ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY

XXVII GIORNATE CARDIOLOGICHE TORINESI

AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

JMC JOINT MEETING OF CARDIOLOGY

Chronic Angina: how to treat it when untreatable

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Turin
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Centro Congressi
Unione Industriale di Torino

HOW MANY PATIENTS STILL HAVE ANGINA?

untreatable

WHAT STRATEGY FOR THIS PATIENT?

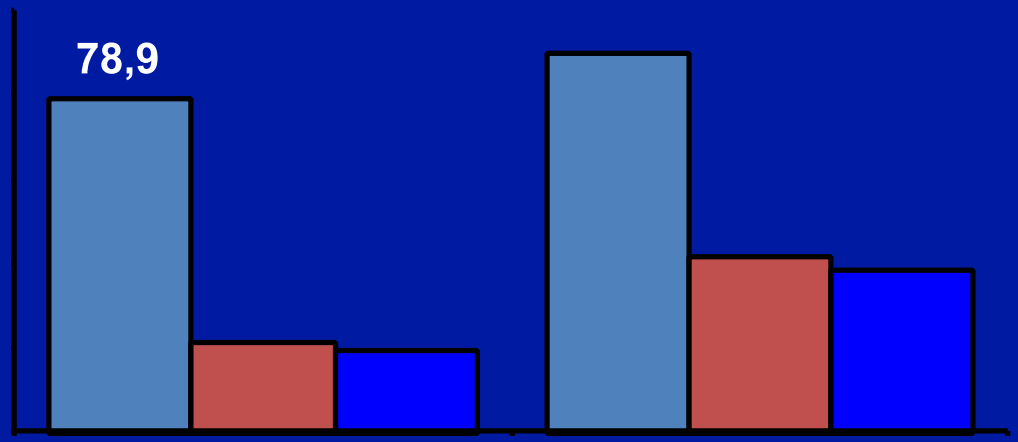
Epidemiology of chronic ischemia (angina)

- 6.5–16.5 million Americans suffer with angina pectoris
- Despite therapeutic advances
  - >13 million episodes of angina per week in the US
  - >1000 episodes of angina every minute
- Growing prevalence of chronic ischemia (angina) due to residual CAD after PCI and CABG
- Improved treatment of recurring ischemia (angina) is an important goal

AHA. *Heart Disease and Stroke Statistics–2006 Update*.
Gibbons RJ et al. ACC/AHA 2002 guidelines. www.acc.org/clinical/guidelines/stable/stable.pdf.
Pepine CJ et al. *Am J Cardiol.* 1994;74:226-31.

Persistent ischemia (angina) despite optimal revascularization

Arterial Revascularization Therapies Study



~60% to 80% taking antianginal medication

~10 to 20% had angina

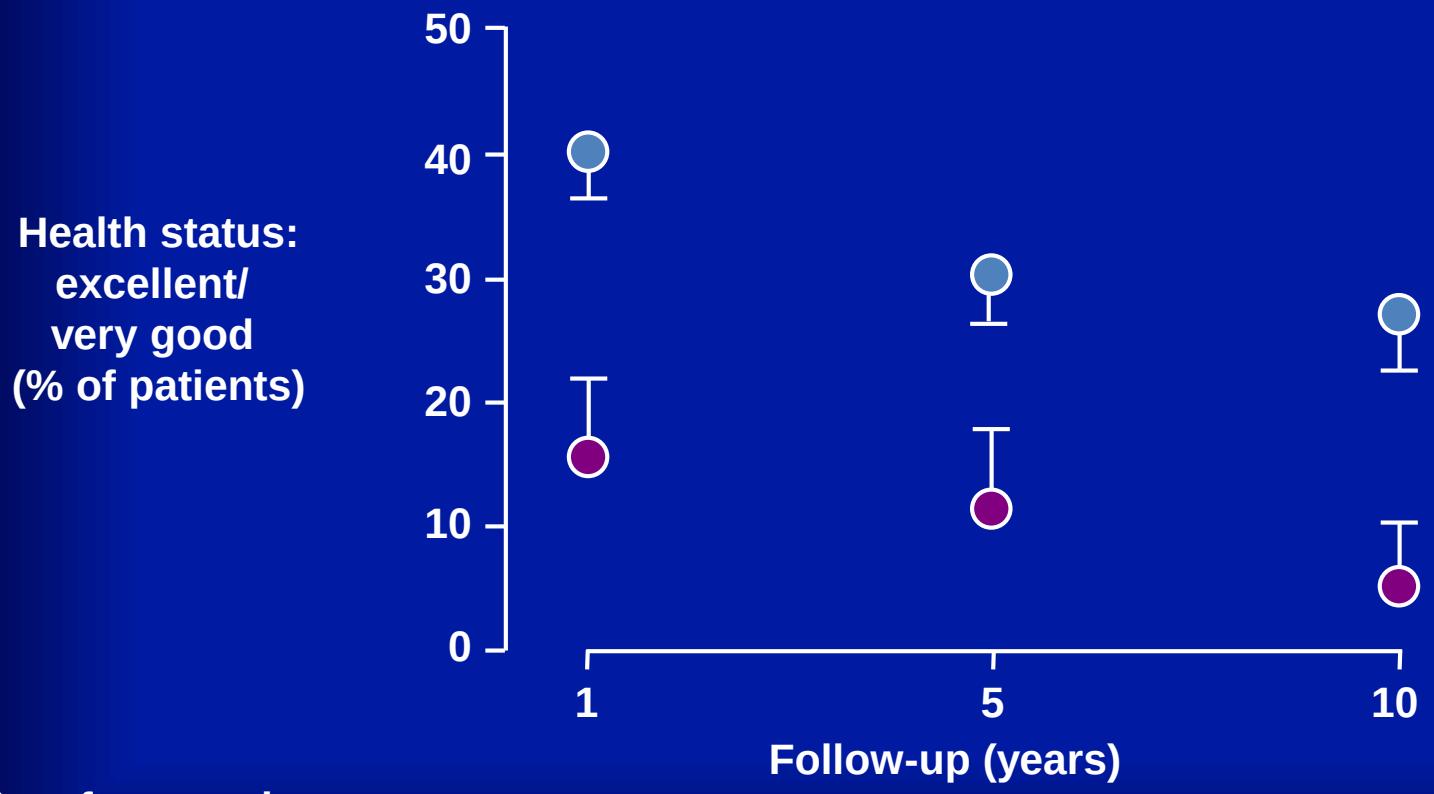
gina and antianginal medication

***1 year after optimal revascularization (stenting or surgery) for ischemia relief (not to prolong survival)**

Serruys PW et al. *N Engl J Med.* 2001;344:1117-24.

Myocardial ischemia reduce quality of life

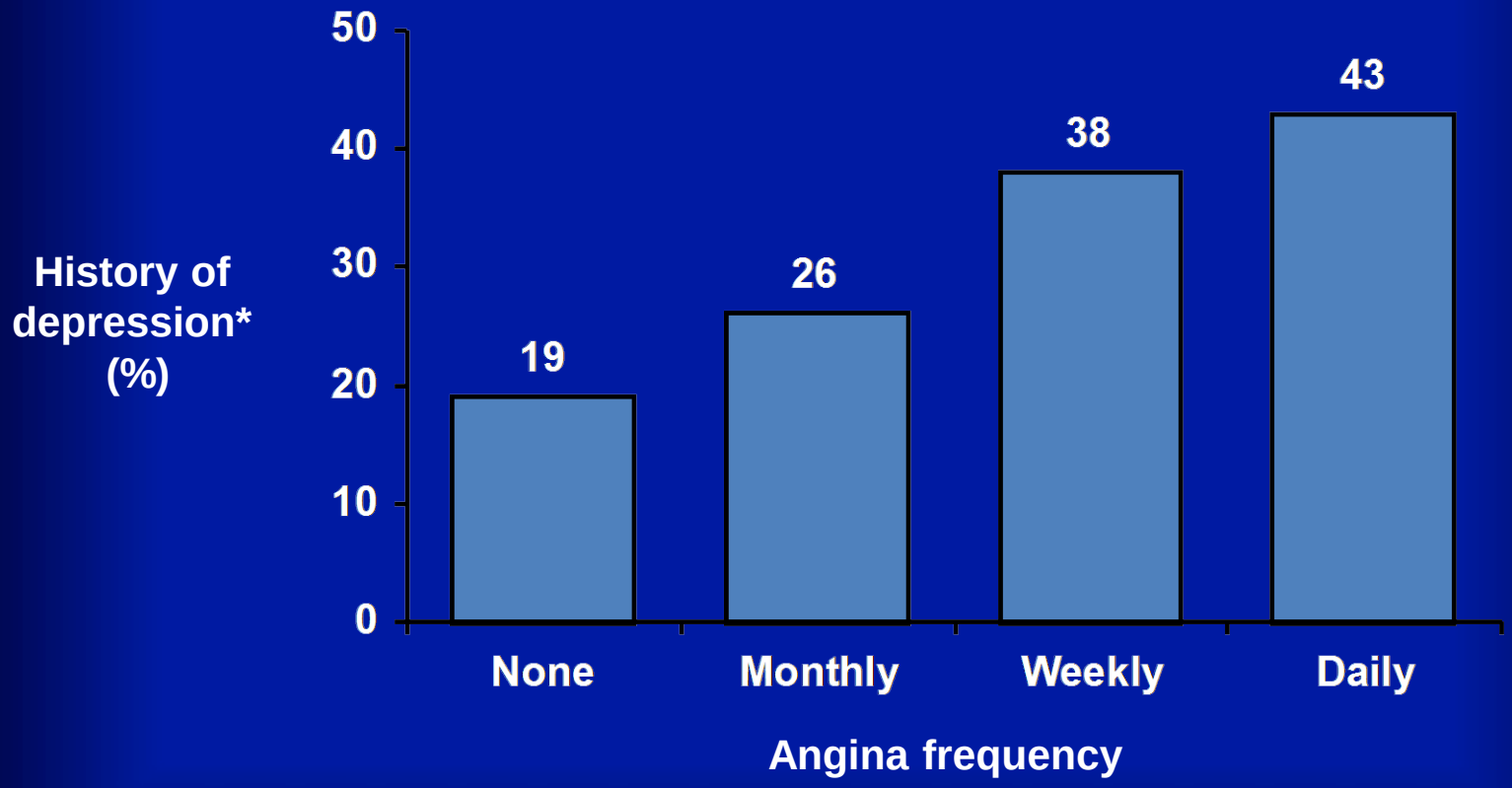
N = 934 post-PCI/CABG
Assessment of general health status during follow-up visits



Hlatky MA et al. *Circulation.* 2004;110:1960-6.

Coexistence of Angina and depression

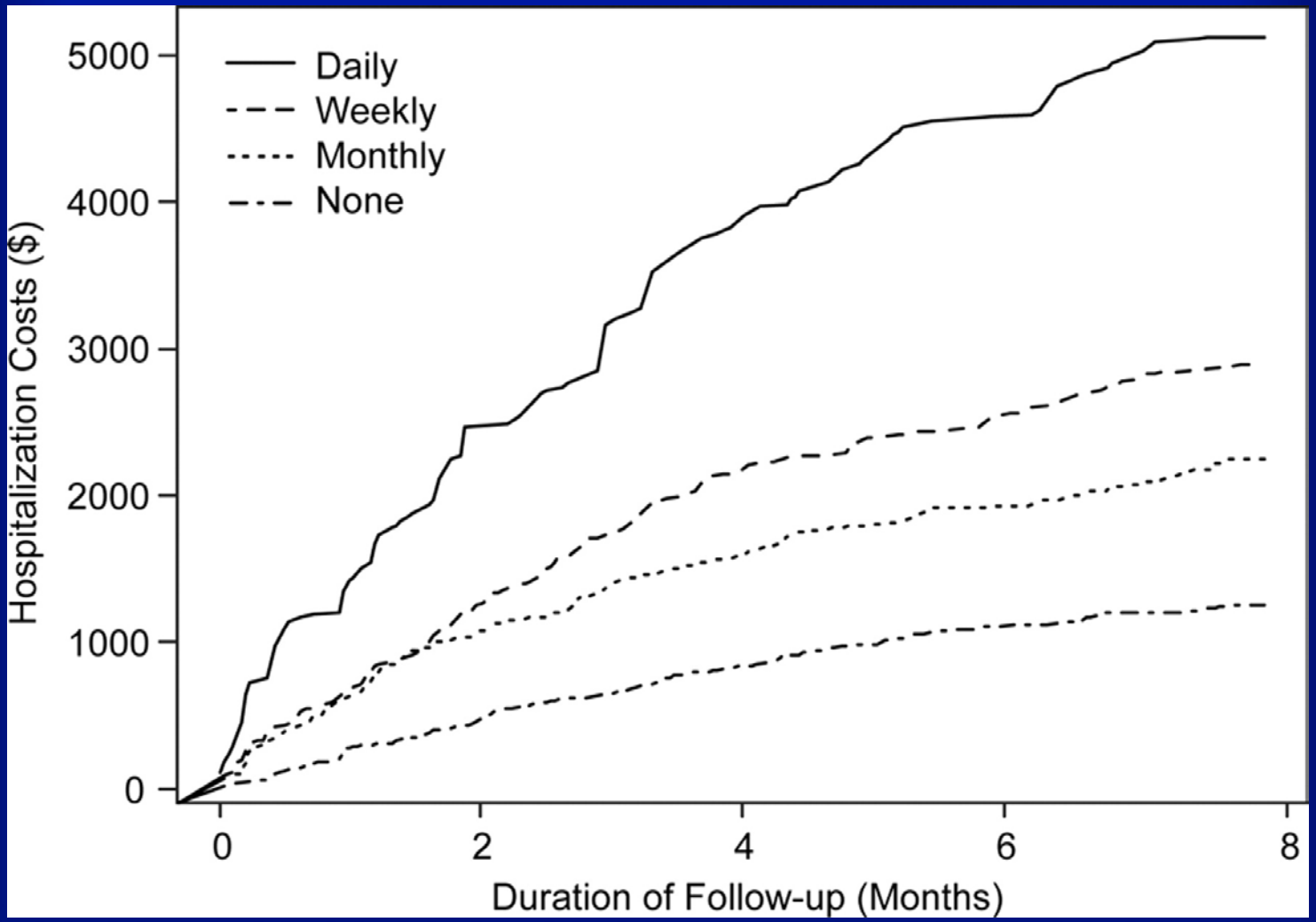
N = 1957; 7 months post-discharge following MI/UA



***Seattle Angina Questionnaire**

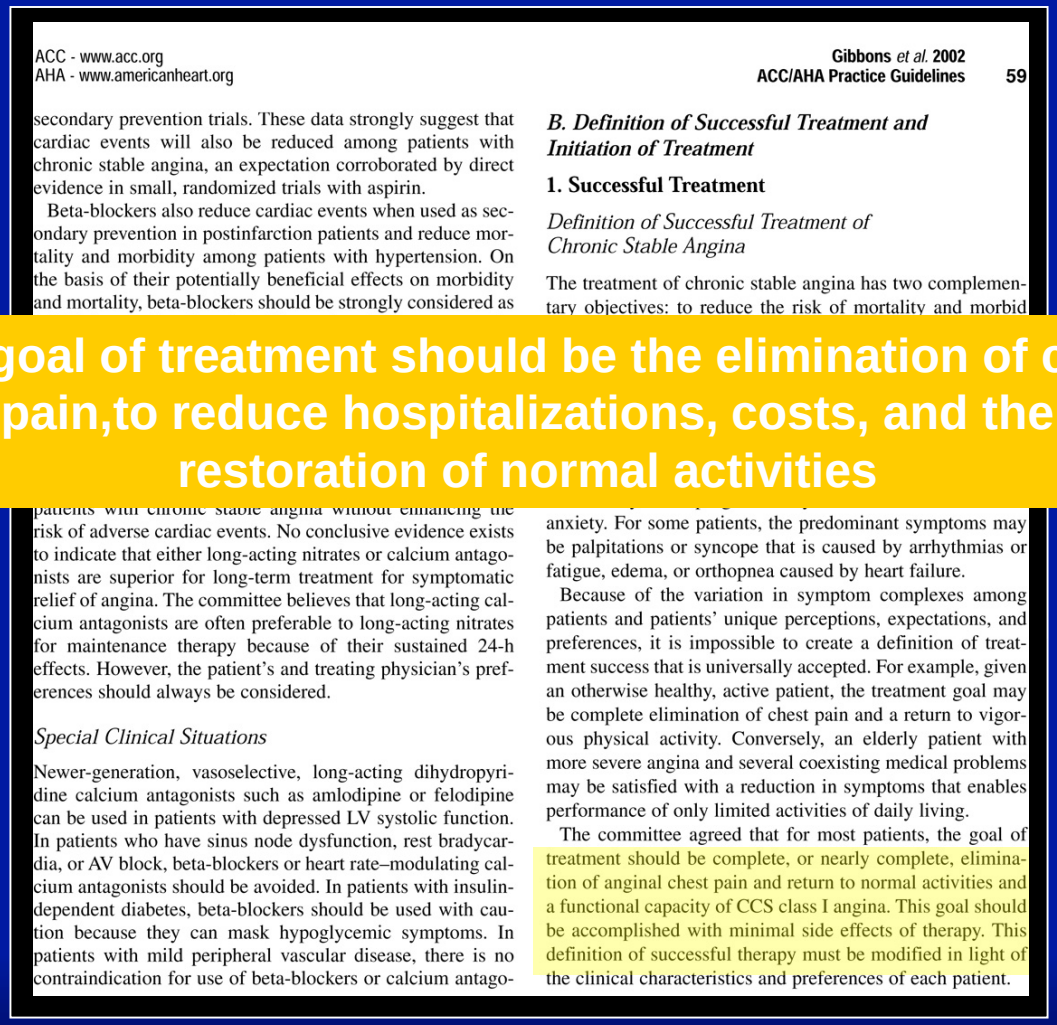
Rumsfeld JS et al. *Am Heart J.* 2003;145:493-9.

Hospitalization Costs based on the frequency of angina attacks



Arnold S V et al. Circ Cardiovasc Qual Outcomes 2009;2:344-353

ACC/AHA guidelines on the management of chronic stable angina



secondary prevention trials. These data strongly suggest that cardiac events will also be reduced among patients with chronic stable angina, an expectation corroborated by direct evidence in small, randomized trials with aspirin.

Beta-blockers also reduce cardiac events when used as secondary prevention in postinfarction patients and reduce mortality and morbidity among patients with hypertension. On the basis of their potentially beneficial effects on morbidity and mortality, beta-blockers should be strongly considered as

patients with chronic stable angina without enhancing the risk of adverse cardiac events. No conclusive evidence exists to indicate that either long-acting nitrates or calcium antagonists are superior for long-term treatment for symptomatic relief of angina. The committee believes that long-acting calcium antagonists are often preferable to long-acting nitrates for maintenance therapy because of their sustained 24-h effects. However, the patient's and treating physician's preferences should always be considered.

Special Clinical Situations

Newer-generation, vasoselective, long-acting dihydropyridine calcium antagonists such as amlodipine or felodipine can be used in patients with depressed LV systolic function. In patients who have sinus node dysfunction, rest bradycardia, or AV block, beta-blockers or heart rate–modulating calcium antagonists should be avoided. In patients with insulin-dependent diabetes, beta-blockers should be used with caution because they can mask hypoglycemic symptoms. In patients with mild peripheral vascular disease, there is no contraindication for use of beta-blockers or calcium antago-

B. Definition of Successful Treatment and Initiation of Treatment

1. Successful Treatment

Definition of Successful Treatment of Chronic Stable Angina

The treatment of chronic stable angina has two complementary objectives: to reduce the risk of mortality and morbid

anxiety. For some patients, the predominant symptoms may be palpitations or syncope that is caused by arrhythmias or fatigue, edema, or orthopnea caused by heart failure.

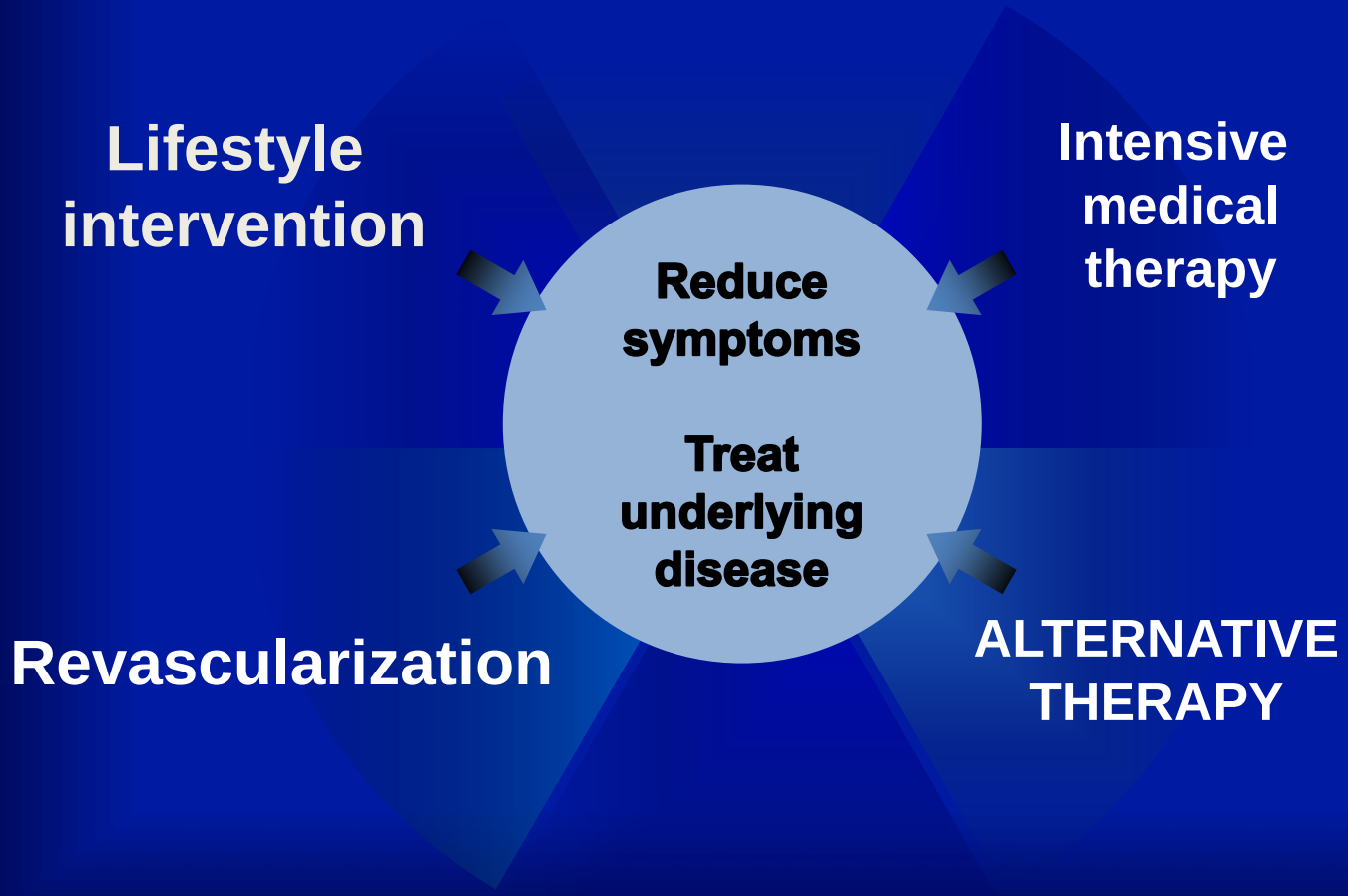
Because of the variation in symptom complexes among patients and patients' unique perceptions, expectations, and preferences, it is impossible to create a definition of treatment success that is universally accepted. For example, given an otherwise healthy, active patient, the treatment goal may be complete elimination of chest pain and a return to vigorous physical activity. Conversely, an elderly patient with more severe angina and several coexisting medical problems may be satisfied with a reduction in symptoms that enables performance of only limited activities of daily living.

The committee agreed that for most patients, the goal of treatment should be complete, or nearly complete, elimination of anginal chest pain and return to normal activities and a functional capacity of CCS class I angina. This goal should be accomplished with minimal side effects of therapy. This definition of successful therapy must be modified in light of the clinical characteristics and preferences of each patient.

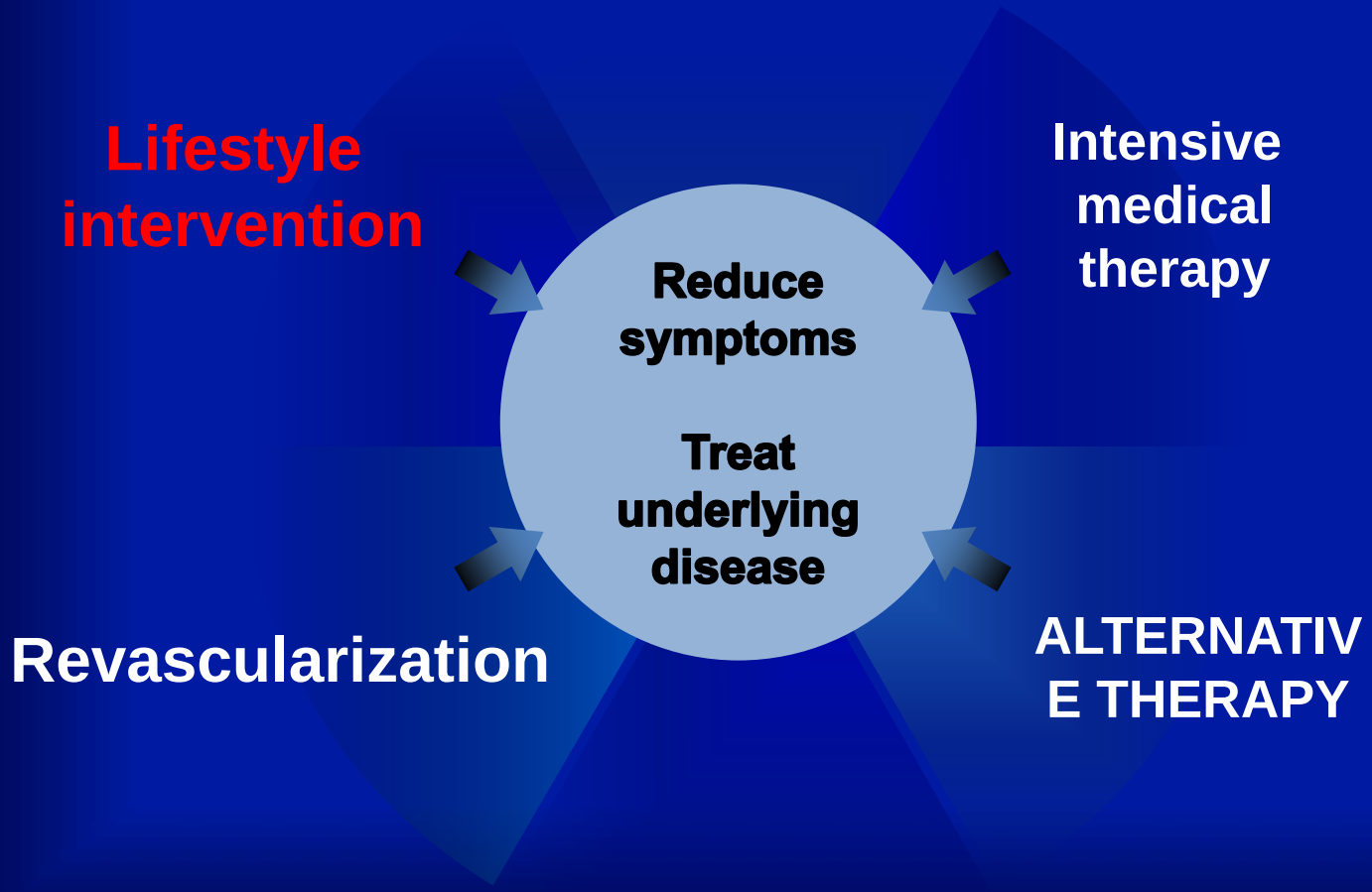
The goal of treatment should be the elimination of chest pain,to reduce hospitalizations, costs, and the restoration of normal activities

Gibbons RJ, et al. *ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina*

CAD: Multiple treatment options

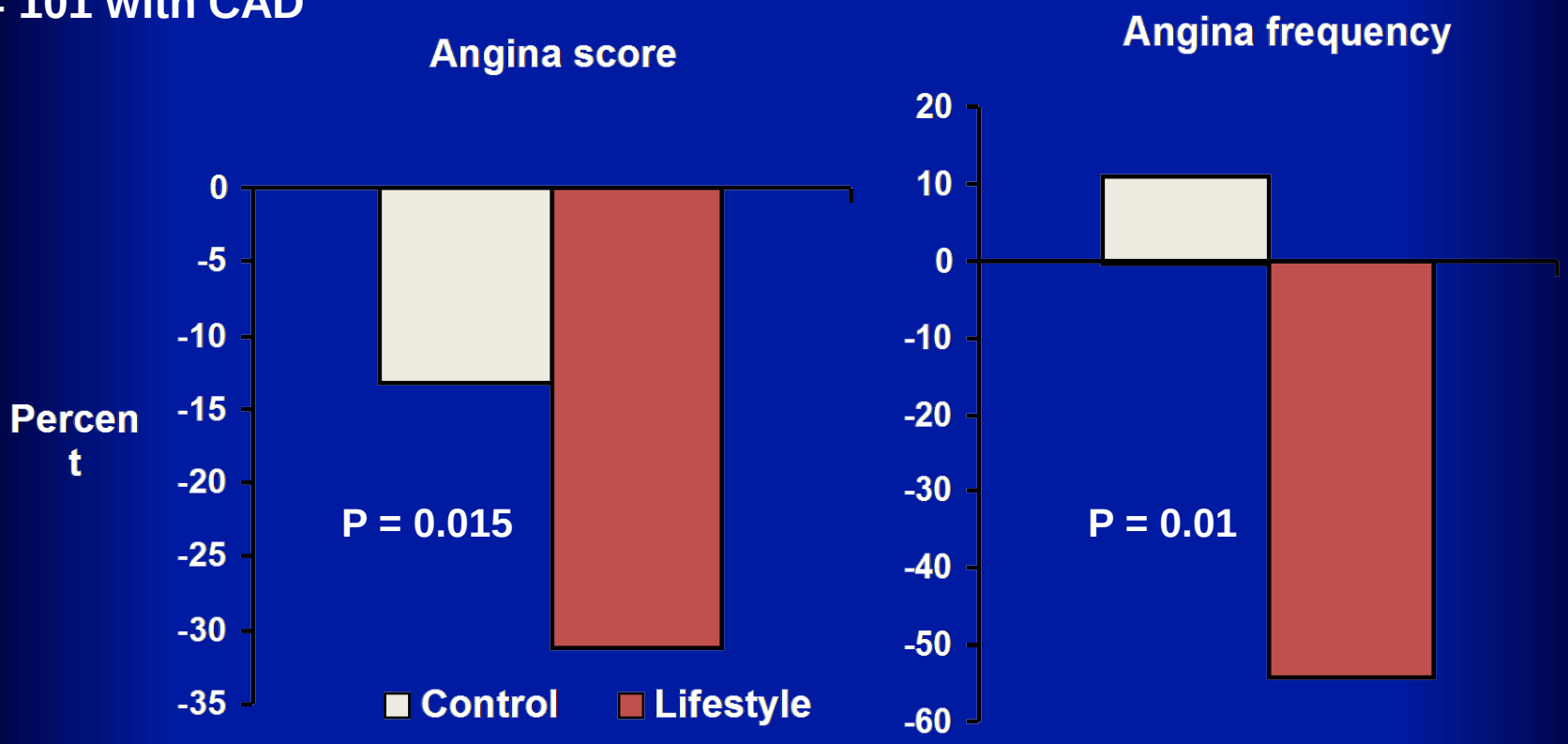


CAD: Multiple treatment options



SAFE-LIFE: Reduction in angina at 1 year with intensive lifestyle intervention

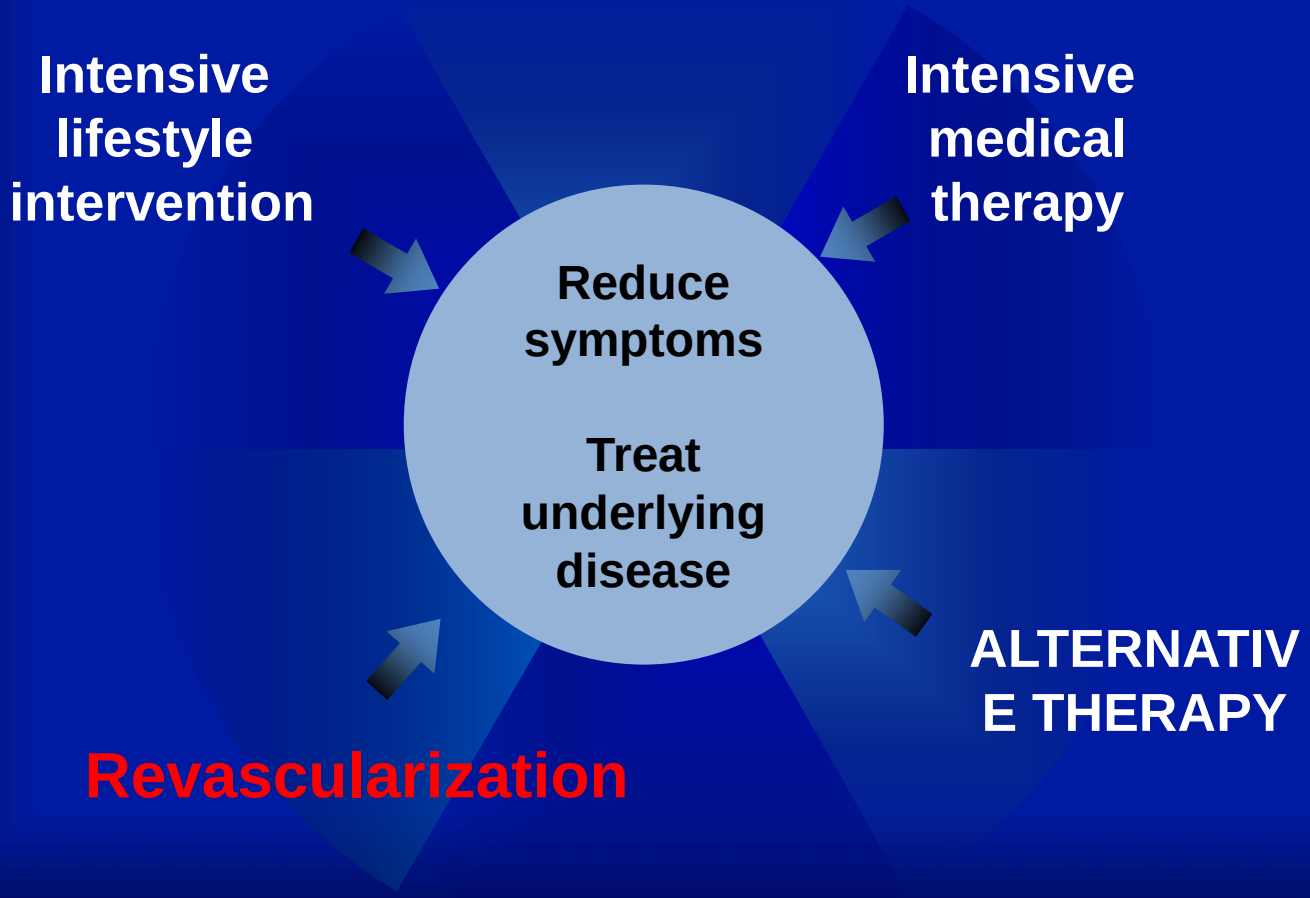
N = 101 with CAD



Michalsen A et al. *Am Heart J.* 2006;151:870-7.

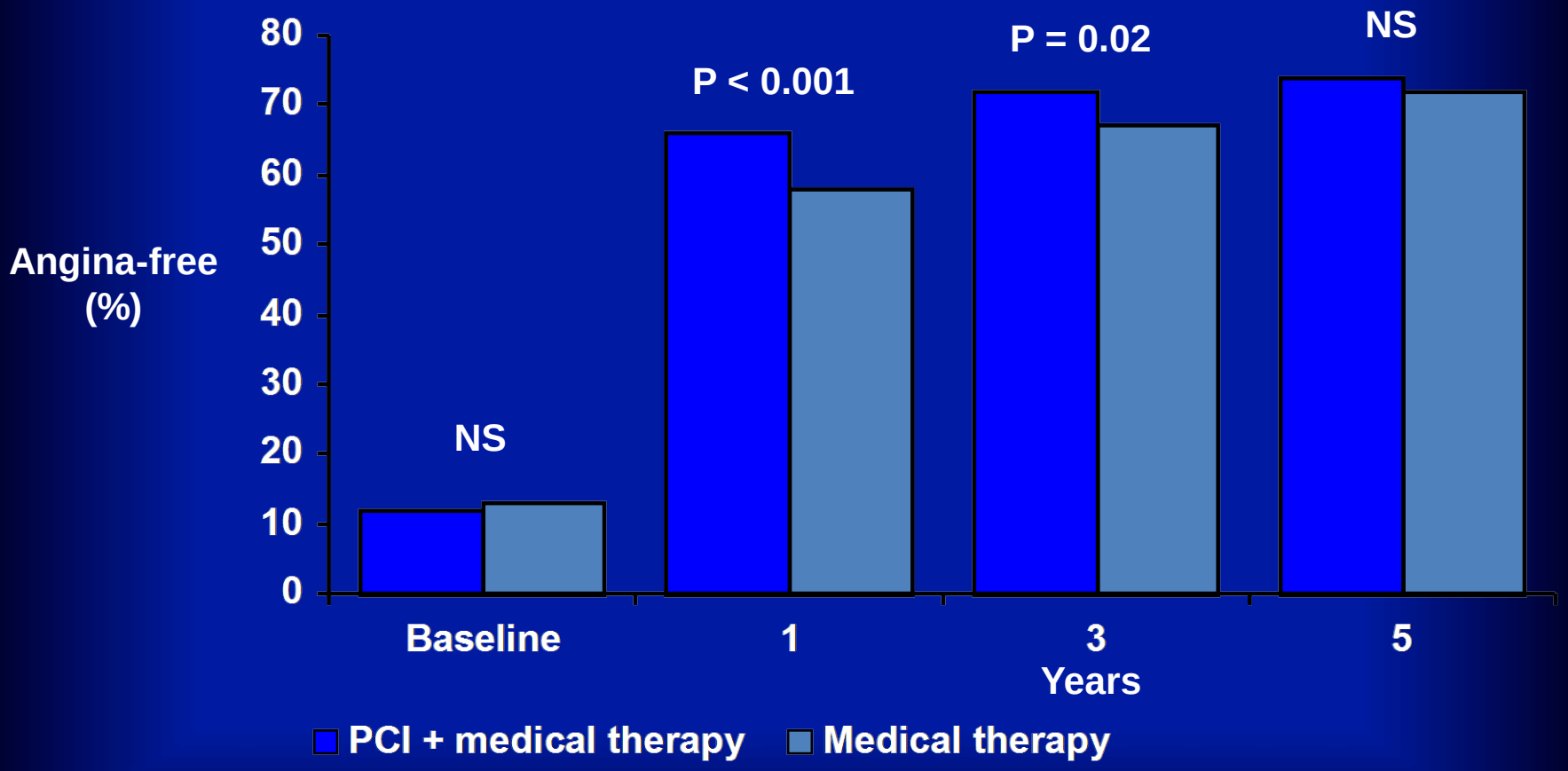
CAD: Multiple treatment options

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation



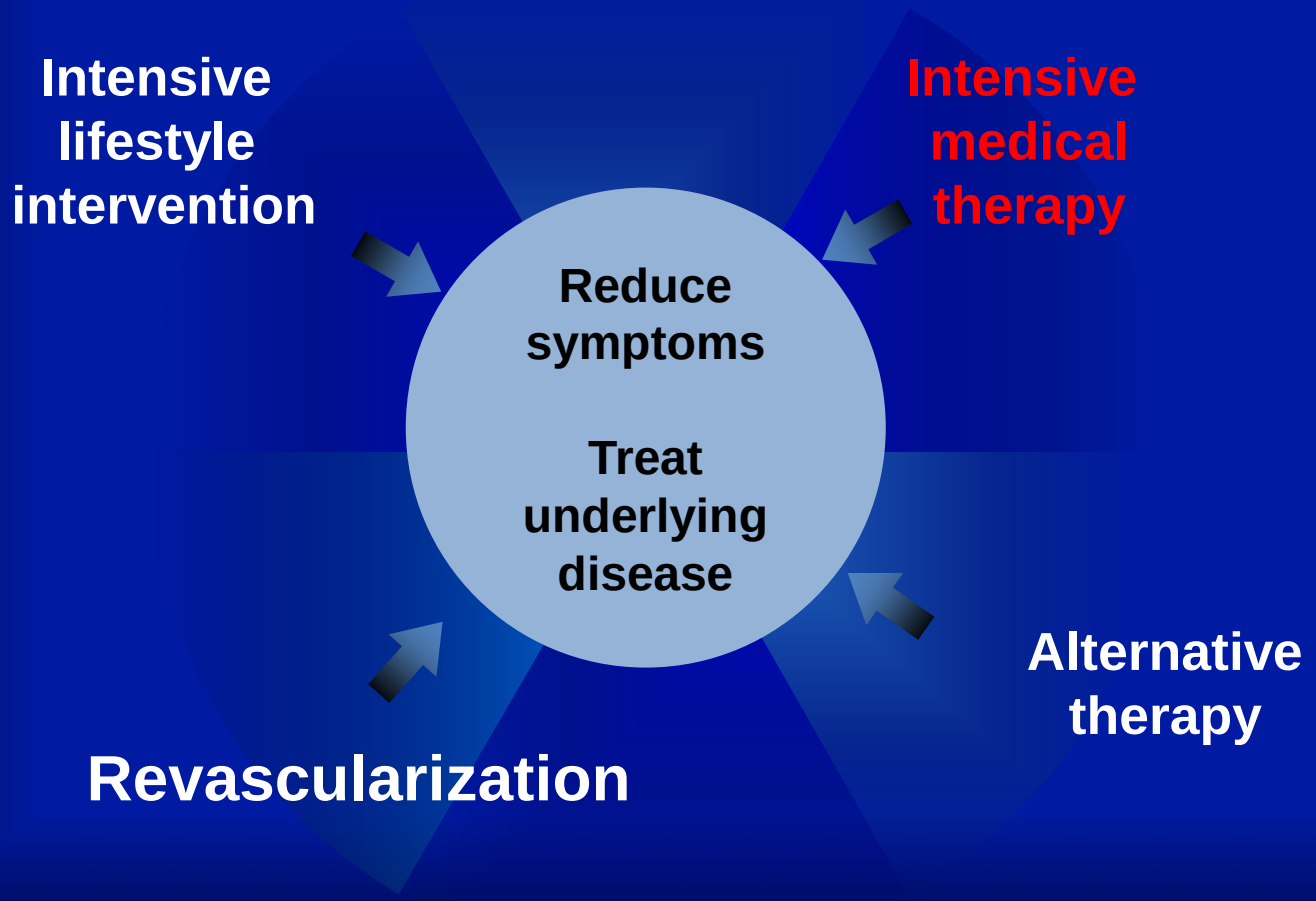
COURAGE: Treatment effect on angina

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation

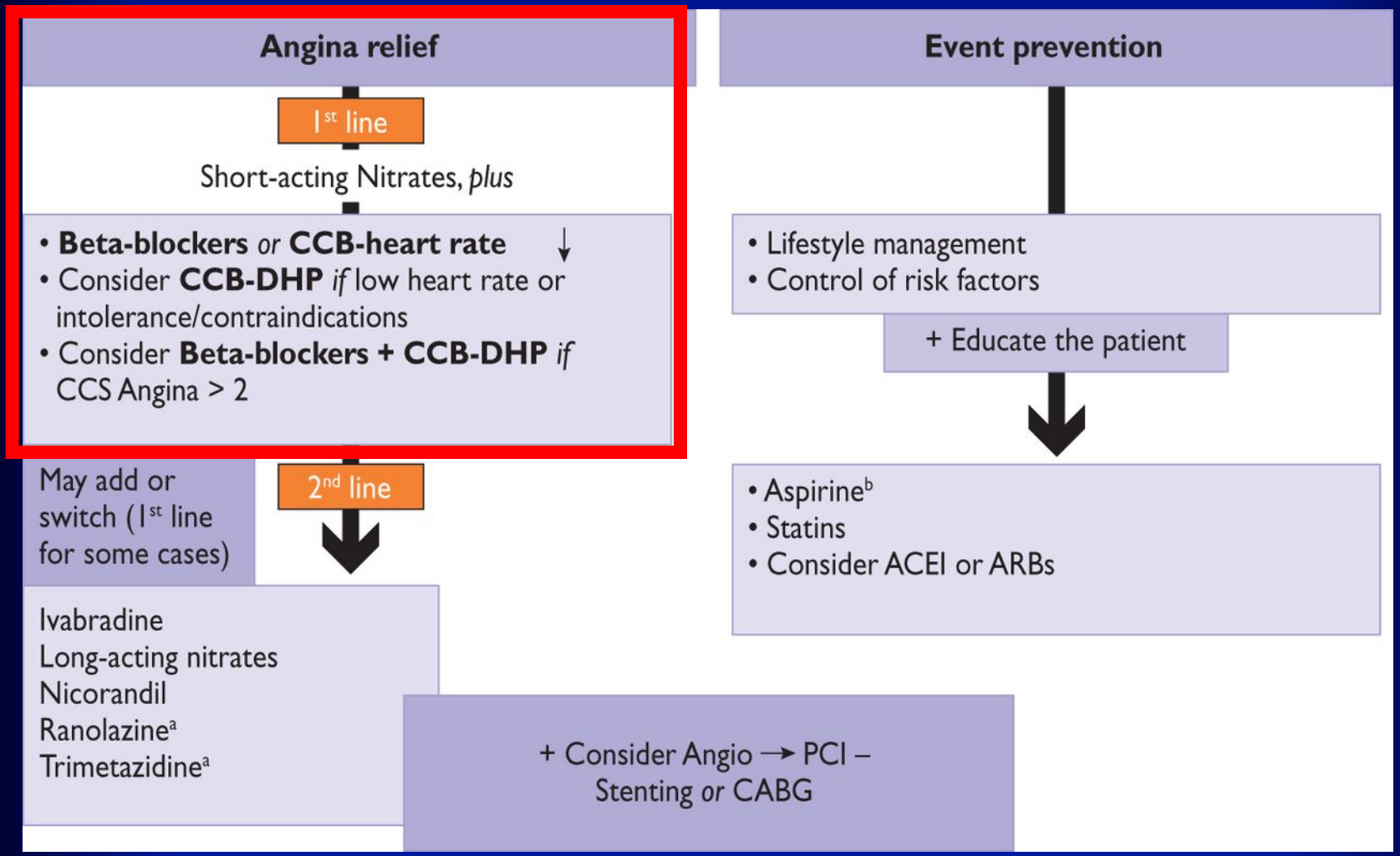


Boden WE et al. *N Engl J Med.* 2007;356:1503-16.

CAD: Multiple treatment options



Medical management of patients with stable coronary artery disease.



ESC Guidelines. Eur Heart J 2013; 34: 2949-3003

Chronic ischemic heart disease: Treatment gaps

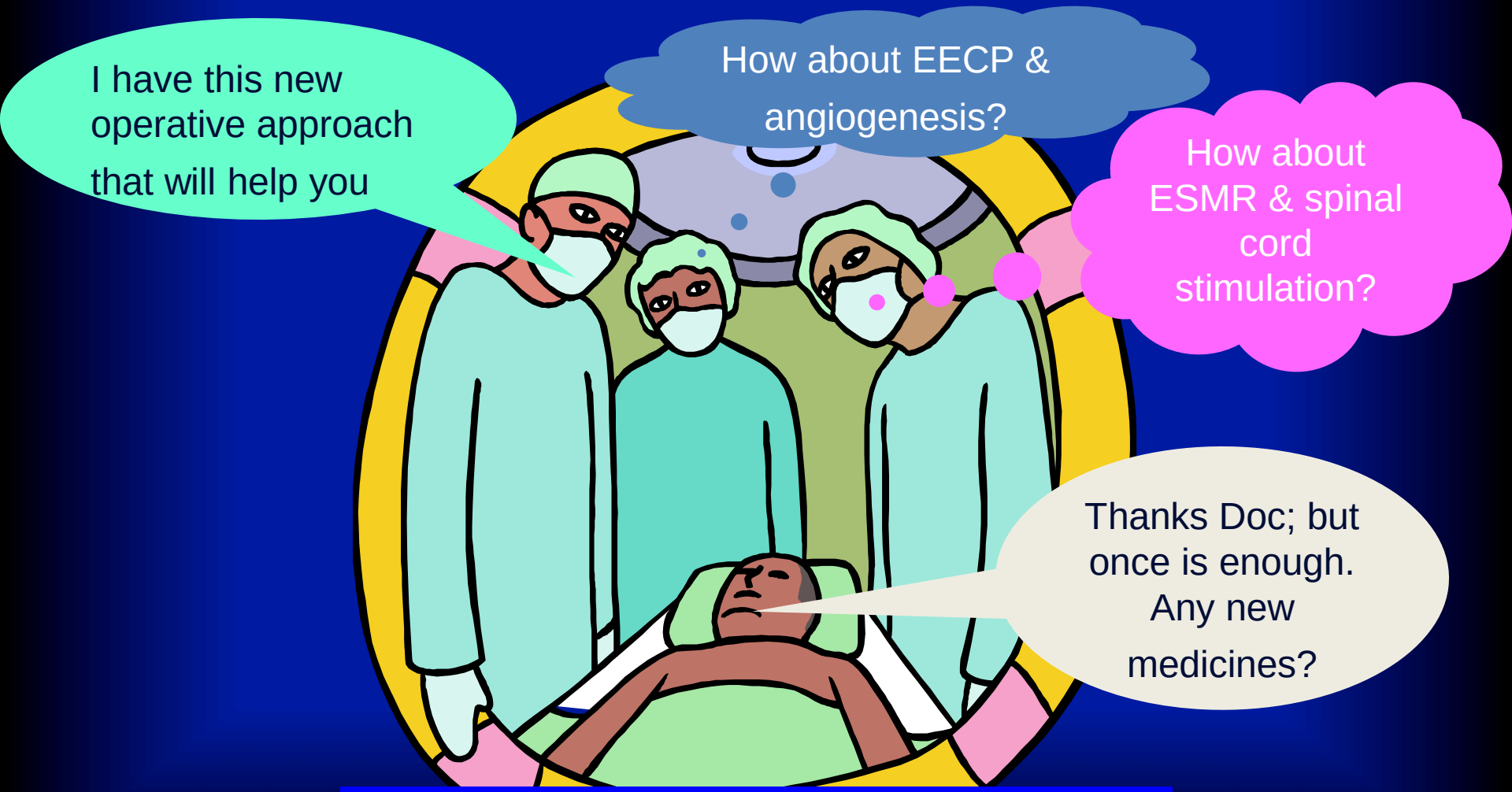
- Most patients have relative intolerances to maximum doses of traditional antianginal agents (β-blockers, CCBs, and nitrates)

- **Patients continue to experience myocardial ischemia**
- **β-blockers and many CCBs have similar depressive hemodynamic and electrophysiologic effects**

- **Antianginal drugs without these limitations are needed**

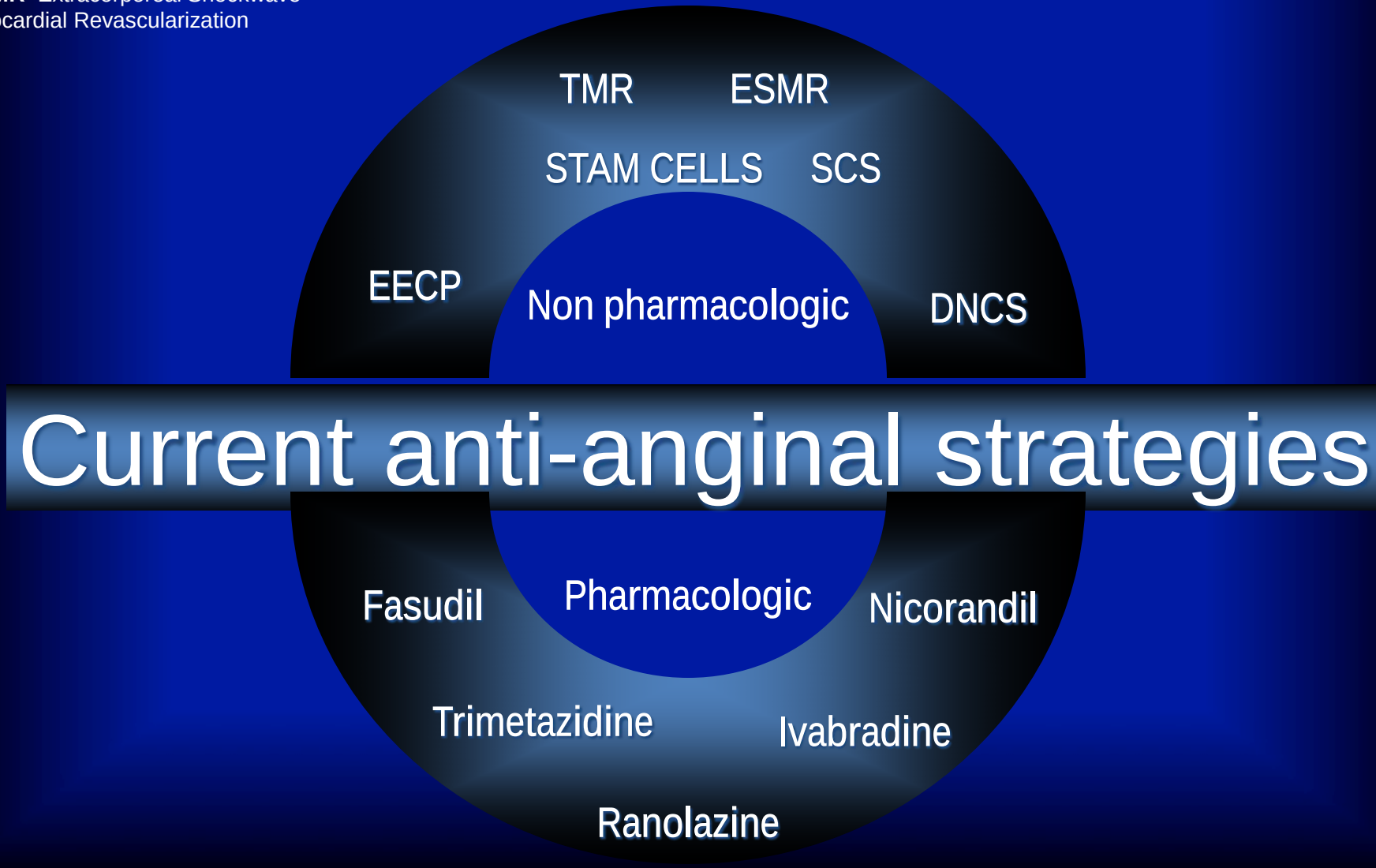
Pepine CJ et al. *Am J Cardiol*. 1994;74:226-31.
Gibbons RJ et al. www.acc.org.

Correlation – doctor's demands and patient expectations



The patient-centered approach

TMR = transmyocardial revascularization
EECP = enhanced external counterpulsation
SCS = spinal cord stimulation
DNCS=device narrows coronary sinus
ESMR=Extracorporeal Shockwave Myocardial Revascularization



New therapy approaches to myocardial ischemia

- Rho kinase inhibition (fasudil)
- Metabolic modulation (trimetazidine)
- Preconditioning (nicorandil)
- Sinus node inhibition (ivabradine)
- Late Na^+ current inhibition (ranolazine)

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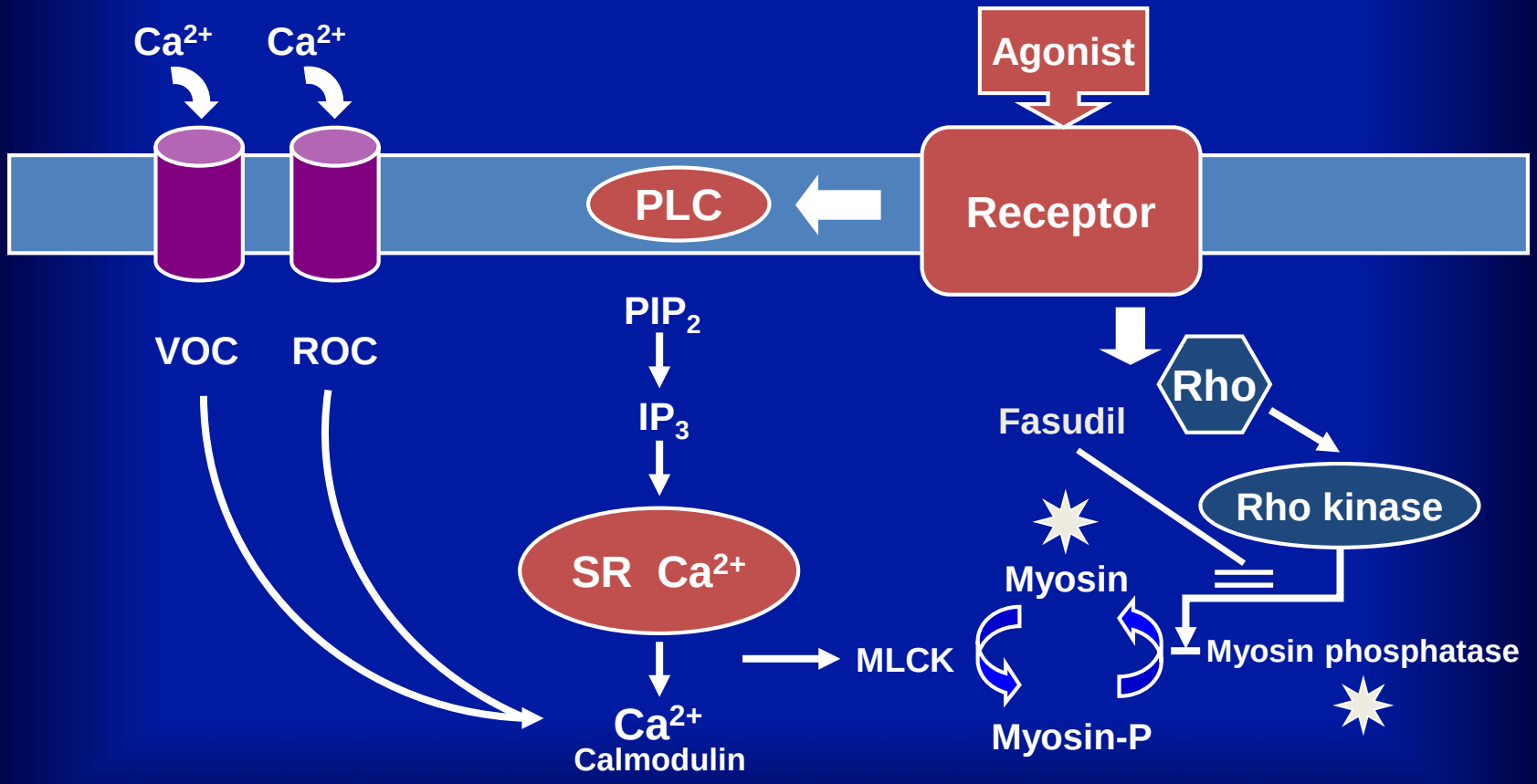
Rho kinase inhibition: Fasudil

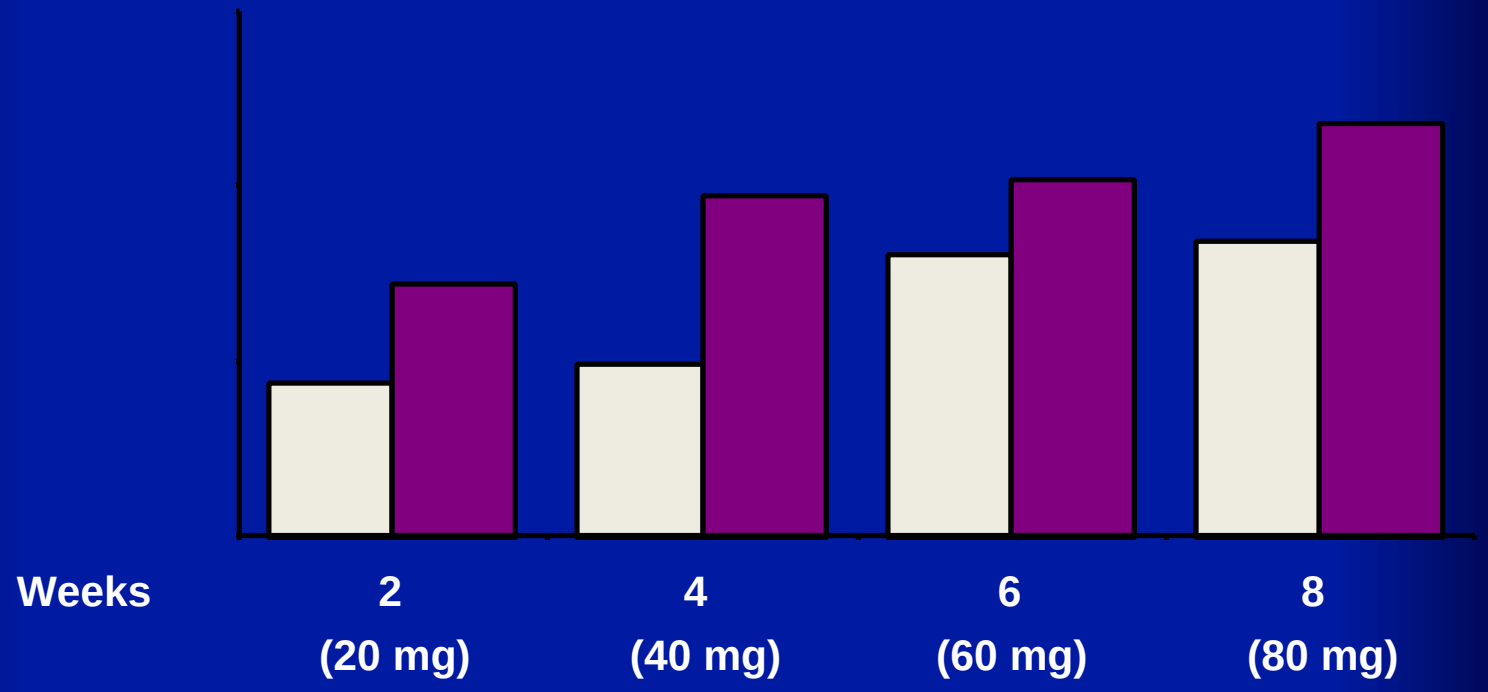
Rho kinase triggers vasoconstriction through accumulation of phosphorylated myosin



Adapted from Seasholtz TM. *Am J Physiol Cell Physiol*. 2003;284:C596-8.

Results: Fasudil improves exercise duration

N = 84



Vicari RM et al. *J Am Coll Cardiol.* 2005;46:1803-11.

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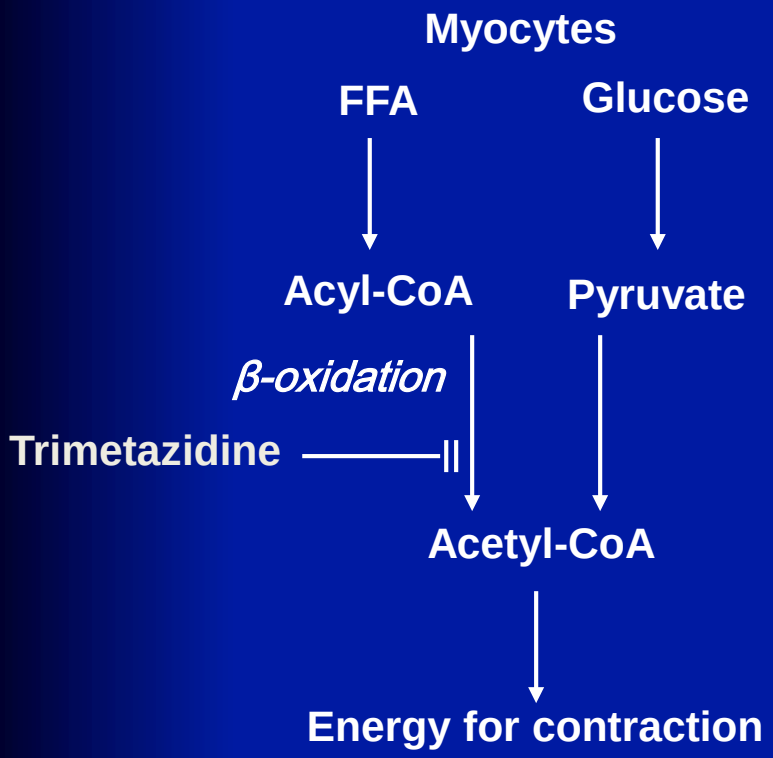
Metabolic modulation (pFOX): Trimetazidine



- O_2 requirement of glucose pathway is lower than FFA pathway
- During ischemia, oxidized FFA levels rise, blunting the glucose pathway

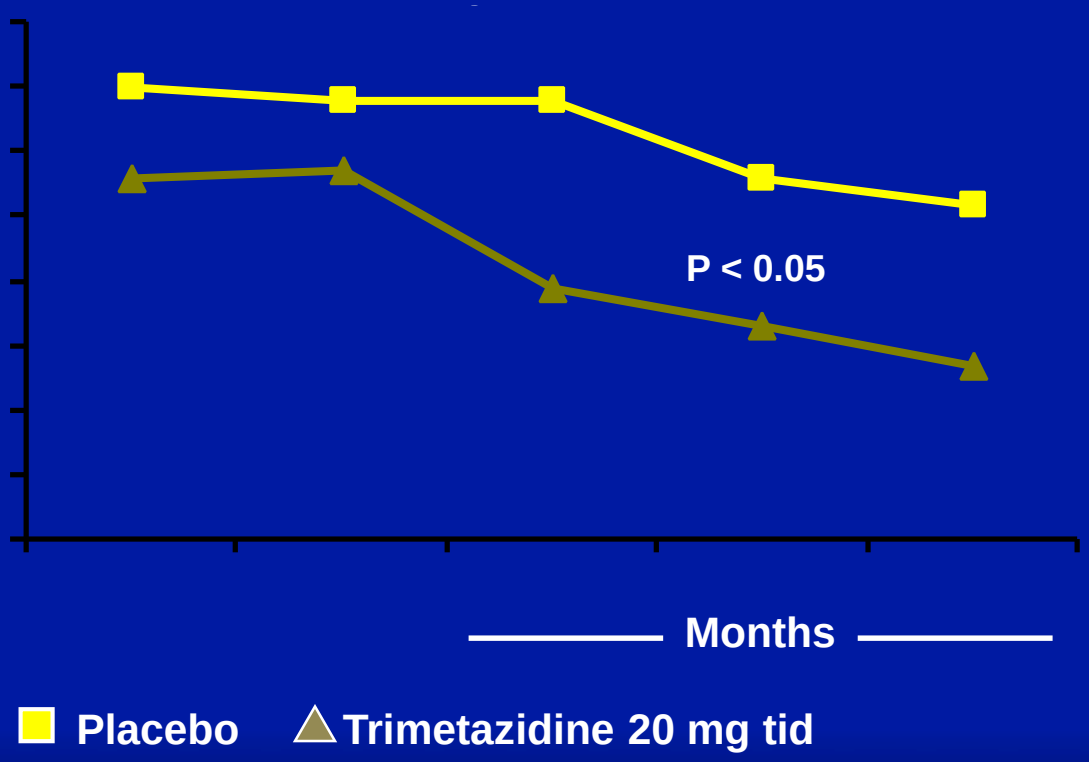
pFOX = partial fatty acid oxidation
FFA = free fatty acid

MacInnes A et al. *Circ Res.* 2003;93:e26-32.
Lopaschuk GD et al. *Circ Res.* 2003;93:e33-7.
Stanley WC. *J Cardiovasc Pharmacol Ther*. 2004;9(suppl 1):S31-45.

TACT: Trimetazidine reduces angina episodes

Trimetazidine in Angina Combination Therapy

N = 166 men with CCS class I–III angina



Chazov EI et al. *Am J Ther.* 2005;12:35-42.

New therapy approaches to myocardial ischemia

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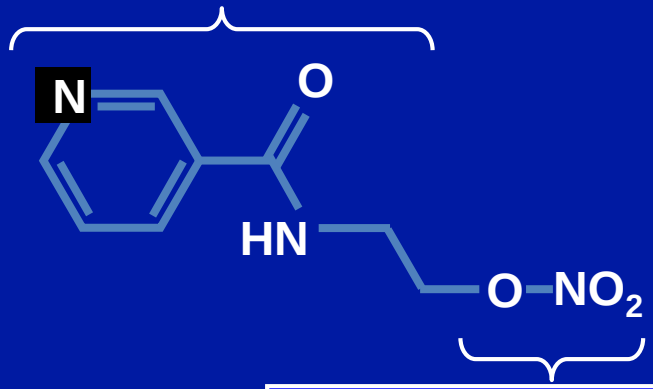
Preconditioning: Nicorandil

Activation of ATP-sensitive K^+ channels
- **Ischemic preconditioning**
- **Dilation of coronary resistance arterioles**

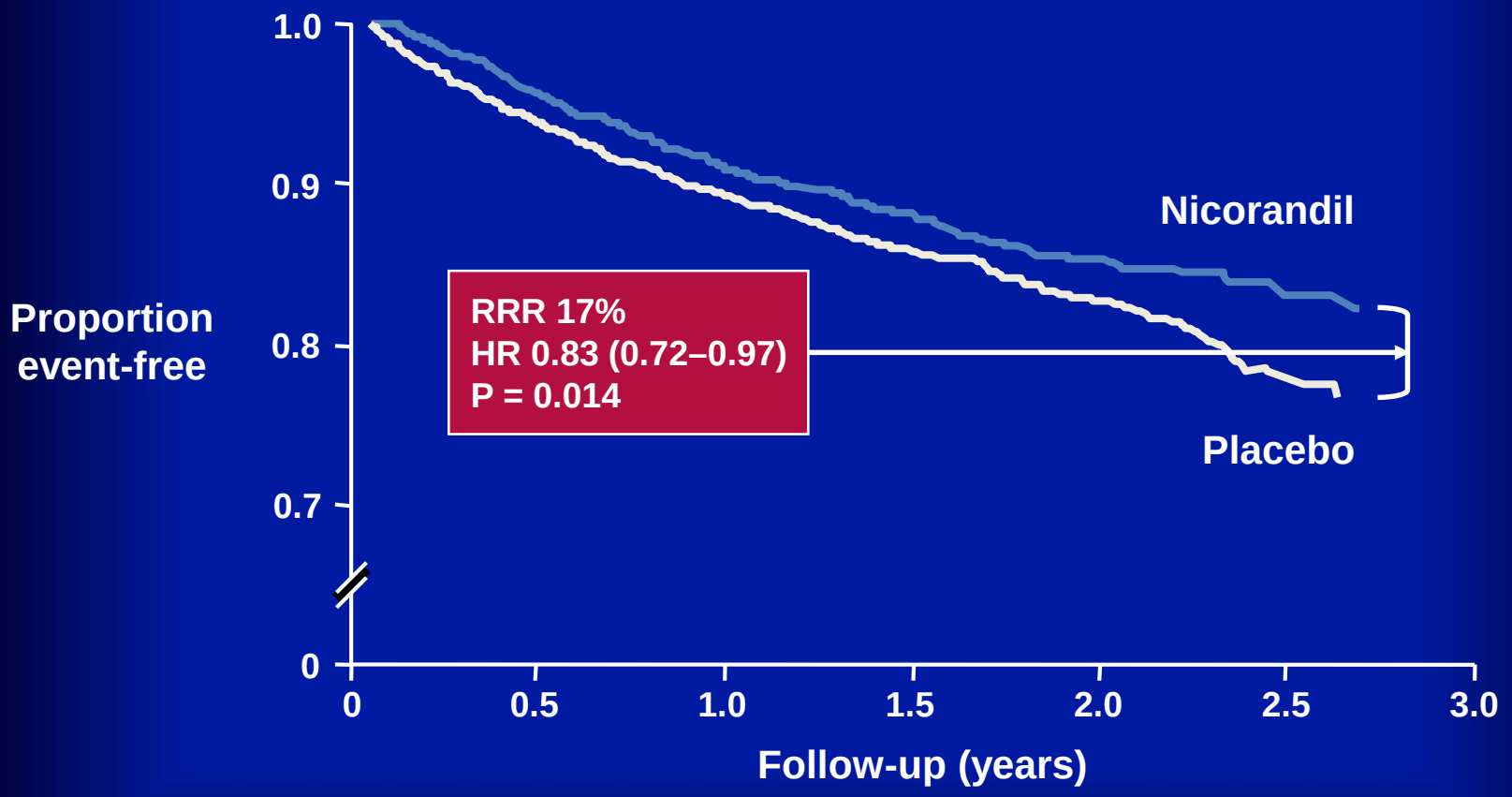


Nitrate-associated effects
- **Vasodilation of coronary epicardial arteries**

IONA Study Group. *Lancet.* 2002;359:1269-75.
Rahman N et al. *AAPS J*. 2004;6:e34.

IONA: Reduction in primary outcome

CHD death, nonfatal MI, hospitalization for chest pain



IONA Study Group. *Lancet.* 2002;359:1269-75.

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- Metabolic modulation (trimetazidine)
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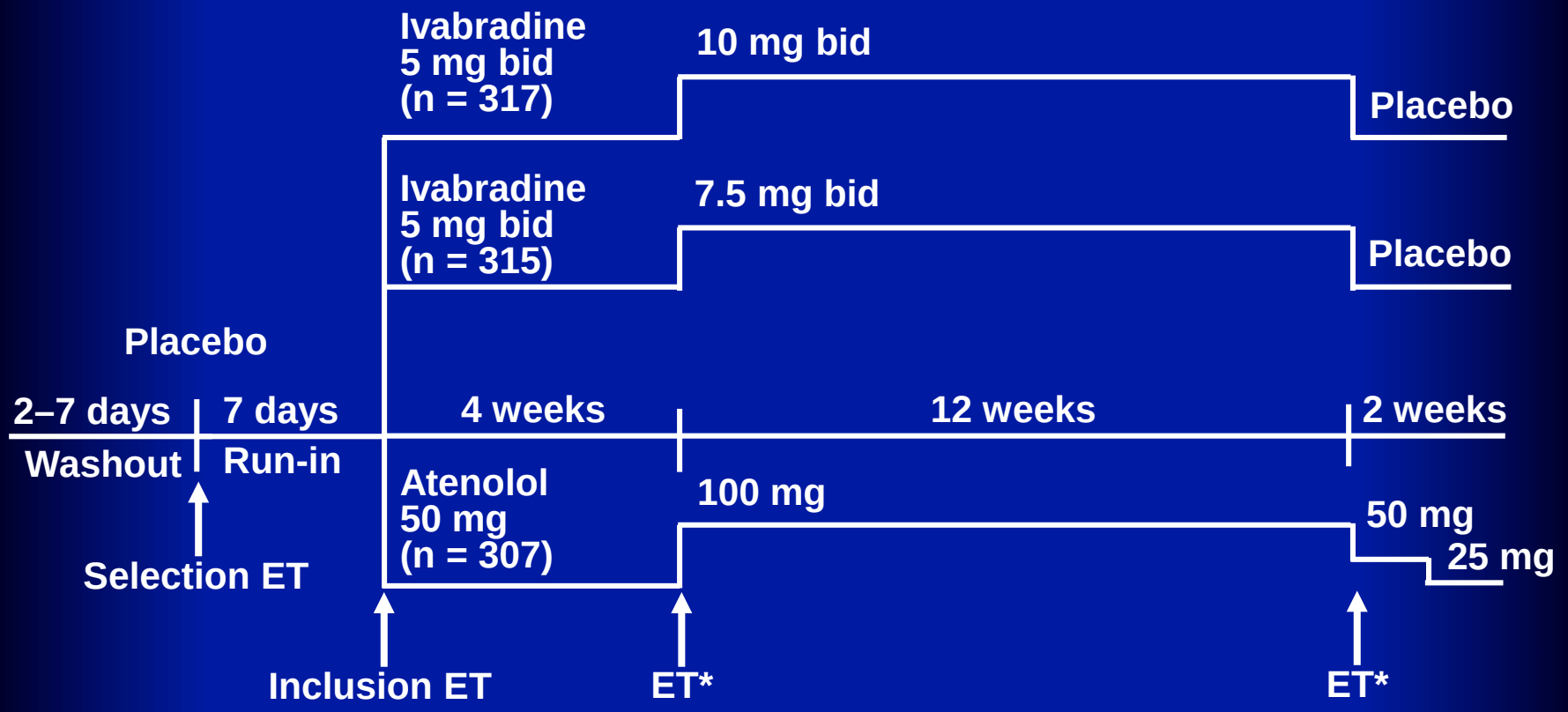
- Sinus node inhibition (ivabradine)
- Late Na^+ current inhibition (ranolazine)

INITIATIVE: Study design

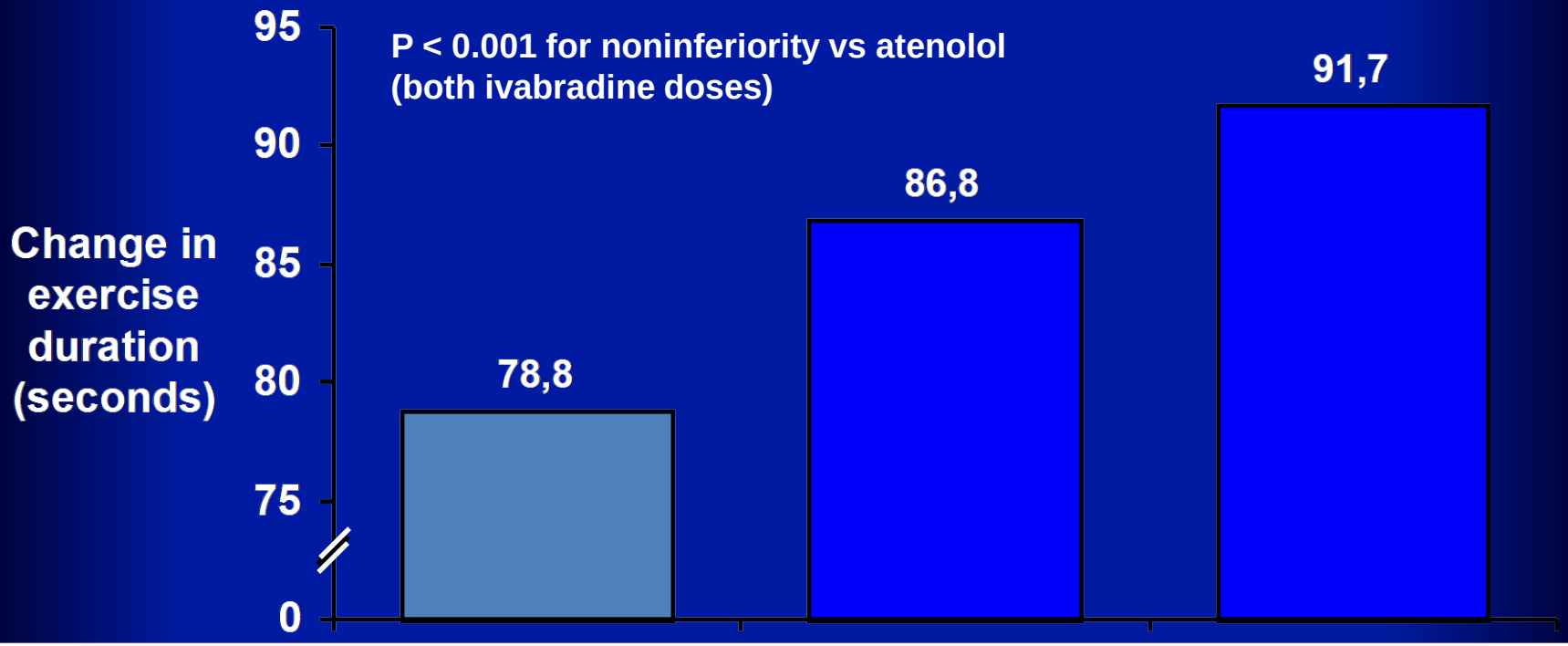
International Trial on the Treatment of Angina with Ivabradine vs. Atenolol



ET = exercise test (treadmill)
***ET at trough and 4 hours post-dose**

Tardif J-C et al. *Eur Heart J*. 2005;26:2529-36.

INITIATIVE: Effects of ivabradine vs β-blockade on primary outcome



I_f current inhibition may be as effective as β-blockade in treatment of stable angina

Patients completing trial

Tardif J-C et al. *Eur Heart J*. 2005;26:2529-36.

New therapy approaches to myocardial ischemia

- Rho kinase inhibition (fasudil)
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- Preconditioning (nicorandil)
- Sinus node inhibition (ivabradine)
- Late Na^+ current inhibition (ranolazine)

Ranolazine: Late Na^+ current inhibitor

- First new class of antianginals to be approved in the US since 1960s
- Antianginal and anti-ischemic effects with no change in HR or BP
- May be used in patients with slow HR, low BP, prolonged AV conduction, CHF, diabetes, or asthma
- Modest prolongation of QTc interval with no known clinical sequelae

Ranolazine: Pathophysiologic effects vs older antianginals

	O_2 Supply	O_2 Demand			
Drug class	**Coronary blood flow**	**Heart rate**	**Arterial pressure**	**Venous return**	**Myocardial contractility**
β-blockers	—	↓	↓	—	↓
DHP CCBs	↑	↑*	↓	—	↓
Non-DHP CCBs	↑	↓	↓	—	↓
Long-acting nitrates	↑	↑ / —	↓	↓	—
Late Na^+ current inhibitors (ranolazine)	—	—	—	—	—†

***Except amlodipine**
†Ranolazine: No direct effect but may prevent ischemia-related decline

Boden WE et al. *Clin Cardiol*. 2001;24:73-9.
Gibbons RJ et al. ACC/AHA 2002 guidelines. www.acc.org/clinical/guidelines/stable/stable.pdf
Kerins DM et al. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10th ed.

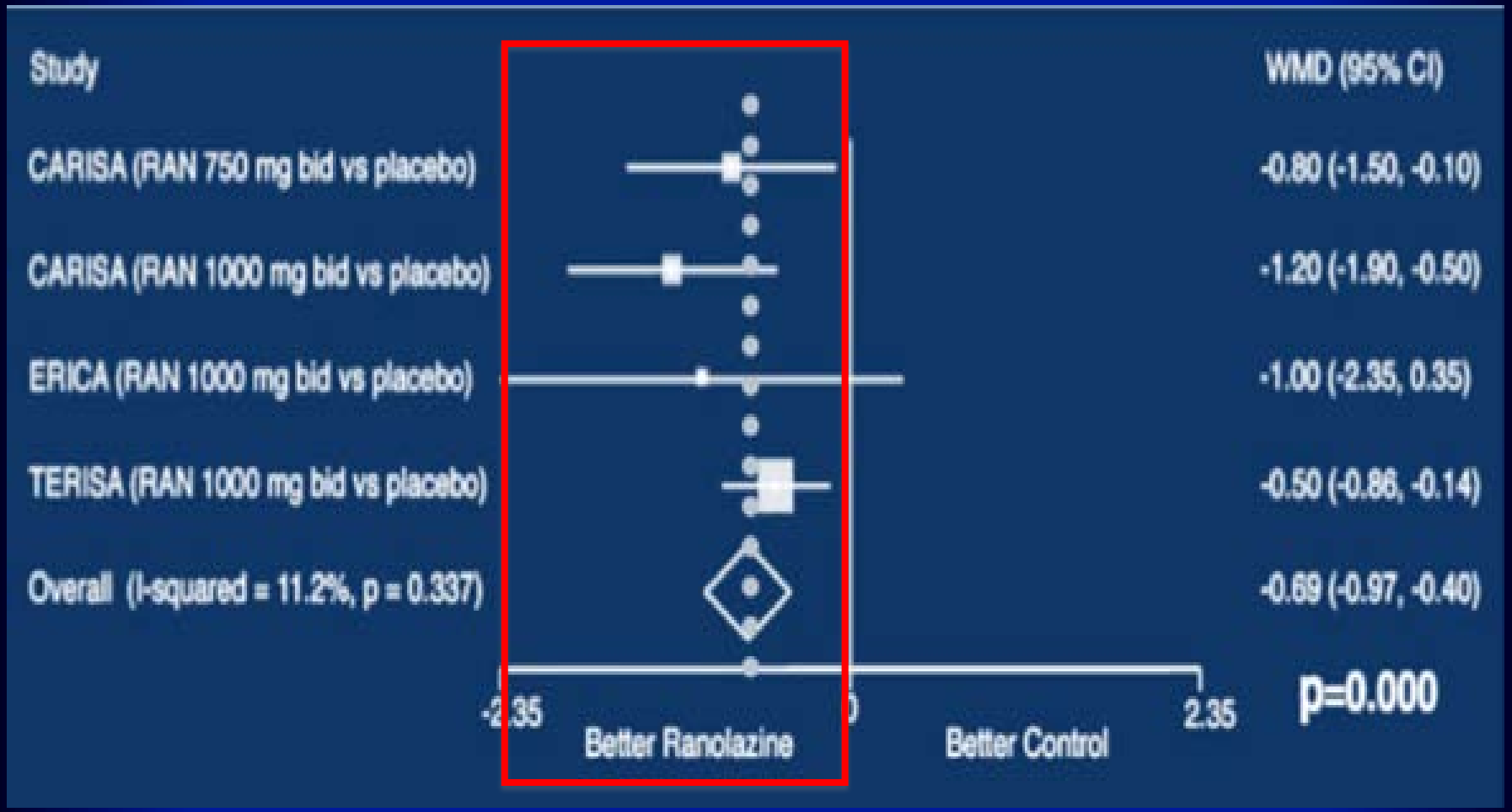
Ranolazine clinical trial program in chronic stable angina

Study	N	Ranolazine dosing (mg bid)	Background antianginal therapy
MARISA	191	500 1000 1500	No
CARISA	823	750 1000	Amlodipine 5 mg Atenolol 50 mg Diltiazem 180 mg
ERICA	565	1000	Amlodipine 10 mg

Monotherapy Assessment of Ranolazine In Stable Angina
Combination Assessment of Ranolazine In Stable Angina
Efficacy of Ranolazine In Chronic Angina

Chaitman BR et al. *J Am Coll Cardiol.* 2004.
Chaitman BR et al. *JAMA.* 2004.
Stone PH et al. *J Am Coll Cardiol.* 2006.

Ranolazine and angina (weekly onset)

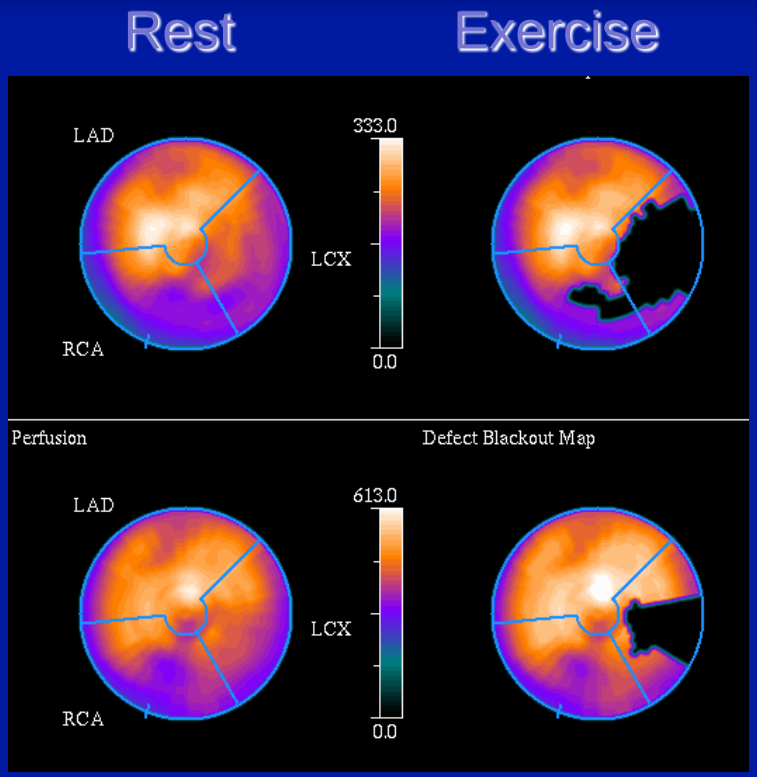


Int J Cardiol 2013

Effects of Ranolazine on Stress MPI

Baseline
Peak HR = 142 bpm

After RAN (3-4 wks)
Peak HR = 142 bpm



25%

10%

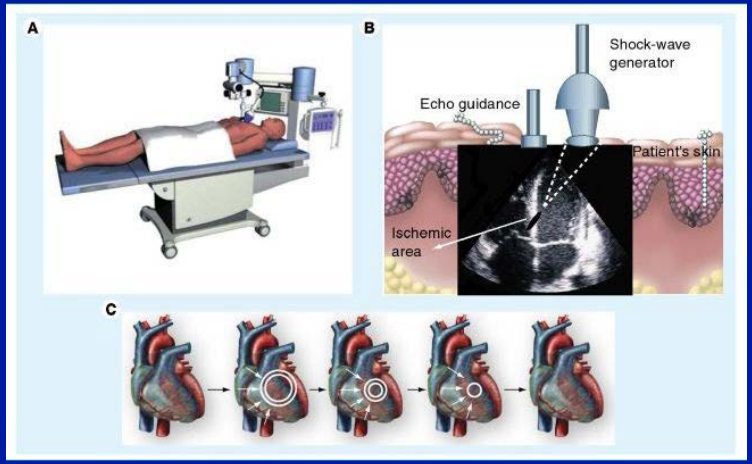
Reversible Perfusion Defect Size

MPI Variables (n=21)	Baseline	After RAN	p Value
Summed difference score	**7.2 ± 5**	**4.7 ± 4**	**0.006**
Total perfusion defect size (PDS)	**24 ± 16**	**17 ± 15**	**0.003**
Ischaemia PDS	***16 ± 11***	***8 ± 5***	***0.005***

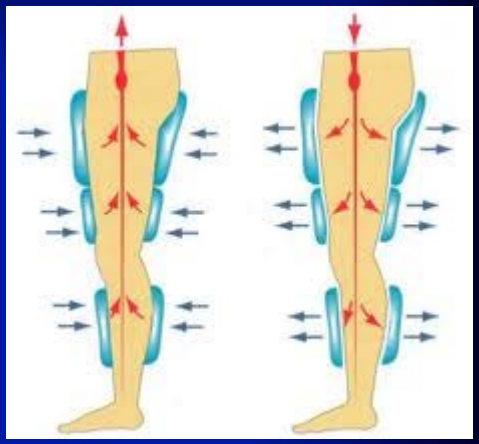
Venkataraman *J. A C C : C ardiovascular Imaging, V O L . 2 , N O . 1 1 , 2 0 0 9*

OTHER OPTIONS

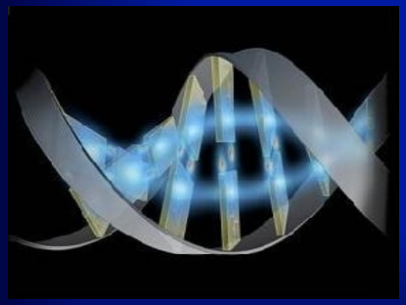
Laser revascularization



Extracorporeal Shockwave Myocardial Revascularization (ESMR)



External couterpulsation



Gene therapy

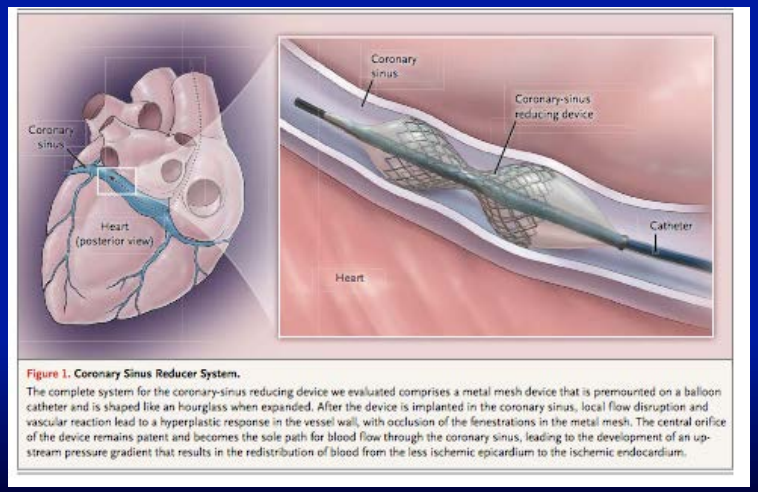
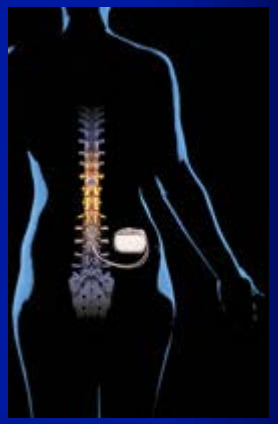
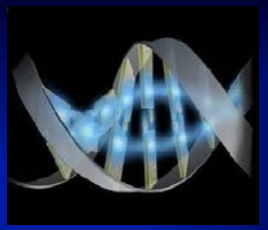


Figure 1. Coronary Sinus Reducer System.
The complete system for the coronary-sinus reducing device we evaluated comprises a metal mesh device that is premounted on a balloon catheter and is shaped like an hourglass when expanded. After the device is implanted in the coronary sinus, local flow disruption and vascular reaction lead to a hyperplastic response in the vessel wall, with occlusion of the fenestrations in the metal mesh. The central orifice of the device remains patent and becomes the sole path for blood flow through the coronary sinus, leading to the development of an upstream pressure gradient that results in the redistribution of blood from the less ischemic epicardium to the ischemic endocardium.



Spinal cord stimulation

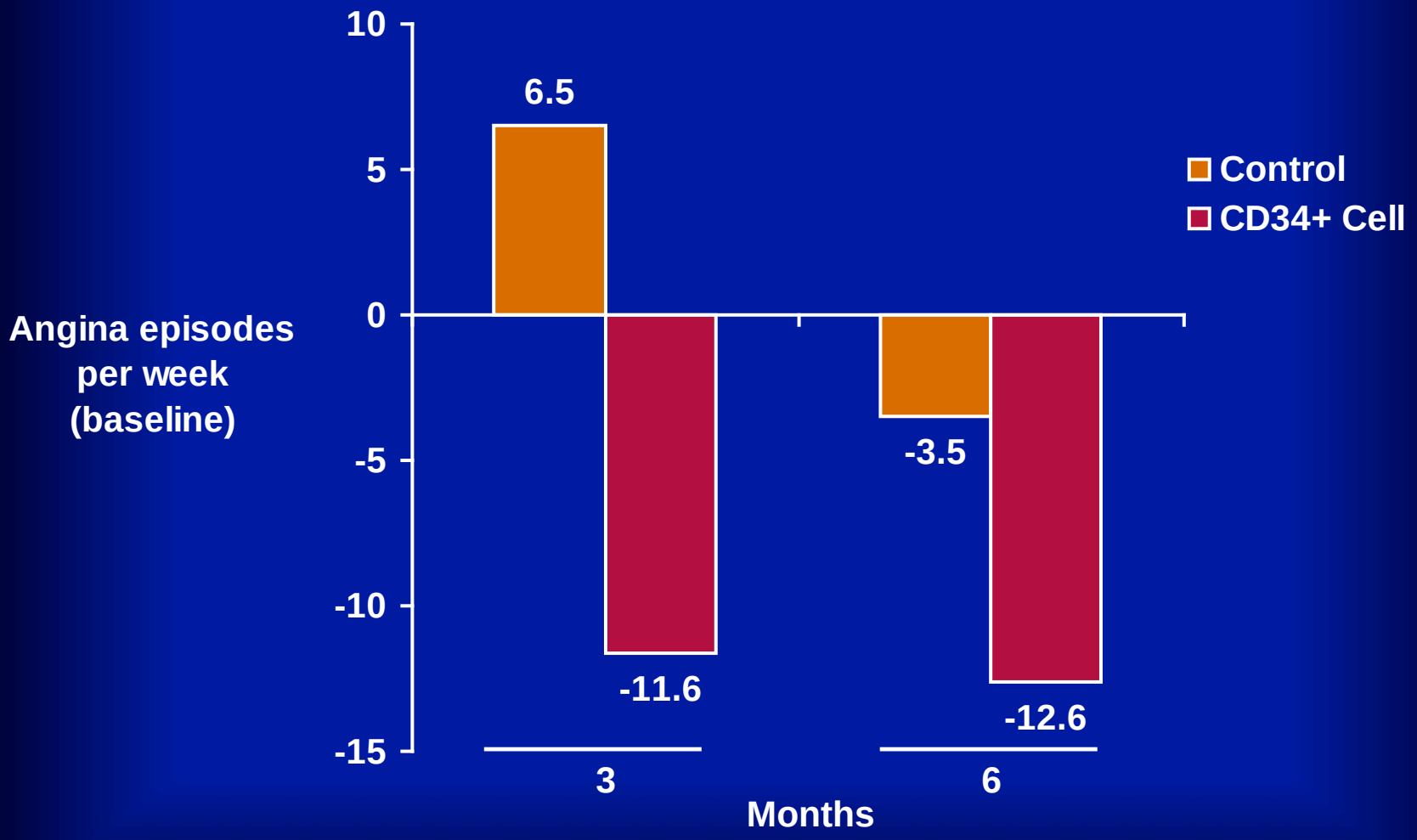


Autologous $CD34^+$ cells for intractable angina

- N = 24 patients with CCS class 3/4 angina
- G-CSF 5 μg/kg/day x 5 days
- Leukapheresis performed on Day 5
- $CD34^+$ cell selection
- NOGA-guided transplantation to zones of myocardial ischemia
- Phase I/IIa double-blind, 3:1 randomization, with crossover of placebo patients using frozen cells

Losordo DW et al. *Circulation.* 2007;115:3165-72.

Decrease in angina frequency with CD34+ cell therapy

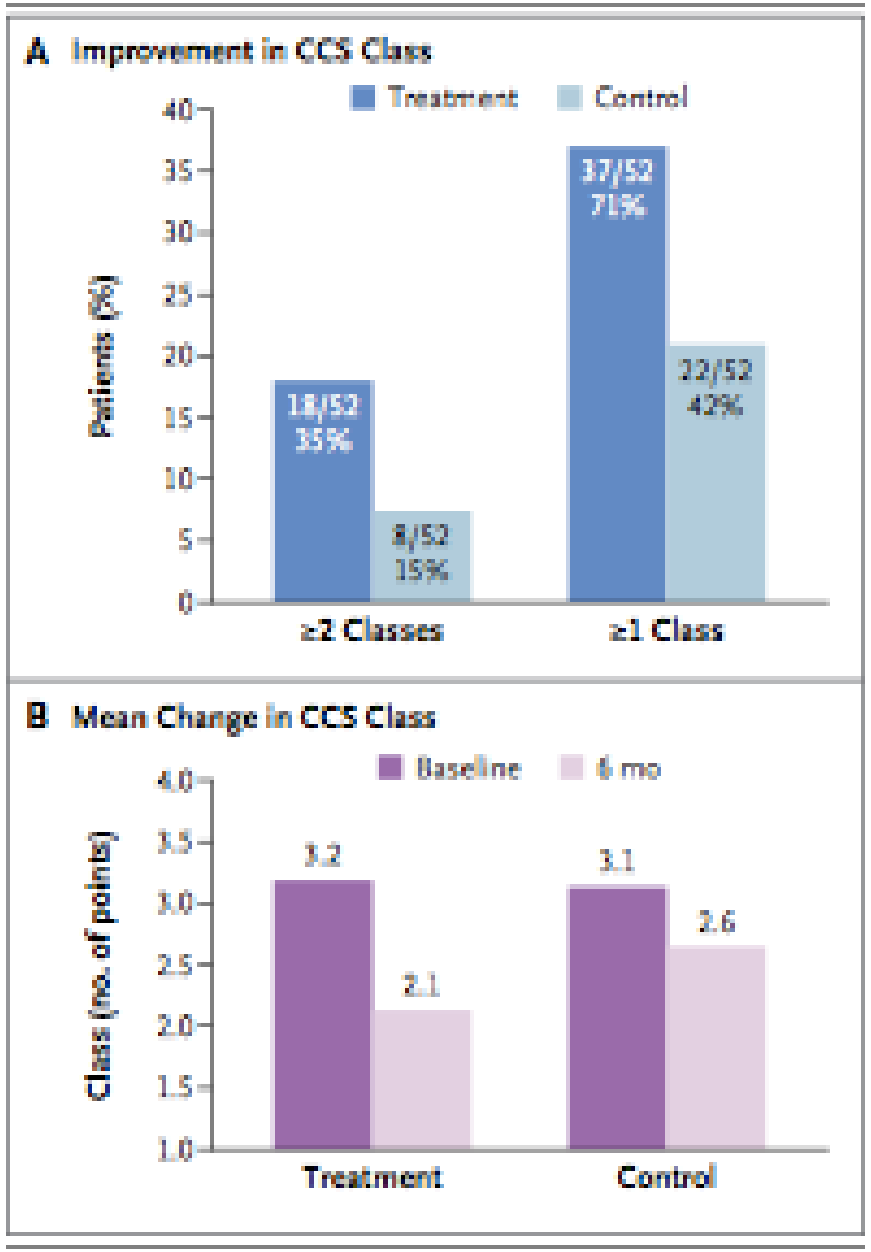


Losordo DW et al. *Circulation.* 2007;115:3165-72.

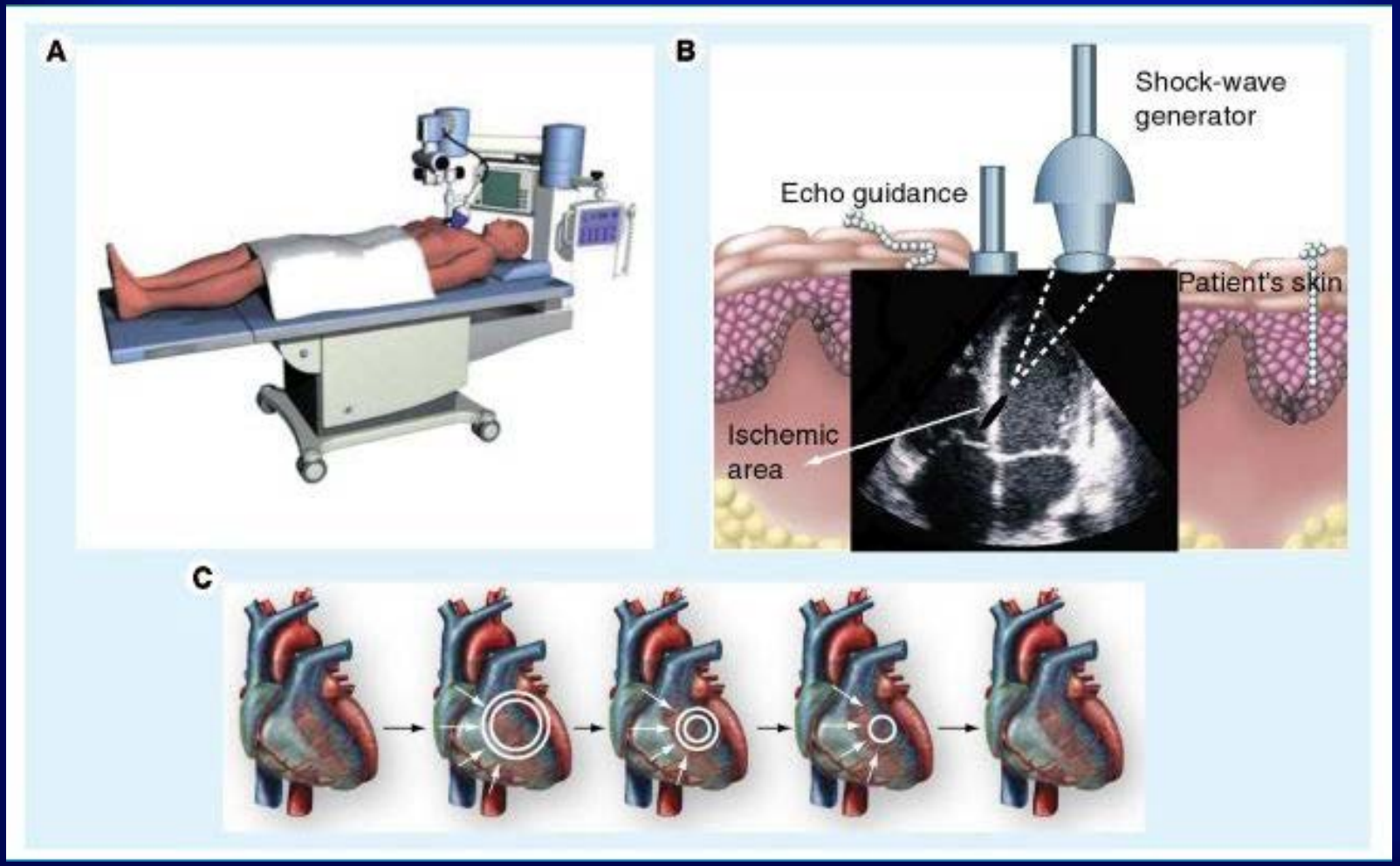
ORIGINA

Efficacy of a Device t
Sinus in Refi

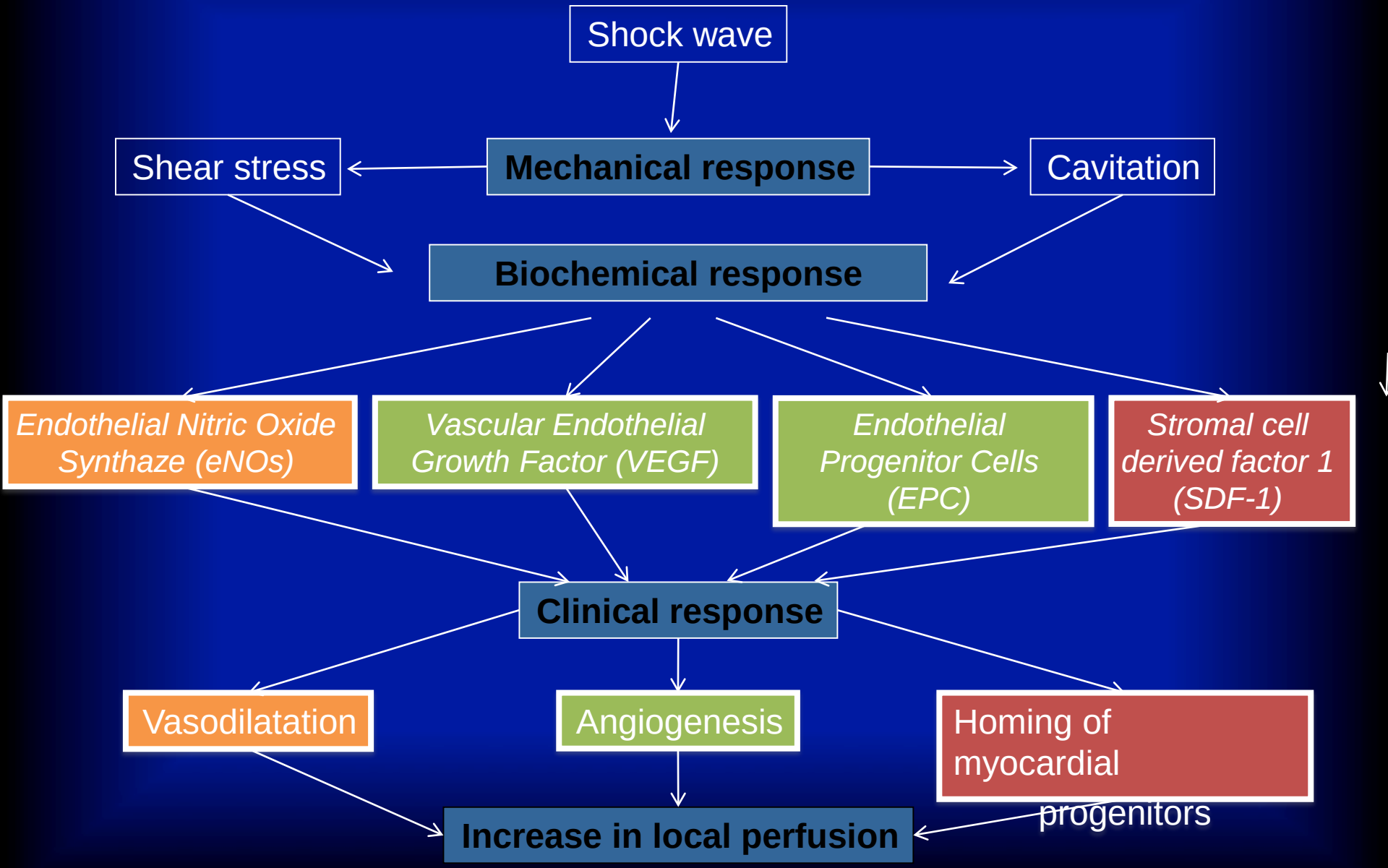
Stefan Verheye, M.D., Ph.D., E. Marc
Thomas Pettersson, M.D., Paul S
Mathias Vrolix, M.D., Pierfrancesco A



Extracorporeal Shockwave Myocardial Revascularization (ESMR)



Low-energy shock waves



Study	Patient group	Placebo-controlled	Effects	Follow-up	Side Effects
Gutersohn et al. 2006	14	No	↓ CCS class ↑ Exercise tolerance ↑ Perfusion (SPECT)	12 months	None
Schmid et al. 2006	15	Yes	↑ Ischemic threshold ↑ Exercise tolerance	6 months	None
Naber et al. 2007	25	No	↓ CCS class ↑ Exercise tolerance ↑ Perfusion (SPECT)	3 months	None
Zuoziene et al. 2010	16	No	↓ CCS class ↑ Perfusion (SPECT)	6 months	1 CABG repeated
Kikuchi et al. 2010	8	Yes	↓ CCS class ↓ NTG use ↑ 6MWT distance ↑ LEVF (MRI)	3 months	None
Fu et al. 2010	27	No	↓ CCS class ↑ Exercise tolerance ↑ Perfusion (SPECT)	6 months	1 discontinuation
Faber et al. 2010	16	No	↓ CCS class ↑ Myocardial blood flow (PET)	3 months	None
Vainer et al. 2010	27	No	↓ CCS class ↓ NTG use ↑ Exercise tolerance ↑ Perfusion (SPECT)	4 months	Transient dizziness in 4 patients,
Leibowitz et al 2010	18	Yes	↑ SAQ ↑ Exercise tolerance ↑ Perfusion (SPECT)	3 months	1 hospitalized with ACS (and underwent PCI
Vasyuk et al. 2010	24	No	↓ NYHA, CCS class ↓ NTG use ↑ LEVF (SPECT) ↑ Perfusion (SPECT)	6 months	1 discontinuation

Improvement in CCS class

* n=361

The beneficial effect of extracorporeal shockwave myocardial revascularization in patients with refractory angina

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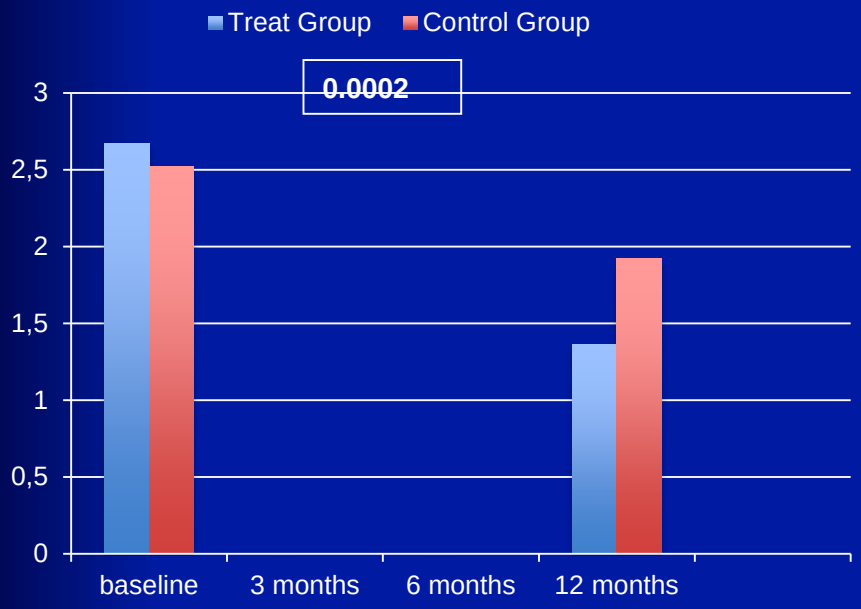
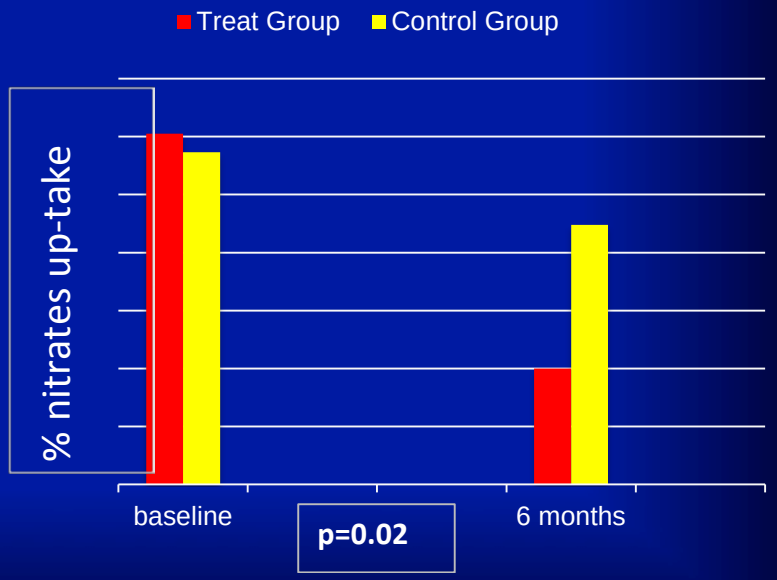
	Cases group (n 43)	Control group (n 29)	p
Mean age (years)	70 ± 5.3	71 ± 5.3	0.4
M/F	36/9 (83.7%)	24/5 (79%)	0.9
Hypertension	43 (100%)	29 (100%)	1
Diabetes mellitus	14 (32.5%)	8 (27%)	0.65
Hyperlipidemia	41 (95.3%)	28 (96%)	0.8
Previous STEMI	22 (51.1%)	11 (38%)	0.26
Previous NSTEMI	16 (37.2%)	12 (41%)	0.7
Previuous PCI	38 (88.4%)	21 (72%)	0.08
Prevoius CABG	21 (48.8%)	9 (31%)	0.13
Previous stroke	3 (7%)	1 (3%)	0.5
Beta blockers	39 (90%)	26 (89%)	0.8
Clopidogrel	18 (41.8%)	11 (37%)	0.7
ASA	40 (93%)	28 (96%)	0.5
Statins	39 (90%)	27 (93%)	0.7
chronic therapy with nitrates	31 (72%)	20 (69%)	0.7
Ranolazine	11 (25.8%)	8 (27%)	0.8
Mean CCS class Score	2.67 ± 0.75	2.52 ± 0.78	0.41
Mean NYHA score	2.51 ± 0.74	2.32 ± 0.79	0.3
LV ejection fraction (%) by echocardiography	56.40 ± 10.3	57.3 ± 9.6	0.7
Nitrates up-take	26 (60.5%)	18 (41%)	0.8
Previous Hospitalization	14 (32.5%)	9 (31%)	0.8

Cardiovasc Revasc Med. 2015 Jan-Feb;16(1):6-11.

Results: CCS Class



Results: NTG up-take



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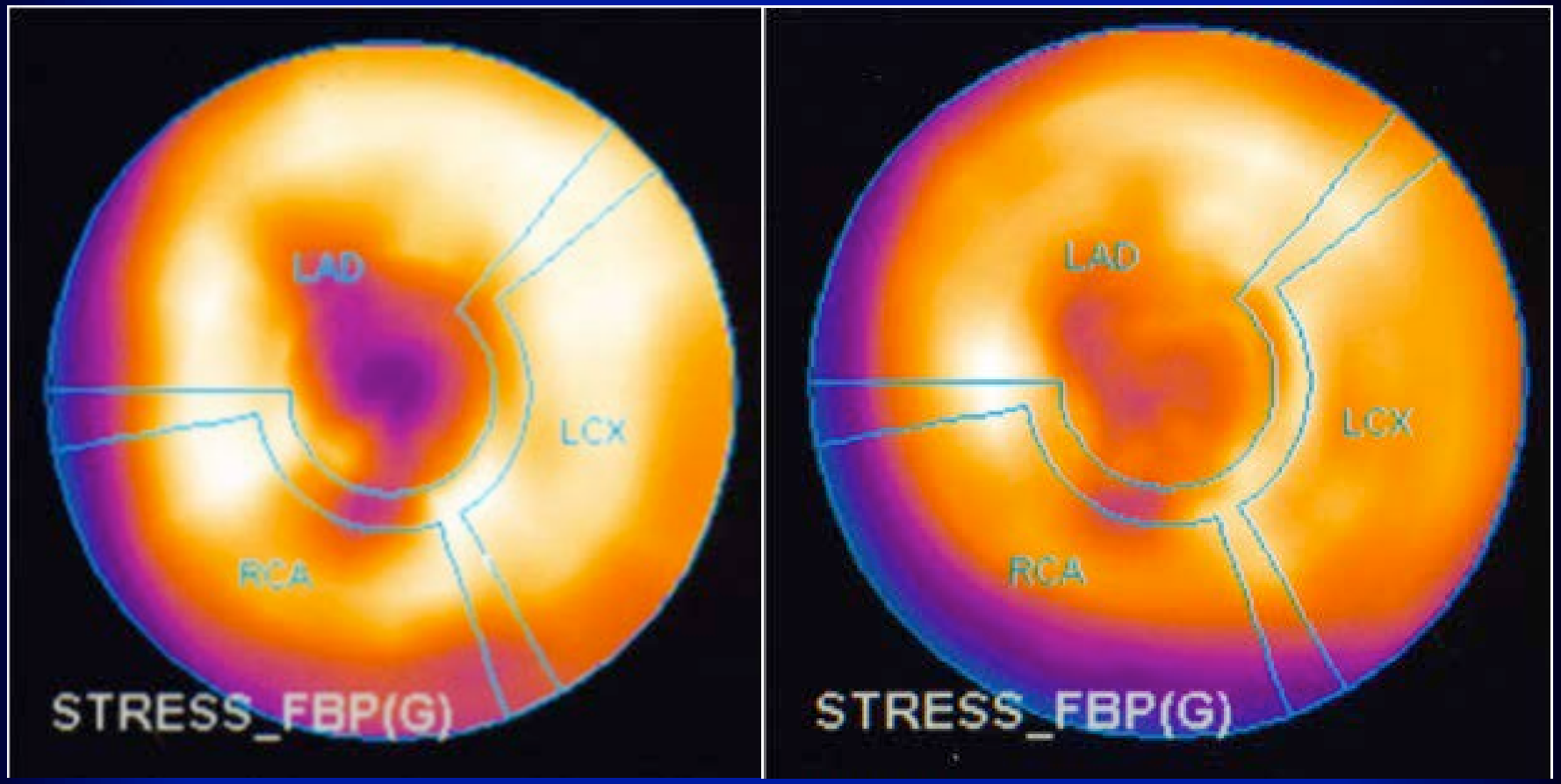
Results: Perfusion SPECT



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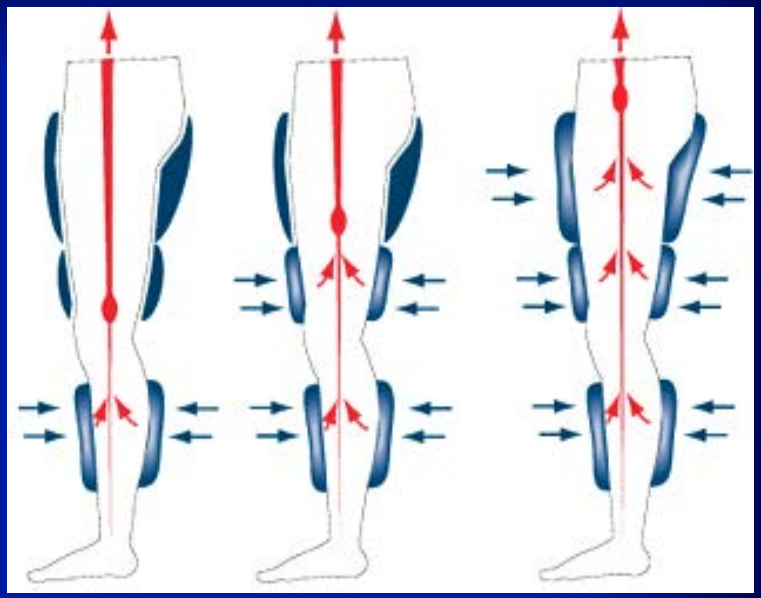
The EECP Procedure

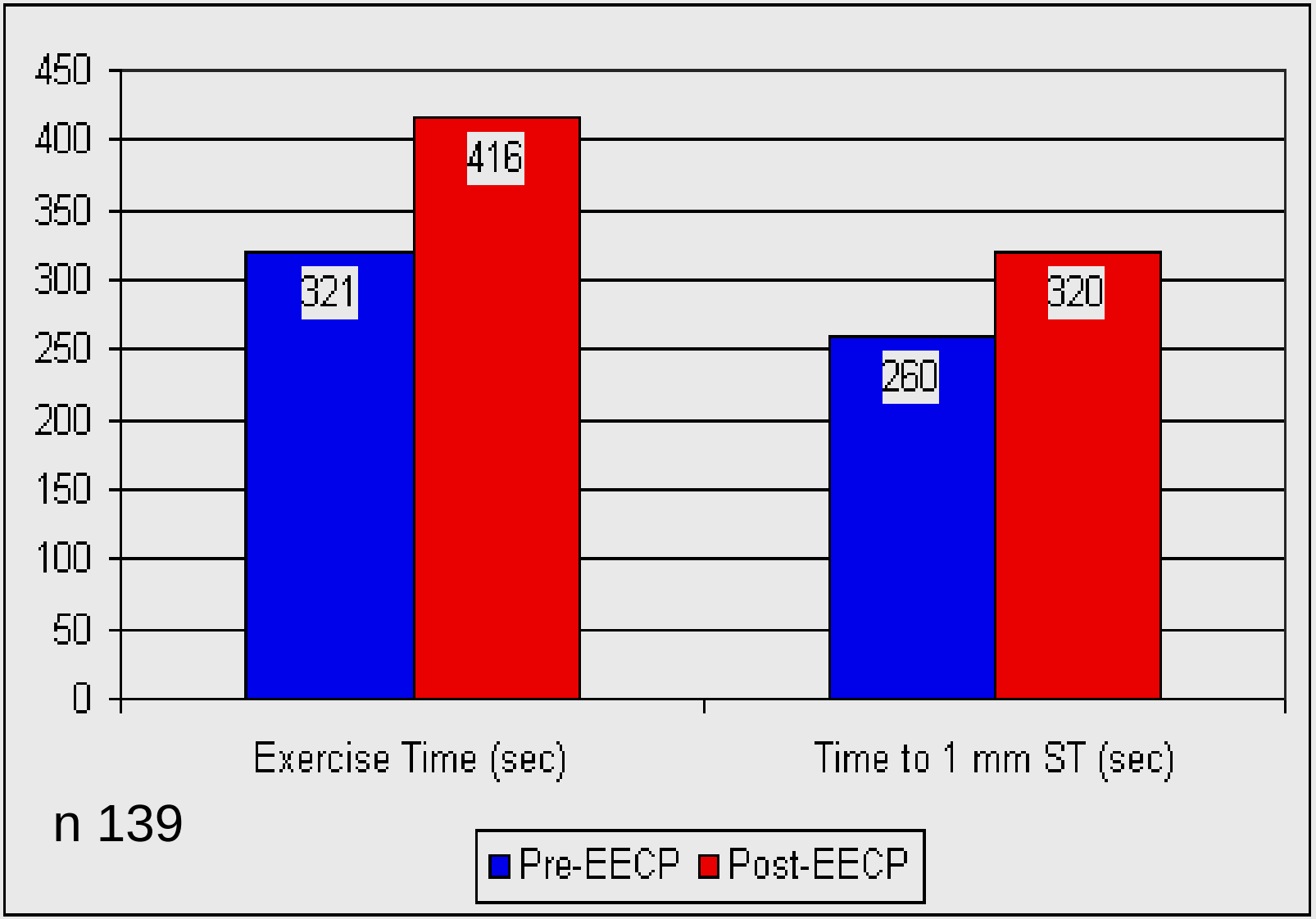


Noninvasive procedure:

- Series of 3 cuffs wrapped around calves, lower thighs, upper thighs and buttocks
- Sequential distal to proximal compression upon diastole, and
- Simultaneous release of pressure at end-diastole

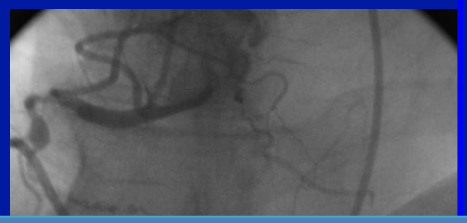
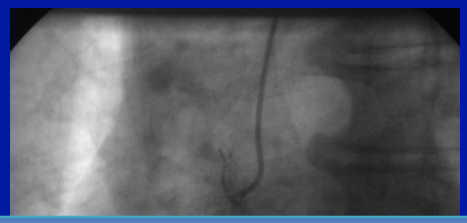
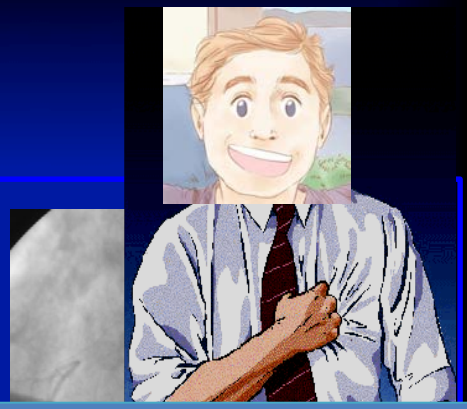
Produces:

- Increased diastolic pressure and retrograde aortic flow
- Increased venous return and...
- Systolic unloading, resulting in increased cardiac output



J Am Coll Cardiol. 1999;33(7):1833-1840. doi:10.1016/S0735-1097(99)00140-0

THE GOAL OF TREATMENT

- For most patients is to be completely free of angina
- A return to normal activities and functional capacity
- Improved understanding of ischemia has prompted new therapeutic approaches
  - Ranolazina, Ivabradina
  - ECCP
  - ESMR?
  - Stam cells?
- They are potentially complementary to traditional medications (beta-blockers, calcium channel blockers, and nitrates).
- The choice of treatment should be mainly based on a careful assessment of the balance between the benefits for the disabling symptoms of patients and the risk associated with the different treatment option

THANKS FOR YOUR ATTENTION