

Relationship of C-Reactive Protein Levels With Angiographic Findings and Markers of Necrosis in Non-ST-Segment Elevation Acute Coronary Syndrome

Juan Sanchís, Vicent Bodí, Ángel Llácer, Lorenzo Facila, Ángel Martínez-Brotons, Luis Insa, and Francisco J. Chorro

Servei de Cardiologia, Hospital Clínic Universitari, Universitat de València, València, Spain.

Introduction and objectives. The mechanism responsible for elevated C-reactive protein levels (inflammation of the ruptured atherosclerotic plaque or myocardial necrosis) in acute coronary syndromes is controversial. The aim of this study was to investigate the relationship between C-reactive protein levels and angiographic complexity of the culprit lesion and troponin elevation in patients with non-ST elevation acute coronary syndromes.

Patients and method. The study group consisted of 125 patients with single-vessel disease. Troponin-I and C-reactive protein were measured, and the complexity of the culprit lesion was analyzed (TIMI flow and thrombus). Information on age, sex, smoking habit, hypertension, hypercholesterolemia and diabetes was obtained from the medical record.

Results. The quartile distribution of C-reactive protein showed more patients with TIMI flow < 3 (31%, 28%, 18%, and 55%; $P=.02$), thrombus (3%, 6%, 7%, and 28%; $P=.007$) and troponin-I elevation (19%, 44%, 50%, and 66%; $P=.003$) in the fourth quartile. Multivariate analysis showed both thrombus (OR = 4.1; 95% CI, 1.2-14.3; $P=.03$) and troponin elevation (OR = 2.6; 95% CI, 1.1-6.3; $P=.03$) to be associated with C-reactive protein > 18 mg/L (fourth quartile cut-off). When treated as a continuous variable, higher levels of C-reactive protein were also associated with thrombus ($P=.02$) and troponin elevation ($P=.003$). No other clinical variables were related with C-reactive protein levels.

Conclusions. Both angiographic complexity of the culprit lesion and elevated troponin level are related with increased C-reactive protein levels in non-ST elevation acute coronary syndromes.

Key words: Inflammation. C-reactive protein. Unstable angina. Coronary angiography. Troponin.

Full English text available at: www.revespcardiol.org

SEE EDITORIAL ON PAGES 375-8

Correspondence: Dr. J. Sanchís Forés.
Servei de Cardiologia. Hospital Clínic Universitari.
Blasco Ibáñez, 17. 46010 València. España.
E-mail: sanchis_juafor@gva.es

Received 12 January, 2004.

Accepted for publication 17 March, 2004.

Relación de los valores de proteína C reactiva con los hallazgos angiográficos y los marcadores de necrosis en el síndrome coronario agudo sin elevación del segmento ST

Introducción y objetivos. El mecanismo implicado en la elevación de la proteína C reactiva (PCR) en los síndromes coronarios agudos (inflamación en la placa de ateroma o necrosis miocárdica) es motivo de controversia. Se investigó la relación de la PCR con la complejidad angiográfica de la lesión causante y con la elevación de la troponina en el síndrome coronario agudo sin elevación del segmento ST.

Pacientes y método. Se estudió a 125 pacientes consecutivos con enfermedad de un vaso. Se determinaron la troponina I y la PCR, y se analizó la complejidad angiográfica de la lesión causante (flujo TIMI y trombo). De la historia clínica se recogieron la edad, el sexo, el tabaquismo, la hipertensión, la hipercolesterolemia y la diabetes.

Resultados. La distribución de la PCR por cuartiles evidenció en el cuarto cuartil más pacientes con flujo TIMI < 3 (31, 28, 18 y 55%; $p = 0,02$), trombo (3, 6, 7 y 28%; $p = 0,007$) y elevación de troponina (19, 44, 50 y 66%; $p = 0,003$). Mediante análisis multivariable, el trombo (*odds ratio* [OR] = 4,1; intervalo de confianza [IC] del 95%, 1,2-14,3; $p = 0,03$) y la elevación de la troponina (OR = 2,6; IC del 95%, 1,1-6,3; $p = 0,03$) se asociaron con una PCR > 18 mg/l (punto de corte del cuarto cuartil). Cuando fue tratada como una variable continua, una mayor concentración de PCR también se asoció con el trombo ($p = 0,02$) y con la elevación de la troponina ($p = 0,003$). Ninguna variable clínica se relacionó con la PCR.

Conclusiones. Tanto la complejidad angiográfica de la lesión causante como la elevación de la troponina están relacionadas con los valores de la PCR en los síndromes coronarios agudos sin elevación del segmento ST.

Palabras clave: Inflamación. Proteína C reactiva. Angina inestable. Coronariografía. Troponina.

ABBREVIATIONS

CRP: C-reactive protein.

OR: odds ratio.

CI: confidence interval.

TIMI: thrombolysis in myocardial infarction.

INTRODUCTION

In recent years, new serum markers have been used in the diagnosis and risk stratification of patients with acute ischemic heart disease. These markers of myocardial damage are systematically employed in the diagnosis and prognosis of acute coronary syndromes.¹ However, it has been suggested that inflammation influences the pathogenesis of atherosclerosis and the progression of acute coronary syndromes.² If this is so, inflammation of the vessel wall might be the principal cause of the rupture of atherosclerotic plaque, causing severe stenosis or acute coronary occlusion. Consequently, markers of inflammation are also used in prognostic stratification of acute coronary syndromes.³ Among these markers, C-reactive protein (CRP) is preferred because of its availability, stability, and prolonged average life.⁴

The cause of inflammation marker elevation in acute coronary syndromes is controversial. In theory, inflammatory activity may originate in complicated atherosclerotic plaque or foci of myocardial necrosis. Some studies point to inflammation of the coronary vessel wall⁵ whereas others suggest myocardial necrosis may be the principal mechanism.⁶

The objective of the present study was to analyze the relationship of CRP elevation with angiographic complexity of the culprit lesion and troponin elevation in non-ST segment elevation acute coronary syndrome. To facilitate identification of the culprit lesion, we enrolled patients who had undergone angiographic study and presented with single-vessel disease. Hypothetically, the angiographic complexity of the culprit lesion might be a marker of vascular inflammation, whereas troponin elevation constitutes a marker of myocardial necrosis.

PATIENTS AND METHODS

Study Group

The study group consisted of 125 consecutive patients admitted to the Cardiology Service of our hospital in Valencia, Spain. All patients were diagnosed with non-ST segment elevation acute coronary syndrome

and underwent cardiac catheterization showing significant single vessel coronary stenosis ($\geq 50\%$). We excluded patients with electrocardiogram ST segment elevation or CRP elevation possibly caused by kidney failure (creatinine >1.5 mg/dL) or presence of known inflammatory, infectious or neoplastic disease. All patients presented at the emergency room with chest pain of possible coronary origin and were examined according to our Chest Pain Unit protocol.⁷⁻¹⁰ Diagnosis of non-ST segment elevation acute coronary syndrome was based on clinical presentation of chest pain and some of the following criteria: *a*) troponin I elevation (≥ 1 ng/mL; $n=55$); *b*) normal troponin but electrocardiogram suggesting ischemia for ST segment depression ≥ 1 mm or T wave inversion 1 mm ($n=20$); *c*) normal troponin but positive early exercise test ($n=27$), or *d*) normal troponin, high probability of acute coronary syndrome due to clinical history with contraindication to early exercise test ($n=23$). On admission, patients were treated with beta blocking agents (unless contraindicated), aspirin (clopidogrel if aspirin was contraindicated) and low molecular weight heparin. Coronary angiography was carried out at 4.5 ± 3 days after admission.

Determination of Markers

Troponin I was determined (Immulite, Los Angeles, CA, USA) on arrival at the emergency room and at 8, 12, and every 24 hours after the onset of pain until the maximum level was reached. C-reactive protein was measured at median 72 hours after presentation at the emergency room (high sensitivity nephelometric method, Behring Diagnostics, Marburg, Germany). Upper limits for normality recommended by our laboratory are: troponin I 1 ng/mL and CRP 5 mg/L. We calculated reference values with a coefficient of variation $<10\%$.

Angiographic Study

Analysis of coronary angiograms was carried out by a single observer (JS) blinded to serum marker values. In quantitative analysis of coronary stenosis we considered $>50\%$ as significant (Philips Integris 3000). Given that, according to our protocol, all patients had single-vessel disease, we assumed the culprit lesion was the diseased vessel and analyzed this for intra-arterial flow and presence of thrombus. Flow grade was classified as TIMI (Thrombolysis In Myocardial Infarction) 0 to 3. Angiographic thrombus was narrowly defined as a filling defect, intraluminal ultrasound images without visible calcification in at least 2 orthogonal projections, ultrasound images of a convex border of an occlusion, or embolus in the distal territory of the diseased vessel.¹¹ When more than one significant stenosis of the diseased

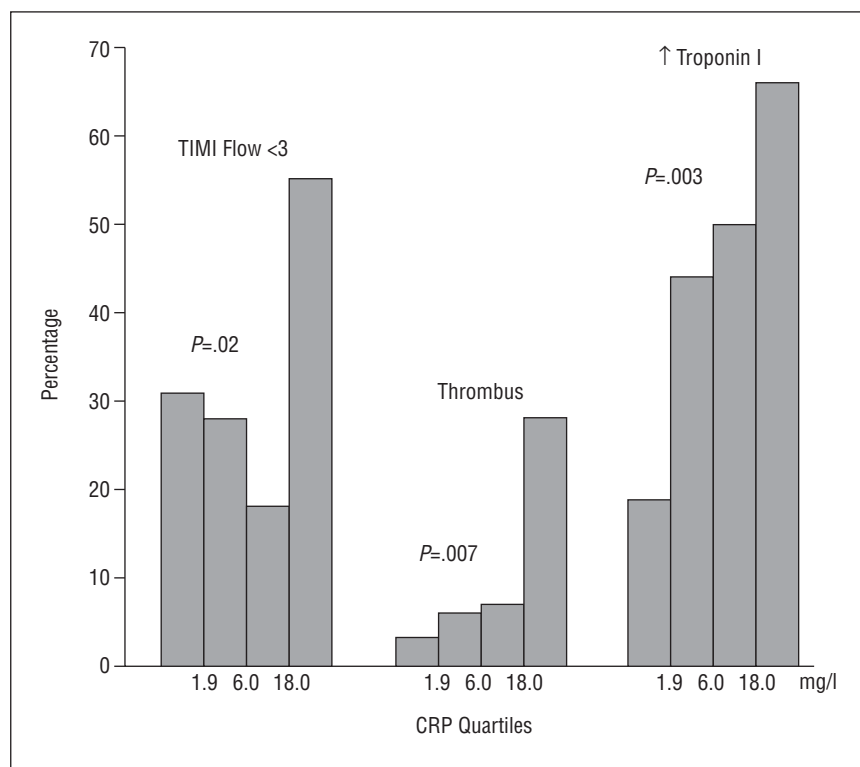


Fig. 1. C-reactive protein (CRP) distribution by quartiles. Percentages of patients with TIMI flow <3 in the culprit vessel (31%, 28%, 18%, and 55%; *P* for trend =.02), thrombus (3%, 6%, 7%, and 28%; *P* for trend =.007), and troponin I elevation (19%, 44%, 50%, and 66%; *P* for trend =.003) were greater in the fourth quartile.

sed vessel was observed, we identified as the culprit lesion that which had thrombus or more severe stenosis.

Statistical Analysis

C-reactive protein was determined both as a qualitative variable, for which we established a cutoff point, and as a continuous variable. To analyze CRP as a qualitative variable, the study group was divided into quartiles and we established a cutoff point corresponding to the fourth quartile of the distribution. Univariate (chi-square) and multivariate logistic analysis were used to evaluate the relationship of clinical factors (age, gender, current smoking habit, high blood pressure, hypercholesterolemia and diabetes mellitus), angiographic findings and troponin I elevation with increased CRP in the fourth quartile. We calculated odds ratio (OR) and 95% confidence intervals (CI). To compare CRP as a continuous variable of a non-normal distribution, we used the Mann-Whitney U nonparametric test of subgroups defined by categorical variables: clinical characteristics, angiographic findings and troponin elevation. Multivariate analysis was carried out by stepwise multiple regression, introducing the variables associated with CRP (*P*<.1) in univariate analysis. For stepwise multiple regression we used the logarithmic transformation of CRP values as an independent variable, given the bias towards the right in the distribution.¹²

RESULTS

Characteristics of the Study Group

Average age was 63±12 years and 77% were men. Coronary risk factor frequencies were: current smoking habit, 30%; high blood pressure, 54%; history of hypercholesterolemia, 50%; and diabetes, 23%.

Elevated troponin (≥1 ng/mL) was found in 55 patients (44%). The diseased vessel was: anterior descending artery (61 patients, 49%); circumflex artery (40 patients, 32%), and right coronary artery (24 patients, 19%). Analysis of angiographic complexity of the culprit lesion showed impaired flow (TIMI <3) in 41 patients (33%) and thrombus in 13 patients (10%).

We found TIMI flow <3 in 23 patients who had troponin elevation, 5 patients with ischemia in the electrocardiogram, 7 patients with abnormal early exercise test, and 6 patients with high probability of acute coronary syndrome and contraindication to early exercise test. In these subgroups, angiographic thrombus was identified in 11 patients who had elevated troponin, 1 patient with electrocardiographic ischemia, and 1 patient with high probability of acute coronary syndrome.

Distribution of C-Reactive Protein by Quartiles

Average CRP value was 15±24 mg/L and median was 6 mg/L (inter-quartile interval 1.9-18 mg/L).

Analysis of CRP distribution by quartiles (0-1.9, n=32; 2-6, n=36; 6.1-18, n=28; >18, n=29, mg/L; Figure 1) revealed that TIMI flow <3 in the culprit vessel was most frequent in the fourth quartile (31%, 28%, 18%, and 55%; *P* for trend =.02, significant differences between fourth and third quartiles [*P*=.03; 95% CI, 0.03-0.7]). Similarly, thrombus was more frequent in the fourth quartile (3%, 6%, 7%, and 28%; *P* for trend =.007, significant differences between fourth and first quartiles [*P*=.02; 95% CI, 0.03-0.46]; between fourth and second quartiles [*P*=.03; 95% CI, 0.01-0.43]; between fourth and third quartiles [*P*=.08; 95% CI, -0.02 to 0.43]). In the fourth quartile, the proportion of patients with troponin I elevation was also greater (19%, 44%, 50%, and 66%; *P* for trend =.003, significant differences between fourth and first quartiles [*P*=.003; 95% CI, 0.12-0.81]).

Variables Associated With C-Reactive Protein Elevation

We established a CRP cutoff point at >18 mg/L corresponding to the fourth quartile. Univariate analysis results are shown in Table 1. The independent variables used were clinical factors (age, gender, current smoking habit, high blood pressure, and diabetes mellitus), angiographic findings (TIMI flow <3 and thrombus) and troponin I elevation. Only angiographic data and troponin I associated with CRP >18 mg/L. In logistic regression analysis, thrombus (OR=4.1; 95% CI, 1.2-14.3; *P*=.03) and troponin I elevation (OR=2.6; 95% CI, 1.1-6.3, *P*=.03) were significantly associated. We entered troponin I (peak) into the logistic model as a continuous not a qualitative variable. Thrombus (OR=3.7; 95% CI=1.1-13.7; *P*=.04) and troponin (per 0.1 ng/mL; OR=1.03; 95% CI, 1.01-1.06; *P*=.01) were independent variables. When thrombus was removed from the multivariate model, TIMI flow <3 (OR=2.9; 95% CI, 1.2-6.8; *P*=.02) and troponin elevation (OR=2.9; 95% CI, 1.2-7.0; *P*=.02) associated with CRP >18 mg/L.

Analysis of C-Reactive Protein as a Continuous Variable

The highest CRP values associated (Table 2) with troponin I elevation (11 [3.4-29.1] vs 4.5 [1.2-8.9] mg/L; *P*=.0001) and a more complex culprit lesion both with TIMI flow <3 (10.5 [2.2-35.7] vs 5.5 [1.7-12.5] mg/L; *P*=.05) and with thrombus (29.0 [6.1-65.0] vs 5.3 [1.7-15.2] mg/L; *P*=.0001). We found no correlation between age and CRP (*r*=0.05, *P*=.6) and no association between clinical data and CRP values (Table 2). In stepwise multiple regression analysis, angiographic thrombus (*P*=.02), and troponin I elevation (*P*=.003) were independent factors. This association was maintained on introducing troponin I peak as a

TABLE 1. Relationship of Clinical Factors, Angiographic Findings and Troponin Elevation (>1 ng/mL), With CRP Elevation (>18 mg/L)*

	CRP>18 mg/L	CRP<18 mg/L	P
Age, years	63±10	63±13	1
Men	75%	77%	.8
Smokers	34%	29%	.7
Hypertension	50%	55%	.7
Hypercholesterolemia	41%	51%	.4
Diabetes mellitus	19%	25%	.6
TIMI flow <3	53%	26%	.008
Thrombus	25%	5%	.004
Troponin >1 ng/mL	66%	37%	.007

*CRP indicates C-reactive protein; TIMI, thrombolysis in myocardial infarction.

continuous variable (*P*=.03 for thrombus and *P*=.001 for troponin I).

DISCUSSION

The results of the present study indicate that angiographic complexity of the culprit lesion and troponin elevation are associated with increased CRP in non-ST segment elevation acute coronary syndromes.

Mechanisms Causing C-Reactive Protein Elevation

In recent years, the arterial inflammation hypothesis has focused attention on explaining the pathogenesis and progression of atherosclerosis as well as acute coronary events.² Several studies have shown the prognostic value of CRP in acute coronary syndromes.¹³⁻¹⁸ The mechanism behind inflammation marker elevation in patients with worse prognosis is not clear. Inflammation secondary to myocardial damage, vascular inflammatory activity linked to the rupture of atherosclerotic plaque, or both, may be related. Some studies indicate that myocardial necrosis might be the underlying mechanism^{6,19} and the association of troponin elevation with CRP values we have observed seems to support this. Moreover, we found that angiographic complexity of the culprit lesion was independently associated with increased CRP. This would support the additional influence of vascular inflammation. Few studies of markers of inflammation and angiographic findings in acute coronary syndromes have been made. In a group of patients with suspected coronary heart disease, Katritsis et al²⁰ revealed an association of CRP and a high risk culprit lesion defined by angiographic thrombus or eccentric or irregular morphology.

Time of Determination of C-Reactive Protein

The partial contribution of atherosclerotic plaque

TABLE 2. Relationship of C-Reactive Protein Values, as a Continuous Variable, With Clinical and Angiographic Data, and Troponin I Elevation (>1 ng/mL)*

	CRP (mg/L)
Gender	
Men	5.3 (1.6-17.7)
Women	8.7 (3.4-19.5)
P	.2
Smoking habit	
Yes	6.9 (2.0-18.2)
No	5.5 (1.8-16.7)
P	.6
Hypertension	
Yes	5.5 (1.9-16.7)
No	6.0 (1.8-18.2)
P	1
Hypercholesterolemia	
Yes	5.5 (1.6-13.6)
No	6.0 (2.2-20.5)
P	.6
Diabetes	
Yes	6.0 (1.7-14.1)
No	5.8 (2.0-18.0)
P	.8
TIMI 3	
Yes	5.5 (1.7-12.5)
No	10.5 (2.2-35.7)
P	.05
Thrombus	
Yes	29.0 (6.1-65.0)
No	5.3 (1.7-15.2)
P	.002
Troponin I >1 ng/mL	
Yes	11.0 (3.4-29.1)
No	4.5 (1.2-8.9)
P	.0001

Values are given as median and interquartile intervals. *CRP indicates C-reactive protein; TIMI, thrombolysis in myocardial infarction.

or necrotic myocardium to inflammation marker elevation may depend on the time these markers are determined. C-reactive protein values increase progressively until they peak at 48-72 hours after onset of acute coronary syndrome.²¹ Theoretically, if myocardial necrosis occurs at admission it is only in its initial stages, so CRP values should be linked to vascular inflammation. Once myocardial necrosis has occurred, inflammation of necrotic foci induces CRP peak.²² In patients with pure unstable angina without necrosis (confirmed by normal troponin), CRP elevation at admission reflects vascular inflammation and remains high during the days that follow without significant variation.²³ This suggests that inflammation is maintained without any additional stimulus such as myocardial necrosis. If myocardial infarction occurs, necrosis would constitute another source of inflam-

mation.⁶ We have observed that CRP elevation is greater in acute coronary syndromes with troponin elevation than in unstable angina with normal troponin.²⁴ In the present study, CRP was determined late, when inflammatory reaction in necrotic foci should already have occurred, which would explain the relationship between troponin elevation and CRP. However, angiographic complexity of the coronary lesion was also independently associated and this suggests that vascular inflammation might also play a part.

Limitations

The principal limitation of this study is the assumption that the degree of angiographic complexity of the culprit lesion, defined by presence of thrombus and intra-arterial TIMI flow, might be a marker of the inflammatory activity in the underlying plaque. Angiography has two limitations: in patients with myocardial infarction without Q wave, multiple vessel disease is frequent, which makes it difficult to identify the culprit lesion.²⁵ To avoid this, we only enrolled patients with single-vessel disease. Moreover, angiography only permits detection of unstable plaque when anatomic rupture is sufficient for it to appear.²⁶ Furthermore, analysis of morphological characteristics supposedly typical of unstable plaque (ulceration, eccentricity, fissure, or irregularity) is subjective. We analyzed two relatively objective parameters: intra-arterial TIMI flow and presence of thrombus. Both parameters should permit us to identify very unstable lesions that hypothetically could be associated with highly inflammatory activity, although TIMI flow might also be compromised by non-unstable plaque. The degree of instability of lesions with less marked morphological changes (without thrombus and with normal TIMI flow) is difficult to establish by angiography.

CONCLUSIONS

In non-ST segment elevation acute coronary syndromes, troponin elevation and angiographic complexity of culprit coronary lesions are related to elevated CRP. This is consistent with inflammatory activity of the vessel wall and necrotic foci contributing to the pathogenesis of inflammation marker elevation.

REFERENCES

1. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined. A consensus document of the joint European Society of Cardiol-

- gy/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;21:1502-13.
2. Bhatt DL, Topol E. Need to test the arterial inflammation hypothesis. *Circulation* 2002;106:136-40.
3. Pearson ThA, Mensah GA, Alexander RW, Anderson JL, Cannon III RA, Criqui M, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation* 2003;107:499-511.
4. Yeh ETH, Willerson JT. Coming of age of C-reactive protein. Using inflammation markers in cardiology. *Circulation* 2003;107:370-2.
5. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med* 2002;347:5-12.
6. Cusack MR, Marber MS, Lambiase PD, Bucknall CIA, Redwood SR. Systemic inflammation in unstable angina is the result of myocardial necrosis. *J Am Coll Cardiol* 2002;39:1917-23.
7. Sanchís J, Bodí V, Llácer A, Núñez J, Ferrero JA, Chorro FJ. Valor de la prueba de esfuerzo precoz en un protocolo de unidad de dolor torácico. *Rev Esp Cardiol* 2002;55:1089-92.
8. Sanchís J, Bodí V, Llácer A, Facila L, Núñez J, Bertomeu V, et al. Usefulness of concomitant myoglobin and troponin elevation as biochemical marker of mortality in non-ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2003;91:448-51.
9. Sanchís J, Bodí V, Llácer A, Facila L, Nuñez J, Roselló A, et al. Predictors of short-term outcome in acute chest pain without ST-segment elevation. *Int J Cardiol* 2003;92:193-9.
10. Sanchís J, Bodí V, Llácer A, Facila L, Pellicer M, Bertomeu V, et al. Estratificación del riesgo de los pacientes con dolor torácico sin elevación del segmento ST en la puerta de urgencias. *Rev Esp Cardiol* 2003;56:955-62.
11. Alfonso F, Rodríguez P, Philips P, Goicolea J, Hernández R, Pérez-Vizcaíno MJ, et al. Clinical and angiographic implications of coronary stenting in thrombus-containing lesion. *J Am Coll Cardiol* 1997;29:725-33.
12. Blake GJ, Rifai N, Buring JE, Ridker PM. Blood pressure, C-reactive protein, and risk of future cardiovascular events. *Circulation* 2003;108:2993-9.
13. Morrow DA, Rifal N, Atman EM, Weiner DL, McCabe CH, Cannon ChP, 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. *J Am Coll Cardiol* 1998;31:1460-5.
14. Ferrerirós ER, Boissonnet CP, Pizarro R, García PF, Corrado G, Cagide A, et al. Independent prognostic value of elevated C-reactive protein in unstable angina. *Circulation* 1999;100:1958-63.
15. Heeschen Ch, Hamm CH, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. *J Am Coll Cardiol* 2000;35:1535-42.
16. 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. *N Engl J Med* 2000;343:1139-47.
17. Bodí V, Facila L, Sanchís J, Llácer A, Núñez J, Mainar L, et al. Pronóstico a corto plazo de los pacientes ingresados por probable síndrome coronario agudo sin elevación del segmento ST. Papel de los nuevos marcadores de daño miocárdico y de los reactantes de fase aguda. *Rev Esp Cardiol* 2002;55:823-30.
18. James SK, Armstrong P, Barnathan E, Califf R, Lindahl B, Siegbadhn A, et al. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome. A GUSTO-IV substudy. *J Am Coll Cardiol* 2003;41:916-24.
19. Bodí V, Núñez J, Sanchís J, Llácer A, Facila L, Chorro FJ. Why does C-reactive protein increase in non-ST elevation acute coronary syndromes? Role of myocardial damage. *Int J Cardiol* 2003;92:129-35.
20. Katritsis D, Korovesis S, Giazitzoglou E, Parissis J, Kalivas P, Webb-People MM, et al. C-reactive protein concentrations and angiographic characteristics of coronary lesions. *Clin Chem* 2001;47:882-6.
21. Oldgren J, Wallentin L, Grip L, Linder R, Norgaard BL, Siegbahn A. Myocardial damage, inflammation and thrombin inhibition in unstable coronary artery disease. *Eur Heart J* 2003;24:86-93.
22. De Winter RJ, Fisher J, Bholasingh R, Van Straalen JP, De Jong TH, Tijssen JGP, et al. C-reactive protein and cardiac troponin T in risk stratification: differences in optimal timing of tests early after the onset of chest pain. *Clin Chem* 2000;46:1597-603.
23. Liuzzo G, Biasucci LM, Rebuzzi AG, Gallimore R, Caligiuri G, Lanza GA, et al. Plasma protein acute-phase response in unstable angina is not induced by ischemic injury. *Circulation* 1996;94:2373-80.
24. Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein in unstable coronary artery disease. *Circulation* 1997;96:4204-10.
25. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ. Revisiting the culprit lesion in non-Q-wave myocardial infarction: results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol* 2002;39:1456-63.
26. Goldstein JA. Angiographic plaque complexity: the tip of the unstable plaque iceberg. *J Am Coll Cardiol* 2002;39:1464-7.