SPECIAL ARTICLE

Inflammation Markers and Risk Stratification in Patients With Acute Coronary Syndromes. Design of the SIESTA Study (Systemic Inflammation. Evaluation in Patients With Non-ST Segment Elevation Acute Coronary Syndromes)

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Background and objective. Evidence is growing regarding the prognostic value of markers of inflammation in unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI). However, the independent value of these variables has not been systematically investigated in prospective studies. The main objective of the SIESTA study is to assess the relative prognostic roles of C-reactive protein, fibrinogen, neopterin, interleukins 6, 8, 10 and 18, tumor necrosis factor, e-selectin, endothelin 1, tissue factor, VCAM-1, ICAM-1, pregnancy-associated plasma protein-A, B-type natriuretic peptide, leukocytes, troponin I or T and serum creatine kinase-MB (CKMB) in UA/NSTEMI patients.

Patients and method. SIESTA is a prospective, multicenter trial involving patients with chest pain suggestive of acute coronary syndrome (ACS) within 48 hours of enrolment and at least one of the following: abnormal troponin levels, electrocardiographic signs of ischaemia or previously documented vascular disease. Clinical outcome data and serial biochemical determinations will be assessed during hospital admission and at 30, 180 and 365 days of follow-up. The TIMI (Thrombolysis In Myocardial Infarction) and PEPA (Proyecto de Estudio del Pronóstico de la Angina) risk scores will be also validated. Study variables will include death due to any cause, cardiac death, non-fatal myocardial infarction, unstable angina requiring re-admission, emergency revascularization and a composite of death, myocardial infarction and need for emergency hospitalization or myocardial revascularization. Each of these conditions will be treated as secondary end-points when assessed individually.

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This study will provide valuable prospective information about the prognostic value of inflammatory markers in «real life» ACS patients of Mediterranean origin.

Key words: *Acute coronary syndromes. Unstable angina. Inflammation markers. Risk stratification.*

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Marcadores de inflamación y estratificación de riesgoen pacientes con síndrome coronario agudo: diseño del estudio SIESTA (Systemic Inflammation Evaluation in patients with non-STsegment elevation Acute coronary syndromes)

Introducción y objetivos. A pesar de que se conoce el valor pronóstico de varios marcadores de inflamación en el síndrome coronario agudo sin elevación del segmento ST (SCASEST), aún se ignora qué subconjunto de éstos proporciona mejor información y qué grado de asociación existe entre ellos.

El objetivo del estudio SIESTA es establecer el valor pronóstico de la proteína C reactiva, fibrinógeno, neopterina, interleucinas 6, 8, 10 y 18, factor de necrosis tumoral, e-selectina, endotelina 1, factor tisular, molécula de adhesión celular vascular-1 (VCAM-1) e intercelular-1 (ICAM-1), proteína plasmática-A asociada al embarazo (PAPP-A), péptido natriurético ventricular (tipo B), troponina I o T, leucocitos e isoforma MB de la creatinfosfocinasa (CK-MB), en pacientes con SCASEST.

Pacientes y método. SIESTA es un estudio prospectivo, multicéntrico, que incluirá a pacientes que hayan presentado dolor torácico sugestivo de síndrome coronario agudo en las últimas 48 h y alguna de las siguientes condiciones: signos electrocardiográficos de isquemia miocárdica, enfermedad vascular documentada o elevación de la concentración de troponinas. Se realizará un seguimiento clínico durante un año, con determinaciones hematológicas y bioquímicas en el momento del ingreso, del alta, y a los 30, 180 y 365 días. Se validarán las escalas TIMI (Thrombolysis In Myocardial Infarction) y PEPA (Proyecto de Estudio del Pronóstico de la Angina).

La variable principal estará compuesta de muerte por cualquier causa, muerte de origen cardíaco, infarto de

ABBREVIATIONS

NSTEACS: non-ST segment elevation acute coronary syndrome.
CRP: C-reactive protein.
PAPP-A: pregnancy-associated plasma protein-A.
BNP: brain natriuretic peptide.
NFkB: nuclear factor kappa-B.
PCTA: percutaneous coronary transluminal angioplasty.

miocardio no letal y angina inestable que requiera hospitalización o revascularización urgente. La evaluación individual de cada una de las variables se considerará como objetivo secundario.

Este estudio ofrecerá valiosa información prospectiva acerca del valor pronóstico de un importante número de marcadores inflamatorios en pacientes de origen mediterráneo asistidos en la práctica médica habitual.

Palabras clave: *Síndrome coronario agudo. Angina inestable. Marcadores de inflamación. Estratificación de riesgo.*

INTRODUCTION

Acute coronary syndrome is one of the most severe forms of heart disease, and is the most frequent cause of morbidity and mortality in the western world.[1,2] Patients with ACS are at serious risk of developing cardiovascular events within the first year of acute coronary syndrome.[2,3]

Recently, Marrugat et al[2] estimated that in the year 2002 more than 40 000 patients will have been admitted to Spanish hospitals with a diagnosis of acute myocardial infarction (60% of the total estimated admissions). The mortality rate of these patients in the first 28 days (excluding the pre-hospital phase) will be close to 25%.[2] Nearly 33 000 individuals will be hospitalized with the diagnosis of non-ST segment elevation acute coronary syndrome (NSTEACS), of which 4.5% will die within the first 3 months.[2]

Adequate risk classification would allow for more precise therapeutic management of these patients.[4,5]

The problem, however, is the heterogeneity of this syndrome, as it includes patients with varying clinical pictures. In addition, prognosis depends on various clinical, electrocardiographic, biochemical, and angiographic variables[4] which, to a degree, reveal the presence of ischemia or myocardial necrosis, frequently associated with heart disease. In patients with ACS, distinct complex physiopathological mechanisms,[6-9] including erosion and rupture of atherosclerotic plaque,[10,11] cause acute obstruction of coronary flow. The principal events associated with clinical instability in patients with NSTEACS[12,13] are the degree of inflammatory activity, increase in vasomotor tone, and plaque activation; similarly, systemic inflammation is found to be associated with the development of atherosclerosis, changes in hemostasis, and acute coronary thrombosis.[14,15] The presence of inflammatory cells within the atheromatous plaque plays an important role in the process that leads to fissure, coronary thrombosis, and vascular occlusion characteristic of ACS.[16,17] The activation of macrophages, T cells, and nuclear factor kappa-B (NF/B), as well as the production and freeing of pro-inflammatory cytokines and neurohumoral substances, significantly contribute to the presence f clinical symptoms in these patients.[18]

Currently, risk classification of patients with NSTEACS is mainly based on clinical, electrocardiographic, and angiographic data, along with markers for cardiac damage.[4,19,20]

The TIMI (Thrombolysis In Myocardial Infarction)[21] and PEPA (Proyecto de Estudio del Pronóstico de la Angina—Project for the Study of Angina Prognosis) risk scores, which combine many of these variables, have recently been proposed and seem to be useful for making treatment decisions. These risk scores, however do not include markers of inflammation and it is possible that the incorporation of these markers may increase the prognostic value of the risk scores since in recent years evidence indicates that markers of inflammation are useful in evaluating prognosis in heart disease. Cytokines such as interleukin-6[22,23] and interleukin-18,[24] and acute phase reactants, such as amyloid protein A[25] and C-reactive protein (CRP),[26-29] are markers of risk and predictors of cardiovascular events.

Recently, researchers and clinicians have been principally focused their attention on the role of CRP as a marker for risk since it has been shown that elevation of CRP concentrations in plasma is a reliable predictor of death, myocardial infarct, and the need for urgent myocardial revascularization.[30-32] For example, in the TIMI 11 A study, the mortality rate at 14 days was significantly higher in patients with CRP of more than 1.55 mg/dL than in patients with lower values (5.6% vs 0.3%).[28] In other studies, an elevated CRP value in a hospital setting was shown to be a powerful predictor of risk at 3 and 24 months.[27,31] It has also been reported that CRP and troponin concentrations are independent markers of risk, and that their presence in combination can predict cardiovascular events more precisely than the presence of either variable alone.[24,28,29,33]

In spite of these findings, reports are contradictory and the controversy continues regarding the usefulness of CRP in everyday clinical practice.[12,13,34-36] CRP va lues are good predictors of future, later cardiovascular events, but not of early cardiovascular events.[27] In addition, it is unknown how often values should be obtained in patients with NSTEACS, given the spontane-

ous variations that can occur in the same patient; it is also unknown what cut point is appropriate for CRP to be considered elevated. Recently, other biochemical markers for risk have been proposed, such at brain natriuretic peptide (BNP) and pregnancy-associated plasma protein-A (PAPP-A)[37,38]; these markers must be validated in the context of markers already studied, as is the case with various markers of inflammation whose possible independent prognostic value is unknown.

Cardiac risk in Mediterranean patients and the role of markers for inflammation in risk stratification

The Mediterranean population has a lower incidence of myocardial infarction and mortality than other populations,[39,40] despite the fact that the prevalence of conventional risk factors in this population is similar to that in other areas of Europe and in the United States. In Spain, the mortality rate due to cardiovascular disease is lower than in other regions of the world,[41] and it is believed that genetic factors and dietary habits (Mediterranean diet) may play an important role. Whether markers for inflammation are of independent prognostic value in patients with ACS in the Mediterranean population has not been systematically studied.

The PEPA registry provides useful data on risk classification in patients with NSTEACS through the use of conventional variables, but does not provide data on the role of markers for inflammation.[5]

SIESTA (Systemic Inflammation Evaluation in Patients with Non-ST Segment Elevation Acute Coronary Syndromes) is a multicenter, observational, prospective Spanish study of patients admitted with a diagnosis of NSTEACS; the goal of the study is to determine the prognostic value of various markers of inflammation as well as markers of endothelial activation in patients with NSTEACS.

Objectives

The principle objectives of the SIESTA study are to:

1. Compare the prognostic value of CRP with other markers for inflammation, including pro- and anti-inflammatory cytokines, chemokines, adhesion molecules, neopterin, fibrinogen, serum amyloid A protein, endothelin 1, and the recently described PAPP-A and BNP.

2. Compare the prognostic value of markers for inflammation with other established risk indicators (clinical, electrocardiographic, and biochemical [troponin]).

3. Establish the predictive value of a single test result vs repeated measurement of various markers of inflammation.

A secondary objective is to establish the prognostic usefulness of the TIMI21 and PEPA5 risk scores.

Hypotheses

The SIESTA study will attempt to confirm the following hypotheses:

- The presence of elevated values of circulating markers for inflammation, chemokines, and markers for endothelial activation are valuable for establishing prognosis for patients with NSTEACS.
- BNP and PAPP-A are independent risk markers in the population studied.
- The presence of persistently elevated values of markers for inflammation is associated with prognosis in patients with NSTEACS.
- The TIMI or PEPA risk scores, or both, are clinically useful for classification of risk in patients of Mediterranean origin with NSTEACS.

Patients and methods

Patients of both sexes will be included in the study, not limited by age, who have chest pain suggestive of ACS during the previous 48 hours and at least 1of the following conditions:

1. Electrocardiographic signs of myocardial ischemia (decline of the ST segment or T-wave inversion, or both).

2. Documented heart, cerebrovascular, or peripheral vascular disease.

3. Percutaneous coronary transluminal angioplasty (PCTA) or myocardial revascularization surgery, or both, performed no less than 12 weeks prior to the current episode.

4. Elevated cardiac troponin values.

Patients will not be included in the study who present with: *a)* ST segment elevation; *b)* complete left branch block; *c)* moderate or severe aortic stenosis; *d)* hypertrophic or dilated myocardiopathy; *e)* myocardial infarct during the last 12 weeks; *f)* PCTA or revascularization surgery, or both, during the prior 12 weeks; *g)* a history of heart failure; *h)* cerebrovascular or peripheral accident during the prior 12 weeks, and *i)* uncontrolled arterial hypertension, anemia, evidence of infection, tyrotoxicosis, local or systemic inflammatory disease, terminal renal insufficiency, neoplasia, or any other disease that seriously compromises the prognosis for survival or generates a systemic inflammatory response, or both.

Sample size

In patients with NSTEACS, the incidence of new cardiovascular events during the first year ranges

from 16% to 30%.[42,43] To calculate the sample size for this study, we assumed that the probability of patients presenting with new cardiovascular events was 20%, and we chose CRP as the variable to calculate in the sample size, as CRP is the value that presents with the greatest variability (in different studies its standard deviation ranged from 5 mg/dL to 10 mg/dL).[44] We assumed a loss rate of 5%, a bilateral alpha risk of 0.05, and a beta error of less than 0.10, we would require 1044 of patients without events and 313 of patients with events in order to detect a difference equal to 1.5 mg/dL in the concentration of CRP between the 2 groups.

Therapeutic management and clinical followup

Patients will be treated in accordance with the recommendations of the Spanish Cardiology Society,[45] and will receive aspirin, beta, blockers, heparin, clopidogrel, nitrates, hypolipemiants, and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (ARA II). Glycoprotein inhibitors IIb/IIIa will be used in high-risk patients, those with elevated troponin, or those about to undergo angiography and possible PCTA.

Data will be collected on any other medications–cardiologic or not–used during the study. The decisions regarding the treatment of patients will be left to the judgment of the attending physician, and the results of markers of inflammation in this study will not be available for patient management. It is expected that all patients with refractory or incapacitating angina that persists despite optimal medical treatment, and patients with signs of serious ischemia will undergo coronary angiography in order to provide PCTA or revascularization surgery. In patients who undergo cardiac catheterization, the ejection fraction, the severity of coronary lesions, and the number of occluded vessels will be noted.

The ethics committee of each participating hospital has approved the study protocol, and the patients will sign informed consent forms before their admission to the study, signifying their agreement to participate in the SIESTA study. Patient recruitment began in June, 2002, and the last patients are expected to be admitted at the end of 2003. The patients will be followed for 1 year.

Demographic and clinical variables that will be analyzed are shown in Table 1.

TABLE 1. **Demographic and clinical variables**

Risk factors
Smoking (habitual, ex-smoker, never smoked; years smoking), hypertension, hyperlipidemia, diabetes mellitus, history of myocardial infarction,NSTEACS, ATCP, revascularization surgery, cerebrovascular accident or peripheral vascular disease, family history of cardiovascular disease
Medication at the time of admission
Aspirin, beta blockers, heparin, IIb/IIIa inhibitors, clopidogrel, nitrates, calcium antagonists, hypolipemiants, angiotensin converting enzyme inhibitors, ARA II, hormone replacement therapy, diuretics, digoxin, others
Coronary angiography
Left ventricular ejection fraction, severity of coronary stenosis and number of diseased vessels
Blood samples (on admission and hospital discharge, at 1, 6 and 12 month followup)
CK-MB, cardiac troponins, lipid profile, high sensitivity CRP, leukocytes, fibrinogen, interleukin 6, 8, 10, and 18, serum amyloid A protein, TNF-alpha, tissue factor, ICAM-1, VCAM-1, von Willebrand factor, e-selectin, metalloproteinase 1, 2, and 9, neopterin, endothelin 1, PAPP-A, and BNP
Variables
The principle variable will consist of death due to any cause, death of cardiac origin, non-lethal myocardial infarction and unstable angina that requires urgent hospitalization or,revascularization. Individual evaluation of each variable isconsidered to be a secondary objective

Blood analysis

Peripheral venous blood will be obtained and immediately centrifuged. Hemogram and biochemistry will be determined, to include: MP isoenzyme of creatinkinase (MB-CK), troponin, lipid profile, creatinine concentrations, urea, etc., at each participating hospital. The samples collected will be quickly frozen and maintained at –70 ºC until they are sent to the central laboratories, which will produce a complete lipid profile, high sensitivity CRP, fibrinogen, serum amyloid protein A, interleukins 6, 8, 10 and 18, tumoral necrosis factor alpha (TNF-alpha), intracellular cellular adhesion molecule 1 (ICAM-1);vascular cellular adhesion molecule 1 (VCAM-1); e-selectin; von Willebrand factor; metalloproteinase 1, 2, and 9; tissue factor; neopterin; PAPPA; BNP; neopterin; and endothelin 1. Blood samples will be obtained at the time of admission and hospital discharge, and at 6 months and 1 year followup.

Two laboratories, the Instituto Carlos III de Madrid and Saint George's of London, have been selected to analyze the samples. The Madrid lab will perform lipid studies and will keep the frozen samples until they are transferred to London, where the markers of inflammation will be determined. The blood samples will be codified in a manner that masks the identity and clinical characteristics of the patients to the laboratories.

Study variables

The principal variable will be death due to any cause, death of cardiac origin, non-lethal myocardial infarction, and angina that requires hospitalization, PCTA, or urgent revascularization surgery. Each component of the principal variable will be a secondary variable when evaluated individually.

Patients who are discharged will be seen in clinic by the research physicians at 1 month, 6 months, and 1 year after discharge. During this followup period, an independent committee will analyze the events, defining death according to the criteria of the International Classification of Diseases (ICD).[46]

Definitions

The definitions used in this study are based on the recent guidelines of the American College of Cardiology/American Heart Association (ACC/AHA)47: a «new» episode of angina is defined as an episode of pain that occurs at rest and last no less than 5 minutes, with ST segment elevation or decline greater than 1 mm or inversion of the T-wave, or both, in 2 contiguous leads, with the exception of the aVR lead. Myocardial infarct is defined as an increase in CK-MB or of troponin values that are double the upper limits of normal or the development of new Q-waves ≥0.04 seconds in 2 leads, in the setting of persistent precordial pain that lasts more than 20 minutes. Death is defined as death independent of any cause, and cardiovascular death indicates that death was due to ACS or was sudden death. Cardiac arrest is classified as «death» (including when the patient survives the event) for the purpose of statistical analysis.

The TIMI risk score21 is a new risk scale that includes variables easily obtained from patients with NSTEACS: age greater than 65 years, the presence of 3 or more risk factors (smoking, diabetes, hypercholesterolemia, arterial hypertension, family history), heart disease with lesions >50%, the use of aspirin during the last 7 days, acute symptoms of angina (more than 2 episodes of angina during the last 24 hours), elevated cardiac enzymes, and changes in the ST segment greater than 0.5 mm. A point was assigned to each of these variables, with 0 being the lowest score and 7 the maximum possible score.

The PEPA risk scale5 includes clinical, electrocardiographic, and biochemical variables: age ≥65 years, diabetes, peripheral vascular disease, more than 2 episodes of angina during the 24 hours prior to admission, post-infarct angina within the first 30 days, Killip class ≥2, ST segment decline, and elevation of markers of cardiac necrosis.

Discussion

This study will answer a number of important clinical questions about the prognostic role of markers of inflammation in patient of Mediterranean origin. The prospective studies in these populations are eagerly anticipated due to the specific characteristics of the population, which are different from Anglo-Saxon and Scandinavian populations who comprise the majority of epidemiological studies in the field of cardiovascular disease.

The patients who comprise this study will be a representative sample of the general population with

NSTEACS who are treated in Spanish hospitals. The SIESTA study will include patients from everyday medical practice who present with NSTEACS and, therefore, the results could be extrapolated to everyday medical practice.

For the first time a comparative study will be performed that analyzes the prognostic role of various markers of inflammation, of variables that indicate endothelial activation of conventional risk factors, in the context of NSTEACS. The SIESTA study will, in addition, allow us to answer, questions about the prognostic value of persistently elevated values vs values that are only transiently elevated.

The prognostic clinical and electrographic markers of risk have also not been compared previously or systematically with markers of inflammation or with markers most recently proposed (BNP and PAPP-A) in Mediterranean patients with NSTEACS.

The SIESTA study will provide the possibility of validating scoring indices such as TIMI in Mediterranean patients. When an increased number of biochemical markers are noted, our findings may help to establish new scoring indexes that are more in accordance with the lifestyle and diet of the Spanish population. Patient recruitment has already started, and we hope that at the beginning of 2004 the first results will be analyzed.

PARTICIPANT IN THE SIESTA STUDY

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REFERENCES

1. American Heart Association 2002. Heart and stroke statistical update. Dallas: American Heart Association, 2001. Disponible en: Publications and Resources. Statistics.
2. Marrugat J, Elosua R, Martí H. Epidemiología de la cardiopatía isquémica en España: estimación del número de casos y de las tendencias entre 1997 y 2005. Rev Esp Cardiol 2002;55:337-46.
3. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable Angina Pectoris. N Engl J Med 2000;342:101-14.
4. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST elevation myocardial infarction. J Am Coll Cardiol 2000;36:970-1062.
5. López de Sá E, López Sendón JL, Anguera I, Bethencourt A, Bosch X. Prognostic value of clinical variables at presentation in patients with non-ST segment elevation acute coronary syndrome. Medicine 2002;81:434-42.
6. Swanson GD, Denson KWE, Wells AJ, Jamrozik K, Colditz GA, Fuster V, et al. Passive smoking and coronary heart disease. N Engl J Med 1999;341:697-700.
7. Fischer A, Gutstein DE, Fuster V. Thrombosis and coagulation abnormalities in the acute coronary syndromes. Cardiol Clin 1999;17:283-94.
8. Forrester JS. Role of plaque rupture in acute coronary syndromes. Am J Cardiol 2000;86:J15-23.
9. Plutzky J. Inflammatory pathways in atherosclerosis and acute coronary syndromes. Am J Cardiol 2001;88:K10-5.
10. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. Circulation 1996;94:2013-20.
11. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276-82.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
13. Kaski JC. Inflamación, infección y enfermedad coronaria: mitos y realidades. Conferencia especial del XXXV Congreso Nacional de la Sociedad Española de Cardiología. Rev Esp Cardiol 2000;53:1311-7.
14. Buffon A, Biasucci LM, Liuzzo G, Dónofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. N Engl J Med 2002;347:5-12.
15. Zouridakis EG, Schwartzman R, García-Moll X, Cox ID, Fredericks S, Holt DW, et al. Increased plasma endothelin levels in angina patients with rapid coronary artery disease progression. Eur Heart J 2001;22:1578-84.
16. Libby P. Coronary artery injury and the biology of atherosclerosis: inflammation, thrombosis, and stabilization. Am J Cardiol 2000;86(Suppl 2):3-8.
17. Shebuski RJ, Kilgore KS. Role of inflammatory mediators in thrombogenesis. J Pharmacol Exp Ther 2002;300:729-35.
18. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999;340:115-26.
19. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljundahl L, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146-50.
20. Antman EM. Decision making with cardiac troponin tests. N Engl J Med 2002;346:683-93.
21. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835-42.
22. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94:874-7.
23. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. JAMA 2001;286:2107-13.
24. Blankemberg S, Tiret L, Bickel C, Peetz D, Cambien F, Meyer J, et al. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. Circulation 2002;106:24-30.
25. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. Serum amyloid A predicts early mortality in acute coronary syndromes: a TIMI 11A substudy. J Am Coll Cardiol 2000;35:358-62.
26. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994;331:417-24.
27. Ferreiros ER, Boissonnet CP, Pizarro R, Merletti PF, Corrado G, Cagide A, et al. Independent prognostic value of elevated C-reactive protein in unstable angina. Circulation 1999;100:1958-63.
28. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1998;31:1460-5.
29. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139-47.
30. Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. Circulation 1997;96:4204-10.
31. Zebrack JS, Anderson JL, Maycock CA, Horne BD, Bair TL, Muhlestein JB. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol 2002;89:145-9.
32. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory to standard treatment trial. J Am Coll Cardiol

2000;35: 1535-42.
33. Rebuzzi AG, Quaranta G, Liuzzo G, Caligiuri G, Lanza GA, Gallimore JR, et al. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. Am J Cardiol 1998;82:715-9.
34. Kaski JC, García-Moll X. C-reactive protein as a clinical marker of risk. Circulation 2000;102:63-4.
35. Koenig W. C-reactive protein and cardiovascular risk: has the time come for screening the general population? Clin Chem 2001;47:9-10.
36. Perez Fernández R, Kaski J. Interleukin-10 and coronary disease. Rev Esp Cardiol 2002;55:738-50.
37. De Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary sindromes. N Engl J Med 2001;345:1014-21.
38. Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR Jr, et al. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. N Engl J Med 2001;345:1057-59.
39. Marrugat J, Senti M. Why mortality from heart disease is low in France. High cholesterol may not have same effect on cardiovascular risk in southern Europe as elsewhere. BMJ 2000;320:250.
40. Masia R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, et al. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. REGICOR Investigators. J Epidemiol Community Health 1998;52: 707-15.
41. Perez G, Pena A, Sala J, Roset P, Masia R, Marrugat J. Acute myocardial infarction case fatality, incidence and mortality rates in a population registry in Girona, Spain, 1990-1992. REGICOR Investigators. Int J Epidemiol 1998;27:599-604.
42. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
43. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, López-Sendón J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 2002;359:373-7.
44. Wong ND, Pio J, Valencia R, Thakal G. Distribution of C-reactive protein and its relation to risk factors and coronary heart disease risk estimation in the National Health and Nutrition Examination Survey (NHANES) III. Prev Cardiol 2001;4:109-14.
45. López-Bescós L, Aros Borau F, Lidón CR, Cequier FA, Bueno H, Alonso JJ, et al. Actualización de las Guías de Práctica Clínica de la Sociedad Española de Cardiología en angina inestable/infarto sin elevación del segmento ST. Rev Esp Cardiol 2002;55:631-42.
46. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. ACC key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001; 38:2114-30.
47. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction 2002; summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of patients with unstable angina). Circulation 2002:106: 1893-900.