



1^{as} Jornadas Lusófonas de Cardiologia

Cidade da Praia, 22 de Janeiro de 2009

Mesa redonda:

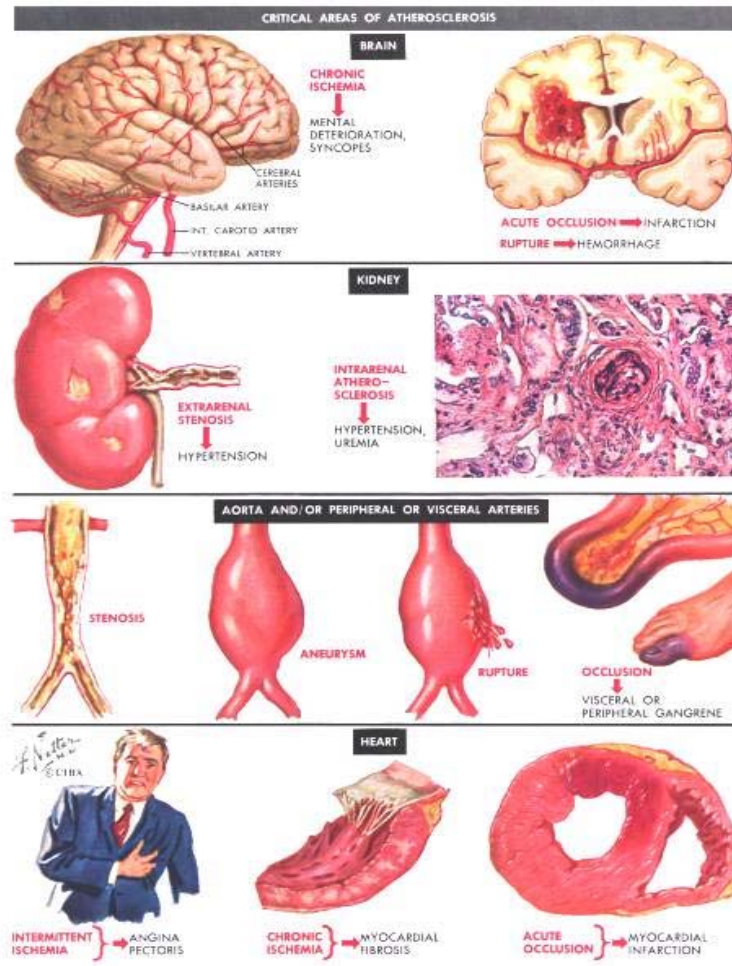
Doença das Artérias Coronárias

Etiopatogenia da Doença das Artérias Coronárias



Miguel Mendes

Aterosclerose = d. sistémica



Artérias de localização preferencial

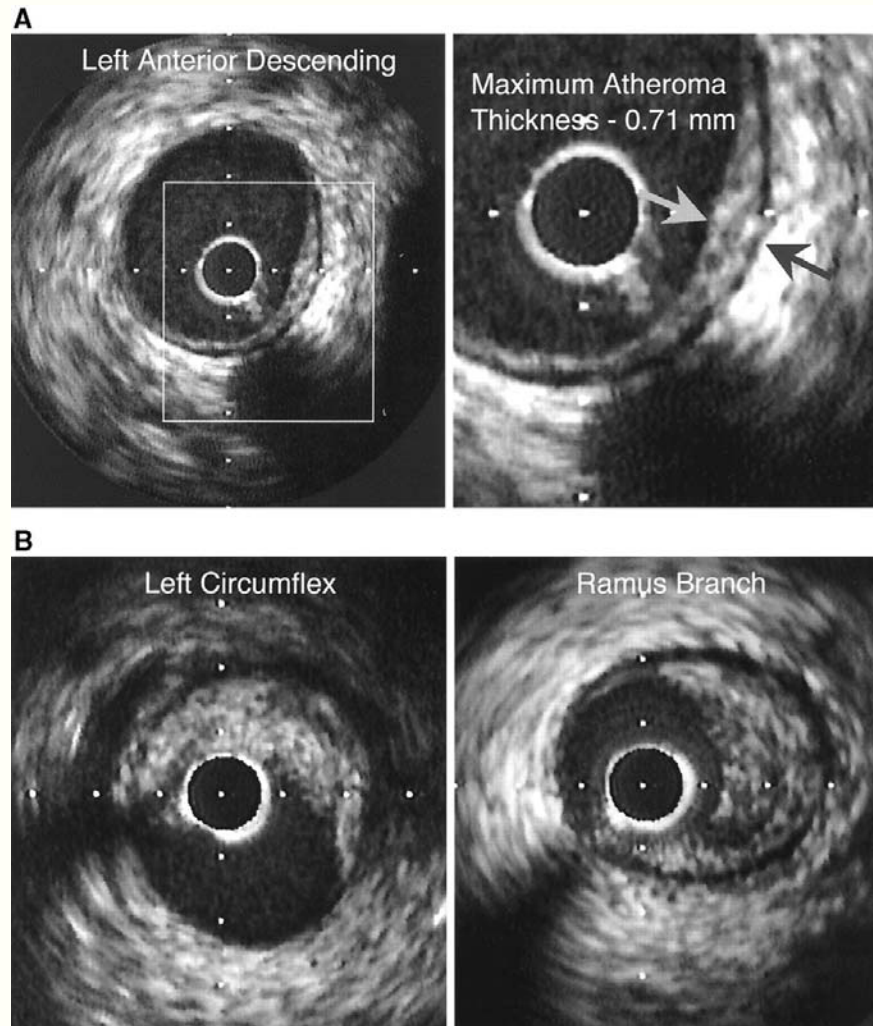
- Cerebrais médias
- Carótidas e artérias vertebrais
- Coronárias
- Aorta
- Membros inferiores

- Em zonas proximais, bifurcações e pequenas curvaturas

INTER-HEART: Risk of acute MI associated with risk factors in the overall population

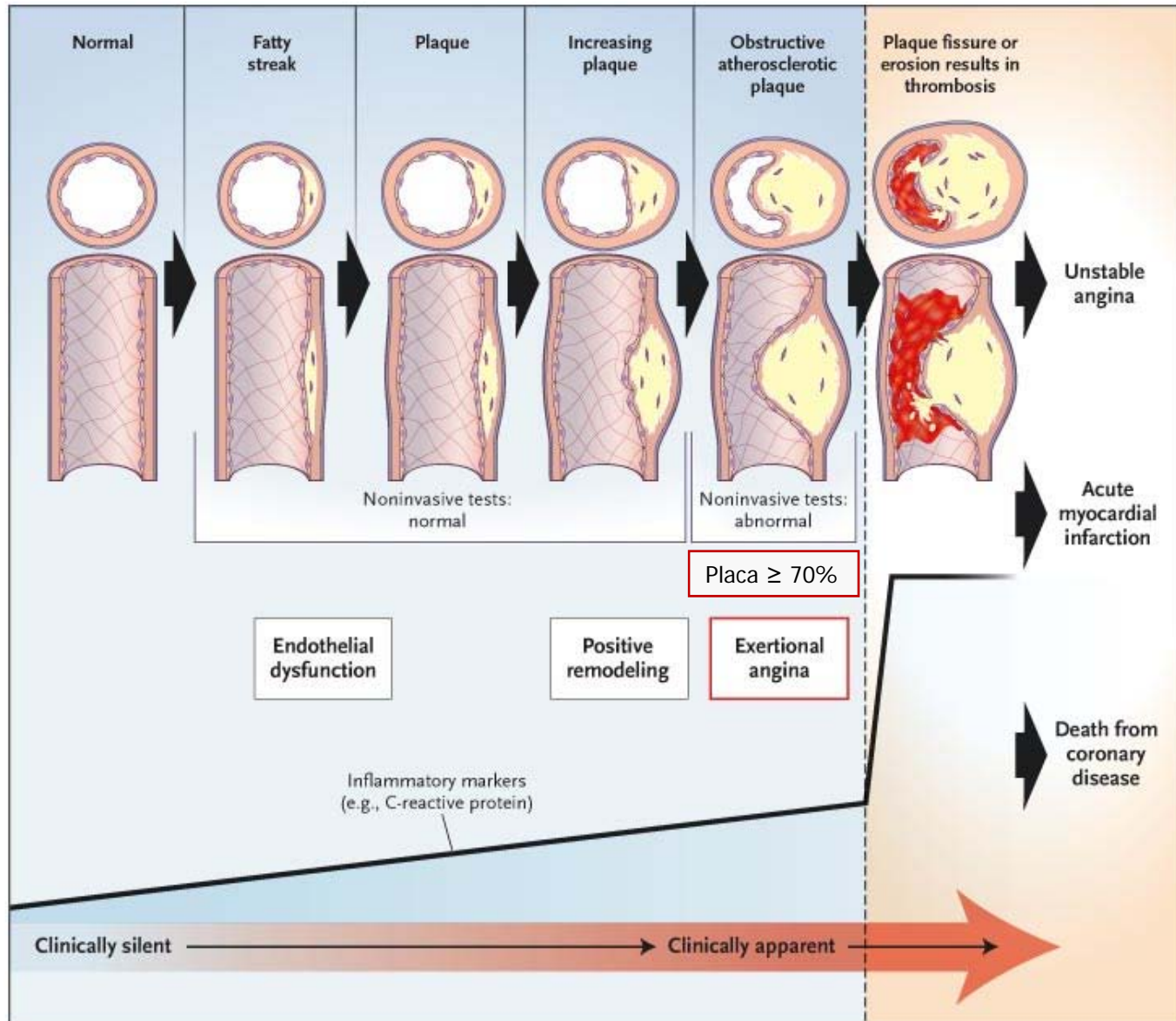
Risk factor	Odds ratio adjusted for age, sex, and smoking (99% CI)	Odds ratio adjusted for all (99% CI)
ApoB/ApoA-1 (fifth quintile compared with first)	3.87 (3.39-4.42)	3.25 (2.81-3.76)
Current smoking	2.95 (2.72-3.20)	2.87 (2.58-3.19)
Diabetes	3.08 (2.77-3.42)	2.37 (2.07-2.71)
Hypertension	2.48 (2.30-2.68)	1.91 (1.74-2.10)
Abdominal obesity	2.22 (2.03-2.42)	1.62 (1.45-1.80)
Psychosocial	2.51 (2.15-2.93)	2.67 (2.21-3.22)
Vegetable and fruits daily	0.70 (0.64-0.77)	0.70 (0.62-0.79)
Exercise	0.72 (0.65-0.79)	0.86 (0.76-0.97)
Alcohol intake	0.79 (0.73-0.86)	0.91 (0.82-1.02)
All combined	129.2 (90.2-185.0)	129.2 (90.2-185.0)

A, Example of atherosclerosis in LAD of 17-years-old man
B. Example of atherosclerosis lesion in Cx artery in a 32 years-old woman

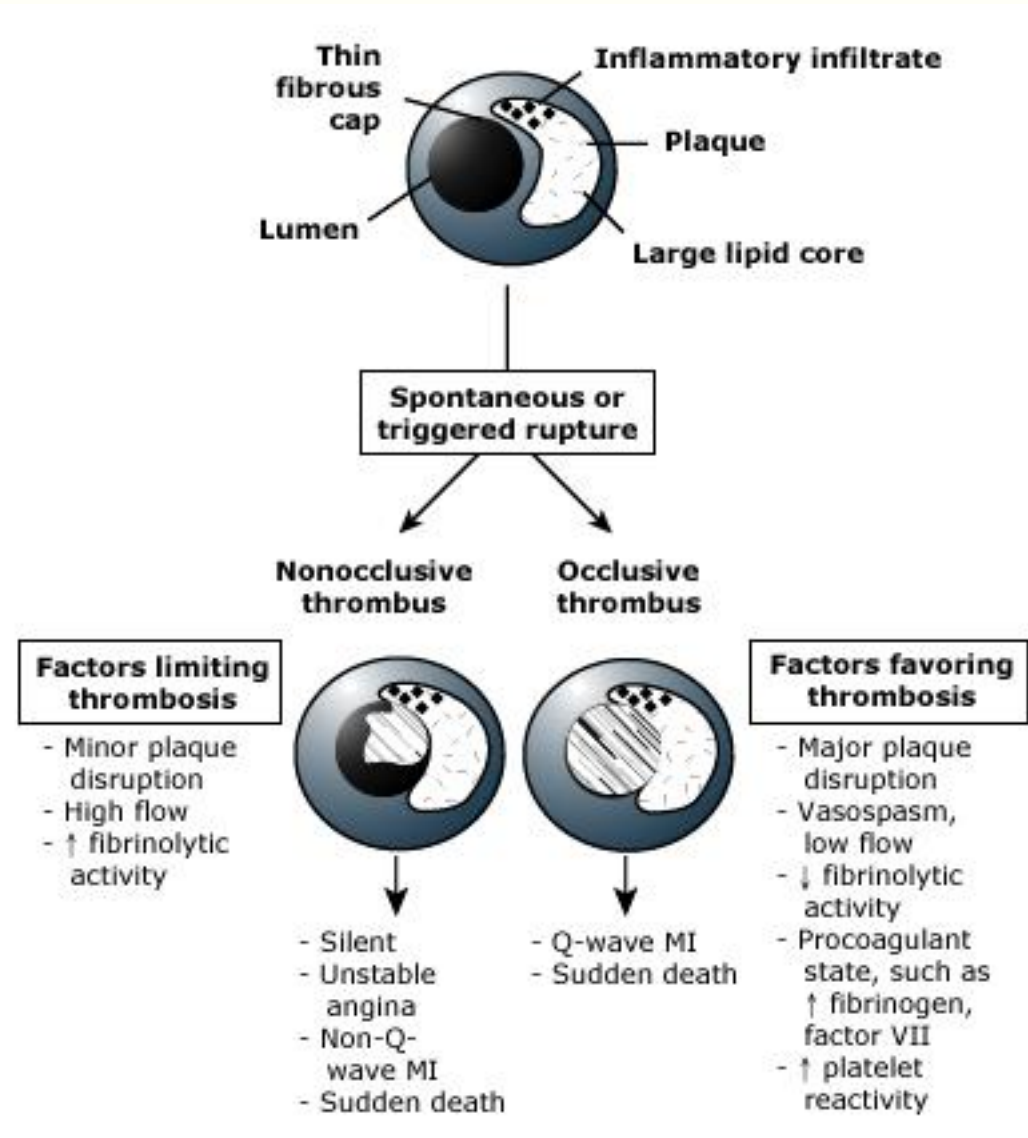


Tuzcu, E. M. et al. *Circulation* 2001;103:2705-2710

Progression of Coronary Atherosclerosis



Unstable Fibrous Plaques in Atherosclerosis



hipóteses etiológicas

- degenerativa / hemodinâmica
- inflamatória/auto-imune
- infecciosa

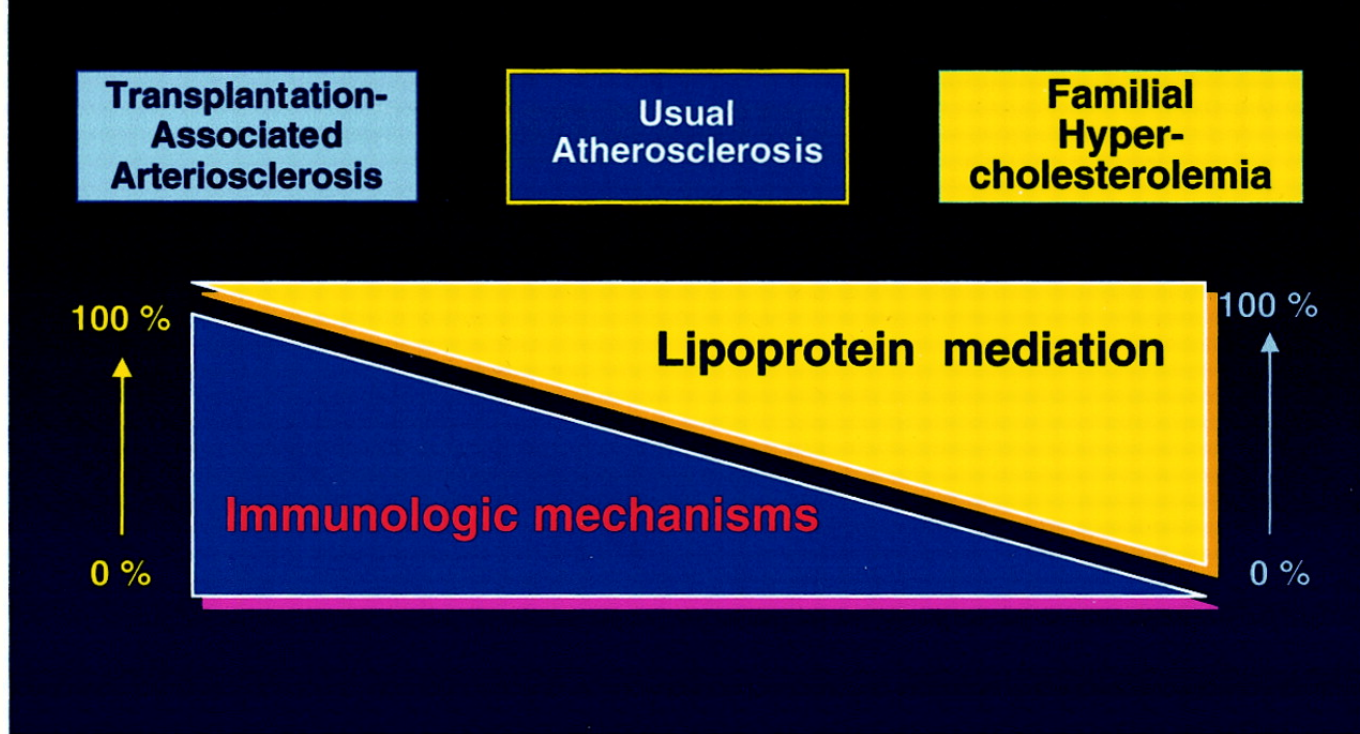
hipótese da infecção

Table 1. Large and Intermediate-Size Trials of Antibiotics for the Secondary Prevention of Coronary Heart Disease.*

Trial†	Year	No. of Patients	Indication or Setting	Antibiotic	Duration of Therapy and Follow-up	Result
ACADEMIC ⁶	2000	302	Coronary heart disease	Azithromycin	3 mo; 2 yr	Negative
ISAR-3 ⁷	2001	1020	Post-percutaneous coronary intervention	Roxithromycin	1 mo; 6–12 mo	Negative
CLARIFY ⁸	2002	148	Acute coronary syndromes	Clarithromycin	3 mo; 18 mo	Trend
ANTIBIO ⁹	2003	872	Myocardial infarction	Roxithromycin	6 wk; 12 mo	Negative
AZACS ¹⁰	2003	1450	Acute coronary syndromes	Azithromycin	5 days; 6 mo	Negative
WIZARD ¹¹	2003	7724	Coronary heart disease	Azithromycin	3 mo; 3 yr	Negative
ACES ¹	2005	4012	Coronary heart disease	Azithromycin	12 mo; 4 yr	Negative
PROVE IT–TIMI ²	2005	4162	Acute coronary syndromes	Gatifloxacin	18 mo; 24 mo	Negative

Allograft arteriosclerosis: one end of the continuum

Multifactorial Mechanisms in Atherogenesis



Libby, P. et al. *Circulation* 2003;107:1237-1239

ORIGINAL ARTICLE

Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease

Steven E. Nissen, M.D., E. Murat Tuzcu, M.D., Paul Schoenhagen, M.D., Tim Crowe, B.S., William J. Sasiela, Ph.D., John Tsai, M.D., John Orazem, Ph.D., Raymond D. Magorien, M.D., Charles O'Shaughnessy, M.D., and Peter Ganz, M.D., for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators*

N ENGL J MED 352:1 WWW.NEJM.ORG JANUARY 6, 2005

Table 4. Rates of Progression According to the Change in LDL Cholesterol and CRP Levels.*

Subgroup	No. of Patients	Percent Atheroma Volume [†]			Total Atheroma Volume (mm ³) [‡]		
		Median	95% CI	Mean ±SD	Median	95% CI	Mean ±SD
Reduction in LDL cholesterol and CRP both greater than median	141	0.24 (-2.8 to 3.5) [‡]	-0.77 to 0.54	0.33±5.3	-1.98 (-23.0 to 10.8) [‡]	-6.26 to 3.67	-2.41±31.6
Reduction in LDL cholesterol greater than median, reduction in CRP less than median	106	0.81 (-2.0 to 4.8)	-0.32 to 1.81	1.62±4.7	2.06 (-12.8 to 21.5)	-3.26 to 6.41	4.04±28.7
Reduction in LDL cholesterol less than median, reduction in CRP greater than median	108	1.21 (-2.0 to 4.0)	-0.31 to 2.08	0.91±4.9	-1.04 (-18.6 to 22.5)	-6.78 to 8.74	1.42±29.2
Reduction in LDL cholesterol and CRP both less than median	141	1.82 (-1.5 to 5.1)	1.0 to 2.84	2.25±5.0	8.21 (-11.8 to 27.5)	0.40 to 13.05	7.49±27.5

CONCLUSIONS

For patients with coronary artery disease, the reduced rate of progression of atherosclerosis associated with intensive statin treatment, as compared with moderate statin treatment, is significantly related to greater reductions in the levels of both atherogenic lipoproteins and CRP.

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M. Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

ABSTRACT

BACKGROUND

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

METHODS

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

RESULTS

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; $P < 0.00001$), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; $P = 0.0002$), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; $P = 0.002$), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; $P < 0.00001$), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; $P < 0.00001$), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; $P = 0.02$). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

From the Center for Cardiovascular Disease Prevention (P.M.R., E.D., J.G.M., R.J.G.) and Division of Cardiovascular Medicine (P.M.R., P.L.), Brigham and Women's Hospital, Harvard Medical School, Boston; Universidade Federal de São Paulo, São Paulo (F.A.H.F.); McGill University Health Center, Montreal (J.G.); Weill Cornell Medical College of Cornell University, New York (A.M.G.); Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.); University of Ulm Medical Center, Ulm, Germany (W.K.); Hospital Cordoba, Cordoba, Argentina (A.J.L.); Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark (B.G.N.); University of Glasgow, Glasgow, Scotland (J.S.); and St. Luke's Episcopal Hospital-Texas Heart Institute, Houston (J.T.W.). Address reprint requests to Dr. Ridker at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, MA 02215, or at pridker@partners.org.

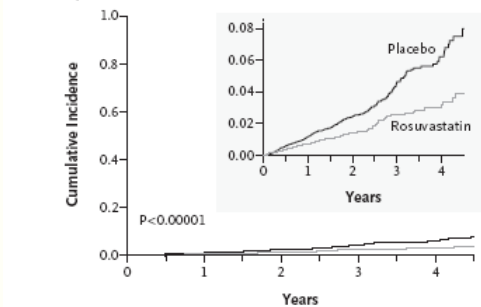
*Members of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study group are listed in the Appendix and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0807646) was published at www.nejm.org on November 9, 2008.

N Engl J Med 2008;359:2195-2027.

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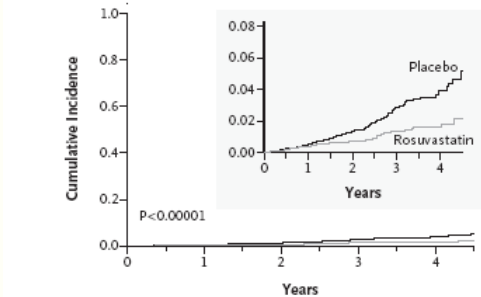
A Primary End Point



No. at Risk

Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

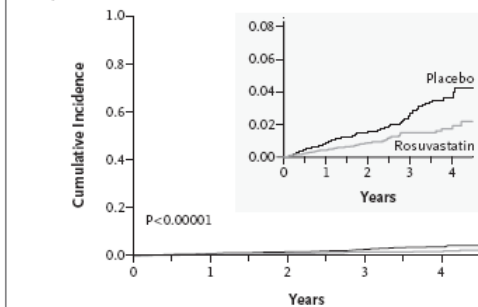
C Revascularization or Hospitalization for Unstable Angina



No. at Risk

Rosuvastatin	8901	8640	8426	6550	3905	1966	1359	989	541	158
Placebo	8901	8641	8390	6542	3895	1977	1346	963	535	176

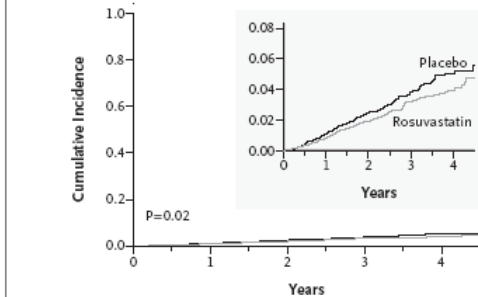
B Myocardial Infarction, Stroke, or Death from Cardiovascular Causes



No. at Risk

Rosuvastatin	8901	8643	8437	6571	3921	1979	1370	998	545	159
Placebo	8901	8633	8381	6542	3918	1992	1365	979	547	181

D Death from Any Cause



No. at Risk

Rosuvastatin	8901	8847	8787	6999	4312	2268	1602	1192	676	227
Placebo	8901	8852	8775	6987	4319	2295	1614	1196	681	246

AHA/CDC Scientific Statement

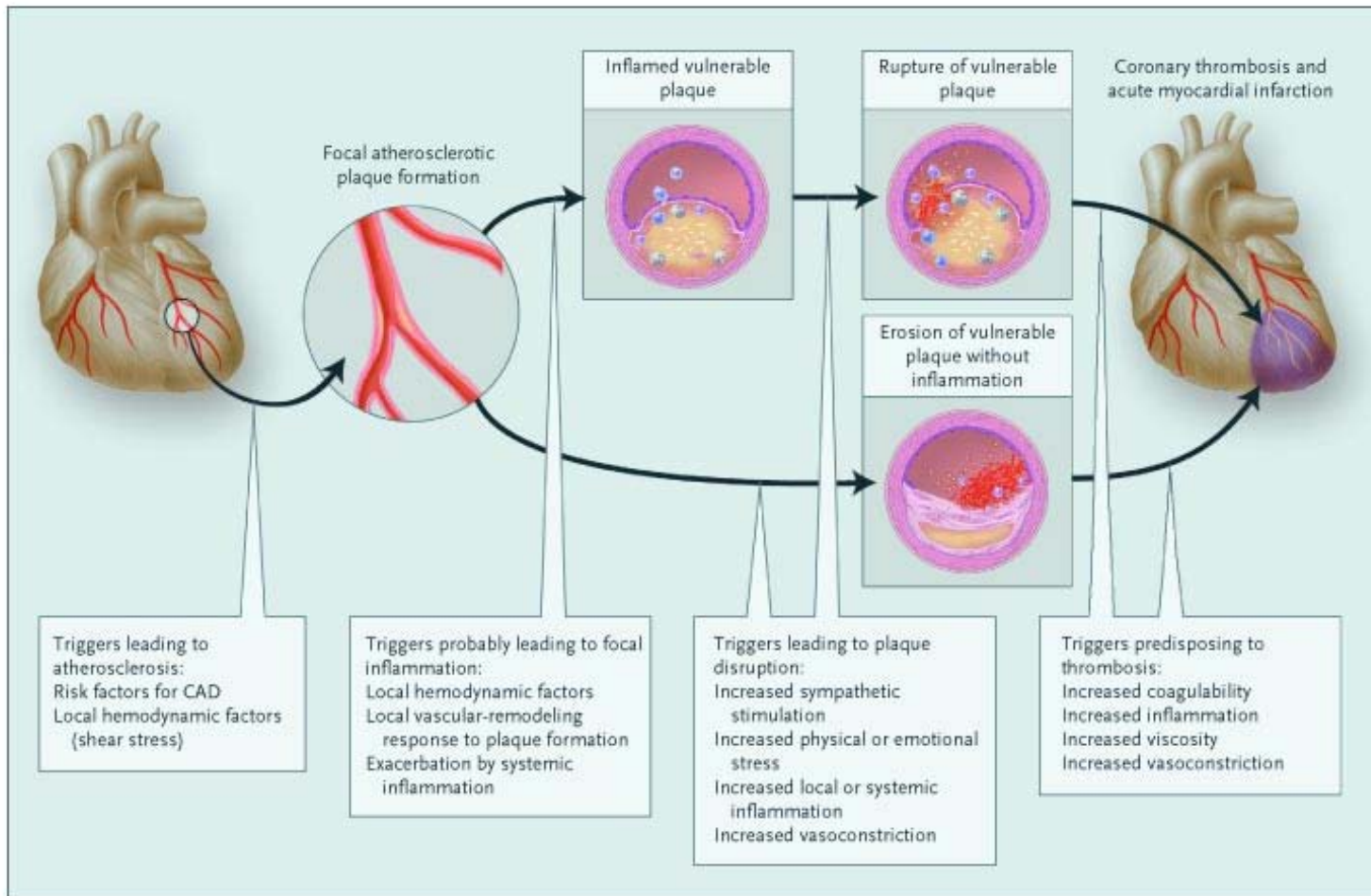
(*Circulation*. 2003;107:499-511.)

Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice

TABLE 3. Patient Characteristics and Conditions Associated With Increased or Decreased Levels of hs-CRP

Increased Levels	Decreased Levels
Elevated blood pressure	
Elevated body mass index	Moderate alcohol consumption
Cigarette smoking	Increased activity/endurance exercise
Metabolic syndrome/diabetes mellitus	Weight loss
Low HDL/high triglycerides	Medications
Estrogen/progestogen hormone use	Statins
Chronic infections (gingivitis, bronchitis)	Fibrates
Chronic inflammation (rheumatoid arthritis)	Niacin

Cascade of Triggers Culminating in Acute Myocardial Infarction



hipótese de resposta à lesão

1. A ***disfunção endotelial*** é a primeira etapa qualquer que seja o processo ou o factor de risco que induz inflamação.
2. A ***inflamação***, se excessiva ou mantida, provocará uma lesão avançada e mais tarde uma lesão complicada.
3. A ***trombose*** é o denominador comum das complicações sérias da doença aterosclerótica.

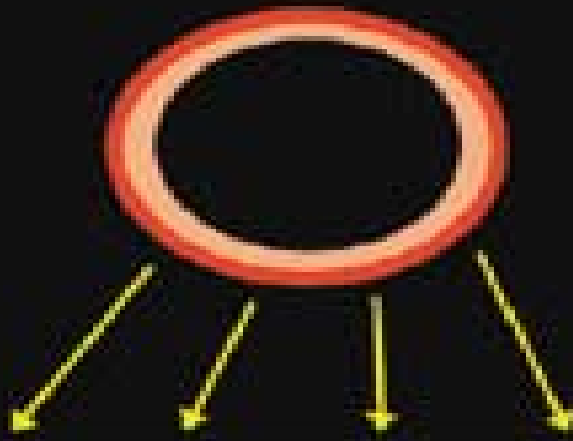
Ross R. Science 1973; 180: 1332-9

Ross R. NEJM 1999; 340: 115-26

Karnicki K. Arterioscler Throm Vasc Biol 2002; 22: 1495-9

Endothelial Dysfunction: Imbalance of Normal Vascular Processes

NORMAL ENDOTHELIUM



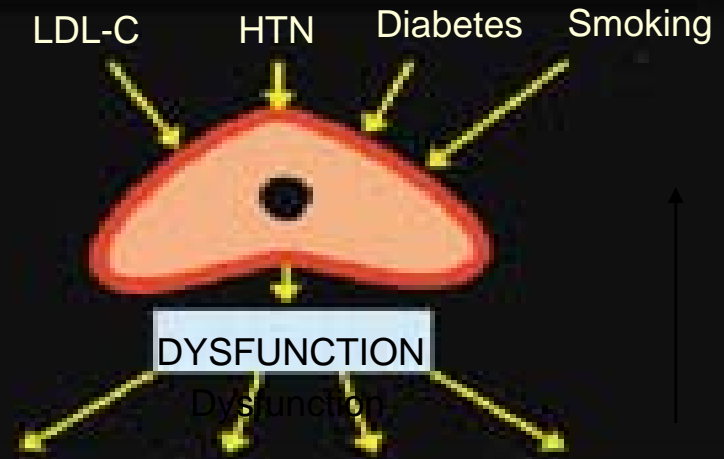
Vascular tone

Retard platelet & leukocyte adhesion

Inhibit SMC migration/proliferation

Barrier to LDL-C
Degrade VLDL-C & chylotriglyceride (lipase)

ABNORMAL ENDOTHELIUM



Vasoconstriction

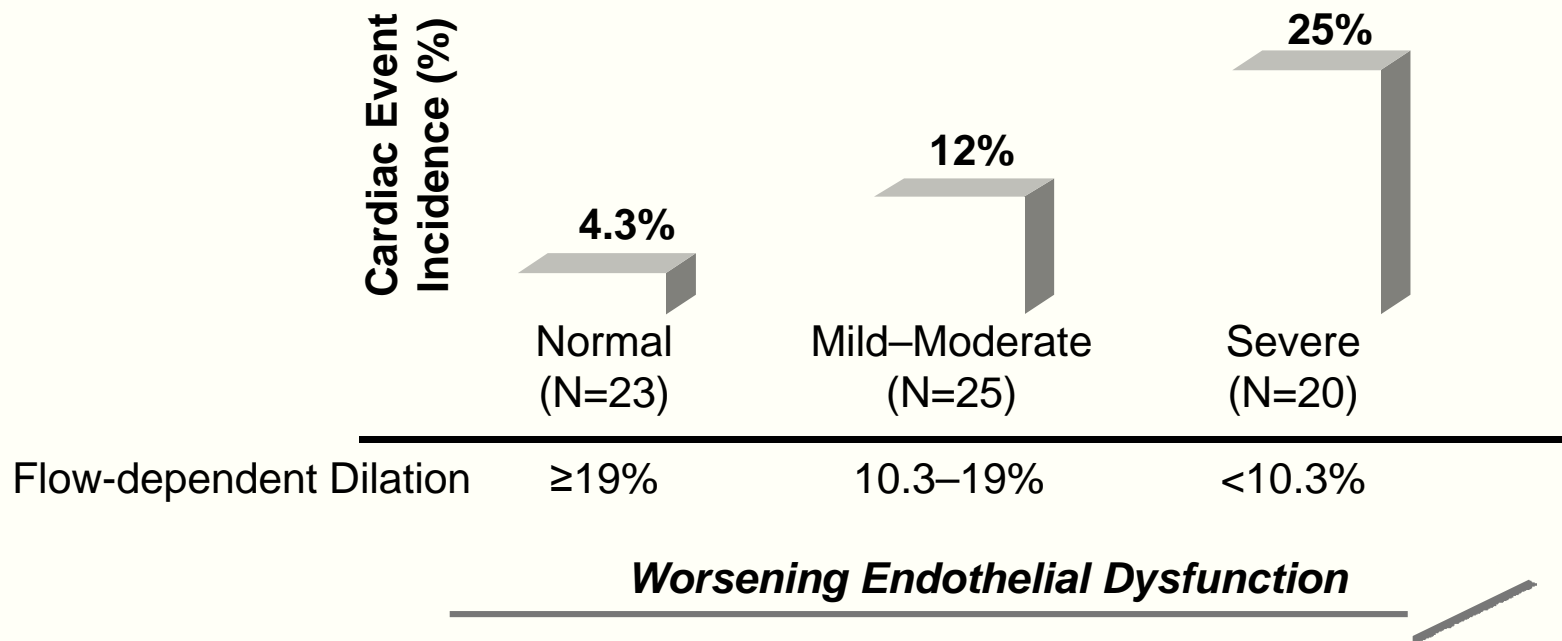
↑ Platelet leukocyte adhesion

SMC migration & growth

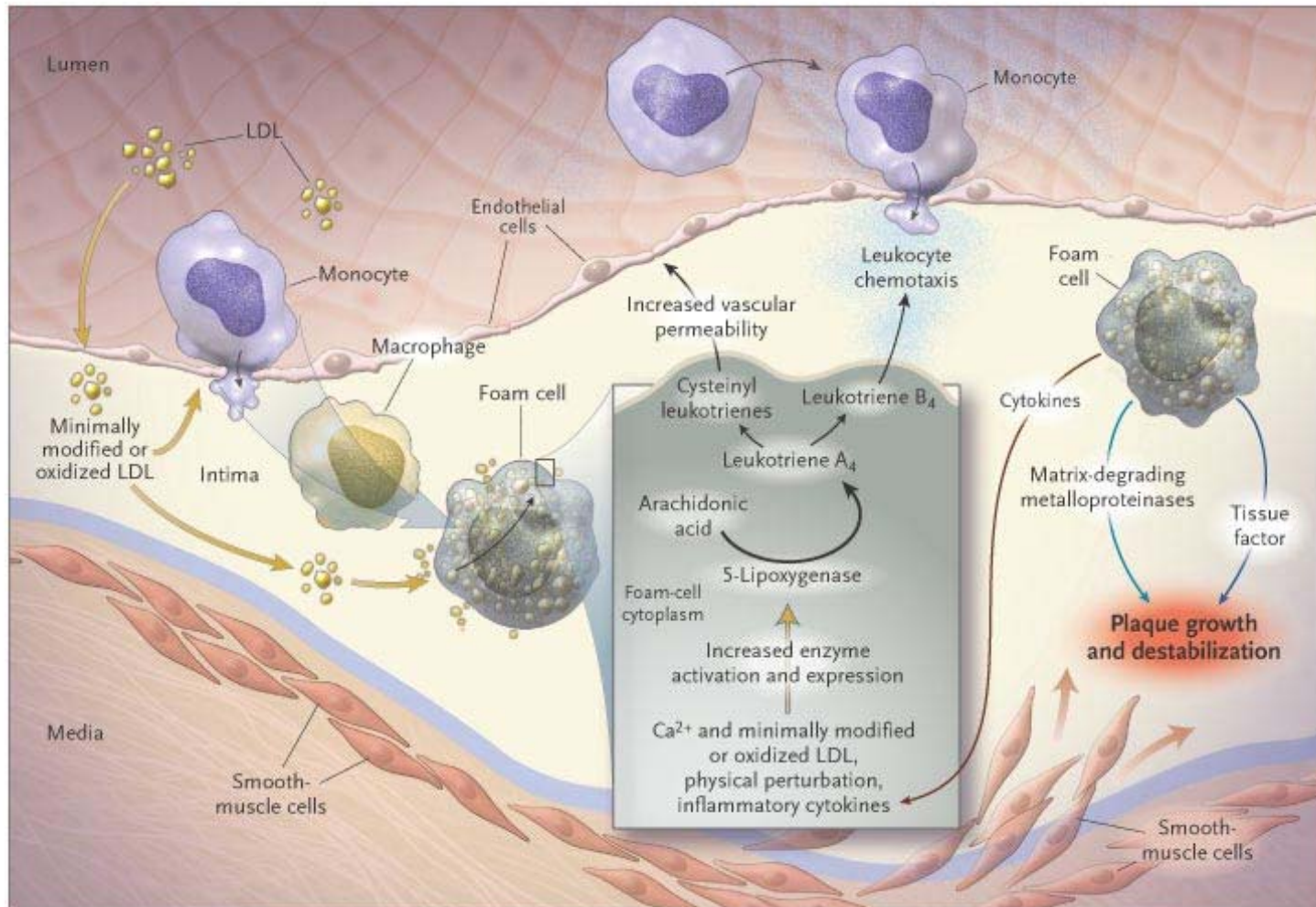
↑ Lipid deposition
↓ Clearance

Endothelial Dysfunction May Be Associated With Adverse Clinical Outcomes

- 147 patients after routine diagnostic cath or PTCA. 7.7 years follow-up
- Cardiac events: CV death, unstable angina, MI, PTCA, CABG, ischemic stroke, peripheral artery revascularization



Formação da placa

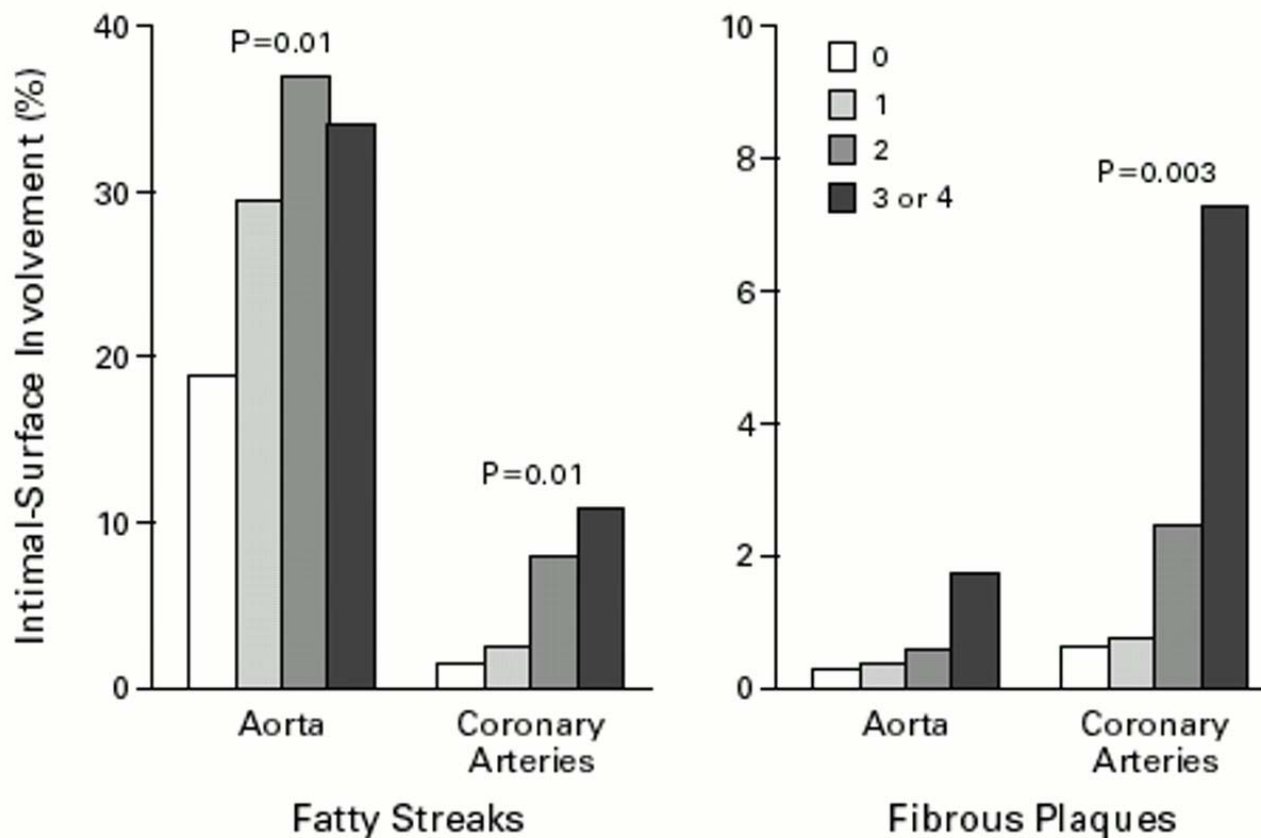


Estria gorda em artéria coronária



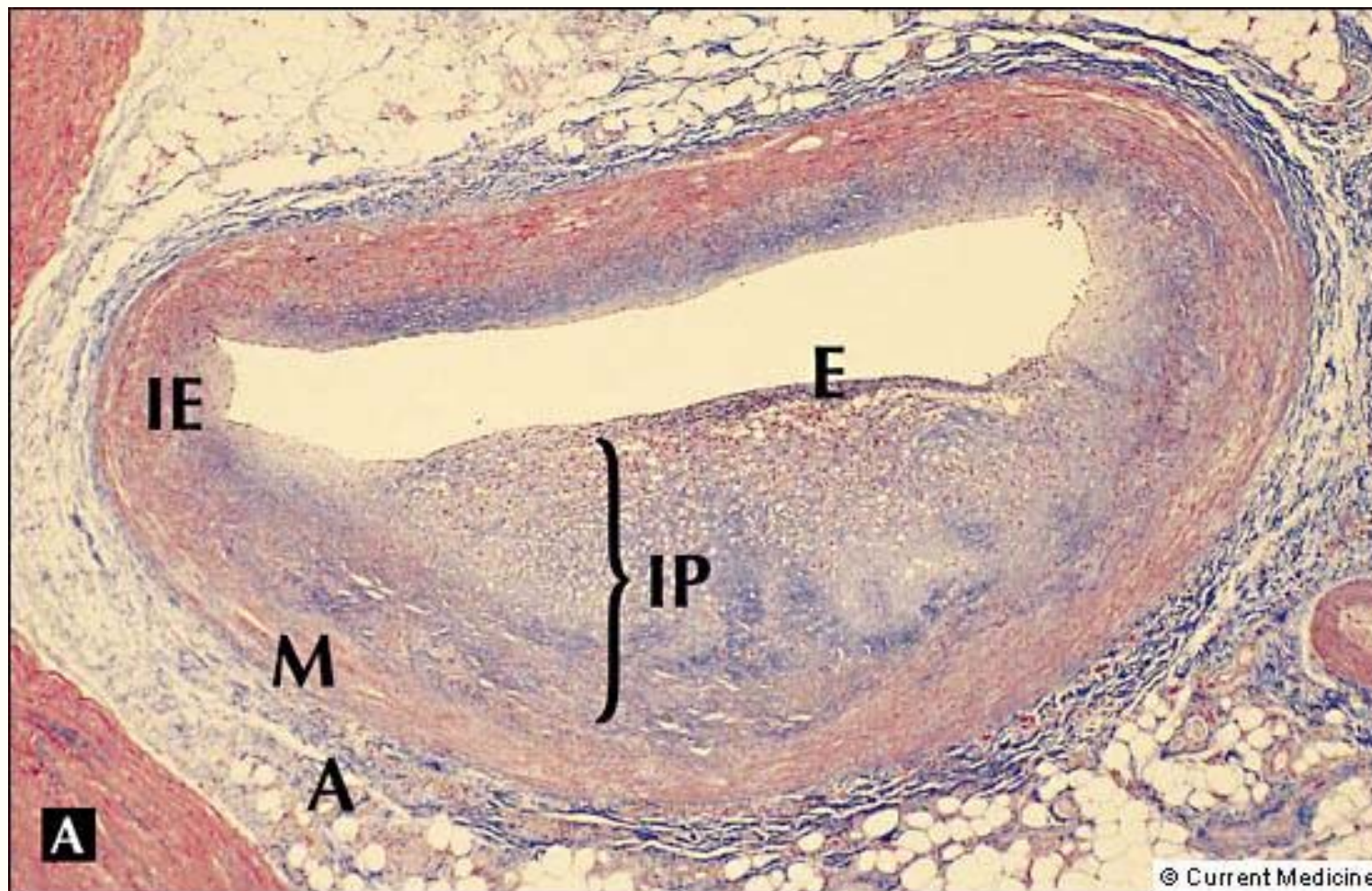
The Effect of Multiple Risk Factors on the Extent of Atherosclerosis in the Aorta and Coronary Arteries in Children and Young Adults

Risk factors: body-mass index, systolic blood pressure, and serum triglyceride and LDL cholesterol

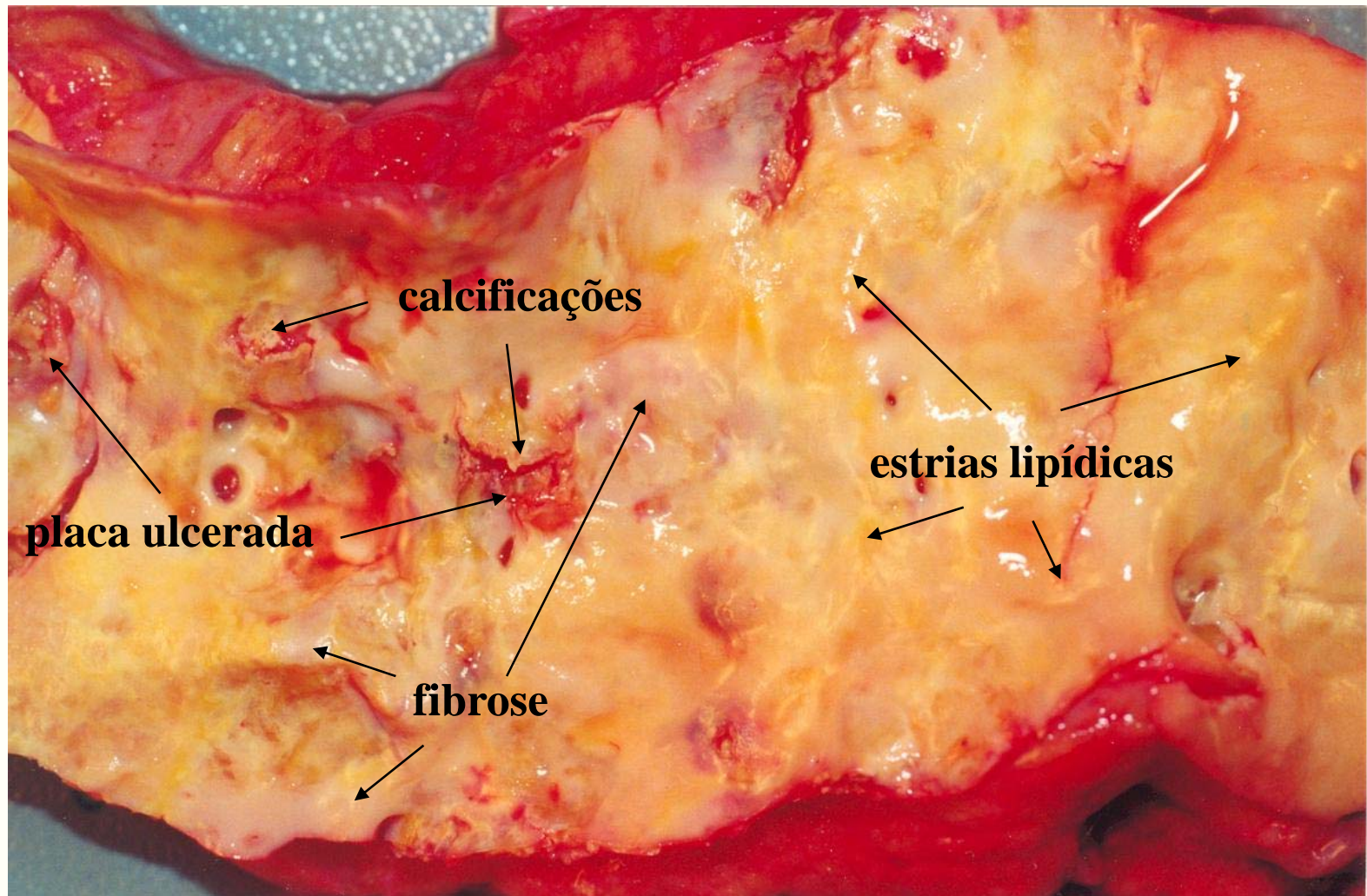


Berenson, G. S. et al. N Engl J Med 1998;338:1650-1656

Progressão da lesão coronária



placa complicada



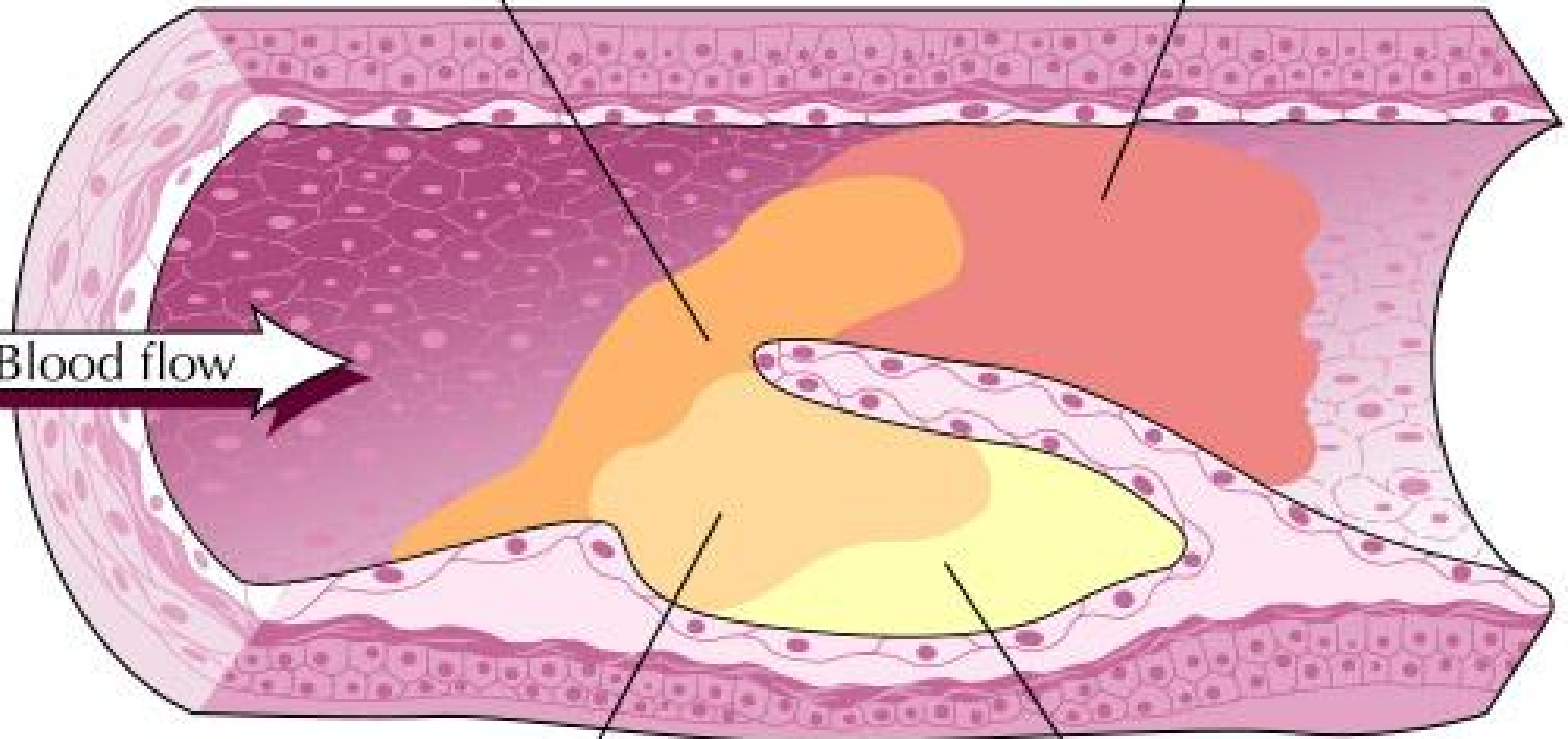
Intraluminal thrombus

Propagation of thrombus

Blood flow

Intraplaque thrombus

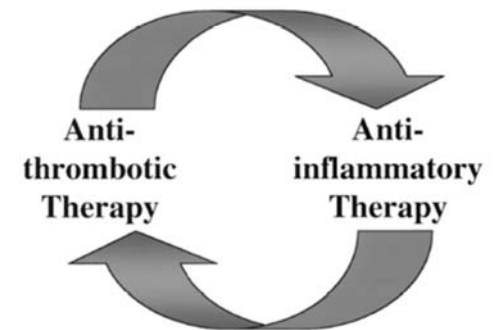
Lipid pool

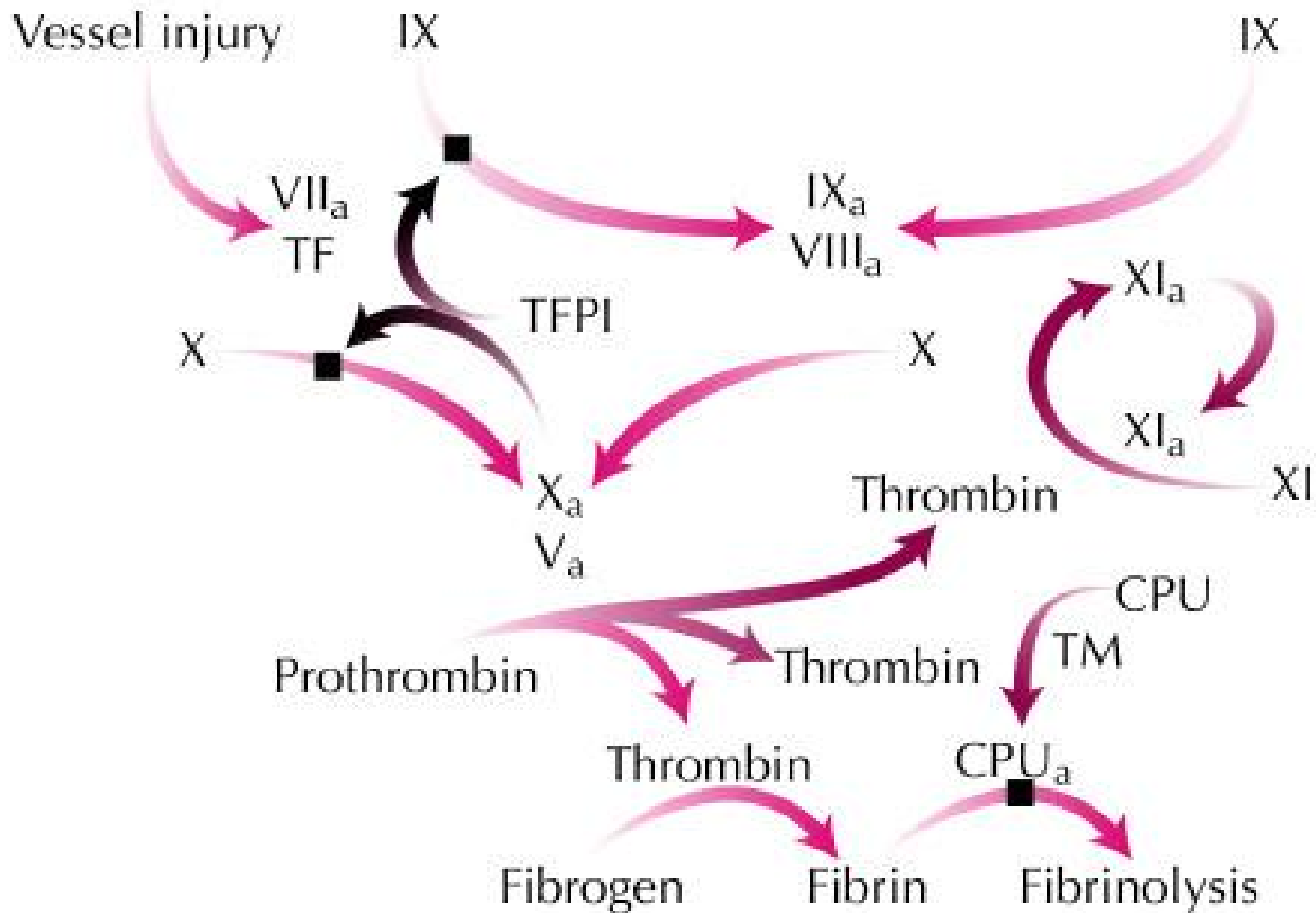


Inflammation and Thrombosis The Clot Thickens

Peter Libby, MD; Daniel I. Simon, MD

- Inflammatory modulators produced by platelets
 - platelet derived growth factor
 - platelet factor 4
 - CD 154 (CD 40 ligand)
 - RANTES
 - Thrombospondin
 - Transforming growth factor – β
 - Nitric oxide





© Current Medicine

Broze GJ. The tissue factor pathway of coagulation. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage*. Philadelphia: Lippincott Williams & Wilkins; 1998:77-104.

Microvascular Obstruction with Troponin Elevation Following Plaque Rupture

Quiescent plaque



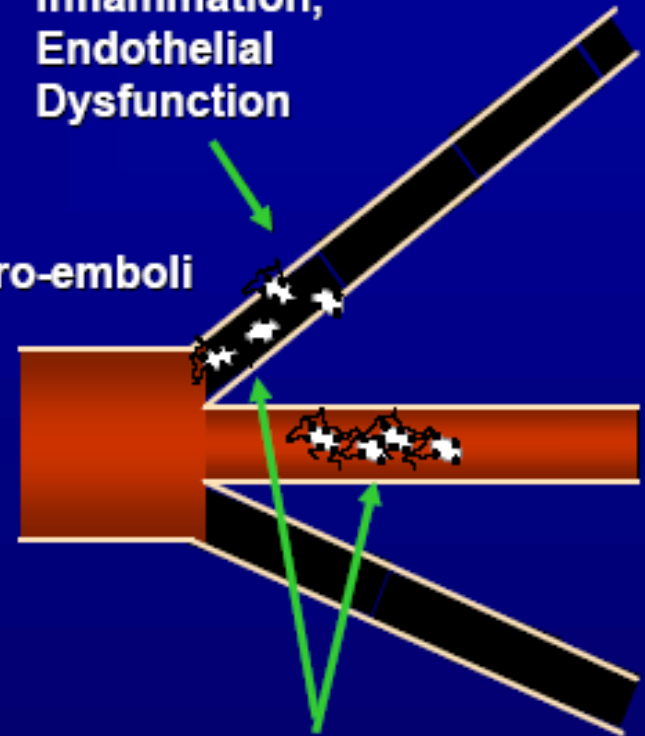
Plaque rupture



Occlusive thrombus



Inflammation,
Endothelial
Dysfunction



Microvascular
Obstruction



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

- Newby & Ohman, JACC 2003

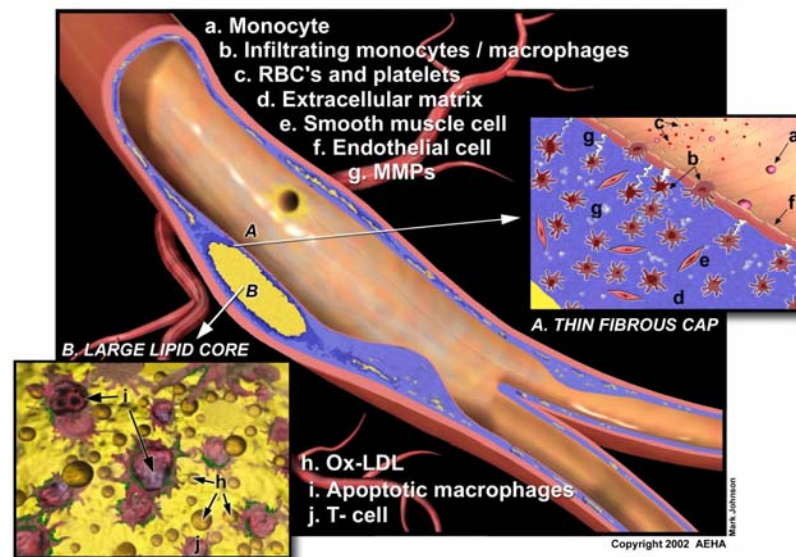
Placas responsáveis por eventos

Placas com rotura (~ 70%)

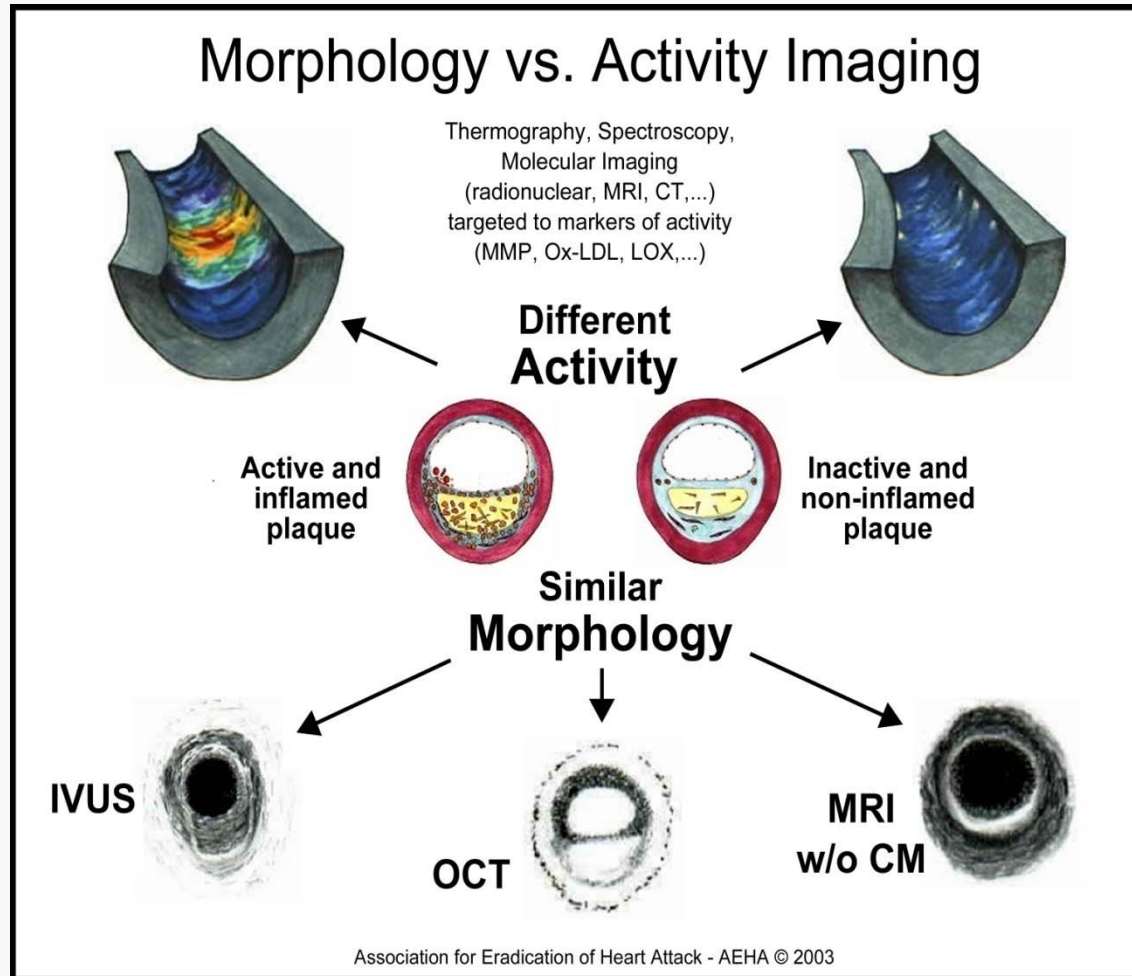
- Estenóticas (20%)
- Não-estenóticas (50%)

Placas sem rotura (~ 30%)

- Erosão
- Nódulo calcificado
- Outras/desconhecido



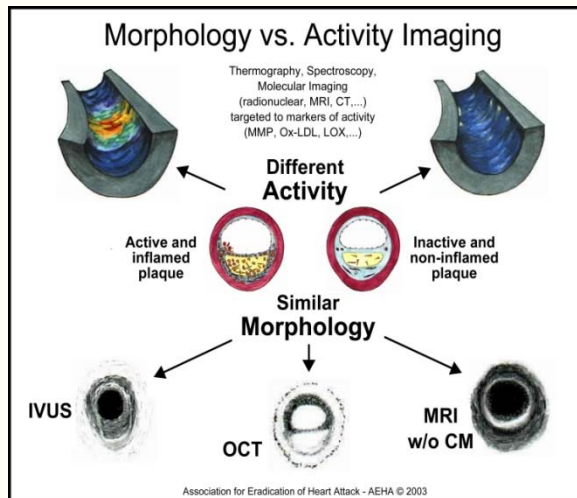
Identificação de placa vulnerável



Definição de placa vulnerável

■ Critérios major

- actividade inflamatória (monócito/macrófago e infiltração de linfocitos T)
- cápsula fibrosa fina e “core” lipídico volumoso
- erosão endotelial c/agregação plaquetária na superfície
- presença de fissura
- estenose crítica



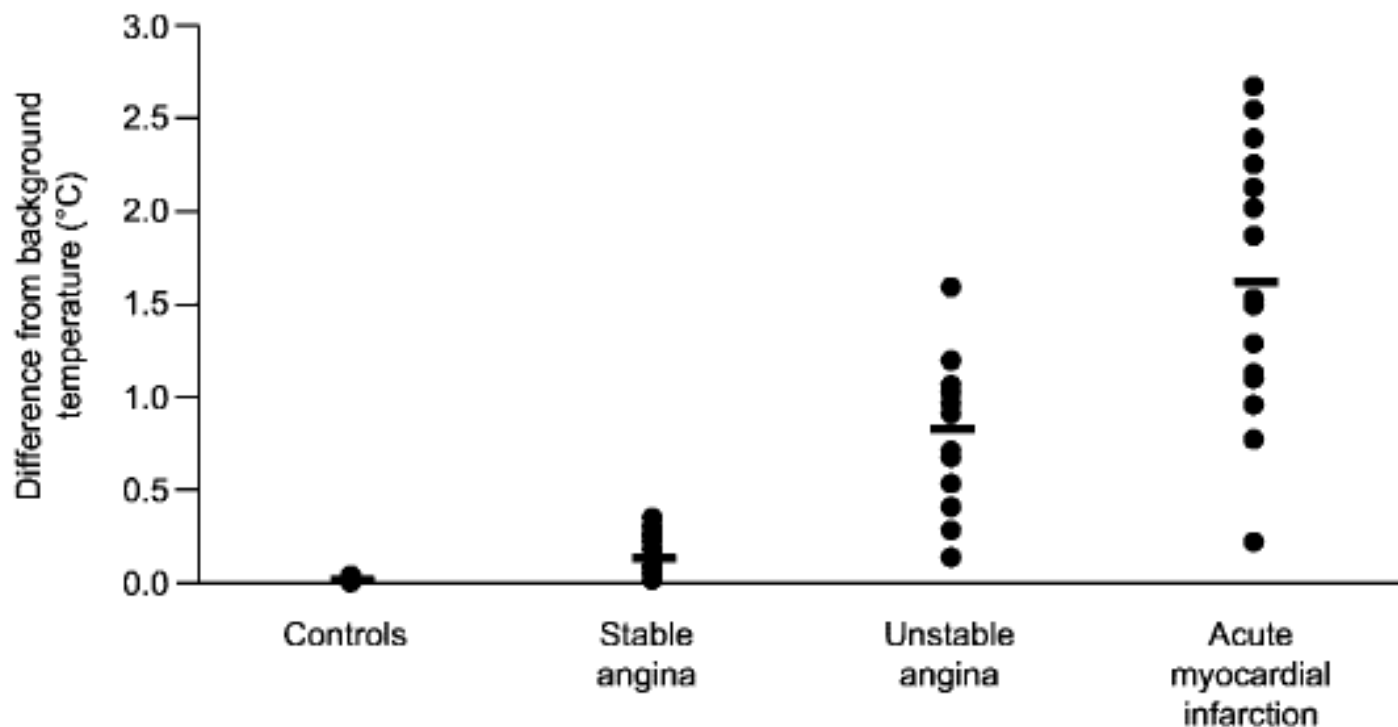
■ Critérios minor

- nódulo superficial calcificado
- hemorragia intra-placa
- disfunção endotelial

Inflammation as a Cardiovascular Risk Factor

James T. Willerson, MD; Paul M. Ridker, MD, MPH

Abstract—Inflammation occurs in the vasculature as a response to injury, lipid peroxidation, and perhaps infection. Various risk factors, including hypertension, diabetes, and smoking, are amplified by the harmful effects of oxidized low-density-lipoprotein cholesterol, initiating a chronic inflammatory reaction, the result of which is a vulnerable plaque, prone to rupture and thrombosis. Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events. Inflammation can potentially be detected locally by imaging techniques as well as emerging techniques, such as identification of temperature or pH heterogeneity. It can be detected systemically by measurement of inflammatory markers. Of these, the most reliable and accessible for clinical use is currently high-sensitivity C-reactive protein. A combination of methods may provide the best identification of persons at risk for cardiovascular events who would benefit from treatment. In randomized, controlled trials, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in the form of statins, have been shown to provide effective therapy for lowering CRP, in conjunction with their lipid-lowering effects. Although



estabilização da placa

- **estatinas:**
 - melhoram a função endotelial reduzem a inflamação
 - diminuem a trombogenicidade, a agregação plaquetária.
- **bloqueantes-beta:**
 - reduzem o stress parietal circunferencial, através da diminuição da pressão arterial, frequência cardíaca, massa VE e dos picos catecolaminérgicos secundários ao stress e ao esforço.
- **iECA:**
 - reduzem a pressão arterial e podem ter efeitos directos de estabilização ao diminuírem a síntese de angiotensina II.
- **antiagregantes e varfarina:**
 - limitam a trombose.