Prognostic Markers of Non-ST Elevation Acute Coronary Syndromes

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Objectives. We analyzed whether the study of systolic function by echocardiography adds independent information to that afforded by biochemical markers in predicting six-month major events after non-ST elevation acute coronary syndrome.

Patients and method. Baseline clinical and electrocardiographic data as well as serum concentrations of troponin, myoglobin, C-reactive protein, fibrinogen and homocysteine were recorded prospectively in 515 consecutive patients admitted because of non-ST elevation acute coronary syndrome. Ejection fraction (echocardiogram) was determined in 248 cases (48%). Predictors of cardiac death or infarction within the following six months were analyzed.

Results. In the 248 patients in whom ejection fraction was analyzed, 38 major events were recorded. Increased biochemical markers were related to major events ($p < 0.05$ for all markers). In the final multivariate model, which included clinical, electrocardiographic, serological and systolic function data, ejection fraction was the most powerful predictor of six-month major events: age > 70 years ($p = 0,04$), insulin-dependent diabetes ($p = 0.03$), C-reactive protein > 11 mg/l ($p = 0.004$) and ejection fraction < 50% ($p < 0.0001$); C-statistic = 0.80.

Conclusions. Apart from the clinical and biochemical profile, analysis of systolic function is advisable for correct risk stratification of patients with non-ST elevation acute coronary syndrome.

Key words: *Unstable angina. Infarction. Prognosis. Systole. Troponin. C-reactive protein.*

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Indicadores pronósticos del síndrome coronario agudo sin elevación del segmento ST

Objetivos. Analizamos si el estudio de la función sistólica mediante ecocardiografía añade información independiente a la aportada por los marcadores bioquímicos para predecir episodios mayores durante los primeros 6 meses tras un síndrome coronario agudo.

Pacientes y método. Los datos clínicos y electrocardiográficos basales, así como los valores de troponina, mioglobina, proteína C reactiva, fibrinógeno y homocisteína, se determinaron prospectivamente en 515 pacientes consecutivos ingresados por síndrome coronario agudo sin elevación del segmento ST. Se estudió la fracción de eyección (ecocardiograma) en 248 casos (48%). Se analizaron los predictores de muerte cardíaca o infarto durante los 6 meses siguientes.

Resultados. En los 248 casos con análisis de la fracción de eyección se registraron 38 episodios mayores. La elevación de los marcadores serológicos se relacionó con la presencia de episodios mayores ($p < 0,05$ para todos los marcadores). En el modelo multivariado definitivo que incluía los datos clínicos, electrocardiográficos, serológicos y de función sistólica, la fracción de eyección fue el predictor más potente de episodios mayores a los 6 meses: edad > 70 años ($p = 0,04$), diabetes insulinodependiente ($p = 0,03$), proteína C reactiva > 11 mg/l ($p = 0,004$) y fracción de eyección < 50% ($p < 0,0001$); estadístico C del modelo = 0,80.

Conclusiones. Además del estudio del perfil clínico y bioquímico, el análisis de la función sistólica es aconsejable para una correcta estratificación de riesgo de los pacientes con síndrome coronario agudo sin elevación del segmento ST.

Palabras clave: *Angina inestable. Infarto. Pronóstico. Sístole. Troponina. Proteína C reactiva.*

INTRODUCTION

The prognostic risk stratification of patients with non-ST elevation acute coronary syndrome has evolved continuously over the past ten years[1] and has focused on the development of chest pain units,[2] early

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ABBREVIATIONS

ECG: electrocardiogram.
EF: ejection fraction.
95% CI: 95% confidence interval.
NS: nonsignificant.
OR: odds ratio.
ROC: receiver operator characteristic.

stress testing[3] and electrocardiographic analysis,[4] and, in particular, the role of biochemical markers.[5-9]

Systolic function is a solid prognostic marker in patients with ischemic heart disease.[10] The interest in biochemical markers has, however, to some extent overshadowed its use, and in many studies its prognostic value is not analyzed. Recent guidelines[11] assign the analysis of systolic function a less important role in risk stratification than other variables which have only recently been incorporated into daily clinical practice. A considerable proportion of patients are therefore discharged from hospital without an analysis of their systolic function.[12]

The objective of the present study was to investigate whether echocardiographic assessment of ejection fraction during hospital stay provides additional independent information in predicting six-month major cardiac events after non-ST elevation acute coronary syndrome. The analysis was performed after adjusting for clinical and electrocardiographic variables, biochemical markers of myocardial damage (myoglobin and troponin) and inflammatory markers (C-reactive protein and fibrinogen), and homocysteine levels.

PATIENTS AND METHODS

Study population

Between November 1st 2000 and December 31st 2001 a total of 515 consecutive patients admitted to the cardiology department with a diagnosis of non-ST elevation acute coronary syndrome were included. The definition of non-ST elevation acute coronary syndrome was based on a clinical diagnosis carried out by the on-call cardiologist. To be included, patients also had to meet at least one of the following criteria: *a)* electrocardiographic findings suggestive of ischemia: depression of the ST segment (>1 mm, 80 ms after the J point) or inversion of the T wave (>1 mm); *b)* evidence of myocardial damage (troponin I>1 ng/mL or myoglobin>70 ng/mL); *c)* a positive stress test result performed within the first 24 h in the chest pain unit; d) fifty-eight patients who did not meet any of the above criteria, but in whom there was a strong suspect of having an acute coronary syndrome by the on-call cardiologist, were also included. In these cases, an early ergometric stress test was not performed because of clinical or electrocardiographic contraindication or due to logistic difficulties. Patients with a potential increase in C-reactive protein levels due to inflammatory diseases, neoplasias, infections or hepatic or renal insufficiency, were excluded from the study.

All prognostic analyses in the present study were carried out using data from 248 patients (48% of the 515 patients admitted) in which an echocardiogram was performed to analyze ejection fraction during the hospital stay. Baseline characteristics of these patients are shown in Table 1.

The attending cardiologist decided patient management strategies. In general, a noninvasive strategy was used. Cardiac catheterization was performed in patients with recurring angina, cardiac insufficiency or a positive stress test. Percutaneous revascularization was carried out when anatomically possible, and all decisions regarding the revascularization strategy were of the attending cardiologist. Aspirin, low molecular weight heparin, and beta-blockers were administered to all patients, except when contraindicated. Other me-

TABLE 1. **Study population baseline characteristics**

Number	248
Clinical observation	
Age, years	68 ± 12
Age >70 years	127 (51%)
Male	167 (67%)
Hypertension	166 (67%)
Hypercholesterolemia 99 (40%)	
Diabetes mellitus	84 (34%)
Type 1 diabetes mellitus	37 (15%)
Smoker	58 (23%)
History of ischemic heart disease	93 (37%)
History of infarct	46 (18%)
Killip class >1	57 (23%)
Electrocardiogram	
Reduced ST segment	76 (31%)
Inverted T wave	25(10%)
Positive ergometric stress test (<24 h)	21 (8%)
Markers	
Troponin Y >1 ng/mL	190 (77%)
Myoglobin >70 ng/mL	139 (56%)
C-reactive protein >11 mg/L	122 (49%)
Fibrinogen >5 g/L	140 (56%)
Homocysteine >12 mmol/L	133 (54%)
Interventions	
Pre-discharge catheterism	71 (29%)
Pre-discharge angioplasty	20 (8%)
Pre-discharge bypass surgery	8 (3%)
Pre-discharge revascularization	27 (11%)
Events	
Cardiac death	13 (5%)
Myocardial infarction	32 (13%)
Major event	38 (15%
Episodio mayor	38 (15%)

dications were prescribed on an individual basis by the attending cardiologist. All clinical and electrocardiographic variables were collected prospectively upon admission.

Biochemical markers

Troponin I, myoglobin, C-reactive protein, fibrinogen and homocysteine levels were determined prospectively in all patients.

Troponin I and myoglobin (immunometric method, DPC, Los Angeles, California, USA) were analyzed on arrival at the emergency department and 6 h later (in patients arriving within the first 2 h of symptom onset), as well as at 8, 12, 18, and 24 h (until the maximum level was detected). As recommended by the hospital laboratory, cut-off points of 1 ng/mL and 70 ng/mL, respectively, were adopted for troponin I and myoglobin.

C-reactive protein values, fibrinogen and homocysteine (single determinations) were determined in all patients in the first analysis performed after admission (median of 48 h after symptom onset). On the basis of their respective ROC curves for predicting major events, a cut-off value of 11 mg/L was selected for C-reactive protein (highly sensitive nephelometric method, Behring Diagnostics, Marburg, Germany), 5 g/L for fibrinogen (DG-FIB, Grifols, Barcelona, Spain), and 12 μmol/L for homocysteine (Axsym System; Abbot, Oslo, Norway). The same method was used to establish a cut-point of 70 years for age.

Ejection fraction

Ejection fraction was studied by performing a B-mode (area-length method) echocardiograph (Agilent Sonos 5500, Phillips, Holland) in 248 patients (48% of the study population). In all cases, the attending cardiologist was responsible for deciding whether to determine ejection fraction by echocardiogram. A mean ejection fraction of 59±13% (median 61% and range 20-85%) was observed. An ejection fraction of <50% (n=58; 23%) was interpreted as depressed.

The ejection fraction was analyzed using a quantitative contrast ventriculography in 181 cases (35% of the total; 103 of those without echocardiogram). In total, information on systolic function during hospital stay was available for 351 patients (68% of the total). To ensure a uniform sample, only patients in whom systolic function was determined by echocardiography (n=248) were included in the prognosis analyses.

Major events and follow-up

Major events were defined as cardiac death and myocardial infarction (excluding that which led to hospital admission). The occurrence of either of these events (or the first of them, when both occurred) was considered as a major event. Myocardial infarction was defined according to current recommendations.[11] Follow-up was performed in the outpatient department, via telephone contact or review of computerized clinical records. All patients were followed up for 6 months.

Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD) and were compared using Student's *t*-test for unpaired data. Categorical variables were expressed as percentages of the study population and were compared using χ^2.

Three different multivariate models (each employing the Cox proportional hazards method) were used to determine which variables provided independent information to predict major events. The 3 models only incorporated data from the 248 patients with echocardiographic analysis of the ejection fraction. In order to take into account the order in which data is received by clinicians, the first model included clinical and electrocardiographic variables, the second model included clinical, electrocardiographic and biochemical markers, and the third and definitive model included all of these together with the ejection fraction. Variables with an adjusted value of $P<.05$ were considered independent and their odds ratio (OR) and respective 95% confidence intervals (95% CI) were calculated. The explanatory power of each of the models was analyzed using the C-statistic test (equivalent to the area under the ROC curve of the model).

All calculations were performed using the SPSS 9.0 statistical package (Chicago, Illinois, USA). Values of $P<.05$ were considered statistically significant in all cases.

RESULTS

Univariate analysis

Table 1 shows the baseline characteristics of the study population, i.e. of the 248 patients with echocardiographic analysis of the ejection fraction. The rate of major events was identical in patients with (28/248, 15%) and without (40/267, 15%) analysis of the ejection fraction by echocardiogram.

In patients in which ejection fraction had been analyzed (n=248), 38 primary major events (15%), 13 cardiac deaths (5%) and 32 myocardial infarctions (13%) were observed. Variables associated with the occurrence of a major event are shown in Table 2. Patients who suffered a major event were older (73 ± 11 vs 68 ± 12 years; $P=.02$), had higher myoglobin values (226 ± 217 vs 145 ± 182 ng/mL; $P=.03$), hig-

TABLE 2. **Percentage of major events as a function of clinical, electrocardiographic, biochemical variables and systolic function. Univariate analysis**

	Yes	No	*P*
Clinical observation			
Age >70 years	21%	9%	.01
Male	17%	11%	NS
Hypertension	13%	19%	NS
Hypercholesterolemia	15%	15%	NS
Diabetes	20%	13%	NS
Type 2 diabetes mellitus 30%	13%	.02	
Smoker	14%	16%	NS
History of ischemic heart disease	17%	14%	NS
History of infarct	20%	14%	NS
Killip class >1	32%	10%	<.0001
Electrocardiogram			
Reduced ST segment	21%	13%	.1
Negative T wave	4%	17%	NS
Markers			
Troponin I >1 ng/mL	18%	5%	.02
Myoglobin >70 ng/mL	20%	9%	.03
C-reactive protein >11 mg/L	21%	9%	.01
Fibrinogen >5 g/L	21%	8%	0.01
Homocysteine >12 µmol/L	23%	8%	.002
Systolic function			
Ejection fraction <50%	36%	9%	<.0001

Yes indicates the percentage of events when the variable is present; No, the percentage of events when the variable is absent; for example, 21% of patients >70 years of age had major events compared to 9% in patients aged <70 years.

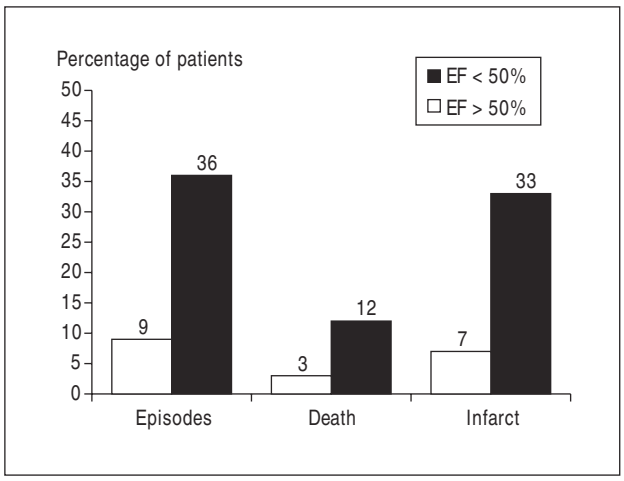

Fig. 1. Percentage of major events, cardiac death, and infarct during 6 months of follow-up as a function of ejection fraction analyzed by echocardiogram. Patients with an ejection fraction of <50% (n=58; 23%) had a higher percentage of primary major events (*P*<.0001), cardiac death (*P*=.02) and myocardial infarction (*P*<.0001) than those with an ejection fraction of >50% (n=190; 77%).

her C-reactive protein (39 ± 57 vs 22 ± 36 mg/L; *P*=.02) and fibrinogen (6 ± 2 vs 5 ± 2 g/L; *P*=.01) levels, and a tendency towards higher concentrations of troponin I (23 ± 32 vs 16 ± 26 ng/mL; *P*=0.1) and homocysteine (1 ± 9 vs 14 ± 10 µmol/L; *P*=0.1). They also had a more depressed ejection fraction (49 ± 13 vs 61 ± 13%; *P*<.0001).

Patients with an ejection fraction of <50% (n=58; 23%) had a higher rate of major events (36% vs 9%; *P*<.0001), cardiac death (12 vs 3; *P*=.02) and myocardial infarctions (33% vs 7%; *P*<.0001) than those with an ejection fraction of >50% (n=190; 77%) (Figure 1).

Multivariate analysis

In the first multivariate model (which included only clinical and electrocardiographic data), variables providing independent information to predict major events were: age >70 years (*P*=.02); Killip class >1 (*P*<.004); and, type 1 diabetes mellitus (*P*=.02). The C-statistic was 0.73 (0.64-0.83]) (Table 3).

In the second model (when values for biochemical markers were added), statistically significant variables were: age >70 years (*P*=.04); Killip class >1 (*P*=.02); type 1 diabetes mellitus (*P*=.03), and C-reactive protein >11 mg/L (*P*=.01). The C-statistic was 75 (0.67-0.83) (Table 3).

Lastly, in the third, and definitive model (when ejection fraction was added) statistically significant variables were: age >70 years (OR=2.3 [95% CI, 1.1-5.3]; *P*=.04); type 1 diabetes mellitus (OR=2.6 [95% CI, 1.1-6.5]; *P*=.03); C-reactive protein >11 mg/L (OR, 3.4 [95% CI, 1.5-7.8] *P*=.004), and; ejection fraction <50% (OR, 5.1[95% CI, 2.4-11.1]; *P*<.0001). The C-statistic was 0.80 (0.72-0.87) (Table 3).

DISCUSSION

The present study shows that classifying patients with non-ST elevation acute coronary syndrome for risk of major cardiac events requires the use of clinical**,** electrocardiographic and biochemical data, as well as data on systolic function in an integrated fashion. On arrival at the emergency department, the collection of demographic data such as age or presence of diabetes, data from the physical exploration, such as signs of cardiac insufficiency, and electrocardiographic data, such as a decrease in the ST segment, quickly provide a large amount of prognostic information. In the hours following the initial examination, determining biochemical variables can help to more precisely define prognosis. Ejection fraction analysis prior to hospital discharge is also advisable as it provides adjunctive information useful in accurately stratifying the risk of a major event over the following months.

TABLE 3. **Predictors of major events. Multivariate analysis**

	First model		Second model		Third model	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Clinical observation-ECG						
Age >70 years	2.6 (1.2-5.8)	.02	2.3 (1.01-5.1)	.04	2.3 (1.1-5.3)	.04
Male		NS		NS		NS
Hypertension		NS		NS		NS
Hypercholesterolemia		NS		NS		NS
Diabetes		NS		NS		NS
Type 1 diabetes mellitus	2.8 (1.1-6.8)	.02	2.6 (1.1-6.1)	.03	2.6 (1.1-6.5)	.03
Smoker		NS		NS		NS
History of ischemic heart disease		NS		NS		NS
History of infarction		NS		NS		NS
Killip class >1	3.1 (1.4-6.6)	.004	2.6 (1.2-5.5)	.02		NS
Reduced ST segment		NS		NS		NS
Negative T wave		NS		NS		NS
Markers						
Troponin I >1 ng/mL				NS		NS
Myoglobin >70 ng/mL				NS		NS
C-reactive protein >11 mg/L			2.9 (1.3-6.5)	.01	3.4 (1.5-7.8)	.004
Fibrinogen >5 g/L				NS		NS
Homocysteine >12 µmol/L				NS		NS
Systolic function						
Ejection fraction <50%					5.1 (2.4-11.1)	<.0001
C-statistic	0.73 (0.64-0.83)		0.75 (0.67-0.83)		0.80 (0.72-0.87)	

ECG indicates electrocardiogram; NS, non-significant; OR (CI 95%), odds ratio with 95% confidence intervals.
First model: multivariate analysis including clinical and electrocardiographic variables.
Second model: multivariate analysis including clinical and electrocardiographic variables and biochemical markers.
Third and final model: multivariate analysis including clinical and electrocardiographic variables, biochemical markers and ejection fraction.
The last row shows the C-statistic for each model.

Clinical and electrocardiographic variables

The results of this study show that, even before the assessment of biochemical markers, a substantial amount of prognostic information can be obtained from anamnesis, physical exploration and electrocardiographic analysis. When considering variables available to the clinician prior to performing any serological analyses in the multivariate analysis (model 1), older age, insulin dependent diabetes mellitus (probably because it represents a late stage of this disease), and signs of cardiac insufficiency were all independently associated with prognosis. The aggregate predictive power of these variables was only slightly improved when values for biochemical markers were introduced (C-statistic, 0.73 vs 0.75).

The greater risk in older patients and those with diabetes or signs of cardiac insufficiency has been observed in previous studies,[4,7,9,13-15] and demonstrates that patients can, to a large extent, be stratified for risk in the initial contact with the patient. Including biochemical markers when stratifying patients for risk can help in decision-making, though it should not be the only criteria used. Clearly, the initial patient assessment can provide valuable information such as the presence of comorbidities or the patient's compliance for a more aggressive treatment strategy) which, although not always «quantifiable,» may be essential for patient management.

Biochemical markers

In recent years, a considerable number of studies have analyzed the prognostic role of different biochemical markers. Many of these have focused on troponin, which is now frequently used in daily clinical practice, both for diagnostic and prognostic purposes.[6-9,13,16,17] Any study currently intending to analyze the prognostic performance of other biochemical markers is obliged to consider whether they provide independent, complementary or redundant information when compared to troponin. For this reason, in the present study the maximum peaks of troponin I and myoglobin were carefully analyzed. Myoglobin is another marker of myocardial damage widely used in emergencies because of its sensitivity and ability to provide fast results.

As observed in other recent studies, patients with elevated troponin I levels had a higher rate of major car-

diac events. The prognostic value of troponin was very similar to that of myoglobin. Two recent studies, the CHECKMATE study[18] and a meta-analysis performed by de Lemos et al[19] obtained similar results, although in both studies single determinations were used, while in the present study, where possible, maximum peak values were determined using successive analyses. As with troponin,[16] elevated myoglobin levels are associated with both the presence of embolic coronary lesions[18] as well as greater myocardial damage.[20] Although the prognostic value of myoglobin is theoretically limited by its fast plasma clearance, de Lemos et al[19] observed that, even in patients presenting more than 12 h after symptom onset, myoglobin provided independent prognostic information. Since myoglobin reaches peak plasma levels very quickly, it is remarkable that it can be useful in risk stratification in the early hours after patient presentation.

Fibrinogen is an acute-phase reactant with direct, procoagulant activity which is known to be associated with a poor short- and long-term prognosis.[9,13,21] Homocysteine, on the other hand, is associated with the presence of thrombotic material and a greater tendency towards reinfarction,[22] though it is not clear whether it acts as an epiphenomenon or as a precipitating factor in these coronary syndromes. The predictive capacity of these variables was confirmed but, after adjusting for other parameters, it was found that they did not provide independent information.

Over the past decade, arteriosclerosis and inflammation have been closely linked,[23-25] and C-reactive protein as an acute-phase reactant and non-specific marker of inflammation has been widely studied.[7,9,26,27] Its independent short- and long-term prognostic power is undeniable, although there are still gaps in our knowledge regarding this marker. For example, it is not clear whether elevated values stem from unstable plaques,[28] rupture of multiple plaques,[29] myocardial damage,[30] etc.; whether it acts via proinflammatory mechanisms, or by provoking endothelium dysfunction, or as a simple epiphenomenona.[23,24,28,29,31] Likewise, the management trategy in unstable patients with elevated C-reactive protein values is not well-defined, for example whether they should be treated with statins,[32] or more invasive strategies,[26] etc. Nevertheless, its undeniable prognostic power has led recent guidelines to classify it as providing a type A evidence for risk stratification.[33]

In the present study, the poorer prognosis over 6 months in patients with elevated C-reactive protein values was confirmed. The predictive value of this variable was maintained even after adjusting for the most predictive biochemical markers and for systolic function. Furthermore, the information provided appears to complement that provided by markers indicating myocardial damage.[7] In this series, the only biochemical marker which provided independent information was C-reactive protein.

Systolic function

Similar to findings observed in a recent register-based study[12], approximately one-third of patients in the present study were discharged from the hospital without data on the ejection fraction (echocardiogram or ventriculography) after the episode leading to admission. Echocardiographic assessment of systolic function was performed in 248 patients (48% of patients admitted) prior to hospital discharge. These patients were included in the multivariate analyses to determine which variables best predicted prognosis. Patients without data on systolic function or having ejection fraction assessed by ventriculography (103 patients, were excluded from the multivariate analysis.

Systolic function is a classic predictor of prognosis in ischemic heart disease.[10] Unlike some variables which have only recently been incorporated into clinical practice, it meets all of the criteria for a good prognostic marker:[34] Its physiopathological mechanisms are well-understood, it is quantifiable, its consequences are known, and it can be treated in different ways. Despite this, however, most recent studies which have analyzed the prognostic capacity of different markers have not adjusted the information obtained from these markers by systolic function, and widely distributed guidelines[11] only assign it a secondary role in risk stratification.

It is commonly believed that ejection fraction only has prognostic value in very high-risk patients (e.g. those with considerable regional dysfunction, ST segment elevation, or who urgently require a coronary intervention). In our study population, however, which did not have a notably depressed ejection fraction (median of 61%) or require, in general, revascularization prior to discharge (11%), echocardiographic analysis of ejection fraction was the most powerful predictor of major cardiac events. Therefore, at a time when biochemical markers play a central role in risk assessment, it is convenient to remember that the study of systolic function prior to hospital discharge can help to correctly classify patients.

As previously mentioned, the inclusion of biochemical markers in the multivariate analysis led only to a modest improvement compared to the information provided by clinical and electrocardiographic variables (the C-statistic only showed an absolute increase of 2% between models 1 and 2: 0.73 vs 0.75). However, including data on the ejection fraction this was a 7% improvement in the model's predictive power in absolute terms and to an almost 10% improvement in relative terms (0.73 vs 0.80).

Limitations

The principal limitation of the present study was that the ejection fraction was not analyzed by echocardio-

gram in the 515 patients admitted with a diagnosis of non-ST elevation acute coronary syndrome during the study period. When interpreting the results, therefore, it should be remembered that the study only included patients with an echocardiographic analysis of the systolic function prior to hospital discharge, and that the criteria for performing this type of analysis may vary between centers.

CONCLUSIONS

When stratifying patients with non-ST elevation acute coronary syndrome for risk of major cardiac events, combined clinical, electrocardiographic, biochemical and systolic function data should be used. A considerable amount of prognostic information can be obtained very quickly from clinical and electrocardiographic data. The analysis of biochemical markers (and, in our series, particularly C-reactive protein) helps to better define prognosis. In those patients in whom an echocardiographic assessment of systolic function was performed, this may also be useful in stratifying patients for risk of major cardiac events.

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