

*Instituto de Cardilogía de Corrientes*

# Biomarcadores en SCA



Dra. Stella Maris Macin



Marcadores disponibles



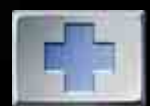
TnT



ProBNP



Otros



## Classical (well demonstrated) and some novel (or suggested) cardiovascular risk factors.

### ■ Classical risk factors (1, 2, 45, 46)

- Age
- Sex
- Positive family history for cardiovascular disease
- Systemic hypertension
- Smoking
- Dyslipidemia
- Exercise and obesity
- Insulin resistance and diabetes
- Mental stress and psychosocial factors
- Estrogenous status

### ■ Novel risk factors

- Cardiac specific troponins (cTnI, cTnT) (3–6)
- Natriuretic peptides (BNP, NT-proBNP) (7–9)
- Homocysteine (21, 30, 34, 36)
- Fibrinogen (21, 26)
- Lipoprotein(a) (22, 23)
- Microalbuminuria (33, 35)
- $\zeta$ -Glutamyltransferase (27)
- Angiotensin II (31)
- Uric acid (38)

### • Markers of coagulation and fibrinolytic function

- PAI-1 (21)
- t-PA (21)
- Clot lysis (21)
- d-Dimer (21)
- Factor V Leiden (21)

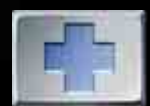
### • Markers of inflammation

- CRP (32)
- Adhesion molecules (VICAM, ICAM) (24)
- Proinflammatory cytokines (IL-6 and TNF $\alpha$ ) (28, 29)

### • Infectious agents

- Cytomegalovirus (40)
- Herpes simplex virus (40)
- *Chlamydia pneumoniae* (41)
- *Helicobacter pylori* (40)

PAI-1, plasminogen activator inhibitor-1; t-PA, tissue-type plasminogen inhibitor; CRP, C-reactive protein; VICAM, vascular intercellular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; IL-6, interleukin-6; TNF $\alpha$ , tumor necrosis factor- $\alpha$ .



Desirable pre-analytical, analytical and post-analytical features of **an ideal biomarker**.

- **Acceptable to patient**
- **Stability in vivo and in vitro**
- **Adequate analytical sensitivity (functional sensitivity)**
- **Good degree in reproducibility and accuracy**
- **Easy to perform**
- **Complete automation of assay**
- **International standardization**
- **Low cost**
- **Low biological variation**
- **Reference range and cut-off values tested for gender, age, and ethnicity dependence**
- **Good diagnostic and prognostic accuracy**
- **Cost-benefit ratio favorable**



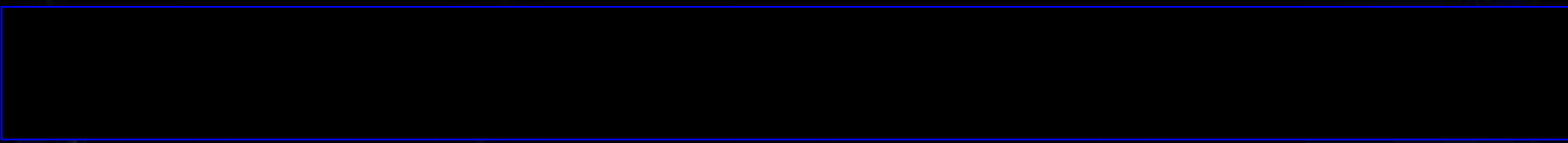
❖ Biomarkers that have either proven or potential utility in acute coronary syndromes.

- Markers of ischemia
- Troponin
- Myoglobin
- Ischemia-modified albumin
- Hemodynamic markers
- N-terminal pro-brain natriuretic peptide
- Brain natriuretic peptide
- Inflammatory markers
- High-sensitivity C-reactive protein
- Myeloperoxidase
- Placental growth factor
- Soluble CD40 ligand
- Interleukin-10
- Interleukin-6
- Monocyte chemoattractant protein-1

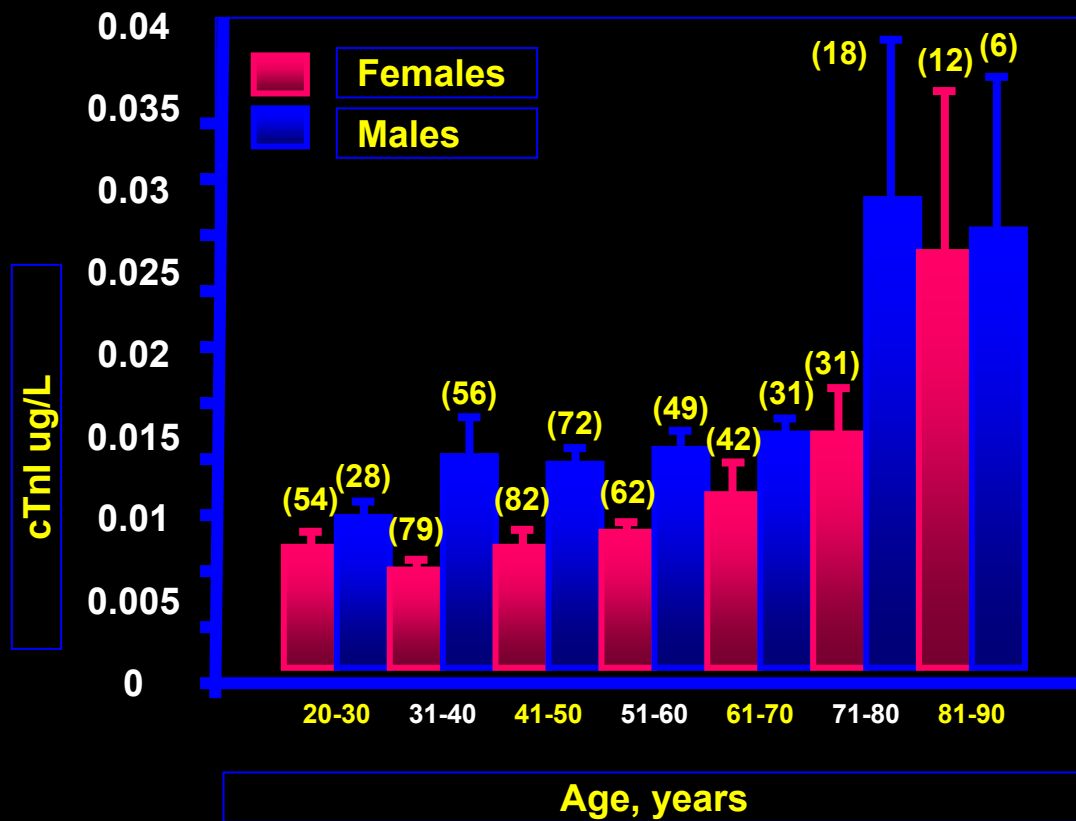


# Clinical utility-based classification of cardiac biomarkers

Inflammation and plaque destabilization	Ischemia	Early necrosis	Intermediate/late necrosis	Heart failure
C-reactive protein (CRP) hs-CRP	Ischemia-modified albumin	Myoglobin	CK-MB	Brain natriuretic peptide (BNP)
Myeloperoxidase	Glycogen phosphorylase enzyme BB (GPBB)	Creatinine kinase MB isoforms-CKMB2	Cardiac troponins (cTn) cTnT cTnI	Terminal fragment of prohormone of BNP
Matrix metalloproteinases Soluble CD-40L (sCD40L) Pregnancy-associated plasma protein A	Free fatty acids Fatty acid binding proteins Phospholipase enzymes (A-D) Lipoprotein associated phospholipase A2			
Placenta growth factor Interleukin-6				

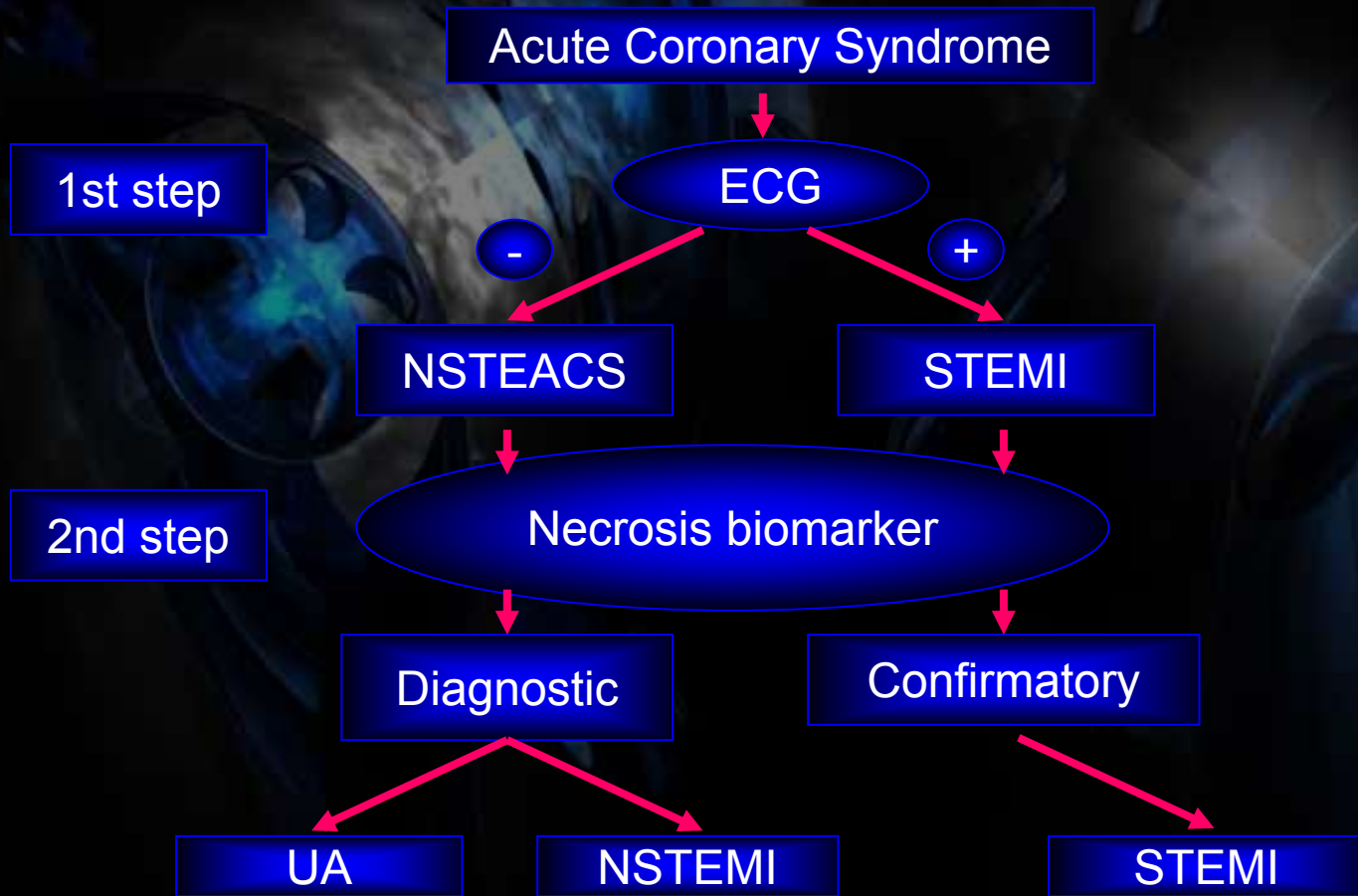


# Distribution of cTnI values in healthy adult subjects divided according to gender and age



February 23, 2004





**Categorization and differential diagnosis of acute coronary syndromes (ACSs). UA, unstable angina; NSTEMIACS, clinical conditions with ST segment depression, T-wave changes, or no electrocardiogram (ECG) abnormalities (non-ST elevation ACS); NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, acute ST-segment elevation myocardial infarction according to Morrow et al. (92)x. The symbol “q” in the circle indicates an ECG with ST-segment elevation, while the symbol “-” in the circle indicates an ECG without ST-segment elevation.**



The most frequent clinical conditions in which the circulating levels of cardiac troponins are increased, **without** overt artery coronary disease.

- Myocarditis/pericarditis
- Congestive heart failure
- Systemic arterial hypertension
- Systemic arterial hypotension
- Especially if associated with cardiac arrhythmias
- Critically ill patients
- Hypothyroidism
- Cardiac trauma
- Myocardial toxicity from cancer therapy
- Pulmonary embolism
- Episode rejection of a cardiac transplant
- Postoperative non-cardiac surgery
- Chronic renal failure
- Amyloidosis
- Sepsis



The most frequent clinical conditions in which the circulating levels of cardiac troponins are increased, **without** overt artery coronary disease.

Comparison of ANP, BNP and CNP biological characteristics.

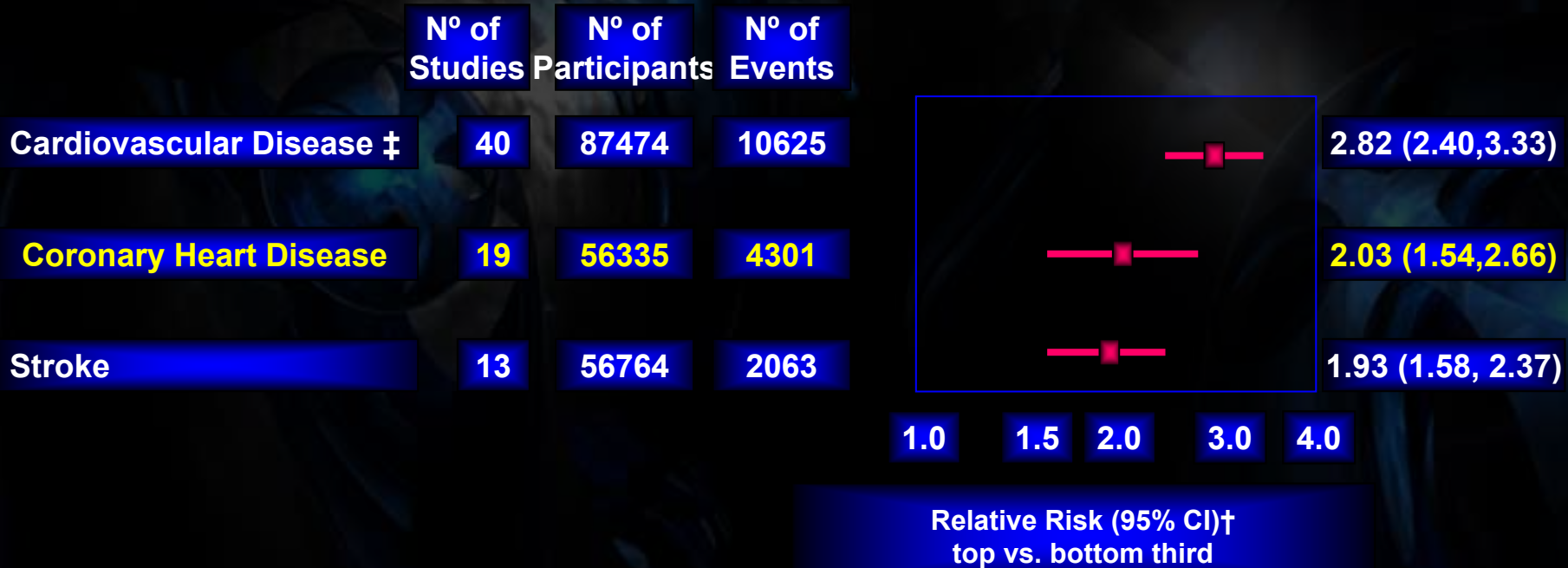
Precursor	pro-ANP		pro-BNP		pro-CNP	
Main synthesis site	Heart		Heart		Endothelial vessels	
Molecules in blood	ANP	NT-proANP	BNP	NT-proBNP	CNP	NT-proCNP
Amino acids	28	98	32	76	CNP-22 (CNP <sub>82-103</sub> ) CNP-53 (CNP <sub>51-103</sub> )	50
Weight, Da	3078	10,615	3462	8457	2199 5802	~5000
Biological activity	Yes	Not yet found	Yes	Not yet found	Yes Yes	Not yet found
Plasma half-life, min	2-4	40-50	15-25	60-120	1-3	Unknown
Mean±SD, ng/L	17.8±10.6		10.0±8.6	50.0±35.9		
Range, ng/L <sup>a</sup>	0.5-63.9		0.4-44.4	6.7-178.7		
97.5th percentile, ng/L <sup>a</sup>	44.9		33.1	158.3		



Some common diseases, in which plasma **cardiac natriuretic peptides** have been found to be altered, compared to healthy subjects.

Diseases	Hormone levels
A) Cardiac diseases	
Heart failure	↑ ↑
AMI (first 2–3 days)	↑ ↑
Essential hypertension with CMP	↑
B) Pulmonary diseases	
Acute dyspnea	↑
Obstructive pulmonary disease	↑
C) Endocrine-metabolic diseases	
Hyperthyroidism	↑
Hypothyroidism	=or ↓
Cushing's syndrome	↑
Primary aldosteronism	↑
Addison's disease	=or ↑
Diabetes mellitus	=or ↑
D) Liver cirrhosis with ascites	↑
E) Renal failure (acute or chronic)	↑ ↑
F) Paraneoplastic syndrome	=or ↑
G) Subarachnoid hemorrhage	↑
H) Inflammatory diseases (acute or chronic)	↑
I) Use of cardiotoxic drugs	↑

# Metaanálisis (9 ensayos con BNP o proBNP)

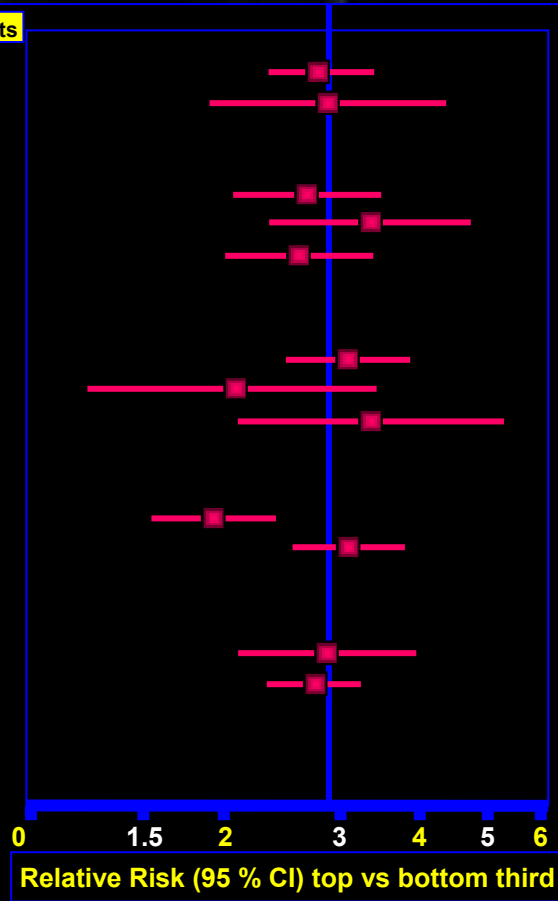


Relative risk for CVD in individuals in the top vs bottom third of baseline BNP or NT-proBNP levels. From random effects meta-analysis. Nineteen studies did not report estimates for CHD and stroke separately. Assessment of heterogeneity: cardiovascular disease:  $I^2$ , 83; 95% CI, 77 to 87;  $P < 0.0001$ ; CHD:  $I^2$ , 88; 95% CI, 83 to 92;  $P < 0.001$ ; stroke:  $I^2$ , 55; 95% CI, 15 to 76;  $P < 0.001$ .



# Relative risks for CVD in individuals in the top vs bottom third of baseline BN or NT-proBNP according to different study level characteristics.

Subgroup	N° of Studies	N° of CVD events
NT - proBNP	33	9940
BNP	7	685
<b>Baseline Population</b>		
General Population	11	1271
Defined by having elevated CVD risk factors	11	2040
With manifest stable CVD	18	7314
<b>Location ¶</b>		
Europe	23	7901
North America	6	930
Asia Pacific	7	511
<b>Events, n°</b>		
≥ 250	6	7329
< 250	34	3296
<b>Average follow up</b>		
≥ 5 years	16	6471
1 – 5 years	24	4154

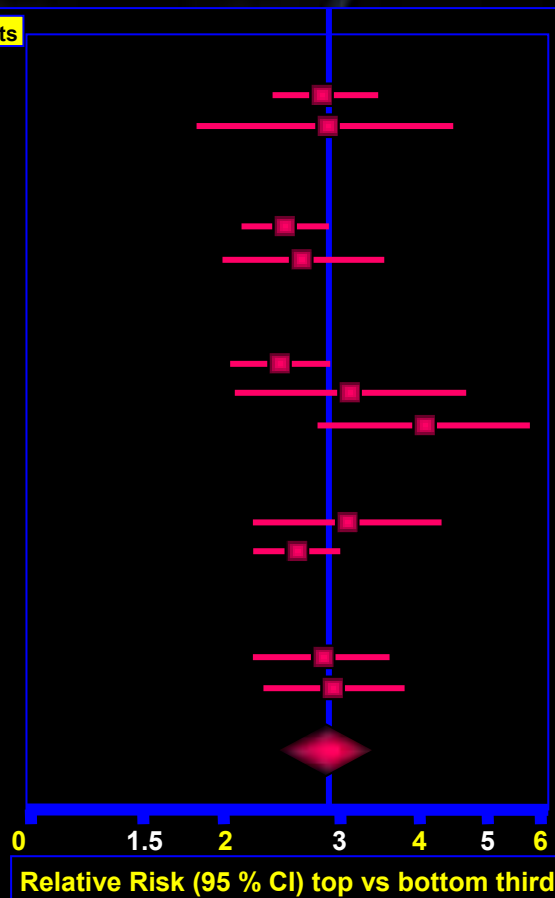


$P > 0.05$  from meta-regression analyses on each of the covariates unless otherwise specified. Four multicenter studies were excluded. \* $P = 0.011$  from meta-regression analysis. Levels of adjustment in multivariate models. Adjusted for conventional cardiovascular factors (ie, age, sex, smoking, history of diabetes mellitus, blood pressure [and/or history of hypertension], total cholesterol [or non-high-density lipoprotein cholesterol], and high-density lipoprotein cholesterol). Further adjusted for other potential risk factors (ie, further adjustment for serum creatinine, left ventricular ejection fraction, or C-reactive protein). Five studies did not specify sample type.



# Relative risks for CVD in individuals in the top vs bottom third of baseline BNP or NT-proBNP according to different study level characteristics.

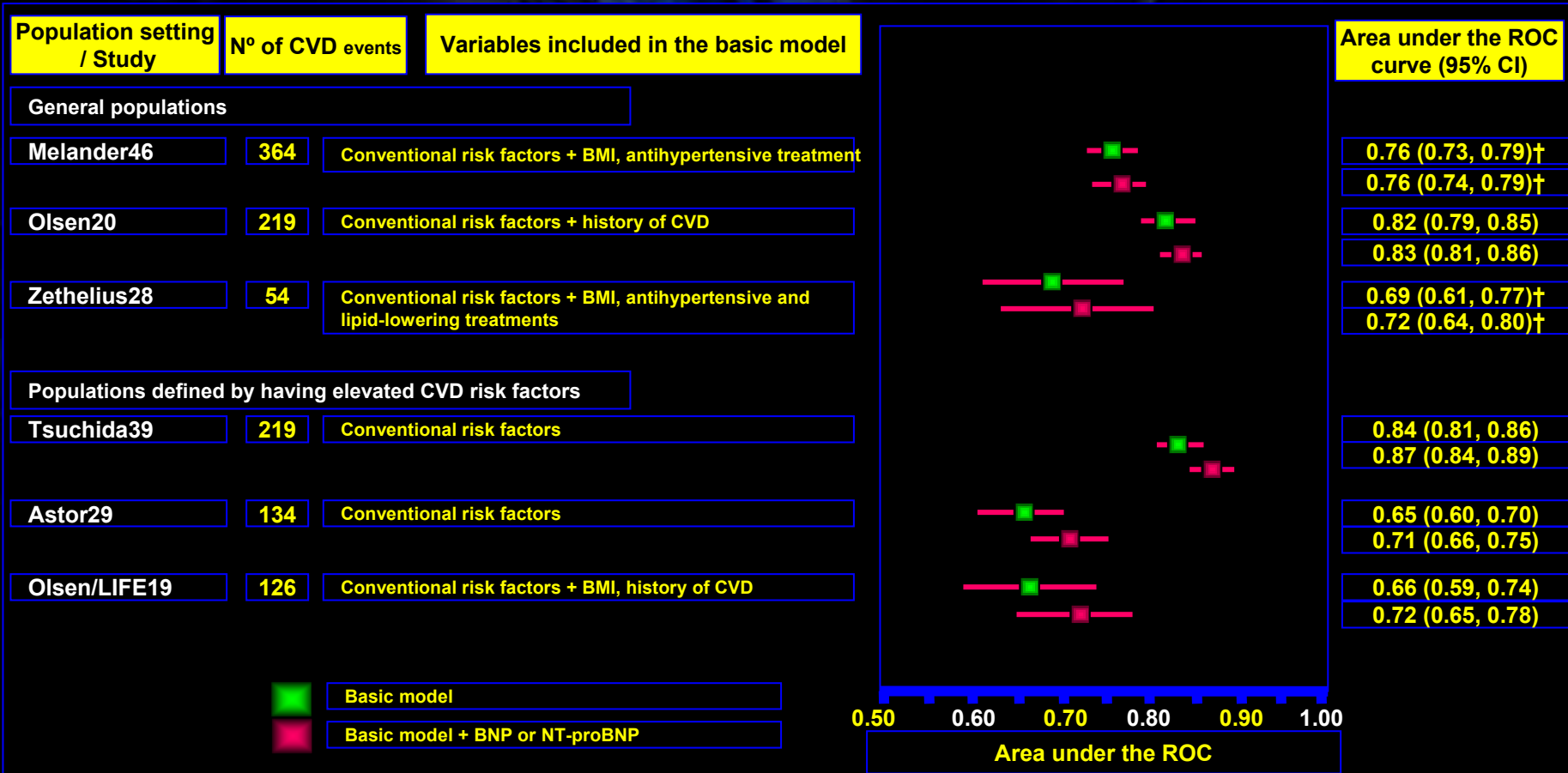
Subgroup		N° of Studies	N° of CVD events
Adjustment ‡	++	33	10017
	+	7	608
Sample type†	Plasma	32	8588
	Serum	3	414
Storage temperature	< -70°	26	8236
	-20° / Unspecified	8	796
	Fresh	6	1593
Data source	Tabular data from investigators	17	6665
	Data from publication	23	3960
Heart failure included in CVD endpoint	No	19	7208
	Yes	21	3417
Overall		40	10625



.  $P > 0.05$  from meta-regression analyses on each of the covariates unless otherwise specified. ¶¶ Four multicenter studies were excluded. \* $P = 0.011$  from meta-regression analysis. Levels of adjustment in multivariate models. Adjusted for conventional cardiovascular factors (ie, age, sex, smoking, history of diabetes mellitus, blood pressure [and/or history of hypertension], total cholesterol [or non-high-density lipoprotein cholesterol], and high-density lipoprotein cholesterol). Further adjusted for other potential risk factors (ie, further adjustment for serum creatinine, left ventricular ejection fraction, or C-reactive protein). Five studies did not specify sample type.



# Relative risks for CVD in individuals in the top vs bottom third of baseline BN or NT-proBNP according to different study level characteristics.

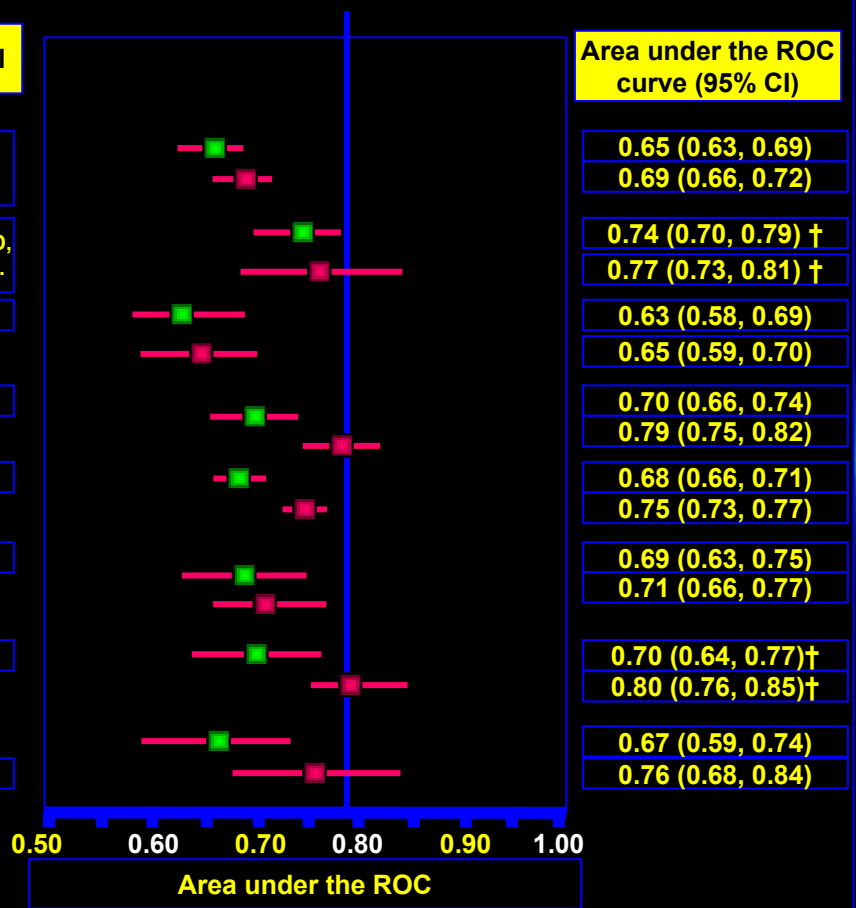


Increment in risk prediction ability by adding BNP or NT-proBNP for cardiovascular disease. Conventional risk factors include age, sex (when appropriate), smoking, history of diabetes mellitus, blood pressure (and/or history of hypertension), total cholesterol (or non-high-density lipoprotein cholesterol), and high-density lipoprotein cholesterol. BMI indicates body mass index; WHR, waist-to-hip ratio; and ROC, receiver-operating characteristic curve. C index (95% CI).



Increment in risk prediction ability by adding BNP or NT-proBNP for cardiovascular disease. Conventional risk factors include age, sex (when appropriate), smoking, history of diabetes mellitus, blood pressure (and/or history of hypertension), total cholesterol (or non-high-density lipoprotein cholesterol), and high-density lipoprotein cholesterol

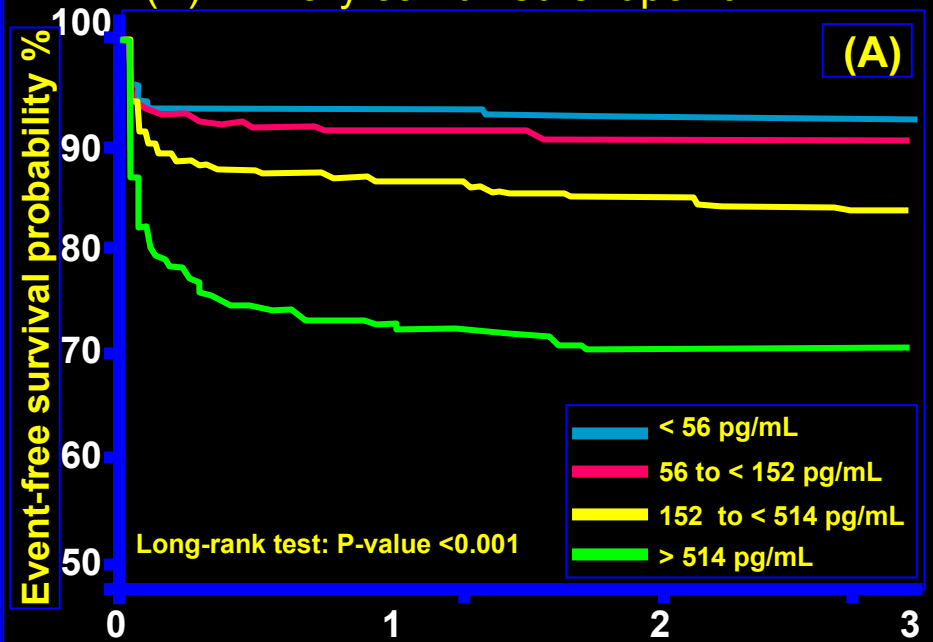
Population setting / Study	N° of CVD events	Variables included in the basic model
<b>Populations with manifest stable CVD</b>		
Blankenberg41	501	Conventional risk factors + WHR, glucose level, renal function, antihypertensive and lipid-lowering treatments
Omland43	431	Convent. risk factors + BMI, renal function, history of CVD, C-reactive protein, antihypertensive & lipid-lowering treat.
Lindahl16	143	Conventional risk factors
Bibbins-Domingo30	142	Conventional risk factors
Marz17	129	Conventional risk factors
Rothenbacher23	95	Conventional risk factors + lipid-lowering treatments
Pfister21	71	Conventional risk factors
Dai35	56	Conventional risk factors + lipid-lowering treatments
		Basic model
		Basic model + BNP or NT-proBNP



# Survival curves for N-terminal pro-brain natriuretic peptide quartiles.

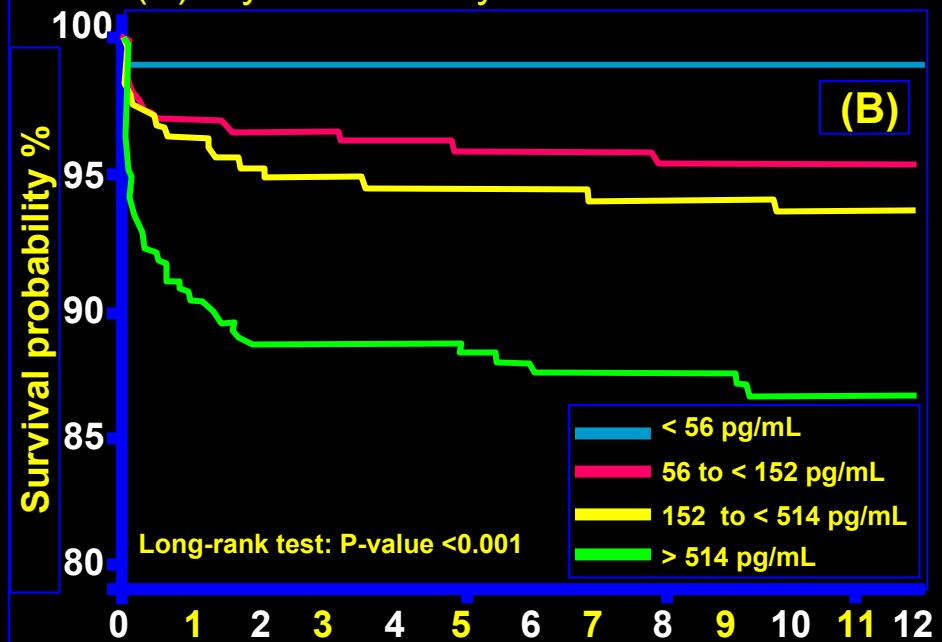


(A) Primary combined endpoint.



Patients at risk	Months since Randomization			
	0	1	2	3
<56 pg/mL	256	239	236	236
56to<152pg/mL	253	231	228	228
152to<514pg/mL	260	225	220	217
>514pg/mL	259	189	181	181

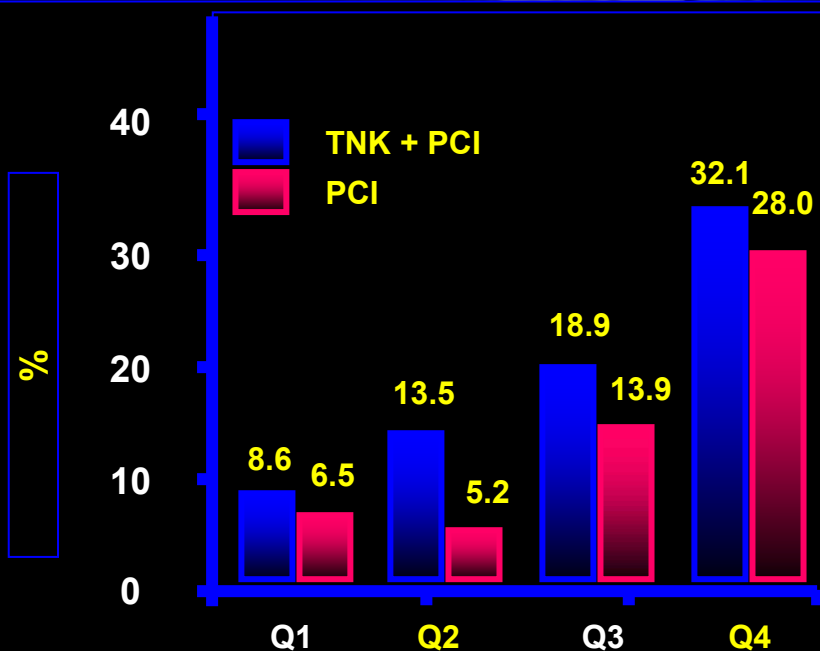
(B) 1-year mortality



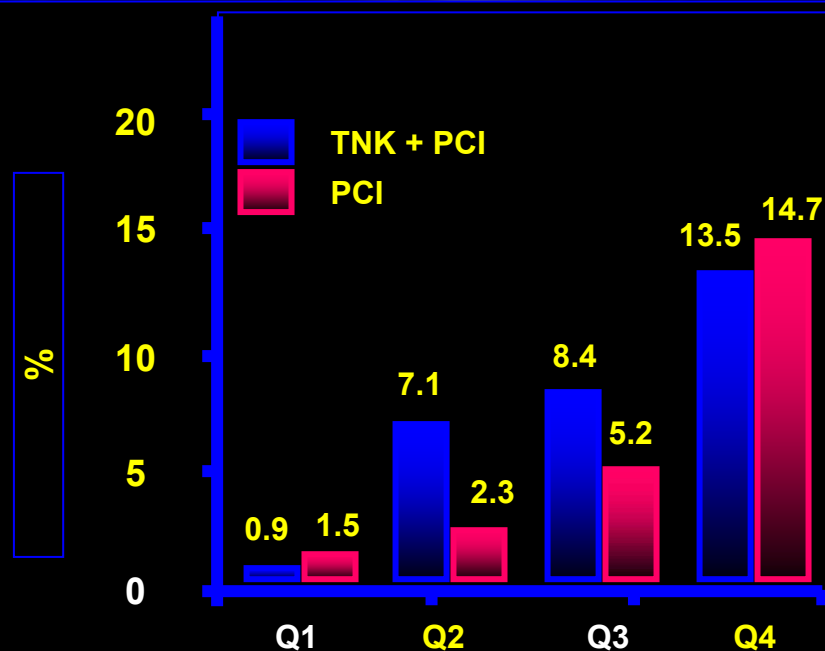
Survival probability %	Months since Randomization												
	0	1	2	3	4	5	6	7	8	9	10	11	12
< 56 pg/mL	256	252	243	243	241	241	241	241	241	241	241	241	241
56 to < 152 pg/mL	253	243	233	232	231	230	230	230	230	230	230	230	230
152 to < 514 pg/mL	260	247	232	232	231	230	230	230	230	230	230	230	230
> 514 pg/mL	259	228	219	217	216	214	214	214	214	214	214	214	214

**Ninety-day combined endpoint and (B) 1-year mortality rates according to treatment allocation and N-terminal pro-brain natriuretic peptide value.**

**(A)** 90 day combined endpoint



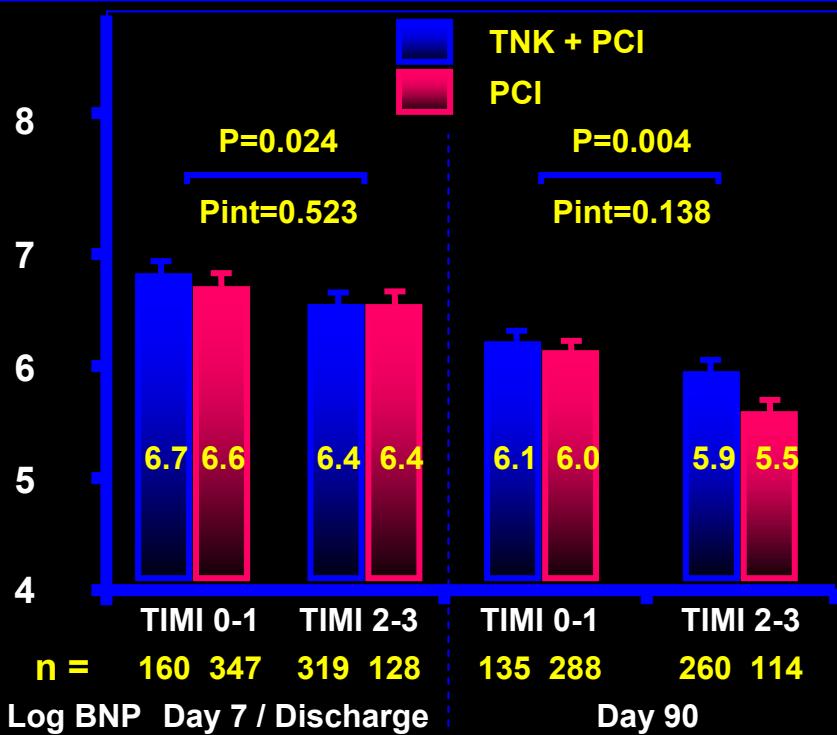
**(B)** One year mortality



**There was no significant interaction between treatment and N-terminal pro-brain natriuretic peptide (P = 0.499 and P = 0.390, respectively).**

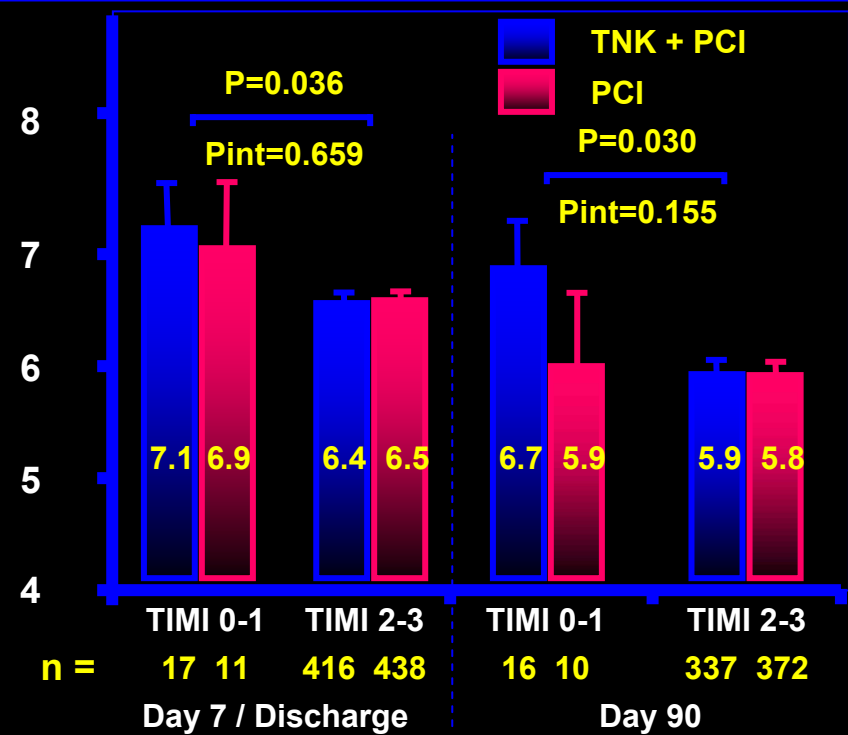
(A)

TIMI flow before PCI



(A)

TIMI flow after PCI



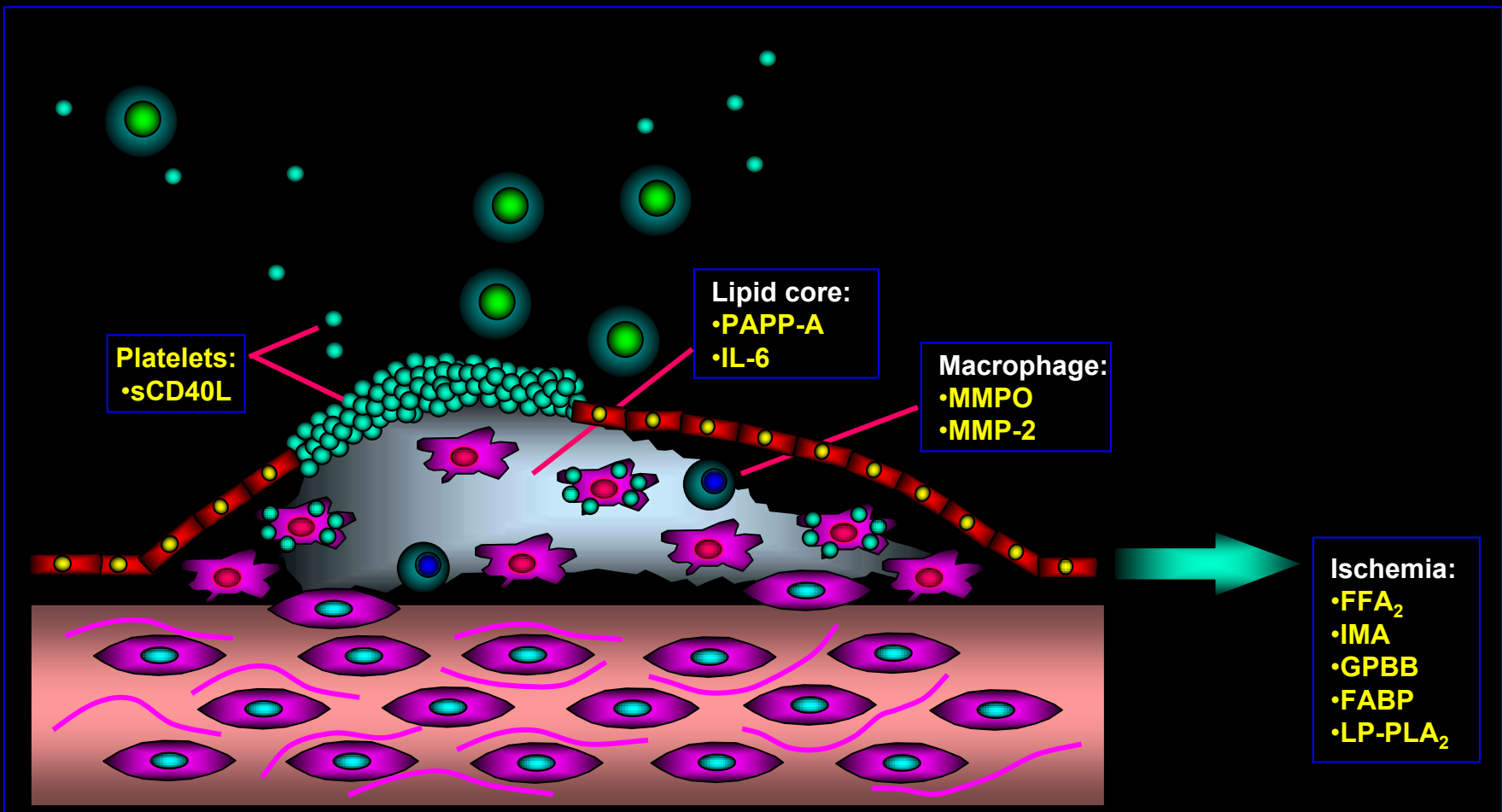


**Stepwise Cox regression model showing associations between significant baseline clinical variables and hazard ratios for all-cause mortality in 870 patients admitted with chest pain**

	<b>Multivariable analysis <sup>a</sup></b>		
	<b>BNP included in analysis (excluded XIIaA)</b>	<b>XIIaA included in analysis (excluded BNP)</b>	<b>Both XIIaA and BNP included in analysis</b>
	<b>Hazard ratio (95% CI)</b>		
BNP quartile 4 vs. quartile 1–3	<b>1.78 (1.24–2.55)</b>		
XIIaA quartile 4 vs. quartile 1–3		<b>1.43 (1.01–2.03)</b>	
XIIaA and BNP in quartile 4 vs. Quartile 1-3			<b>2.30 (1.51–3.50)</b>
Age	<b>1.07 (1.05–1.10)</b>	<b>1.08 (1.06–1.10)</b>	<b>1.08 (1.06–1.10)</b>
History of CHF	<b>1.47 (1.03–2.10)</b>		
NYHA III		<b>2.19 (1.44–3.35)</b>	<b>2.38 (1.50–3.77)</b>
Index diagnosis STEMI			<b>1.82 (1.05–3.15)</b>
Admission TnT>0.01 ng/mL	<b>2.07 (1.38–3.09)</b>	<b>2.21 (1.48–3.29)</b>	<b>1.88 (1.21–2.92)</b>

**XIIaA, activated factor XII type A; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CI, confidence interval; NYHA, New York Heart Association class; STEMI, ST-elevation myocardial infarction; TnT, troponin T. a Independent predictors following adjustment for all the baseline variables on admission.**

# Biomarkers for plaque destabilization and ischemia.

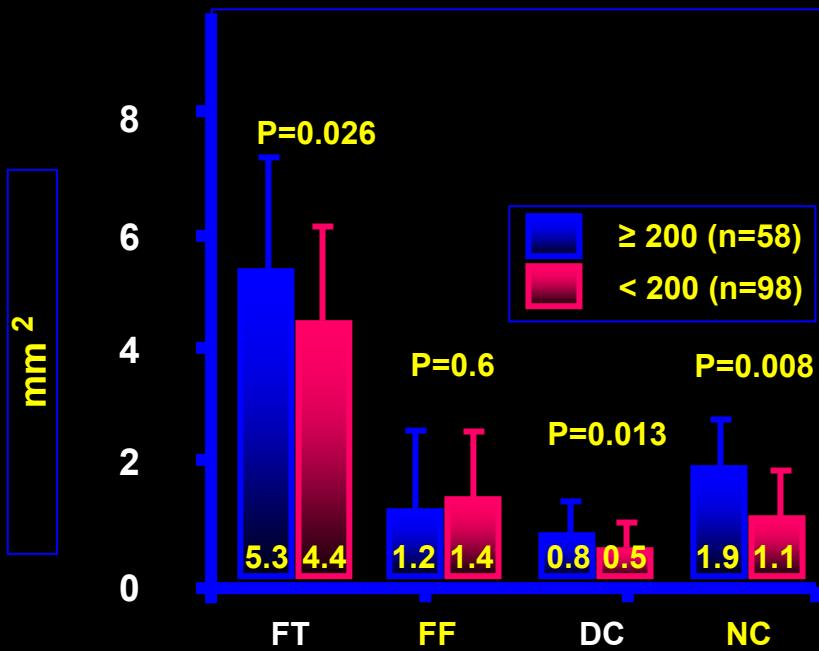


FABP, fatty acid binding protein; FFA, free fatty acids; GPBB, glycogen phosphorylase enzyme BB in brain; IL-6, interleukin-6; IMA, ischemia-modified albumin; LP-PLA<sub>2</sub>, lipoprotein-associated phospholipase A<sub>2</sub>; MMP, matrix metalloproteinase; PAPP-A, pregnancy-associated plasma protein A; sCD40L, soluble CD40 ligand.

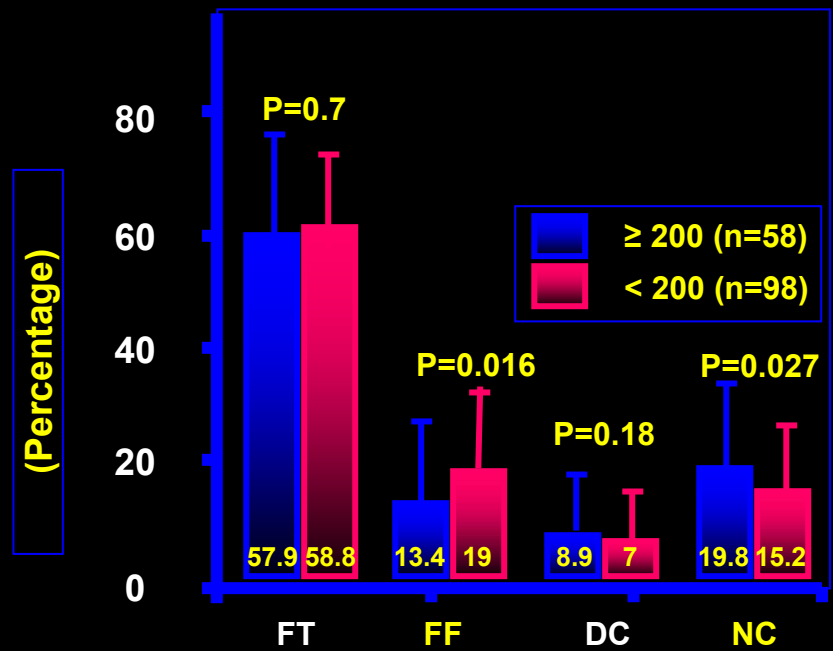


# The absolute (a) and relative (b) plaque components at the minimum lumen site.

**(A)** Minimum lumen site absolute plaque area



**(B)** Minimum lumen site relative plaque area



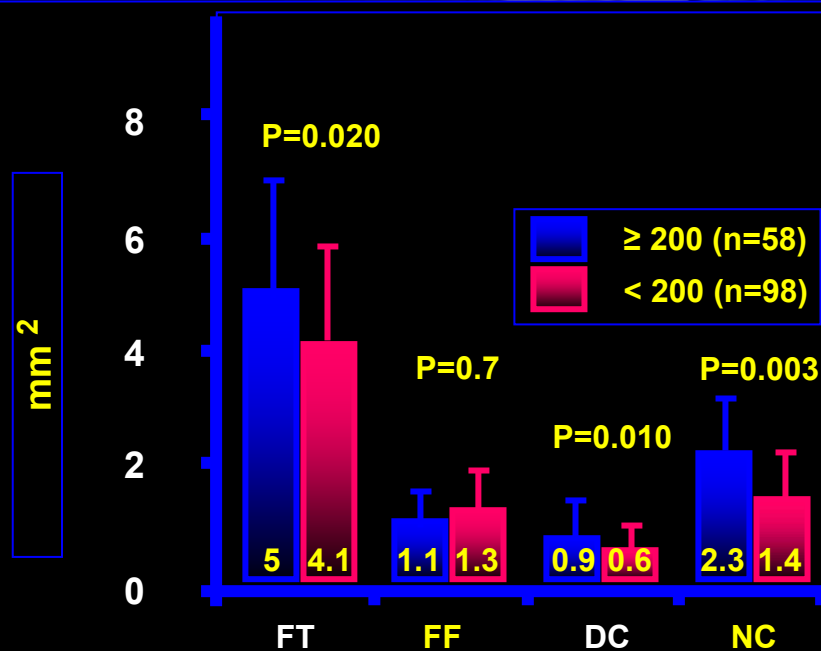
Virtual histology-intravascular ultrasound analysis classified the color-coded tissue into four major components: green [fibrotic (FT)]; yellow-green [fibro-fatty (FF)]; white [dense calcium (DC)]; and red [necrotic core (NC)]. At the minimum lumen site, the absolute and relative NC areas, absolute DC area, and absolute FT area were significantly greater in group I than in group II; conversely the relative FF area was significantly smaller in group I than in group II.

(Percentage)

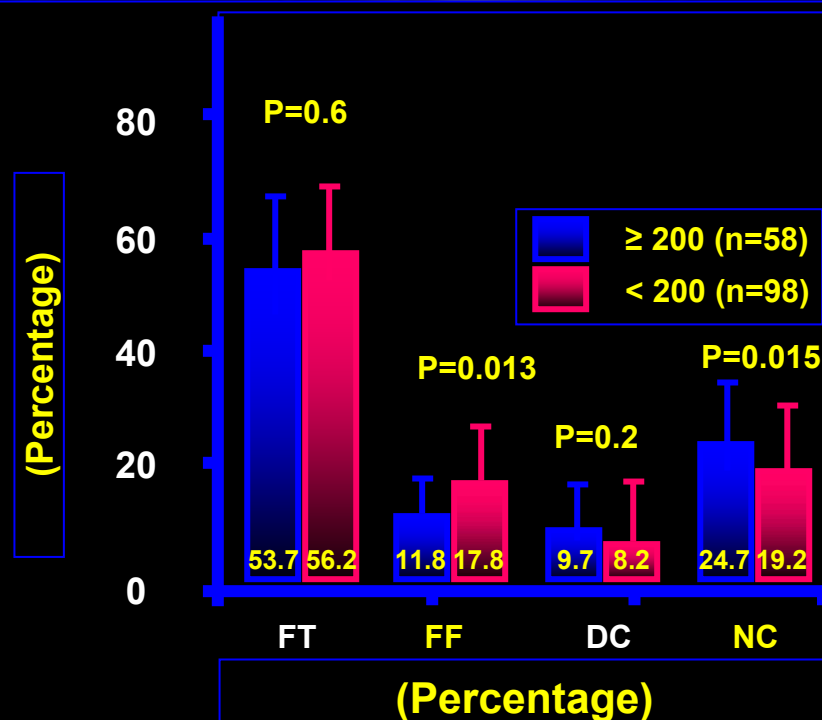


# The absolute (a) and relative (b) plaque components at the minimum lumen site.

**(A)** Largest necrotic core site absolute plaque area



**(B)** Largest necrotic core site relative plaque area

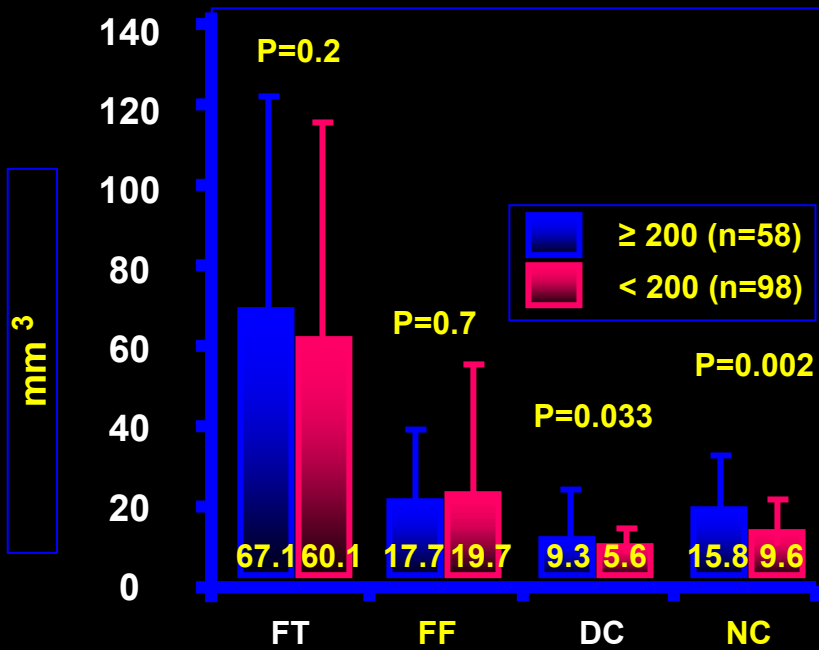


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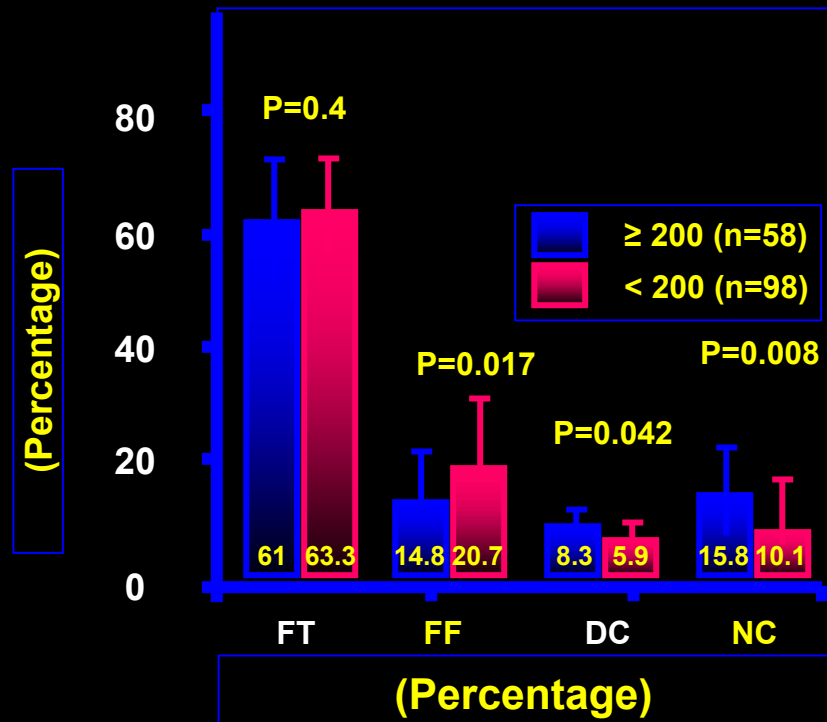


# The absolute (a) and relative (b) plaque components at the minimum lumen site.

**(A)** Absolute plaque volume

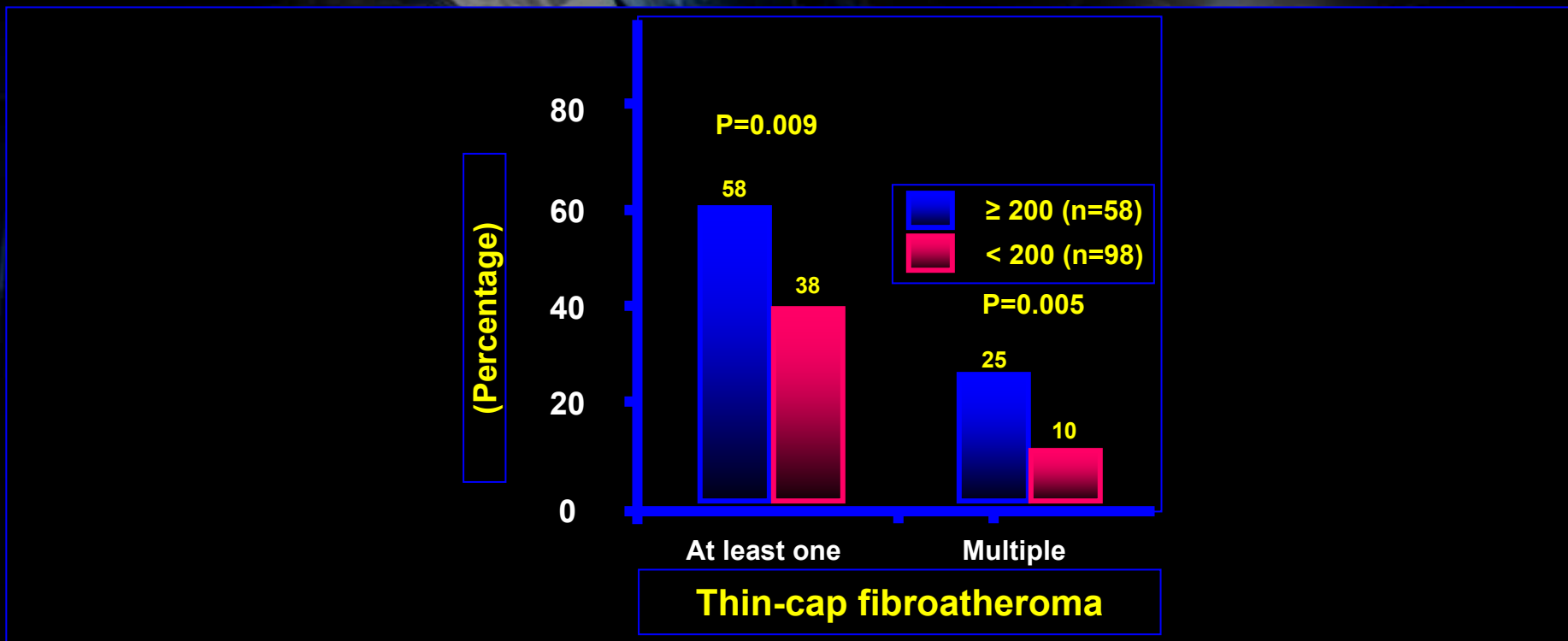


**(B)** Relative plaque volume



Virtual histology-intravascular ultrasound analysis classified the color-coded tissue into four major components: green [fibrotic (FT)]; yellow-green [fibro-fatty (FF)]; white [dense calcium (DC)]; and red [necrotic core (NC)]. At the minimum lumen site, the absolute and relative NC areas, absolute DC area, and absolute FT area were significantly greater in group I than in group II; conversely the relative FF area was significantly smaller in group I than in group II.

# The incidence of thin-cap fibroatheromas.

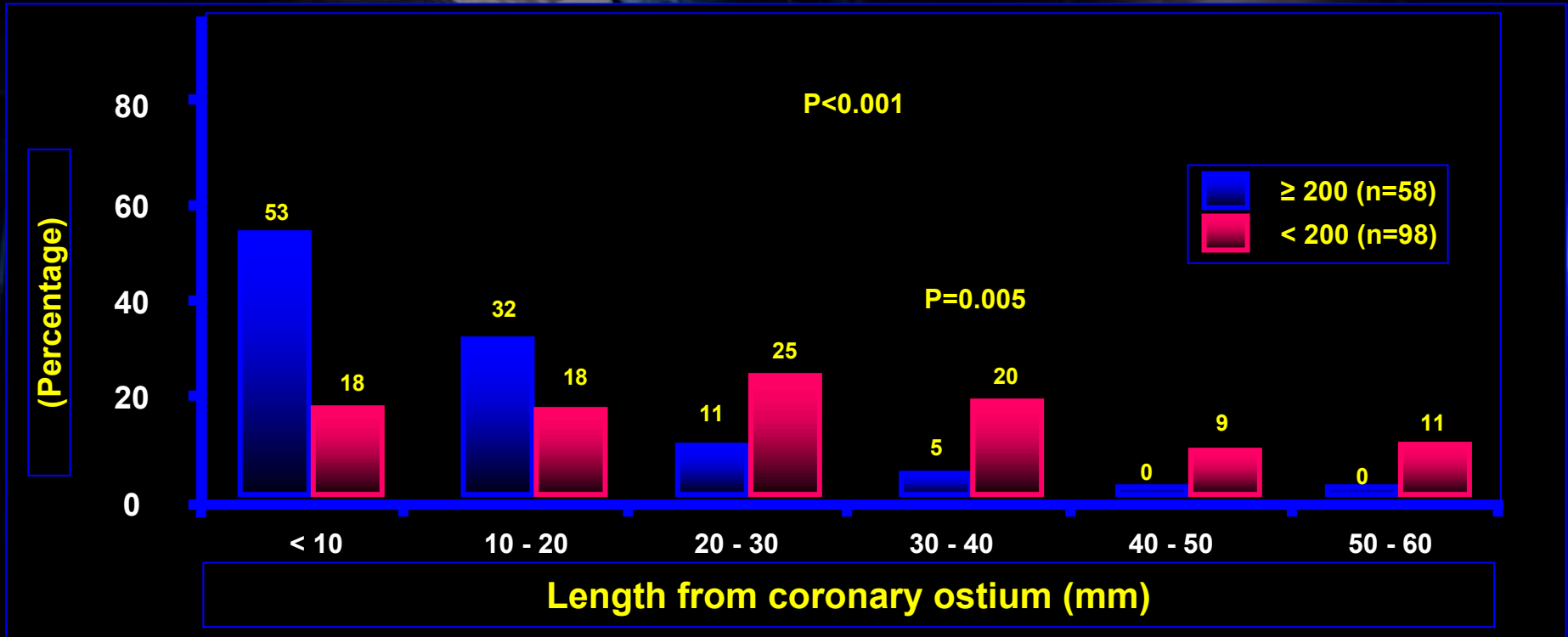


Intravascular ultrasound detected thin-cap fibroatheroma was defined as a necrotic core  $\geq 10\%$  of plaque area in at least three consecutive frames without overlying fibrous tissue in the presence of  $\geq 40\%$  plaque burden. The presence of at least one thin-cap fibroatheroma and multiple thin-cap fibroatheromas within culprit lesions were observed more frequently in group I than in group II.



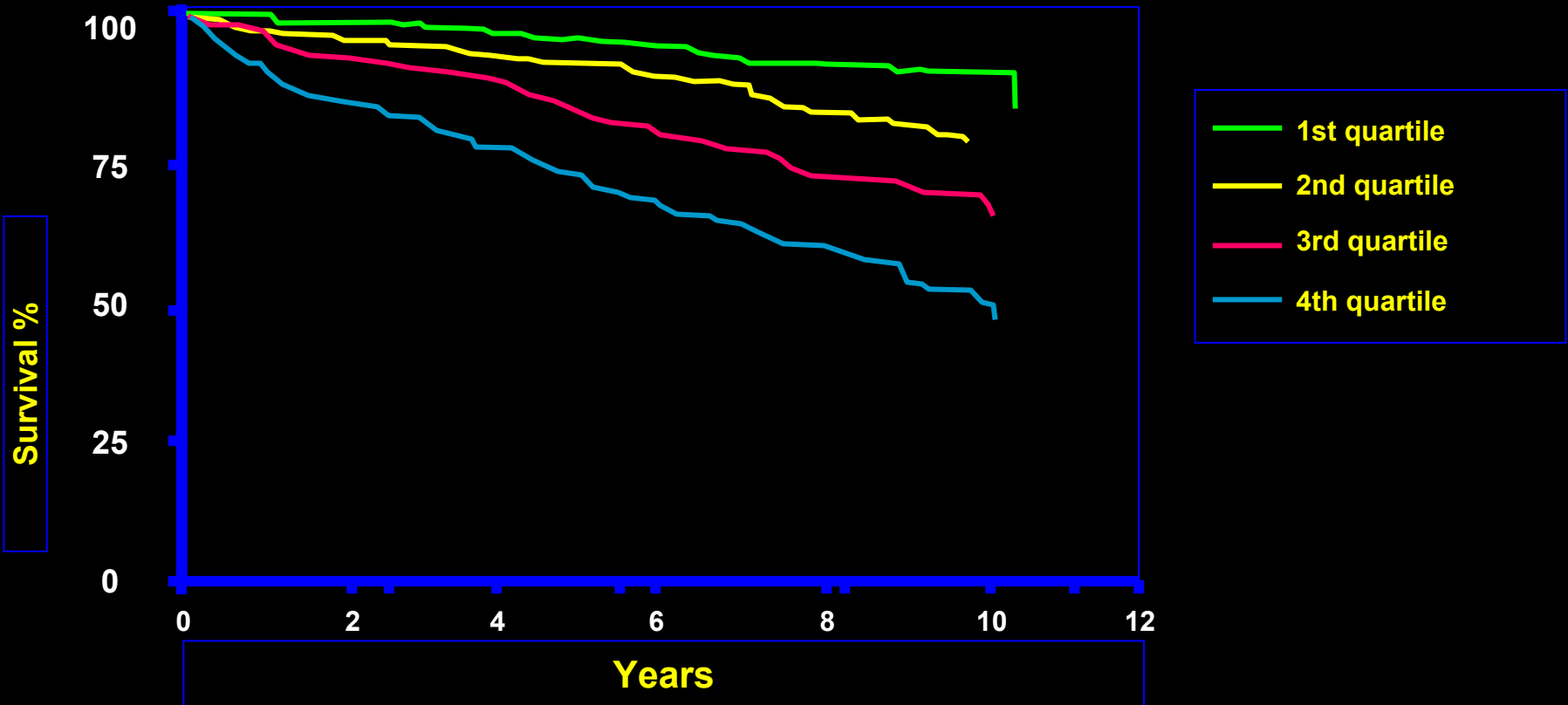
# The length from coronary ostium to thin-cap fibroatheromas.

## Thin-cap fibroatheroma



Intravascular ultrasound-detected thin-cap fibroatheroma was defined as a necrotic core  $\geq 10\%$  of plaque area in at least three consecutive frames without overlying fibrous tissue in the presence of  $\geq 40\%$  plaque burden. The total number of observed thin-cap fibroatheromas was 38 in group I and 56 in group II. Most thin-cap fibroatheromas were located proximally in group I and evenly distributed in group II.

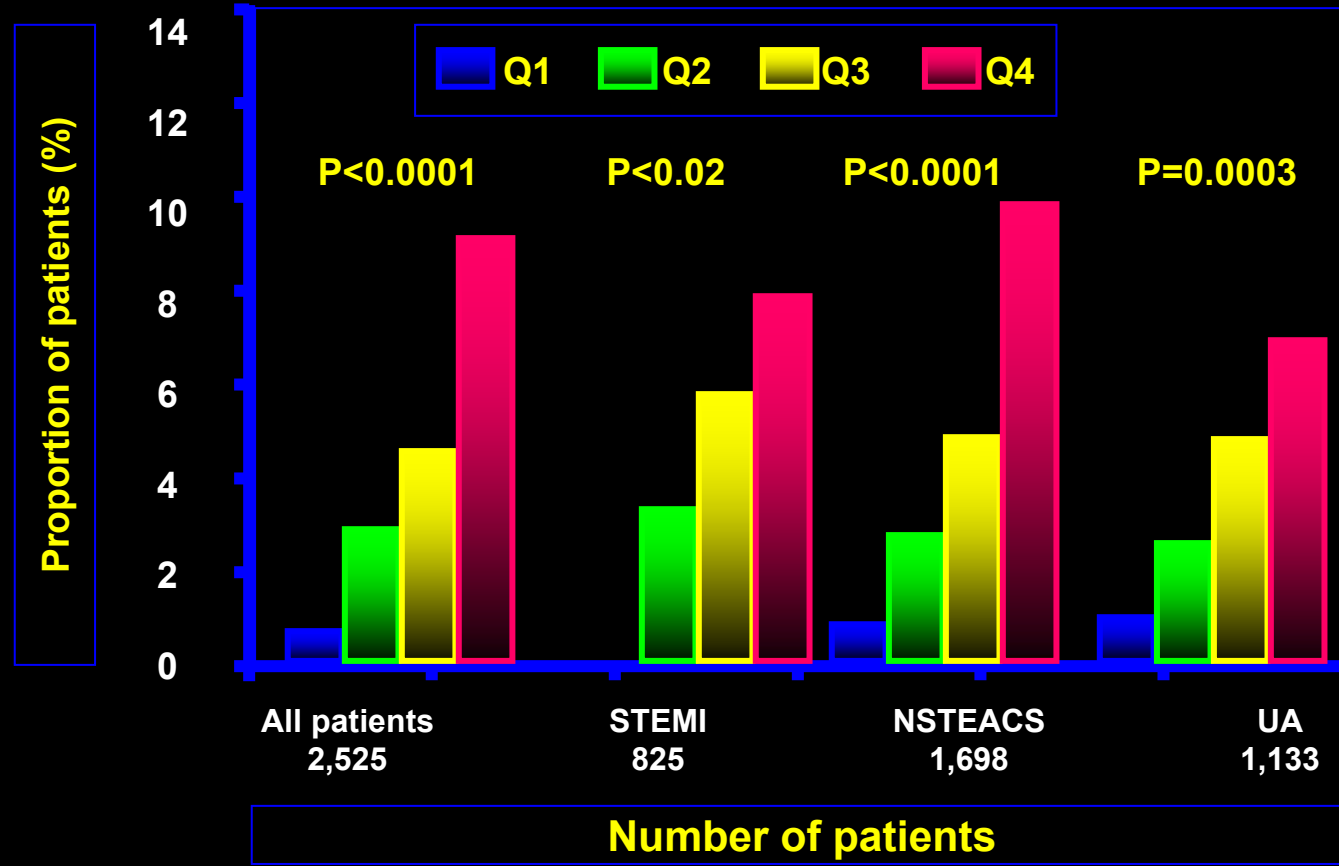
# Overall Survival among Patients with Stable Coronary Artery Disease, According to Quartiles of NT-pro-BNP.



The NT-pro-BNP levels were as follows: first quartile, less than 64 pg per milliliter; second quartile, 64 to 169 pg per milliliter; third quartile, 170 to 455 pg per milliliter; and fourth quartile, more than 455 pg per milliliter.  $P < 0.001$  by the log-rank test for the overall comparison among the groups.



# Relationship between brain natriuretic protein concentrations by quartile and risk of mortality in patients with acute coronary syndromes

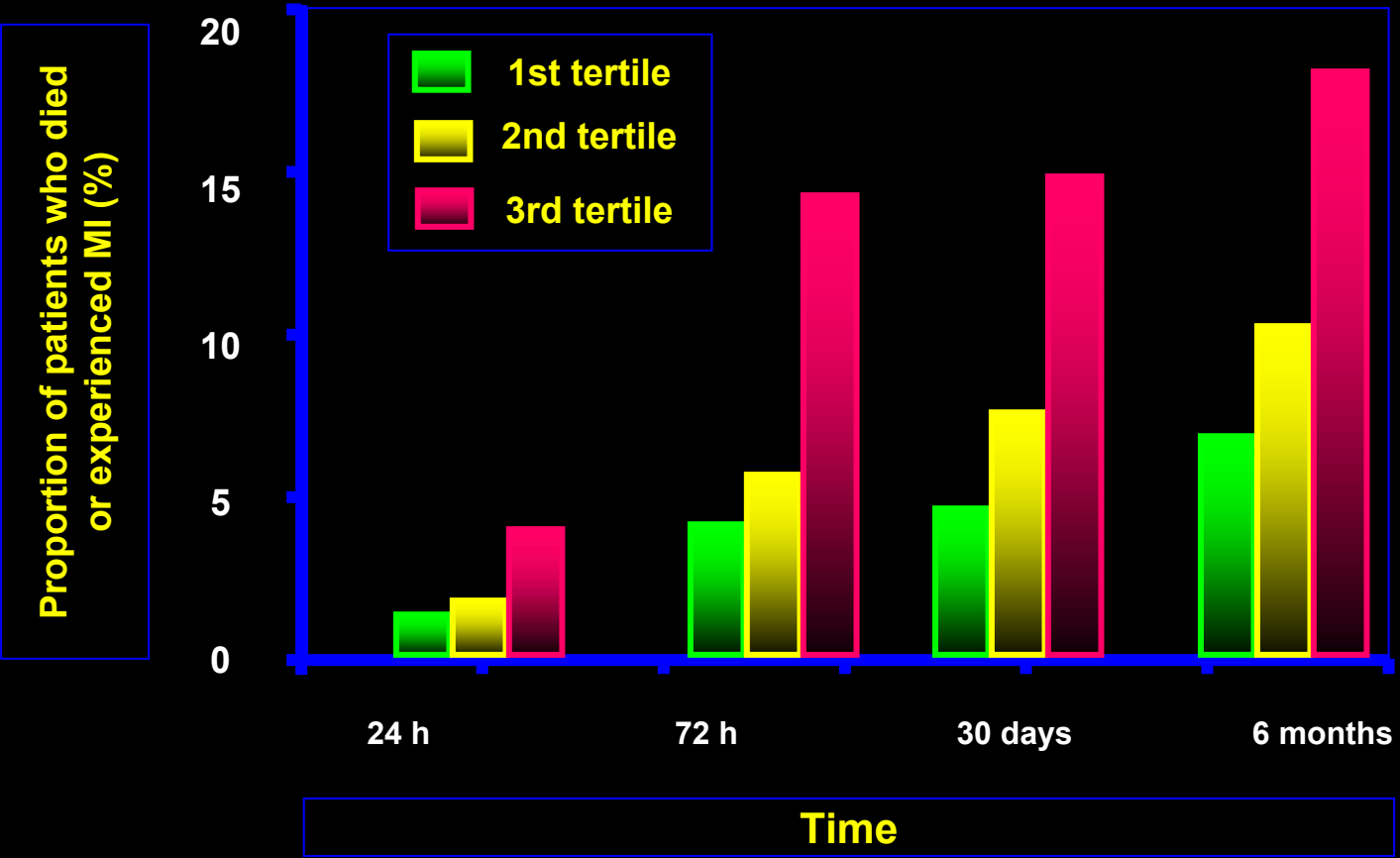


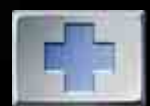
NSTEMI, non-ST-segment elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Reproduced with permission from reference 34 © (2001) Massachusetts Medical Society.



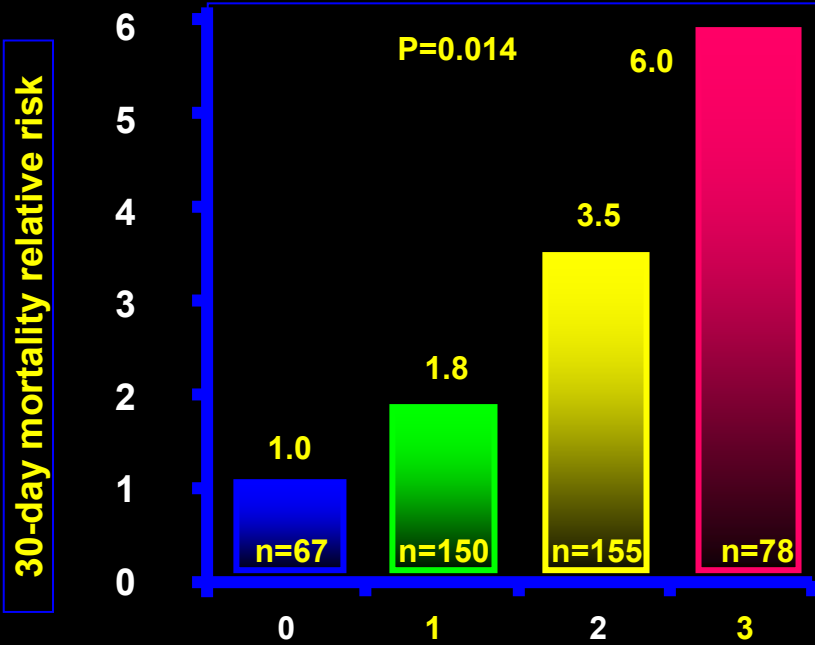
# Association between myeloperoxidase serum levels in different tertiles and cardiac event rate in patients with acute coronary syndromes short term and long term after onset



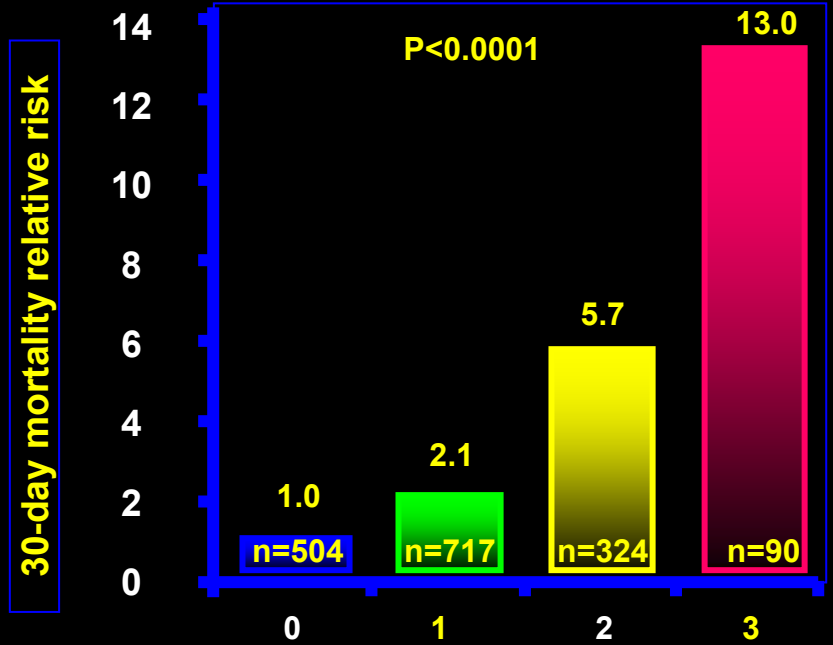


# Mortality risk at 30 days after onset of acute coronary syndromes, assessed by measurement of no, single and multiple cardiac biomarkers.

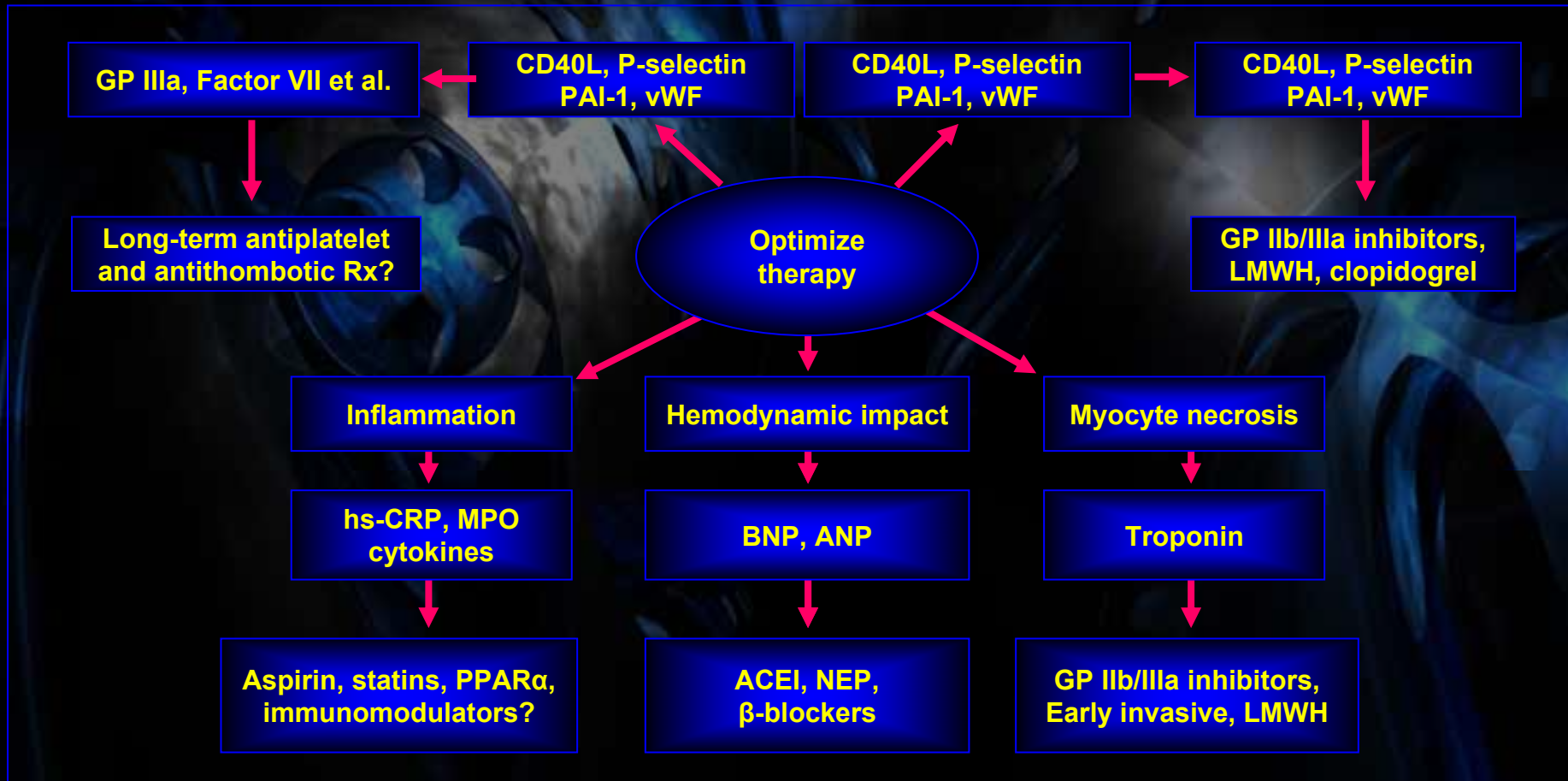
(A) Myocardial infarction.



(B) Congestive heart failure.



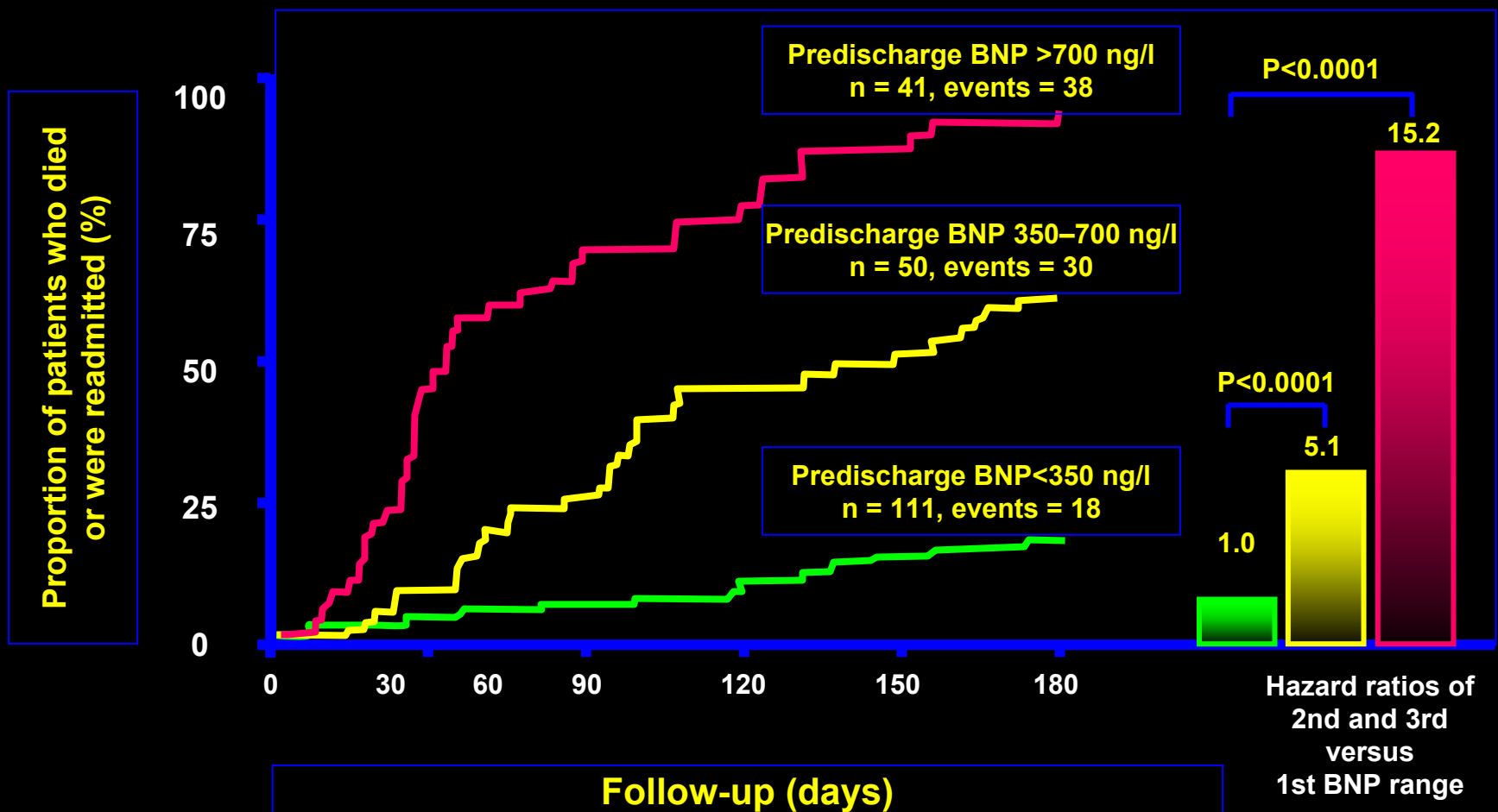
Number of elevated cardiac biomarkers



Possible routes of research into biomarker-guided, individualized management strategies. ACEI, angiotensin-converting-enzyme inhibitor; ANP, atrial natriuretic peptide; ASA, aspirin; BNP, brain natriuretic peptide; CD40L, CD40 ligand; GP, glycoprotein; hsCRP, high-sensitivity C-reactive protein; LMWH, low-molecular-weight heparin; MPO, myeloperoxidase; NEP, neutral endopeptidase; PAI-1, plasminogen activator-1; PPAR $\alpha$ , peroxisome proliferative activator $\alpha$ ; Rx, research; vWF, von Willebrand factor.

Reproduced with permission from reference 4 © (2003) Lippincott Williams & Wilkins.

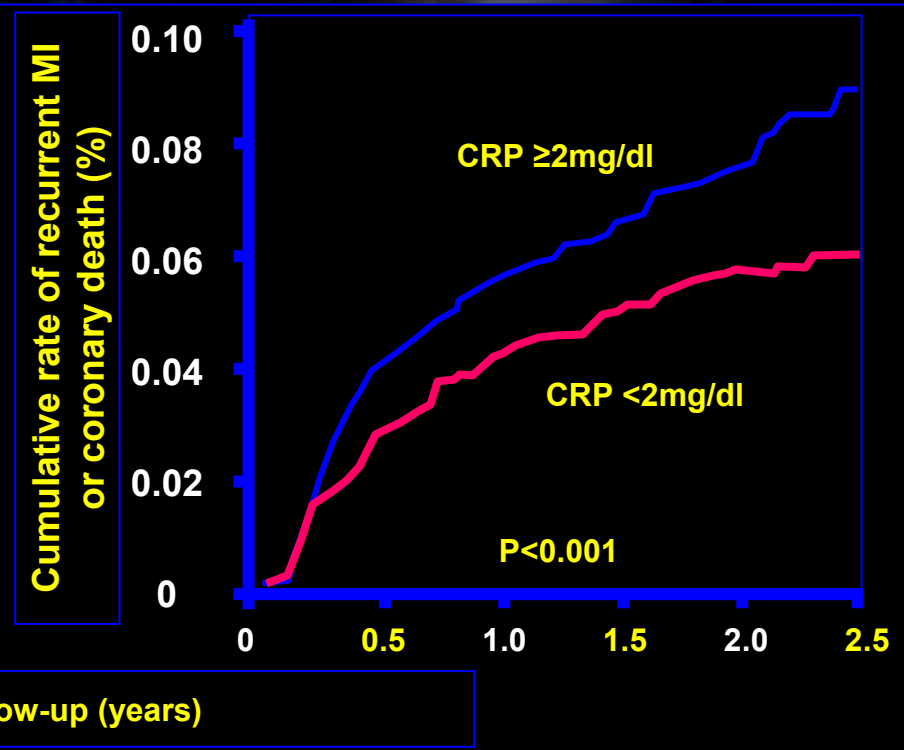
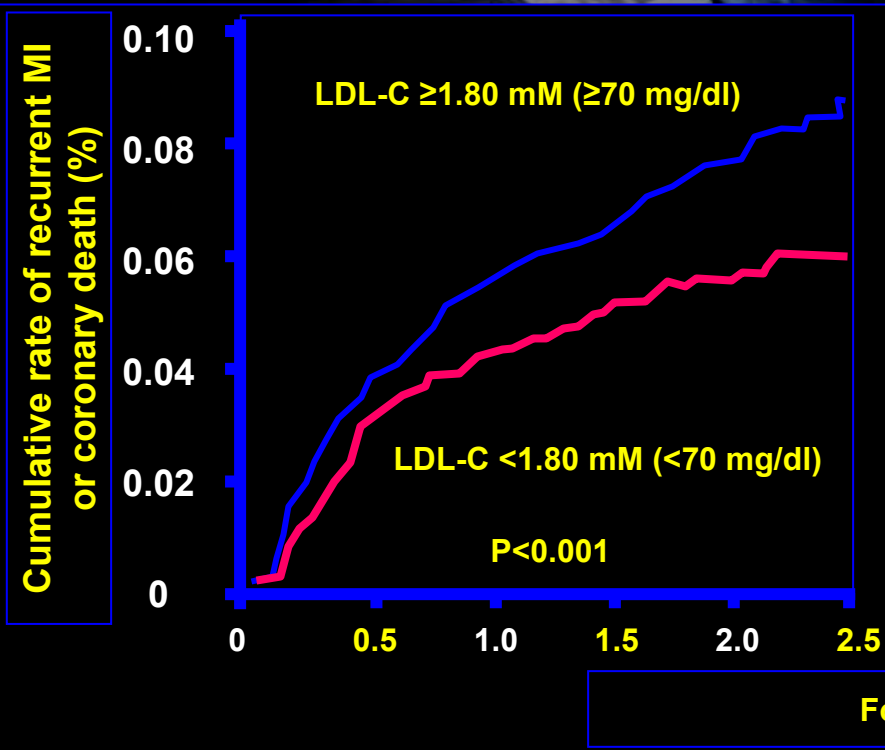
# Association of predischARGE brain natriuretic peptide levels and risk of rehospitalization or death during 6-month follow-up.



Patients with brain natriuretic peptide concentrations <350 ng/l had the best outcome (16.2% of events at 6 months; hazard ratio 1.0) compared with patients with concentrations of 350–700 ng/l (60.0%; hazard ratio 5.1; 95% CI 2.8–9.1;  $P < 0.0001$ ) and >700 ng/l (92.7%; hazard ratio 15.2; 95% CI 8.5–27;  $P < 0.0001$ ).  
Reproduced with permission from reference 64 © (2004) American College of Cardiology Foundation.



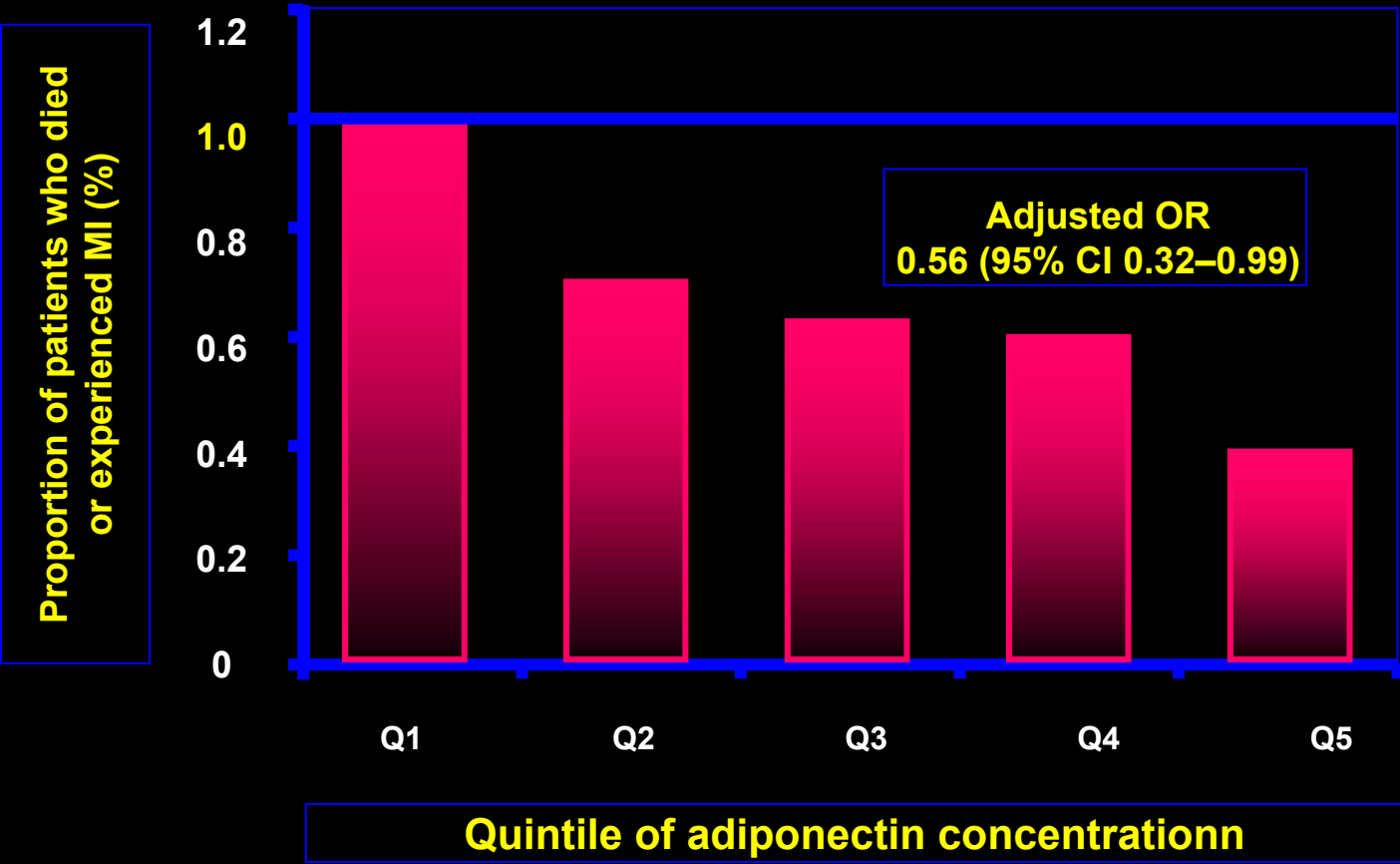
# Clinical relevance of achieved level of low-density lipoprotein cholesterol and C-reactive protein concentration after treatment with statins for recurrent myocardial infarction or death in long-term follow-up



. The lower the C-reactive protein concentration, the better the outcome, irrespective of the low-density lipoprotein cholesterol level achieved. CRP, C-reactive protein; LDL-C, LDL cholesterol; MI, myocardial infarction. Reproduced with permission from reference 65 © (2005) Massachusetts Medical Society.



Association between **adiponectin** concentrations in different quintiles and risk of myocardial infarction in 532 men aged 45–75 years during 6-year follow-up. OR, odds ratio.





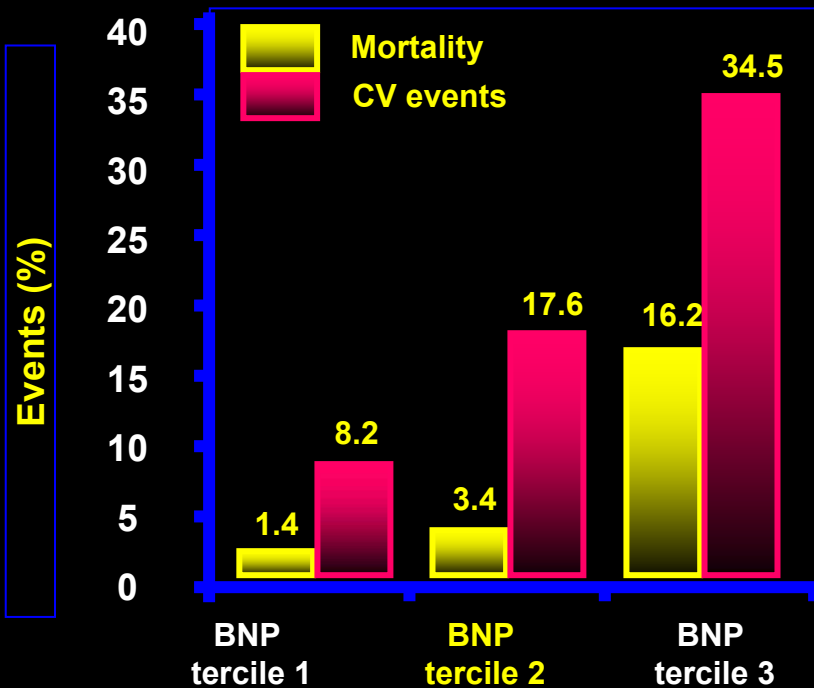
# The usefulness of inflammatory biomarkers in diagnosis and risk stratification in acute coronary syndromes

	Biomarker						
	CK-MB	cTnI/T	hsCRP	BNP/ NT-proBNP	IMA	MPO	CD40L
<b>Diagnosis</b>	Yes	Yes	No	No	Yes	Result unclear	No
<b>Outcomes</b>	Death	Death/	Death/ MI/RI	Death/ MI/RI	No CHF	Death/ MI	Death/ MI
<b>Short term</b>	Yes	Yes	Yes	Yes	—	Yes	Yes
<b>Long term</b>	Yes	Yes	Yes	Yes	—	Yes	Yes
<b>Independent</b>	Yes	Yes	Yes	Yes	—	Yes	Yes
<b>FDA Approval</b>	Yes	Yes	Yes	Yes <sup>a</sup>	Yes	No	No
<b>Guidelines</b>	Class I	Class I	Class IIa	Yes	No	No	No

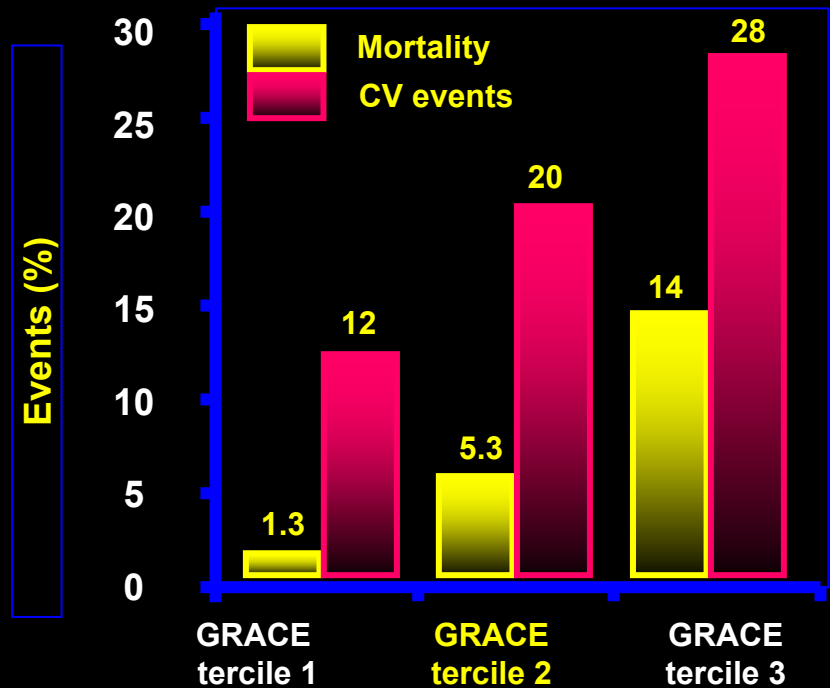
<sup>a</sup> N-terminal pro-brain natriuretic peptide has yet to be approved by the FDA for risk stratification purposes in acute coronary syndromes. BNP, brain natriuretic peptide; CD40L, CD40 ligand; CHF, congestive heart failure; CK-MB, creatine kinase MB; cTnI/T, cardiac troponin I or T; hsCRP, high-sensitivity C-reactive protein; IMA, ischemia-modified albumin; MI, myocardial infarction; MPO, myeloperoxidase; NT-proBNP, N-terminal pro-brain natriuretic peptide; RI, recurrent infarction.

# Biomarkers for plaque destabilization and ischemia.

(A)



(B)

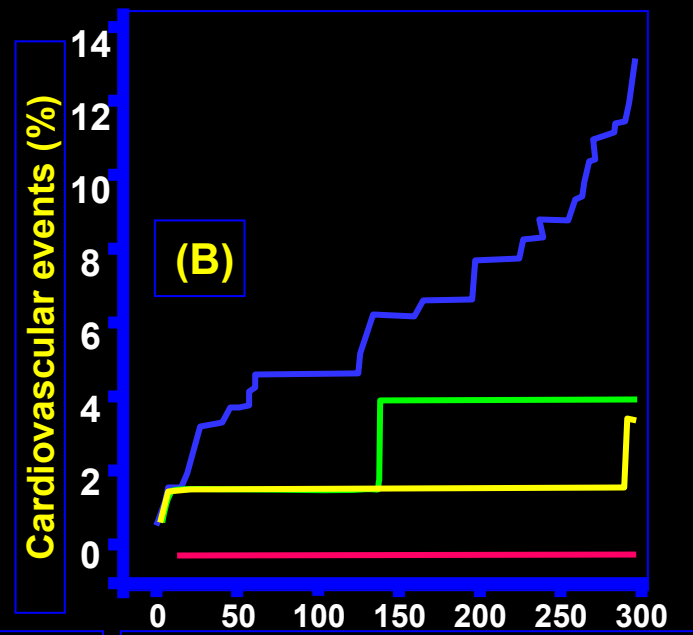
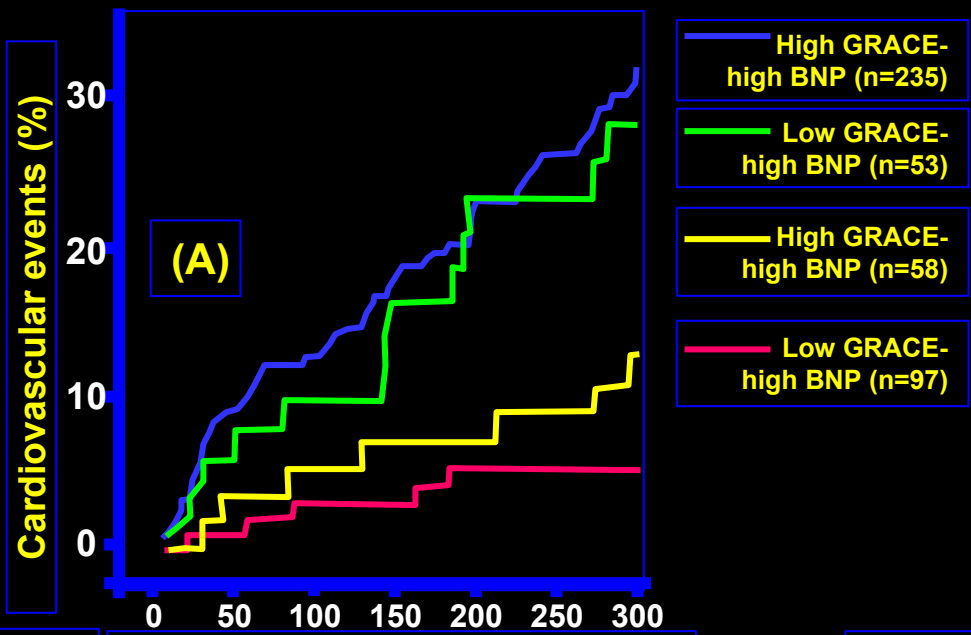


- (A) Distribution of 10-month cardiovascular events and mortality according to different tertiles of B-type natriuretic peptide (BNP) ( $p < 0.001$  for both mortality and cardiovascular events).
- (B) Distribution of 10-month cardiovascular events and mortality according to different tertiles of the GRACE (Global Registry of Acute Coronary Events) score ( $p = 0.003$  for cardiovascular events and  $p < 0.001$  for mortality).



# (A) Kaplan-Meier survival curves for cardiovascular events

# (B) Kaplan-Meier survival curves for mortality.



No at risk	Time = days						
	0	50	100	150	200	250	300
Low G-Low B	97	96	94	94	92	92	92
High G-Low B	58	56	55	54	54	53	51
Low G-high B	53	49	48	45	42	42	40
High G-high B	235	214	207	197	188	181	171

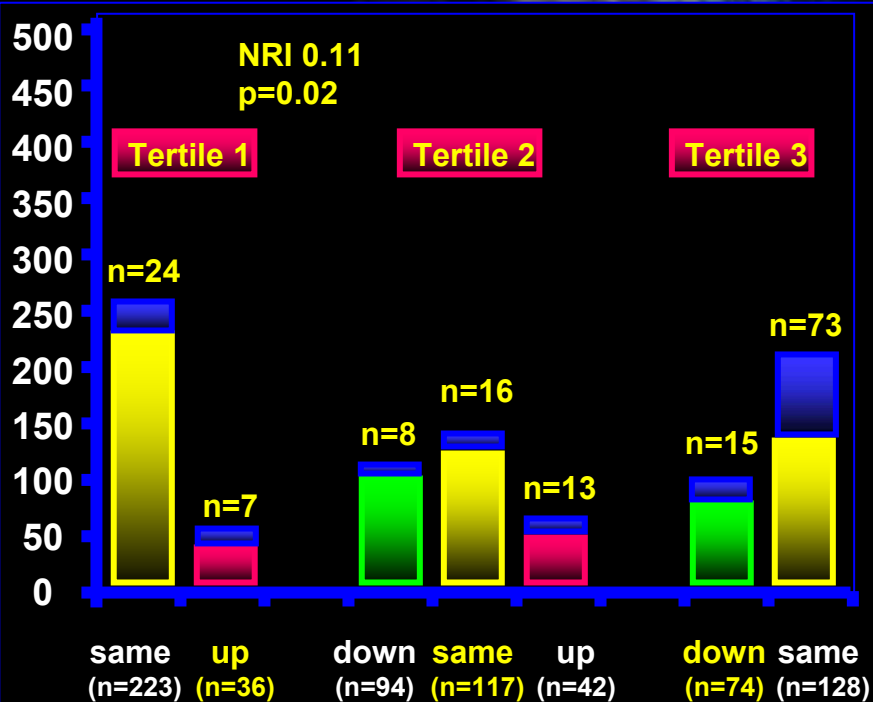
No at risk	Time = days						
	0	50	100	150	200	250	300
Low G-Low B	97	97	97	97	97	97	97
High G-Low B	58	57	57	57	57	57	56
Low G-high B	53	53	53	51	51	51	51
High G-high B	235	226	224	221	219	216	208

High BNP defined as  $.80 \text{ pg/ml}$  and high GRACE score defined as  $.119$  points. High GRACE-high BNP (RR 6.00 (95% CI 2.40 to 14.83)), low GRACE-high BNP (RR 5.27 (95% CI 1.88 to 14.77)) and high GRACE-low BNP (RR 2.40 (95% CI 0.76 to 7.56)). Log-rank test  $p,0.001$ .

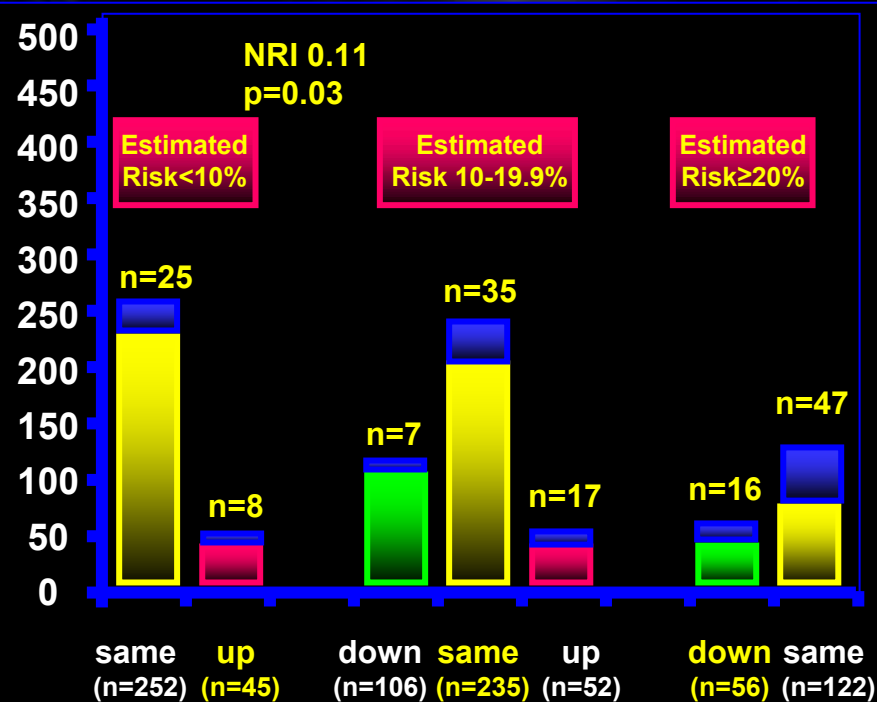
High BNP defined as  $.80 \text{ pg/ml}$  and high GRACE score defined as  $119$  points. High GRACE-high BNP (RR 12.81 (95% CI 1.74 to 94.31)), low GRACE-high BNP (RR 4.12 (95% CI 0.37 to 45.39)) and high GRACE-low BNP (RR 3.45 (95% CI 0.31 to 38.07)). Log-rank test  $p=0.002$ . BNP, B-type natriuretic peptide; GRACE, Global Registry of Acute Coronary Events; TIMI, thrombolysis in myocardial infarction.

# NRI Regarding the Composite of Death or Myocardial Infarction During 5-Year Follow-Up After Addition of NT-proBNP Levels at 6 Weeks to Conventional Risk Indicators

**(A) Risk categories defined by estimated risk tertiles.**



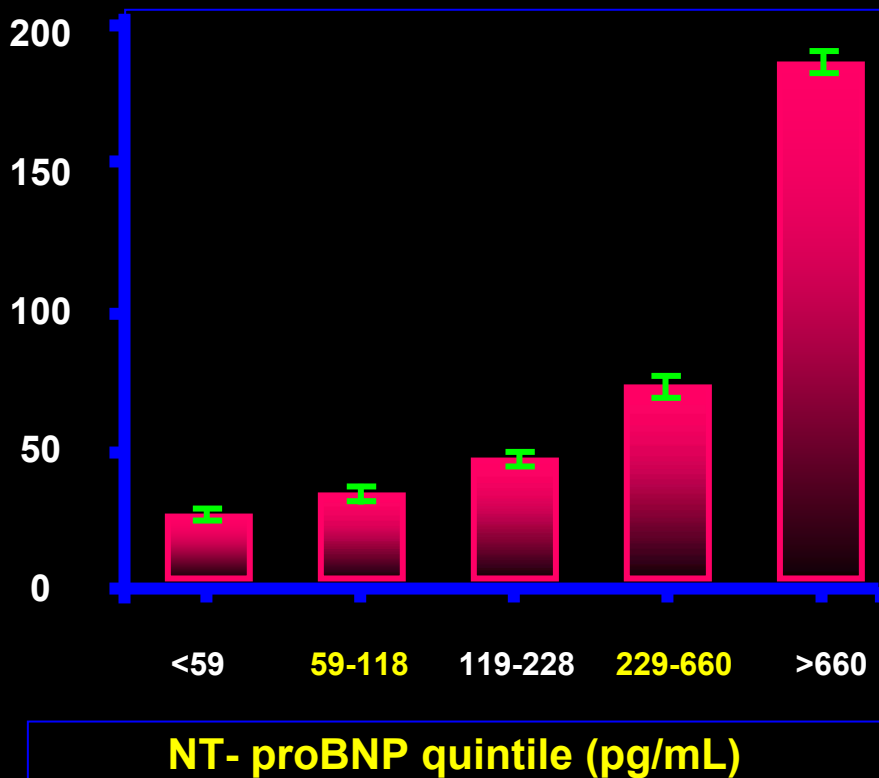
**(B) Risk categories defined by estimated risks of 10%, 10% to 19.9%, and 20%.**



Bars indicate numbers of patients within the respective risk categories, considering those who had been downgraded or upgraded and those who remained within the same risk category at 6 weeks after the addition of In N-terminal pro-brain natriuretic peptide (NT-proBNP) levels to conventional risk indicators (age, sex, diabetes, heart failure, previous myocardial infarction). The solid parts of the bars depict the proportion of patients who met the composite end point after 6 weeks and within 5 years of follow-up. The number of patients with an event is given at the top of each bar. NRI net reclassification improvement.

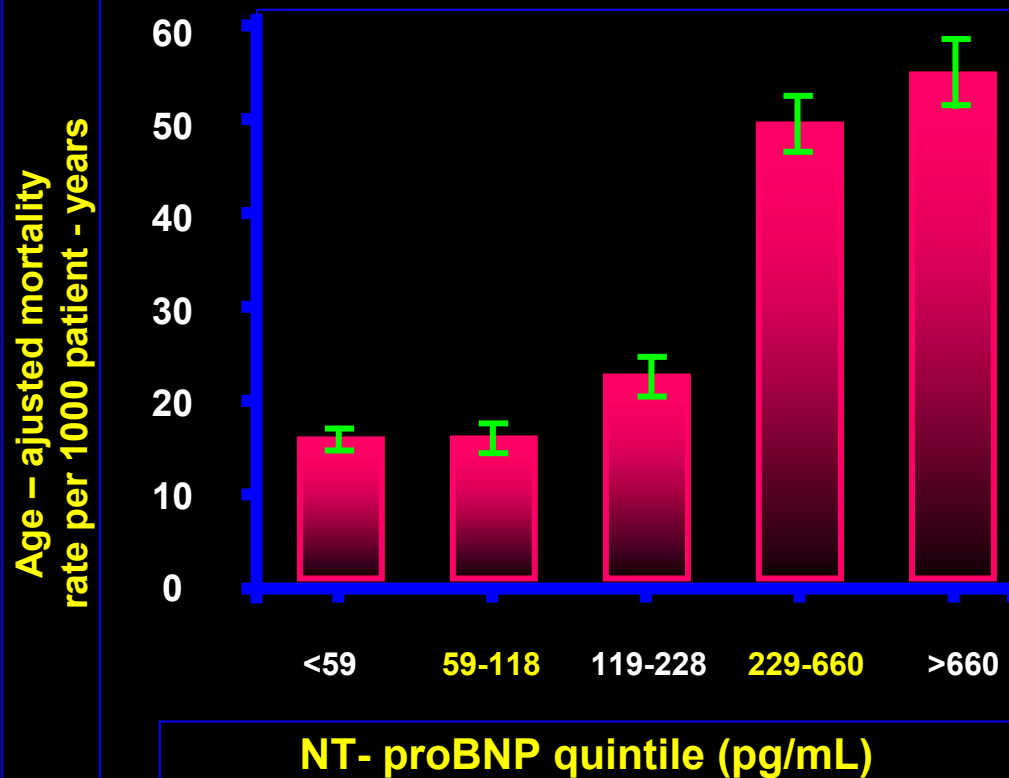
# measurement of NT-proBNP

Age – adjusted cardiovascular hospitalization rate per 1000 patient - years



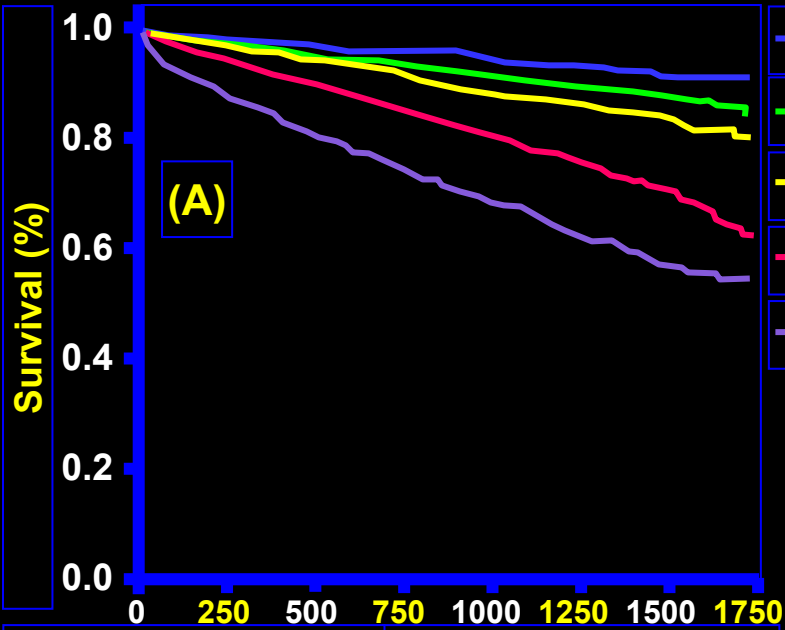
Directly age-adjusted rates of cardiovascular hospitalization with 95% CI in patients referred from primary care for measurement of NT-proBNP on the suspicion of chronic heart failure by NT-proBNP quintiles.

# Directly age-adjusted mortality rates

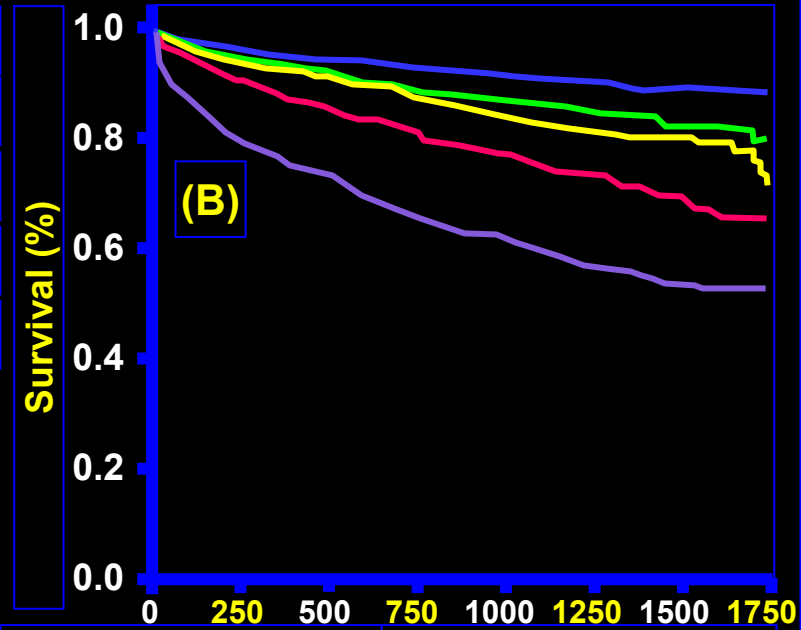


Directly age-adjusted mortality rates with 95% CI in patients referred from primary care for measurement of NT-proBNP on the suspicion of chronic heart failure by NT-proBNP quintiles.

**Cumulative survival curves stratified by NT-proBNP quintile. (A) Survival, (B) probability of no cardiovascular (CV) hospitalization.**



Peptide quintile at risk	Time = days							
<59	1175	1159	1144	1137	856	497	189	15
59-118	1160	1137	1110	1088	780	499	168	15
119-228	1135	1110	1079	1050	453	461	178	16
229-660	1221	1154	1103	1052	765	437	176	16
>660	1184	1046	963	884	613	332	123	18

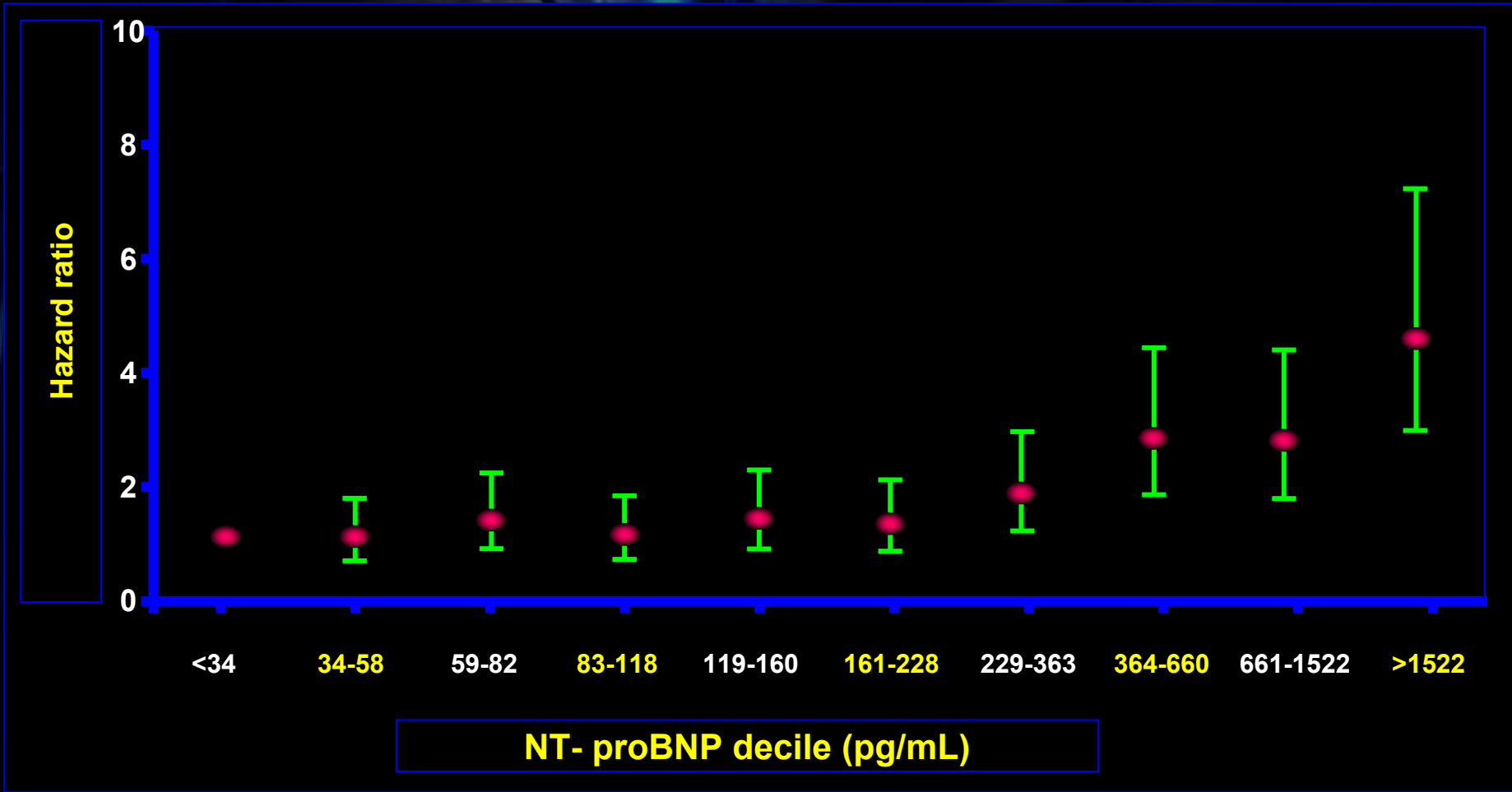


Peptide quintile at risk	Time = days							
<59	1175	1128	1099	1077	795	452	165	13
59-118	1160	1094	1041	994	697	441	146	11
119-228	1135	1054	1004	945	641	373	135	13
229-660	1221	1069	970	888	618	344	128	11
>660	1184	877	748	642	426	212	83	13

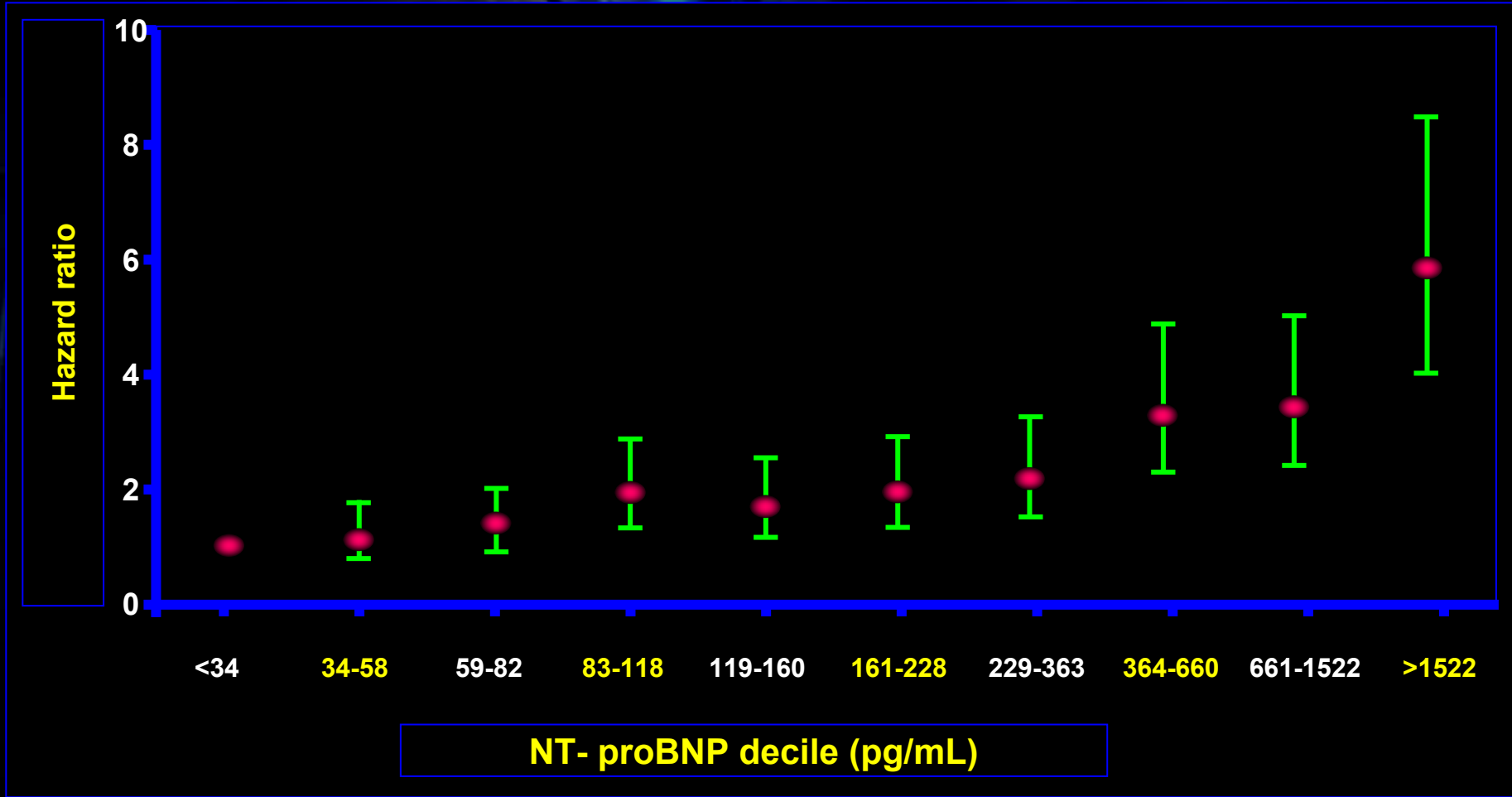
**Cumulative survival curves stratified by NT-proBNP quintile. (A) Survival, (B) probability of no cardiovascular (CV) hospitalization.**



Effect of NT-proBNP decile on the hazard ratio with 95% CI for **all-cause mortality** in patients referred from primary care for NT-proBNP measurement on the suspicion of congestive heart failure.

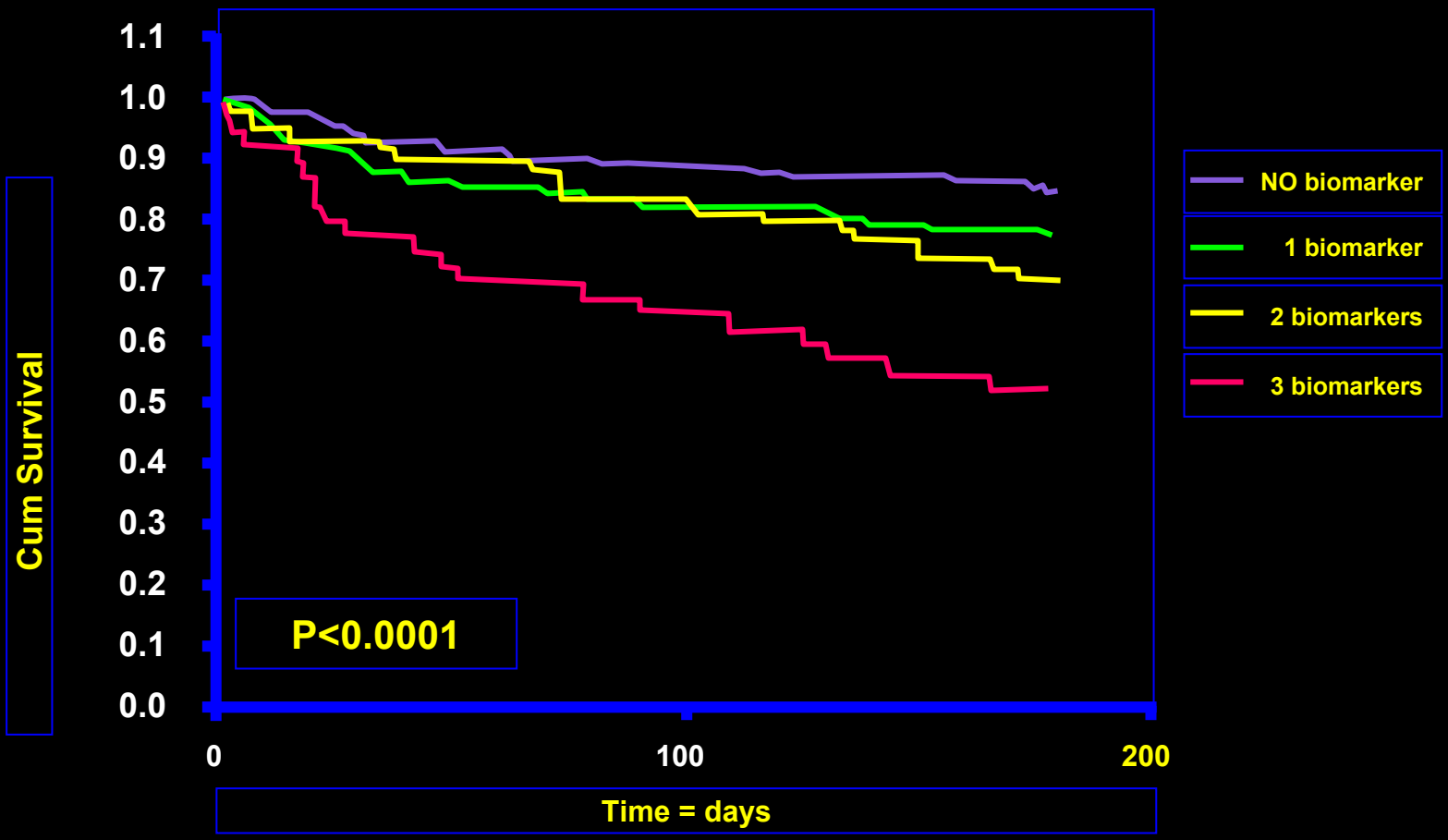


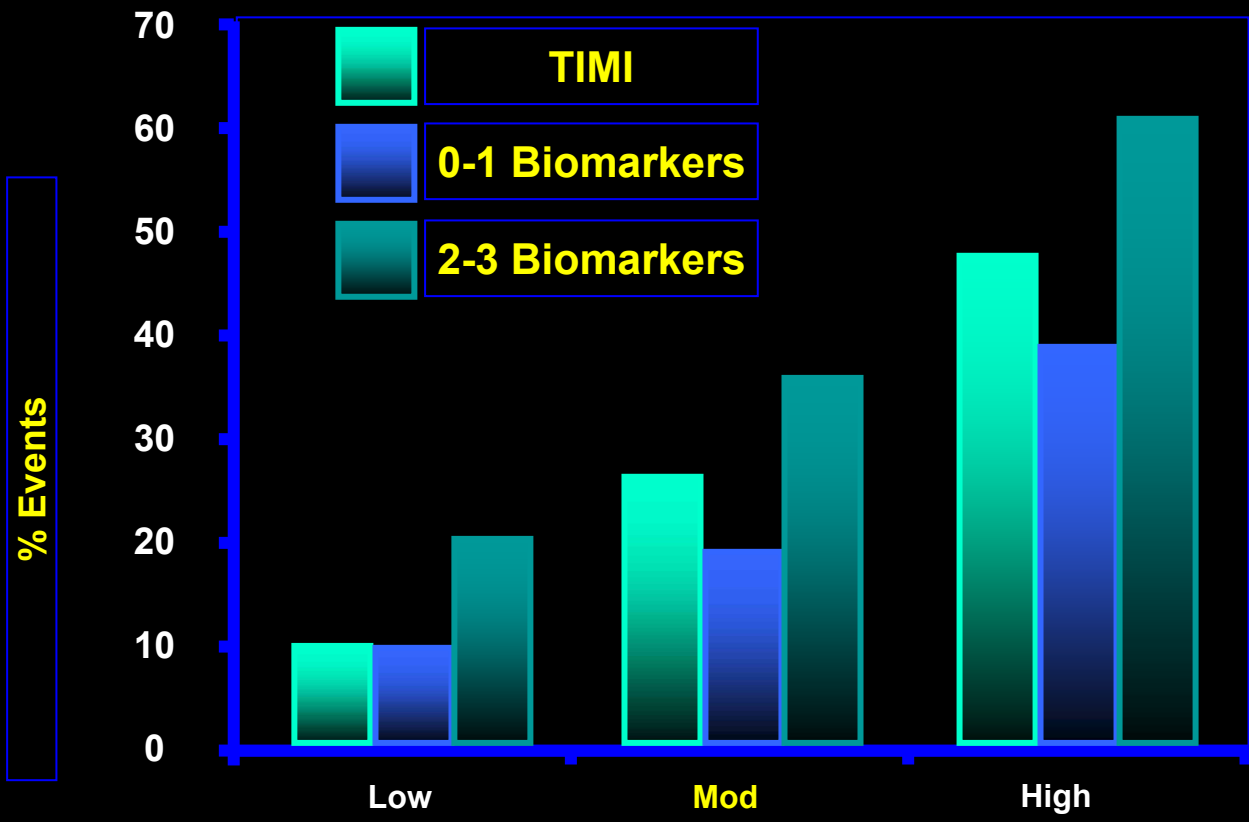
Effect of NT-proBNP decile on the hazard ratio with 95% CI for cardiovascular hospitalization in patients referred from primary care for NT-proBNP measurement on the suspicion of congestive heart failure.



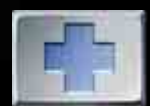


# Kaplan–Meier curves showing the relationship between positive number of biomarkers (addition) and cumulative event-free survival.





Relationship between patients' risk and events at 6 months' follow-up. Percentage of events divided by patients risk in TIMI risk score (all patients, light blue bar). When divided by the number of positive biomarkers (dark blue and green bars), the risk is increased principally in low and moderate (Mod) risk patients (see text).

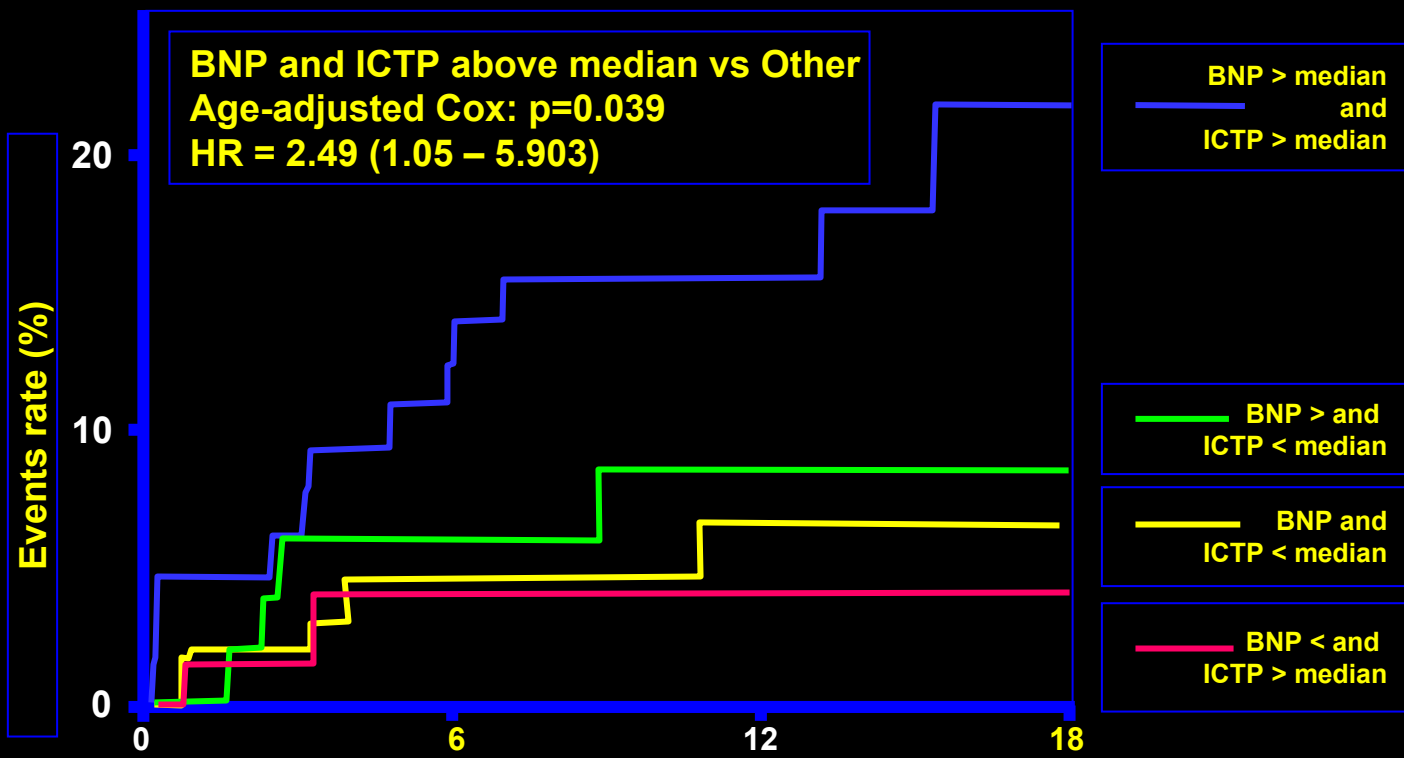


## Event rate at 6 months' follow-up. Influence of number of elevated biomarkers

	Low risk (%)	Moderate risk (%)	High risk (%)
<b>Entire group</b>	<b>10.3</b>	<b>26.4</b>	<b>47.8</b>
<b>0–1 biomarker</b>	<b>9.8</b>	<b>19.0</b>	<b>39.1</b>
<b>2–3 biomarkers</b>	<b>20.0</b>	<b>35.9</b>	<b>61.1</b>

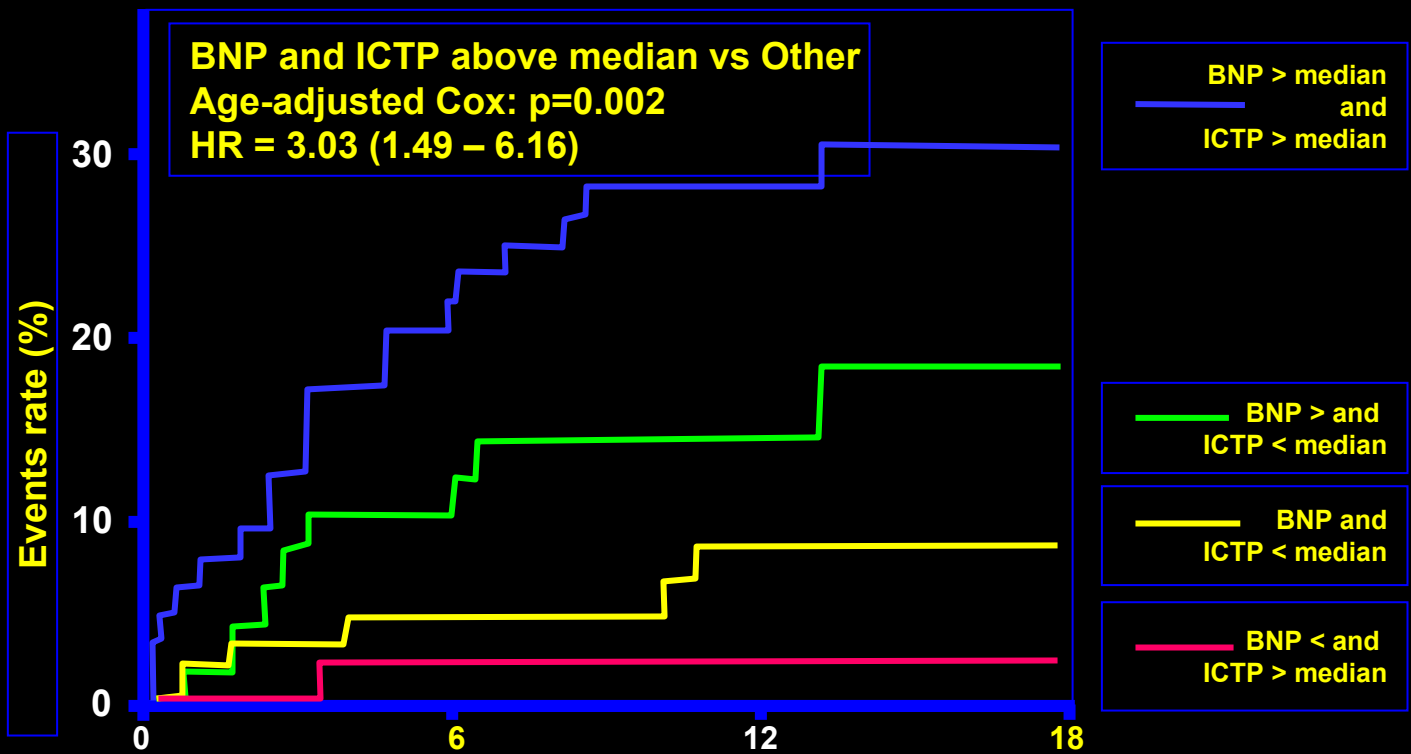
This table shows the adverse event rate amongst groups divided according to the TIMI risk score and the increase in this rate, when we divided the groups depending on the number of elevated biomarkers in each group (see text for explanation).

# Kaplan-Meier curves showing all-cause mortality in the placebo group.



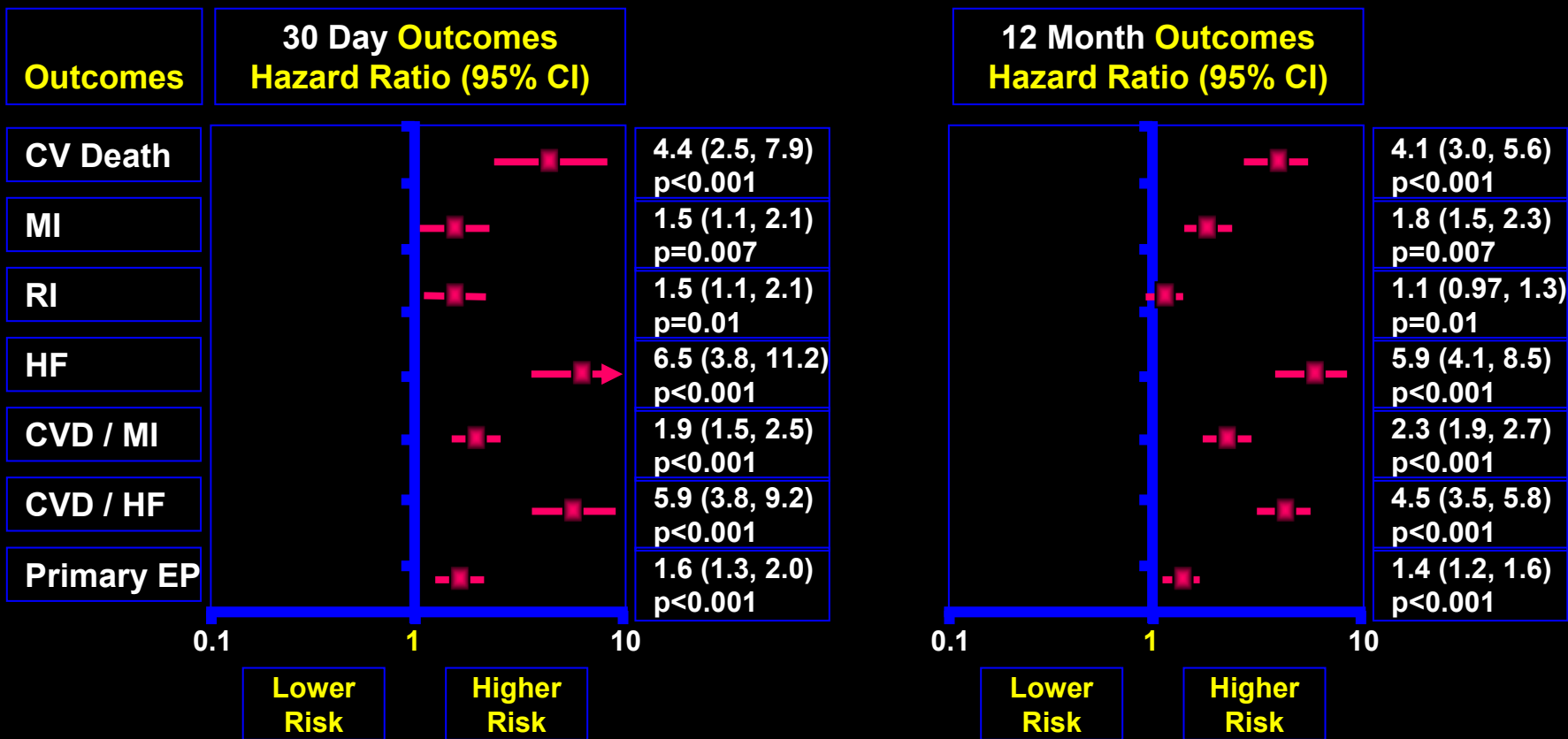
	Patients left at risk (events rate %)		months	
	0	6	12	18
<b>BNP/ICTP high</b>	64 (0)	55 (14)	39 (16)	10 (22)
<b>BNP high/ICTP low</b>	49 (0)	46 ( 6)	26 ( 9)	6 ( 9)
<b>BNP low/ICTP high</b>	48 (0)	46 ( 4)	28 ( 4)	4 ( 4)
<b>BNP low/ICTP low</b>	65 (0)	62 ( 5)	37 ( 7)	9 ( 7)

# Kaplan-Meier curves showing cardiovascular death or hospitalization for HF worsening in the placebo group.



Patients left at risk (events rate %)	months			
	0	6	12	18
<b>BNP/ICTP high</b>	64 (0)	49 (23)	34 (28)	10 (30)
<b>BNP high/ICTP low</b>	49 (0)	43 (12)	23 (14)	6 (18)
<b>BNP low/ICTP high</b>	48 (0)	46 ( 2)	28 ( 2)	4 ( 2)
<b>BNP low/ICTP low</b>	65 (0)	61 ( 5)	35 ( 9)	9 ( 9)

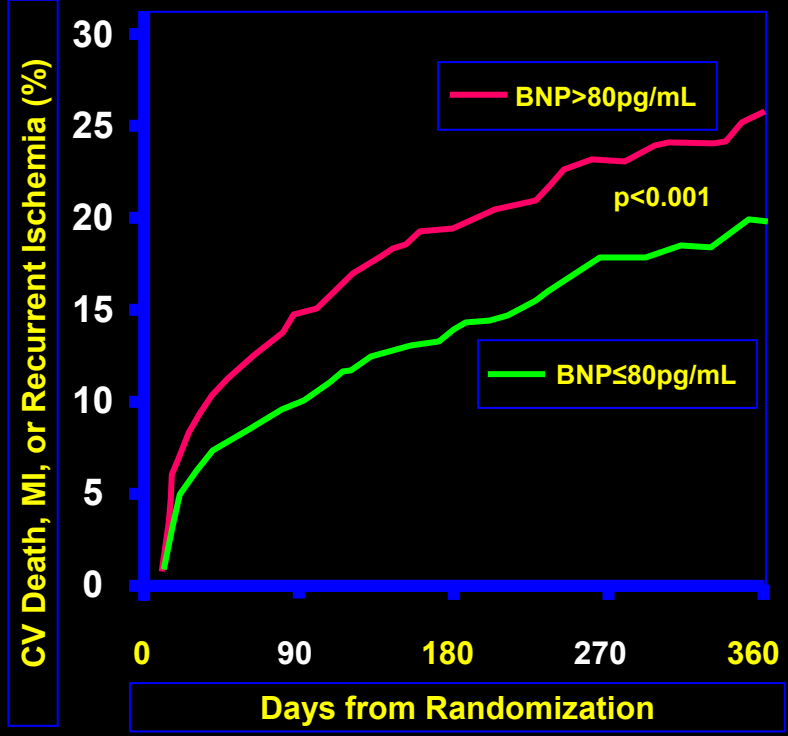
# Risk of 30-Day and 1-Year Adverse CV Outcomes Associated With Baseline BNP >80 pg/ml.



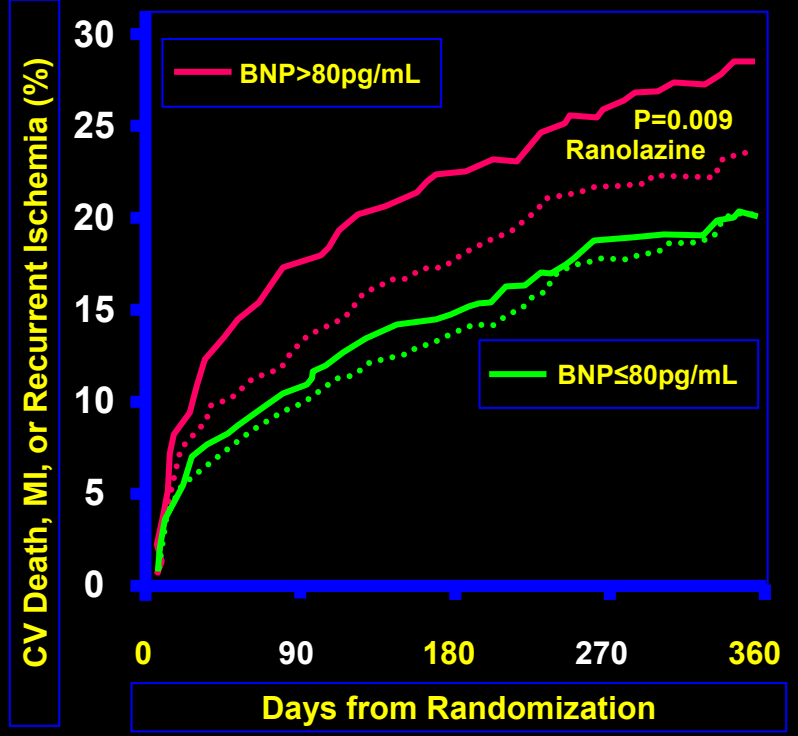
Primary end point (EP) is the composite of cardiovascular death (CVD), myocardial infarction (MI), or recurrent ischemia (RI). BNP B-type natriuretic peptide; CI confidence interval; CV cardiovascular; HF heart failure.



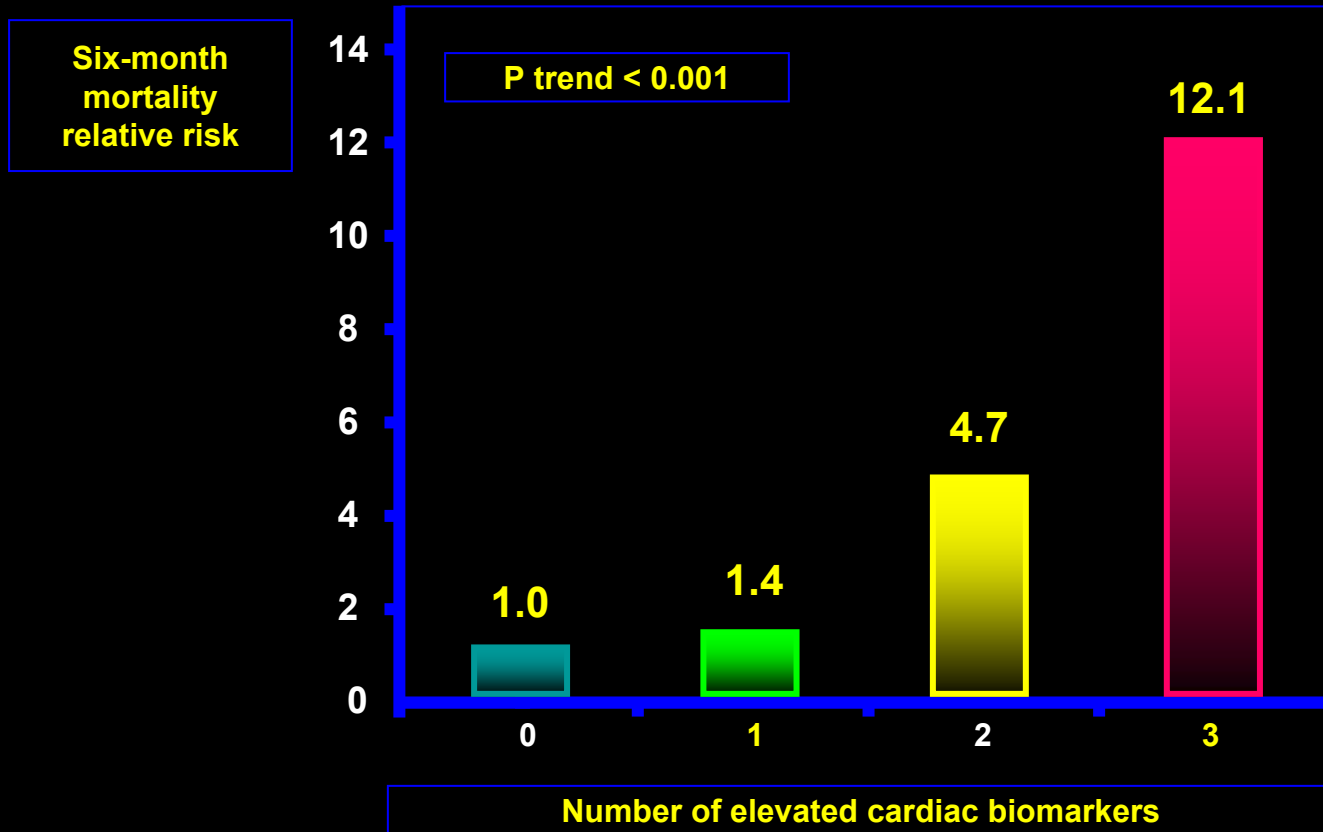
(A)



(B)



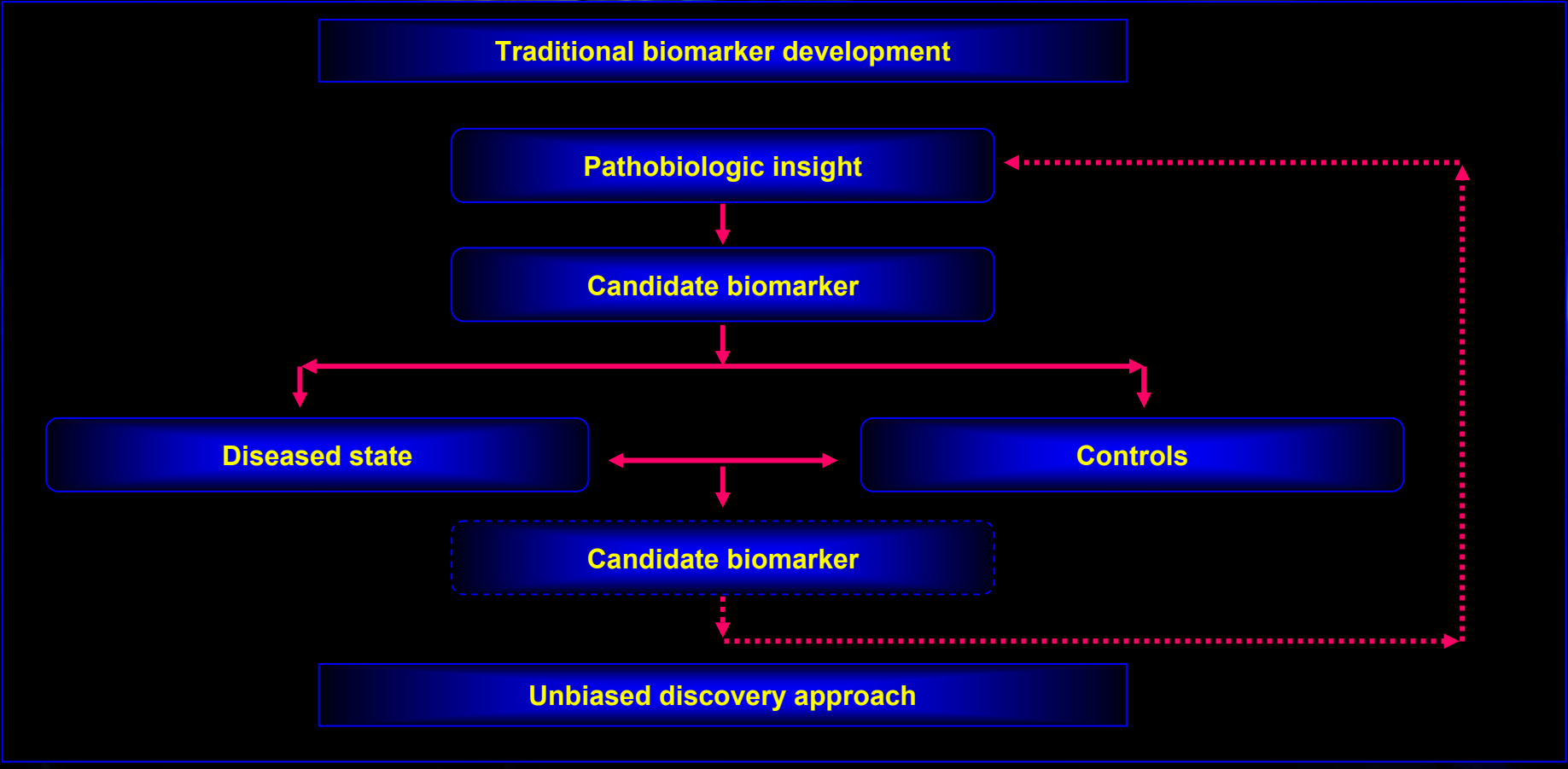
# TACTICS-TIMI 18 trial



Relative 6-month mortality in the TACTICS-TIMI 18 trial stratified by the number of elevated biomarkers, including troponin I, B-type natriuretic peptide and C-reactive protein



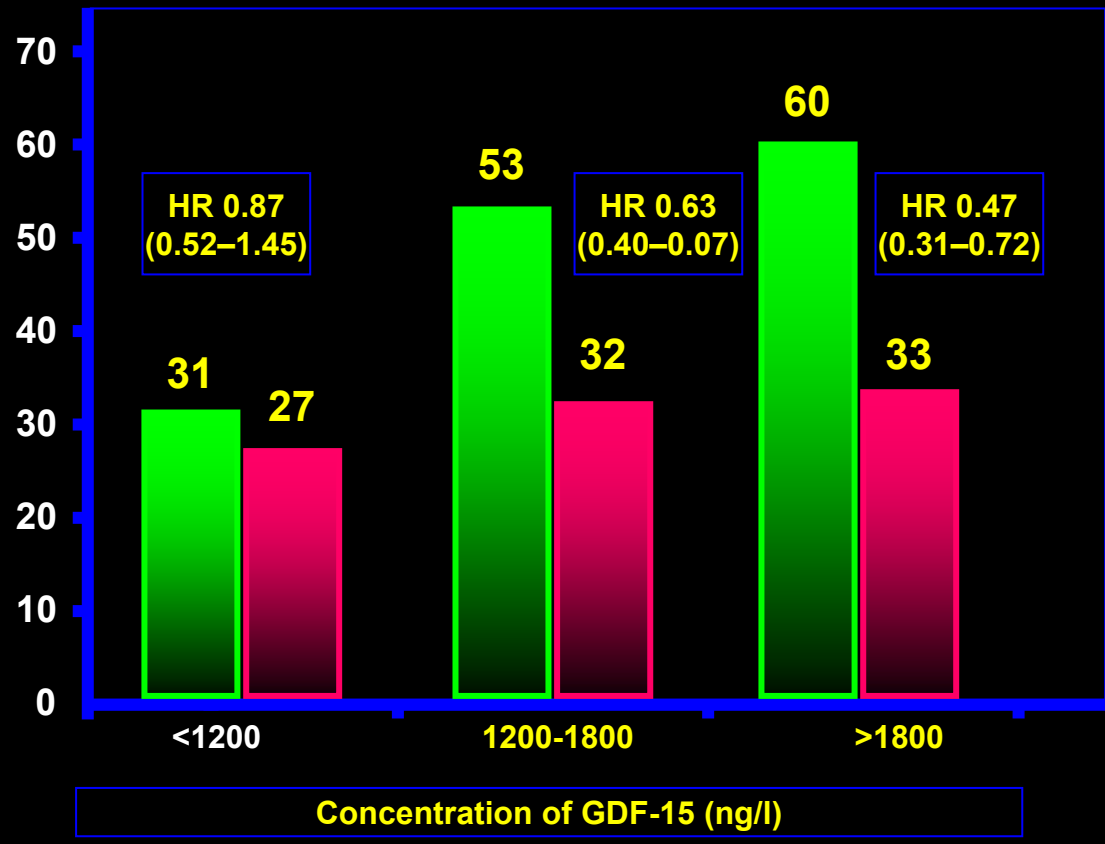
**Traditionally, many biomarkers are identified as a logical extension of what is already understood about the pathobiology of acute coronary syndromes**



**Relative 6-month mortality in the TACTICS-TIMI 18 trial stratified by the number of elevated biomarkers, including troponin I, B-type natriuretic peptide and C-reactive protein**



Rate of death or MI (%)

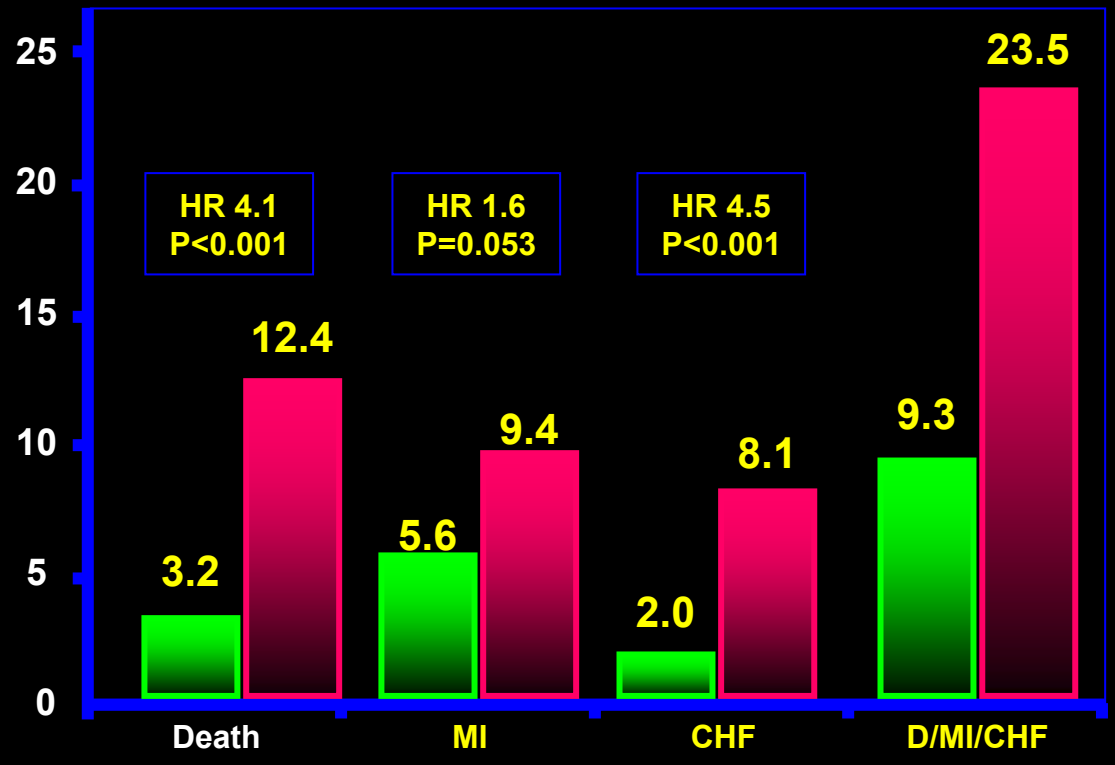


GDF, growth differentiation factor; HR, hazard ratio; MI, myocardial infarction. Rising levels of GDF-15 were useful for helping to discriminate patients who may benefit most from an invasive strategy (P=0.08).

Event rates for the risk of death or MI through 2 years of follow-up for patients randomized to an invasive or conservative treatment strategy with a baseline troponin T >0.01µg/l



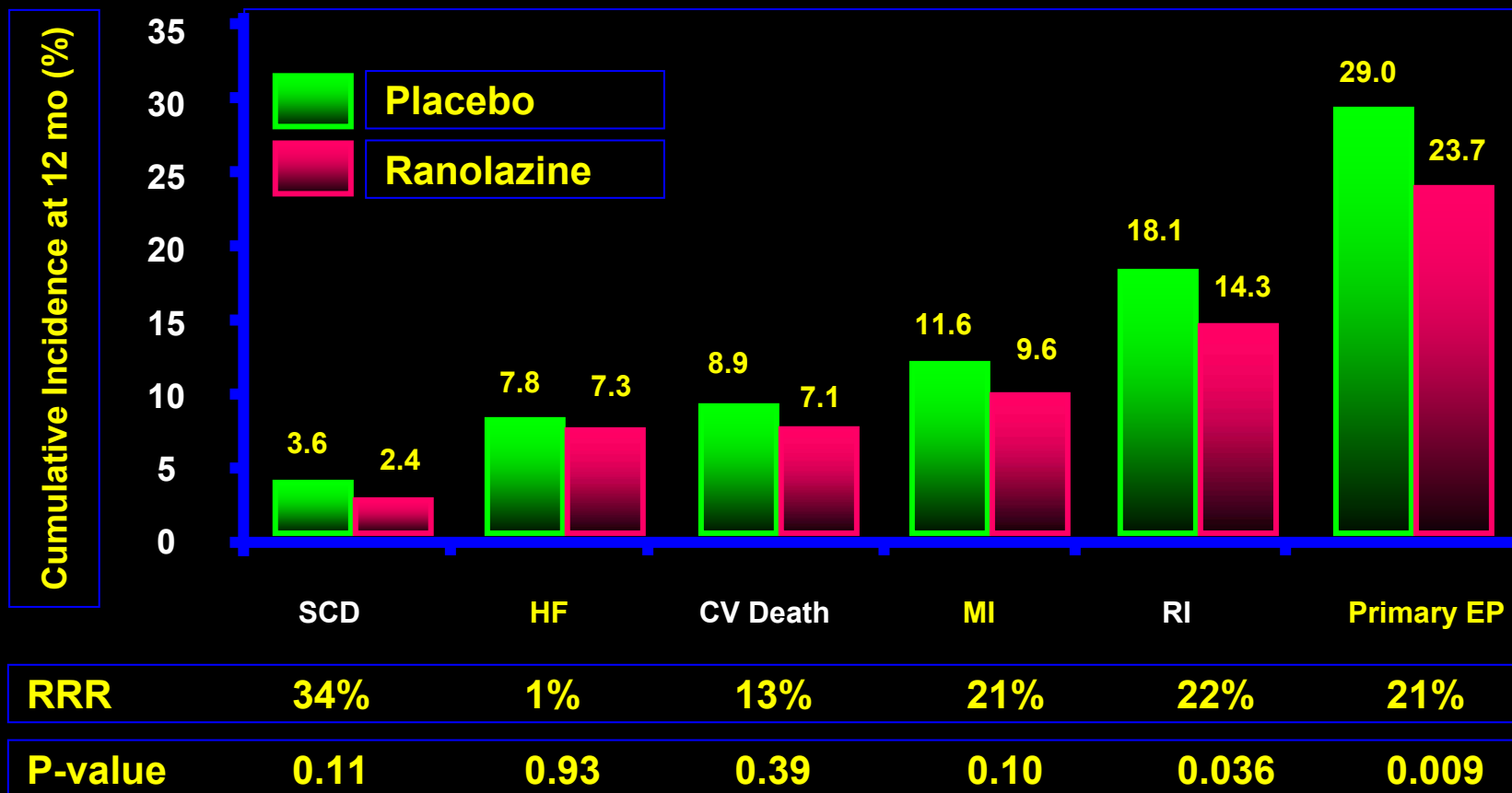
Event rate through 10 months



CHF, congestive heart failure; D, death; FABP, fatty acid-binding protein; HR, hazard ratio; MI, myocardial infarction.

Event rates for the risk of death, MI, CHF and the composite of these endpoints through 10 months of follow-up in OPUS-TIMI 16 stratified by baseline H-FABP ≤ 8 or >8ng/ml

# Kaplan-Meier Estimated 1-Year Incidence of CV Events

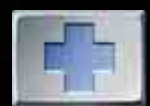


Sudden cardiac death (SCD), myocardial infarction (MI), recurrent ischemia (RI), and new or worsening heart failure (HF) with ranolazine compared with placebo among patients with baseline BNP results 80 pg/ml. RRR relative risk reduction;

# Incidence of clinical outcomes at 1 month in patients with normal and elevated plasma BNP levels.

Variable	Plasma BNP Level ≤80 pg/mL (n=62)	Plasma BNP Level >80 pg/mL (n=84)	p
New heart failure	1 (2%)	26 (31%)	<0.00001
Recurrent MI or angina pectoris	13 (21%)	12 (14%)	NS
All-cause mortality	0 (0%)	08 (10%)	<0.01500

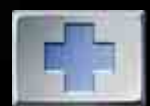
BNP: B-type natriuretic peptide; MI: myocardial infarction; NS: not statistically significant. Numbers in parentheses signify percentage of patients in the plasma BNP subgroup listed at the head of the column.



# Effect of myocardial revascularization on clinical outcomes in patients with normal and elevated plasma BNP levels.

Clinical Outcome	Normal Plasma BNP Subgroup			Elevated Plasma BNP Subgroup		
	Revascularized (n=28)	Unrevascularized (n=34)	p	Revascularized (n=39)	Unrevascularized (n=41)	p
<b>New heart failure</b>	<b>0</b>	<b>1</b>	<b>NS</b>	<b>7</b>	<b>19</b>	<b>&lt;0.01</b>
Recurrent MI or ischemia	3	10	NS	3	9	NS
<b>All-cause mortality</b>	<b>0</b>	<b>0</b>	<b>NS</b>	<b>1</b>	<b>7</b>	<b>&lt;0.05</b>

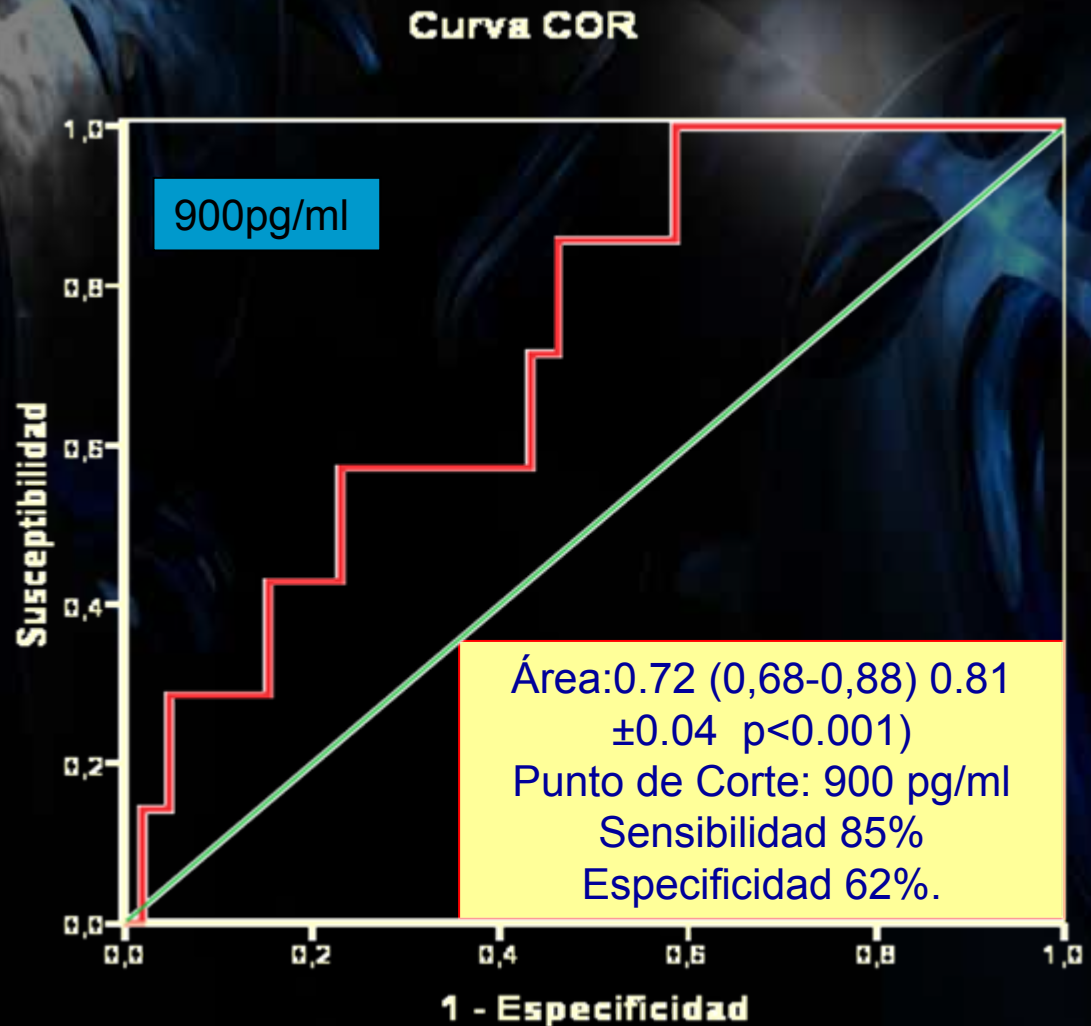
**BNP: B-type natriuretic peptide; MI: myocardial infarction; NS: not statistically significant; myocardial revascularization: percutaneous intervention or coronary artery bypass grafting, normal plasma BNP level is  $\leq 80$  pg/mL, elevated plasma BNP level is  $>80$  pg/mL.**

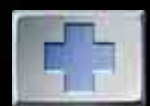


# Eventos y Curvas ROC

## NT-Pro BNP

A 542 días: 7 muertes (6.3%), y 20 muertes/infarto.

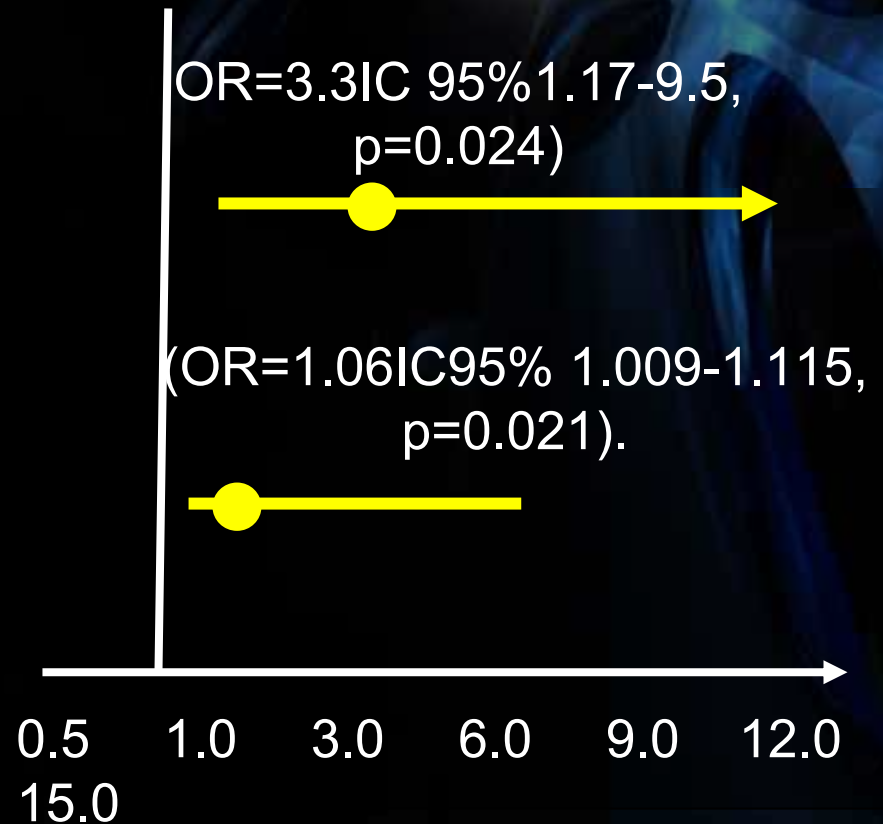


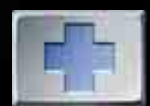


## Modelo multivariado predictores de pro BNP elevado

Localización anterior

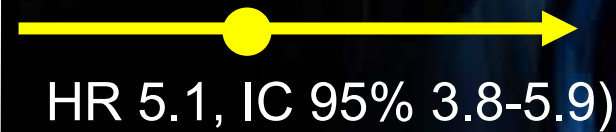
Edad



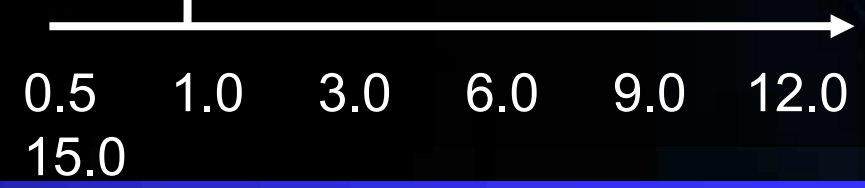


# Modelo Proporcional de Cox

Uremia

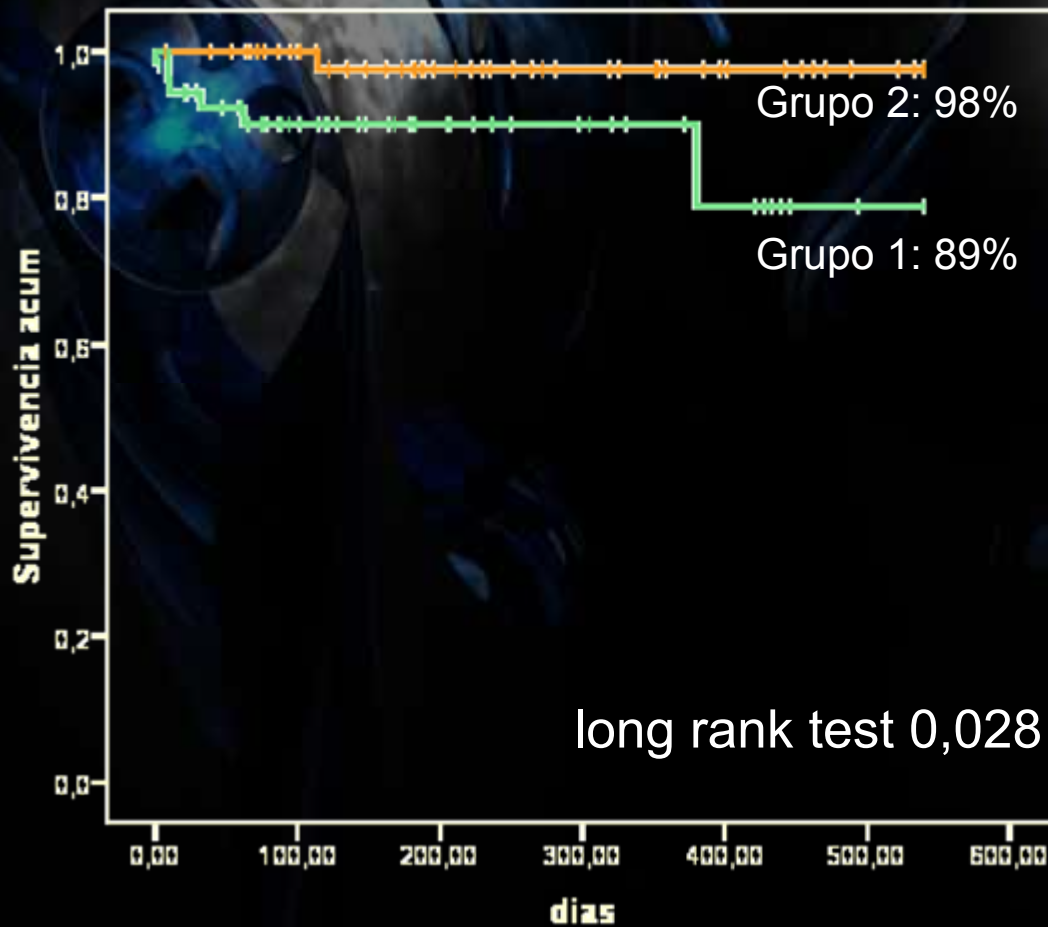


Rales





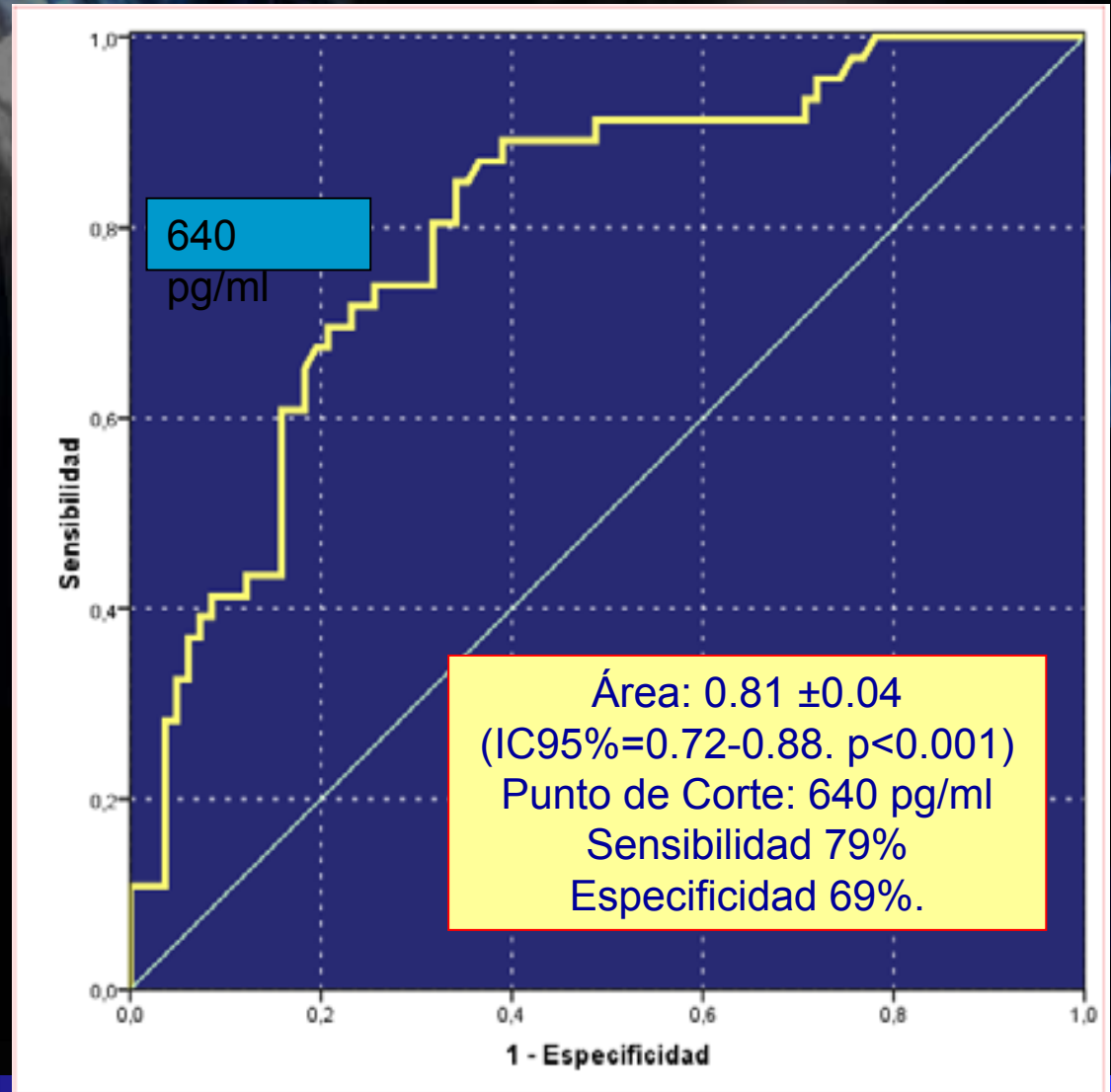
# Supervivencia por Kaplan Meyer



# Eventos y Curvas ROC

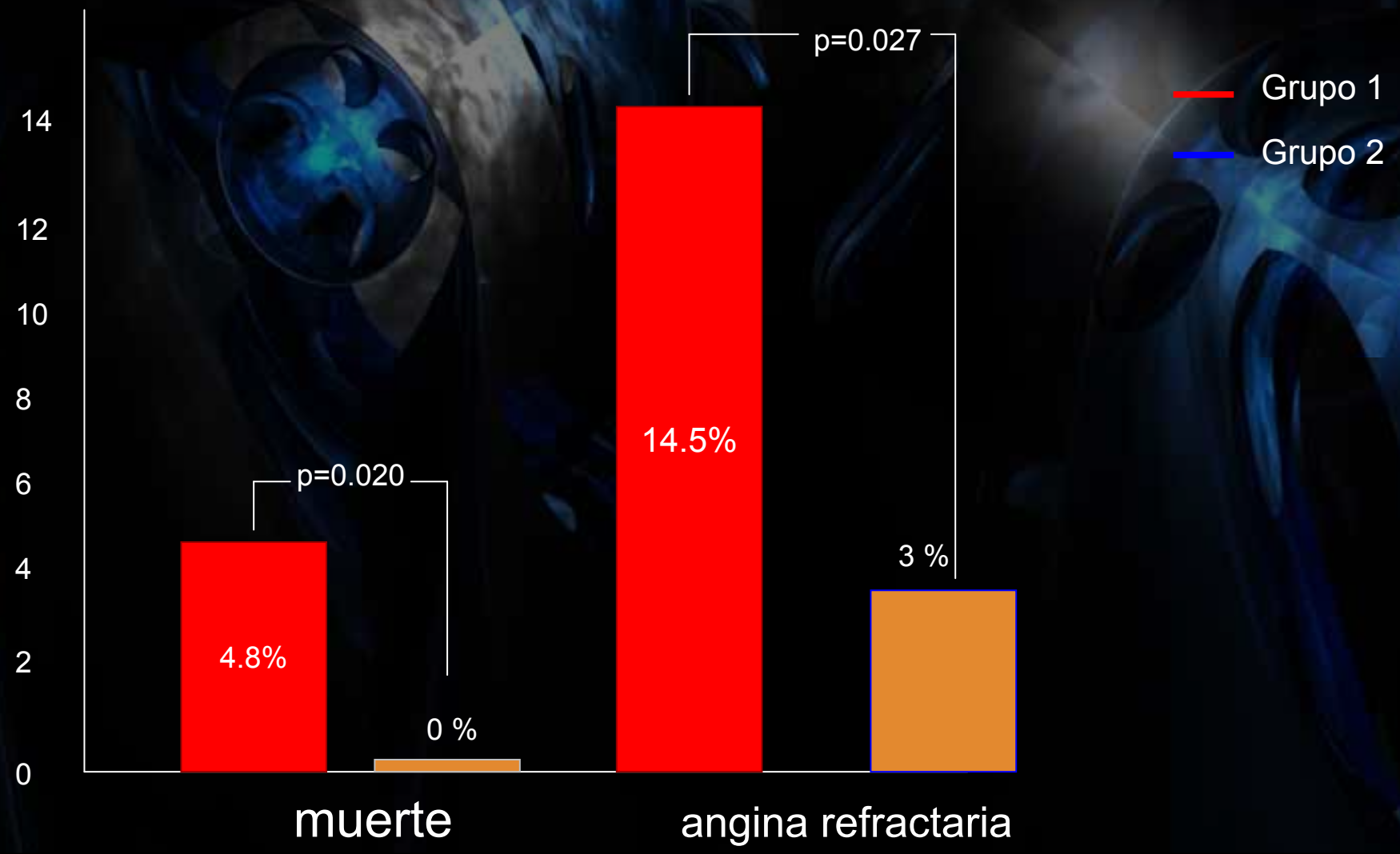
## NT-Pro BNP

A 7 días: 28 eventos  
(muerte/IAM-reIAM-  
Angina recurrente).



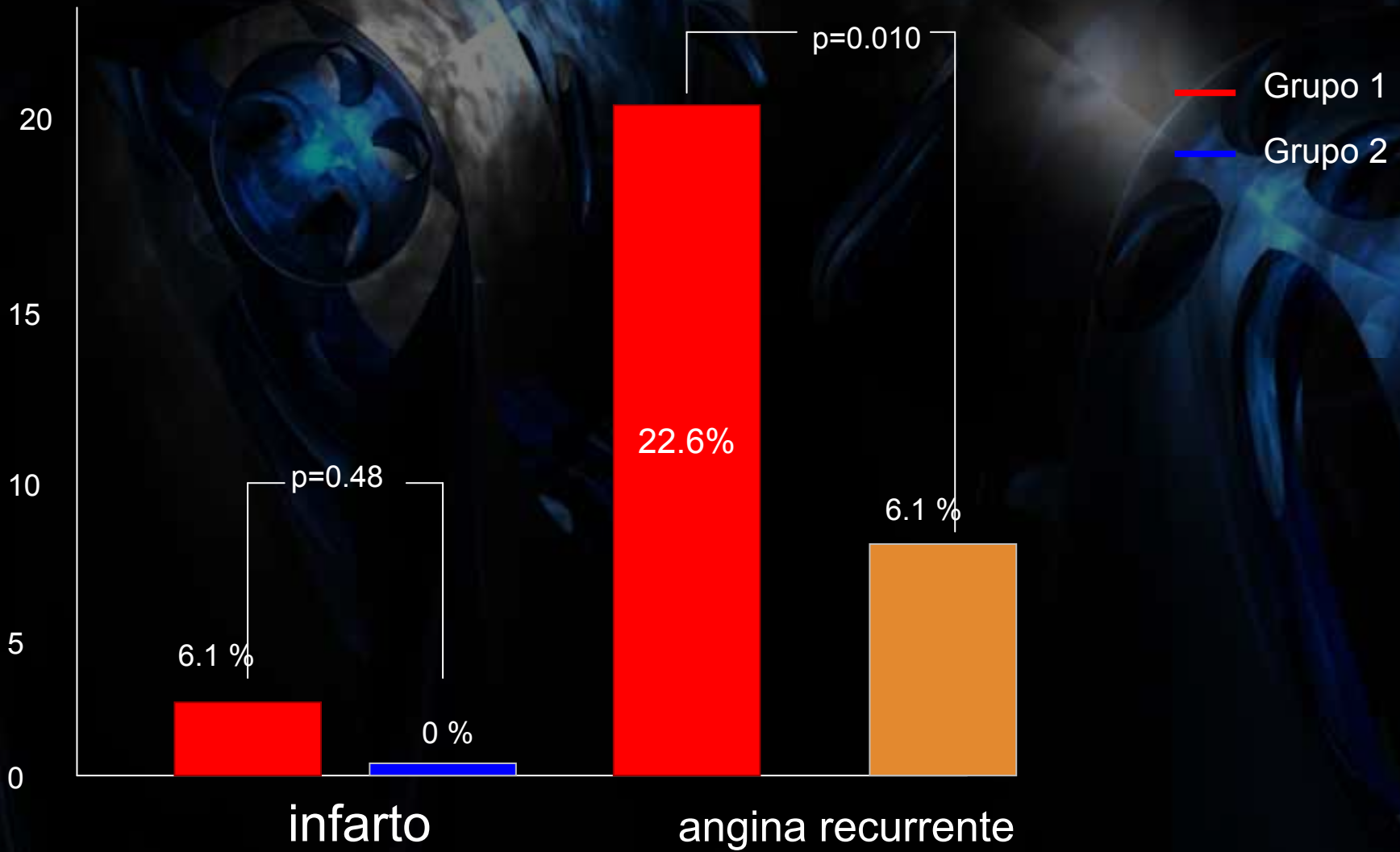


# Eventos





# Eventos



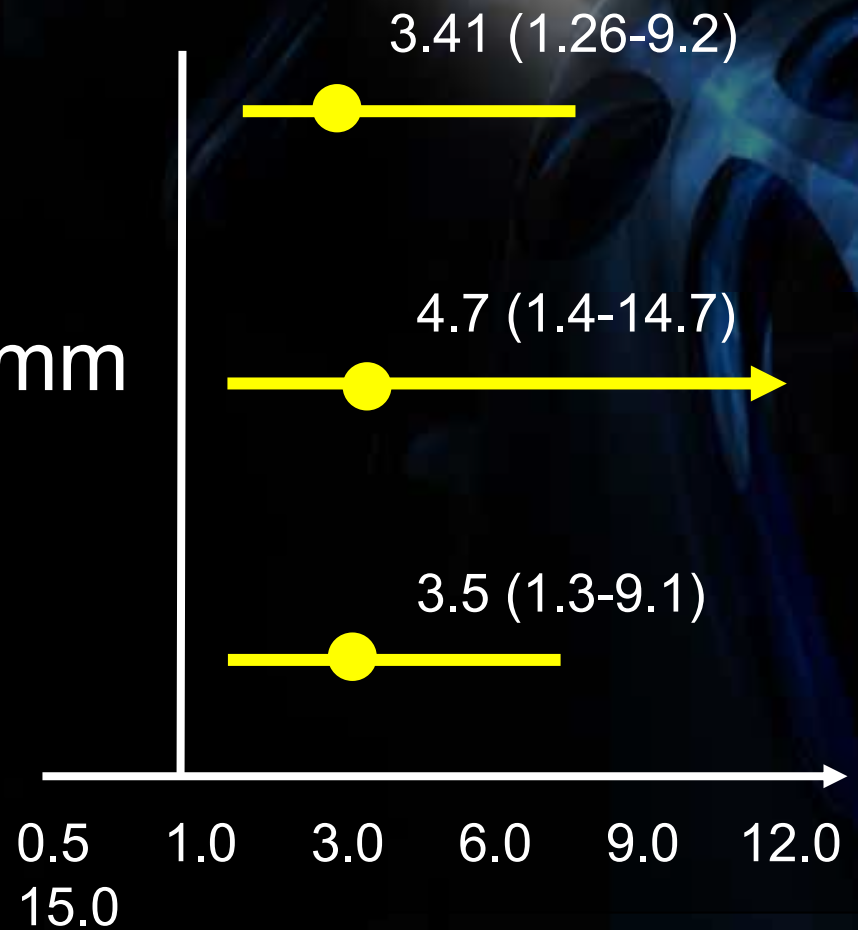


Modelo multivariado

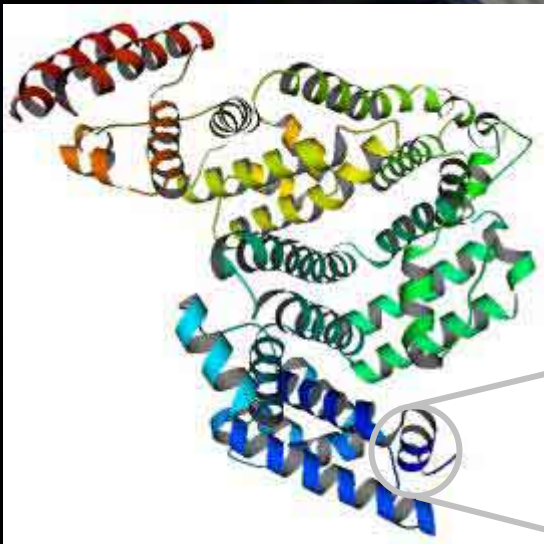
Score Grace >160

Infradesnivel del ST >2mm

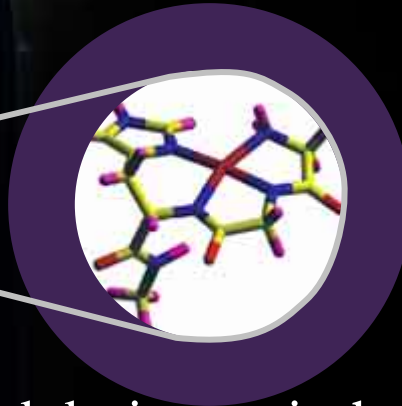
Angina previa



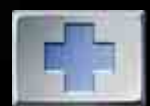
# What is IMA?



Human Serum Albumin (HSA) is a circulating protein in blood with a metal binding site at the N-terminus.



The N-terminus is altered during an ischemic event, resulting in Ischemia Modified Albumin (IMA<sup>TM</sup>). IMA is unable to bind metals at the N-terminus.



# Ischemia Modified Albumin (IMA)

- ❖ During ischemia, N-terminus of albumin is altered through a series of chemical reactions that cause free radical damage to albumin

## Strengths

- ❖ IMA is indicated for ED patients with chest pain, low to moderate risk for ACS, non-diagnostic ECG, normal troponin at presentation

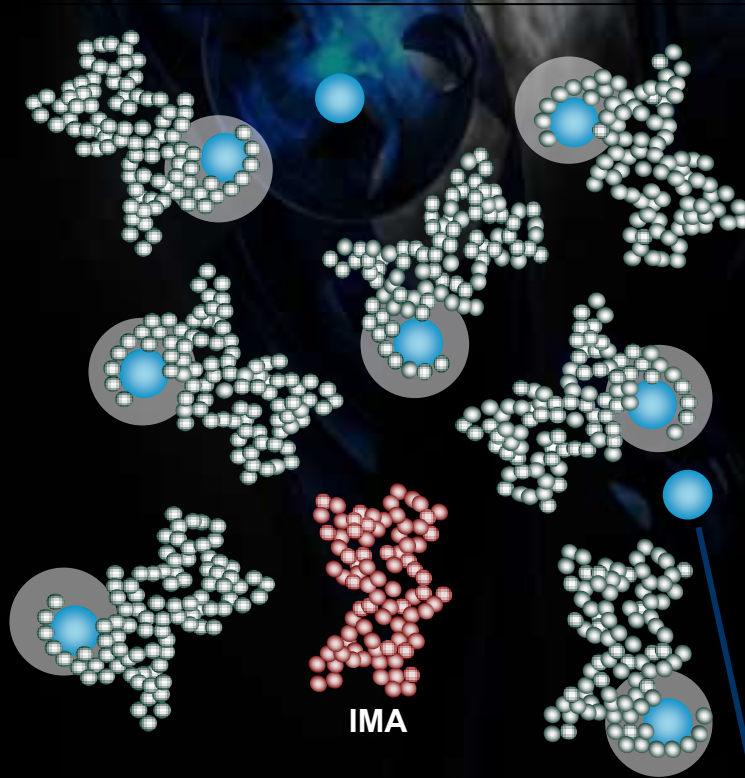
## Limitations

- ❖ Current data suggests that it may not be specific for cardiac ischemia
  - elevated in patients with cancer, infection, end-stage renal disease, liver disease and brain ischemia
- ❖ Limited published research available

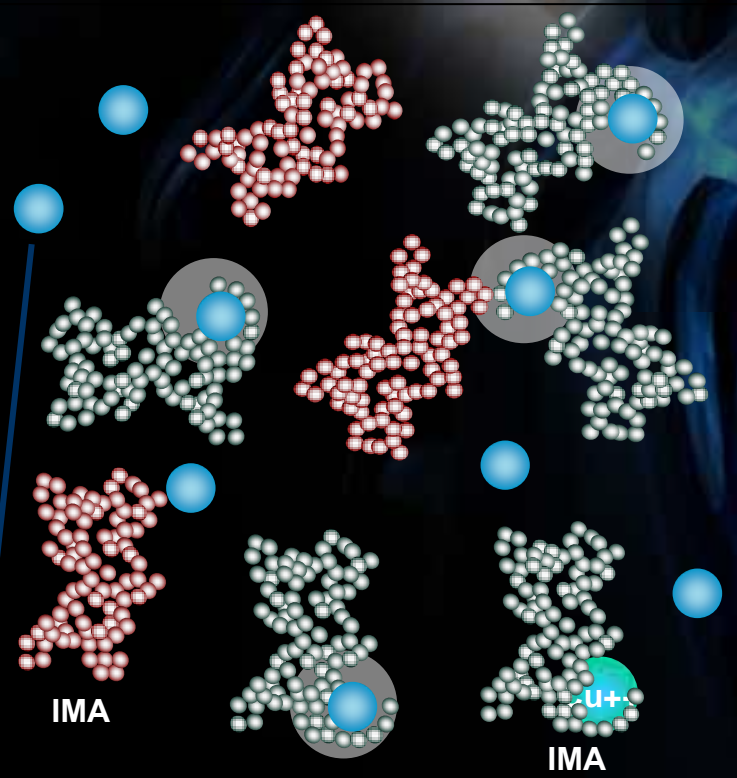


# ACB Test is an Indirect Measure of IMA

Normal Sample



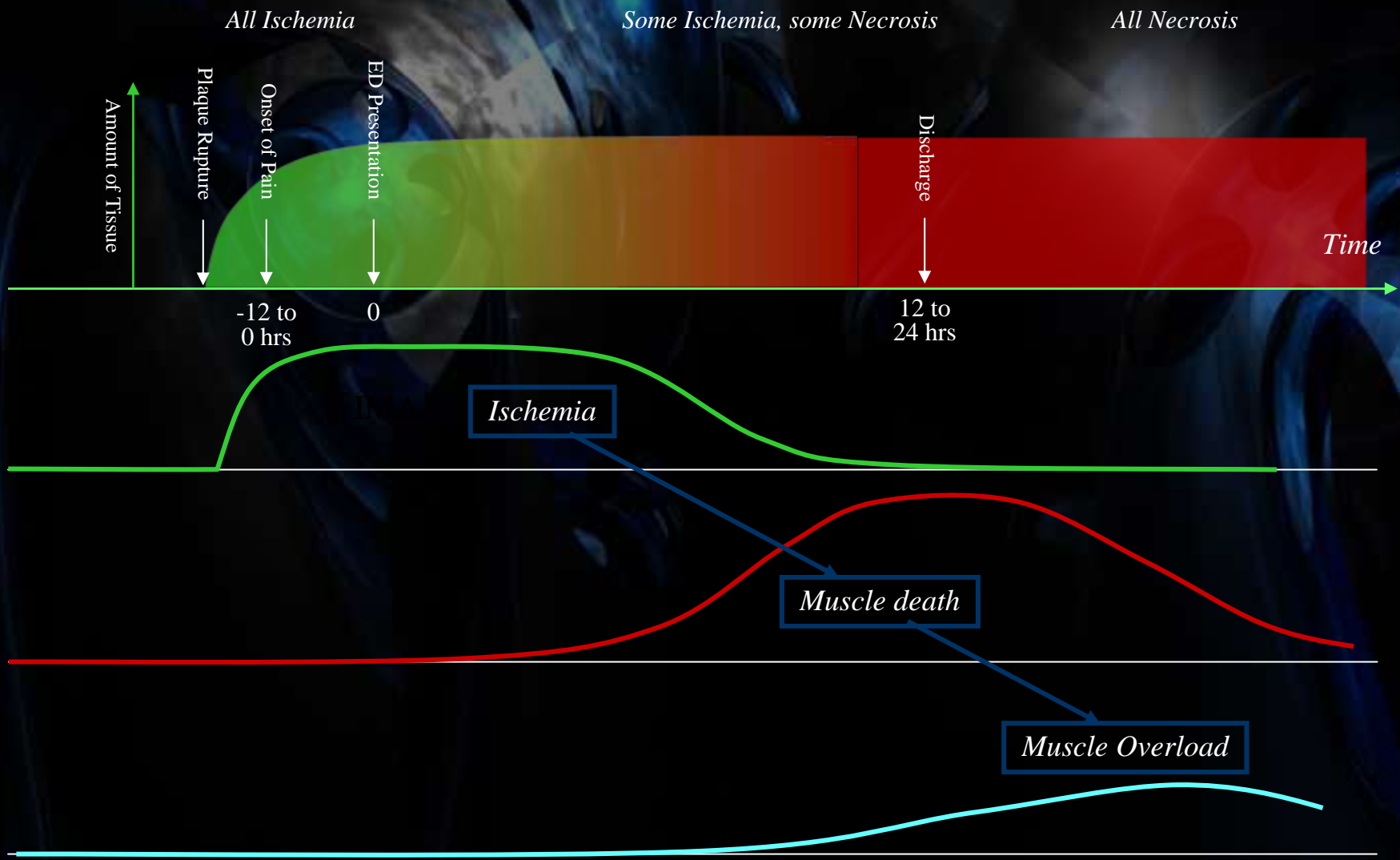
Ischemic Sample



ACB Test measures unbound cobalt

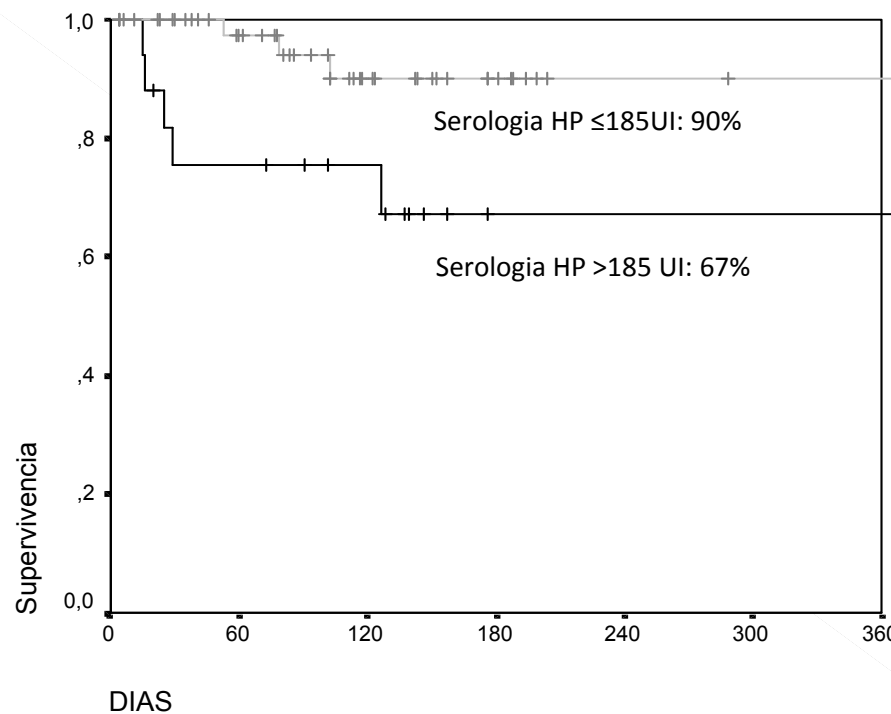
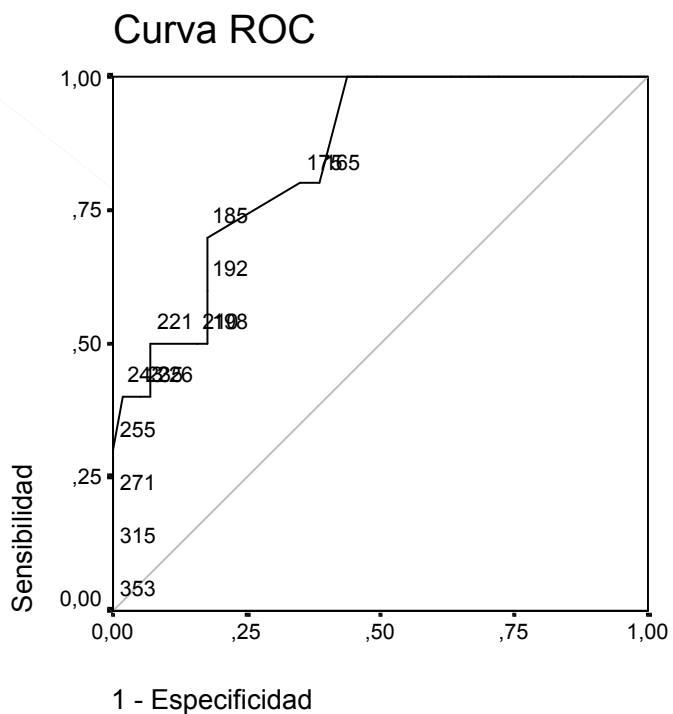


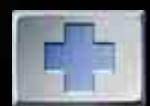
# ACS Sequence and Timing



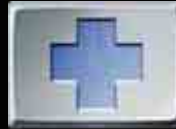


# Helicobacter pylori y SCA





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**Thank You !**

Dra. Stella Maris Macin