

Short-Term Prognosis of Patients Admitted for Probable Acute Coronary Syndrome without ST-Segment Elevation. Role of New Myocardial Damage Markers and Acute-Phase Reactants

Vicent Bodí, Lorenzo Facila, Juan Sanchis, Ángel Llácer, Julio Núñez, Luis Mainar^a, Ricardo Gómez-Aldaraví^a, José V. Monmeneu^b, María L. Blasco^c, Rafael Sanjuan^c, Luis Insa and Francisco J. Chorro

Servei de Cardiologia. Hospital Clínic i Universitari. València. Universitat de València. ^aUnidad de Cardiología. Hospital de Requena. ^bUnidad de Cardiología. Hospital de Xàtiva. ^cUnidad Coronaria. Hospital Clínic i Universitari. València.

Objectives. The relative value of classic markers, myocardial damage variables, and levels of acute-phase reactants in establishing the pre-discharge prognosis of acute coronary syndrome without ST-segment elevation was analyzed.

Method. We prospectively studied 385 consecutive patients admitted from our chest pain unit with a high-probability diagnosis of acute coronary syndrome without ST-segment elevation. The clinical and electrocardiographic data, myocardial damage markers (troponin I, CK-Mb mass, myoglobin), and acute-phase reactants (high-sensitivity C-reactive protein, fibrinogen) were recorded.

Results. During admission, 15 deaths (3.9%) and 16 complicative infarctions (4.2%) occurred, for a total of 31 major events (death and/or infarction: 8.1%). Age ($p = 0.03$), insulin-dependent diabetes ($p = 0.009$), and C-reactive protein ($p = 0.05$) were independently related to death. Fibrinogen was related to infarction ($p = 0.01$); by fibrinogen quartiles: 1.4%; 1.4%; 2.9%, and 11.7% ($p = 0.02$). Age ($p = 0.01$), insulin-dependent diabetes ($p = 0.02$), and C-reactive protein ($p = 0.04$) were independent predictors of major events; by C-reactive protein quartiles: 1.4%; 5.5%; 5.4%, and 16.7% ($p = 0.004$). Troponin I was related to major events ($p = 0.03$), but it was not an independent predictor.

Conclusions. Acute-phase reactants add independent information to clinical variables in the short-term risk stratification of patients with an acute coronary syndrome. The predictive power of troponins is lower than that of other variables.

Key words: *Unstable angina. Infarction. Prognosis. Fibrinogen. Enzymes.*

Full English text available at: www.revespcardiol.org

Correspondence: Dr. V. Bodí Peris.
Servei de Cardiologia. Hospital Clínic i Universitari.
Avda. Blasco Ibáñez, 17. 46010 Valencia. España.
E-mail: vicentbodi@hotmail.com

Received 17 October 2001.
Accepted for publication 23 April 2002.

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

Objetivos. Se analiza el papel relativo de los marcadores clásicos, de las variables de daño miocárdico y reactantes de fase aguda en el pronóstico prealta del síndrome coronario agudo sin elevación del segmento ST.

Método. Se estudió prospectivamente a 385 pacientes consecutivos ingresados desde nuestra unidad de dolor torácico con el diagnóstico de alta probabilidad de síndrome coronario agudo sin elevación del segmento ST. Se recogieron las variables clínicas, electrocardiográficas, indicadores de daño miocárdico (troponina I, Ck-Mb masa, mioglobina) y reactantes de fase aguda (proteína C reactiva de alta sensibilidad y fibrinógeno).

Resultados. Durante el ingreso hospitalario se detectaron 15 fallecimientos (3,9%), 16 infartos complicativos (4,2%) y 31 episodios mayores (fallecimiento y/o infarto: 8,1%). Fueron predictores independientes de fallecimiento la edad ($p = 0,03$), la diabetes insulino dependiente ($p = 0,009$) y la proteína C reactiva ($p = 0,05$). El fibrinógeno ($p = 0,01$) predijo infarto; por cuartiles: 1,4; 1,4; 2,9, y 11,7% ($p = 0,02$). La edad ($p = 0,01$), la diabetes insulino dependiente ($p = 0,02$) y la proteína C reactiva ($p = 0,04$) fueron predictores independientes de episodio mayor; por cuartiles de proteína C reactiva: 1,4; 5,5; 5,4, y 16,7% ($p = 0,004$). La troponina I se relacionó con una mayor tasa de episodios mayores ($p = 0,03$), pero no fue un predictor independiente.

Conclusiones. Los reactantes de fase aguda añaden información independiente a las variables clínicas en la estratificación de riesgo a corto plazo de los pacientes con síndrome coronario agudo. El poder predictor de la troponina disminuye al ser comparado con otras variables.

Palabras clave: *Angina inestable. Infarto. Pronóstico. Fibrinógeno. Enzimas.*

ABBREVIATIONS

IDDM: insulin dependent diabetes mellitus.
ECG: electrocardiogram.
95% CI: 95% confidence interval.
OR: odds ratio.
hsCRP: high sensitivity reactive protein C.
ROC: receiver operator characteristic.

INTRODUCTION

The classic concepts of the pathogenesis of acute coronary syndromes have changed rapidly over the last decade.¹ In this sense, the definition of an infarct has also changed.² The pathophysiology of the process is increasingly better understood and thus, along with thrombosis, inflammation appears to be important.^{1,3,4} Patient treatment has changed and shows a greater tendency toward invasive procedures.⁵⁻⁷ Given the great prevalence and enormous costs of acute coronary syndromes,⁸⁻¹⁰ specific hospital units have been created for dealing with chest pain.⁸⁻¹⁰

Therefore, early prognostic classification of patients who are admitted with chest pain is indispensable; together with the classic markers,¹¹ in recent years there have been new developments in this field. Among these, troponin stands out;⁸ nevertheless there are opinions that a more precise validation of their role is required with respect to other variables.¹²⁻¹⁶ Finally, the reactants of the acute phase have been proposed as predictors of episodes in patients with unstable heart disease.^{3,17-19}

In this study we analyzed the short term prognosis (inpatient) of a consecutive series of patients admitted with a diagnosis of highly suspected acute coronary syndrome without elevation of the ST segment who received treatment according to an actualized protocol. The clinical power of the new parameters as predictors of myocardial damage and inflammation was determined by comparing them with the classic clinical and electrocardiographic (ECG) variables.

METHODS

Study group

The study group consisted of 385 patients admitted consecutively between November 1, 2000 and September 13, 2001 with a high suspicion of acute coronary syndrome without ST segment elevation.

Following the protocol established by our chest pain unit, the admission criteria for a patient with suspected

coronary syndrome were: *a*) ECG indicative of acute ischemic heart disease (decline of the ST segment or T-wave inversion); *b*) elevation of the markers for myocardial damage; *c*) positive ergometry (performed on patients without electrocardiographic changes and without an increase in markers for myocardial damage), and *d*) in the absence of the first 3 criteria, cause for admission was also those patients with a suggestive clinical history: chest pain at rest or, in the case of effort-induced chest pain, of less than a week's duration, or with a clear decrease in the appearance threshold (in patients with chronic angina). The characteristics of the chest pain were quantified by use of a previously validated protocol;²⁰ as a function of our initial experience,²¹ admission was advised if the score was higher than 9.

Variables considered

Clinical variables

In all cases, a history was obtained of both the ischemic heart disease and risk factors. A score was assigned to each patient following the method used by Geleijnse et al²⁰ with the aim of quantifying the characteristics of the chest pain according to the patient report.

Electrocardiogram

An ECG was performed when the patient arrived at the emergency room (whether they had pain or not) and every time the chest pain reappeared. Electrocardiographic changes that were considered significant were: *a*) decline in the ST segment, if a level higher than 1 mm at 80 ms was observed from the J point, and *b*) changes in the T-wave, if an inversion of the T-wave peak greater than 1 mm was observed. Electrocardiographic changes described had to be dynamic (the existence of an ECG with and another without changes).

Biochemical markers

With respect to markers for myocardial damage, the myoglobin values were determined (in 352 cases; in 33 cases these were not measured as the episode of chest pain had occurred more than 6 hours previously), and troponin I (in all cases) when the patient presented to the emergency room. In the case of troponin I, another test was performed 8 hours after the episode of chest pain and again at 12, 18, and 24 hours (until the maximum peak was detected). When troponin I was elevated during 1 of the tests the CK-Mb mass was also analyzed (in 233 cases) during the same test and during all following tests. The upper

limits of normal in our center are 0.5 ng/mL for troponin I, 70 ng/mL for myoglobin, and 5 ng/mL for the Ck-Mb mass.

We analyzed the C-reactive protein values in the acute phase (hsCRP, 294 cases) and fibrinogen (in 268 cases). A high-sensitivity nephelometric method (Behring Diagnostics) was used, with a detection limit of 0.2 mg/L. In 73 cases general analysis of the hsCRP and fibrinogen values was not available due to various reasons (early discharge, analysis obtained more than 5 days after the acute episode, technical failure); in the remaining cases where these values were not considered this was due to the possible interference of other associated diseases. The percentage of patients whose values were not taken into consideration was greater in those cases where a final diagnosis of acute coronary syndrome was not made (30% versus 15%), probably due to the greater prevalence in this subgroup of associated diseases that resulted in rejection of said values and which, in turn, caused rejection of a complete study (stress or coronary angiography) to demonstrate ischemia.

The cut-off points for the hsCRP (11 mg/L) and fibrinogen (6 g/L) values were established by receiver operator characteristic (ROC) curves (for a major episode in the first case and for infarct in the second case). These data were collected in addition to the general analysis performed between 24 hours and 72 hours after the episode that motivated the hospital admission (average, 48 hours; interquartile range 24 to 48 hours). As has been seen in previous studies,¹⁸ the acute phase reactants in the context of an acute coronary syndrome showed a slow increase, without reaching a plateau until after the first 24 hours had passed; for this reason we chose this window of time to determine these values.

Treatment of patients admitted

The patients admitted with suspected acute coronary syndrome without ST segment elevation were treated with aspirin (96% of cases), enoxaparin (1 mg/kg/12 hours in 89% of cases), nitrites (oral or intravenous, in 94% of cases), and beta-blockers (in 78% of cases; calcium antagonists if beta-blockers were contraindicated). A conservative strategy was followed, with cardiac catheterization being performed in the case of recurrent angina, hemodynamic or electrical instability; or, if the patient remained stable a pre-discharge stress test was performed; coronary angiography was also performed if the results were positive.

Final diagnostic definitions

The criteria established to define the final diagnosis were as follows: *a*) acute myocardial infarct: if an an

elevation of the Ck-Mb mass above normal (>5 ng/mL) was detected; *b*) unstable angina: if the Ck-Mb mass was normal but there was demonstrated evidence of ischemia by stress test or a pathological coronary angiogram; *c*) chest pain without evidence of ischemic cardiopathy: if the Ck-Mb mass was normal and there was no objective evidence of ischemia (normal stress test or normal coronary angiography), and *d*) without a definitive diagnosis: if the Ck-Mb mass was normal and a stress test or coronary angiography had not been performed.

Definition of episodes

Episodes considered by the present study were: *a*) inpatient cardiac death; *b*) complicating infarct: refers to those cases in whom after the initial diagnosis of angina (determined by Ck-Mb mass after 8 hour of negative pain) a new episode of chest pain occurs with an elevation in the Ck-Mb mass >5 ng/mL, or in those cases with an initial diagnosis of infarct in whom, after a new episode of chest pain (more than 8 hours after the episode that motivated the admission), a new increase in the Ck-Mb mass was detected, and *c*) major episode: if an infarct and/or cardiac death occurred.

Statistical analysis

The quantitative variables that were adjusted to normal were expressed as mean±standard deviation (SD) and were compared by non-paired Student *t* test, while those that were not adjusted to normal were expressed as median (25th to 75th percentile) and were compared by the Mann-Whitney U test. The qualitative variables were expressed as percentages and compared by χ^2 .

Multivariate analysis for the prediction of episodes was performed by logistical regression analysis. Following the chronology with which the clinic received the information, those variables were included in 3 successive models that on univariate analysis showed a value of $P<.1$. In the first step, clinical and electrocardiographic variables were included; in the second model those variables that had turned out to be significant in the first step and the variables for myocardial damage were included; and finally, in the third and definitive model, in addition to the variables that were considered significant in the second model the acute phase reactant values were added (if on univariate analysis they were $P<.1$). In this definitive model we calculated the odds ratio (OR) and the 95% confidence interval (CI) for those variables that were shown to be independent for the prediction of episodes. The quantitative variables were included as such (without converting them into qualitative values). In all cases, the final analysis

included the variables of age, insulin-dependent diabetes mellitus (IDDM), and ST segment decline per previous studies.

In all cases a finding of $P < .05$ was considered significant. The SPSS 9.0 (Chicago, Illinois) statistical package was used for statistical analysis.

RESULTS

Study Groups

The mean patient age of the study group was 68 ± 12 years (range, 35 to 94 years). Sixty-five percent of the subjects were male; 32% had diabetes, 10% had IDDM, 45% dyslipidemia, 65% hypertension, and 20% were smokers. Fifty percent of the patients had a history of ischemic cardiopathy and 30% had a history of infarct. In 84% of cases the angina was at rest and in 13% with effort (present for less than 1 week and with a clear decrease in effort threshold), and in 3% was post-infarct. The chest pain score was 10.2 ± 2.8 .

A decline in ST segment was detected on ECG in 23% of the cases and T-wave in 10%. Fifty-four percent of cases showed an increase in troponin and 20% simultaneously showed electrocardiographic changes and troponin I elevation. Coronary angiography, angioplasty, and surgery were performed in 34%, 12% and 3% of patients, respectively. The final diagnosis was acute infarct in 52% of cases, unstable angina in 18%, chest pain without evidence of ischemia in 17%, and 13% of cases did not have a definitive diagnosis.

The chest pain score was similar in cases with and without episodes: cardiac death (9.9 ± 1.4 versus 10.2 ± 2.8 ; $P = \text{NS}$), infarct (10.2 ± 3 versus 10.2 ± 2.8 ; $P = \text{NS}$), or major episode (10.1 ± 2.4 versus 10.2 ± 2.8 ; $P = \text{NS}$).

Cardiac death

There were 15 deaths (3.9%) during hospital admission among our cases. The patients who died showed on univariate analysis significantly increased age ($P < .0001$), IDDM ($P = .01$), myoglobin ($P = .01$) and hsPRC ($P = .006$) (Table 1). Upon inclusion in a multivariate study of all these variables as well as those in the univariate study showing a $P < .1$ (Table 1), the independent predictors of death were age ($P = .03$), IDDM ($P = .009$) and hsCRP ($P = .05$).

Infarct

There were 16 cases of infarct (as a complication of the initial diagnosis) during admission (4.2%). In the univariate analysis (Table 2), the patients with infarct showed higher myoglobin ($P = .03$), hsCRP ($P = .05$), and fibrinogen ($P = .008$) values. In the multivariate study (Table 2) the only independent predictor of infarct was fibrinogen ($P = .01$).

Major episode

During admission 31 major episodes took place (8.1%). These patients were characterized on univariate analysis by greater age ($P = .002$), more IDDM ($P = .04$), and higher troponin I ($P = .03$), myoglobin ($P = .001$), hsCRP ($P = .001$) and fibrinogen ($P = .005$) values. In the multivariate study the only variables that were included in the definitive model were age ($P = .01$), IDDM ($P = .02$) and hsCRP ($P = .04$) (Table 3).

Upon analyzing only the 270 patients who had a final diagnosis was acute coronary syndrome, confirmed by evidence of ischemia according to the criteria established in our protocol, once again the

TABLE 1. Death predictors. Univariate and multivariate analysis

	Death	Survival	P	Multivariate			OR (95% CI)	P
				Model 1	Model 2	Model 3		
				P	P			
Clinical-ECG								
Age, years	79 \pm 7	68 \pm 12	<.0001	.0006	.0005	1.1 (1.01-1.2)		.03
IDDM, %	33	9	.01	.03	.03	8.6 (1.7-42.8)		.009
Hypertension, %	87	65	.1	–	–			–
ST decline, %	31	23	.7	–	–			–
Myocardial damage								
Troponin I, ng/mL	3.9 (0.6-25.7)	1.1 (0-10.9)	.08		–			–
Myoglobin, ng/mL	228 (41-405)	43 (27-109)	.01		–			–
Analytical								
HsCRP, mg/L	33 (16-102)	8.8 (3.4-26)	.006			1.01 (1-1.02)		.05

A multivariate study was performed progressively, including in 3 steps the ECG-clinical variables (model 1), myocardial damage enzymes (model 2), and analytical variables (model 3, definitive) that on univariate analysis showed a value of $P < .1$ (in addition to the variable of ST decline) – indicates not included in the multivariate analysis; IDDM, non-insulin-dependent diabetes mellitus; ECG: electrocardiogram; 95% CI, 95% confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

TABLE 2. Predictors of infarct. Univariate and multivariate analysis

	Infarct	No infarct	P	Multivariate		
				Model 1	Model 2	Model 3
				P	P	OR (95% CI)
Clinical-ECG						
Age, years	70±11	68±12	.5	–	–	–
IDDM, %	12	10	.8	–	–	–
ST decline, %	36	22	.4	–	–	–
Myocardial damage						
Myoglobin, ng/mL	94 (47-153)	48 (30-119)	.03		–	–
Analytical						
HsCRP, mg/L	32 (6-109)	8.8 (3.4-26)	.05			–
Fibrinogen, g/L	6.7 (5.6-7.6)	4.9 (3.9-6.1)	.008			1.47 (1.07-2) .01

A multivariate study was performed progressively including in 3 steps the ECG-clinical variables (model 1), myocardial damage enzymes (model 2), and analytical variables (model 3, definitive) that on univariate analysis showed a value of $P < .1$ (in addition to the variables of age, IDDM, and ST decline) – indicates not included in the multivariate analysis; IDDM, non-insulin dependent diabetes mellitus; ECG, electrocardiogram; 95% CI, 95% confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

independent predictors of a major episode on multivariate analysis were age (OR=1.08 [1.02-1.14]; $P=.02$); IDDM (OR=5.1 [1.3-19.8]; $P=.02$) and hsCRP (OR=1.01 [1.01-1.02]; $P=.006$).

Role of myocardial damage markers

The patients with elevated troponin I values (>0.5 ng/mL; $n=207$) showed a tendency toward higher mortality rates (5.8% versus 1.7%; OR=3.6 [0.99-12.9]; $P=.07$), more infarcts (5.8% versus 2.3%; OR=2.7 [0.8-8.4]; $P=.1$), and significantly more major episodes (12% versus 4%; OR=3.2 [1.4-7.6]; $P=.01$) than those cases with normal troponin I values ($n=178$). In the multivariate studies (Tables 1-3) troponin I was not included as an independent predictor of any of the episodes analyzed.

The patients with elevated myoglobin values (>70

ng/mL; $n=142$) showed a tendency toward higher mortality rates (7% versus 2.4%; OR=3.1 [1-9.3]; $P=.06$) and significantly more complicating infarcts (7.7% versus 2.4%; OR=3.4 [1.2-10.1]; $P=.04$) and more major episodes (14.8% versus 4.8%; OR=3.5 [1.6-7.6]; $P=.002$) than those cases with normal myoglobin values ($n=210$). In the multivariate studies myoglobin was not included as an independent predictor (Tables 1-3).

Role of the acute phase reactants

Patients with elevated fibrinogen levels (>6 g/L; $n=78$) showed significantly more infarcts (10.3% versus 1.6%; OR=7.1 [1.8-27.6]; $P=.004$) and a tendency toward more major episodes

12.8% versus 5.3%; OR=2.6 [1-6.6]; $P=.06$), without differences in mortality rate (2.5% versus

TABLE 3. Predictors of major episodes. Univariate and multivariate analysis

	Infarct	No infarct	P	Multivariate		
				Model 1	Model 2	Model 3
				P	P	OR (95% CI)
Clinical-ECG						
Age, years	74±11	68±12	.002	.0009	.0009	1.07 (1.01-1.12) .01
IDDM, %	23	9	.04	.05	.05	4.1 (1.3-13.5) .02
ST decline, %	33	22	.3	–	–	–
Myocardial damage						
Troponin I, ng/mL	4.5 (0.6-18)	0.9 (0-10.8)	.03		–	–
Myoglobin, ng/mL	103 (45-291)	47 (30-113)	.001		–	–
Analytical						
HsCRP, mg/L	33 (12-102)	8 (3-24)	.001			1.007 (1.0003-1.01) .04
Fibrinogen, g/L	6 (5.4-7.5)	4.9 (3.9-6.1)	.005			–

A multivariate study was performed by progressively including in 3 steps the ECG-clinical variables (model 1), myocardial damage enzymes (model 2), and analytical variables (model 3, definitive) which on univariate analysis showed a value of $P < .1$ (in addition to the variables of age, IDDM, and ST decline) – indicates not included in the multivariate analysis; IDDM, non-insulin dependent diabetes mellitus; ECG, electrocardiogram; 95% CI, 95% confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

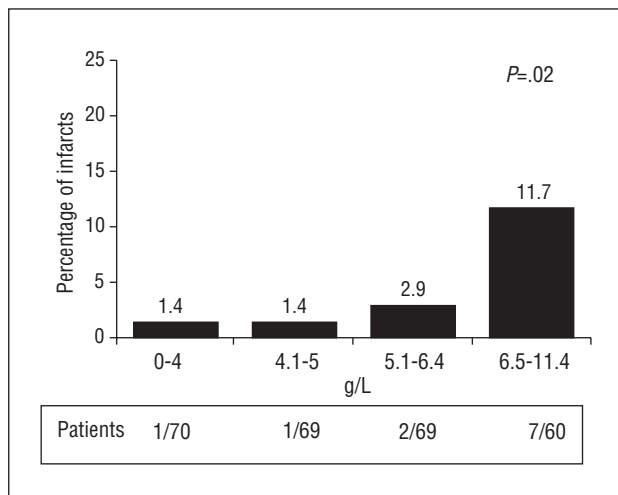


Fig. 1. The percentage of patients who presented with a complicating infarct during admission is shown by dividing the group in quartiles as a function of the fibrinogen values. The abscissa axis shows the fibrinogen values in each quartile and the number of patients in each subgroup.

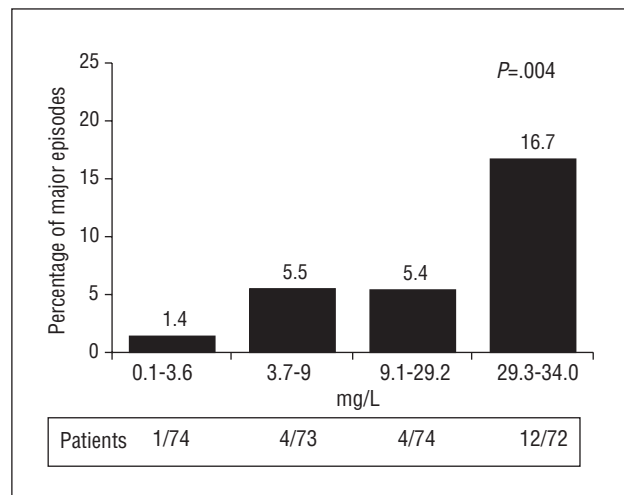


Fig. 2. The percentage of patients who presented with a major episode during admission is shown by dividing the group in quartiles as a function of the hsCRP values. The abscissa axis shows the hsCRP values in each quartile and the number of patients in each subgroup.

3.7%) with regard to those patients with a fibrinogen level <6 g/L (n=190). On multivariate analysis, fibrinogen was included as the only independent predictor of infarct (as a continuous variable, Table 2), but not as a predictor of death or major episodes (Tables 1 and 3). Upon dividing the group into fibrinogen quartiles, a progressive increase in the rate of infarct was noted (1.4, 1.4, 2.9 and 11.7%; $P=0.02$; Figure 1).

Patients with an elevated hsCRP value (>11 g/l; n=120) showed significantly greater mortality rates (6.6% versus 0.6%; OR=12.2 [1.5-98.7]; $P=0.009$) and more major episodes (13% versus 3%; OR=5.2 [1.8-14.5]; $P=0.001$) and a tendency toward more infarcts (6.7% versus 2.3%; OR=3 [0.9-10.3]; $P=0.1$) than those with hsCRP values <11 g/l (n=173). In the multivariate study hsCRP was an independent predictor of death and major episodes (as a continuous variable, Tables 1 and 3), but not for infarct (Table 2). Upon analyzing the group in quartiles of hsCRP values, a progressive increase in the mortality rate (0, 1.4, 2.7, and 8.2%; $P=0.02$) and in major episodes (1.4, 5.5, 5.4, and 16.7%; $P=0.004$; Figure 2) was noted.

DISCUSSION

We studied the predictive value in the short-term of clinical and ECG variables, the new markers for myocardial damage, and the acute phase reactants in patients who were admitted with suspected acute coronary syndrome without ST segment elevation. We observed that, in accordance with the majority of prior studies, the baseline clinical characteristics (age and IDDM) were predictors of major episodes. The acute

phase reactants added independent information for the prediction of death and major episodes (in the case of hsCRP values) and infarct (in the case of fibrinogen values). Troponin was related to a greater rate of major episodes, but was not an independent predictor in the multivariate analysis.

Clinical and ECG variables

The diagnosis, prognostic stratification, and treatment of acute coronary syndromes have changed rapidly in recent years. Therefore, the new diagnostic² and physiopathological concepts,^{1,3} more interventional treatment,^{5,6} and the introduction of new medications^{6,7} and new prognostic markers¹²⁻¹⁹ makes it necessary to periodically review those factors that can help us categorize the risk of patients who are admitted with suspected acute coronary syndrome. Given that the majority of episodes are going to occur in the first days after destabilization occurs, a correct definition of the risk profile would have great therapeutic, economic, emotional, and even legal implications.⁸

In spite of the introduction of new markers, including the most exhaustive multivariate analysis,¹⁷ the clinical variables (particularly age and diabetes) continue to be fundamental prognostic factors.²² In the same manner, electrocardiographic changes and, above all, the decline in ST markers,¹¹ are also related to an increased episode rate.

We observed that, in accordance with previous studies, age and IDDM emerged as independent predictors of death and major episodes. This shows the elevated risk of these patients (quickly identified from

the first moment). On the other hand, the existence of electrocardiographic changes is not related to a higher rate of episodes, although more aggressive treatment of these patients could have caused an «improvement» in the natural evolution of the disease. A fact that without doubt limits the prognostic power (and the diagnostic sensitivity of the ECG is that there are few patients who arrive at the emergency room with chest pain in whom electrocardiographic changes can be detected (23% with ST segment decline in our series). On the other hand, treatment of these patients according to the protocol of a chest pain unit protocol permits the exclusion of false cases of acute coronary syndrome; by not analyzing these patients (all of whom had a very good prognosis and did not have electrocardiographic changes), the predictive power of ECG is probably decreased. Finally, we need longer-term follow-up on our series of patients in order to evaluate the predictive power of electrocardiographic changes with respect to the rest of the variables that were analyzed.

Markers for myocardial damage

The introduction of specific markers capable of detecting minimal myocardial damage has caused important changes in the concepts² and treatment^{8,9,13-15} of patients with suspected acute coronary syndrome. Apart from their great diagnostic utility, troponins have been shown to be, including in multivariate analyses,¹⁷ medium-term independent risk predictors.

Nevertheless, over the last months several authors have expressed their concern about the excessive use of troponins as the principal protagonist at the moment of deciding whether or not early discharge is advisable,^{12,14} in the classification of admitted patients,¹⁶ and when deciding whether or not to perform interventional procedures.⁵ On the other hand, the design and interpretation of the studies that show the usefulness of these markers have also been the object of study.¹³ It is for these reasons that new studies are being performed to analyze the role of troponins as predictors as compared to other variables.^{13,15}

In our series, increased troponin I values showed a significant tendency toward a higher mortality, infarct, and major episode rate. Nevertheless, on multivariate analysis these values did not provide independent information in any of the cases studied. As is explained in the protocol, the elevation of troponin I values was not an indicator for more aggressive treatment, so that different treatment regimens do not appear to be the cause of the relatively low value of this parameter. It is possible that, as others have shown,¹⁷ on longer-term follow-up the prognostic power of troponin values is increased (as there is a progressive increase in episodes in those cases with

more myocardial damage). Therefore, our results underline the fact that troponin is useful, but does not appear to be the most important variable in the categorization of short-term risk for this type of patient.

The other new parameter for myocardial damage that we analyzed (myoglobin) showed an even greater prognostic capacity than troponin I. It had a significant relationship in all the episodes analyzed in the univariate analysis although it did not provide independent information in the multivariate analyses. The usefulness of this value for risk stratification short-term has already been observed in another study,²³ and we can assume that it has the capacity to aid in early diagnosis of myocardial damage.

Acute phase reactants

During the last few years inflammation has been identified as a primordial element in the arteriosclerotic process;^{3,4,18,24} this had led cardiologists to identify inflammation markers as predictors of episodes in individuals without antecedents⁴ and of complications following an acute coronary syndrome.^{19,25}

In summary, in addition to a focus of inflammation (unstable plaque, myocardial lesion, adipose tissue) cytokines are liberated (interleukine [IL] 1 and 6 or alpha tumor necrosis factor [TNF- α], among others) that stimulate the liver to produce acute phase reactants (CRP, fibrinogen, amyloid substance); a major inflammation would cause a greater liberation of reactants, which could supposedly be an indicator of greater risk.^{3,4,18} On the other hand, these reactants have been related to specific functions such as favoring coagulation and aggregation by fibrinogen 1 or the intensification and extension of the inflammatory response by CRP.^{3,24}

Various studies have shown the important predictor role of hsCRP and fibrinogen in acute coronary syndromes. Therefore, in the FRISC (Fragmin during instability in coronary artery disease) study in the medium-term (6 months) observed that fibrinogen is an independent predictor of death and infarct, while hsCRP is only a predictor of death;¹⁹ with long-term (3 years) follow-up of the same group, it was observed that hsCRP was an independent predictor of death.¹⁷ Recent studies²⁵ support the predictive role of these reactants.

Our results confirm the importance of hsCRP and fibrinogen in the prognosis of patients admitted for highly suspected acute coronary syndrome included in the very short term (inpatient) and after correction by the classic clinical, ECG, and myocardial damage markers. Even more so, utilizing practically the same cut-off points as the FRISC study, we observed that a

hsCRP value >11 mg/mL multiplied by 5.2 (1.8 to 14.5) and a fibrinogen value >6 g/L multiplied by 7.1 (1.8 to 27.6) the risk of suffering a major episode. In the multivariate analysis the hsCRP value was related to a greater rate of death and major episodes, and the fibrinogen was related to a greater rate of infarction (probably as a consequence of its role in aggregation and coagulation).

Our study shows that the prognostic usefulness of the acute phase reactants in the medium- and long-term as shown in previous studies^{17,19,25} also applies in periods that are as critical for risk stratification as inpatient hospital stays, and that they probably should be systematically included in daily practice due to the ease low cost involved in obtaining these values.

Finally, new questions such as the real cause (inflammatory focus) of the increase in the values of these reactants in coronary syndromes,^{3,18} their application for individual treatment (usefulness of aspirin²⁵ and statins²⁴ in those cases where elevated hsCRP values are present), or in the genetic identification of patients at greater risk (polymorphisms related to increased fibrinogen values¹) shows the breadth of the field that has opened up for the clinical application of these markers.

CONCLUSIONS

Our study shows that in a time when more markers for risk stratification are constantly being introduced, 2 classic variables (age and IDDM) continue to be included as first-degree prognostic factors. Troponin I is related to a greater rate of episodes but, on multivariate analysis, its predictive power in the short-term seems to be inferior to that of other variables. Finally, the acute phase reactants are confirmed as first-degree markers and it appears to be advisable to include them in the tools habitually used for the prognostic stratification of patients admitted with suspected acute coronary syndrome.

REFERENCES

- Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001;104:365-72.
- Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined. A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;21:1502-13.
- Rader DJ. Inflammatory markers of coronary risk. *N Engl J Med* 2000;343:1179-82.
- Best PJ, Gersh BJ. Cell adhesion molecules and inflammation in acute coronary syndromes: markers and emerging risk factors. *Eur Heart J* 2001;22:1155-9.
- Hod HH, Kleiman NS, Sequeira RF, Voipio-Pulkki LM. Issues in cardiac intervention for UA/NSTEMI. *Eur Heart J* 2001;3(Suppl J):J32-J9.
- Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
- Boden WE, McKay RG. Optimal treatment of acute coronary syndromes—an evolving strategy. *N Engl J Med* 2001;344:1939-42.
- Hutter AM, Amsterdam EA, Jaffe AS. Task force 2: acute coronary syndromes: section 2B—chest discomfort evaluation in the hospital. *J Am Coll Cardiol* 2000;35:825-80.
- Bassan R, Gibler WB. Unidades de dolor torácico: estado actual del manejo de pacientes con dolor torácico en los servicios de urgencias. *Rev Esp Cardiol* 2001;54:1103-9.
- Lee TH, Goldman L. Evaluation of the patient with acute chest pain. *New Engl J Med* 2000;342:1187-95.
- Kaul P, Fu Y, Chang WCh, Harrington RA, Wagner GS, Goodman SG, et al. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. *J Am Coll Cardiol* 2001;38:64-71.
- Bodí V, Sanchis J, Llàcer A, Graells ML, Llorca L, Chorro FJ, et al. ¿Es la troponina I útil para predecir el riesgo hospitalario en pacientes con angina inestable ingresados en un hospital comarcal? Resultados de un estudio prospectivo. *Rev Esp Cardiol* 2002; 55:100-6.
- Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol* 2001;38:478-85.
- Gibler WB. Understanding true risk: evaluating troponins in the emergency setting. *Am Heart J* 1999;137:985-6.
- De Winter RJ. Risk stratification with cardiac troponin I in acute coronary syndromes. *J Am Coll Cardiol* 2000;36:1824-6.
- Antman EM, Corbalán R, Huber K, Jaffe AS. Issues in early risk stratification for UA/NSTEMI. *Eur Heart J* 2001;3(Suppl J):J6-J14.
- 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.
- De Winter RJ, Fischer J, Bholasingh R, Van Straalen JP, De Jong T, 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.
- Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable artery disease. *Circulation* 1997;96:4204-10.
- Geleijnse ML, Elhendy A, Kasprzak JD, Rambaldi R, Van Domburg RT, Cornel JH, et al. Safety and prognostic value of early dobutamine-atropine stress echocardiography in patients with spontaneous chest pain and a non-diagnostic electrocardiogram. *Eur Heart J* 2000;21:397-406.
- Sanchis J, Llàcer A, Plancha E, Navarro A, Ferrero A, Blasco E, et al. Diagnóstico de síndrome coronario agudo en una unidad de dolor torácico [resumen]. *Rev Esp Cardiol* 2001;54:4.
- López Bescos L, Fernández-Ortiz A, Bueno Zamora H, Coma Canella I, Lidón Corbi RM, Cequier Fillat A, et al. Guías de práctica clínica de la Sociedad Española de Cardiología en la angina inestable/infarto sin elevación ST. *Rev Esp Cardiol* 2000;53:838-50.
- Sonel A, Sasseen BM, Fineberg N, Bang N, Wilensky RL. Prospective study correlating fibrinopeptide A, troponin I, myoglobin, and myosin light chain levels with early and late ischemic events in consecutive patients presenting to the emergency department with chest pain. *Circulation* 2000;102:1107-13.
- Munford RS. Statins and the acute-phase response. *N Engl J Med* 2001;344:2016-8.
- Kennon S, Price CP, Mills PG, Ranjadayan K, Cooper J, Clarke H, et al. The effect of aspirin on C-reactive protein as a marker of risk in unstable angina. *J Am Coll Cardiol* 2001;37:1266-70.