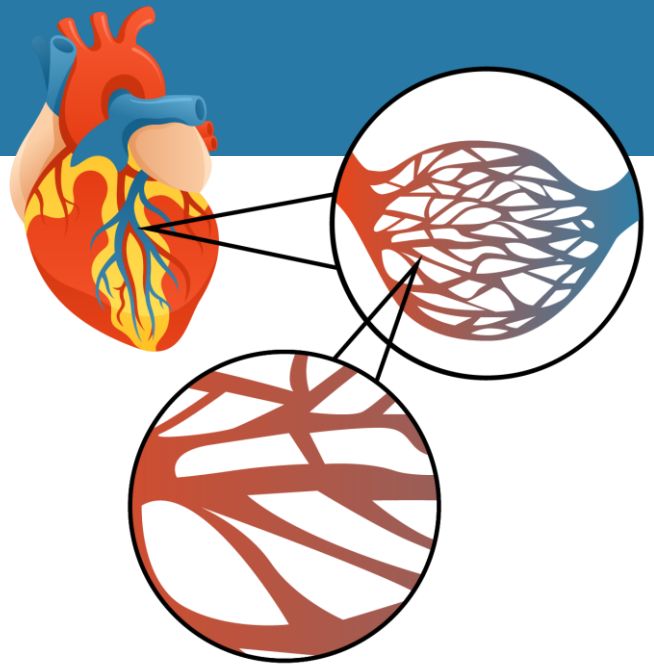
# Advancing Cell Therapies for Coronary Microvascular Dysfunction: Experts Roundtable



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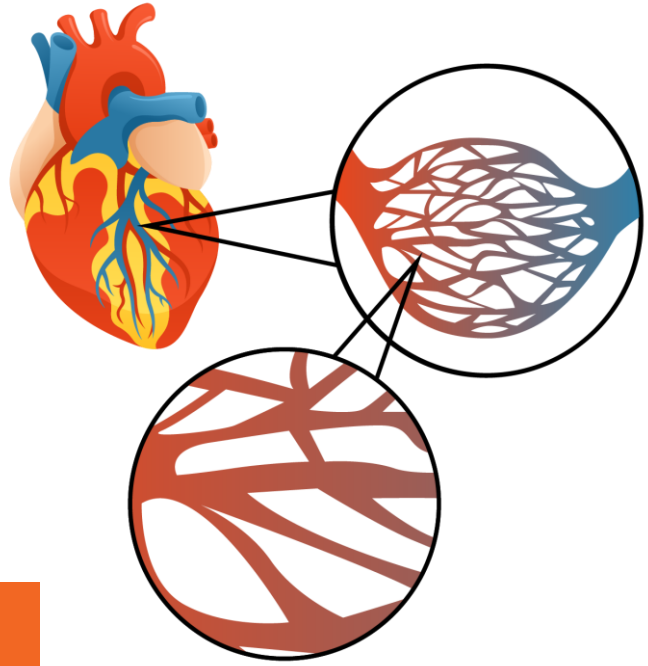
# Program Overview



**Michael Gibson, MD (Co-Chair)**
**&**
**Peter H. Stone, MD (Co-Chair)**

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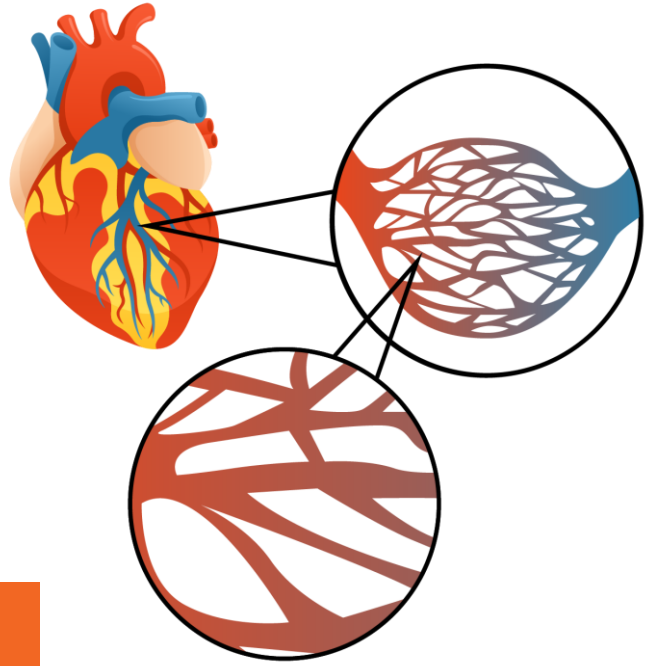
# Stable Angina: State of the Art



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# Faculty Disclosure

**Peter H. Stone, MD**

RESEARCH SUPPORT: NIH, AstraZeneca, St. Jude Medical, Infraredx

# Guideline Based β-Blocker Therapy
## *Secondary Prevention*


β-blocker therapy should be started and continued for 3 years in all patients with normal LV function after MI or ACS.


β-blocker therapy should be used in all patients with LVEF ≤40% with heart failure or prior MI, unless contraindicated. (Documented benefit with carvedilol, metoprolol succinate, or bisoprolol)


β-blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease.



(Fihn SD, et al. *JACC* 2012;60:e44-e164)

# **β-Blockers** for Secondary Prevention of CV Disease

*Meta-Analysis of Selective and Non-Selective β-Blockers*
*33 Trials, 34,622 Patients*

~ 20-30% reduction in mortality and vascular events

| Group of Pts: Outcome | β1 Blockers **Relative Risk** (95% CI) | β1+2 Blockers Relative Risk (95% CI) |
|---|---|---|
| ACS: Total mortality | 0.84 (0.67-1.05) | 0.72 (0.63-0.81) |
| ACS: Vascular Events | 0.68 (0.42-1.11) | 0.74 (0.66-0.84) |
| Heart Failure: Total mortality | 0.75 (0.66-0.85) | 0.74 (0.56-0.96) |
| Heart Failure: Vascular Events | 1.34 (0.82-2.18) | 0.79 (0.61-1.03) |

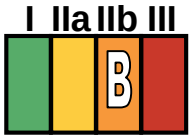
(de Peuter OR, et al. Neth J Med 2009;67:284)

# Guideline-Based Antiplatelet Therapy

## *Secondary Prevention*


**Aspirin** 75 to 162 mg daily indefinitely.


**Clopidogrel** is reasonable when aspirin is contraindicated.




Aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD.


Dipyridamole is not recommended as antiplatelet therapy.

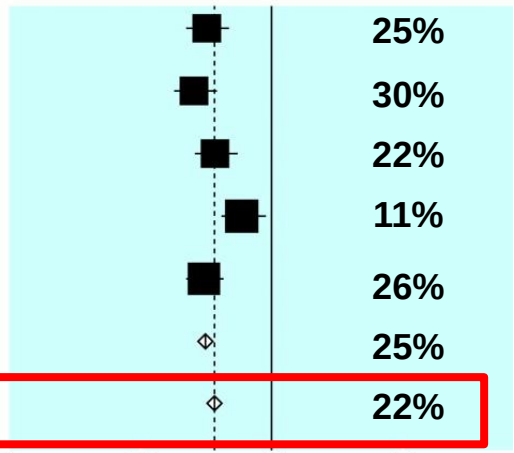


(Fihn SD, et al. JACC 2012;60:e44-e164)

# Benefit of **Antiplatelet Therapy** for Secondary Prevention of CV Disease

## (non-fatal MI, non-fatal stroke, vascular death)

| Category of trial | No of trials with data | No (%) of vascular events: Allocated antiplatelet | No (%) of vascular events: Adjusted control | % Odds Reduction |
|---|---|---|---|---|
| Previous myocardial infarction | 12 | 1345/9984 (13.5) | 1708/10 022 (17.0) | 25% |
| Acute myocardial infarction | 15 | 1007/9658 (10.4) | 1370/9644 (14.2) | 30% |
| Previous stroke/transient ischaemic attack | 21 | 2045/11 493 (17.8) | 2464/11 527 (21.4) | 22% |
| Acute stroke | 7 | 1670/20 418 (8.2) | 1858/20 403 (9.1) | 11% |
| Other high risk | 140 | 1638/20 359 (8.0) | 2102/20 543 (10.2) | 26% |
| Subtotal: all except acute stroke | 188 | 6035/51 494 (11.7) | 7644/51 736 (14.8) | 25% |
| **All trials** | **195** | **7705/71 912 (10.7)** | **9502/72 139 (13.2)** | 22% |



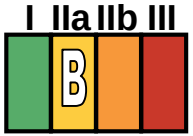

Heterogeneity of odds reductions between:
5 categories of trial: $\chi^2$=21.4, df=4; P=0.0003
Acute stroke *v* other: $\chi^2$=18.0, df=1; P=0.00002

(Antithrombotic Trialists' Collaboration. BMJ 2002;324:71-86)

# Guideline-Based Renin-Angiotensin-Aldosterone Blocker Therapy

## *Secondary Prevention*

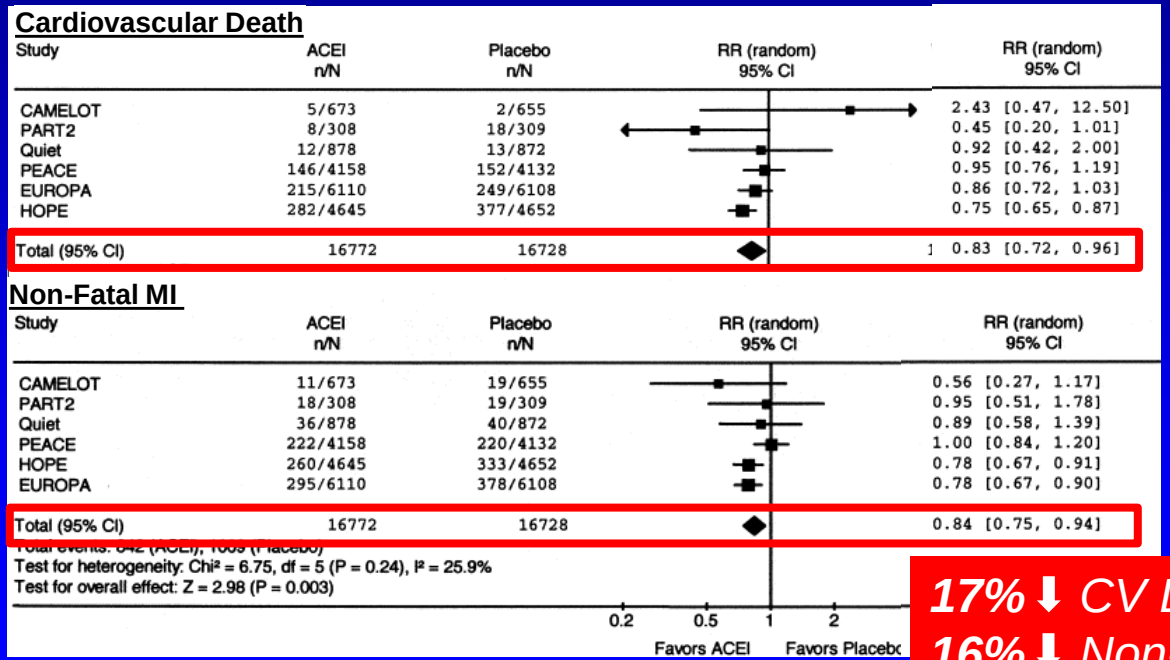

**ACE inhibitor** (or **ARB** if ACEI intolerant) should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF ≤40%, or CKD, unless contraindicated.




**ACE inhibitor** (or **ARB** if ACEI intolerant) is reasonable in patients with both SIHD and other vascular disease (vascular protection).

# Benefit of ACEI for Secondary Prevention of CV Disease

*Meta-Analysis of RCTs of Patients with **CAD and Preserved LVEF***
*6 Trials with 33,500 Patients*




***17%*** ⬇ *CV Death*
***16%*** ⬇ *Non-Fatal MI*

(Al-Mallah, et al. JACC 2006;47:1576)

# ***Treatment of Symptoms (Angina):***
# Determinants of Myocardial $O_2$ Supply:Demand Balance

## ***$O_2$ Demand***

- Heart Rate
- Contractility
- Ventricular Wall Tension
  - Preload
  - Afterload

## ***$O_2$ Supply***

- Diastolic blood flow
- Resistances
  - Regulation
  - Metabolic control
  - Endothelial function
  - Myogenic/ extravascular compression

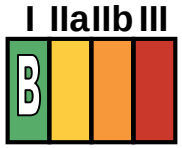
# Guideline-Based Anti-Ischemic Medications *for Angina*


**β-blockers** should be prescribed as initial therapy.

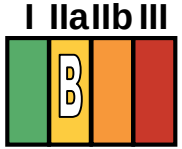

**$Ca^{++}$-channel blockers** or **long-acting nitrates** should be prescribed when β-blockers are contraindicated or cause unacceptable side effects


**$Ca^{++}$-channel blockers or long-acting nitrates, in combination with β-blockers**, should be prescribed when initial treatment with β-blockers is unsuccessful.

# Guideline-Based Anti-Ischemic Medications *for Angina* (cont.)




Sublingual **NTG** or spray for immediate relief of angina.




Long-acting **verapamil or diltiazem** instead of a β-blocker as initial therapy is reasonable.


**Ranolazine** can be useful as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects, is ineffective or is contraindicated.

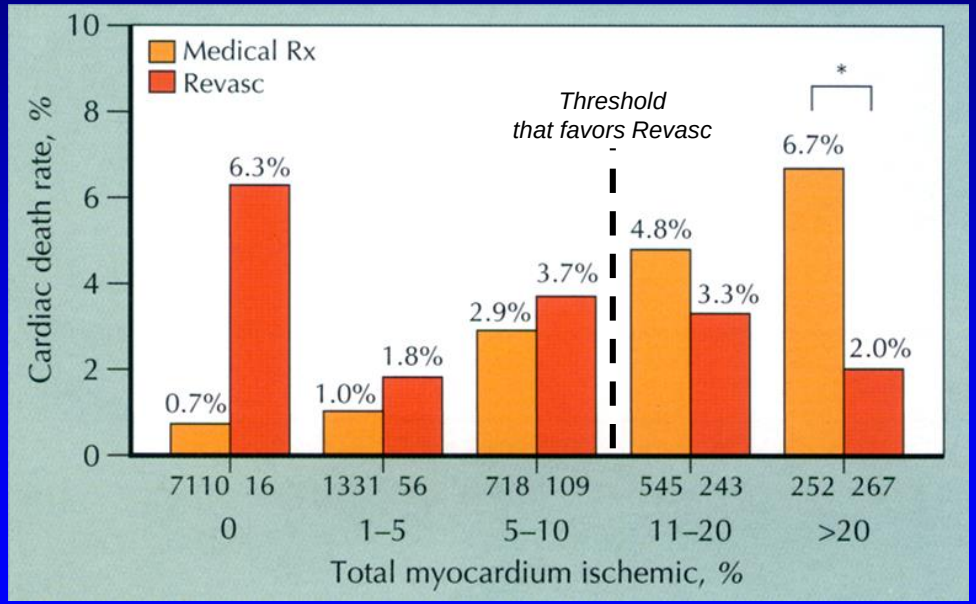

Ranolazine in combination with β-blockers can be useful when initial treatment with β-blockers is not successful.



(Fihn SD, et al. JACC 2012;60:e44-e164)

# Benefit of Medical vs Revascularization Therapy Based on Amount of Ischemic Myocardium

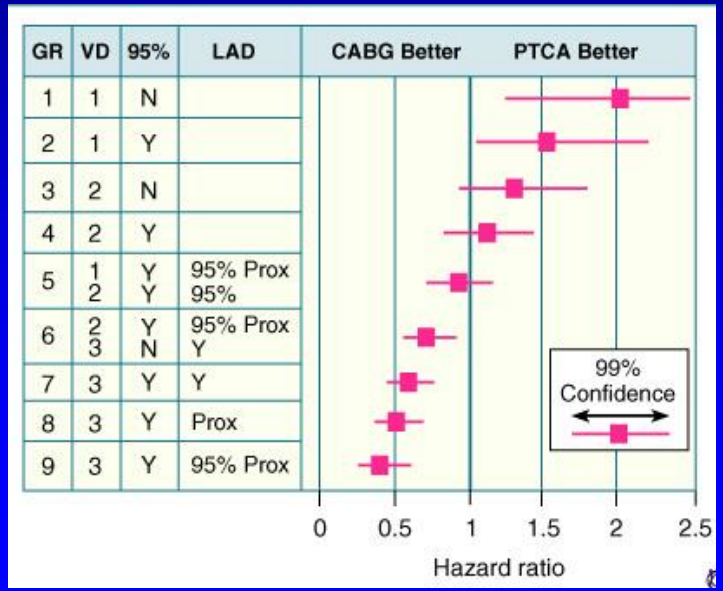
*10,627 consecutive patients, myocardial stress perfusion imaging (exercise or adenosine), with followup 1.9±0.6 years*




(Hachamovitch, et al. Circulation 2003;107:2900)

# 5-Year Survival Based on Revascularization by CABG vs PTCA

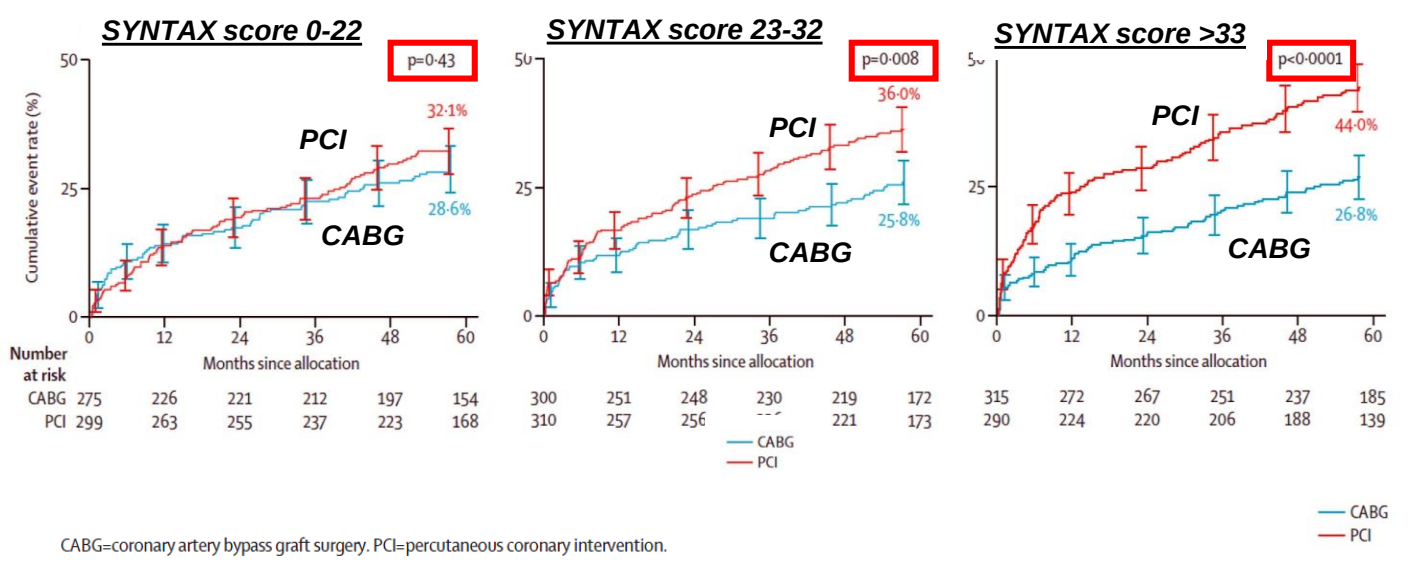
*Least severe CAD, survival better with PTCA,*
*Intermediate risk, no difference*
*More severe CAD, survival better with CABG*




(Jones, et al. *J Thorac CV Surg* 1996;111:1013.)

# CABG vs PCI: SYNTAX
## *Overall Cohort*

*Highest-risk patients generally do better with CABG vs PCI*




(Mohr FW et al. *Lancet* 2013;381:629-638)

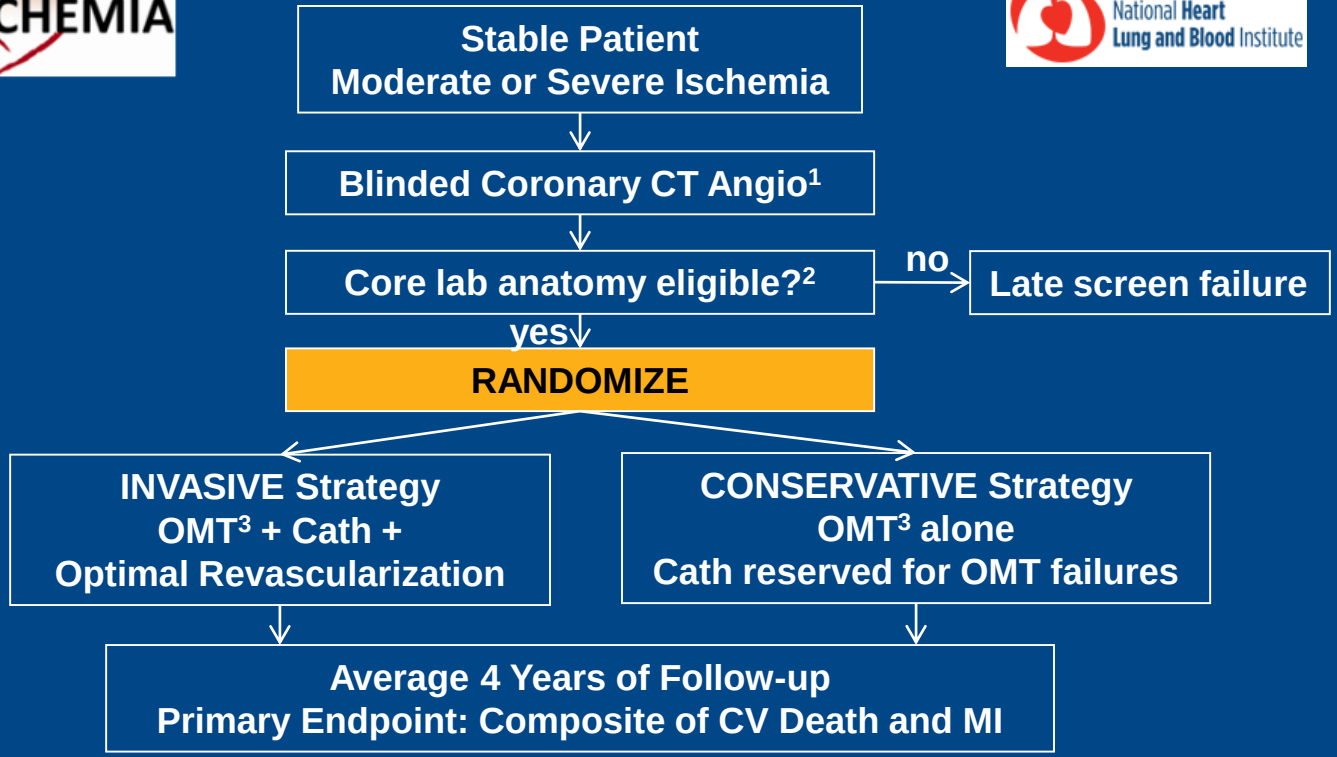
# Revascularization of Stable CAD 2012

## *Revascularization Indications in Stable Angina*

| FOR **PROGNOSIS** | | |
|---|---|---|
| **SUBSET OF CAD BY ANATOMY** | **CLASS** | **LEVEL** |
| **Left main >50%** | **I** | **A** |
| **Any proximal LAD >50%** | **I** | **A** |
| **2VD or 3VD with impaired LV function** | **I** | **B** |
| **Proven large area of ischemia (>10% LV)** | **I** | **B** |
| **Single remaining vessel >50% stenosis** | **I** | **C** |
| **1VD without proximal LAD and without >10% ischemia** | **III** | **A** |

| FOR **SYMPTOMS** | | |
|---|---|---|
| **SUBSET OF CAD BY ANATOMY** | **CLASS** | **LEVEL** |
| **Any stenosis >50% with limiting angina or angina equivalent, unresponsive to GDMT** | **I** | **A** |
| **Dyspnea/CHF and >10% LV ischemia/viability supplied by >50% stenotic artery** | **IIa** | **B** |
| **No limiting symptoms with GDMT** | **III** | **C** |

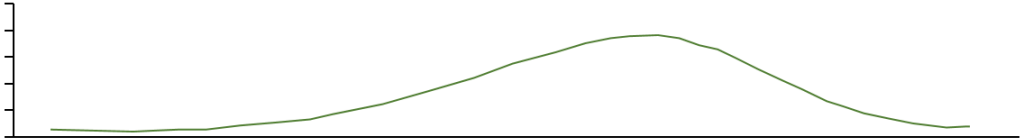
(Fihn SD, et al. JACC 2012;60:e44-e164; ESC Guidelines for Revascularization 2010. *EHJ.* 2010;31:2501-55)




[1]CCTA will be performed in all patients with eGFR ≥60 mL/min
[2]Exclude patients with LM disease or no obstructive disease
[3]OMT=Optimal medical therapy

# Coronary Macro- and Micro-circulation

*New and Evolving Understanding of Inter-relationships of Macrocirculation (Epicardial) and Microcirculation (Microvascular)*

| | Macrocirculation | Microcirculation | | |
|---|---|---|---|---|
| **Segment and size:** | Epicardial arteries >400 μM | Small arteries <400 μM | Arterioles <100 μM | Capillaries <10 μM |
| |  | | | |
| **Main stimulus for vasomotion:** | **Flow** | **Pressure** | **Metabolites** | |
| **Main function:** | **Transport** | **Regulation** | | **Exchange** |
| **Percentage of total flow resistance:** |  | | | |

(De Bruyne B, et al. JACC 2016;67:1170)

# Microvascular and Epicardial Endothelial Function Results (n=65 pts w Stable CAD)

***Definitions:***

Microvascular endothelial dysfcn: max% increase CBF <50% by ACh

Epicardial endothelial dysfcn: decrease lumen diameter >20% by ACh

| | | Epicardial Endothelial Function | |
|---|---|---|---|
| | | Normal (48) | Abnormal (17) |
| Microvascular Endothelial Function | Normal (32) | 26 | 0 |
| | Abnormal (39) | 22 | 17 |

*No patient with normal microvascular endothelial function had abnormal epicardial endothelial function*

*Of patients with abnormal microvascular endothelial function:*
*56% had abnormal epicardial endothelial function and*
*44% had normal epicardial endothelial function*

(Siasos G, et al. JACC 2018;71:2092-2102)

# Continuum of Endothelial Dysfunction from **Microvascular** to **Macrovascular**/Plaque Development

*Among Patients with Microvascular Endothelial Dysfunction:*
*(n=39; defined as lack of increase in coronary blood flow to ACh)*

| Characteristic | Normal | Abnormal | P value |
|---|---|---|---|
| **Concomitant Epicardial Endothelial Dysfcn** (Δ coro diam after acetylcholine infus) | -3.02 ± 7.45 | -14.73 ±26.36 | 0.01 |
| **Blood Flow in Epicardial Artery** | | | |
| Low flow (Pro-atherogenic, Lowest ESS, Pa) | 0.72 ± 0.32 | 0.54 ±0.25 | 0.01 |
| **Plaque Characteristics** | | | |
| Plaque Area ($mm^2$) | 2.72 ± 1.74 | 3.78 ±2.34 | <0.0001 |
| Plaque Burden (%) | 21.33 ± 9.72 | 26.43 ±12.59 | <0.0001 |
| Plaque Thickness (mm) | 0.28 ± 0.18 | 0.39 ±0.24 | <0.001 |

**Worse epicardial endothelial dysfunction**

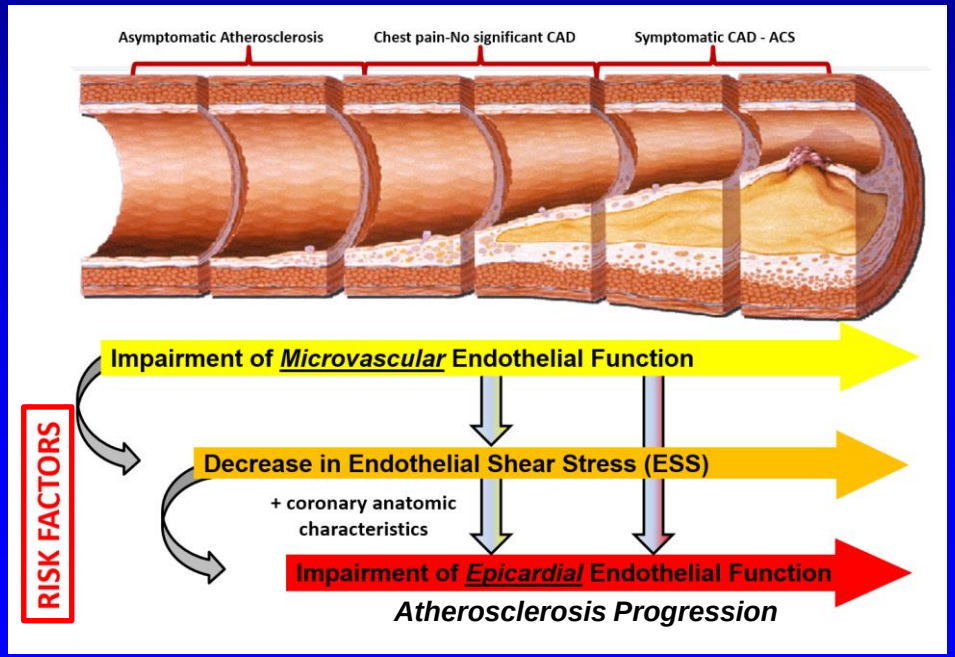
**Lower flow** (shear stress) **in epicardial arteries**

**More abnormal epicardial plaque** features:
- ↑ plaque **area**
- ↑ plaque **burden**
- ↑ plaque **thickness**

(Siasos G, et al. JACC 2018;71:2092-2102)

# Continuous Natural History of Coronary Atherosclerosis: Opportunities for Therapeutic Intervention

CAD is an evolving process that progresses from **microvascular** to **epicardial** endothelial dysfunction over time, with mechanistic contributions by Low blood flow (low shear stress) at multiple time points



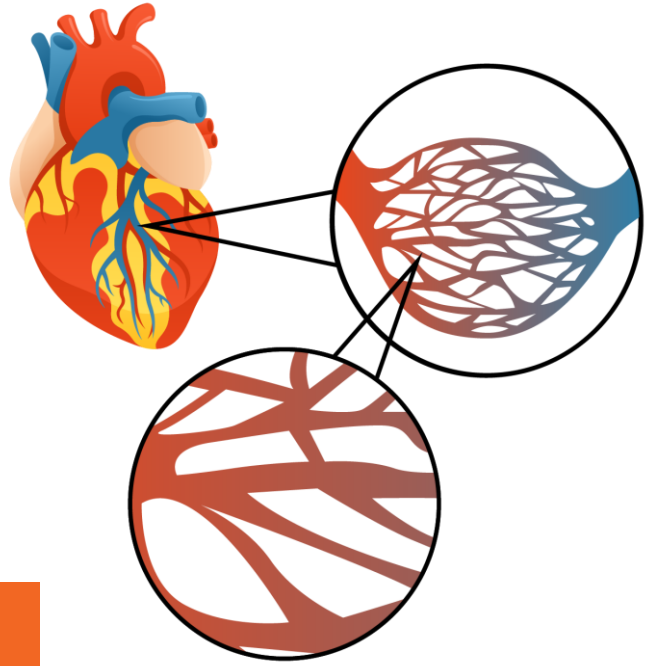

(Siasos G, et al. JACC 2018; 71:2092-2102)

# Stable Ischemic Heart Disease: State of the Art

## *Summary and Conclusions*

- Goals of management strategy includes strategies to:
  - modify disease (secondary prevention: statins, BP control, Anti-plt Rx, ACEI/ARBs) and,
  - improve quality of life (anti-anginal Rx)
- Revascularization strategies include PCI for less severe ischemic jeopardy, and CABG for highest risk ischemic jeopardy (ISCHEMIA trial may change that!)
- New appreciation of continuum of phenotypic atherosclerosis process from microvascular to macrovascular manifestations
  - **Opportunities (and Needs) for therapeutic intervention!**

# Microvascular Disease: Prevalence and Unmet Needs



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# Faculty Disclosure

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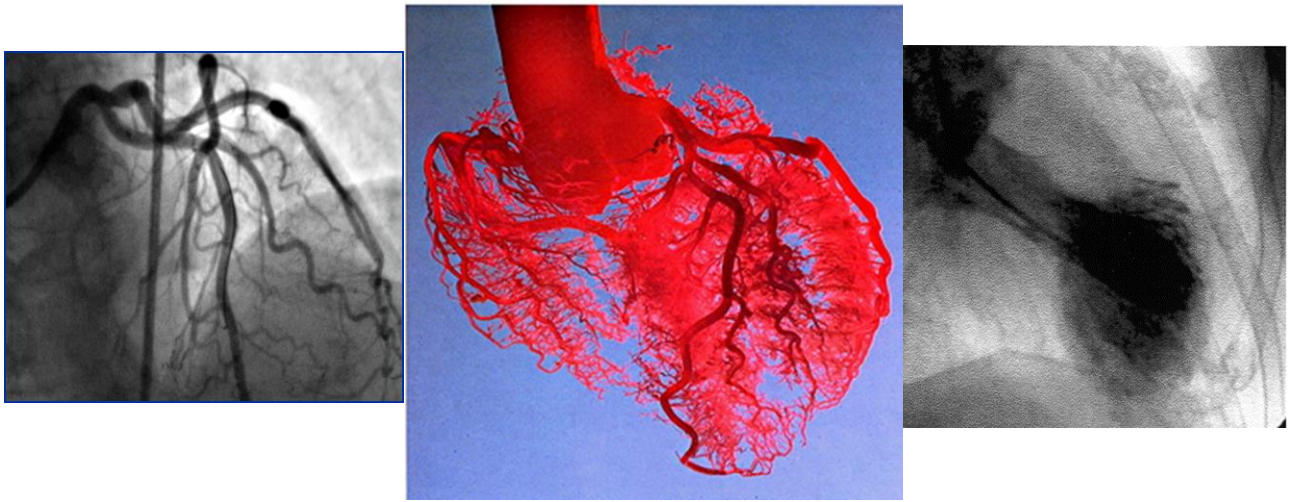
CONSULTING: Medscape*, Sanofi-Vascular*, NIH CSR and NIH ORWHAB*, iRhythm, Caladrius

HONORARIUM*: Abbott Diagnostics

GRANT SUPPORT*: NHLBI, Louis B Mayer Foundation, NIH-CTSI, CMDRP-DoD, NIH-Caladrius, California Institute for Precision Medicine (CIAPM), Sanofi-Vascular

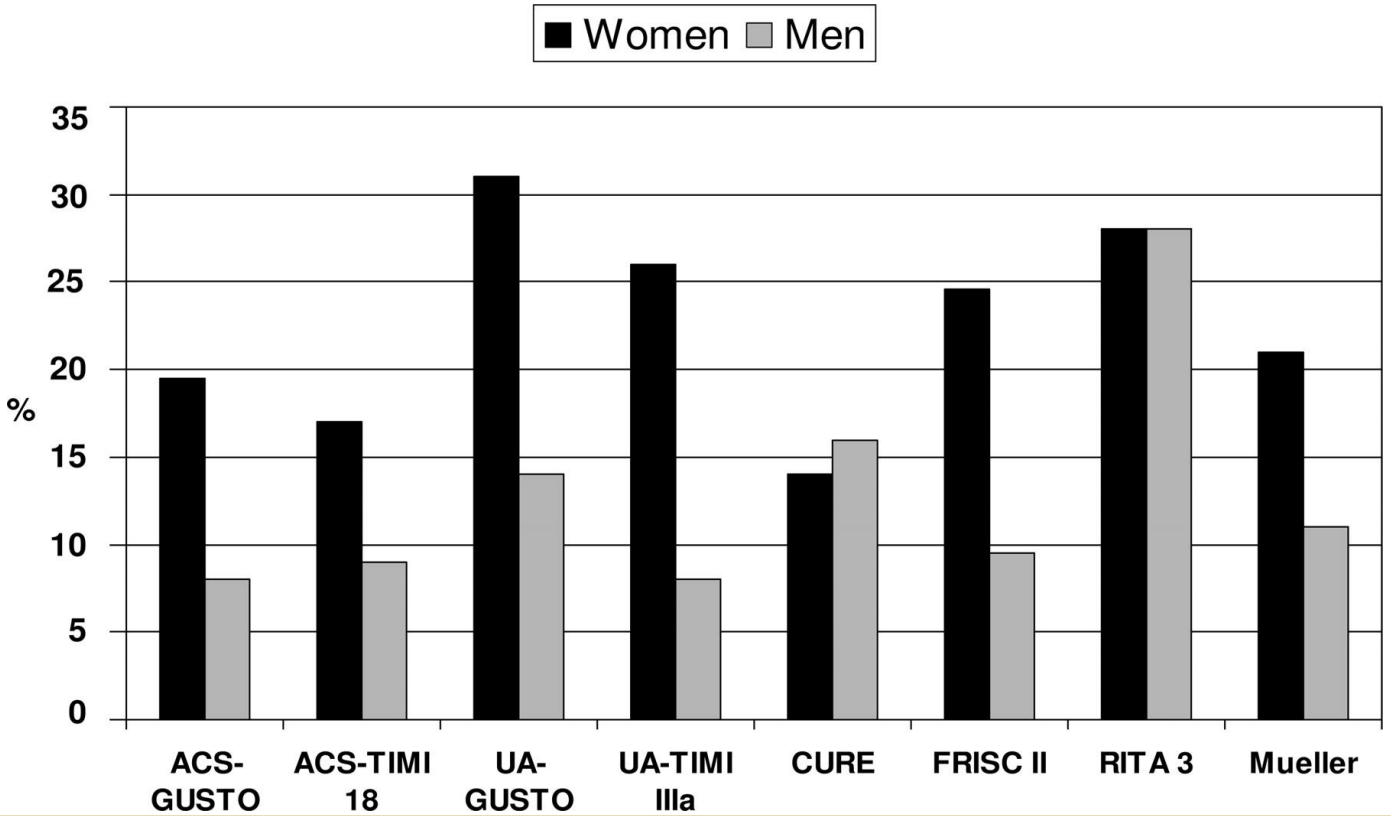
*paid to CSMC

# Women and Coronary Microvascular Dysfunction
# INOCA/MINOCA



Ischemia with No Obstructive CAD (INOCA)
Myocardial Infarction with No Obstructive CAD (MINOCA)

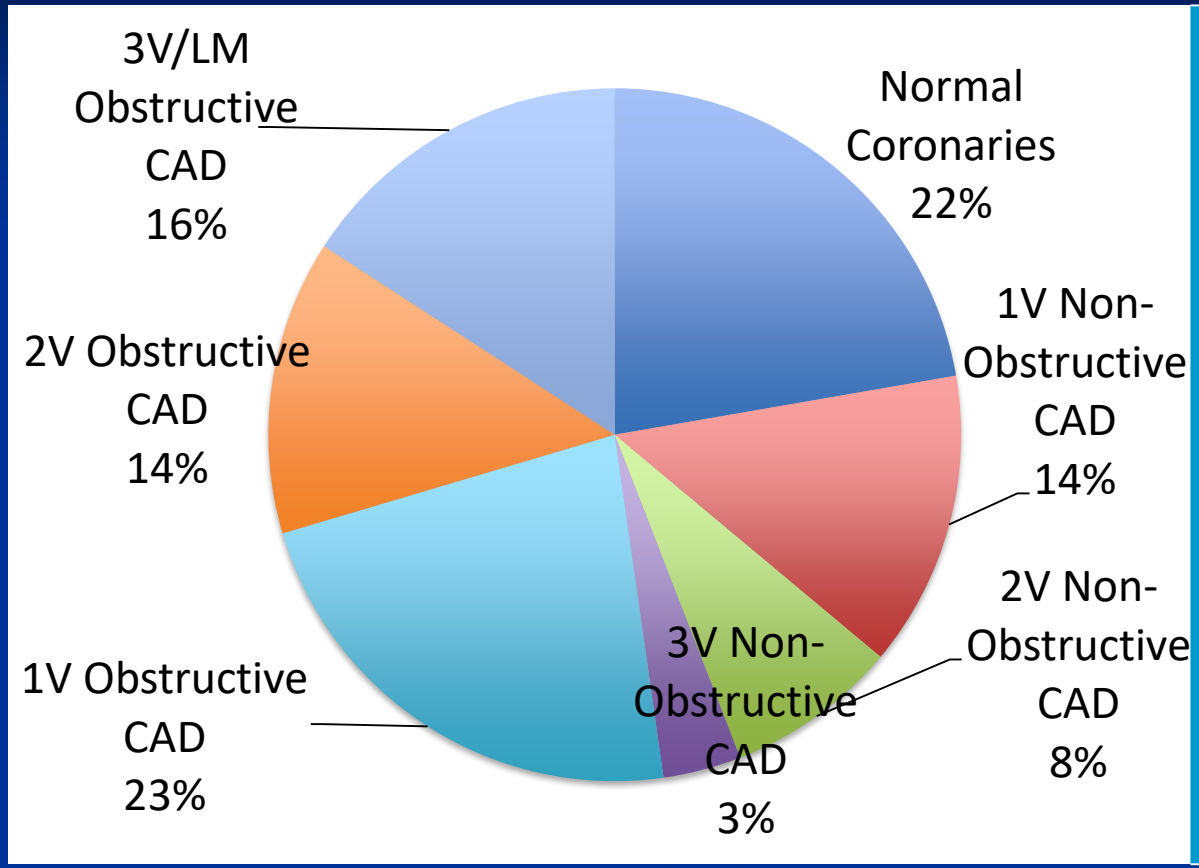
# Prevalence of normal or non-obstructive coronary arteries: common in women






Anderson RD et al. *Circulation* 2007;115:823-826

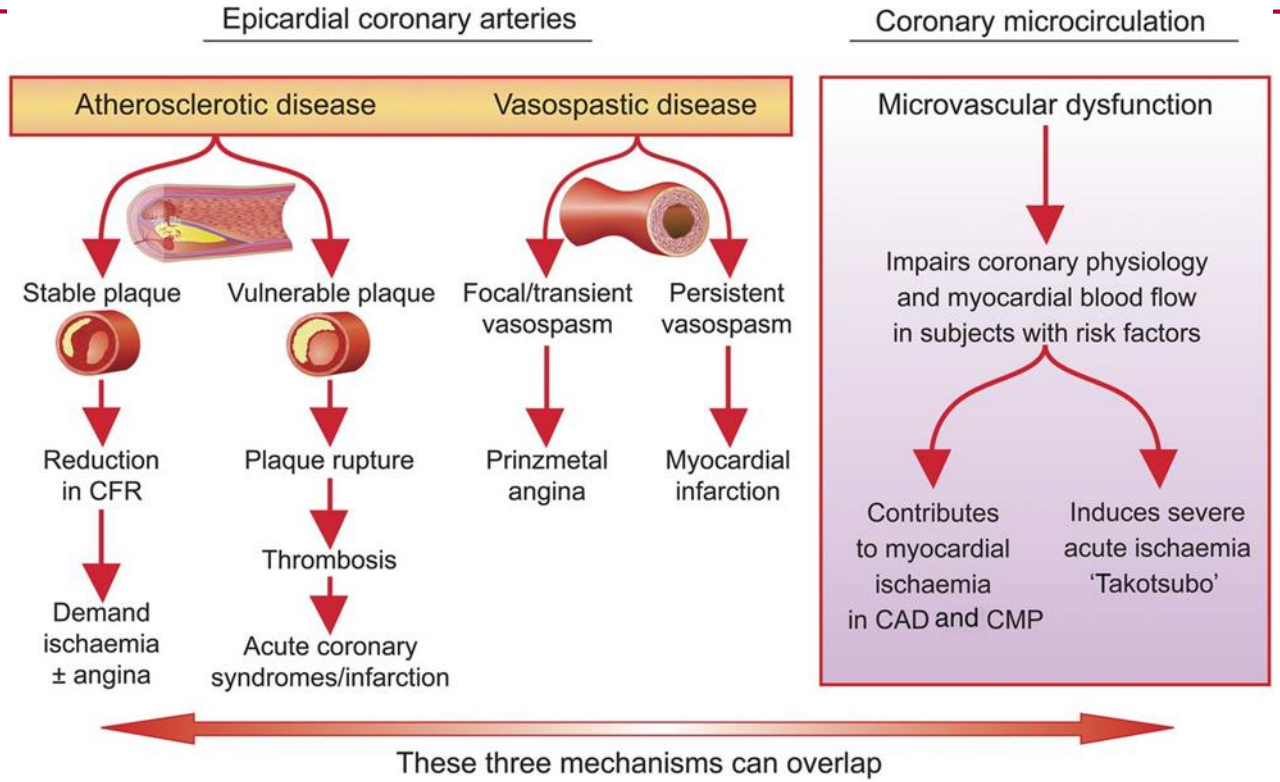
# VA CART 37,674 male patients – 47% non-obstructive or normal coronary arteries




Now common in men!

CART VA CLINICAL ASSESSMENT REPORTING & TRACKING PROGRAM

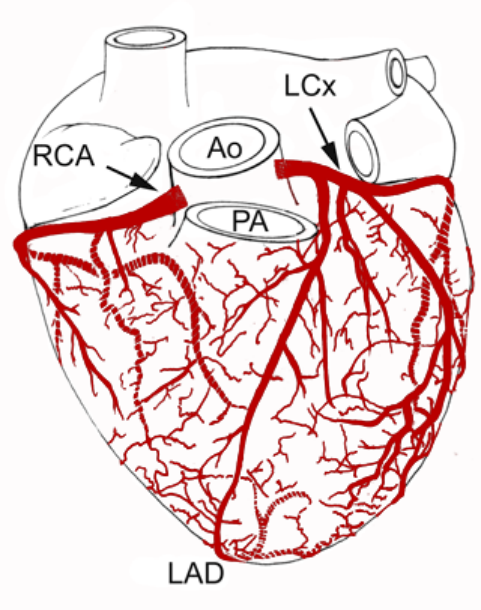
# Mechanisms of Myocardial Ischemia (including INOCA)






Crea, Filippo, Paolo G. Camici, and Cathleen Noel Bairey Merz. "Coronary microvascular dysfunction: an update." European heart journal (2013): eht513.

# Coronary Vascular Resistance



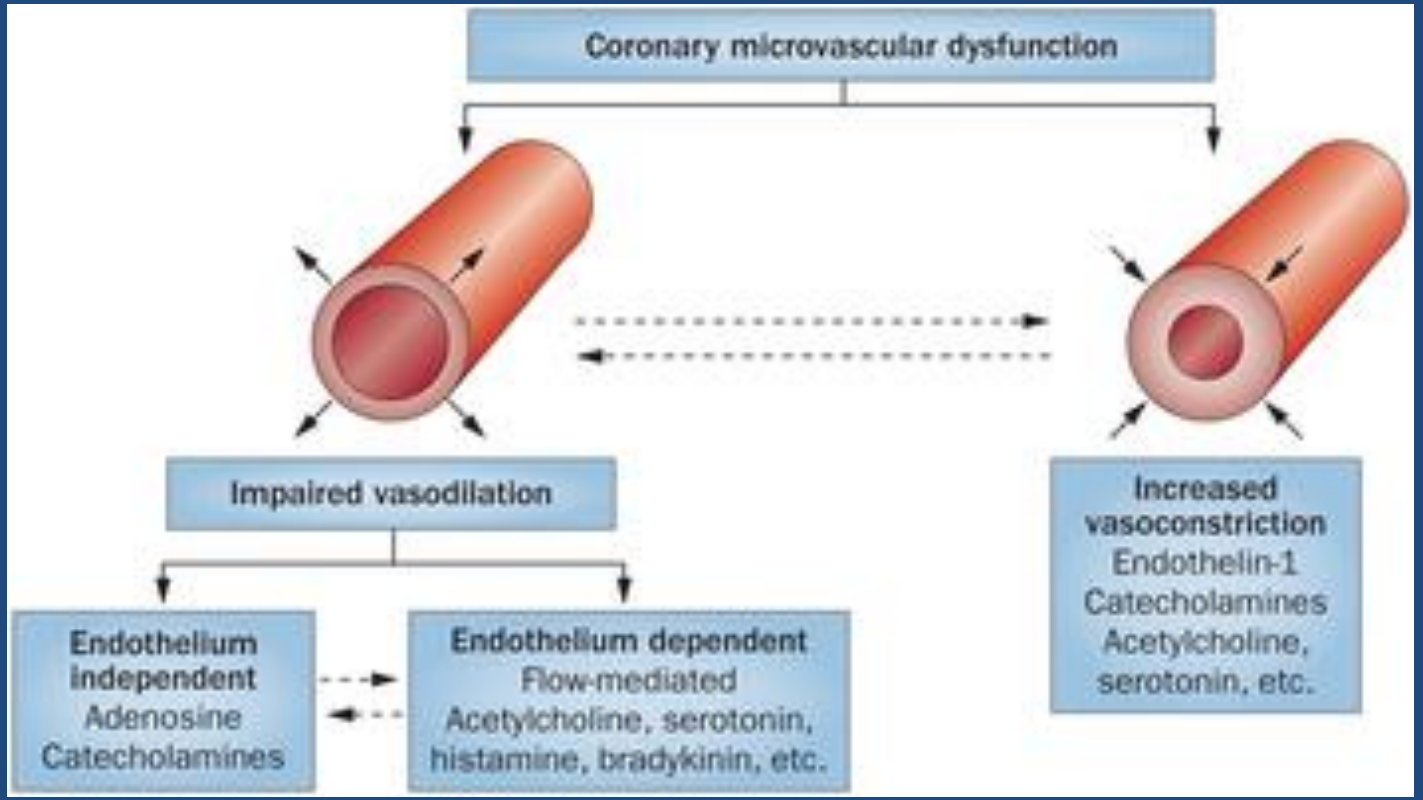

www.vhlab.umn.edu/

- Epicardial arteries normally contribute <10% of the coronary vascular resistance
  - –hemodynamic significance when >70% of the lumen is obstructed
- Coronary microvasculature is responsible for >70% of the coronary resistance under physiological circumstances.



Gould KL et al. *Am J Cardiol*. 1974;33:87–94.
Camici P et al. *Heart, Lung, and Circ.* 2009;18:19-27

# Coronary Microvascular Dysfunction

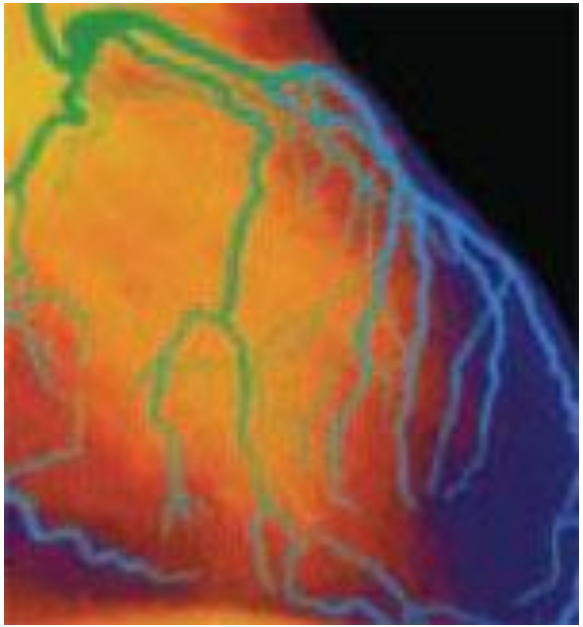



Crea, F, et al. Nature Reviews Cardiology. 2015;12:48–62.

# Mechanisms: Coronary Microvascular Dysfunction (CMD) is Prevalent in INOCA

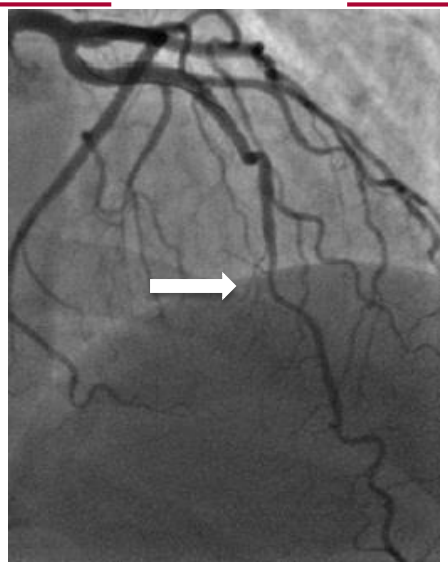
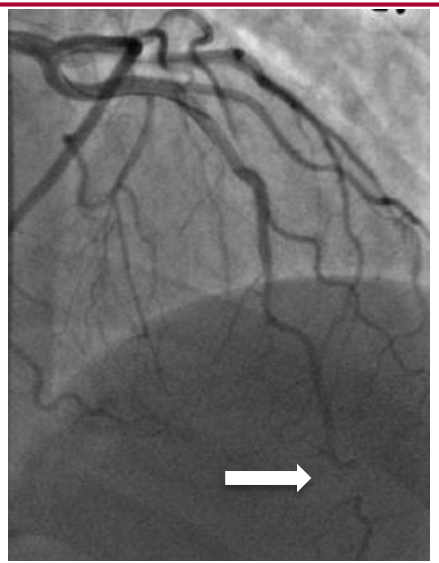
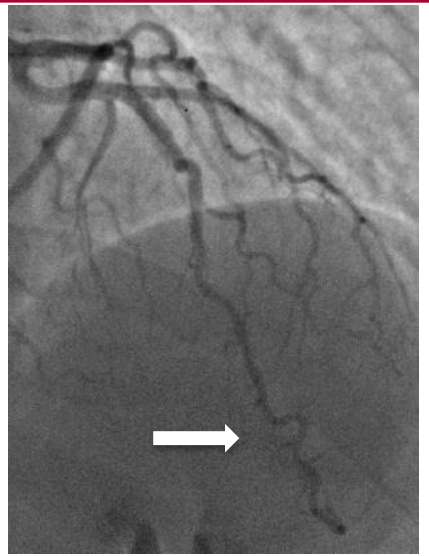
- Approximately 50% of patients with:
  - persistent chest pain
  - non-obstructive coronary artery disease

- have physiologic evidence of coronary microvascular dysfunction measured by abnormal coronary flow reserve (CFR) or coronary blood flow (CBF)
- prevalence is higher (70%) with evidence of myocardial ischemia

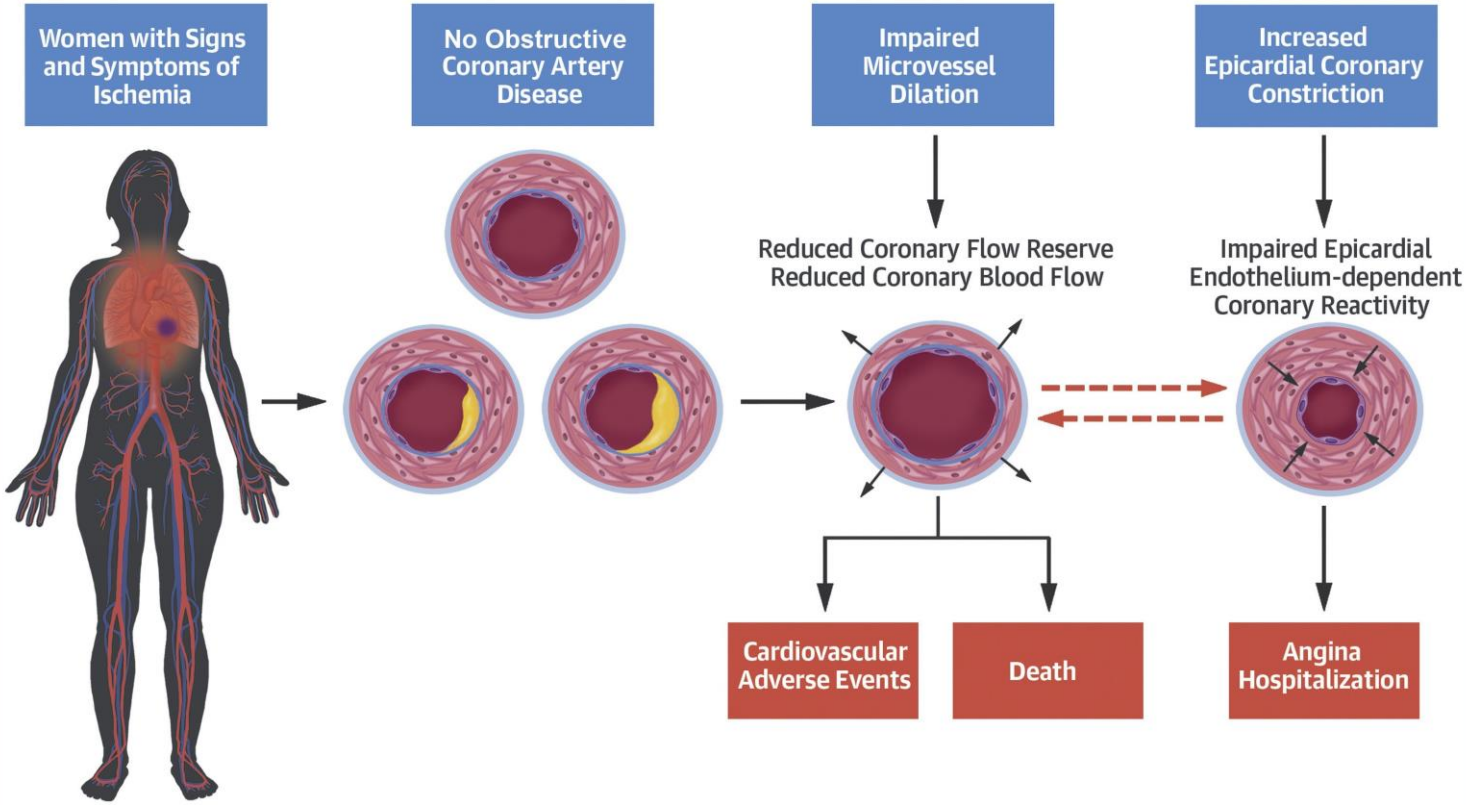


Hasdai D et al. *Mayo Clin Proc.* 1998;73:1133-1140
Wei J et al. JACC Interventions. 2012;6(5):64

# Case: Functional Coronary Angiography

| Baseline | Adenosine | Nitroglycerin |
|---|---|---|
|  |  |  |
| mid LAD bridging and plaque on IVUS | Abnormal CFR 1.8, adenosine-induced vasoconstriction, chest pain but no ST-T changes | Resolution of vasoconstriction<br>Abnormal LVEDP = 18 |

**CENTRAL ILLUSTRATION: Women With Signs and Symptoms of Ischemia With No Obstructive Coronary Artery Disease and the Potential Role of Coronary Reactivity Testing**



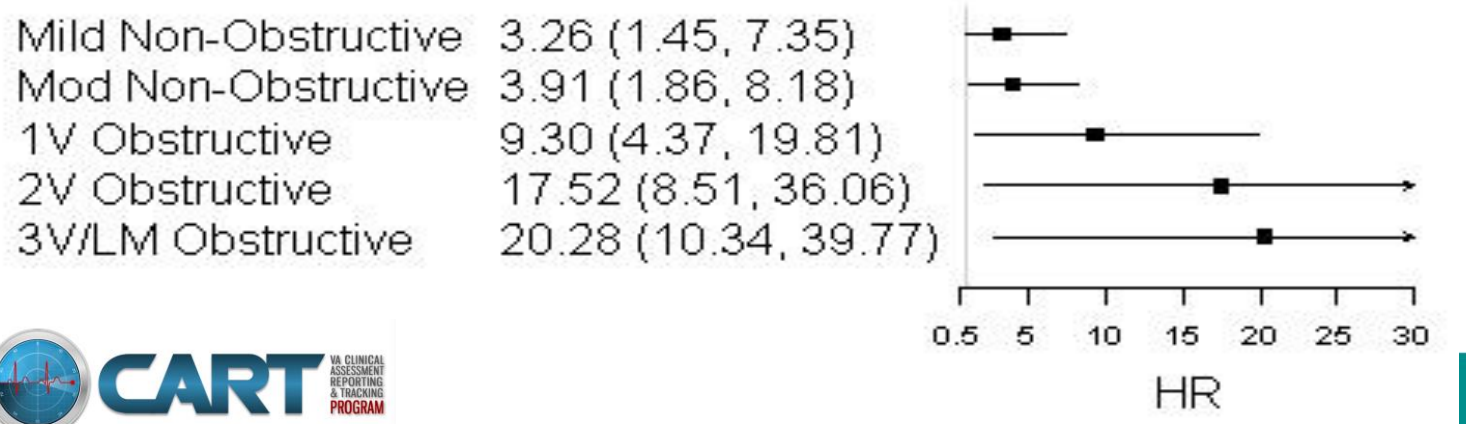

AlBadri, A. et al. J Am Coll Cardiol. 2019;73(6):684–93.

# INOCA Treatment Knowledge Gaps

1. Coronary Microvascular Dysfunction is associated with elevated major cardiac event rate, persistent angina and elevated health costs
2. Observational and randomized intermediate outcome trials support therapeutic strategies
3. Existing guidelines focus on symptom management and current clinical practice is reassurance
4. Therapeutic clinical trials are needed

# Observational Outcomes: Low use of optimal medical therapy and elevated 1-year MI rate following INOCA angiogram

| | Normal Coronaries | 1V Non-Obstructive CAD | 2V Non-Obstructive CAD | 3V Non-Obstructive CAD | 1V Obstructive CAD | 2V Obstructive CAD | 3V/LM Obstructive CAD | P-Value |
|---|---|---|---|---|---|---|---|---|
| IHD | 100 (1.2%) | 119 (2.3%) | 73 (2.4%) | 40 (2.9%) | 618 (7.2%) | 443 (8.5%) | 545 (9.1%) | |
| Stable Angina | 281 (3.3%) | 188 (3.6%) | 101 (3.3%) | 60 (4.4%) | 391 (4.6%) | 254 (4.9%) | 232 (3.9%) | |
| **Discharge Medications** | | | | | | | | |
| Statins | 3,758 (44.8%) | 3,129 (60.1%) | 1,920 (63.5%) | 885 (64.4%) | 6,395 (74.9%) | 3,893 (75.1%) | 4,359 (73.1%) | <.0001 |
| Beta-blockers | 3,142 (37.4%) | 2,506 (48.2%) | 1,591 (52.6%) | 733 (53.3%) | 5,831 (68.3%) | 3,745 (72.3%) | 4,440 (74.4%) | <.0001 |
| ACE/ARB | 2,848 (33.9%) | 2,341 (45.0%) | 1,399 (46.3%) | 694 (50.5%) | 4,414 (51.7%) | 2,747 (53.0%) | 2,928 (49.1%) | <.0001 |
| Thienopyridines | 109 (1.3%) | 258 (5.0%) | 196 (6.5%) | 125 (9.1%) | 4,283 (50.2%) | 2,502 (48.3%) | 1,773 (29.7%) | <.0001 |




CART VA CLINICAL ASSESSMENT REPORTING & TRACKING PROGRAM

# WISE CMD Randomized Pharmacologic PROBE Trials

| Trial (n) | Intervention | Results |
|---|---|---|
| **QWISE[1] (n=78)** | **quinipril** | ↑ CFR; ↓ angina |
| **FemHRT-WISE [2](n=35)** | **ethinyl estradiol and norethindrone acetate** | → MRS; ↓ angina |
| **EWISE[3] (n=41)** | **eplenerone** | →CFR; →angina |
| **SWISE[4] (n=23)** | **sildenafil** | →CFR; →angina |
| **RWISE Pilot[5] (n=20)** | **ranolazine** | ↗MPRI; ↓angina |
| **RWISE[6] (n=128)** | **ranolazine** | →MPRI; →angina |

CFR = coronary flow reserve, MRS = magnetic resonance spectrosopy; myocardial perfusion reserve index; WISE = Women's Ischemia Syndrome Evaluation. 1. Pauley AHJ 2011; 2. Bairey Merz AHJ 2010; 3. Bavry AHJ 2014; Denardo Clin Card 2011; 5. Mehta JACC Imaging; 6. Bairey Merz EHJ 2015

# DES in Stable Angina: ORBITA Trial

| Change from Baseline | PCI | Sham | P Value |
|---|---|---|---|
| Exercise time (sec) | 28.4 | 11.8 | 0.200 |
| Peak oxygen uptake (ml/min) | -2.0 | 10.9 | 0.741 |
| SAQ Physical Limitation | 7.4 | 5.0 | 0.420 |
| SAQ Angina Frequency | 14.0 | 9.6 | 0.260 |
| SAQ Angina Stability | -4.2 | -5.1 | 0.851 |
| Quality of Life | 0.03 | 0.03 | 0.994 |
| Duke Treadmill Score | 1.22 | 0.10 | 0.104 |
| Complete Freedom from Angina | 49.5% | 31.5% | <0.05 |

Compared with placebo, PCI improved stress echo by 1.07 segment units ($p<0.00001$), with larger improvements in stress echo with lower levels of FFR and iFR ($p_{interaction}$ <0.00001)



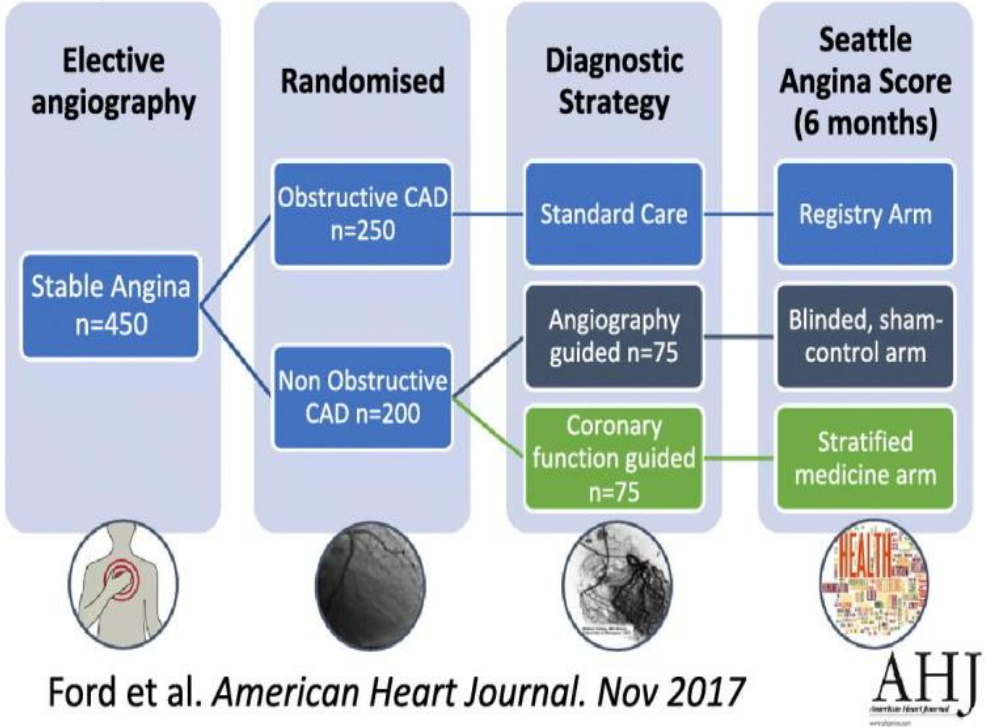
Al-Lamee R et al. Lancet 2018; 391: 31–40

# Randomized CRT Protocol Improves Angina Outcomes

## The BHF CorMicA Study Design

**Coronary Microvascular Angina – a randomised clinical trial of stratified medicine**

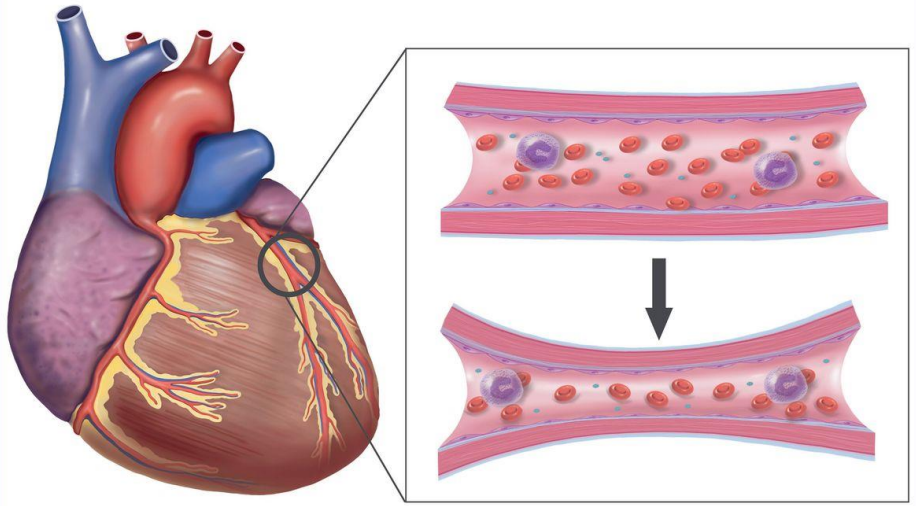
British Heart Foundation




Ford et al. *American Heart Journal*. Nov 2017

AHJ

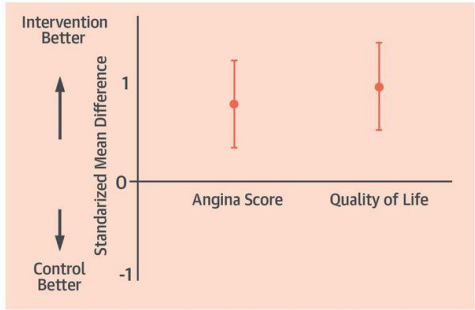
## CENTRAL ILLUSTRATION: Invasive Coronary Function Testing in Angina: Study Design and Results



**Stratified Medicine in Patients with INOCA:**

- Microvascular Angina
- Vasopastic Angina
- Non-Cardiac Chest Pain

**Improved Angina and Quality of Life**




Ford, T.J. et al. J Am Coll Cardiol. 2018;72(23):2841-55.

# WARRIOR: Women's IschemiA TReatment Reduces Events In Non-ObstRuctive CAD Trial

Carl Pepine MD
Noel Bairey Merz MD
Eileen Handberg PhD
Rhonda Cooper-DeHoff PharmD
Janet Wei MD
John Spertus MD
Bernard Chaitman MD
William Weintraub MD

4,422 subjects with angina, no obstructive CAD randomized to IMT (intensive statin and ACE/ARB) vs GMT (guideline directed risk factor management) for reduction of MACE (all-cause death, non-fatal-MI, -stroke, or hospitalization for angina or HF)

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

Women's Ischemia Syndrome Evaluation
WISE

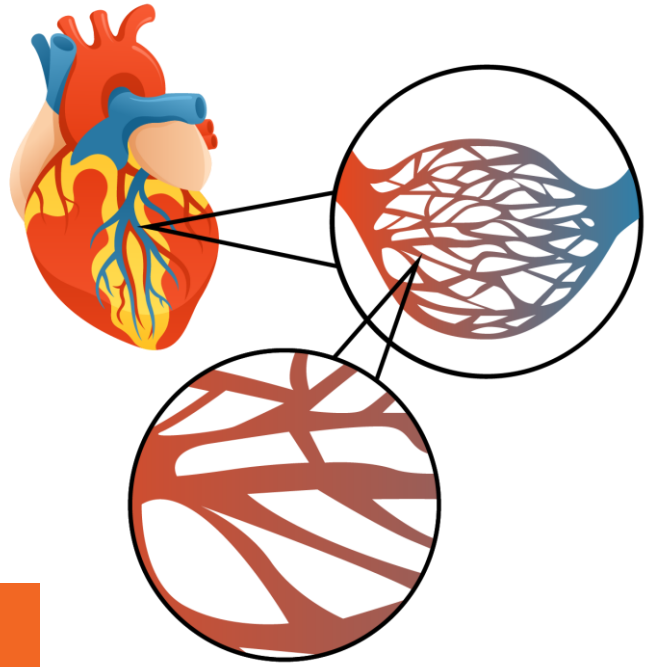
WARRIOR

# Coronary Microvascular Dysfunction: Prevalence and Unmet Needs

- CMD is prevalent in >50% INOCA patients
- ESC guidelines endorse treatment consistent with stable angina (SIHD) guidelines[1]
- Diagnostic testing and use of anti-anginal therapy improved angina and quality of life
- Additional, novel anti-ischemic/anti-anginal therapies are needed
- Large outcome trials are needed

[1]Fox K et al. Eur Heart J 2006;27:1341-1381

# Defining Refractory Angina: Epicardial and Microvascular



**Amir Lerman, MD**
Barbara Woodward Lips Professor
Associate Chair, Cardiovascular Medicine
Director, Cardiovascular Research Center, Mayo Clinic
Rochester, MN

medtelligence℠

# Faculty Disclosure

**Amir Lerman, MD**

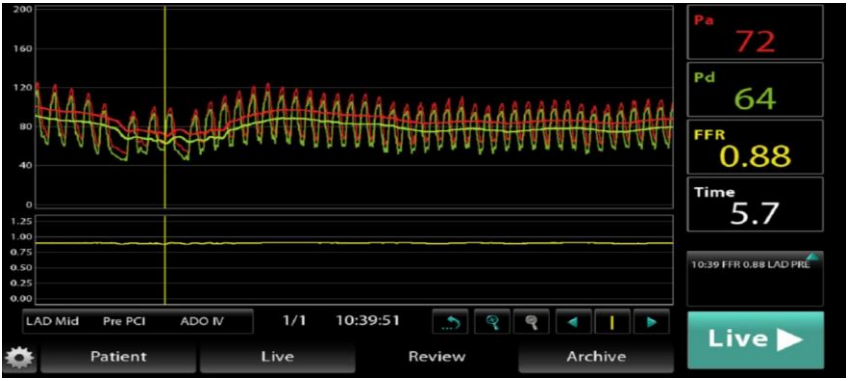
CONSULTING FEE: Itamer Medical, Philips

# 50-Year-Old Female With Chest Pain

- Had a severe episode of CP while driving on highway 110 with her window open on her way for dental appointment.
- Arrived at the ER: MI was ruled out
- History of obesity and PCO syndrome
- She continues to complain on recurrent episodes of chest pain

# 67 year old male with Chest Pain

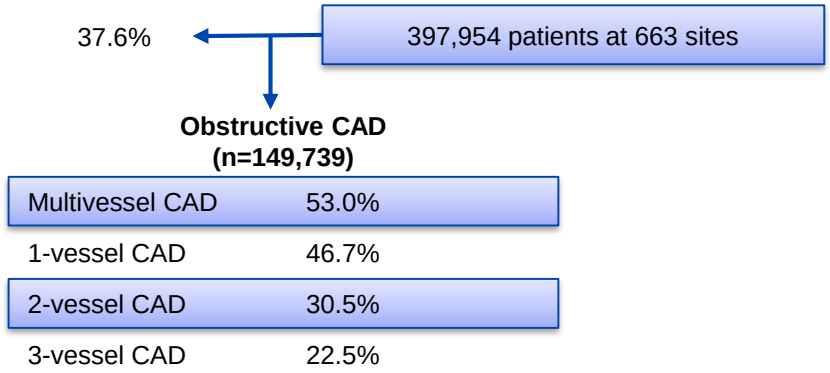
- S/P NSTEMI and stent to LAD
- Continue to complain on progressive chest pain during exertion
- Several ER visits with ECG changes

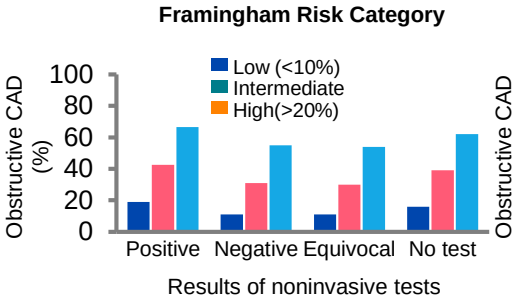


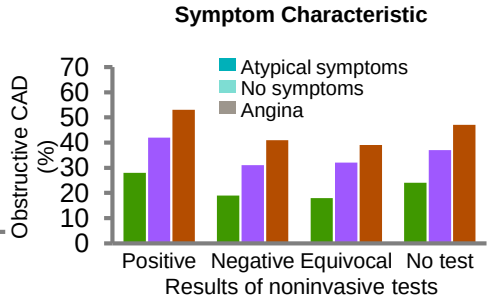
ORIGINAL ARTICLE

# Low Diagnostic Yield of Elective Coronary Angiography

## Study Population and Rates of Obstructive Coronary Artery Disease




Patel et al: N Engl J Med 362:886, 2010

Research

Original Investigation

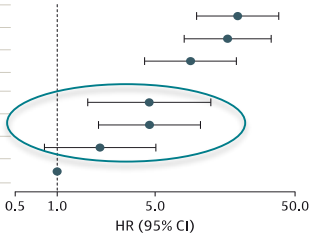
# Nonobstructive Coronary Artery Disease and Risk of Myocardial Infarction

Among 37 674 patients, 8384 patients (22.3%) had non obstructive CAD

Figure 2. Adjusted Cox Model Results for 1-Year Myocardial Infarction, Mortality, and Combined Myocardial Infarction and Mortality by CAD Extent, Relative to No Apparent CAD

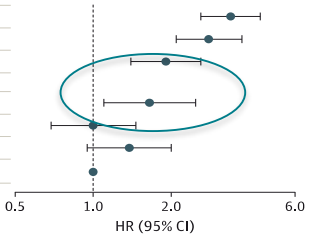
## –1year myocardial infarction

| | Events | Patients | HR (95% CI) |
|---|---|---|---|
| Obstructive CAD | | | |
| 3-Vessel or left main | 137 | 6036 | 19.5 (9.9-38.2) |
| 2-Vessel | 110 | 5452 | 16.5 (8.1-33.7) |
| 1-Vessel | 101 | 9411 | 9.0 (4.2-19.0) |
| Nonobstructive CAD | | | |
| 3-Vessel | 6 | 1133 | 4.5 (1.6-12.5) |
| 2-Vessel | 13 | 2605 | 4.6 (2.0-10.5) |
| 1-Vessel | 10 | 4646 | 2.0 (0.8-5.1) |
| No apparent CAD | 8 | 8391 | 1 [Reference] |




## –1year mortality

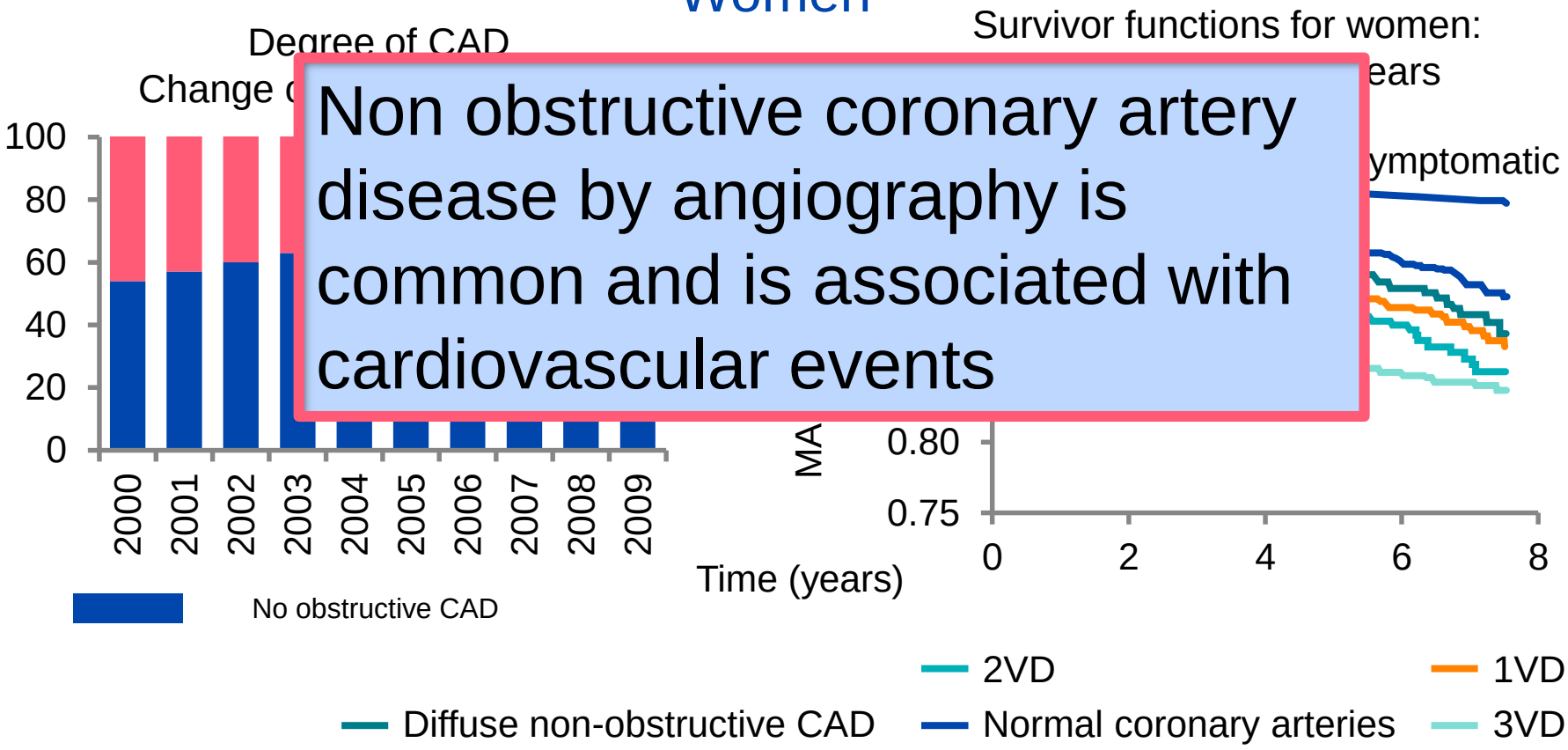
| | Events | Patients | HR (95% CI) |
|---|---|---|---|
| Obstructive CAD | | | |
| 3-Vessel or left main | 239 | 6036 | 3.4 (2.6-4.4) |
| 2-Vessel | 164 | 5452 | 2.8 (2.1-3.7) |
| 1-Vessel | 192 | 9411 | 1.9 (1.4-2.6) |
| Nonobstructive CAD | | | |
| 3-Vessel | 27 | 1133 | 1.6 (1.1-2.5) |
| 2-Vessel | 35 | 2605 | 1.0 (0.7-1.5) |
| 1-Vessel | 85 | 4646 | 1.4 (1.0-2.0) |
| No apparent CAD | 103 | 8391 | 1 [Reference] |




Maddox,JAMA. 2014;312(17):1754-1763..

1-Year combined myocardial infarction and mortality

# Major Adverse Cardiovascular Event-Free Survivor Functions Women

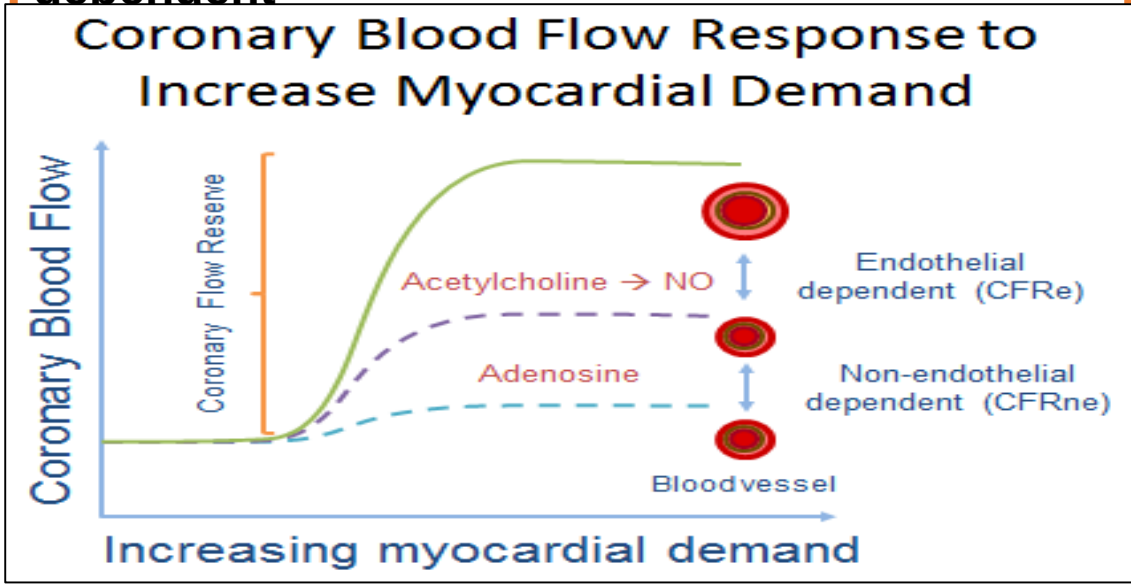



Non obstructive coronary artery disease by angiography is common and is associated with cardiovascular events

Jespersen: European Heart Journal (2012) 33, 734-744

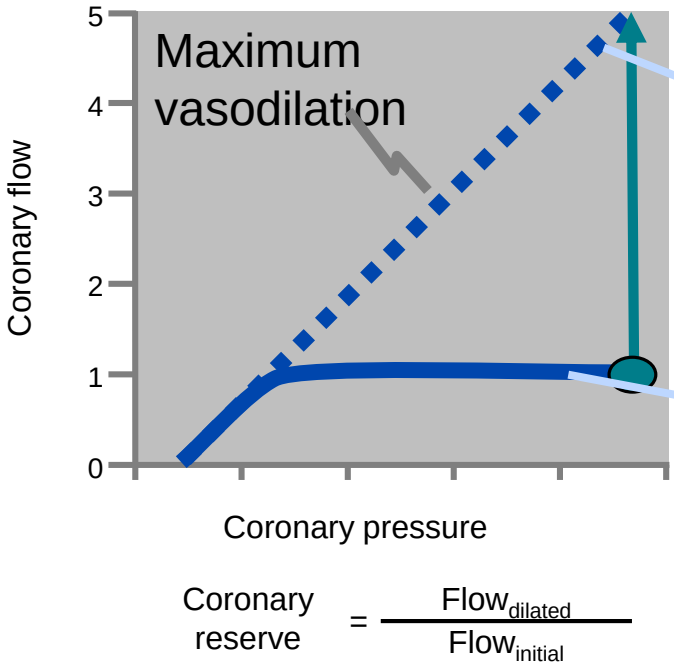
# Coronary Microcirculation

**High oxygen extraction 60-80% vs. 20-30% in skeletal muscle: coronary perfusion is flow dependent**

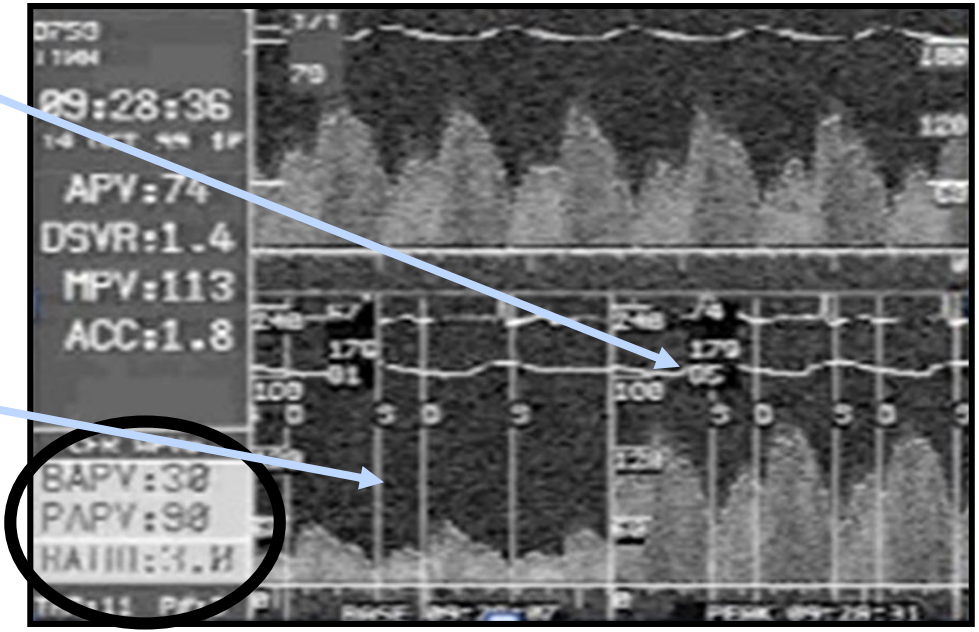


# Coronary Flow Reserve

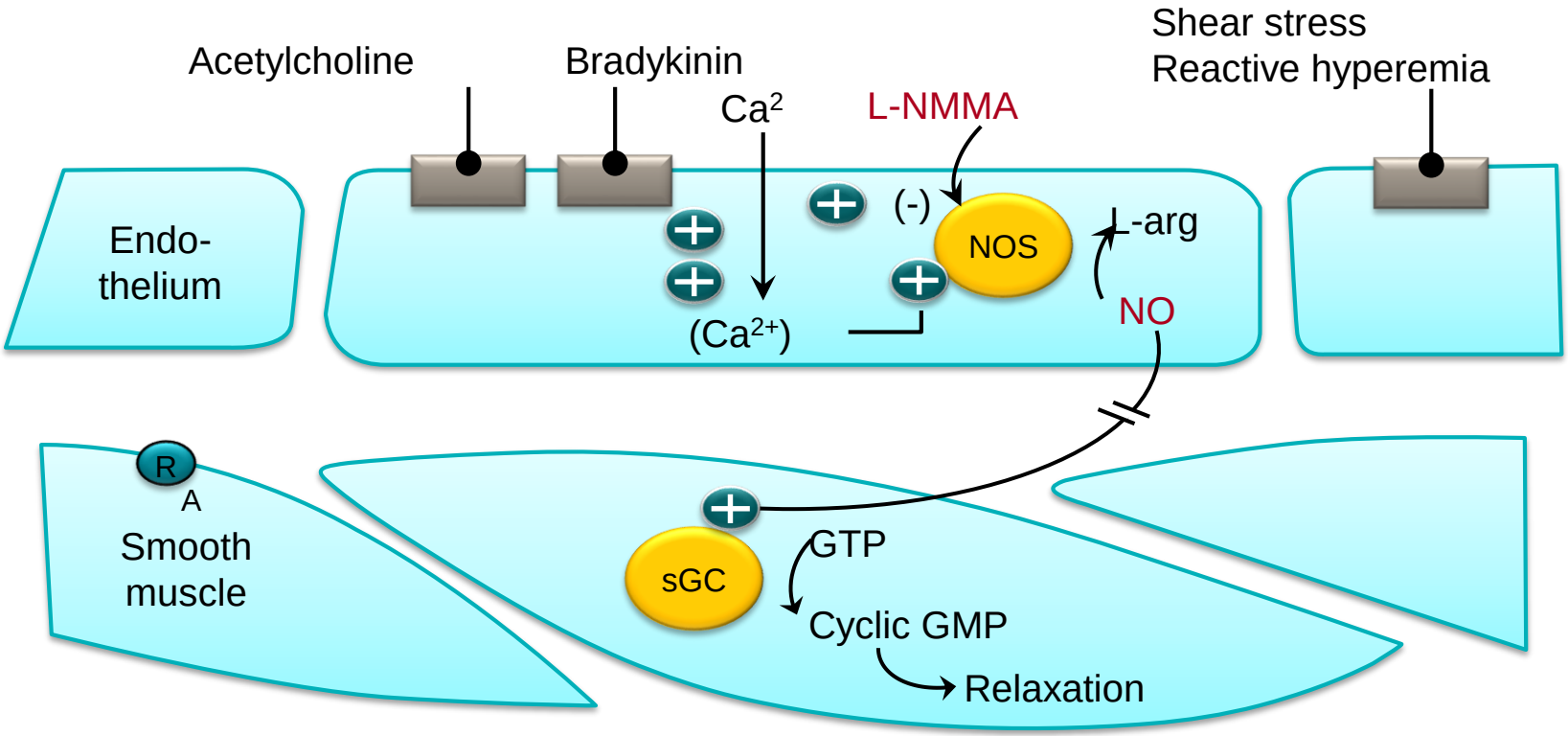
## Response to Adenosine is Non-Endothelial Dependent




$$\text{Coronary reserve} = \frac{\text{Flow}_{\text{dilated}}}{\text{Flow}_{\text{initial}}}$$



# How to assess endothelial function?



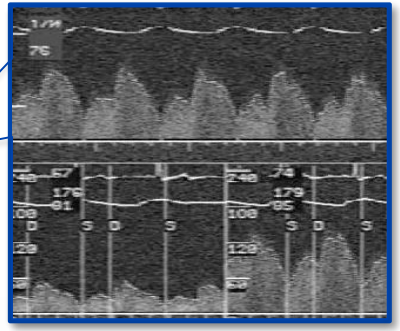

Coronary blood flow increase in response to exercise and mental stress is endothelium dependent and parallels the response to intracoronary acetylcholine.

# Functional Angiogram Protocol

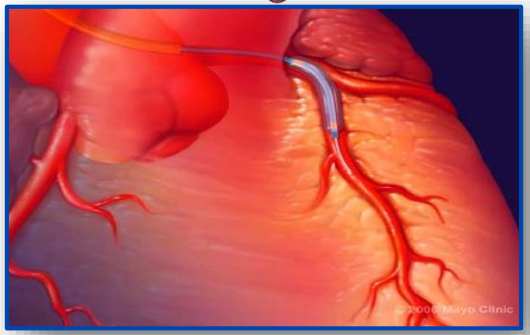
Diagnostic angiography

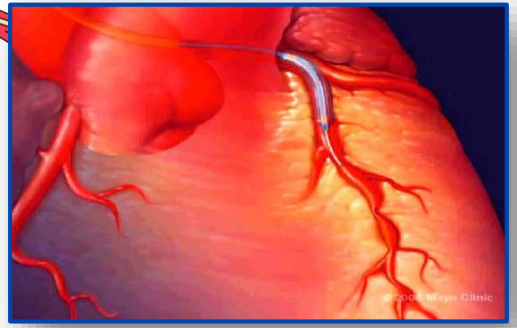
Adenosine IC 24-72 μg

CFR: Non endothelium **microcirculation**

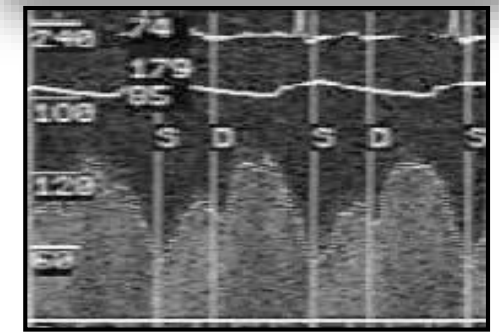


Acetylcholine (endothelium dependent vasodilator)

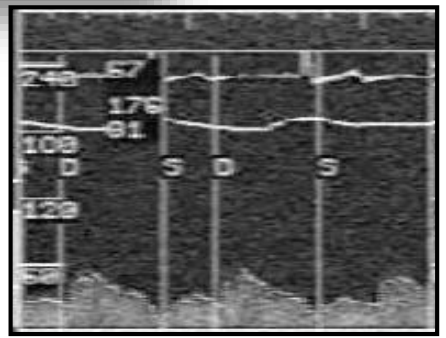




**Epicardial**



**Microcirculation**



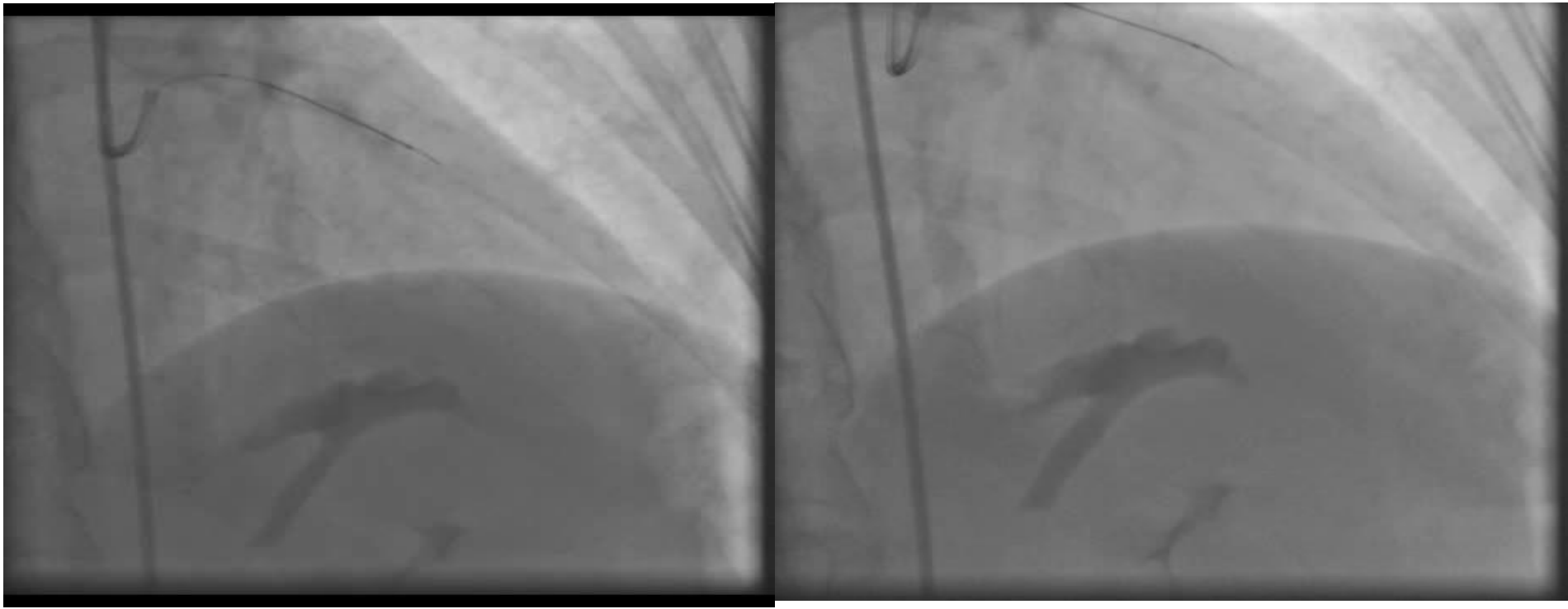
| Mechanism/drug | Non-Endothelium | Endothelial function Epicardial | Endothelial function Microcirculation |
|---|---|---|---|
| **Adenosine**<br>Microcirculation | % Δ in CBF<br>Doppler<br>>2.5 | – | – |
| **Acetylcholine** | – | % Δ in CAD<br>>20% | % Δ in CBF<br>>50% |
| **NTG**<br>Epicardial | % Δ in CAD<br>QCA | – | – |

CAD: coronary artery diameter, CBF coronary blood flow

# 50-Year-Old Female With Chest Pain: Functional coronary angiography

*Baseline*

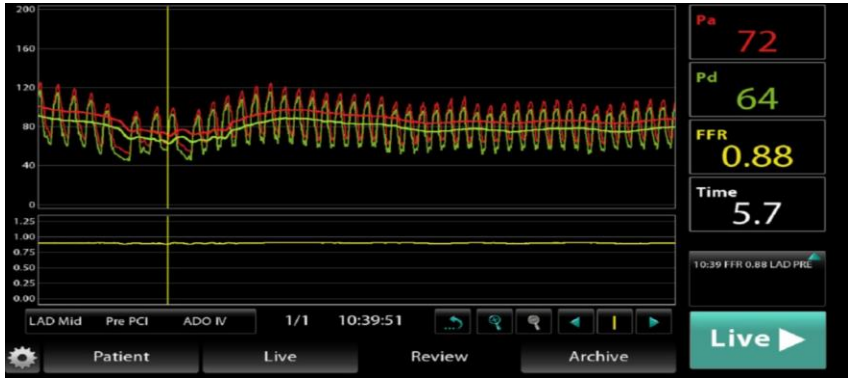
*Acetylcholine 10-4M*



CFR to adenosine 2.2 changes in CBF to Ach -10 %

# 67-year-old male with Chest Pain

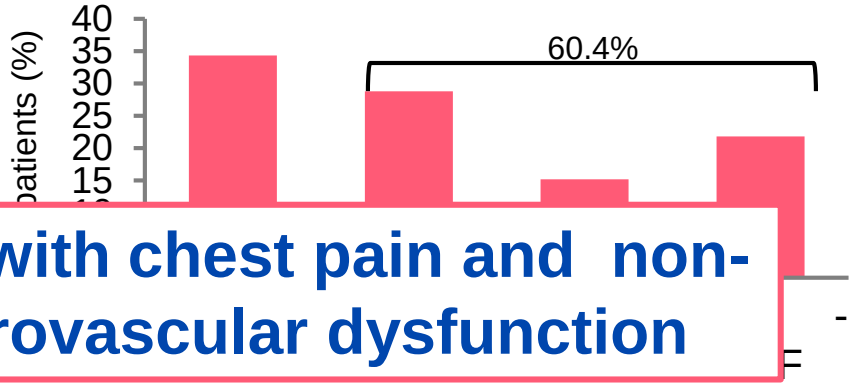
- CFR= 2.5
- Response to IC acetylcholine
- % change of CBF 10%



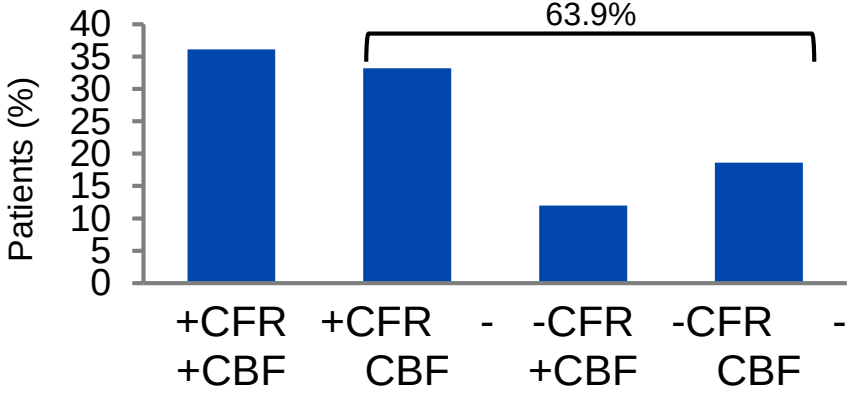
# Prevalence of Microvascular Dysfunction in Patients With Non-Obstructive CAD

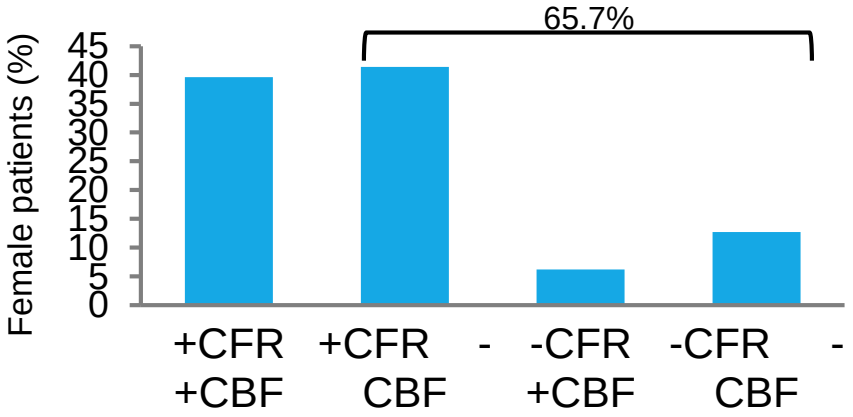
1,439 patients with chest pain and non-obstructive

Microvessel endothelial-dependent and independent function was examined by evaluating changes in coronary blood flow after intracoronary administration of adenosine a




**The majority of the patients with chest pain and non-obstructive CAD have microvascular dysfunction**

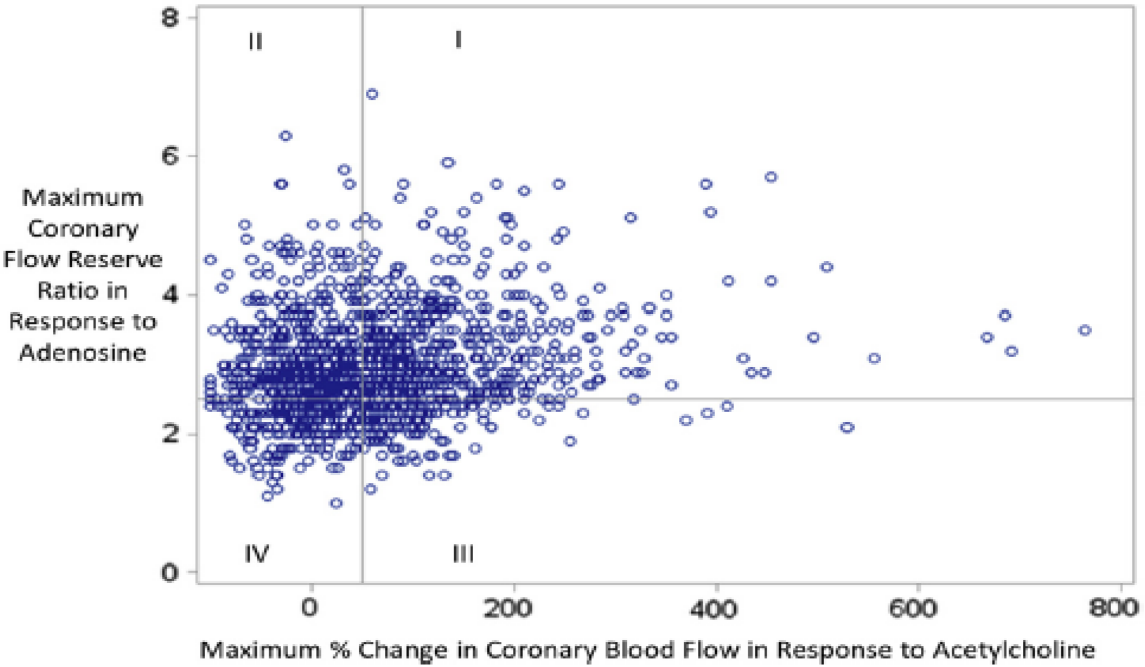



Sara and Lerman JACC Int. 2015

# Coronary microvascular dysfunction among patients with chest pain and non-obstructive coronary artery disease

1,439 patients with measurements available for both CBF and CFR.




Two-thirds of all patients had some sort of microvascular dysfunction.

Sara & Lerman et al JACC 2015

MAYO CLINIC

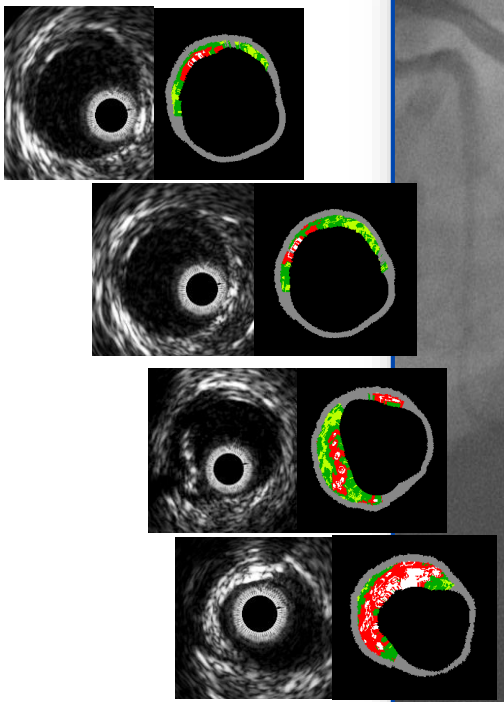
# Endothelial dysfunction is associated with tissue chaptalization of vulnerable plaque

ht166017 Module 1 Heart 12/8/09 16:35:24 Topics:

Original article

Segmental coronary endothelial dysfunction in patients with minimal atherosclerosis is associated with necrotic core plaques

S Lavi,[1,2*] J-H Bae,[1,3*] C S Rihal,[1] A Prasad,[1] G W Barsness,[1] R J Lennon,[4] D R Holmes Jr,[1] A Lerman[1]

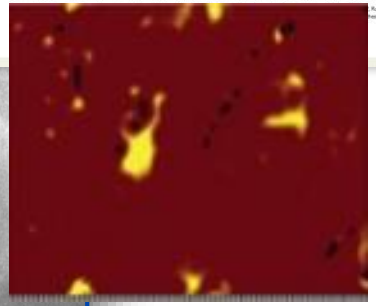


European Heart Journal Advance Access published April 7, 2013

CLINICAL RESEARCH

Coronary endothelial dysfunction in patients with early coronary artery disease is associated with the increase in intravascular lipid core plaque†

Byoung-Joo Choi[1,2], Abhiram Prasad[1], Rajiv Gulati[1], Patricia J. Best[1], Ryan J. Lennon[3], Gregory W. Barsness[1], Lilach O. Lerman[4], and Amir Lerman[1]*



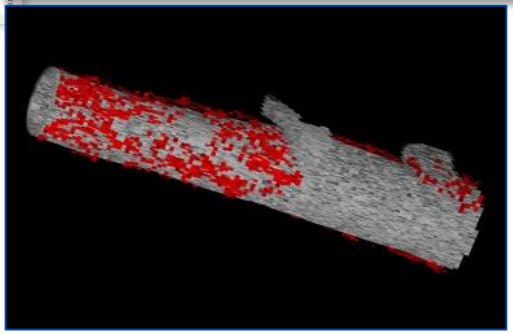
Arteriosclerosis, Thrombosis, and Vascular Biology

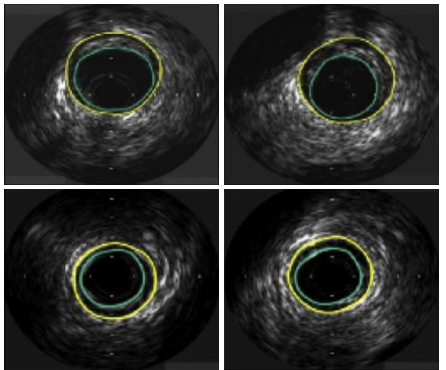
Journal of the American Heart Association

American Heart Association

Coronary Endothelial Dysfunction Is Associated With Inflammation and Vasa Vasorum Proliferation in Patients With Early Atherosclerosis

Byoung-Joo Choi, Yoshiki Matsuo, Tatsuo Aoki, Taek-Geun Kwon, Abhiram Prasad, Rajiv Gulati, Ryan J. Lennon, Lilach O. Lerman and Amir Lerman

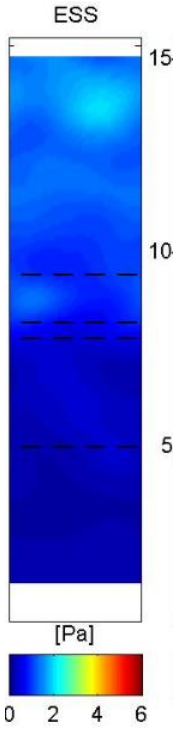




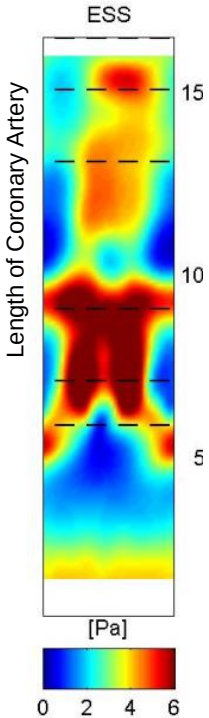
# Local Low Shear Stress and Endothelial Dysfunction in Patients With Nonobstructive Coronary Atherosclerosis

- 65 patients with nonobstructive coronary atherosclerosis
- Microvascular and epicardial coronary endothelial function was assessed by using intracoronary acetylcholine infusion
- Each reconstructed artery was divided into sequential 3-mm segments and analyzed for local ESS with computational fluid dynamics

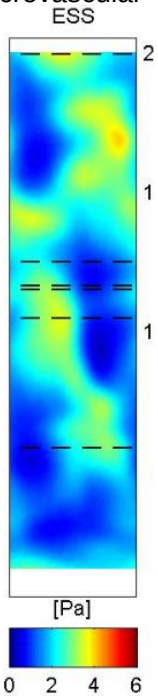
LAD with ***Normal*** Epicardial Endothelial Function



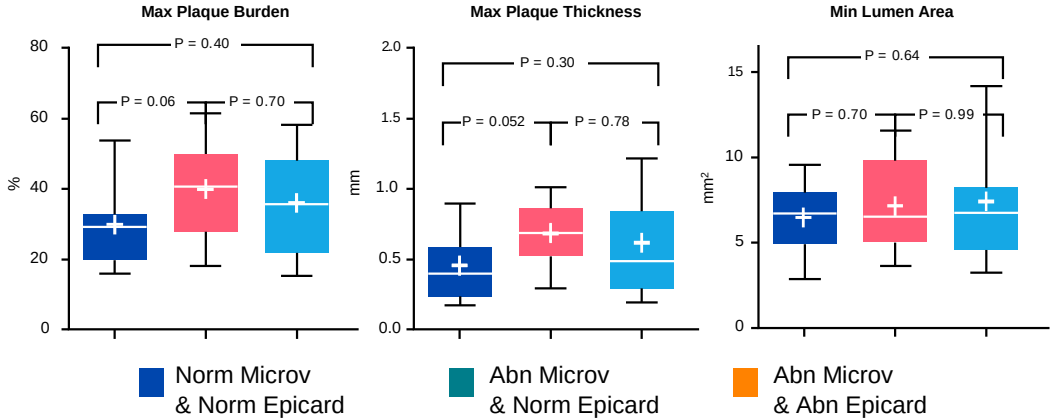

LAD with ***Abnormal*** Epicardial Endothelial Function




LAD with ***Normal*** Epicardial Endothelial Function and **abnormal** microvascular function

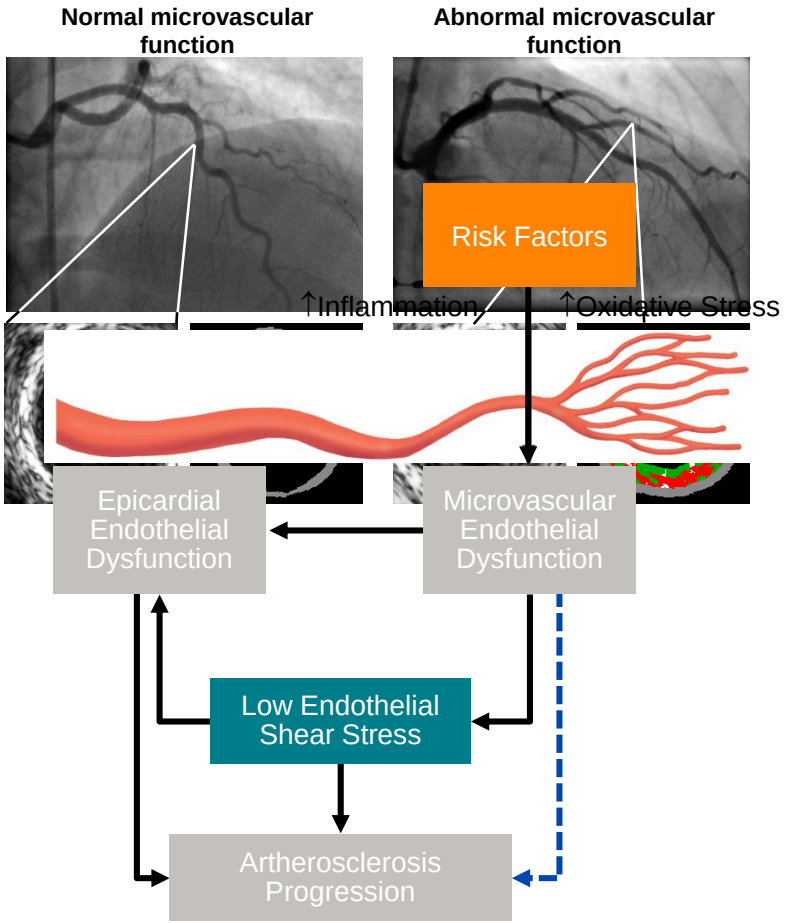



**Plaque Characteristics in 1 Segment Per Artery: Analysis Based on Both Microvascular and Epicardial Endothelial Function**

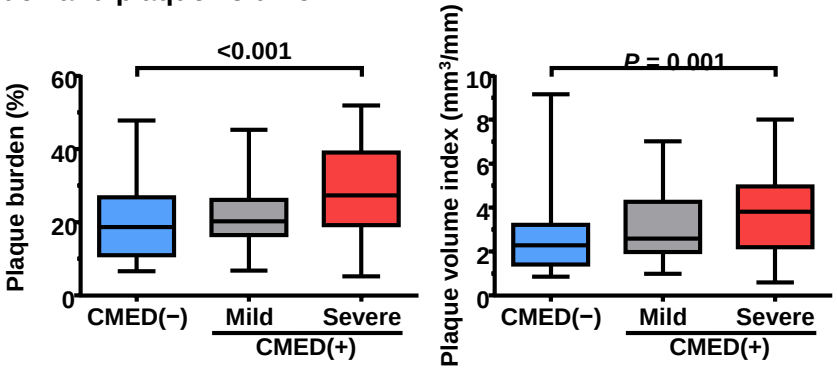



Siasos et al: J Am Coll Cardiol 2018;71:2092–102

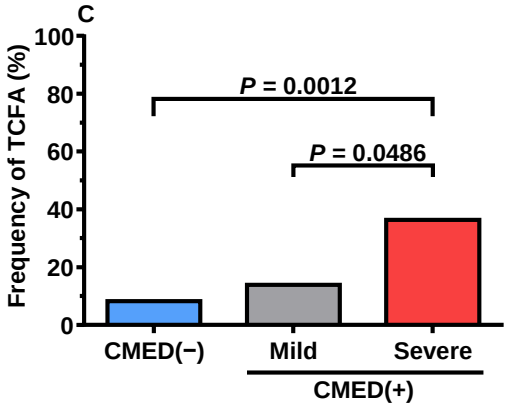
# The Relationship between the Microcirculation and Epicardial Disease




**Association of coronary microvascular endothelial function with plaque burden and plaque volume.**

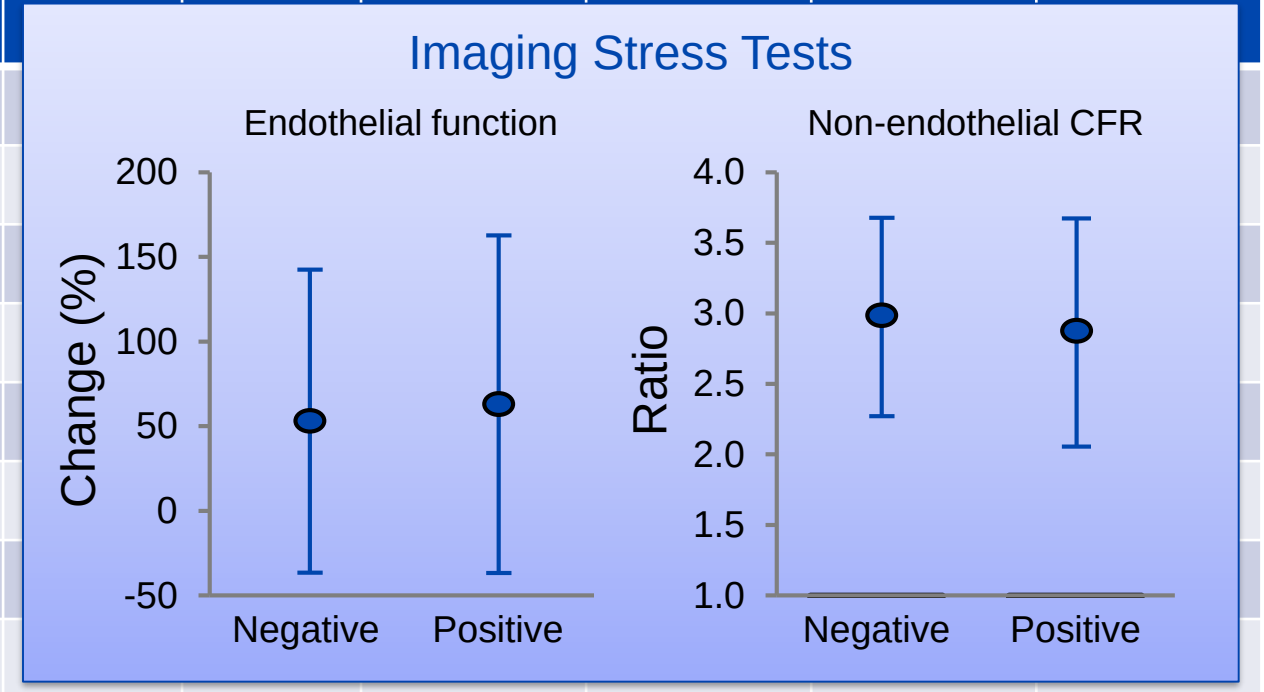



**Association of coronary microvascular endothelial function with plaque composition and vulnerability.**



# Association Between Noninvasive Tests and Coronary Flow Reserve

| Test |
| --- |
| Exercise Echo |
| Dobutamine Echo |
| Exercise SPECT |
| Vasodilator SPECT |
| Vasodilator PET |
| All imaging |
| Exercise ECG |
| All imaging + ECG |




Cassar: Circ, 2009

European Heart Journal (2011) 32, 2758–2765
doi:10.1093/eurheartj/ehr221

CLINICAL RESEARCH
*Coronary heart disease*

**Myocardial ischaemia in patients with coronary endothelial dysfunction: insights from body surface ECG mapping and implications for invasive evaluation of chronic chest pain**

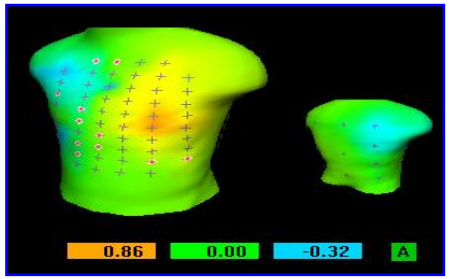
Matthew R. Summers[1], Amir Lerman[1], Ryan J. Lennon[2], Charanjit S. Rihal[1], and Abhiram Prasad[1]*

**Coronary endothelial function in response to acetylcholine**

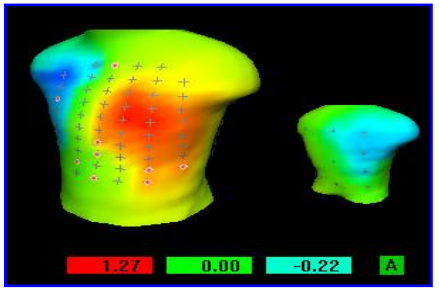
**Eighty lead body surface ECG**

## Coronary Endothelial Function: Prime ECG

**Baseline**

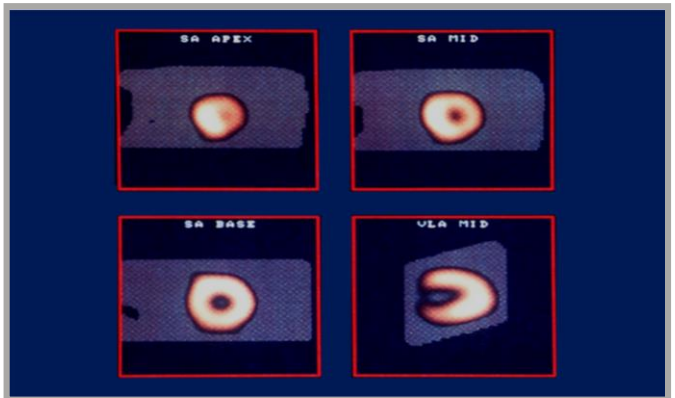


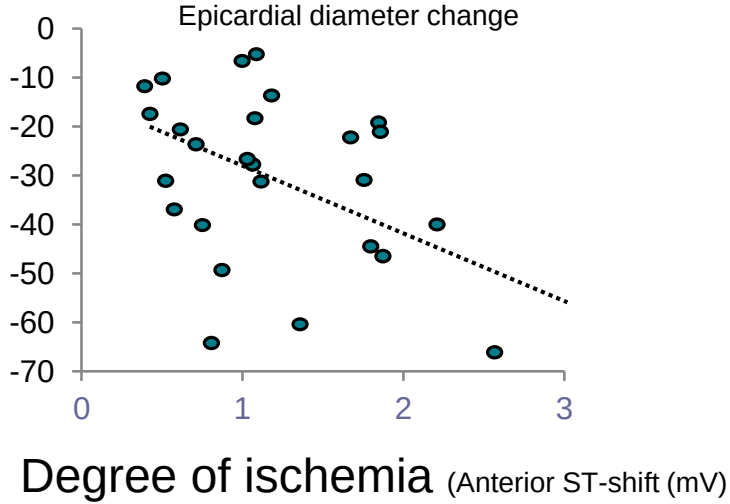

**ACH $10^{-4}$M**




## Coronary Endothelial Dysfunction in Humans Is Associated With Myocardial Perfusion Defects

David Hasdai, MD; Raymond J. Gibbons, MD; David R. Holmes, Jr, MD;
Stuart T. Higano, MD; Amir Lerman, MD



# Coronary Microvascular Dysfunction

Coronary endothelial dysfunction

Epicardial endothelial dysfunction

Vulnerable plaque

Plaque rupture or erosion

ACS

Plaque progression

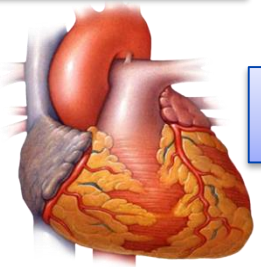
Shear stress

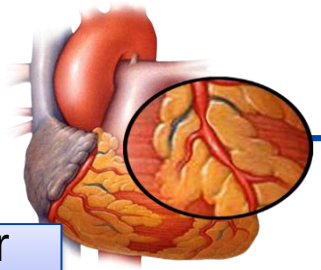
Myocardial ischemia

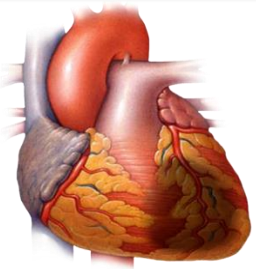
Angina

Microcirculatory endothelial dysfunction

Cardiomyopathy, diastolic dysfunction, apical ballooning







**Coronary endothelial function testing provides superior discrimination compared with standard clinical risk scoring in prediction of cardiovascular events**

Martin Reriani, Jaskanwal D. Sara, Andreas J. Flammer, Rajiv Gulati, Jing Li, Charanjit Rihal, Ryan Lennon, Lilach O. Lerman and Amir Lerman

***Background*** Endothelial dysfunction is regarded as the

microvascular CEF correctly reclassified 11.3% of patients

intracoronary acetylcholine in 470 patients who presented with chest pain and nonobstructive coronary artery disease. CV events were assessed after a median follow-up of 9.7 years. The association between CEF and CV events was examined, and the net reclassification improvement index (NRI) was used to compare the incremental contribution of CEF when added to FRS. The mean age was 53 years, and 68% of the patients were women with a median FRS of 8. Complications (coronary dissection) occurred in three (0.6%) and CV events in 61 (13%) patients. In univariate analysis, microvascular CEF [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.72–0.97, $P=0.032$] and epicardial CEF (HR 0.73, 95% CI 0.59–0.90, $P=0.01$) were found to be significant predictors of CV events, whereas FRS was not (HR 1.05, 95% CI 0.85–1.26, $P=0.61$). When added to FRS,

compared with FRS alone in patients presenting with chest pain or suspected ischemia. ***Coron Artery Dis*** 27:213–220



Coronary Artery Disease 2016, 27:213–220

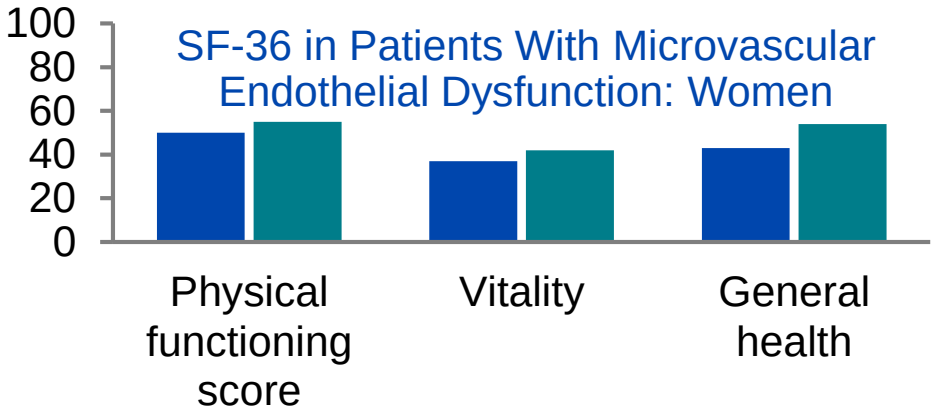
Keywords: cardiovascular events, endothelial dysfunction, endothelium, myocardial infarction, prognosis

Division of Cardiovascular Diseases, Mayo Clinic Rochester, Rochester, Minnesota, USA

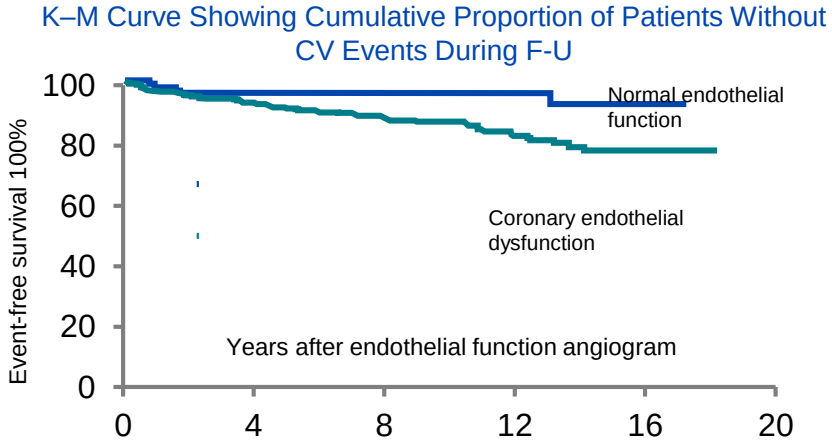
Correspondence to Amir Lerman, MD, Division of Cardiovascular Diseases, Mayo Clinic Rochester, 200 First Street, SW, Rochester, MN 55905, USA
Tel: +1 507 255 4152; fax: +1 507 255 2550; e-mail: lerman.amir@mayo.edu

**Received** 12 November 2015 **Revised** 8 December 2015
**Accepted** 23 December 2015

CV events were assessed after a median follow-up of 9.7 years




| Variable (events) | NRI |
|---|---|
| FRS + microvascular CEF | 0.11 |
| FRS + epicardial CEF | 0.12 |
| FRS + microvascular and epicardial CEF | **0.228** |



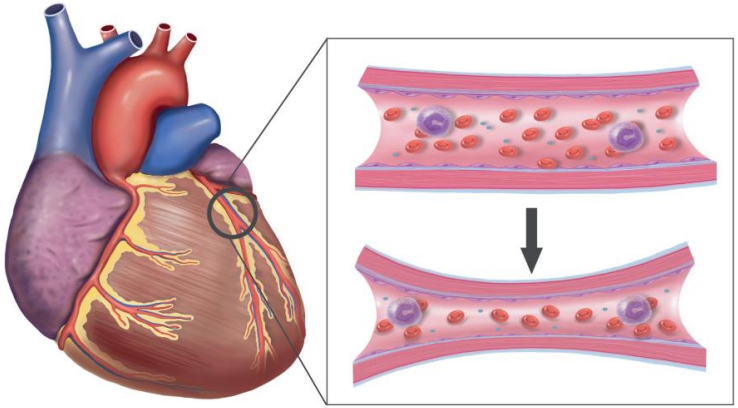

Reriani et al: Coronary Art Dis 27(3):213, 2016

# Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

## The CorMicA Trial

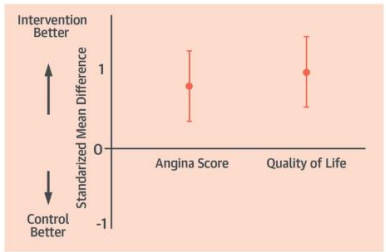
**OBJECTIVES** The purpose of this study was to test whether an interventional diagnostic procedure (IDP) linked to stratified medicine improves health status in patients with INOCA.

### Stratified Medical Therapy Guided by an IDP in Patients With Angina but No Obstructive CAD

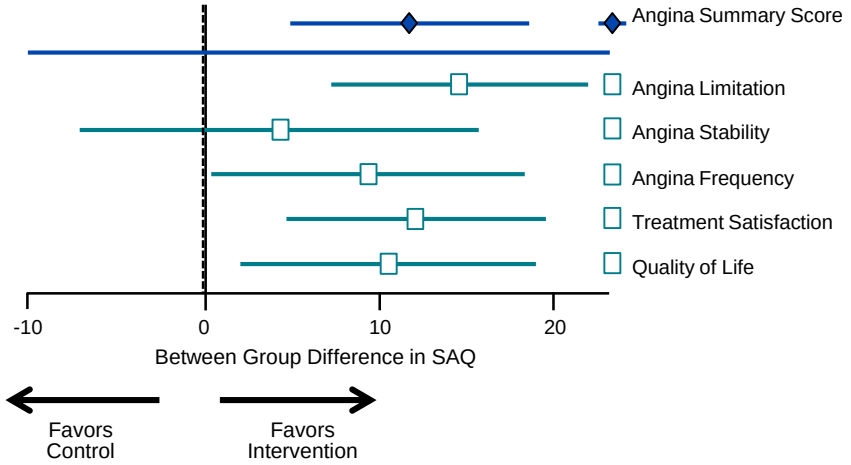


**Stratified Medicine in Patients with INOCA:**
- Microvascular Angina
- Vasopastic Angina
- Non-Cardiac Chest Pain

→ **Improved Angina and Quality of Life**



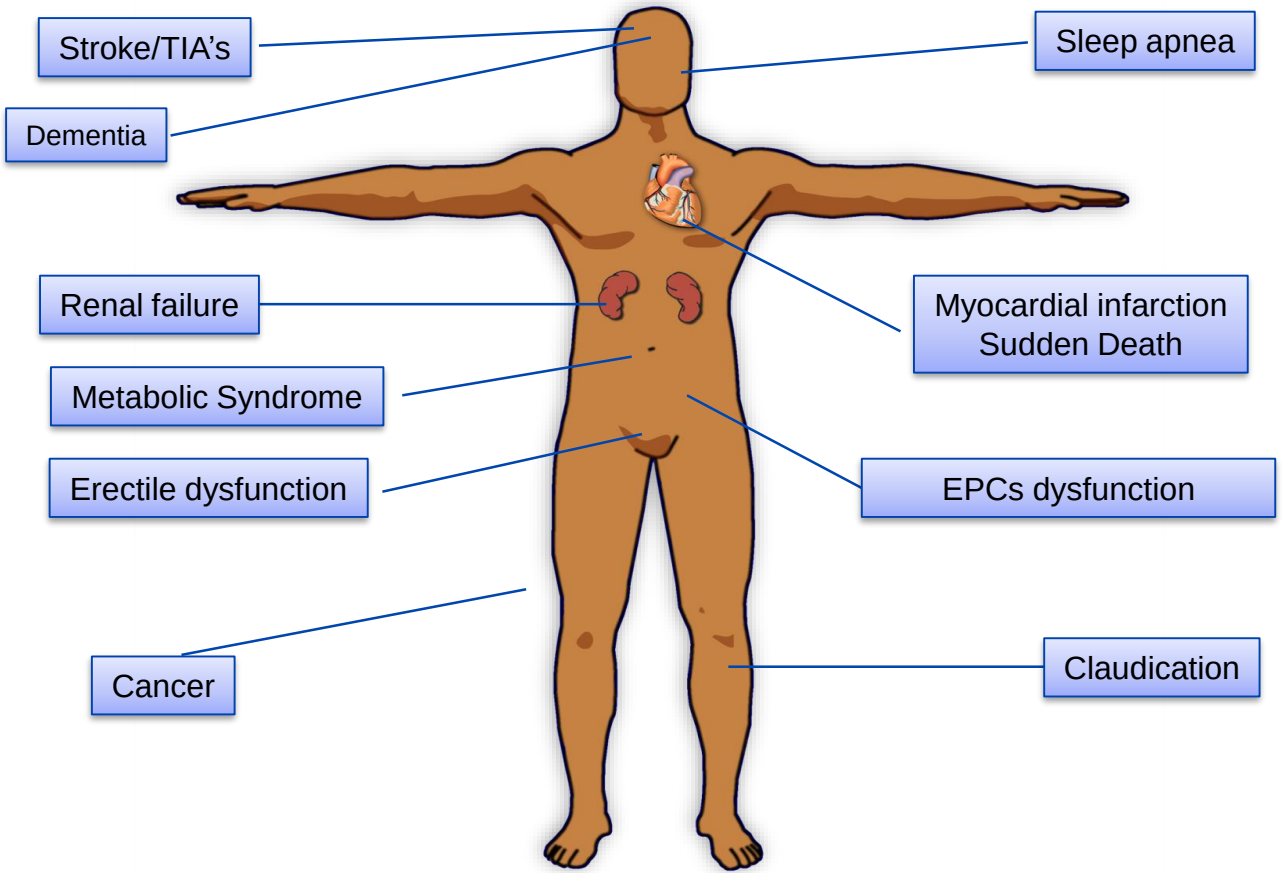

### Primary Efficacy Outcome: Treatment Difference in the 6-Month SAQ Summary Score



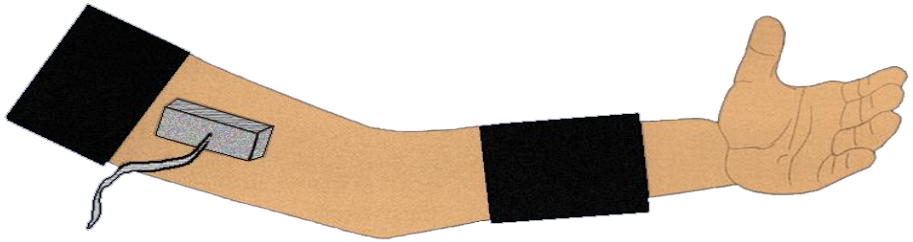

Ford et al: J Am Coll Cardiol; 72:2841-55, 2018

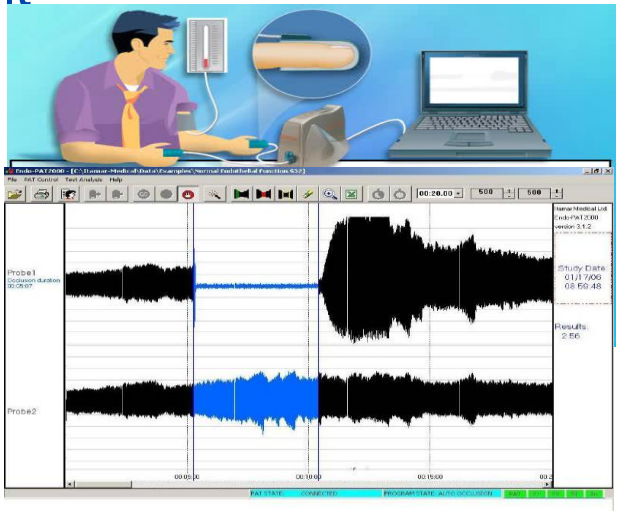
# Systemic Manifestation of Endothelial Dysfunction

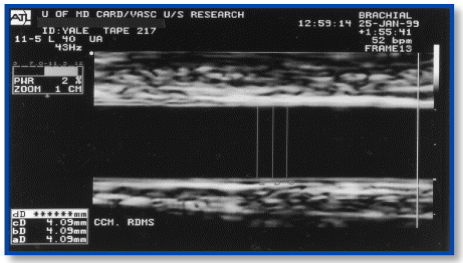
## The Vulnerable Patient



# Reactive Hyperemia: Endothelium Dependent







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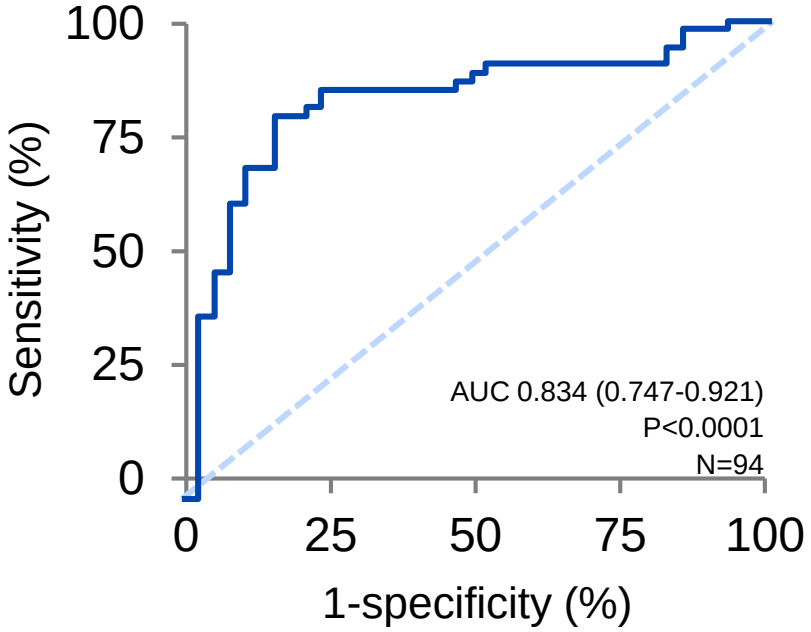
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.08.062

Coronary Artery Disease

# Noninvasive Identification of Patients With Early Coronary Atherosclerosis by Assessment of Digital Reactive Hyperemia

Piero O. Bonetti, MD,* Geralyn M. Pumper, RN,* Stuart T. Higano, MD, FACC,*
David R. Holmes, JR, MD, FACC,* Jeffrey T. Kuvin, MD, FACC,† Amir Lerman, MD, FACC*
*Rochester, Minnesota; and Boston, Massachusetts*

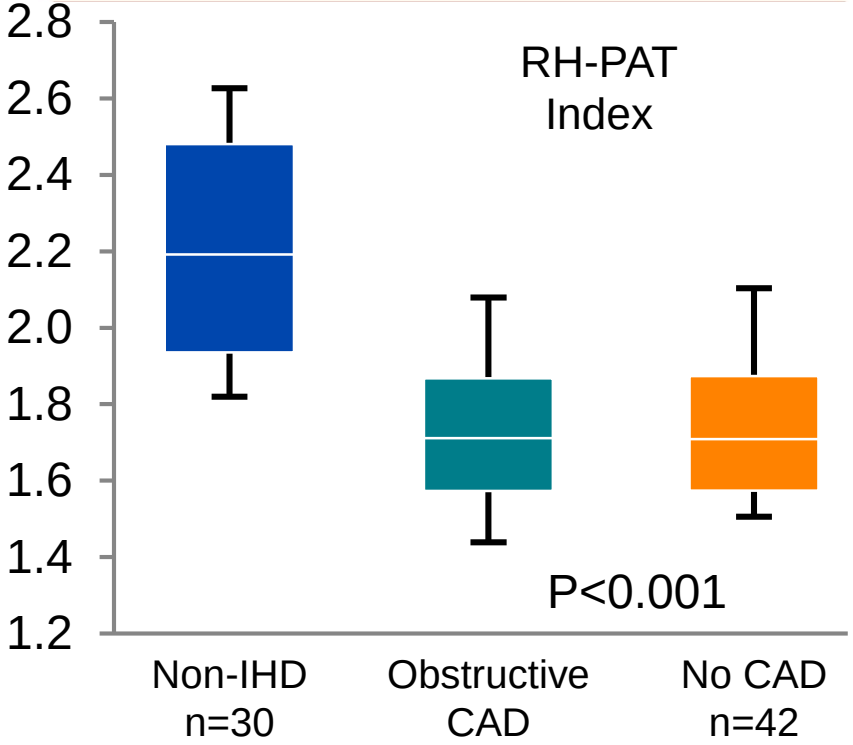



Bonetti & Lerman: JACC, 2004



# Digital Assessment of Endothelial Function and Ischemic Heart Disease in Women

Yasushi Matsuzawa, MD,* Seigo Sugiyama, MD, PHD,* Koichi Sugamura, MD, PHD,*
Toshimitsu Nozaki, MD,* Keisuke Ohba, MD,* Masaaki Konishi, MD,* Junichi Matsubara, MD,*
Hitoshi Sumida, MD, PHD,* Koichi Kaikita, MD, PHD,* Sunao Kojima, MD, PHD,*
Yasuhiro Nagayoshi, MD, PHD,* Megumi Yamamuro, MD, PHD,* Yasuhiro Izumiya, MD, PHD,*
Satomi Iwashita, MT,* Kunihiko Matsui, MD, PHD,† Hideaki Jinnouchi, MD, PHD,‡
Kazuo Kimura, MD, PHD,§ Satoshi Umemura, MD, PHD,‖ Hisao Ogawa, MD, PHD*
*Kumamoto and Yokohama, Japan*



ORIGINAL RESEARCH

American Heart Association | American Stroke Association

# Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis

Yasushi Matsuzawa, MD, PhD; Taek-Geun Kwon, MD, PhD; Ryan J. Lennon, MS; Lilach O. Lerman, MD, PhD; Amir Lerman, MD

***Background***—Endothelial dysfunction plays a pivotal role in cardiovascular disease progression, and is associated with adverse events. The purpose of this systematic review and meta-analysis was to investigate the prognostic magnitude of noninvasive peripheral endothelial function tests, brachial artery flow-mediated dilation (FMD), and reactive hyperemia—peripheral arterial tonometry (RH-PAT) for future cardiovascular events.

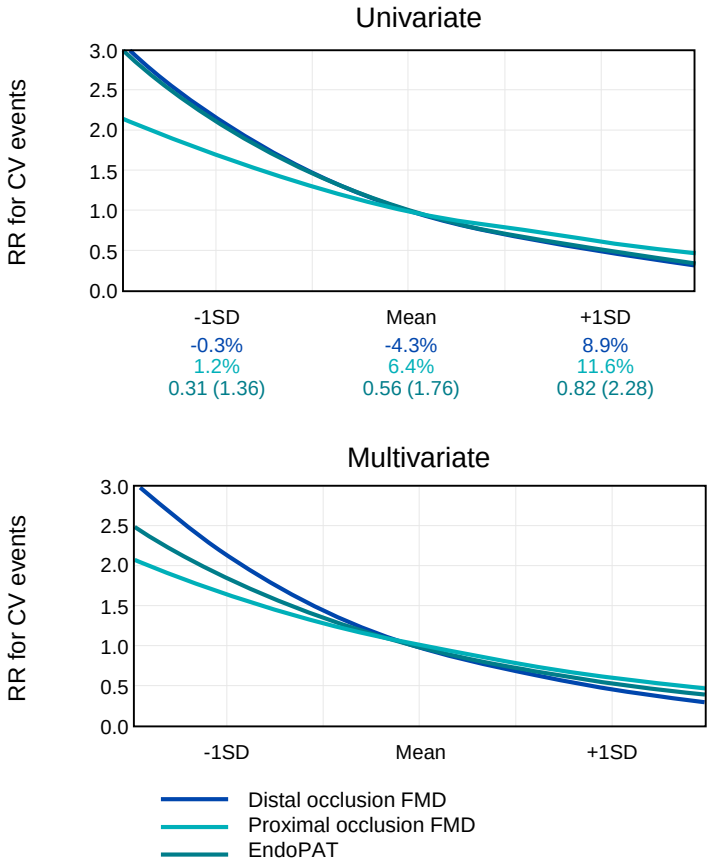
***Methods and Results***—Databases of MEDLINE, EMBASE, and the Cochrane Library were systematically searched. Clinical studies reporting the predictive value of FMD or RH-PAT for cardiovascular events were identified. Two authors selected studies and extracted data independently. Pooled effects were calculated as risk ratio (RR) for continuous value of FMD and natural logarithm of RH-PAT index (Ln RHI) using random-effects models. Thirty-five FMD studies of 17 280 participants and 6 RH-PAT studies of 602 participants were included in the meta-analysis. Both endothelial function tests significantly predicted cardiovascular events, with similar prognostic magnitude. The magnitude of the prognostic value in cardiovascular disease subjects was comparable between these 2 methods; a 1 SD worsening in endothelial function was associated with doubled cardiovascular risk.

***Conclusions***—Noninvasive peripheral endothelial function tests, FMD and RH-PAT, significantly predicted cardiovascular events, with similar prognostic magnitude. Further research is required to determine whether the prognostic values of these 2 methods are

Thirty-five FMD studies of 17 280 participants and 6 RH-PAT studies of 602 participants were included in the meta-analysis.

The magnitude of the prognostic value in cardiovascular disease subjects was comparable between these 2 methods; a 1 SD worsening in endothelial function was associated with double cardiovascular risk.

## Relative Risk for FMD and Endo PAT



# Can We use Endothelial Function to Individualize Therapy?

Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 40, No. 3, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01976-9

**Women and Cardiovascular Disease**

## Prognostic Role of Reversible Endothelial Dysfunction in Hypertensive Postmenopausal Women

Maria G. Modena, MD, FESC, FACC, Lorenzo Bonetti, MD, Francesca Coppi, MD, Francesca Bursi, MD, Rosario Rossi, MD

*Modena, Italy*

Journal of the American College of Cardiology
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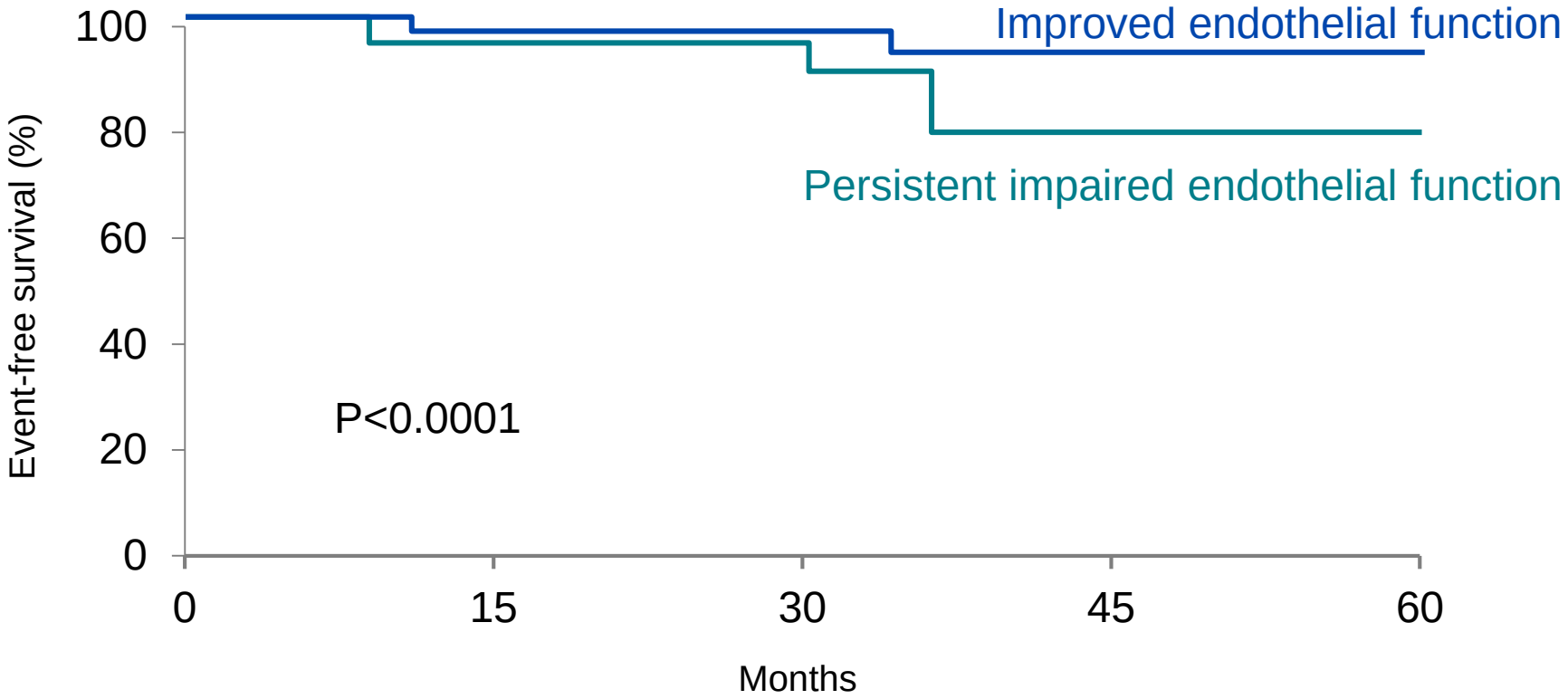
Vol. 53, No. 4, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.08.074

## Persistent Impairment of Endothelial Vasomotor Function Has a Negative Impact on Outcome in Patients With Coronary Artery Disease

Yoshinobu Kitta, MD, PHD, Jyun-ei Obata, MD, PHD, Takamitsu Nakamura, MD, Mitsumasa Hirano, MD, Yasushi Kodama, MD, Daisuke Fujioka, MD, PHD, Yukio Saito, MD, Ken-ichi Kawabata, MD, PHD, Keita Sano, MD, Tsuyoshi Kobayashi, MD, Toshiaki Yano, MD, Kazuto Nakamura, MD, PHD, Kiyotaka Kugiyama, MD, PHD

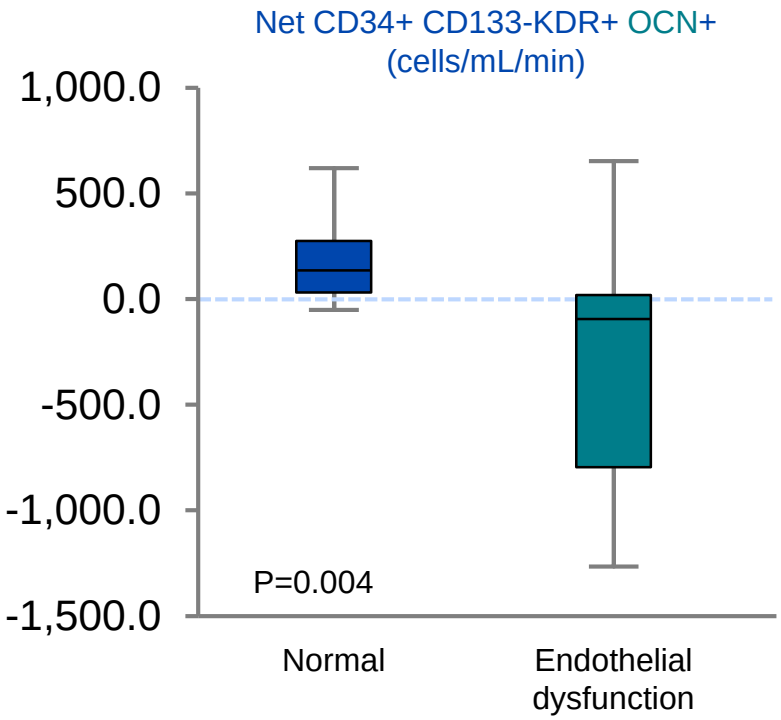
*Yamanashi, Japan*

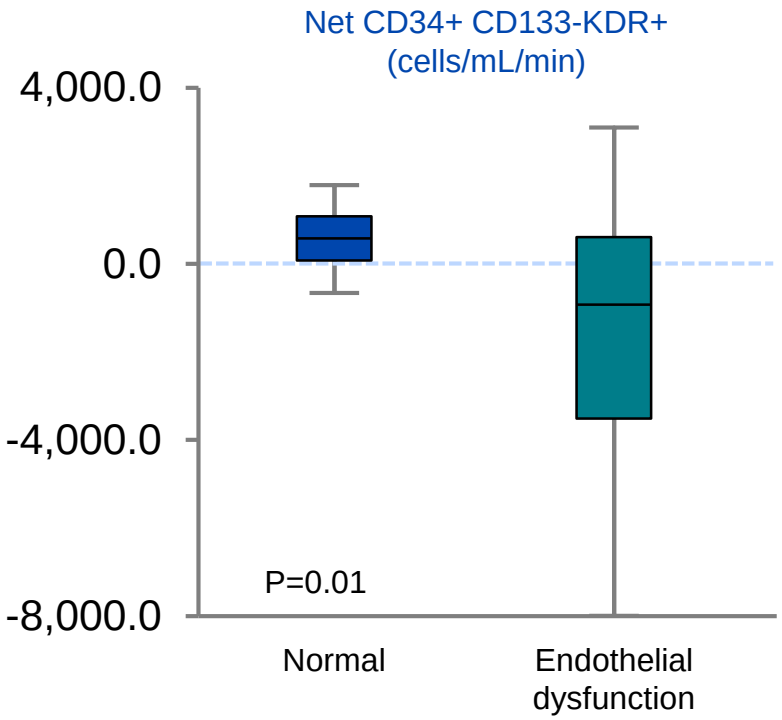
# Event-Free Rate According to Persistent Endothelial Dysfunction in Patients With Mild CAD




Modena et al: JACC 40, 2002

# Osteogenic EPCs are Retained by Myocardium in Early Atherosclerosis



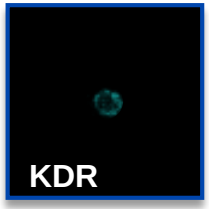

## The Retention of OCN+ Cells is Associated with Coronary Calcification

Gössl & Lerman et al: European Heart J, 2010

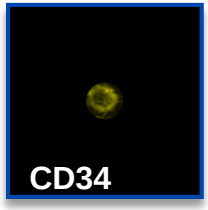
# Multicolor Flowcytometry

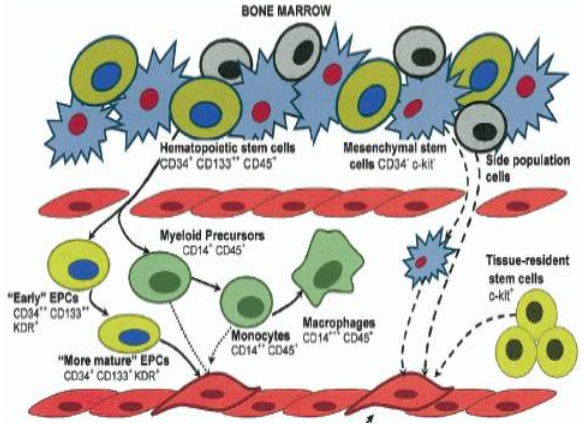
## Classification EPCs

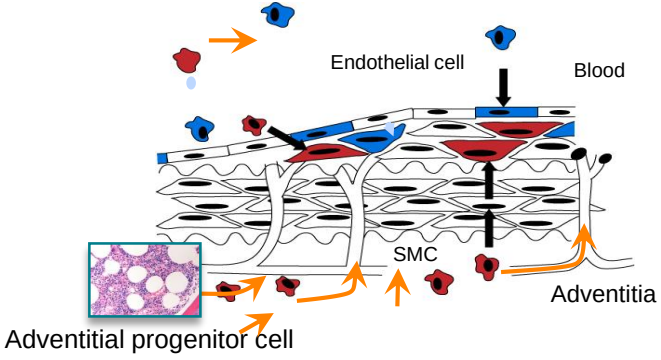
- VEGFR2/KDR (endothelial marker)
- CD133 (hematopoietic/endothelial stem cell marker)
- CD34 (hematopoietic/endothelial stem cell marker)







# Risk factors and Atherosclerosis

Smoking | Hypertension | Hypercholesterolemia | Age | Diabetes

Environmental

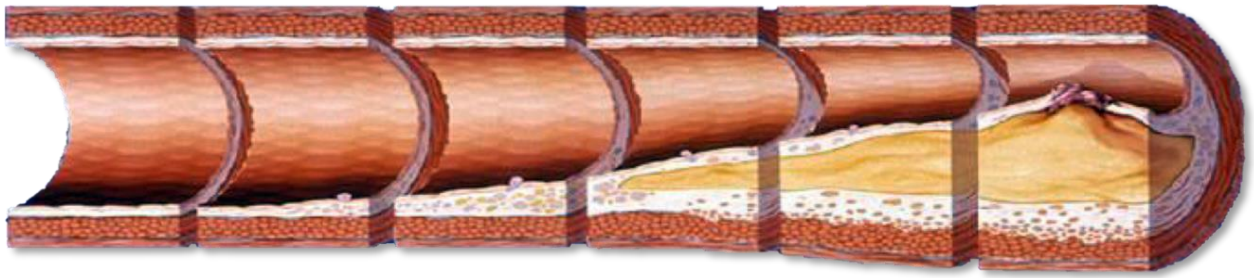
Vascular injury

**EPCs**

Mental stress

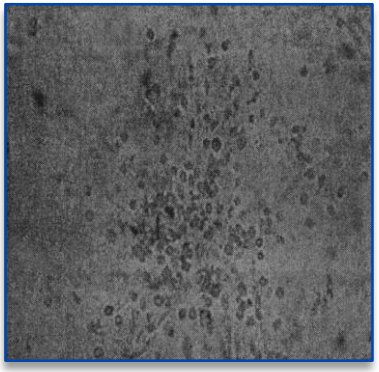
Inflammation & oxidative stress

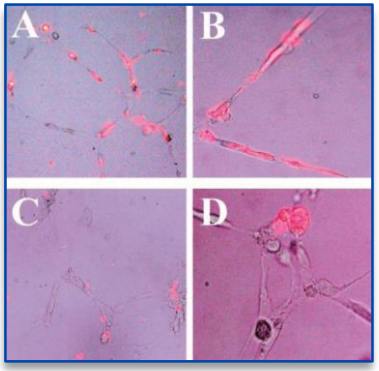
Endothelial dysfunction: The risk of the risk factors



# How Do We Assess Role of EPCs?

- Number of EPCs
- The function of the EPCs
- Colony formation unit
- Tube formation





# Relation Between the Number of Endothelial Progenitor Cells and Endothelial Function

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Circulating Endothelial Progenitor Cells, Vascular Function, and Cardiovascular Risk

Jonathan M. Hill, M.R.C.P., Gloria Zalos, R.N., Julian P.J. Halcox, M.R.C.P., William H. Schenke, B.A., Myron A. Waclawiw, Ph.D., Arshed A. Quyyumi, M.D., and Toren Finkel, M.D., Ph.D.

ABSTRACT

BACKGROUND
Cardiovascular risk factors contribute to atherogenesis by inducing endothelial-cell injury and dysfunction. We hypothesized that endothelial progenitor cells derived from bone marrow have a role in ongoing endothelial repair and that impaired mobilization or depletion of these cells contributes to endothelial dysfunction and cardiovascular disease progression.

METHODS
We measured the number of colony-forming units of endothelial progenitor cells in peripheral-blood samples from 45 men (mean [±SE] age, 50±2 years). The subjects had various degrees of cardiovascular risk but no history of cardiovascular disease. Endothelium-dependent and endothelium-independent function was assessed by high-resolution ultrasonography of the brachial artery.

RESULTS
We observed a strong correlation between the number of circulating endothelial progenitor cells and the subjects' combined Framingham risk factor score (r=−0.47, P=0.001). Measurement of flow-mediated brachial-artery reactivity also revealed a significant relation between endothelial function and the number of progenitor cells (r=0.59, P<0.001). Indeed, the levels of circulating endothelial progenitor cells were a better predictor of vascular reactivity than was the presence or absence of conventional risk factors. In addition, endothelial progenitor cells from subjects at high risk for cardiovascular events had higher rates of in vitro senescence than cells from subjects at low risk.

CONCLUSIONS
In healthy men, levels of endothelial progenitor cells may be a surrogate biologic marker for vascular function and cumulative cardiovascular risk. These findings suggest that endothelial injury in the absence of sufficient circulating progenitor cells may affect the progression of cardiovascular disease.

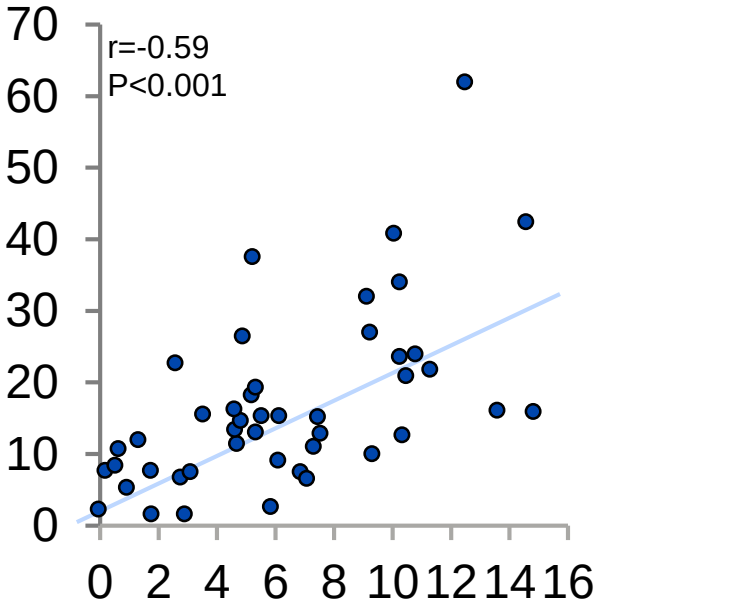
From the Cardiovascular Branch (J.M.H., G.Z., J.P.J.H., W.H.S., T.F.) and the Office of Biostatistics Research (M.A.W.), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.; and Emory University Hospital, Atlanta (A.A.Q.). Address reprint requests to Dr. Finkel at the Cardiovascular Branch, NIH, Bldg. 10/6N-240, 10 Center Dr., Bethesda, MD 20892-1622, or at finkelt@nih.gov.

N Engl J Med 2003;348:593-600.





Endothelial Progenitor Cells (Colony-Forming Units)




Change in brachial reactivity (%)

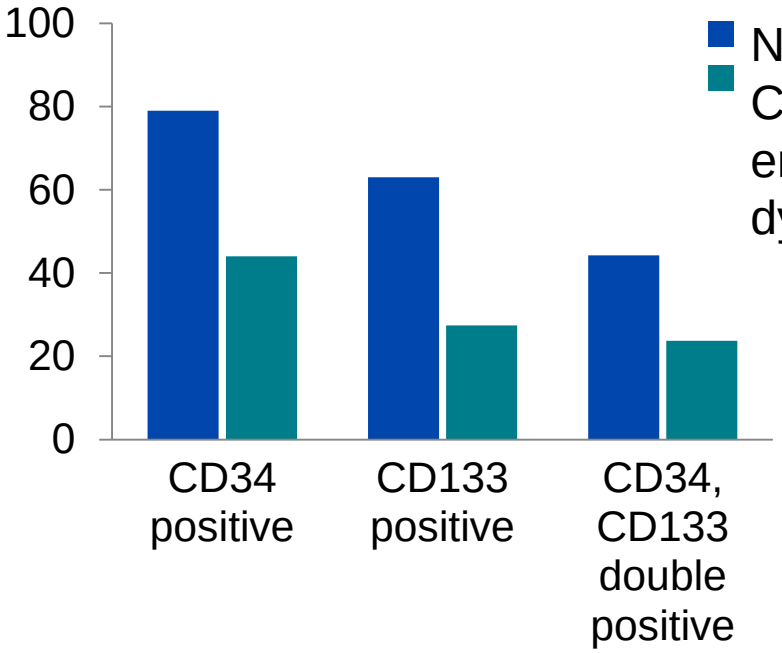
Hill et al: NEJM 348(7):597, 2003

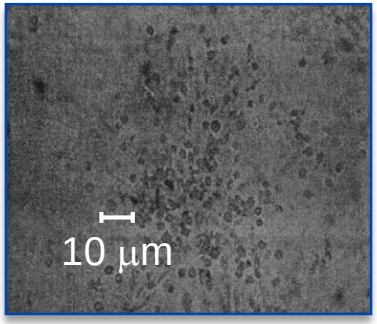
CLINICAL RESEARCH

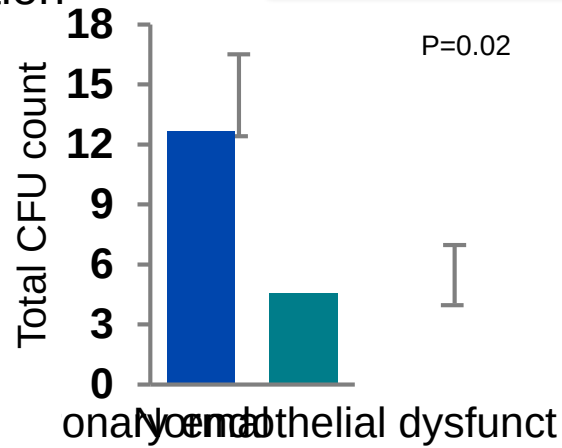
www.nature.com/clinicalpractice/cardio

## Circulating CD34$^+$ cell subsets in patients with coronary endothelial dysfunction

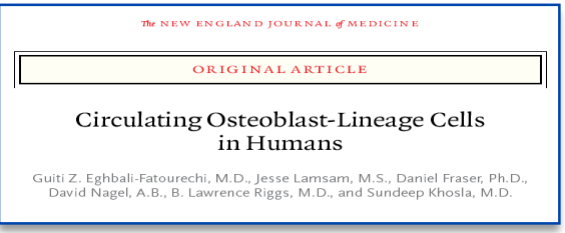
Barry A Boilson,[1] Thomas J Kiernan,[1] Adriana Harbuzariu,[1] Rebecca E Nelson,[1] Amir Lerman[1] and Robert D Simari[1]*




Boilson &, Lerman A: Nat Cardiovasc Med, 2009

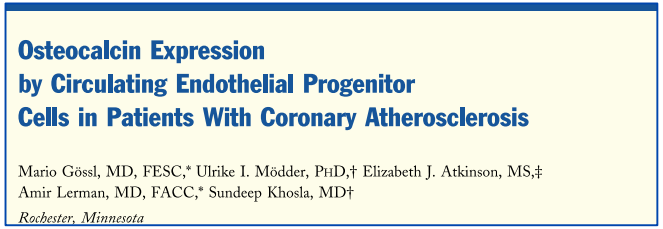


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Circulating Osteoblast-Lineage Cells in Humans

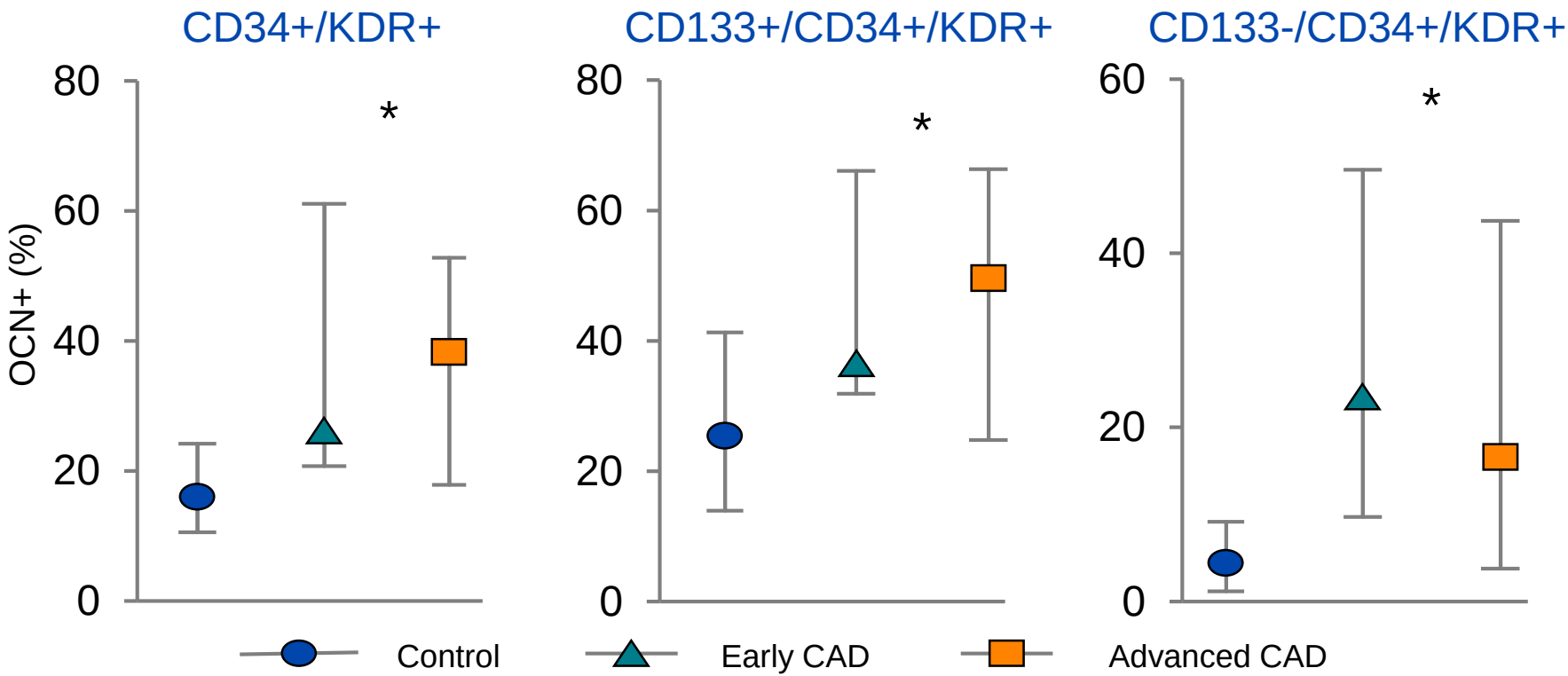
Guiti Z. Eghbali-Fatourechi, M.D., Jesse Lamsam, M.S., Daniel Fraser, Ph.D., David Nagel, A.B., B. Lawrence Riggs, M.D., and Sundeep Khosla, M.D.



Osteocalcin Expression by Circulating Endothelial Progenitor Cells in Patients With Coronary Atherosclerosis

Mario Gössl, MD, FESC,* Ulrike I. Mödder, PHD,† Elizabeth J. Atkinson, MS,‡ Amir Lerman, MD, FACC,* Sundeep Khosla, MD†

*Rochester, Minnesota*



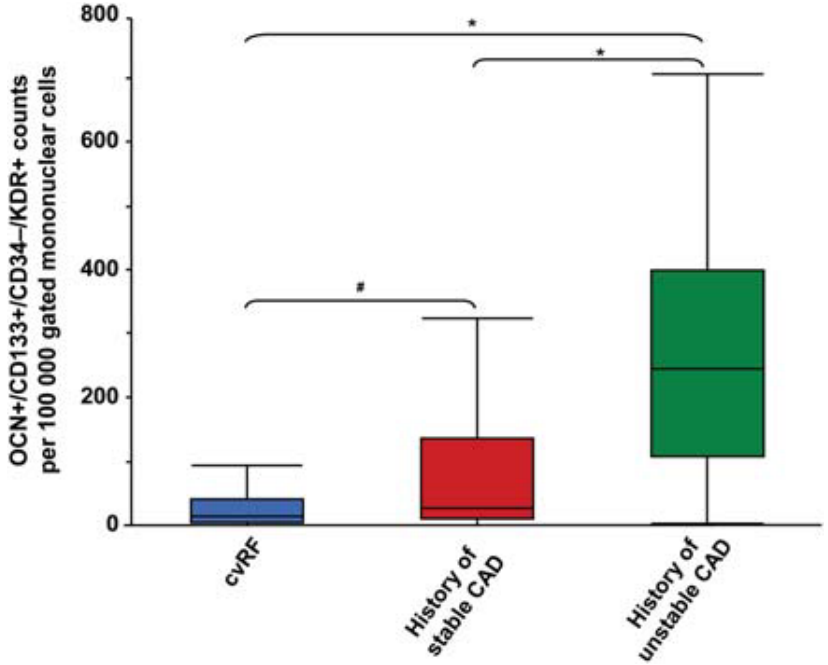

Gössl & Lerman: JACC 52:1314, 2008

European Heart Journal (2012) 33, 2963–2969
doi:10.1093/eurheartj/ehs234

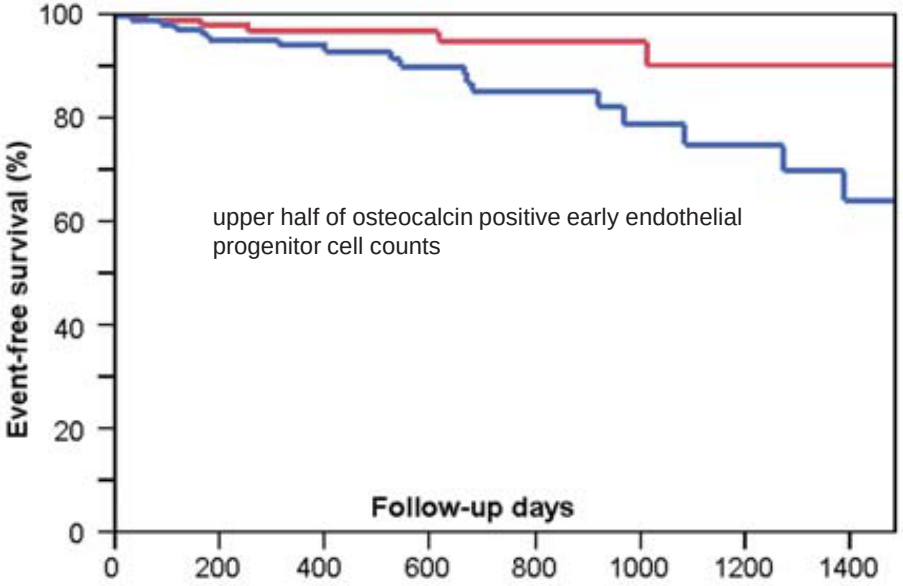


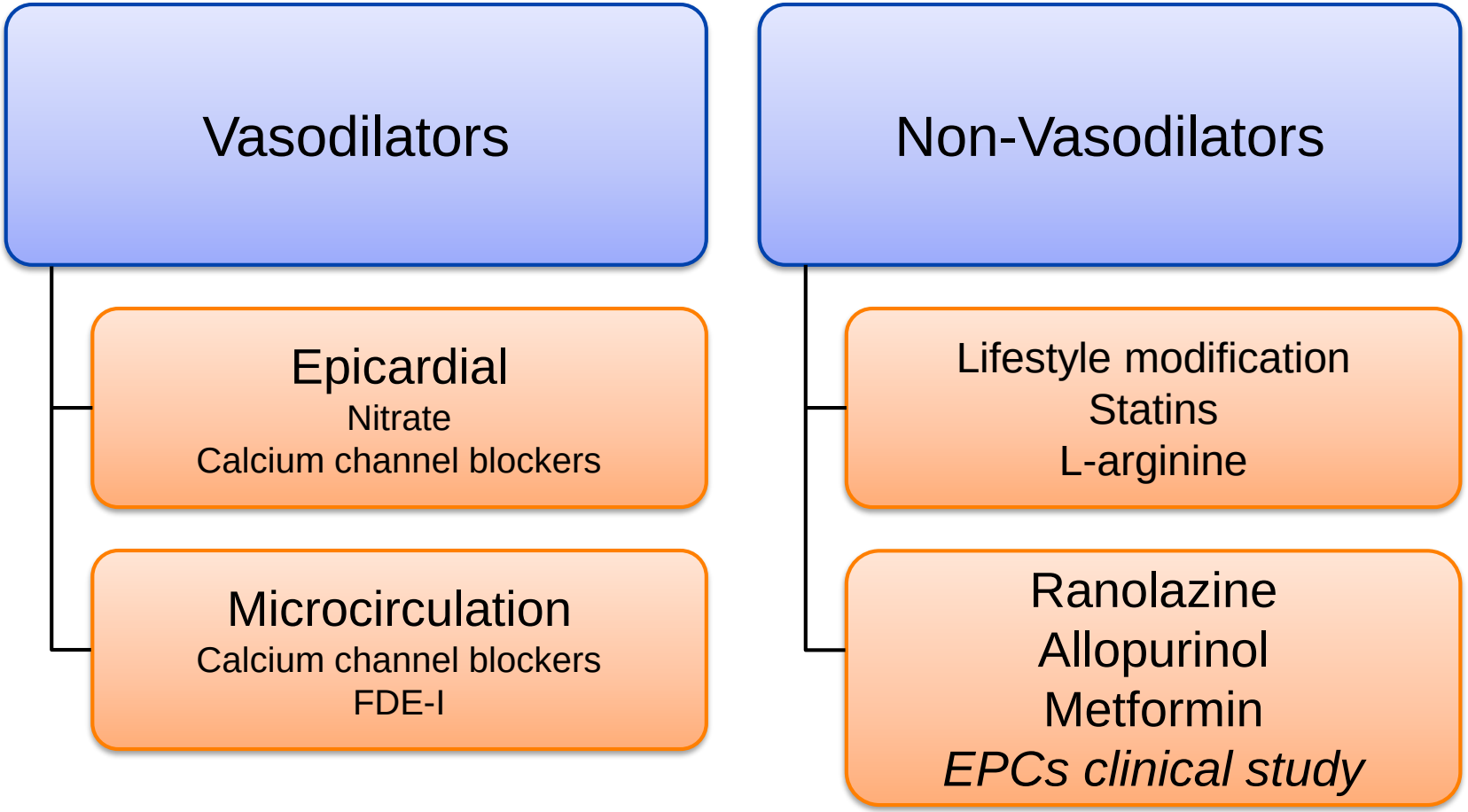
# Osteocalcin positive CD1331 /CD342 /KDR1 progenitor cells as an independent marker for unstable atherosclerosis

Osteocalcin positive ‘early’ endothelial progenitor cells.



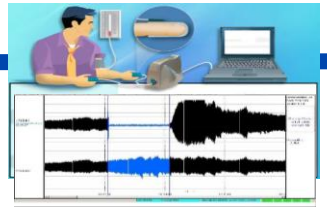

Event-free survival according to the level of osteocalcin positive ‘early’ endothelial progenitor cells.




Vasodilators
Epicardial
Nitrate
Calcium channel blockers
Microcirculation
Calcium channel blockers
FDE-I
Non-Vasodilators
Lifestyle modification
Statins
L-arginine
Ranolazine
Allopurinol
Metformin
EPCs clinical study

Traditional CV risk factors

Normal endothelial Function



Endothelial Dysfunction

Continue current management

**Ongoing CV risk and Events**

Sleep Apnea

Metabolic syndrome


Inflammation

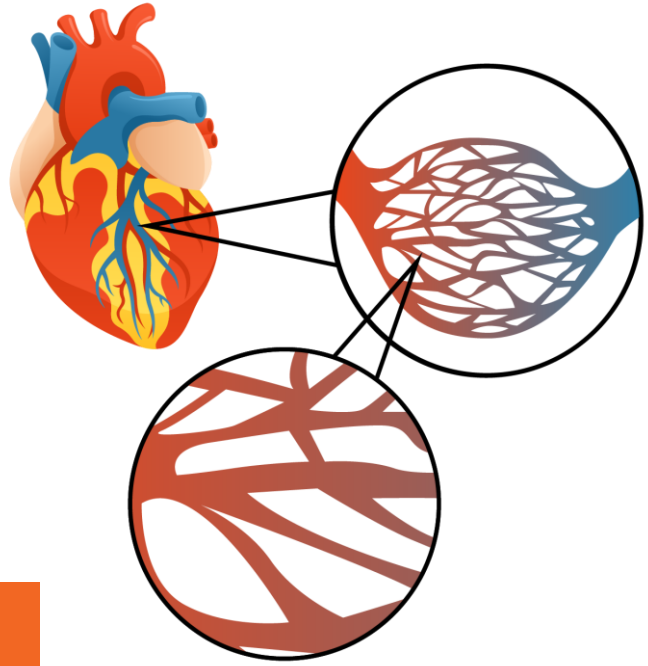
Mental stress

Modify current management

Thank you

Lerman.amir@mayo.edu

# Pioneering Advancements in Cell Therapies



**Thomas J. Povsic, MD, PhD**
Interventional Cardiologist
Duke University Medical Center
Durham, NC

medtelligence℠

# Faculty Disclosure

**Thomas J. Povsic, MD, PhD**

SALARY: Sanofi-Aventis, Orbus-Neich, CSL Boering, Intracellular Therapies, Janssen Pharmaceuticals, Eli Lilly, Merck, Amgen, GSK, St. Jude Medical, Regeneron

CONSULTING: Caladrius Biosciences, Ventrix, Cytosorbents, NovoNordisk

CONTRACTED RESEARCH: CSL Boehring, Intracellular Therapies

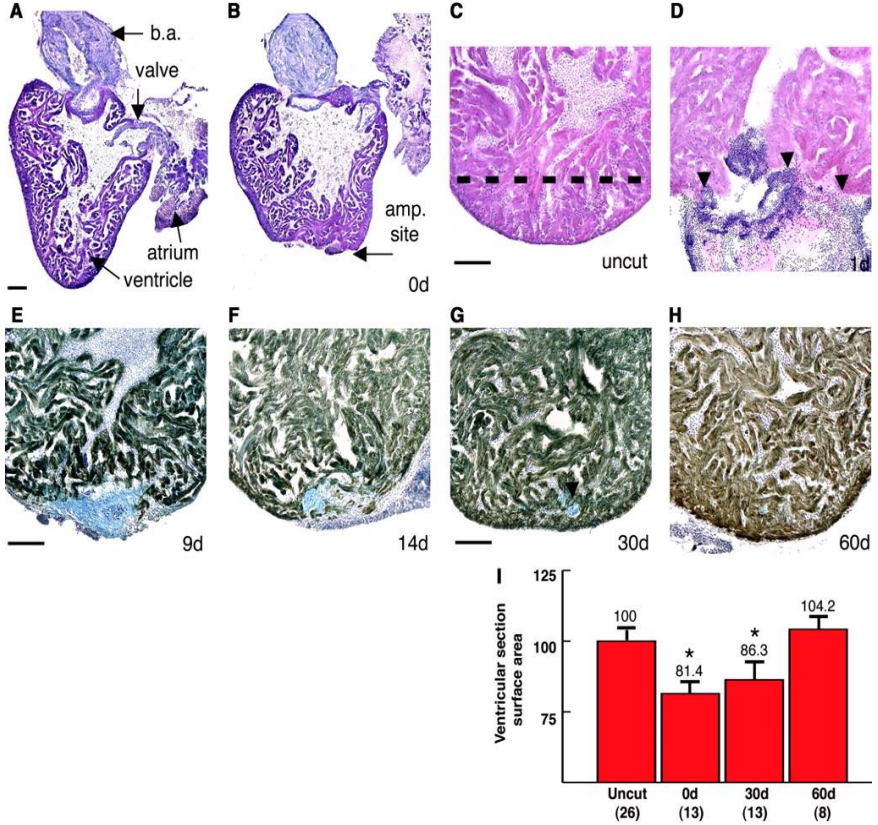
# Where are we?

In the context of developing therapies for serious unmet clinical needs, the best approach is to think of clinical and statistical plausibility together.

- Mechanistic plausibility
- Preclinical models
- Reducing risk (autologous products)
- Consistency of effect
- Totality of data
- Clinical need

# The promise…..

- Zebrafish fully regenerate hearts within 2 months of 20% ventricular resection
- Robust proliferation of myocytes at epicardial edge of new myocardium
- ? Model to illuminate factors to induce regeneration in man



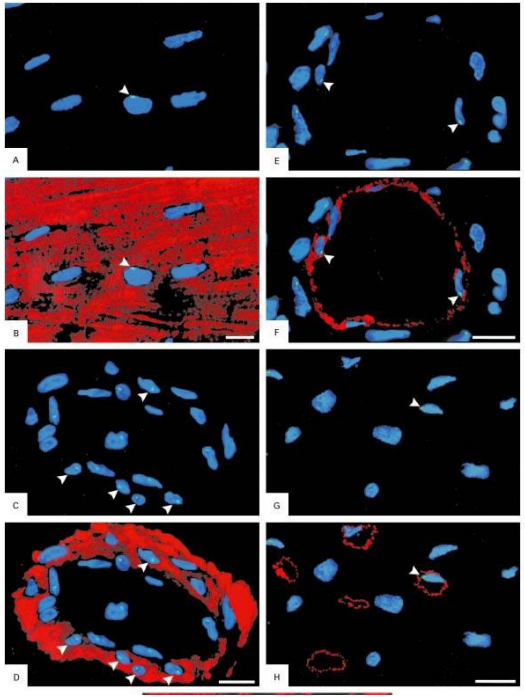

-- Ross KD et al, Science, 2002

# *Myocardial Repair*

The Y Chromosome in
Transplanted Hearts:

Myocytes

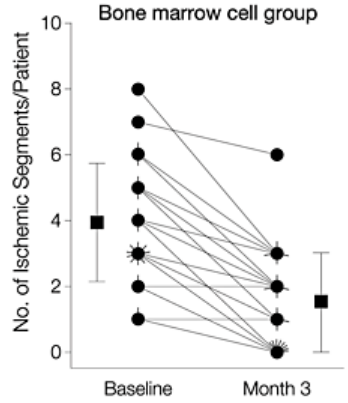
SMCs

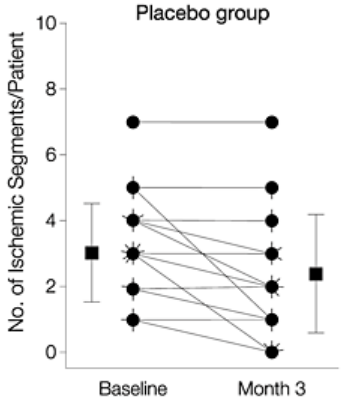


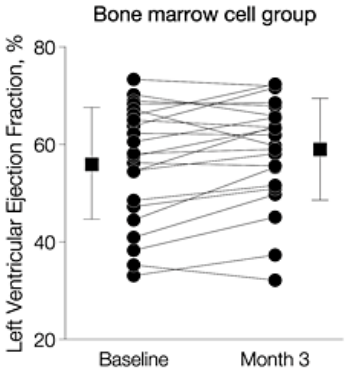

Endothelial Cells

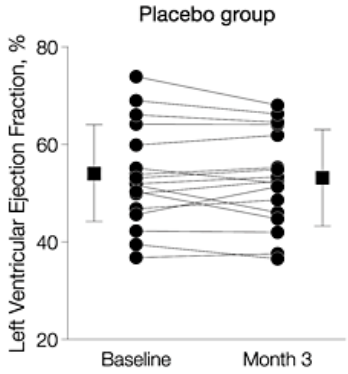
Capillary Endothelium

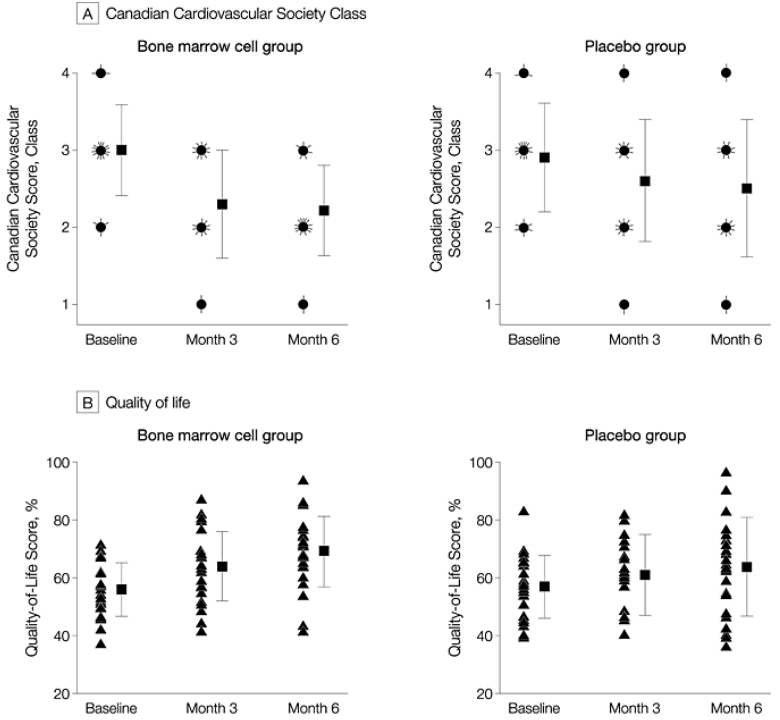
Quaini, F. et al. N Engl J Med 2002;346:5-15



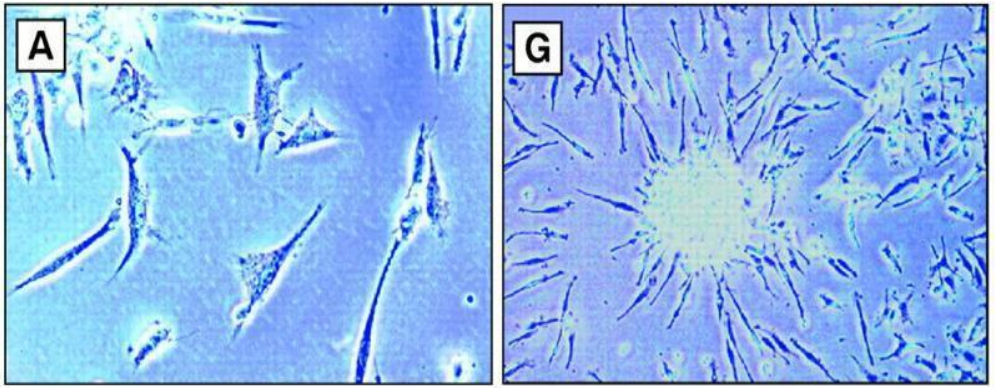




van Ramshorst, J. et al. JAMA 2009;301:1997-2004

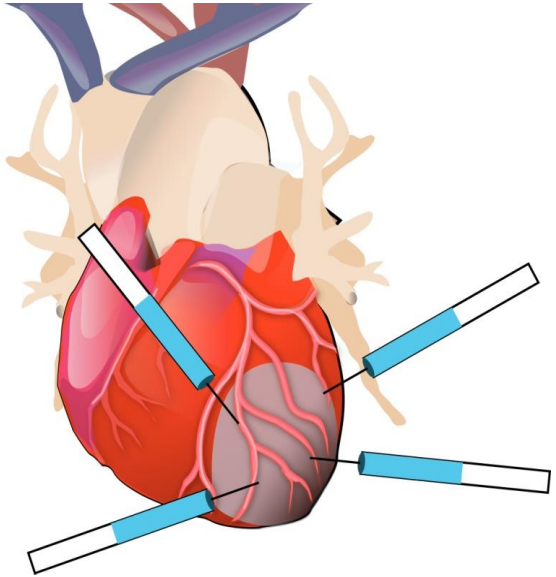
# Original Description of Endothelial Progenitor Cells (EPC) in Adults

- CD34+ cells isolated
- Cultured on fibronectin
- Grew into colonies resembling embryonic blood islands




*Asahara et al. Science 1997;275:964-7*

# Pre-clinical Experience of Transplanted CD34+ Human Progenitor Cells in a Chronic Myocardial Ischemia Rat Model



## Treatment Groups

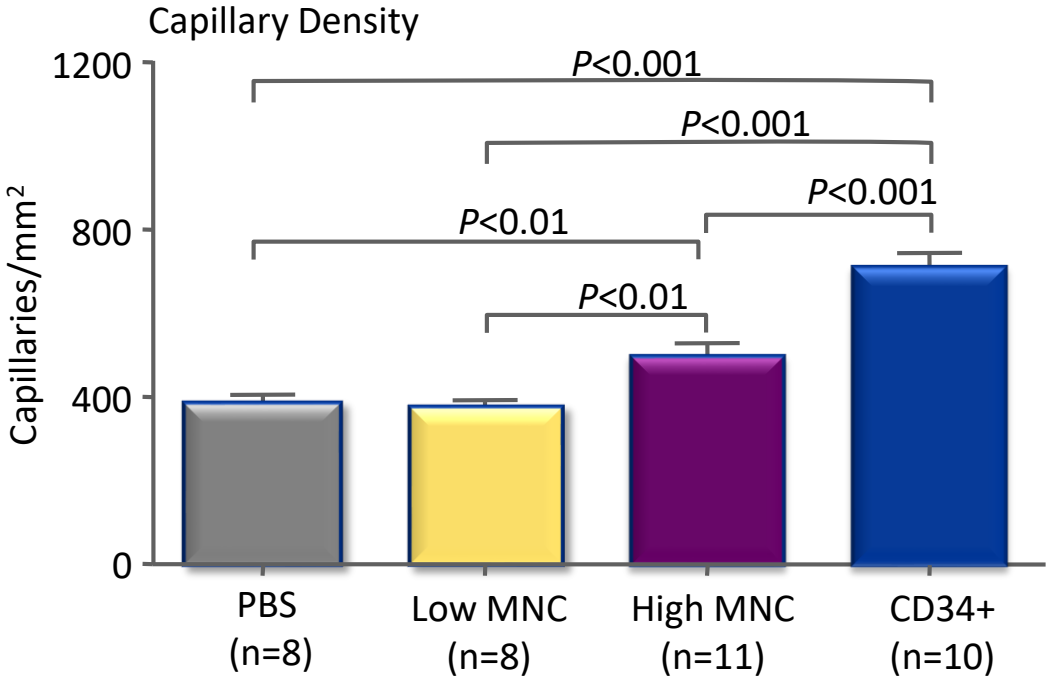
1. **PBS**: 100 µl
2. **Low MNC**: $5\times10^5$ cells/rat kg
3. **High MNC**: total MNCs containing CD34+ dose
4. **CD34+**: $5\times10^5$ cells/rat kg

- n=8~11 rats in each group

PBS = Phosphate-buffered saline; MNC = mononuclear cells.

Kawamoto A, et al. *Circulation*. 2003;107:461-468

# Pre-clinical Experience Results: Treatment with CD34+ Cells Increases Myocardial Capillary Density

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Kawamoto A, et al. *Circulation*. 2003;107:461-468

# CD34+ Cells Are Associated with Aerobic Physical Function

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | Estimate | p-value | Estimate | p-value |
| Usual Gait Speed | 0.055 | 0.005 | 0.046 | 0.015 |
| Rapid Gait Speed | 0.092 | 0.007 | 0.079 | 0.020 |
| 6MWD | 90.6 | 0.004 | 71.7 | 0.012 |
| 5-chair stand | -0.66 | 0.031 | -0.50 | 0.10 |
| Balance Time | 0.188 | 0.25 | 0.124 | 0.40 |
| Grip Strength | 0.663 | 0.33 | 0.743 | 0.26 |
| SPPB summary score | 0.211 | 0.073 | 0.172 | 0.15 |
| SF-36 Phys. Fxn Score | 4.38 | 0.009 | 3.07 | 0.045 |

*Adjusted for age, arm, BMI, 8 comorbid conditions, and IL-6 level.
$CD34^+$ cells were more tightly associated than $CD133^+$ or $ALDH^{br}$ cells

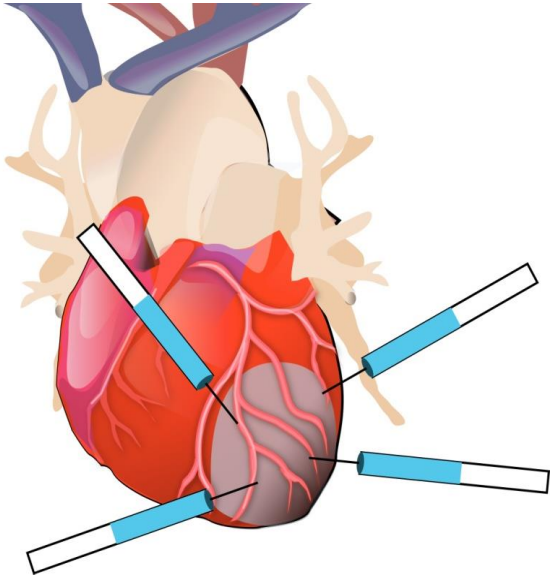
*Povsic et al. J. Geron. Med. Sci.* **2013**,16:1559-1566

# CD34+ Cells Predict Future Physical Function

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | Estimate | p-value | Estimate | p-value |
| 3-month | | | | |
| Usual Gait Speed | 0.073 | 0.002 | 0.065 | 0.003 |
| Rapid Gait Speed | 0.101 | 0.006 | 0.086 | 0.014 |
| 6MWD | 74.4 | 0.027 | 59.6 | 0.036 |
| 12-month | | | | |
| Usual Gait Speed | 0.057 | 0.032 | 0.041 | 0.087 |
| Rapid Gait Speed | 0.141 | 0.001 | 0.126 | 0.003 |
| 6MWD | 100.3 | 0.023 | 701 | 0.028 |
| Change | | | | |
| Usual Gait Speed | 0.026 | 0.035 | 0.025 | 0.034 |
| Rapid Gait Speed | 0.056 | 0.007 | 0.056 | 0.006 |
| 6MWD | 4.29 | 0.774 | 14.02 | 0.228 |

*Adjusted for age, arm, BMI, 8 comorbid conditions, and IL-6 level.

# Pre-clinical Experience of Transplanted CD34+ Human Progenitor Cells in a Chronic Myocardial Ischemia Rat Model



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- n=8~11 rats in each group

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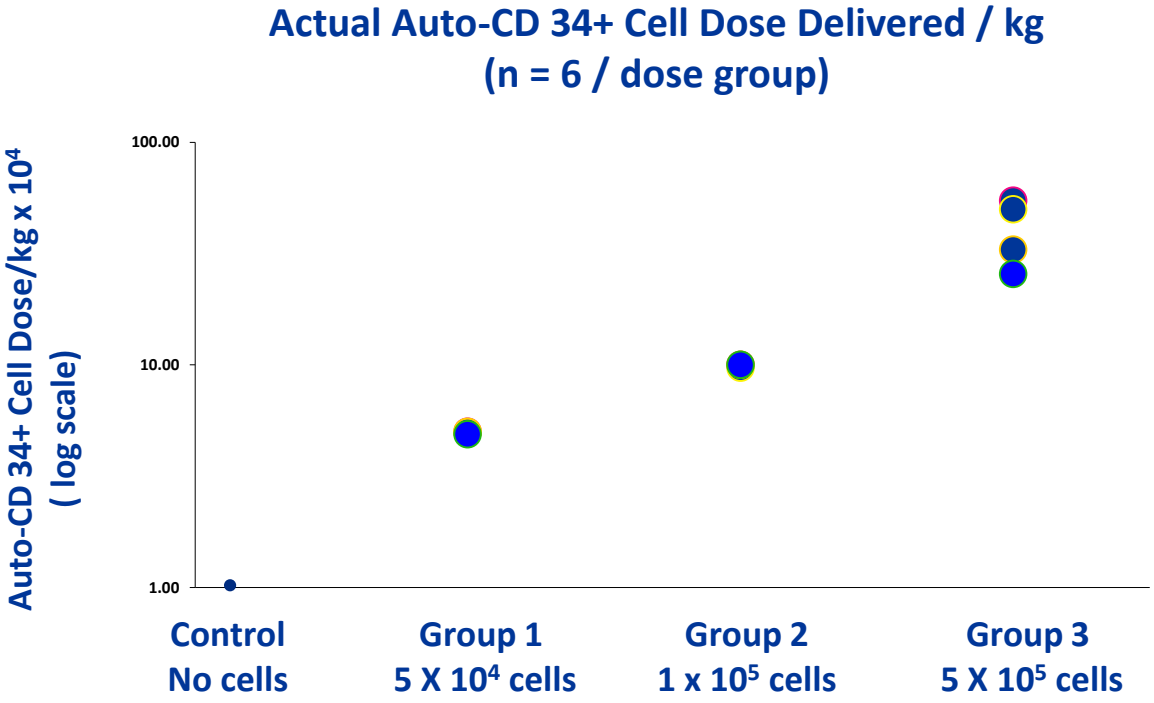
Kawamoto A, et al. *Circulation*. 2003;107:461-468

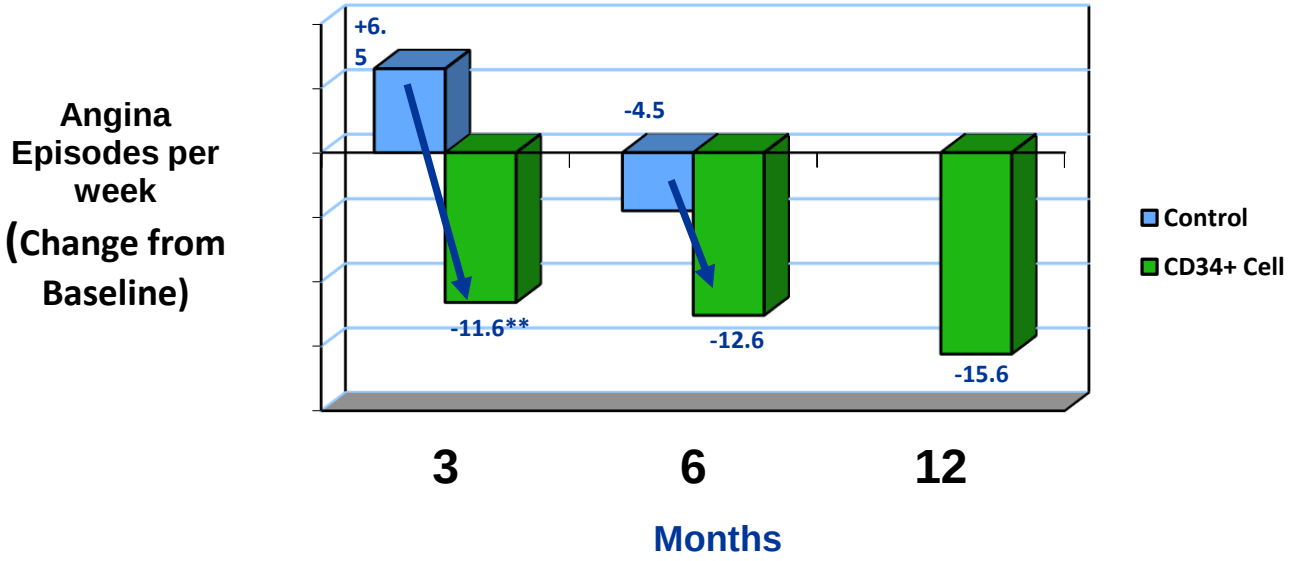
# Phase I: The Dose Range is Feasible




Losordo D W et al. Circulation 2007;115:3165-3172

# Phase I: Angina Frequency

## Episodes per Week




12 month control data is not represented due to control patient cross-over after 6 months

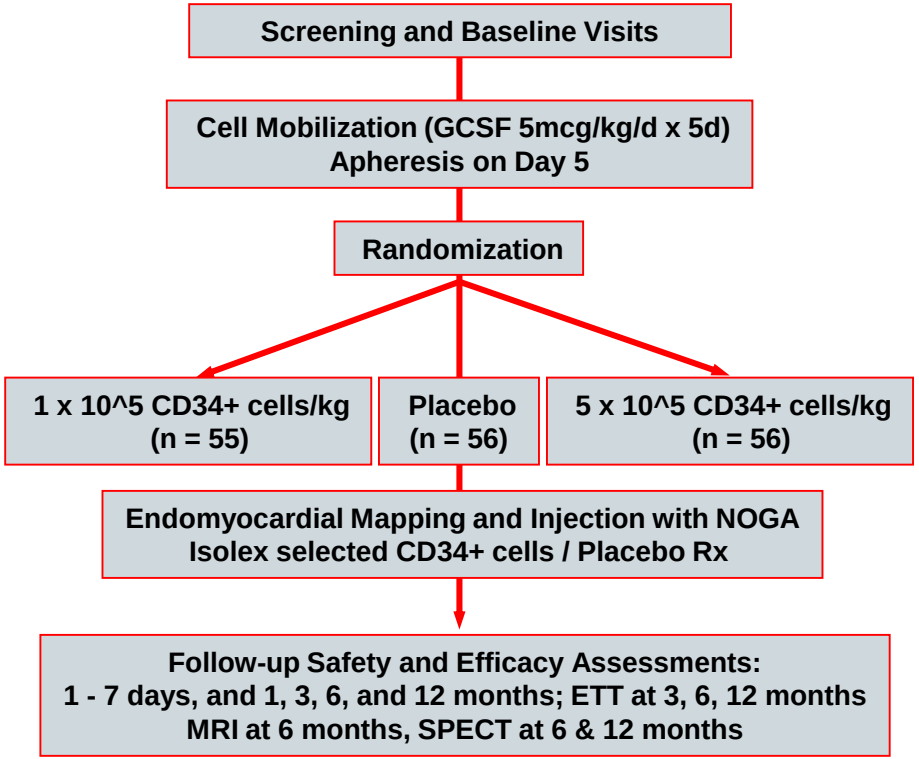
**p=0.053 ANOVA between treatment groups

Losordo D W et al. Circulation 2007;115:3165-3172

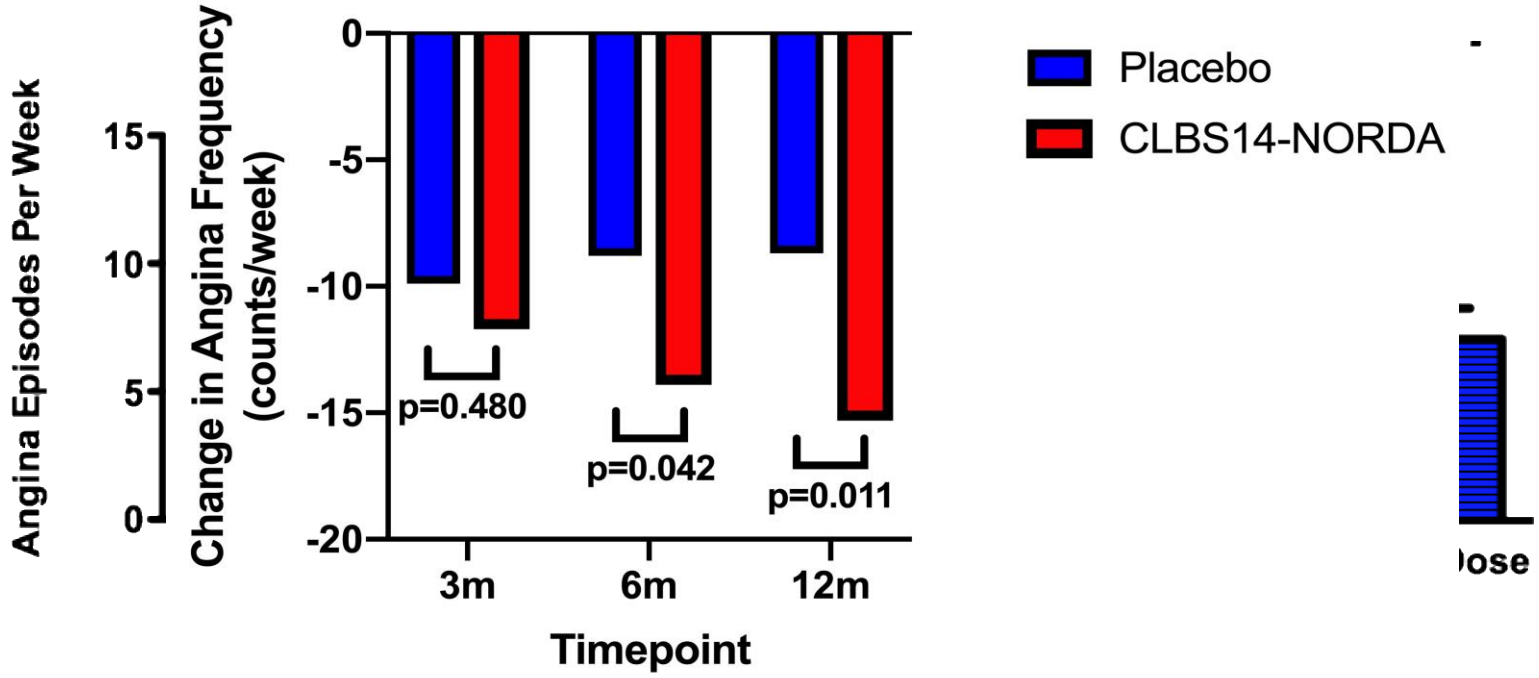
# Randomized, Double-Blind, Placebo Controlled Trial of Autologous CD34+ Cell Therapy for Refractory Myocardial Ischemia

**Subject population**
**(n=167)**

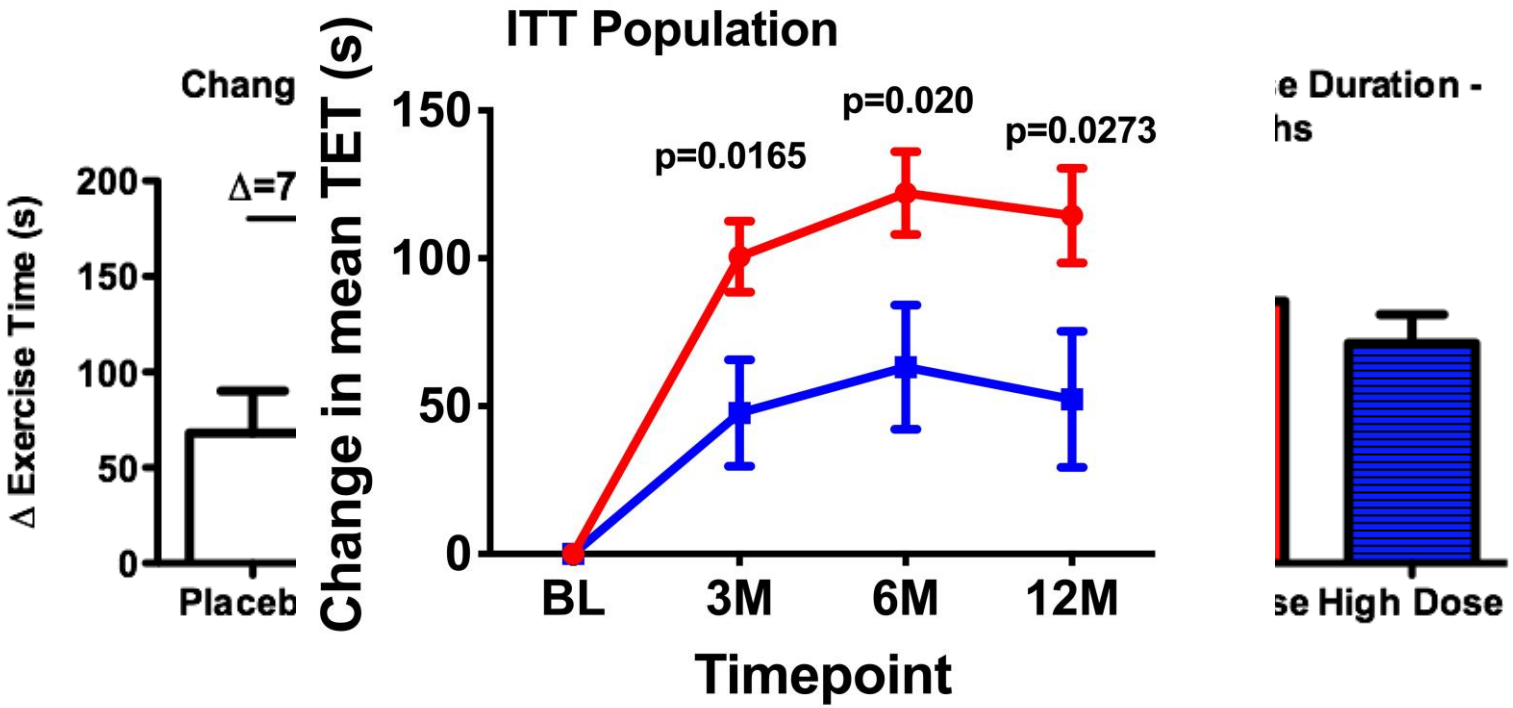
- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia on SPECT
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline



# Change in Angina Counts



# Change in Exercise Capacity

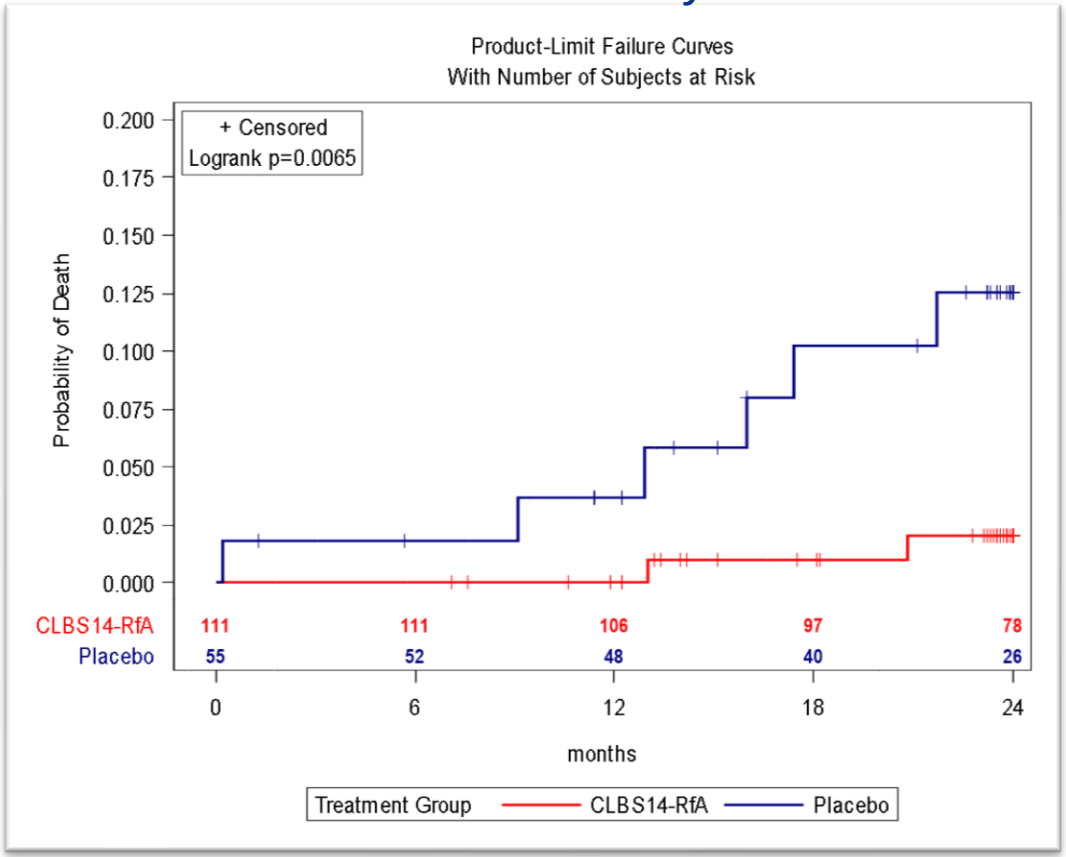


# Major Adverse Cardiac Events (12 Months)

| | Control | $1x10^5$ $CD34^{+cells}$/kg | $5x10^5$ $CD34^{+cells}$/kg | p-value* |
|---|---|---|---|---|
| Death | 3 (5.4%) | 0 (%) | 0(%) | 0.107 |
| MI | 7 (12.5%) | 3 (5.5%) | 3 (5.4%) | 0.305 |
| Death, MI | 10 (17.9%) | 3 (5.5%) | 3 (5.4%) | 0.058 |
| Death, MI, Urgent Revasc | 11 (19.6%) | 5 (9.1%) | 4 (7.1%) | 0.106 |
| Death, MI, Urgent Revasc, Worse CHF, ACS | 15 (26.8%) | 7 (12.7%) | 7 (12.5%) | 0.093 |

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

# ACT-34 Mortality

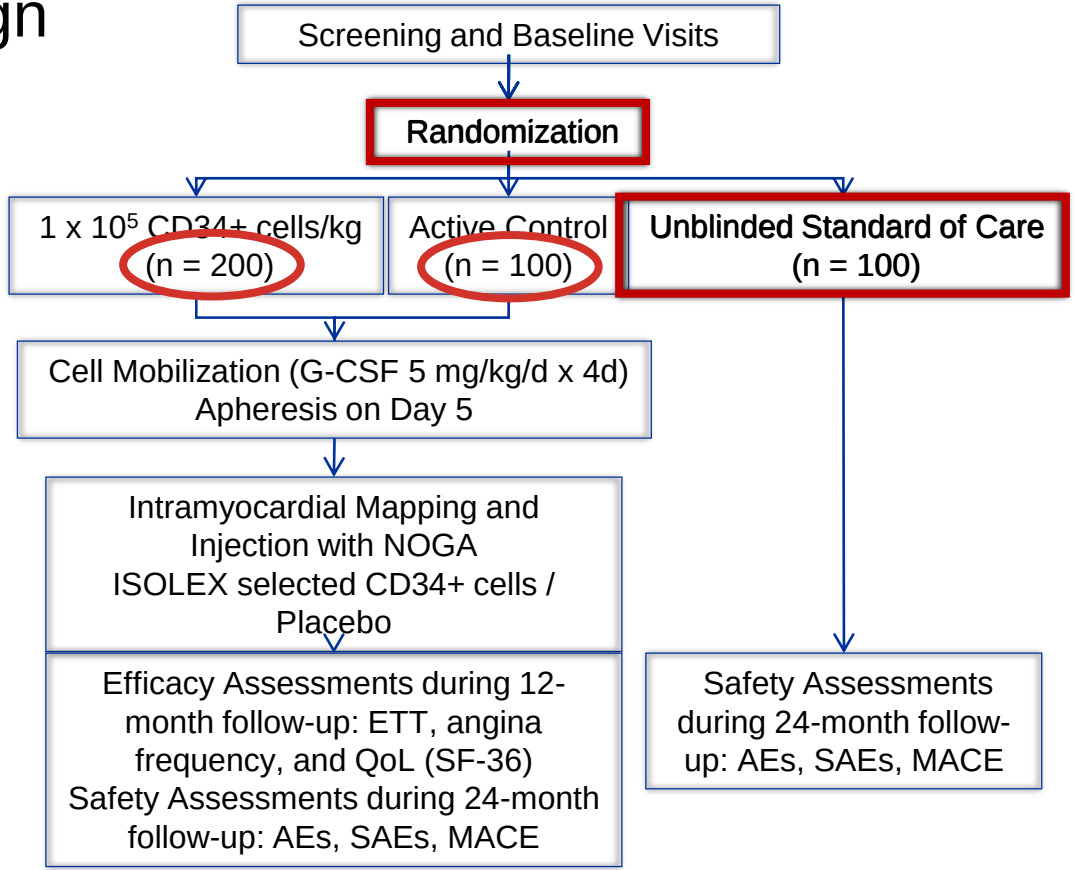


# RENEW Study Design

**Inclusion Criteria:**
- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia w/stress
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline
- ETT reproducible <20%
- 7 angina/wk

**Exclusion Criteria:**
- Recent hospitalization
- Other angiogenic trials
- Must forgo other txt x 2 years

**Pre-Qual Committee Central Review**



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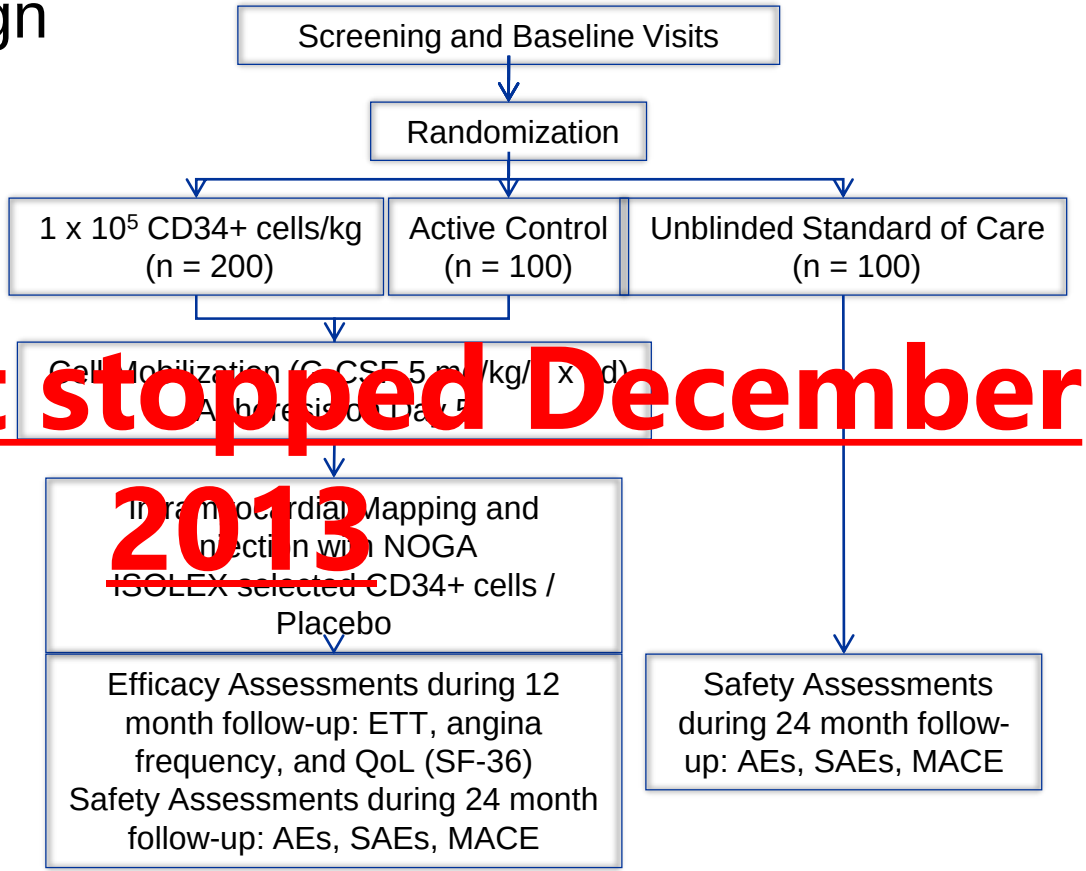
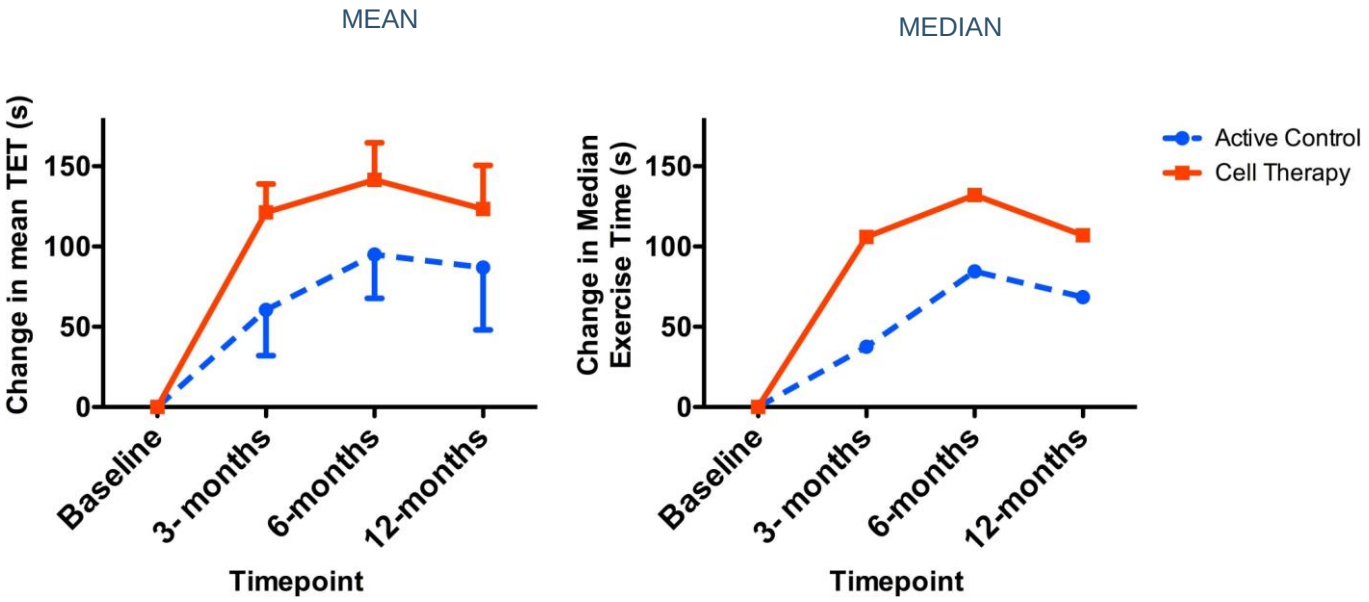


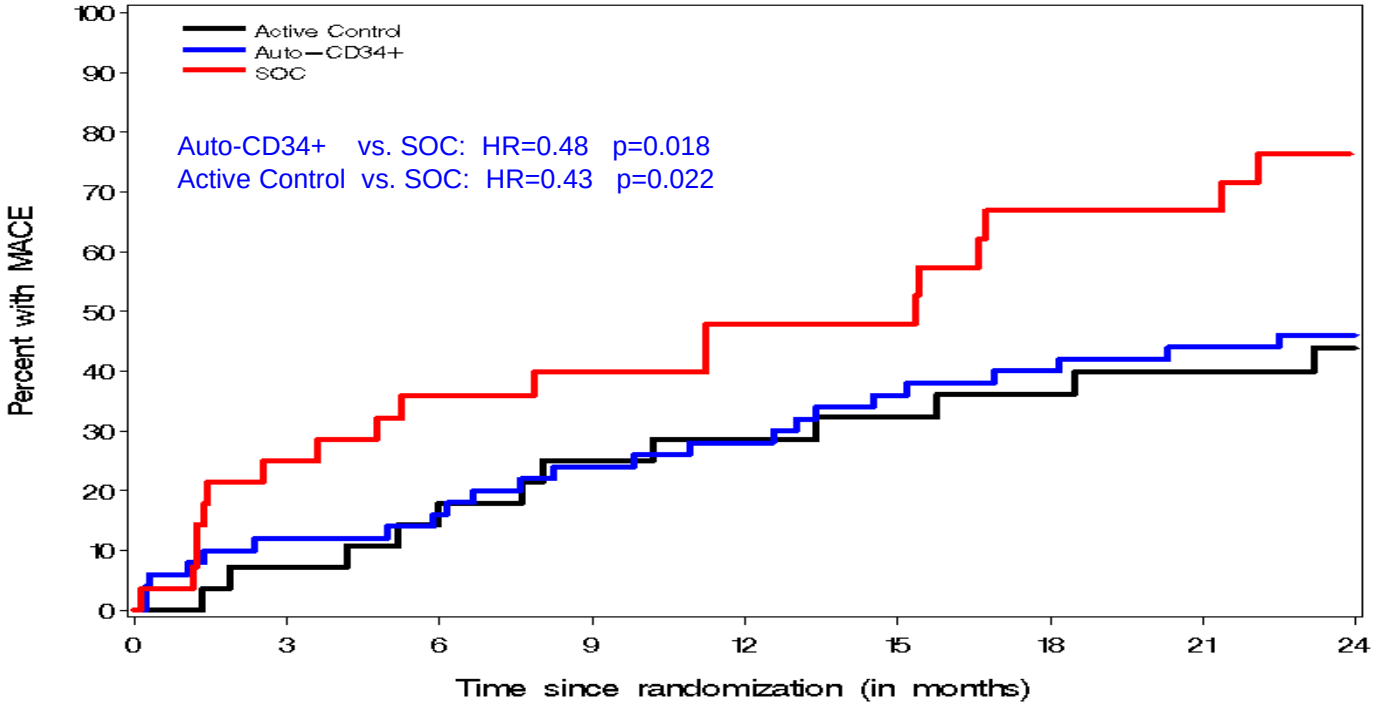

**Enrollment stopped December 2013**

# RENEW: Primary Endpoint as Treated



# Kaplan-Meier Curves: Cumulative Risk of MACE

As Treated



# 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%) |

Goals: Combine patient level data from 3 trials of Auto-CD34$^{+}$ cell therapy for refractory angina

- All trials:
  - Double-blind randomized design
  - IM injection of CD34$^{+}$ cells vs. placebo
  - Assessed exercise capacity (ETT) and angina frequency at 3-, 6- and 12- months
  - Collected MACE to 24 months

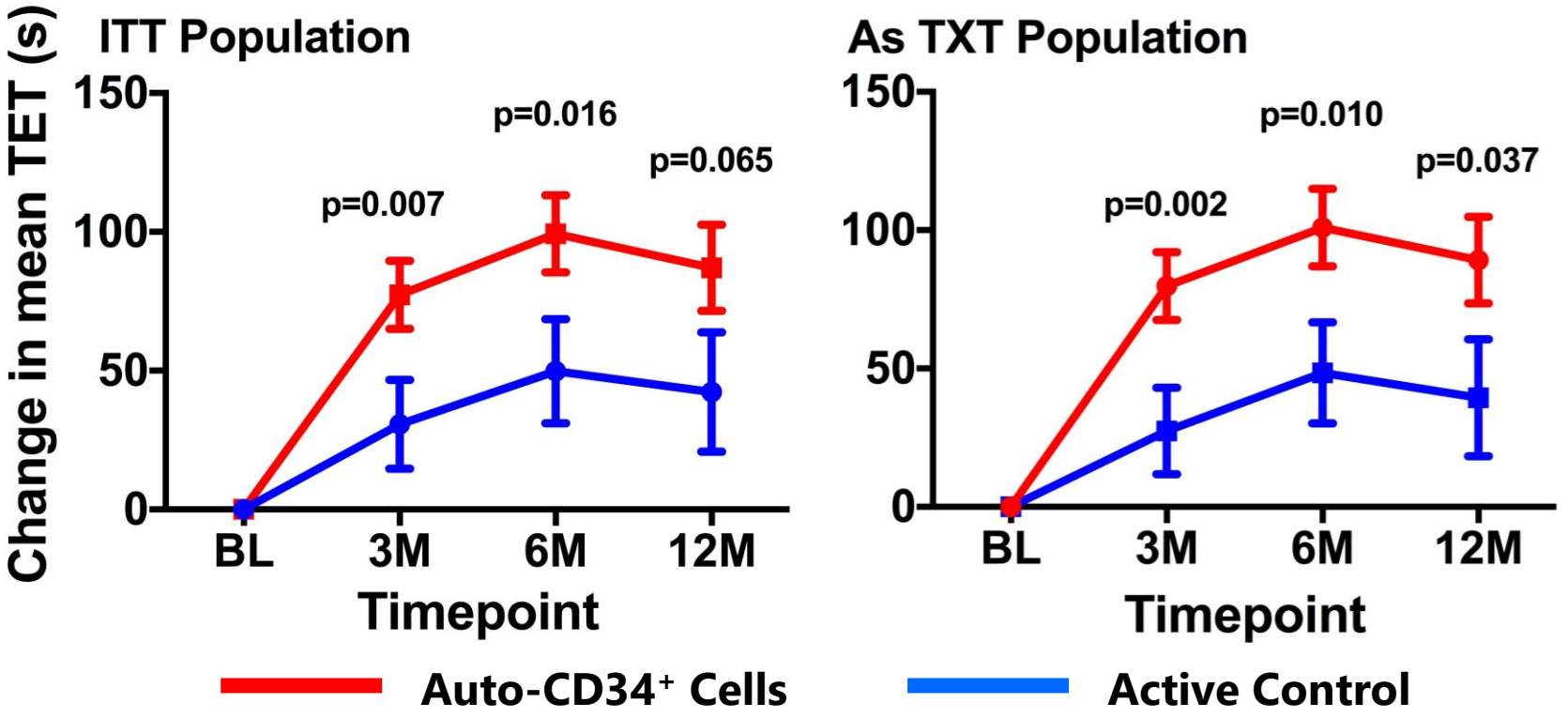
# Baseline Characteristics

| | Placebo (n=89) | CD34+ (n=187) | SOC (n=28) | Total (n=304) |
|---|---|---|---|---|
| Age (median) | 64 (56,69) | 62 (56,68) | 63 (55,69) | 63 (56,69) |
| Female | 11 (12%) | 30 (16%) | 4 (4%) | 45 (15%) |
| Caucasian | 80 (90%) | 171 (91%) | 27 (96%) | 278 (91%) |
| Diabetes | 50 (56%) | 95 (51%) | 16 (57%) | 161 (53%) |
| Hypertension | 77 (87%) | 163 (87%) | 24 (86%) | 264 (87%) |
| Hyperlipidemia | 74 (83%) | 154 (82%) | 27 (96%) | 255 (84%) |
| CHF | 31 (35%) | 50 (27%) | 8 (29%) | 89 (29%) |
| PVD | 24 (27%) | 44 (24%) | 4 (14%) | 72 (24%) |
| h/o PCI | 78 (88%) | 162 (87%) | 26 (93%) | 266 (88%) |
| h/o CABG | 80 (90%) | 173 (93%) | 23 (82%) | 276 (91%) |

# Medication use

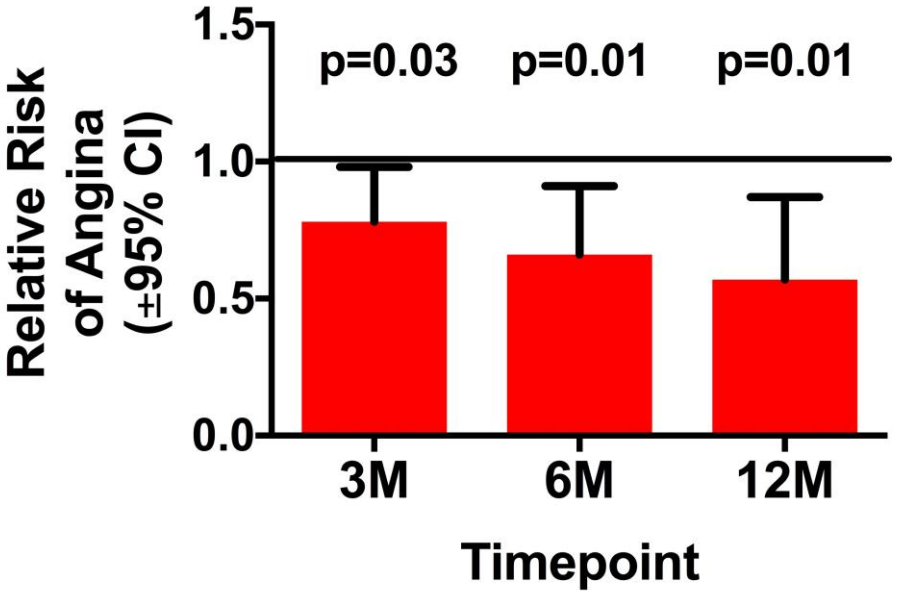
| | Placebo (n=89) | CD34⁺ (n=187) | SOC (n=28) | Total (n=304) |
|---|---|---|---|---|
| β-blockers | 82 (92%) | 169 (90%) | 26 (93%) | 277 (91%) |
| Nitrates | 70 (79%) | 138 (74%) | 24 (86%) | 232 (76%) |
| Ranolazine | 29 (33%) | 66 (35%) | 18 (64%) | 113 (37%) |
| Ca-blockers | 34 (38%) | 79 (42%) | 13 (46%) | 126 (41%) |
| Acel/ARB | 47 (53%) | 104 (56%) | 15 (54%) | 166 (55%) |
| Statins | 70 (79%) | 154 (82%) | 25 (89%) | 249 (82%) |

# Results: Total Exercise Time

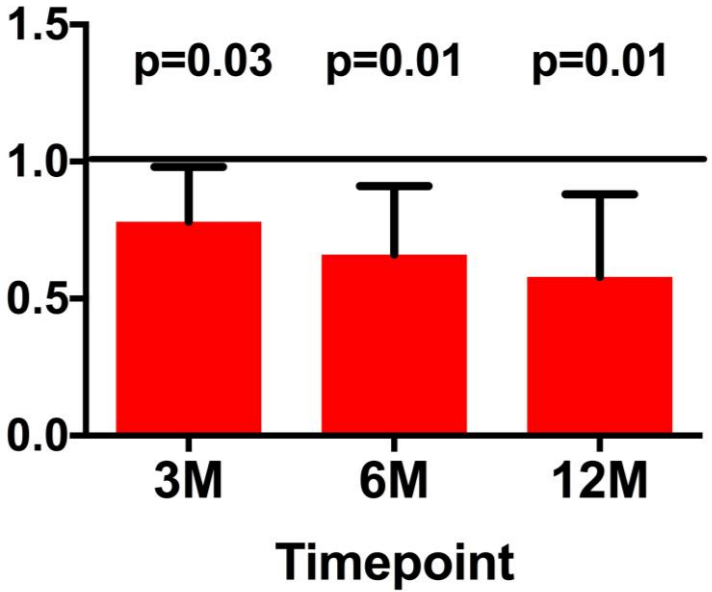


# Relative Risk of Angina*

## ITT Analysis

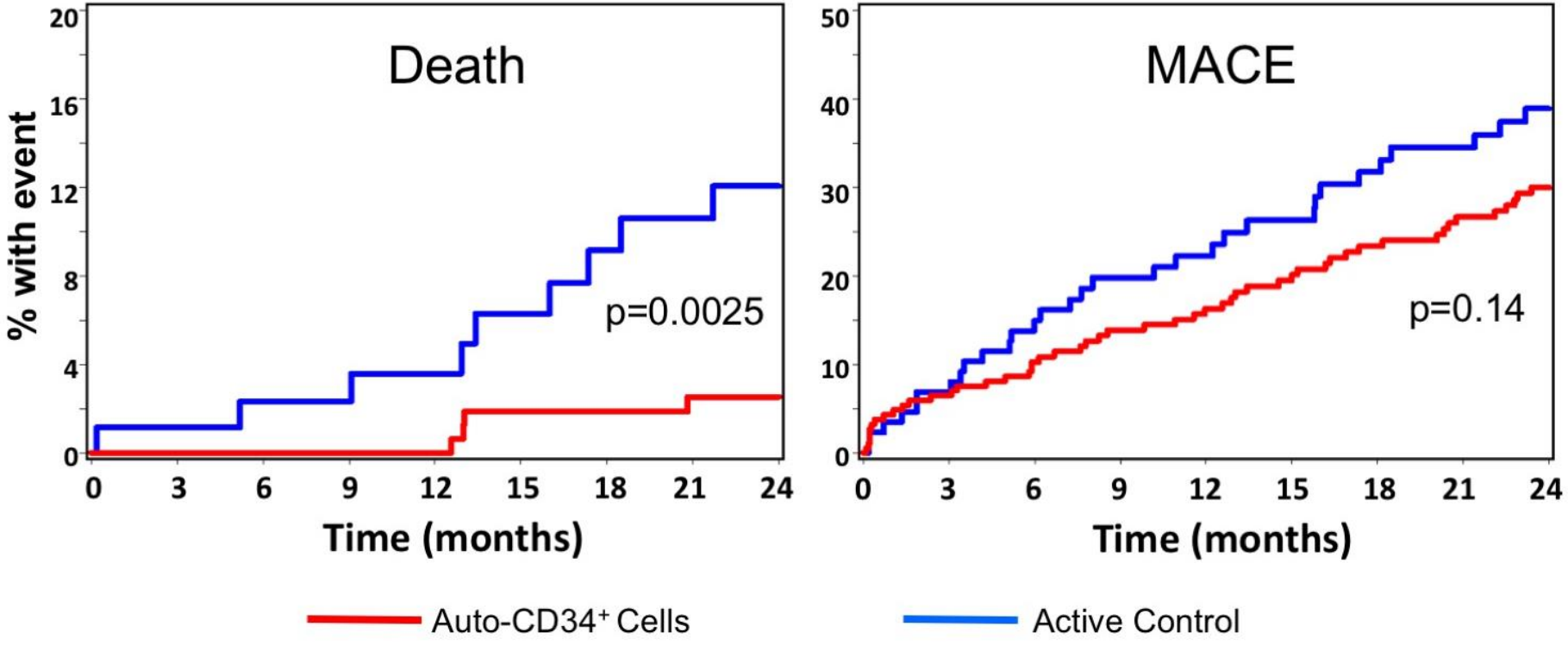



## As Txt Analysis

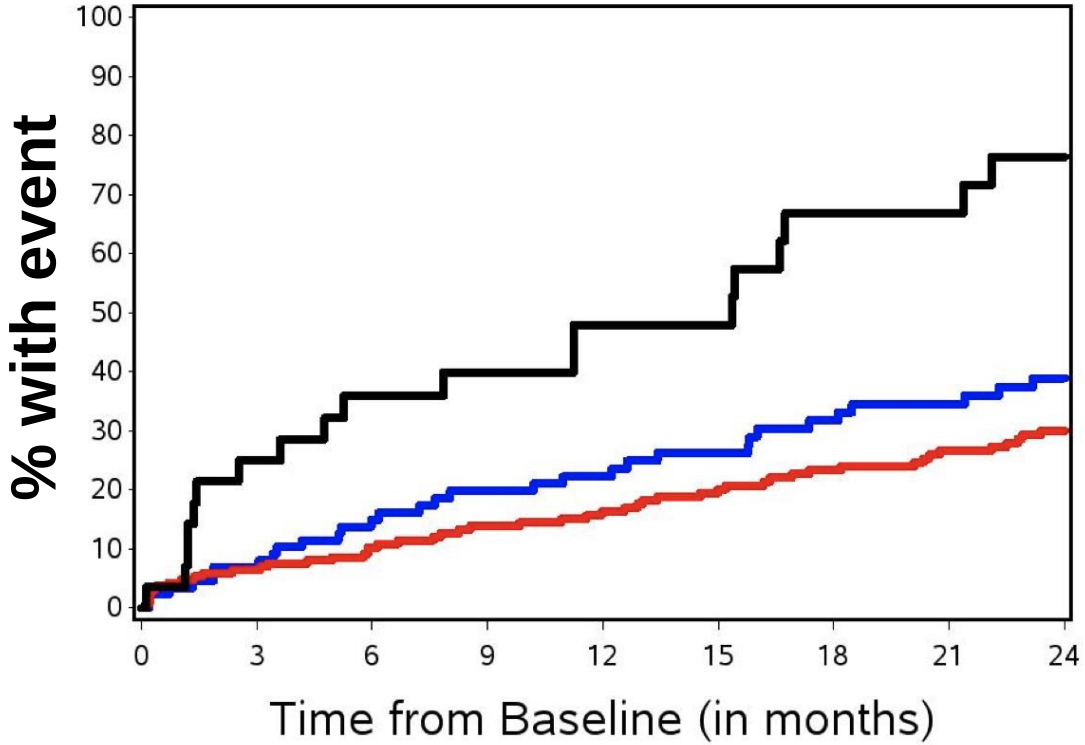



*Prespecified Poisson Distribution

# Kaplan-Meier Analysis

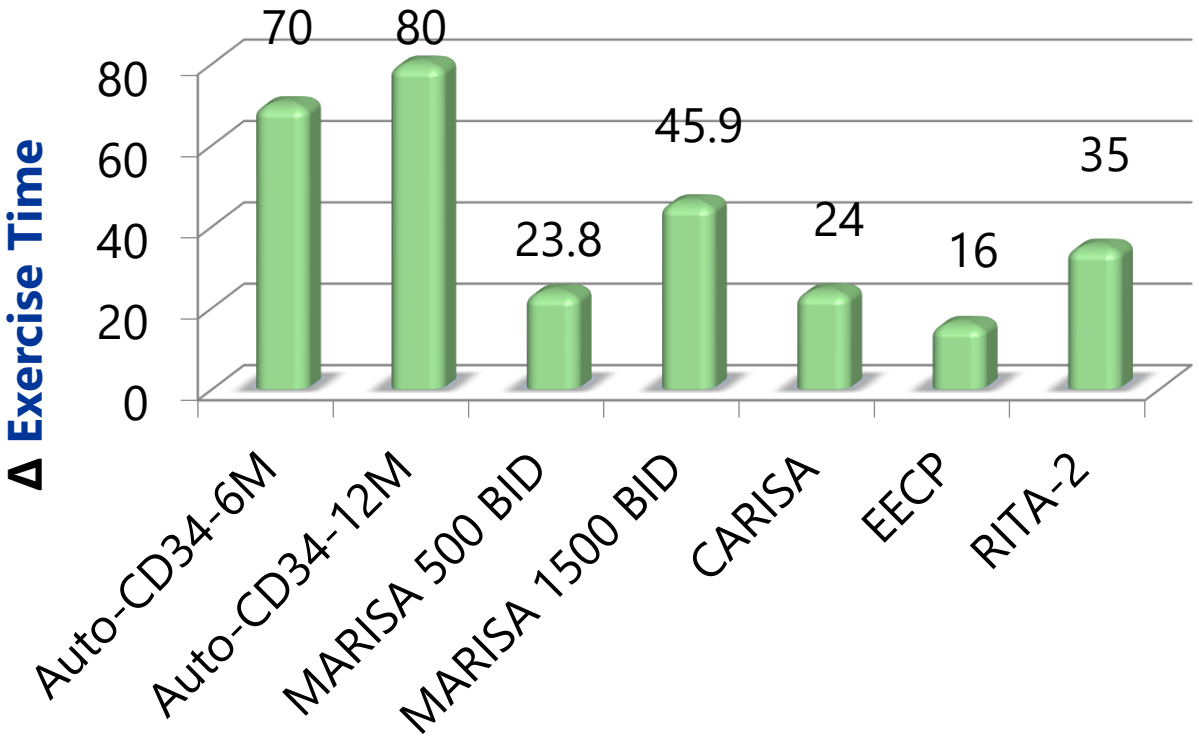


# Kaplan-Meier Analysis

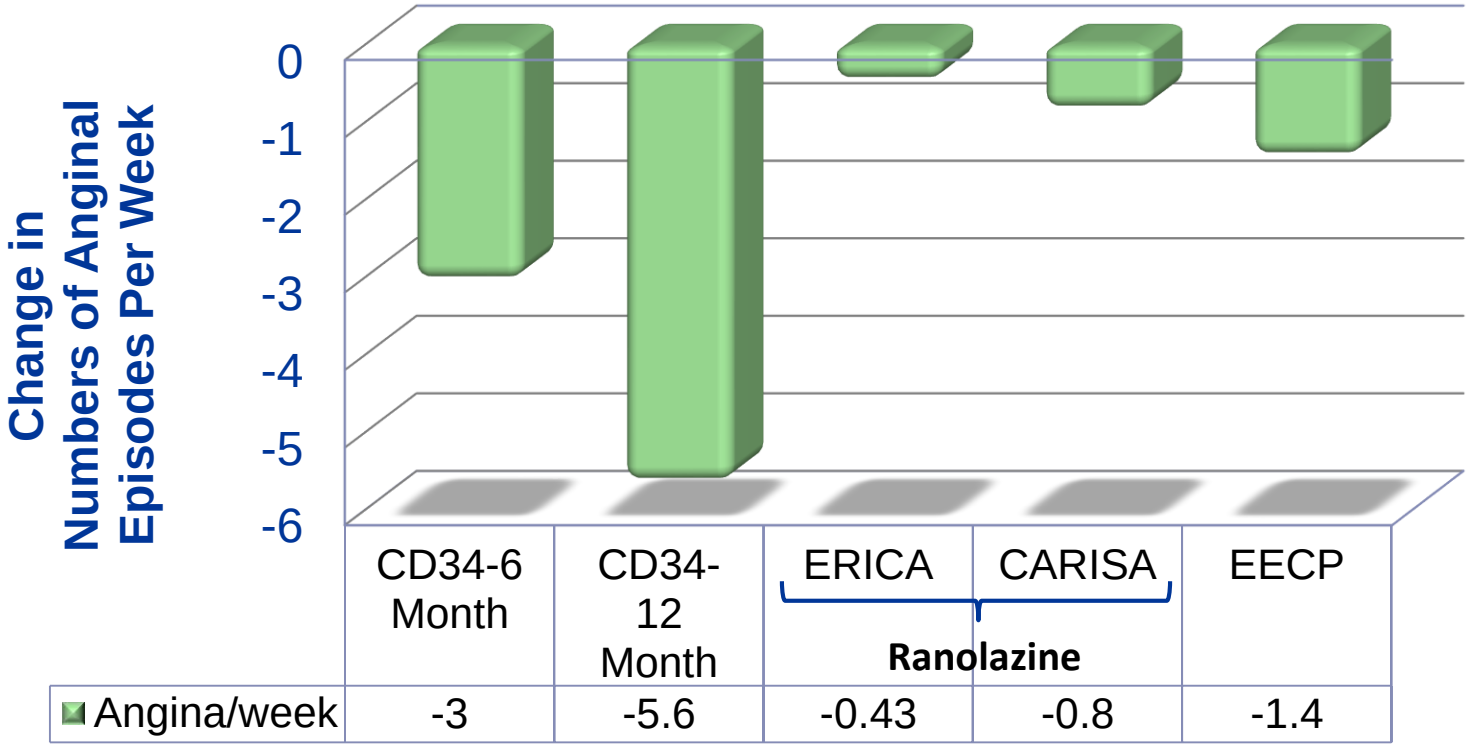



**Auto-CD34⁺ Cells** **Active Control** **Open Label SOC**

# Efficacy Comparison: Change in ETT



# Efficacy Comparison: Change in Angina Frequency



# Conclusions

- $CD34^+$ cells, compared with placebo injections, result in:
  - Clinically and statistically significant durable improvements in exercise capacity to at least 12 months
  - Overall improvements in angina frequency
  - MACE events favor cell therapy
  - Statistically significant improvement in mortality with cell therapy
  - SOC arm faired poorly
  - Effect larger than other accepted therapies for angina

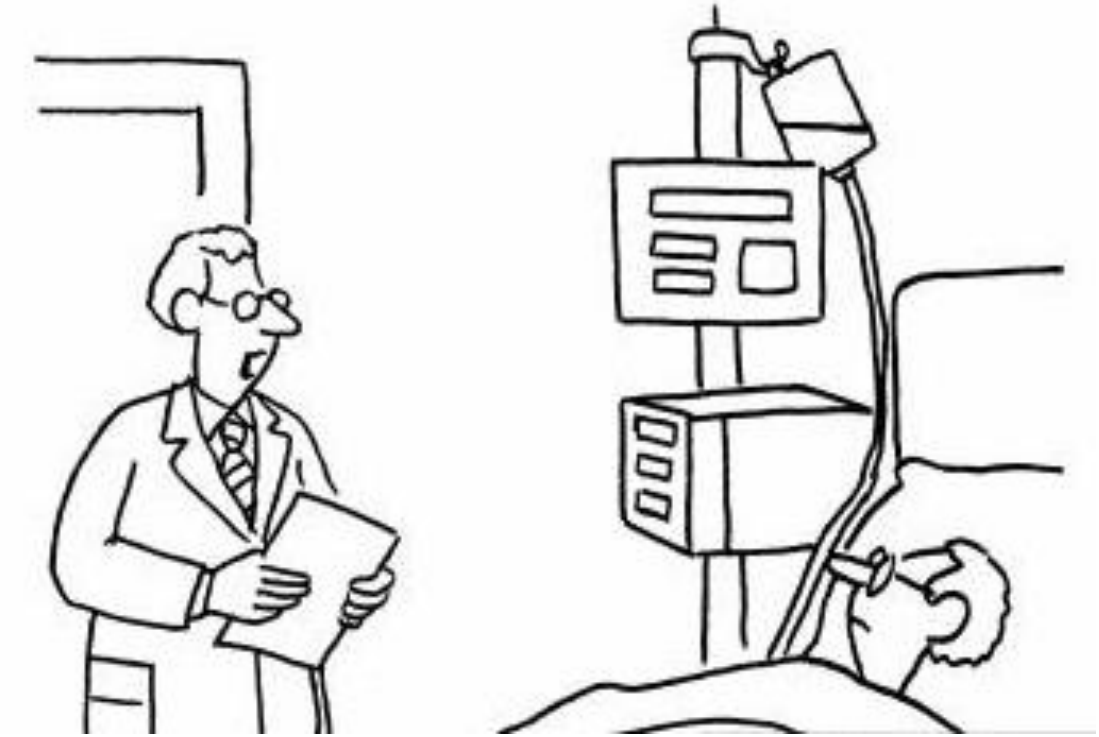
# Where are we?

In the context of developing therapies for serious unmet clinical needs, the best approach is to think of clinical and statistical plausibility together.

- ✓ Mechanistic plausibility
- ✓ Preclinical models
- ✓ Reducing risk (autologous products)
- ✓ Consistency of effect
- ✓ Totality of data
- ✓ Clinical need

# 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 imperative to explore methods to bring this therapy to patients with high clinical need and limited if any other options



"It's nothing a few stem cells and another 75 years of research can't fix."