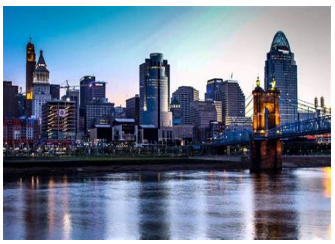
OPTIONS FOR THE NO OPTION PATIENT EVALUATION/TREATMENT OF REFRACTORY ANGINA



Timothy Henry, MD

Medical Director, The Carl and Edyth Lindner Center for Research and Education
The Carl and Edyth Lindner Family Distinguished Chair in Clinical Research
Director of Programmatic and Network Development

The Christ Hospital Health Network

1

DISCLOSURES

The Christ Hospital Health Network

2

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%

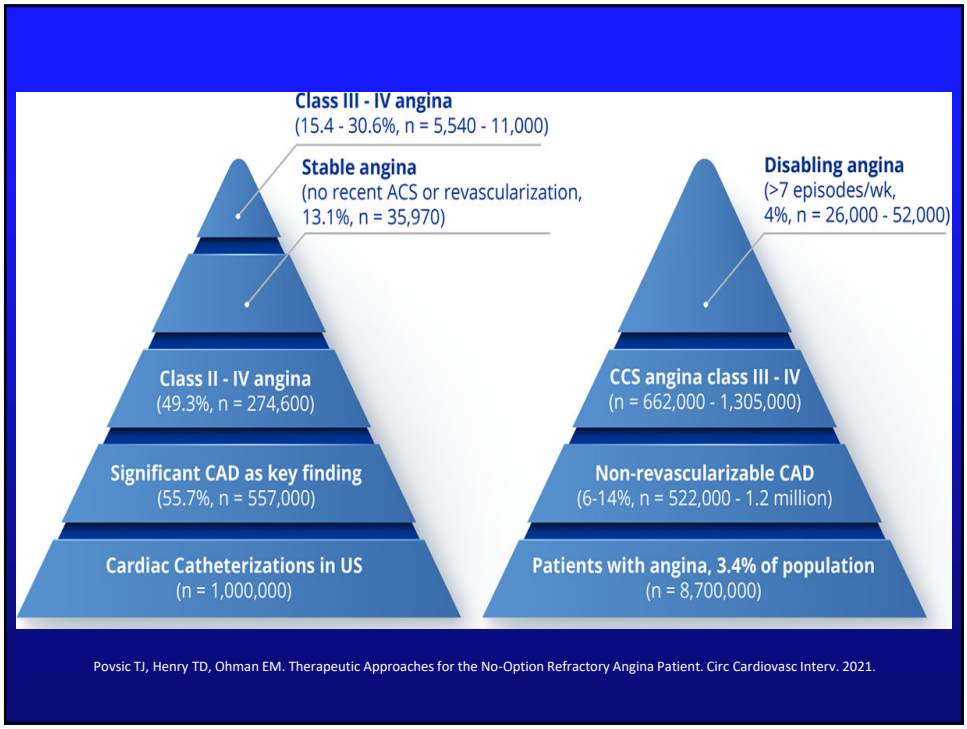
3

Refractory Angina
Current Challenges

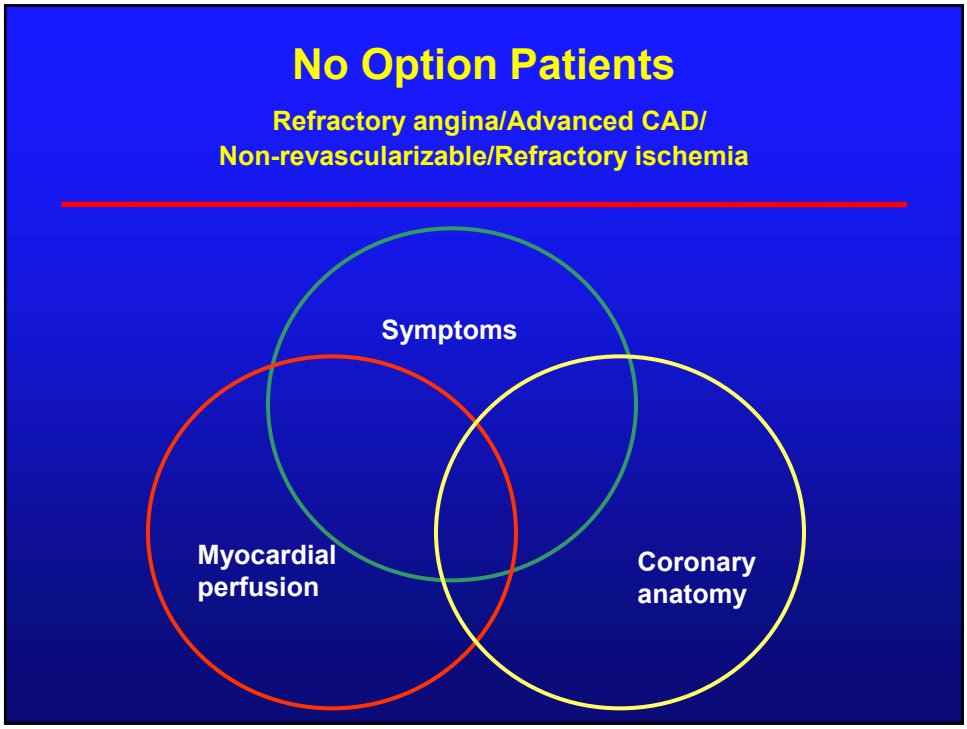
- Current terminology is confusing:
  - "No Option Patients"
  - Refractory Angina - Refractory Ischemia
  - Non-Revascularizable - Advanced CAD
- Limited natural history data
- No large national database or registry
- ? High morbidity and mortality

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

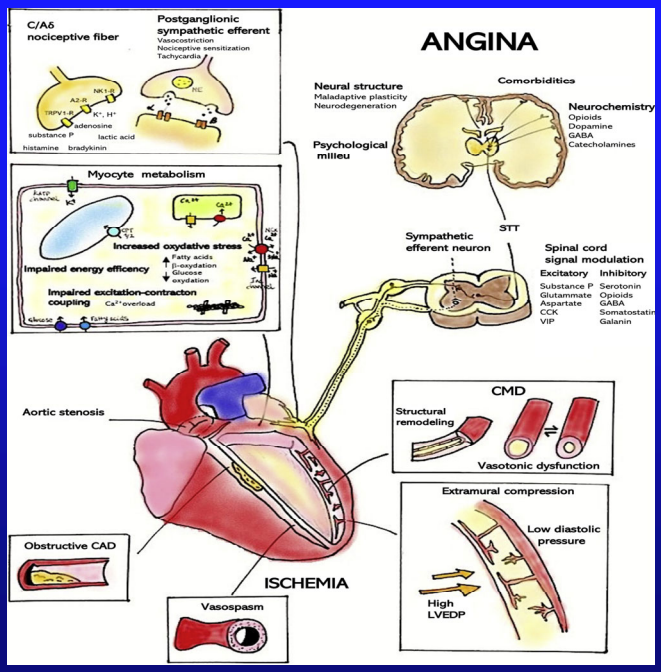
4


Class III - IV angina
(15.4 - 30.6%, n = 5,540 - 11,000)
Stable angina
(no recent ACS or revascularization,
13.1%, n = 35,970)
Disabling angina
(>7 episodes/wk,
4%, n = 26,000 - 52,000)
Class II - IV angina
(49.3%, n = 274,600)
CCS angina class III - IV
(n = 662,000 - 1,305,000)
Significant CAD as key finding
(55.7%, n = 557,000)
Non-revascularizable CAD
(6-14%, n = 522,000 - 1.2 million)
Cardiac Catheterizations in US
(n = 1,000,000)
Patients with angina, 3.4% of population
(n = 8,700,000)
Povsic TJ, Henry TD, Ohman EM. Therapeutic Approaches for the No-Option Refractory Angina Patient. Circ Cardiovasc Interv. 2021.

5


No Option Patients
Refractory angina/Advanced CAD/
Non-revascularizable/Refractory ischemia
Symptoms
Myocardial perfusion
Coronary anatomy

6



Gallone G, Baldetti L, Tzanis G, Gramegna M, Latib A, Colombo A, Henry TD, Giannini F. Refractory Angina: From Pathophysiology to New Therapeutic Nonpharmacological Technologies. JACC Cardiovasc Interv. 2020 Jan 13;13(1):1-19.

7

OPTIMIST PROGRAM GOALS

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

8

Why Call it the OPTIMIST Clinic??

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

9

"No Option" Patients

- Are these patients really out there?
- Are they high risk?
- Can you stratify the risk?
- Are they always no option?

10

"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

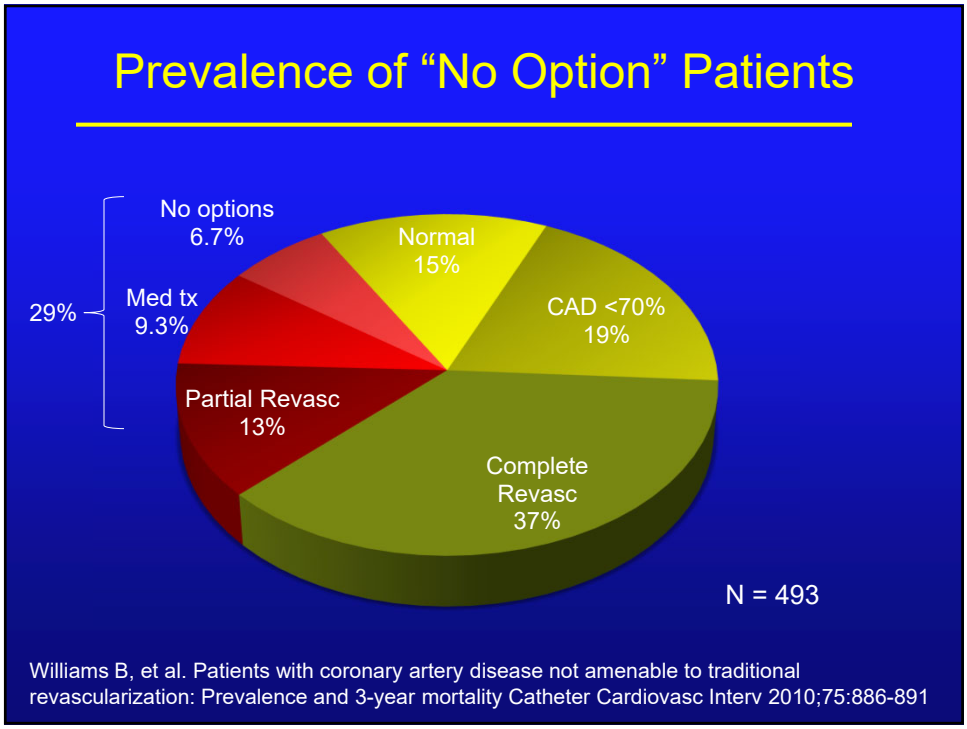
11

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

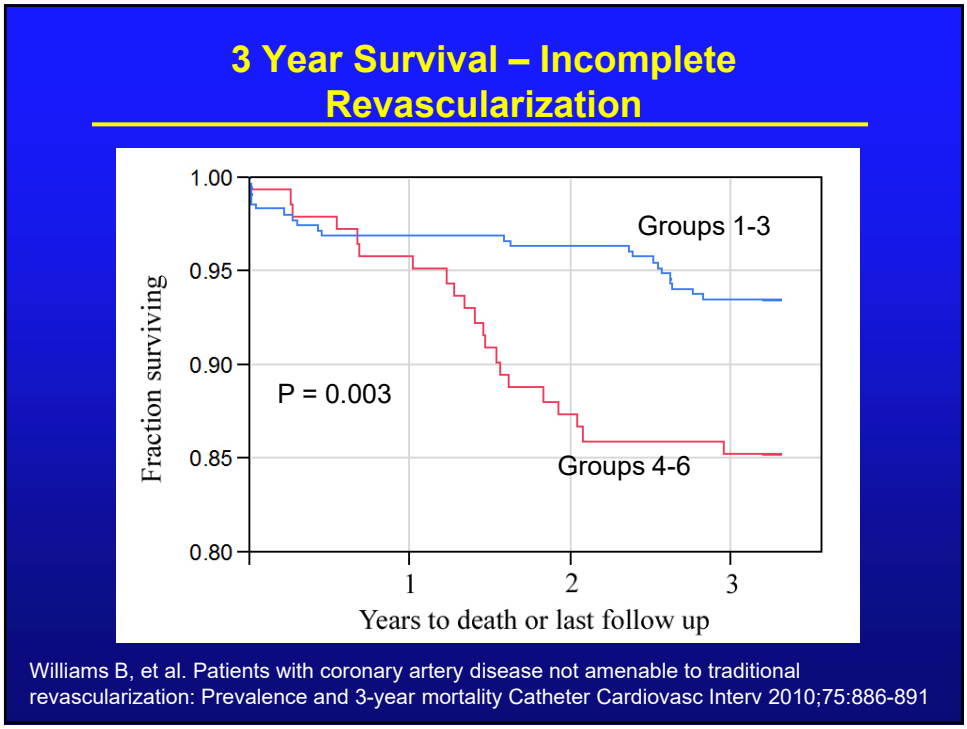
Results Fifty-nine patients of the 500 studied were identified who had refractory ischemia but were not candidates for traditional revascularization. The 59 patients ineligible for traditional methods of revascularization had a rehospitalization rate of 128% (76 total hospitalizations), a 25.5% rate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

12


Prevalence of "No Option" Patients
No options
6.7%
Normal
15%
29%
Med tx
9.3%
CAD <70%
19%
Partial Revasc
13%
Complete
Revasc
37%
N = 493
Williams B, et al. Patients with coronary artery disease not amenable to traditional revascularization: Prevalence and 3-year mortality Catheter Cardiovasc Interv 2010;75:886-891

13


3 Year Survival – Incomplete Revascularization
1.00
0.95
0.90
0.85
0.80
Fraction surviving
Groups 1-3
P = 0.003
Groups 4-6
1
2
3
Years to death or last follow up
Williams B, et al. Patients with coronary artery disease not amenable to traditional revascularization: Prevalence and 3-year mortality Catheter Cardiovasc Interv 2010;75:886-891

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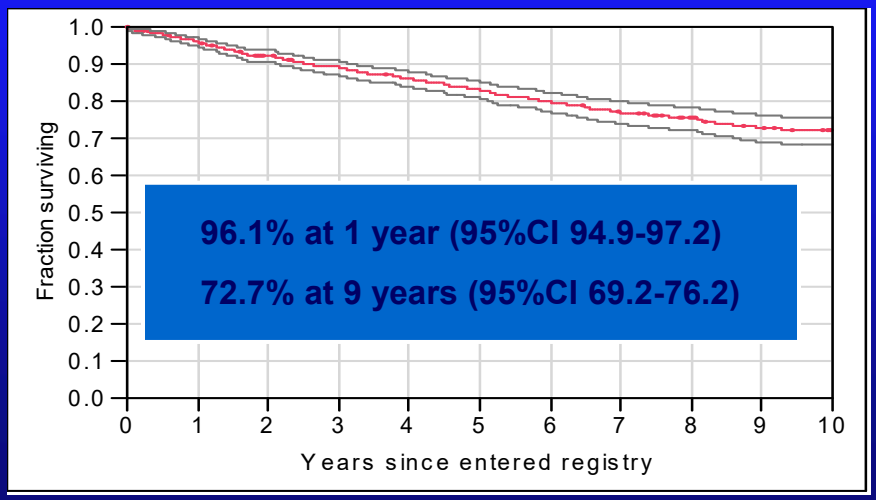
The OPTions In Myocardial Ischemic Syndrome Therapy (OPTIMIST) Program

- 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

15

MHI OPTIMIST PROGRAM Long-Term Survival



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

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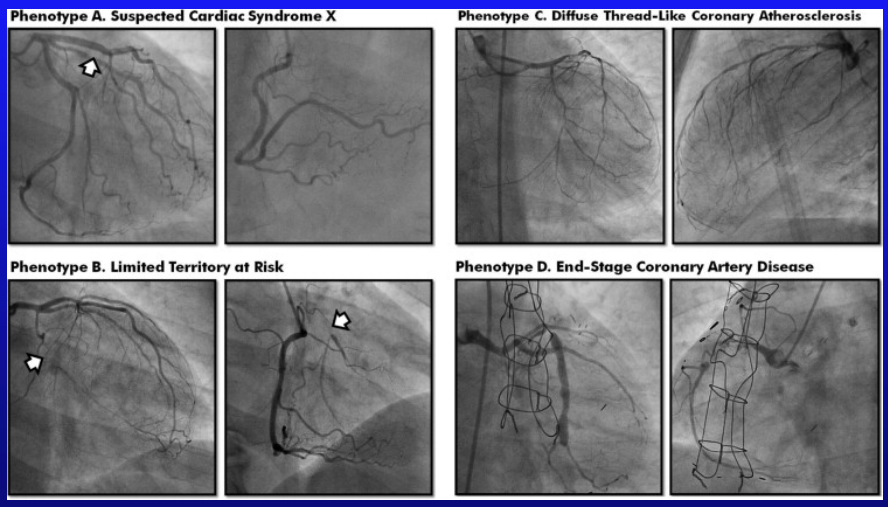
Refractory Angina Classification Scheme



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

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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

Tradewell M, et al. Subsequent Revascularization in "No Option" Patients with Refractory Angina: Etiology and Outcome. Circulation. 2012;126

18

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

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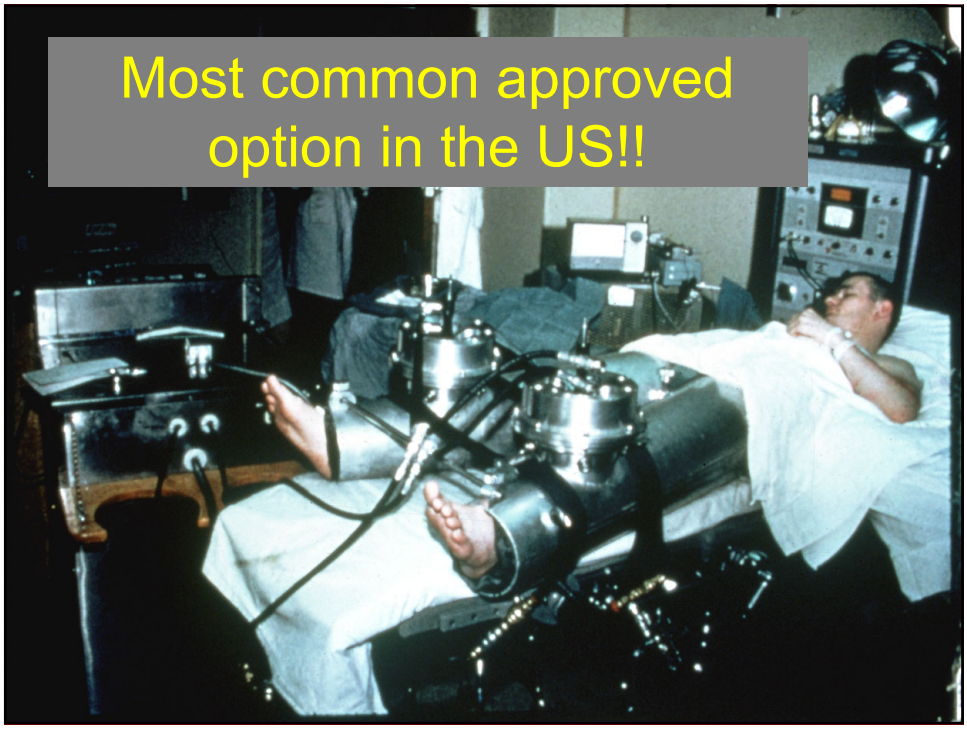
EECP

Enhanced External Counterpulsation

20



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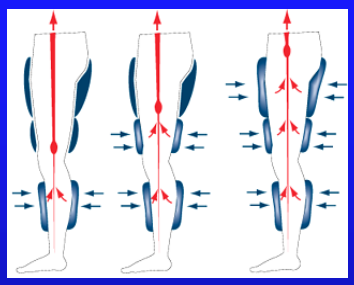
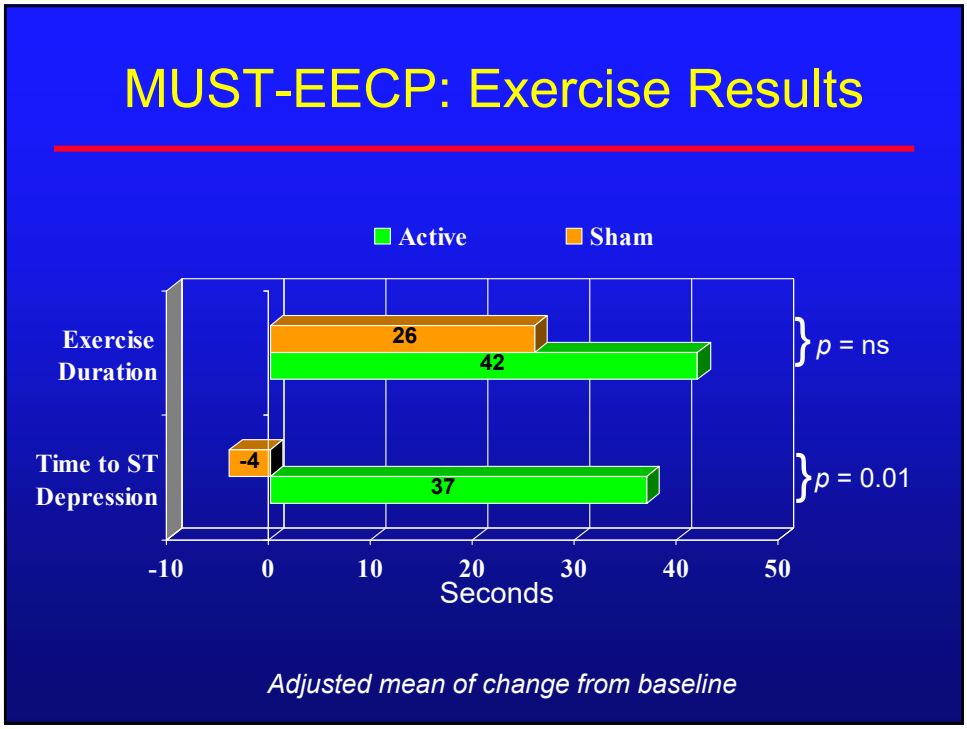
The EECP Procedure

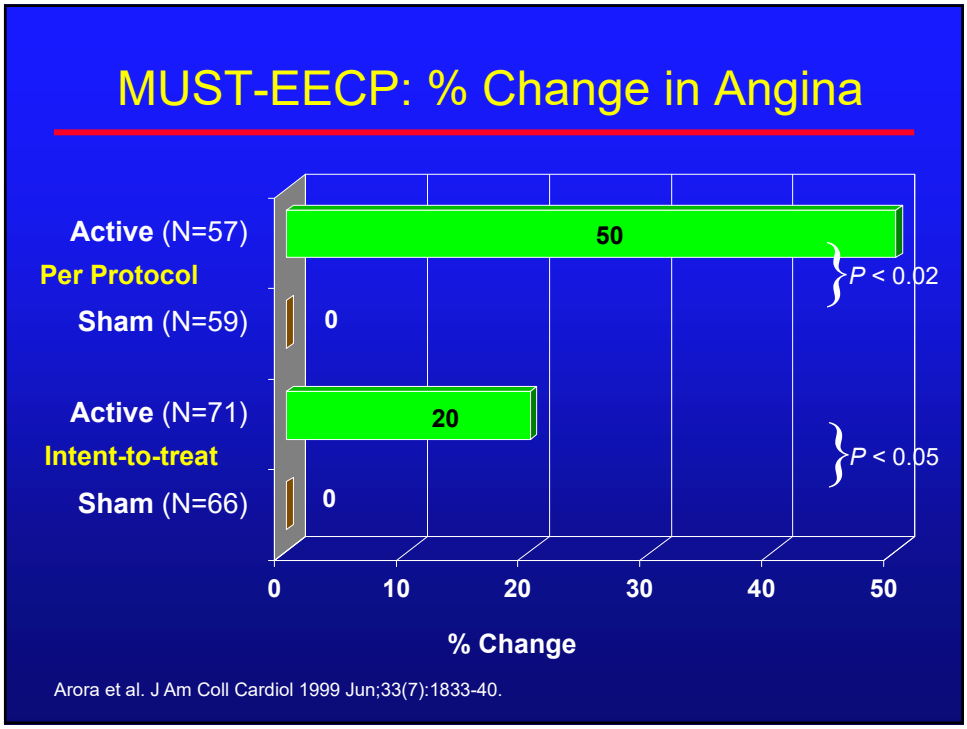


- Series of 3 cuffs wrapped around calves, lower thighs, upper thighs and buttocks
- Sequential distal to proximal compression upon diastole, and
- Simultaneous release of pressure at end-diastole
- Increased diastolic pressure and retrograde aortic flow
- Increased venous return and...
- Systolic unloading,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

22


MUST-EECP: Exercise Results
Active
Sham
Exercise Duration
Time to ST Depression
26
42
-4
37
p = ns
p = 0.01
-10
0
10
20
30
40
50
Seconds
Adjusted mean of change from baseline

23


MUST-EECP: % Change in Angina
Active (N=57)
Per Protocol
Sham (N=59)
Active (N=71)
Intent-to-treat
Sham (N=66)
50
0
20
0
P < 0.02
P < 0.05
0
10
20
30
40
50
% Change
Arora et al. J Am Coll Cardiol 1999 Jun;33(7):1833-40.

24

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

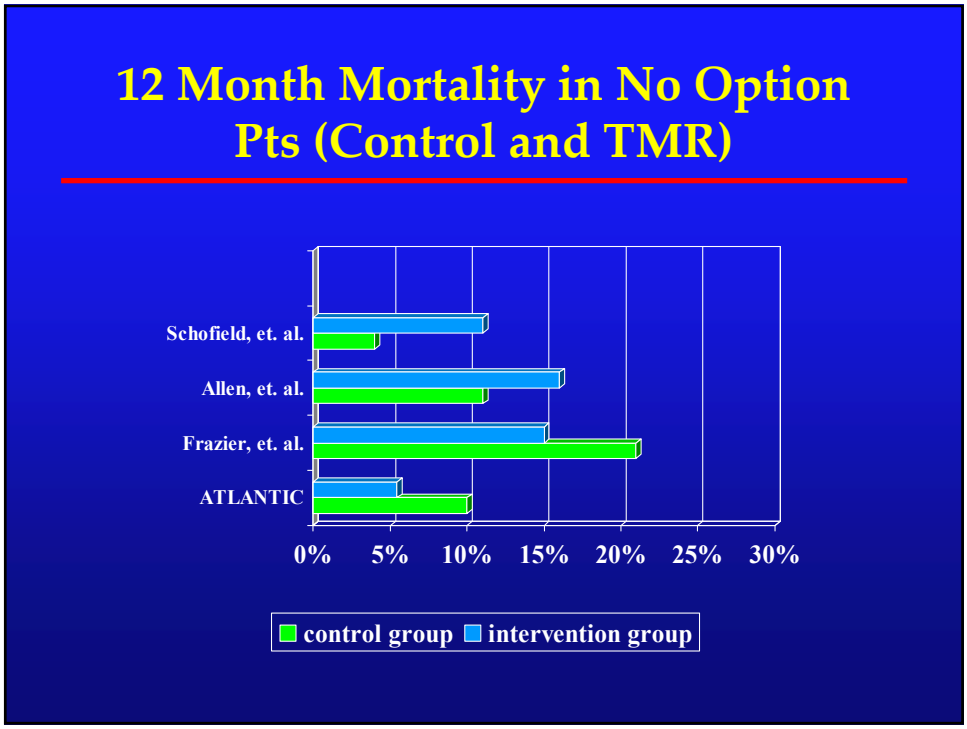
It is recommended that 2 hours daily treatment sessions are separated by a 30 minutes rest interval.

25

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

26


12 Month Mortality in No Option Pts (Control and TMR)
Schofield, et. al.
Allen, et. al.
Frazier, et. al.
ATLANTIC
0%
5%
10%
15%
20%
25%
30%
control group
intervention group

27


Neurostimulation Devices
Percutaneous Leads

28

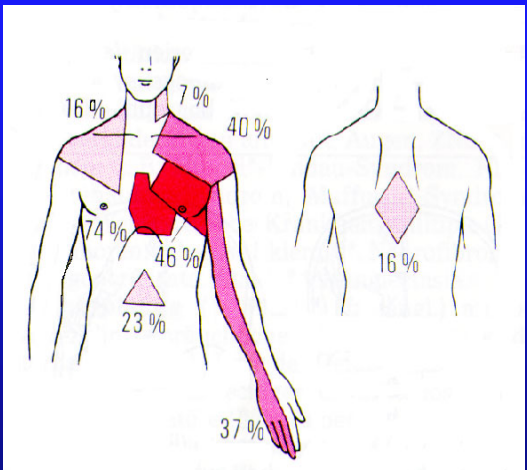
Theorized Mechanisms of Action

- 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

29

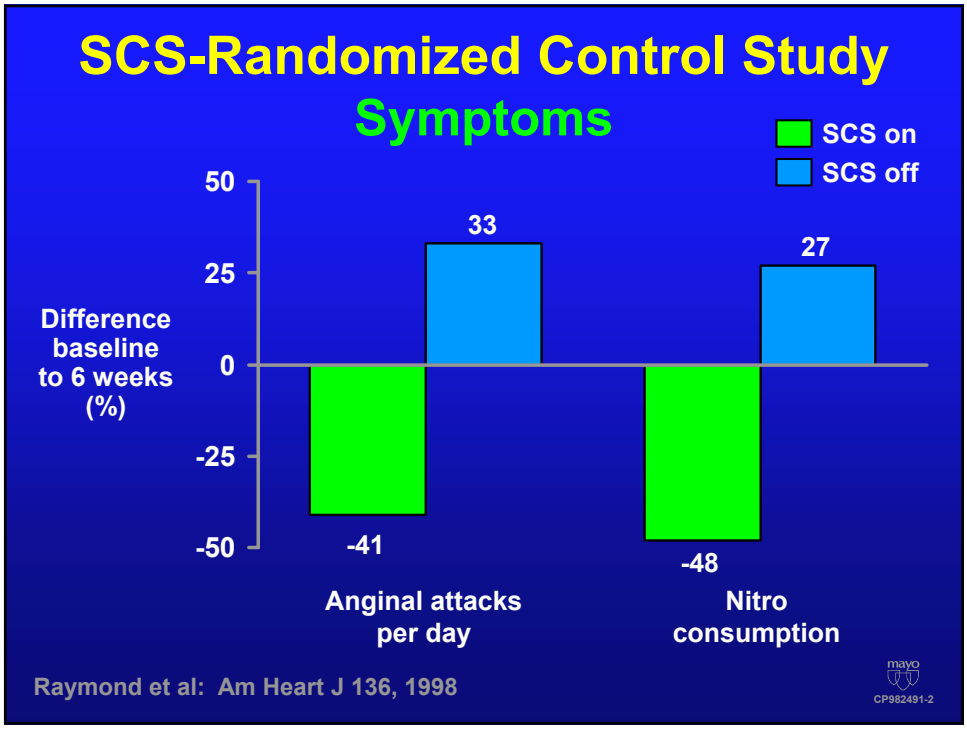
Angina Pectoris



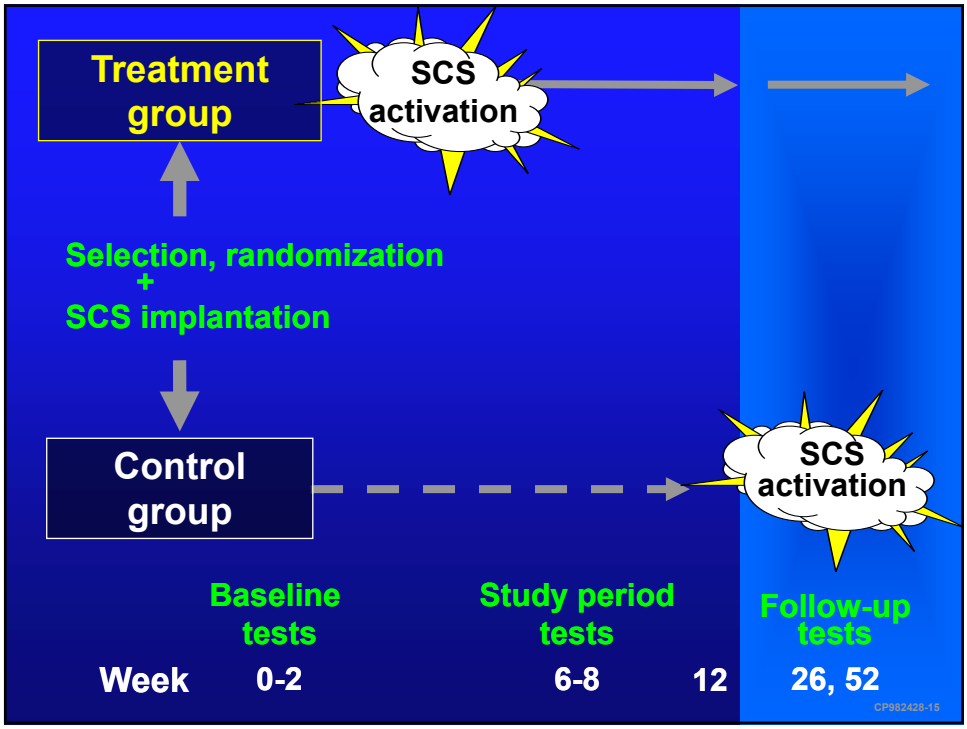
Typical Localisation

Source: "Pschyrembel", Clinical Dictionary, Edition 257, pp. 69-70. German Text published by Walter de Gruyter, 1994.[35]

30


SCS-Randomized Control Study
Symptoms
SCS on
SCS off
Difference baseline to 6 weeks (%)
50
25
0
-25
-50
33
27
-41
-48
Anginal attacks per day
Nitro consumption
Raymond et al: Am Heart J 136, 1998
CP982491-2

31


Treatment group
SCS activation
Selection, randomization
+
SCS implantation
Control group
SCS activation
Baseline tests
Study period tests
Follow-up tests
Week
0-2
6-8
12
26, 52
CP982428-15

32

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)

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L-arginine supplementation

Beneficial Effects Reported in the Literature

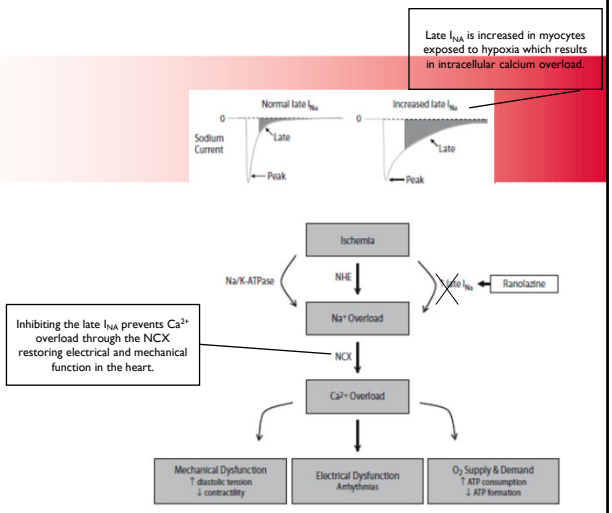
- ⇑ EDNO production
- ⇑ coronary blood flow in CAD
- ⇓ ST segment depression in CAD
- ⇑ work performed in CAD, claudication and heart failure
- ⇑ erectile function
- ⇓ pain of Raynaud's Disease
- ⇑ wound healing
- ⇓ symptoms of cystitis
- ⇓ symptoms of esophageal dysmotility

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

34

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_{Kr}) which prolongs the ventricular action potential
  - ★ Ranolazine can prolong the QT interval in a concentration-dependent manner



Hasenfuss and Maier, 2007

CORZYNA™

KYE Pharmaceuticals

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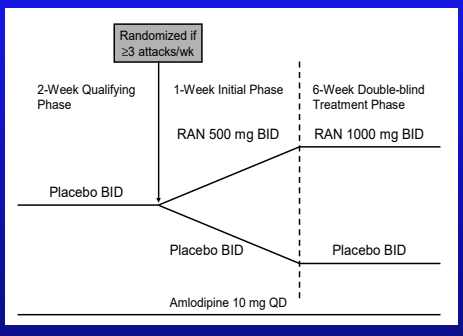
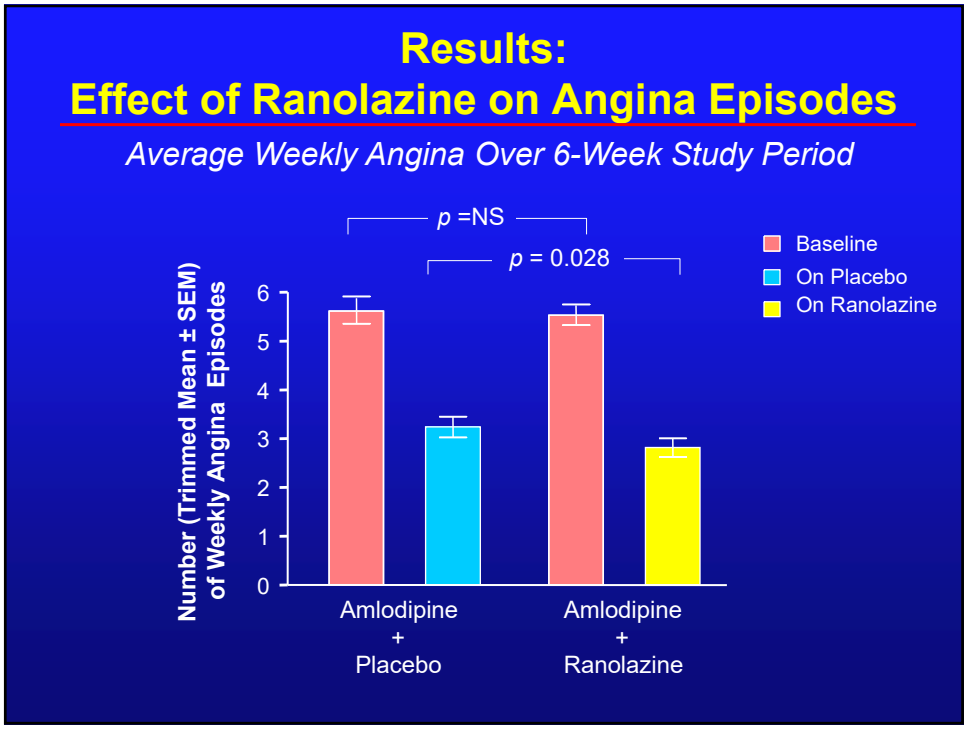
ERICA: Study Design

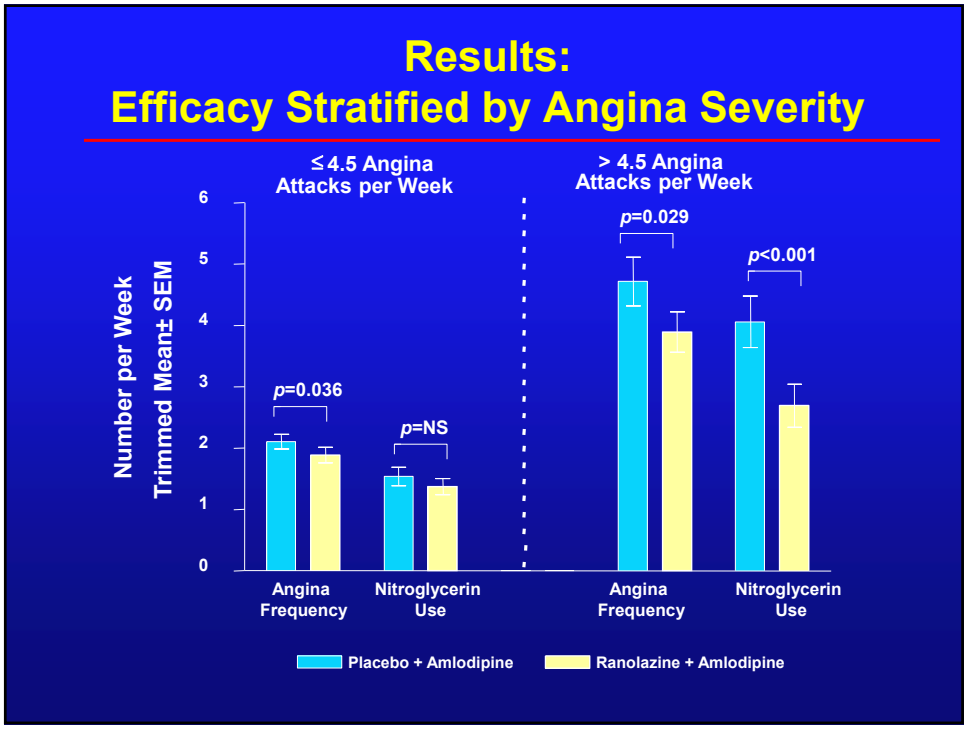


Stone PH, Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566-75.

36


Results:
Effect of Ranolazine on Angina Episodes
Average Weekly Angina Over 6-Week Study Period
p =NS
p = 0.028
Baseline
On Placebo
On Ranolazine
Number (Trimmed Mean ± SEM) of Weekly Angina Episodes
0
1
2
3
4
5
6
Amlodipine + Placebo
Amlodipine + Ranolazine

37


Results:
Efficacy Stratified by Angina Severity
≤ 4.5 Angina Attacks per Week
> 4.5 Angina Attacks per Week
Number per Week Trimmed Mean± SEM
0
1
2
3
4
5
6
p=0.036
p=NS
p=0.029
p<0.001
Angina Frequency
Nitroglycerin Use
Angina Frequency
Nitroglycerin Use
Placebo + Amlodipine
Ranolazine + Amlodipine

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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).

Bennett NM et al. Ranolazine Refractory Angina Registry Trial: 1-Year Results. Crit Pathw Cardiol. 2014 Sep;13(3):96-8

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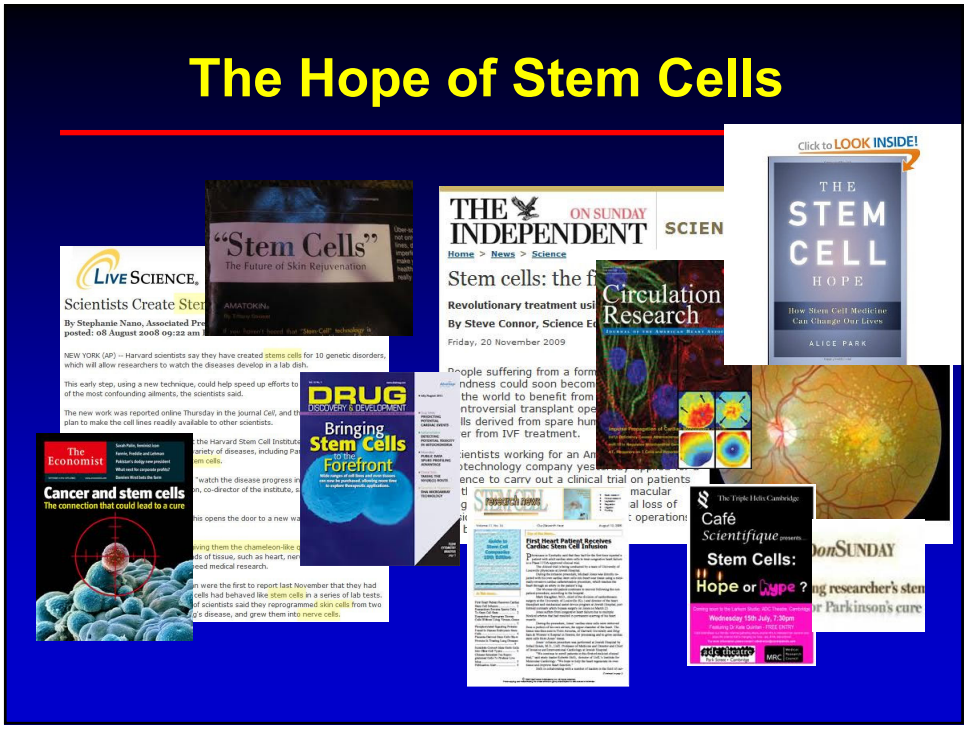
MHIF Ranolazine Refractory Angina Registry Trial

Table 1. One Year Follow-Up Information

	Continued Ranolazine	Discontinued Ranolazine	P-Value
Angina Class Improvement			
No Change, %	3 (5.3)	20 (48.8)	<0.001
One Class, %	22 (38.6)	11 (26.8)	
Two Classes, %	26 (45.6)	9 (22.0)	
Three Classes, %	6 (10.5)	1 (2.4)	
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

Bennett NM et al. Ranolazine Refractory Angina Registry Trial: 1-Year Results. Crit Pathw Cardiol. 2014 Sep;13(3):96-8

40

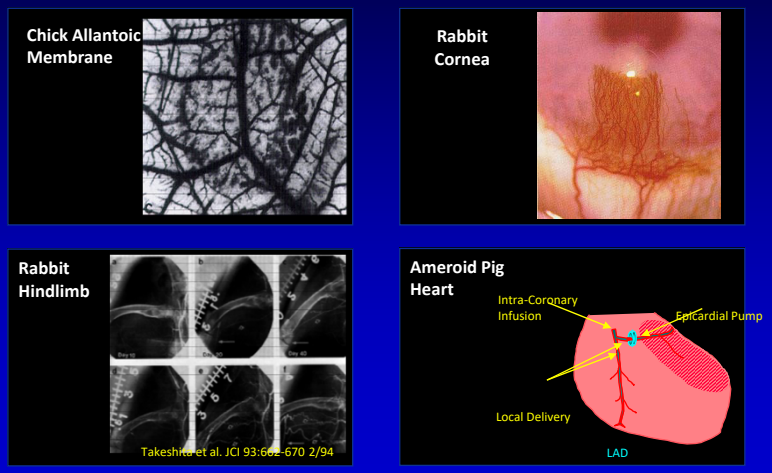

The Hope of Stem Cells
"Stem Cells"
The Future of Skin Rejuvenation
LIVE SCIENCE
Scientists Create Stem
THE INDEPENDENT
ON SUNDAY
SCIEN
Home > News > Science
Stem cells: the f
Revolutionary treatment usi
By Steve Connor, Science Ed
Friday, 20 November 2009
Circulation Research
Click to LOOK INSIDE!
THE STEM CELL HOPE
How Stem Cell Medicine Can Change Our Lives
ALICE PARK
DRUG DISCOVERY & DEVELOPMENT
Bringing Stem Cells to the Forefront
The Economist
Cancer and stem cells
The connection that could lead to a cure
The Triple Helix Cambridge
Café Scientifique presents...
Stem Cells:
Hope or Hype ?
Wednesday 15th July, 7.30pm
First Heart Patient Receives Cardiac Stem Cell Infusion
SUNDAY
researcher's stem
Parkinson's cure

41


Can We Really Grow New Blood Vessels?

42

Angiogenesis Really, Really, Really Works!



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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=88** — **IM BM Cells**
  - **ADVANCE: n=24** — **IM CD34+ Cells**
  - **ACT-34: n=162** — **IM CD34+Cells**
  - **PRECISE: n=27** — **IM Adipose derived Cells**

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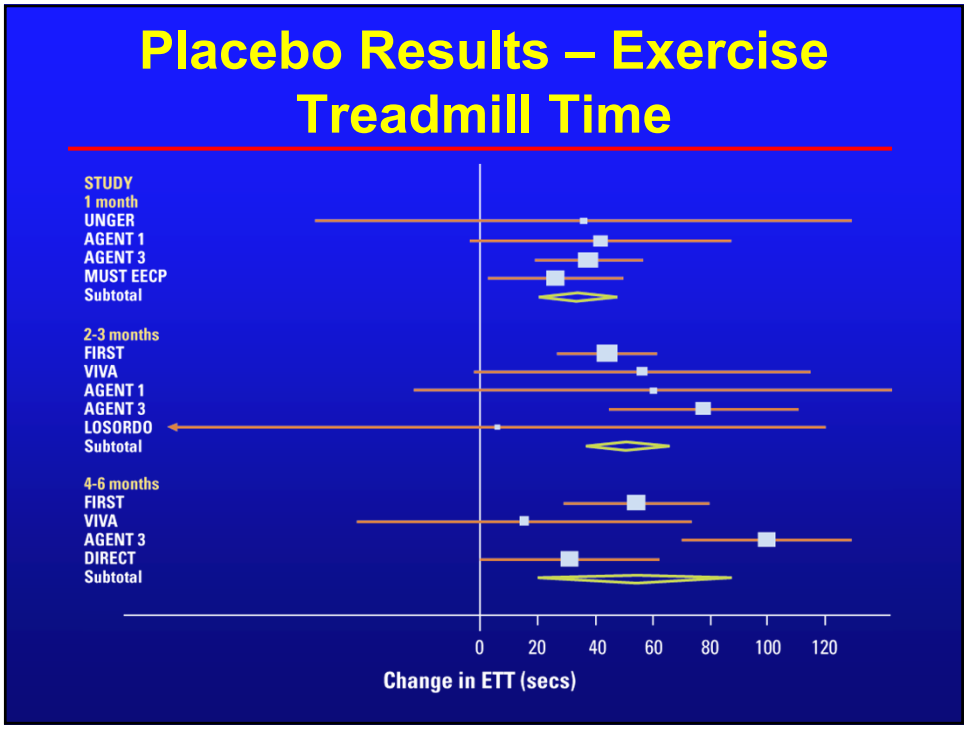
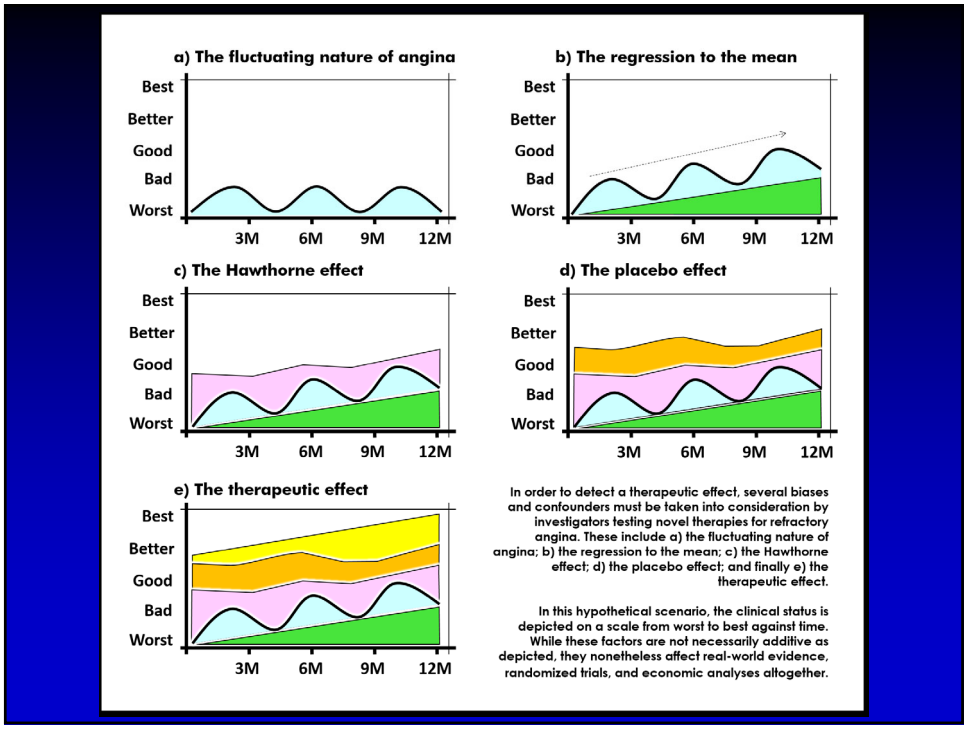

Placebo Results – Exercise Treadmill Time
STUDY
1 month
UNGER
AGENT 1
AGENT 3
MUST EECP
Subtotal
2-3 months
FIRST
VIVA
AGENT 1
AGENT 3
LOSORDO
Subtotal
4-6 months
FIRST
VIVA
AGENT 3
DIRECT
Subtotal
0
20
40
60
80
100
120
Change in ETT (secs)

45


a) The fluctuating nature of angina
b) The regression to the mean
c) The Hawthorne effect
d) The placebo effect
e) The therapeutic effect
Best
Better
Good
Bad
Worst
3M
6M
9M
12M
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.

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AGENT 3

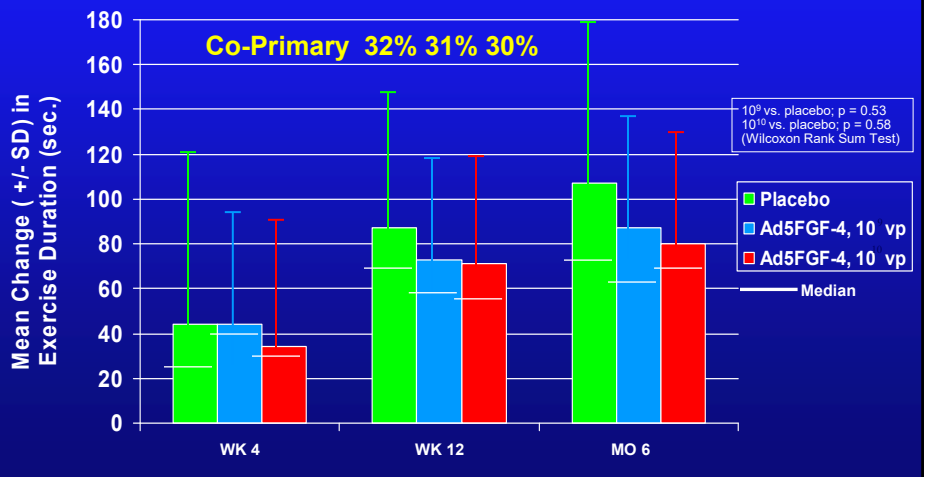
A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Patients with Stable Angina

Henry et al. JACC 2007

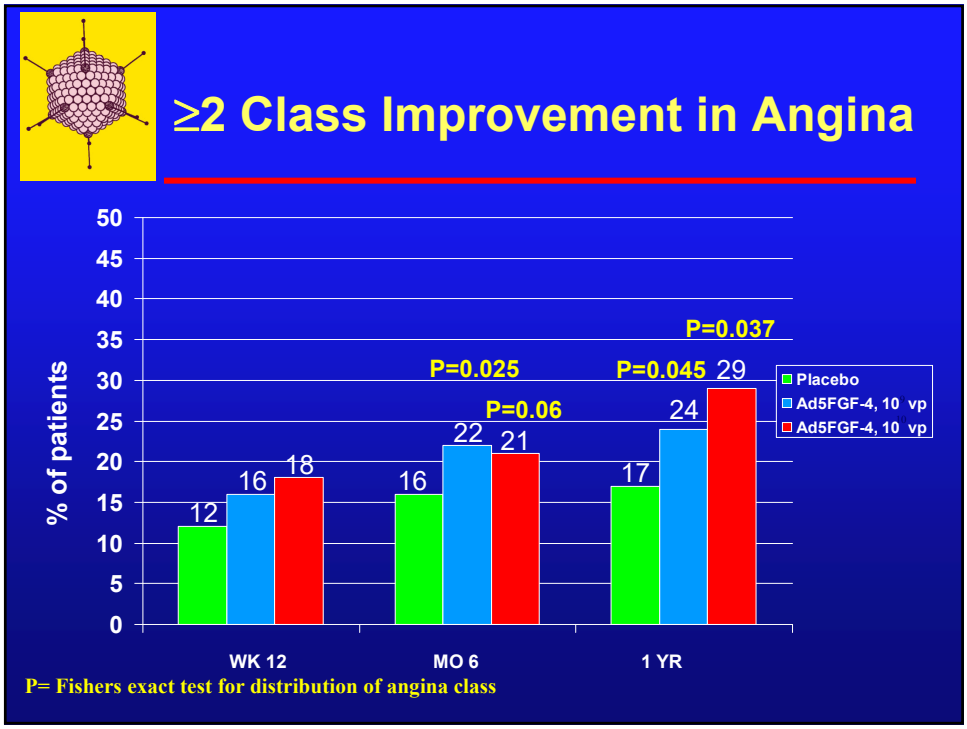
47

Primary Endpoint

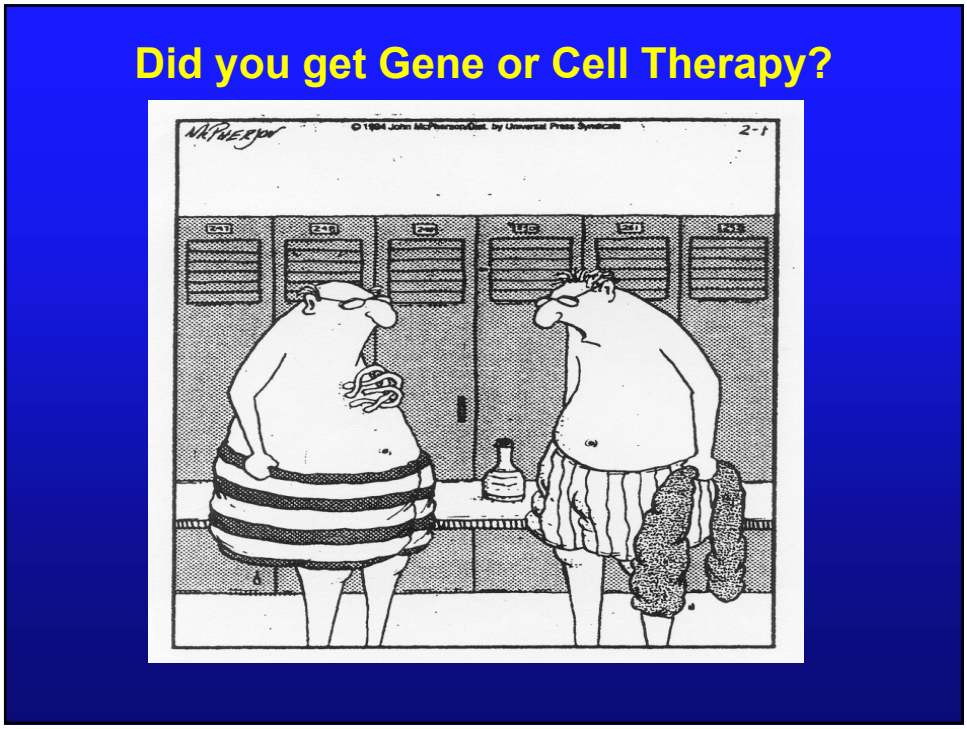
Change in Exercise Duration from Baseline (sec.)



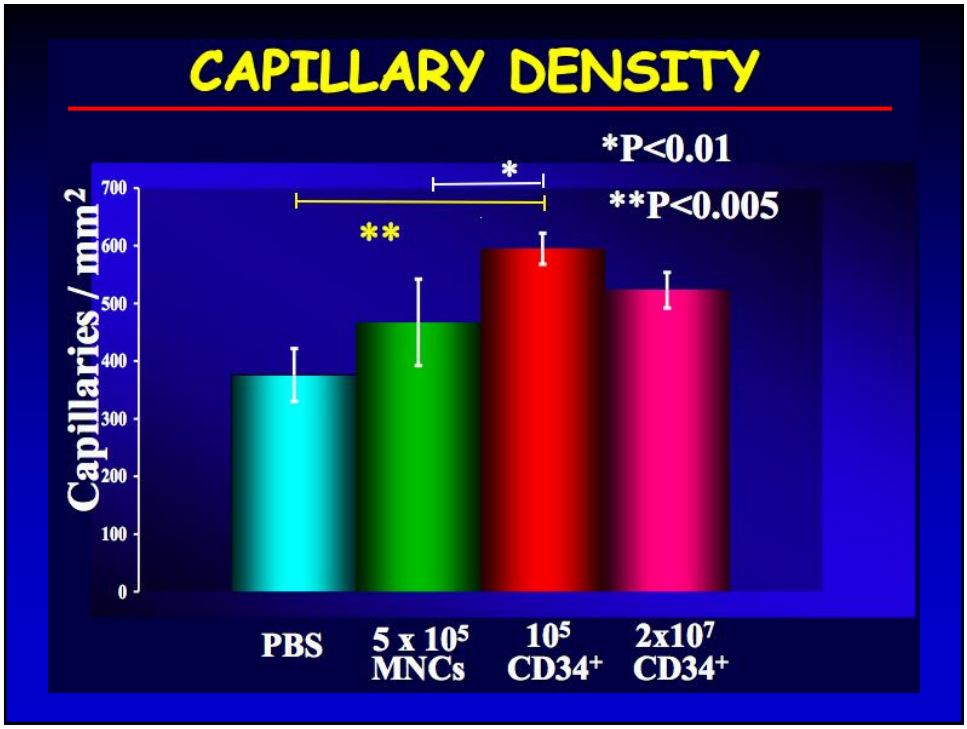
48


≥2 Class Improvement in Angina
% of patients
50
45
40
35
30
25
20
15
10
5
0
12
16
18
16
22
21
17
24
29
P=0.025
P=0.06
P=0.045
P=0.037
WK 12
MO 6
1 YR
Placebo
Ad5FGF-4, 10 vp
Ad5FGF-4, 10 vp
P= Fishers exact test for distribution of angina class

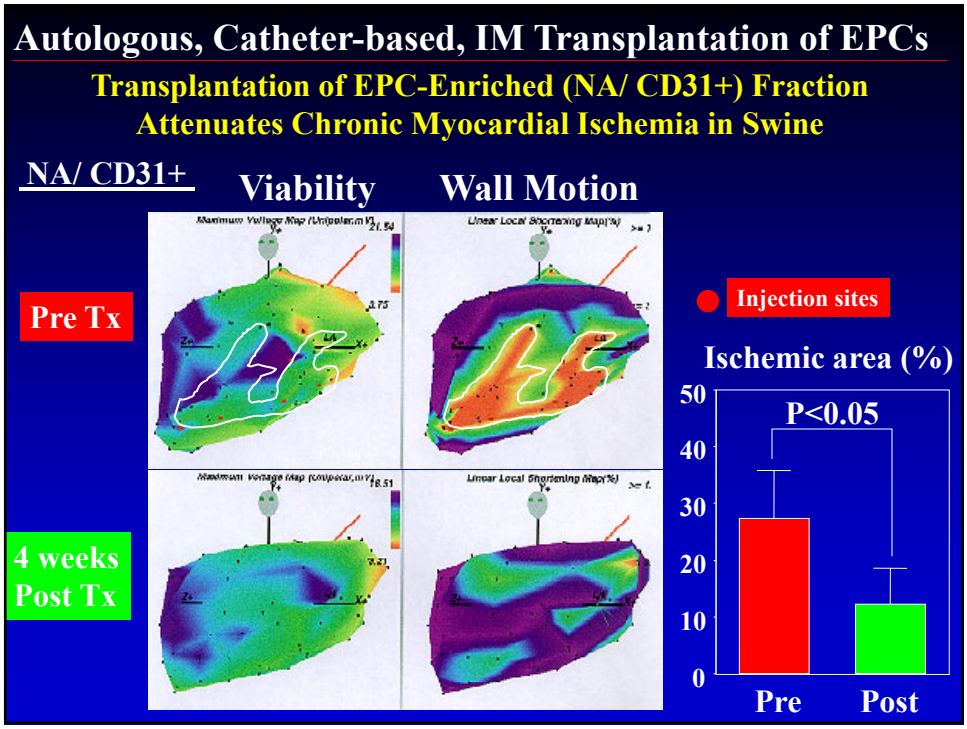
49


Did you get Gene or Cell Therapy?

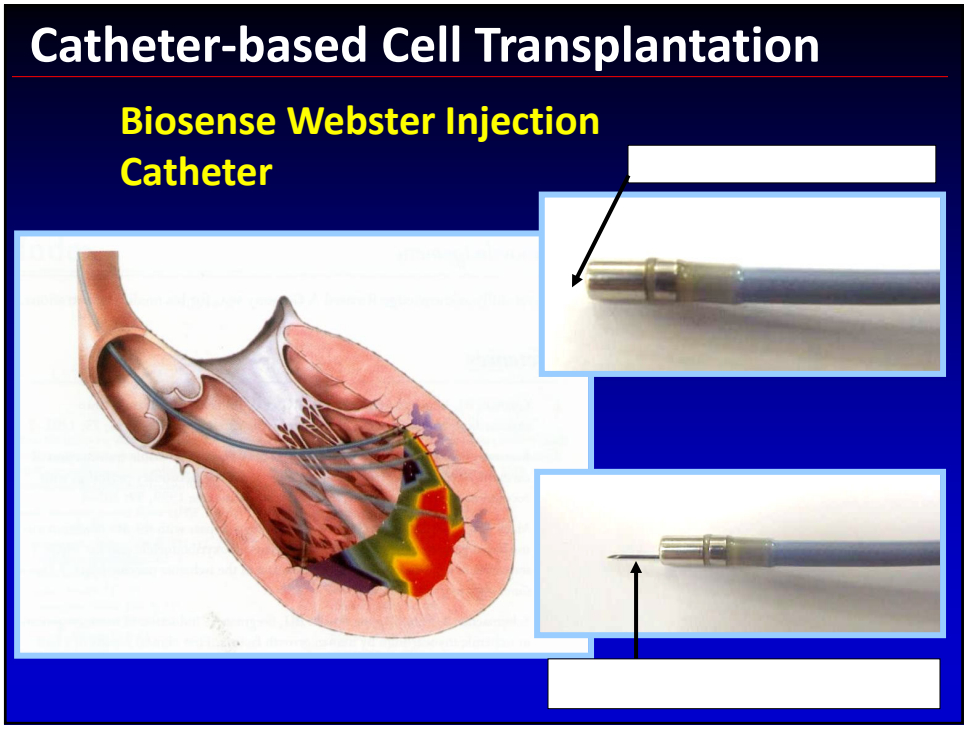
50


CAPILLARY DENSITY
*P<0.01
**P<0.005
Capillaries / mm2
700
600
500
400
300
200
100
0
*
**
PBS
5 x 10^5 MNCs
10^5 CD34+
2x10^7 CD34+

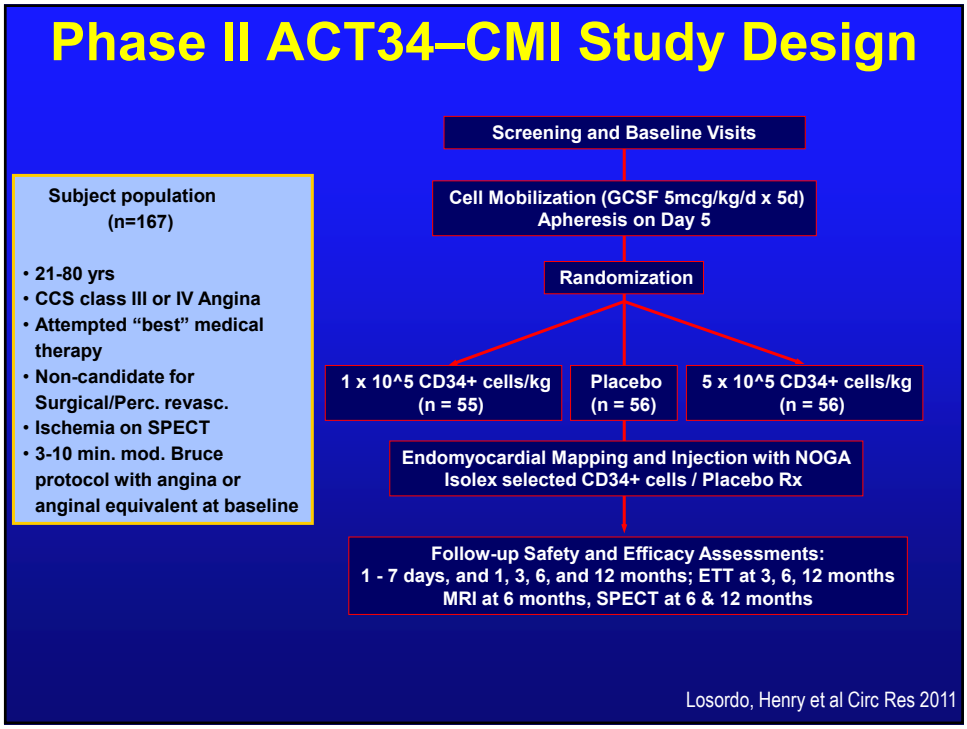
51


Autologous, Catheter-based, IM Transplantation of EPCs
Transplantation of EPC-Enriched (NA/ CD31+) Fraction
Attenuates Chronic Myocardial Ischemia in Swine
NA/ CD31+
Viability
Wall Motion
Pre Tx
4 weeks Post Tx
Injection sites
Ischemic area (%)
50
40
30
20
10
0
P<0.05
Pre
Post

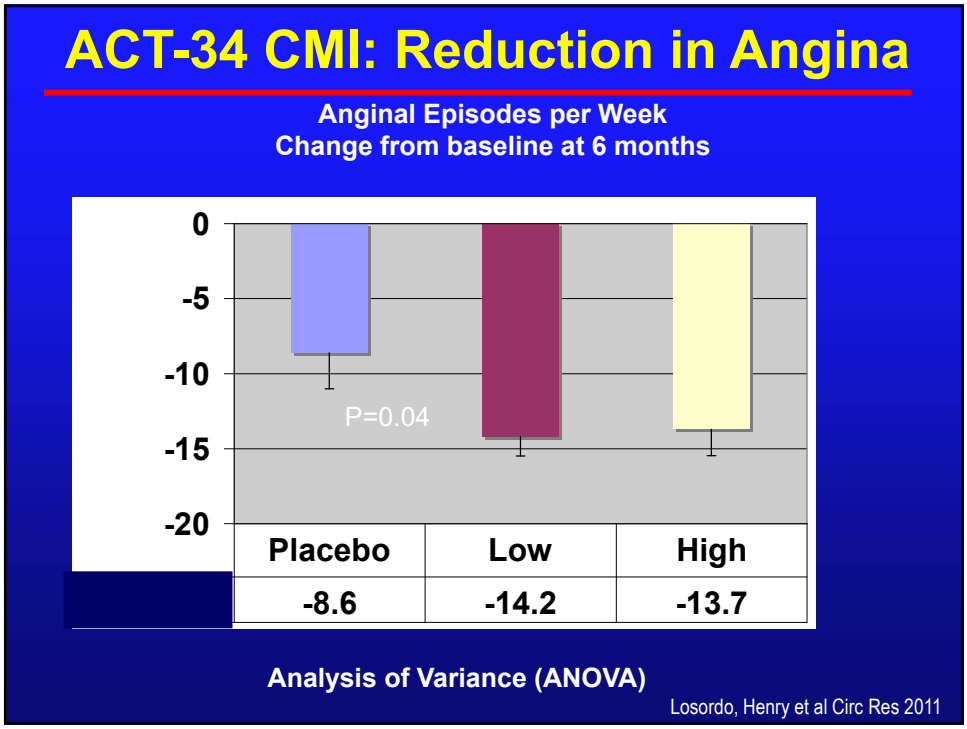
52


Catheter-based Cell Transplantation
Biosense Webster Injection Catheter

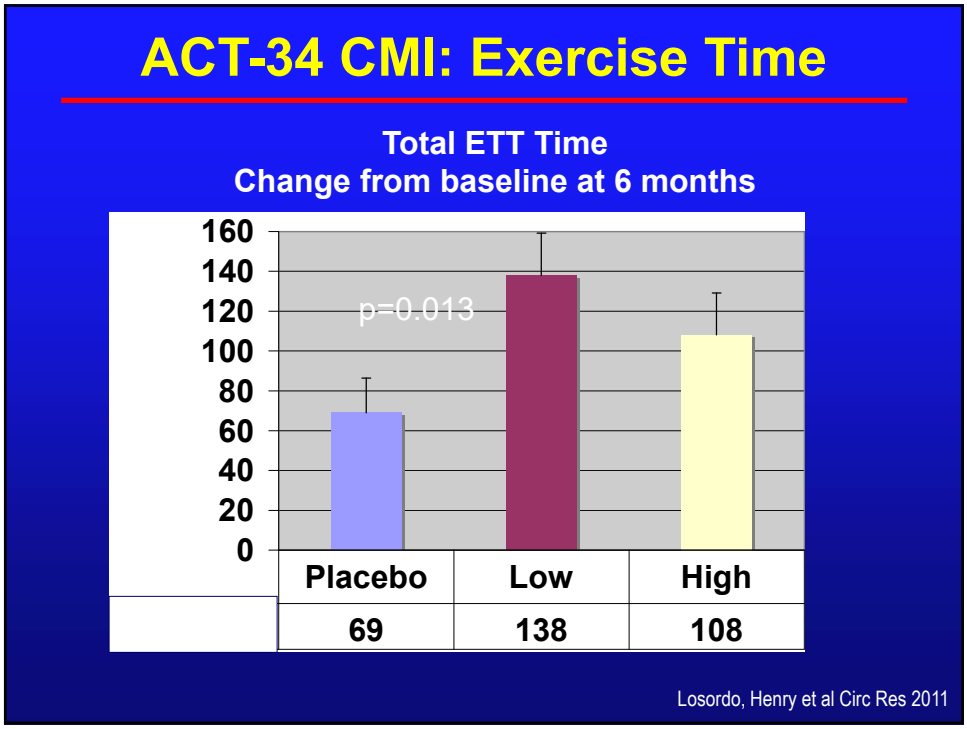
53


Phase II ACT34–CMI Study Design
Subject population (n=167)
• 21-80 yrs
• CCS class III or IV Angina
• Attempted "best" medical therapy
• Non-candidate for Surgical/Perc. revasc.
• Ischemia on SPECT
• 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline
Screening and Baseline Visits
Cell Mobilization (GCSF 5mcg/kg/d x 5d) Apheresis on Day 5
Randomization
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

54


ACT-34 CMI: Reduction in Angina
Anginal Episodes per Week
Change from baseline at 6 months
0
-5
-10
-15
-20
P=0.04
Placebo
Low
High
-8.6
-14.2
-13.7
Analysis of Variance (ANOVA)
Losordo, Henry et al Circ Res 2011

55


ACT-34 CMI: Exercise Time
Total ETT Time
Change from baseline at 6 months
160
140
120
100
80
60
40
20
0
p=0.013
Placebo
Low
High
69
138
108
Losordo, Henry et al Circ Res 2011

56

Major Adverse Cardiac Events (24 Months)

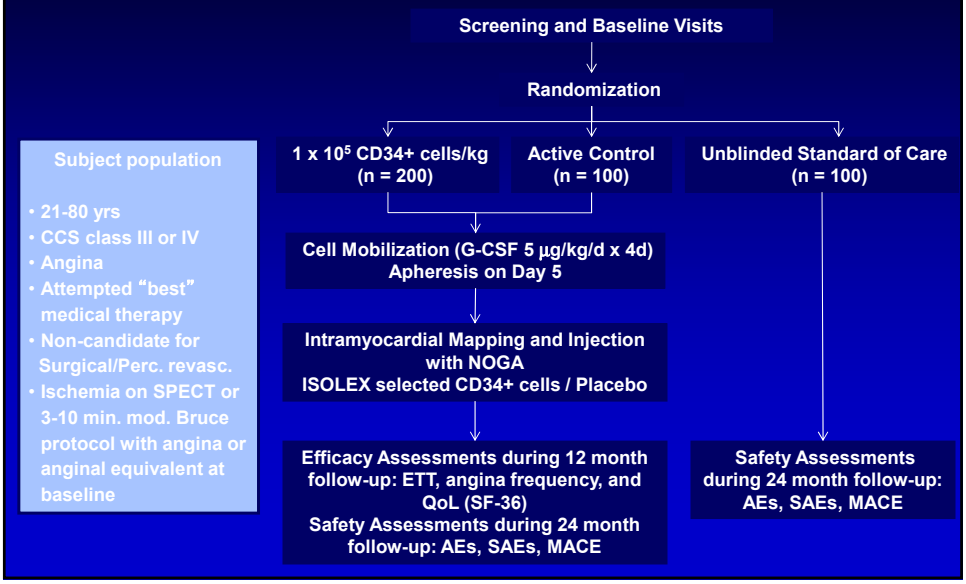
	Control	$1x10^5$ $CD34^{+cells}/kg$	$5x10^5$ $CD34^{+cells}/kg$	p-value*
Death	7(12.5%)	1(1.8%)	2(3.6%)	0.081
MI	10 (17.9%)	9(16.4%)	6(10.7%)	0.587
Death, MI	15(26.8%)	10(18.2%)	6(10.7%)	0.096
Death, MI, ACS Hospitalization	17(30.4%)	10(18.2%)	8(14.3%)	0.101
Death, MI, ACS or Worse CHF Hospitalization	19(33.9%)	12(21.8%)	9(16.1%)	0.078

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

57

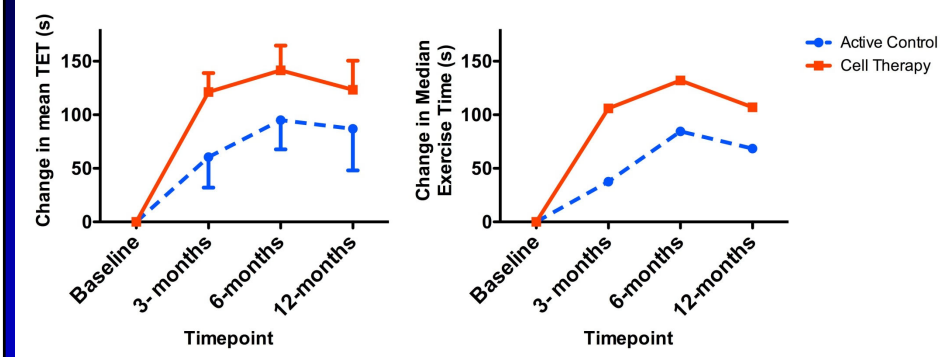
Refractory Angina Phase III RENEW Study Design



58

RENEW: PRIMARY ENDPOINT AS TREATED

MEAN MEDIAN



RENEWstudy

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

59

RENEW: ANGINA FREQUENCY

6 months Relative Risk

As Treated	ITT
0.63 P=0.05	0.58 P=0.02

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

60

RENEW RESULTS: 2-YEAR MACE

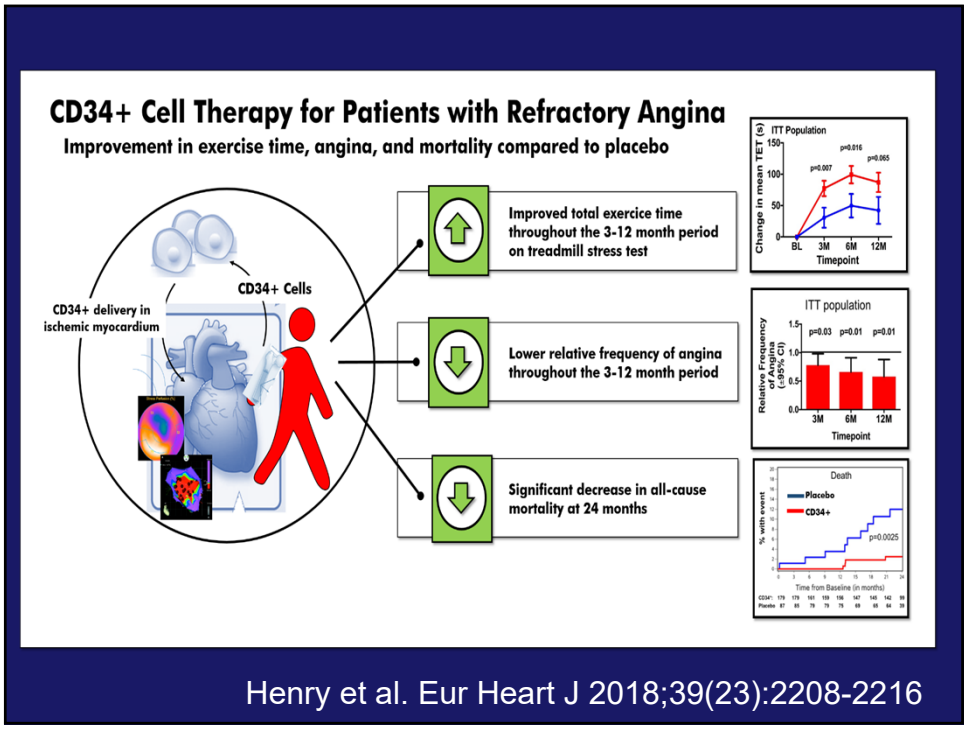
	Standard of Care (n=28)	Active Control (n=28)	CD34+ Cell Txt (n=50)	Started Mobilization but Not Injected (n=6)
Patients with MACE	19 (67.9%)	12 (42.9%)	23 (46.0%)	2 (33.3%)
Death	2 (7.1%)	3 (10.7%)	2 (4.0%)	0
MI	2 (7.1%)	3 (10.7%)	5 (10.0%)	2 (33.3%)
Perforation	0	0	2 (4.0%)	1* (16.7%)
Stroke	-	-	-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

RENEW study

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

61

62



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

63

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

64

- We belie… cell therapy for refra… cularly promisi… both function… ity
- It is imp… ethods to bring th… s

65

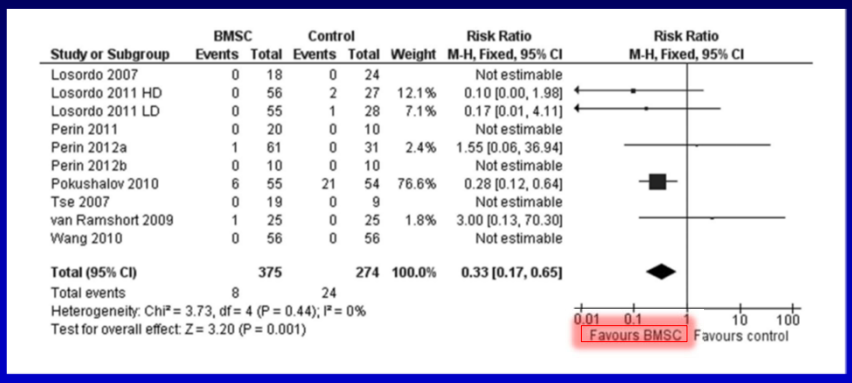
Bone Marrow Stem Cell Treatment for Ischemic Heart Disease in Patients with No Option of Revascularization: A Systematic Review and Meta-Analysis

Sheila A. Fisher[1,2], Carolyn Dorée[1,2], Susan J. Brunskill[1,2], Anthony Mathur[3], Enca Martin-Rendon[2,4]*

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

66

Mortality

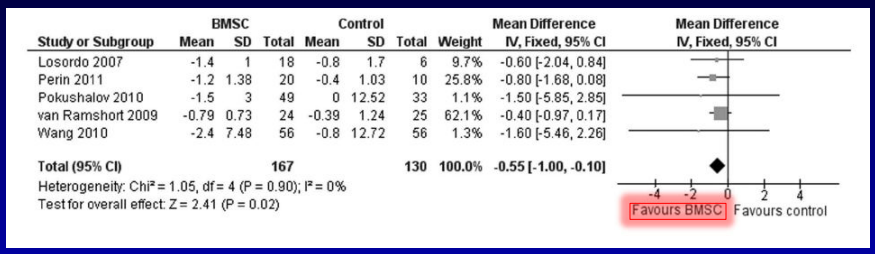


PLoS One 2013 Jun 19;8(6):e64669

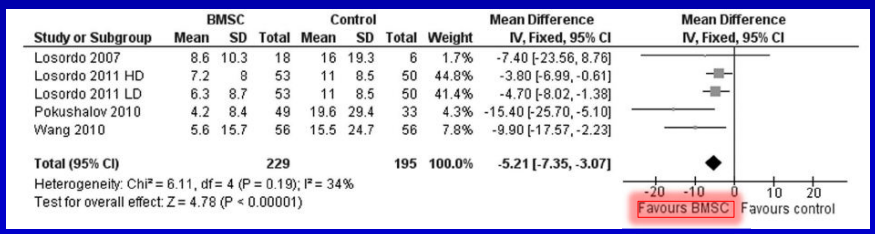
67

Martin-Rendon Meta-analysis

Angina Class



Angina Frequency

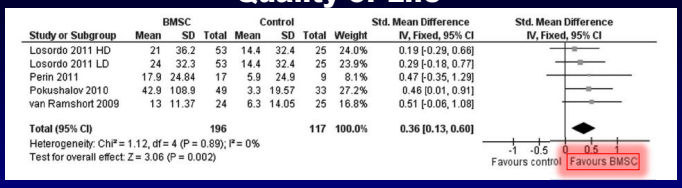


PLoS One 2013 Jun 19;8(6):e64669

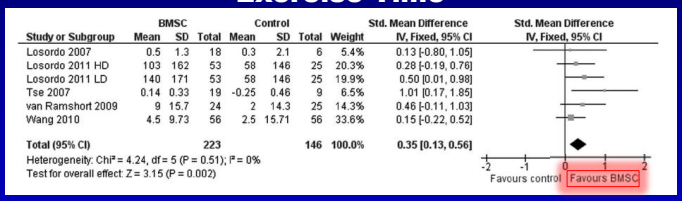
68

Martin-Rendon Meta-analysis

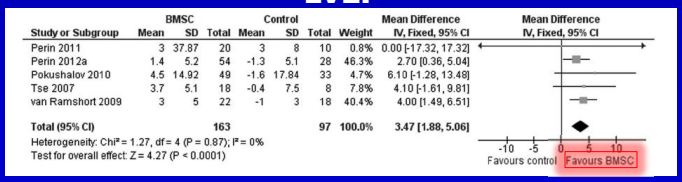
Quality of Life



Exercise Time



LVEF



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

69

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 a 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 metanalysis which demonstrate consistent results with other angiogenic cells
- SAFE!!!
- Limited treatment options

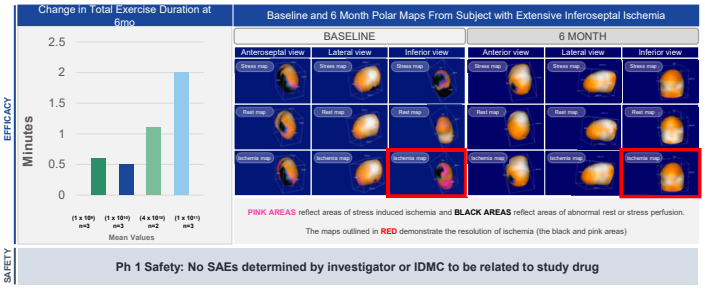
70

Why is this not available for our Patients?

71

PHASE 1 GENE THERAPY TRIAL: XYLOCOR

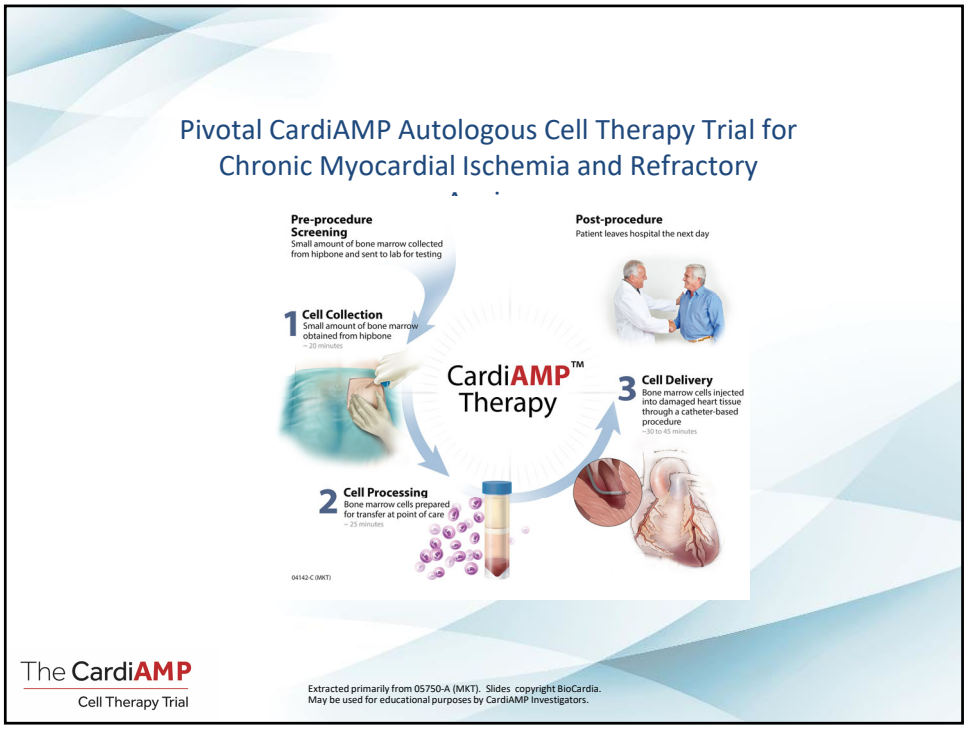
Dose dependent improvements in PET and Angina
CIRC CARD INTERVENTIONS: In Press



Source: 2022 AATS presentation

XyloCor Therapeutics

72


Pivotal CardiAMP Autologous Cell Therapy Trial for Chronic Myocardial Ischemia and Refractory
Pre-procedure Screening
Small amount of bone marrow collected from hipbone and sent to lab for testing
Post-procedure
Patient leaves hospital the next day
1 Cell Collection
Small amount of bone marrow obtained from hipbone
~ 20 minutes
CardiAMP™ Therapy
3 Cell Delivery
Bone marrow cells injected into damaged heart tissue through a catheter-based procedure
~30 to 45 minutes
2 Cell Processing
Bone marrow cells prepared for transfer at point of care
~ 25 minutes
04142-C (MKT)
The CardiAMP Cell Therapy Trial
Extracted primarily from 05750-A (MKT). Slides copyright BioCardia.
May be used for educational purposes by CardiAMP Investigators.

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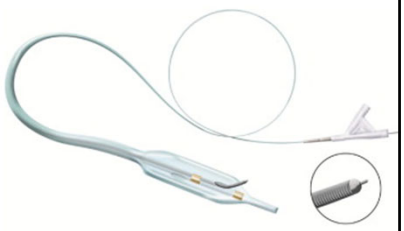
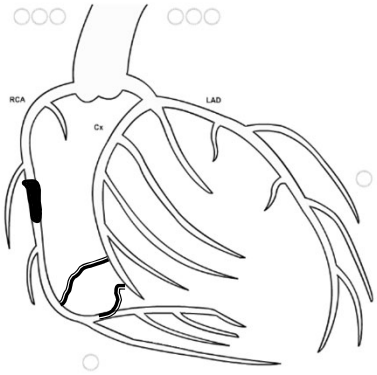
Proliferation of Stem Cell Clinics
The Center for Regenerative Medicine
The Procedure
- Knee Joint
- Back Pain
- Shoulder Pain
The Knee Diaries
Federal Regulatory Oversight of US Clinics Marketing Adipose-Derived Autologous Stem Cell Interventions: Insights From 3 New FDA Draft Guidance Documents
Leigh G. Turner, PhD
21 CFR 1271 and the Same Surgical Procedure Exception
Treatment Process
Contact Us
All websites accessed June 8, 2015.

74

PCI Options

- Facilitated Antegrade Steering Technique (FAST-CTO)
  - Bridgepoint System (3 parts)



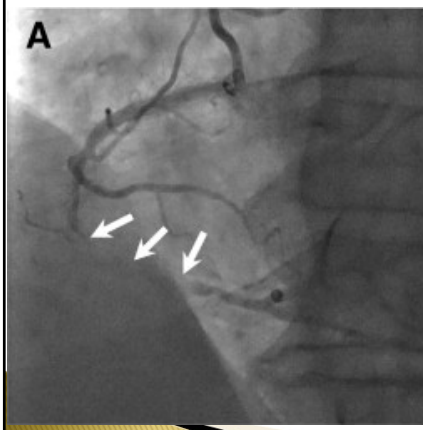


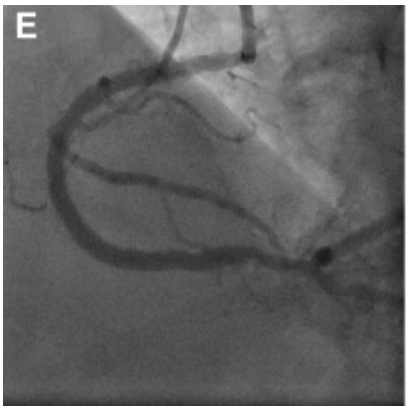
- Retrograde
  - Find true Lumen using collaterals

75

Results

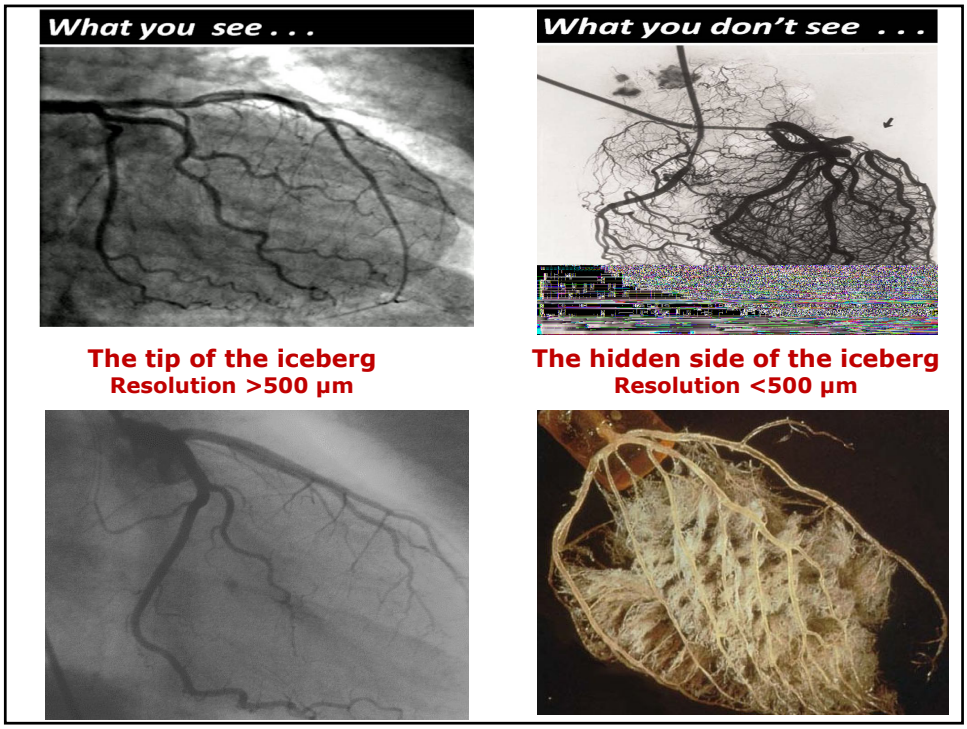
BEFORE



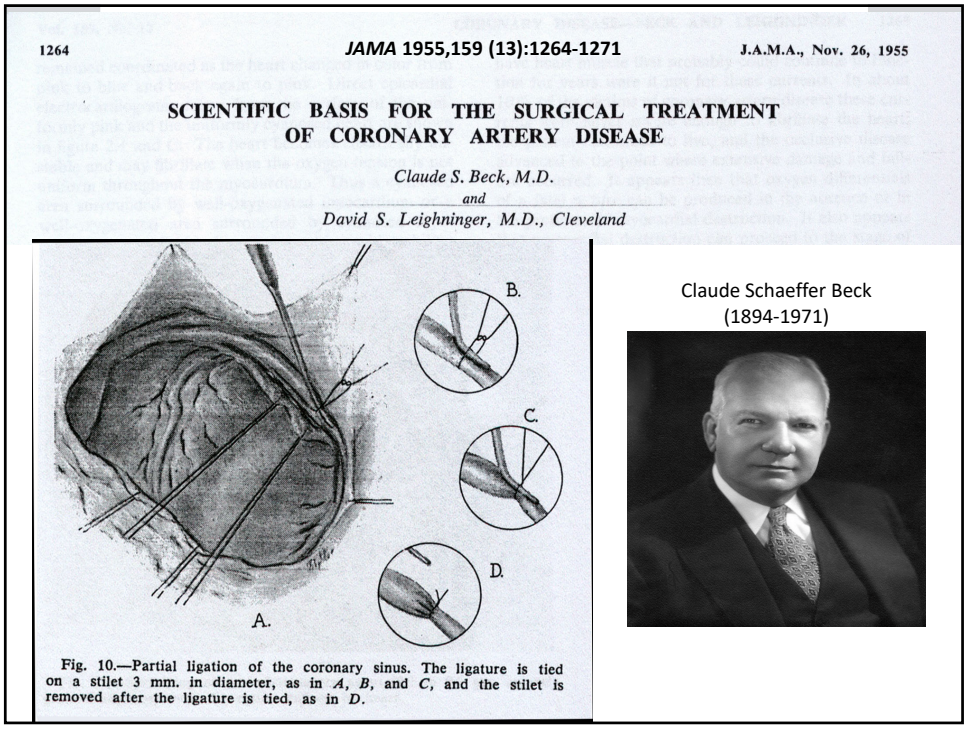


AFTER

76


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

77


1264
JAMA 1955,159 (13):1264-1271
J.A.M.A., Nov. 26, 1955
SCIENTIFIC BASIS FOR THE SURGICAL TREATMENT OF CORONARY ARTERY DISEASE
Claude S. Beck, M.D.
and
David S. Leighninger, M.D., Cleveland
B.
C.
D.
A.
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.
Claude Schaeffer Beck
(1894-1971)

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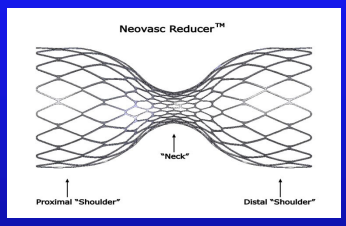
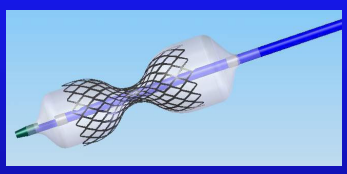
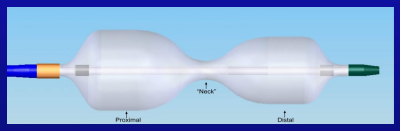
Generation II Reducer System

Inflated

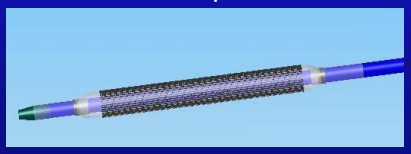




Delivery System



Crimped



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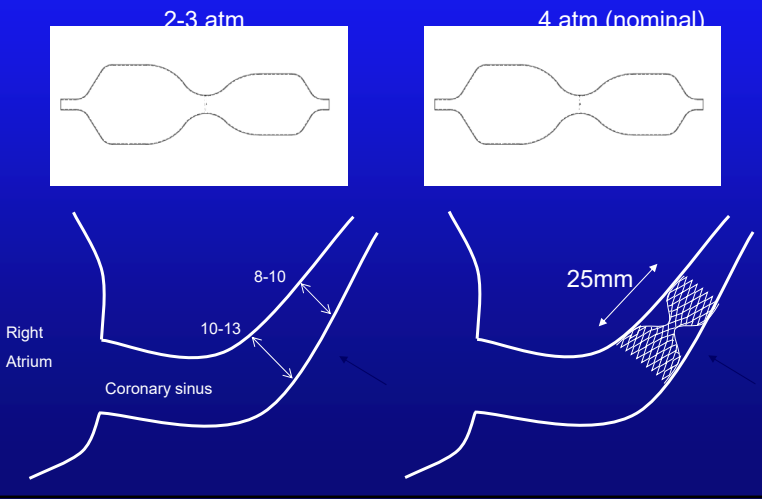
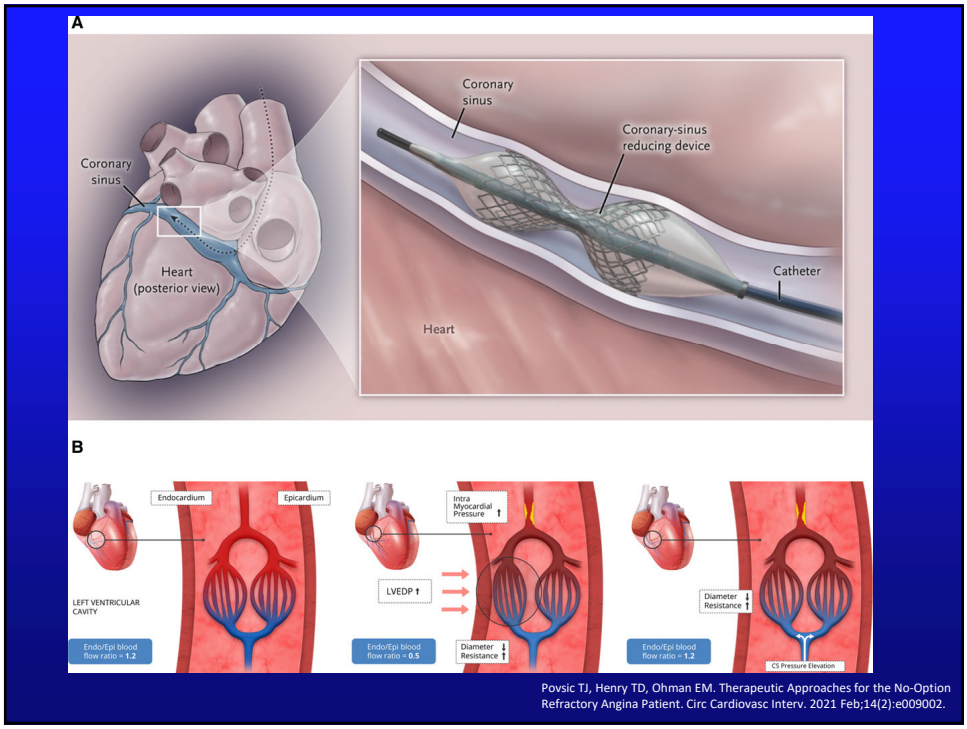
Reducer Implantation

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

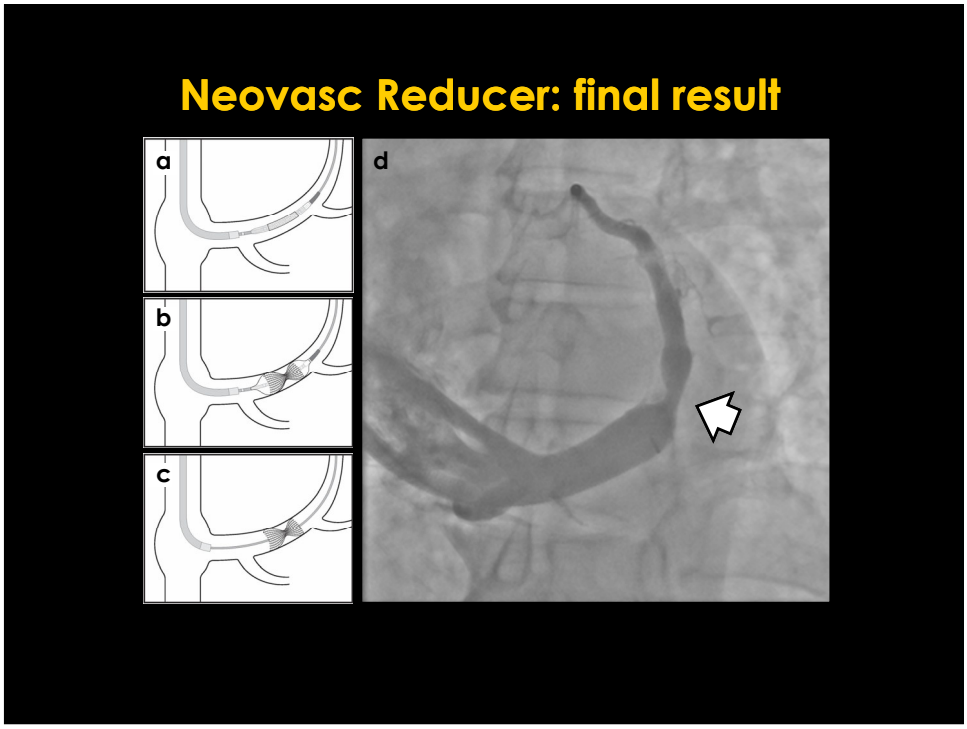


80



Povsic TJ, Henry TD, Ohman EM. Therapeutic Approaches for the No-Option Refractory Angina Patient. Circ Cardiovasc Interv. 2021 Feb;14(2):e009002.

81



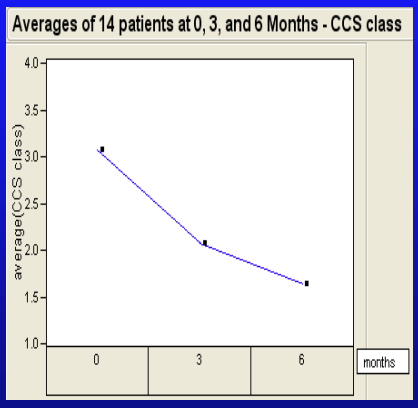
82

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



83

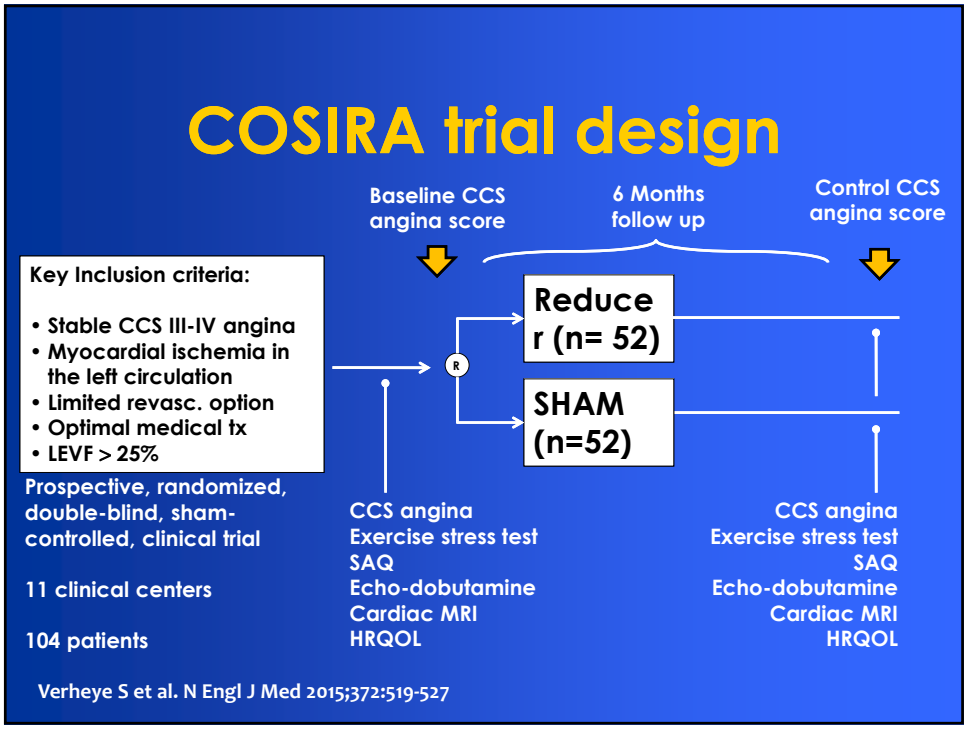
ORIGINAL ARTICLE

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

Stefan Verheye, 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.

N Engl J Med 2015;372:519-27.

84



85

Change in Canadian Cardiovascular Society (CCS) Angina Class, According to Study Group

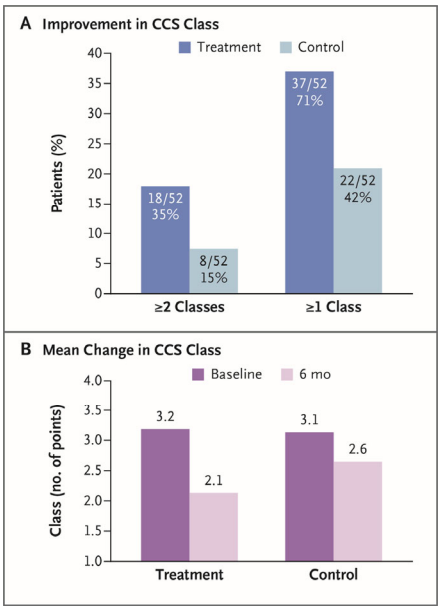
Panel A

- 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

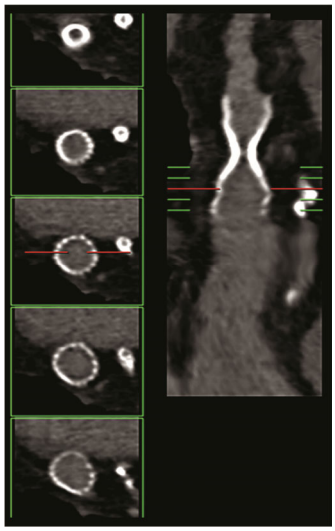
- The mean (±SD) CCS class was reduced from 3.2±0.4 at baseline to 2.1±1.0 at 6 months of follow-up in the Reducer group, as compared with a reduction from 3.1±0.3 to 2.6±0.9 in the control group, P=0.001

Verheye S et al. N Engl J Med 2015;372:519-527



86

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



Verheye S et al. N Engl J Med 2015;372:519-527

The NEW ENGLAND JOURNAL of MEDICINE

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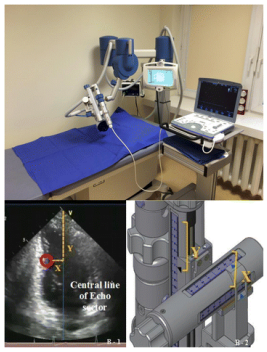
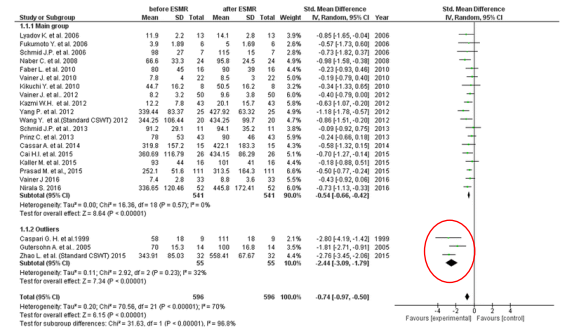
Shockwave Therapy





Bumeikaute et al, Cardiovasc Ultrasound. 2017 Apr 12;15(1):11.

ACC.23 TOGETHER WITH WCC

88

Just for the Record!

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

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Current Trials

- Xylocor: Triple gene for VEGF
- Imbria: novel metabolic inhibiter
- Stem Cell: CD34+ and BMC Selected
- Coronary Sinus Reducer: COSIRA-2

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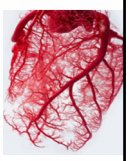
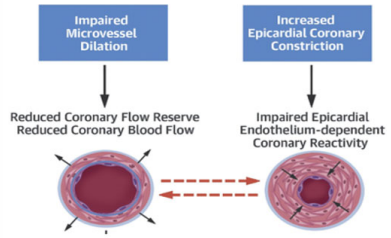
INOCA (Ischemia & Non-obstructive coronary artery disease) & Coronary Microvascular dysfunction (CMD)





- 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

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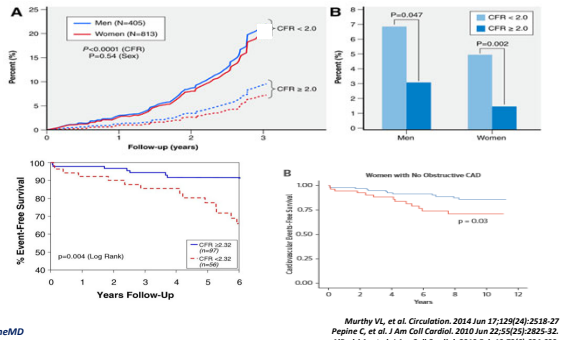
Long-term Outcomes in INOCA

Non-endothelial Dependent CMD predicts MACE



@OdaymeMD

Murthy VL, et al. Circulation. 2014 Jun 17;129(24):2518-27
Pepine C, et al. J Am Coll Cardiol. 2010 Jun 22;55(25):2825-32.
AlBadri A, et al. J Am Coll Cardiol. 2019 Feb 19;73(6):684-693.

ACC.23 TOGETHER WITH WCC

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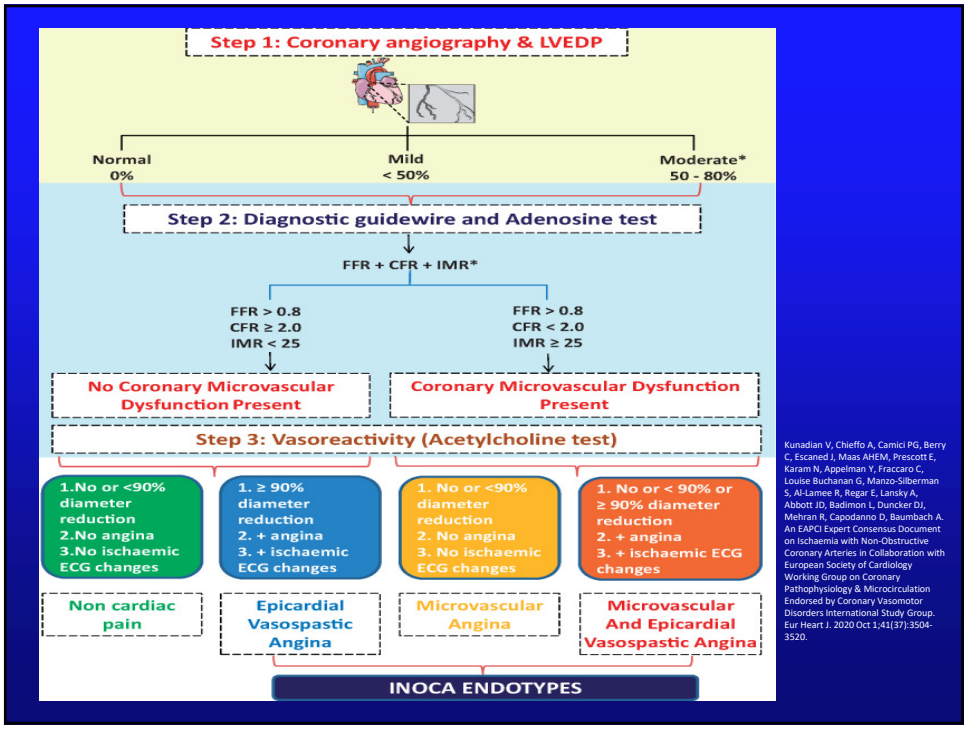
Step 1: Coronary angiography & LVEDP
Normal 0%
Mild < 50%
Moderate* 50 - 80%
Step 2: Diagnostic guidewire and Adenosine test
FFR + CFR + IMR*
FFR > 0.8 CFR ≥ 2.0 IMR < 25
FFR > 0.8 CFR < 2.0 IMR ≥ 25
No Coronary Microvascular Dysfunction Present
Coronary Microvascular Dysfunction Present
Step 3: Vasoreactivity (Acetylcholine test)
1.No or <90% diameter reduction 2.No angina 3.No ischaemic ECG changes
1. ≥ 90% diameter reduction 2. + angina 3. + ischaemic ECG changes
1. No or <90% diameter reduction 2. No angina 3. No ischaemic ECG changes
1. No or < 90% or ≥ 90% diameter reduction 2. + angina 3. + ischaemic ECG changes
Non cardiac pain
Epicardial Vasospastic Angina
Microvascular Angina
Microvascular And Epicardial Vasospastic Angina
INOCA ENDOTYPES
Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020 Oct 1;41(37):3504-3520.

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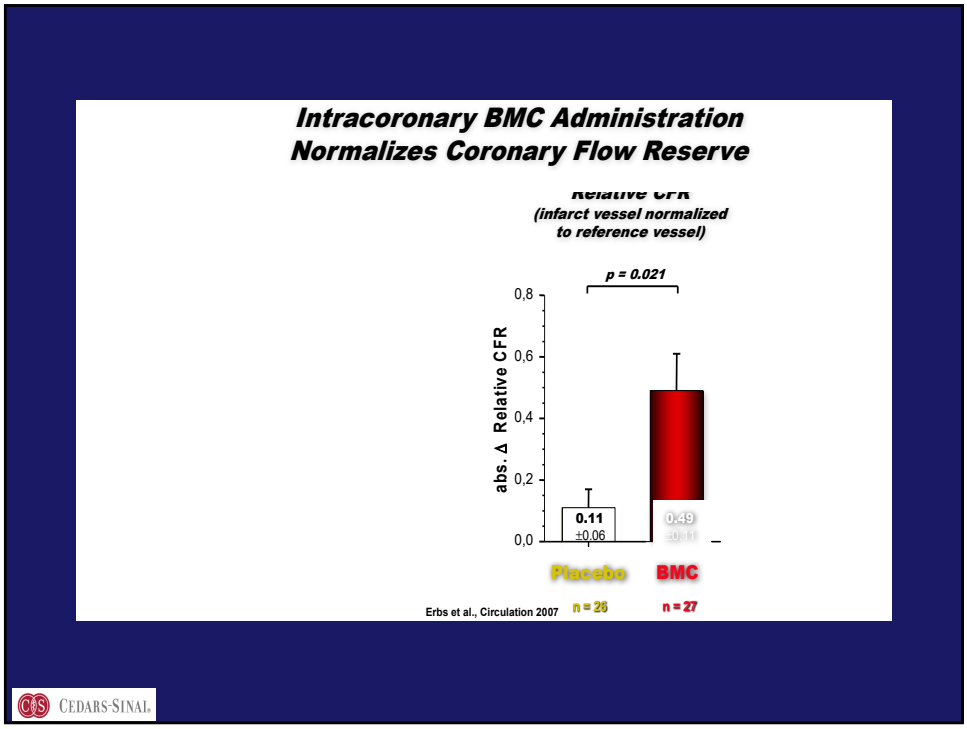
Intracoronary BMC Administration Normalizes Coronary Flow Reserve
(infarct vessel normalized to reference vessel)
p = 0.021
abs. Δ Relative CFR
0,8
0,6
0,4
0,2
0,0
0.11
±0.06
0.49
Placebo
BMC
n = 26
n = 27
Erbs et al., Circulation 2007
CEDARS-SINAI

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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

Henry TD, Lerman A, Wei J, Corban M, Joung S, Kotynski C, Lewis M, Schumacher A, Shah V, Bartel R, Wang J, Sietsema WK, Losordo DW, Bairey-Merz CN

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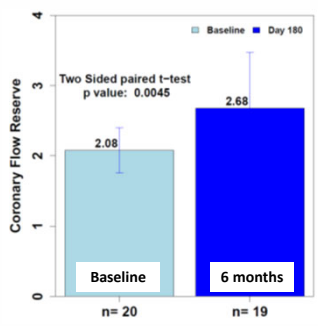
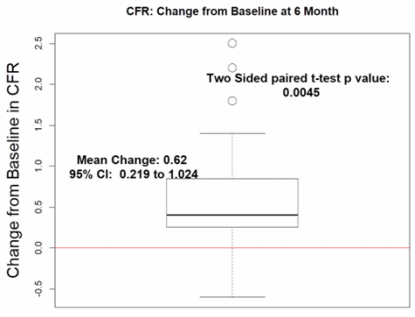
ESCAPE-CMD INCREASES CFR AT 6 MONTHS IN CMD





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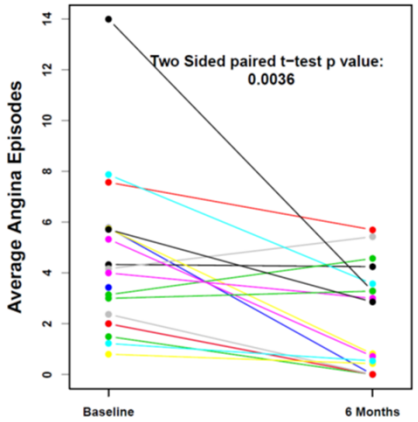
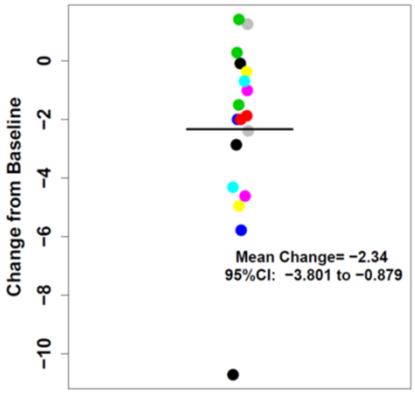
ESCAPE-CMD DECREASES ANGINA FREQUENCY AT 6 MONTHS





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ESCAPE-CMD IMPROVES ANGINA CLASS AT 6 MONTHS

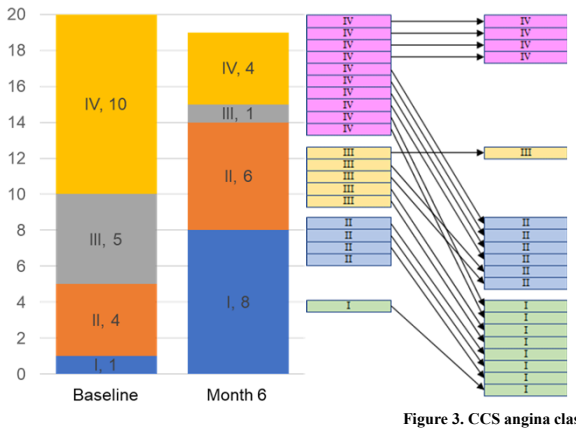

Figure 3. CCS angina class changes from baseline to month 6.

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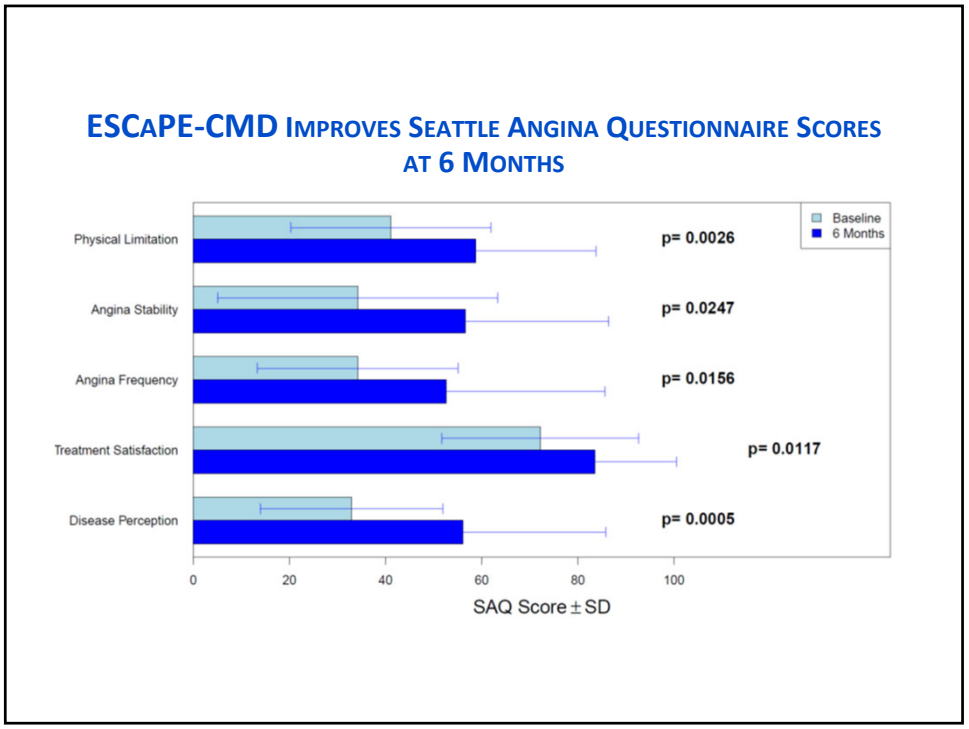
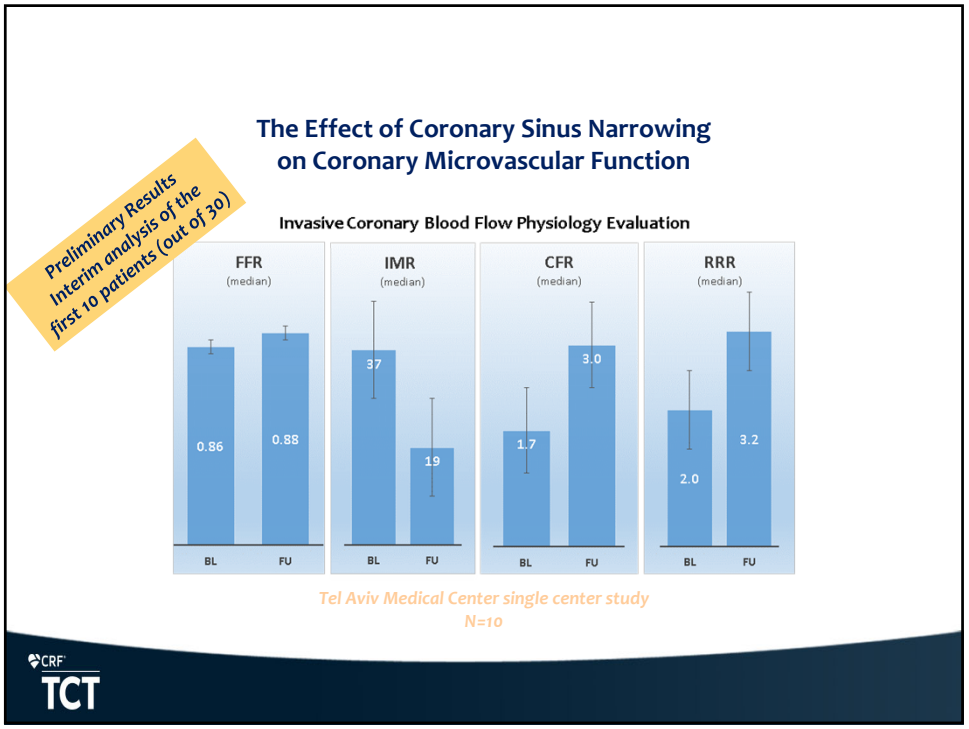
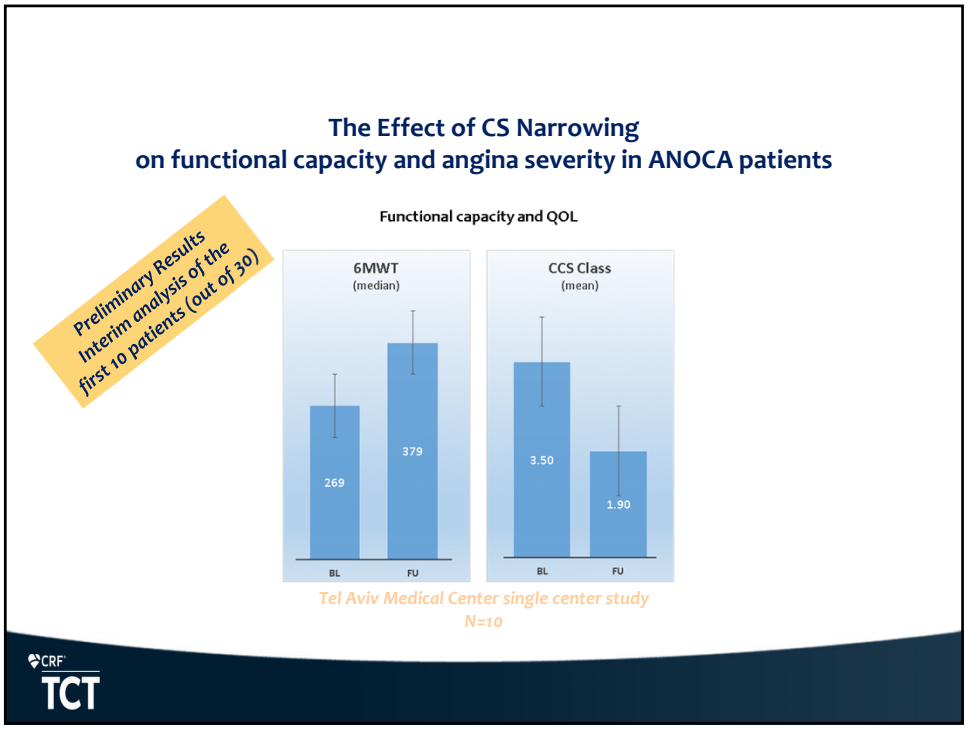

ESCAPE-CMD IMPROVES SEATTLE ANGINA QUESTIONNAIRE SCORES AT 6 MONTHS
Baseline
6 Months
Physical Limitation
Angina Stability
Angina Frequency
Treatment Satisfaction
Disease Perception
p= 0.0026
p= 0.0247
p= 0.0156
p= 0.0117
p= 0.0005
0
20
40
60
80
100
SAQ Score ± SD

99


The Effect of Coronary Sinus Narrowing on Coronary Microvascular Function
Preliminary Results
Interim analysis of the first 10 patients (out of 30)
Invasive Coronary Blood Flow Physiology Evaluation
FFR
(median)
0.86
0.88
IMR
(median)
37
19
CFR
(median)
1.7
3.0
RRR
(median)
2.0
3.2
BL
FU
Tel Aviv Medical Center single center study
N=10
CRF
TCT

100



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Current Microvascular AnginaTrials

- CD34+ stem cell (Phase 2)
- Imbria: novel metabolic inhibiter
- WARRIOR trial
- ?Coronary Sinus Reducer

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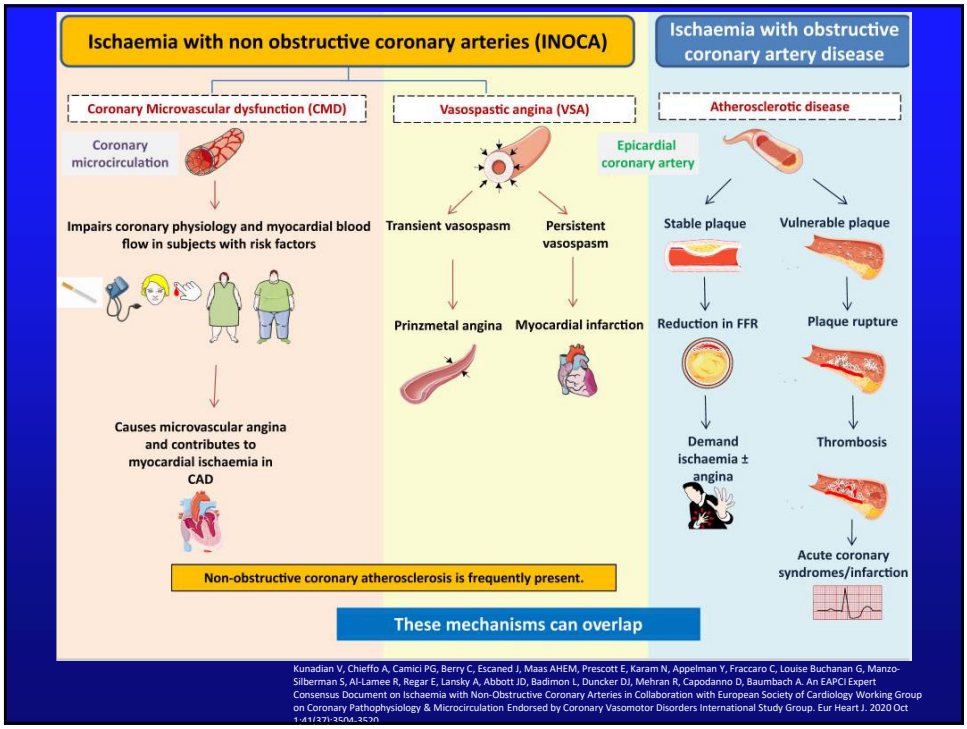
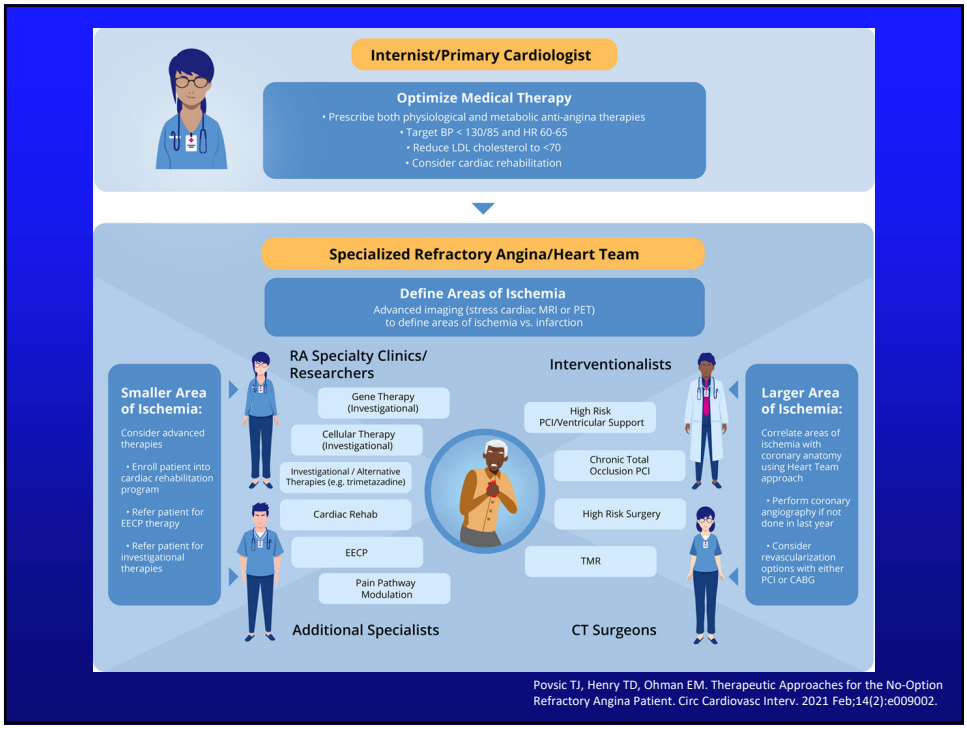


Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020 Oct 1;41(37):3504-3520.

103



Povsic TJ, Henry TD, Ohman EM. Therapeutic Approaches for the No-Option Refractory Angina Patient. Circ Cardiovasc Interv. 2021 Feb;14(2):e009002.

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