Nuevos biomarcadores para la evaluación del riesgo cardiovascular

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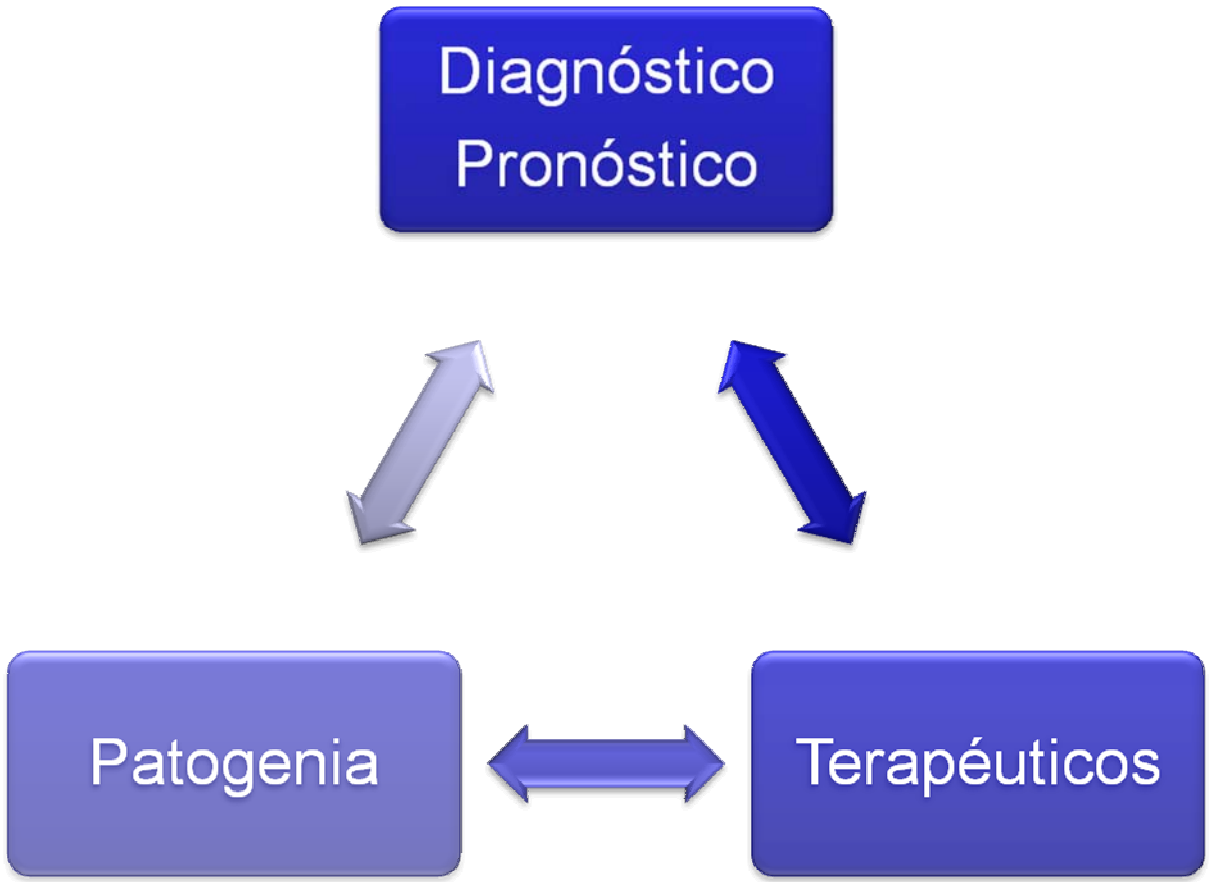
Nuevos biomarcadores



Nuevos biomarcadores

Markers of inflammation and plaque destabilization

CRP C-reactive protein
IL-6 Interleukin-6
IL-18 Interleukin-18
IL-10 Interleukin-10
TNF- Tumor necrosis factor-
SAA Serum amyloid A
MPO Myeloperoxidase
sCD40L Soluble CD40 ligand
Lp-PLA2 Lipoprotein associated phospholipase A2
MMP-9 Matrix metalloproteinases-9
PLGF Placental growth factor
VGEF Vascular endothelial growth factor
PAPP-A Pregnancy-associated plasma protein A
ICAM Intercellular adhesion molecule
VCAM Vascular adhesion molecule
GDF-15 Growth differentiation factor 15
MCP-1 Monocyte chemotactic protein 1
E and P selectins

Markers of ischemia and necrosis

IMA Ischemia mediated albumin
h-FABP Heart-type fatty acid binding protein
Choline Choline
cTnT Cardiac troponin T
cTnI Cardiac troponin I
Myoglobin Myoglobin

Markers of myocardial stress

BNP B-type natriuretic peptide
NT-proBNP N-terminal B-type natriuretic peptide

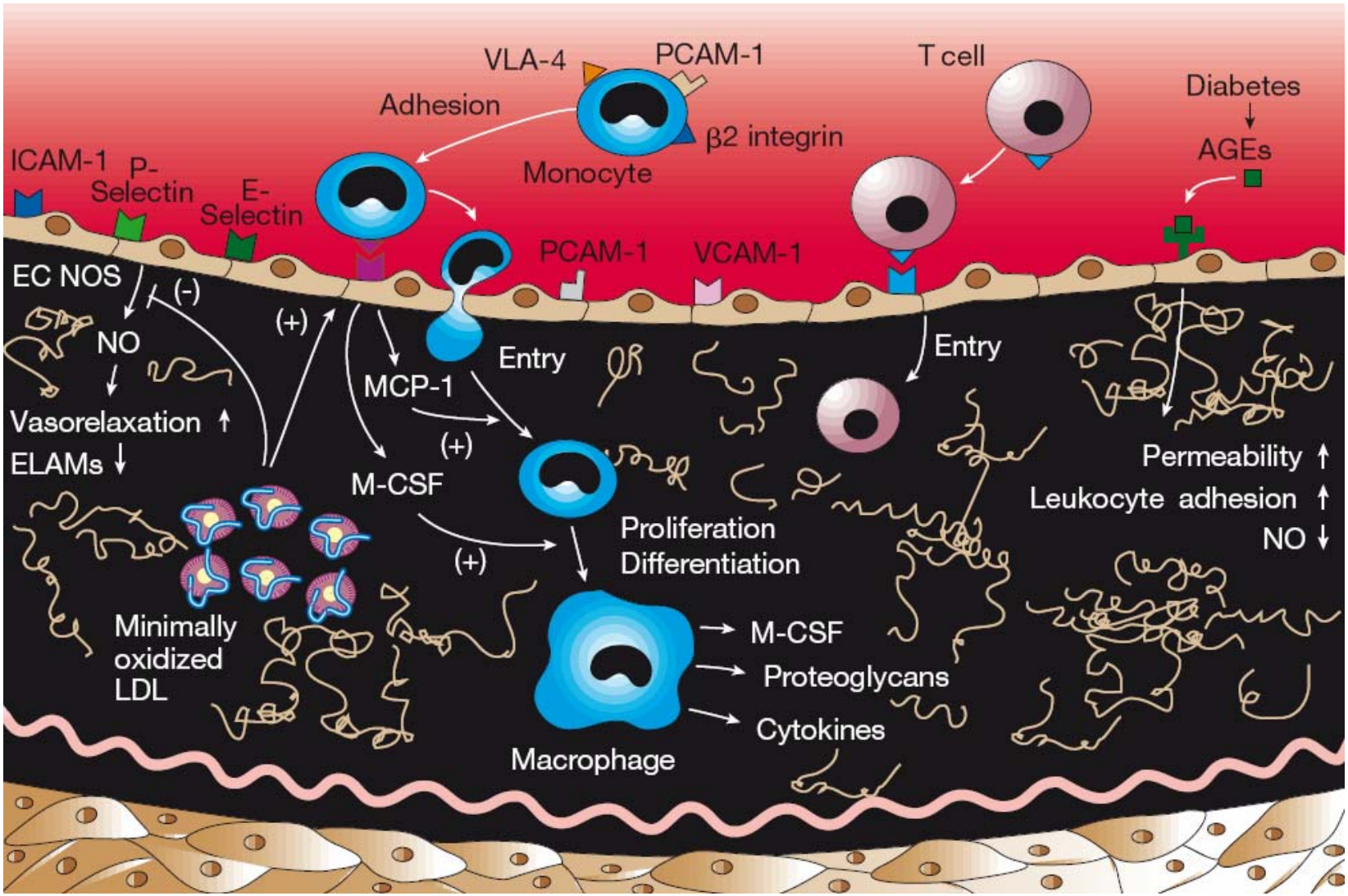
Oxidative stress

LDLox
PON-1
PAF-AH

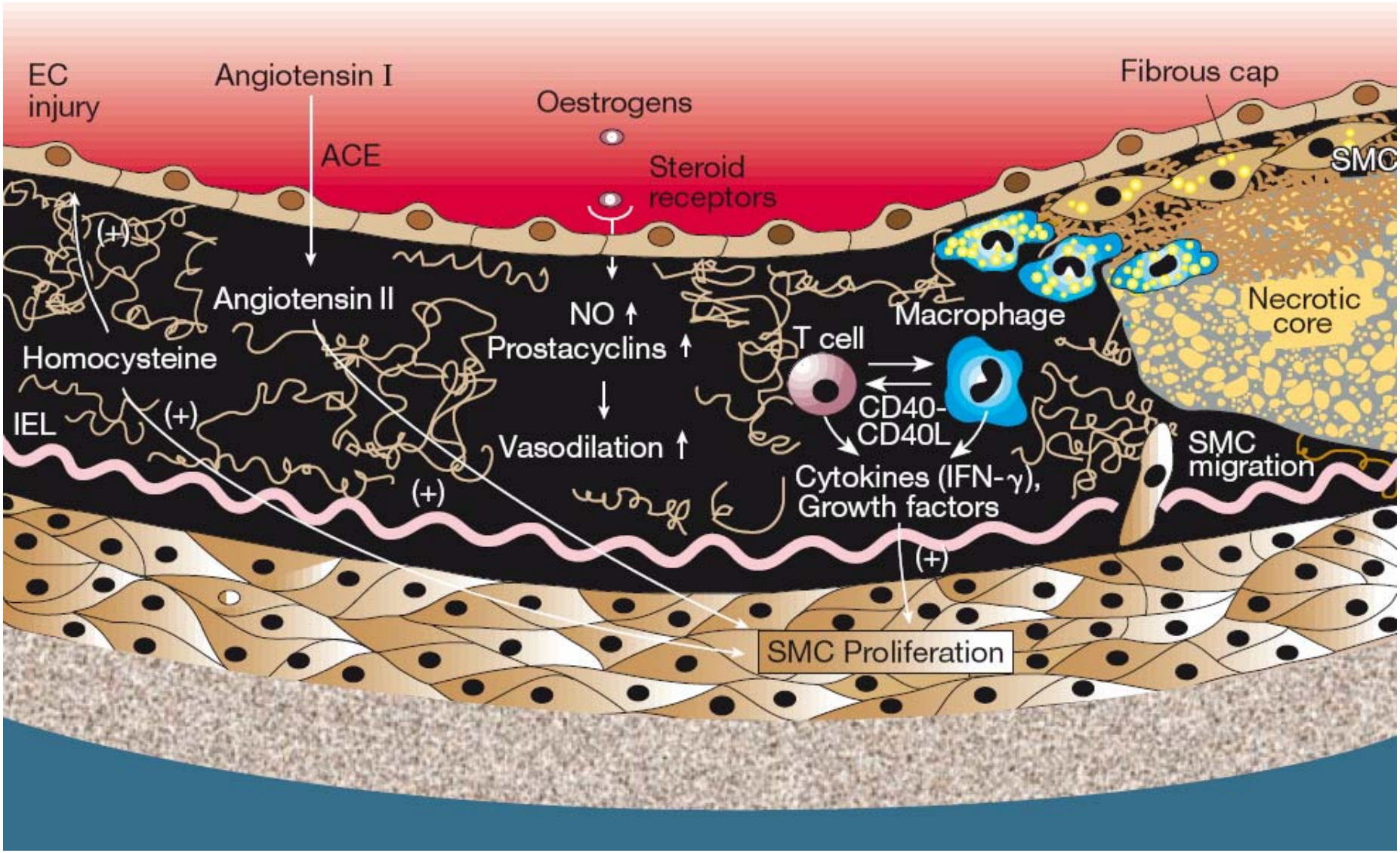
Coagulation factors

Fibrinogen
D dimer
Homocysteine

Joanne D. Schuijf et al. How to Identify the Asymptomatic High-Risk Patient?. *Curr Probl Cardiol* 2009;34:539-577. Modificado.



Lusis AJ. *Nature.* 2000;407:233-241.



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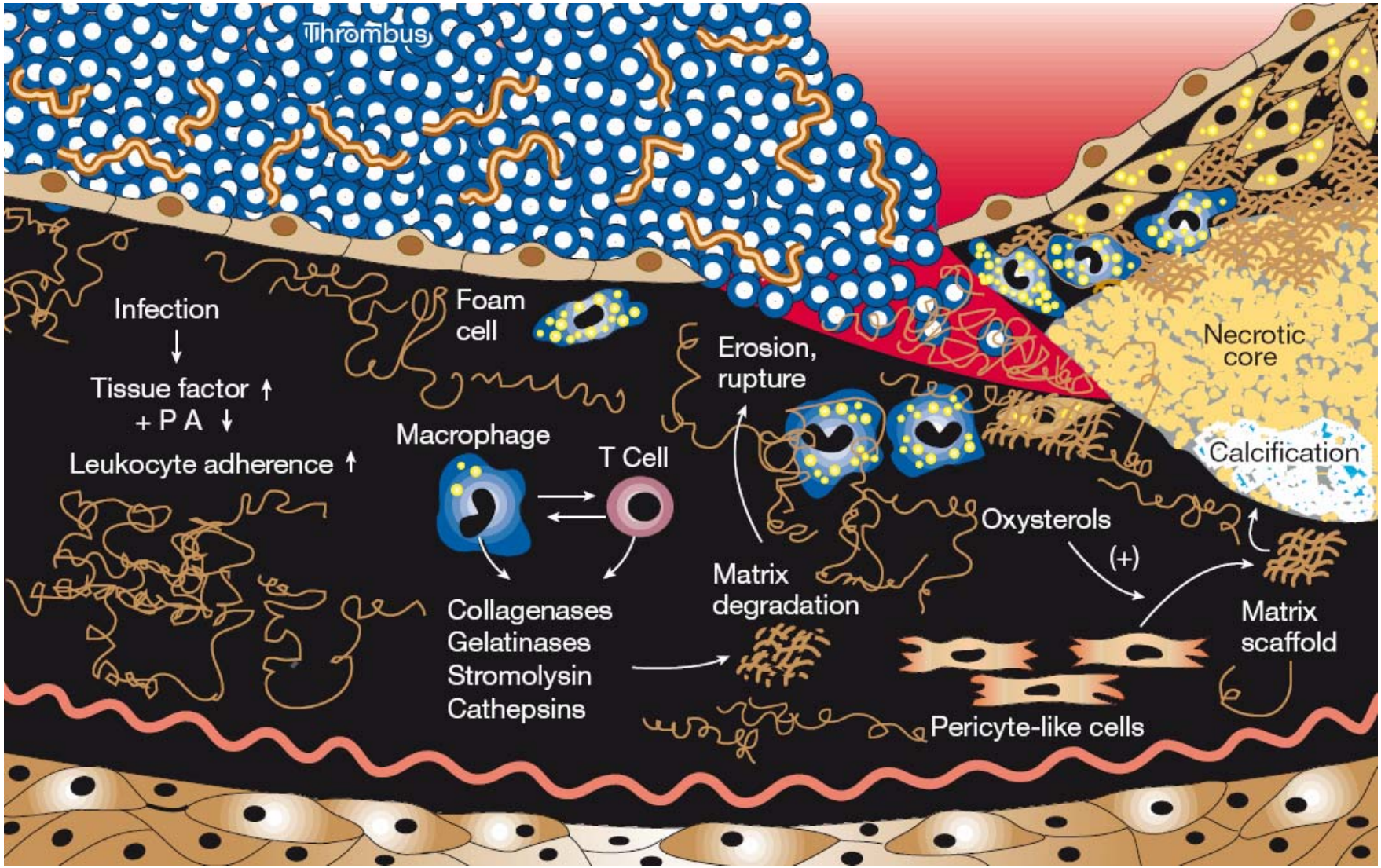

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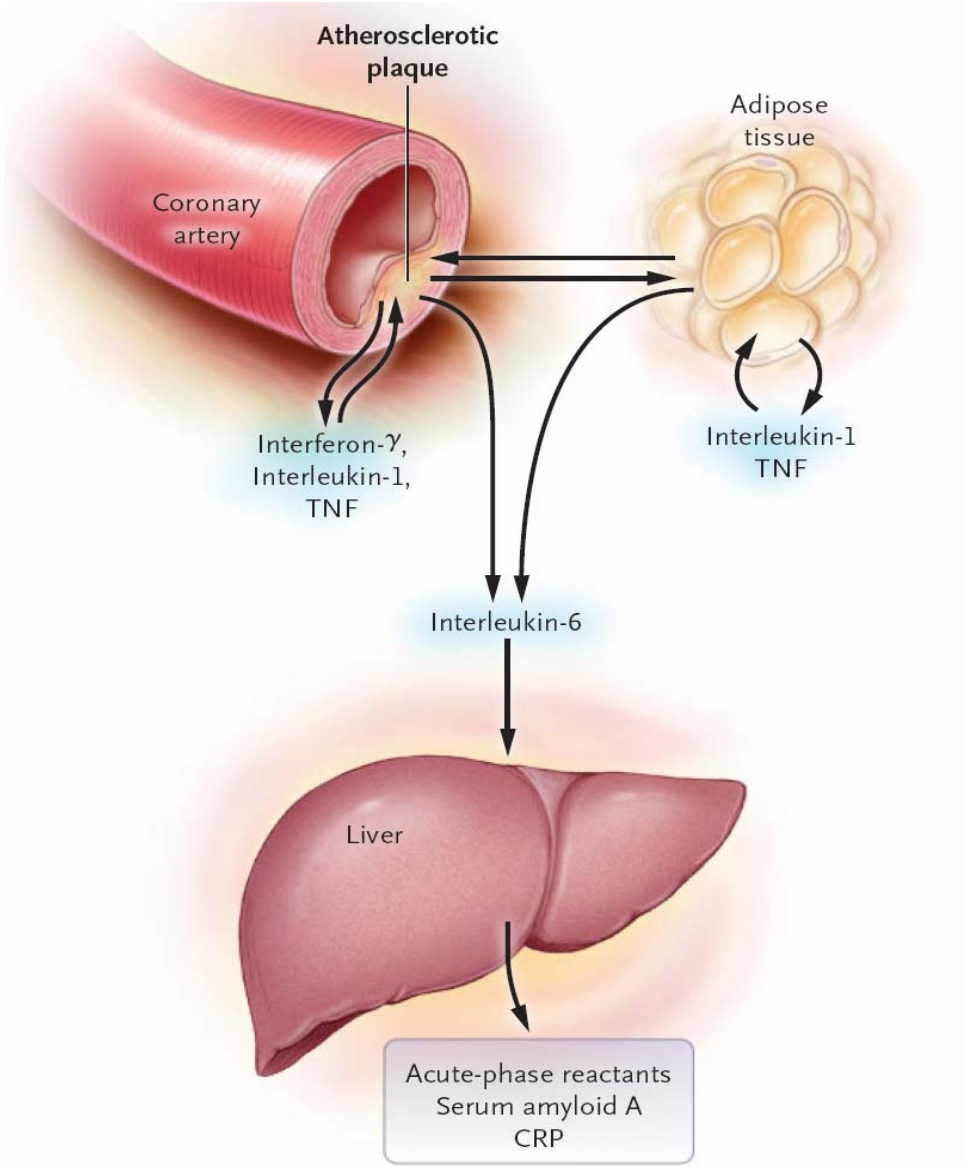
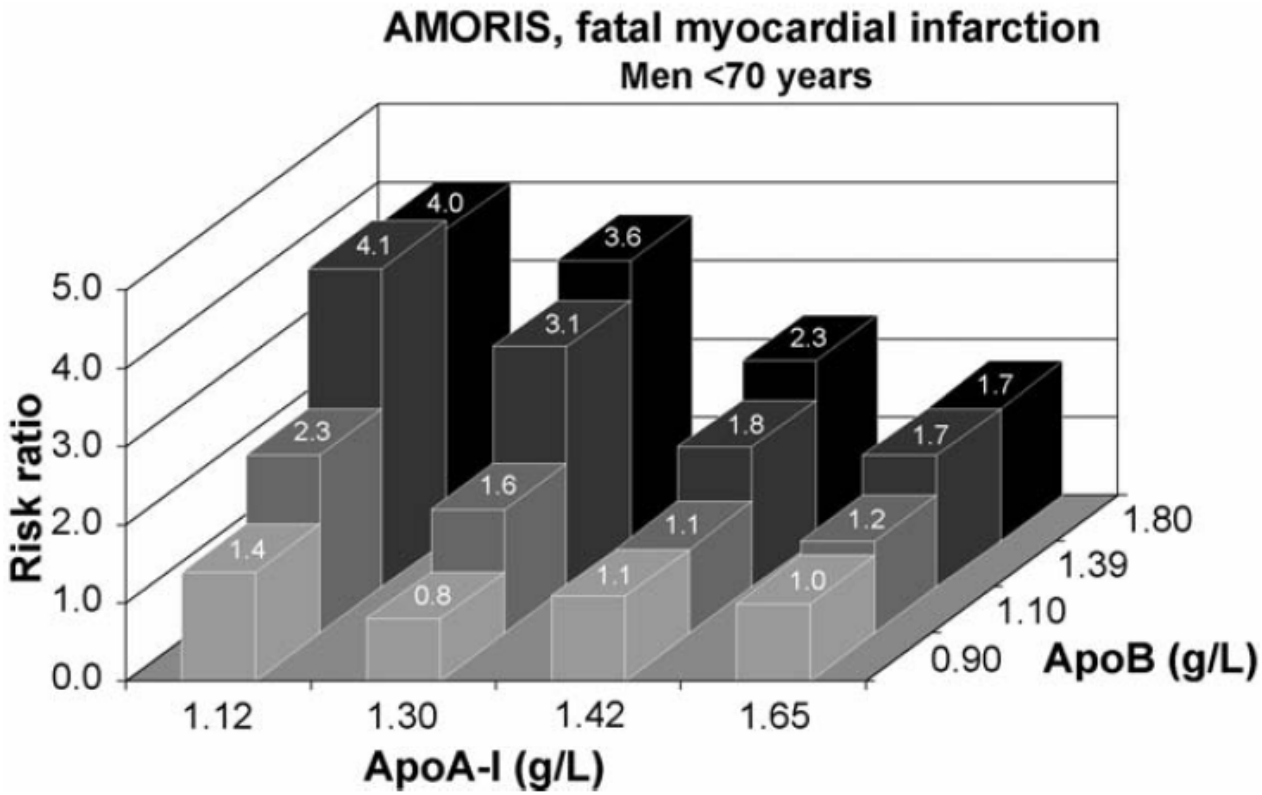


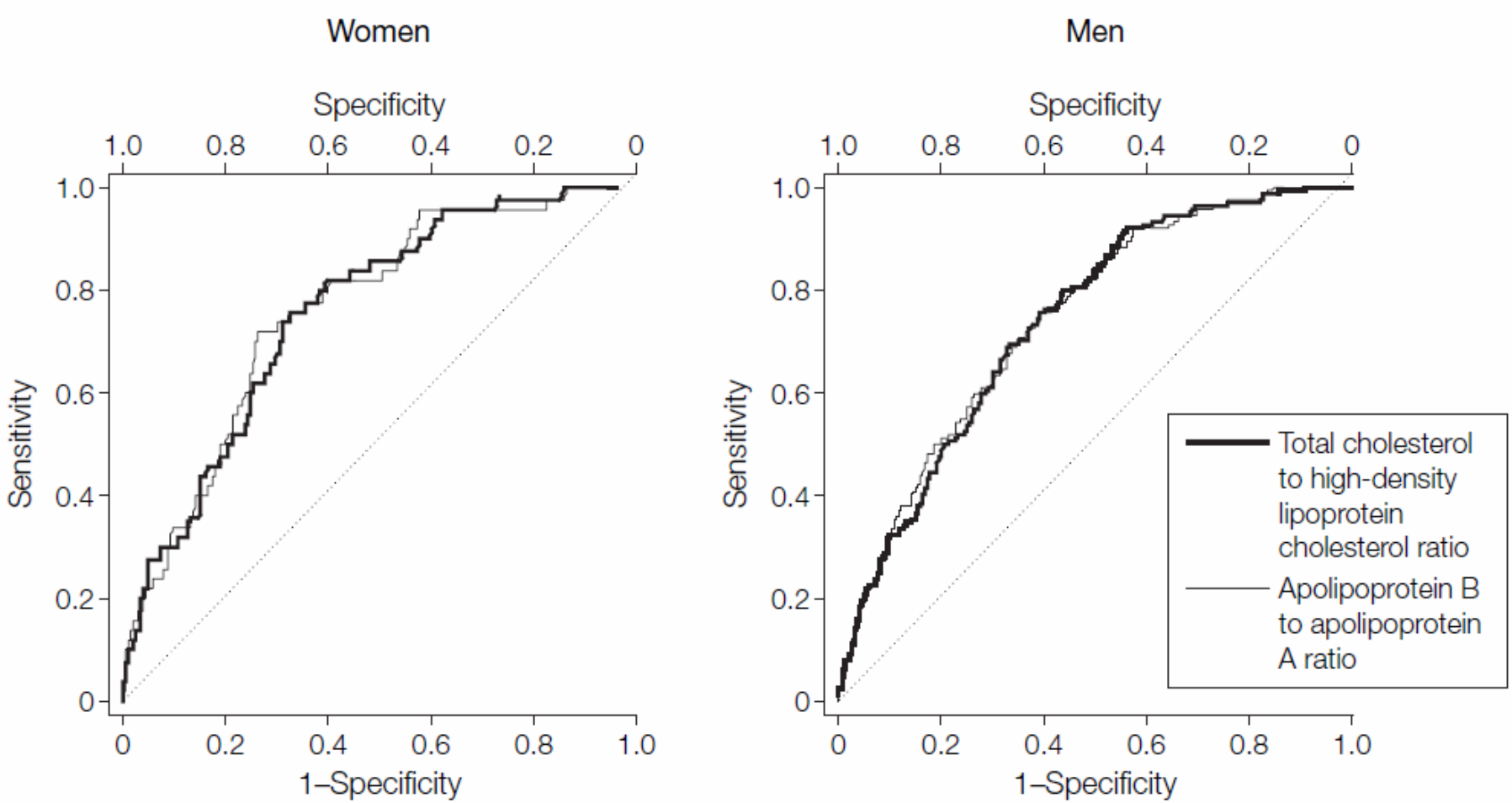
Hansson GK. *N Engl J Med* 2005;352:1685-95.

Lipoproteínas: ApoB



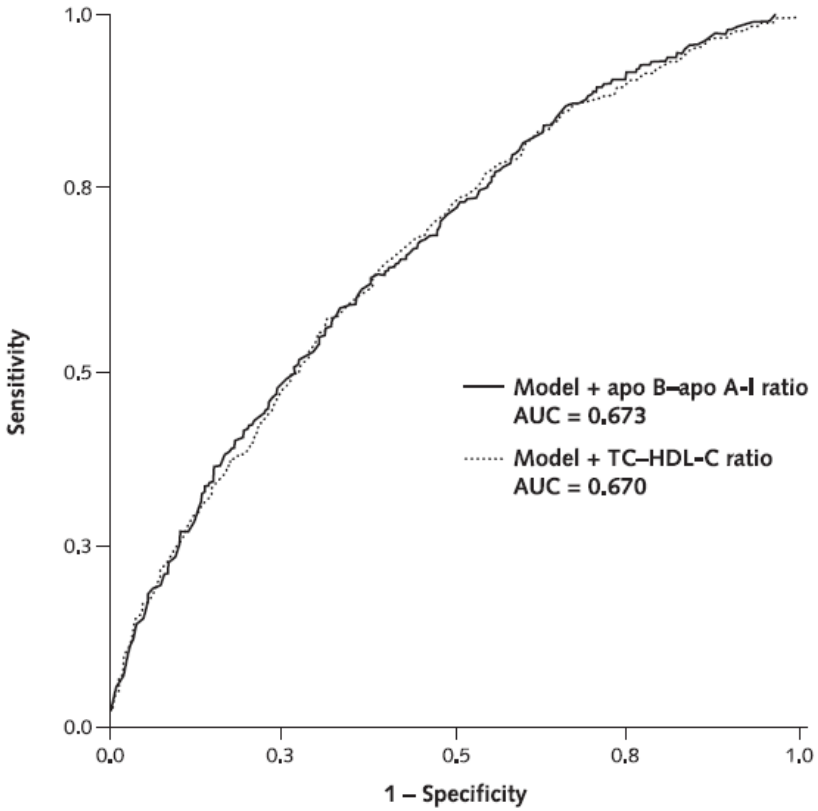
Göran Walldius et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001; 358: 2026–33

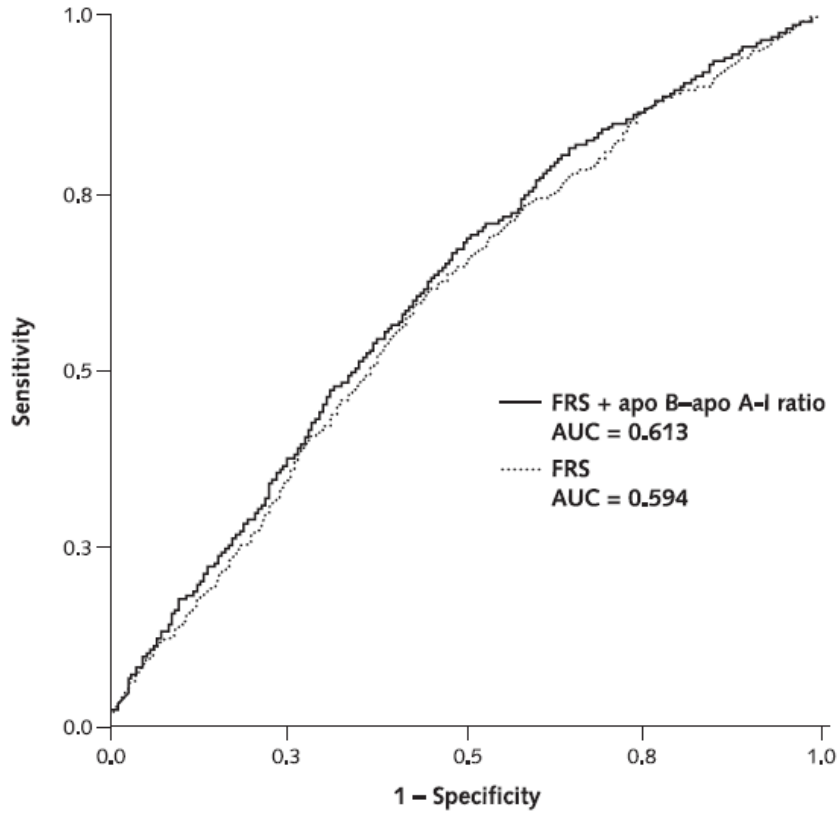
Lipoproteínas: apoB:apoA1



Erik Ingelsson et al. Clinical Utility of Different Lipid Measures for Prediction of Coronary Heart Disease in Men and Women. *JAMA*. 2007;298(7):776-785

Lipoproteínas: apoB:apoA1





Wim A. van der Steeget al. Role of the Apolipoprotein B–Apolipoprotein A-I Ratio in Cardiovascular Risk Assessment: A Case–Control Analysis inEPIC-Norfolk. *Ann Intern Med.* 2007;146:640-648.

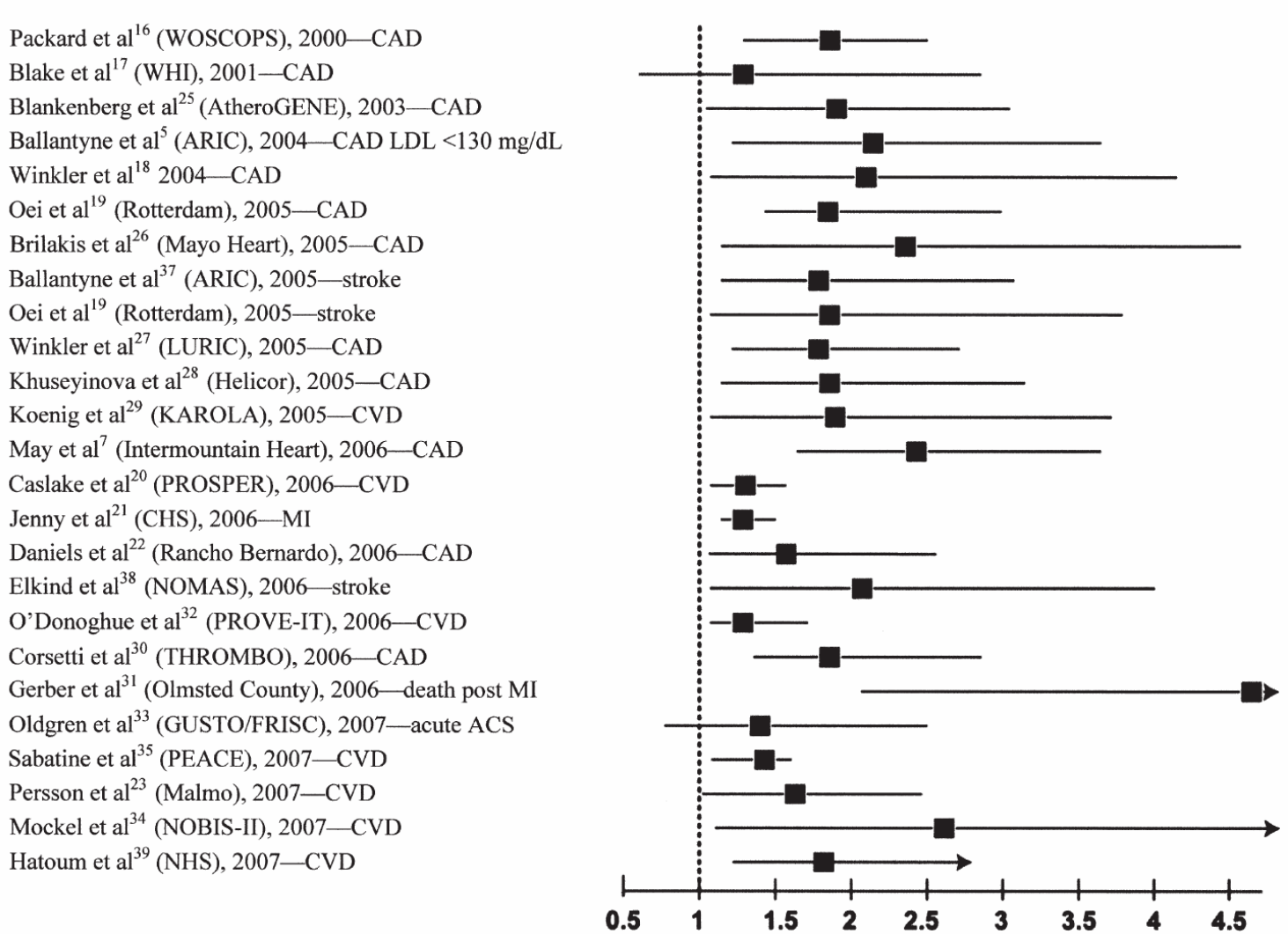
Marcadores inflamatorios: MPO

Odds Ratios for Fatal and Nonfatal Future CAD Events and Gender-Specific Odds Ratios by MPO Quartile (Unadjusted)

	MPO Quartile				
	1	2	3	4	p Value
MPO range (pmol/l)	<454	454–638	638–951	>951	
Fatal	1	1.45 (0.96–2.18)	1.44 (0.95–2.18)	1.82 (1.23–2.70)	0.03
Nonfatal	1	1.17 (0.91–1.51)	1.47 (1.15–1.87)	1.35 (1.04–1.74)	0.01
Male MPO range (pmol/l)	<464	464–657	657–985	>985	
	1	1.34 (1.02–1.75)	1.54 (1.17–2.02)	1.61 (1.23–2.12)	0.003
Female MPO range (pmol/l)	<446	446–607	607–894	>894	
	1	0.91 (0.63–1.30)	1.20 (0.86–1.67)	1.17 (0.84–1.62)	0.3

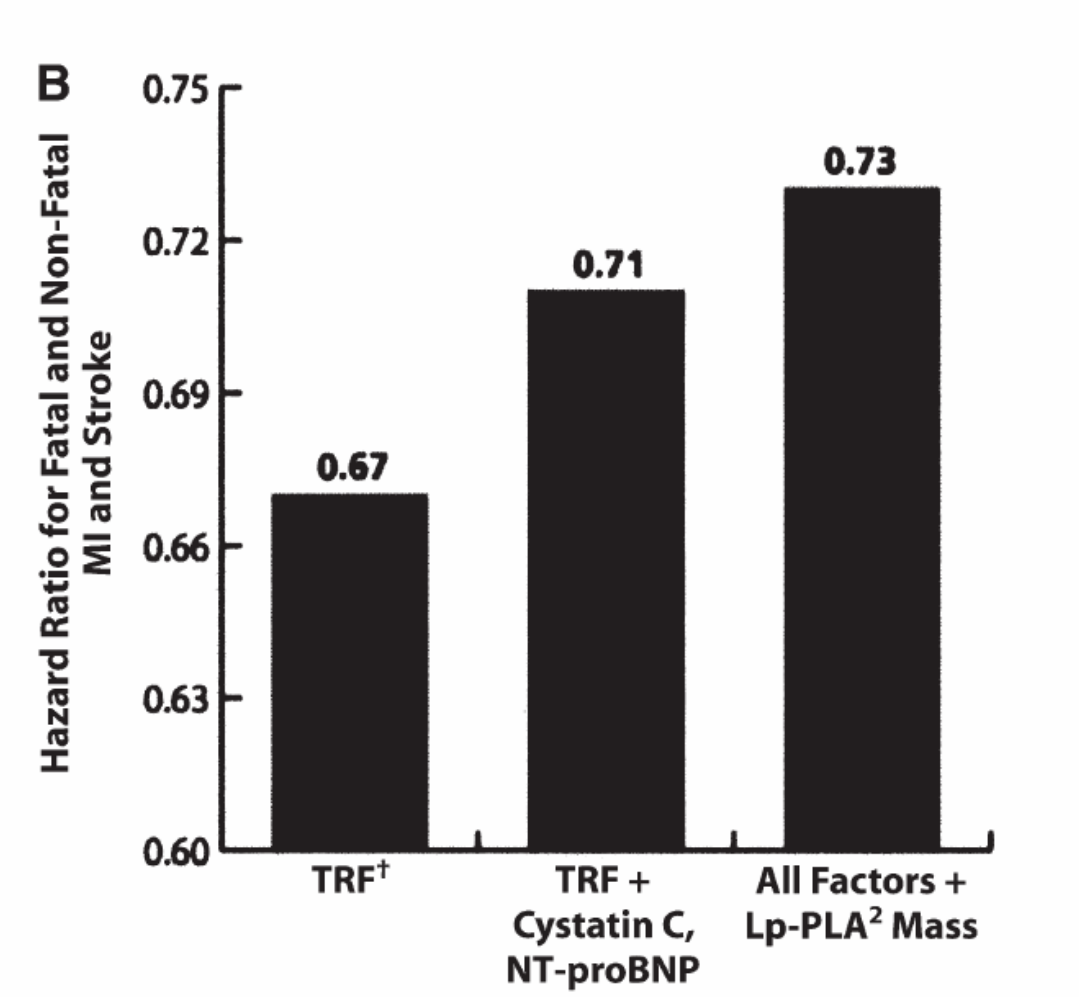
Marijn C. Meuwese et al. Serum Myeloperoxidase Levels Are Associated With the Future Risk of Coronary Artery Disease in Apparently Healthy Individuals The EPIC-Norfolk Prospective Population Study. *JACC* 2007;50:159–65

Marcadores inflamatorios: Lp-LPA$_2$



Marshall A. Corson et al. Review of the Evidence for the Clinical Utility of Lipoprotein-Associated Phospholipase A2 as a Cardiovascular Risk Marker. Am J Cardiol 2008;101[suppl]:41F–50F

Marcadores inflamatorios: Lp-LPA_2



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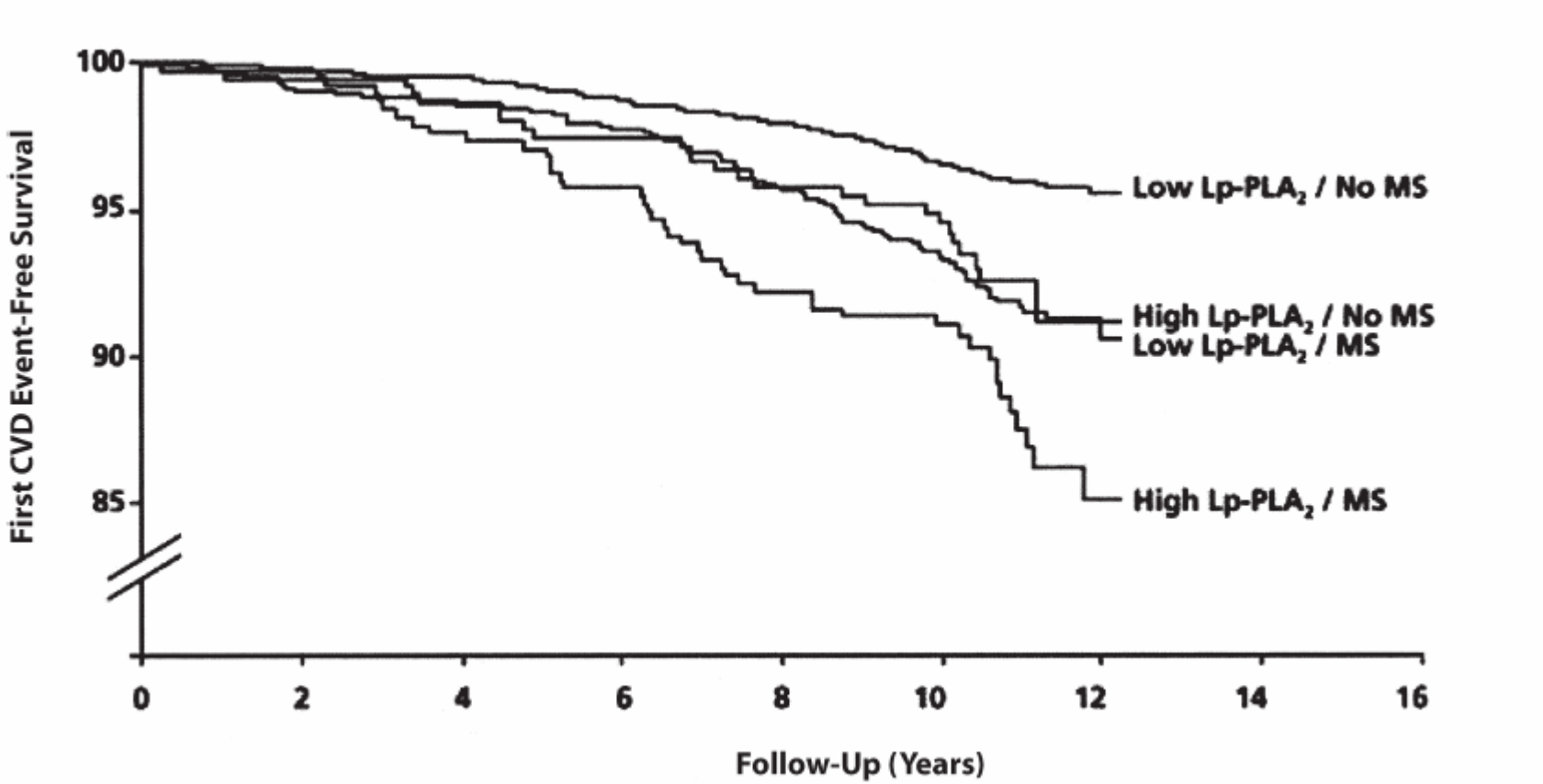
Marcadores inflamatorios: Lp-LPA_2

The ability of cardiac biomarkers, including lipoprotein-associated phospholipase A_2 (Lp-PLA_2), to significantly increase the area under the curve (AUC) for incident coronary artery disease in the Atherosclerosis Risk in Communities (ARIC) study*

Biomarker	p Statistic
Log C-reactive protein	NS
Lp-PLA_2	<0.05
Metalloproteinase-1	NS
Intracellular adhesion molecule–1	NS
E-selectin	NS
Log D-dimer	NS
Log plasminogen activator inhibitor–1	NS
Homocysteine	NS

Marshall A. Corson et al. Review of the Evidence for the Clinical Utility of Lipoprotein-Associated Phospholipase A2 as a Cardiovascular Risk Marker. Am J Cardiol 2008;101[suppl]:41F–50F

Marcadores inflamatorios: Lp-LPA_2



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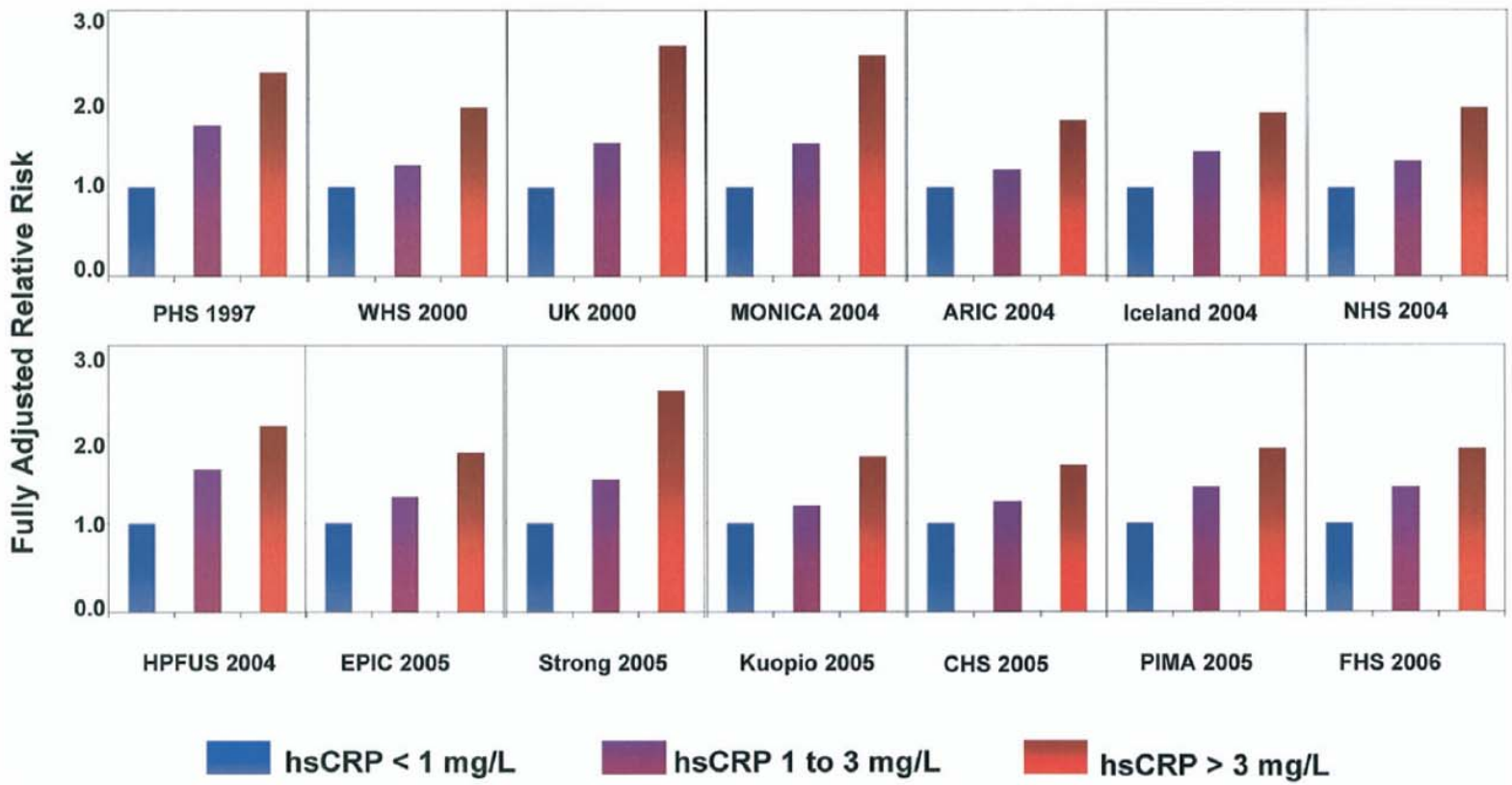
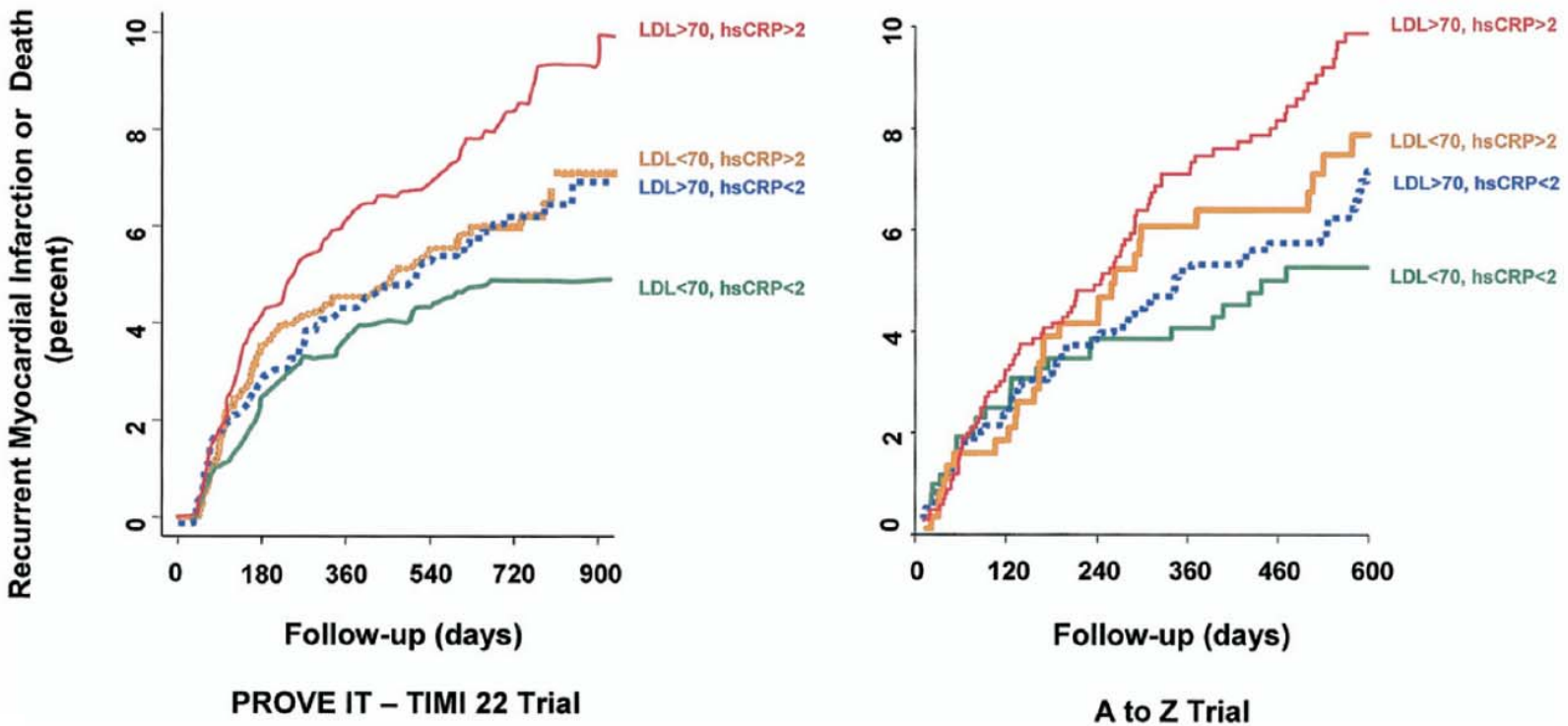
Marcadores inflamatorios: PCR



Independent Impact of hsCRP on Cardiovascular Risk

Paul M Ridker. C-Reactive Protein and the Prediction of Cardiovascular Events Among Those at Intermediate Risk. Moving an Inflammatory Hypothesis Toward Consensus. J Am Coll Cardiol 2007;49:2129–38

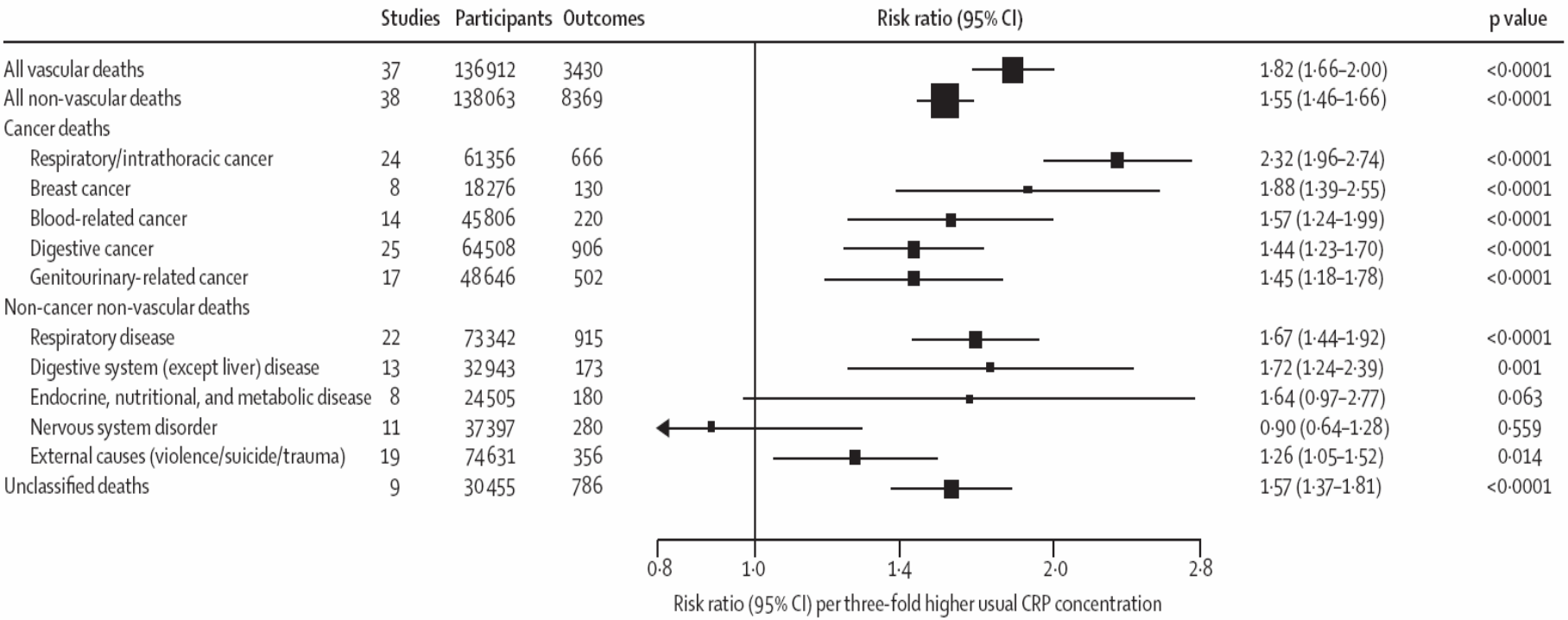
Marcadores inflamatorios: PCR



LDL Cholesterol, hsCRP, and Clinical Outcomes on Statin Therapy

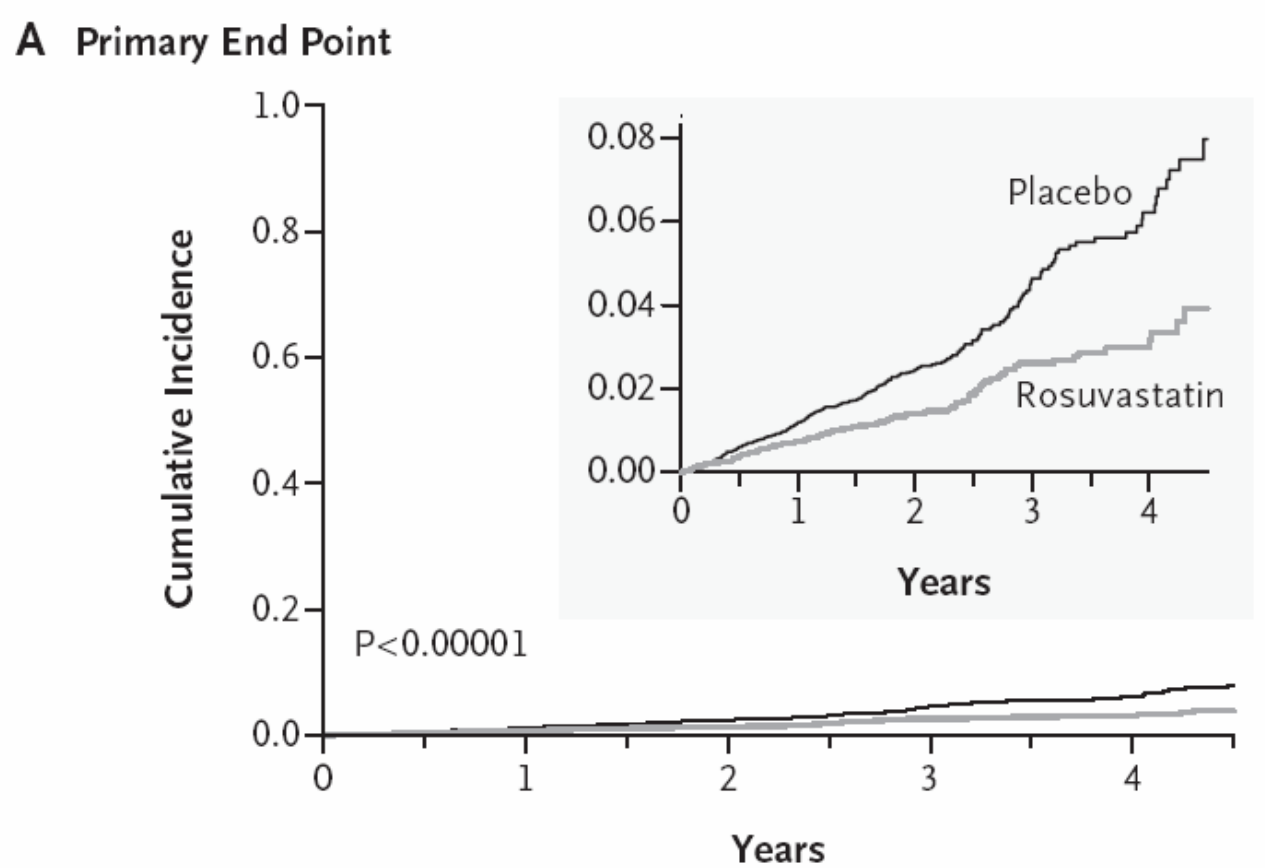
Paul M Ridker. C-Reactive Protein and the Prediction of Cardiovascular Events Among Those at Intermediate Risk. Moving an Inflammatory Hypothesis Toward Consensus. J Am Coll Cardiol 2007;49:2129–38

Marcadores inflamatorios: PCR



The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; 375: 132–40

Marcadores inflamatorios: PCR



Paul M Ridker et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med 2008;359:2195-207.

Marcadores inflamatorios: MCP-1

Chemokine	Population	Numbers	Follow-up	Associated disease/event	Study design	Outcome
IL-8 (36)	Healthy individuals	785 cases 1,570 controls	6 years	Fatal and nonfatal CAD	Nested case-control	Higher levels of IL-8 in cases
MCP-1 (37)	Healthy individuals	3,499		Subclinical athero-sclerosis	Cross sectional	MCP-1 associated with coronary artery calcium score
MCP-1 (38)	CAD/PAD	412/209 cases 733/709 controls		CAD/PAD	Case control	Higher levels of MCP-1 in cases
IL-8, IP-10, MCP-1, RANTES, MIP-1α,eotaxin (39)	CAD	312 cases 472 controls		Angiographically confirmed and stable CAD	Case control	Higher levels of IL-8 and IP-10, lower RANTES in cases
MCP-1 (40)	ACS	2,270	10 months	Death or MI	Prospective	MCP-1 levels above 75th percentile associated with increased event risk
MCP-1 (41)	ACS	183	13 months	Composite (death, MI, unstable angina, revascularization)	Prospective	MCP-1 predicted a new coronary event
Eotaxin-3 (42)	CAD	1,026	2.7–4.1 years	Cardiovascular death, MI	Prospective	Lower eotaxin-3 levels predicted future events

IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein-1; IP-10, interferon (INF)-inducible protein of 10 kd; MIP-1α, macrophage inflammation protein-1; CAD, coronary artery disease; PAD, peripheral artery disease; ACS, acute coronary syndrome; MI, myocardial infarction.

Pål Aukrust et al. Chemokines in cardiovascular risk prediction. *Thromb Haemost* 2007; 97: 748–754

Marcadores cardíacos: BNP, Trop I

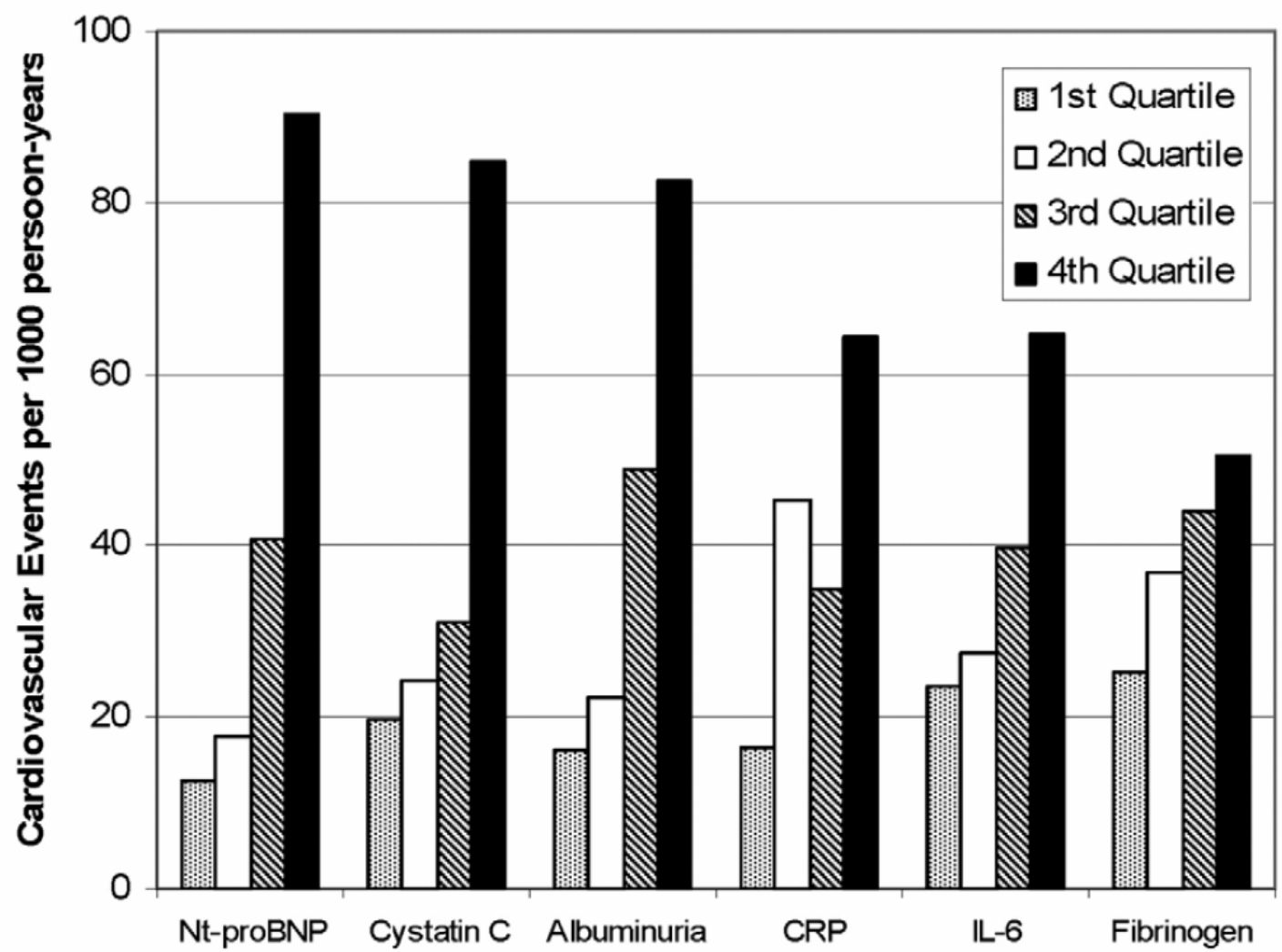
C Statistic for Cox Regression Models Predicting Death from Cardiovascular Causes and from All Causes in the Whole Sample and in the Subsample without Cardiovascular Disease at Baseline.*

Risk Factors and Biomarkers	C Statistic for Death from Cardiovascular Causes	P Value†	C Statistic for Death from All Causes	P Value†
Whole sample				
Established risk factors	0.664	Referent	0.604	Referent
Established risk factors plus troponin I	0.715	0.002	0.634	0.009
Established risk factors plus NT-pro-BNP	0.749	<0.001	0.657	<0.001
Established risk factors plus cystatin C	0.691	0.07	0.626	0.03
Established risk factors plus C-reactive protein	0.689	0.07	0.636	0.008
Established risk factors plus all biomarkers	0.766	<0.001	0.676	<0.001
Estimated difference with the addition of all biomarkers (95% CI)	0.102 (0.056 to 0.147)	<0.001	0.072 (0.041 to 0.104)	<0.001
Participants without CVD at baseline				
Established risk factors	0.688	Referent	0.638	Referent
Established risk factors plus troponin I	0.716	0.15	0.640	0.90
Established risk factors plus NT-pro-BNP	0.722	0.20	0.653	0.32
Established risk factors plus cystatin C	0.700	0.45	0.649	0.38
Established risk factors plus C-reactive protein	0.715	0.20	0.663	0.11
Established risk factors plus all biomarkers	0.748	0.03	0.668	0.09
Estimated difference with the addition of all biomarkers (95% CI)	0.059 (0.007 to 0.112)	0.03	0.030 (–0.005 to 0.064)	0.09

Bjorn Zethelius et al. Use of Multiple Biomarkers to Improve the Prediction of Death from Cardiovascular Causes

N Engl J Med 2008;358:2107-16.

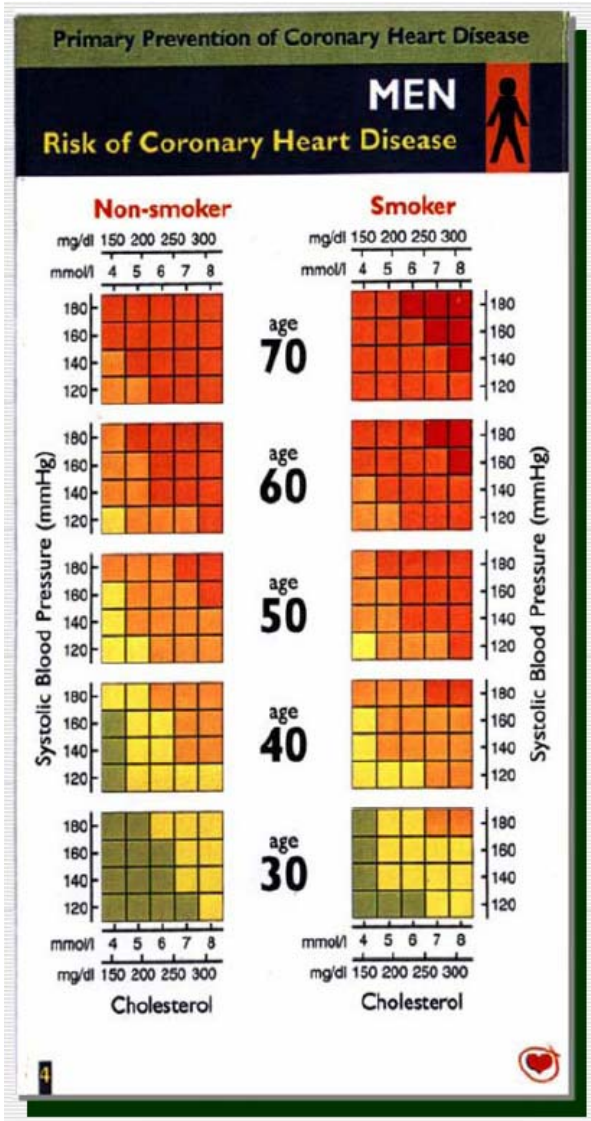
Marcadores renales: Albuminuria, Cistatina C

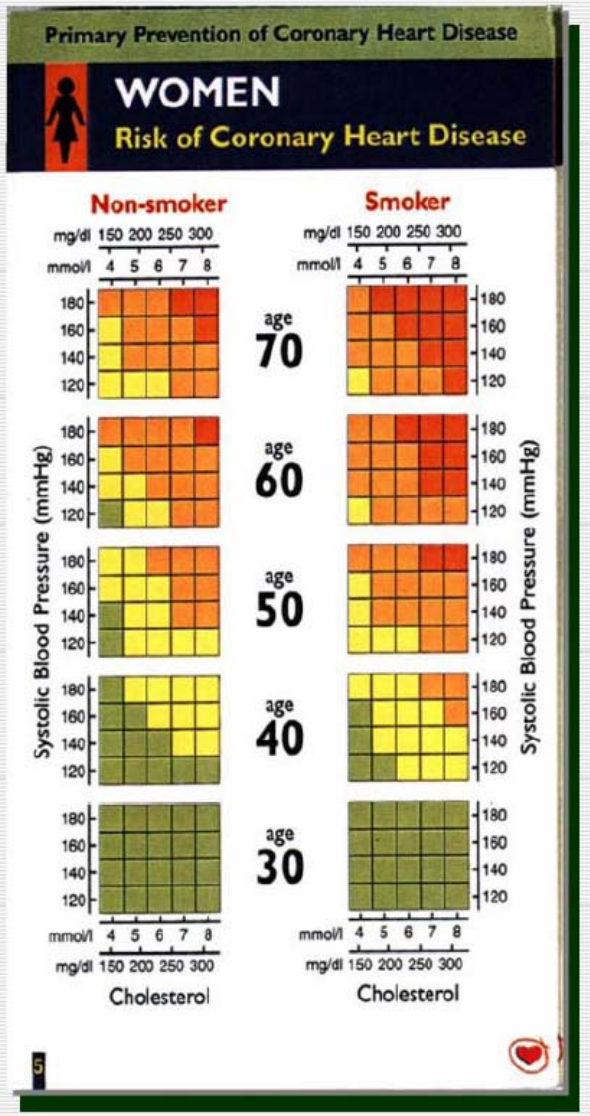


Michael G. Shlipak et al. Biomarkers to Predict Recurrent Cardiovascular Disease: The Heart and Soul Study

Am J Med 2008;121, 50-57

Utilidad clínica





Utilidad clínica

Characteristics of the Study Sample (N = 5067)[a]

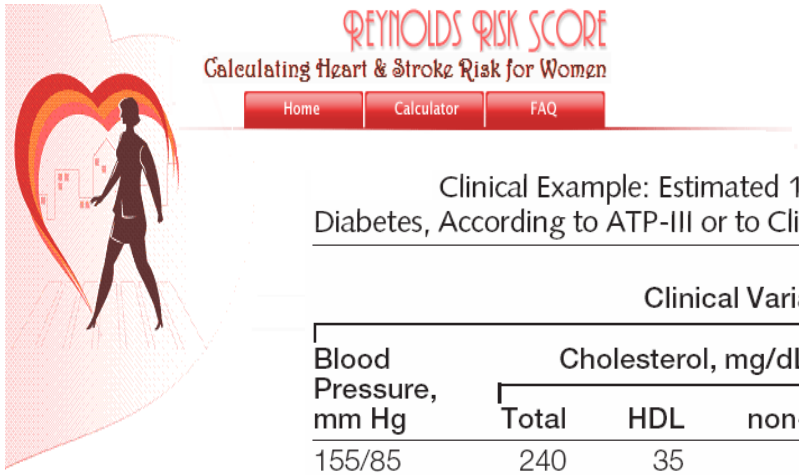
Characteristic	Value
mean (SD), %	

Reclassification of 10-Year Predicted Risk[a]

Model With Conventional Risk Factors Alone	Model With Conventional Risk Factors and Biomarkers, No. With Events/Total (%)			
	<6%	6% to <20%	≥20%	Total
Cardiovascular events				
<6%	65/3092 (2.1)	7/123 (5.7)	0	72/3215 (2.2)
6% to <20%	10/143 (7.0)	109/920 (11.8)	6/35 (17.1)	125/1098 (11.4)
≥20%	0	4/34 (11.8)	37/136 (27.2)	41/170 (24.1)
Total	75/3235 (2.3)	120/1077 (11.1)	43/171 (25.1)	
Coronary events				
<6%	72/3891 (1.8)	9/85 (10.6)	0	81/3976 (2.0)
6% to <20%	3/110 (2.7)	45/443 (10.2)	2/22 (9.1)	50/575 (8.7)
≥20%	0	2/14 (14.3)	11/35 (31.4)	13/49 (26.5)
Total	75/4001 (1.9)	56/542 (10.3)	13/57 (22.3)	

Olle Melander et al. Novel and Conventional Biomarkers for Prediction of Incident Cardiovascular Events in the Community. *JAMA*. 2009;302(1):49-57

Utilidad clínica



Clinical Example: Estimated 10-Year Risk for a 50-Year-Old Smoking Woman Without Diabetes, According to ATP-III or to Clinically Simplified Model B (the Reynolds Risk Score)

Clinical Variables						Estimated 10-Year Risk, %	
Blood Pressure, mm Hg	Cholesterol, mg/dL			hsCRP, mg/L	Parental History*	ATP-III Model	Simplified Model B
	Total	HDL	non-HDL				
155/85	240	35	205	0.1	No	11.5	4.9
155/85	240	35	205	0.5	No	11.5	6.5
155/85	240	35	205	1.0	No	11.5	7.4
155/85	240	35	205	3.0	No	11.5	8.9
155/85	240	35	205	5.0	No	11.5	9.7
155/85	240	35	205	8.0	No	11.5	10.5
155/85	240	35	205	10.0	No	11.5	10.9
155/85	240	35	205	20.0	No	11.5	12.3
155/85	240	35	205	0.1	Yes	11.5	7.5
155/85	240	35	205	0.5	Yes	11.5	9.9
155/85	240	35	205	1.0	Yes	11.5	11.2
155/85	240	35	205	3.0	Yes	11.5	13.4
155/85	240	35	205	5.0	Yes	11.5	14.6
155/85	240	35	205	8.0	Yes	11.5	15.8
155/85	240	35	205	10.0	Yes	11.5	16.4
155/85	240	35	205	20.0	Yes	11.5	18.4

Paul M Ridker et al. Development and Validation of Improved Algorithms for the Assessment of GlobalCardiovascular Risk in Women. The Reynolds Risk Score. *JAMA.* 2007;297:611-619

Utilidad clínica

Reclassifi
Causes or Who Di

Model with Estab

Participants who c	
<6% risk	14
6–20% risk	27
>20% risk	13
Total no.	54
Participants who c	
<6% risk	322
6–20% risk	258
>20% risk	27
Total no.	607

diovascular

Biomarkers

Total No.

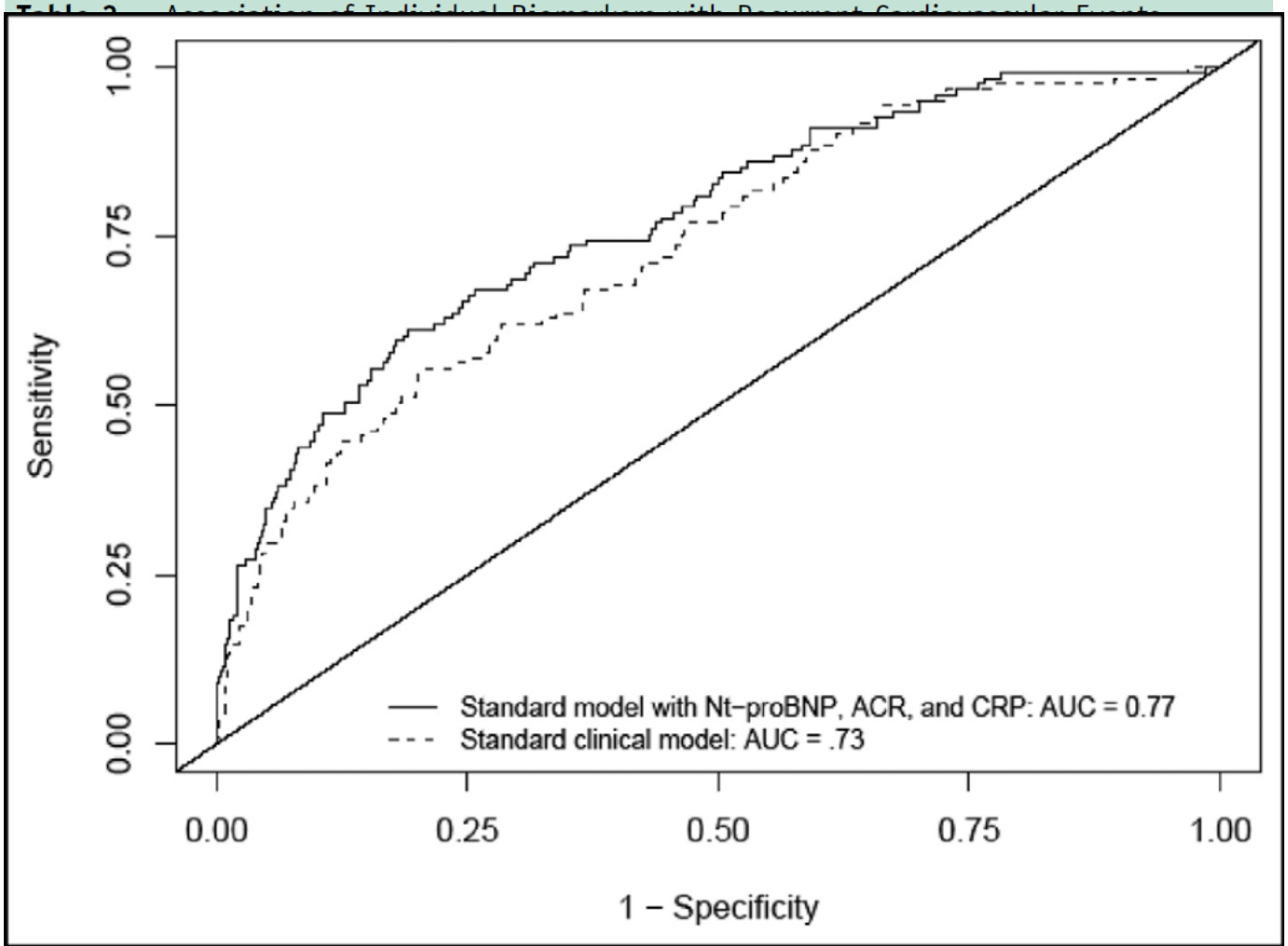
Baseline Characteristics of the Study Cohort.*

Characteristic	Whole Sample	Participants without Cardiovascular Disease
No. of subjects	1135	661
Age — yr	71±0.6	71±0.6
Body-mass index†	26.3±3.4	26.0±3.2
Serum cholesterol — mmol/liter‡		
Total	5.81±0.99	5.77±0.98
HDL	1.28±0.35	1.31±0.35
Blood pressure — mm Hg		
Systolic	147±19	148±19
Diastolic	84±9	84±9
Plasma troponin I — μg/liter	0.021±0.17	0.022±0.22
Plasma NT-pro-BNP — ng/liter	232±397	145±213
Serum cystatin C — mg/liter	1.24±0.27	1.22±0.23
Serum C-reactive protein — mg/liter	3.37±4.77	3.27±4.55
Smoker — no. (%)	235 (20.7)	140 (21.2)
Diabetes — no. (%)	121 (10.7)	58 (8.8)
Hypertension — no. (%)	849 (74.8)	472 (71.4)
Antihypertensive treatment — no. (%)	378 (33.3)	146 (22.1)
ACE-inhibitor treatment — no. (%)	66 (5.8)	25 (3.8)
Dyslipidemia — no. (%)	994 (87.6)	575 (87.0)
Lipid-lowering treatment — no. (%)	106 (9.3)	44 (6.7)
Aspirin treatment — no. (%)	105 (9.3)	8 (1.2)
Previous cardiovascular disease — no. (%)	474 (41.8)	—

Bjorn Zethelius et al. Use of Multiple Biomarkers to Improve the Prediction of Death from Cardiovascular Causes

N Engl J Med 2008;358:2107-16.

Utilidad clínica

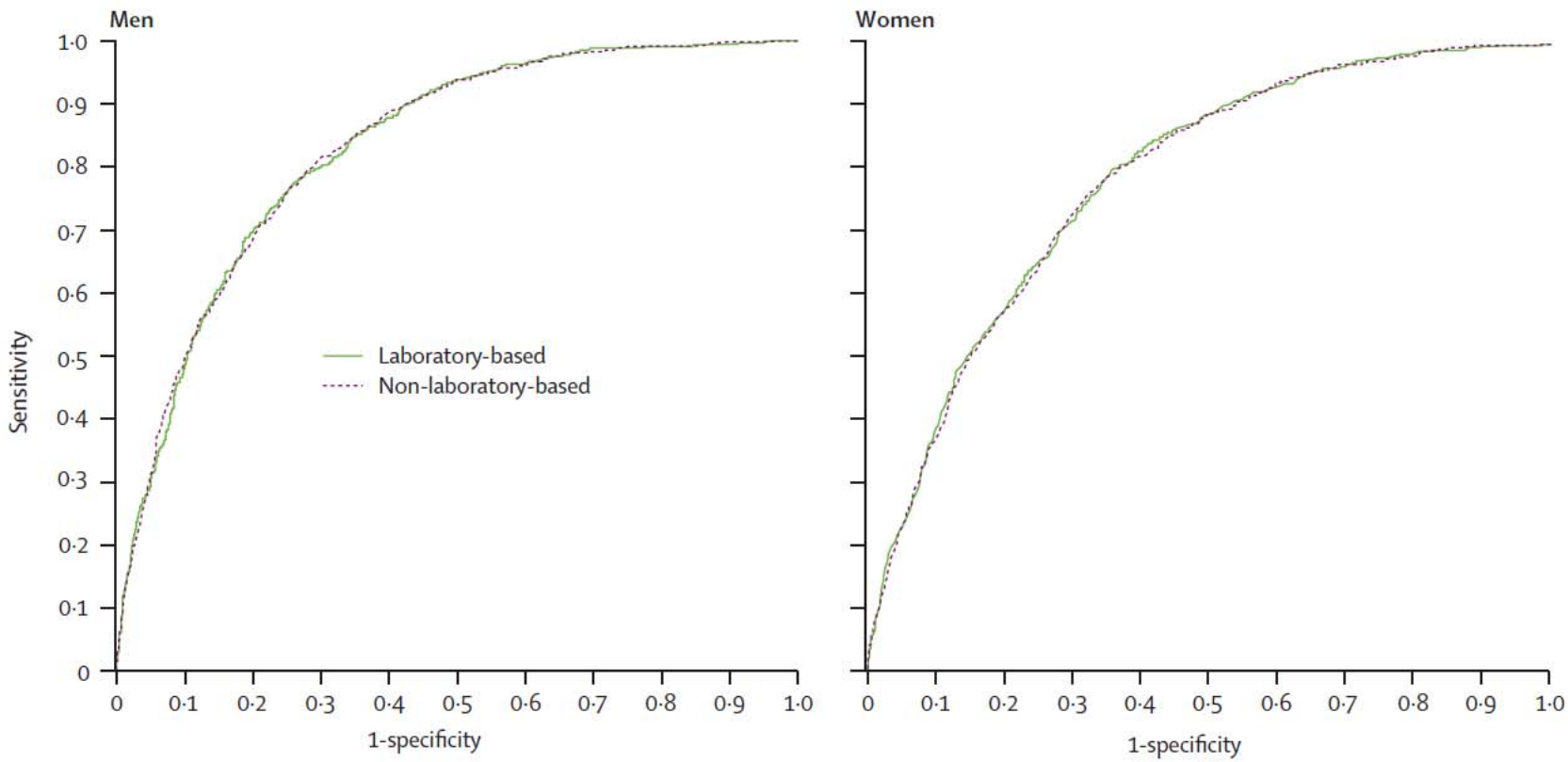


Adjusted‡	1.26 (1.04-1.52)	.02	1.15 (0.78-1.69)	.48

Michael G. Shlipak et al. Biomarkers to Predict Recurrent Cardiovascular Disease: The Heart and Soul Study

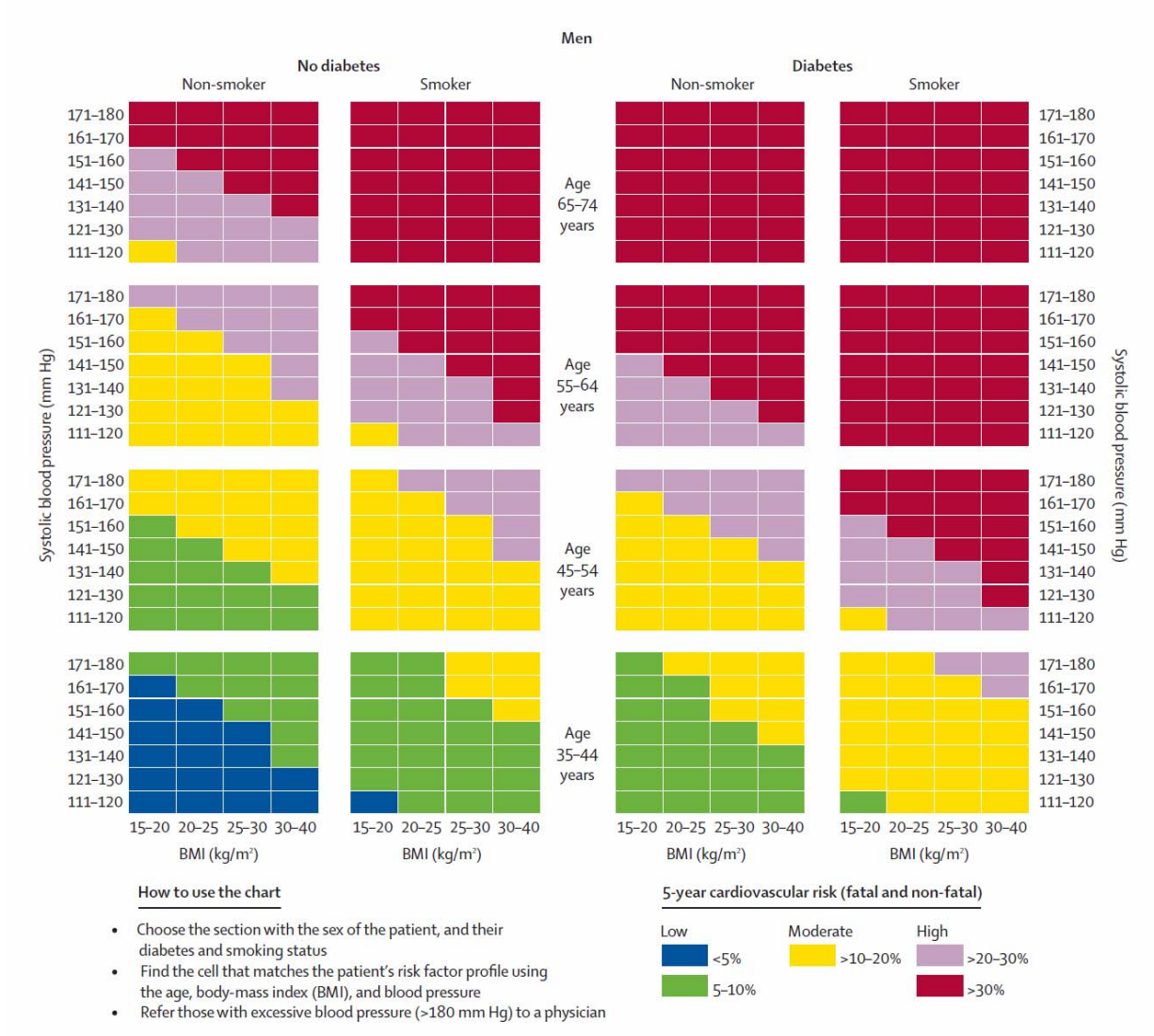
Am J Med 2008;121, 50-57

Tablas de multimarcadores



Thomas A Gaziano et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008; 371: 923–31

Tablas de multimarcadores



Thomas A Gaziano et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008; 371: 923–31

Screening for Atherosclerosis

Risk Factors vs Disease

Numerous Risk Factors

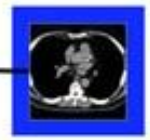
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests

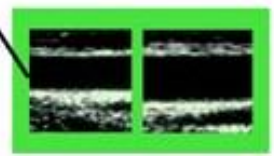
Carotid IMT and Plaque Measured by Ultrasound

Aortic and Carotid Plaque Detected by MRI



Coronary Calcium Score Measured by CT

Ankle Brachial Index



Brachial Vasoreactivity Measured by Ultrasound

Vascular Compliance Measured by Radial Tonometry

Examples of Arterial Function Tests

Microvascular Reactivity Measured by Fingertip Tonometry