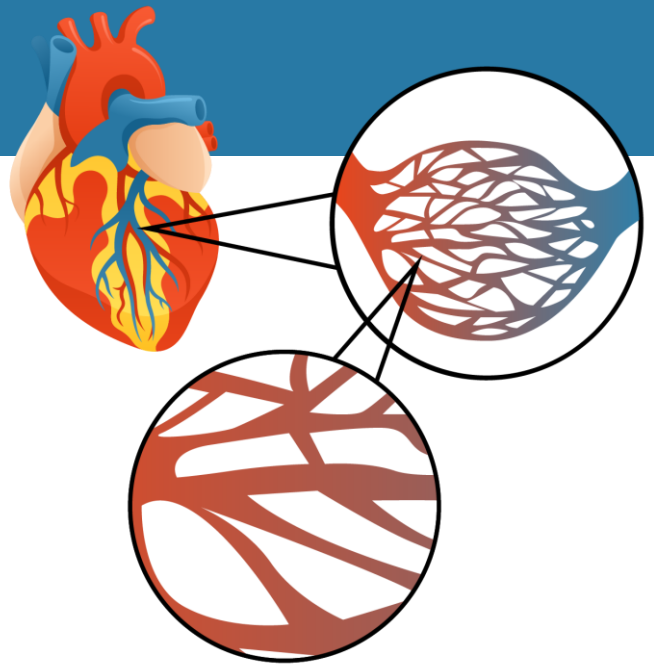
Advancing Cell Therapies for Coronary Microvascular Dysfunction: Experts Roundtable



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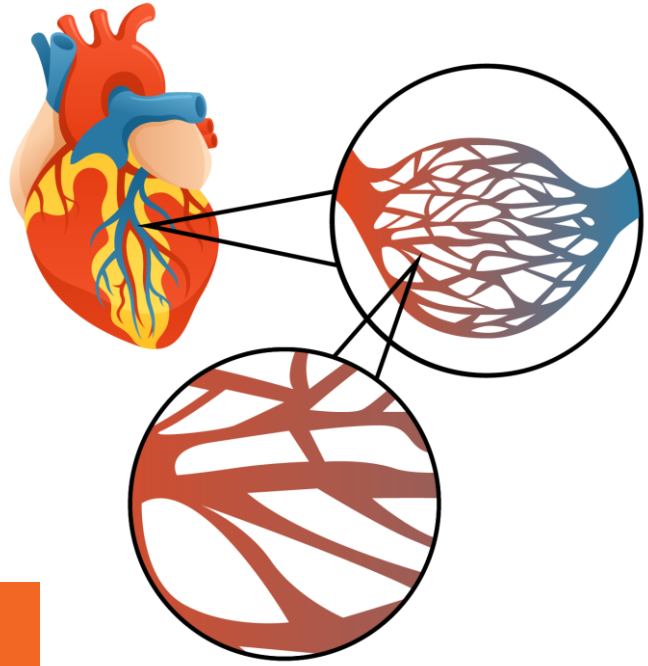
Program Overview



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

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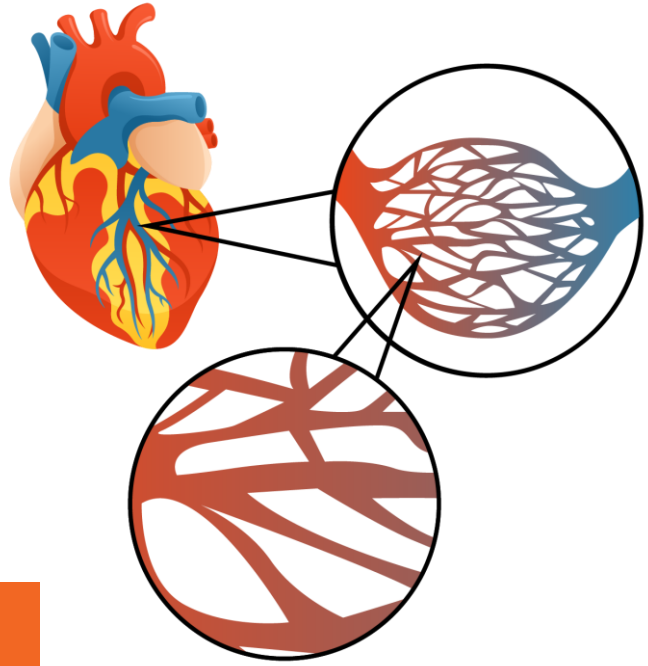
Stable Angina: State of the Art



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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)

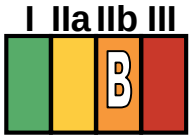
(de Peuter OR, et al. Neth J Med 2009;67:284)

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.

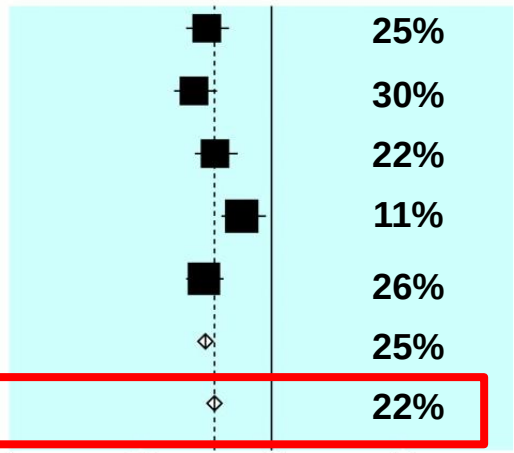
Dipyridamole is not recommended as antiplatelet therapy.

(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%



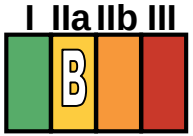
Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002

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

Guideline-Based Renin-Angiotensin-Aldosterone Blocker Therapy

Secondary Prevention

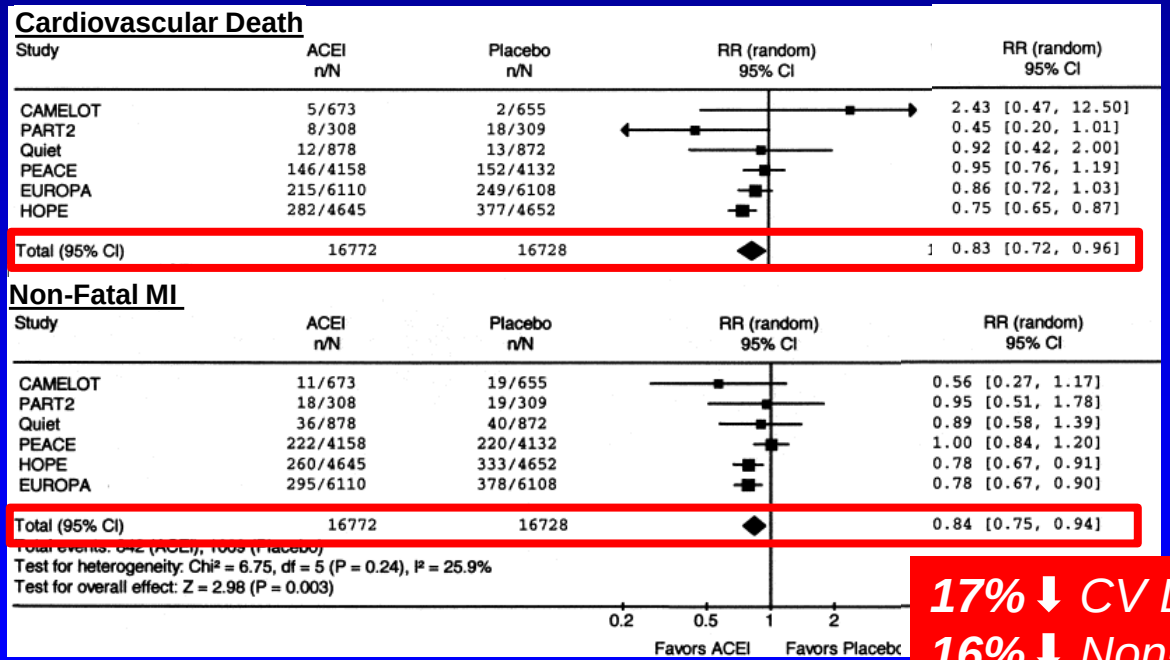
ACE inhibitor (or **ARB** if ACEI intolerant) should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF ≤40%, or CKD, unless contraindicated.



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

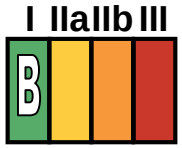
Guideline-Based Anti-Ischemic Medications *for Angina*

β-blockers should be prescribed as initial therapy.

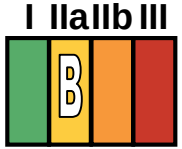
Ca^{++}-channel blockers or **long-acting nitrates** should be prescribed when β-blockers are contraindicated or cause unacceptable side effects

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.

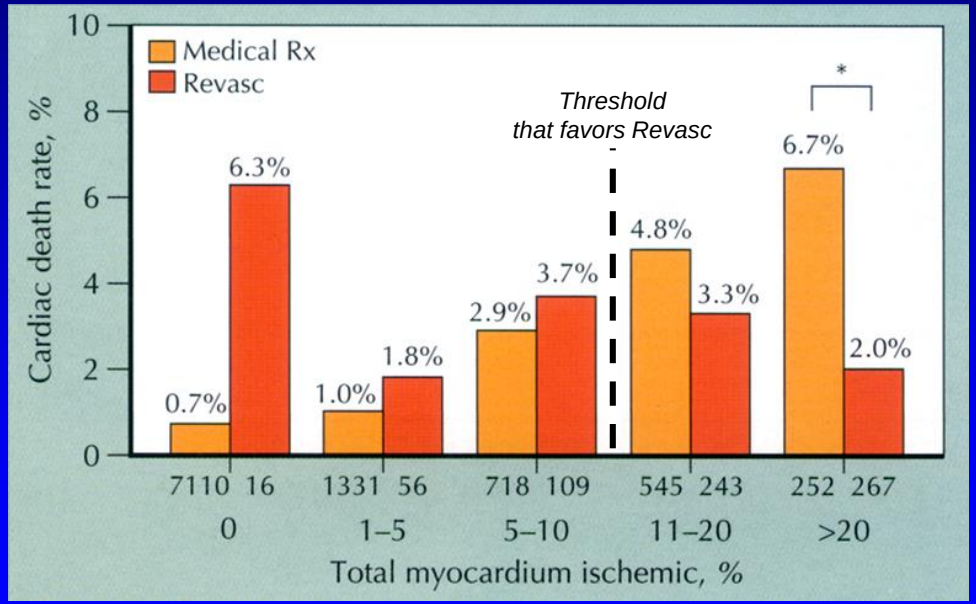
Ranolazine can be useful as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects, is ineffective or is contraindicated.

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

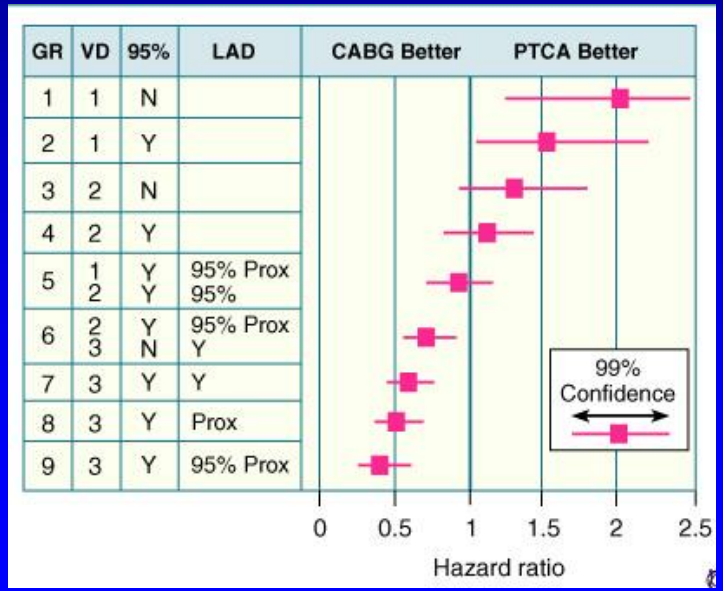
10,627 consecutive patients, myocardial stress perfusion imaging (exercise or adenosine), with followup 1.9±0.6 years



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

5-Year Survival Based on Revascularization by CABG vs PTCA

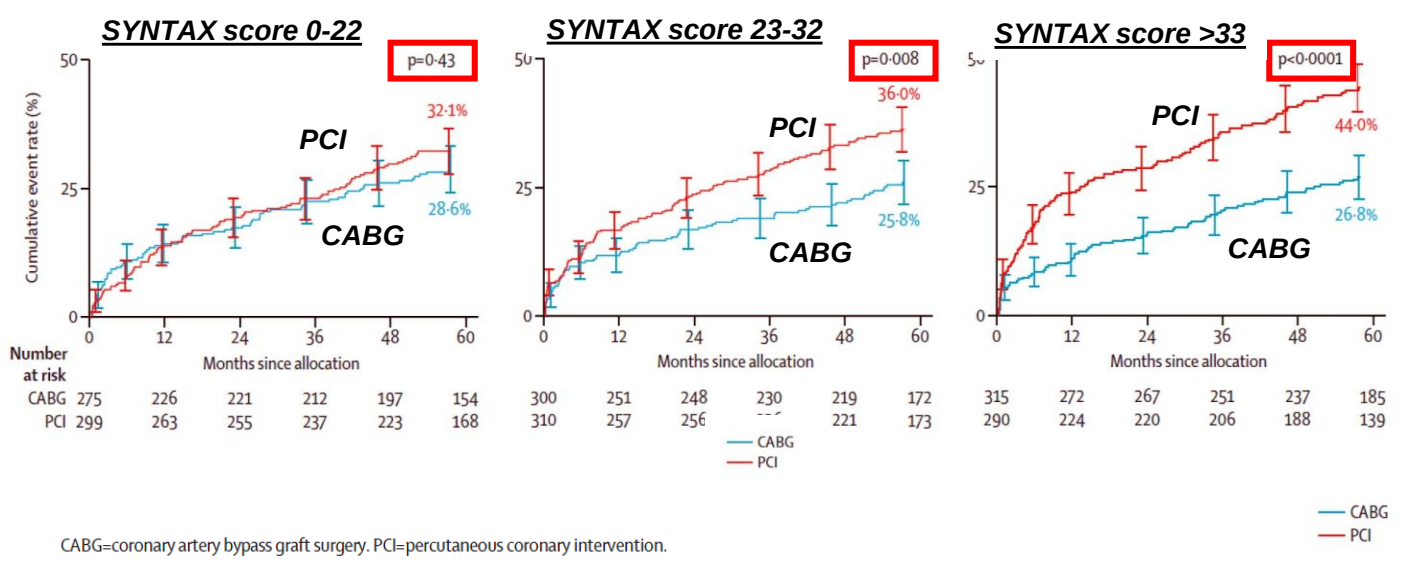
Least severe CAD, survival better with PTCA,
Intermediate risk, no difference
More severe CAD, survival better with CABG



(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)

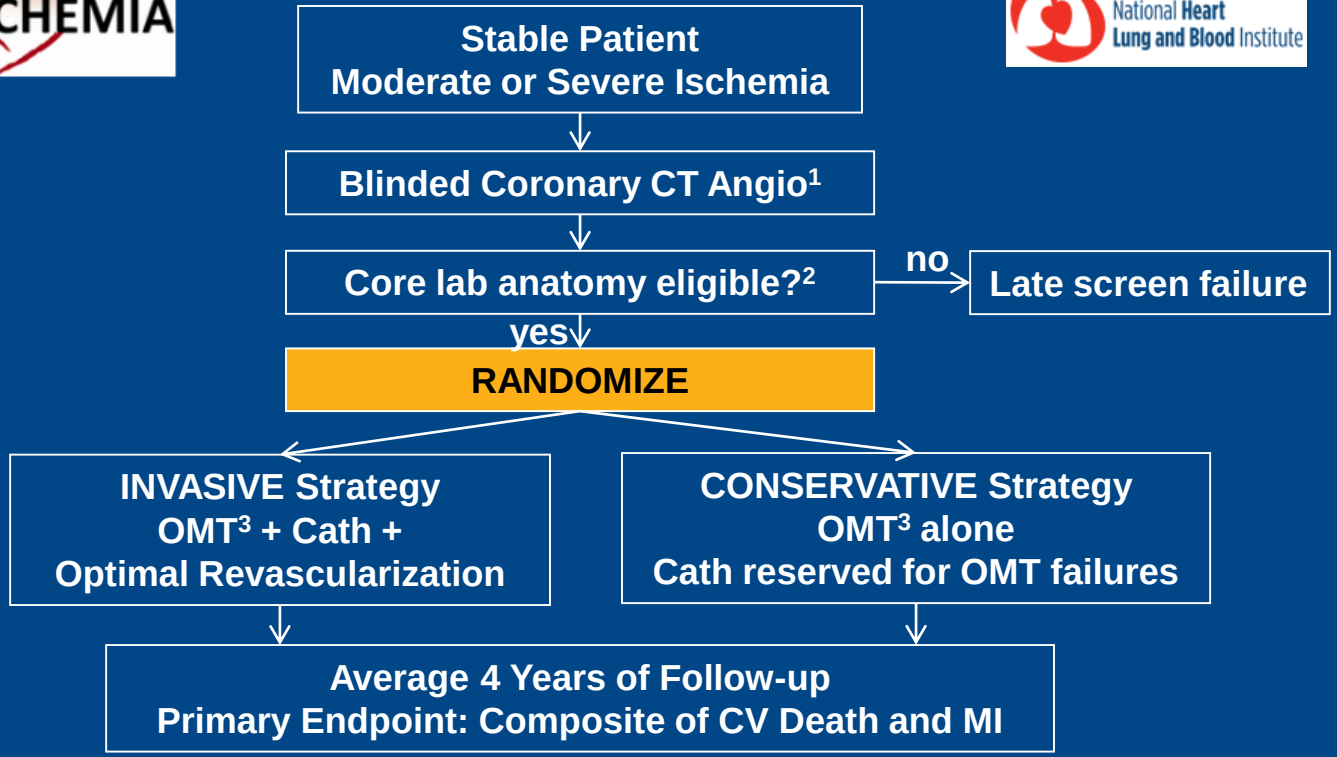
Revascularization of Stable CAD 2012

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**

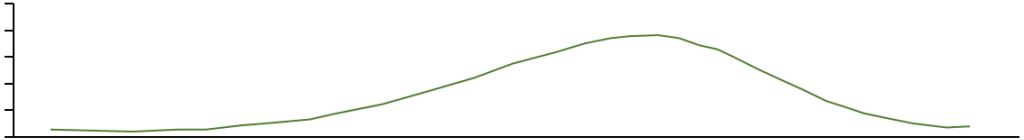
(Fihn SD, et al. JACC 2012;60:e44-e164; ESC Guidelines for Revascularization 2010. *EHJ.* 2010;31:2501-55)



[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

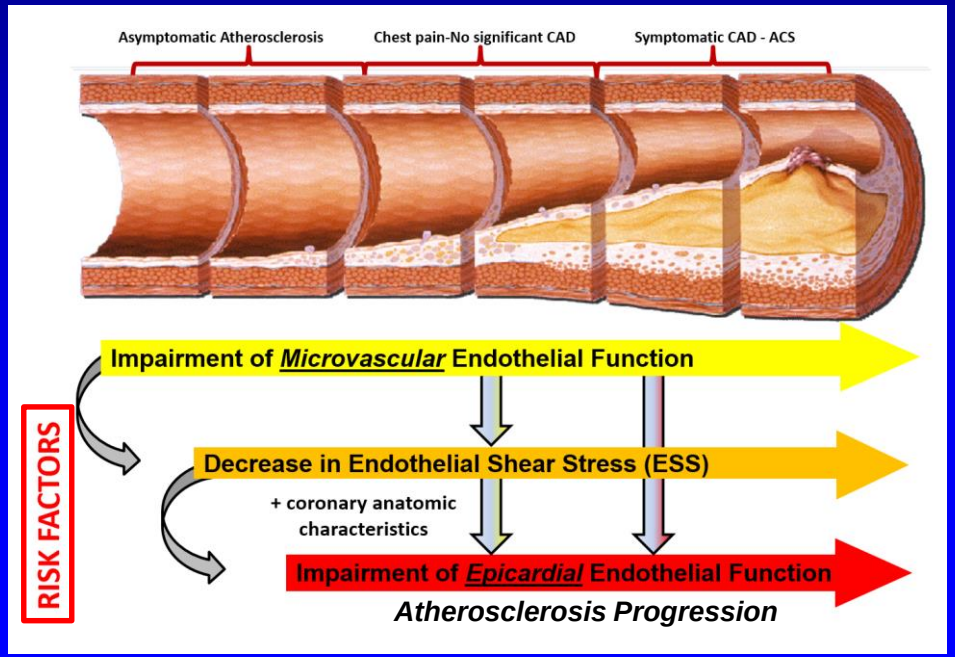
Lower flow (shear stress) **in epicardial arteries**

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



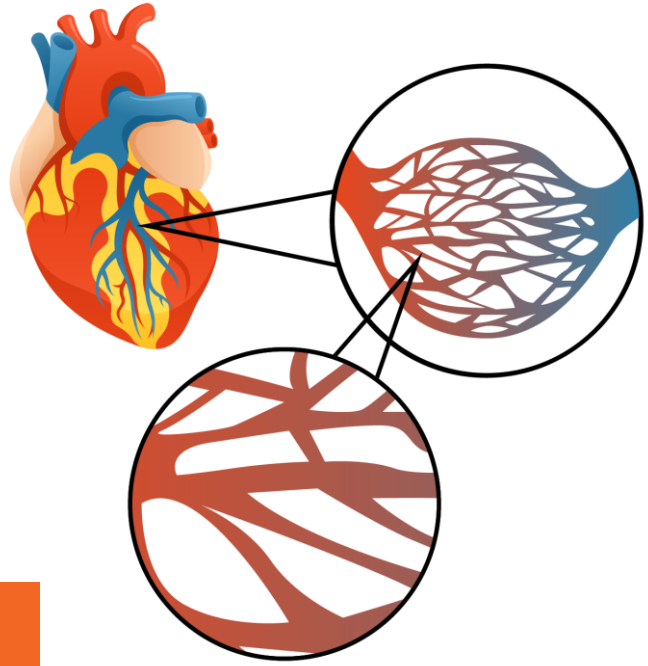
(Siasos G, et al. JACC 2018; 71:2092-2102)

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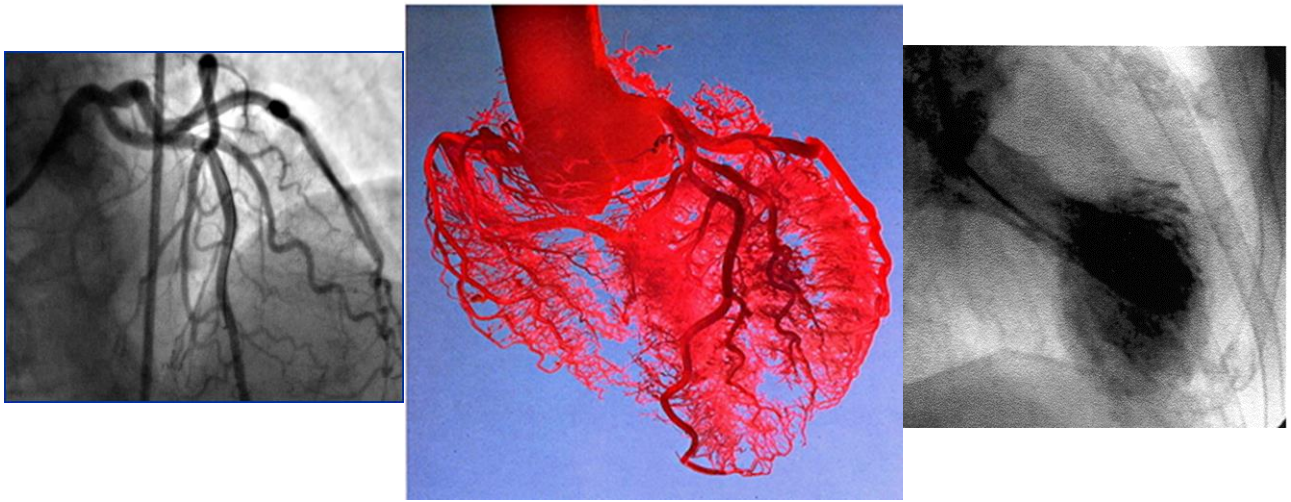
CONSULTING: Medscape*, Sanofi-Vascular*, NIH CSR and NIH ORWHAB*, iRhythm, Caladrius

HONORARIUM*: Abbott Diagnostics

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

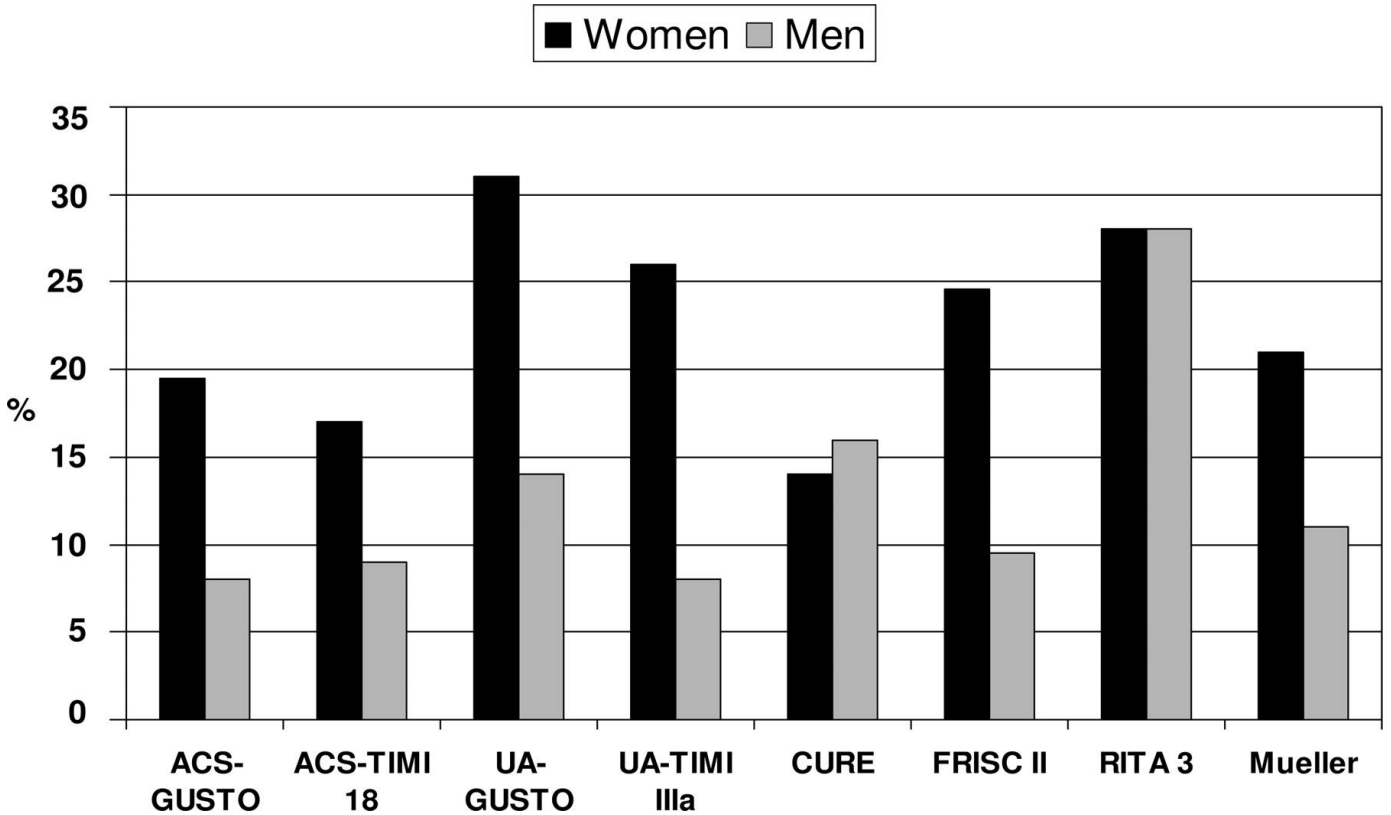
*paid to CSMC

Women and Coronary Microvascular Dysfunction
INOCA/MINOCA



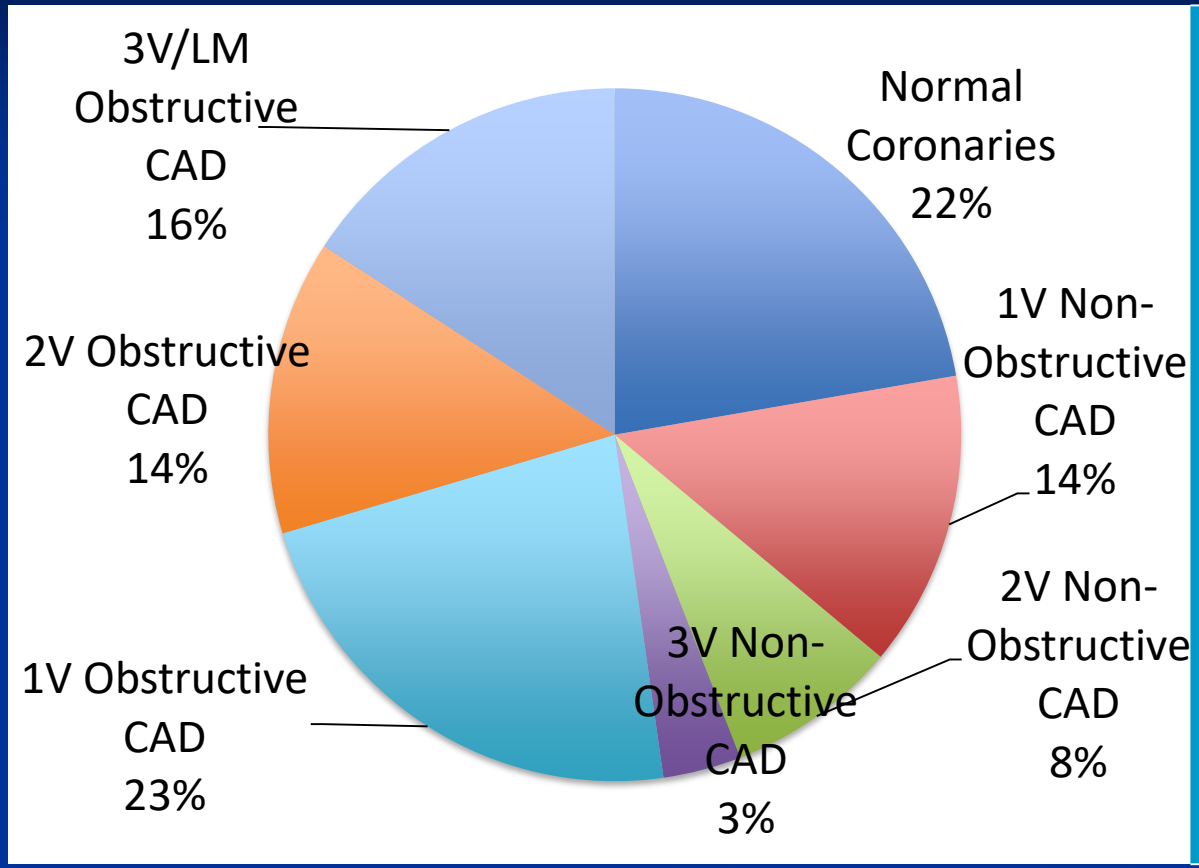
Ischemia with No Obstructive CAD (INOCA)
Myocardial Infarction with No Obstructive CAD (MINOCA)

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



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

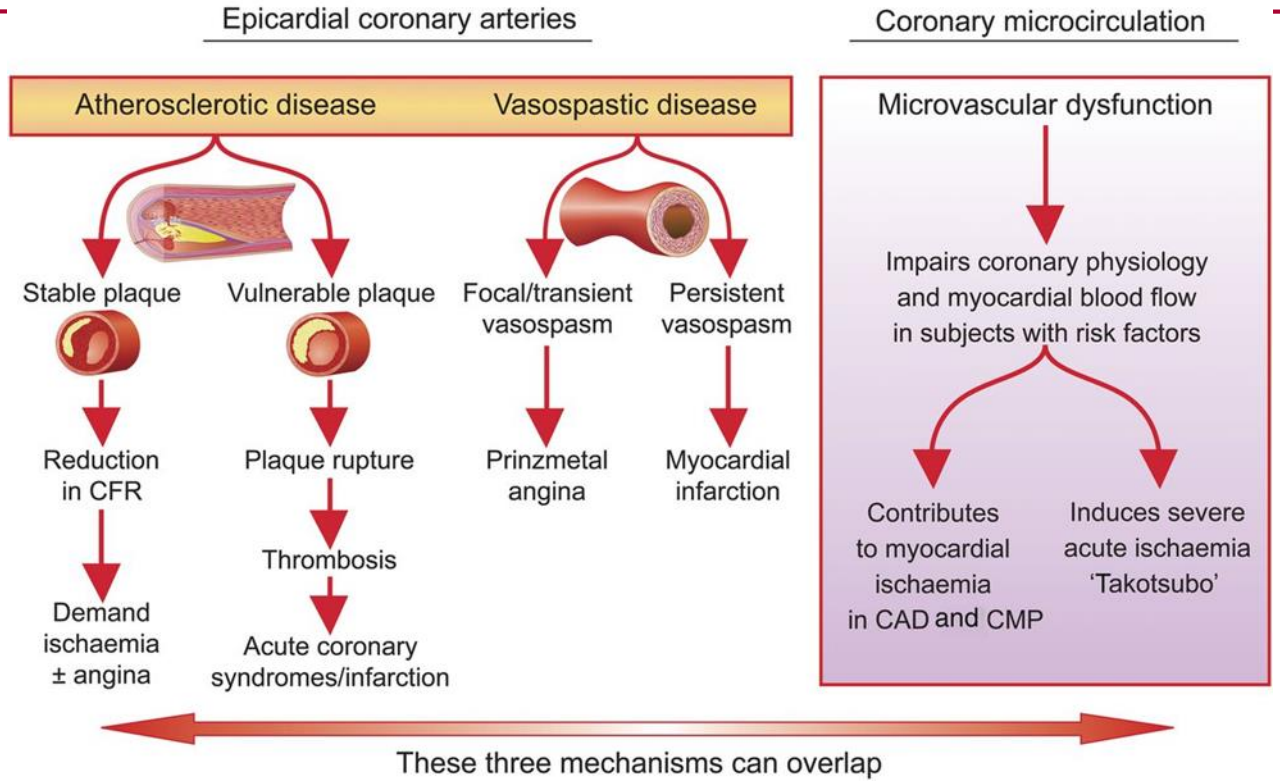
VA CART 37,674 male patients – 47% non-obstructive or normal coronary arteries



Now common in men!

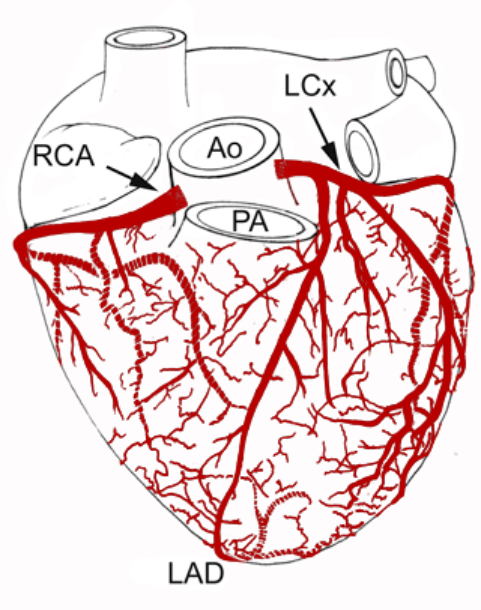
CART VA CLINICAL ASSESSMENT REPORTING & TRACKING PROGRAM

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

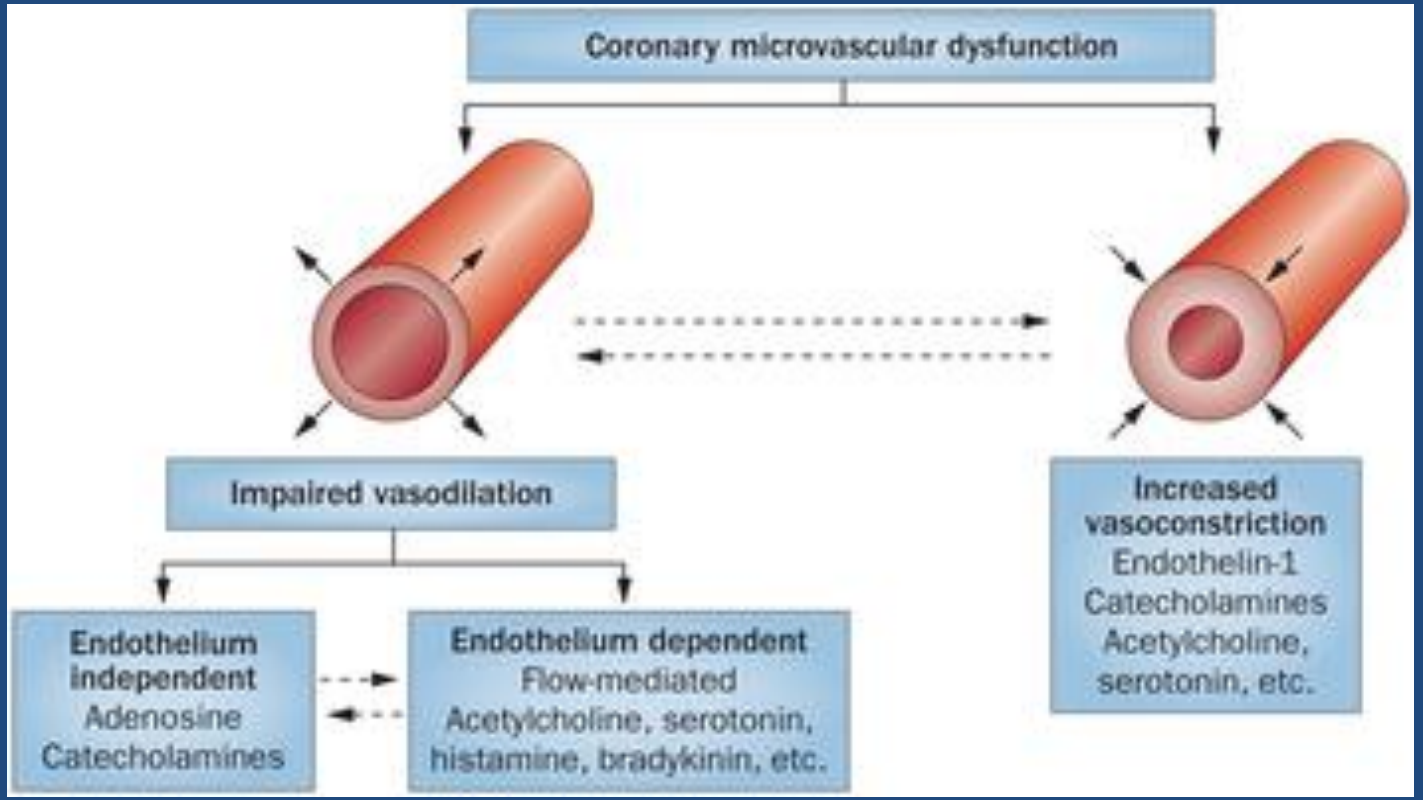


www.vhlab.umn.edu/

- 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

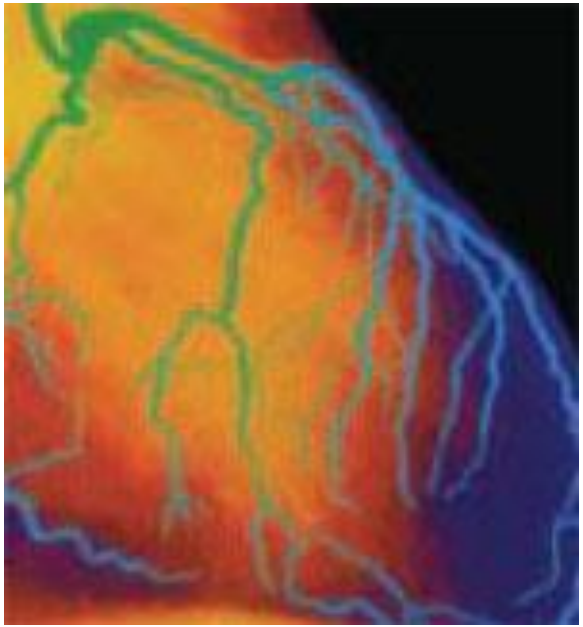


Crea, F, et al. Nature Reviews Cardiology. 2015;12:48–62.

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

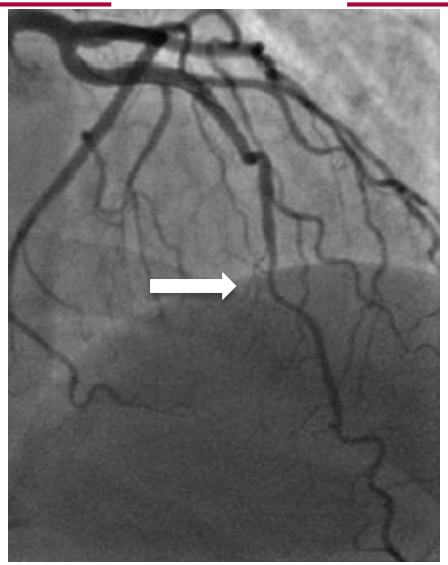
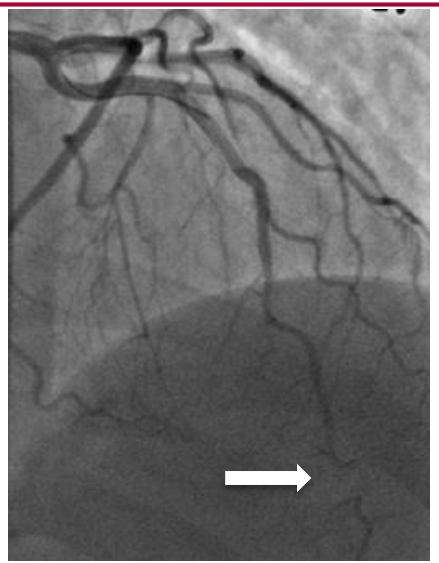
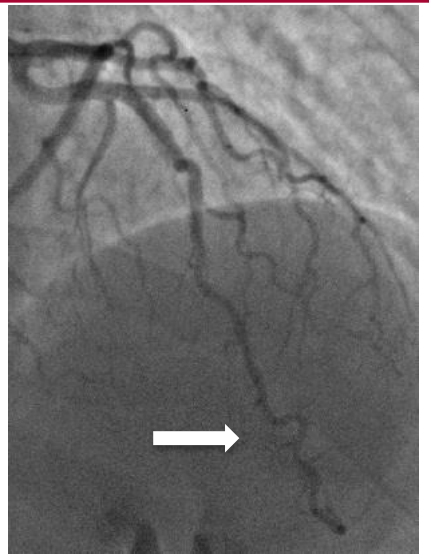
- Approximately 50% of patients with:
  - persistent chest pain
  - non-obstructive coronary artery disease

- 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

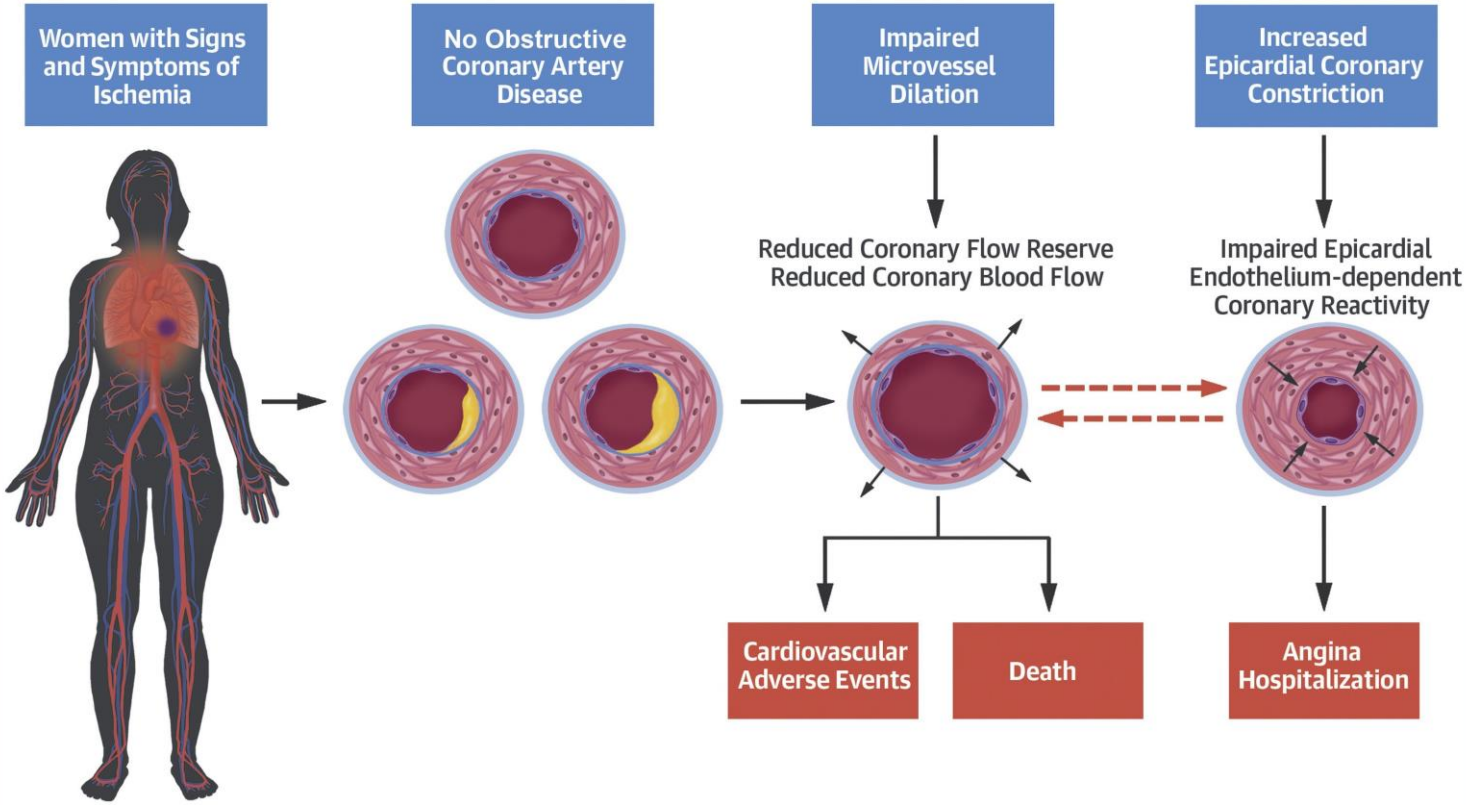


Hasdai D et al. *Mayo Clin Proc.* 1998;73:1133-1140
Wei J et al. JACC Interventions. 2012;6(5):64

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 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



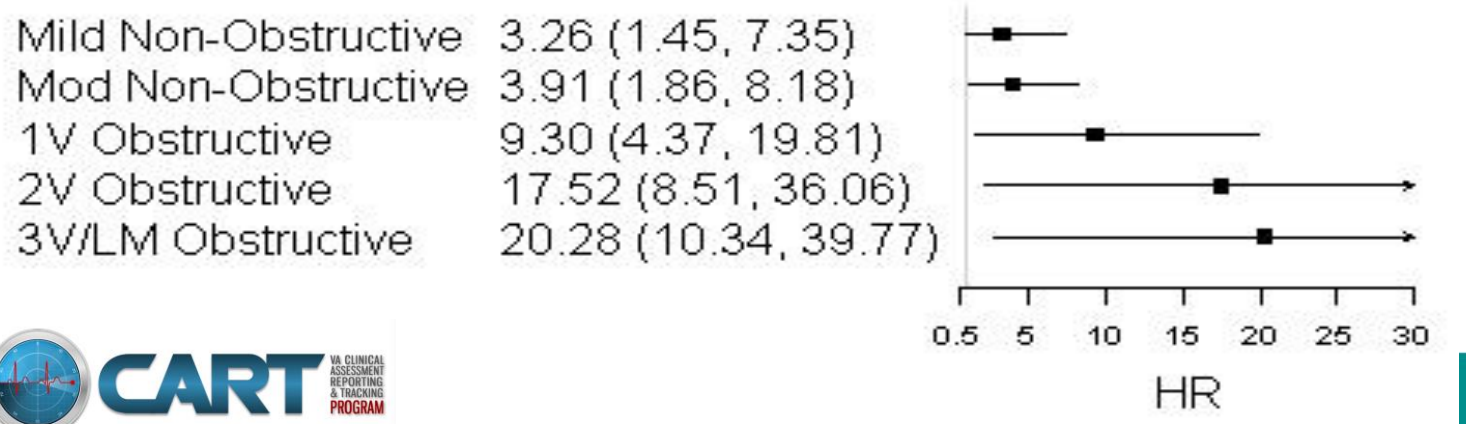
AlBadri, A. et al. J Am Coll Cardiol. 2019;73(6):684–93.

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)

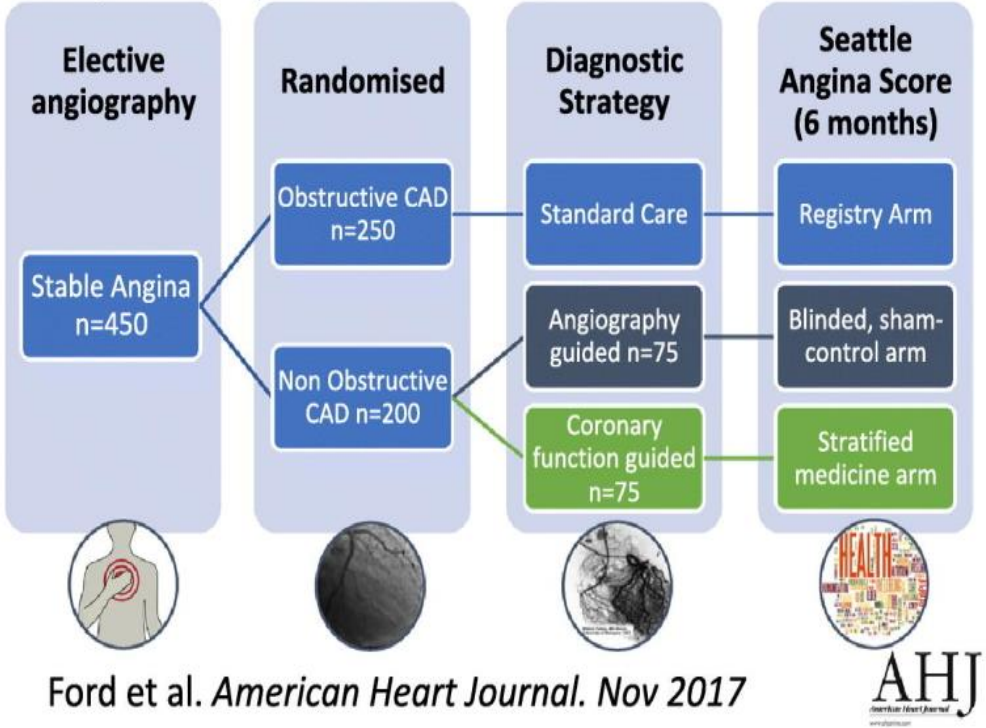
Al-Lamee R et al. Lancet 2018; 391: 31–40

Randomized CRT Protocol Improves Angina Outcomes

The BHF CorMicA Study Design

Coronary Microvascular Angina – a randomised clinical trial of stratified medicine

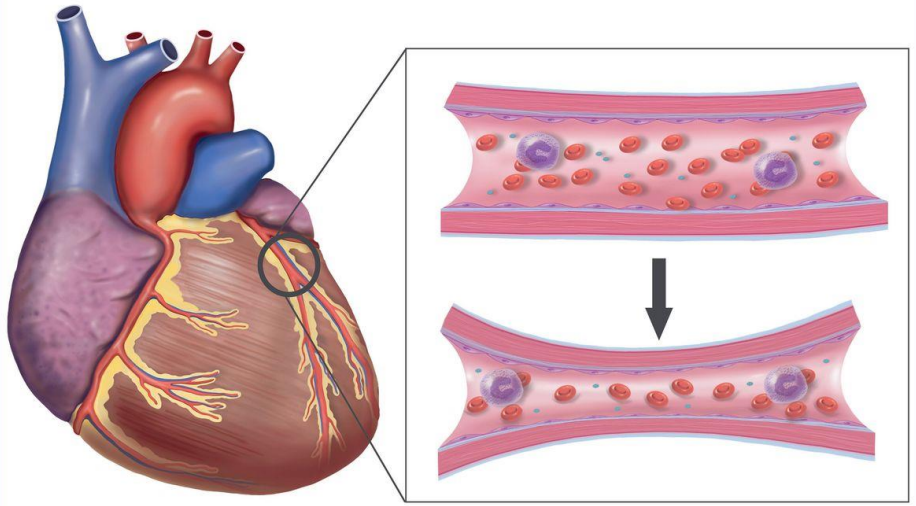
British Heart Foundation



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

AHJ

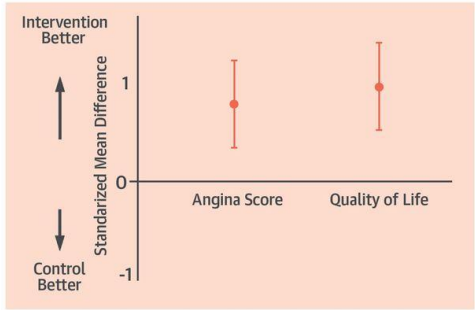
CENTRAL ILLUSTRATION: Invasive Coronary Function Testing in Angina: Study Design and Results



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

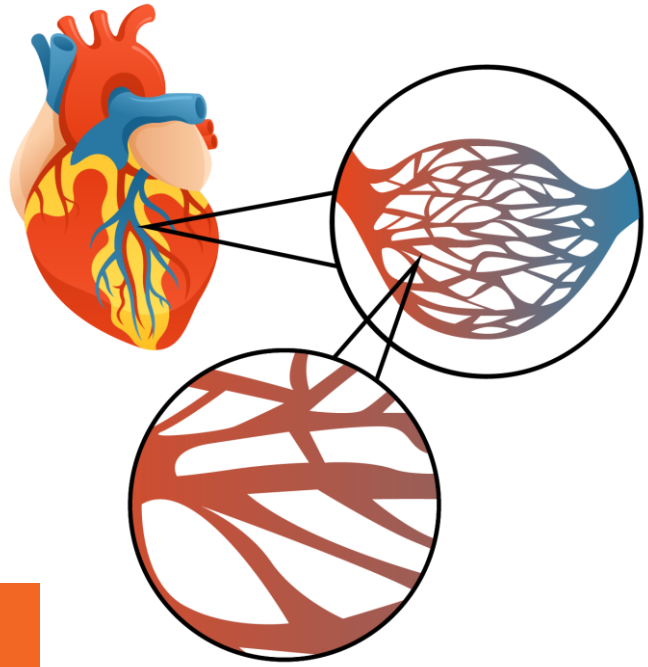
WARRIOR

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

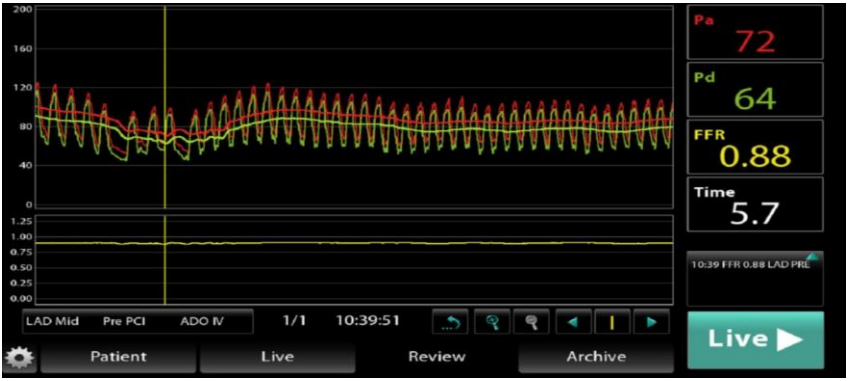
CONSULTING FEE: Itamer Medical, Philips

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

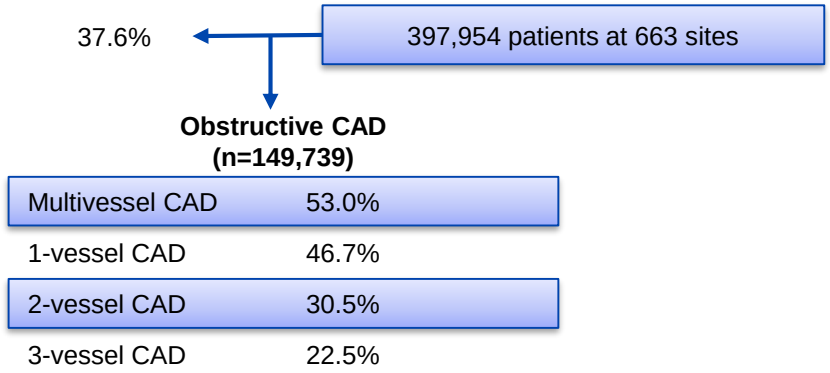
- S/P NSTEMI and stent to LAD
- Continue to complain on progressive chest pain during exertion
- Several ER visits with ECG changes

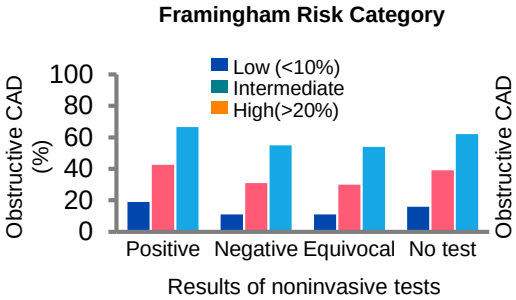


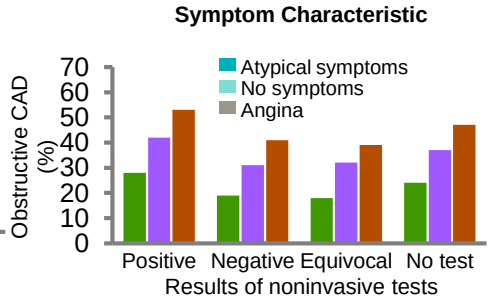
ORIGINAL ARTICLE

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

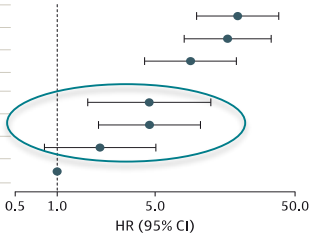
Nonobstructive Coronary Artery Disease and Risk of Myocardial Infarction

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

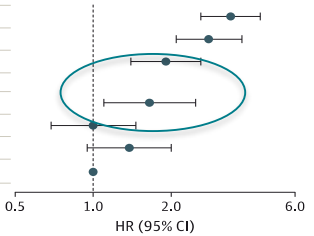
–1year myocardial infarction

	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

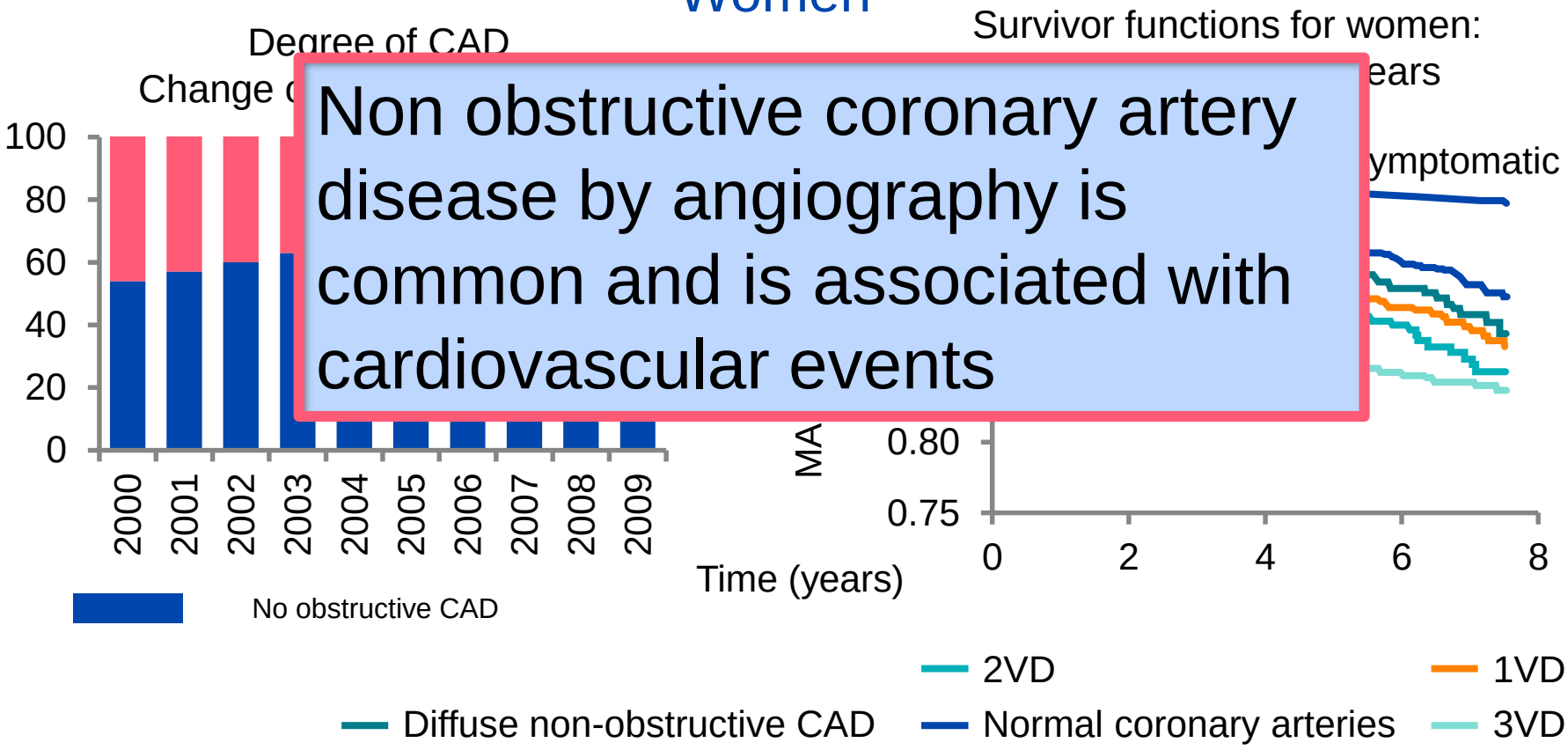
	Events	Patients	HR (95% CI)
Obstructive CAD			
3-Vessel or left main	239	6036	3.4 (2.6-4.4)
2-Vessel	164	5452	2.8 (2.1-3.7)
1-Vessel	192	9411	1.9 (1.4-2.6)
Nonobstructive CAD			
3-Vessel	27	1133	1.6 (1.1-2.5)
2-Vessel	35	2605	1.0 (0.7-1.5)
1-Vessel	85	4646	1.4 (1.0-2.0)
No apparent CAD	103	8391	1 [Reference]



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

1-Year combined myocardial infarction and mortality

Major Adverse Cardiovascular Event-Free Survivor Functions Women

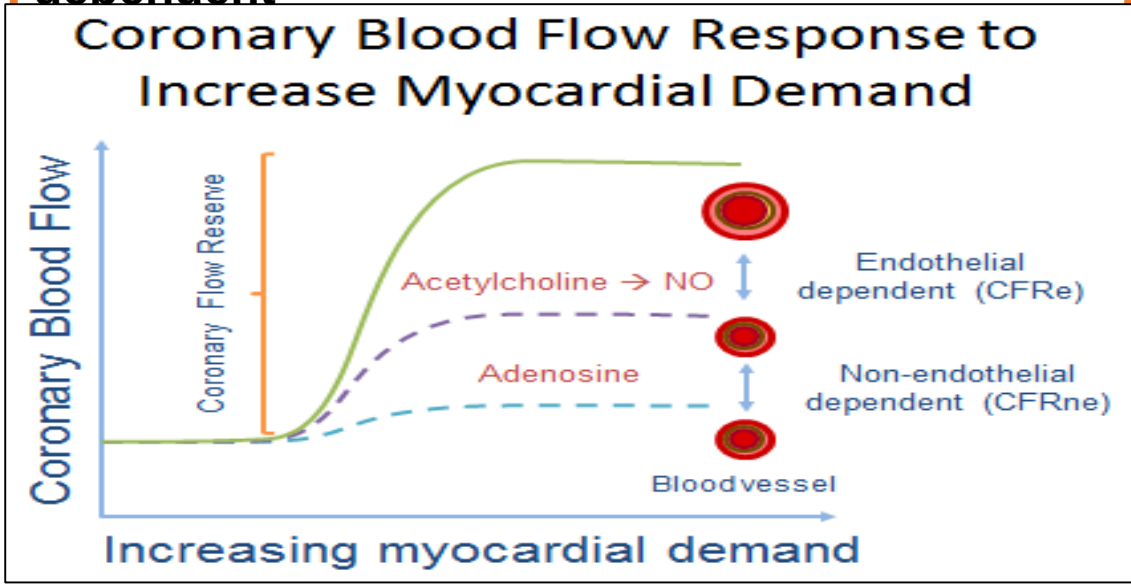


Non obstructive coronary artery disease by angiography is common and is associated with cardiovascular events

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

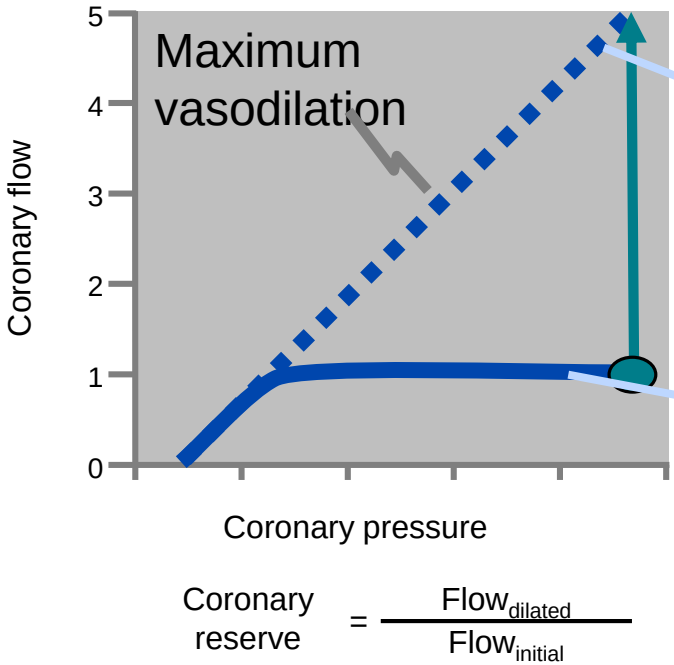
Coronary Microcirculation

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

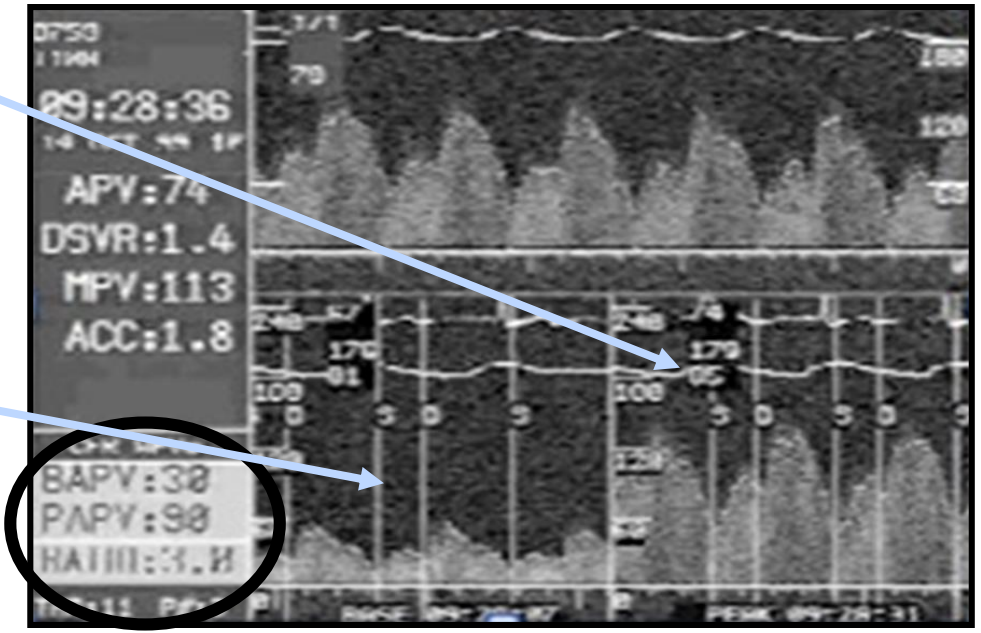


Coronary Flow Reserve

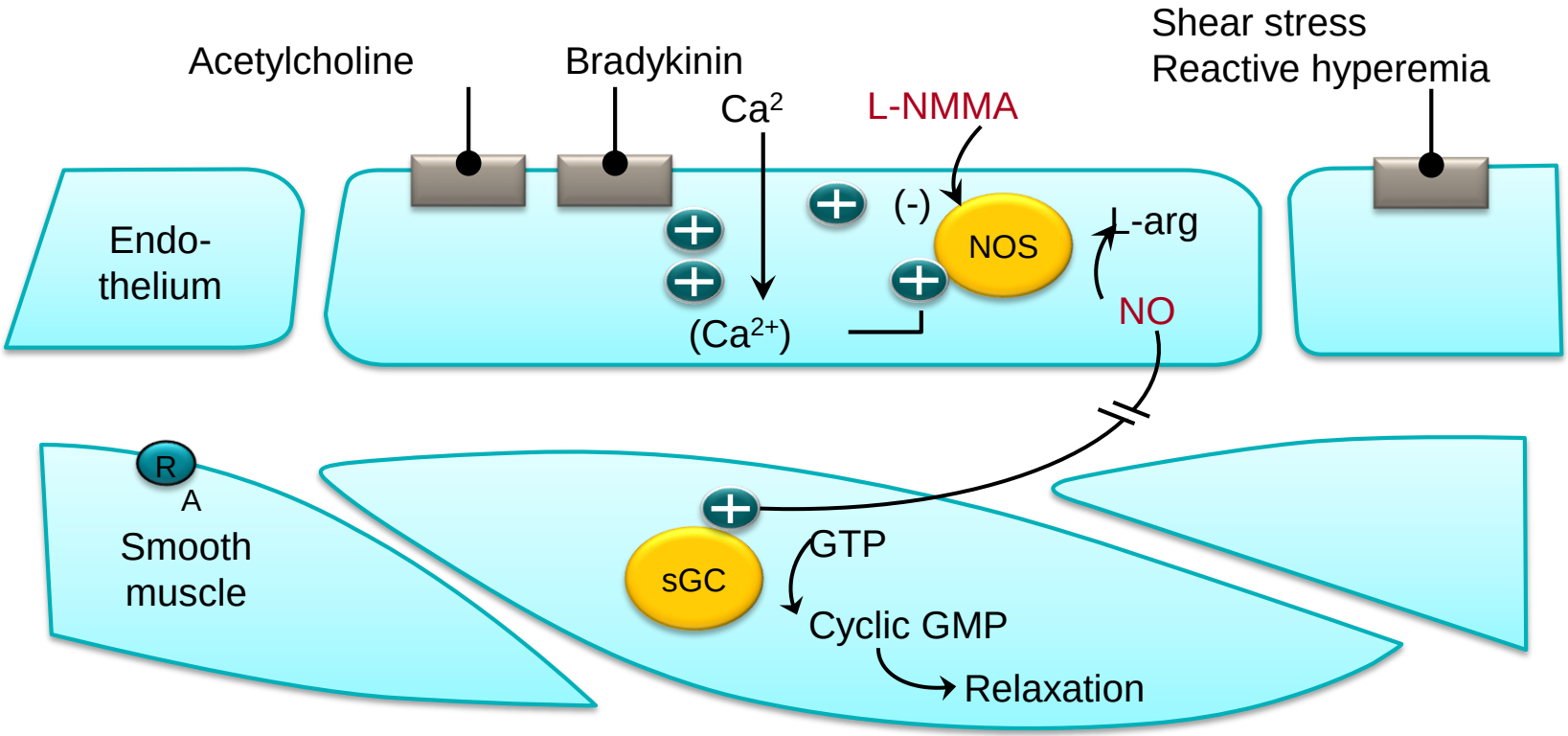
Response to Adenosine is Non-Endothelial Dependent



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



How to assess endothelial function?



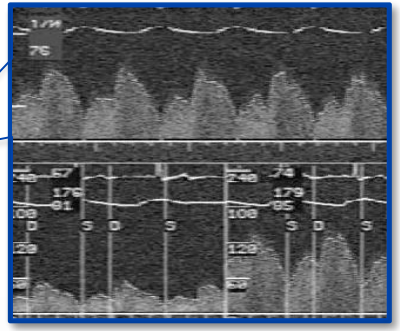
Coronary blood flow increase in response to exercise and mental stress is endothelium dependent and parallels the response to intracoronary acetylcholine.

Functional Angiogram Protocol

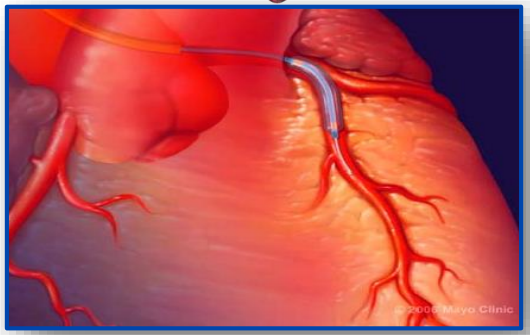
Diagnostic angiography

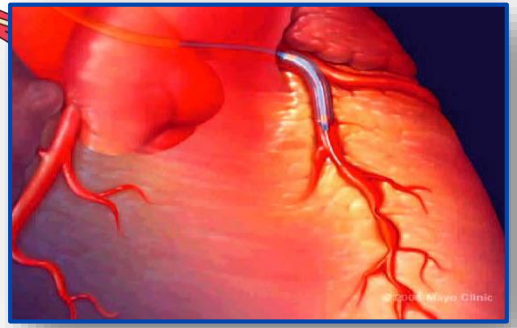
Adenosine IC 24-72 μg

CFR: Non endothelium **microcirculation**

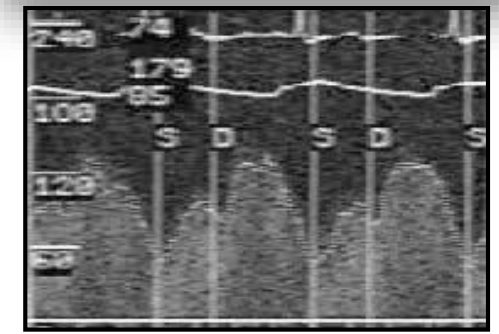


Acetylcholine (endothelium dependent vasodilator)

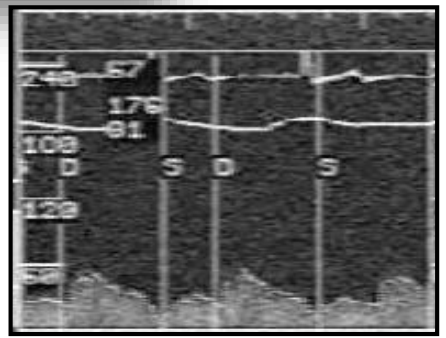




Epicardial



Microcirculation



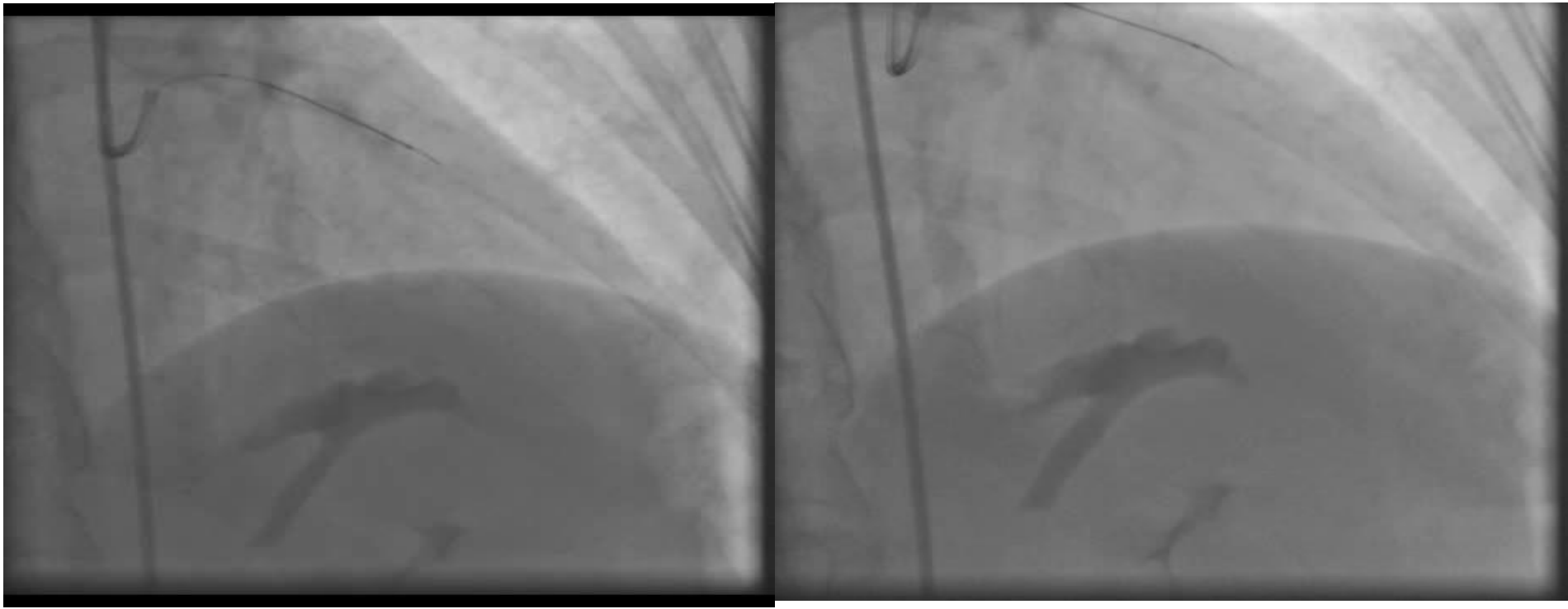
Mechanism/drug	Non-Endothelium	Endothelial function Epicardial	Endothelial function Microcirculation
Adenosine Microcirculation	% Δ in CBF Doppler >2.5	–	–
Acetylcholine	–	% Δ in CAD >20%	% Δ in CBF >50%
NTG Epicardial	% Δ in CAD QCA	–	–

CAD: coronary artery diameter, CBF coronary blood flow

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

Baseline

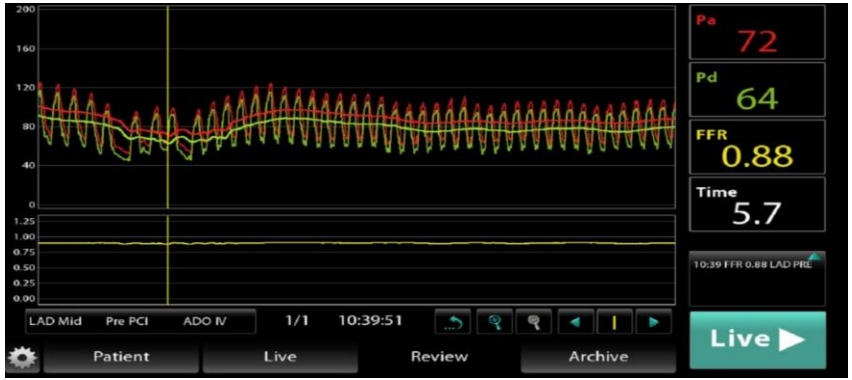
Acetylcholine 10-4M



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

67-year-old male with Chest Pain

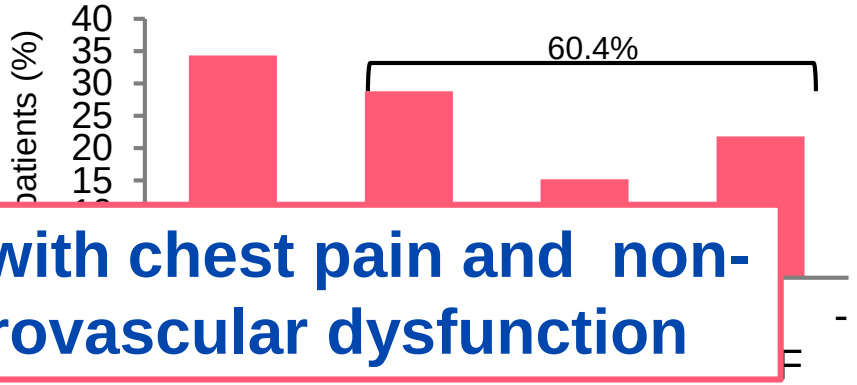
- CFR= 2.5
- Response to IC acetylcholine
- % change of CBF 10%



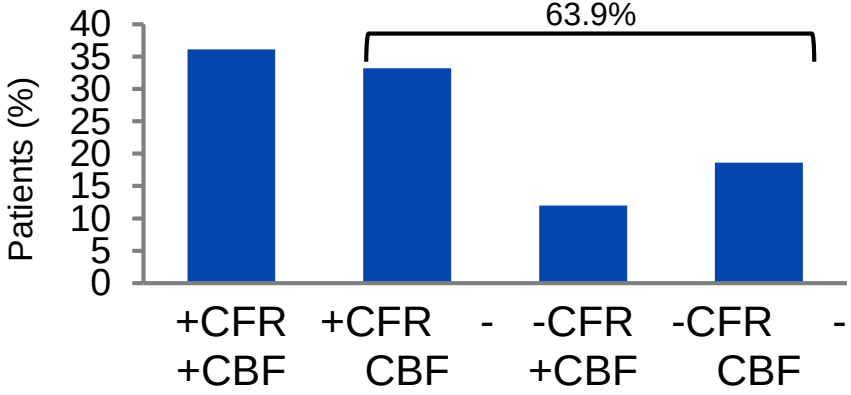
Prevalence of Microvascular Dysfunction in Patients With Non-Obstructive CAD

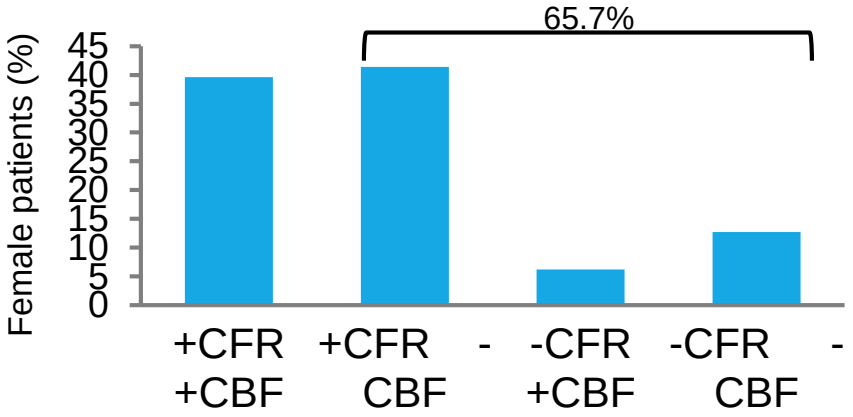
1,439 patients with chest pain and non-obstructive

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

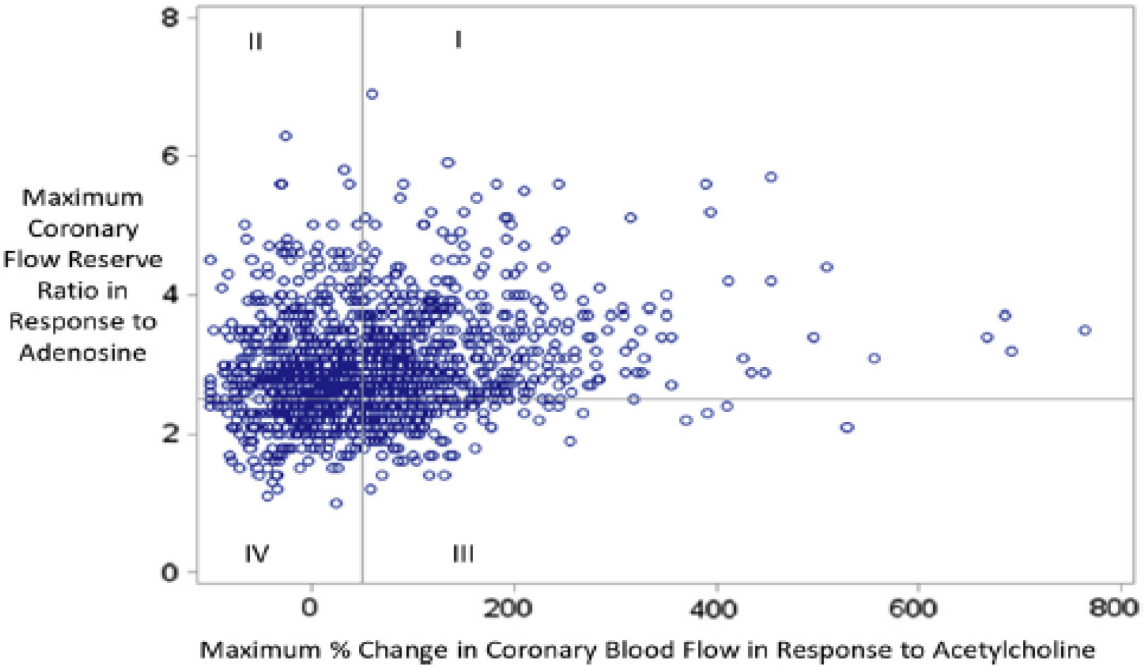




Sara and Lerman JACC Int. 2015

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

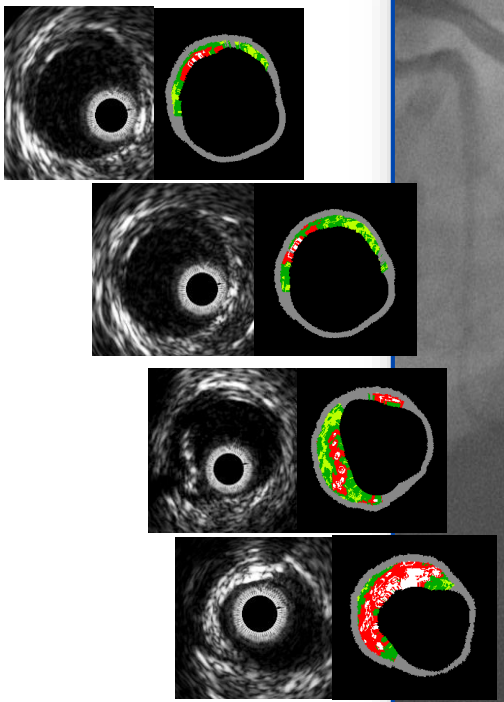
Endothelial dysfunction is associated with tissue chaptalization of vulnerable plaque

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]

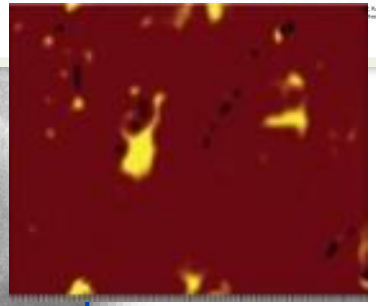


European Heart Journal Advance Access published April 7, 2013

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]*



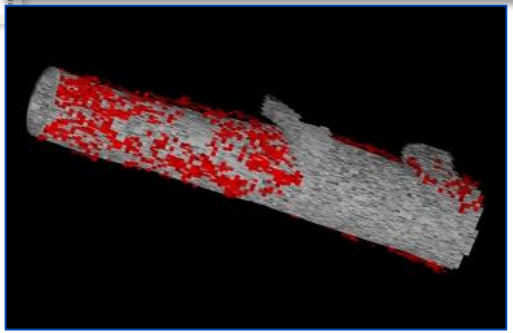
Arteriosclerosis, Thrombosis, and Vascular Biology

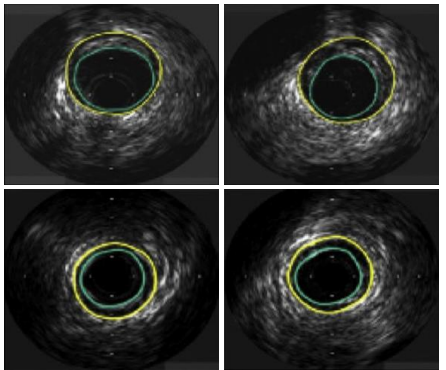
Journal of the American Heart Association

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

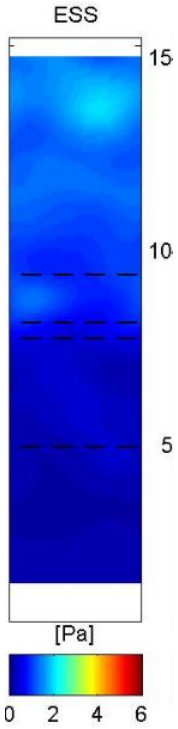




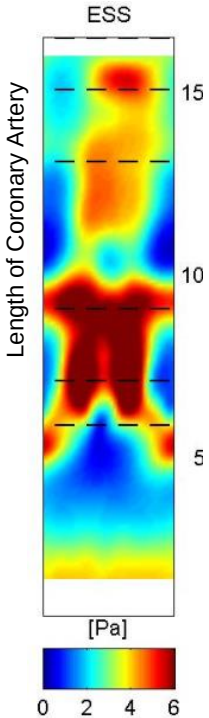
Local Low Shear Stress and Endothelial Dysfunction in Patients With Nonobstructive Coronary Atherosclerosis

- 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

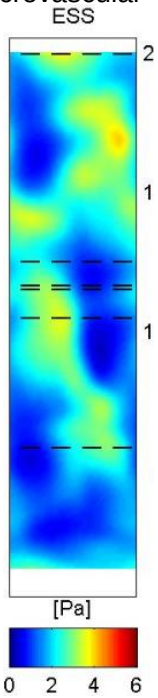
LAD with ***Normal*** Epicardial Endothelial Function



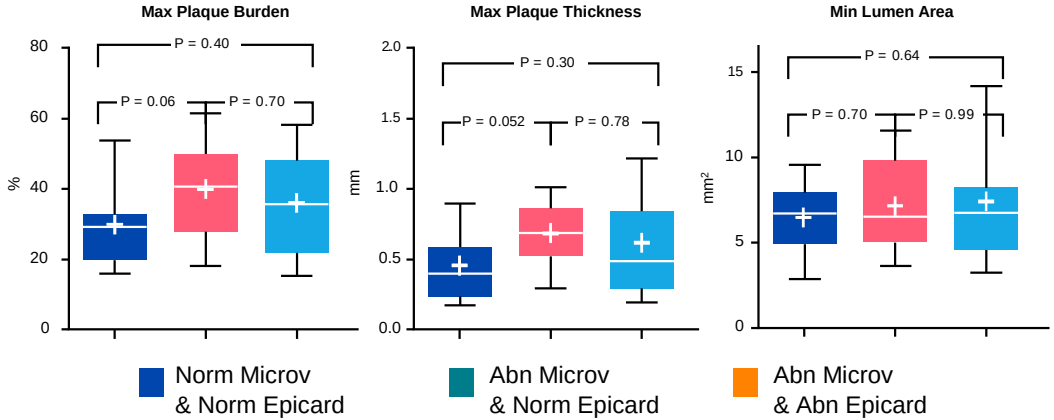
LAD with ***Abnormal*** Epicardial Endothelial Function



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

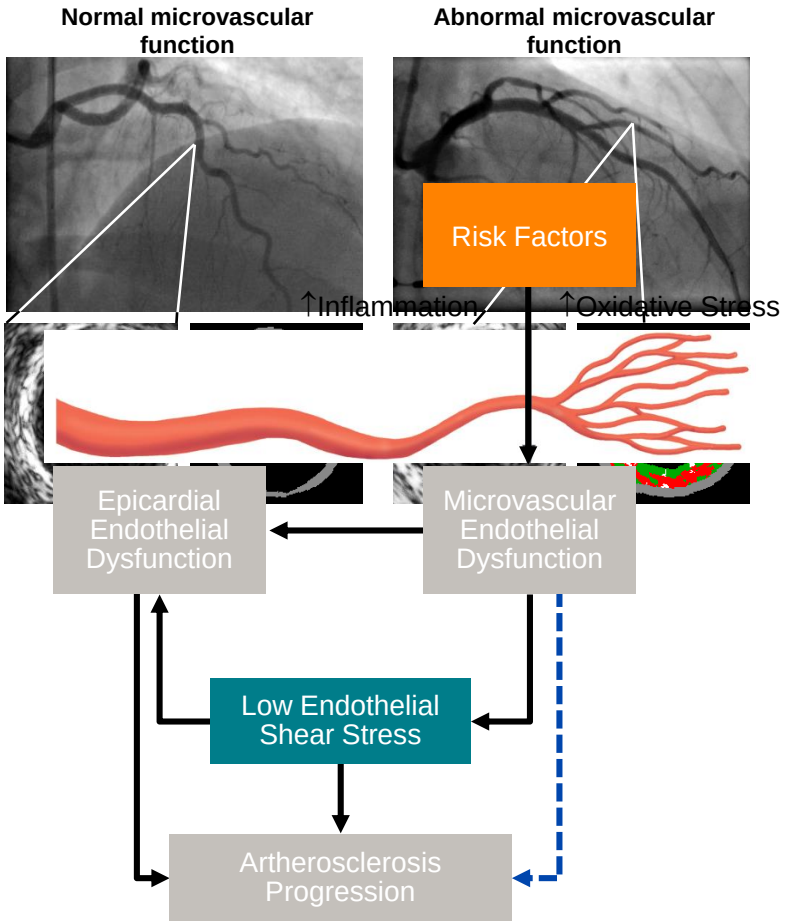


Plaque Characteristics in 1 Segment Per Artery: Analysis Based on Both Microvascular and Epicardial Endothelial Function

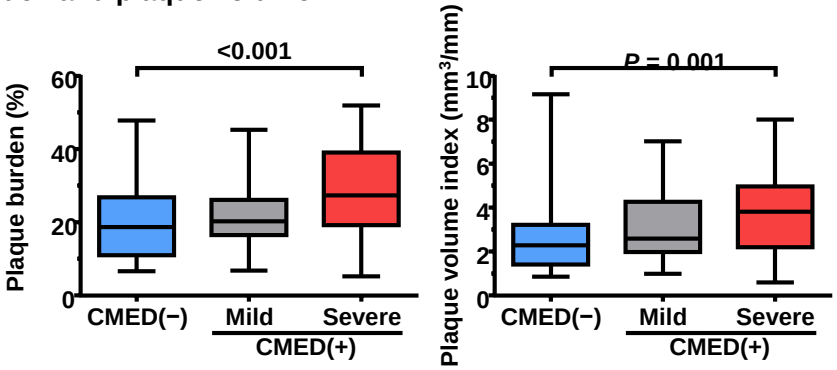


Siasos et al: J Am Coll Cardiol 2018;71:2092–102

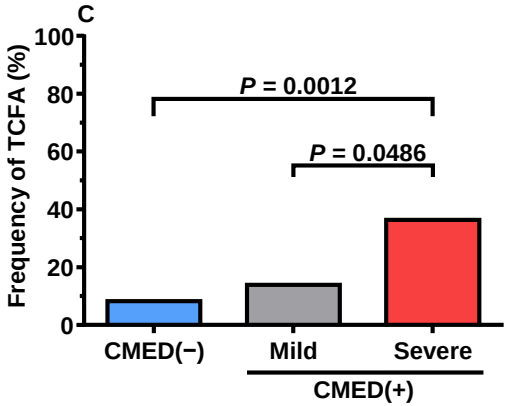
The Relationship between the Microcirculation and Epicardial Disease



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

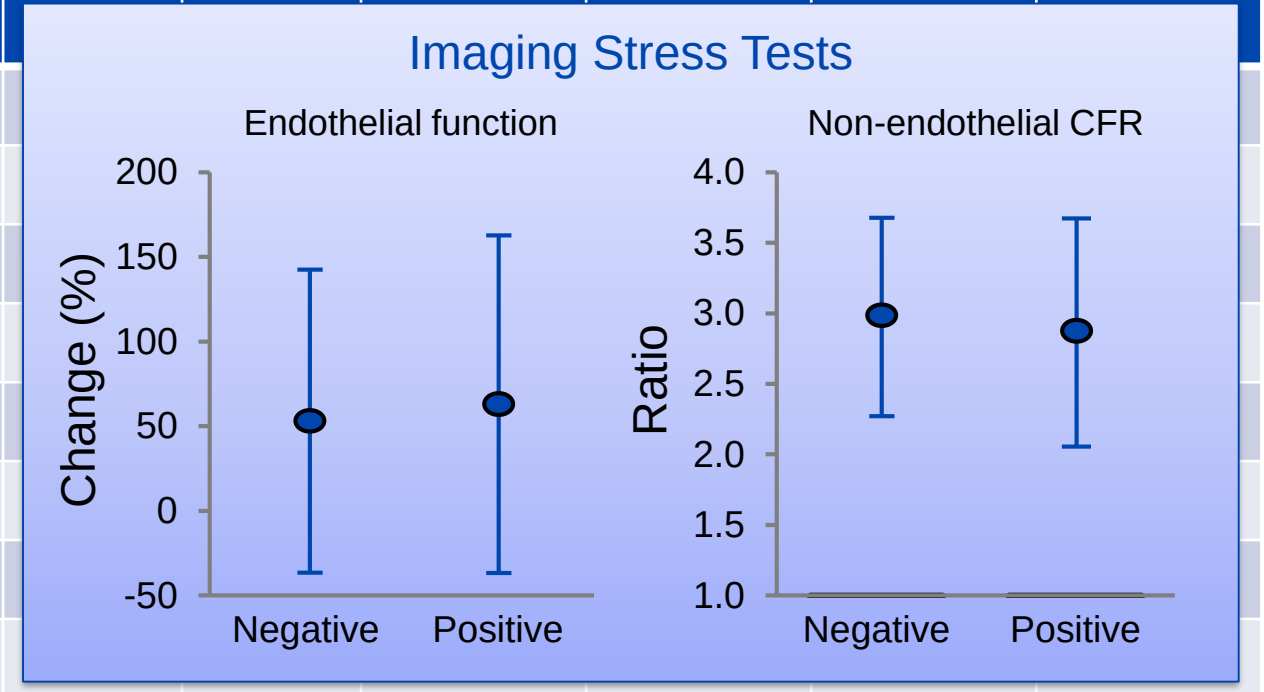


Association of coronary microvascular endothelial function with plaque composition and vulnerability.



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

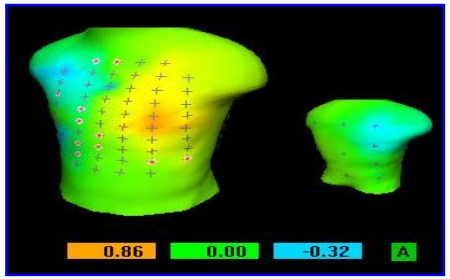
Matthew R. Summers[1], Amir Lerman[1], Ryan J. Lennon[2], Charanjit S. Rihal[1], and Abhiram Prasad[1]*

Coronary endothelial function in response to acetylcholine

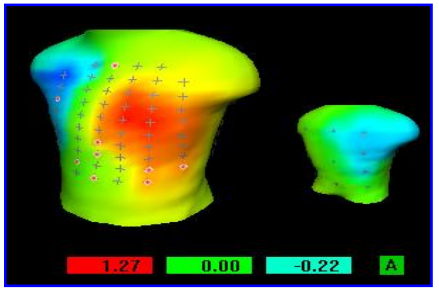
Eighty lead body surface ECG

Coronary Endothelial Function: Prime ECG

Baseline

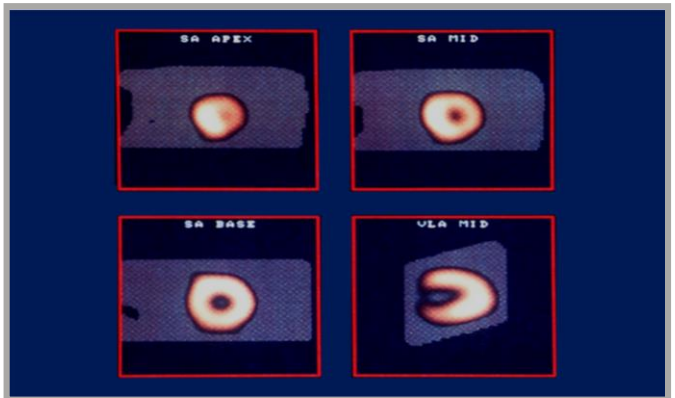


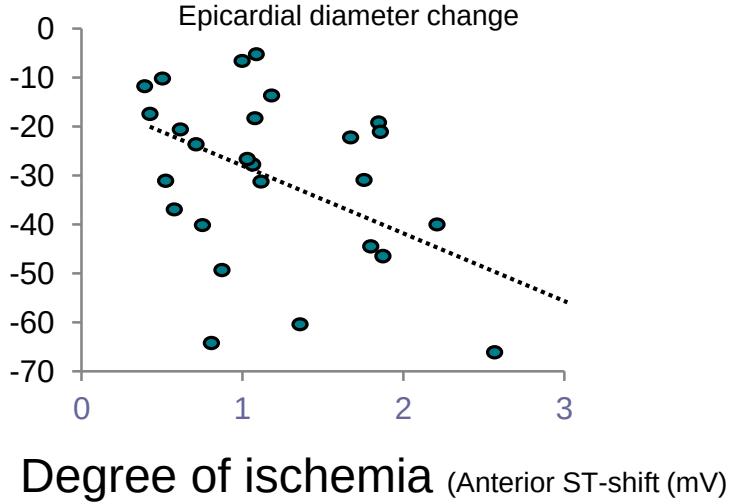
ACH 10^{-4}M



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

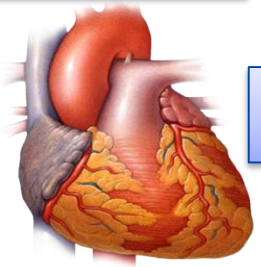
Shear stress

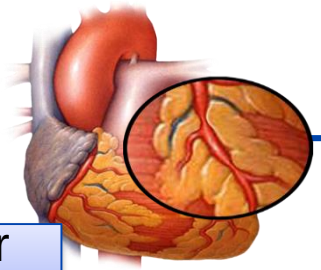
Myocardial ischemia

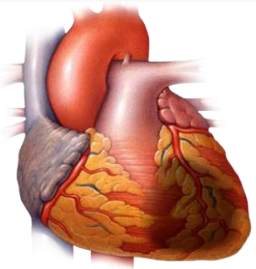
Angina

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

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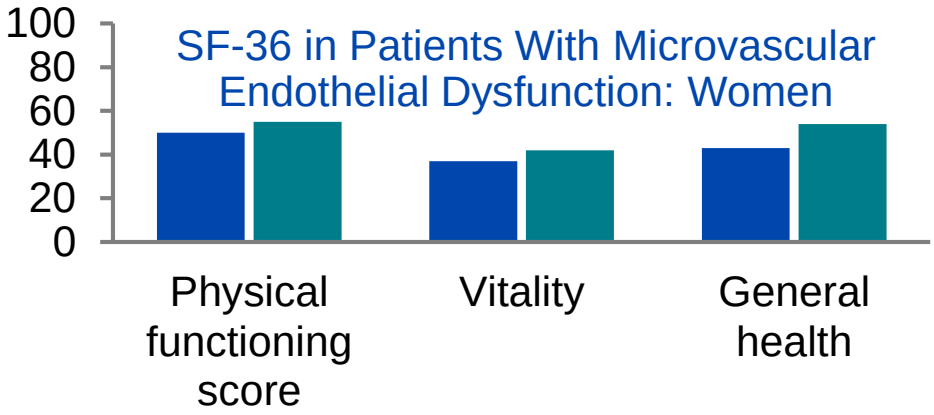
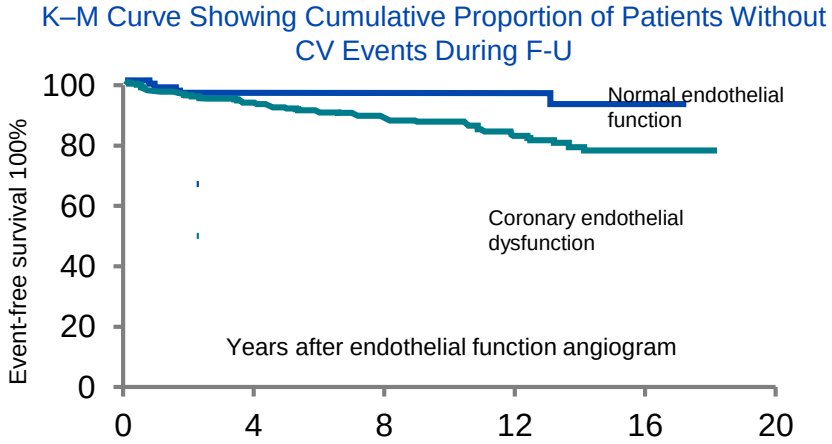
Received 12 November 2015 **Revised** 8 December 2015
Accepted 23 December 2015

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**



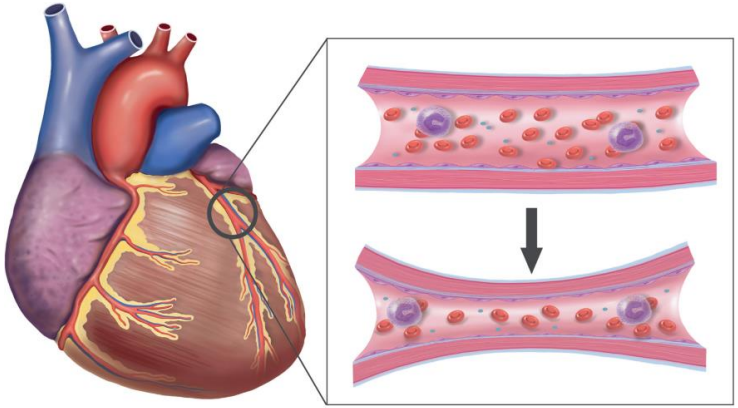
Reriani et al: Coronary Art Dis 27(3):213, 2016

Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

The CorMicA Trial

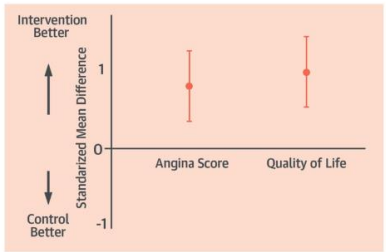
OBJECTIVES The purpose of this study was to test whether an interventional diagnostic procedure (IDP) linked to stratified medicine improves health status in patients with INOCA.

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

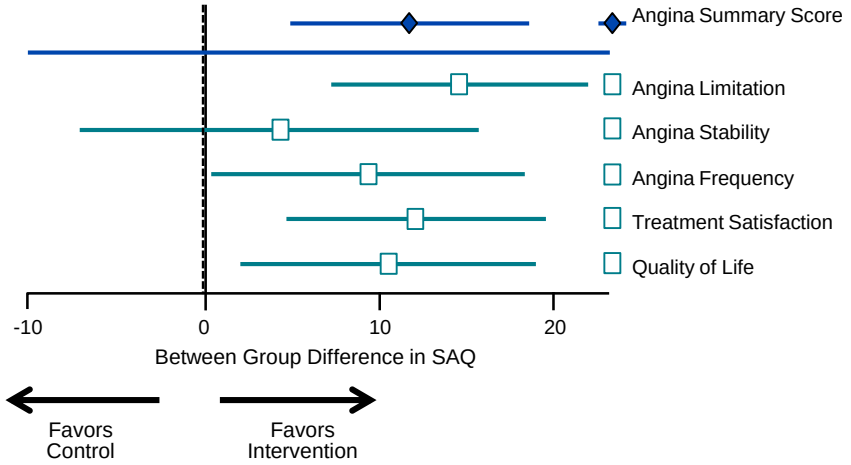


Stratified Medicine in Patients with INOCA:
- Microvascular Angina
- Vasopastic Angina
- Non-Cardiac Chest Pain

→ **Improved Angina and Quality of Life**



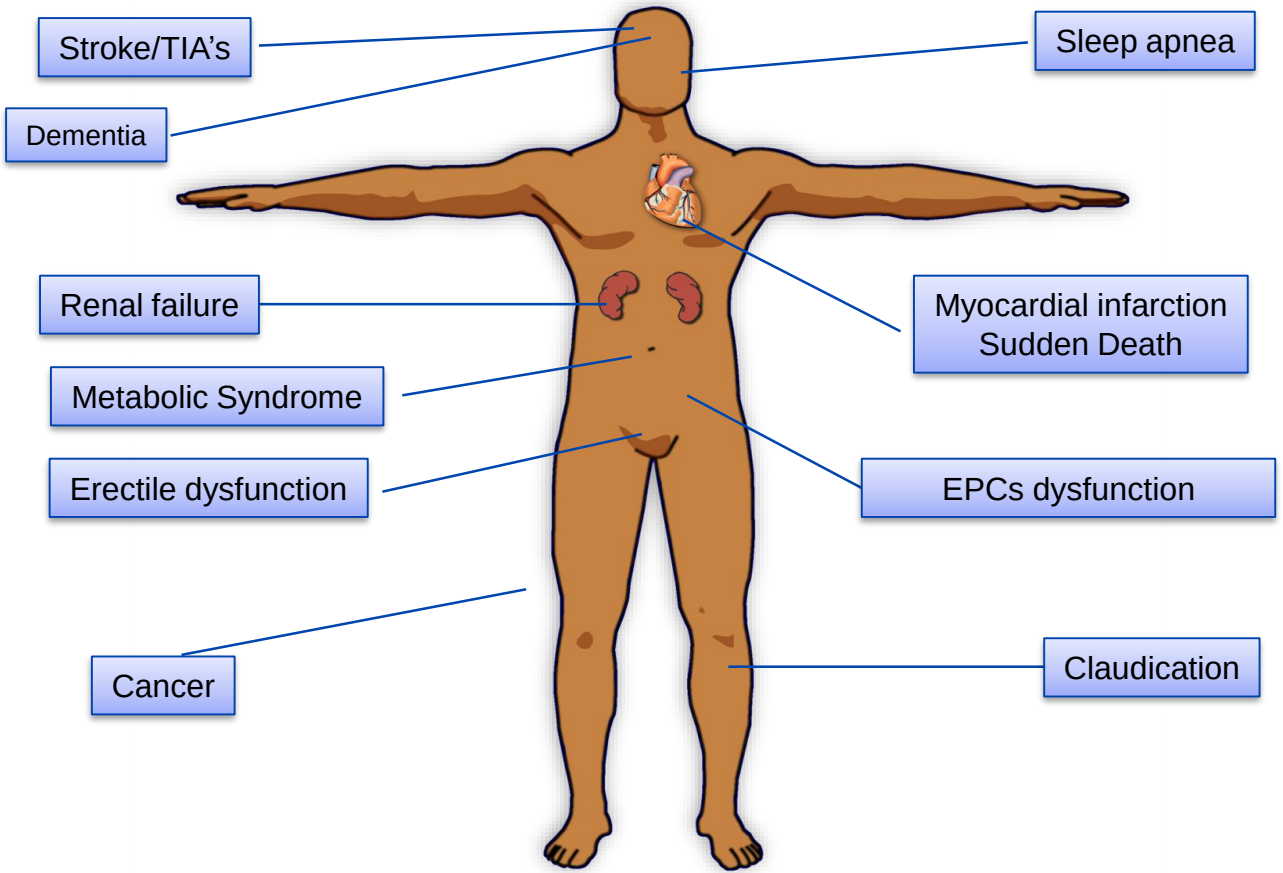
Primary Efficacy Outcome: Treatment Difference in the 6-Month SAQ Summary Score



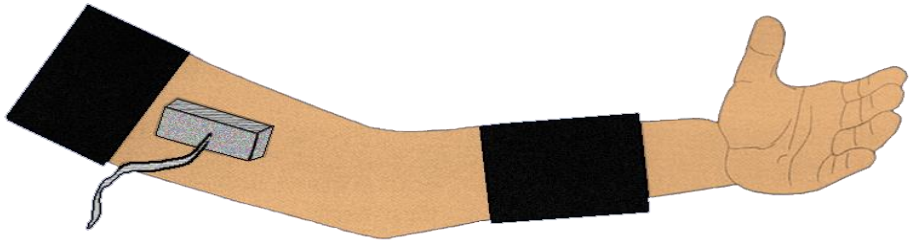
Ford et al: J Am Coll Cardiol; 72:2841-55, 2018

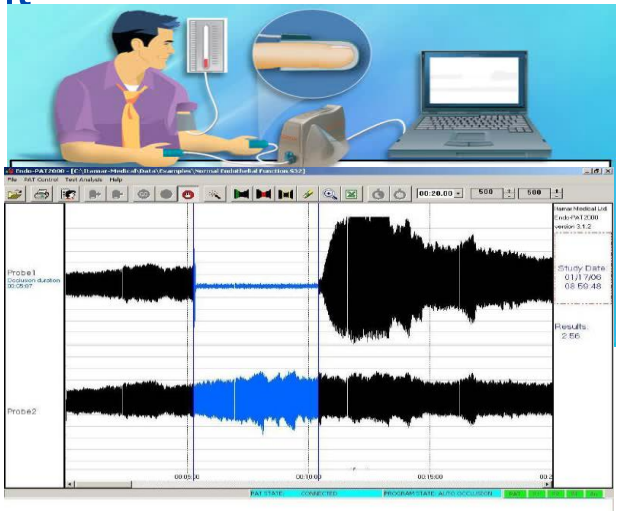
Systemic Manifestation of Endothelial Dysfunction

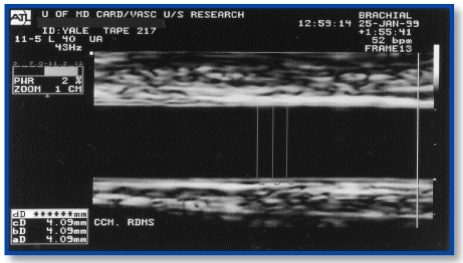
The Vulnerable Patient



Reactive Hyperemia: Endothelium Dependent







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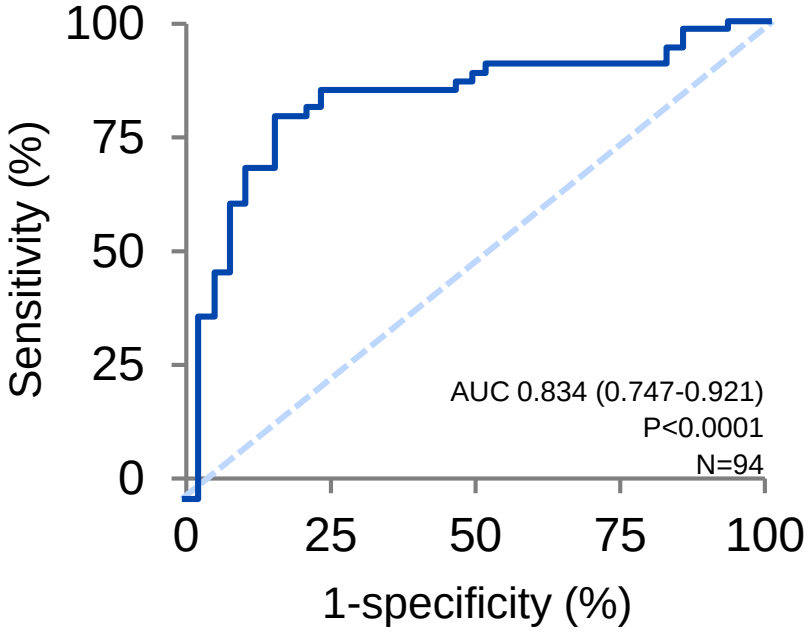
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.08.062

Coronary Artery Disease

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

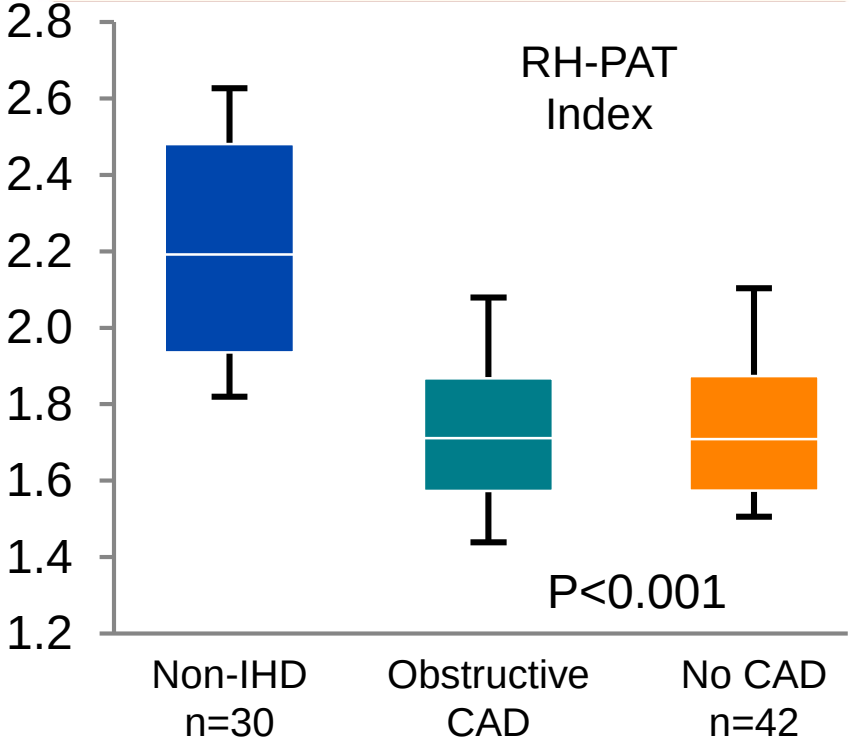
Piero O. Bonetti, MD,* Geralyn M. Pumper, RN,* Stuart T. Higano, MD, FACC,*
David R. Holmes, JR, MD, FACC,* Jeffrey T. Kuvin, MD, FACC,† Amir Lerman, MD, FACC*
Rochester, Minnesota; and Boston, Massachusetts



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.

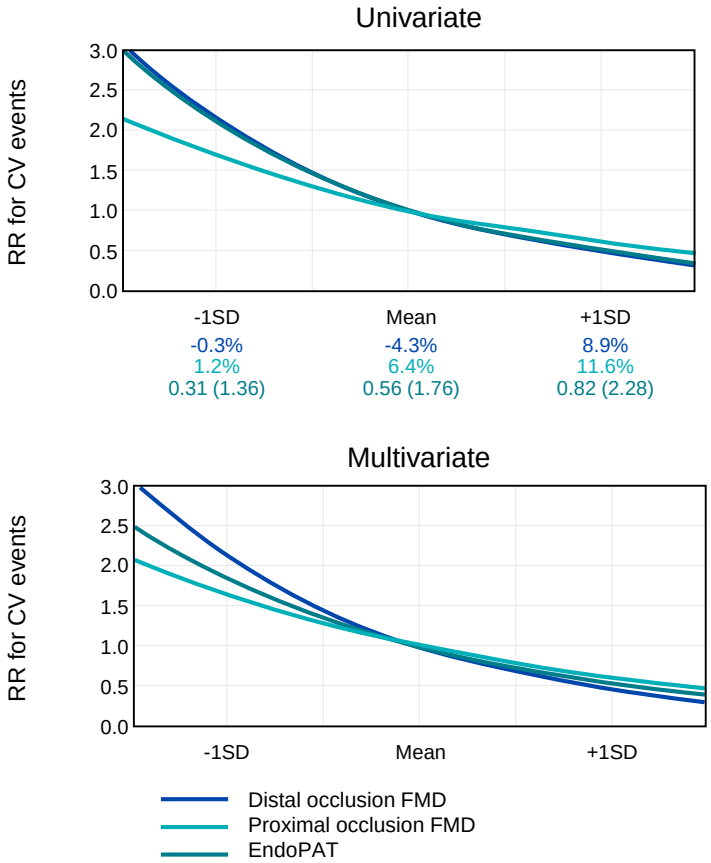
Methods and Results—Databases of MEDLINE, EMBASE, and the Cochrane Library were systematically searched. Clinical studies reporting the predictive value of FMD or RH-PAT for cardiovascular events were identified. Two authors selected studies and extracted data independently. Pooled effects were calculated 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?

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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

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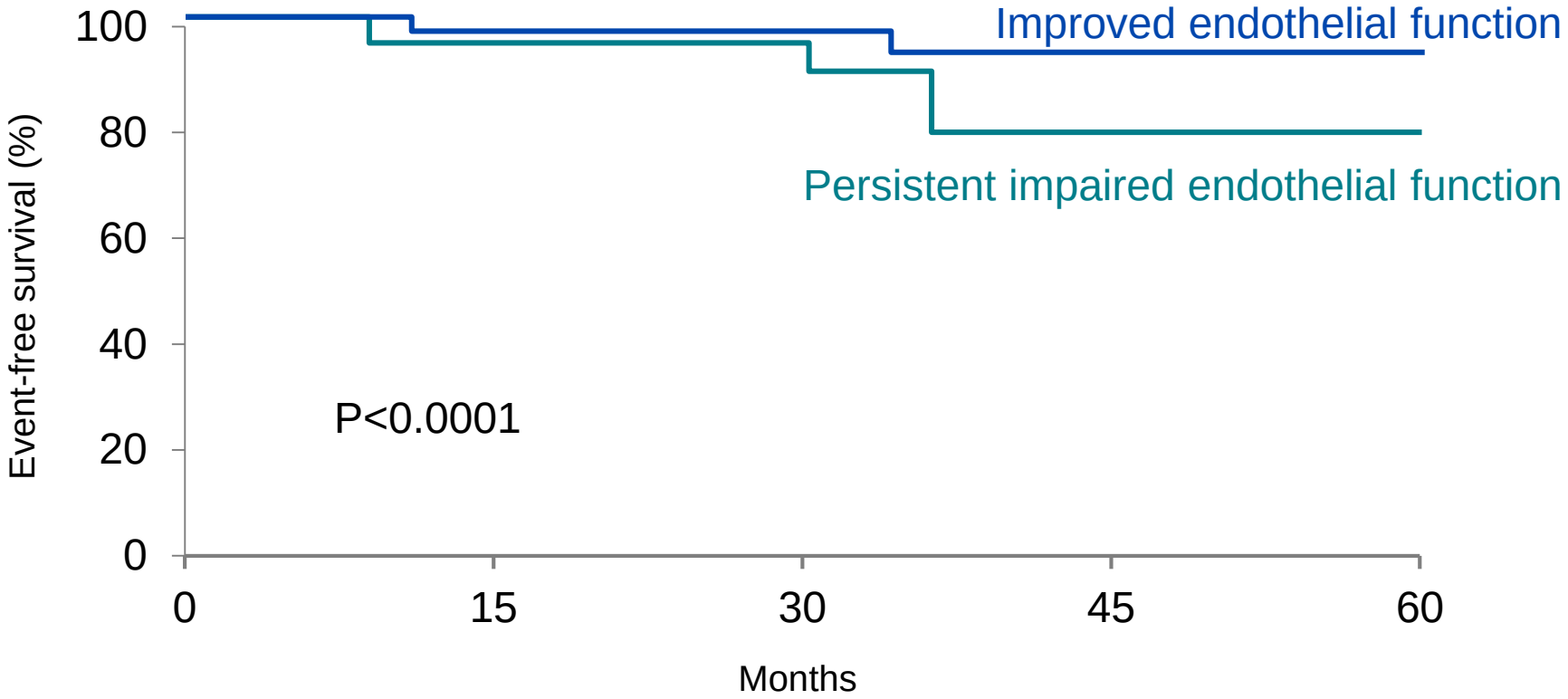
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.08.074

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

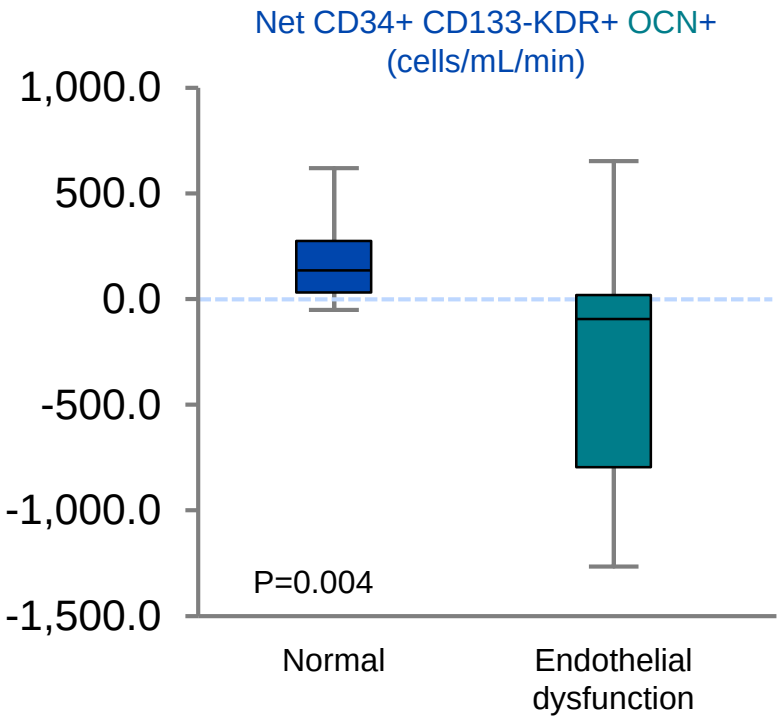
Yamanashi, Japan

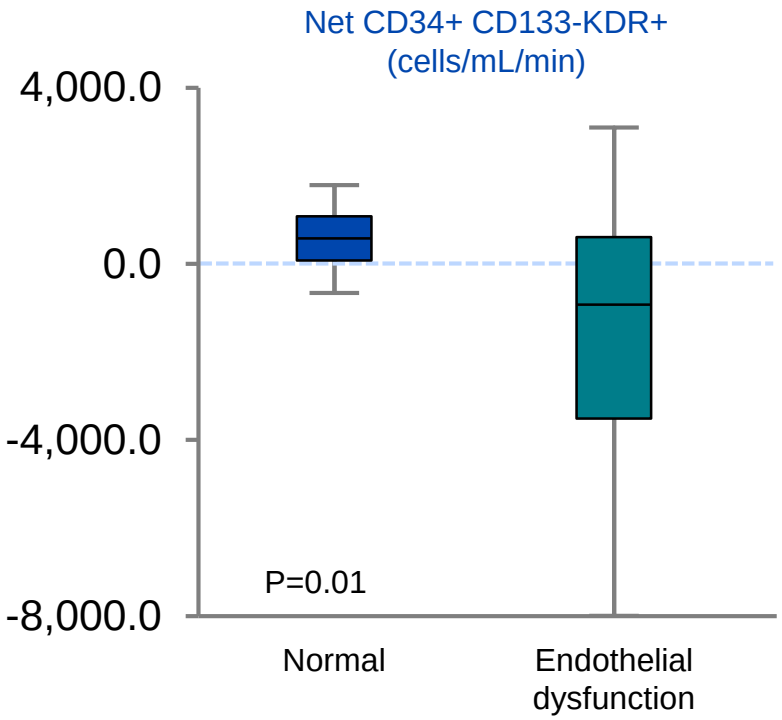
Event-Free Rate According to Persistent Endothelial Dysfunction in Patients With Mild CAD



Modena et al: JACC 40, 2002

Osteogenic EPCs are Retained by Myocardium in Early Atherosclerosis





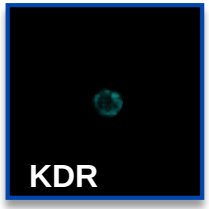
The Retention of OCN+ Cells is Associated with Coronary Calcification

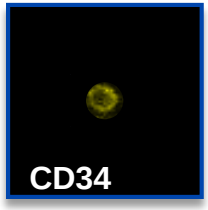
Gössl & Lerman et al: European Heart J, 2010

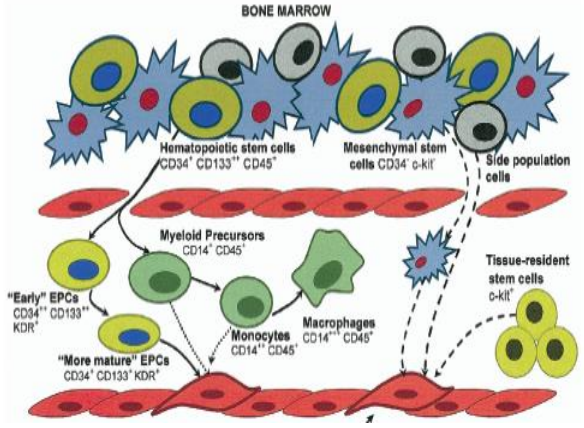
Multicolor Flowcytometry

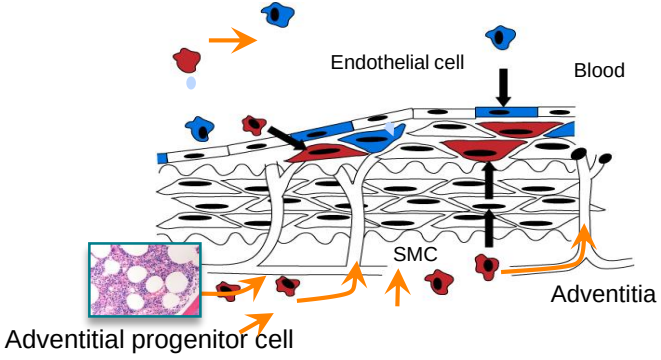
Classification EPCs

- 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

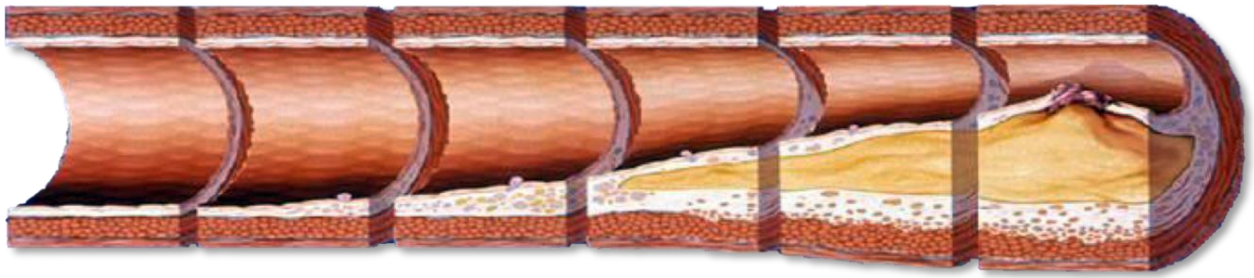
Vascular injury

EPCs

Mental stress

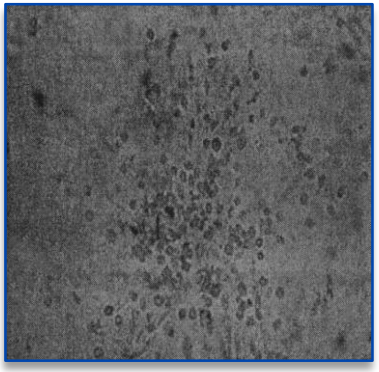
Inflammation & oxidative stress

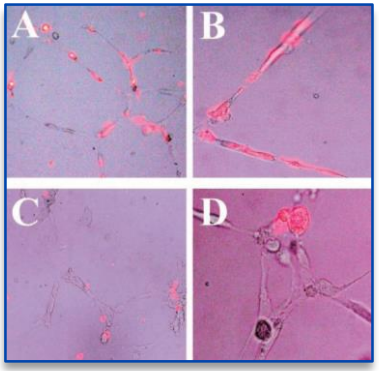
Endothelial dysfunction: The risk of the risk factors



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.

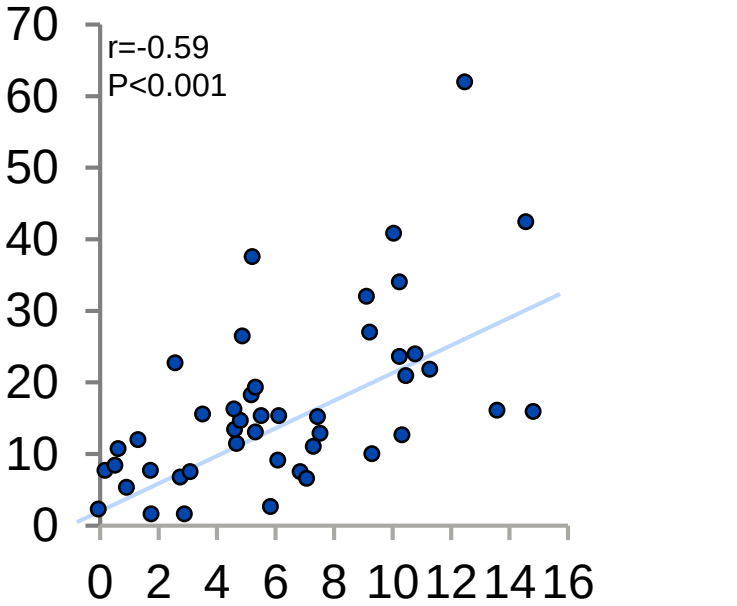
RESULTS
We observed a strong correlation between the number of circulating endothelial progenitor cells and the subjects' combined Framingham risk factor score (r=−0.47, P=0.001). Measurement of flow-mediated brachial-artery reactivity also revealed a significant relation between endothelial function 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 (%)

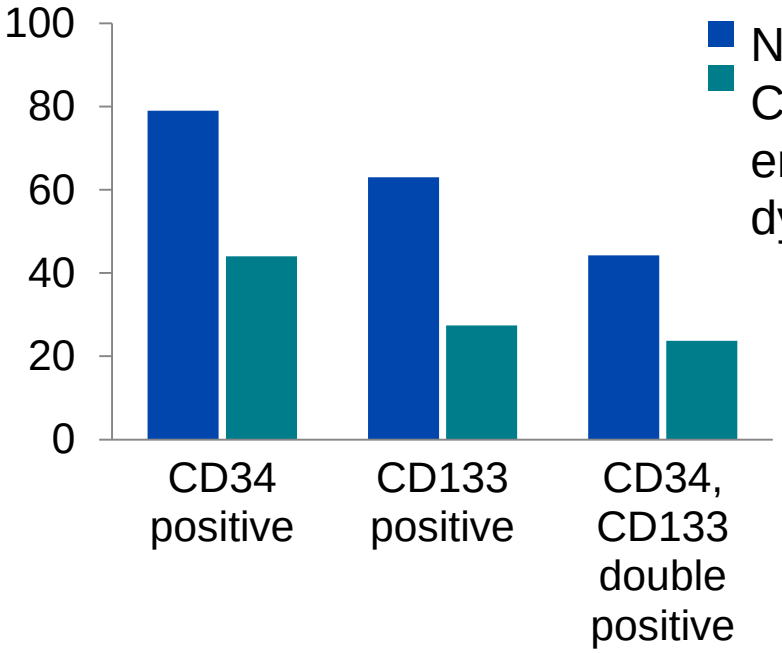
Hill et al: NEJM 348(7):597, 2003

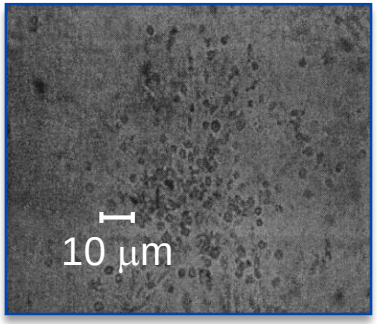
CLINICAL RESEARCH

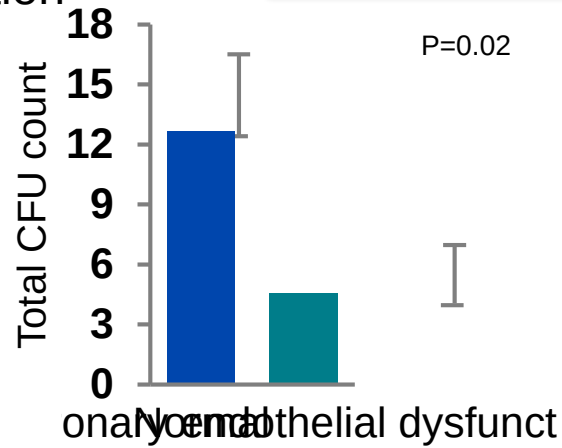
www.nature.com/clinicalpractice/cardio

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

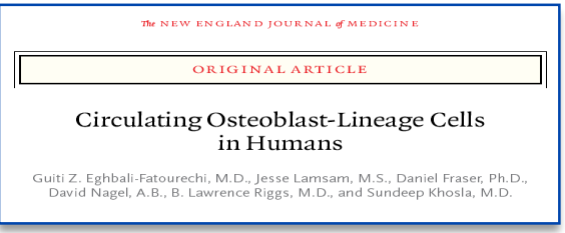
Barry A Boilson,[1] Thomas J Kiernan,[1] Adriana Harbuzariu,[1] Rebecca E Nelson,[1] Amir Lerman[1] and Robert D Simari[1]*







Boilson &, Lerman A: Nat Cardiovasc Med, 2009

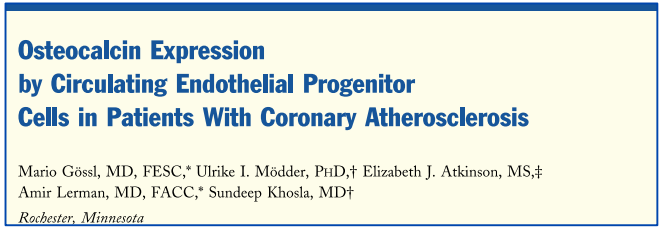


The NEW ENGLAND JOURNAL of MEDICINE

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

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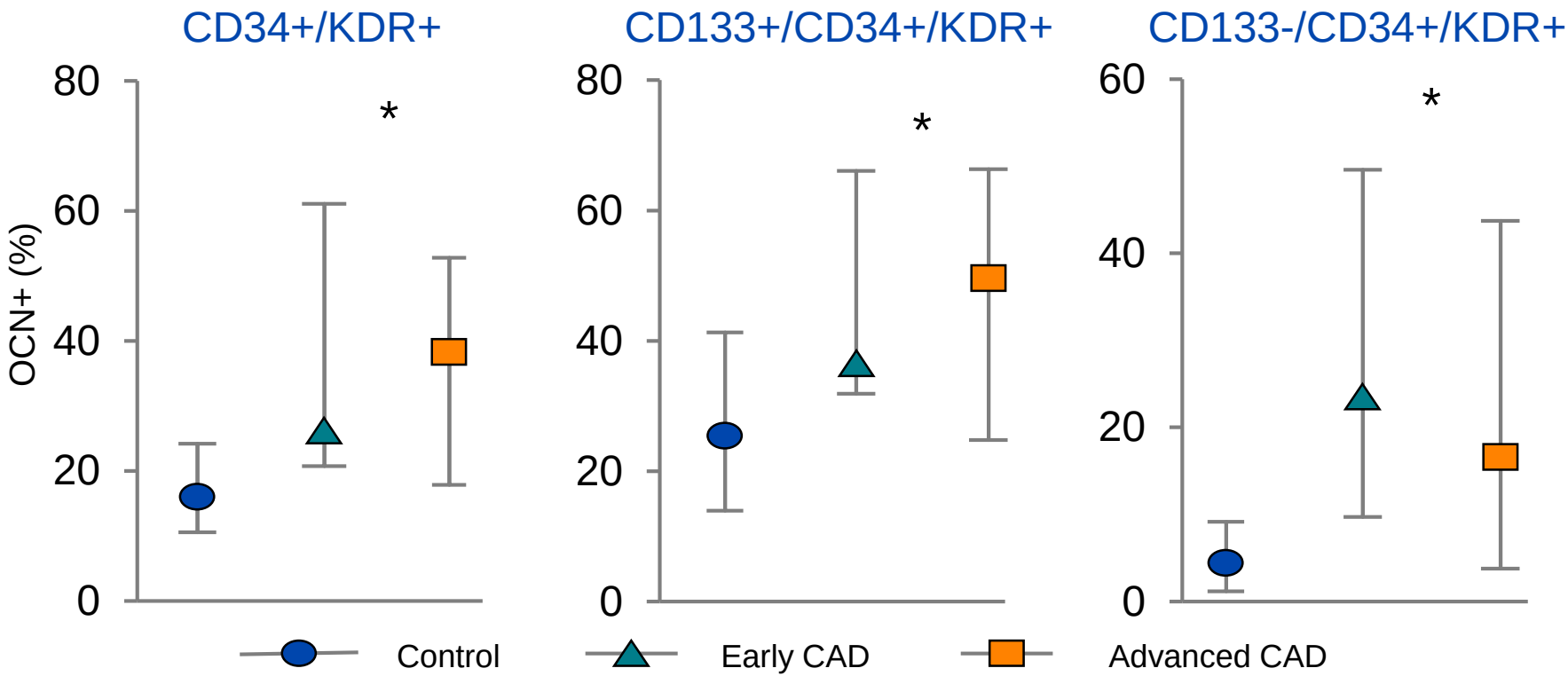
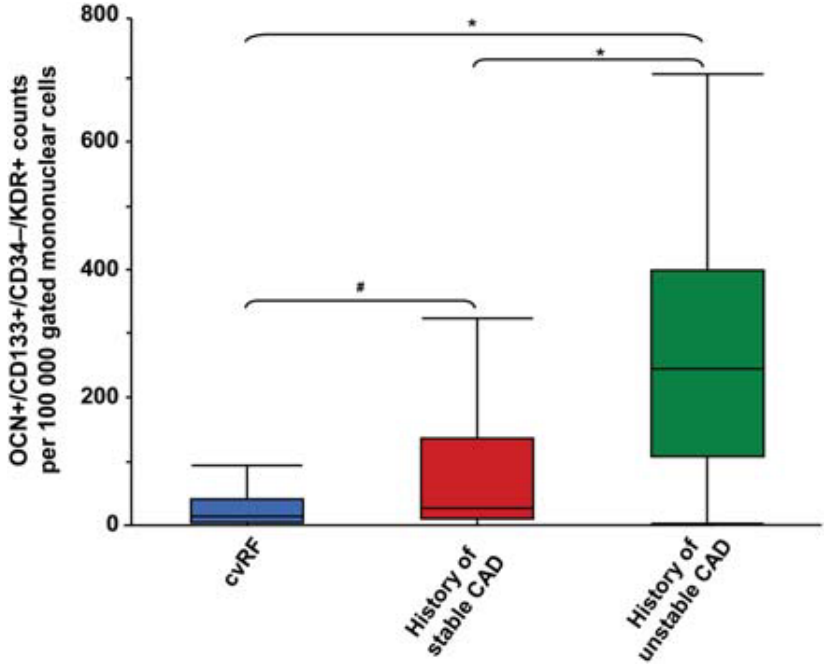


Gössl & Lerman: JACC 52:1314, 2008

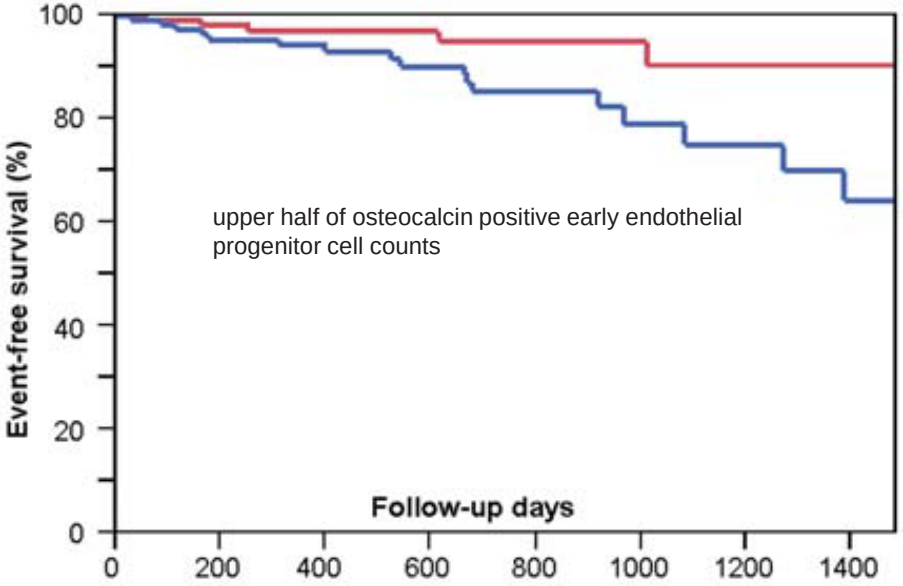
European Heart Journal (2012) 33, 2963–2969
doi:10.1093/eurheartj/ehs234

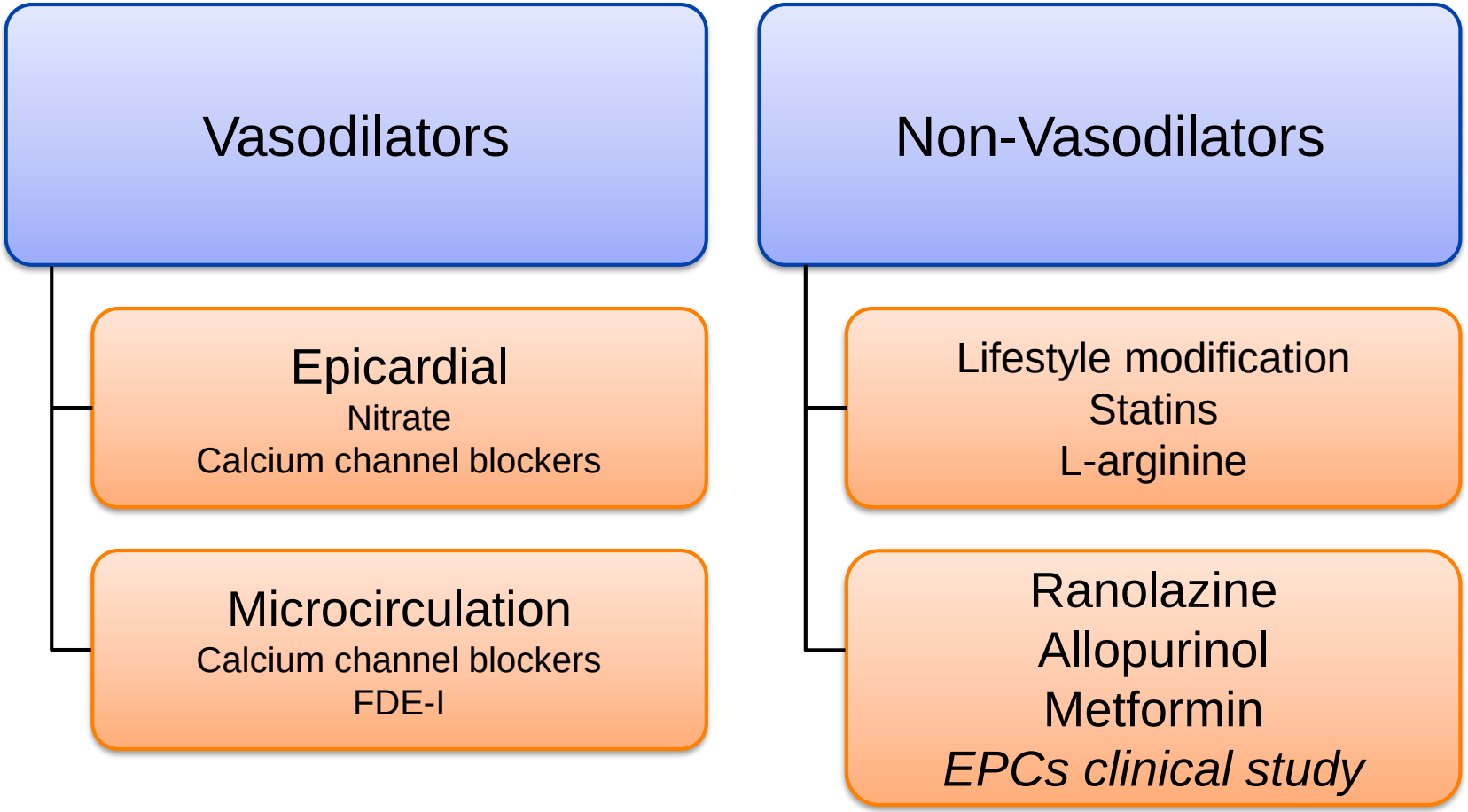
Osteocalcin positive CD1331 /CD342 /KDR1 progenitor cells as an independent marker for unstable atherosclerosis

Osteocalcin positive ‘early’ endothelial progenitor cells.



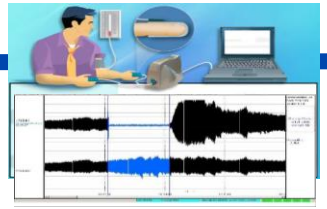
Event-free survival according to the level of osteocalcin positive ‘early’ endothelial progenitor cells.




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

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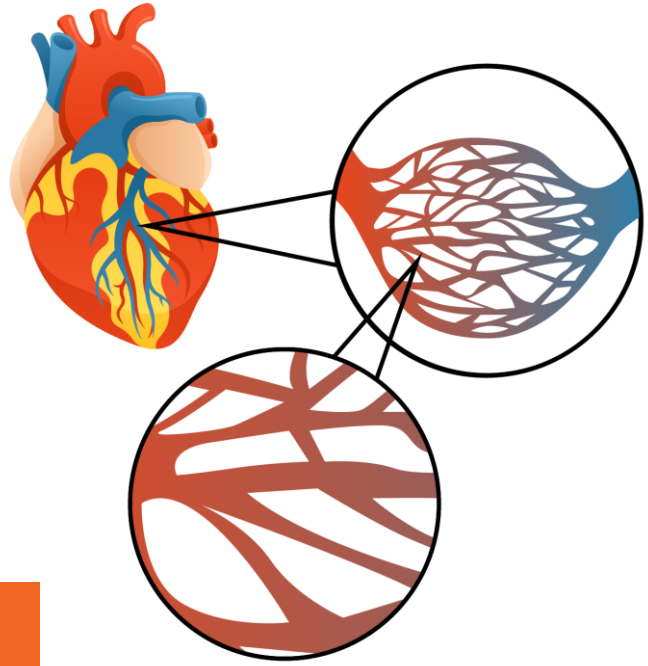
Pioneering Advancements in Cell Therapies



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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

Disclosures

- Baxter Healthcare funded the studies described
- Baxter Healthcare (now Shire Plc) provided research funding to DCRI for ACT-34, RENEW, and partly funded a combined patient level analysis
- Caladrius Biosciences provided research funding to DCRI for additional analyses

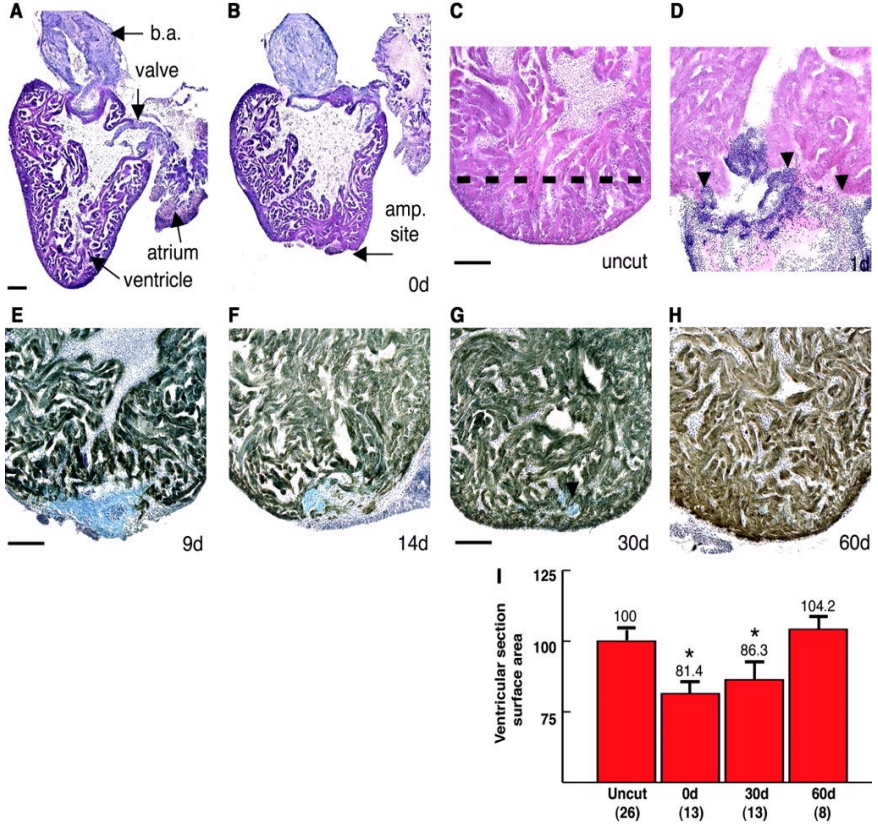
Where are we?

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



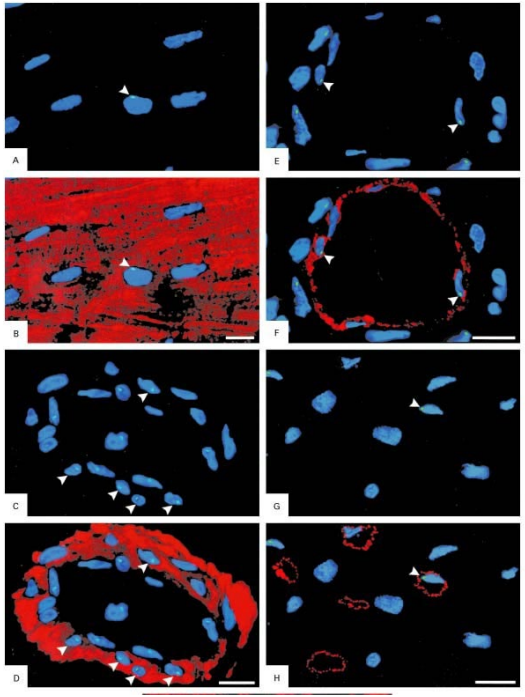
-- Ross KD et al, Science, 2002

Myocardial Repair

The Y Chromosome in Transplanted Hearts:

Myocytes

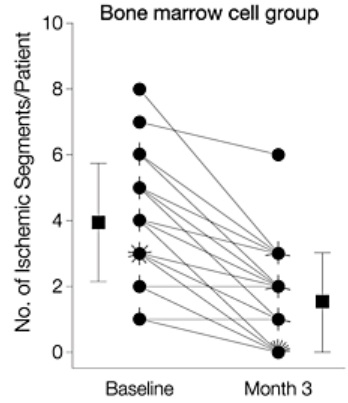
SMCs

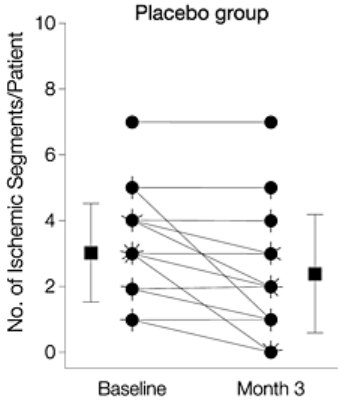


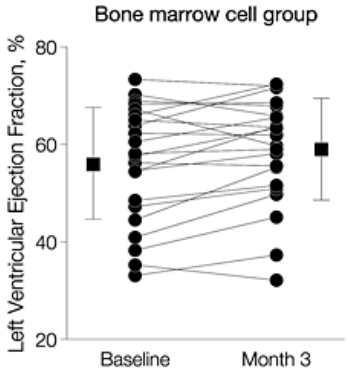
Endothelial Cells

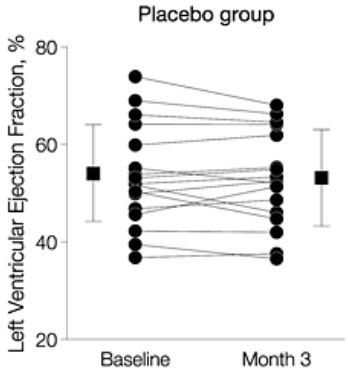
Capillary Endothelium

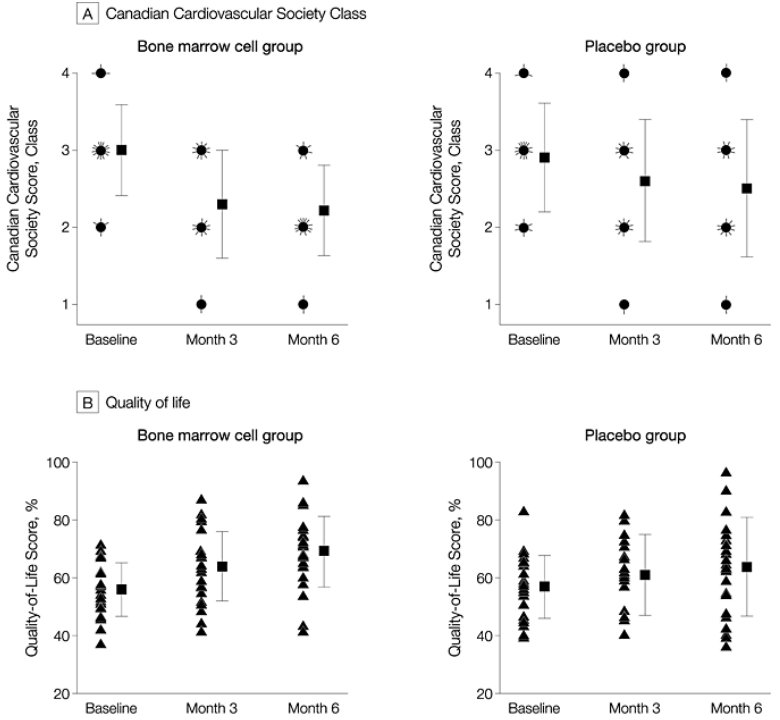
Quaini, F. et al. N Engl J Med 2002;346:5-15







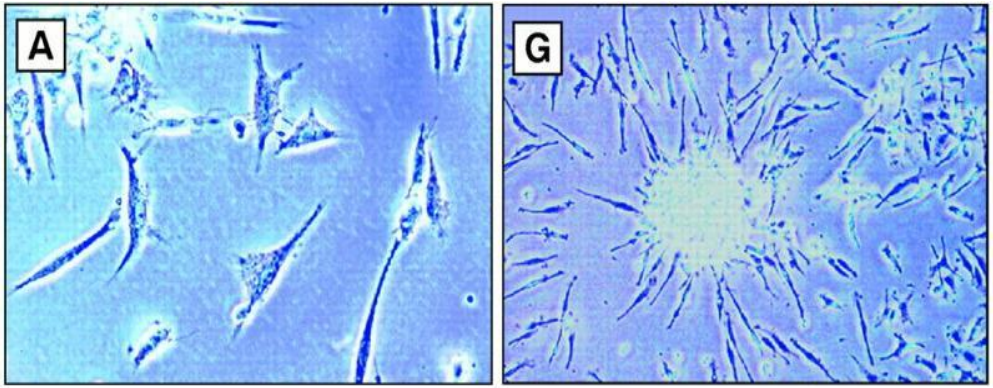




van Ramshorst, J. et al. JAMA 2009;301:1997-2004

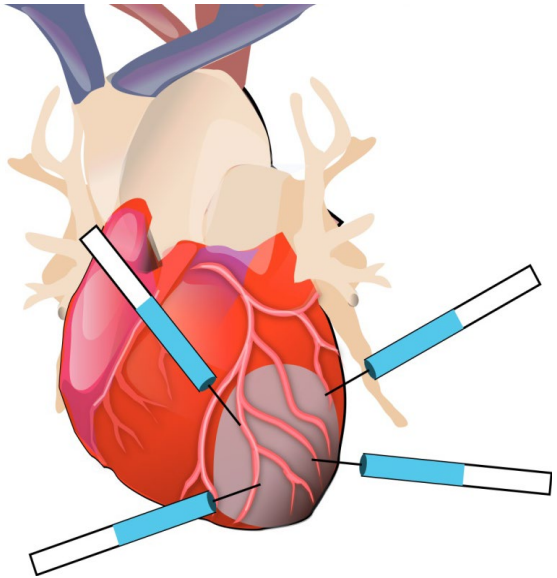
Original Description of Endothelial Progenitor Cells (EPC) in Adults

- 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

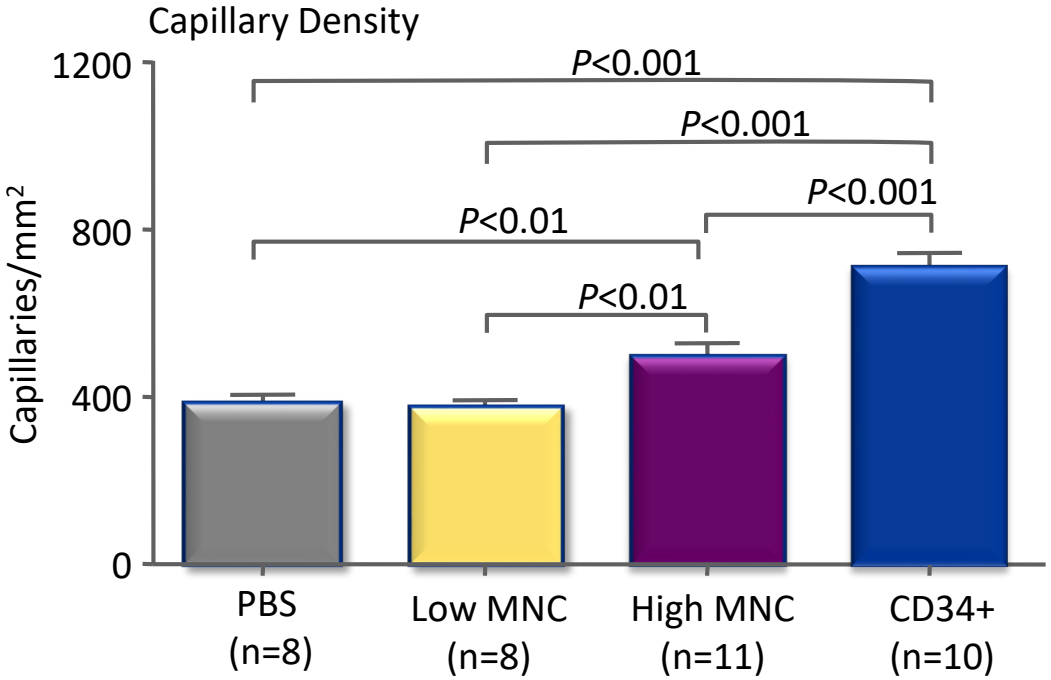
1. **PBS**: 100 µl
2. **Low MNC**: 5×10^5 cells/rat kg
3. **High MNC**: total MNCs containing CD34+ dose
4. **CD34+**: 5×10^5 cells/rat kg

- 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



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

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

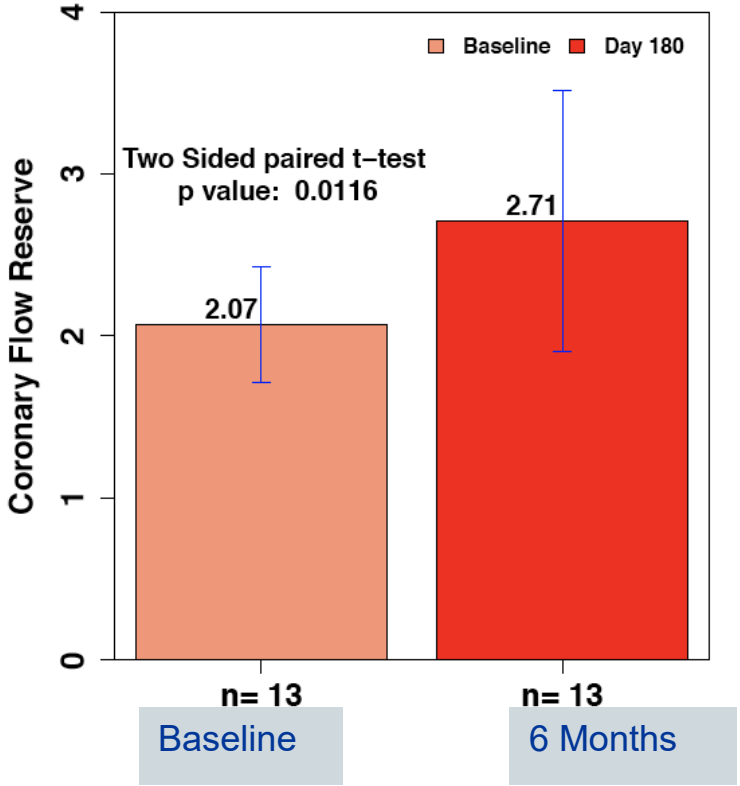
	Unadjusted		Adjusted*	
	Estimate	p-value	Estimate	p-value
3-month				
Usual Gait Speed	0.073	0.002	0.065	0.003
Rapid Gait Speed	0.101	0.006	0.086	0.014
6MWD	74.4	0.027	59.6	0.036
12-month				
Usual Gait Speed	0.057	0.032	0.041	0.087
Rapid Gait Speed	0.141	0.001	0.126	0.003
6MWD	100.3	0.023	701	0.028
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

RVX000222

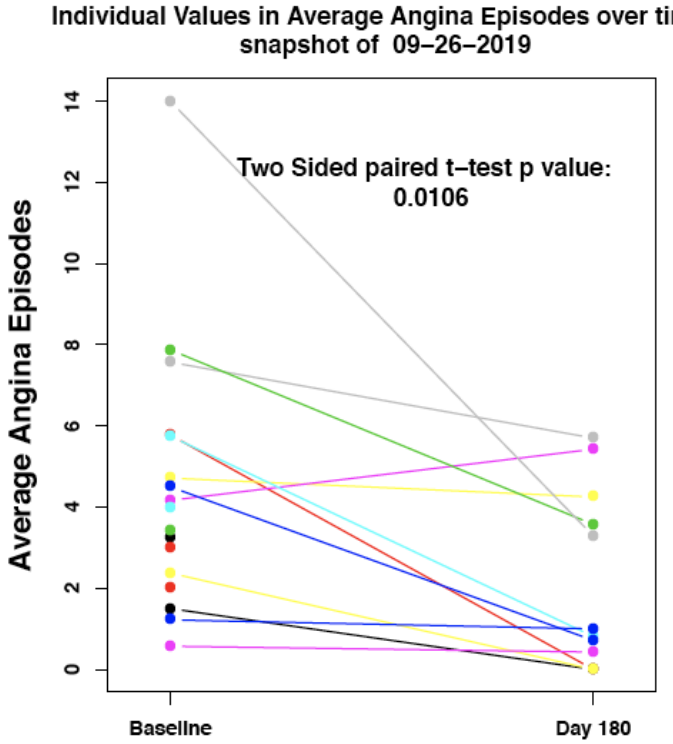
*Adjusted for age, arm, BMI, 8 comorbid conditions, and IL-6 level.

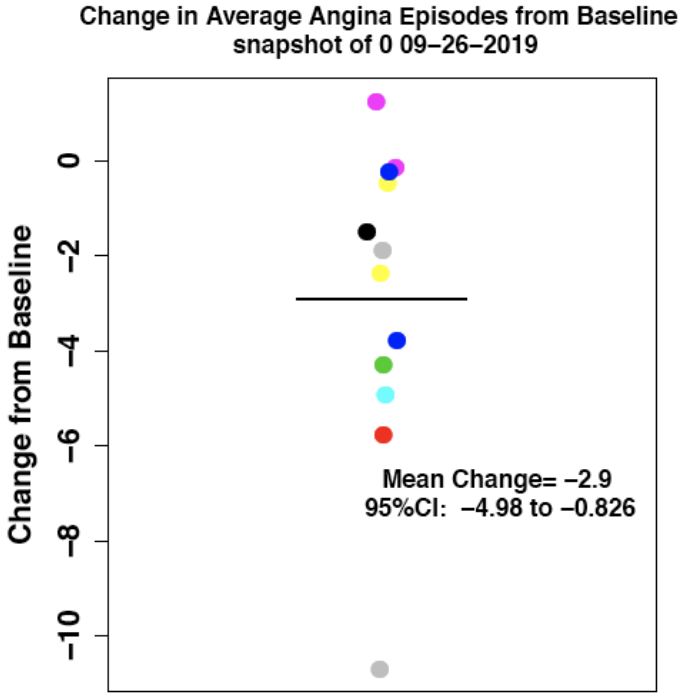
Single Administration of CD34 Cells Significantly Increases CFR in CMD

- *Patient follow-up to date (n=13)*
- *Coronary flow reserve (CFR)*
  - Ratio of maximal to resting coronary blood flow
- *Increased CFR documents improved microvascular function*
- *Presentation at AHA meeting 2019*



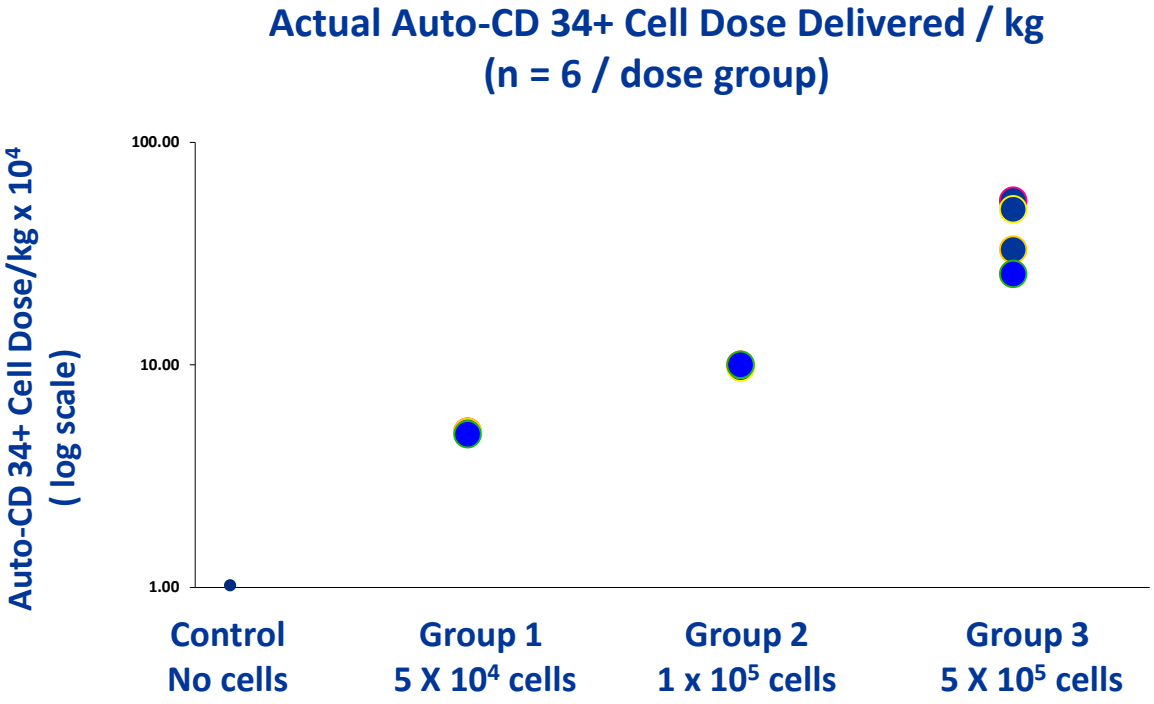
Single Administration of CD34 Cells Significantly Reduces Angina Frequency in CMD





	Study 11196	Study 24779/34976	Study 901001
N	24	167	112
$CD34^+$ treated ptns	18	112	57
AF at baseline	-	≧7 episodes/wk	≧7 episodes/wk
Exercise at baseline	1-6 minutes Bruce Protocol	3-10 minutes mod Bruce Protocol	3-10 minutes mod Bruce Protocol
Cell mobilization	G-CSF 5 mcg/kg/d x 5 d	G-CSF 5 mcg/kg/d x 5 d	G-CSF 5 mcg/kg/d x 4 d
Cell Harvesting	Apheresis day 5	Apheresis day 5	Apheresis day 5
Cell Isolation	Local	Local	Central
Cell Delivery	IM via NOGA Myostar	IM via NOGA Myostar catheter	IM via NOGA Myostar catheter
Cell Dose	1×10^4, 1×10^5, and 5×10^5 cells/kg	1×10^5, and 5×10^5 cells/kg	1×10^5 cells/kg
Randomization	1:1:1:1 to 3 doses vs. placebo	1:1:1 to 2 doses and placebo	2:1:1 to CD34+ cells vs. placebo vs. open label SOC
Efficacy control	Active (cell mobilization, apheresis, placebo injection)	Active (cell mobilization, apheresis, placebo injection)	Active (cell mobilization, apheresis, placebo injection)
Design	Double blind	Double Blind	Double blind (efficacy) with open label SOC arm
AF assessments	Baseline, 3m, 6 m	Baseline, 3m, 6m, 12 m, 24 m	Baseline, 3m, 6m, 12 m
TET Assessments	Baseline, 3 m	Baseline, 3m, 6m, 12 m	Baseline, 3m, 6m, 12 m
Clinical FU	6 m	12 m (24779), 24 m (34976)	24 m
Clinical FU	Investigator reported	CEC adjudicated	CEC adjudicated

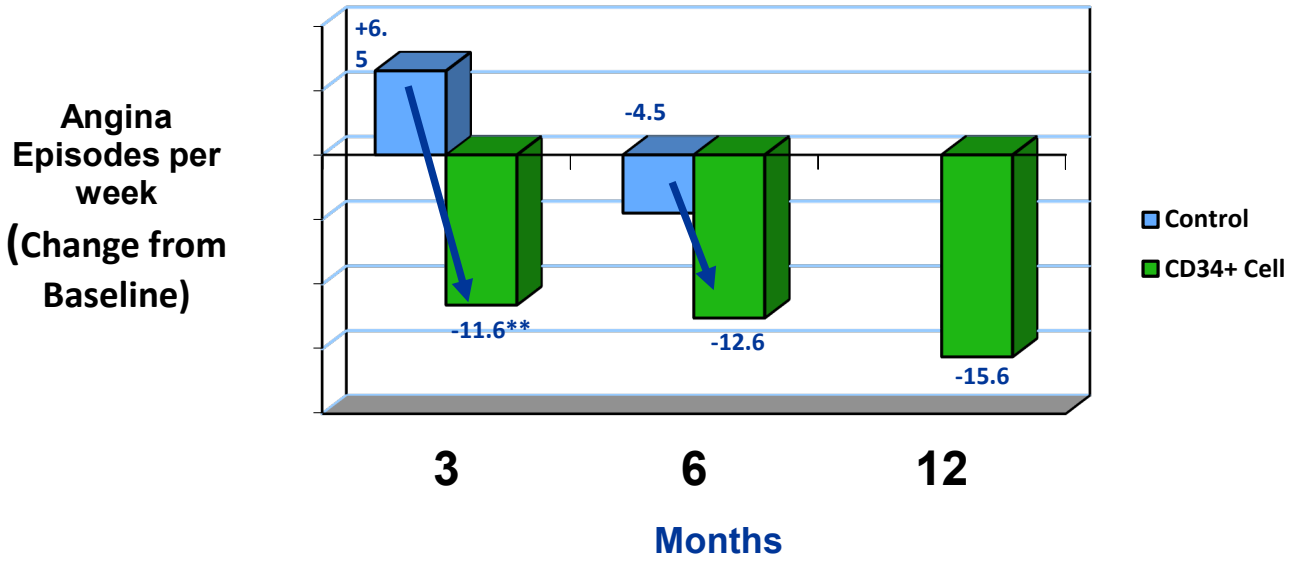
Phase I: The Dose Range is Feasible



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

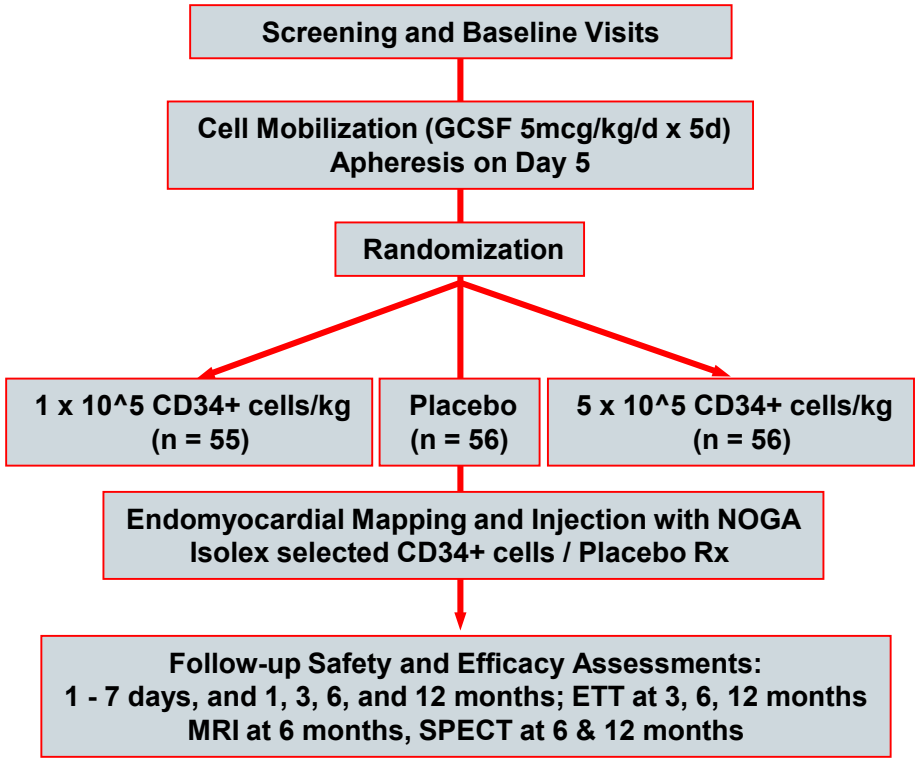
**p=0.053 ANOVA between treatment groups

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

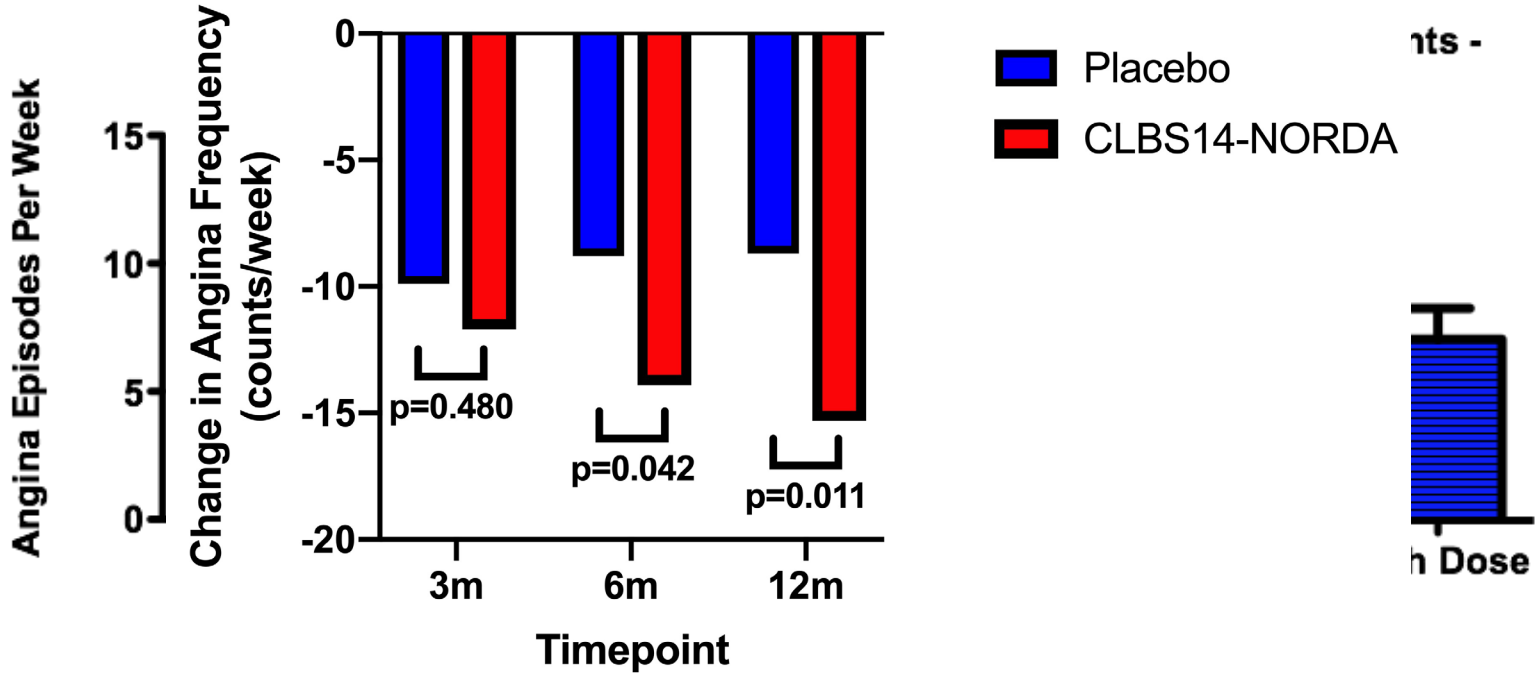
Randomized, Double-Blind, Placebo Controlled Trial of Autologous CD34+ Cell Therapy for Refractory Myocardial Ischemia

Subject population (n=167)

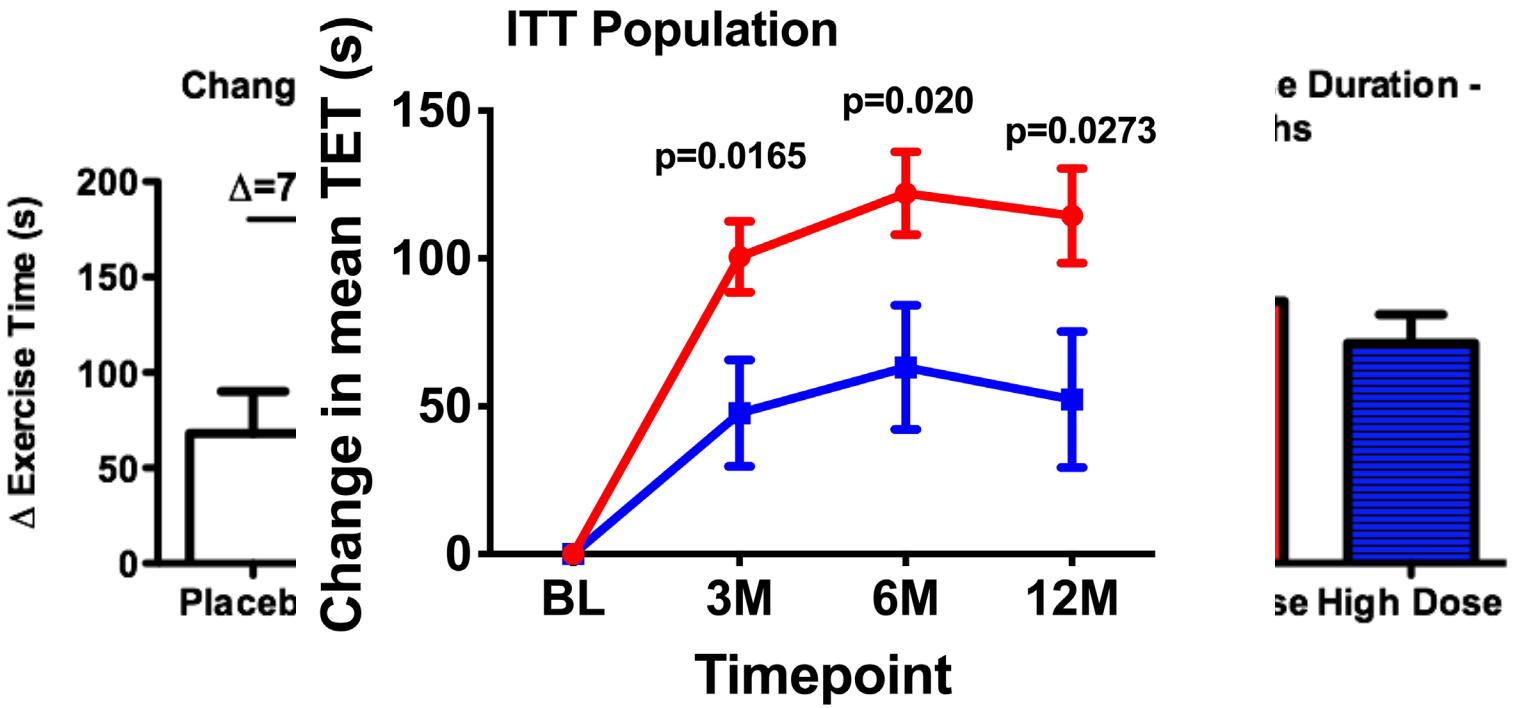
- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia on SPECT
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline



Change in Angina Counts



Change in Exercise Capacity

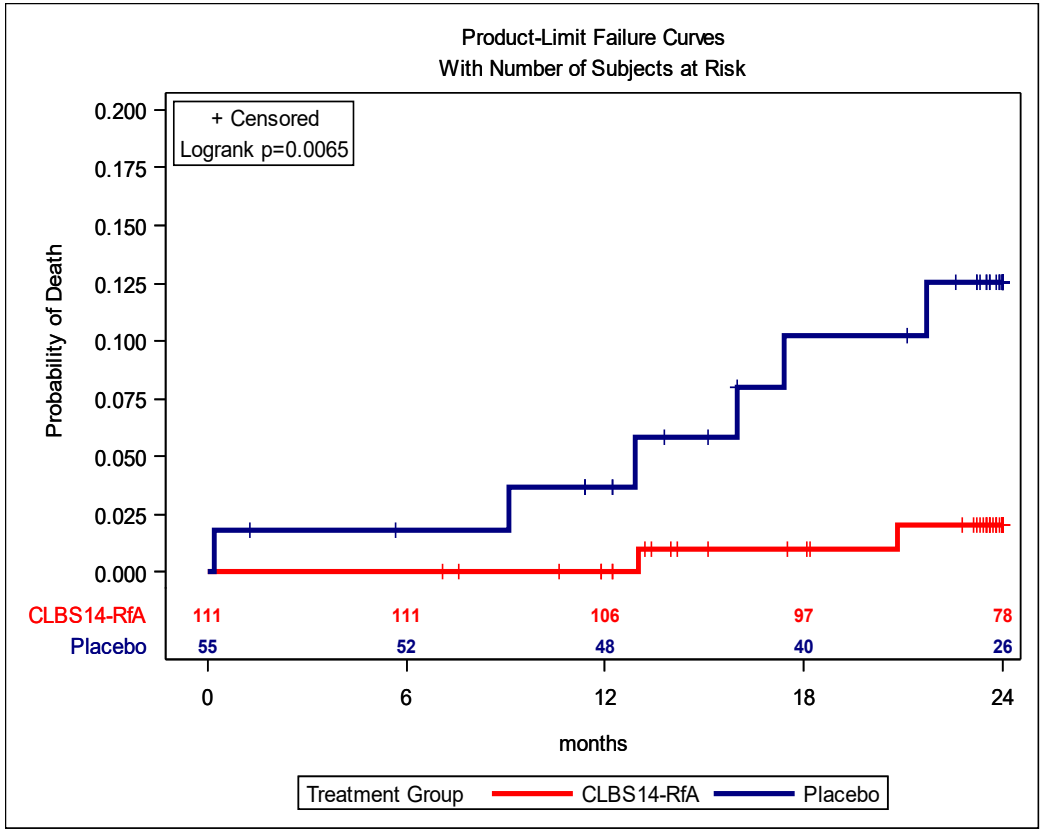


Major Adverse Cardiac Events (12 Months)

	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

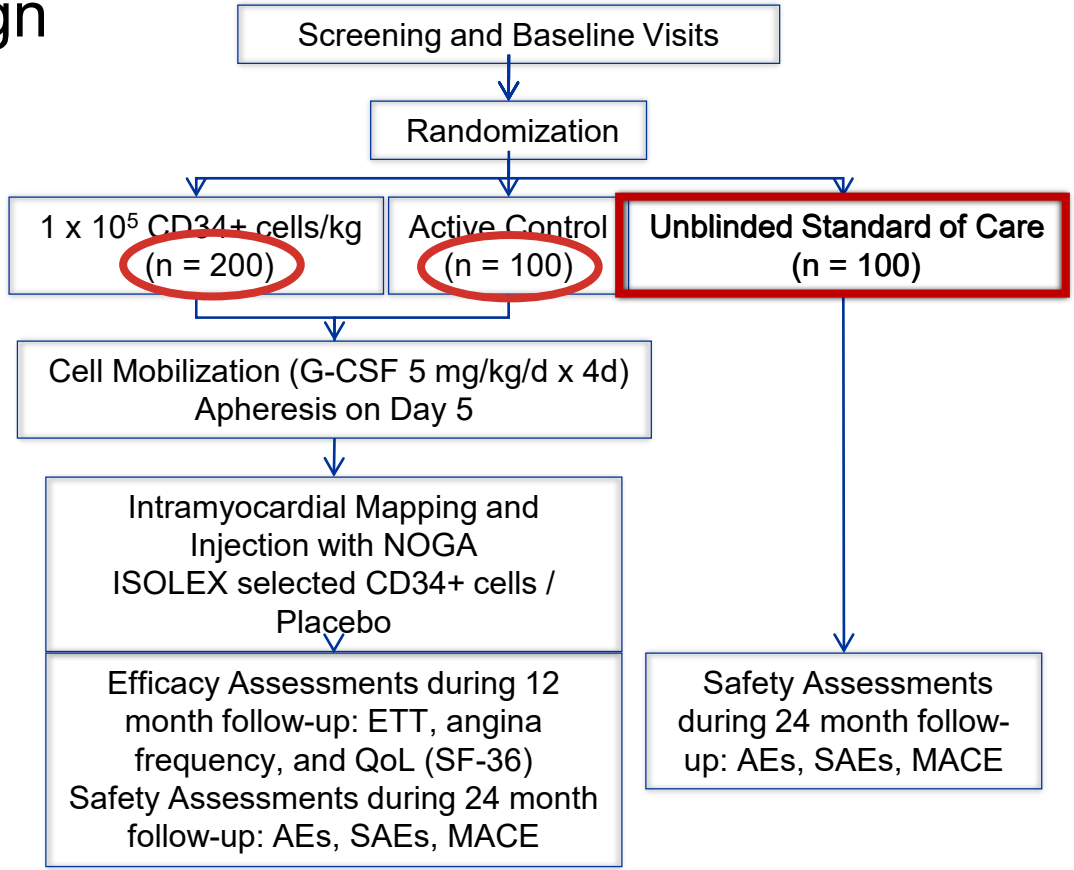


RENEW Study Design

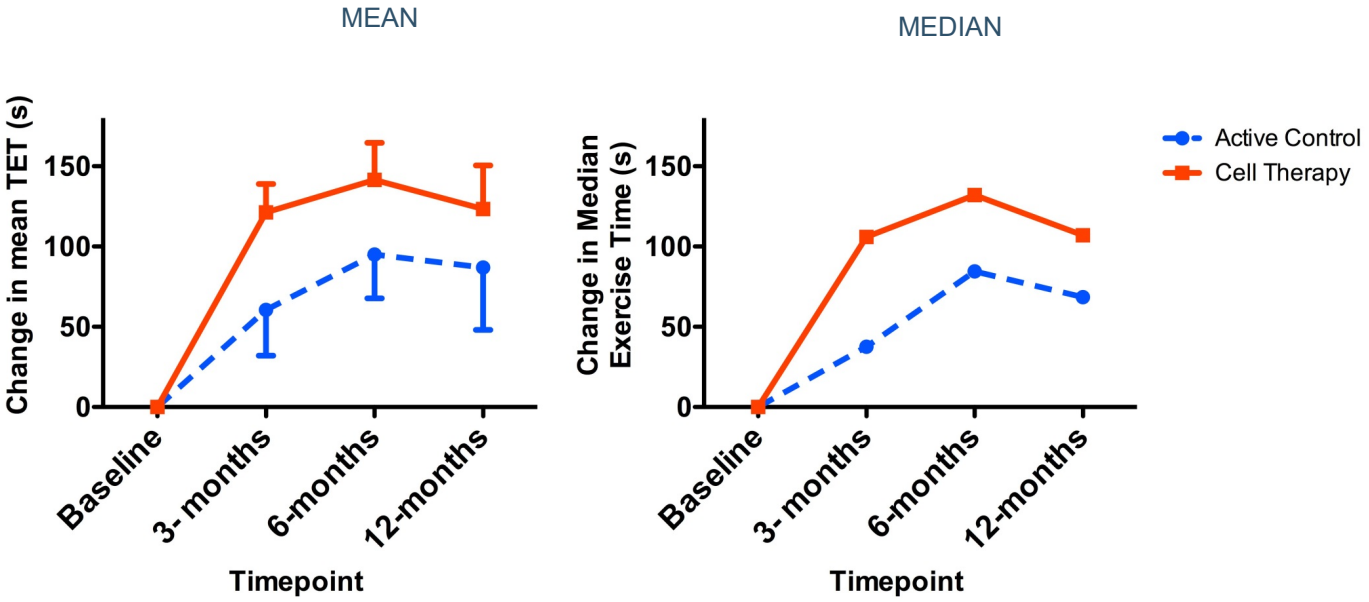
Inclusion Criteria:
- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia w/stress
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline
- ETT reproducible <20%
- 7 angina/wk

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

Pre-Qual Committee Central Review

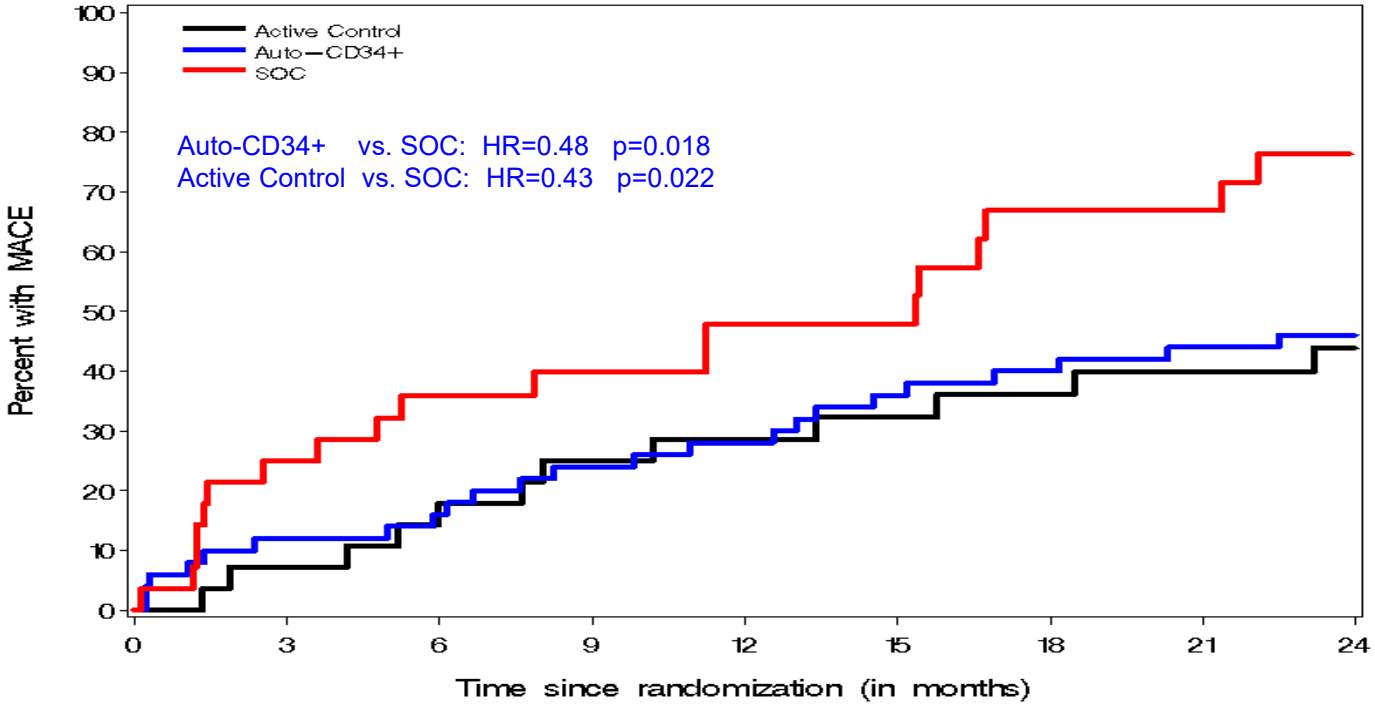


RENEW: Primary Endpoint as Treated



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

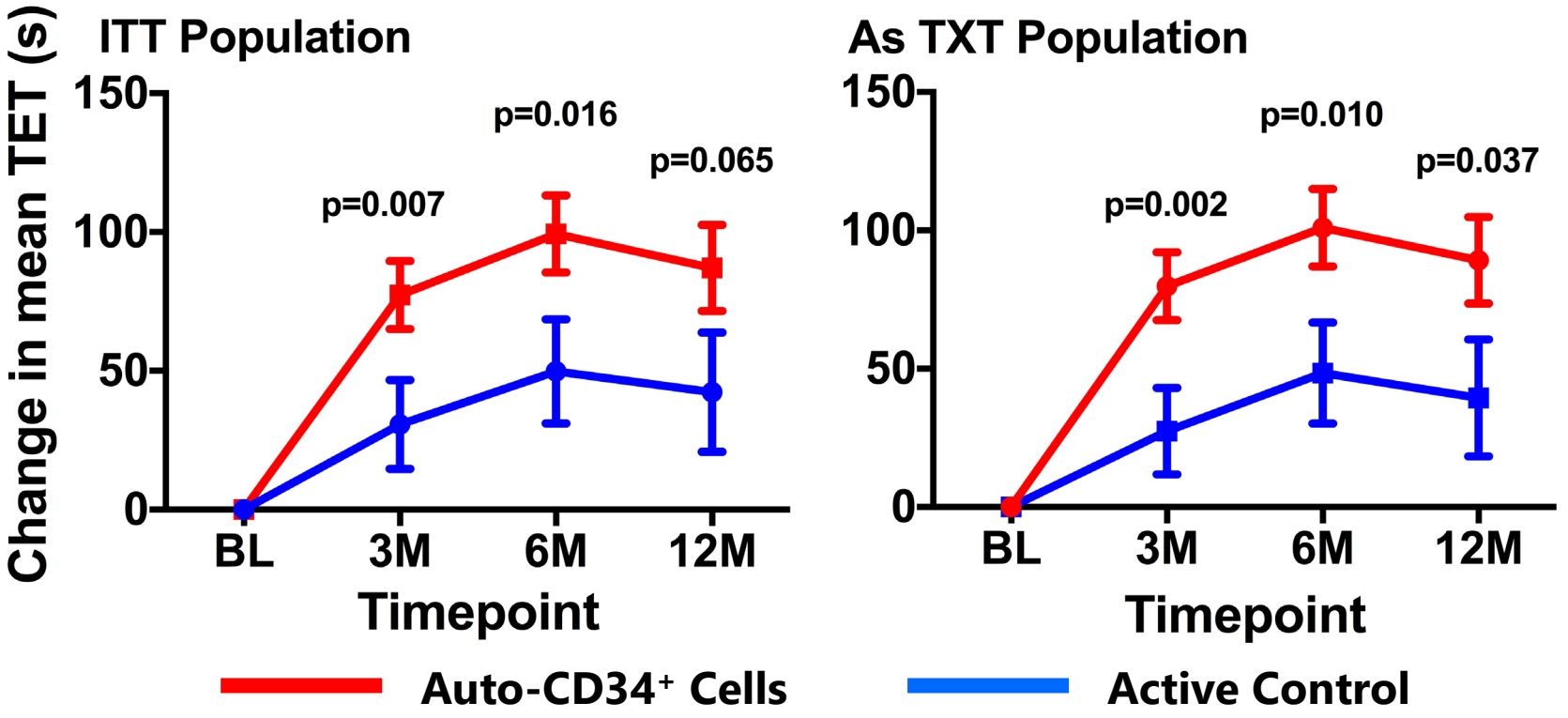
Baseline Characteristics

	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%)

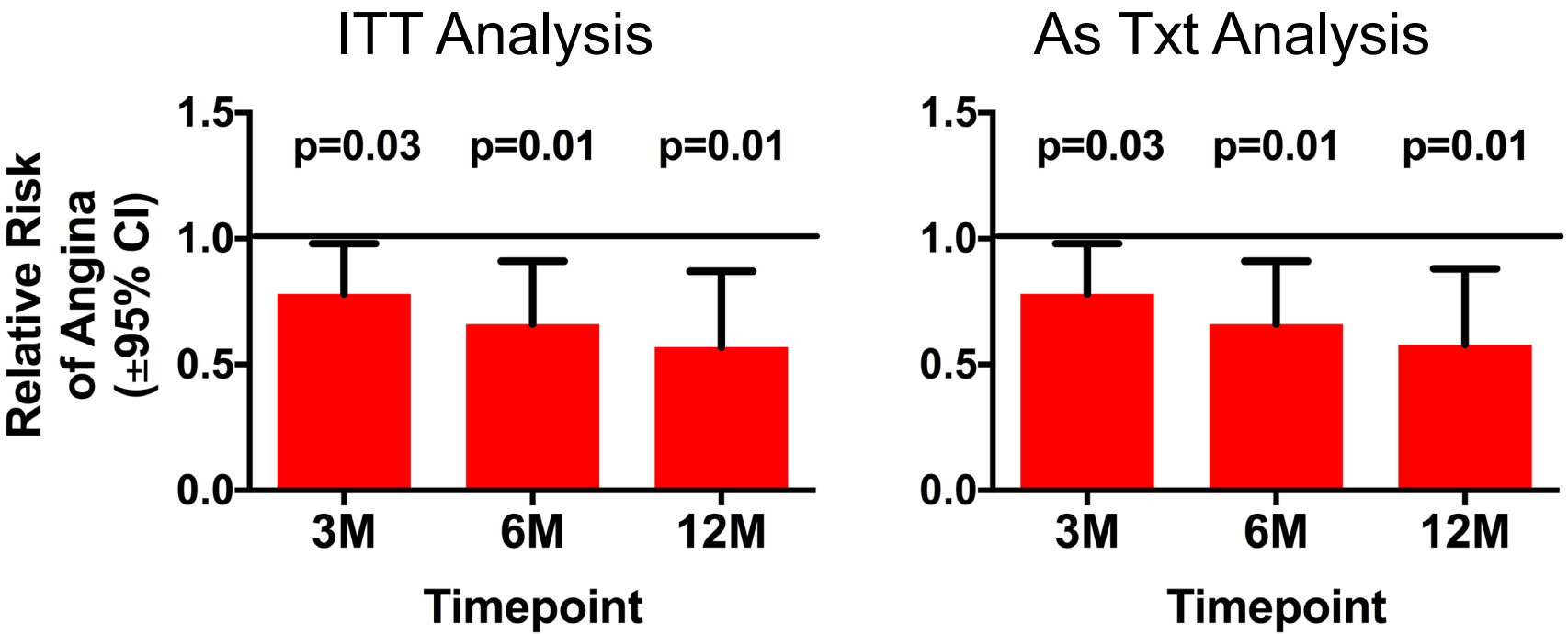
Medication use

	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

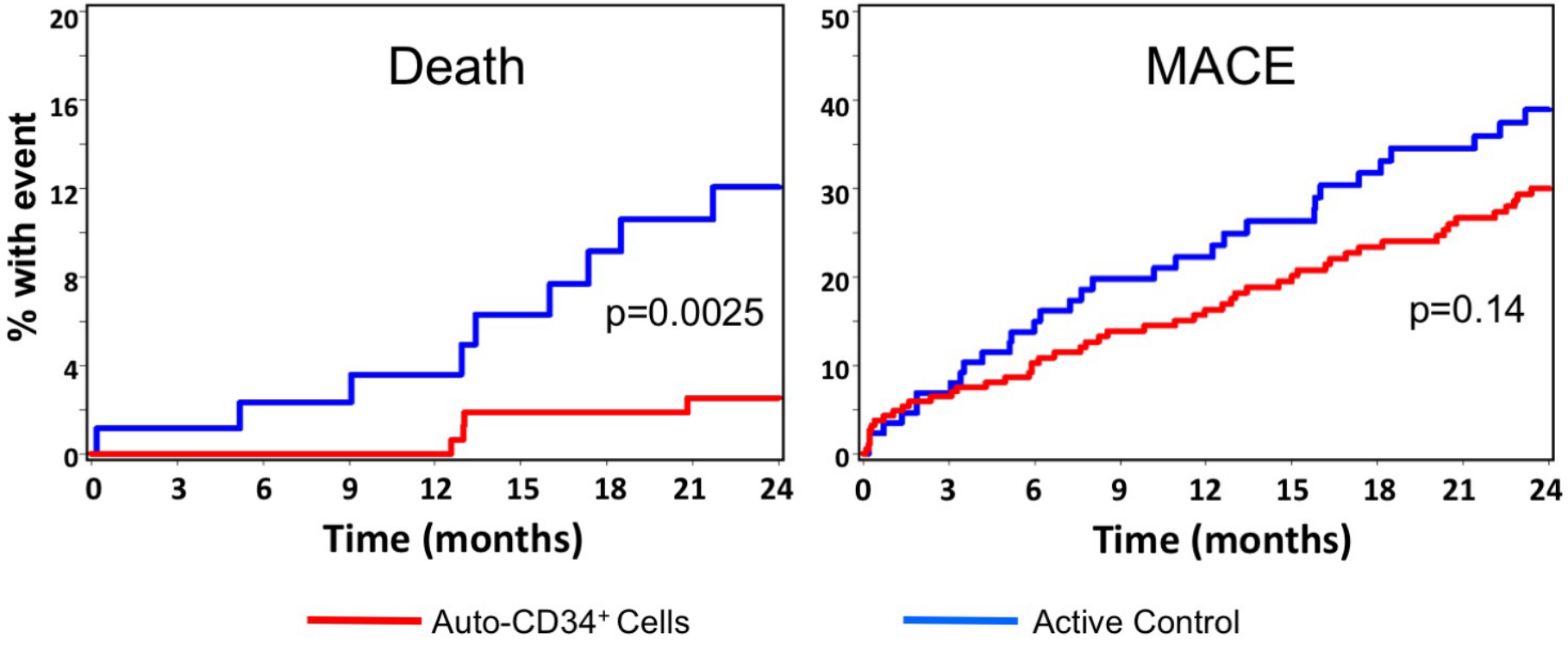


Relative Risk of Angina*

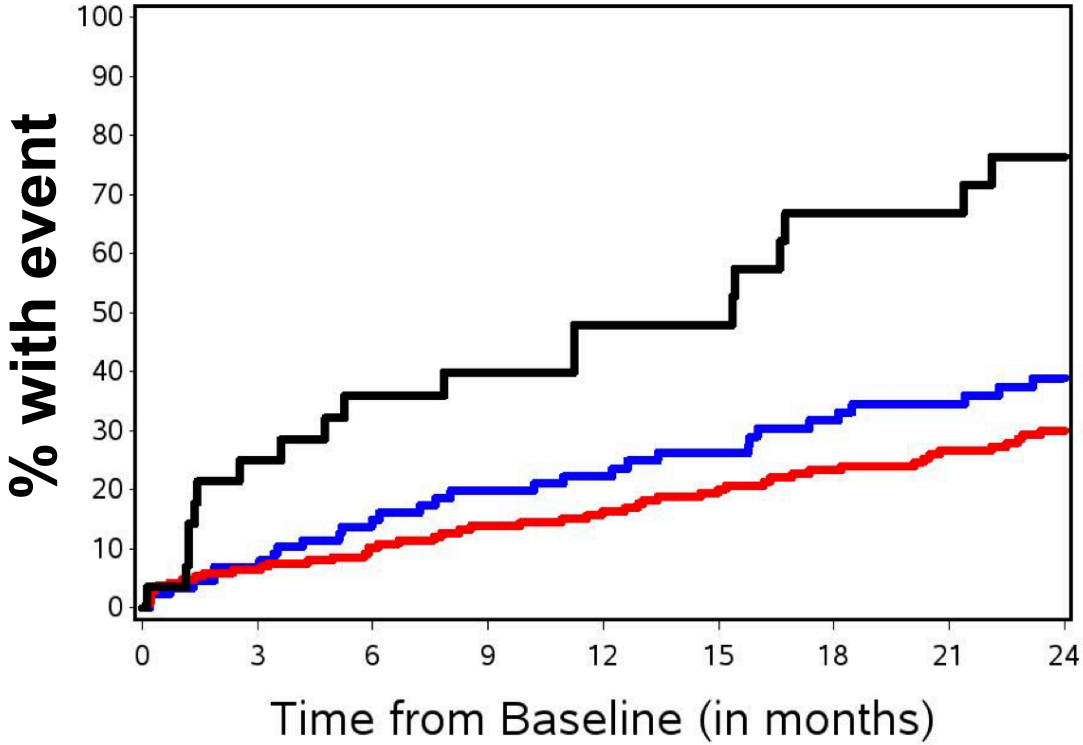


*Prespecified Poisson Distribution

Kaplan-Meier Analysis

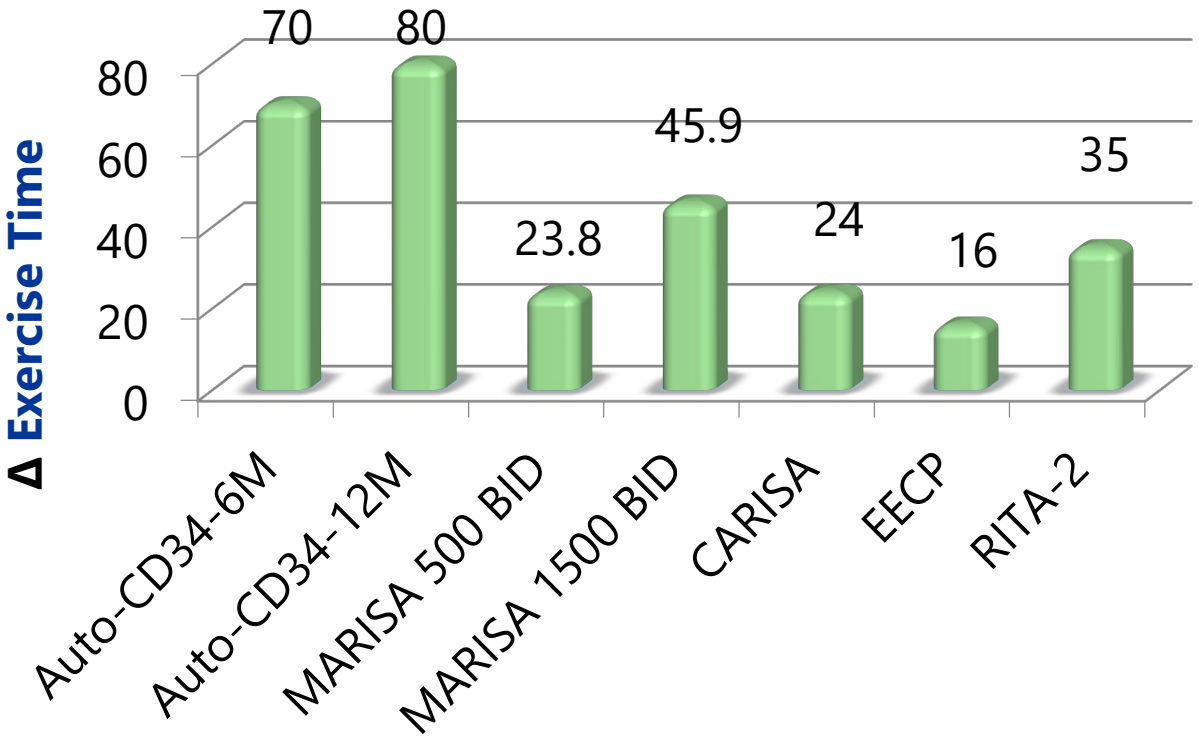


Kaplan-Meier Analysis

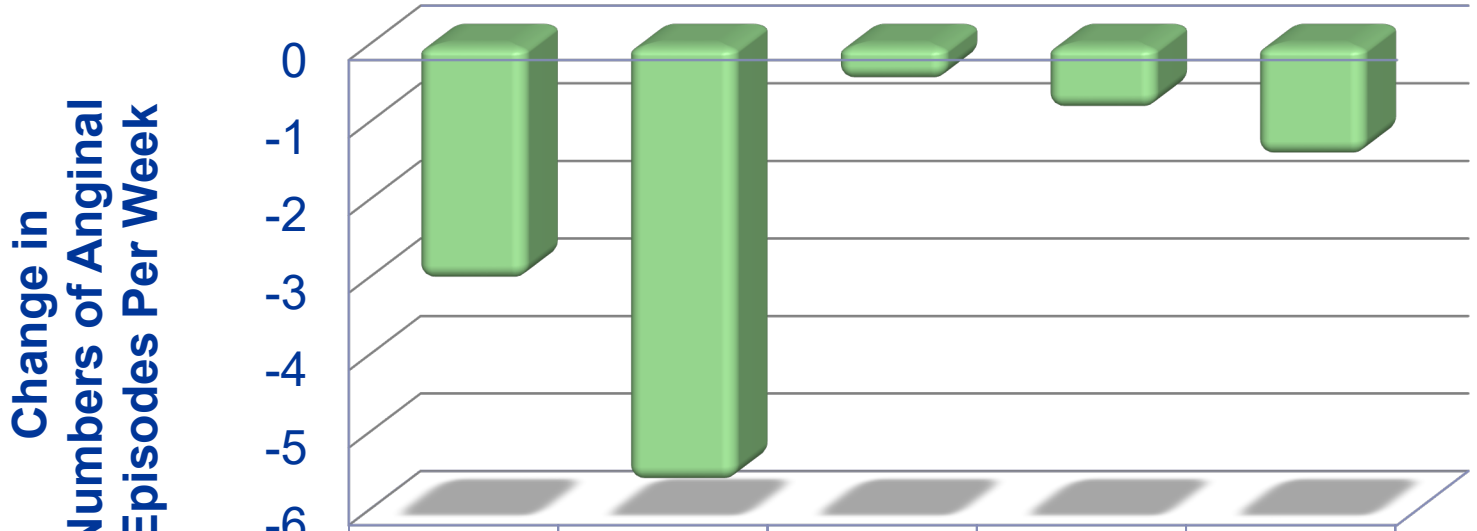


Auto-CD34⁺ Cells **Active Control** **Open Label SOC**

Efficacy Comparison: Change in ETT



Efficacy Comparison: Change in Angina Frequency



	CD34-6 Month	CD34-12 Month	ERICA	CARISA	EECP
			Ranolazine		
Angina/week	-3	-5.6	-0.43	-0.8	-1.4

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

- 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."

Andreas M. Zeiher, MD
Dept. of Internal Medicine III
University of Frankfurt
Germany

The Future of Cell-Based Therapies of Cardiovascular Diseases

Philadelphia, 11 / 2019

Disclosure information:

t2cure (co-founder, advisor)
Sanofi / Pfizer / Amgen (advisor)
Boehringer / Bayer / Servier /
Novartis / St.Jude / Daichi (Speaker)

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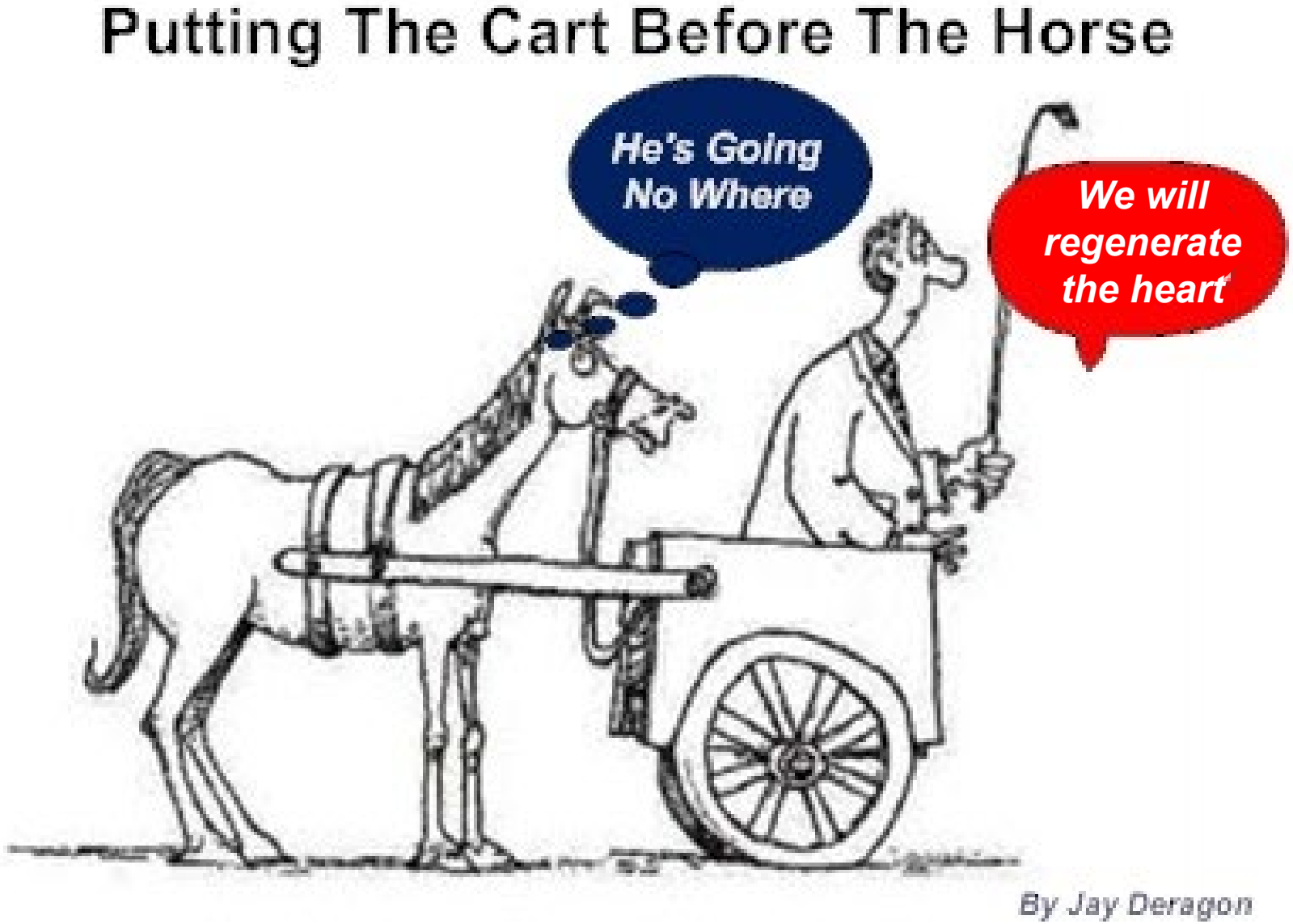
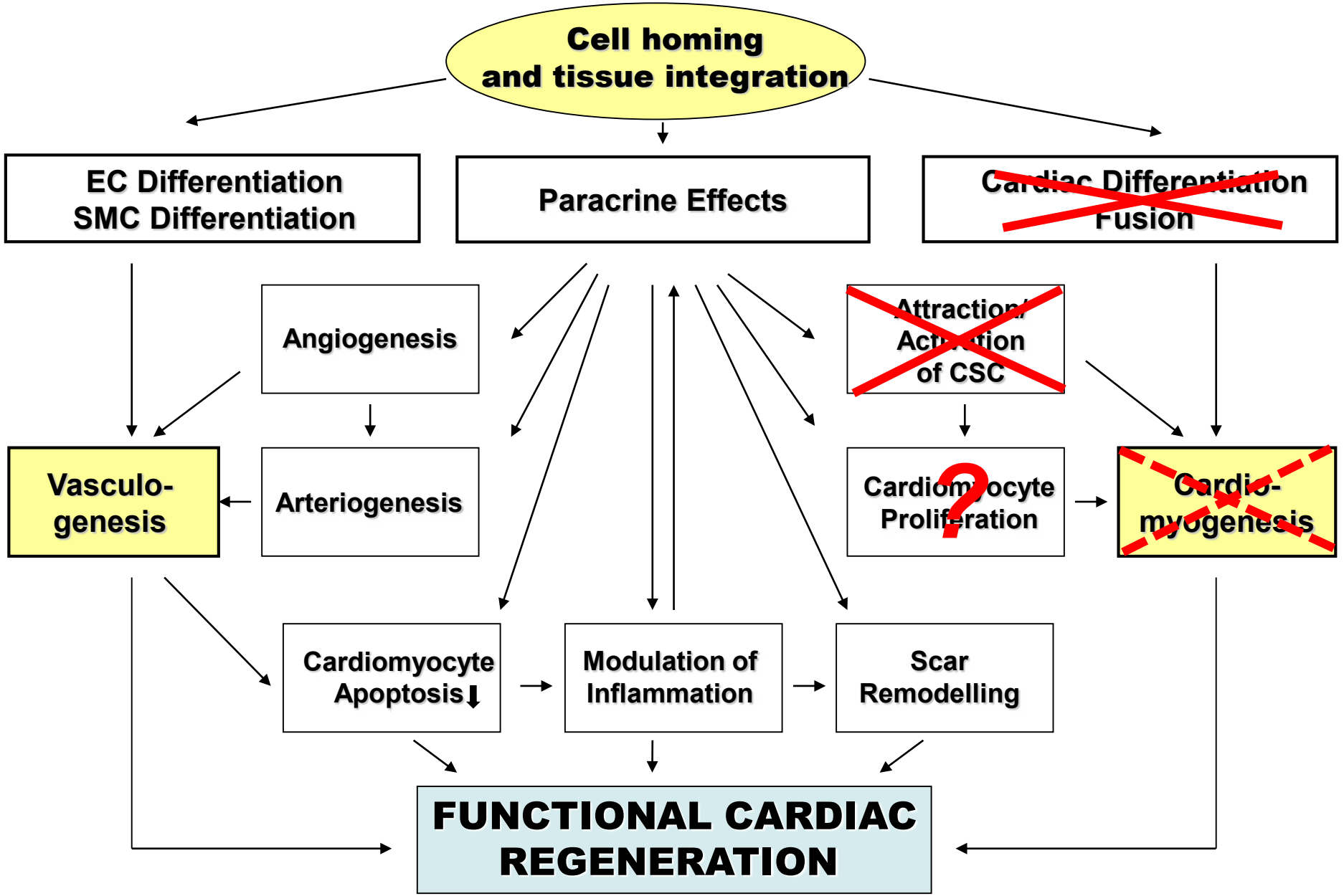
Cell therapy of the heart: the prevailing view 2019



Putative mechanisms for cardiac regeneration



Burchfield, Zeiher, Dimmeler, ATVB 2009

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Cell therapy in cardiovascular diseases

- ⇨ *Refractory Angina*
- ⇨ *Acute Myocardial Infarction*
- ⇨ *Chronic Heart Failure*
- ⇨ *Peripheral Arterial Occlusive Disease*

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Autologous CD34+ cell therapy in no-option refractory angina

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 2208–2216
doi:10.1093/eurheartj/ehx764

Autologous CD34$^+$ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials

Timothy D. Henry[1]*, Douglas W. Losordo[2], Jay H. Traverse[3], Richard A. Schatz[4], E. Marc Jolicoeur[5], Gary L. Schaer[6], Robert Clare[7], Karen Chiswell[7], Christopher J. White[8], F. David Fortuin[9], Dean J. Kereiakes[10], Andreas M. Zeiher[11], Warren Sherman[12], Andrea S. Hunt[13], and Thomas J. Povsic[7]

[1]Cedars-Sinai Heart Institute, Los Angeles, CA, USA; [2]Caladrius Biosciences, Inc., New York, NY, USA; [3]Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, MN, USA; [4]Scripps Clinic Torrey Pines, La Jolla, CA, USA; [5]Montreal Heart Institute, Université de Montréal, Montréal, Quebec, Canada; [6]Rush University Medical Center, Chicago, IL, USA; [7]Duke University School of Medicine, Duke Clinical Research Institute, Durham, NC, USA; [8]Ochsner Clinical School, Ochsner Medical Center, New Orleans, LA, USA; [9]Mayo Clinic Hospital, Phoenix, AZ, USA; [10]The Christ Hospital Heart and Vascular Center, Lindner Research Center, Cincinnati, OH, USA; [11]University of Frankfurt, Frankfurt, Germany; [12]LoneStar Heart Inc., Irvine, CA, USA; and [13]Shire US, Lexington, MA, USA

Received 14 July 2017; revised 31 August 2017; editorial decision 27 October 2017; accepted 13 December 2017; online publish-ahead-of-print 5 January 2018

See page 2217 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx793)

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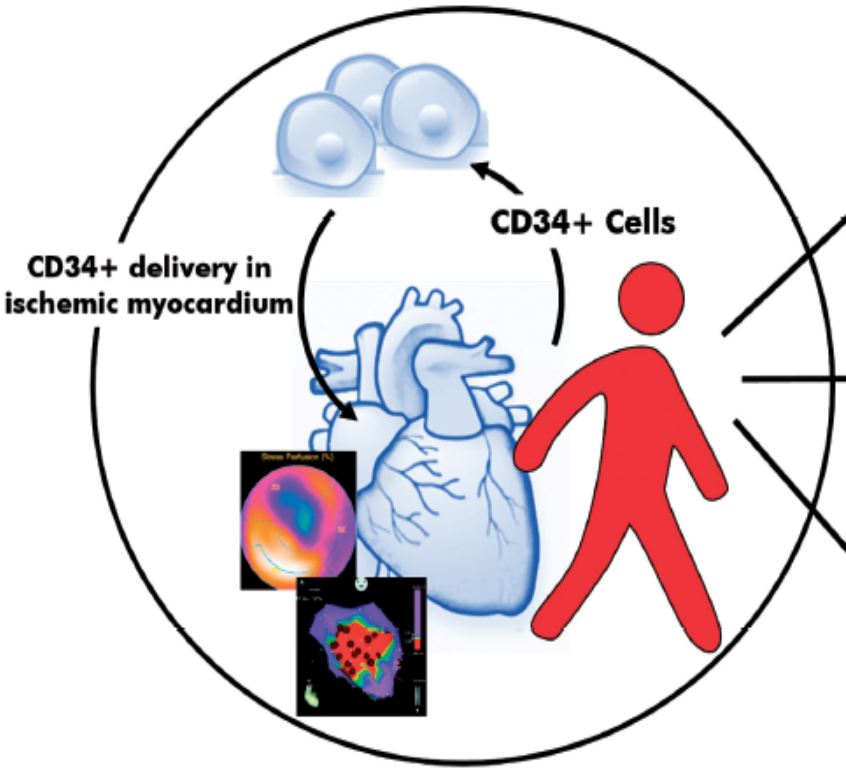
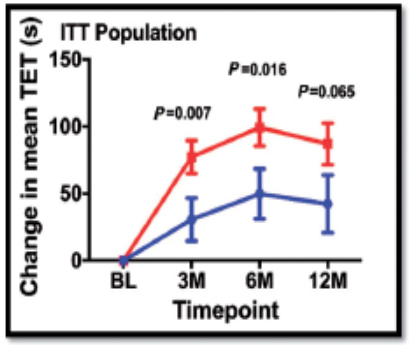
Autologous CD34+ cell therapy in no-option refractory angina

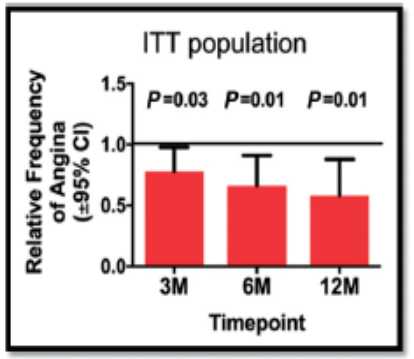
CD34+ Cell Therapy for Patients with Refractory Angina

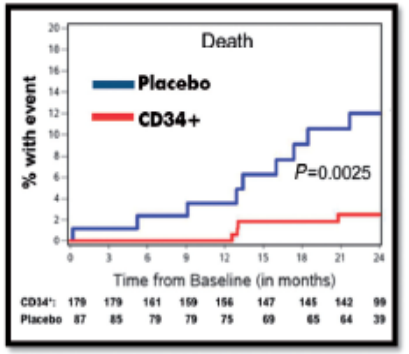
Improvement in exercise time, angina, and mortality compared to placebo



- **Improved total exercice time throughout the 3-12 month period on treadmill stress test**
- **Lower relative frequency of angina throughout the 3-12 month period**
- **Significant decrease in all-cause mortality at 24 months**







Today: *Auto-CD34 Cell Therapy for Microvascular Dysfunction and Non-obstructive coronary arateries / Noel Bairey-Merz*

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The Future of Cell-Based Therapies

⇨ *Refractory Angina = ‚low-hanging fruit‘*

- **Final phase III trial for approval**
- **Necessity for repetitive treatment ?**

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The Future of Cell-Based Therapies

- *Refractory Angina*
- ***Acute Myocardial Infarction***
- *Chronic Heart Failure*
- *Peripheral Arterial Occlusive Disease*

Autologous Bone-Marrow Derived Cell Therapy: A Journey of 17 Years

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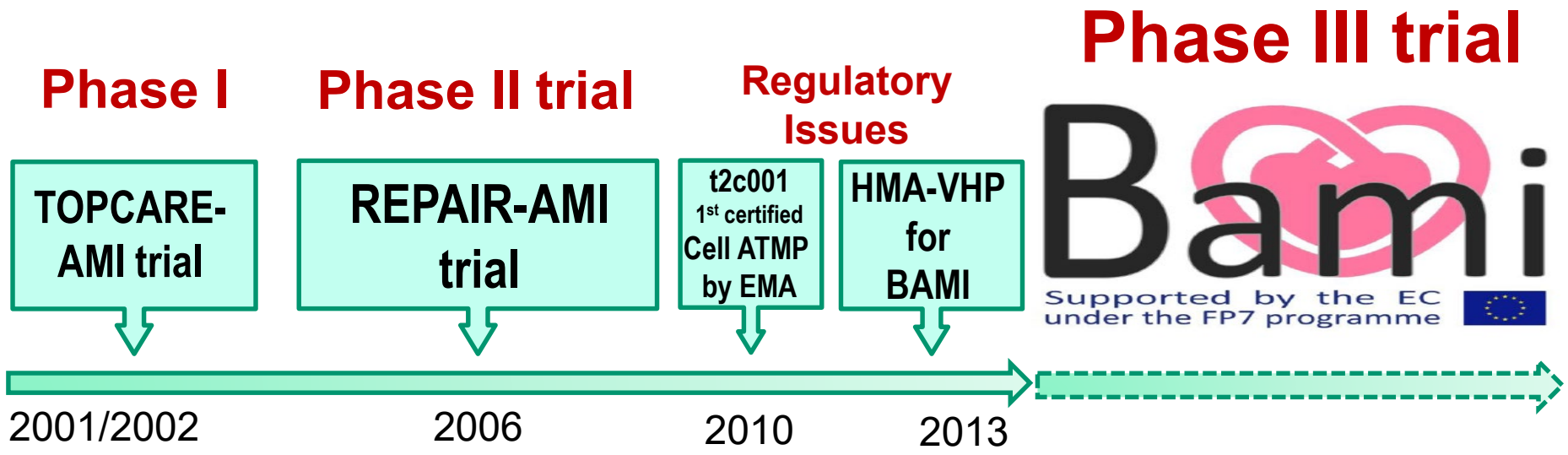


Circulation 2002
Circulation 2003
JACC 2004
ClinResCardiol 2011

NEJM 2006
EHJ 2007
Circulation 2007
CircHeartFail 2010
EHJ 2014

European Journal of Heart Failure (2017) 19, 1545–1550
doi:10.1002/ejhf.829

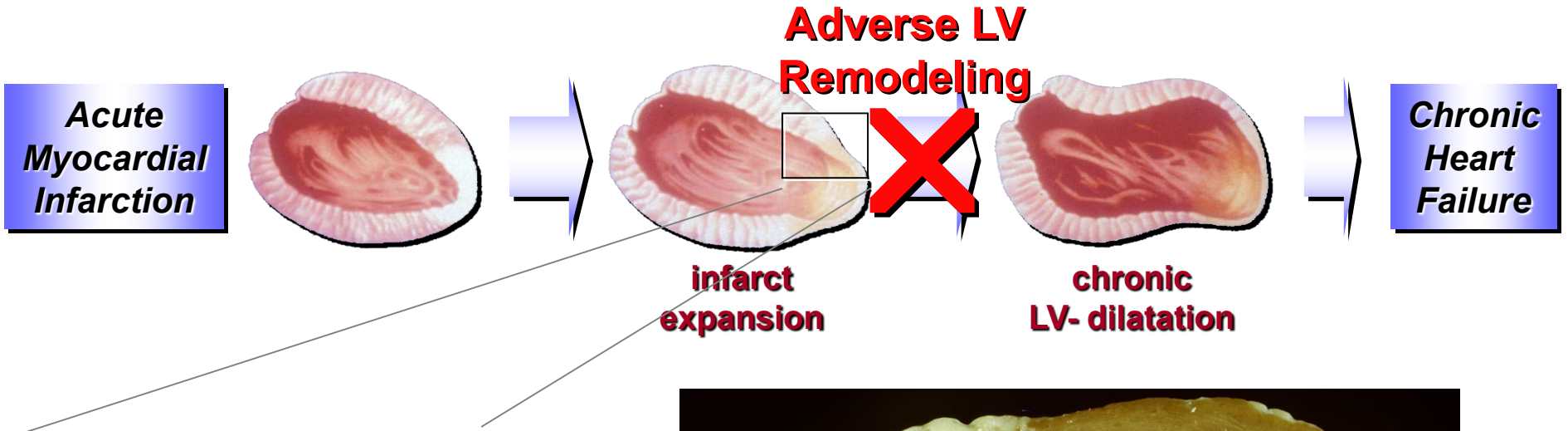
STUDY DESIGN

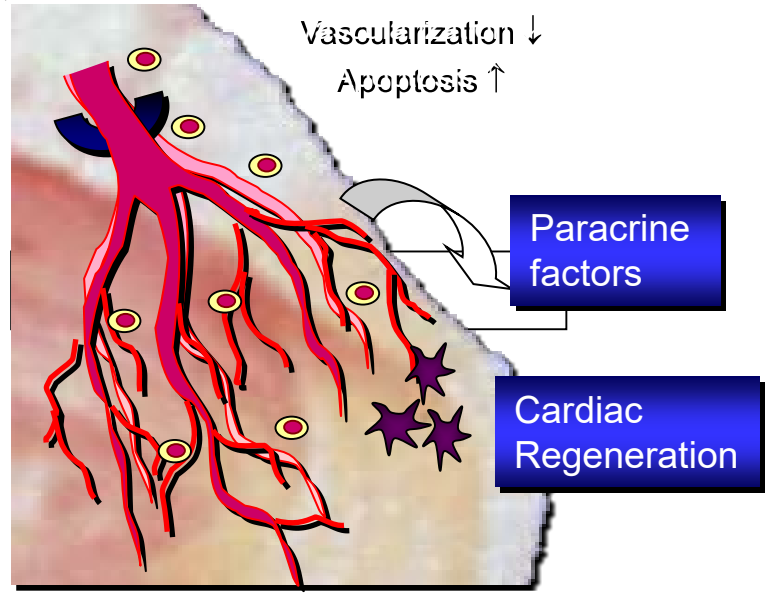
The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: rationale and design of the BAMI trial

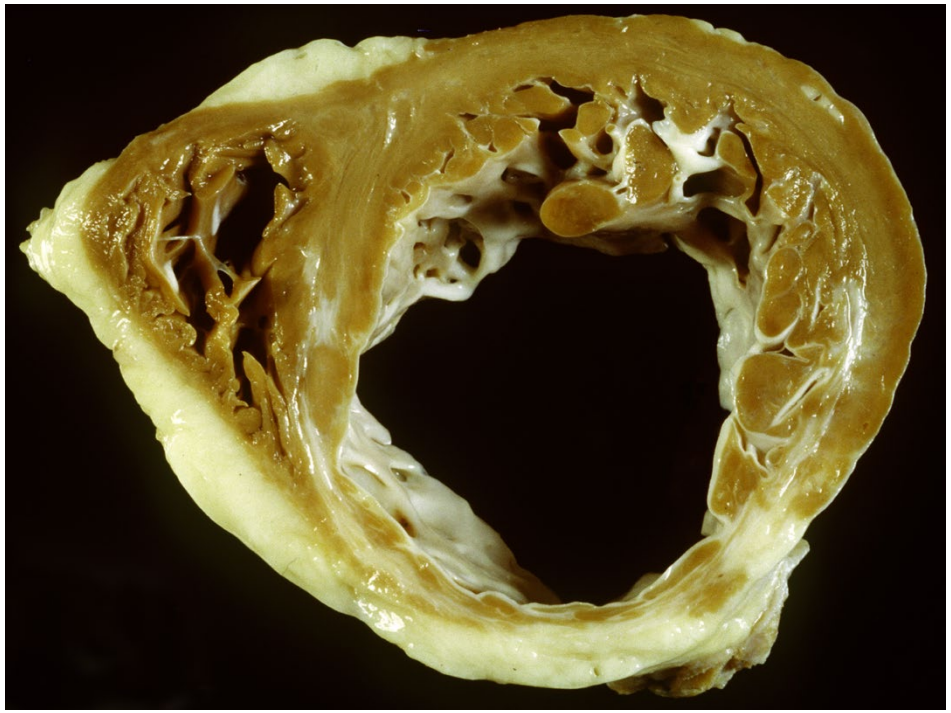
Anthony Mathur[1]*, Roman Arnold[2], Birgit Assmus[3], Jozef Bartunek[4], Ann Belmans[5], Halvard Bönig[6], Filippo Crea[7], Stefanie Dimmeler[3], Sheik Dowlut[1], Francisco Fernández-Avilés[8], Manuel Galiñanes[9], David Garcia-Dorado[9], Juha Hartikainen[10], Jonathan Hill[11], Annette Hogardt-Noll[12], Christian Homsy[13], Stefan Janssens[14], Petr Kala[15], Jens Kastrup[16], John Martin[17], Philippe Menasche[18], Roman Miklik[15], Abdul Mozid[19], J. Alberto San Román[2], Ricardo Sanz-Ruiz[8], Michal Tendera[20], Wojtek Wojakowski[20], Seppo Ylä-Herttuala[10], and Andreas Zeiher[3]

Recruitment completed
Results 2/2020

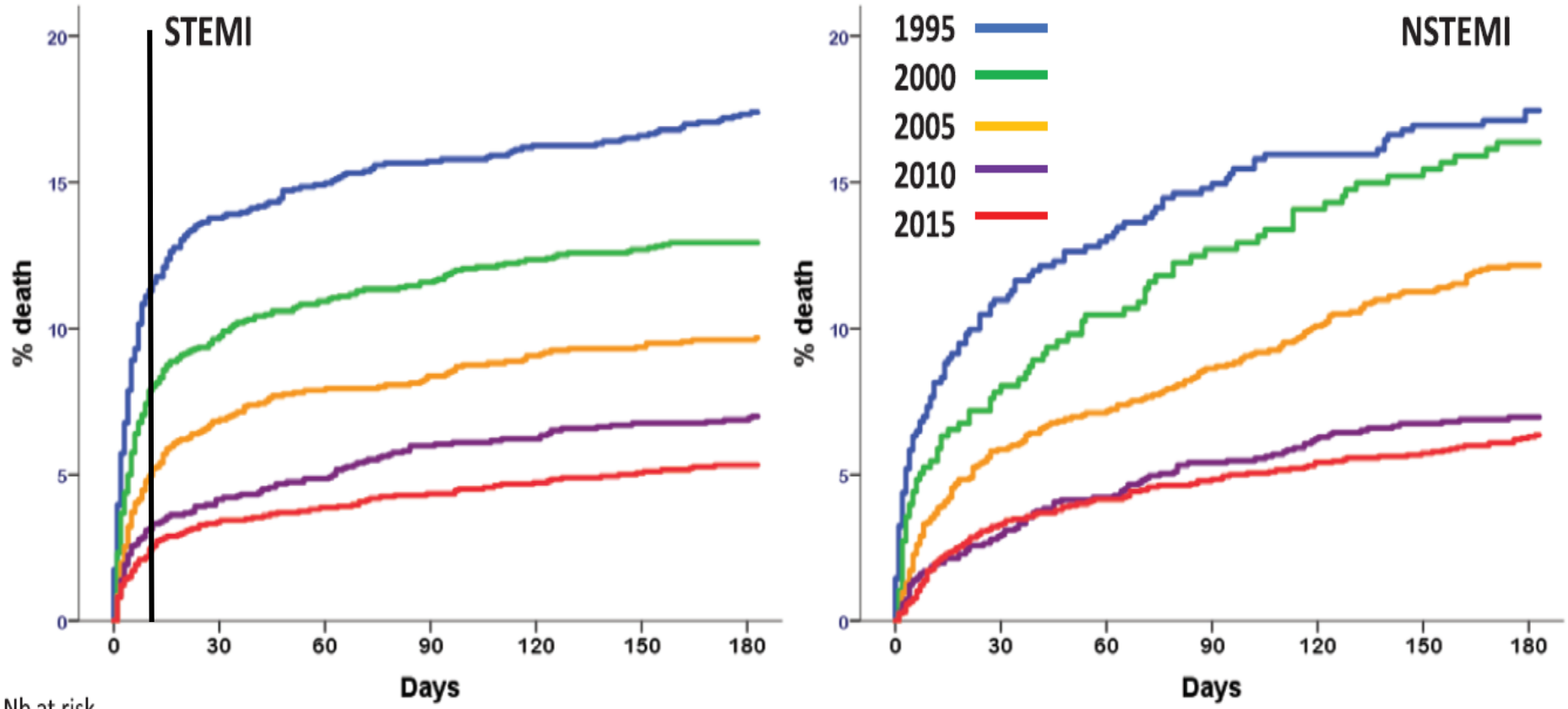
Regenerative therapies in STEMI: do we still need it in 2020 ?







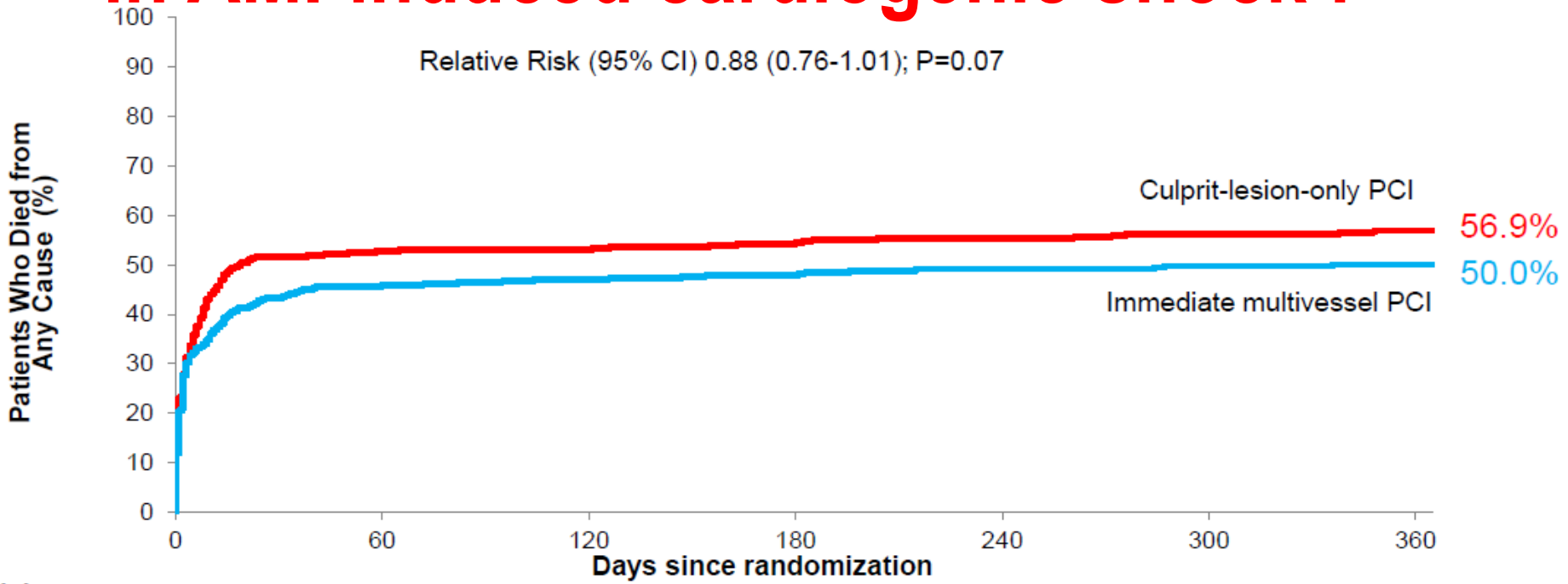
6-months mortality over the past 20 years: FAST-MI program



Nb at risk								
1995	1536	1268	1249	1233	616	525	507	497
2000	1844	1546	1484	1465	476	402	377	363
2005	1611	1485	1466	1457	1448	1346	1303	1273
2010	1716	1610	1587	1576	1363	1291	1263	1252
2015	1872	1780	1761	1736	1941	1835	1811	1779

Puymirat E et al., Circulation 9/2017

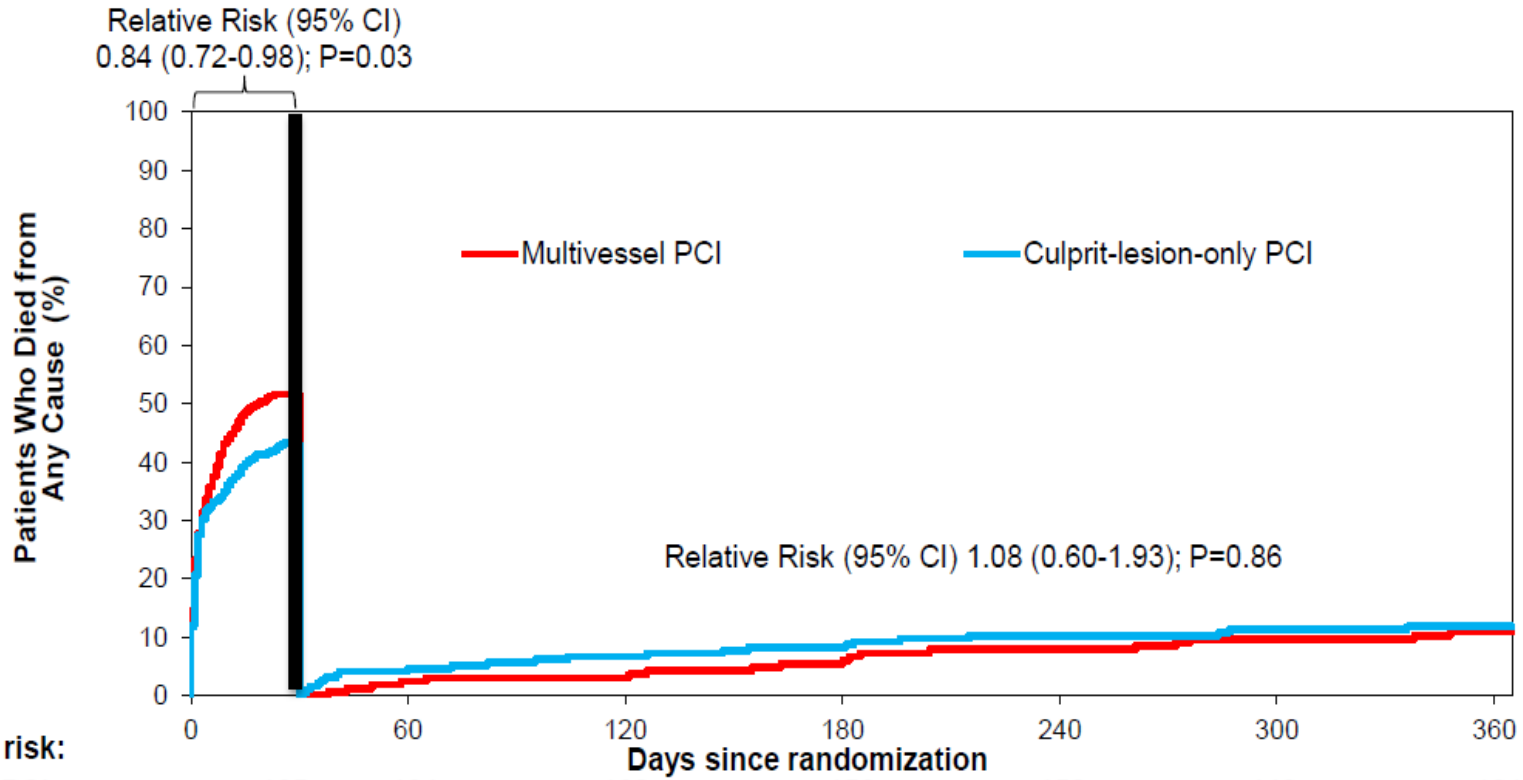
1-Year All-Cause Mortality
in AMI-induced cardiogenic shock !



Number at risk:

Multivessel PCI	341	161	160	156	152	149	131
Culprit-lesion-only PCI	344	186	181	178	174	172	147

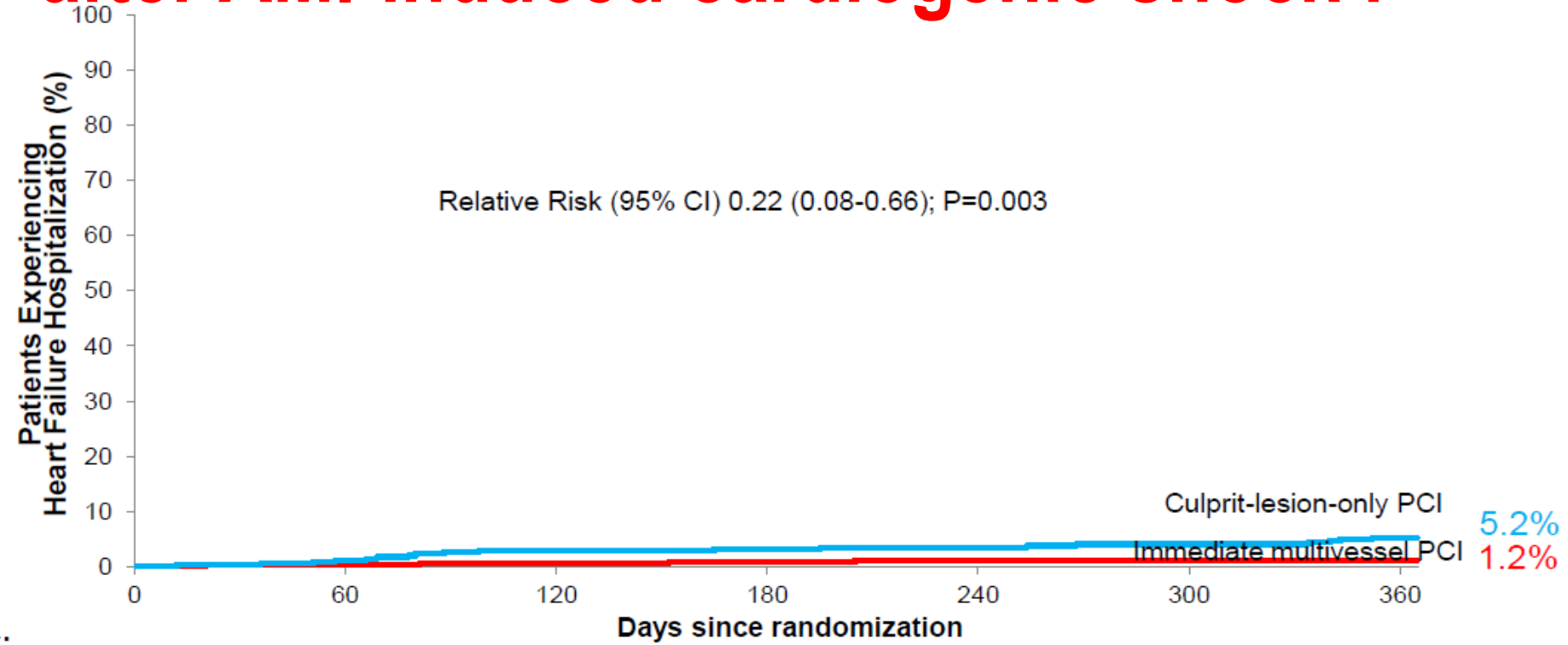
1-Year All-Cause Mortality – Landmark Analysis



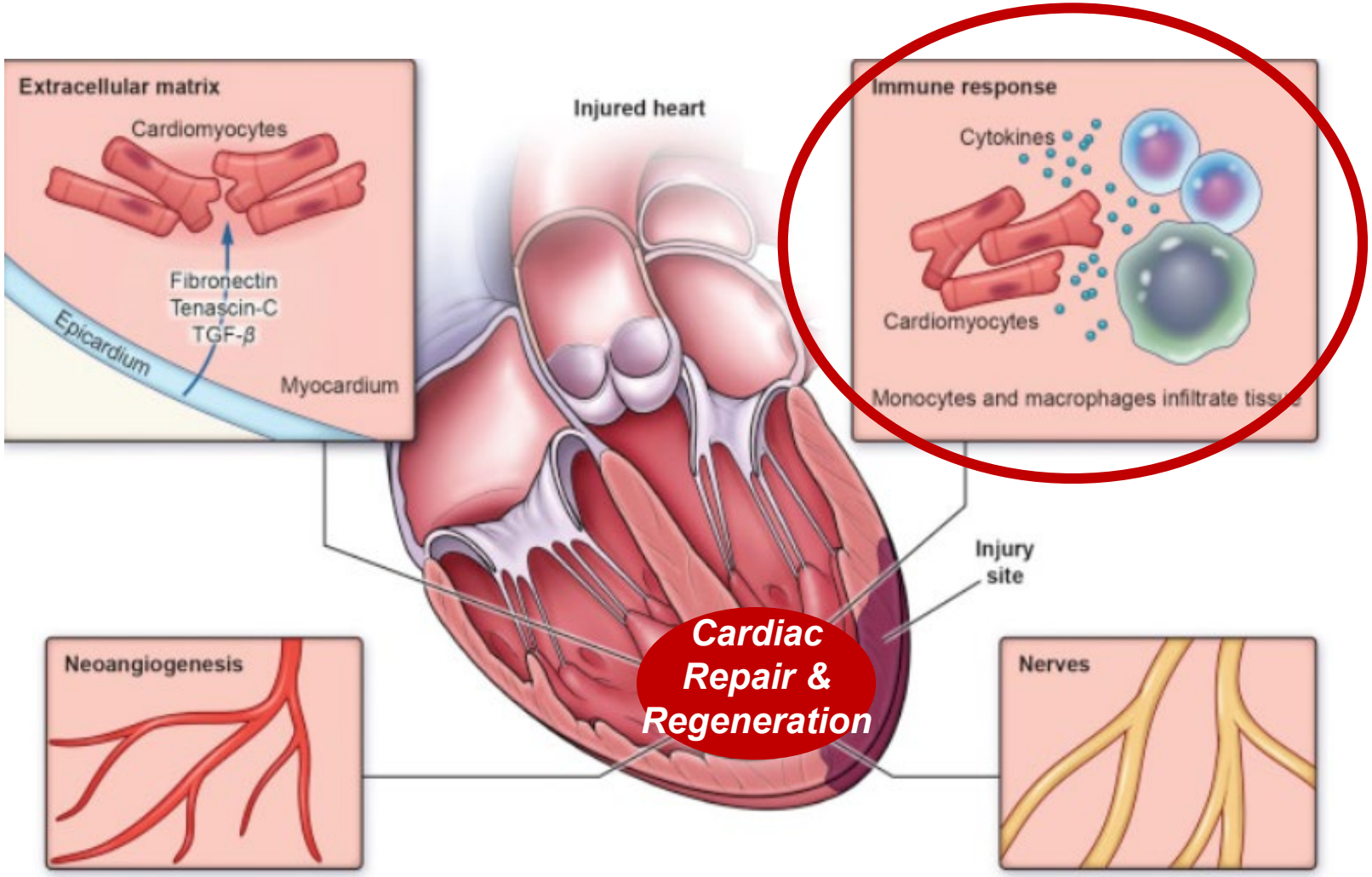
Number at risk:

Multivessel PCI	165	161	160	156	152	149	131
Culprit-lesion-only PCI	195	186	181	178	174	172	147

1-Year Rehospitalization Congestive Heart Failure after AMI-induced cardiogenic shock !



Regulation of post-infarction remodelling



Uygur & Lee, Dev Cell 2016

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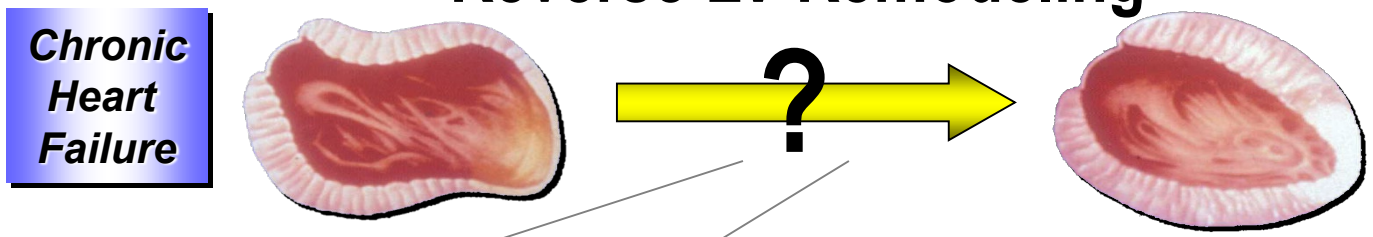
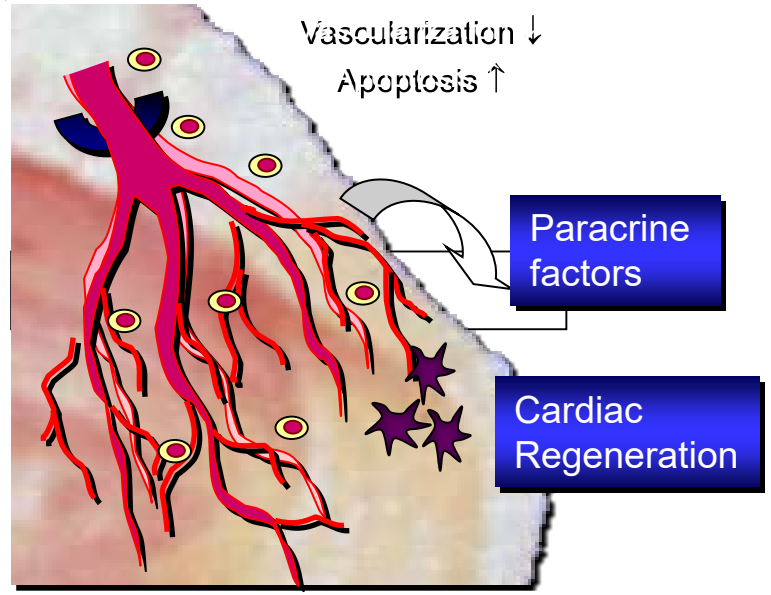
The Future of Cell-Based Therapies

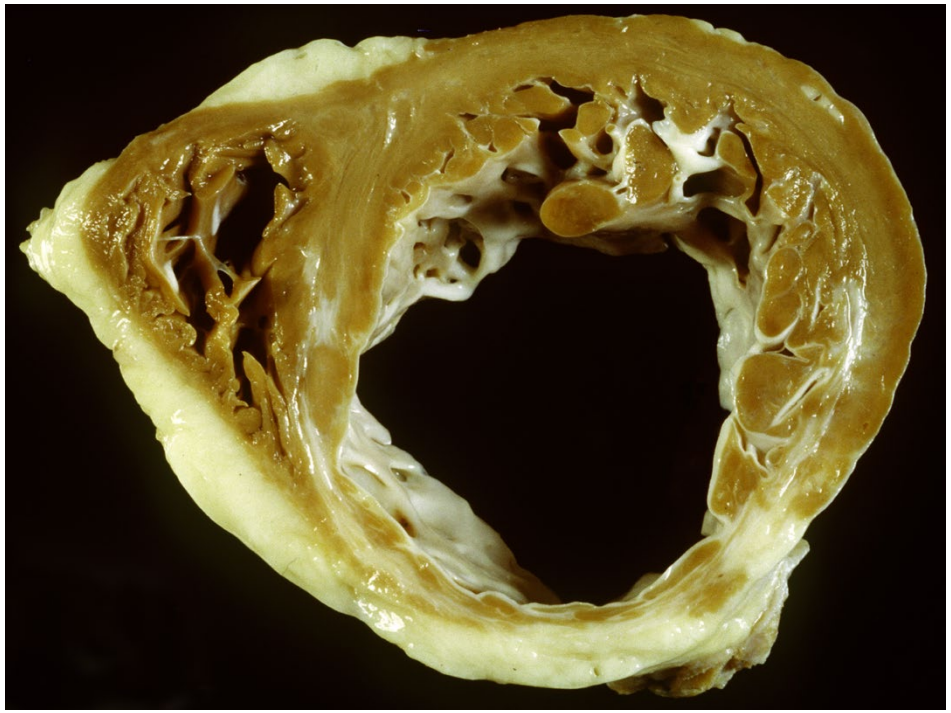
- ⇨ *Refractory Angina*
- ⇨ *Acute Myocardial Infarction*
- ⇨ ***Chronic Heart Failure***
- ⇨ *Peripheral Arterial Occlusive Disease*

Challenges of Cell Therapy in Chronic Post-Infarction Heart Failure

Reverse LV Remodeling







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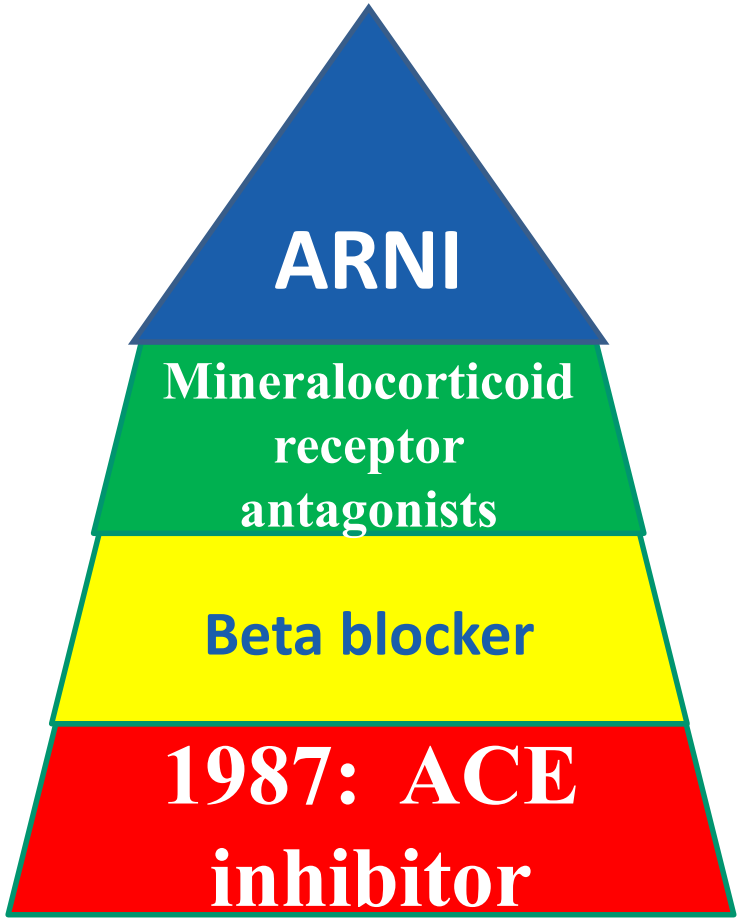
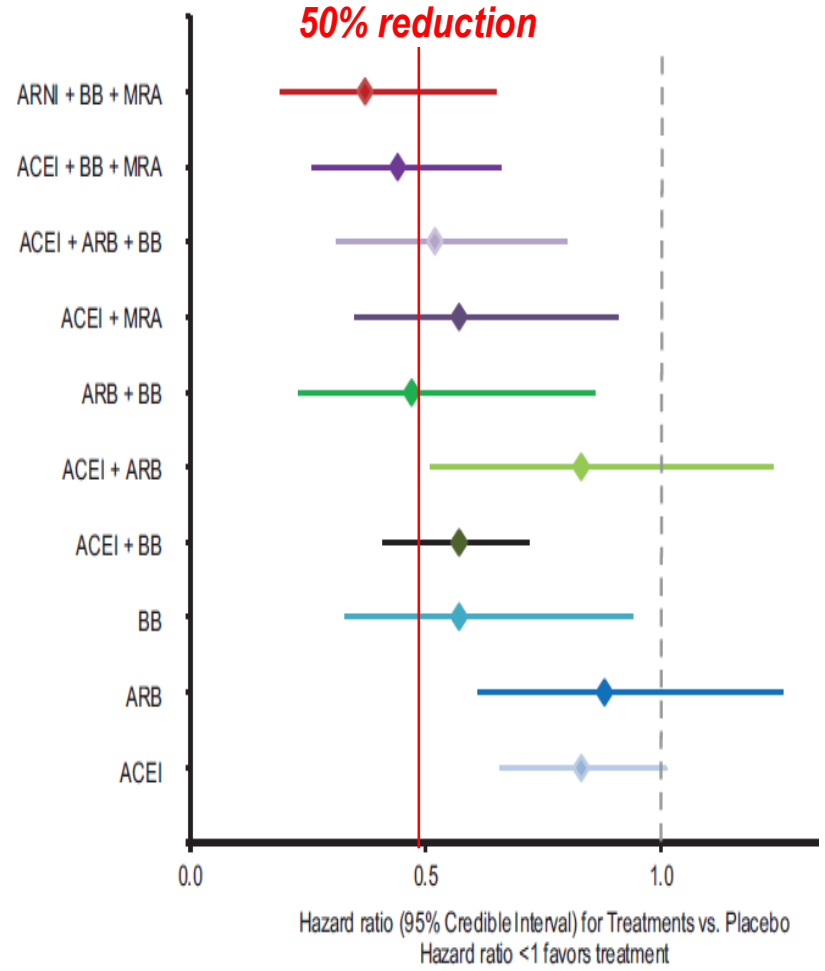
Historical perspective of pharmacological treatment strategies for heart failure (HFrEF)

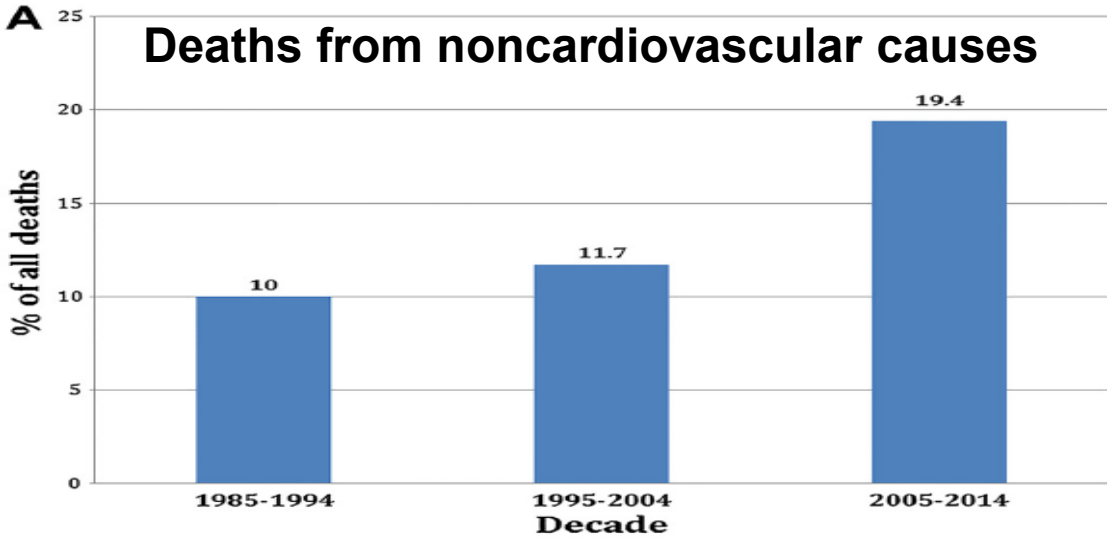
Heart Failure 1987 - 2017

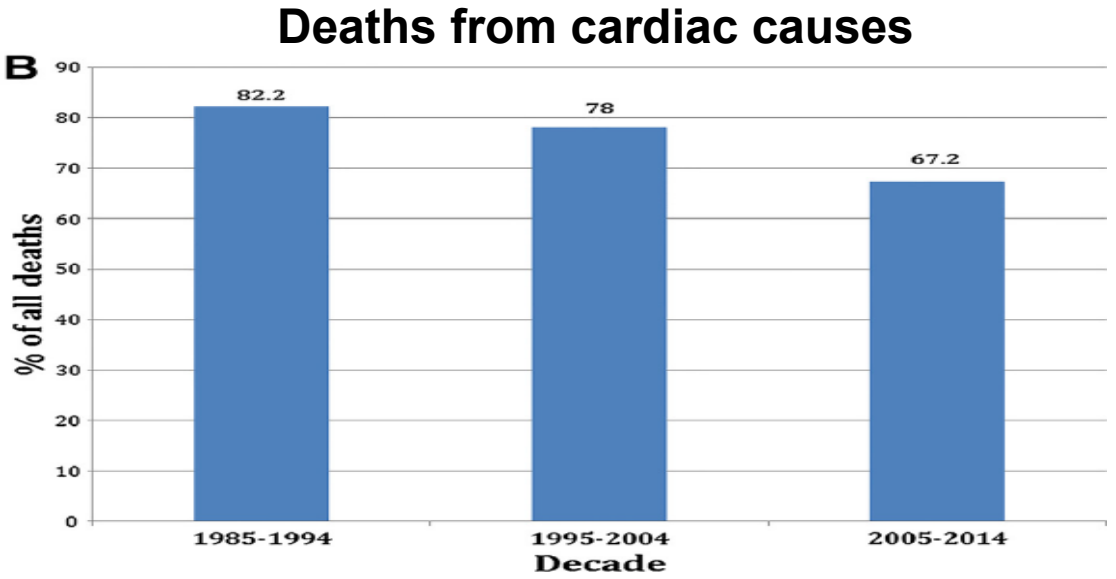




Circ Heart Fail 2017

Trends over time in proportion of all deaths in HFrEF





JACC Heart Fail 2015

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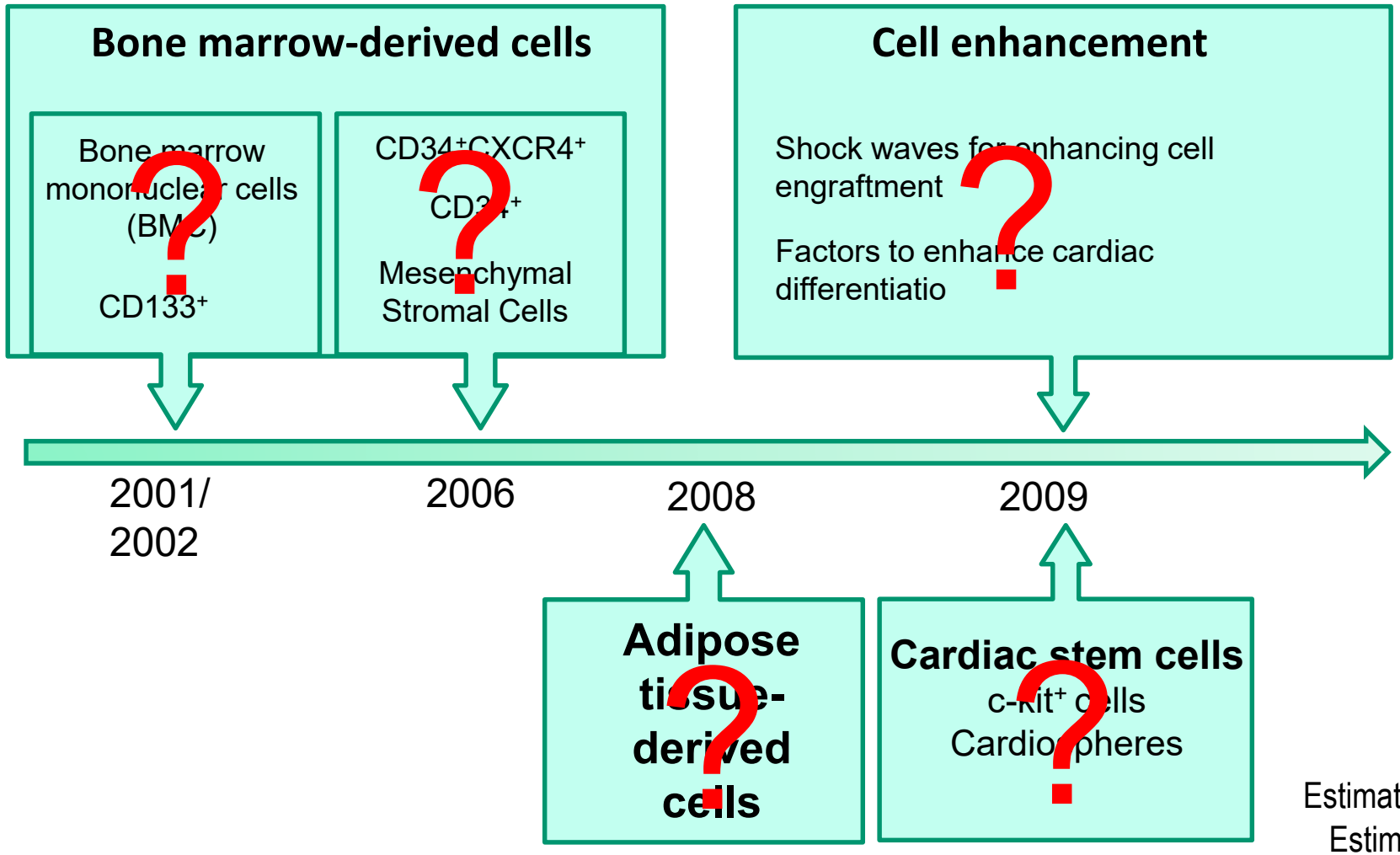
Cell Therapy for Chronic Heart Failure

Cell therapy for chronic heart failure – in clinical trials



Phase II/III trial (ongoing)

DREAM-HF

Mesoblast

600 participants

Double-blind, Randomized, Sham-procedure-controlled, Parallel-Group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (Rexlemestrocel-L) in Chronic Heart Failure Due to LV Systolic Dysfunction (Ischemic or Nonischemic)

Actual Study Start Date :January 2014
Estimated Primary Completion Date :December 2019
Estimated Study Completion Date :December 2019

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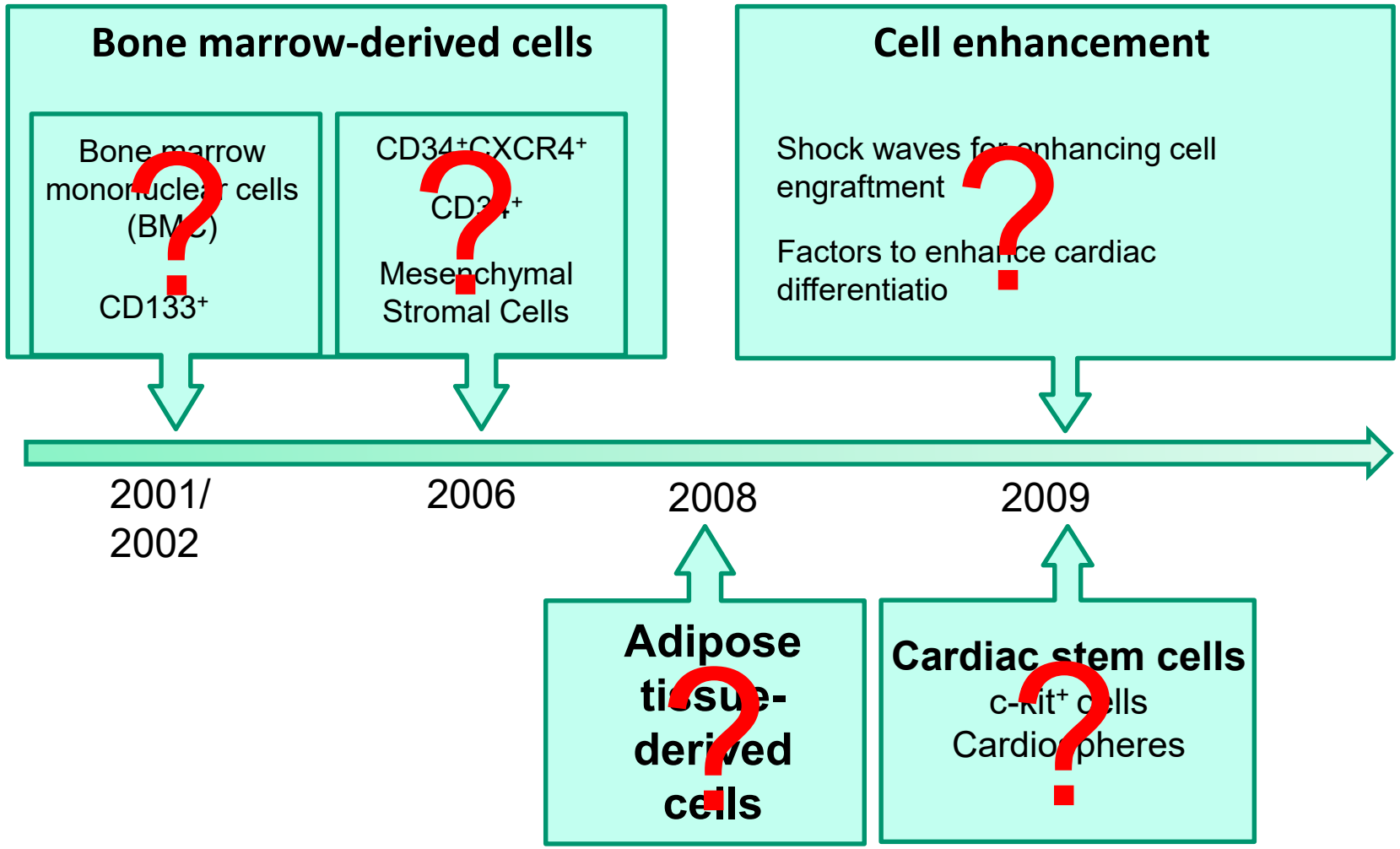
Regenerative Therapeutic Strategies for Chronic Heart Failure

Cell therapy for chronic heart failure – in clinical trials



Future

Other stem cells?
(e.g. iPS, ESC)

Direct reprogramming?

microRNA therapeutics ?

The double-edged sword of pro-regenerative strategies

HEART

Targeting microRNAs can enchance proliferation and regeneration

TUMOR

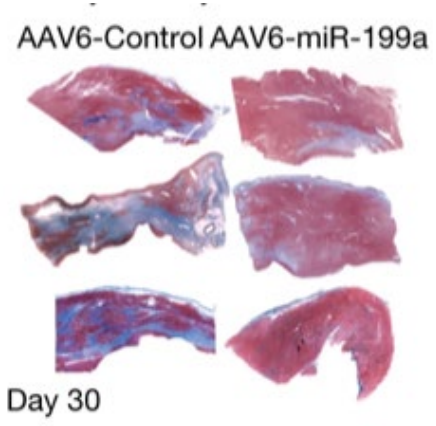
Targeted regenerative microRNAs are often tumor suppressor

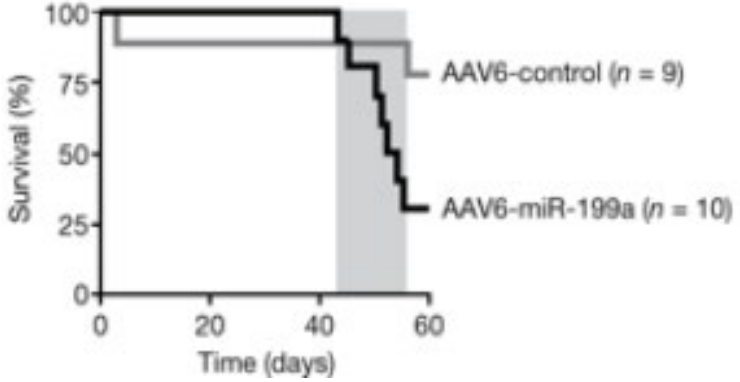
Letter | Published: 08 May 2019

MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs

Khatia Gabisonia, Giulia Prosdocimo, Giovanni Donato Aquaro, Lucia Carlucci, Lorena Zentilin, I Secco, Hashim Ali, Luca Braga, Nikoloz Gorgodze, Fabio Bernini, Silvia Burchielli, Chiara Collesi, Lorenzo Zandonà, Gianfranco Sinagra, Marcello Piacenti, Serena Zacchigna, Rossana Bussani, F A. Recchia & Mauro Giacca

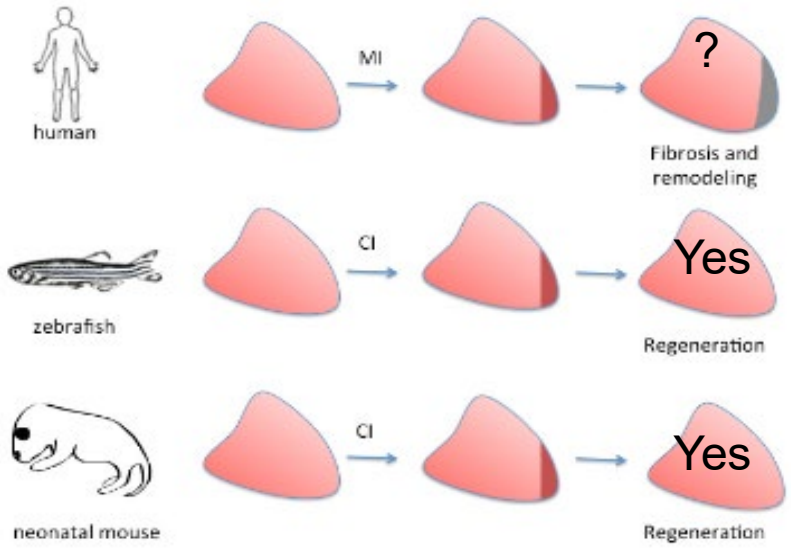
Nature **569**, 418–422 (2019) | Download Citation





The heart is a regenerating organ

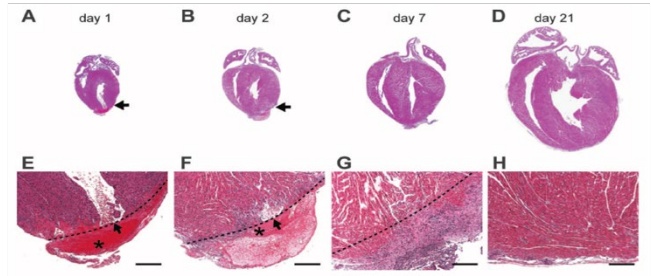
Endogenous cardiac regeneration:



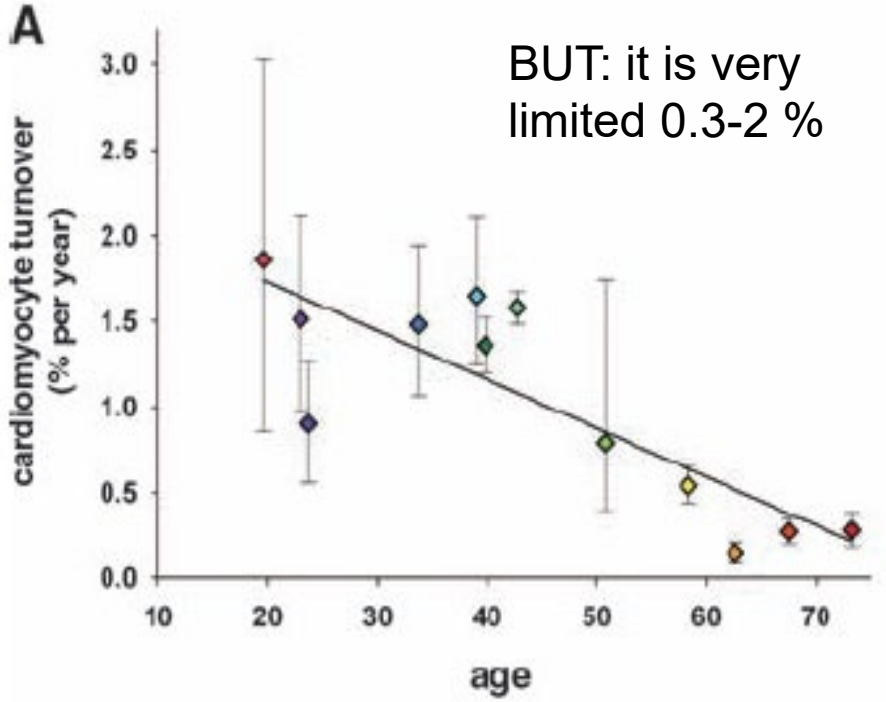
Sanchez-Iranzo et al ESC online

Transient Regenerative Potential of the Neonatal Mouse Heart

Enzo R. Porrello,[1] Ahmed I. Mahmoud,[2] Emma Simpson,[3] Joseph A. Hill,[1,2] James A. Richardson,[1,3] Eric N. Olson,[1*] Hesham A. Sadek[2*]



Myocyte turn over per year



BUT: it is very limited 0.3-2 %

Bergmann et al., Science 2009 324:98-102

- **The human heart is regenerating BUT: The extent of regeneration is very limited particularly during aging**