Diabetes: From Endothelial Dysfunction to Overt Atherosclerosis

1ο Πανελλήνιο Συνέδριο ESODiMESO

October 12, 2014

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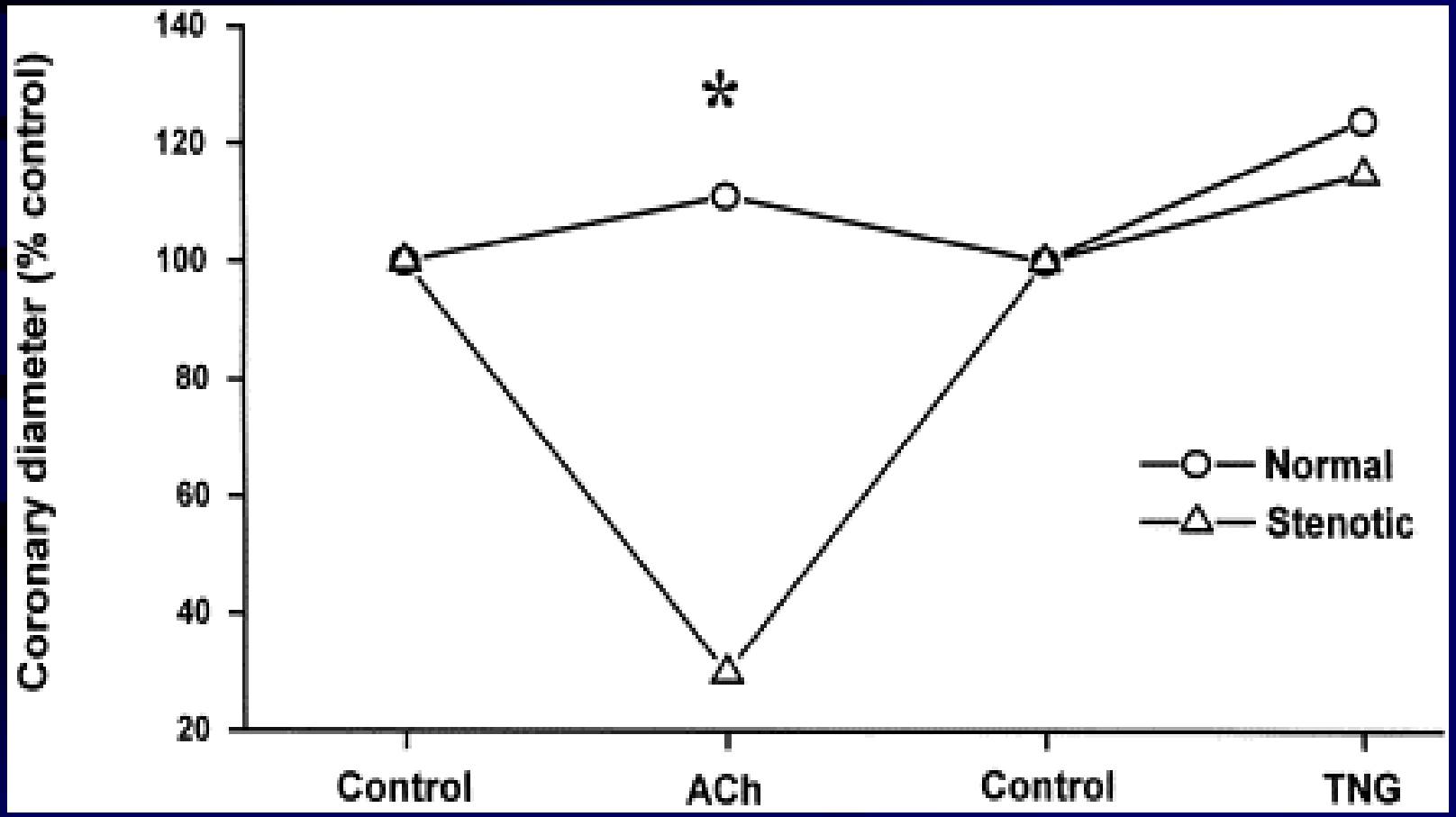
Athens Medical Center

Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries

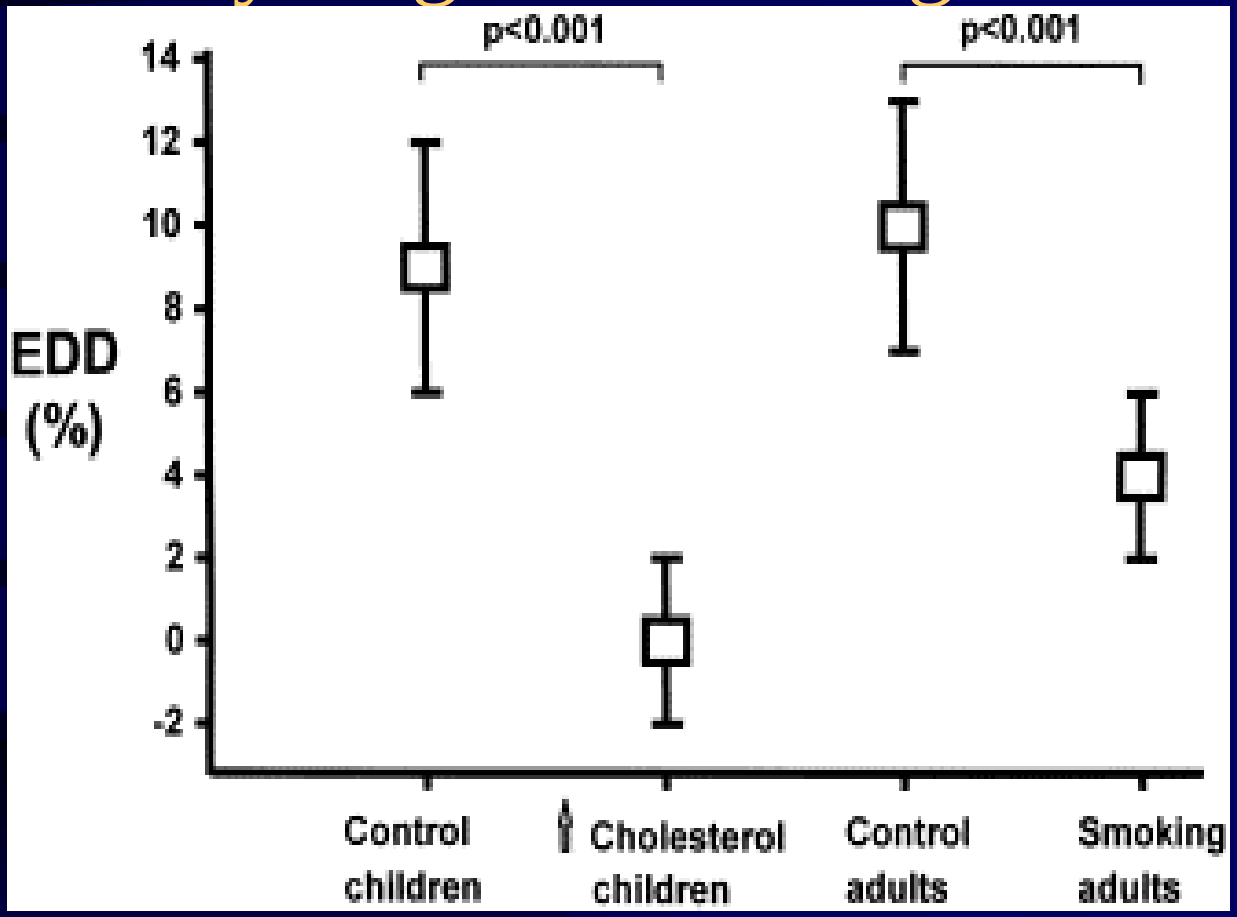


Ludmer et al. N Engl J Med 1986;315:1046-51

Detection of Endothelial dysfunction

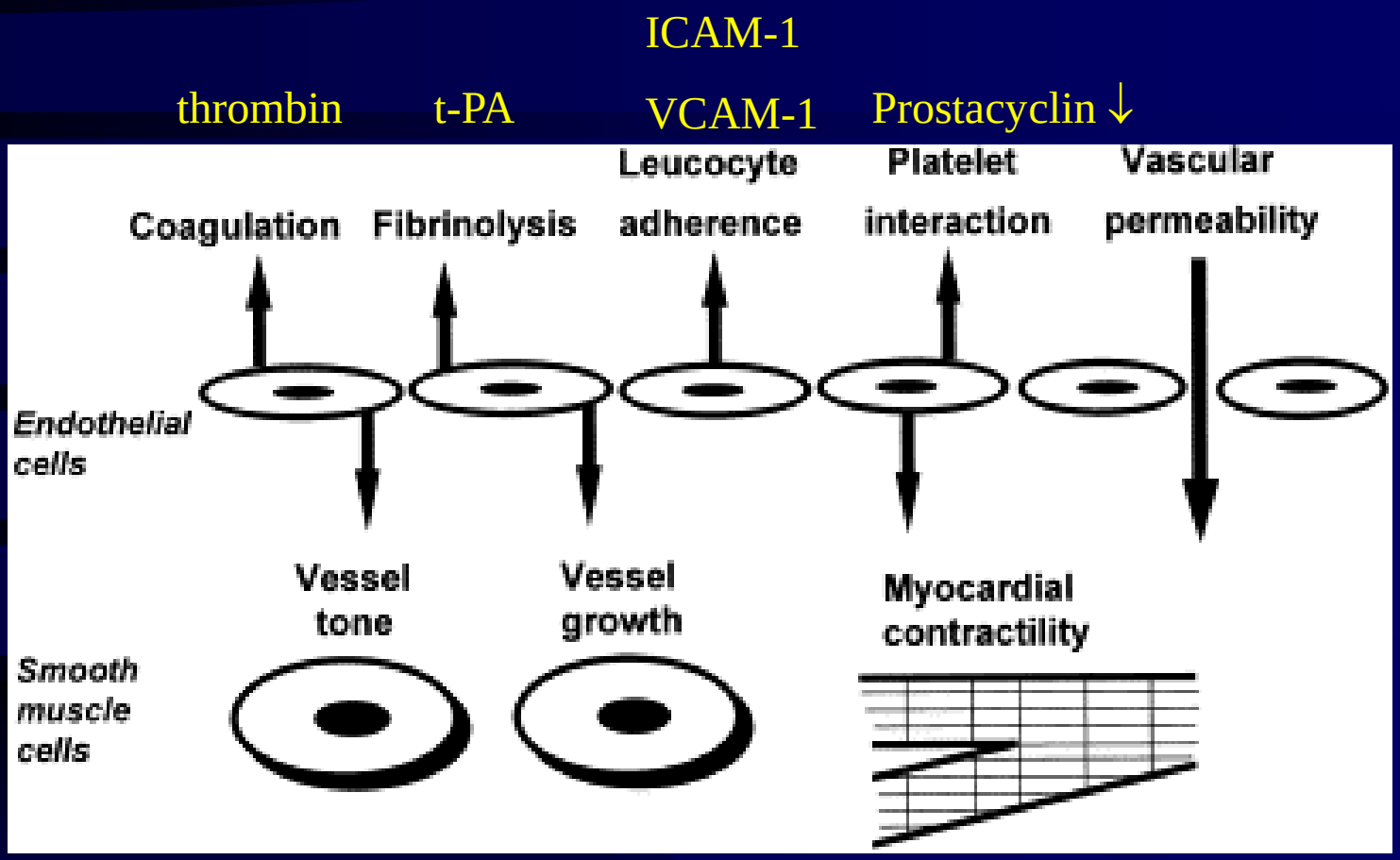
- Selective endothelial dysfunction may occur in the absence of angiographic or ultrasound atherosclerosis and in patients with risk factors for coronary disease (*J Am Coll Cardiol 1994;23:833-43*)
- Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis (*Lancet 1992;340:1111-15*)
- Close relationship of endothelial function in the human coronary and peripheral circulations (*J Am Coll Cardiol 1995;26:1235-41*)

Endothelial dysfunction is important in the early stages of atherogenesis



Significantly impaired endothelium FMD (EDD) is present in asymptomatic children and young adults with risk factors for atherosclerosis. **Celermajer et al, Lancet 1992;340:1111-15.**

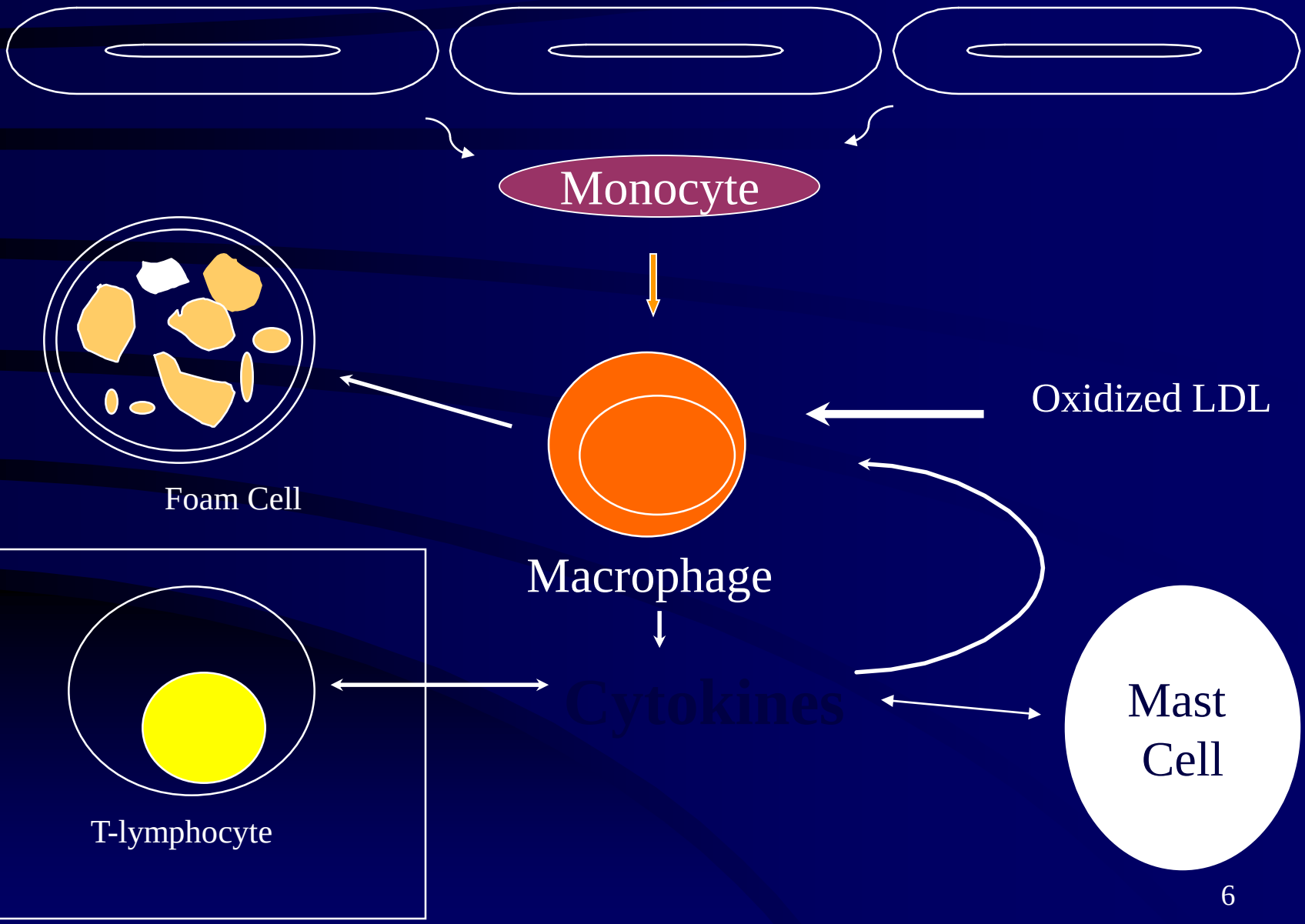
Functions of normal endothelium



NO, Prostacyclin / AT-1, ET-1

J Am Coll Cardiol 1997;30:325-33

Endothelium



Arterial Injury-Endothelial Dysfunction (CAUSES)

- **Traditional** (2/3)
  - Hypertension
  - Smoking
  - DM
  - Hyperlipidemia <50%
  - Family History
  - Obesity, Sedentary, Type A, Male
- **Novel**
- Infection
  - Chlamydial
  - Periodontal
- Allergy/Inflammation
- Homocysteine
- Air Pollution

Endothelial Dysfunction (CONSEQUENCES)

- Loss of vasodilatory ability (⬇ NO)
- Increased platelet aggregation (⬇ NO)
- Increased adhesion molecule expression
- Monocyte, T-lympocyte, and Mast cell recruitment
- Initiation of local inflammation
  - Collagen destruction ("soft-vulnerable plaque")
  - Cytokine production

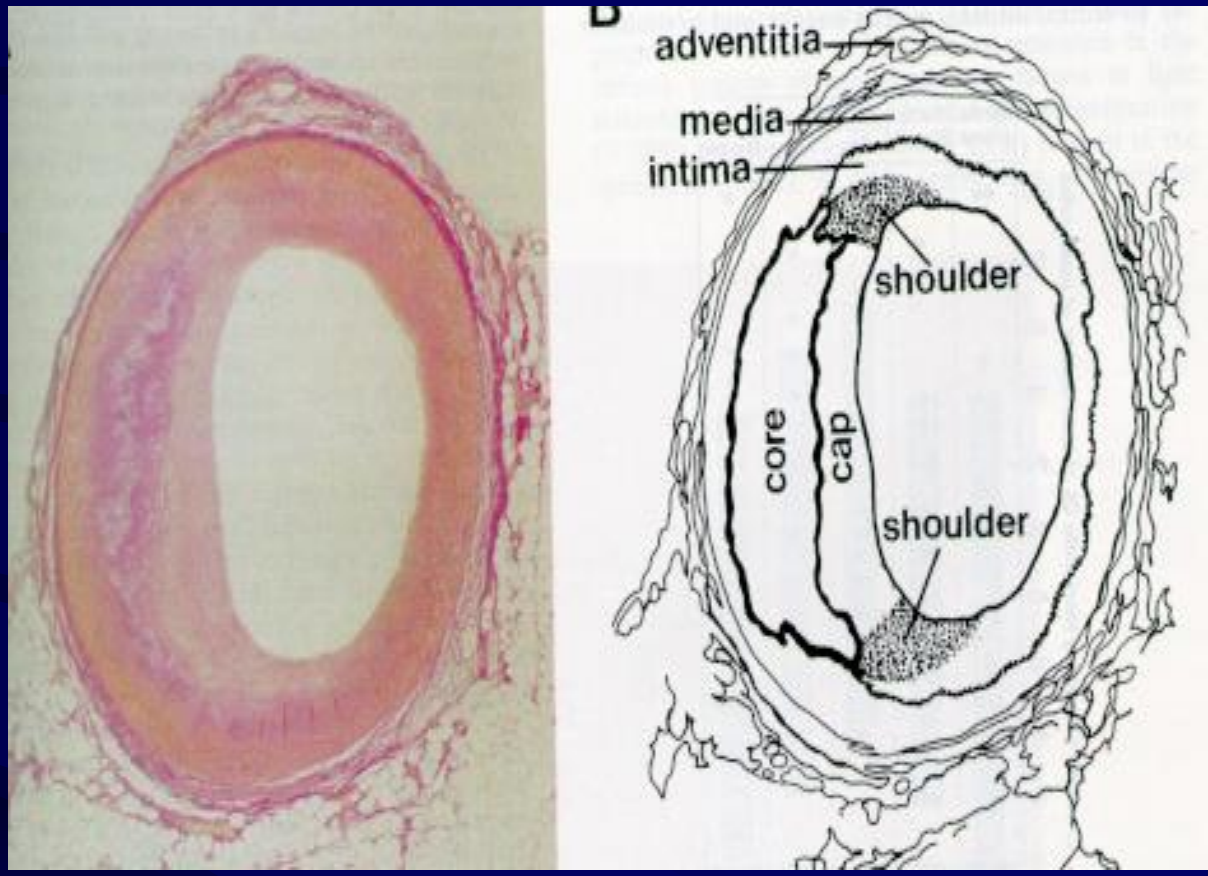
The "Shoulder Region"

Most common site of plaque rupture.

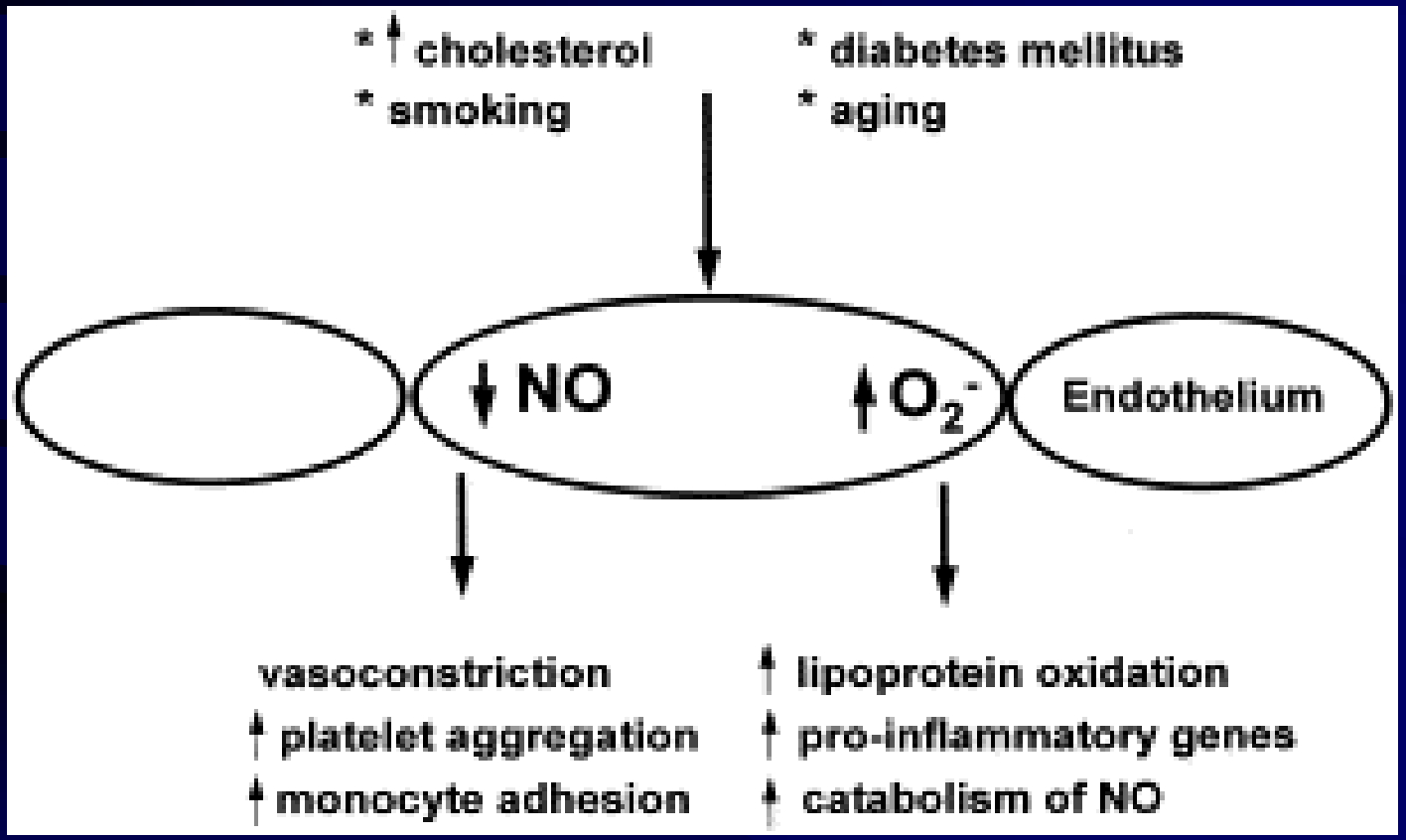
Border of atheroma with normal intima.

Site of intense inflammatory cell accumulation.

Activated mast cells present.



Endothelial dysfunction: The risk of the risk factors



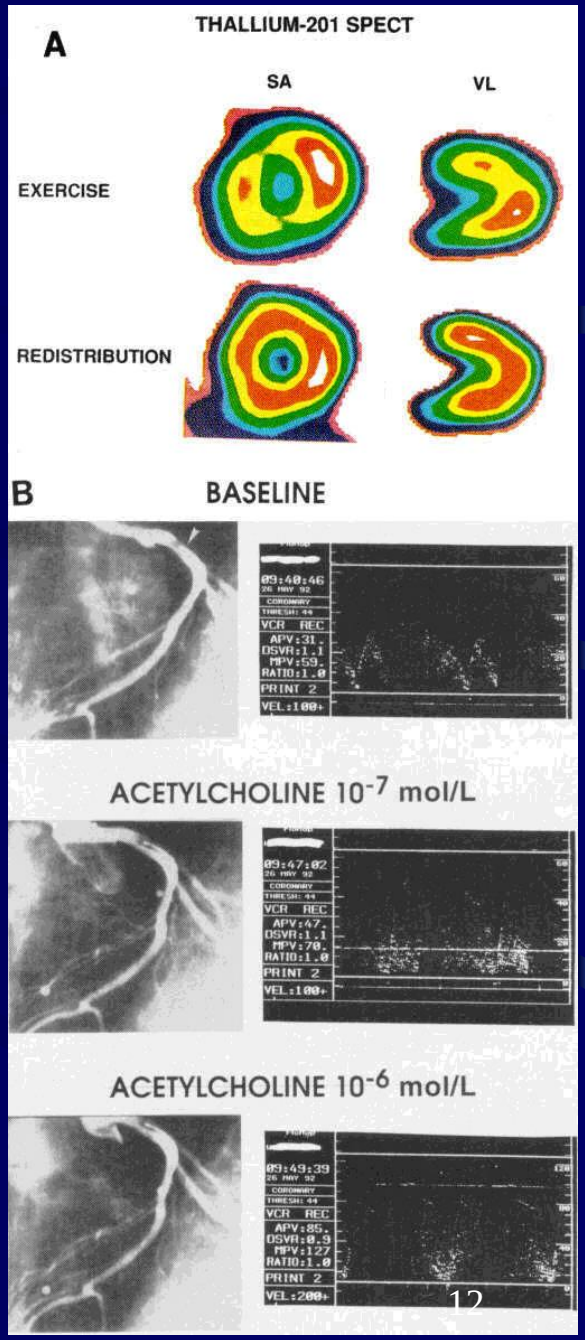
J Clin Invest 1993;92:1886-94

Endothelial dysfunction and clinical applications

- Relation to myocardial ischemia
- Correlation with prognosis
- Effect of therapy on endothelial function
- Improved endothelial function correlates with improved clinical outcomes

Relation with Myocardial ischemia

A: Thallium-201 SPECT imaging during exercise (top) and at redistribution (bottom), demonstrating moderate to severe reduction of uptake of radiotracer indicative of myocardial ischemia in the anterior wall (SA indicates short axis; VL, vertical long axis). **B**: Coronary angiography (left panels) and intracoronary Doppler flow velocity tracings (right panels) at baseline and during increasing acetylcholine infusion into the left anterior descending artery (arrow denotes tip of infusion catheter) of the patient with exercise-induced thallium perfusion abnormality illustrated in A. Note absence of flow-limiting epicardial artery constriction



Zeiher et al. Circulation 1995;91:2345-2352

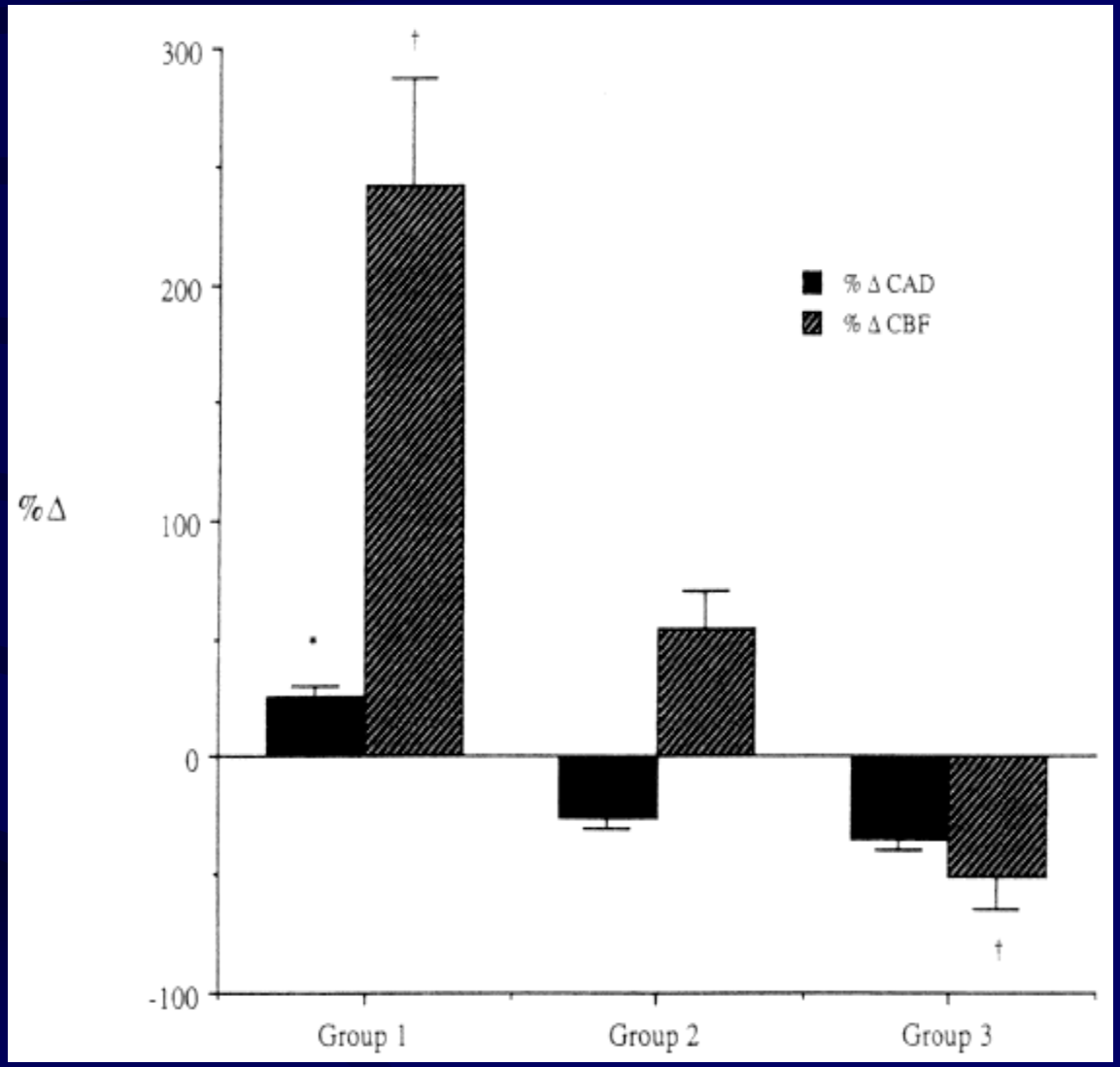
Relation with Myocardial ischemia

Maximal effect of acetylcholine infusion (10^{-4} mol/L) in the LAD expressed as mean percent change in CAD (%Delta CAD) and in CBF (%Delta CBF) relative to baseline. *P < .05 relative to %Delta CAD for group 2; (dagger)P < .05 relative to %Delta CBF for group 2.

Group 1: MPI in non-LAD

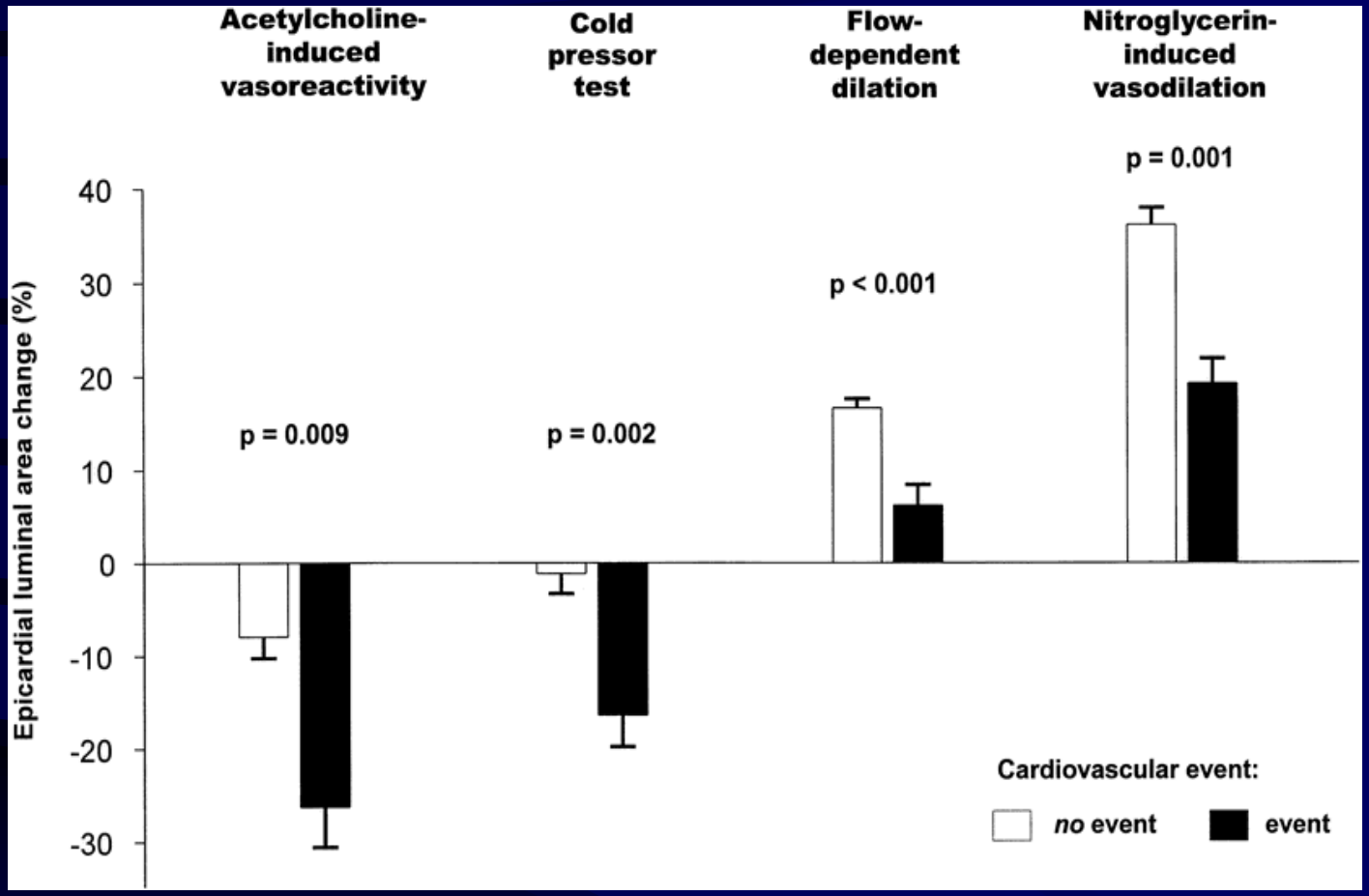
Group 2: No MPI

Group 3: MPI in LAD



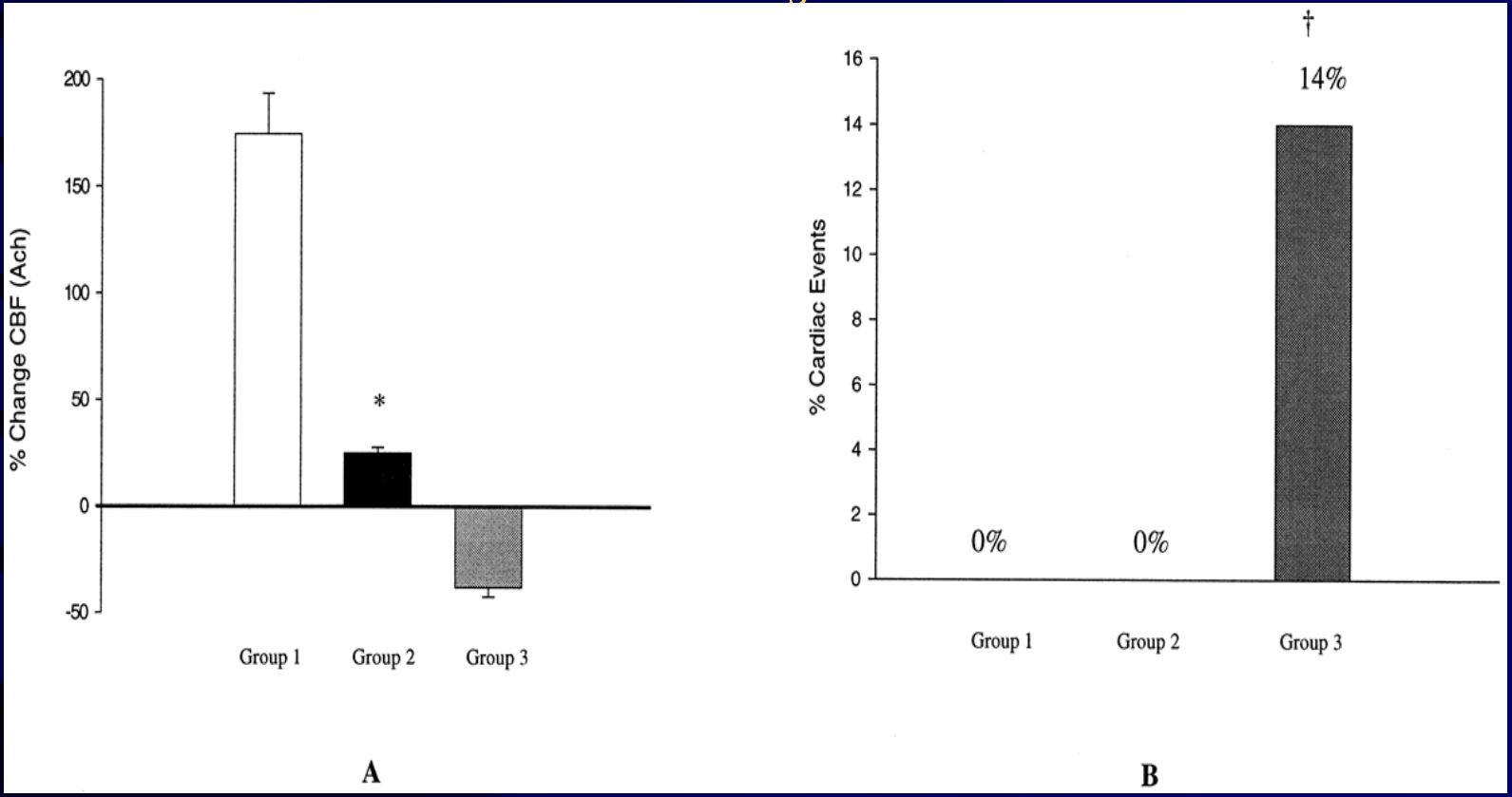
Hasdai et al. Circulation 1997;96:3390-3395

Correlation with prognosis



Epicardial luminal area changes in response to various vasoreactivity tests in patients with (filled columns) and without (open columns) cardiovascular events during long-term follow-up. Data are shown as mean ± SEM. (**Circulation 2000;101:1899-1906**)

Long term follow up of patients with CAD and endothelial dysfunction

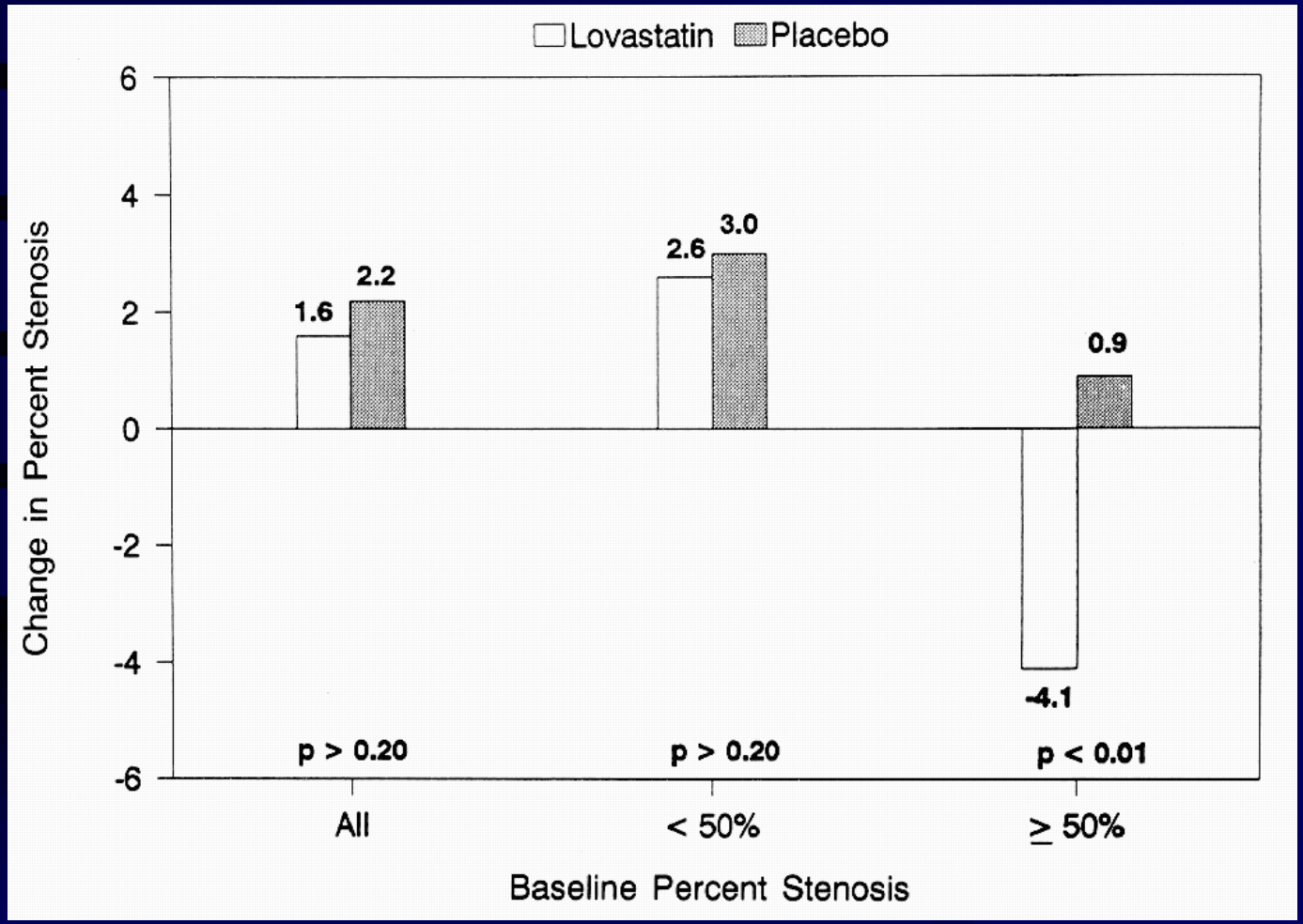


A: Mean percent change in CBF in response to acetylcholine (Ach) among 3 groups. **P* <0.0001 vs groups 1 and 3. B: **Cardiac events** (myocardial infarction, PCI, CABG, and/or cardiac death). †*P* <0.05 vs groups 1 and 2. Groups 1,2,3: Normal, Mild and severe endothelial dysfunction. **Circulation 2000;101:948-954**

Effects of therapy on endothelial dysfunction

- Cholesterol lowering
- Antioxidants
- ACE Inhibitors
- Metformin
- Hormone replacement therapy
- Exercise
- L-arginine

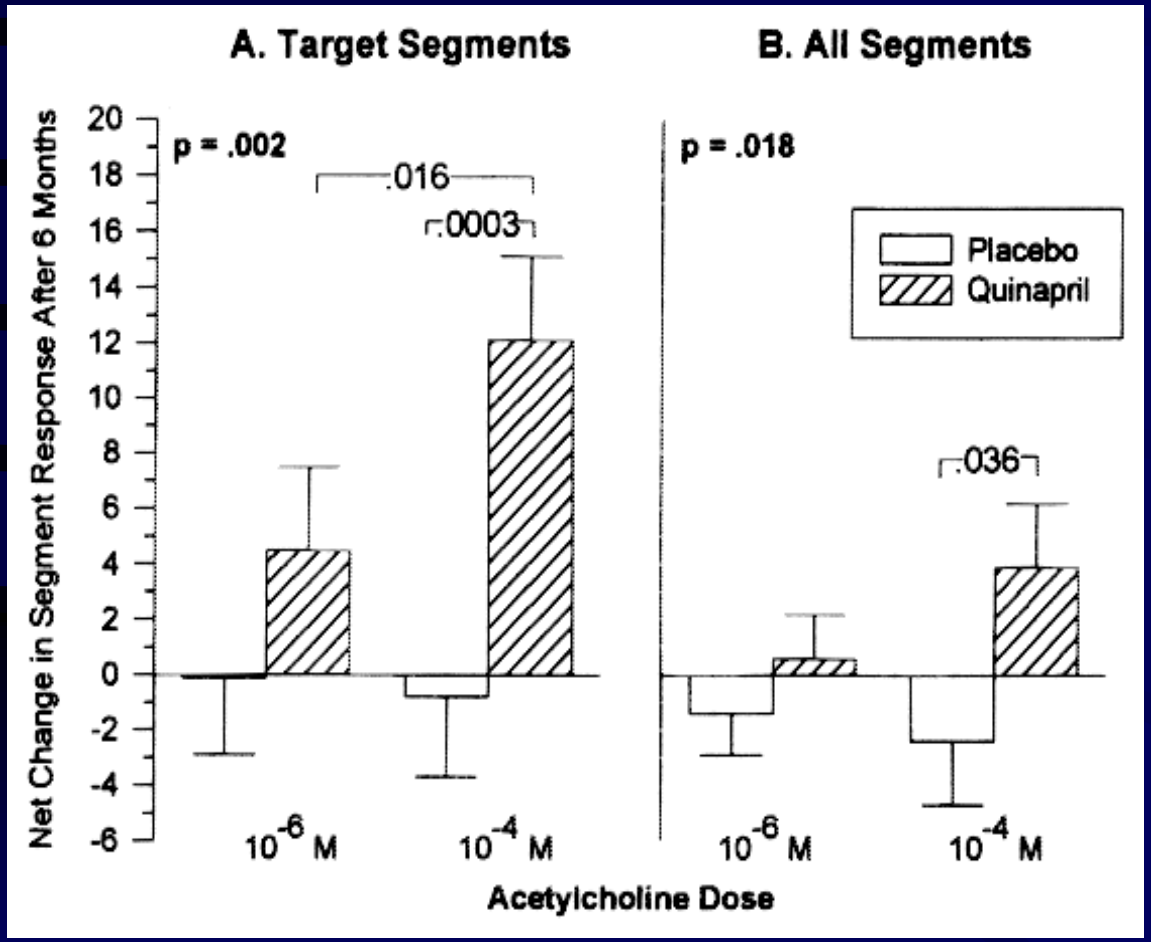
MARS Study: Coronary angiographic changes with Lovastatin therapy



Average change in percent diameter stenosis as determined by quantitative coronary angiography. After adjusting for the percent diameter stenosis at baseline, analysis of covariance was carried out for all lesions (114 patients in the lovastatin group, 106 in the placebo group), small lesions (<50% stenosis) at baseline (112 patients in the lovastatin group, 105 in the placebo group), and large lesions (>=50% stenosis) at baseline (77 patients in the lovastatin group, 79 in the placebo group)

Annals Intern Med 1993;119:969-76

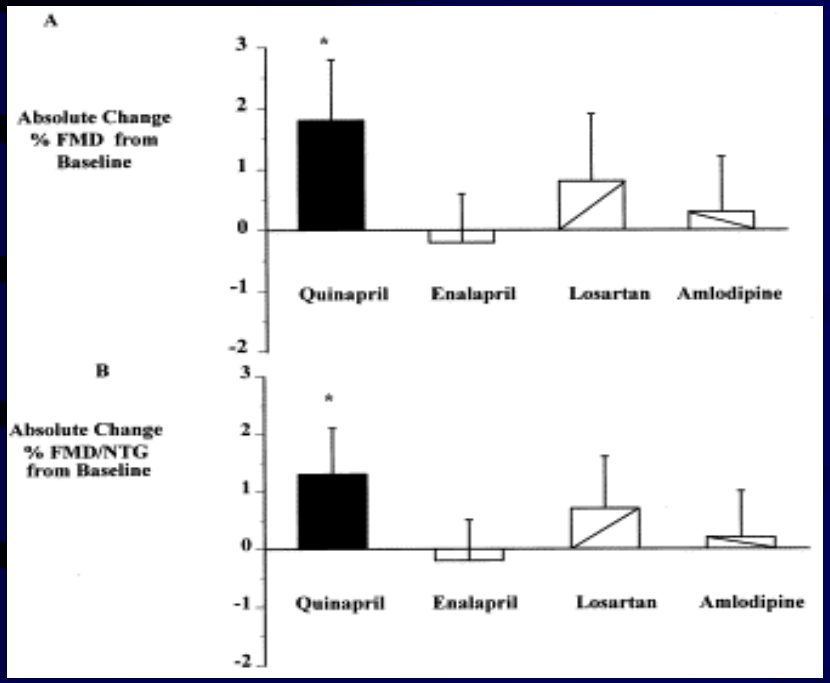
TREND Study: ACE Inhibition with Quinapril improved endothelial dysfunction in normotensive patients without severe hyperlipidemia



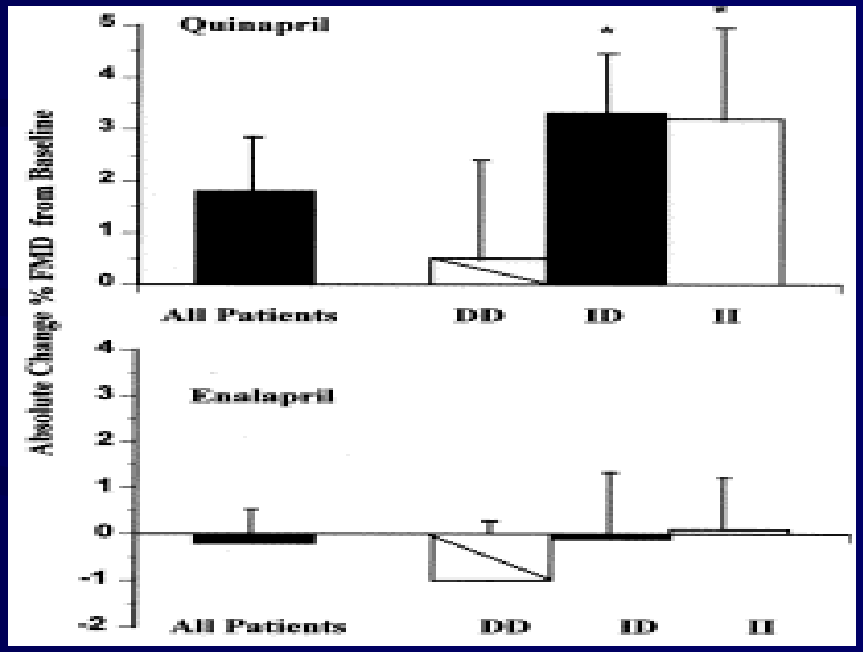
A: The primary efficacy parameter (net change in segment response after 6 months in the target segment, expressed as a percent +/- SE, plotted on y axis) for two concentrations of acetylcholine (x axis). B: Analysis of all segments. Overall differences in response between the placebo and quinapril groups were significant for the target segment analysis (P = .002) and for all segments (P = .018). At the 10 sup -4 mol/L dose, the difference between the placebo and quinapril groups was significant for both the target vessel analysis (P < .0003) and for all segments (P = .036).

Mancini et al. Circulation 1996;94:258-265

BANF Study: ACE Inhibition and endothelial function (J Am Coll Cardiol 2000;35:60-6)



A: The absolute change in percent FMD following therapy compares with pretreatment baseline values. Only quinapril resulted in a significant improvement in brachial flow-mediated vasodilation (*p < 0.02). **B:** The absolute change in the ratio of percent FMD/nitroglycerin-induced vasodilation following therapy compared with baseline values. Again only quinapril resulted in significant improvement (*p = 0.03).



The absolute change in percent FMD following therapy compares with pretreatment baseline values for quinapril and enalapril based on ACE genotype. Significant improvement in FMD seen only in the quinapril group for the ID and II genotype (*p = 0.03).

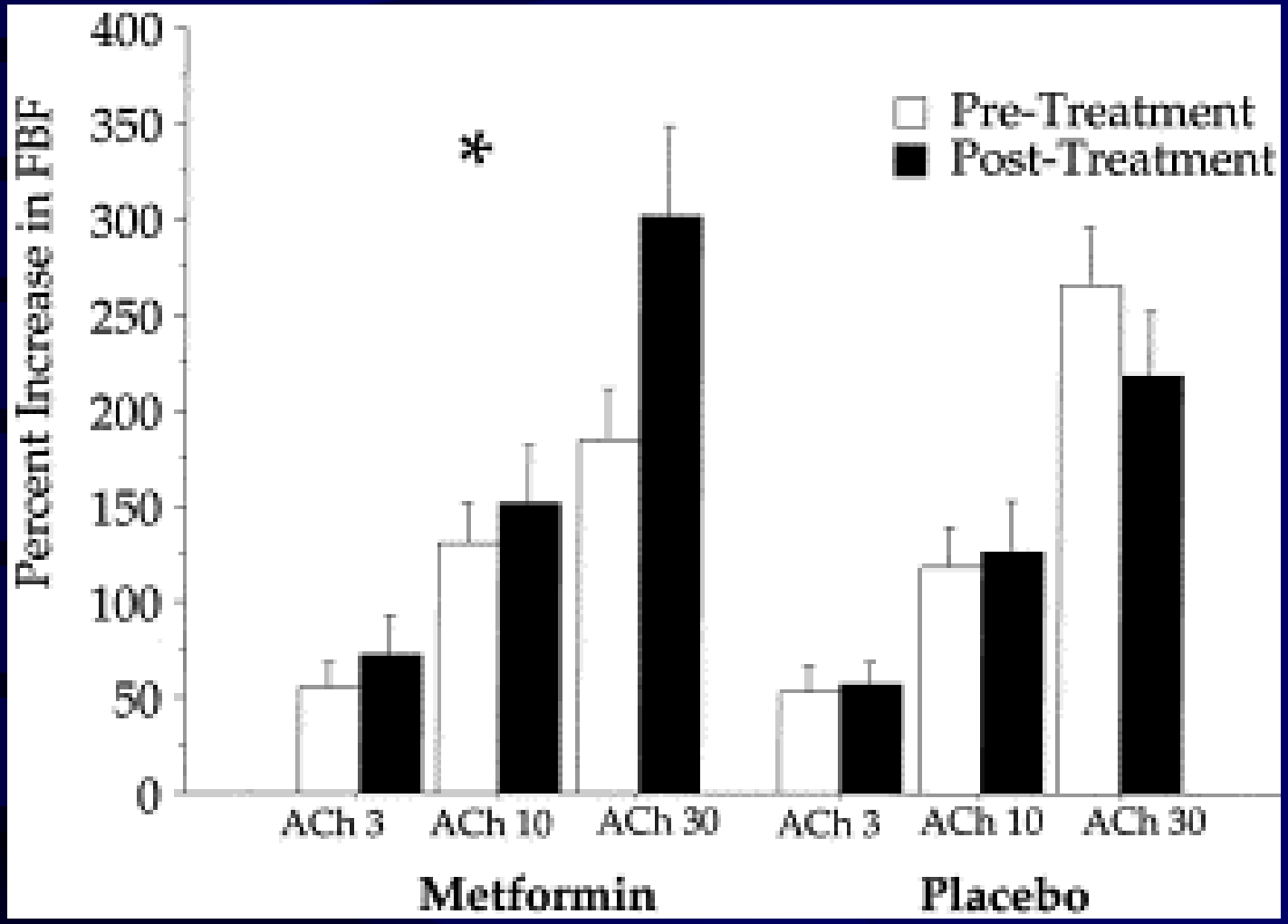


Figure 1. Endothelium-dependent blood flow responses before and after treatment with metformin. Doses are 3, 10 and 30 g/min. p = 0.0027 by two-way analysis of variance, comparing treatment effects in the two groups. ACh = acetylcholine; FBF = forearm blood flow.

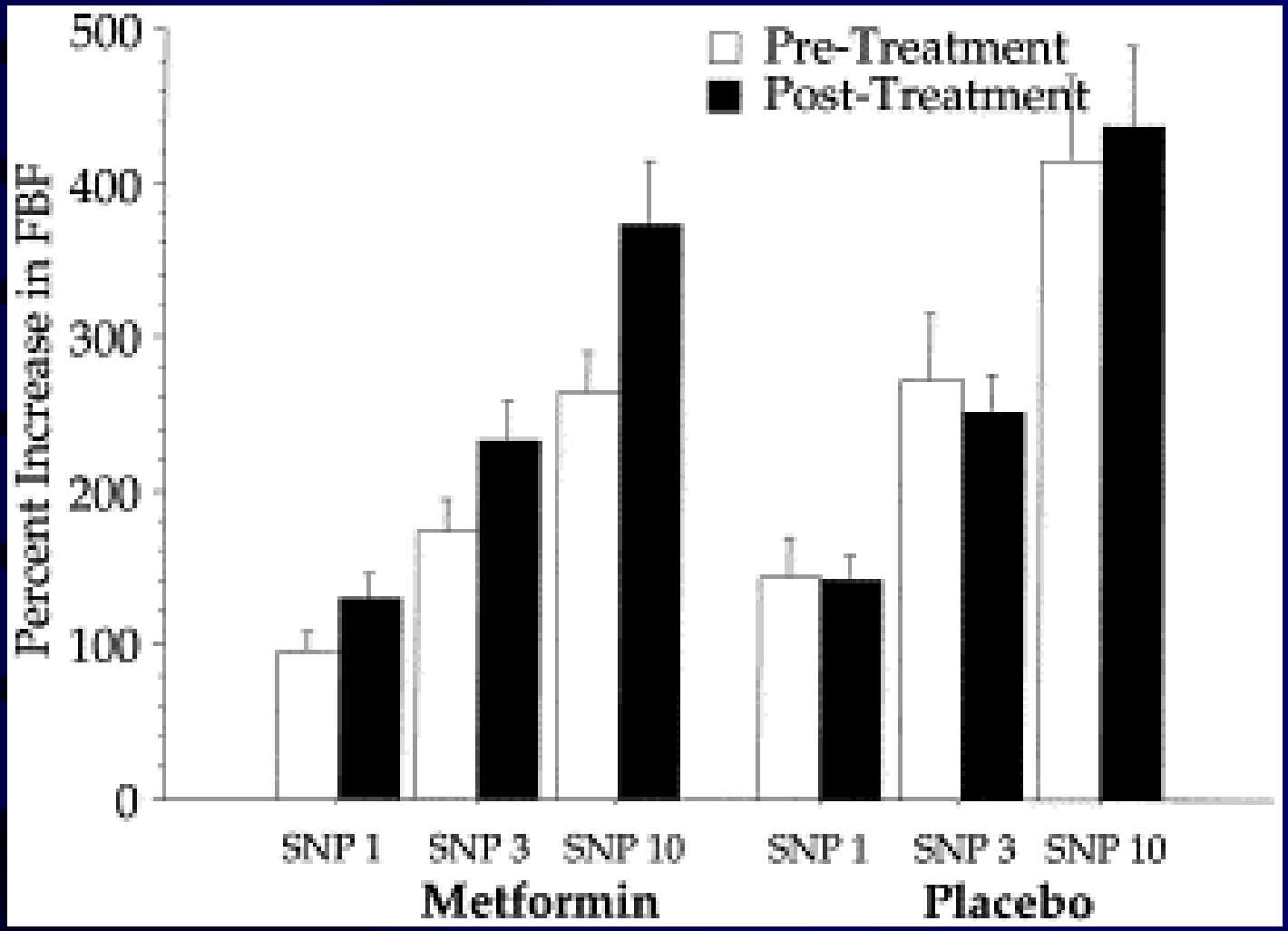


Figure 2. Endothelium-independent blood flow responses before and after treatment with metformin. Doses are 1, 3 and 10 g/min. P = 0.27 by two-way analysis of variance, comparing treatment effects in the two groups. SNP = sodium nitroprusside; FBF = forearm blood flow.

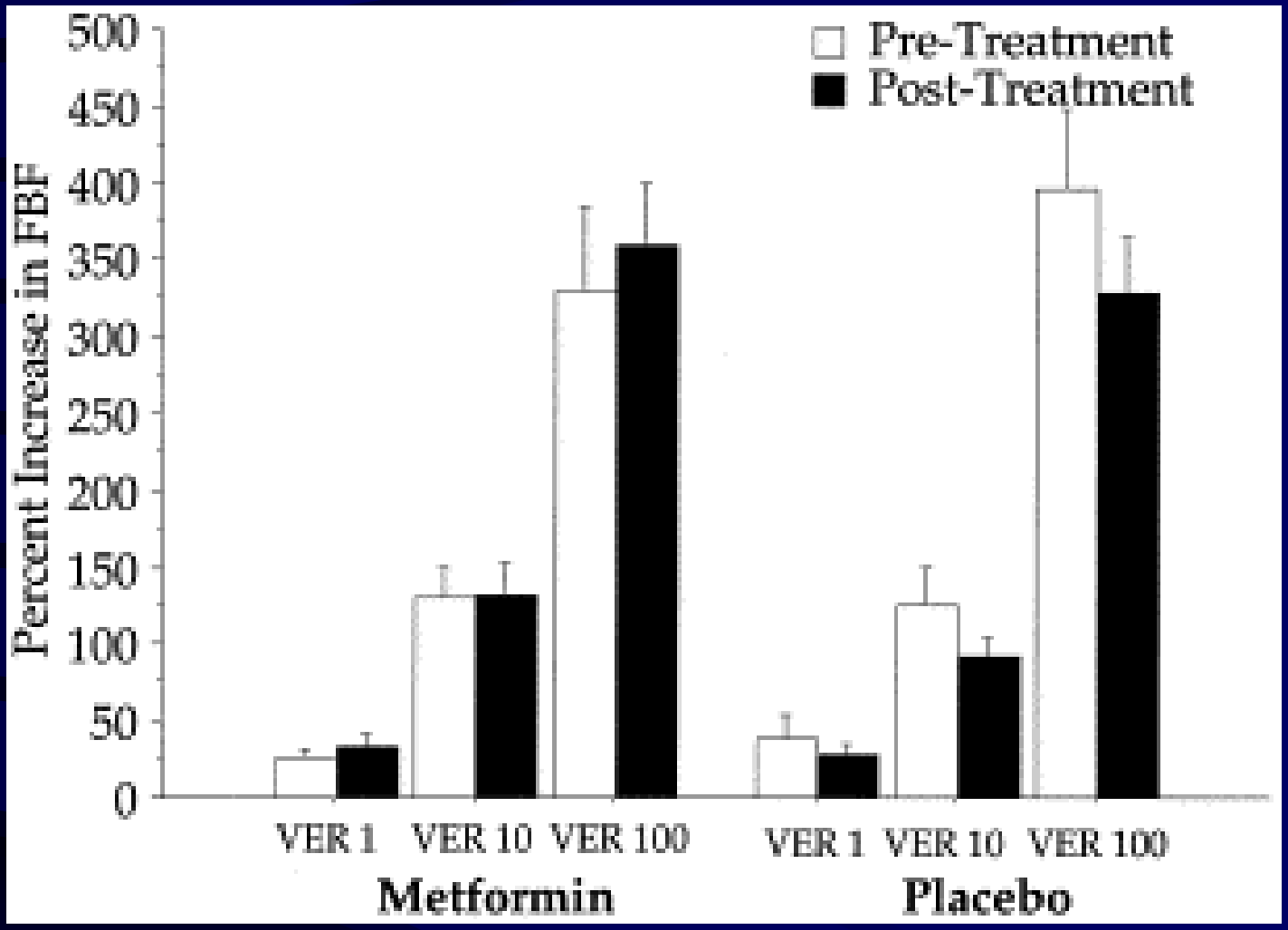
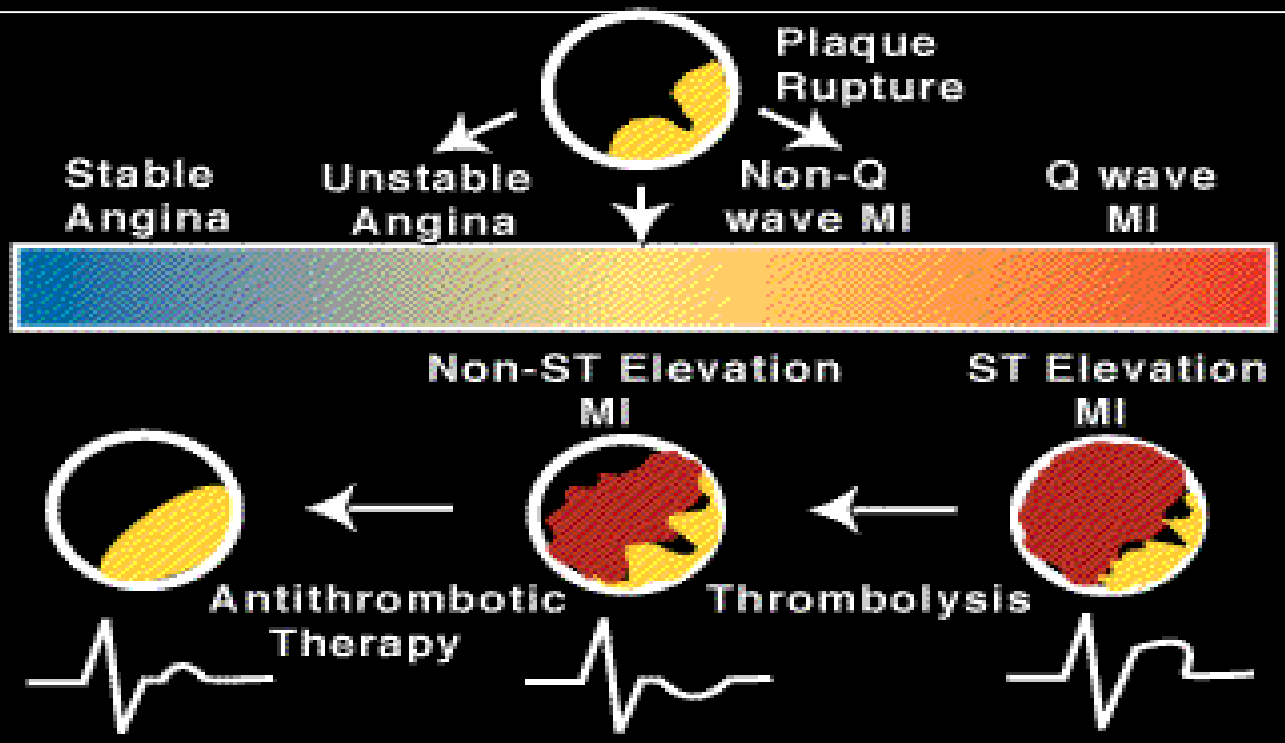


Figure 3. Nitrate-independent blood flow responses before and after treatment with metformin. Doses are 1, 10 and 100 g/min. P = 0.40 by two-way analysis of variance, comparing treatment effects in the two groups. VER = verapamil; FBF = forearm blood flow.

Pathophysiology of Acute Coronary Syndrome

Risk Factors-Endothelial dysfunction-Intima/Media Thickness-Calcification-Atherosclerotic Plaque



Cannon CP: J Thromb Thrombolysis 1995;2:205-218.

BRAZIL 1982 - The team of Dreams

Paolo Roberto Falcao

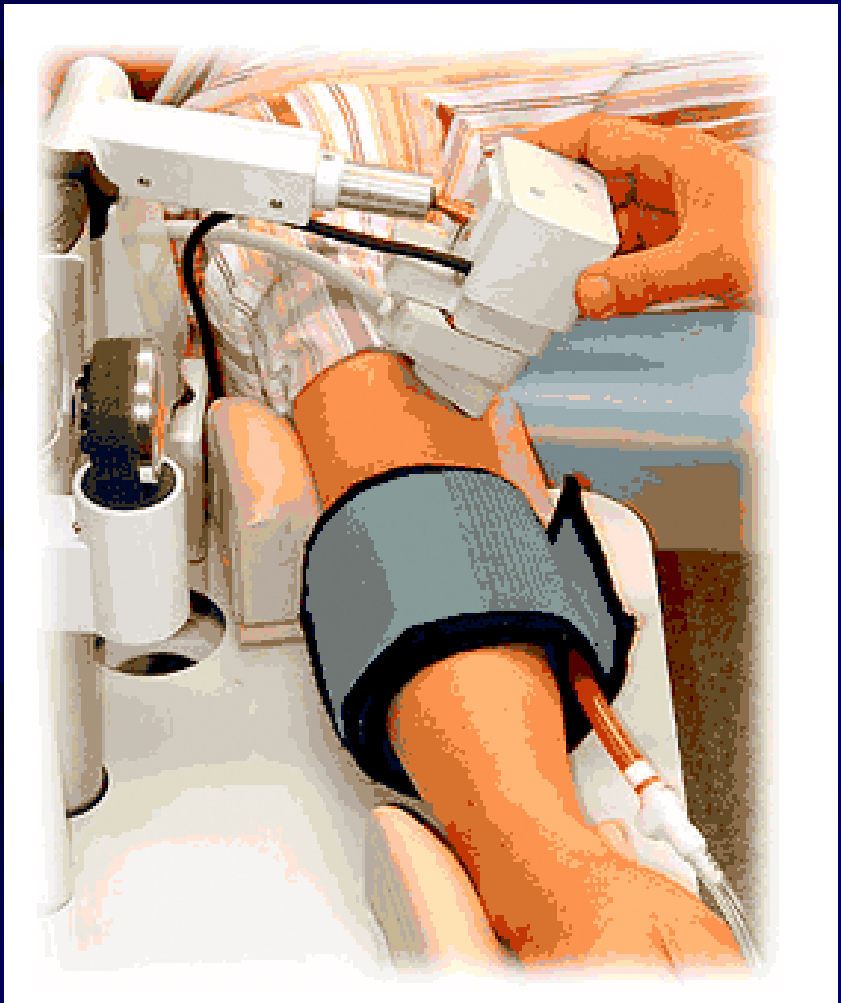
Socrates

Artunes Coimbra Zico

Assessment of Vascular Health (Endothelial Function)

- Brachial artery studies (NO-mediated vasodilatation)
- Coronary flow reserve measurements
- Inflammatory marker measurements (acute phase reactants)
  - C-reactive protein
  - ESR
  - Fibrinogen
  - WBC #

Brachial Artery Reactivity Testing



Why should we study the coronary microcirculation? (I)

- Even the most seminal reactions, autoregulation and metabolic dilatation, are incompletely understood
- CAD is not only an epicardial vessel disease
- There is great difficulty in the clinical evaluation of coronary microcirculation. Remember Syndrome X?
- Animal and human data suggest that dysfunction of coronary microcirculation can produce cardiac abnormalities. (e.g data with coronary infusion of ET1, data with measurement of CFR following PTCA)

Am J Physiol Heart Circ Physiol 2000;279:H2581-84.

Why should we study the coronary microcirculation? (II)

- Identification of patients with paradoxical vasoconstriction during increases in O_2 consumption
- Assess efficacy of various pharmacologic interventions who aim to produce dilation of coronary microcirculation
- Administration of drugs that “target” the coronary circulation can improve outcomes of interventional techniques (PTCA, Stenting)

Am J Physiol Heart Circ Physiol 2000;279:H2581-84.

Mechanisms of Coronary Physiology

Angiographic Epicardial Stenosis

↑ Resistance to Flow

↓

Resting Post-stenotic Flow usually satisfactory

↓ Microvascular Resistance to maintain regional basal flow

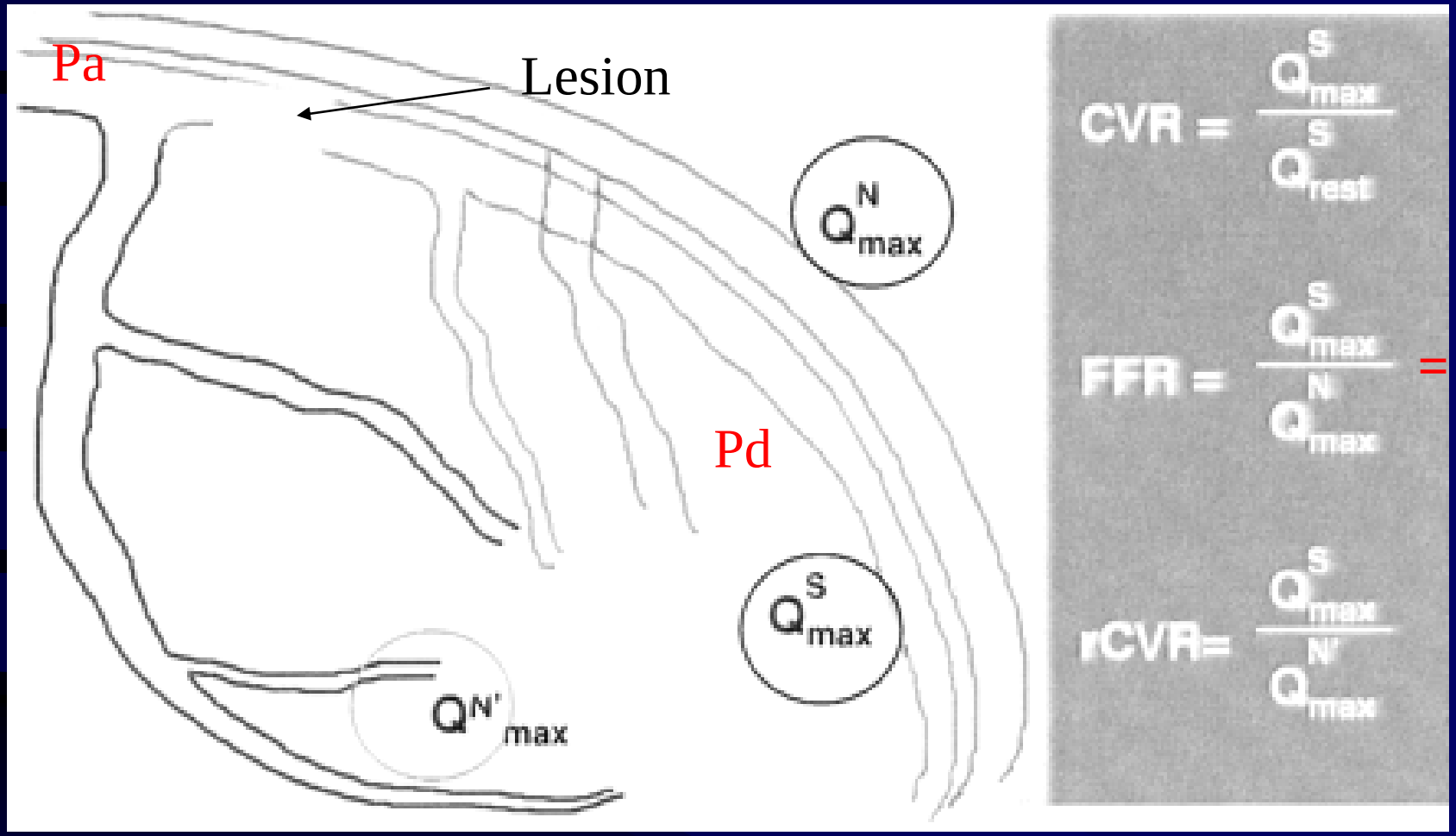
↓

↓ of Potential CVR

↓

Any increase in myocardial O2 demand results in ↓ CVR and ↓ rCVR and ischemia

Diagrammatic definitions of CVR, FFR, and rCVR



A theoretically normal artery is drawn behind the stenotic artery. CVR is determined by maximal stenosis flow (Q^S_{max}) divided by stenosis artery flow at rest (Q^S_{rest}). FFR is determined by maximal stenosis flow (Q^S_{max}) divided by maximal theoretical normal artery flow (Q^N_{max}). rCVR is determined by maximal stenosis flow (Q^S_{max}) divided by maximal normal adjacent artery flow ($Q^{N'}_{max}$) **Circulation 2001;103:3142-3149.**

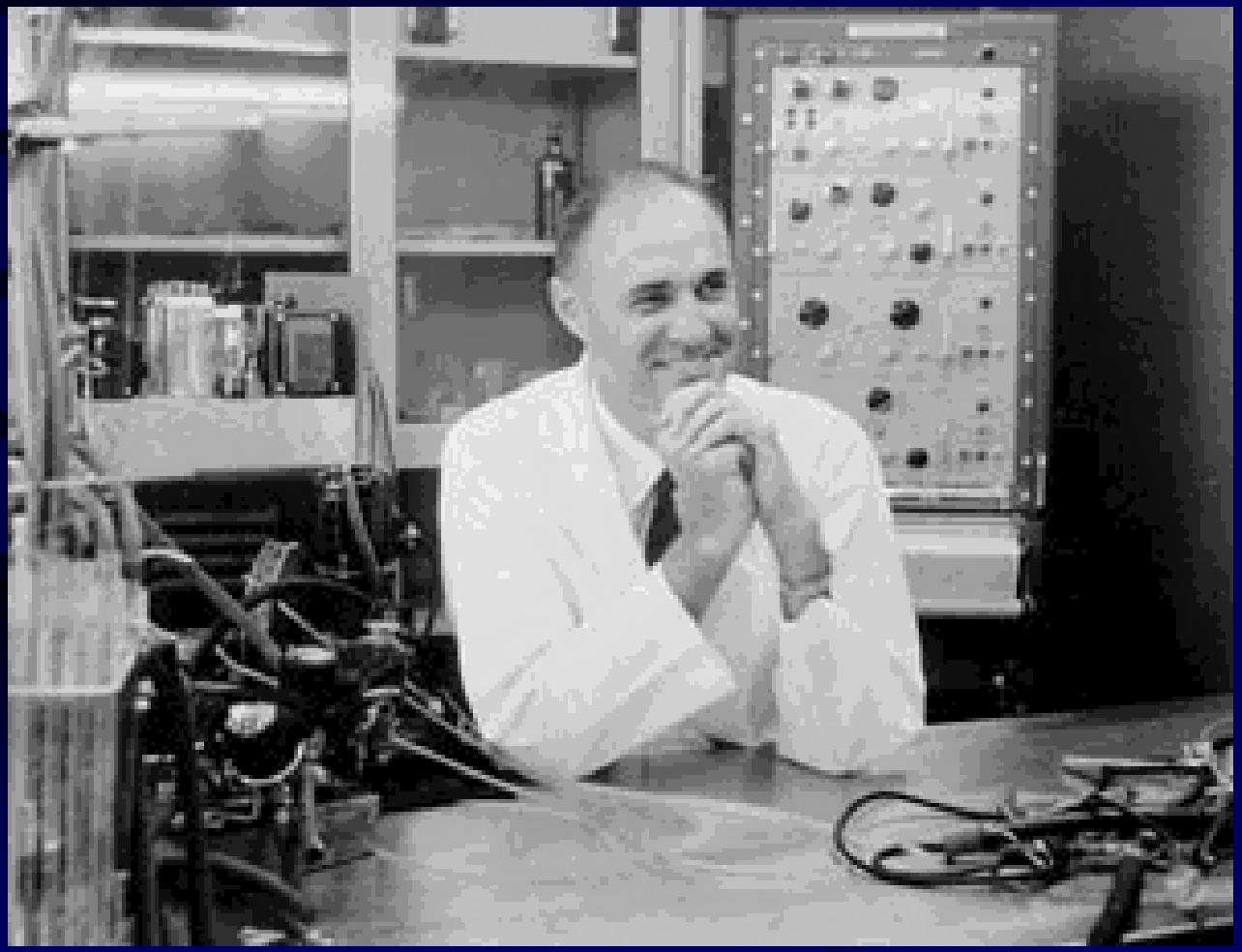
Anatomic and Physiologic Criteria associated with Clinical Outcomes

Application	IVUS	CVR	rCVR	FFR
Ischemia Detection	<3-4 mm^2	<2.0	<0.8	<0.75
Deferred PTCA	>4 mm^2	>2.0	…	>0.75
PTCA Endpoint	…	>2.0-2.5 with <35% DS	…	>0.90
Stenting Endpoint	>9 mm2, >80% of reference area, full apposition	…	…	>0.94

Circulation 2001;103:3147

Arthur C. Guyton, MD: A Legacy of Achievement

AHA 2001 Eugene Braunwald Academic Mentorship Award



Diabetes and CVD

In patients with diabetes, CVD is:

- A leading cause of morbidity and mortality[1]
- Often more advanced at diagnosis[1]
- Commonly silent with little or no pain response to ischemia[2]
- Often manifested as acute MI or cardiac death[3]
- More likely to show multivessel disease at diagnosis or first MI[1]
- Associated with an unfavorable prognosis, particularly in women[3]

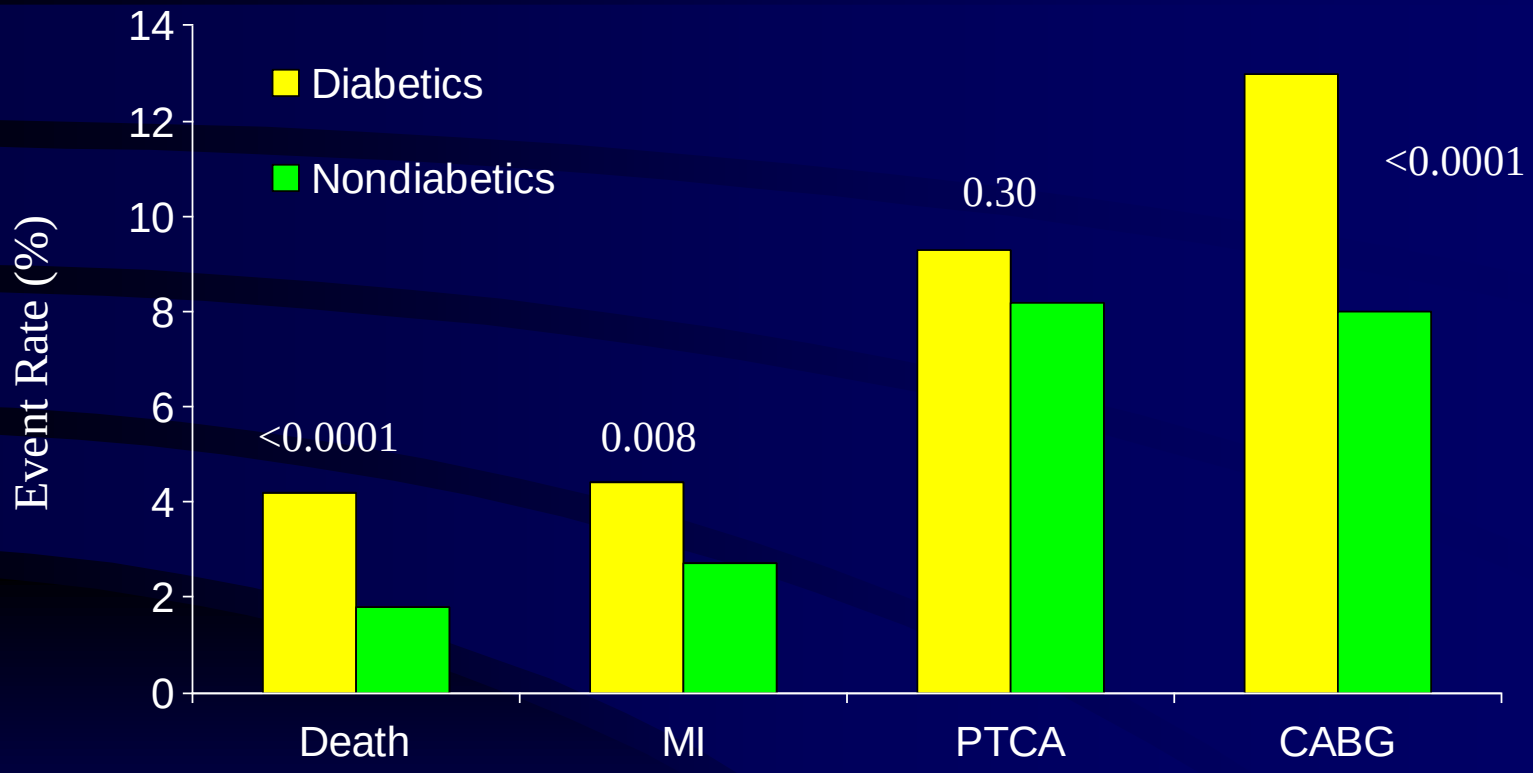
1. American Diabetes Association. *Diabetes Care*. 1998;21:1551-1559.
2. Jacoby RM, Nesto RW. *J Am Coll Cardiol*. 1992;20:736-744.
3. Miettinen H, et al. *Diabetes Care*. 1998;21:69-75.

Diabetes: Increased CAD Risk

- 2-4–fold increased risk of cardiovascular events with diabetes[1]
  - Type 1 and type 2 diabetes are independent risk factors for CAD[2]
  - After MI, diabetic patients have a 2-3–fold greater morbidity and mortality than nondiabetic patients[1]
- Diabetes itself confers a risk equivalent to the presence of established CAD[3]

1. American Diabetes Association. *Diabetes Care*.1998;21:1551-1559.
2. Jacoby RM, Nesto RW. *J Am Coll Cardiol.* 1992;20:736-744.
3. Haffner SM. *N Engl J Med.* 2000;342:1040-1042.

Outcomes Comparison: Diabetic/Nondiabetic Patients Undergoing Stress MPI



Giri S, et al. *Circulation.* 2002;105:32-40.

Diabetes and CAD: Risk Factors

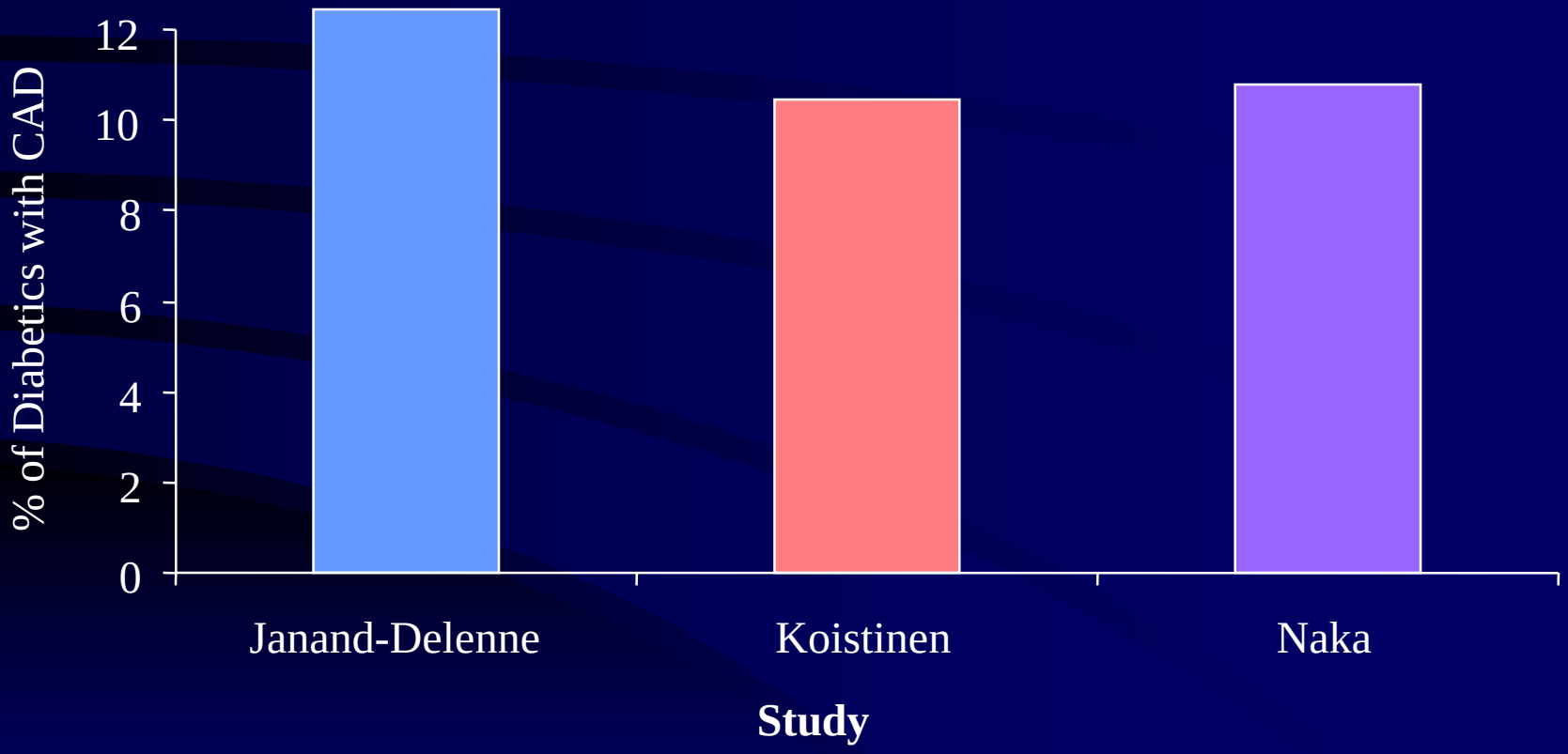
- Traditional risk factors for CAD:
  - Age - Gender
  - Diabetes
  - Hypertension
  - Dyslipidemia
  - Family History of CAD
  - Obesity
  - Smoking
  - Sedentary life-style
- Traditional risk factors account for less than half the excess CAD mortality of diabetics

CAD in Diabetic Patients

- May be associated with generalized endothelial dysfunction and small-vessel abnormalities[1,2]
- Diffuse disease vs more localized involvement in nondiabetics with CAD[1]
- Increased morbidity and mortality rates from MI[1]
- Increased risk for recurrent MI, CHF, cerebrovascular disease, and peripheral vascular disease[1,3]

1. American Diabetes Association. *Diabetes Care.* 1998;21:1551-1559.
2. Clarkson P, et al. *J Am Coll Cardiol.* 1996:28:573-579.
3. Jacoby RM, Nesto RW. *J Am Coll Cardiol.* 1992;20:736-744.

Incidence of Asymptomatic CAD in Type-2 Diabetic Patients



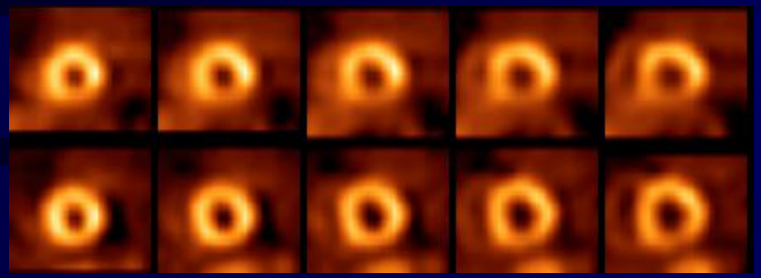
Adapted from Janand-Delenne B, et al. *Diabetes Care.* 1999;22:1396-1400; Koistinen MJ. *BMJ*. 1990;301:92-95; Naka M, et al. *Am Heart J.* 1992;123:46-53.

Diabetes and CAD: Potential Benefits of Early CAD Screening

- Diagnosis of disease, prognostic assessment, and treatment selection
  - Early, modifiable CAD in a lower-risk group in which medical management is possible
  - Advanced disease in which revascularization could prolong life
- Improved compliance with risk factor intervention and treatment with CAD diagnosis[1]
  - Aggressive “secondary” intervention proven to reduce morbidity and mortality[2]

1. Nesto RW. *Diabetes Care*. 1999;22:1393-1395.

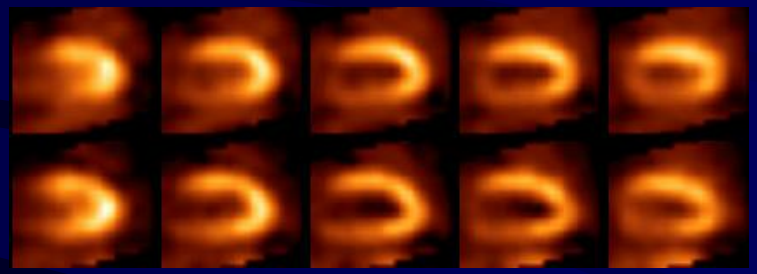
Myocardial Perfusion Images



Stress

Rest

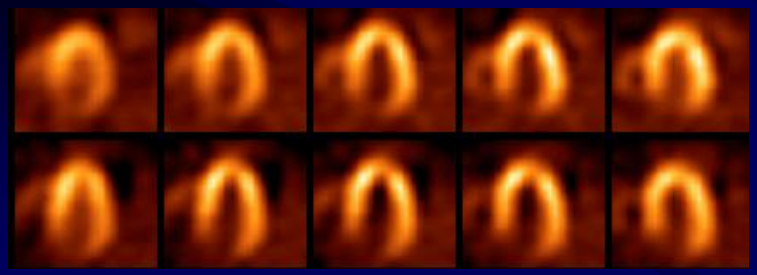
Short Axis



Stress

Rest

Vertical-Long Axis



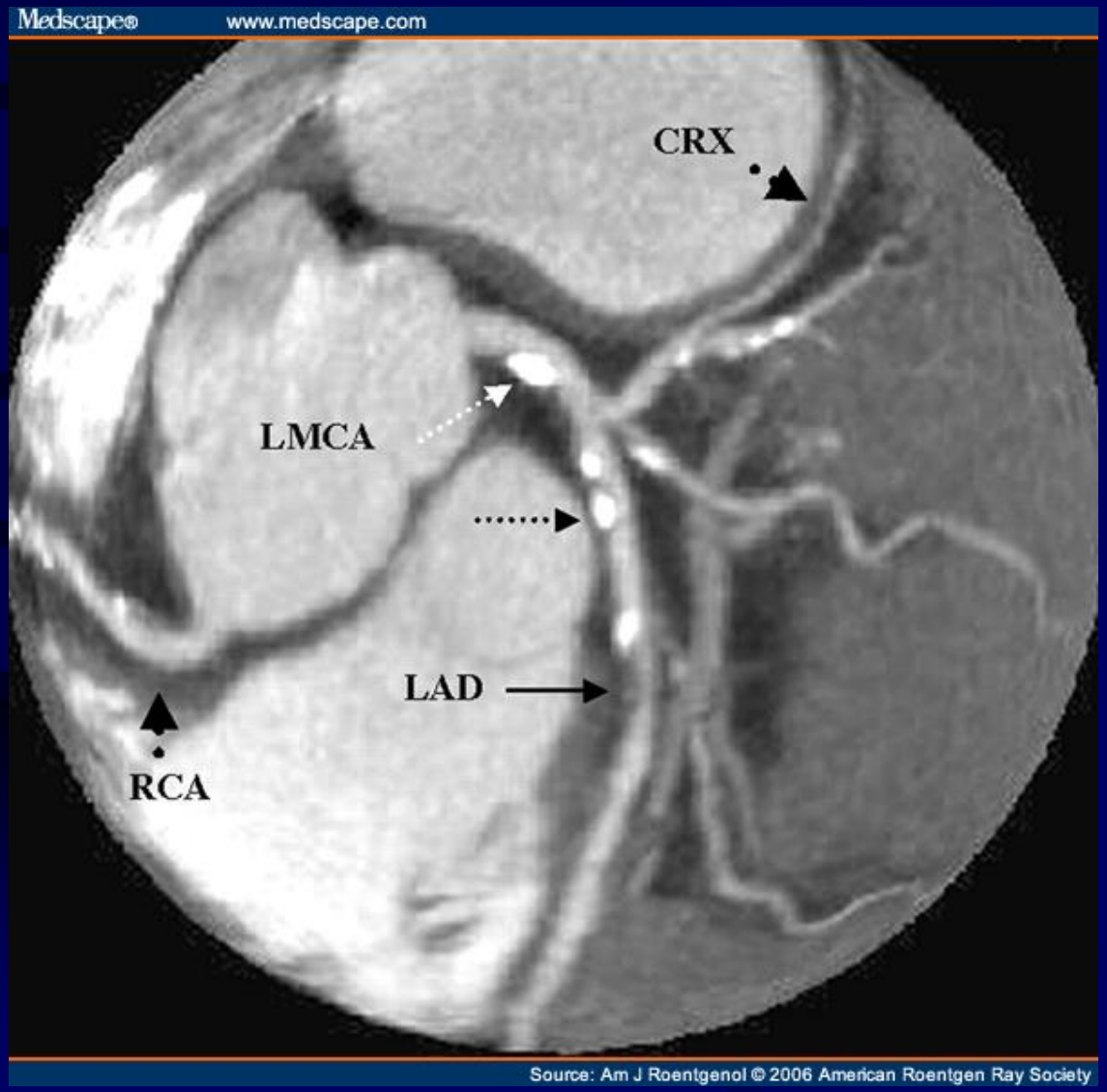
Stress

Rest

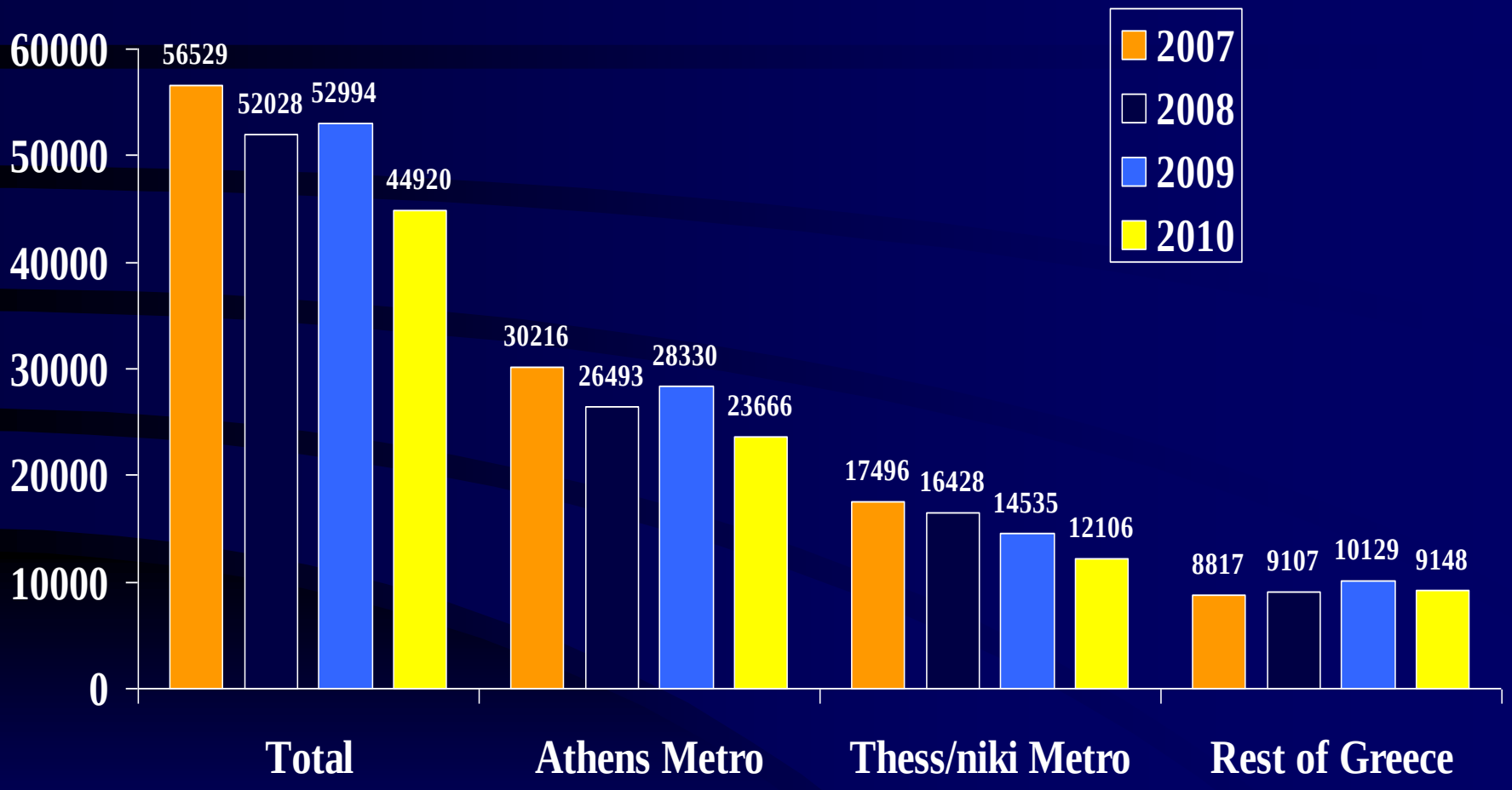
Horizontal-Long Axis

Courtesy of Gary Heller, MD, of the University of Connecticut School of Medicine.

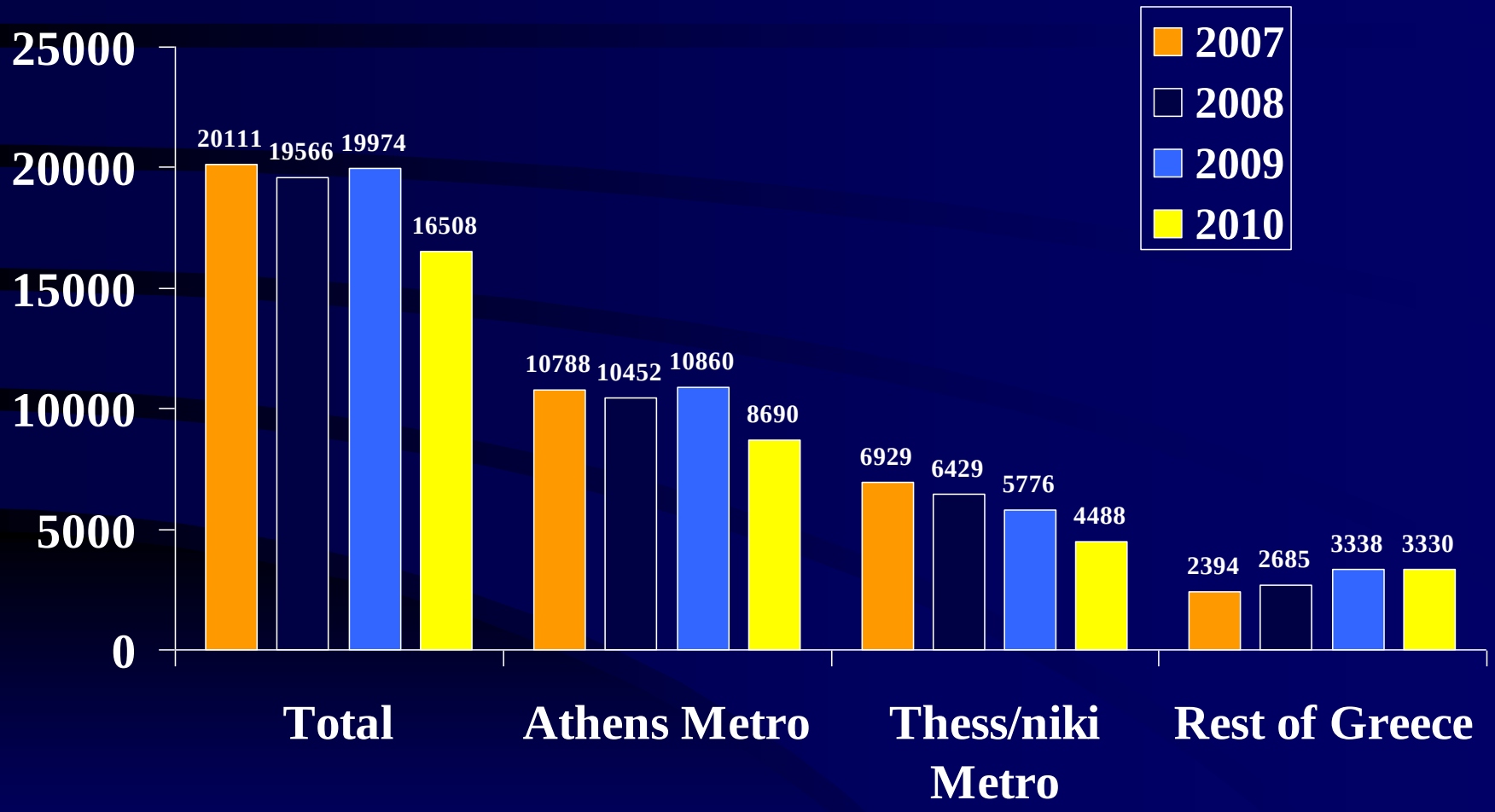
Coronary CT Angiography



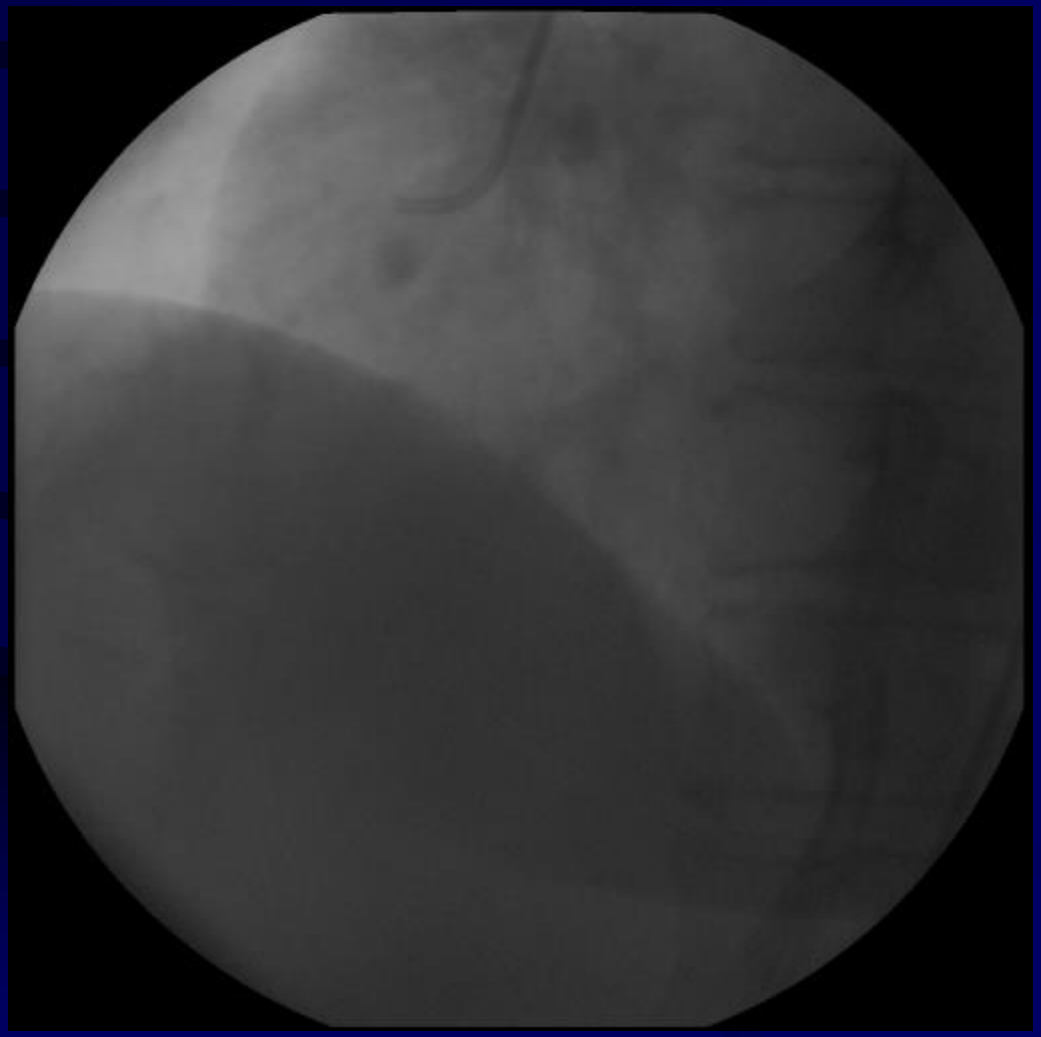
COR Procedures 2007-2010



PCI Procedures 2007-2010



Coronary Angiography



I indeed was in the marines!