Biomarkers of Inflammation as Predictors of CVD

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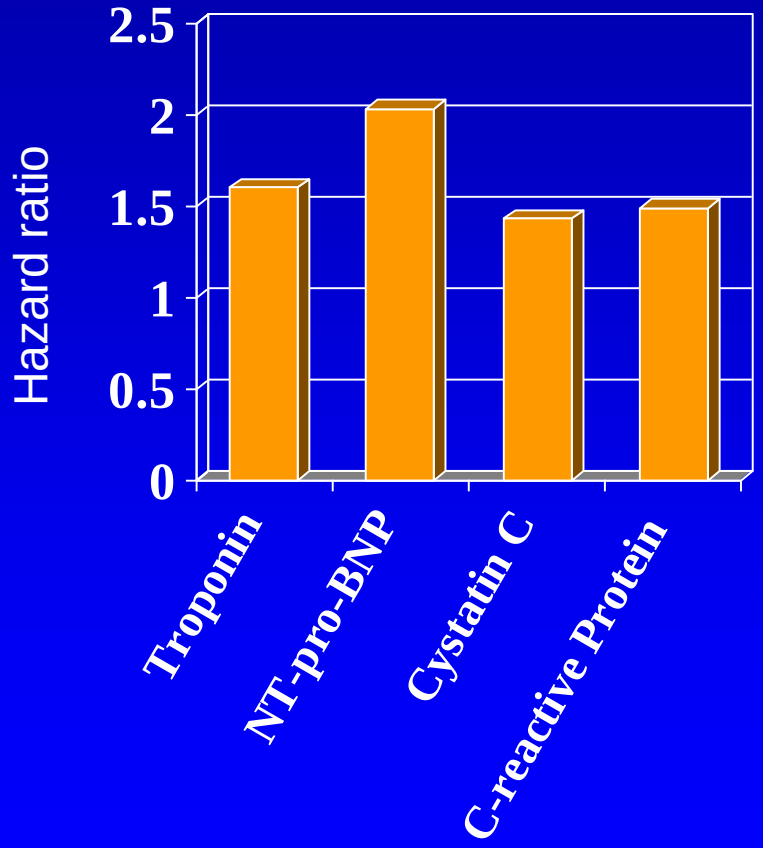
Biomarkers

- Brain natriuretic peptide (NT-pro BNP)
- Serum Amaloid
- Fibrinogen
- Lipoprotein-Associated Phospholipase A2
- Cystatin C
- Troponin-1
- MR-proADM (mid-region pro-adrenomedullin)
- MR-proANP (amino-terminal pro-A-type natriuretic peptide)
- Soluable Tumor Necrosis Factor-Receptor 1 (sTNF-R1)
- Soluable Tumor Necrosis Factor-Receptor 2 (sTNF-R2)
- Interleukin 6
- Coronary Artery Calcium Score (CAC)
  - Electron beam computerized tomography (EBCT)
- C-reactive protein (hs-CRP)

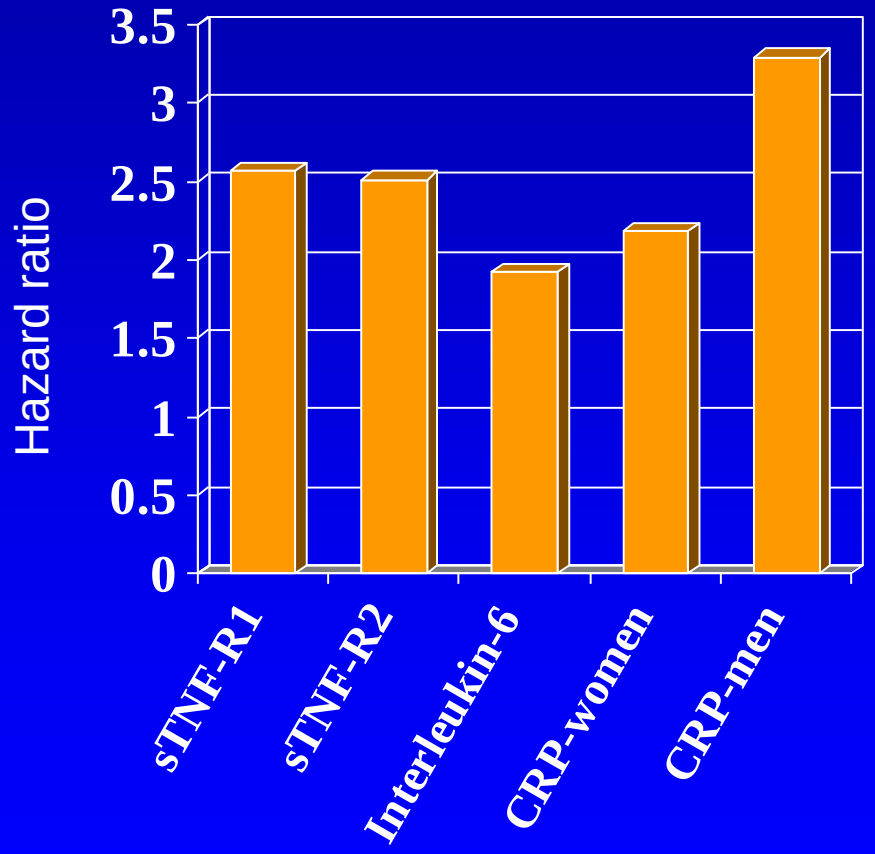
1. Zethelius B, et. al. *N Engl J Med* 2008; 358: 2107-16.
2. Pai KJ, et.al. *N Engl J Med* 2004; 351: 2599-2610.

Biomarkers Predict Cardiovascular Death



Zethelius B, et. al. *N Engl J Med* 2008; 358: 2107-16.

Biomarkers Predict Increased Cardiovascular Event Risk in women



Top quintile vs bottom quintile

sTNF and Interleukin not predictive in men

Pai KJ, et.al. *N Engl J Med* 2004; 351: 2599-2610.

What biomarkers are available in routine clinical practice?

A. hs-CRP
B. coronary artery calcium score (CAC Score)
C. cystatin
D. Both A and B
E. mid-region pro-adrenomedullin (MR-proADM)

C-Reactive Protein

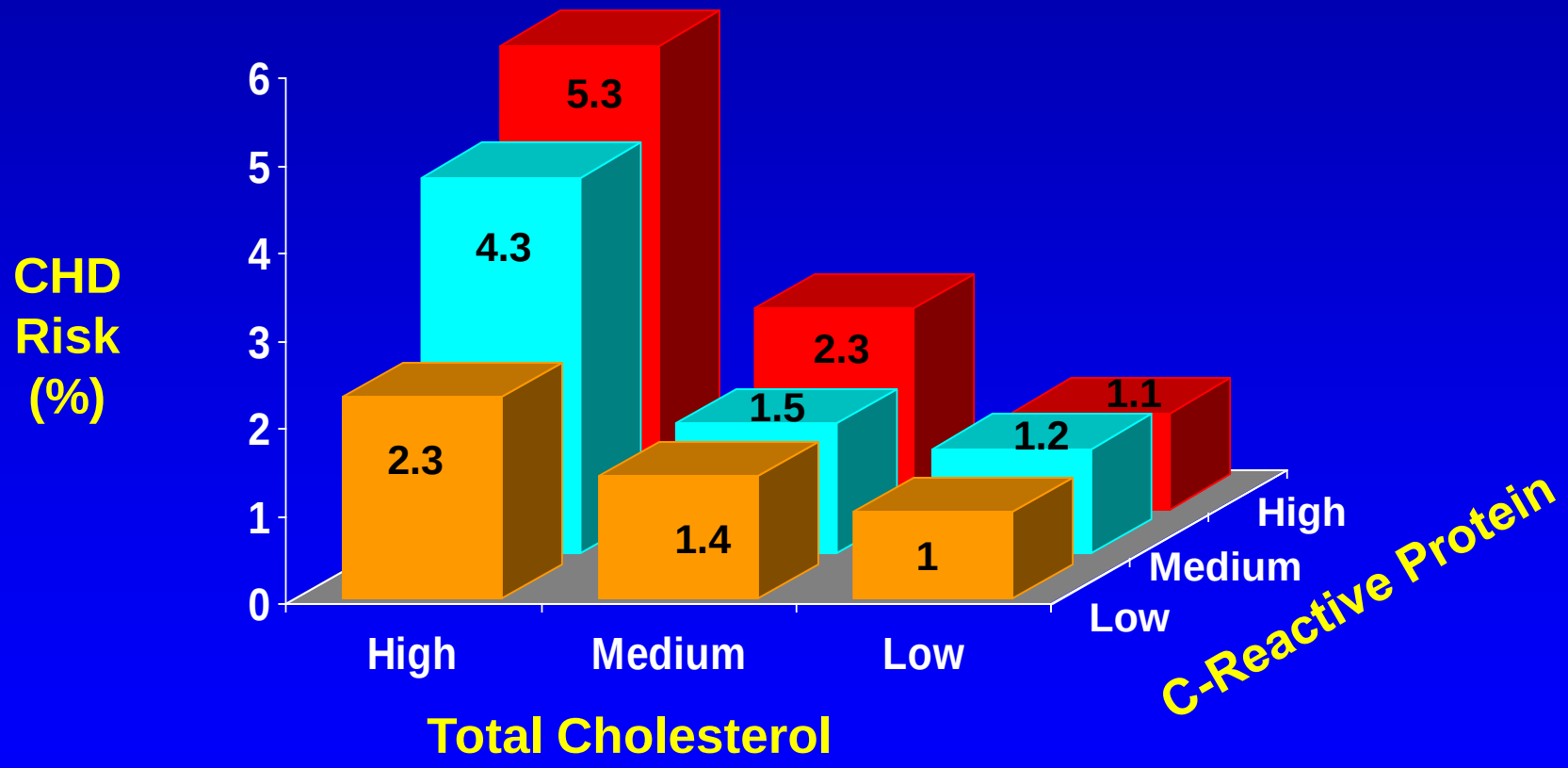
An acute phase reactant in blood:

- **Rises in inflammatory states**
- **Prognostic indicator in acute MI**
- **Predicts prospective coronary risk; possibly better than LDL**
- **May be predictor of new diabetes**

CRP vs hs-CRP

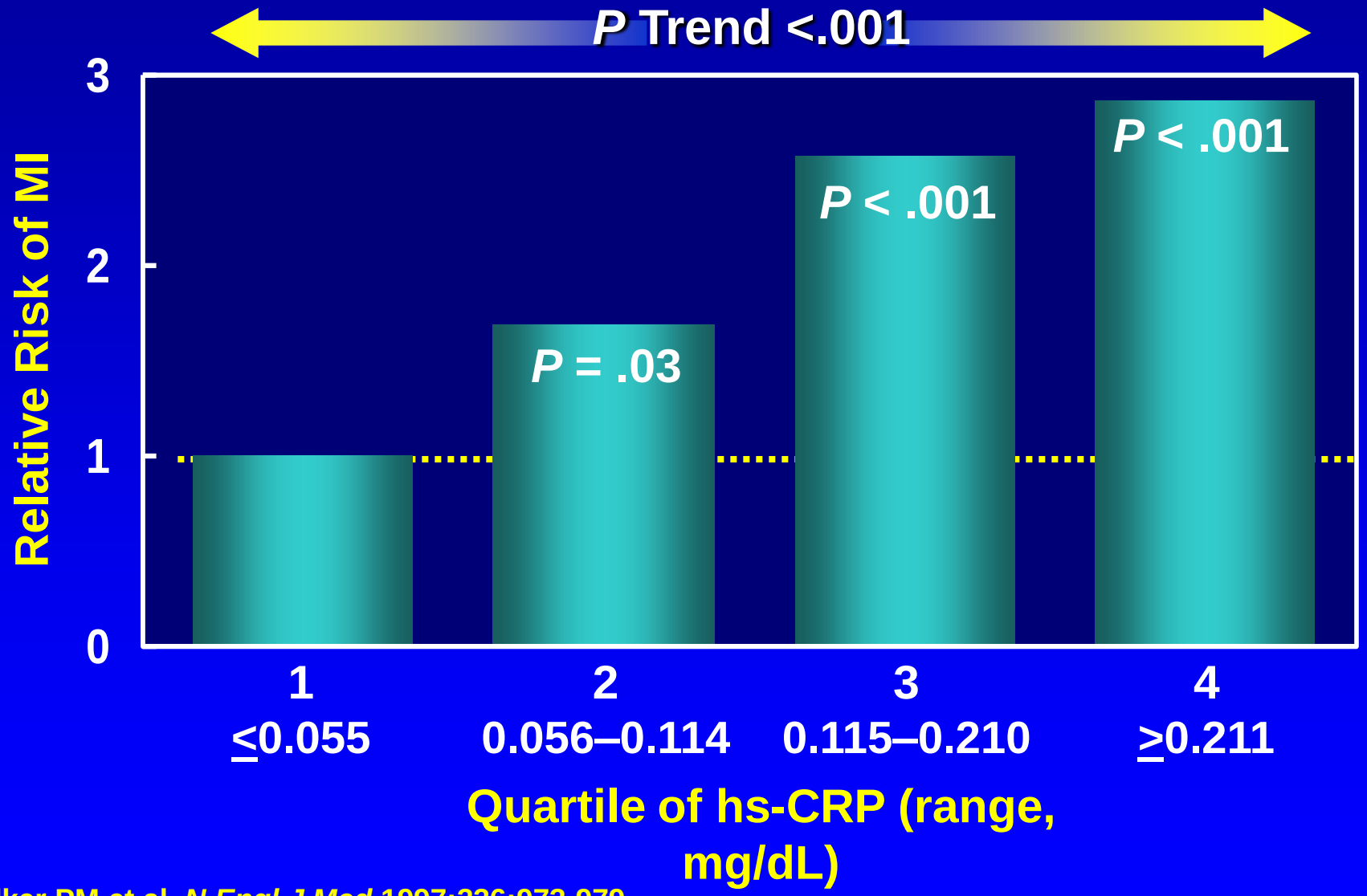
- CRP is an acute-phase protein produced by the liver in response to cytokine production (IL-6, tumor necrosis factor) during tissue injury, inflammation, or infection
- Standard CRP tests determine levels which are increased up to 1,000-fold in response to inflammation or infection but can not adequately assess the normal range
- High-sensitivity CRP (hs-CRP) assays detect levels of CRP within the normal range

C-Reactive Protein Adds to Predictive Value of Total Cholesterol in Determining Risk of First MI



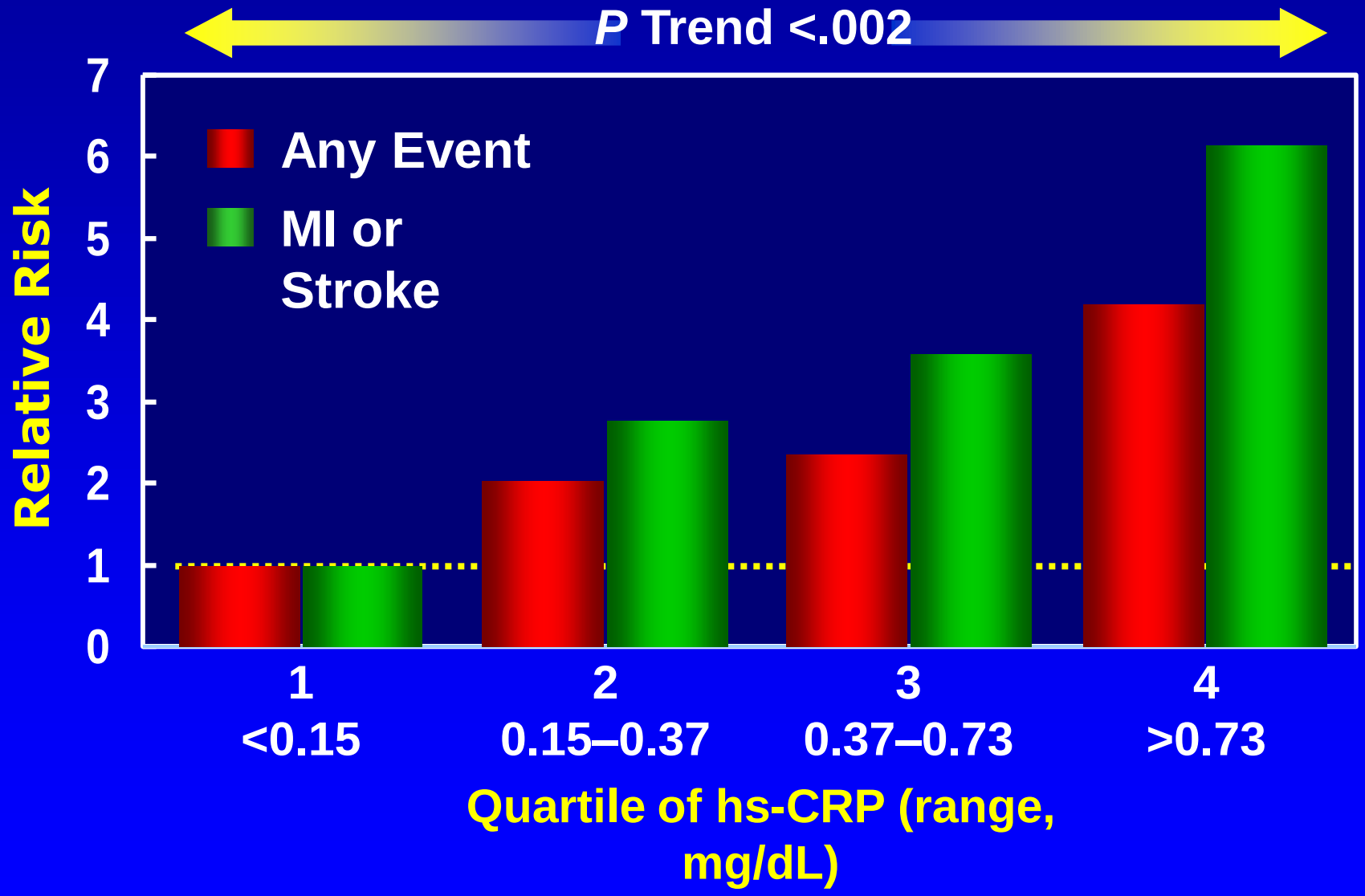
Ridker. *Circulation.* 1998;97:2007-2011.

High Sensitivity CRP and Risk of Future MI in Apparently Healthy Men



Ridker PM et al. *N Engl J Med* 1997;336:973-979.

High Sens CRP and Risk of Future Cardiovascular Events in Apparently Healthy Women



Ridker PM et al. *Circulation* 1998;98:731-733.

- Which of the following is related to CRP?

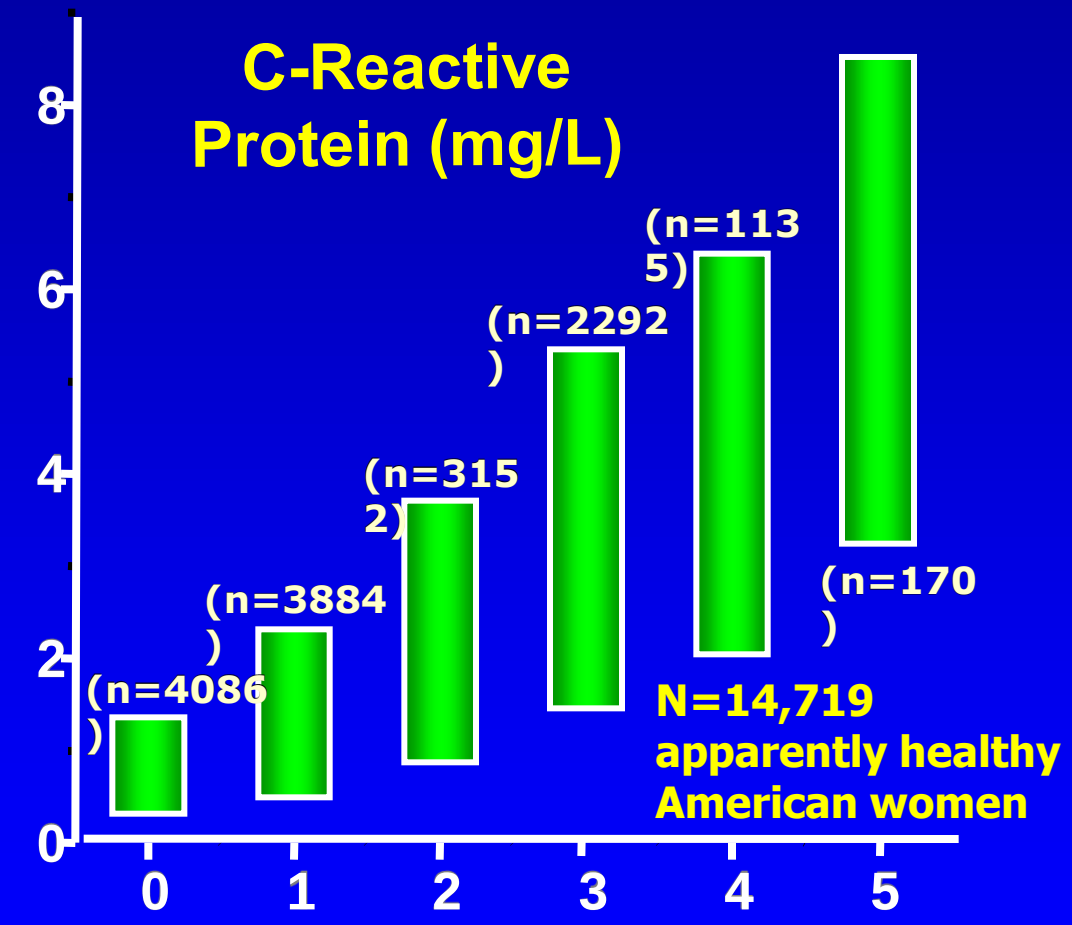
A. Glucose
B. BMI
C. Hypertension
D. Total Cholesterol
E. All of the above

C-Reactive Protein and Insulin Resistance

- Increase in C-reactive protein associated with measures of the metabolic syndrome: (P<.0001)
  - total cholesterol
  - triglyceride
  - body mass index
  - glucose
  - uric acid
  - HDL-C (negative)

Frohlich et al. *Diabetes Care.* 2000;23:1835-1839.

CRP Levels Correlate with ATP III Definition of Metabolic Syndrome



ATP III Definition of Metabolic Syndrome

3 of the following 5 characteristics:

- Midline obesity
- Elevated TG
- Low HDL
- Hypertension
- Abnormal glucose metabolism

Ridker PM et al. *Circulation.* 2003;107:391-397.

Predictive Value of Survival by CRP Level in Patients with Metabolic Syndrome

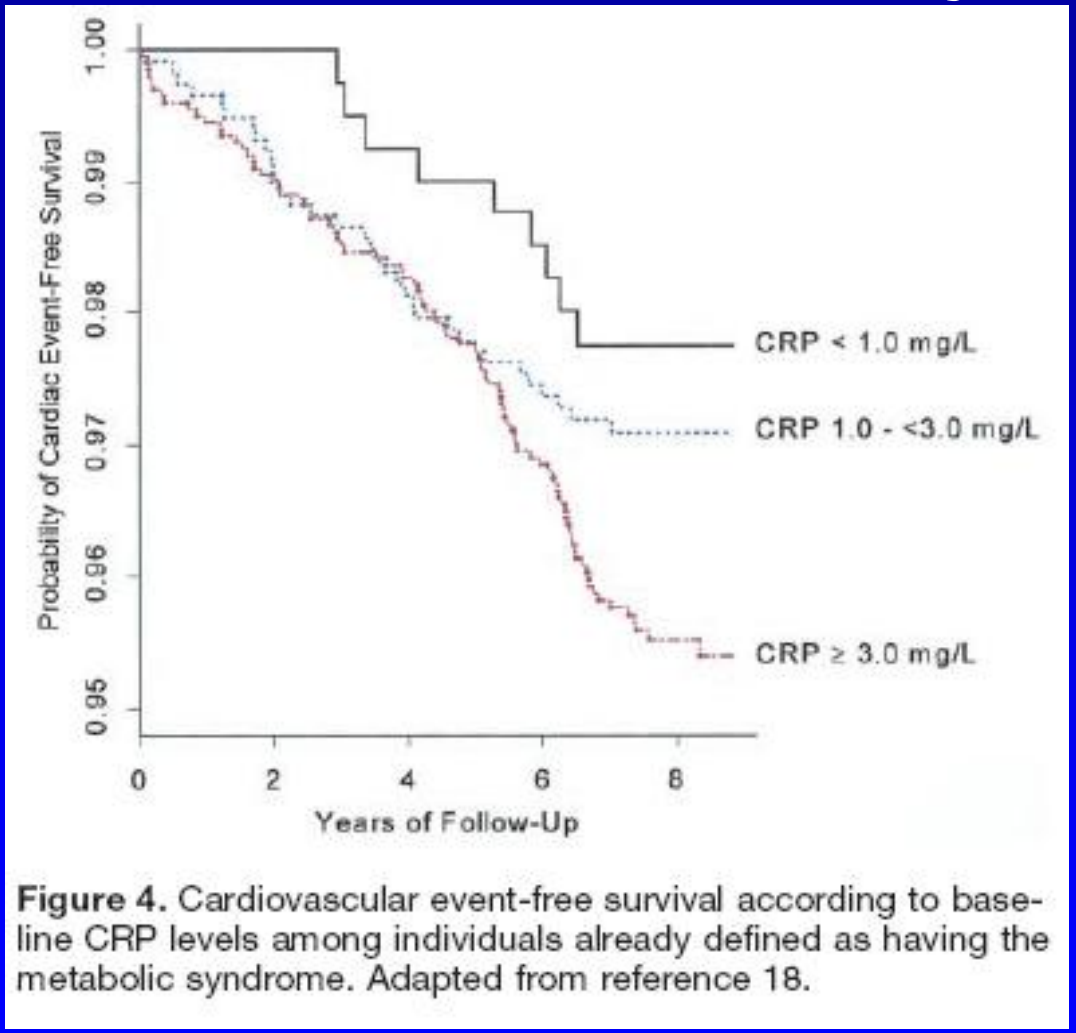


Figure 4. Cardiovascular event-free survival according to baseline CRP levels among individuals already defined as having the metabolic syndrome. Adapted from reference 18.

RIdker et al.Circulation. 2003;107:391-397

CRP and LDL-C Relationship for Risk in the Women's Health Study

Low CRP ≤1.52 mg/L

High CRP > 1.52 mg/L

Low LDL ≤124 mg/dL

High LDL >124 mg/dL

(Study Median Values)

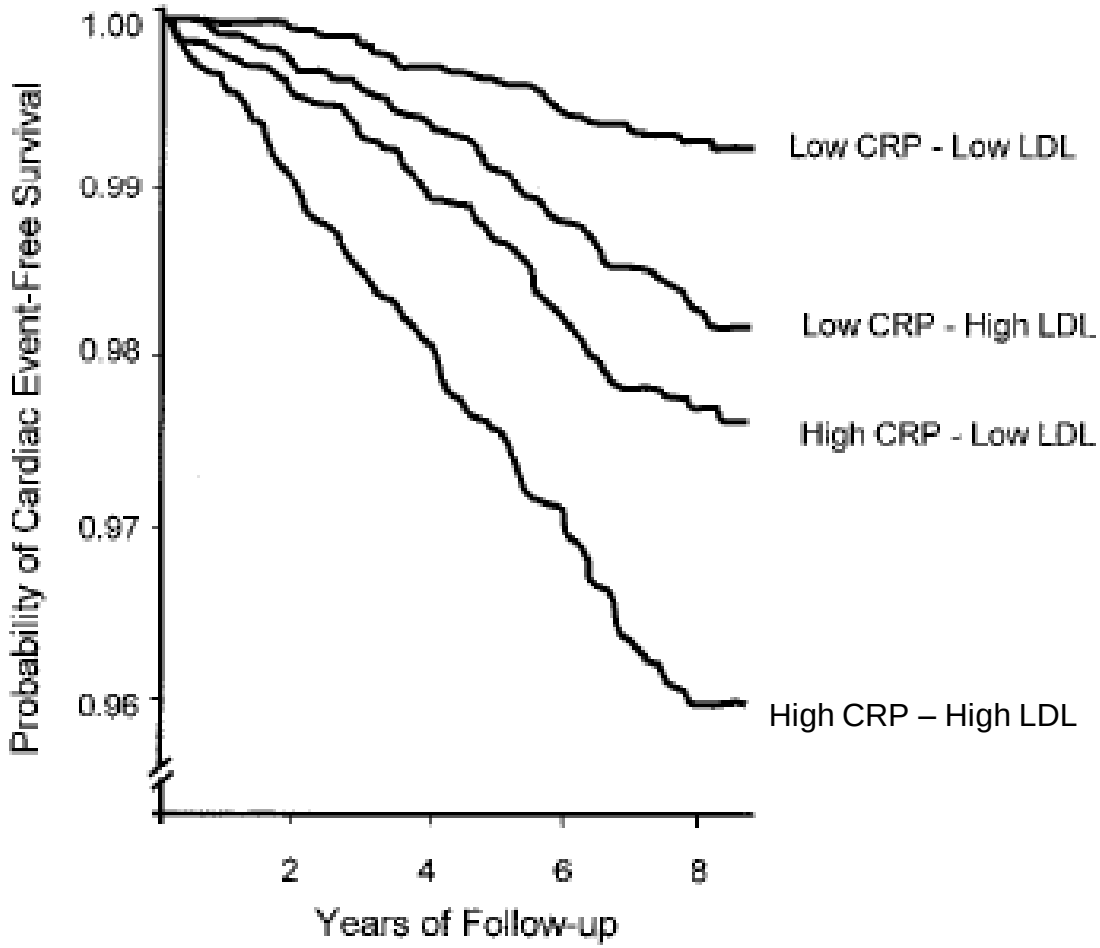


Figure 6. Cardiovascular event-free survival according to baseline levels of CRP and LDL. Adapted from reference 6.

Ridker et al. NEJM.2002;347:1557-1565

AHA/CDC Panel: Recommendations for the Use of hs-CRP in Clinical Practice

- The entire population should not be screened for hs-CRP
- hs-CRP measurement is an independent marker of CVD risk and in those at intermediate risk (10-20% CVD risk per 10 years), it may help direct evaluation and therapy in primary prevention
- Measurement of hs-CRP may be used at the discretion of the physician as part of a global risk assessment, the benefit of this approach remains uncertain
- Serial testing should not be used to monitor effects of therapy

Pearson et al.Circulation. 2004; 110:e499-511

Predictors of Future CV Events

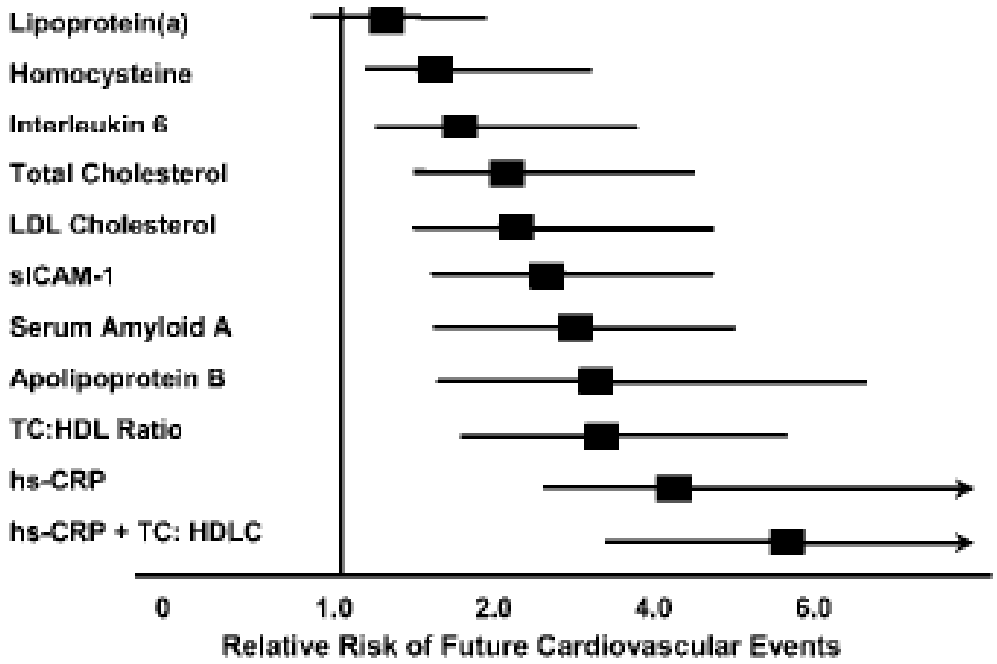


Figure 5. Direct comparison of CRP to several other lipid and non-lipid risk factors for cardiovascular disease. SICAM-1 indicates soluble intercellular adhesion molecule-1; hs-CRP, high-sensitivity CRP; HDL, high-density lipoprotein; and HDLC, high-density lipoprotein cholesterol. Adapted from reference 3.

Ridker et al.NEJM 1997. 336;973-979

The PREDICT Study: Event Rate by Coronary Artery Calcium Score in Diabetes

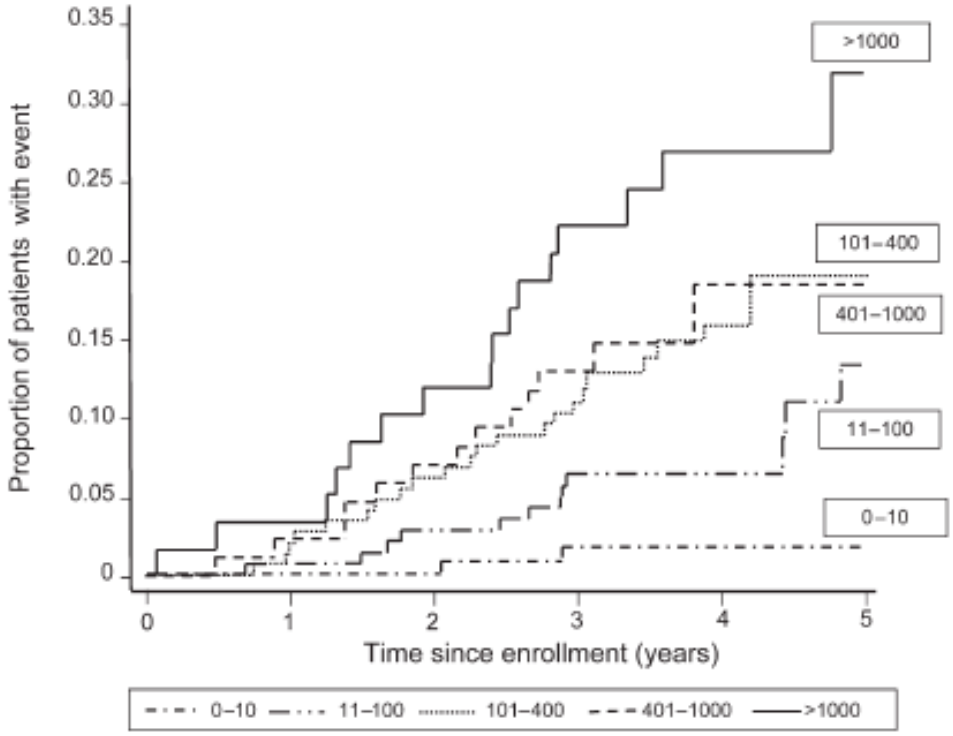
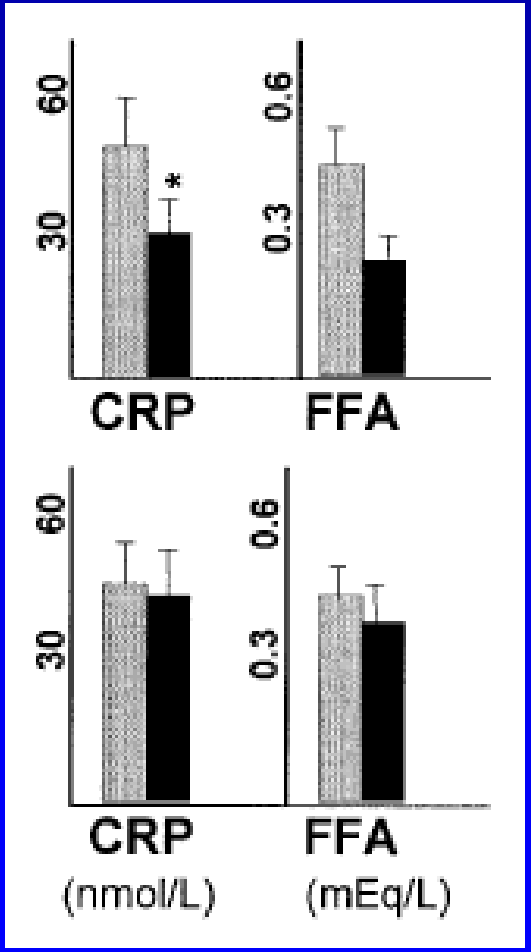


Figure 3 Proportions of patients with an event with increasing time since recruitment into the PREDICT study in successive coronary artery calcification score categories (Agatston units).

Elkeles et al. European Heart Journal (2008) 29, 2244–2251A

Use of antiinflammatory agents to reduce CRP

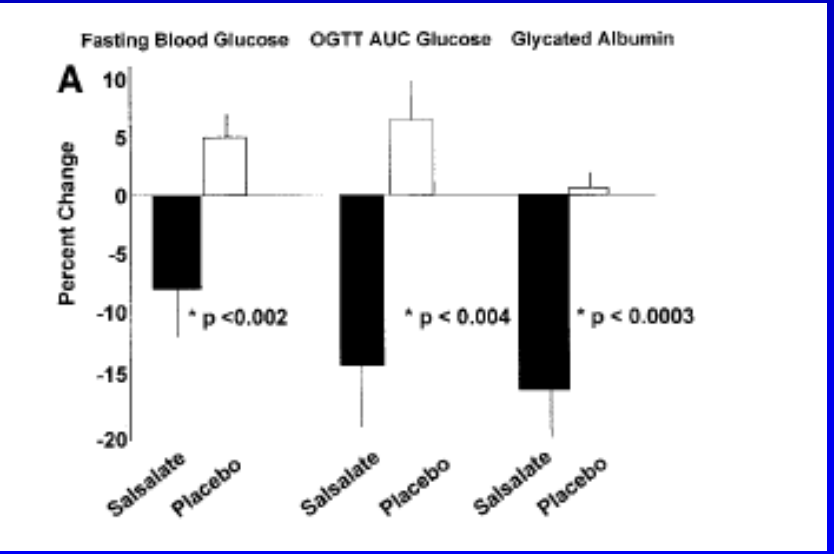
- Salsalate therapy has been shown to reduce inflammatory markers – including CRP
- Improving inflammation should improve insulin resistance
- Improving insulin resistance should have beneficial effects on glucose metabolism



Fleischman A, et.al. Diabetes Care.2008;31:289-94.

Salsalate therapy and glucose metabolism

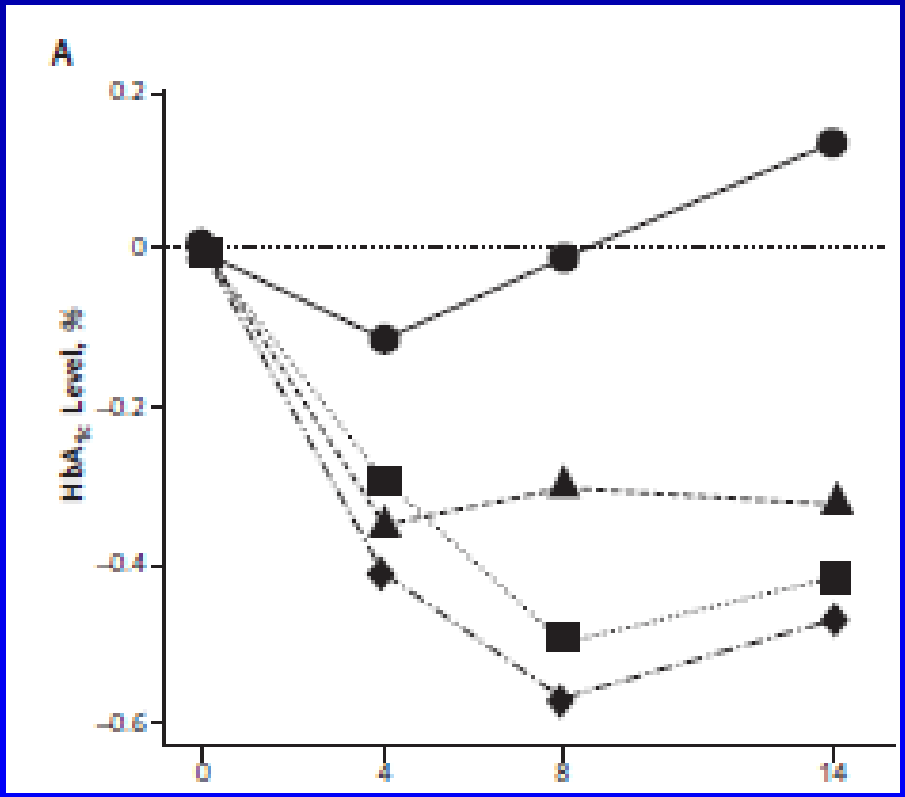
- 20 obese nondiabetic patients treated for 1 month with salsalate
- Treated patients had a decrease in glucose and Glycated albumin
- Insulin levels not increased



Fleischman A, et.al. Diabetes Care.2008;31:289-94.

Salsalate as a Possible Treatment for Diabetes

- Pts with T2 DM
- 3, 3.5 or 4gms salsalate daily
- mean A1c 7.4-7.9%
- Mean decrease in A1c = 0.5% in 4gm group



Goldfine A, et.al. *Ann Intern Med.* 2010;152:346-357.

Future Directions

- Can anti-inflammatory therapy prevent or treat the complications of the insulin resistance syndrome?
  - DM
  - CAD