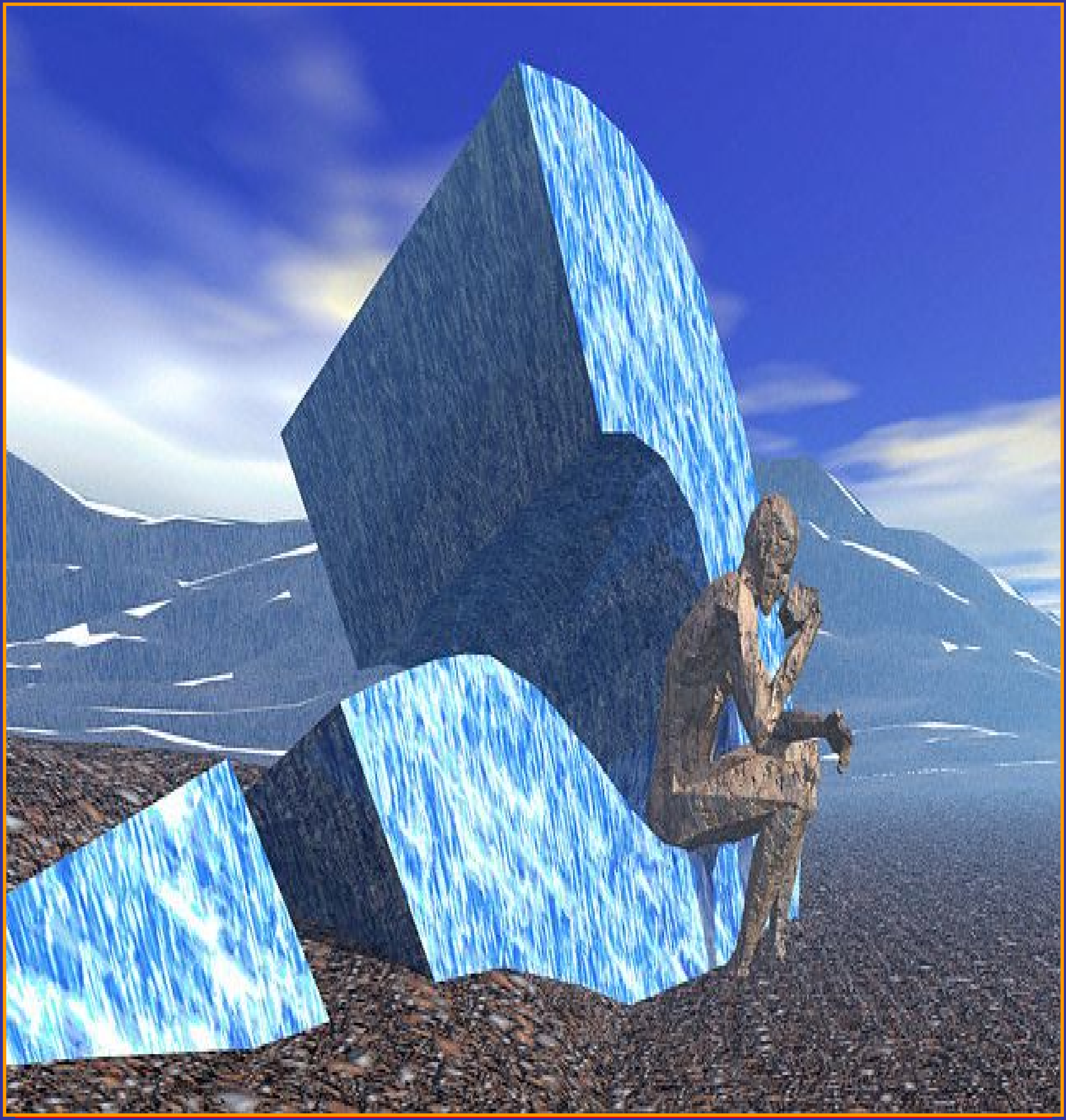
Νεώτεροι δείκτες στή Στεφανιαία Νόσο

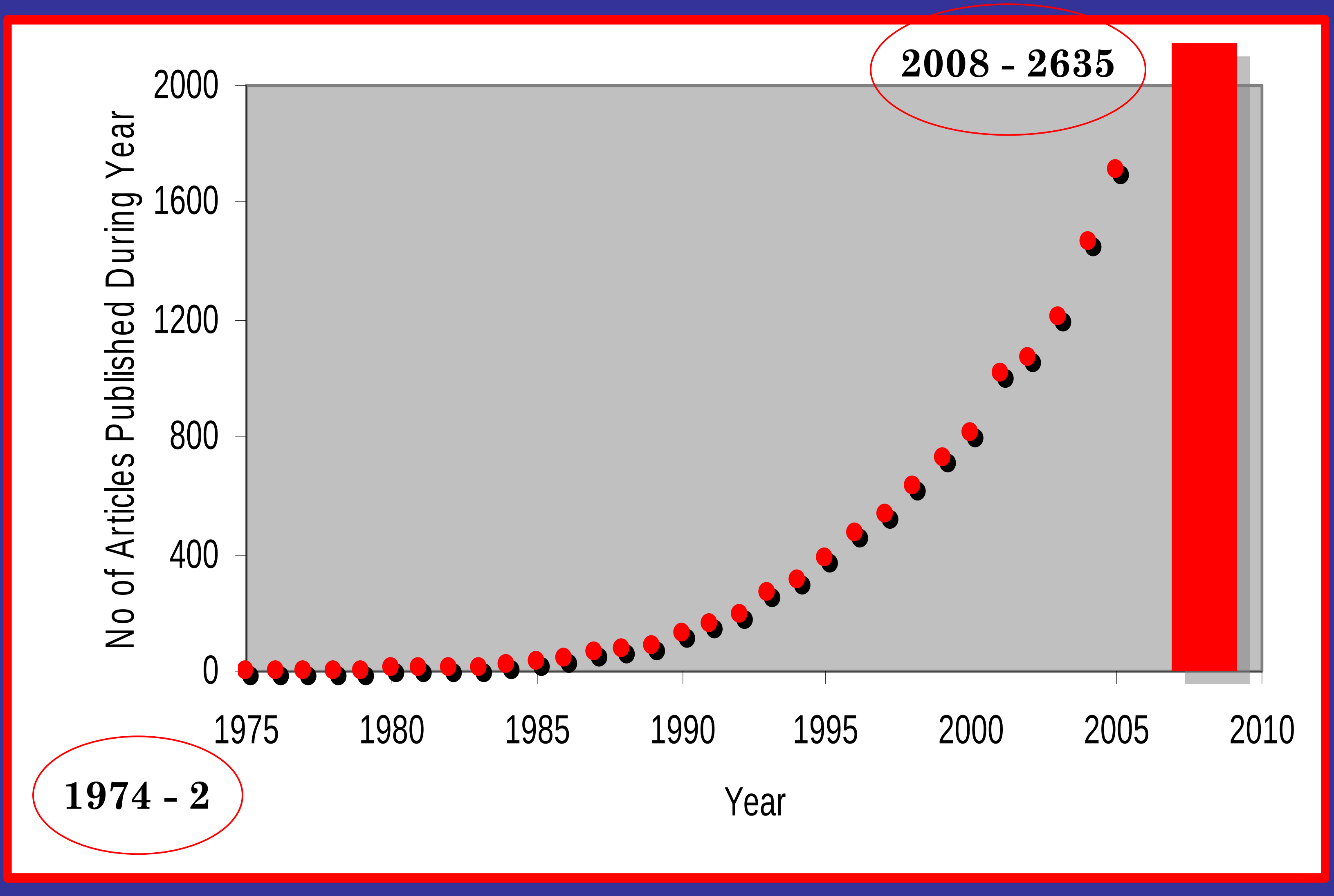
Δημήτριος Ν. Τζιακάς, *MD, FESC, FAHA, FCCP, FACC.*

Επίκουρος Καθηγητής Καρδιολογίας Δ.Π.Θ

www.cardioalex.gr



Δείκτες και Στεφανιαία Νόσος (1975 - 2008)



Δείγμα βιοδεικτών στη Σ.Ν

Leukocytes
ESR
Plasma viscosity
LDL-chol
HDL-chol
Tgl
Ox-LDL
apoB, apo A
LDL particle No
CETP
Lp-PLA,sPLA-IIA
Lp (a)

C-reactive protein
Serum amyloid A
Fibrinogen
Albumin
Plasminogen
PAI-1 / vWF
BNP / NT-pro BNP
D-Dimer
Cytokines
(TNF-a, IL-6, -8, -18, -10)
CAMs
Neopterin
MMPs / TIMPs
Myeloperoxidase

GPX1 activity
sLOX-1
Alpha$_1$-antitrypsin
Haptoglobin
Ceruloplasmin
Nitrotyrosine
C3, C4
IgA, G, M, and E
Sialic acid
CD-40 / CD-40L
Homocysteine
Cystatin
PAPP A

.. be continued

Ένας ιδανικός βιοδείκτης πρέπει…

A

1) Can the clinician measure the biomarker?

a) **Accurate and reproducible analytical method(s)**
b) **Pre-analytical issues (including stability) evaluated and manageable**
c) **Assay is accessible**
d) Available assays provide high through-put and rapid turn-around
e) Reasonable cost

2) Does the biomarker add new information?

a) **Strong and consistent association between the biomarker and the outcome or disease of interest in multiple studies**
b) **Information adds to or improves upon existing tests**
c) Decision-limits are validated in more than one study
d) Evaluation includes data from community-based populations

3) Will the biomarker help the clinician to manage patients ?

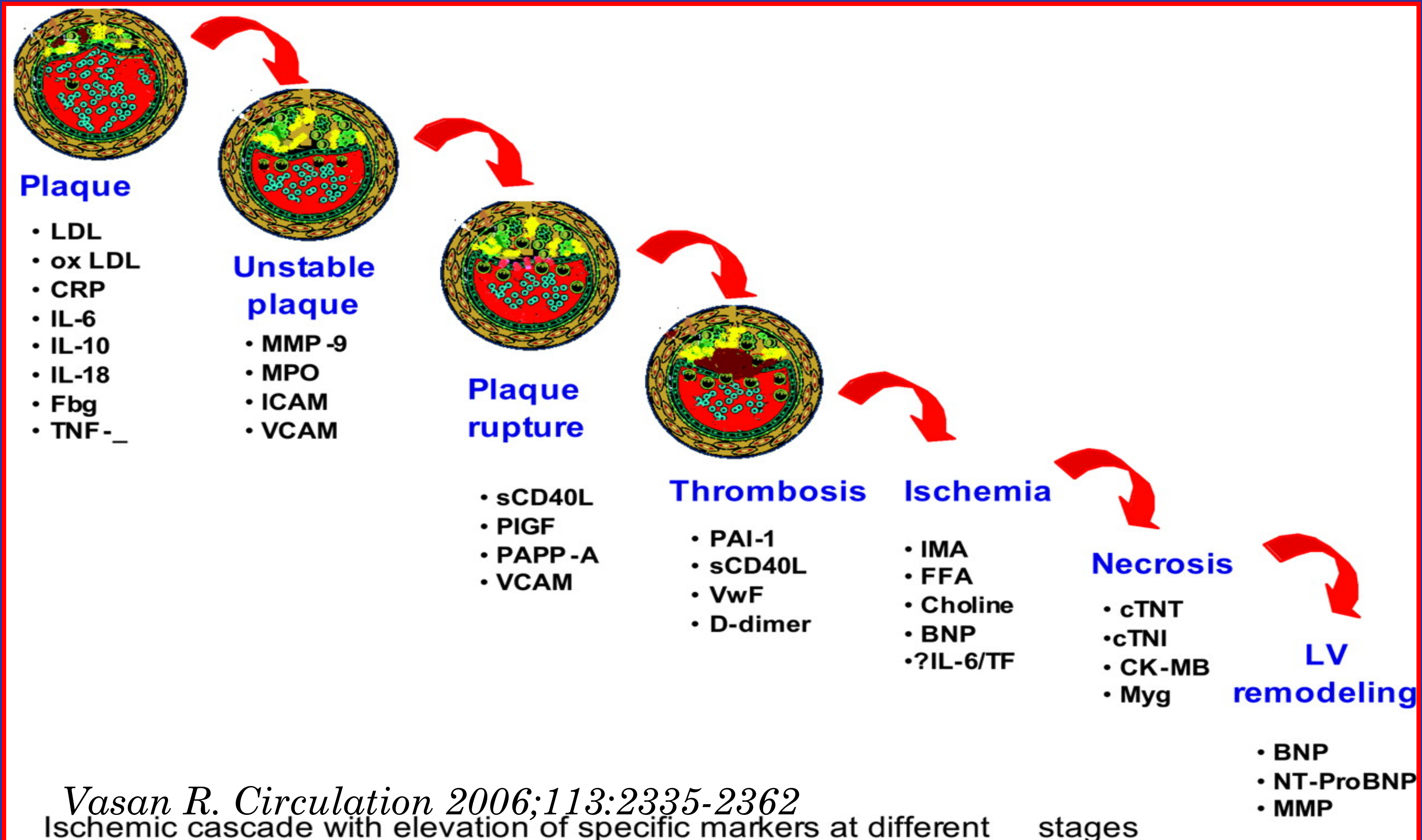
a) **Superior performance to existing diagnostic tests, or**
b) **Evidence that associated risk is modifiable with specific therapy, or**
c) **Evidence that biomarker-guided triage or monitoring enhances care**
d) Consider each of multiple potential uses (SEE PANEL B)

Ένας ιδανικός προγνωστικός δείκτης πρέπει...

TABLE 7. Some Key Questions to Ask Before Using a New Biomarker in Practice

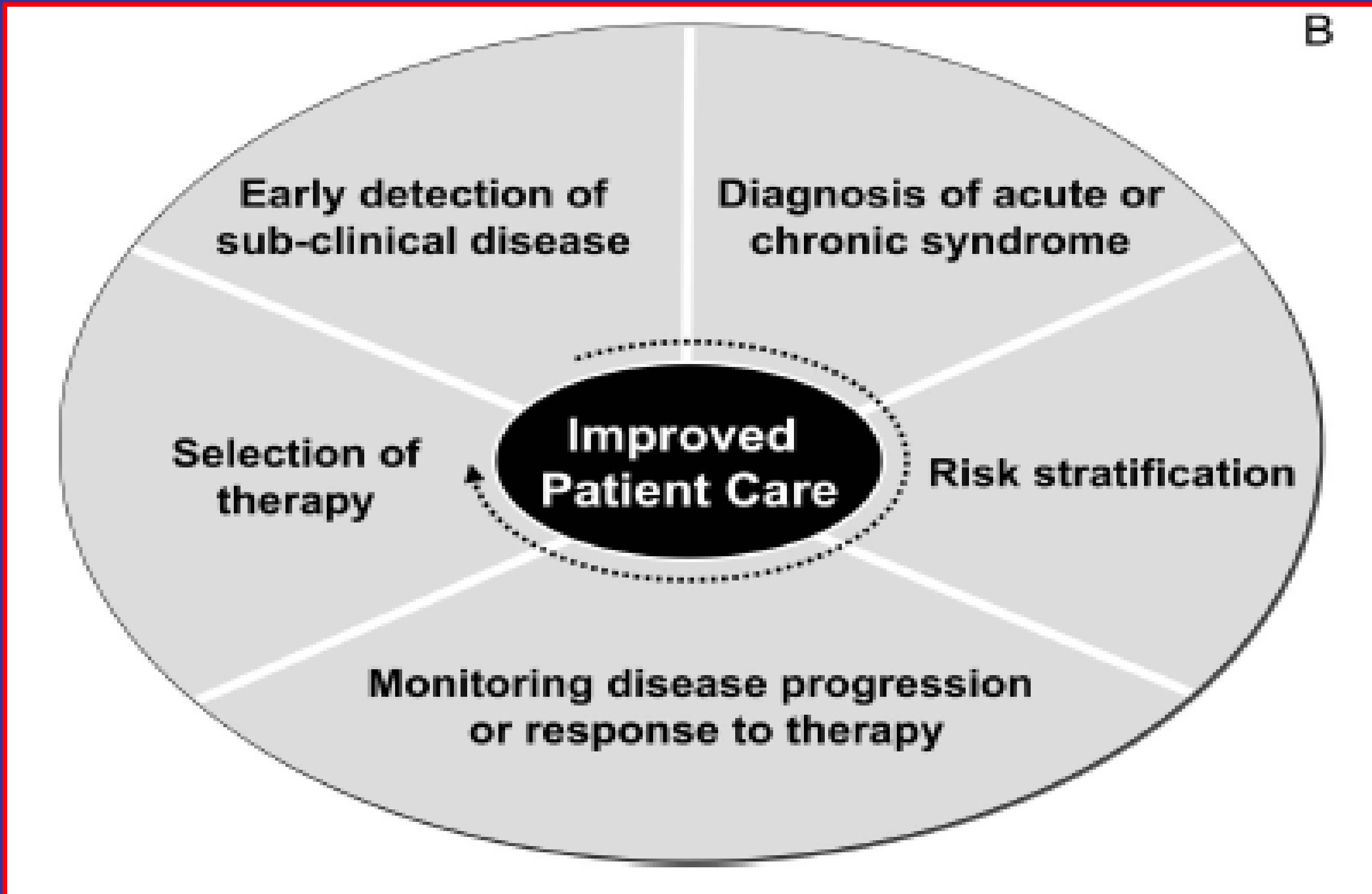
Has the assay been standardized?
Is the assay reproducible, accurate, and available?
Is the distribution of biomarker values in the general population and in select demographic subsets well known?
What are abnormal levels (reference limits and discrimination limits)?
Do biomarker levels correlate with known CVD risk factors?
Does a new biomarker reveal novel mechanisms of CVD initiation or progression?
Does the biomarker predict the outcome of interest?
Has residual confounding been excluded as an explanation for the observed association of a marker with CVD risk?
Is the new biomarker better than or does it have incremental utility over currently established biomarkers considered together?
Will the use of a multimarker strategy using a new biomarker in combination with known biomarkers improve overall testing for CVD?
Do the biomarkers add to the established risk prediction algorithms?
Can a therapeutic course of action or the likelihood of response to an agent be determined with the use of a new biomarker?
Will clinical practice change as a result of use of a new biomarker for screening, diagnosis, prognostication, or treatment?
Is use of the biomarker shown to be cost-effective?

Τύποι Βιολογικών δεικτών
(παθοφυσιολογικός διαχωρισμός)

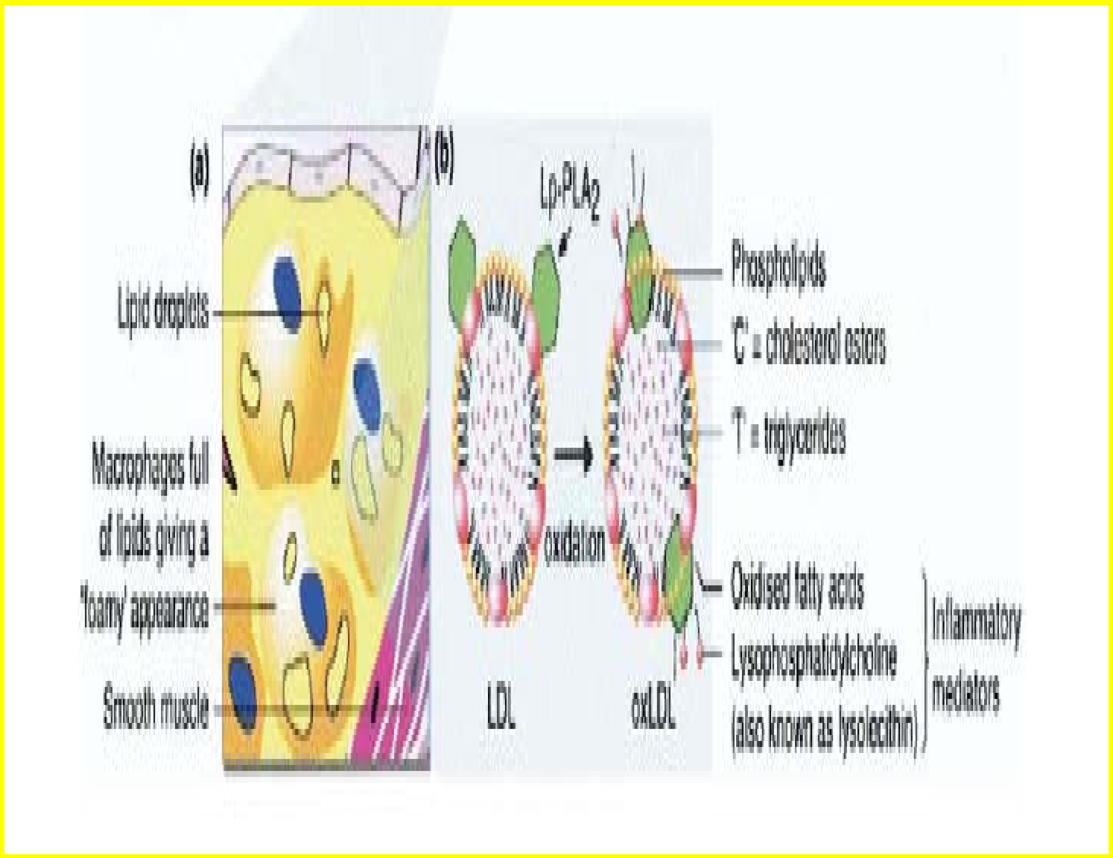


Vasan R. Circulation 2006;113:2335-2362

Τύποι Βιολογικών δεικτών (κλινικός διαχωρισμός)



Lipoprotein – associated phospholipase A2 (LpPLA2)



Lipoprotein – associated phospholipase A2 (LpPLA2)

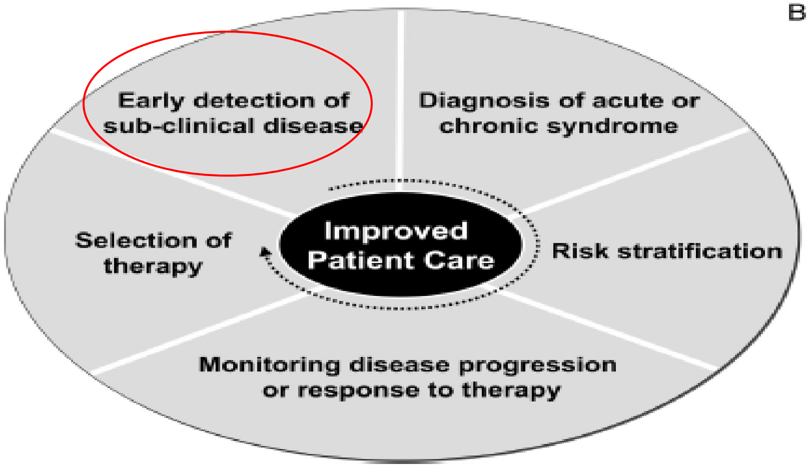


TABLE 4. CHD HRs (95% CI) by Lp-PLA$_2$ Tertiles

	Lp-PLA$_2$ Tertiles*	
	2 (310–422 μg/L)	3 (≥422 μg/L)
Model 1†	1.26 (0.94–1.69)	1.78 (1.33–2.38)
Model 2‡	1.02 (0.73–1.43)	1.16 (0.82–1.65)
Model 2,‡ LDL-C <130 mg/dL	1.83 (1.11–3.00)	1.99 (1.17–3.38)
Model 3§	1.00 (0.71–1.41)	1.15 (0.81–1.63)
Model 3,§ LDL-C <130 mg/dL	1.83 (1.10–3.05)	2.08 (1.20–3.62)

*Lowest tertile (<310 μg/L) is reference.
†Adjusted for age, sex, and race.
‡Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, and diabetes.
§Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, diabetes, and hs-CRP.

<130

TABLE 3. HR for CHD by a 1-SD Increase in Lp-PLA$_2$ or CRP, Each in a Separate Model, or Combined in the Same Model: MONICA/KORA Cohort Study 1984–1998 (n=934)

οπρ

Model	HR (95% CI)	P
Lp-PLA$_2$		
Unadjusted	1.37 (1.16–1.62)	0.0002
Adjusted for age, DM, smoking	1.26 (1.05–1.54)	0.01
Multivariable adjustment*	1.23 (1.02–1.47)	0.03
CRP		
Unadjusted	1.57 (1.30–1.91)	0.0001
Adjusted for age, DM, smoking	1.32 (1.07–1.62)	<0.009
Multivariable adjustment*	1.28 (1.03–1.60)	<0.03
Lp-PLA$_2$ and CRP		
Unadjusted		
Lp-PLA$_2$	1.35 (1.14–1.60)	0.0006
CRP	1.55 (1.28–1.89)	<0.0001
Adjusted for age, DM, smoking		
Lp-PLA$_2$	1.25 (1.04–1.50)	<0.02
CRP	1.31 (1.07–1.62)	0.01
Multivariable adjustment*		
Lp-PLA$_2$	1.21 (1.01–1.45)	0.04
CRP	1.27 (1.01–1.59)	0.04

Circulation 2004;109;837-842

Circulation 2004;110;1903-1908;

Lipoprotein – associated phospholipase A2 (LpPLA2)

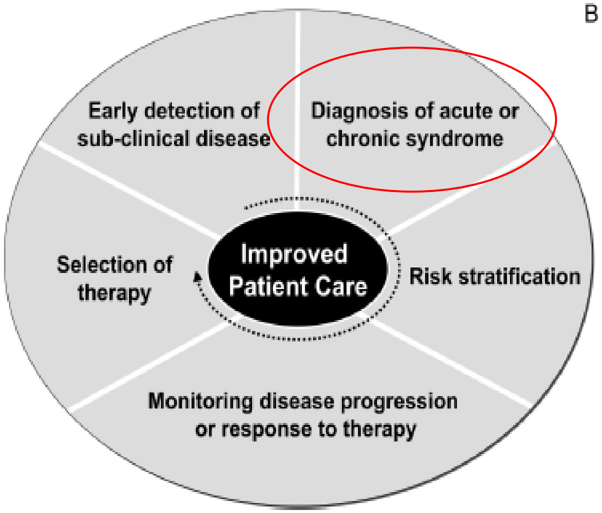
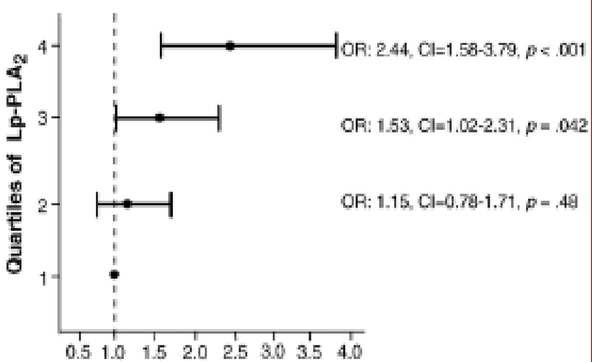


Figure 2



Adjusted ORs of CAD risk for Lp-PLA$_2$ quartiles.

Table 2 Lp-PLA2, CRP, and fibrinogen levels in patients with and without an acute coronary syndrome

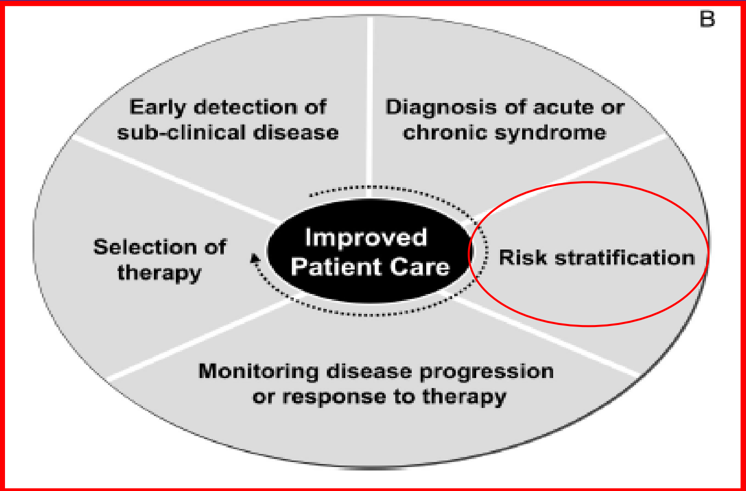
	AMI (n = 41)	UA (n = 128)	Non-ACS (n = 335)	P-value
Lp-PLA2, ng/mL	254 ± 75	245 ± 83	243 ± 97	0.77
CRP, mg/L[a]	13.4 (5.9-32.8)	3.2 (1.3-6.6)	2.2 (1.0-5.6)	<0.001
Fibrinogen, mg/dL	549 ± 164	468 ± 123	438 ± 115	<0.001
Total cholesterol, mmol/L	5.3 ± 1.1	5.4 ± 1.0	5.4 ± 1.2	0.79
Triglycerides, mmol/L[a]	1.7 (1.3-2.10)	1.7 (1.3-2.6)	1.7 (1.3-2.3)	0.74
HDL cholesterol, mmol/L	1.1 ± 0.3	1.2 ± 0.4	1.3 ± 0.4	<0.001
LDL cholesterol, mmol/L	3.4 ± 1.0	3.3 ± 1.0	3.2 ± 0.9	0.39

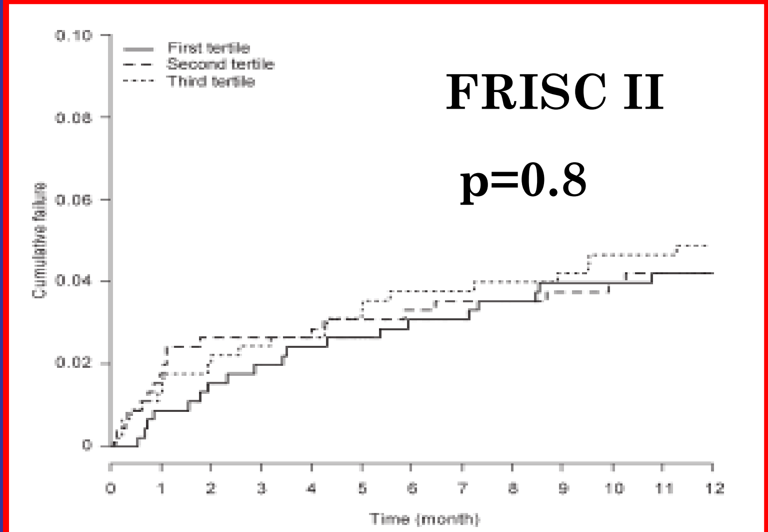
Plus-minus values are mean ± standard deviation.
[a]Median (interquartile range).
ACS, acute coronary syndrome. Other abbreviations as in text and Table 1.

American Heart Journal
Volume 152, Number 5

European Heart Journal (2005) 26, 137-144

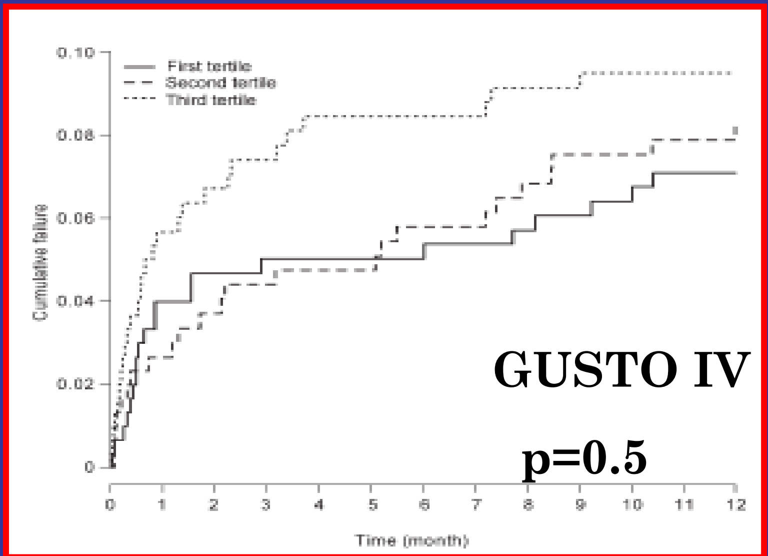
Lipoprotein – associated phospholipase A2 (LpPLA2)





MI
RV

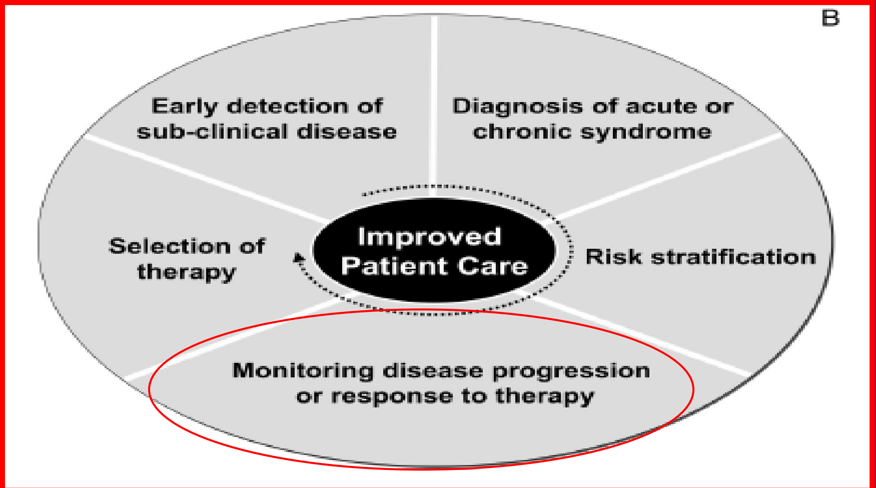
Outcome	Q1 9.2–24.6 (n=654)	Q2 24.6–31.0 (n=649)	Q3 31.0–36.9 (n=657)	Q4 36.9–45.3 (n=654)	Q5 45.3–105.2 (n=651)	P_{trend}	Adjusted HR, Q5:Q1 (95% CI)*
	Unadjusted Event Rates by Quintile, %						
Primary end point	17.6	21.8	22.6	22.6	26.4	0.002	1.33 (1.01–1.74)
Death or MI	5.4	7.8	6.9	7.5	11.3	<0.001	1.70 (1.08–2.68)
Death	1.7	2.5	2.6	2.3	2.8	0.24	1.30 (0.57–2.94)
MI	3.8	5.6	5.0	5.6	9.4	<0.001	1.98 (1.17–3.34)
Unstable angina	3.3	2.7	5.6	2.2	3.4	0.99	0.85 (0.42–1.71)
Revascularization	13.4	16.1	17.7	17.4	20.3	0.006	1.33 (0.97–1.82)
Stroke	0.97	0.99	0.38	0.82	0.97	0.89	1.02 (0.28–3.69)

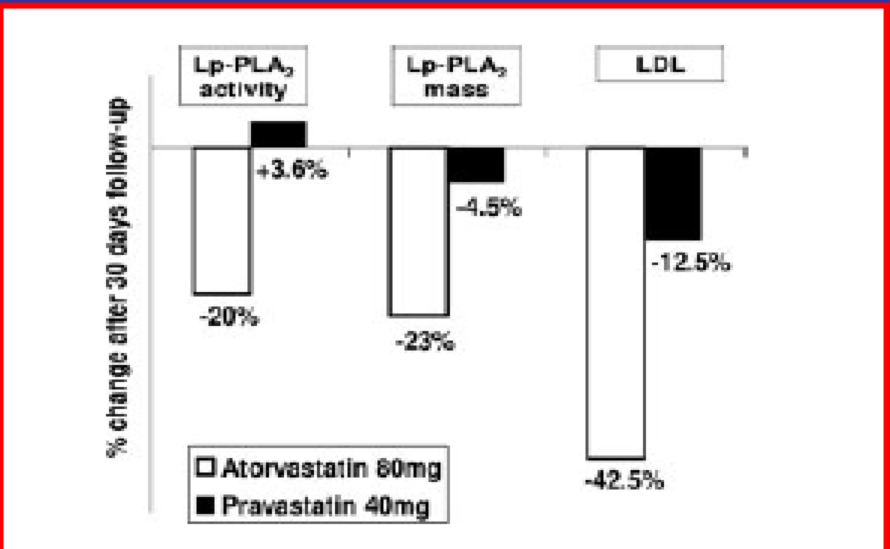


Circulation 2006;113:1745-1752

European Heart Journal (2007) 28, 699-704

Lipoprotein – associated phospholipase A2 (LpPLA2)





Circulation 2006:113:1745-1752

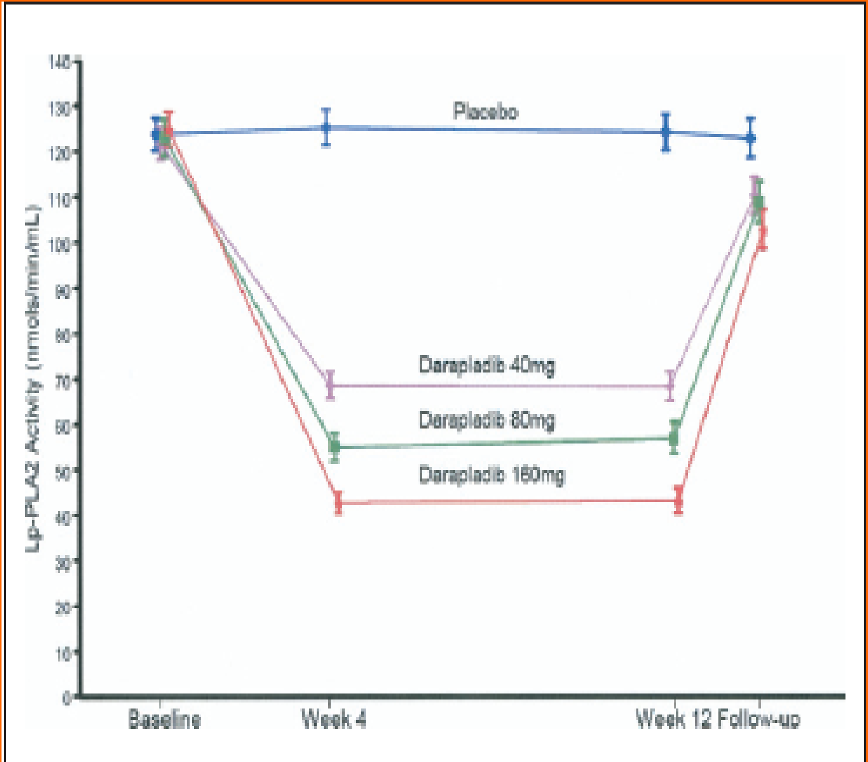


Figure 2 Plasma Lp-PLA$_2$ Activity

CRP-IL6

The results are presented as geometric means with 95% confidence interval. All doses of darapladib produced highly significant inhibition of lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) activity when compared with placebo at weeks 4 and 12 ($p < 0.001$).

JACC Vol. 51, No. 17, 2008
April 29, 2008:1632–41

Νέοι προγνωστικοί δείκτες στην Στεφανιαία Νόσο (2007-2008)

- **Growth differentiation factor -15**
- **Heart type fatty acid binding protein**
- **Thrombus precursor protein**
- **Myeloid-related protein -14**
- **F11R/JAM-A**

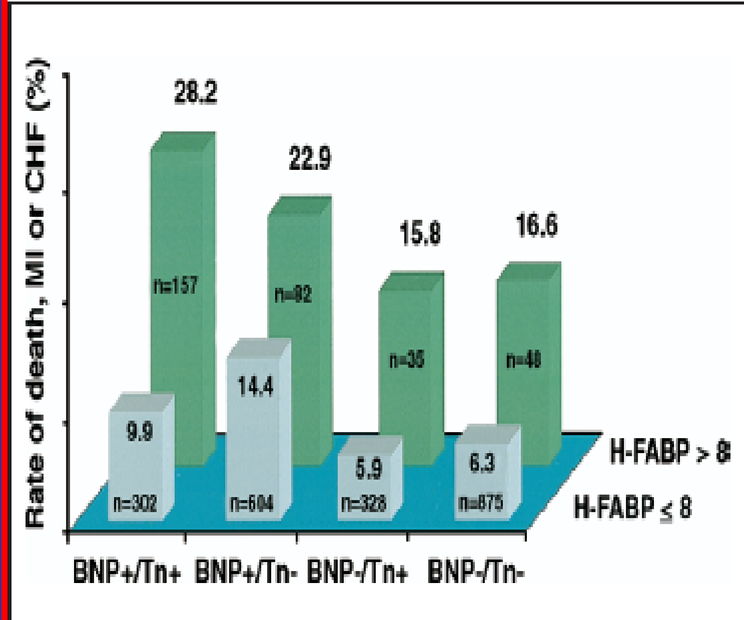


Figure 2 Predictive Value of H-FABP After an Acute Coronary Syndrome

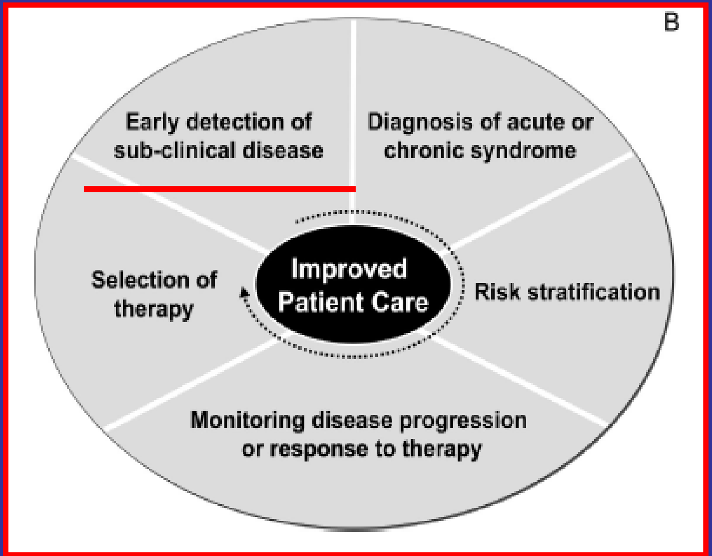
Rates of death, myocardial infarction (MI), or congestive heart failure (CHF) stratified by baseline concentration of brain natriuretic peptide (BNP), troponin I (Tn), or heart-type fatty acid binding protein (H-FABP) in the OPUS-TIMI 16 study. BNP + = BNP >80 pg/ml; Tn + = troponin I >1.5 ng/ml. Reproduced with permission from O'Donoghue et al. (20).

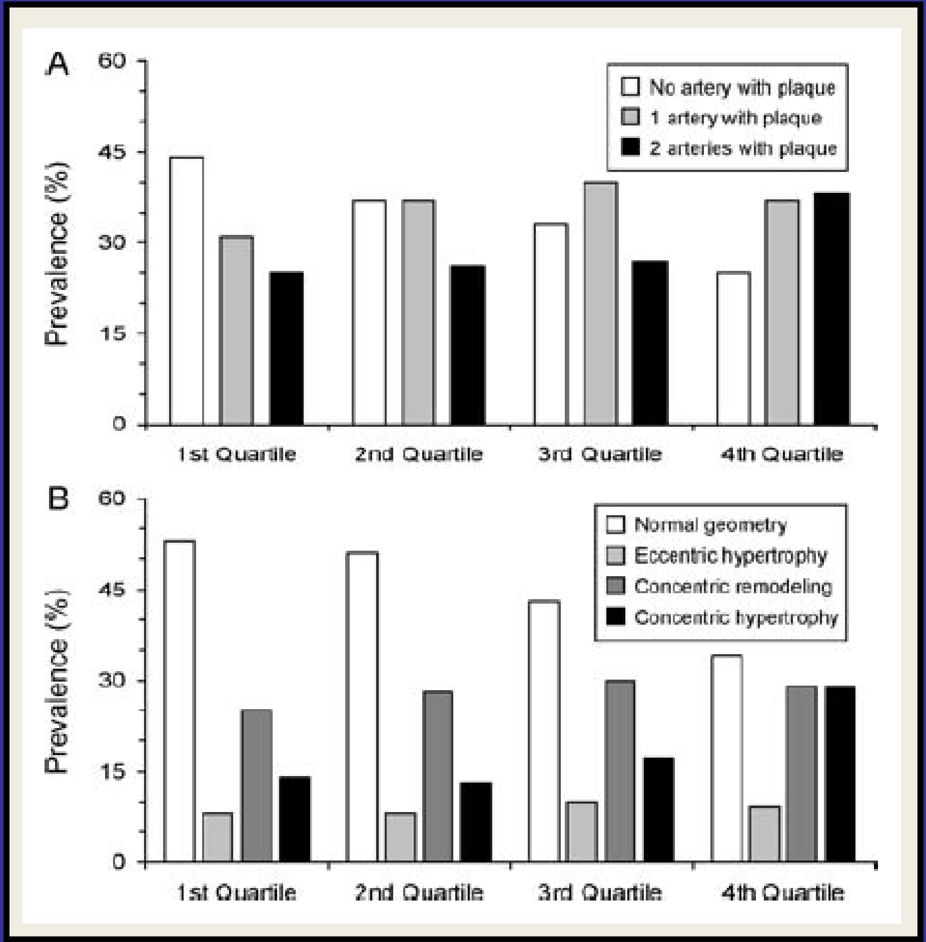
JACC Vol. 49, No. 16, 2007
April 24, 2007:1740–9

Current Opinion in Cardiology 2008, 23:309–314

JACC Vol. 50, No. 18, 2007
October 30, 2007:1777–80

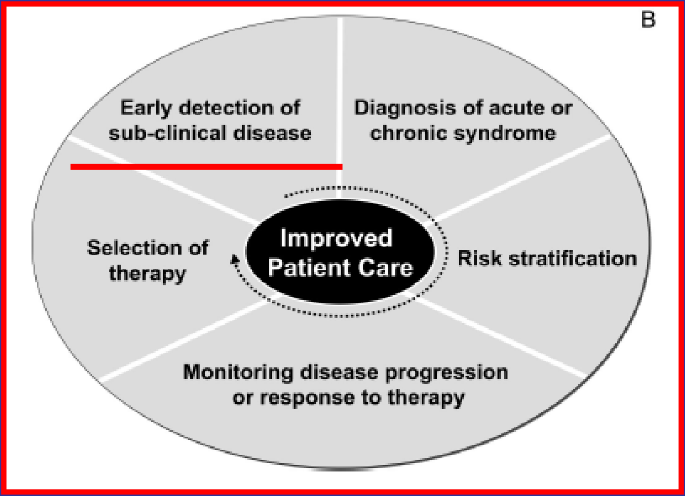
Growth-differentiation factor-15





European Heart Journal (2009) **30**, 2346–2353
doi:10.1093/eurheartj/ehp261

Growth-differentiation factor-15



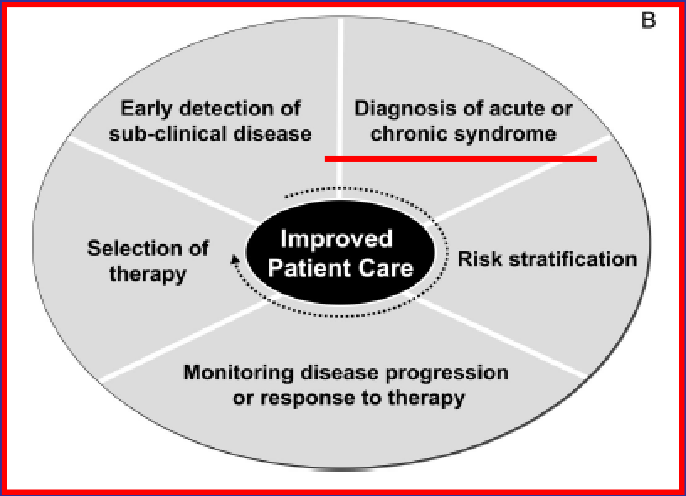
European Heart Journal (2009) **30**, 2346–2353
doi:10.1093/eurheartj/ehp261

Table 4 Predictive value of GDF-15 for any cardiovascular diagnosis

Parameter	Simple model OR (95% CI)	P-value	Multiple model OR (95% CI)	P-value
Framingham score	1.02 (0.97 to 1.07)	0.53	1.00 (0.94 to 1.07)	0.92
EDV	0.81 (0.58 to 1.13)	0.21	0.99 (0.69 to 1.41)	0.96
IMT	1.11 (0.39 to 3.21)	0.84	0.51 (0.13 to 1.91)	0.32
GDF-15	3.95 (2.49 to 6.25)	<0.001	4.08 (2.22 to 7.50)	<0.001

Simple and multiple logistic regressions, any CV diagnosis as outcome variable. All variables were treated as continuous variables. GDF-15 and EDV were ln transformed. The multiple models includes all four variables. ORs refer to a 1-point increase in 10-year risk calculated by the Framingham risk score, an increase of 1 unit in the ln scale for EDV and GDF-15, and a 1 mm increase in IMT.
OR, estimated odds ratio; CI, confidence interval; EDV, endothelium-dependent vasodilation; IMT, intima-media thickness.

Growth-differentiation factor-15



Circulation: Cardiovascular Genetics. 2009;2:286-292
Published online before print March 31, 2009, doi: 10.1161/CIRCGENETICS.108.824870

« Previous Article | Table of Contents | Next Article »

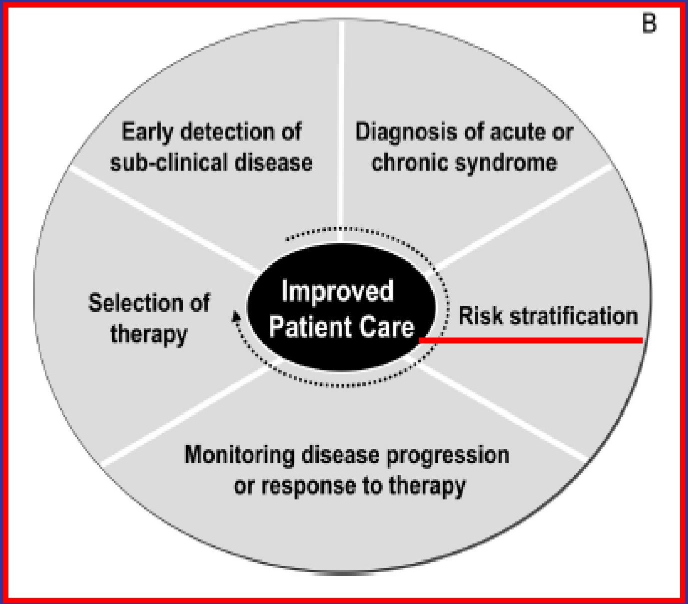
Original Articles

Growth-Differentiation Factor-15 for Risk Stratification in Patients With Stable and Unstable Coronary Heart Disease

Results From the AtheroGene Study

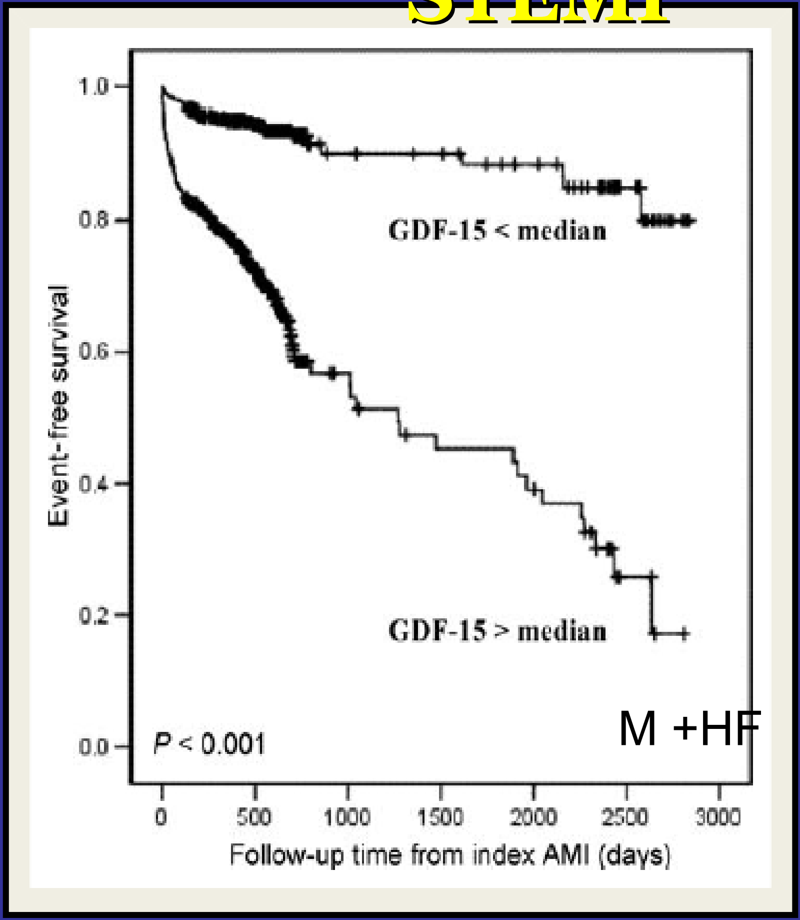
Tibor Kempf, MD; Jan-Malte Sinning, MD; Anja Quint, BSc; Christoph Bickel, MD; Christoph Sinning, MD; Philipp S. Wild, MD; Renate Schnabel, MD; Edith Lubos, MD; Hans J. Rupprecht, MD; Thomas Münzel, MD; Helmut Drexler, MD; Stefan Blankenberg, MD and Kai C. Wollert, MD

Growth-differentiation factor-15

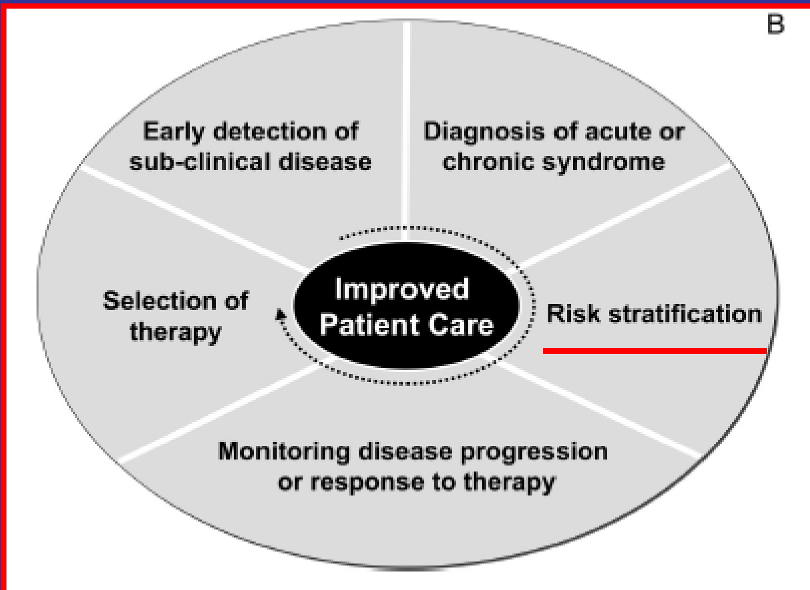


European Heart Journal (2009) **30**, 1057–1065
doi:10.1093/eurheartj/ehn600

STEMI



Growth-differentiation factor-15



European Heart Journal (2007) 28, 2858-2865
doi:10.1093/eurheartj/ehm465

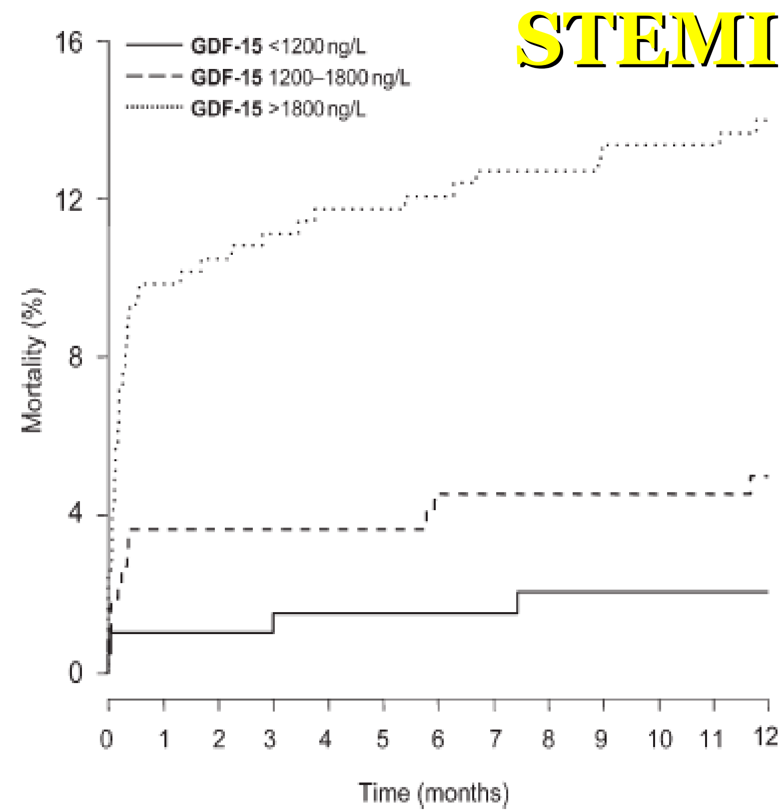
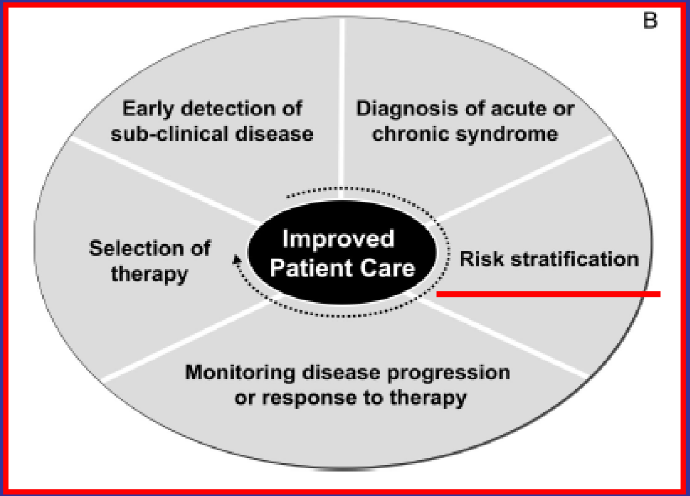


Figure 1 Cumulative probability of death according to levels of growth-differentiation factor-15 at presentation in 730 patients with ST-segment elevation myocardial infarction enrolled in ASSENT-2 or ASSENT-plus ($P < 0.001$ by log-rank test).

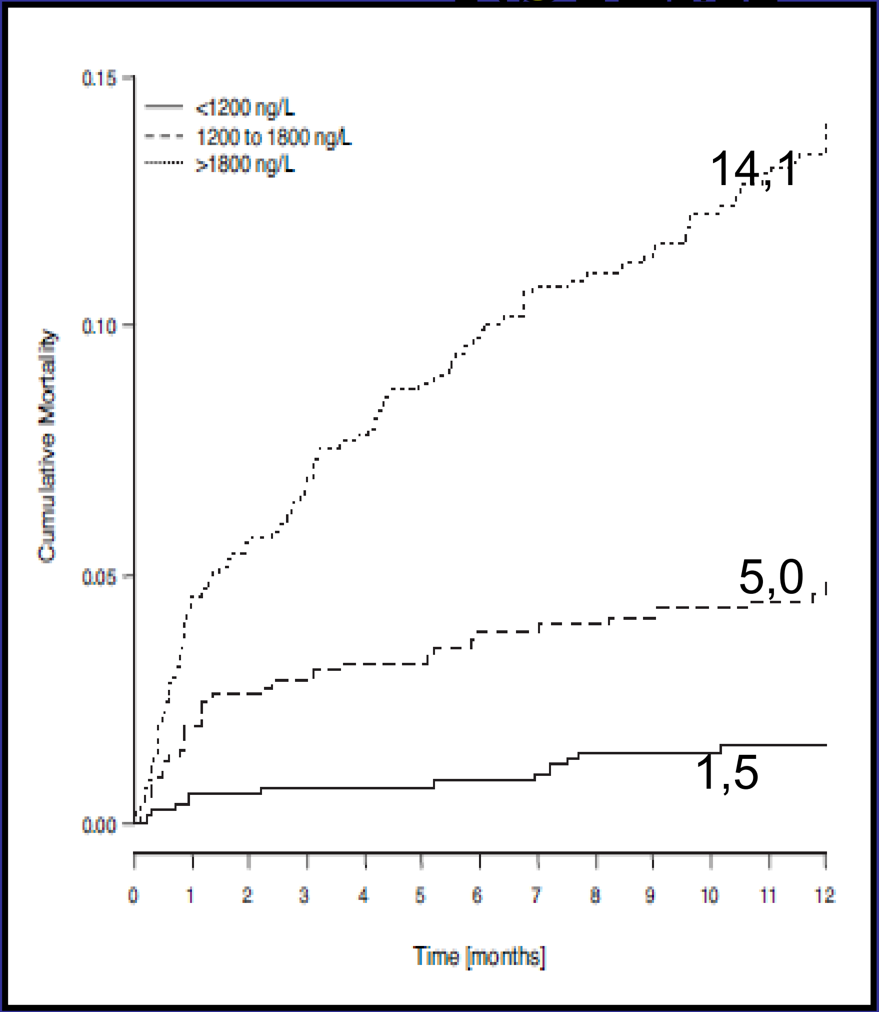
GDF-15 remained an independent predictor of mortality after adjustment for clinical variables, **troponin T, and NT-proBNP**.

Growth-differentiation factor-15



(Circulation. 2007;115:962-971.)

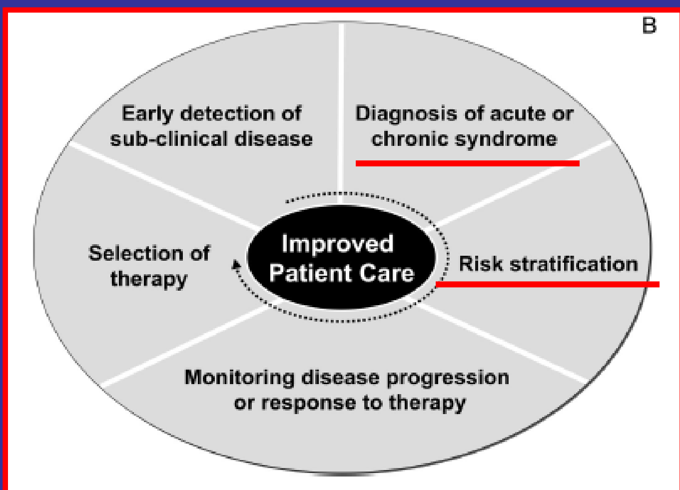
NSTEMI

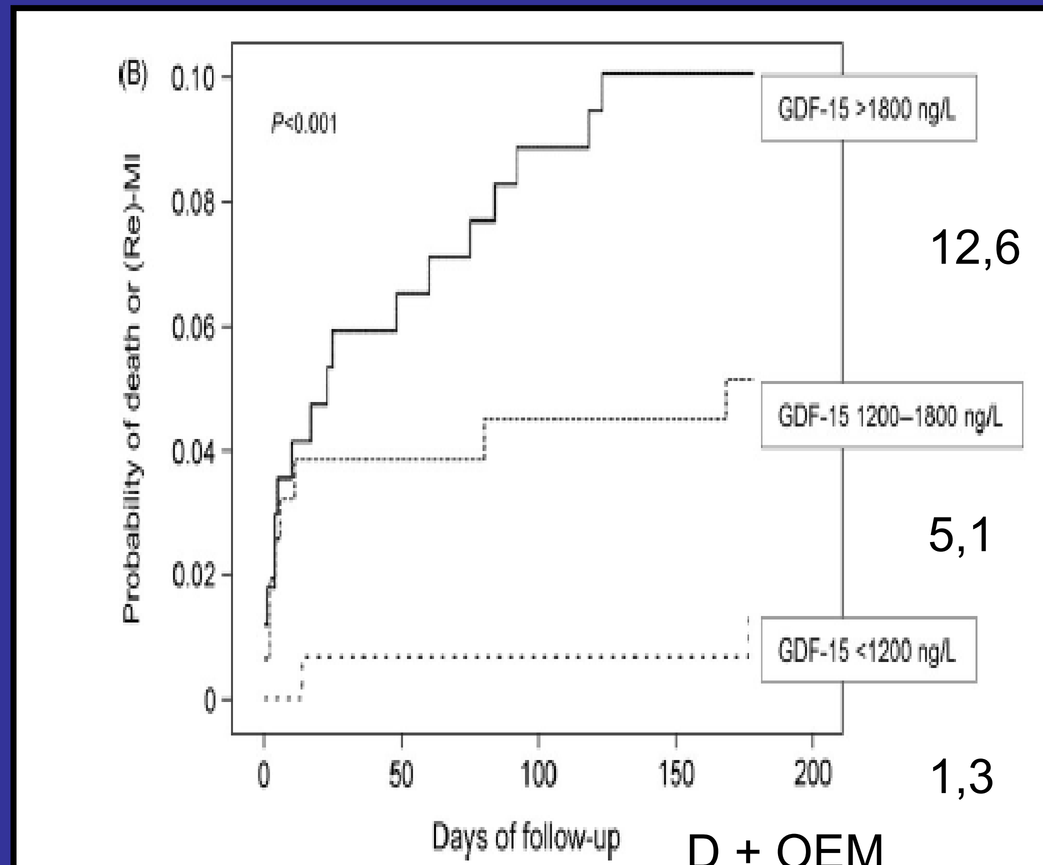


GDF-15 is a strong marker of 1-year mortality risk (area under the curve, 0.757)

Growth-differentiation factor-15

Chest Pain

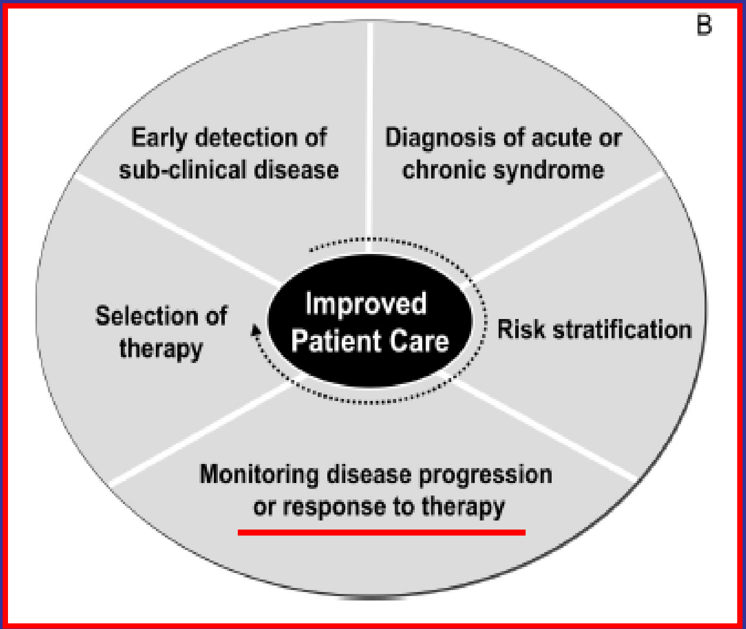


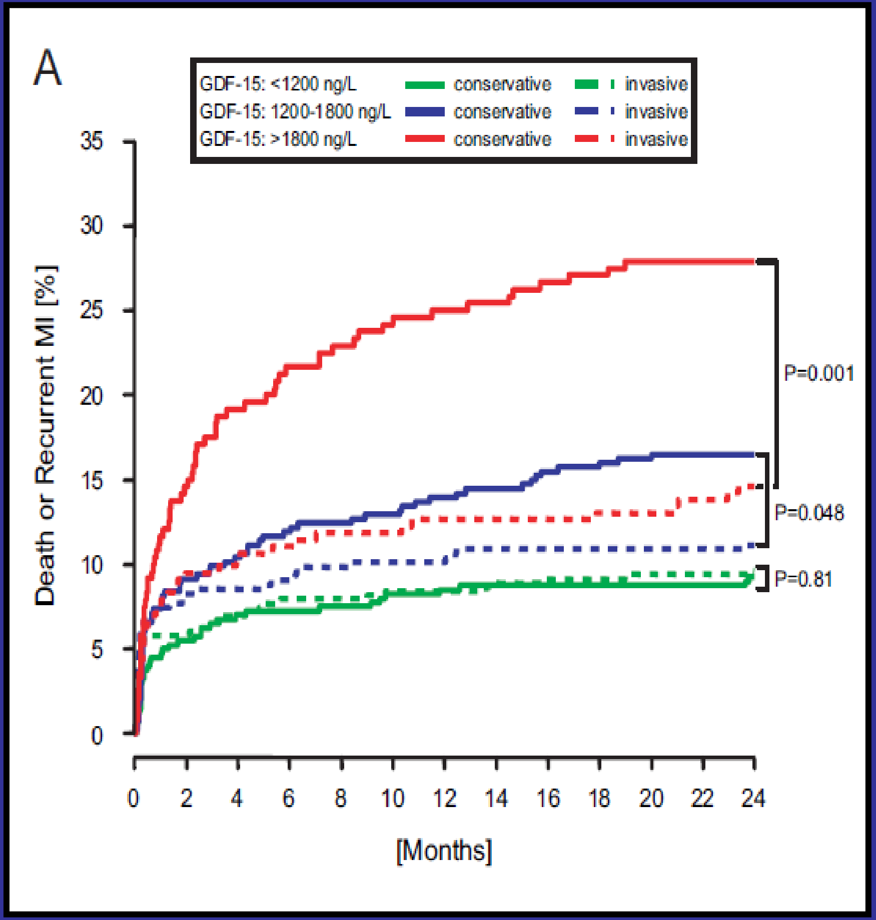


European Heart Journal (2008) **29**, 2327–2335
doi:10.1093/eurheartj/ehn339

Τροπονίνης I, CRP, NT-proBNP

Growth-differentiation factor-15



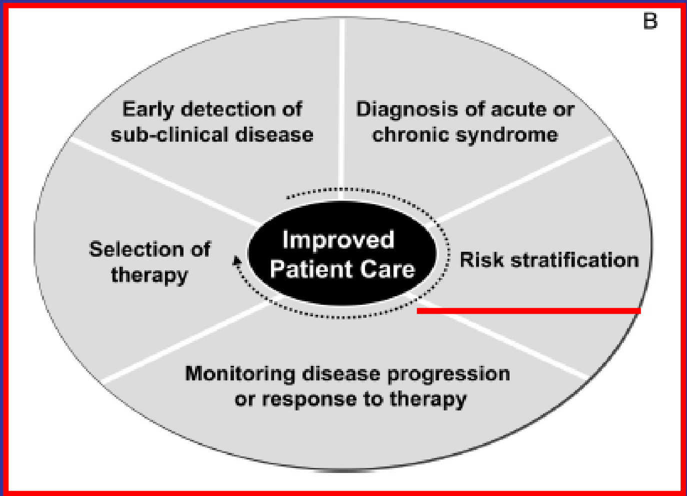


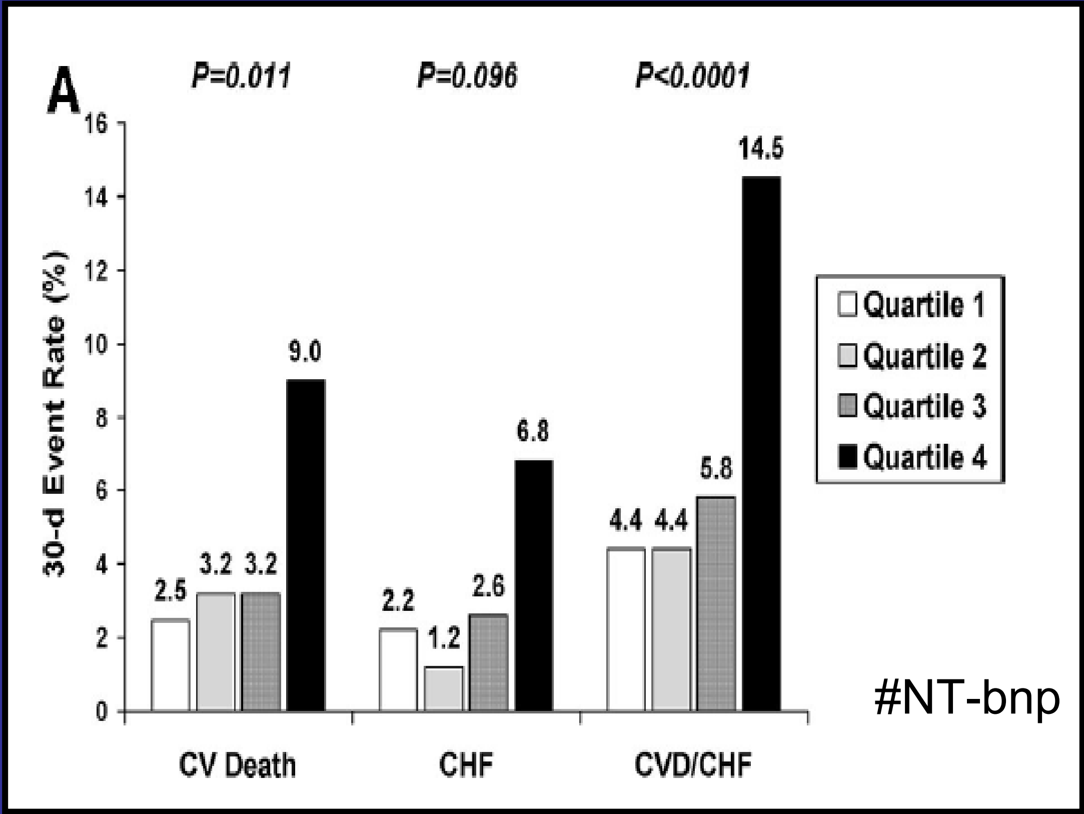
(Circulation. 2007;116:1540-1548.)

ST-2 soluble receptor

Although a heart failure biomarker

STEMI

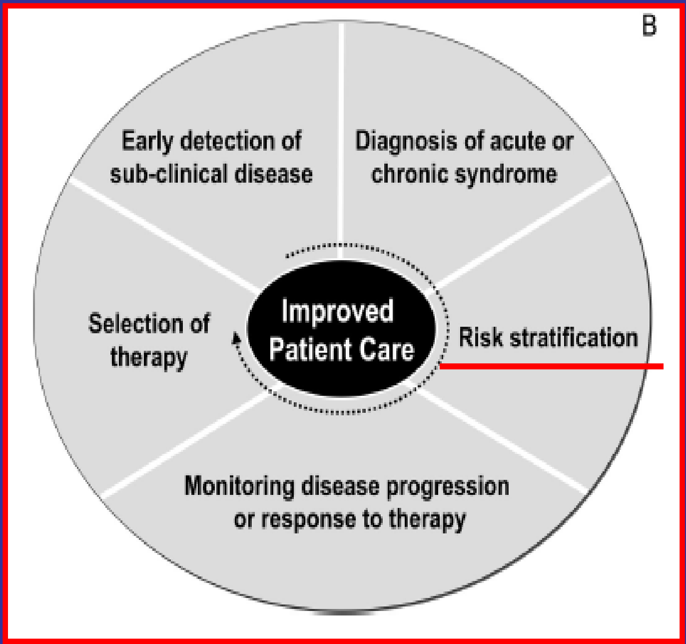




Circulation 2008;117;1936-1944

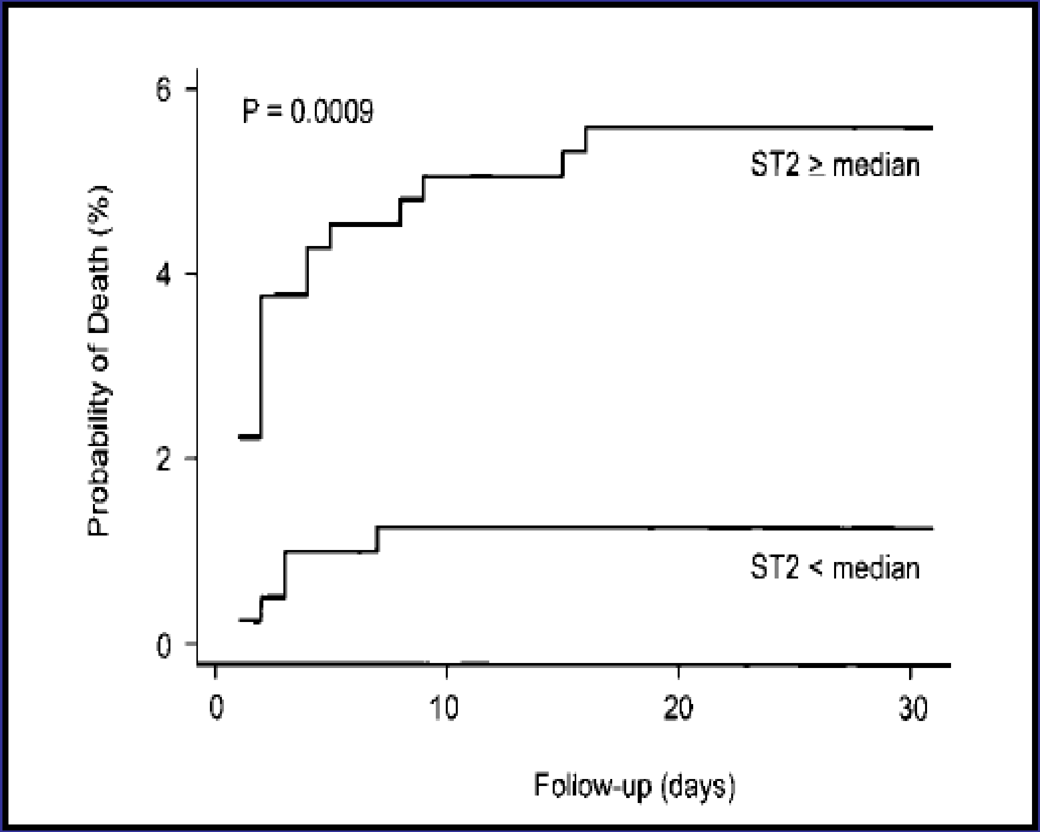
ST-2 soluble receptor

Although a heart failure biomarker



Circulation 2004;109;2186-2190

STEMI



Heart Type Fatty Acid Binding Protein

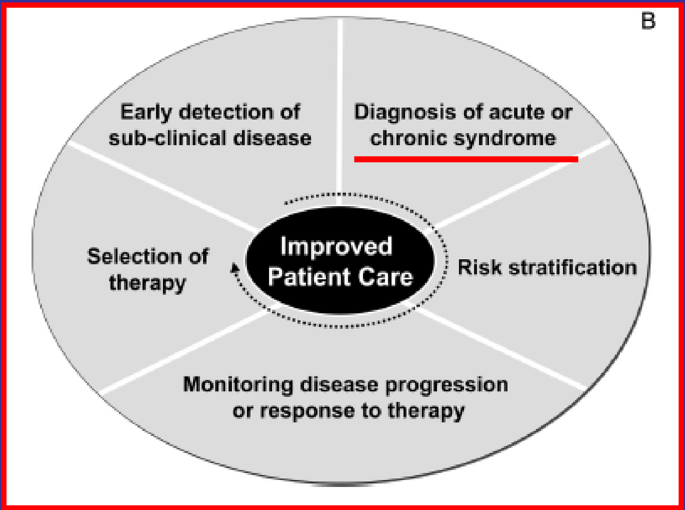
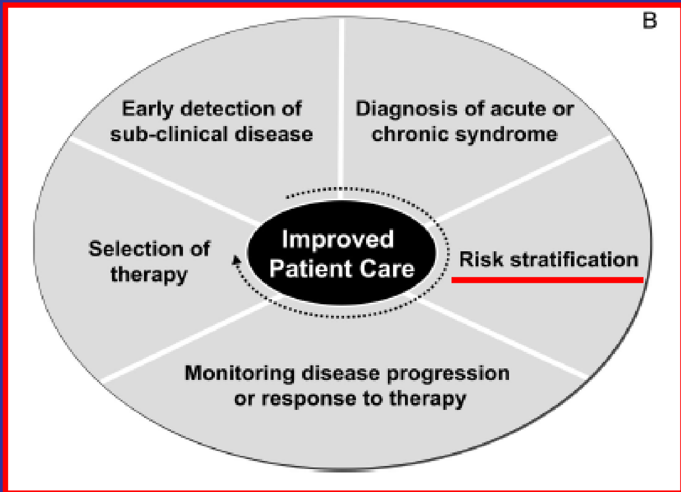


Table 3 Comparison of the diagnostic value of troponin T and H-FABP in patients with AMI and ACS (CI 95%)

	H-FABP (CI)	Troponin T (CI)
AMI (*N*=148)		
Sensitivity	0.60 (0.52–0.68)	0.19 (0.13–0.25)
Specificity	0.88 (0.84–0.91)	0.99 (0.99–1.00)
Positive predictive value	0.72 (0.74–0.80)	0.97 (0.90–1.03)
Negative predictive value	0.80 (0.76–0.85)	0.69 (0.65–0.74)
SCA (*N*=237)		
Sensitivity	0.47 (0.41–0.54)	0.12 (0.08–0.16)
Specificity	0.94 (0.90–0.97)	1 (1–1)
Positive predictive value	0.91 (0.86–0.96)	1 (1–1)
Negative predictive value	0.56 (0.49–0.64)	0.47 (0.42–0.52)

European Journal of Emergency Medicine 2008, Vol 15 No 3

Heart Type Fatty Acid Binding Protein



JACC Vol. 50, No. 21, 2007
November 20, 2007:2061–7

ACS

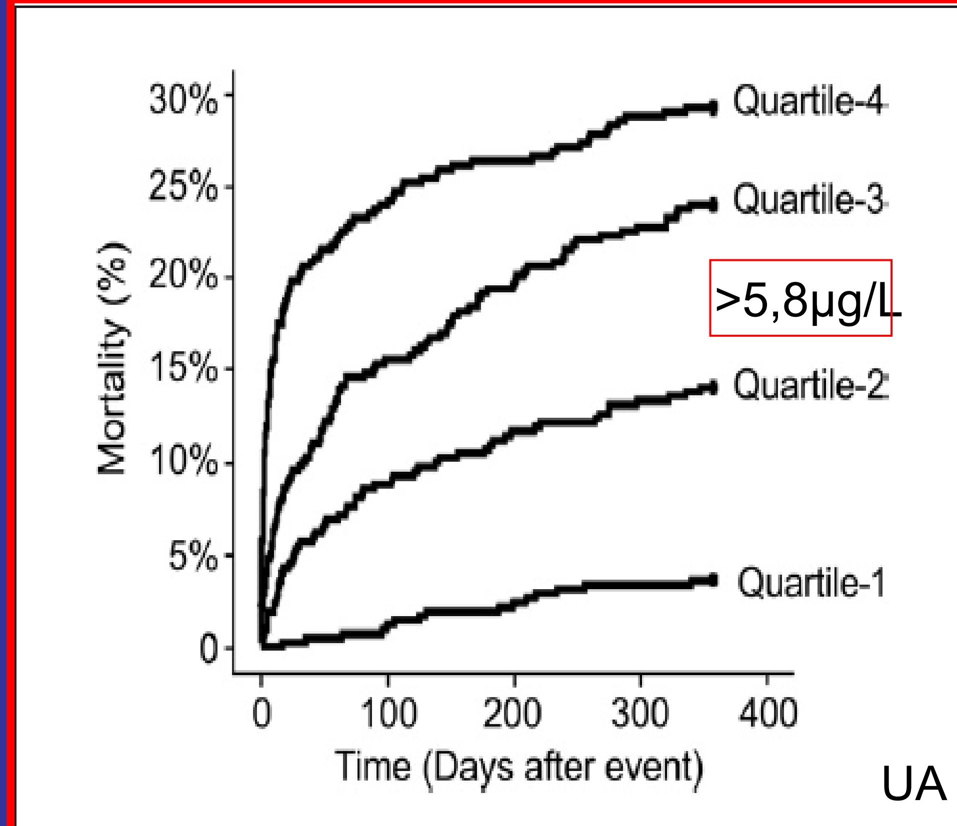
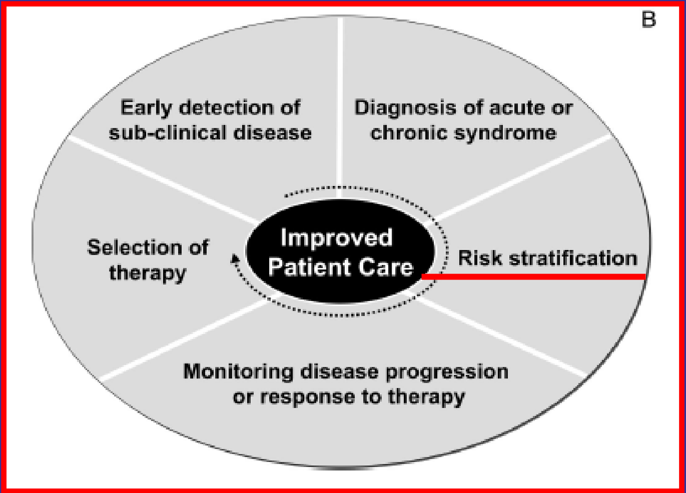
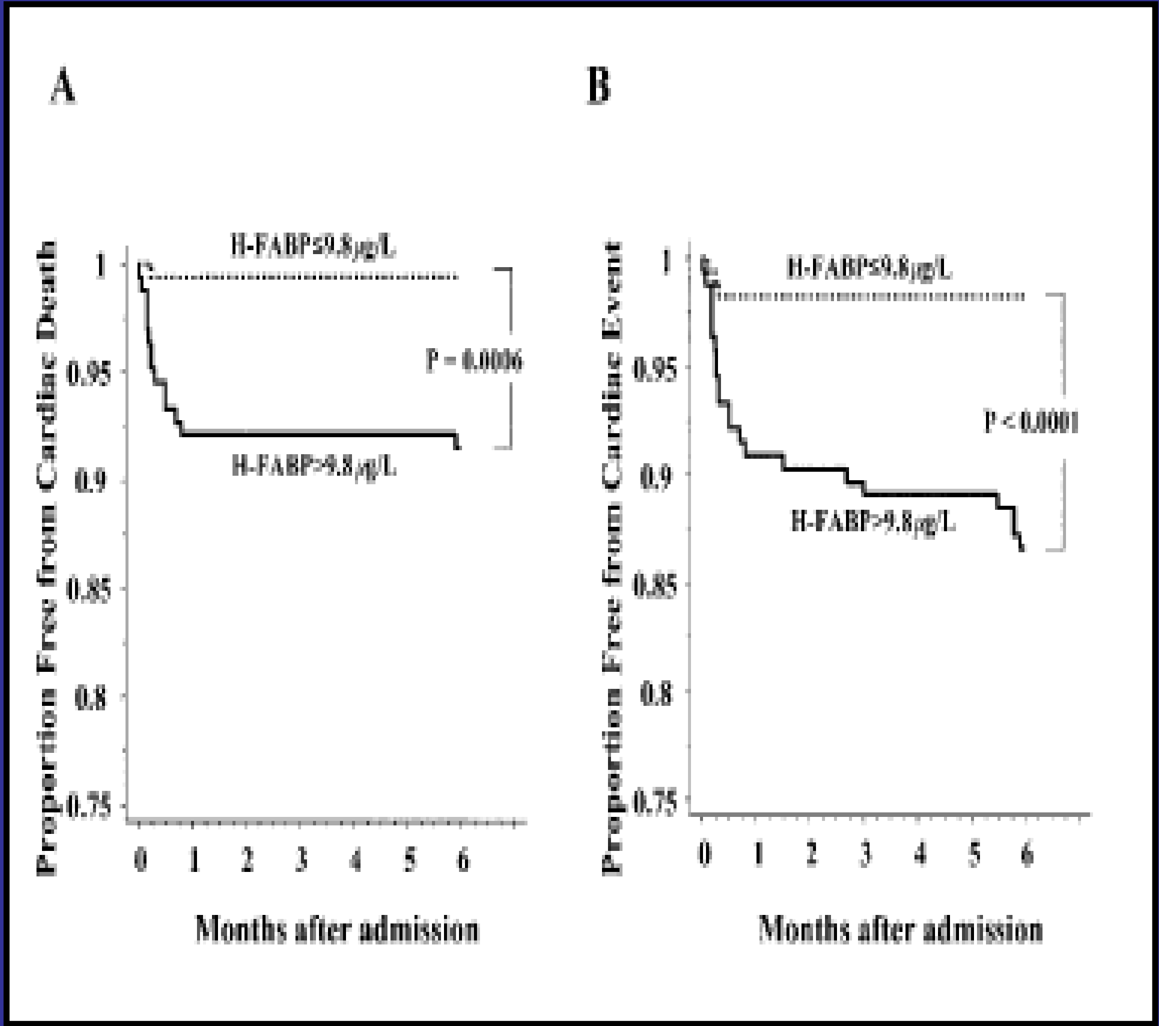


Figure 1 Kaplan-Meier All-Cause Mortality Curves According to H-FABP Quartiles

Heart Type Fatty Acid Binding Protein

ACS (STEMI-NSTEMI)



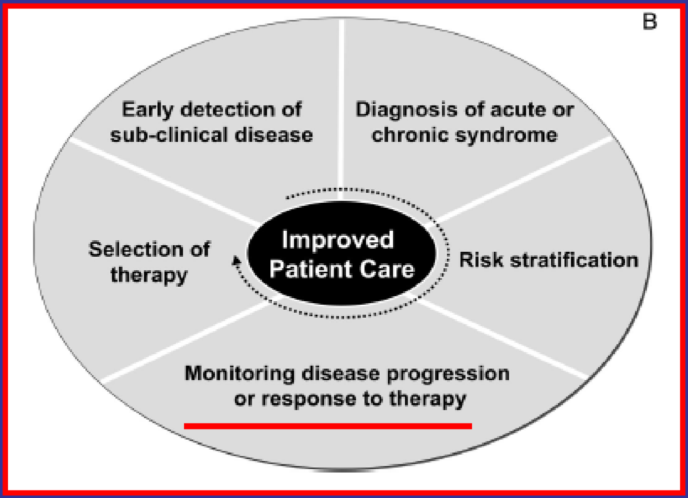


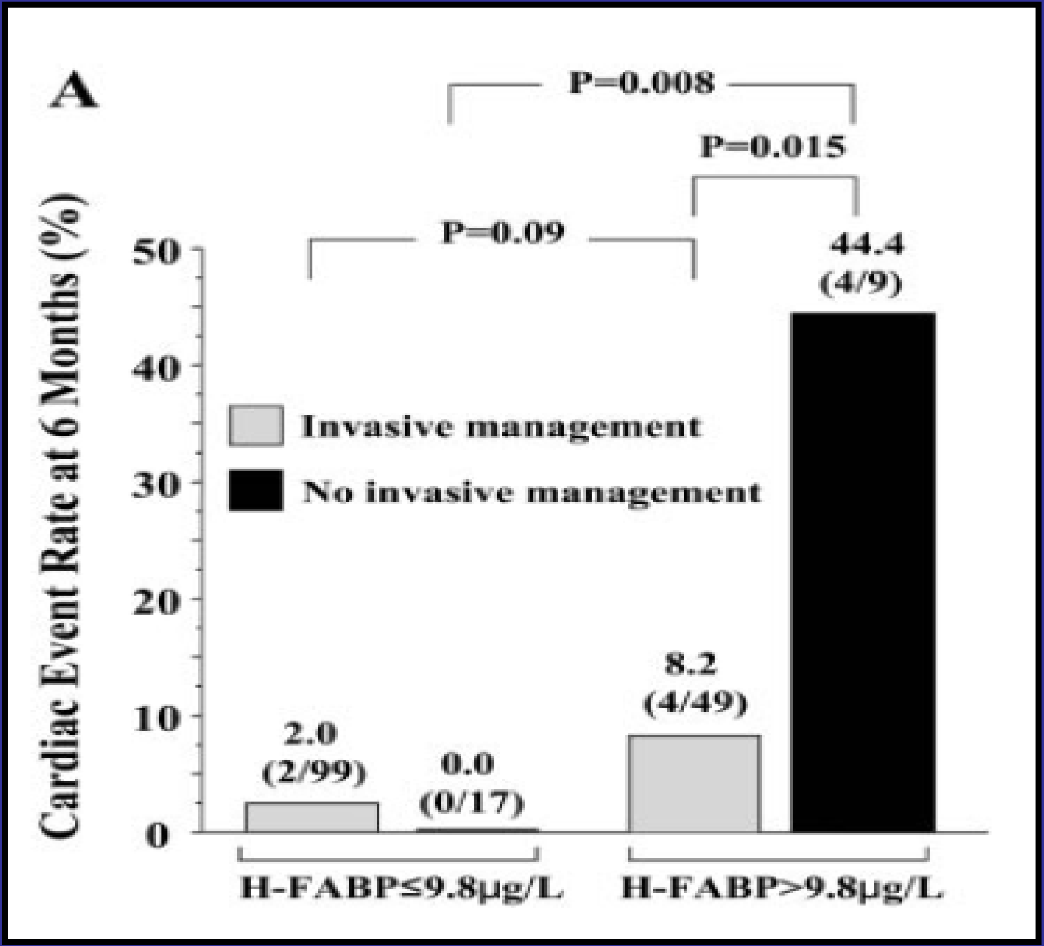
Clinical Chemistry 51:8
1397–1404 (2005)

Σε ROC ανάλυση η AUC ήταν καλύτερη για την H-FABP από ότι για την Τροπονίνη Τ

Heart Type Fatty Acid Binding Protein

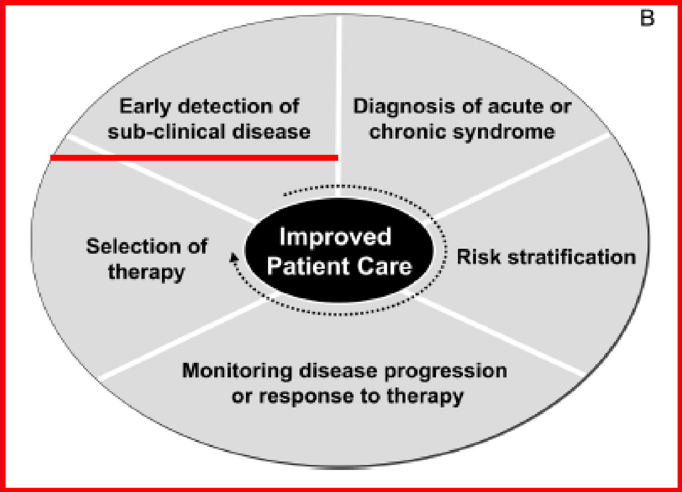
ACS + RV





Clinical Chemistry 51:8 1397–1404 (2005)

F11R / JAM-A



JACC Vol. 50, No. 18, 2007
October 30, 2007:1768–76

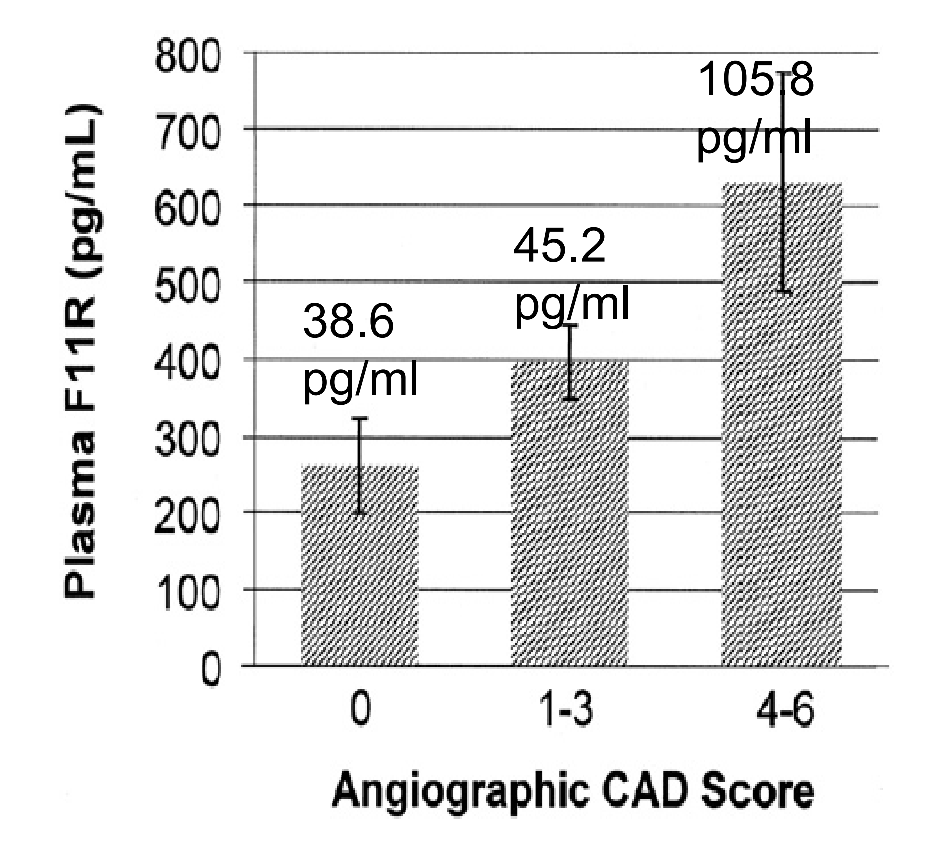
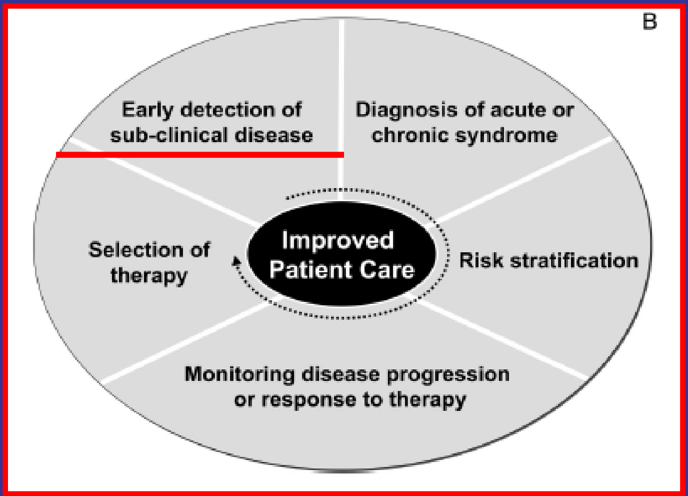


Figure 1 Plasma F11R Levels as a Function of CAD Score

F11R / JAM-A

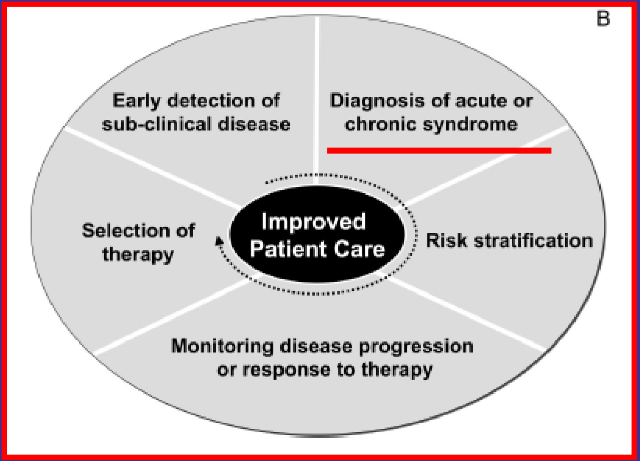


JACC Vol. 50, No. 18, 2007
October 30, 2007:1768–76

Table 5 Multivariate Analysis for CAD Score*

Predictors of CAD Score	p Value
Age/10 yrs	<0.0001
Hyperlipidemia	0.0009
Chronic renal insufficiency	0.0088
LV function	0.0013
Beta-blocker use	0.0203
F11R	0.0091

Thrombus Precursor Protein



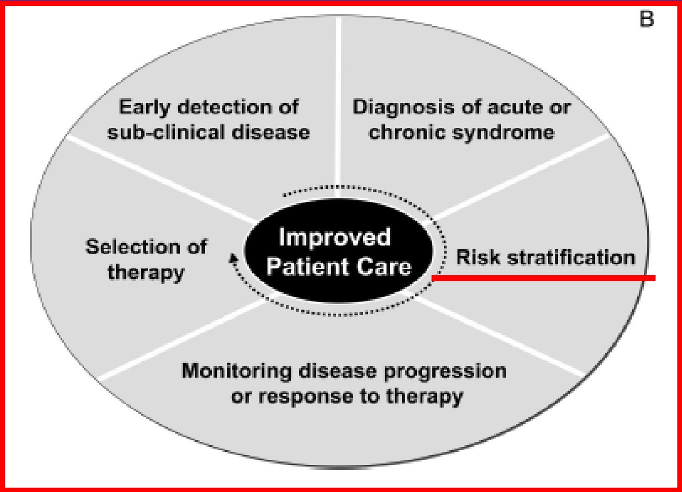
Blood Coagul Fibrinolysis. 2002 Apr;13(3):247-55. DPI

Coagulation indicators in chronic stable effort angina and unstable angina: relationship with acute phase reactants and clinical outcome.

Fiotti N, Di Chiara A, Altamura N, Miccio M, Fioretti P, Guarnieri G, Giansante C.

U.C.O. Clinica Medica Generale e Terapia Medica Dipartimento di Scienze Cliniche, Morfologiche e Tecnologiche, Università degli Studi di Trieste, Trieste, Italy. fiotti@univ.trieste.it

Thrombus Precursor Protein



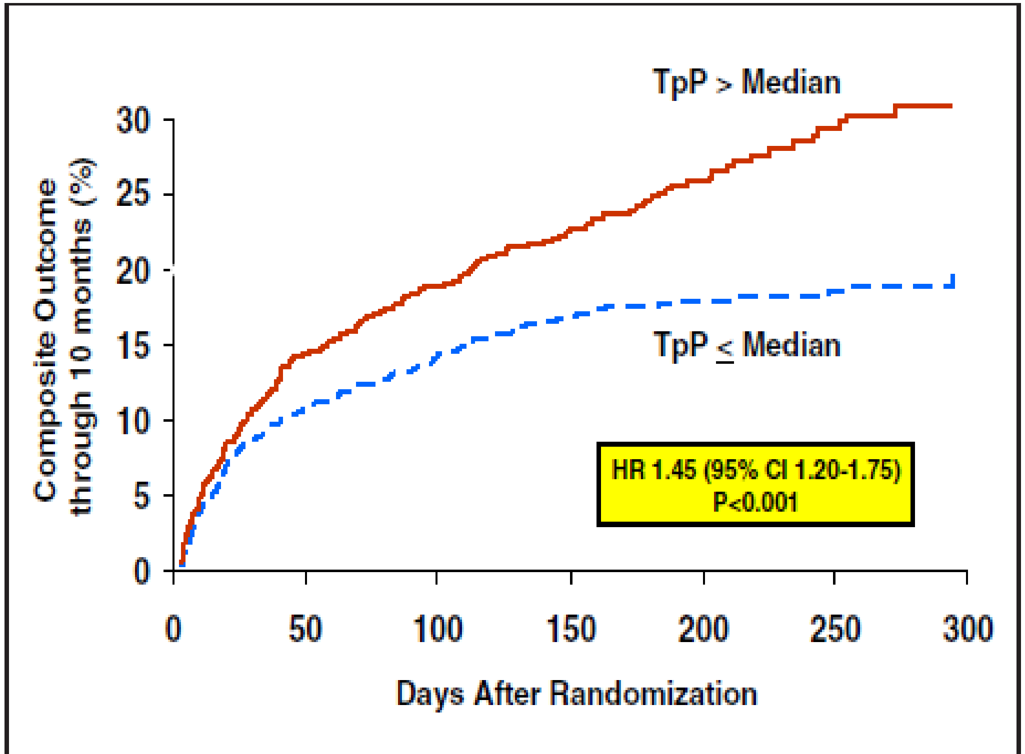
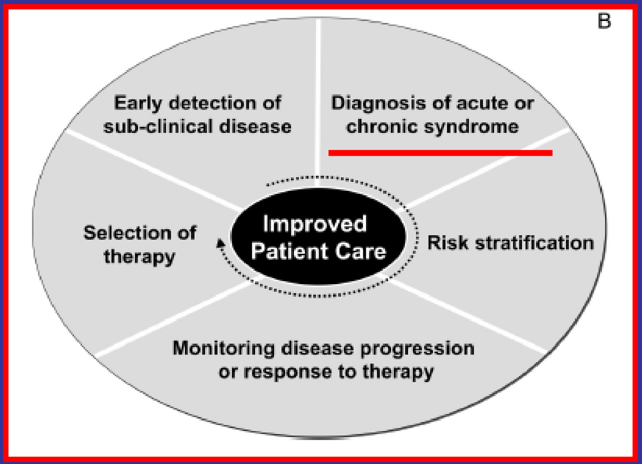


Figure 2 Cumulative Incidence of the Composite Outcome by TpP Level

JACC Vol. 51, No. 25, 2008
June 24, 2008:2422–9

End point: Death,MI,Ischemia>RV # Tr I,CRP,BNP,CC

Myeloid related protein-14



Heart 2008;**94**:1002-1007 doi:10.1136/hrt.2007.121640

Original article

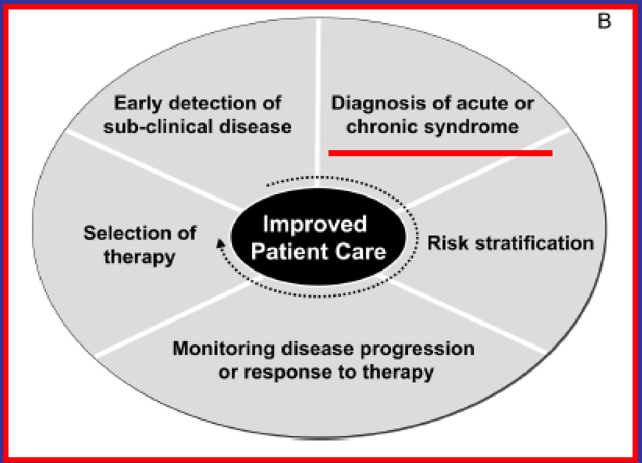
Acute coronary syndromes

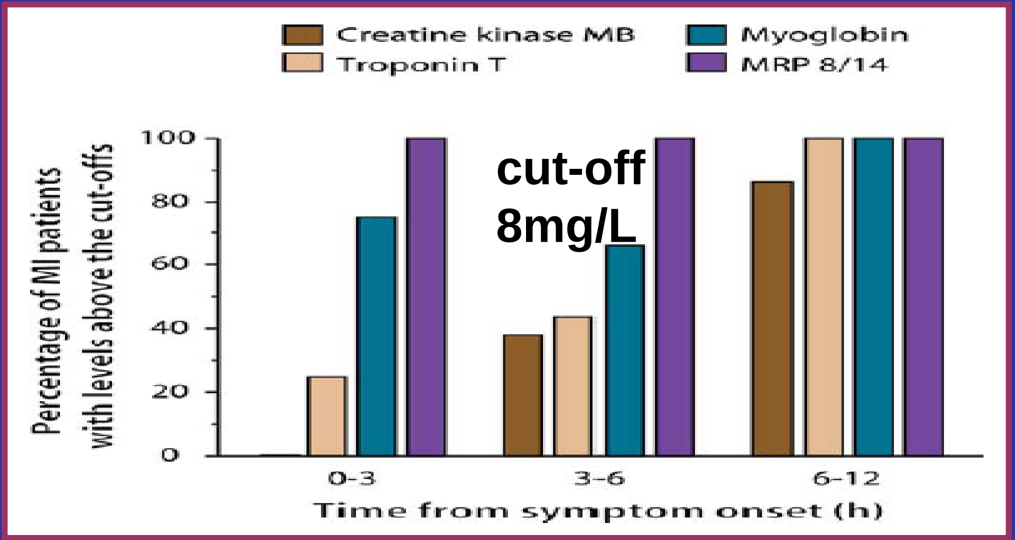
Increased serum levels and expression of S100A8/A9 complex in infiltrated neutrophils in atherosclerotic plaque of unstable angina

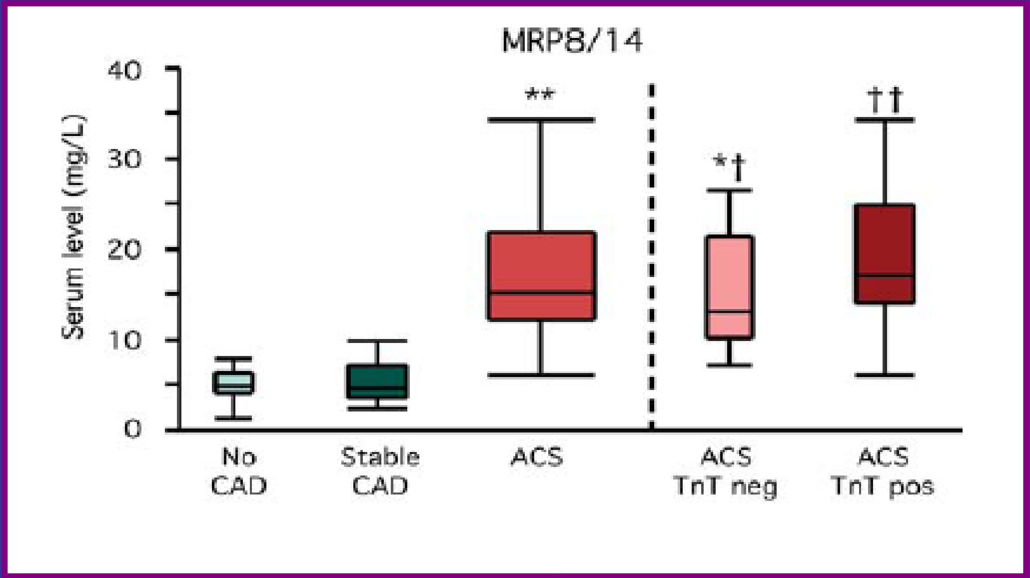
S Miyamoto[1], M Ueda[2], M Ikemoto[3], T Naruko[4], A Itoh[4], S Tamaki[5], R Nohara[1], F Terasaki[6], S Sasayama[7], M Fujita[3]

Myeloid related protein-14

ACS

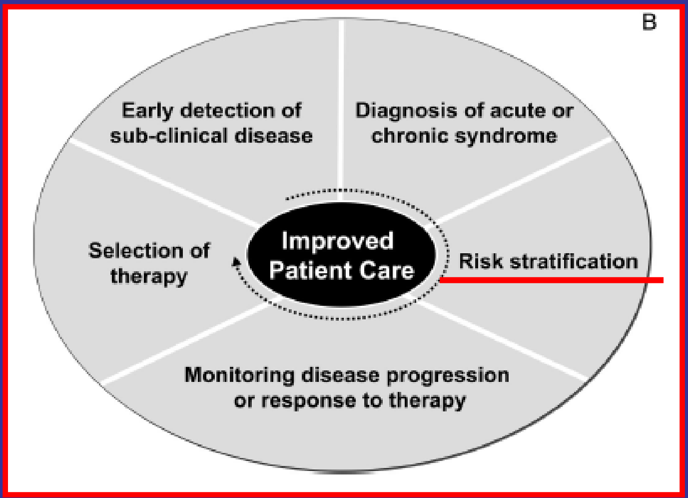


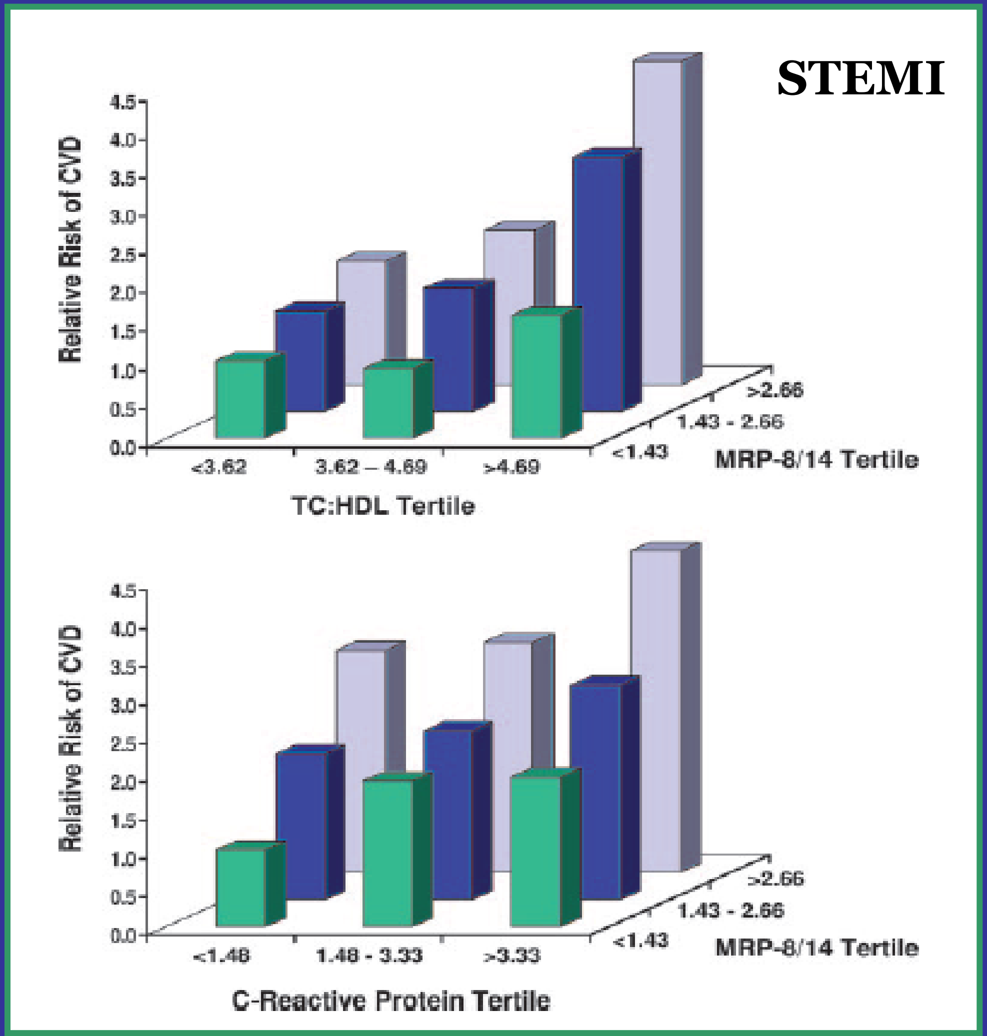




European Heart Journal
doi:10.1093/eurheartj/ehm078

Myeloid related protein-14

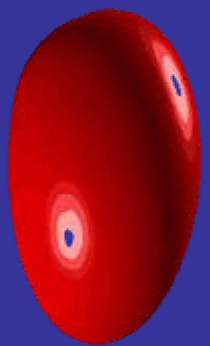


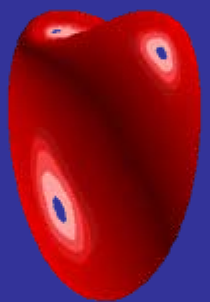


(*Circulation*. 2006;113:2278-2284.)

Νέοι προγνωστικοί δείκτες στην Στεφανιαία Νόσο

(2007-2008)





Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 21, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.08.069

FOCUS ISSUE: PLAQUE NEOVASCULARIZATION, HEMORRHAGE, AND VULNERABILITY

Original Research Paper

Total Cholesterol Content of Erythrocyte Membranes Is Increased in Patients With Acute Coronary Syndrome

A New Marker of Clinical Instability?

Dimitrios N. Tziakas, MD, PhD,* Juan Carlos Kaski, MD, DSc, FACC,* Georgios K. Chalikias, MD, PhD,* Carlos Romero, MD,† Salim Fredericks, PhD,† Ioannis K. Tentes, PhD,‡ Alexandros X. Kortsaris, PhD,‡ Dimitrios I. Hatseras, MD, PhD,‡ David W. Holt, PhD†

London, United Kingdom; and Alexandroupolis, Greece

European Heart Journal
doi:10.1093/eurheartj/ehn382

CLINICAL RESEARCH

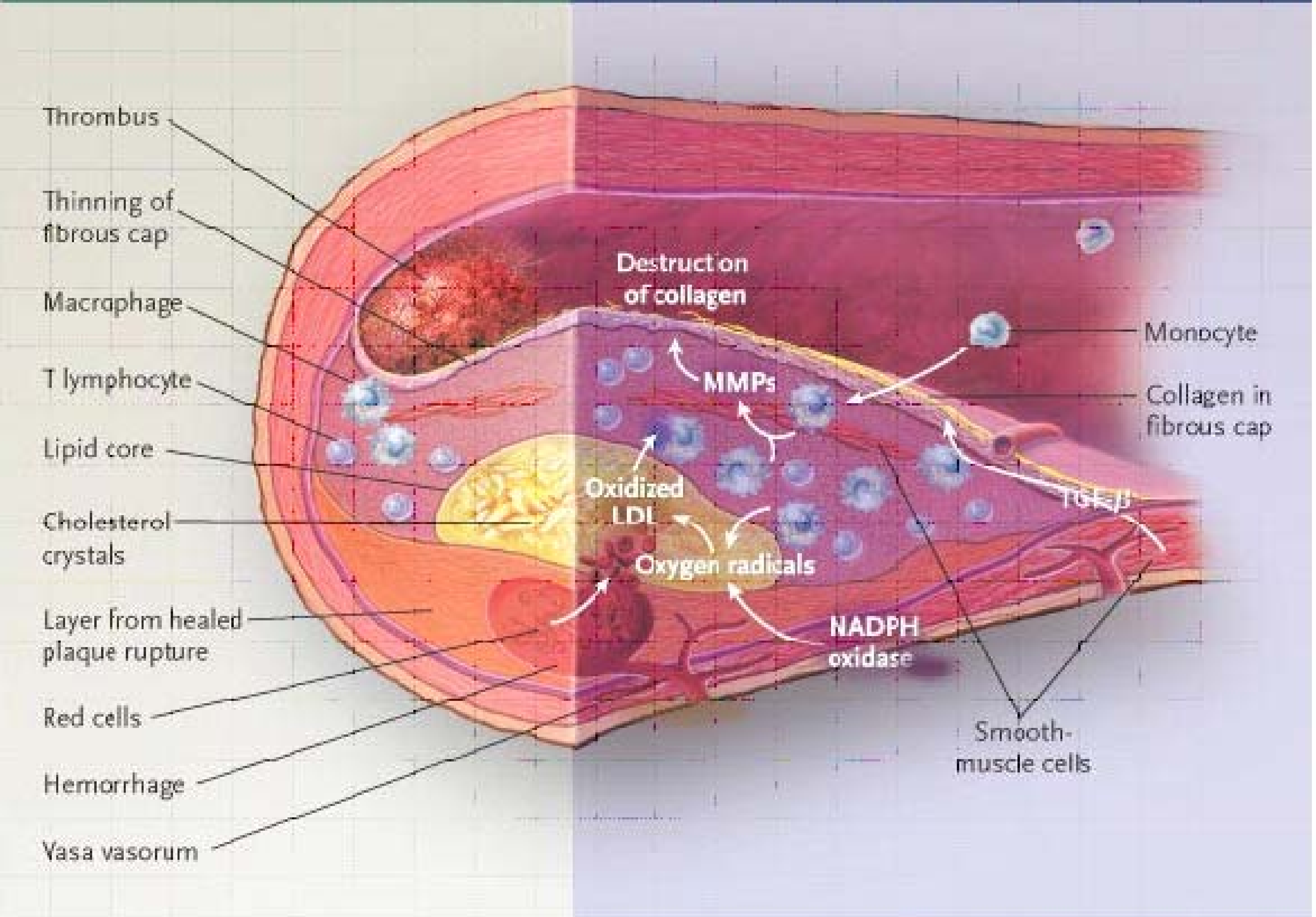
Interleukin-8 is increased in the membrane of circulating erythrocytes in patients with acute coronary syndrome

Dimitrios N. Tziakas[1*], Georgios K. Chalikias[1], Ioannis K. Tentes[2], Dimitrios Stakos[1], Sofia V. Chatzikyriakou[1], Konstantina Mitrousi[1], Alexandros X. Kortsaris[2], Juan Carlos Kaski[3], and Harisios Boudoulas[4]

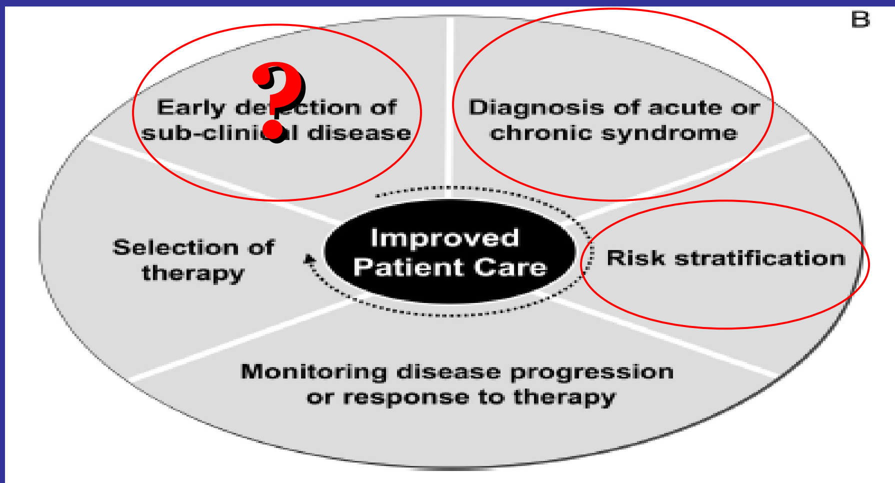
[1]University Cardiology Department, Medical School, Democritus University of Thrace, Voulgaroktonou 23, 68100 Alexandroupolis, Evros, Greece; [2]Biochemistry Department, Medical School, Democritus University of Thrace, Alexandroupolis, Greece; [3]Cardiovascular Biology Research Centre, St George's Hospital, University of London, London, UK; and [4]Clinical Research Center, Biomedical Research Foundation, Academy of Athens, Athens, Greece

Received 19 February 2008; revised 22 July 2008; accepted 25 July 2008

Unstable Arterial Plaque | Mechanisms of Plaque Rupture



Νέοι προγνωστικοί δείκτες στην Στεφανιαία Νόσο (2007-2008)



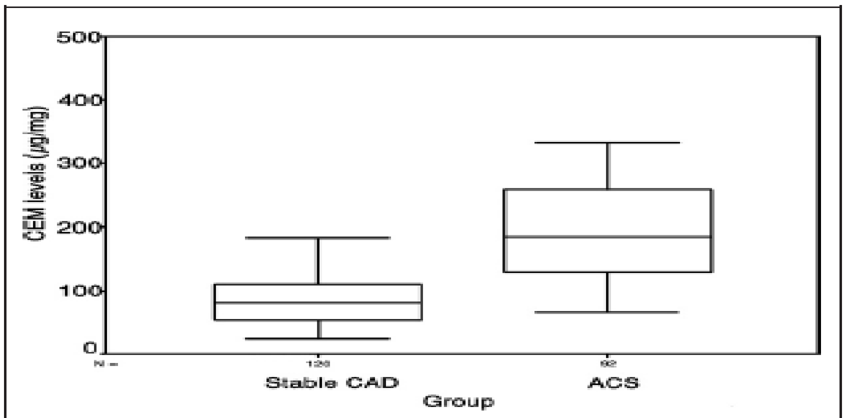


Figure 1 **Total Cholesterol Content of Erythrocyte Membranes in Stable CAD and ACS Patients**

Box plots represent median, quartiles, and range values of total cholesterol content of erythrocyte membranes (CEM). Data do not reflect logarithmic transformation or covariate adjustment as assessed in the analysis of covariance model. ACS = acute coronary syndrome; CAD = coronary artery disease.

JACC Vol. 49, No. 21, 2007
May 29, 2007:2081–9

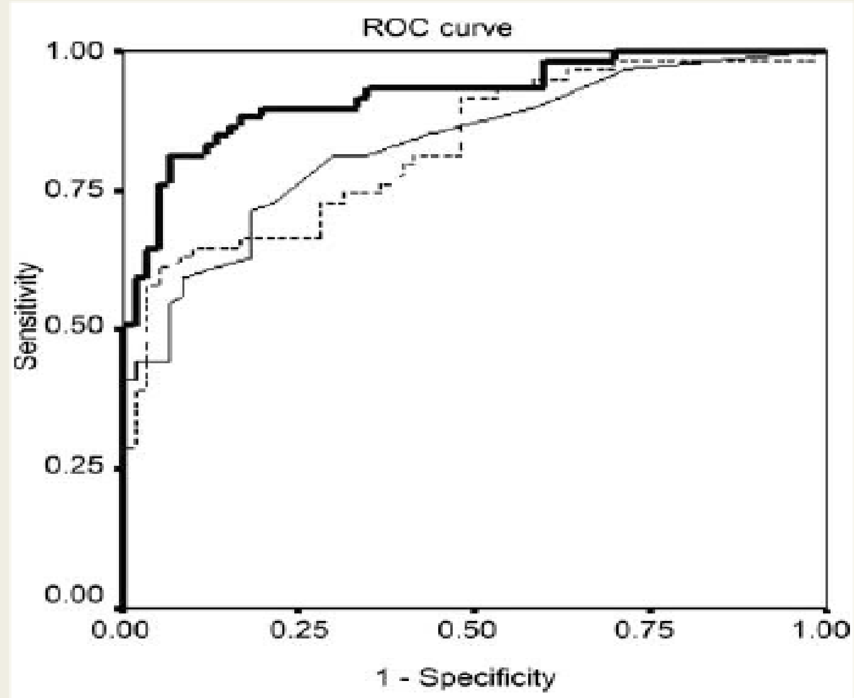
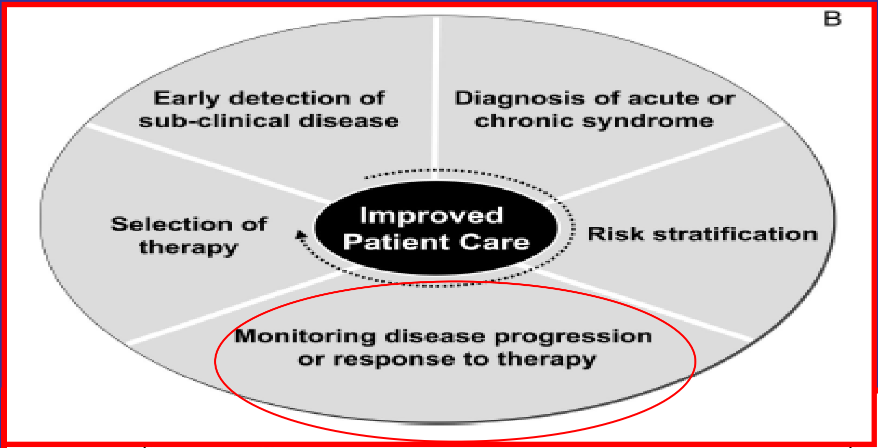
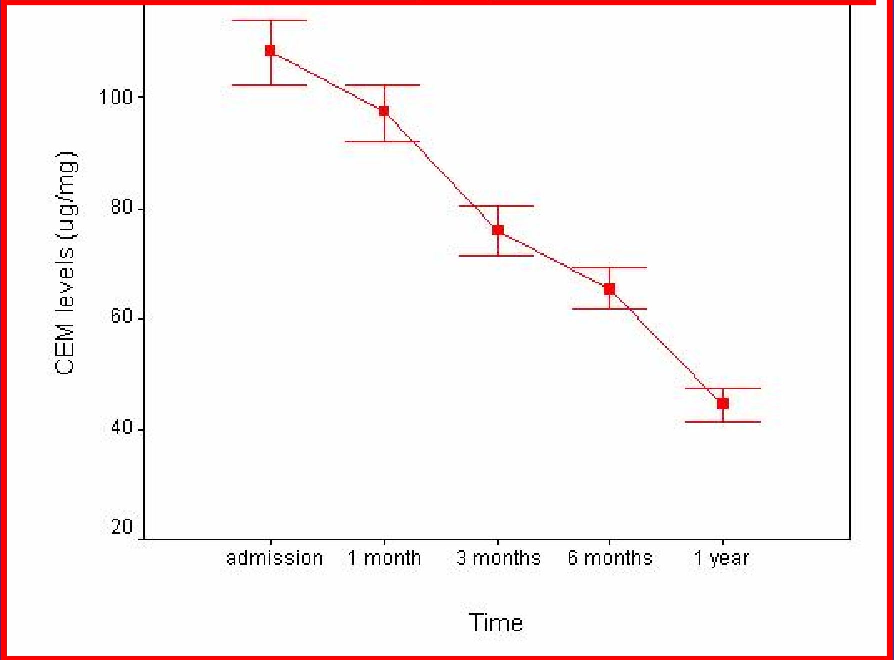


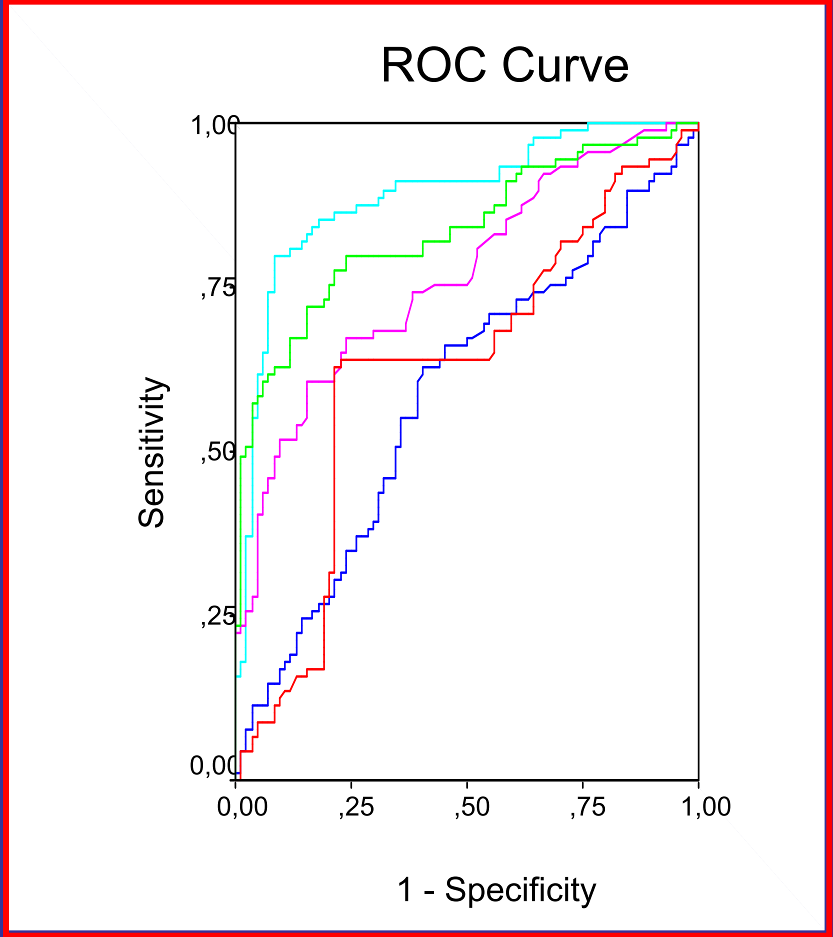
Figure 2 Receiver-operating characteristics (ROC) curve analysis regarding predictive accuracy of acute coronary syndrome. The bold line represents ROC analysis for total cholesterol content of erythrocyte membranes. The continuous line represents ROC analysis for C-reactive protein levels The dotted line represents ROC analysis for rIL-8 (interleukin-8 content of erythrocyte membranes) levels.

European Heart Journal
doi:10.1093/eurheartj/ehn382

Νέοι προγνωστικοί δείκτες στην Στεφανιαία Νόσο (2007-2008)



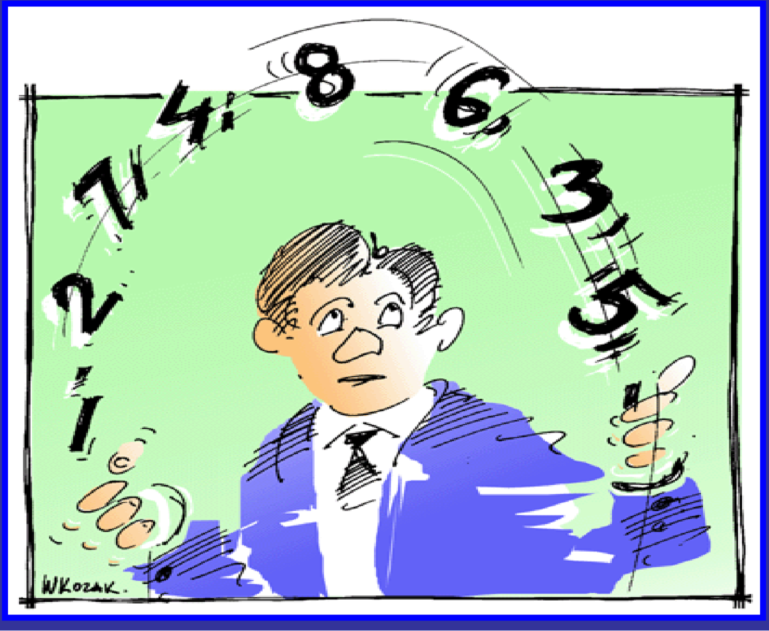




unpublished data, submitted to EHJ

Προβλήματα με τους δείκτες

1) Δυσκολίες στην μέτρηση
2) Μη σταθερά προγνωστικά ευρήματα
3) Ανακολουθία μεταξύ παθοφυσιολογίας και κλινικής εμφάνισης
4) Στατιστικά τρικ
5) Διαφορές μεταξύ πληθυσμών
6) Μηδαμινή κλινική χρησιμότητα



The verdict is still out…