2008년 순환기관련학회
춘계통합학술대회

Interpretation of Cardiac Biomarkers

전남의대

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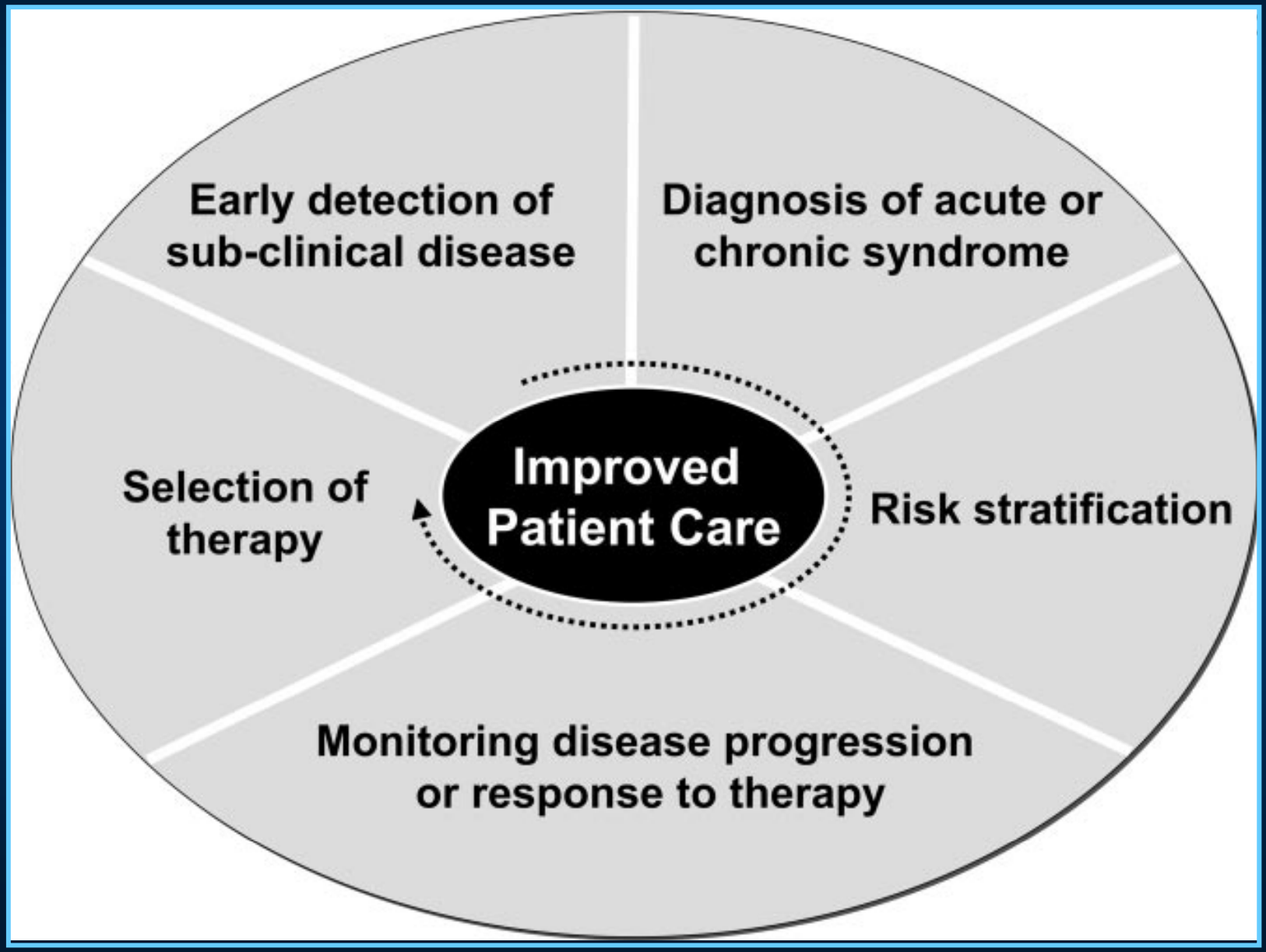
CARDIAC BIOMARKERS

WHAT ARE CARDIAC BIOMARKERS?

- **Located in the myocardium**
- **Released in cardiac injury**
  - **Myocardial infarction**
  - **Unstable angina pectoris**
  - **Other conditions affecting cardiac muscle (trauma, cardiac surgery, myocarditis etc.)**
- **Can be measured in blood samples**

Clinical applications of cardiac biomarkers

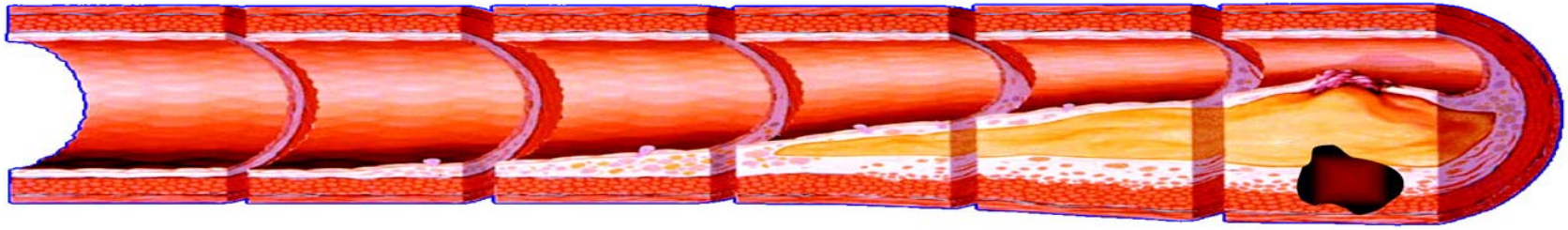


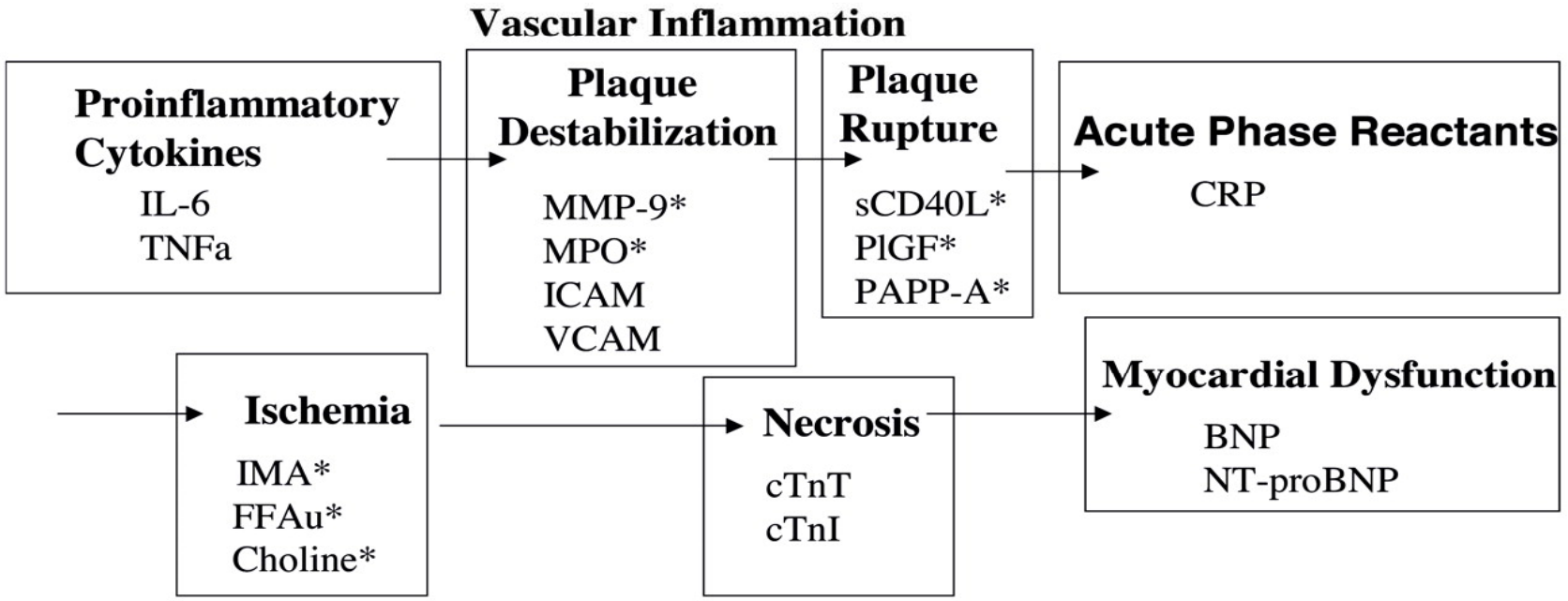
The usefulness of inflammatory biomarkers in diagnosis and risk stratification in ACS

	Biomarker						
	CK-MB	**cTnI/T**	**hsCRP**	**BNP/ NT-proBNP**	**IMA**	**MPO**	**CD40L**
Diagnosis	Yes	Yes	No	No	Yes	Result unclear	No
Outcomes	Death	Death/ MI/RI	Death/MI/ RI	Death/CHF	No	Death/MI	Death/MI
Short term	Yes	Yes	Yes	Yes	—	Yes	Yes
Long term	Yes	Yes	Yes	Yes	—	Yes	Yes
Independent	Yes	Yes	Yes	Yes	—	Yes	Yes
FDA approval	Yes	Yes	Yes	Yes[a]	Yes	No	No
Guidelines	Class I	Class I	Class IIa	Yes	No	No	No

Nature Clinical Practice Cardiovascular Medicine 2006;3:24–34

Biochemical profile in ACS patients: vascular inflammation to plaque rupture to ischemia to cell death to myocardial dysfunction





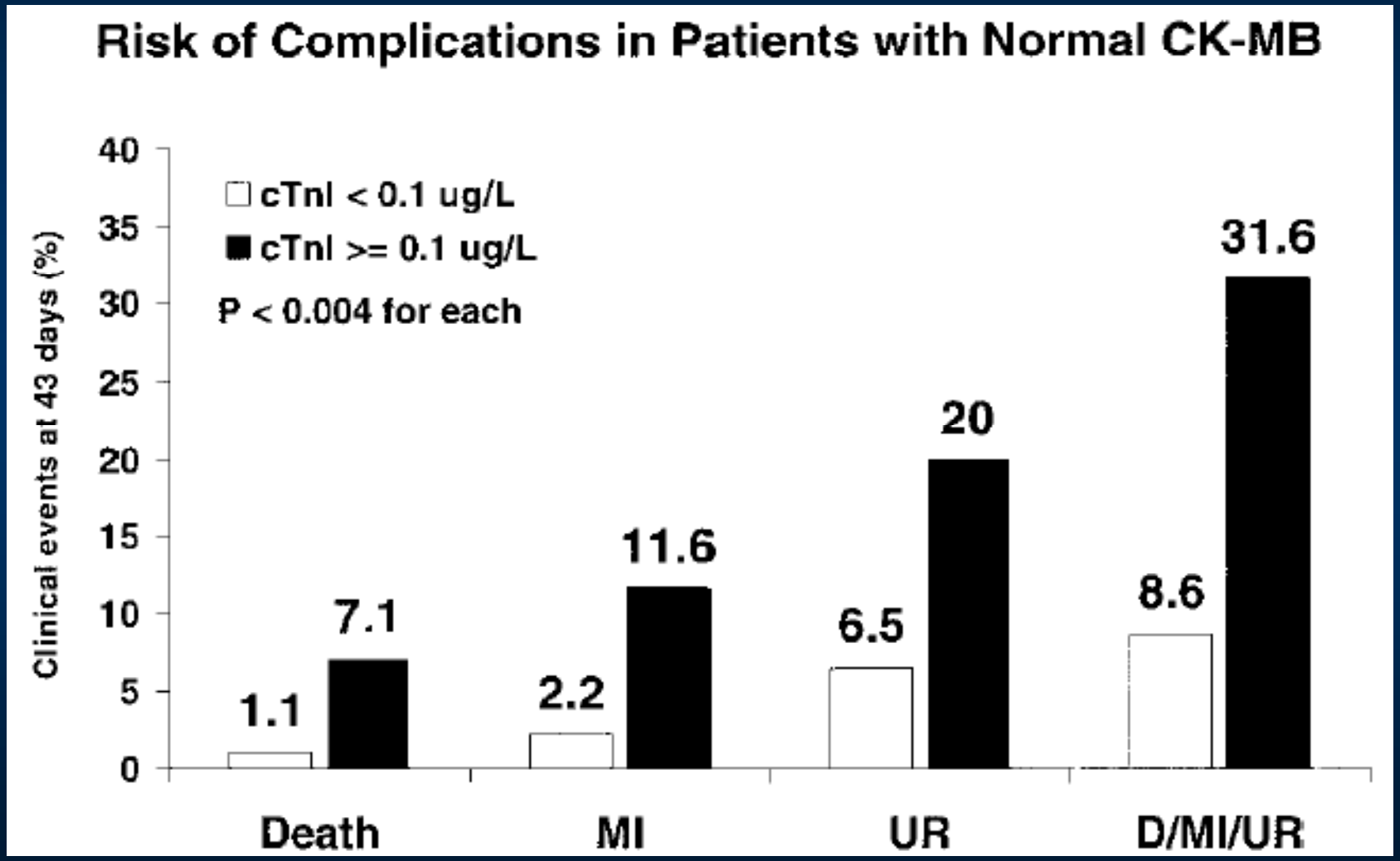
A. BIOCHEMICAL MARKERS OF MYOCARDIAL NECROSIS

I. Cardiac Troponins

II. Creatine Kinase-MB

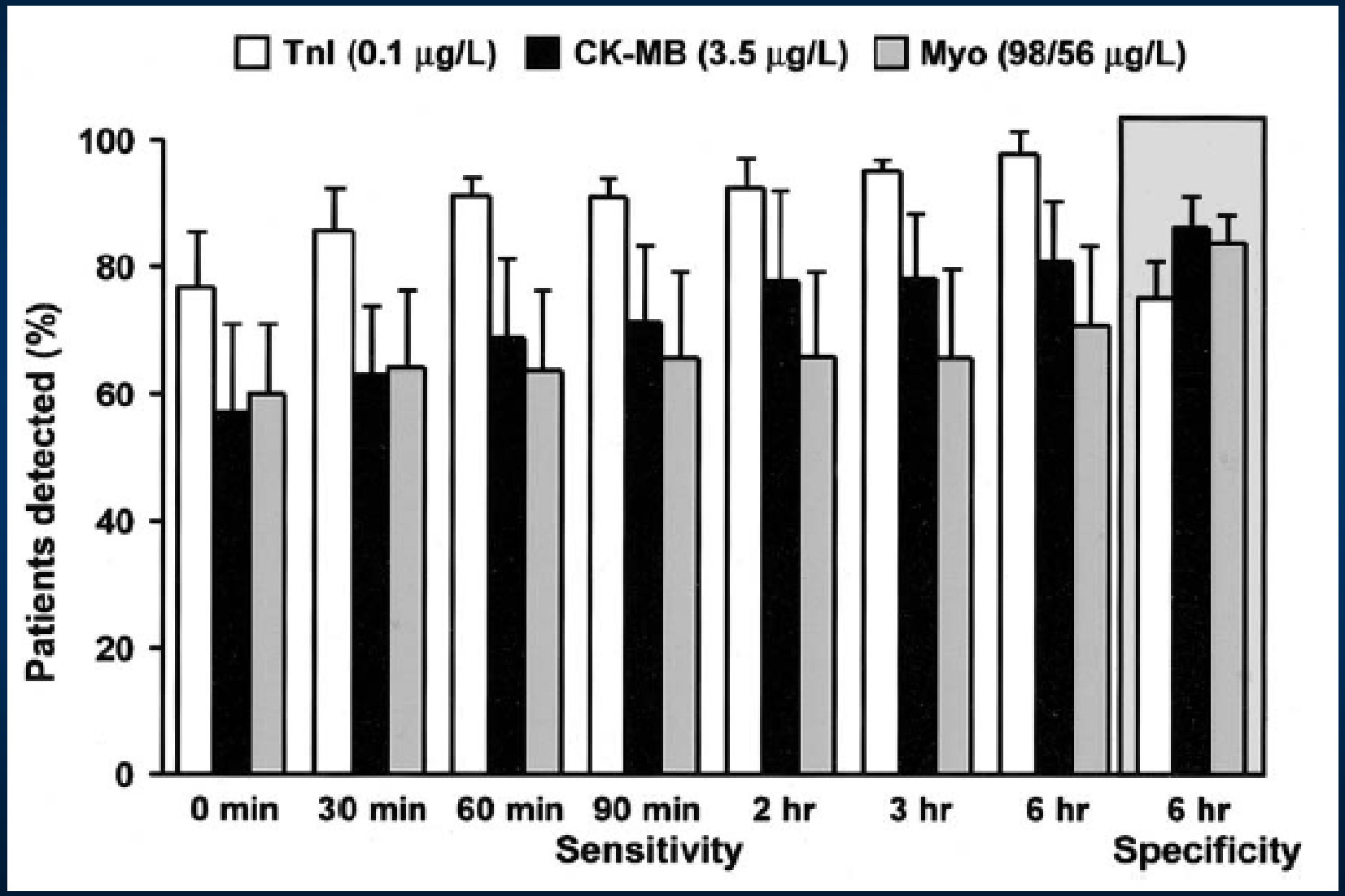
III. Heart-Type Fatty Acid-Binding Protein

Risk of death and recurrent ischemic events among patients with NSTEACS and normal serial CK-MB with and without increase baseline cTn-I



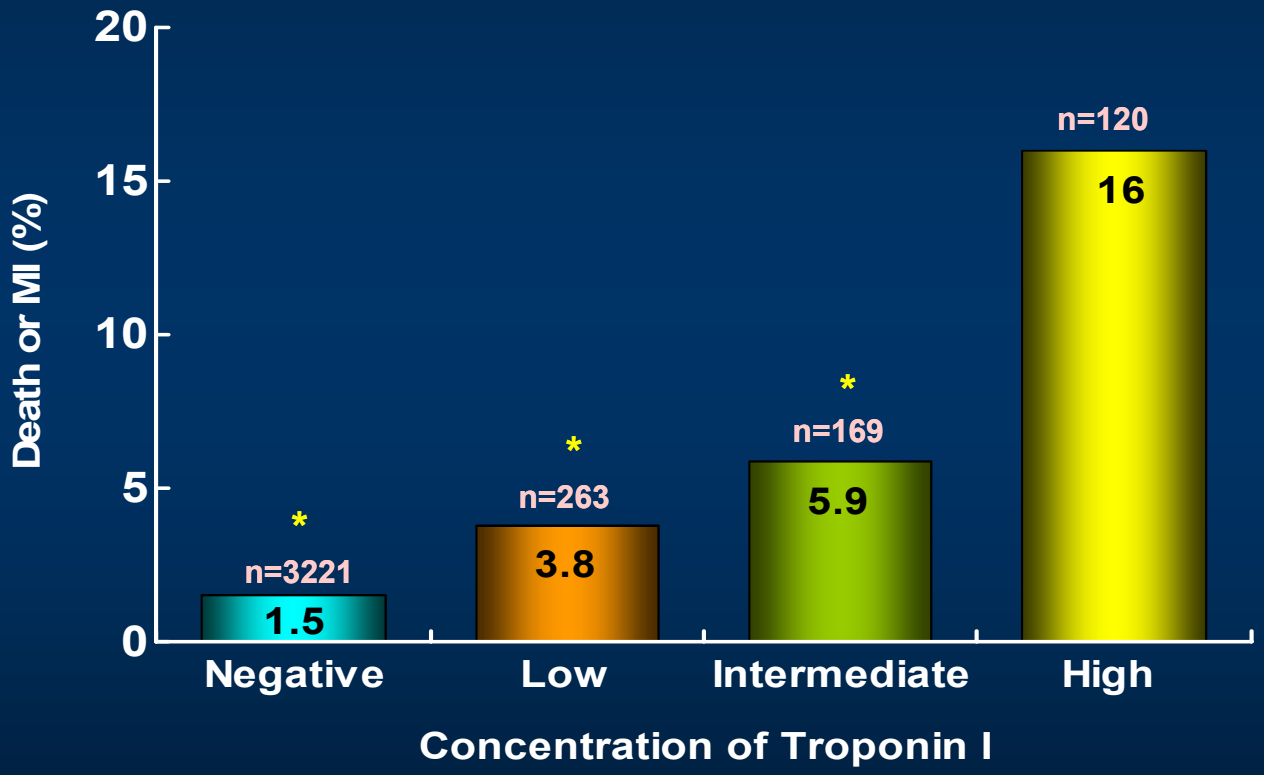
J Am Coll Cardiol 2000;36:1812–7

Sensitivity of cTn-I compared with myoglobin and CK-MB for the detection of myocardial injury



Am Heart J 2004;148: 574–81

Hazard Ratio for Future Cardiovascular Events in Coronary Artery Disease



Negative : no detectable cTnI

low : peak greater than the lower limit of detectability but less than the optimal diagnostic value

intermediate : peak greater than or equal to the optimal diagnostic value but less than the manufacturer's suggested upper reference limit (URL)

high : peak greater than or equal to the URL

The trend toward an increased number of events for increasing peak cTnI values was highly significant . * $p < 0.001$.

JACC 2004;43:958-965

Recommendations for Use of Biochemical Markers for Diagnosis of MI

Class I

1. Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with ACS (C)

2. The patient's clinical presentation (history, physical exam) and ECG should be used in conjunction with biomarkers in the diagnostic evaluation of suspected MI (C).

3. cTn is the preferred marker for the diagnosis of MI. CK-MB by mass assay is an acceptable alternative when cTn is not available (A).

4. Blood should be obtained for testing at hospital presentation followed by serial sampling with timing of sampling based on the clinical circumstances. For most patients, blood should be obtained for testing at hospital presentation and at 6–9 h (C).

5. In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI (C):

a. Maximal concentration of cardiac troponin exceeding the 99th percentile of values for a reference control group on at least 1 occasion during the first 24 h after the clinical event.

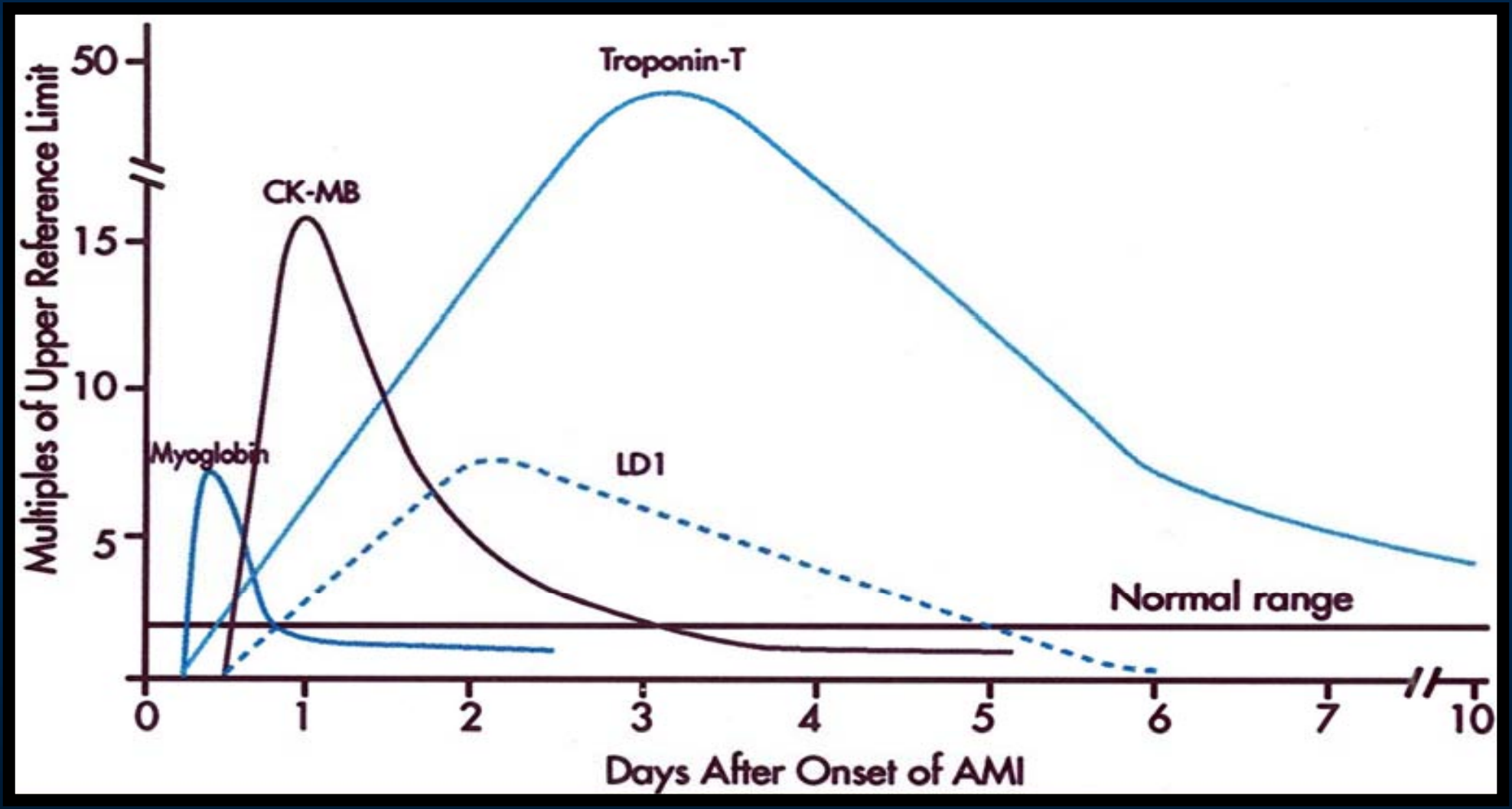
b. Maximal concentration of CK-MB exceeding the 99th percentile of values for a sex-specific reference control group on 2 successive samples

KINETICS OF CARDIAC MARKERS AFTER AMI

MARKER	DETECTION	PEAK	DISAPPEARANCE
Myoglobin	1 – 4 h	6 – 7 h	24 h
CK-MB mass	3 – 12 h	12 – 18 h	2 – 3 days
Total CK	4 – 8 h	12 – 30 h	3 – 4 days
cTnT	4 – 12 h	12 – 48 h	5 – 15 days
cTnI	4 – 12 h	12 – 24 h	5 – 7 days
IMA	few minutes	2 – 4 h	6 hours

*** IMA : Ischemia modified albumin**

BIOCHEMICAL MARKERS IN AMI:
RELEASE, PEAK AND DURATION OF ELEVATION



A. BIOCHEMICAL MARKERS OF MYOCARDIAL NECROSIS

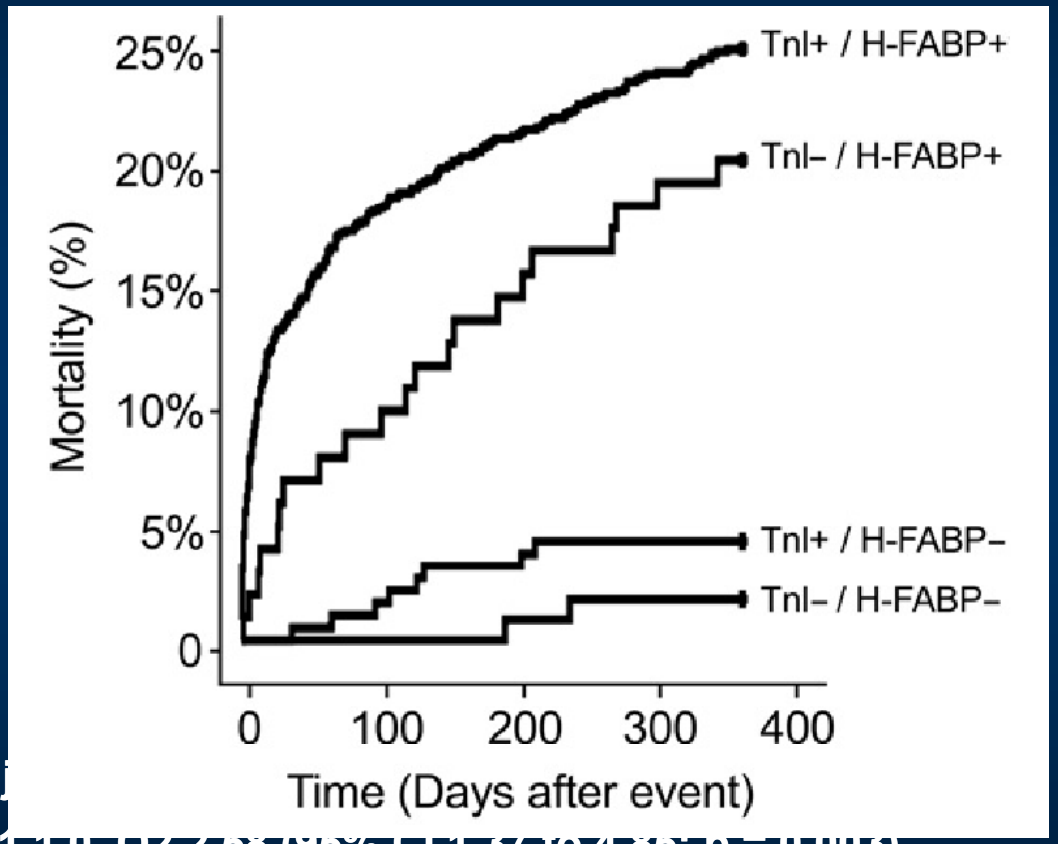
I. Cardiac Troponins

II. Creatine Kinase-MB

III. Heart-Type Fatty Acid-Binding Protein

Kaplan-Meier all-cause mortality curves according to H-FABP Quartiles

12 to 24 h after onset of Sx in 1448 patients with ACS



After adj

HRs : Q1 1.0, Q2 2.58 (95% CI 1.37 to 4.85; p = 0.003)

Q3 3.77 (95% CI 2.01 to 7.07; p = 0.001)

Q4 6.59 (95% CI 3.40 to 12.74; p = 0.001)

JACC 2007;50:2061-7

B. BIOCHEMICAL MARKERS OF INFLAMMATION

I. C-Reactive Protein

Usefulness of CRP in Acute Coronary Syndrome

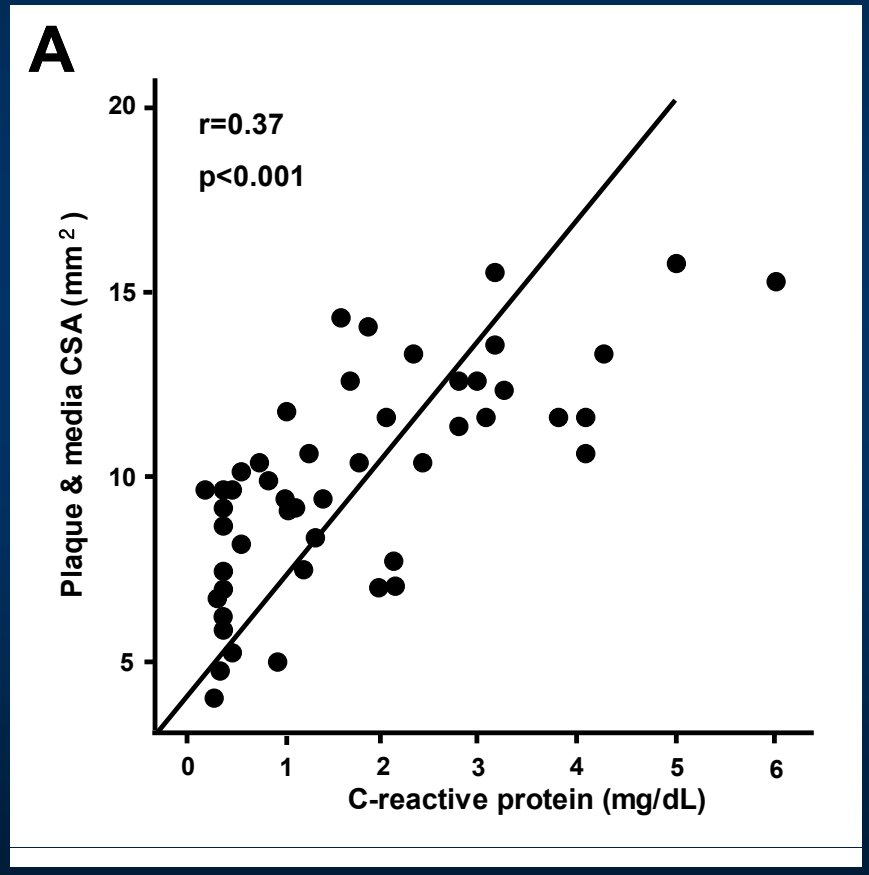
- Indicator of an acute inflammatory process associated with plaque vulnerability and rupture
- To be useful for guiding a therapy such as statin
- Independent predictor for prognosis

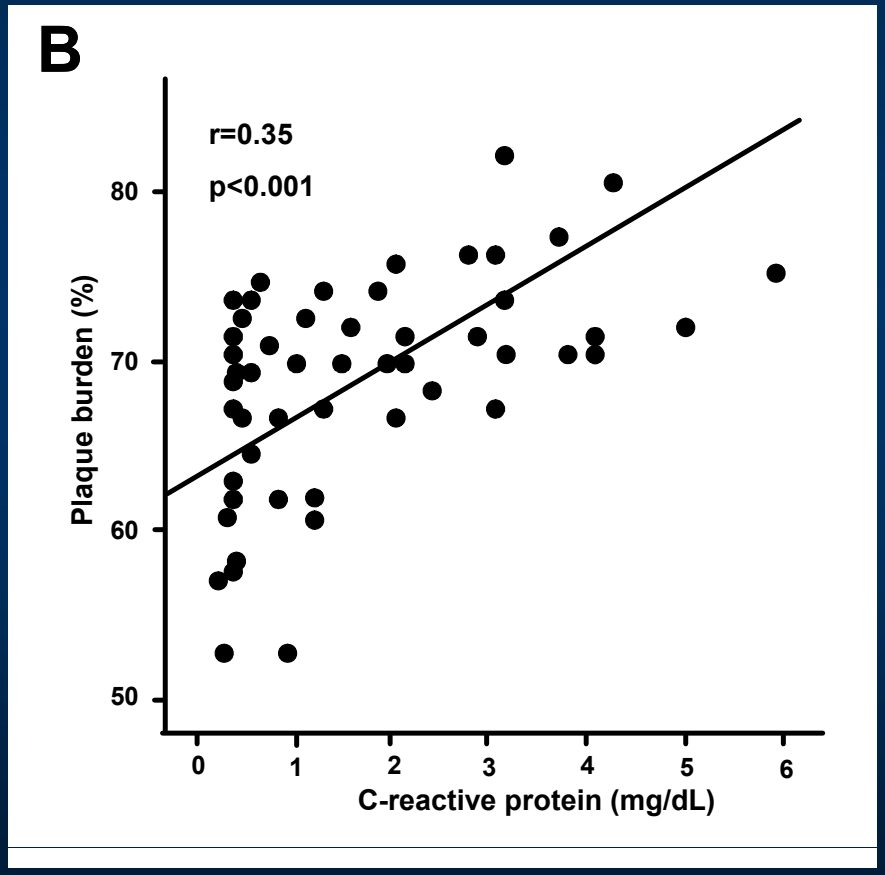
Elevated Preprocedural hsCRP Levels are Associated with NIH and Restenosis Development after Successful PCI

- 100 consecutive patients (100 lesions) who received successful IVUS-guided single stent (MAC) implantation
  → single, de novo lesions in native coronary arteries
- Exclusion
  : LM disease
  : bifurcation lesion
  : graft stenosis
  : LV dysfunction

CNUH data, Cir J 2005;69:1477-1483

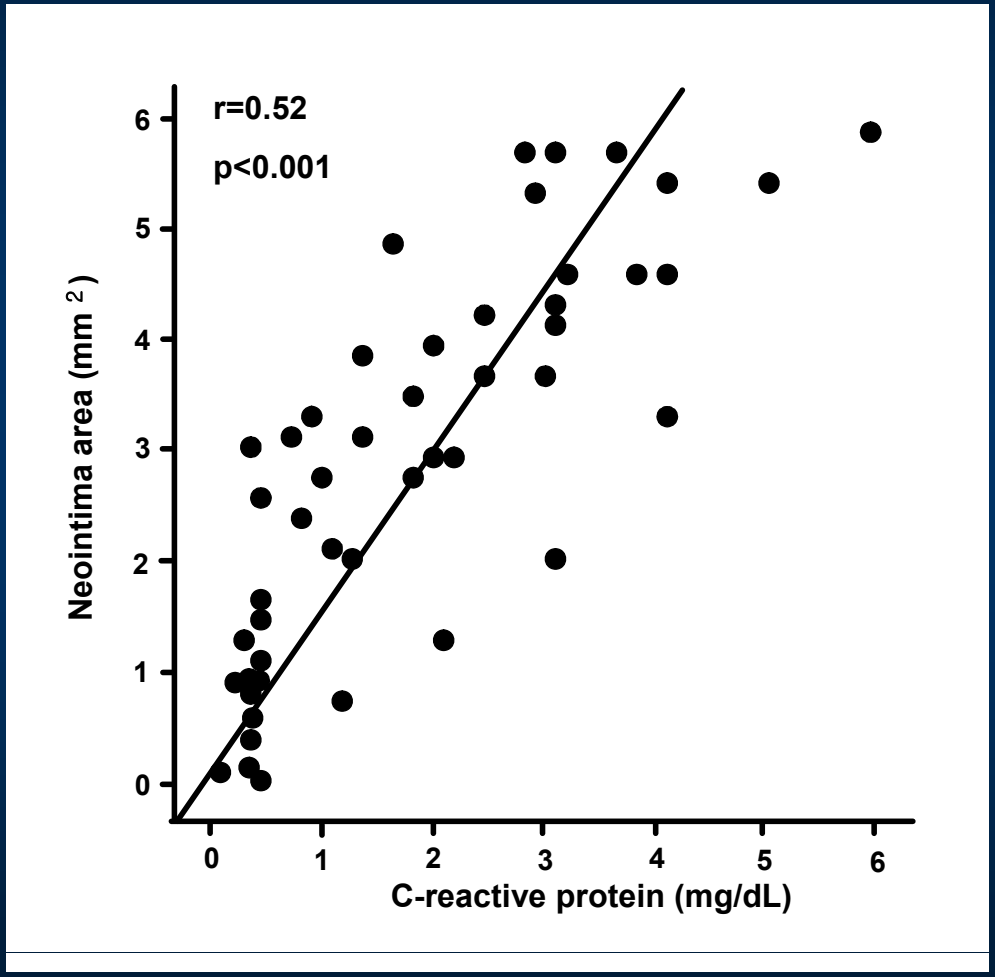
Correlation Between Pre-interventional hsCRP Levels And Pre-interventional Plaque Plus Media CSA (A) And Pre-interventional Plaque Burden (B)





CNUH data, Cir J 2005;69:1477-1483

Correlation Between Pre-interventional hsCRP Level and F/U NIH Area



CNUH data, Cir J 2005;69:1477-1483

Relation of Soft Plaque and Pre-Procedural Elevated hsCRP Levels to Incidence of ISR after Successful Coronary Artery Stenting

- 120 coronary artery disease patients
- Soft plaque group : 50 patients

  Non-soft plaque group : 70 patients
- Exclusion

  : LM disease

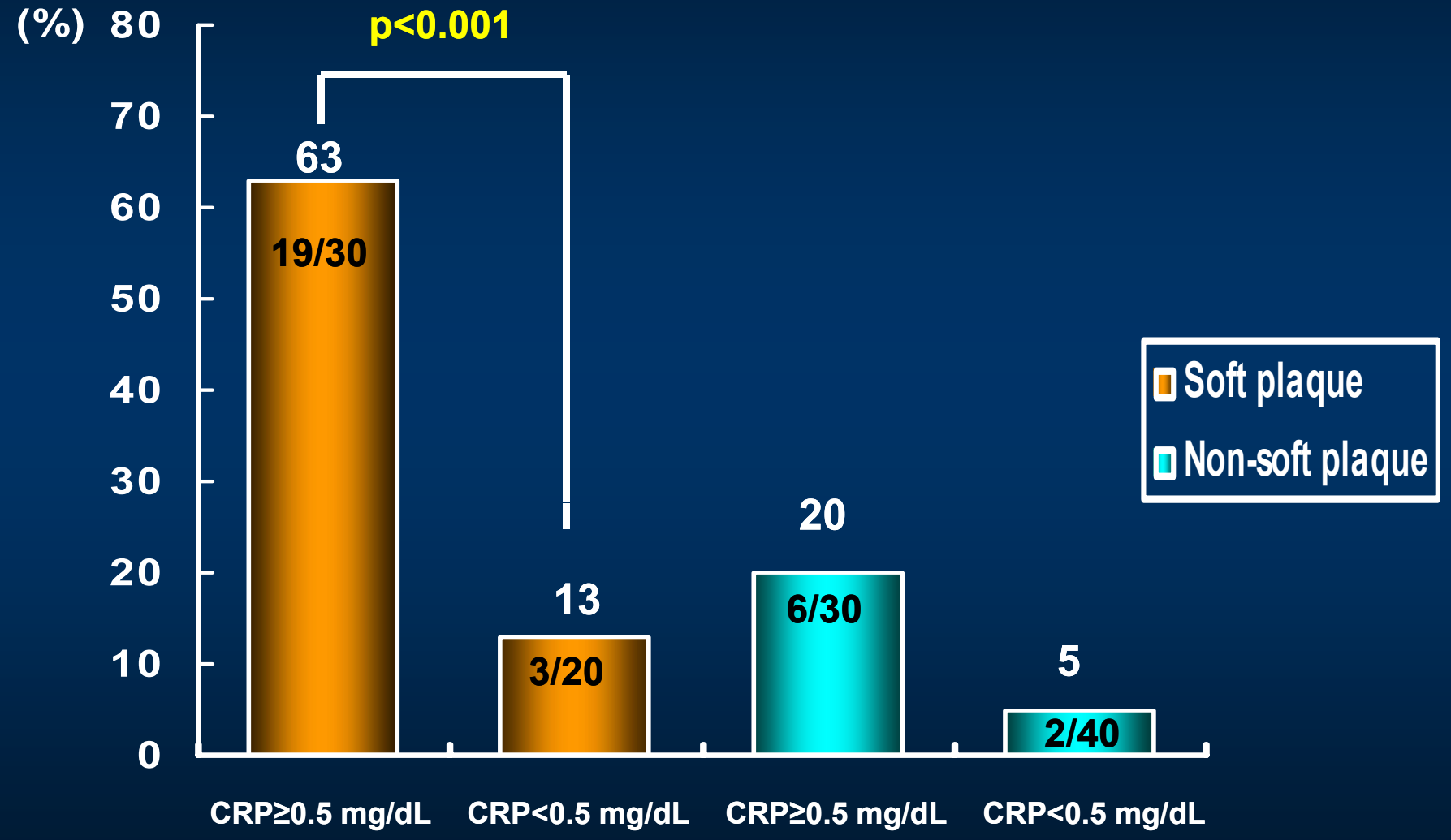
  : Osteal or bifurcation target lesion

  : graft stenosis

  : LV dysfunction

CNUH data, Am J Cardiol 2006;98:341-345

The Incidences of ISR According to Plaque Morphology and Pre-interventional Serum hsCRP



CNUH data, Am J Cardiol 2006;98:341-345

Independent Predictors for ISR

	OR (95% CI)	p Value
Soft plaque + hs-CRP ≥ 0.5 mg/dL	5.435 (1.542-10.423)	0.001
Soft plaque	3.967 (1.456-8.764)	0.010
hs-CRP ≥ 0.5 mg/dL	2.593 (0.954-6.823)	0.059
Pre-intervention positive remodeling	2.453 (0.876-7.234)	0.110
Diabetes mellitus	2.494 (0.714-7.342)	0.154
Lesion length	2.132 (0.683-4.567)	0.243
Post-intervention residual plaque burden	1.865 (0.612-3.567)	0.345
Hypertension	1.714 (0.584-2.682)	0.367
Post-intervention plaque prolapse	1.018 (0.935-1.082)	0.453

CNUH data, Am J Cardiol 2006;98:341-345

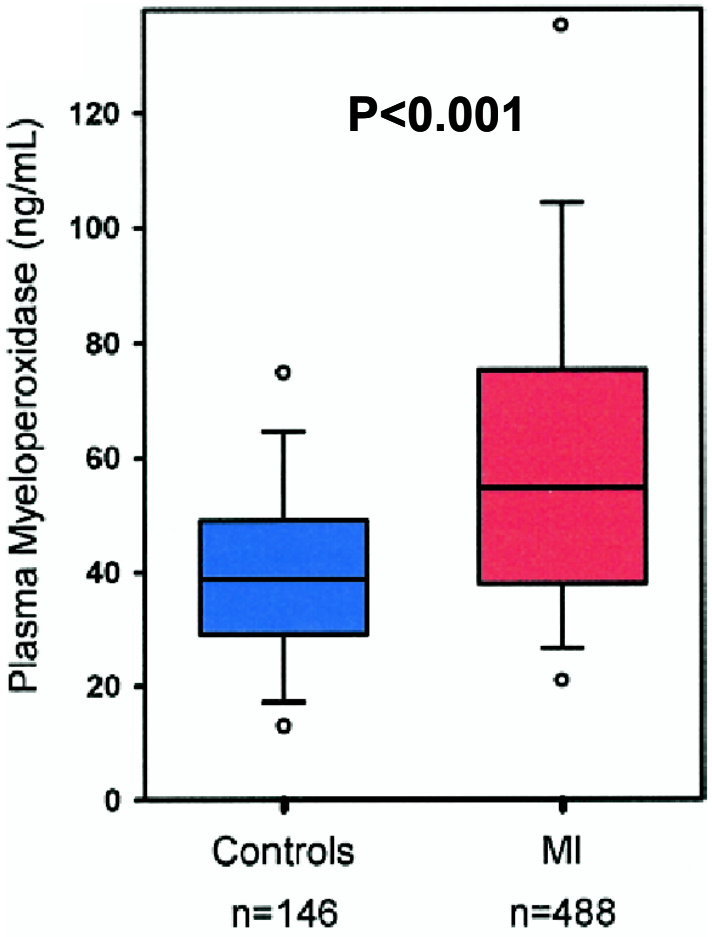
C. BIOCHEMICAL MARKERS OF PLAQUE INSTABILITY

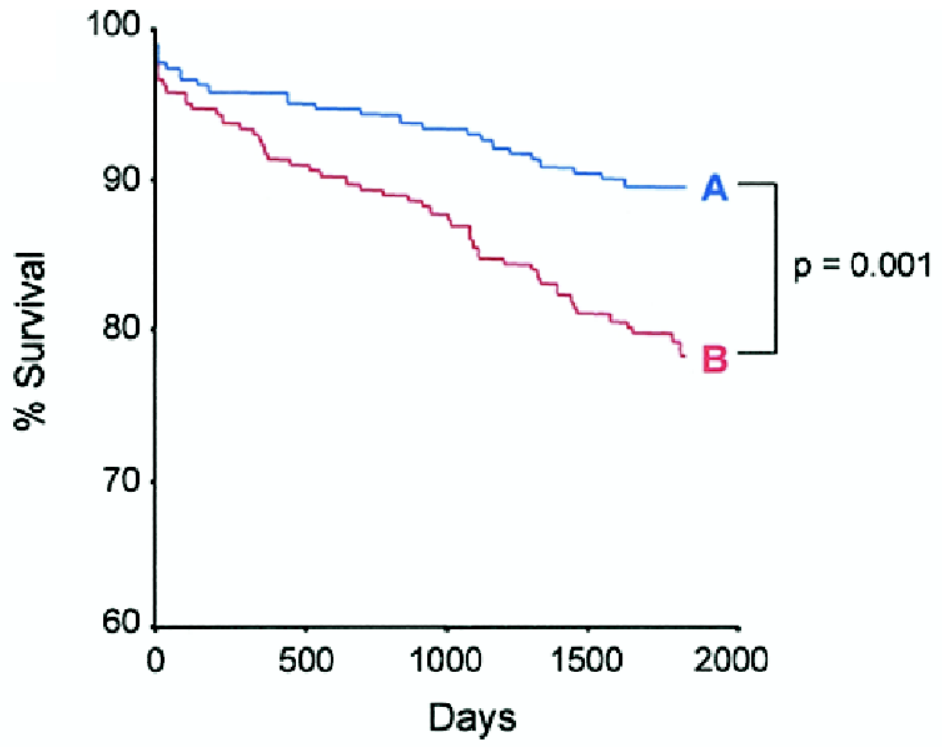
I. Myeloperoxidase

II. Soluble CD40 Ligand

III. Pregnancy-Associated Plasma Protein A

Plasma concentrations of MPO predict mortality after MI

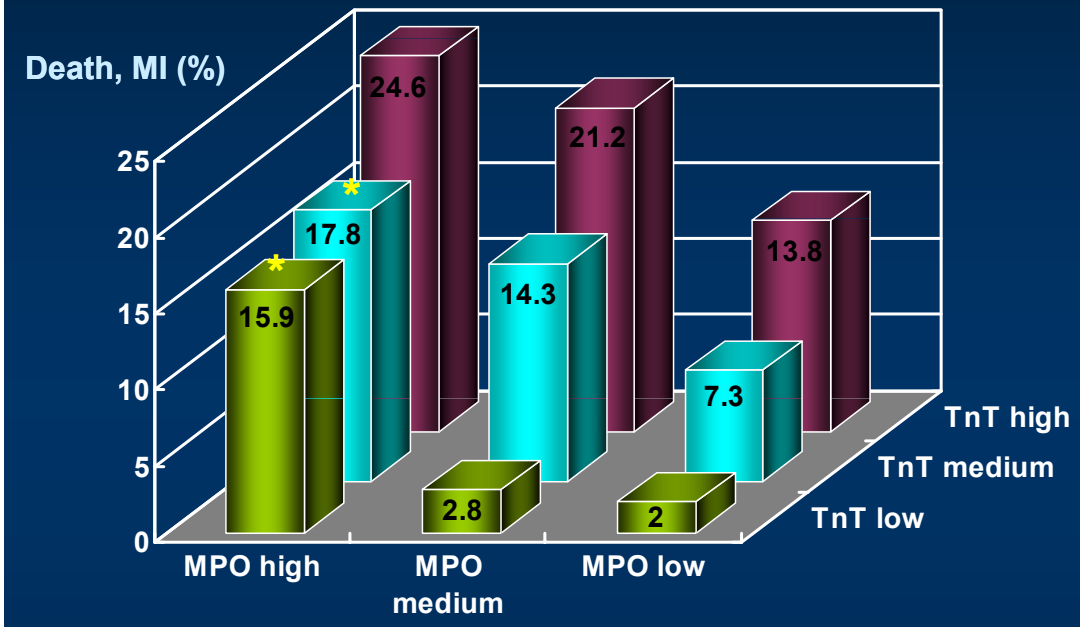




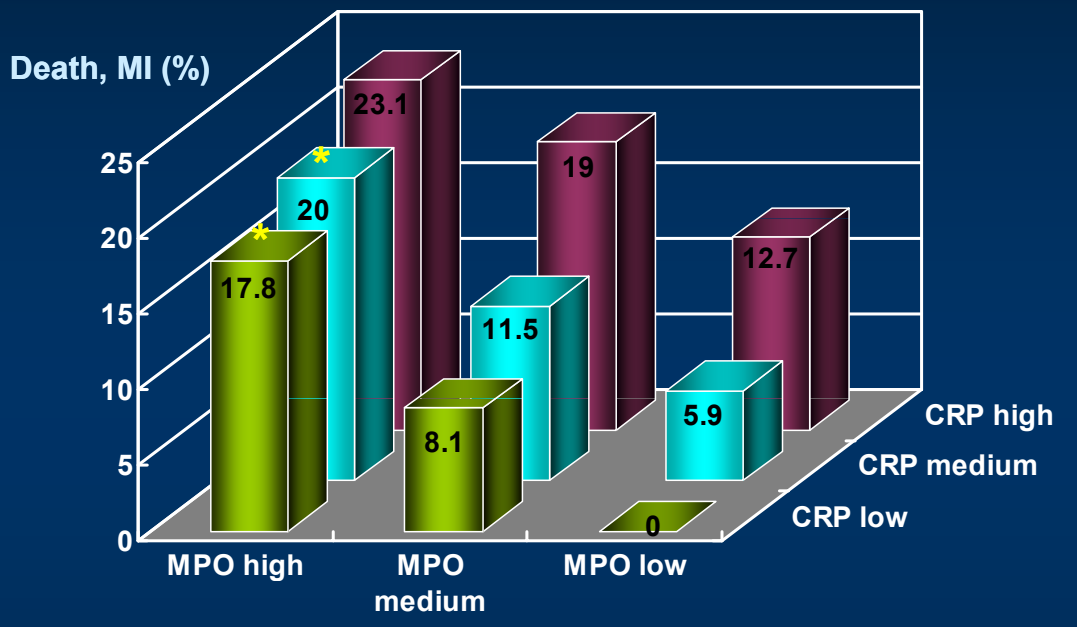
Number at risk at each time point:						Events	%
A MPO < med:	242	230	226	219	217	25	10
B MPO > med:	243	221	213	197	191	52	21

JACC 2007;49:1993-2000

MPO serum levels predict risk in patients with ACS



* p<0.01 vs MPO low



* p<0.01 vs MPO low

Diagnostic threshold levels were 222 and 350 ug/L for MPO, 0.01 and 0.1 ug/L for TnT, 5 and 15 mg/L for CRP

Circulation 2003;108:1440-1445

C. BIOCHEMICAL MARKERS OF PLAQUE INSTABILITY

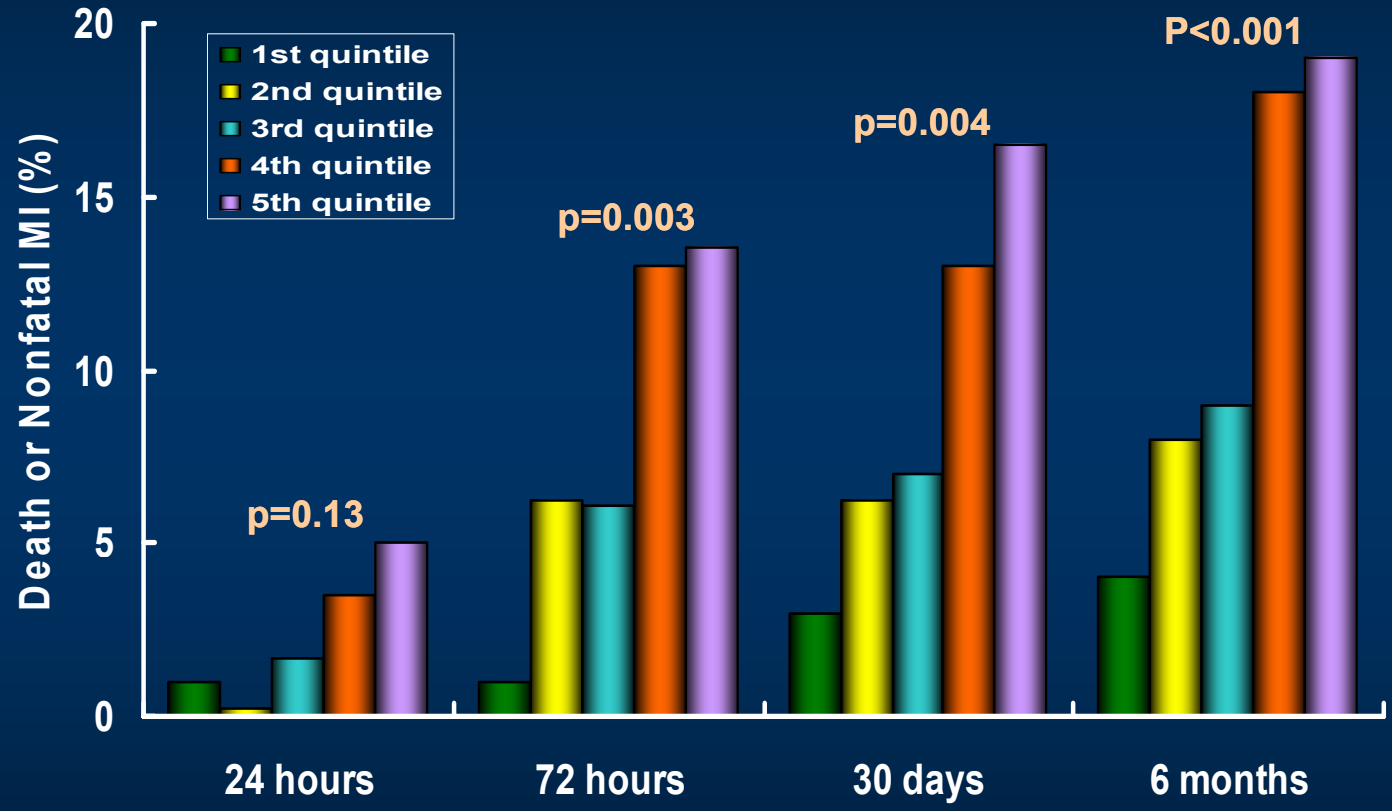
I. Myeloperoxidase

II. Soluble CD40 Ligand

III. Pregnancy-Associated Plasma Protein A

Association between soluble CD40 ligand levels and rate of cardiac events at 24 H, 72 H, 30 D, and 6 M

544 patients with ACS



first quintile : CD40 ligand <1.93 µg/L

second quintile : 1.93 < CD40 ligand < 3.50 µg/L

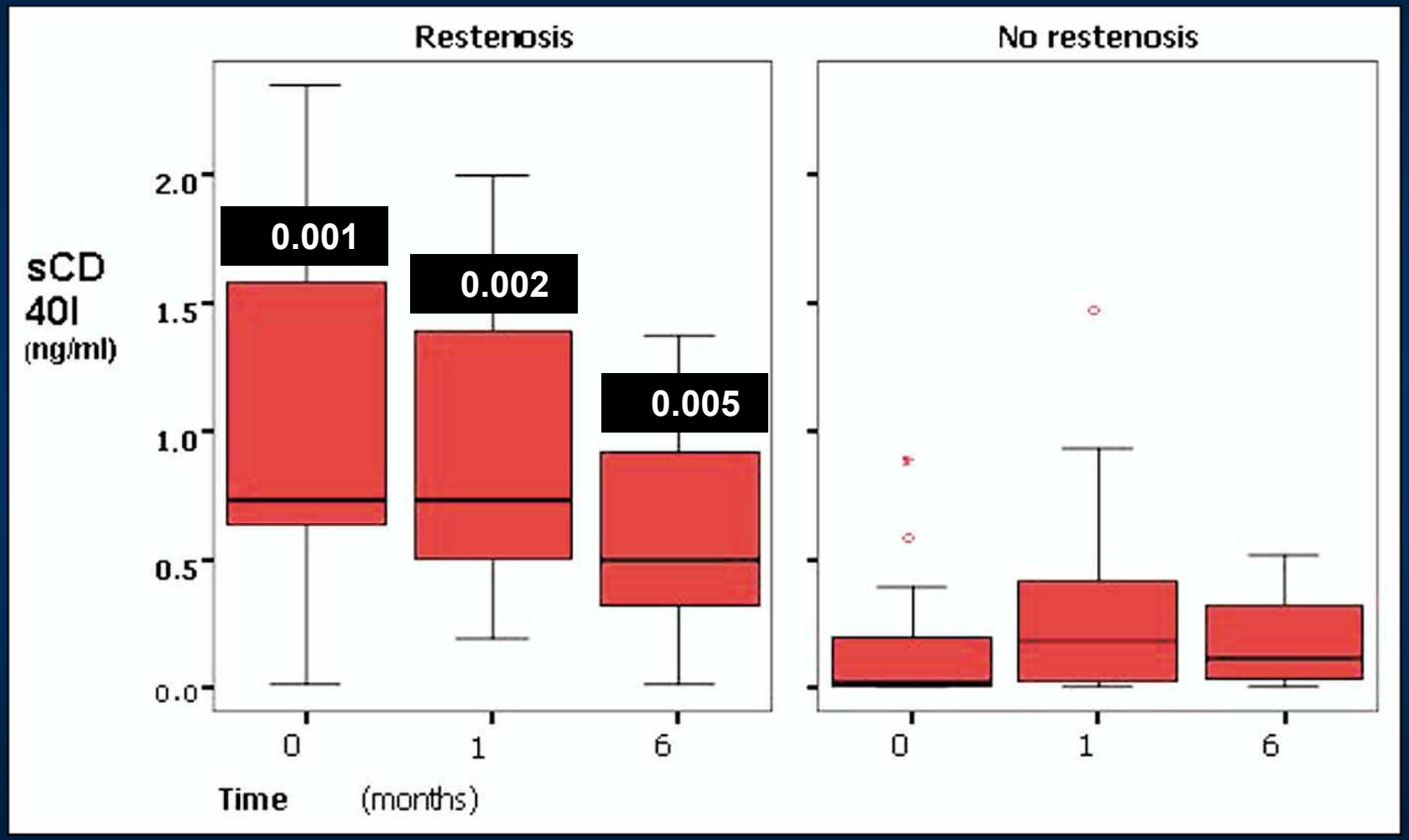
third quintile : 3.51 < CD40 ligand < 5.00 µg/L

fourth quintile : 5.01 < CD40 ligand < 6.30 µg/L

fifth quintile : 6.30 µg/L < CD40 ligand

NEJM 2003;348:1104-11

Usefulness of preprocedural soluble CD 40 ligand for Predicting restenosis in patients with stable CAD



Am J Cardiol 2006;97:198-202

C. BIOCHEMICAL MARKERS OF PLAQUE INSTABILITY

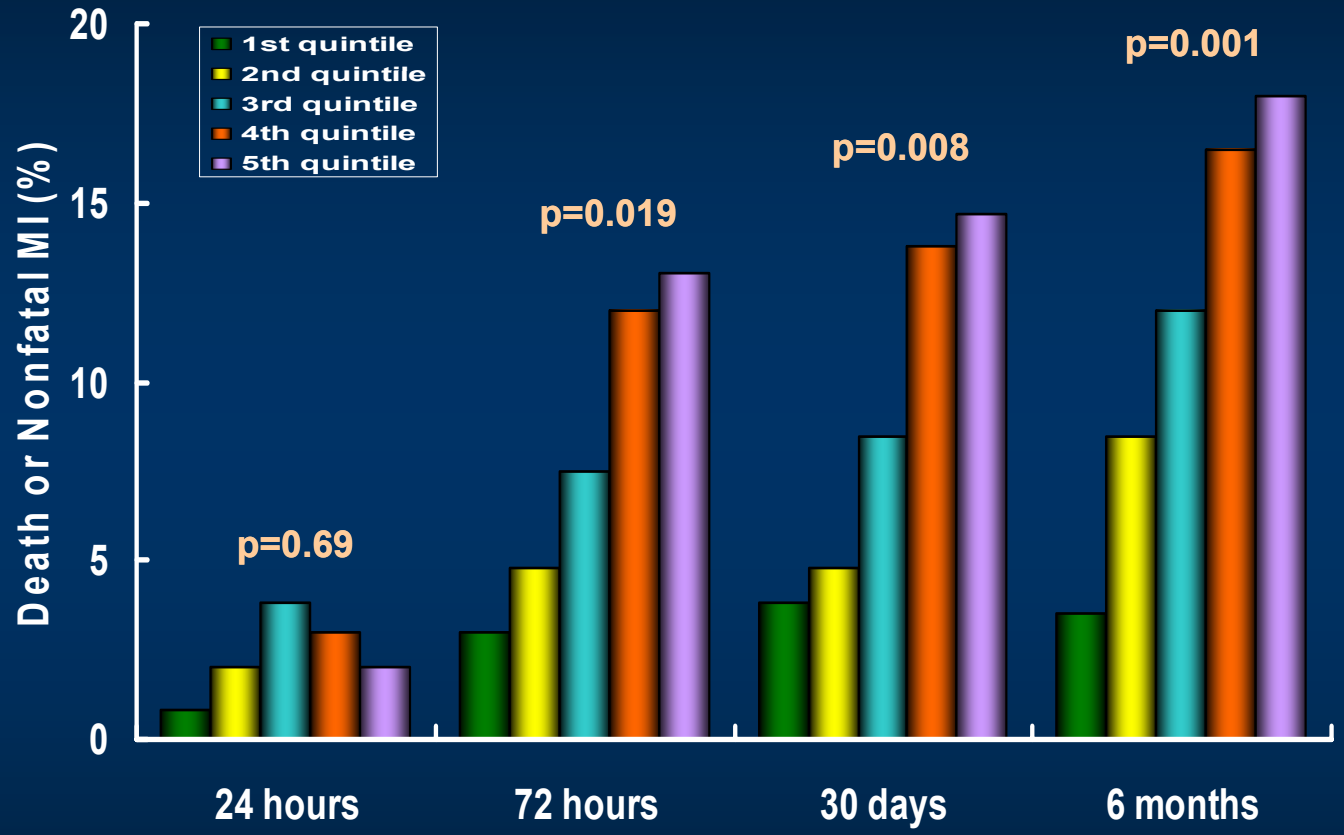
I. Myeloperoxidase

II. Soluble CD40 Ligand

III. Pregnancy-Associated Plasma Protein A

Pregnancy-associated plasma protein-A levels in patients with ACS

547 patients with ACS



first quintile : PAPP-A <4.5 mIU/L

second quintile : 4.5 < PAPP-A < 7.5 mIU/L

third quintile : 7.6 < PAPP-A < 12.6 mIU/L

fourth quintile : 12.7 < PAPP-A < 24.0 mIU/L

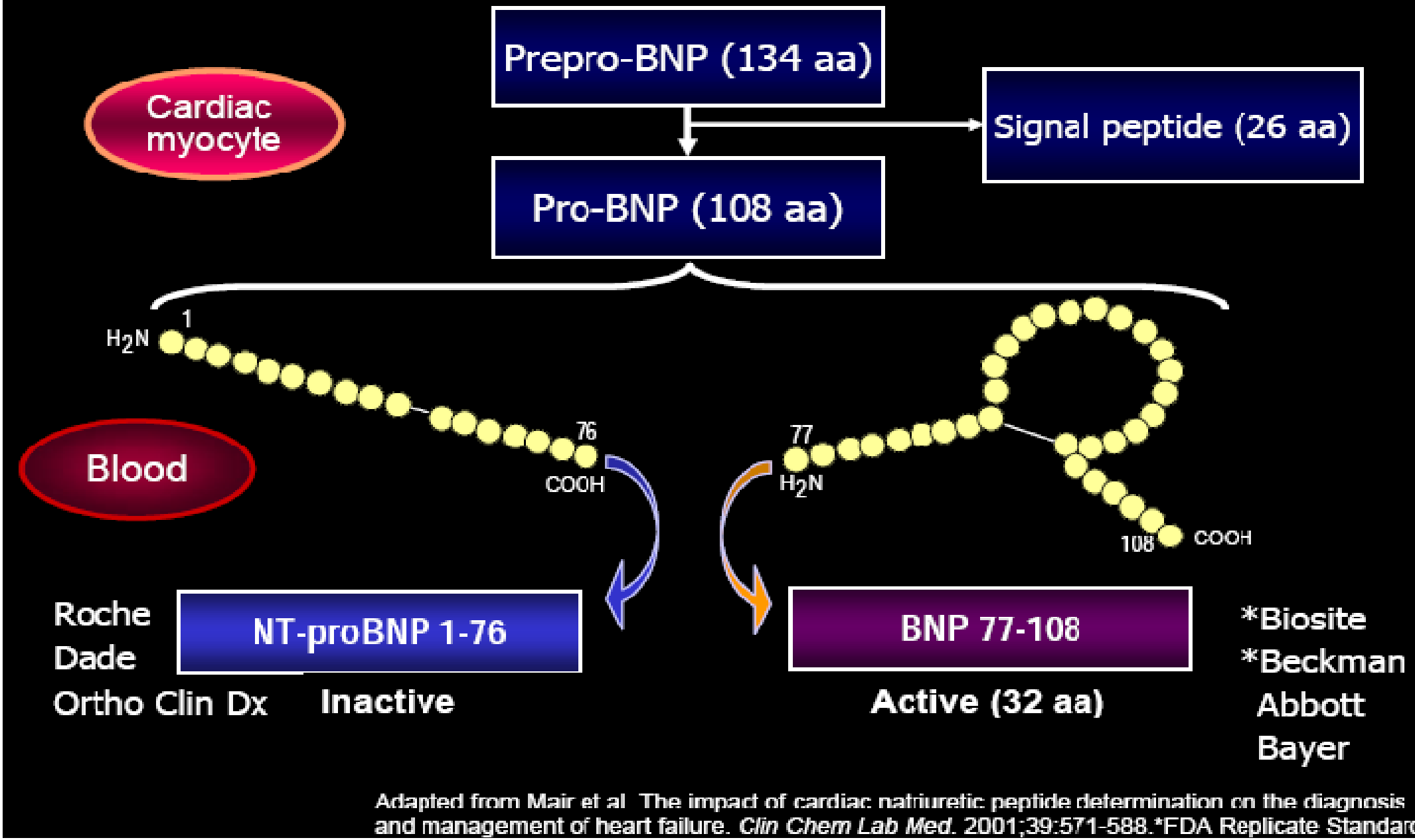
fifth quintile : 24.0 mIU/L < PAPP-A

JACC 2005;45:229-37

D. BIOCHEMICAL MARKERS OF MYOCARDIAL DYSFUNCTION

I. Cardiac Natriuretic Peptides

Release of BNP From Cardiac Myocytes



Adapted from Mair et al The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. *Clin Chem Lab Med.* 2001;39:571-588.*FDA Replicate Standard.

Use of NT-proBNP Versus BNP

BNP has been used in more studies & seems to correlate better with disease status.

NT-proBNP circulates at higher levels

NT-proBNP has a longer half-life (1-2 hours)

BNP has a short half-life (<20 minutes)

NT-proBNP will not cross-react with exogenous BNP

Clearance of NT-proBNP dependent upon renal function

Usefulness of NT-proBNP in ACS

- Reliable biomarker, reflecting myocardial stress caused by various cardiovascular disease
- Closely linked to prognosis and angiographic procedural complication
- Correlated to severity, location, and extent of angiographic coronary disease
- Useful for screening of coronary artery disease
- Superior to CRP or troponin for long-term risk stratification
- Combination of NT-proBNP with creatinine clearance

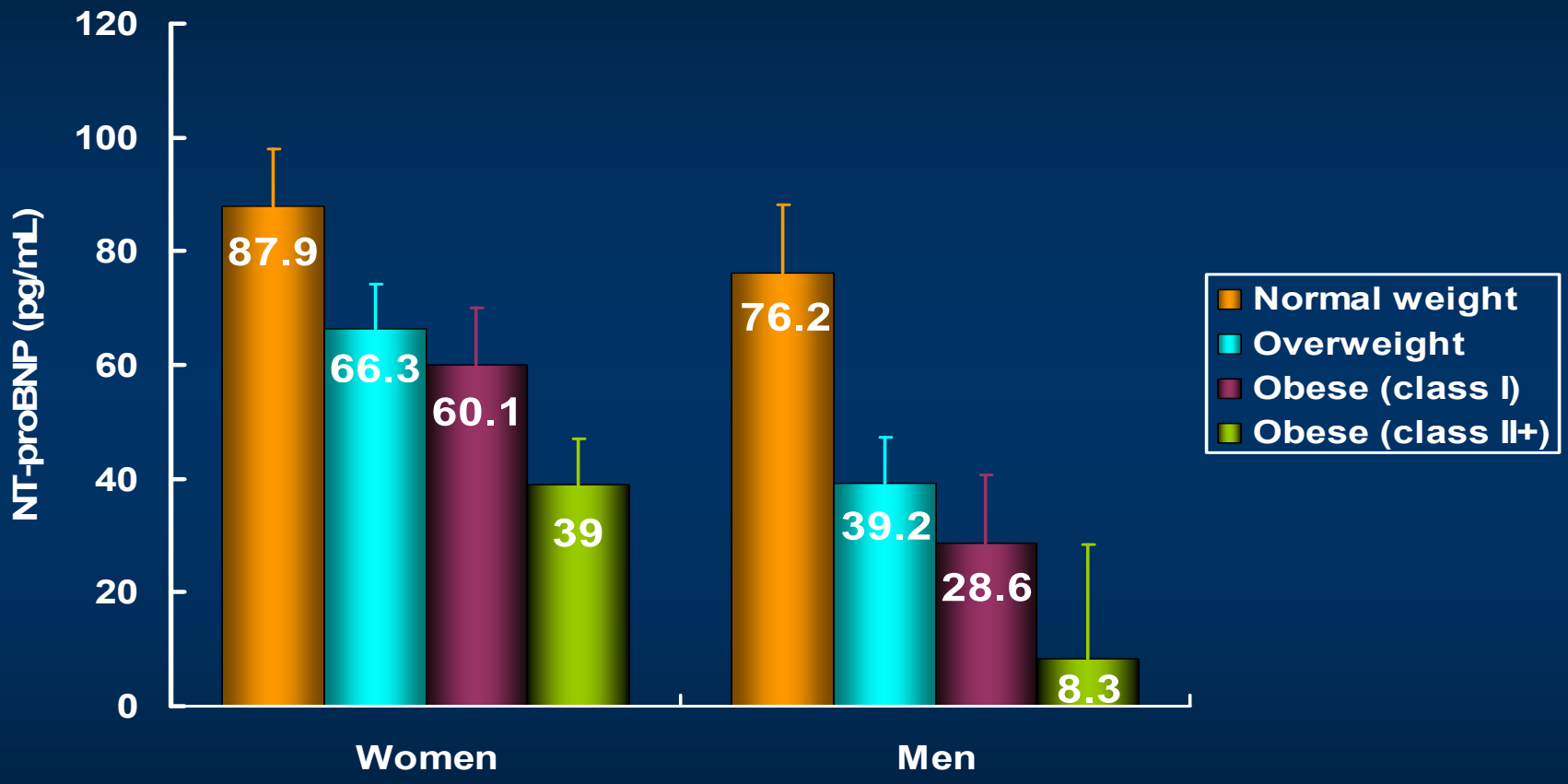
  emerged as the best predictor of 1-year mortality

The Influence of Variables on the Level of NT-proBNP

- Female sex ($p < 0.0001$)
- Greater age ($p < 0.0001$)
- Increasing dyspnea ($p = 0.0001$)
- Diabetes mellitus ($p = 0.01$)
- Valvular heart disease ($p = 0.002$)
- Low heart rate ($p < 0.0001$)
- Left ventricular ejection fraction < 45% ($p < 0.0001$)
- Abnormal ECG ($p < 0.0001$)
- High $\log_{10}$[plasma creatinine] ($p = 0.0009$)
- Low $\log_{10}$[plasma HbA1c] (%) ($p = 0.0004$)
- High $\log_{10}$[urine albumin] (%) ($p < 0.0001$)

Heart 2003;89:745-51

NT-proBNP Levels Stratified by BMI



Normal weight : BMI < 25 kg/m²

Overweight : 25 ≤ BMI < 30 kg/m2

Obese (class I) : 30 ≤ BMI < 35 kg/m2

Obese (class II+) : BMI ≥ 35 kg/m2

Circulation 2005;112:2163-2168

NT-proBNP Predicts Significant Coronary Artery Lesion in Patients with UAP

- 161 unstable angina patients
  with normal ventricular function
  (left ventricular ejection fraction > 55% and
  no regional wall motion abnormality
  by echocardiography)
  normal troponin I level (≤0.05 ng/mL), CRP (mg/dL),
  other cardiac enzymes, ECG finding,
  creatinine clearance rate

- No patient had suffered a myocardial infarction or unstable angina pectoris prior to hospitalization.

CNUH data, Cir J 2005;69:1472-6

Correlation Between NT-proBNP and Gensini Score

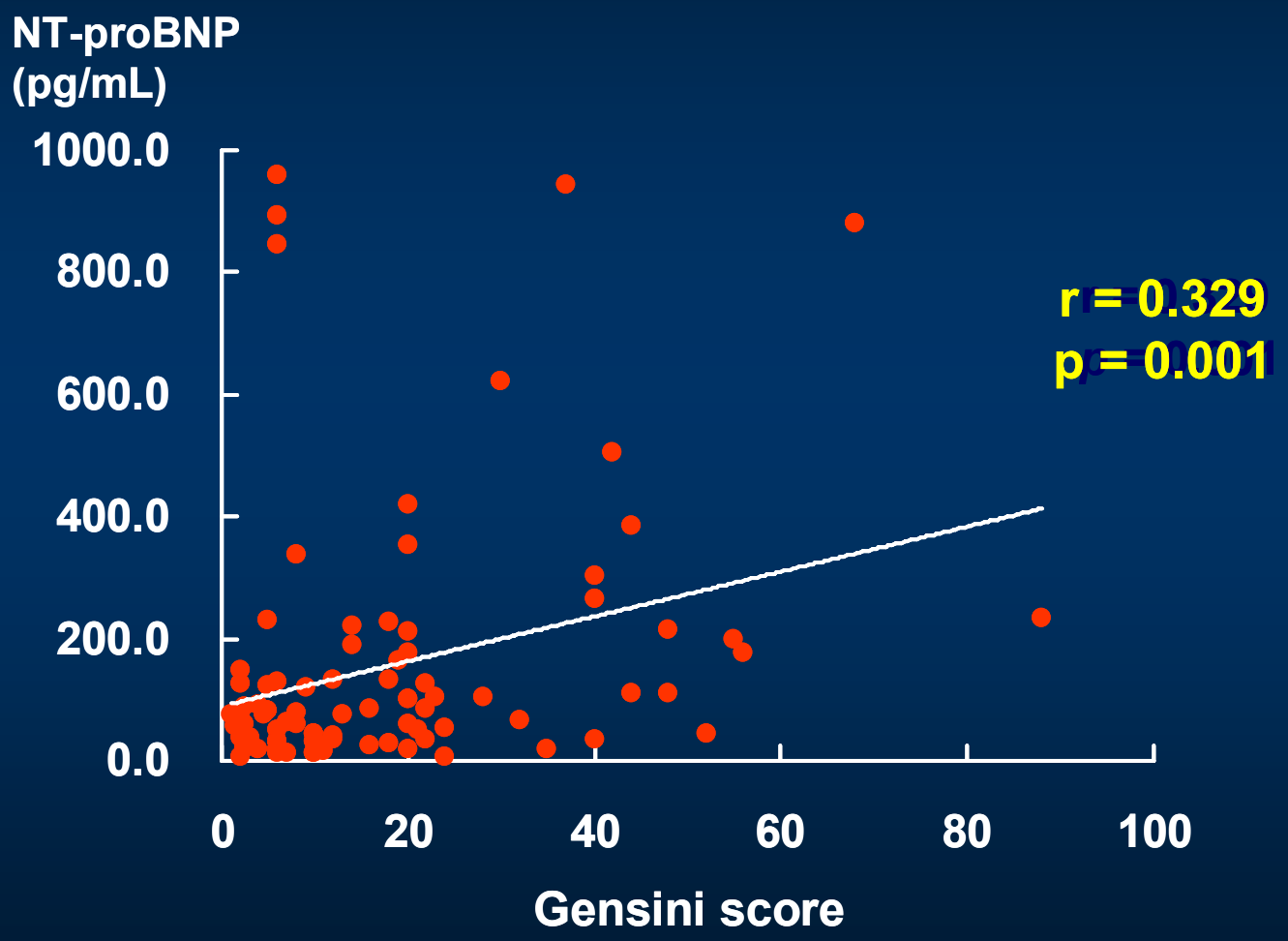
Gensini score = sum of (stenosis score × functional significance score)

Significance score

LM : 5	d-LCx : 1
p-LAD : 2.5	OM : 1
m-LAD : 1.5	p-RCA : 1
d-LAD : 1	m-RCA : 1
1st Dx : 1	d-RCA : 1
2nd Dx : 0.5	PD : 1
p-LCx 2.5	PL : 1

Stenosis score

1 : 25%	2 : 50%
4 : 75%	8 : 90%
16 : 99%	32 : 100%



CNUH data, Cir J 2005;69:1472-1476

Independent Predictors for Coronary Artery Lesion

	OR (95% CI)	p value
Age	1.0 (0.9-1.1)	0.940
Male gender	0.3 (0.1-0.7)	0.006
Hypertension	0.6 (0.3-1.6)	0.319
Diabetes	0.6 (0.2-2.0)	0.433
Smoking	1.4 (0.5-3.9)	0.578
Dyslipidemia	0.1 (0.0-0.2)	0.001
NT-proBNP (>200 pg/mL)	10.1 (2.6-38.7)	0.001

CNUH data, Cir J 2005;69:1472-1476

NT-proBNP Predicts ISR in Asymptomatic Patients with Normal Cardiac Enzymes

- Subjects : 271 asymptomatic patients with preserved LV systolic function who underwent follow-up coronary angiography
- Exclusion criteria
  - : angina > CCS class II
  - : LV EF ≤50 %
  - : elevated cardiac enzymes
  - : CRP >0.5 mg/dL
  - : calculated creatinine clearance rate <80 mL/min/m^2

CNUH data, Am J Cardiol 2007;99:1051-1054

Independent Predictors for ISR

	OR (95% CI)	p value
Age	1.033 (0.977-1.092)	0.252
Hypertension	0.706 (0.168-2.960)	0.634
Diabetes	1.945 (0.497-7.611)	0.339
Dyslipidemia	2.298 (0.965-5.472)	0.060
Smoking	0.637 (0.109-2.404)	0.506
Ejection fraction	0.971 (0.912-1.034)	0.698
hsCRP	1.350 (0.296-1.034)	0.698
DES	1.189 (1.015-1.392)	0.032
NT-proBNP (>200 pg/mL)	3.244 (1.009-10.433)	0.048

CNUH data, Am J Cardiol 2007;99:1051-1054

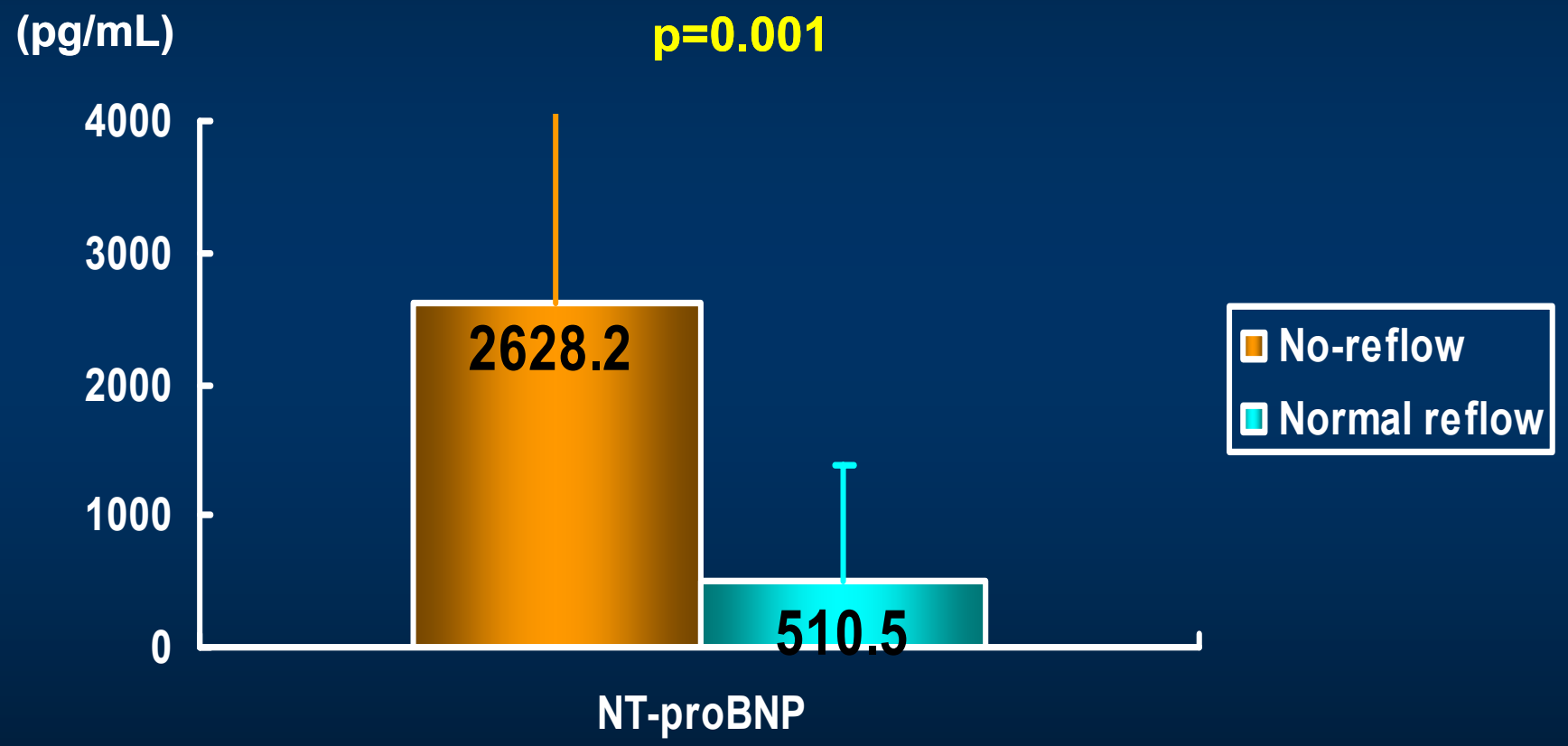
Preprocedural NT-proBNPeptide Predicts Angiographic No-Reflow Phenomenon During Stent Implantation in Patients with ASTEMI

- Subjects : 174 consecutive patients with ASTEMI who underwent primary PCI

- Exclusion criteria
  : Left main disease
  : Killip class ≥ III
  : severe valvular heart disease
  : severe chronic heart failure
  : calculated creatinine clearance rate <80 mL/min/m^2

CNUH data, Am J Cardiol 2007;100:631-634

NT-proBNP according to TIMI Flow Grade



CNUH data, Am J Cardiol 2007;100:631-634

Independent Predictors for No-Reflow

	OR (95% CI)	p value
Age	1.033 (0.977-1.092)	0.252
Hypertension	0.706 (0.168-2.960)	0.634
Diabetes	1.945 (0.497-7.611)	0.339
Smoking	0.637 (0.109-2.404)	0.506
Ejection fraction	0.971 (0.912-1.034)	0.698
Monocyte	2.396 (0.316-18.183)	0.398
hsCRP	1.350 (0.296-1.034)	0.698
Troponin T	1.189 (1.015-1.392)	0.032
NT-proBNP (>500 pg/mL)	5.844 (2.427-14.063)	0.001

CNUH data, Am J Cardiol 2007;100:631-634

The Role of Preprocedural NT-proBNP Level in Patients With ASTEMI Who Underwent Primary Percutaneous Coronary Intervention

- Subject : 163 patients with LV systolic dysfunction [defined as LVEF <45 %] who underwent primary PCI for acute STEMI

- Exclusion criteria
  - : left main disease
  - : Killip class ≥ III
  - : prior MI
  - : prior LV systolic dysfunction
  - : chronic renal failure

CNUH data, 2008 ACC

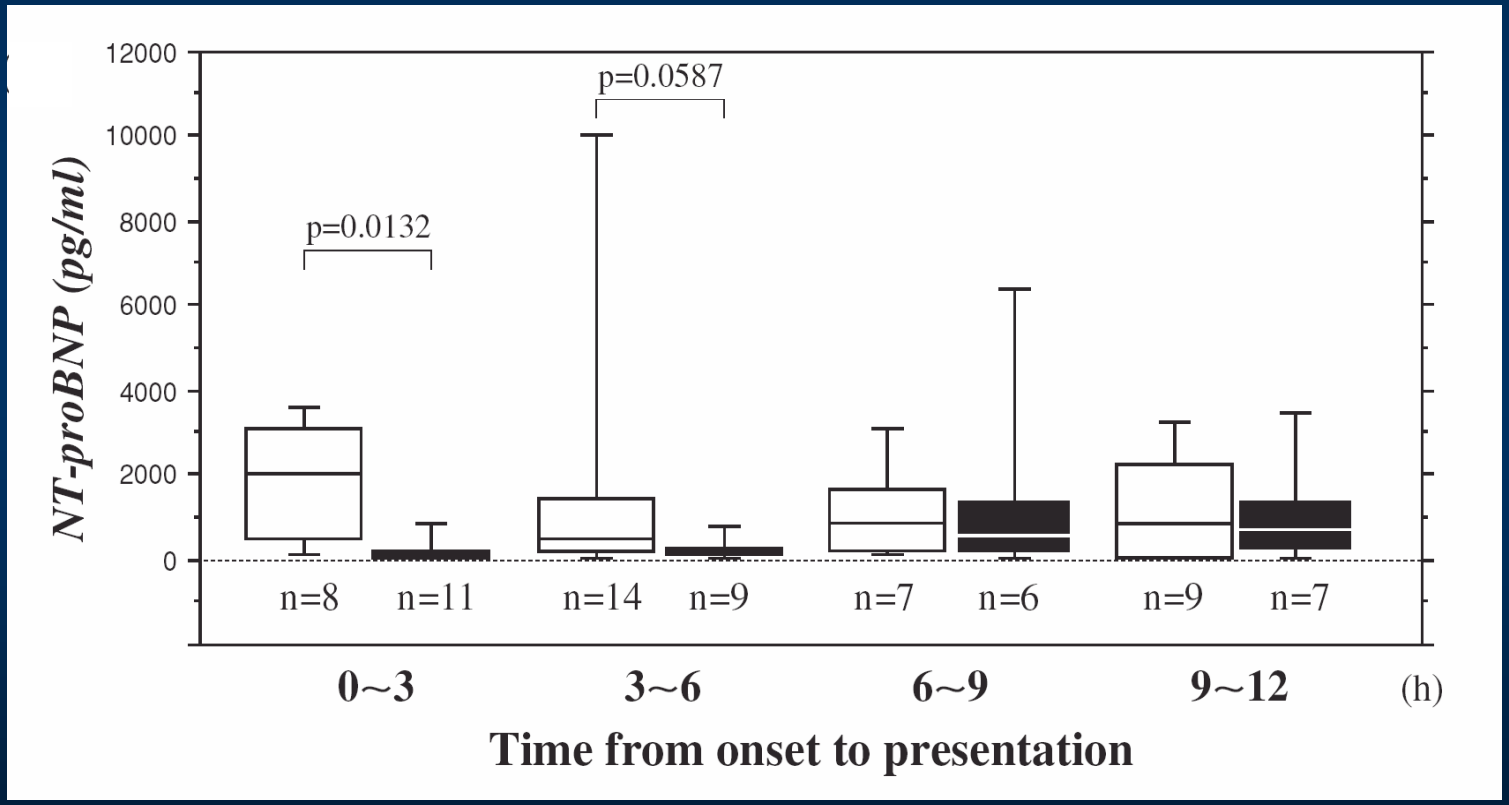
Independent Predictors for Non-recovery of LVEF

	OR (95% CI)	p value
Age	0.05 (0.01-0.72)	0.031
Monocyte	3.47 (1.30-5.98)	0.020
hsCRP	2.23 (1.96-5.47)	0.047
Troponin I	1.02 (0.99-1.01)	0.406
NT-proBNP (>500 pg/mL)	3.24 (1.01-10.43)	0.013

CNUH data, 2008 ACC

Comparison of NT-proBNP in NSTEMI and STEMI

547 patients with ACS



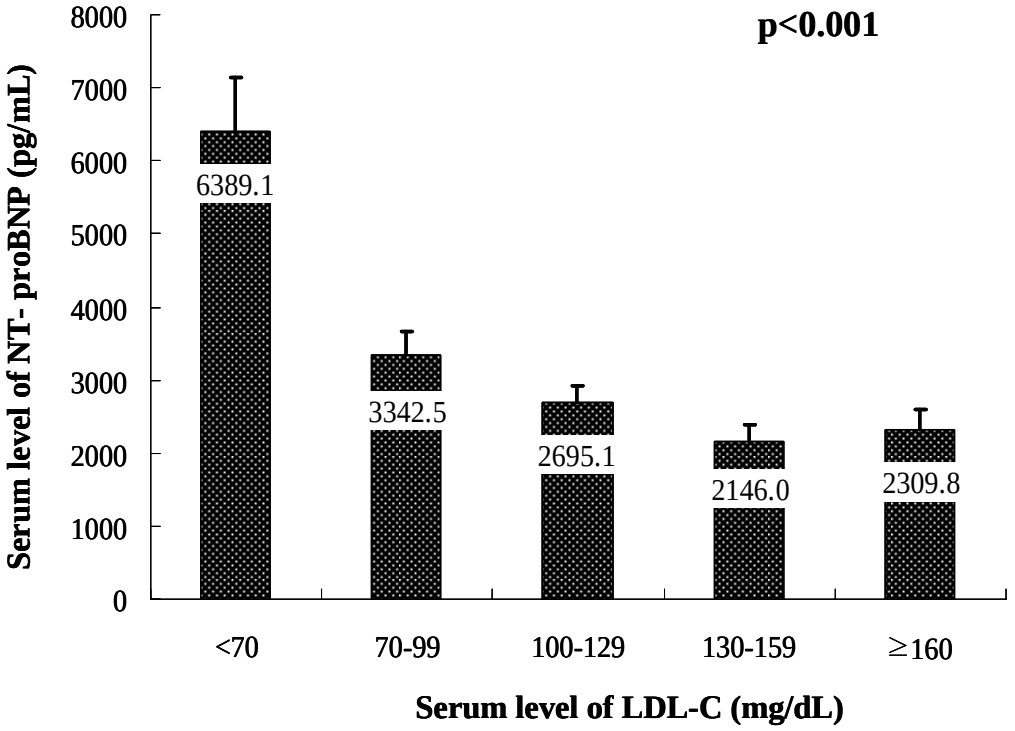
NSTEMI
STEMI

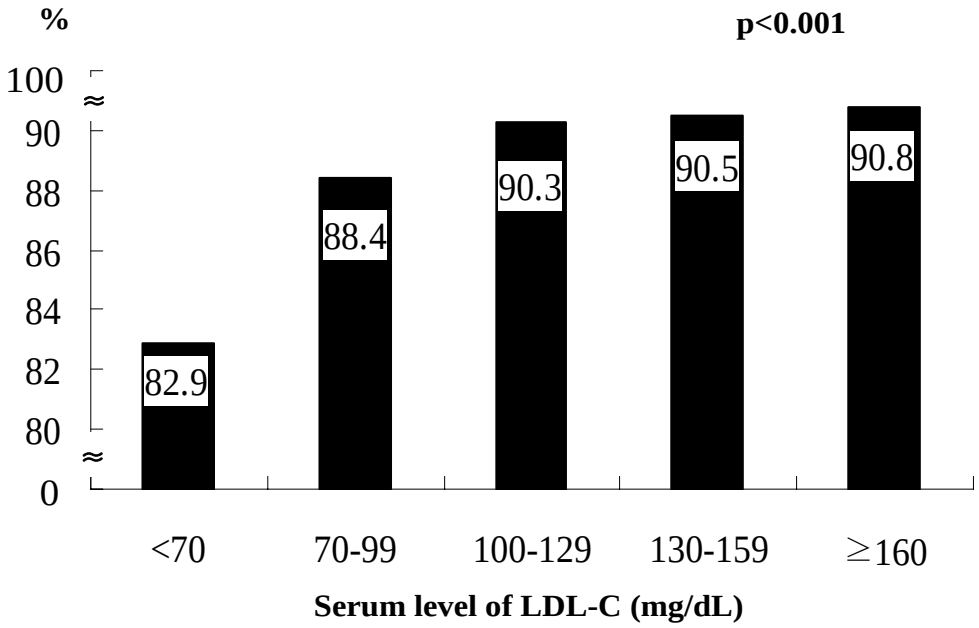
Cir J 2006;70:1372-1378

VH-IVUS analysis demonstrates that ACS patients with elevated NT-pro-BNP levels ≥ 200 pg/ml had more vulnerable plaque component (more necrotic core containing lesions and higher frequency of culprit lesion TCFAs) compared with ACS patients with NT-pro-BNP level < 200 pg/ml.

CNUH data, ESC abstract submitted

N-terminal pro-B-type natriuretic peptide was underlying the potential mechanism for obesity paradox in patients with acute myocardial infarction



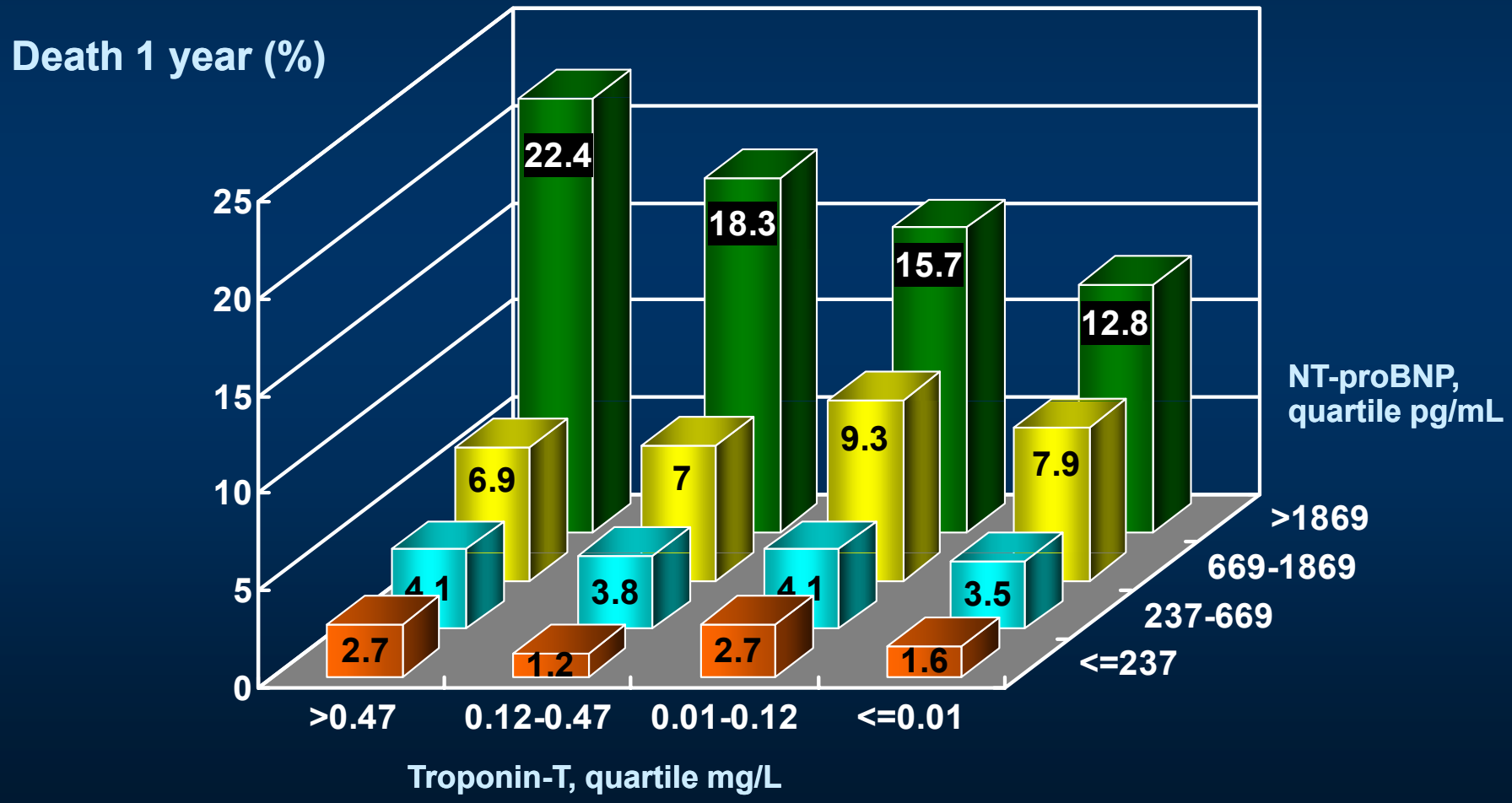


KAMIR data, Am J Cardiol submitted

MULTIMARKER APPROACH

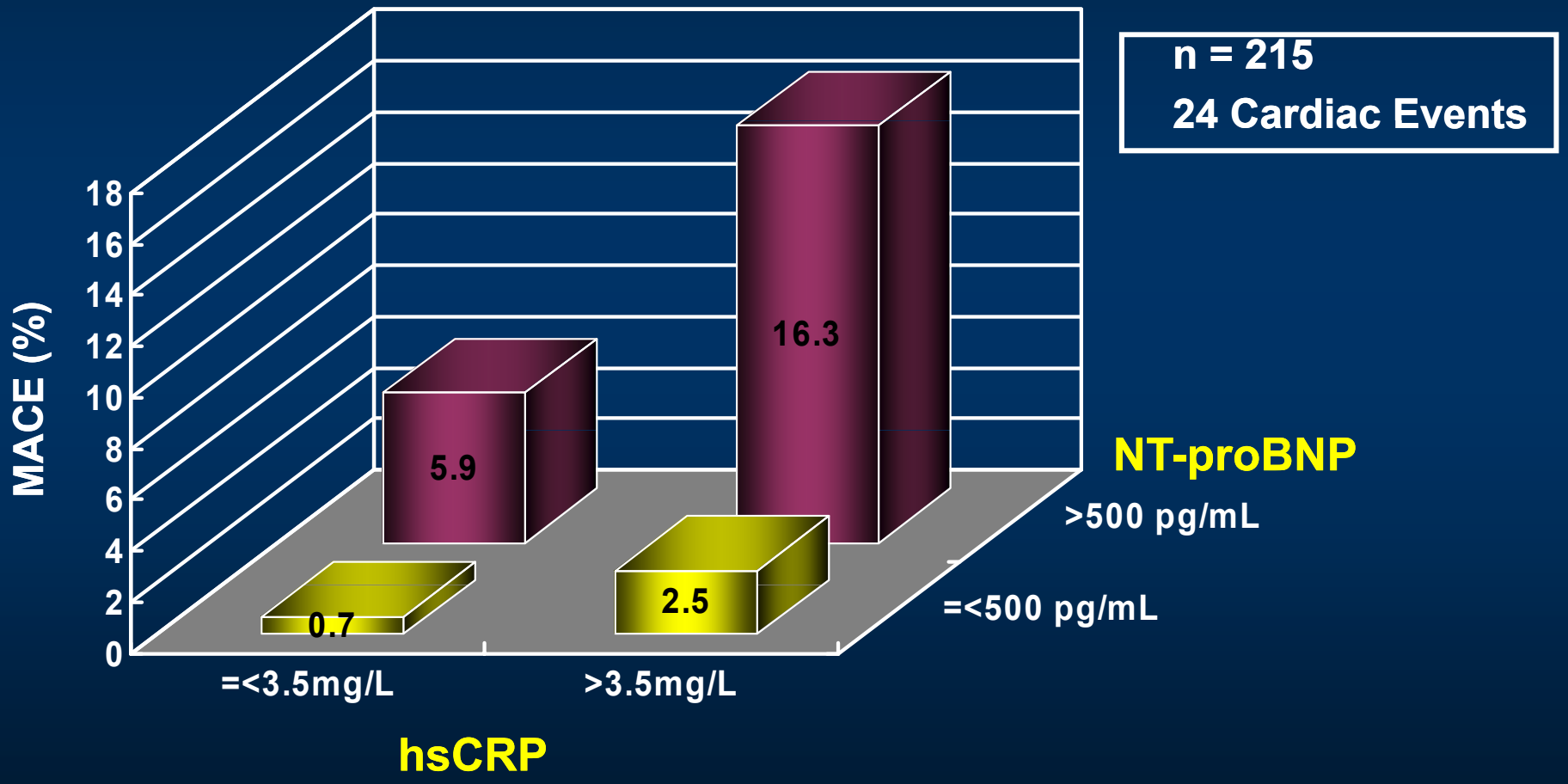
Relationship between Cardiac Markers and Cardiac Events in ACS

NT-proBNP at Median time of 9.5 H after symptom onset in 6809 patients



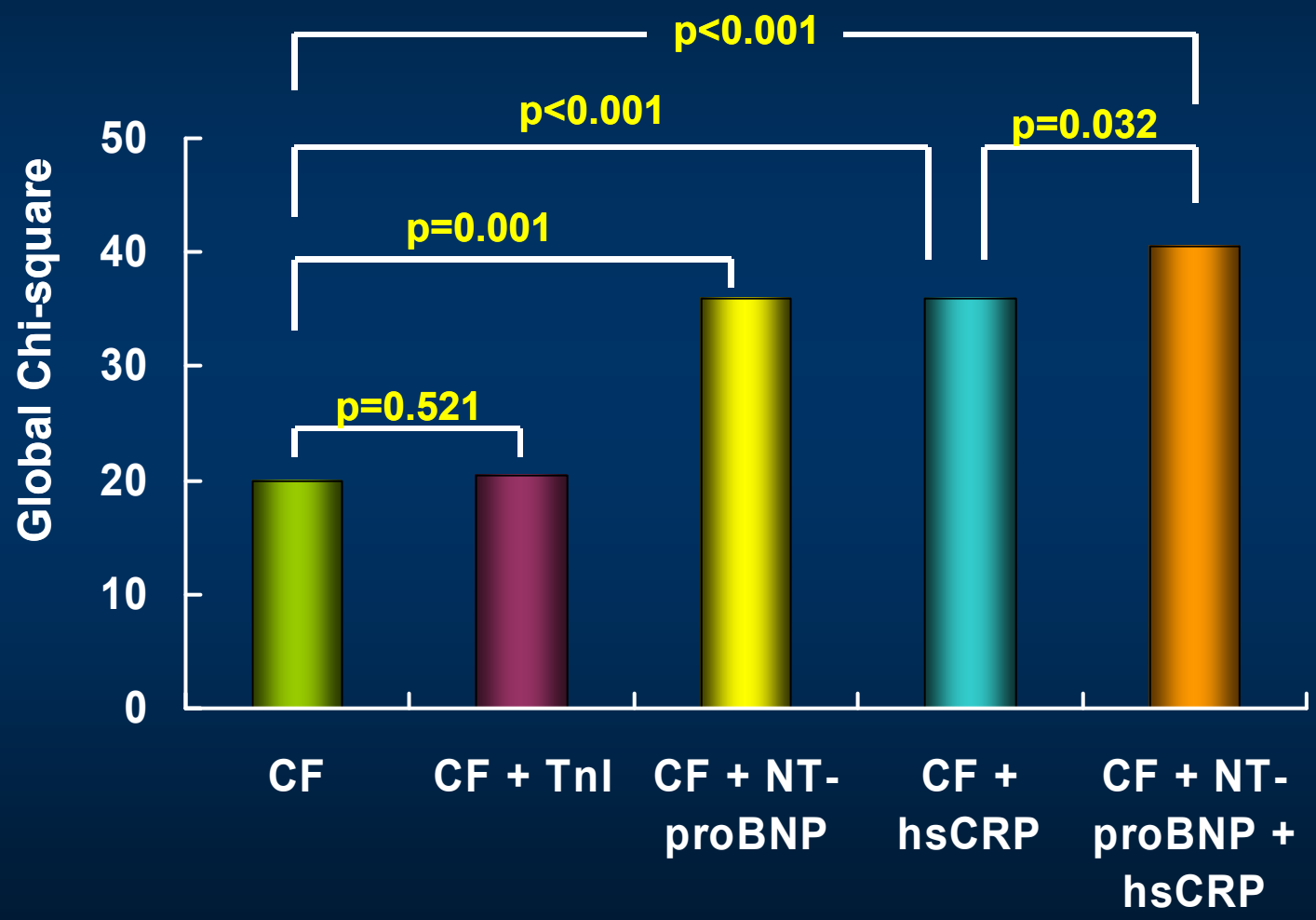
Circulation 2003;108:275-281

Relationship between Cardiac Markers and Cardiac Events in ACS



Cir J 2006;70:1379-1384

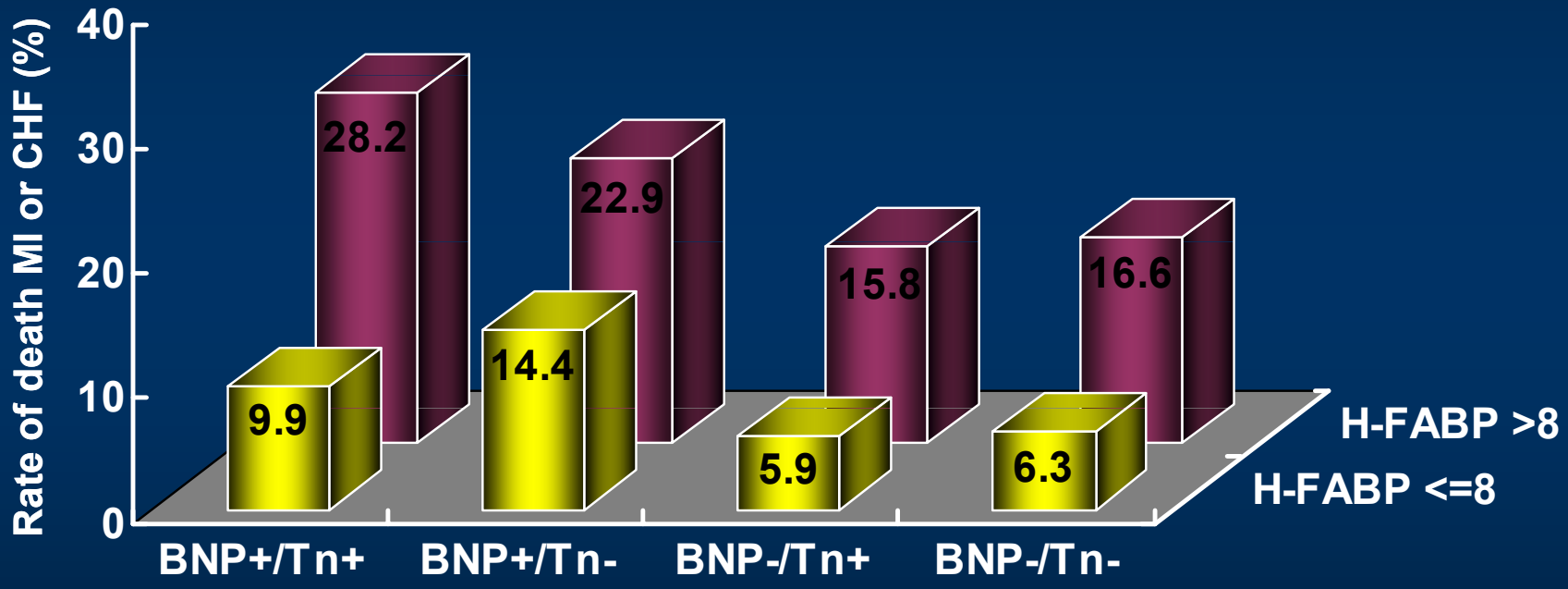
Incremental Prognostic Value of hsCRP and NT-proBNP in ACS



CF : Conventional factors

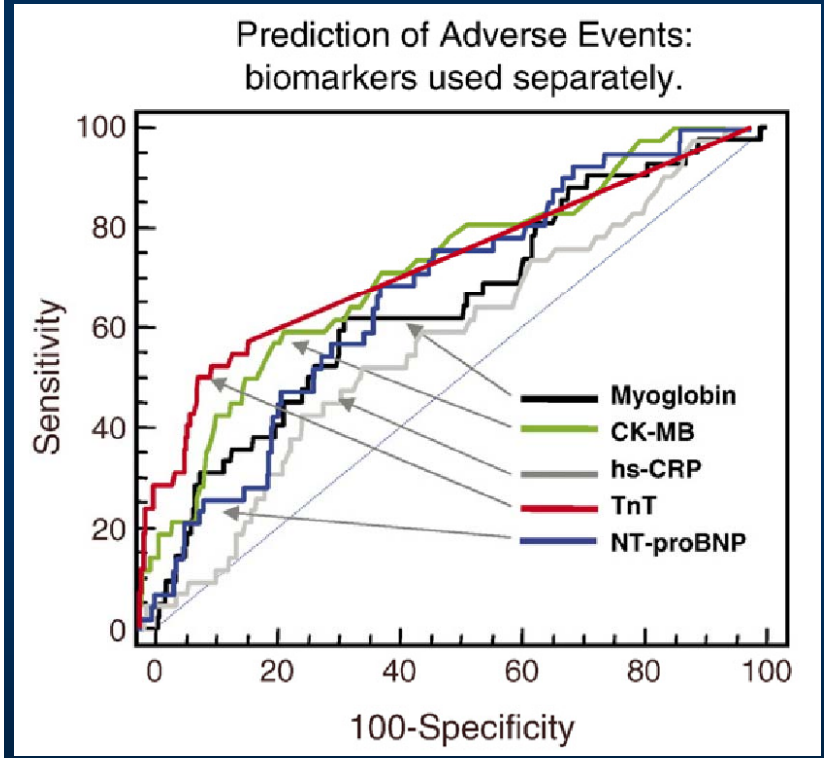
Cir J 2006;70:1379-1384

Incremental Prognostic Value of H-FABP in ACS Regardless of Baseline Troponin or BNP



Circulation 2006;114:550-557

Multi-Marker Approach for the Prediction of Adverse Events in ACS

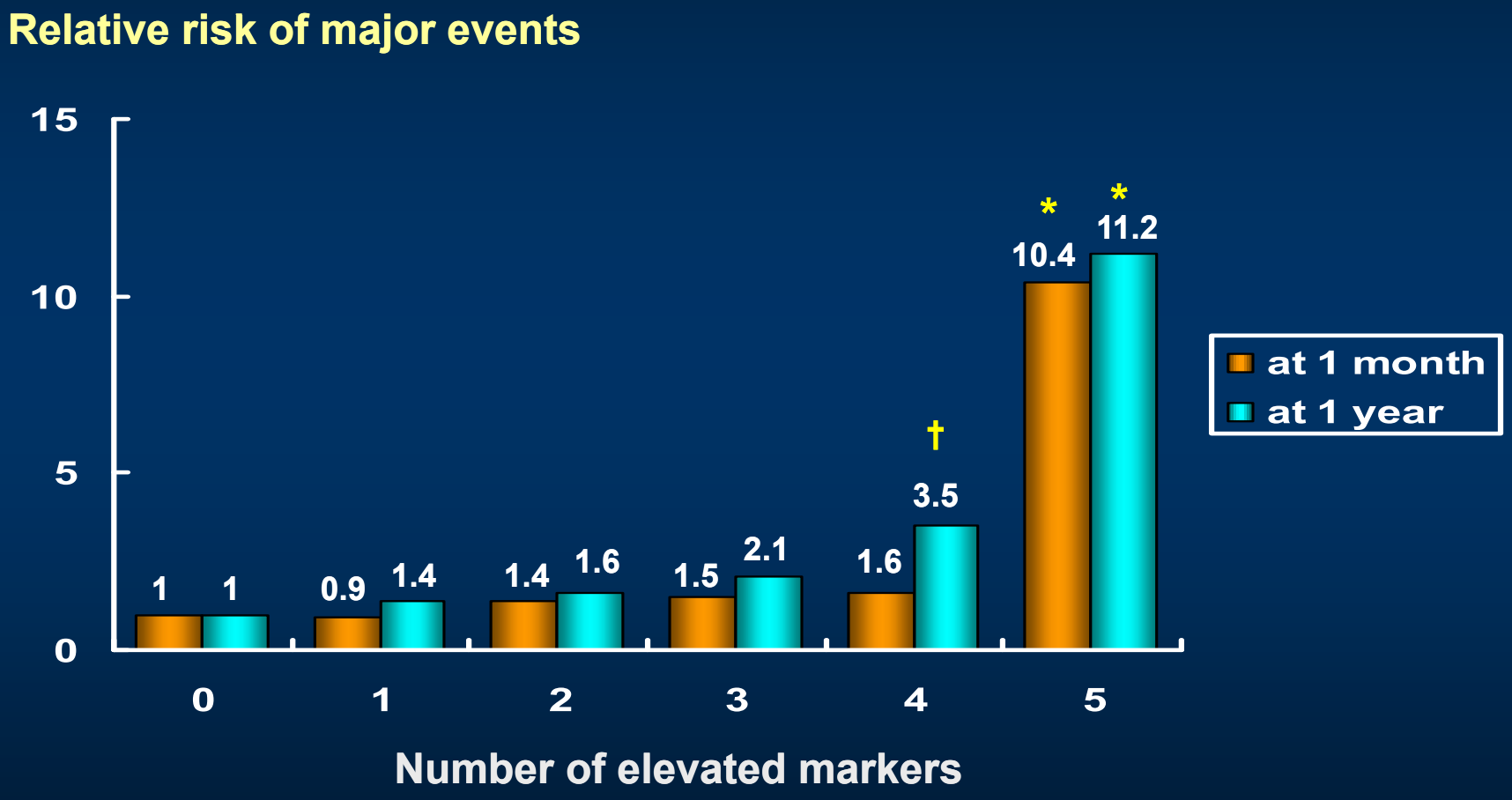


	cTnT + hsCRP	cTnT + NT-proB NP	cTnT + hsCRP + NT-proBNP	Five-marker panel
Sensitivity	66.7 (52.4-80.9)	78.6 (66.2-91.0)	81.0 (69.1-92.8)	88.0 (78.3-98.9)
Specificity	68.4 (63.7-73.1)	59.7 (54.8-64.7)	48.9 (43.9-54.0)	33.4 (28.7-38.2)
PPV	18.9 (12.6-25.2)	17.7 (12.3-23.2)	14.9 (10.2-19.5)	12.8 (8.9-16.6)
NPV	94.9 (92.3-97.5)	96.2 (93.7-98.6)	95.9 (93.1-98.7)	96.2 (93-99.5)
RR	3.7 (2.0-6.8)	4.7 (2.3-9.5)	3.6 (1.7-7.6)	3.4 (1.4-8.4)

Five panel: cTnT, hsCRP, NT-proBNP, CK-MB, Myocglobin

Clinica Chimica Acta 2007;376:168-173

Relative Risk of Presenting MACE Depending on the Number of Elevated Markes in ACS

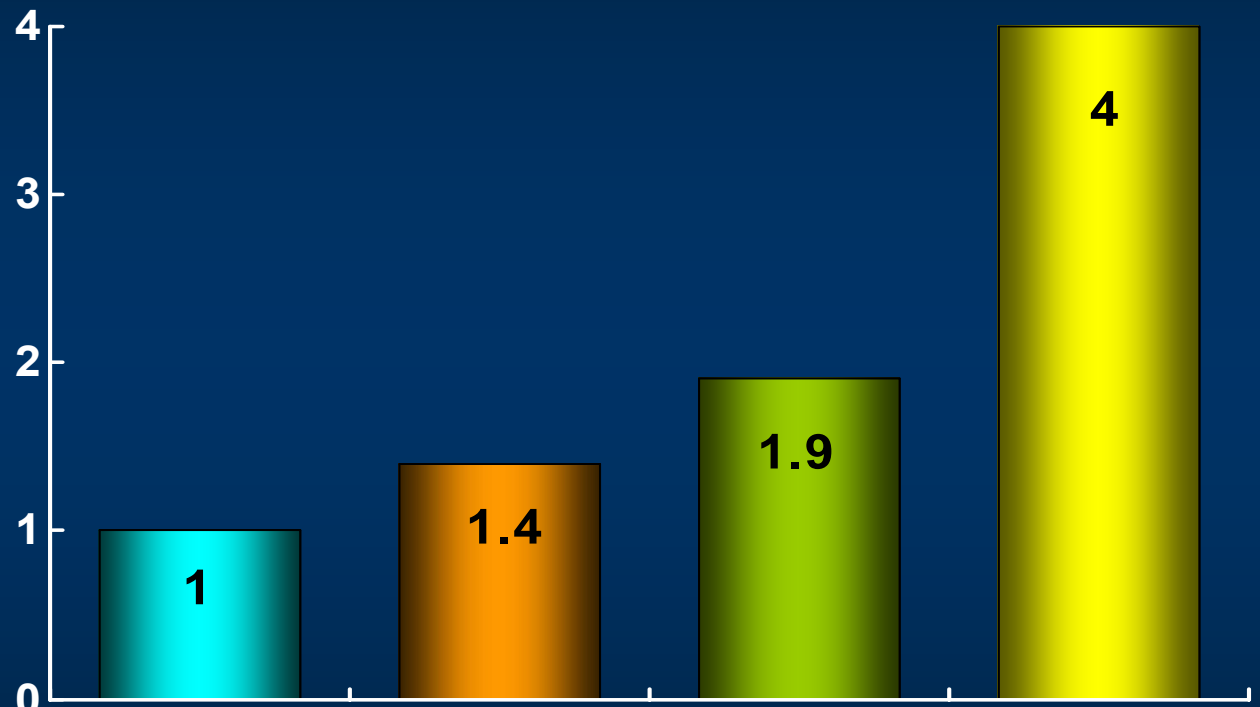


* p < 0.0001 between 5 elevated markers and all other cases

† p =0.01 between 4 and 0 elevated markers

Am Heart J 2005;149:268-274

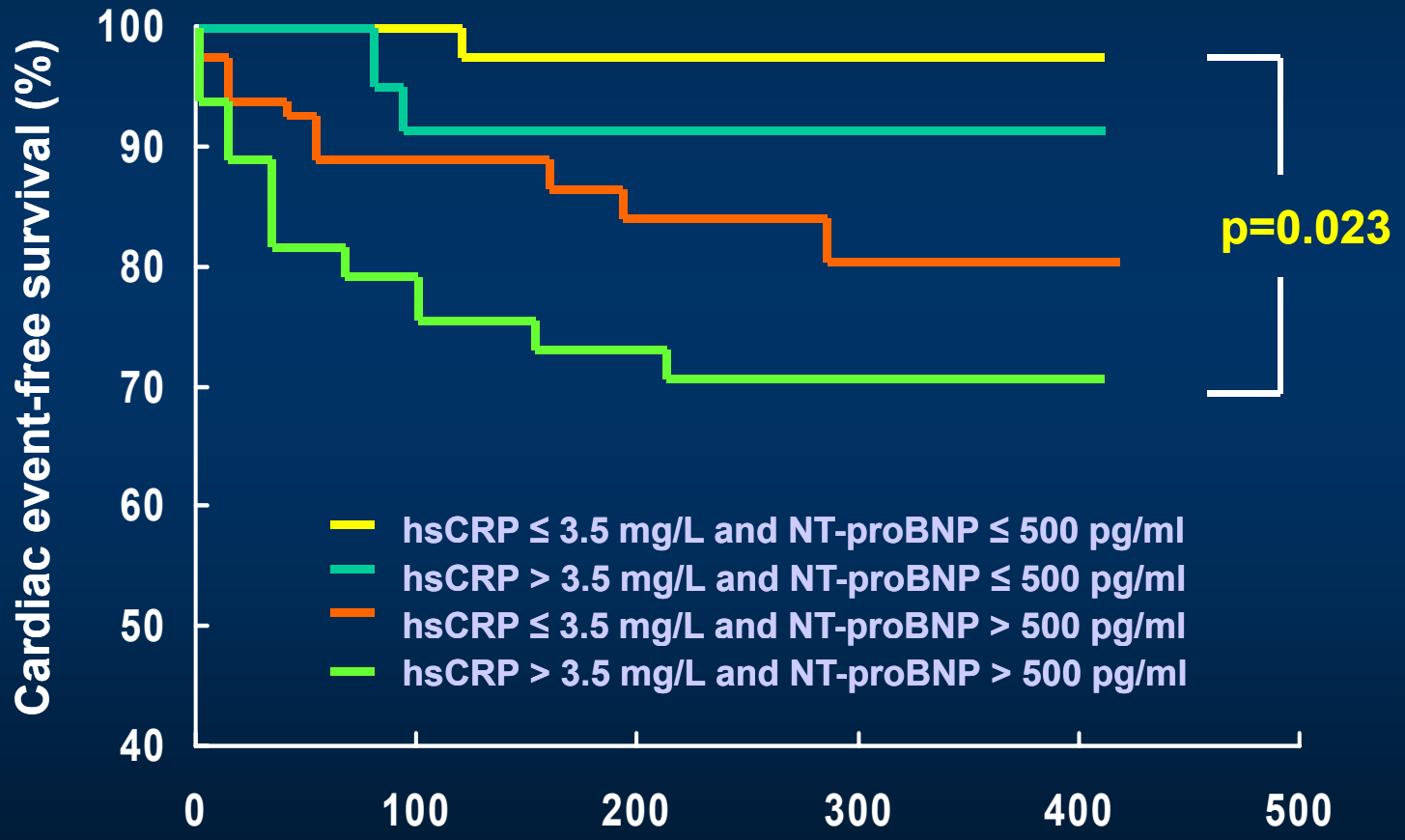
Hazard Ratio for Future Cardiovascular Events in Coronary Artery Disease



NT-proBNP (highest quartile >487.9 pg/mL)	-	-	+	+
hSCRP (highest quartile >6.1 mg/L)	-	+	-	+

Eur Heart J 2005;26:241-249

Cardiac Event Free Survival In ACS (Prognostic Value of hsCRP and NT-proBNP)



Cir J 2006;70:1379-1384

CONCLUSION

- Present and future for cardiac biomarker is exciting
- In the near future, many of these biomarkers will provide important new insights into pathophysiology and aid in the diagnosis and management of CV patients
- It is likely to be able to multiplex assays, personalizing biomarker strategies and providing large numbers of values quickly and cheaply