



Up-date on new biomarkers in ACS: C-REACTIVE PROTEIN

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AHA/CDC Scientific Statement

Markers of Inflammation and Cardiovascular Disease

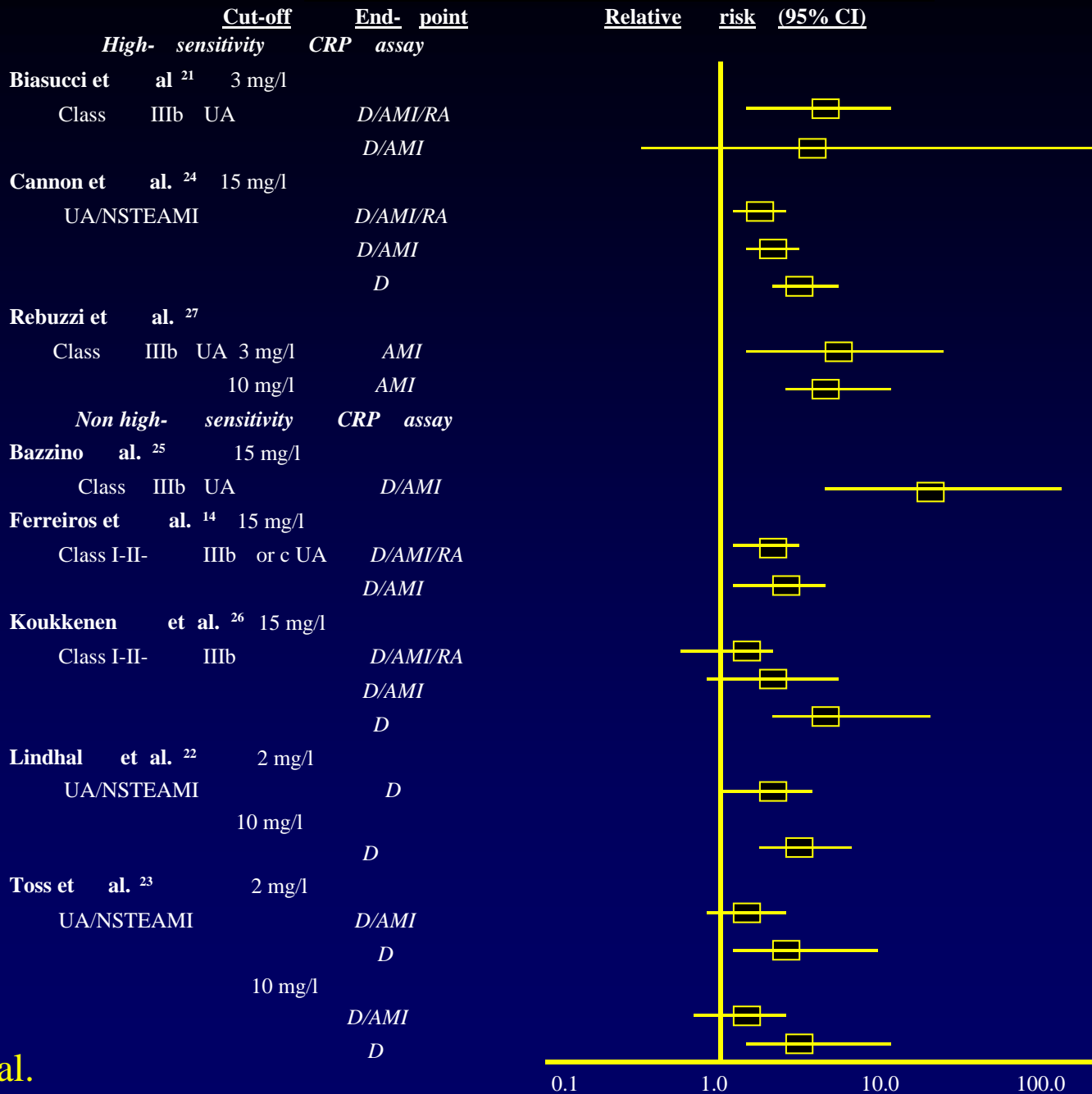
Application to Clinical and Public Health Practice

A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association

Thomas A. Pearson, MD, PhD (Co-Chair); George A. Mensah, MD (Co-Chair);
R. Wayne Alexander, MD, PhD; Jeffrey L. Anderson, MD; Richard O. Cannon III, MD;
Michael Criqui, MD; Yazid Y. Fadi, MD; Stephen P. Fortmann, MD; Yuling Hong, MD, PhD;
Gary L. Myers, PhD; Nader Rifai, PhD; Sidney C. Smith, Jr, MD; Kathryn Taubert, PhD;
Russell P. Tracy, PhD; Frank Vinicor, MD

UA/NSTEAMI:

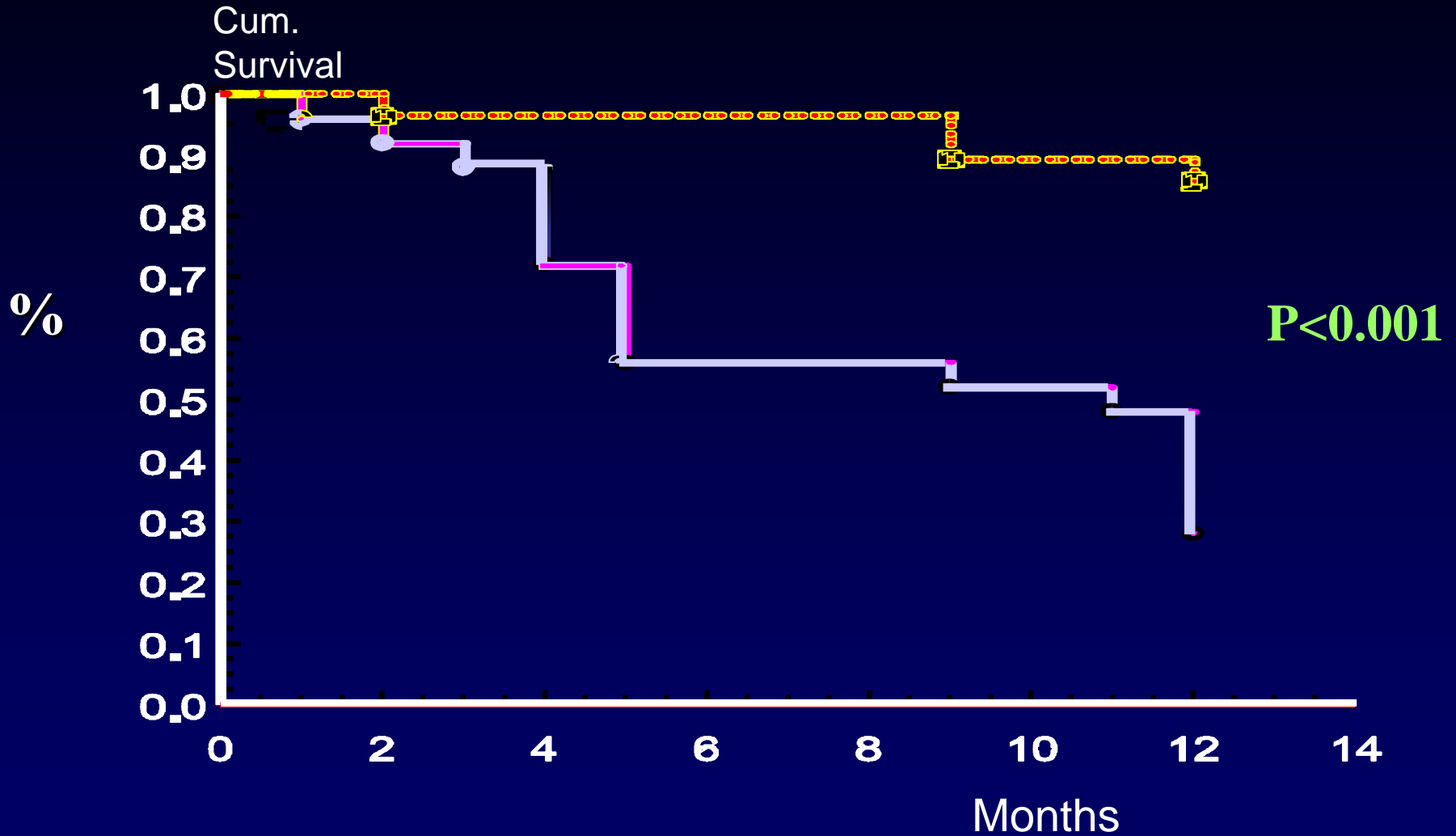
INTERMEDIATE- TO LONG-TERM FOLLOW-UP



Biasucci et al.

WU, Acute Coronary syndromes, 2003

EVENT FREE SURVIVAL ACCORDING TO CRP LEVELS AT DISCHARGE IN UA

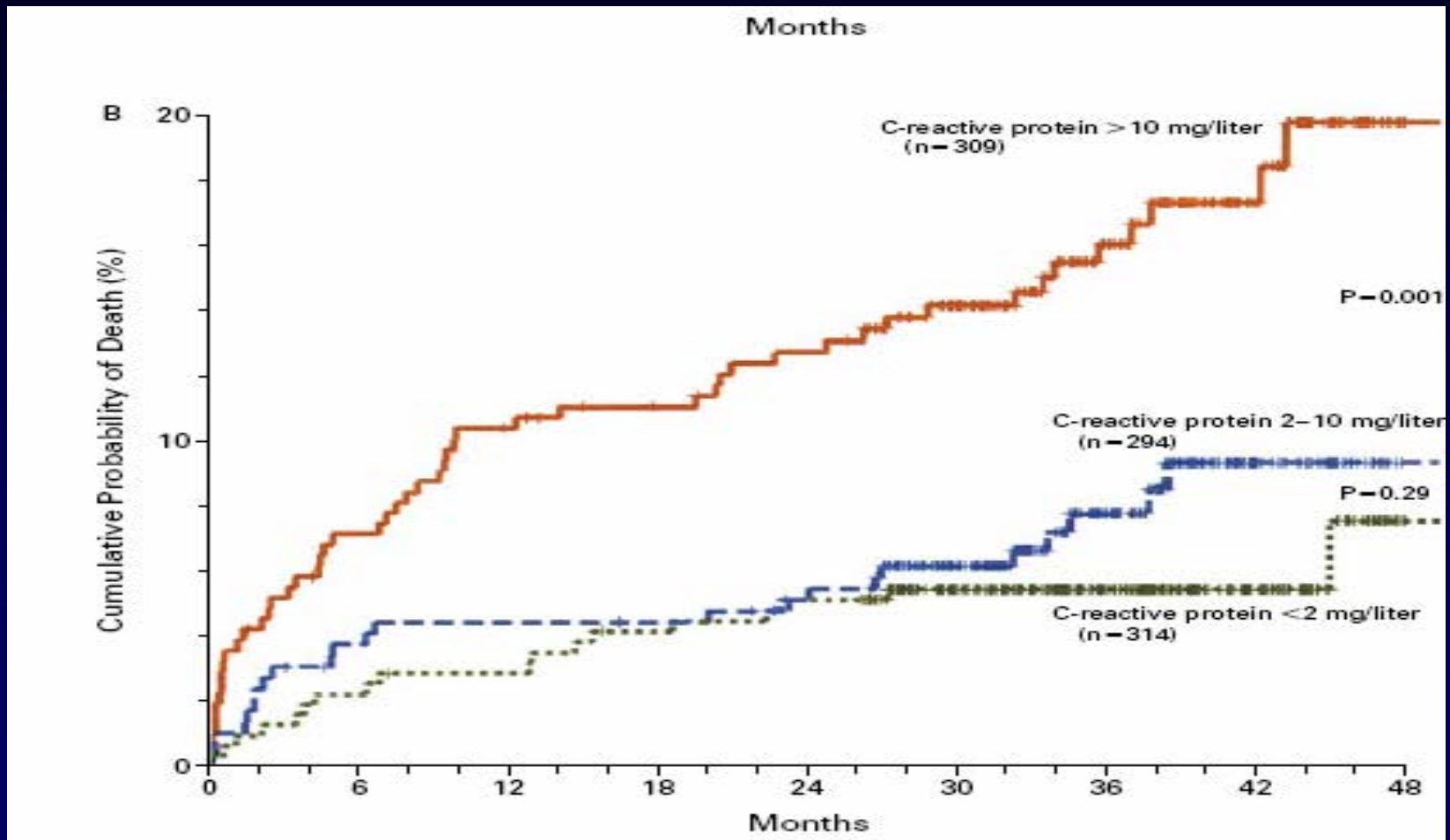


Biasucci Circulation 99,855; 1999



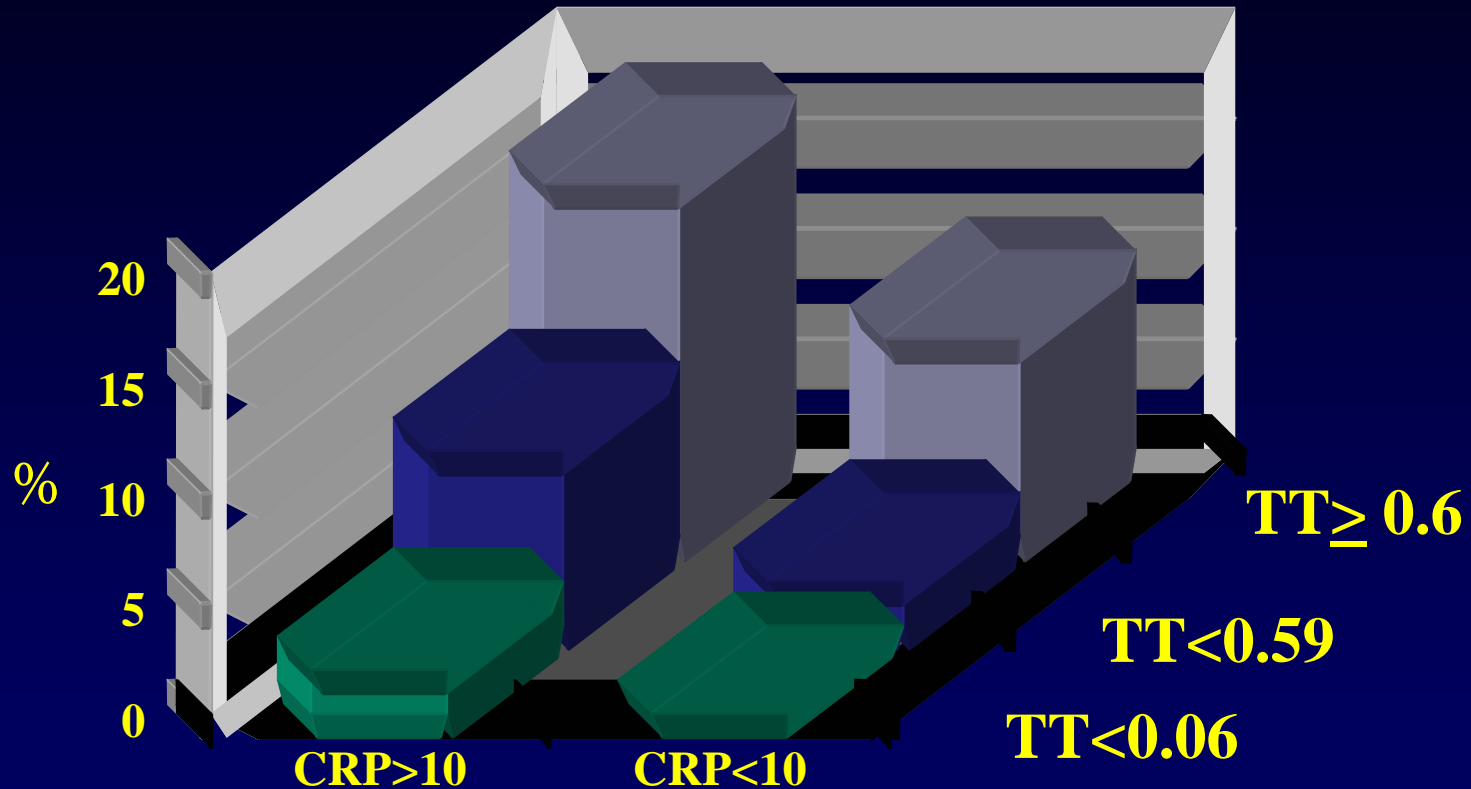
CRP < 3 mg/L
CRP > 3 mg/L

CRP AND 48 MONTHS MORTALITY IN ACUTE CORONARY SYNDROMES



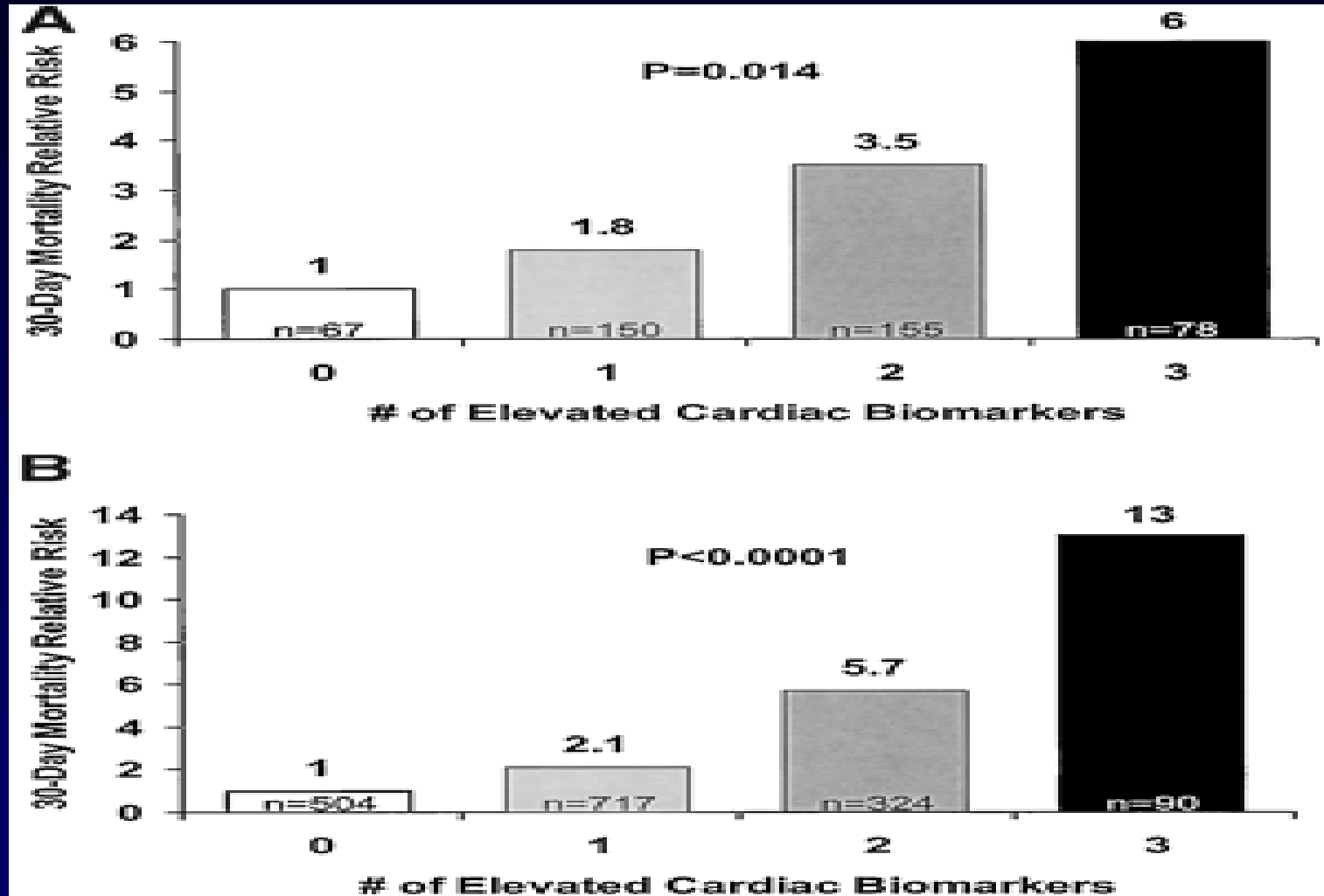
Lindahl NEJM, 2000

INCIDENCE OF CARDIAC DEATH AT TWO YEARS ACCORDING TO CRP AND TT



Lindahl, NEJM 343,16,2000

Multimarker approach to risk stratification in ACS in OPUS-16 (A) and TACTICS-TIMI 18 (B)



(Sabatine et al, Circulation 2002)

TABLE 4. Recommendations for Clinical and Public Health Practice

| Procedure Should Be Performed (Class I) | Conflicting Evidence/Opinion: Weight in Favor of Usefulness/Efficacy (Class IIa) | Conflicting Evidence/Opinion: Usefulness/Efficacy Less Well Established (Class IIb) | Procedure Should Not Be Performed (Class III) |
|---|---|---|--|
| Population Science | | | 1. The entire adult population should not be screened for hs-CRP for purposes of cardiovascular risk assessment. (Class III, Level of Evidence C) |
| Clinical Practice | 1. Measurement of hs-CRP is an independent marker of risk and, in those judged at intermediate risk by global risk assessment (10 to 20% risk of CHD per 10 years), at the discretion of the physician, may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence B) | 2. Measurement of hs-CRP is an independent marker of risk and may be used at the discretion of the physician as part of a global coronary risk assessment in adults without known CVD. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence C) 3. hs-CRP levels may be useful in motivating patients to improve their behaviors. The benefits of this strategy remain uncertain. (Class IIb, Level of Evidence C) | 5. Other inflammatory markers (cytokines, other acute-phase reactants) should not be measured for the determination of coronary risk in addition to hs-CRP. (Class III, Level of Evidence C) |
| | 6. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker of prognosis for recurrent events, including death, MI, and restenosis after PCI. The benefits of therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence B) | | |

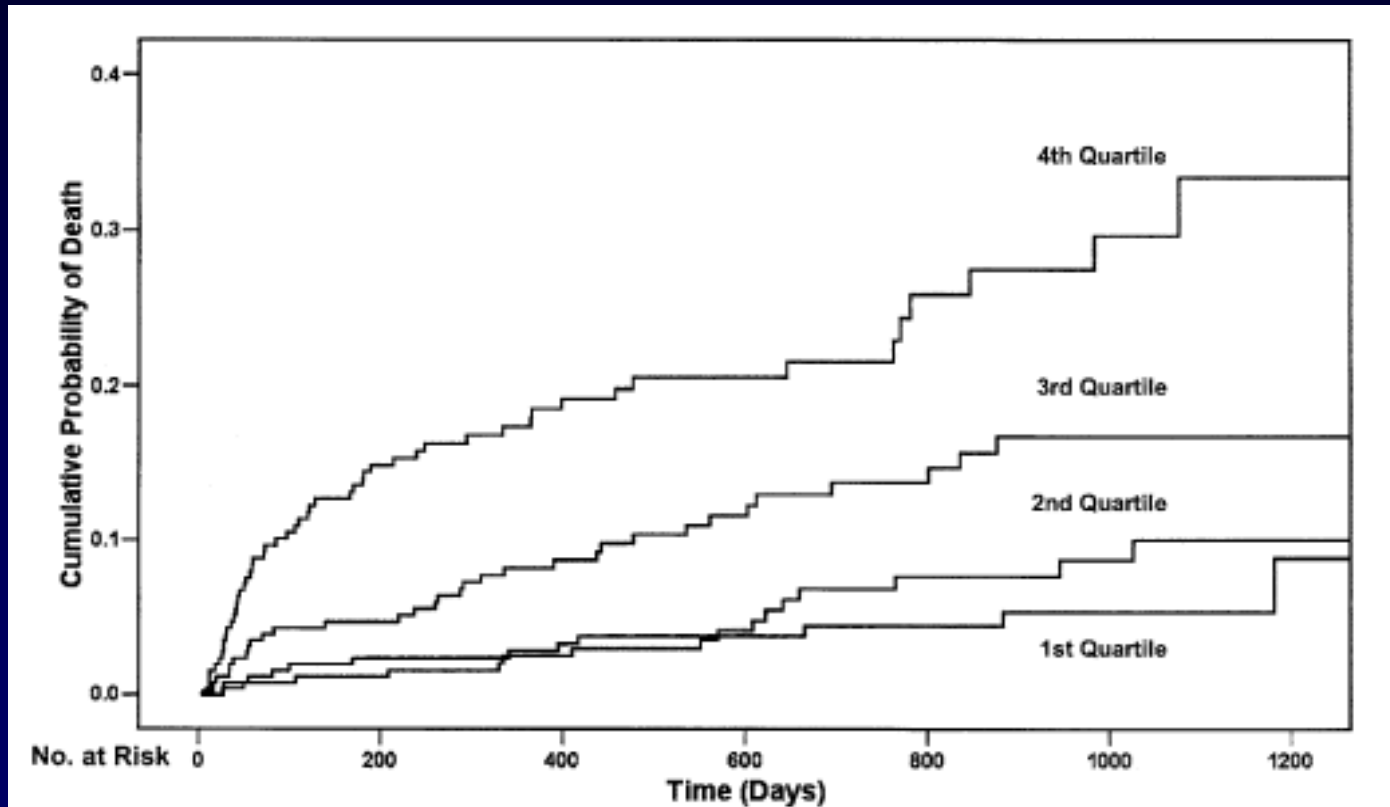
What's new about CRP and ACS?

- Clinical data on short and long term risk prediction and role as a guide for therapy
- CRP and new markers
- Pathophysiological data on role of CRP and inflammation

What's new about CRP and ACS?

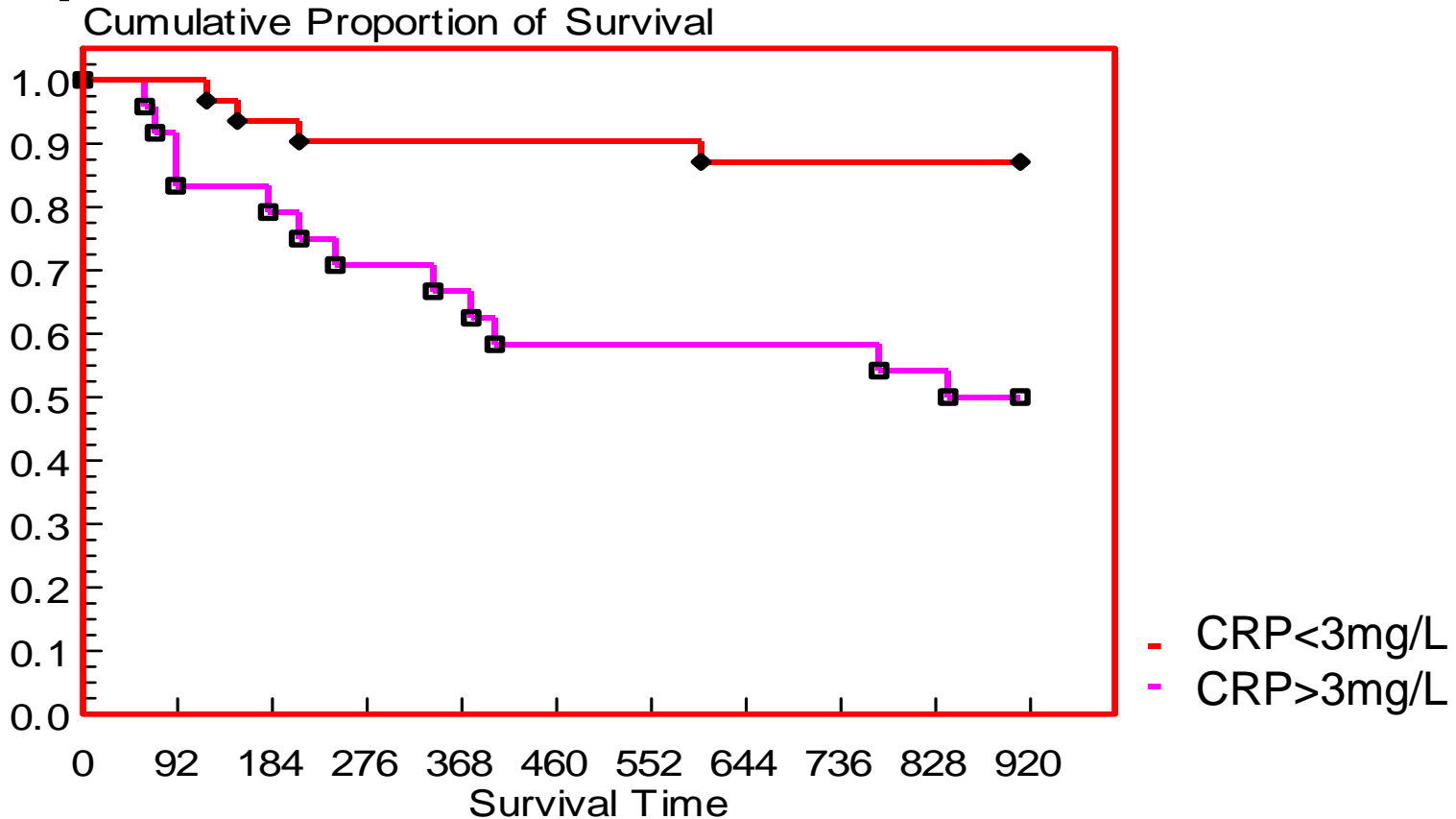
- **Clinical data on short and long term risk prediction and role as a guide for therapy**
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CRP and risk of HF and Death after ACS

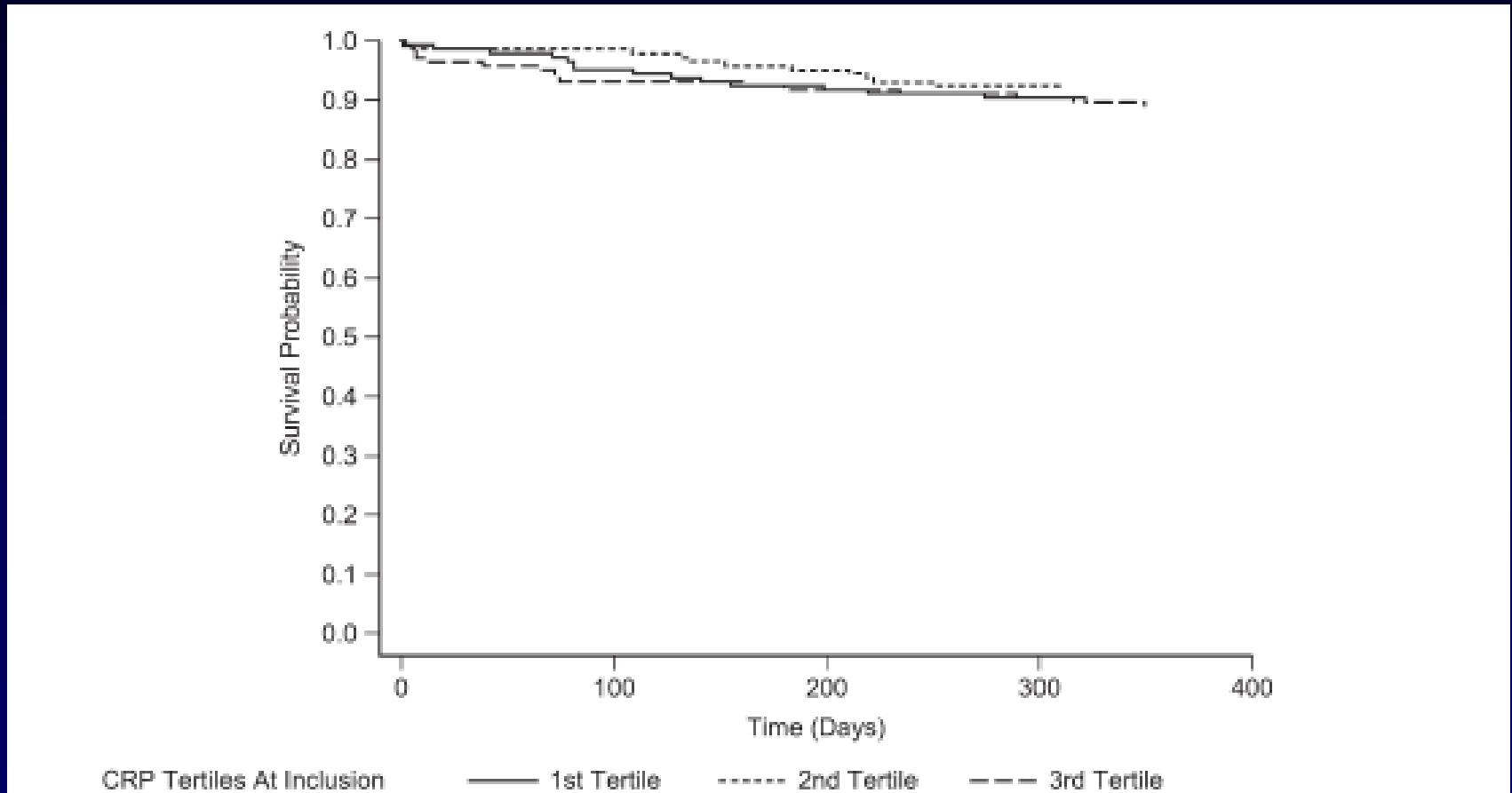


OCCURRENCE OF VT/VF ACCORDING TO CRP LEVELS

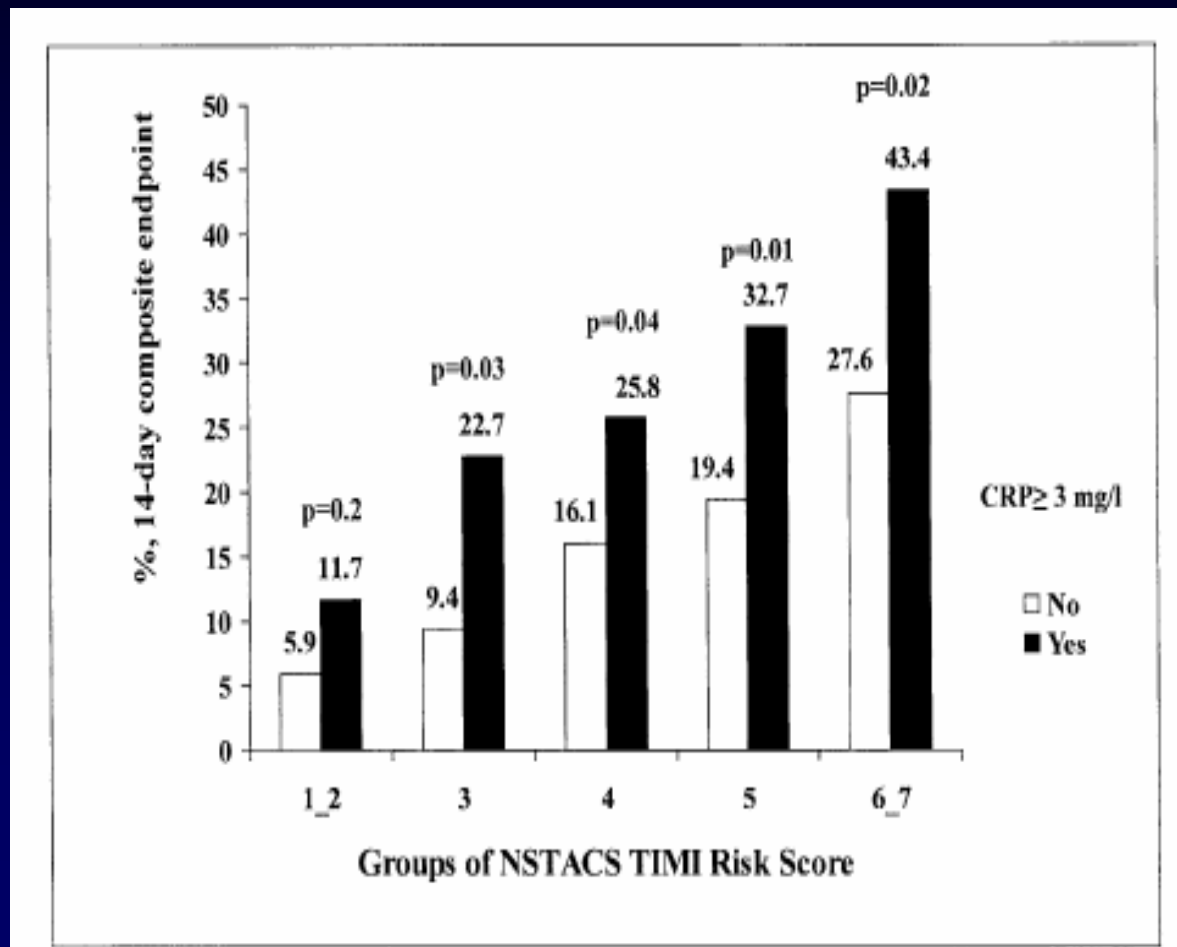
Kaplan-Meier Cumulative Survival Plot



CRP at discharge after ACS and outcome at 1 year



CRP adds prognostic information to TIMI risk score



What's new about CRP and ACS?

- **Role as a guide for therapy**
- CRP and new markers
- Pathophysiological data on role of CRP and inflammation

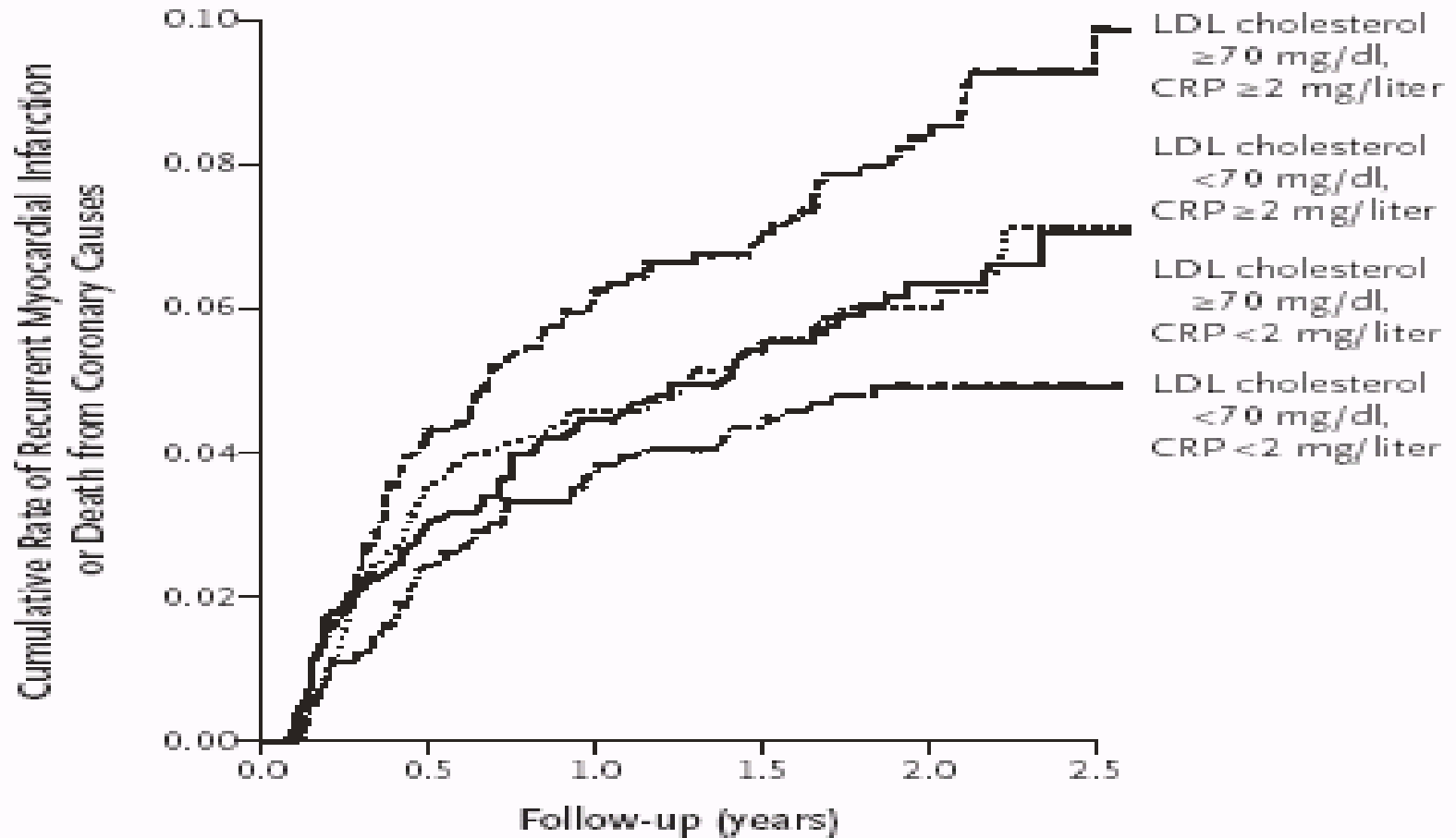
ESC and AHA/ACC ACS Guidelines

on

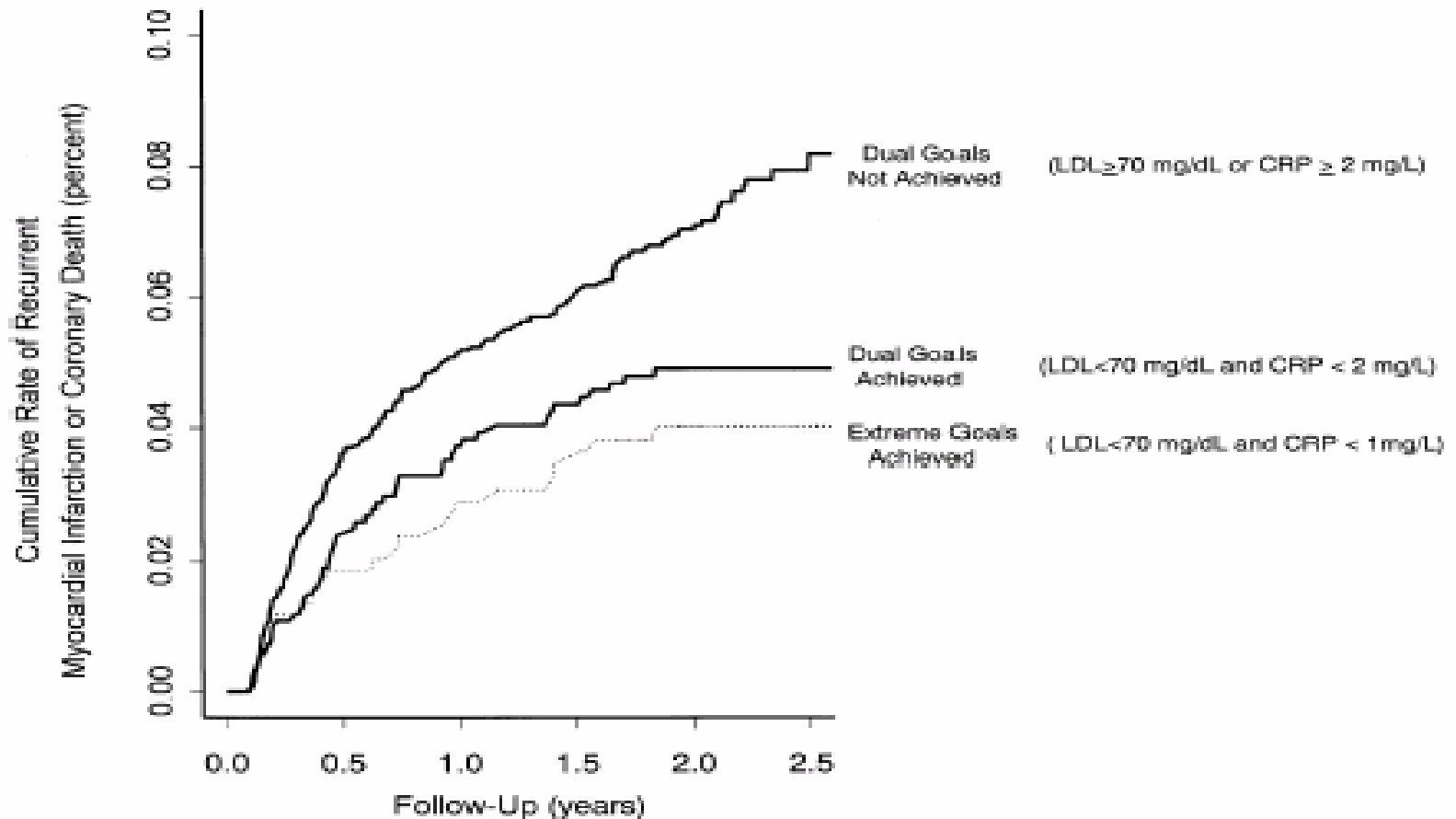
Long term management

- Aggressive and intensive risk factors modification
- Asa(75-100 mg for life) clopidogrel (9-12 months)
- Betablockers
- Lipid lowering drugs; HMG-CoA reductase inhibitors
- ACE inhibitors/AgII inhibitors

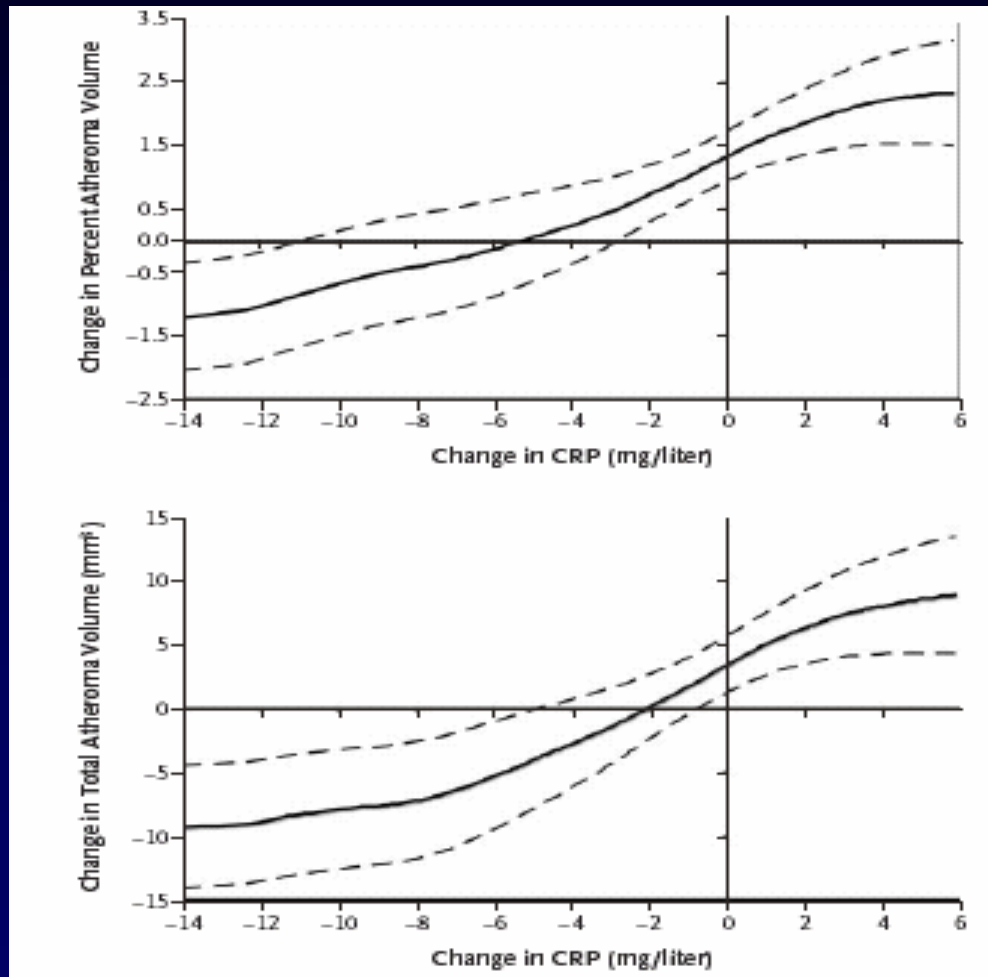
Cumulative rate of D/MI in Prove-it/TIMI 22



LDL cholesterol, hs-CRP and mortality



REVERSAL: changes in CRP and atheroma

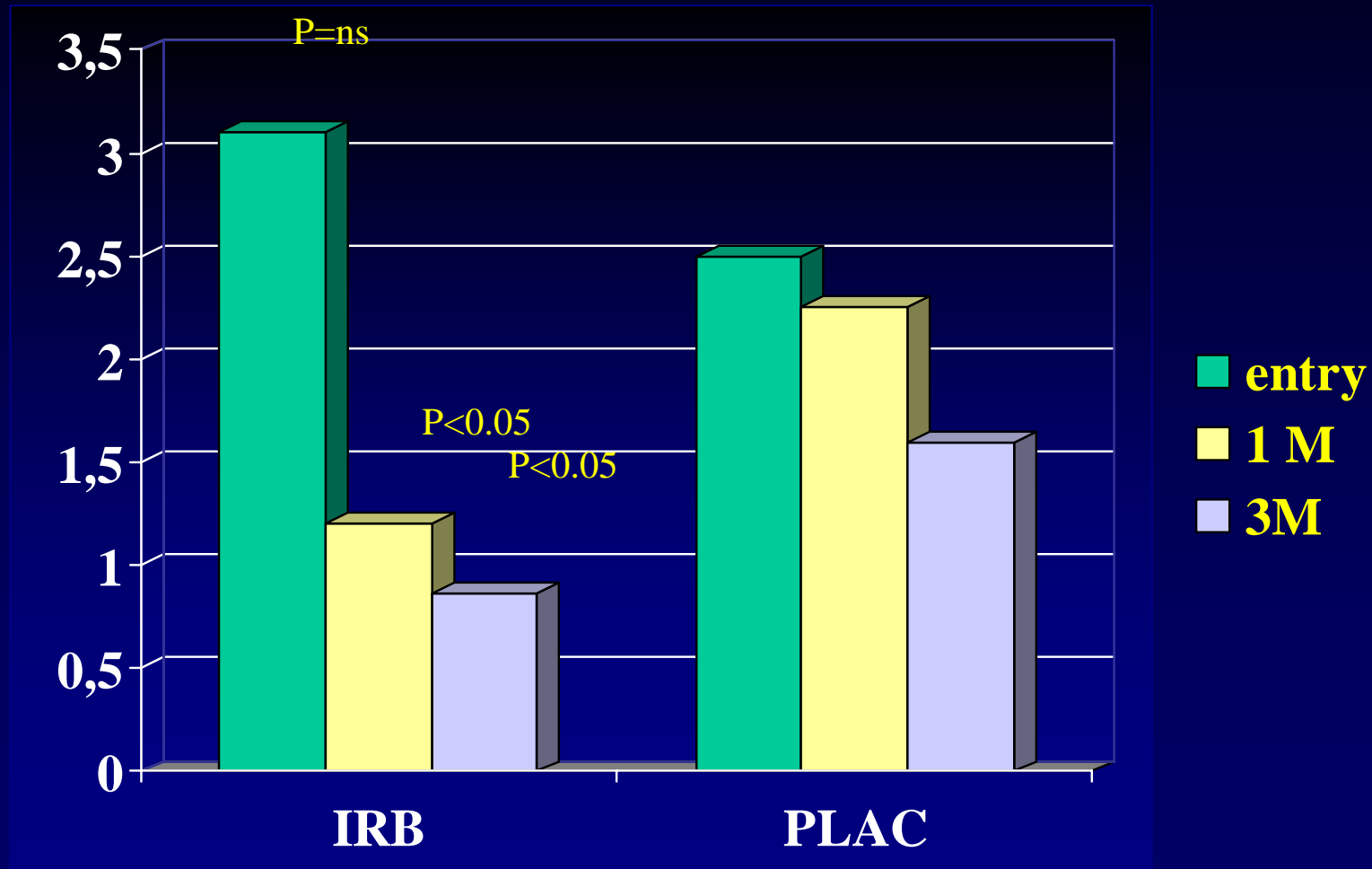


CRP and atheroma reduction after statins in Reversal

| 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 |

Nissen NEJM 2005

Irbesartan significantly reduces CRP levels in ACS



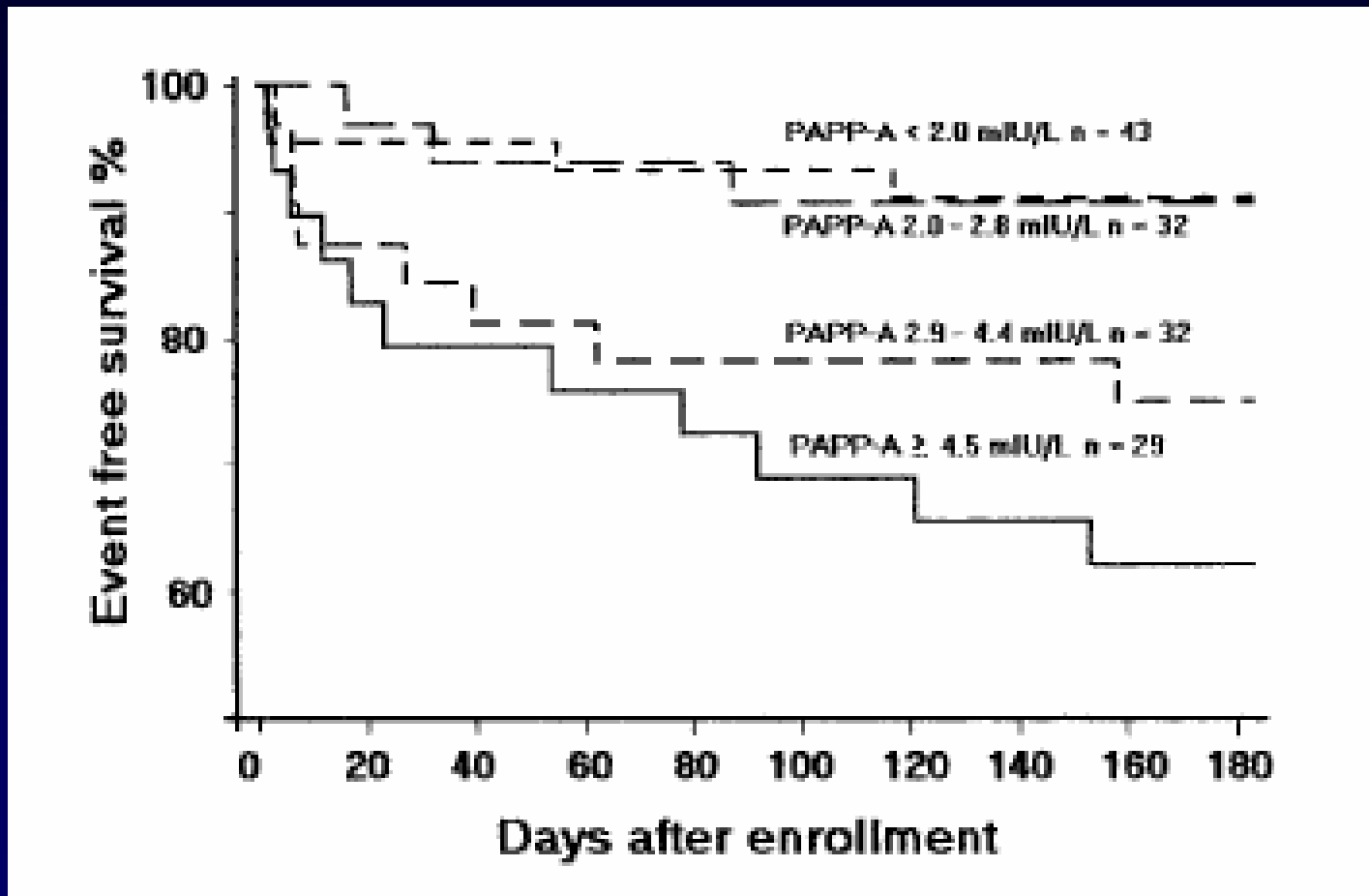
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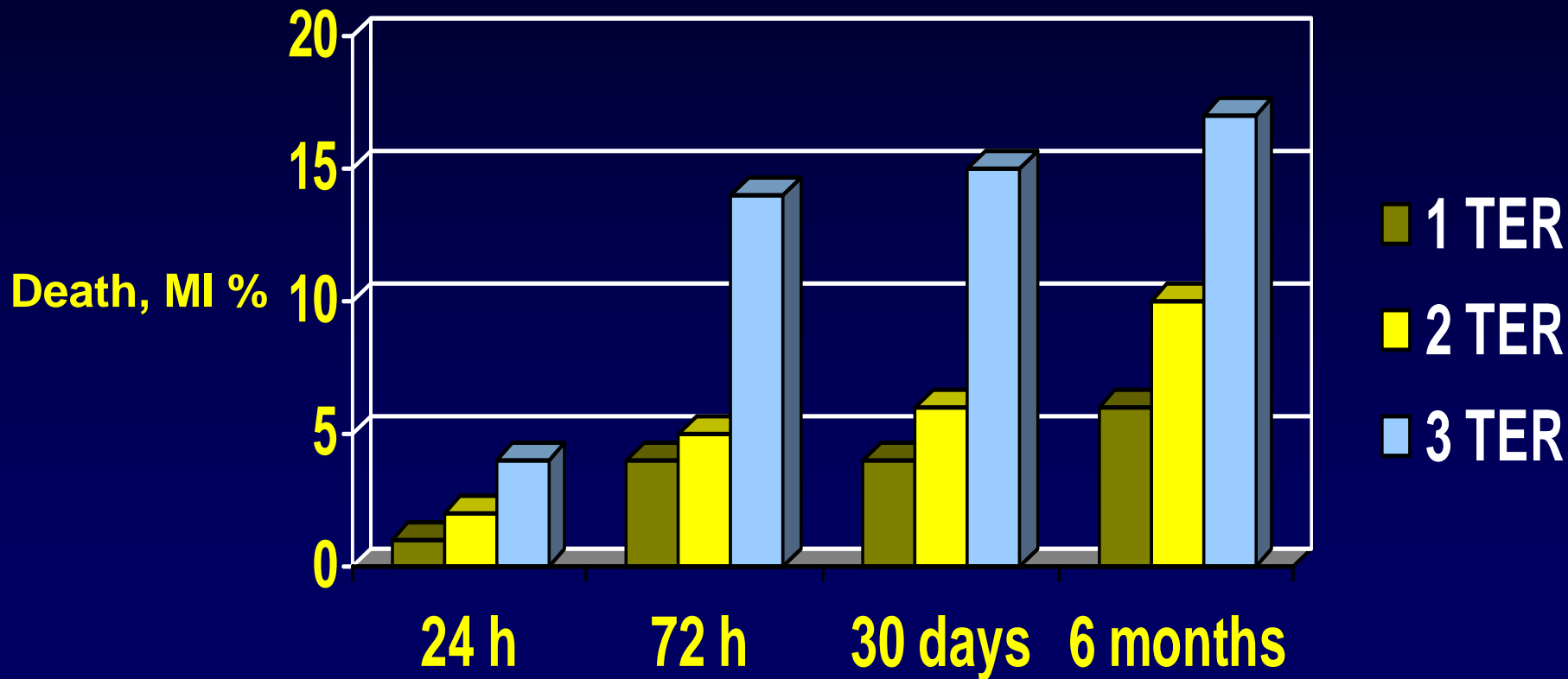
New markers of risk in ACS

- MPO
- PAPP-A
- CD40-L
- IL-18
- IL-6
- Cystatin-C
-

PAPP-A and outcome in cTN- ACS



MIELOPEROXIDASE SERUM LEVELS PREDICT RISK IN ACUTE CORONARY SYNDROMES

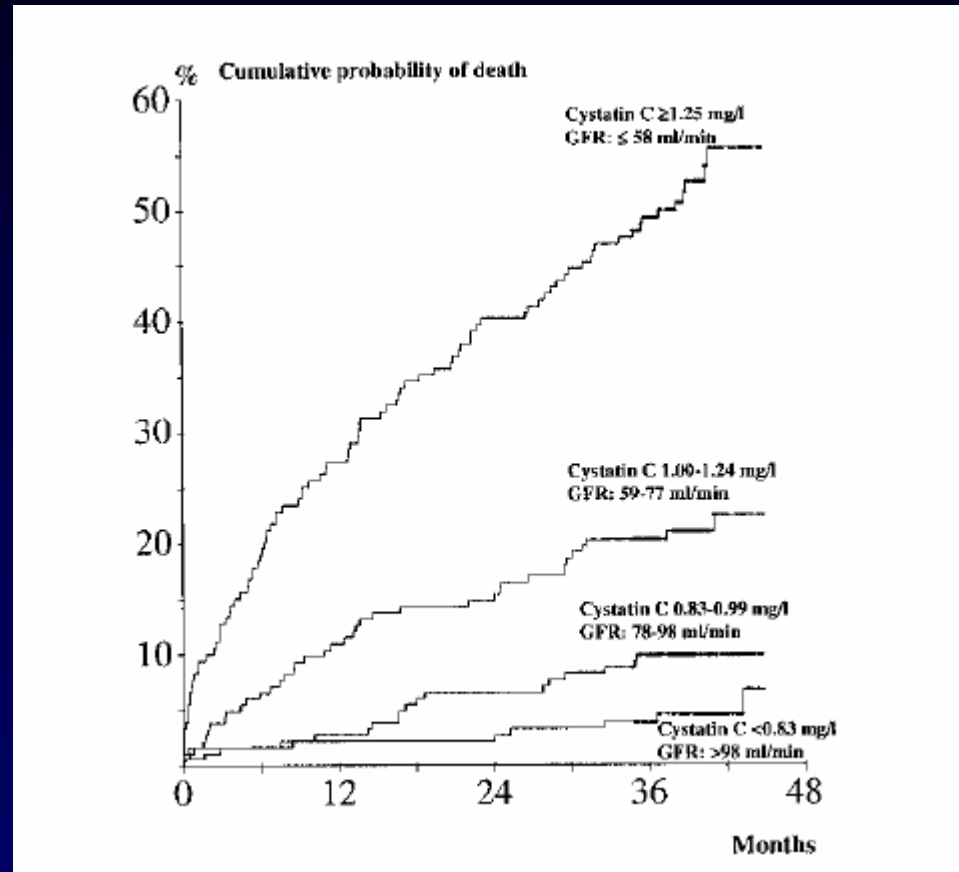


BALDUS , CIRCULATION 2003

ASSESSMENT OF RISK: CHARACTERISTICS OF A NEW TEST

- Simple, noninvasive, commercially available, cost effective
- Reproducible and standardized internationally
- Ability to predict risk in prospective studies
- Population normals as reference and in various populations.
- Add to predictive value of established tests
- Useful in refining the risk of medium-low risk groups

Cystatin-C and outcome in NSTEMI-ACS

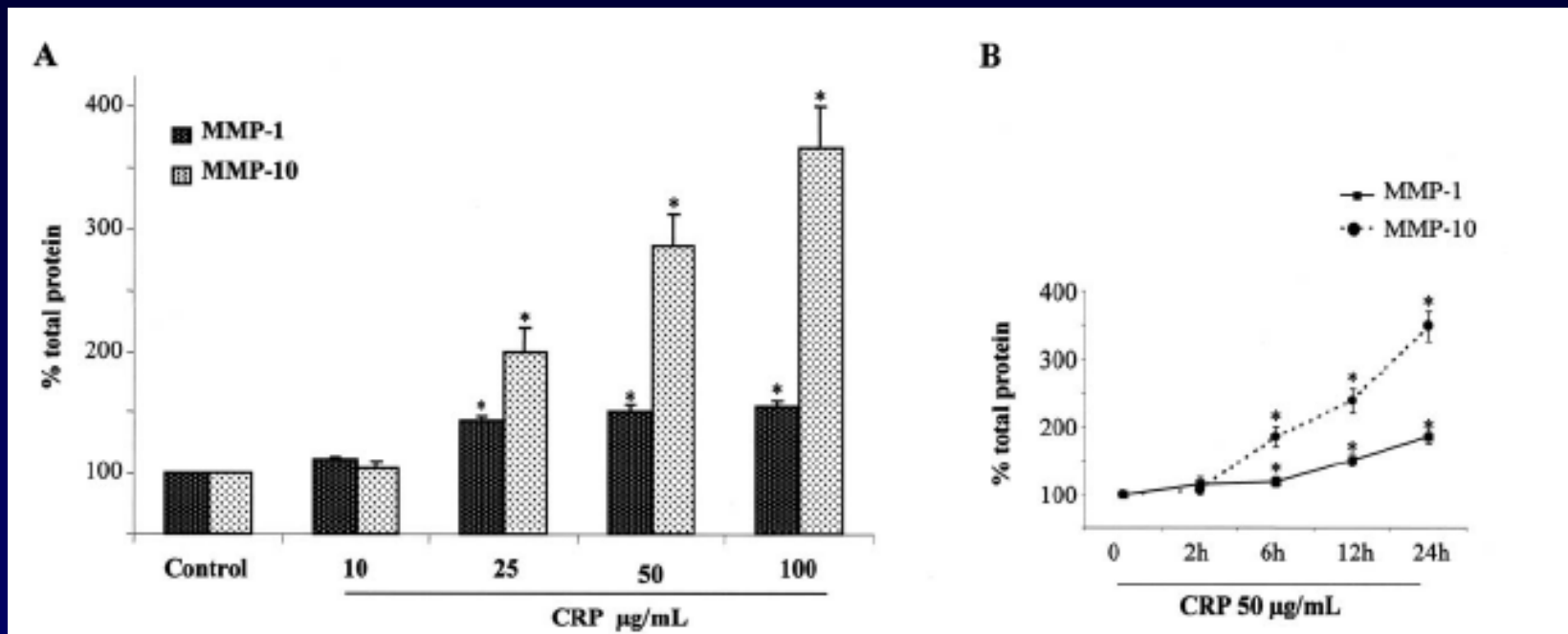


Jernberg, Circulation 2004

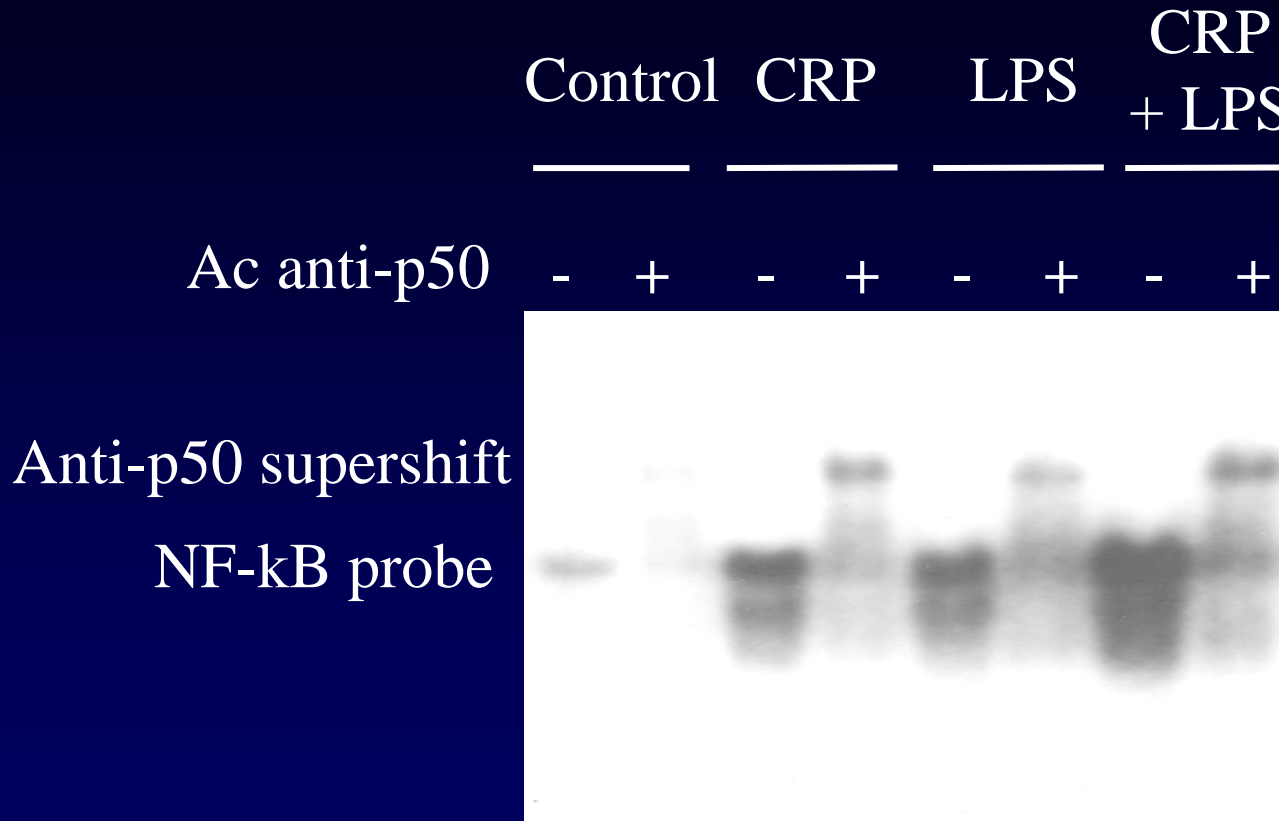
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CRP induces MMP-1 and MMP-10 in a dose and time dependent manner

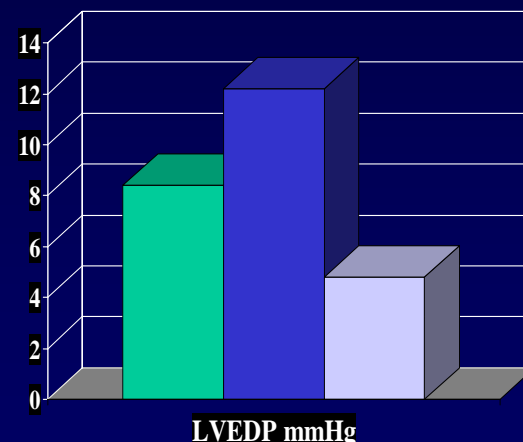
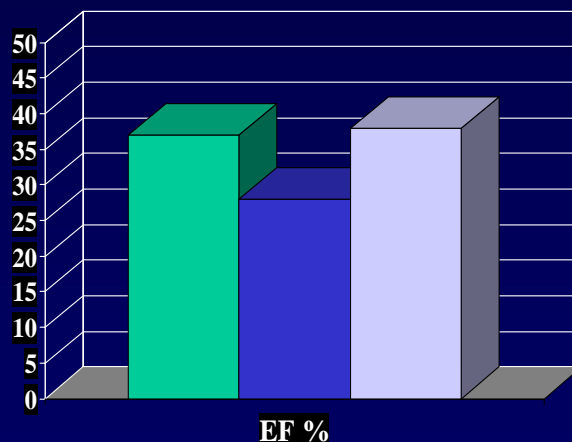
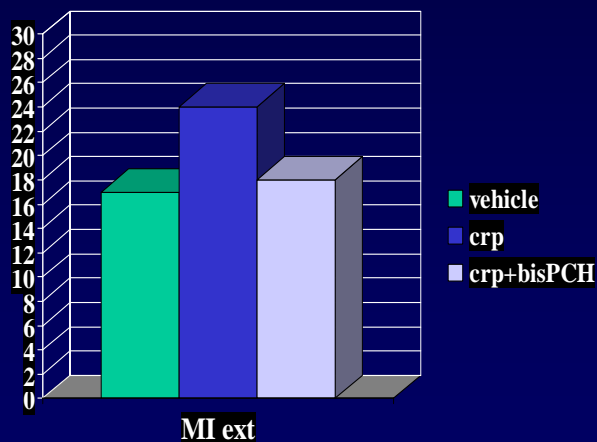


Direct activation of the transcription factor NF- κ B by CRP in human PBMC



Targeting C-reactive protein for the treatment of cardiovascular disease

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CRP or not CRP? That Is the Question

Mark B. Pepys

ATVB2005

- **CRP remains a significant predictor of future events after ACS**
- **CRP adds important information on the top of other biochemical and clinical markers of risk**
- **CRP remains the less expensive, more avoidable and extensively studied marker of inflammation**
- **CRP may represent a useful tool to monitor treatment efficacy**
- **The exact role played by CRP in ACS needs more studies to be elucidated.**

CRP or not CRP? That Is the Question

Mark B. Pepys

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A PROPOSAL

- Measure CRP on admission
- **If CRP > 10 mg/L:**
- initiate an aggressive lipid lowering treatment independently from LDL cholesterol levels
- Initiate ACE-I or Ag-II inh. Independently of the presence of other risk factors
- **If CRP > 3 mg/L at 6 month/1y:**
- continue on full therapy (including clopidogrel?) or increase doses until
- CRP < 3 (1?) mg/L

Association of genotype distribution and MI

TABLE 1. Genotype distribution and allele frequency for +1059G/C CRP SNP in 106 young male patients (< 46 years) and 120 age-related male controls from Sicily

| | GG | GC | CC | +1059G | +1059C |
|----------|-------------|----------|----------|--------------|-------------|
| Patients | 84 (79.3%) | 18 (17%) | 4 (3.7%) | 186 (87.70%) | 26 (12.30%) |
| Controls | 112 (93.3%) | 7 (5.8%) | 1 (0.9%) | 231 (96.25%) | 9 (3.75%) |

The distribution of genotypes was in HWE. Genotype and allele frequencies were significantly different between the two groups ($P = 0.007$ by χ^2 test, 3×2 tables, and, respectively, $P = 0.001$ by χ^2 test with Yate's correction). OR 3.59 (1.64–7.85 95% CI; $P = 0.0007$).

TABLE 2. CRP (γ /mL) serum values in 70 healthy Sicilians analyzed according to CRP genotype

| Genotype | Median (25th–75th percentiles) |
|----------|--------------------------------|
| C+ | 4.5 (1.75–5.01) |
| C– | 0.8 (0.62–2.10) |

CRP serum levels were significantly higher in 6 C+ healthy subjects (CC plus CG) than in 64 C– healthy subjects (GG) ($P = 0.0075$ by Wilcoxon test).