

Usefulness of Clinical Profiling and Exercise Testing in the Prognostic Assessment of Patients Admitted With Chest Pain But Without High-Risk Criteria

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Introduction and objectives. Few data are available on the outcome of patients admitted to hospital with suspected acute coronary syndrome who have no high-risk factors and who undergo exercise testing before discharge. Our objectives were to investigate outcomes in this group of patients and to determine whether clinical history-taking or exercise testing can help to predict outcome.

Patients and methods. The study population comprised 449 patients admitted to hospital with chest pain suggestive of acute coronary syndrome. All were judged to be at low risk of subsequent events (i.e., none had ischemic ECG changes or an elevation in troponin level). They underwent treadmill exercise testing before discharge, after an observation period of at least 12 hours. Exercise testing was performed after clinical evaluation based on an algorithm involving troponin-T level and resting ECG. The median follow-up duration was 479 days. The single combined endpoint was defined as cardiac death, or hospital admission for nonfatal acute myocardial infarction or unstable angina.

Results. Adverse events occurred in 44 (10%) of the 449 patients. A high event rate was associated with four clinical features (i.e., age ≥ 65 years, diabetes, previous acute myocardial infarction, and typical chest pain) and with a positive result on exercise testing.

Conclusions. Adverse events after discharge are not infrequent in patients admitted to hospital with suspected acute coronary syndrome and a low risk profile. Both the patient's clinical characteristics and exercise test results should be taken into account in accurately determining prognosis.

Key words: *Electrocardiography. Exercise. Unstable angina. Myocardial infarction. Prognosis.*

Utilidad del perfil clínico y la ergometría en la valoración del pronóstico de los pacientes ingresados por dolor torácico sin criterios de alto riesgo

Introducción y objetivos. Hay escasa información sobre la evolución de los pacientes hospitalizados por dolor torácico que no presentan criterios de alto riesgo tras su evaluación inicial, a los que se realiza una prueba de esfuerzo para su valoración antes del alta. Nuestro objetivo fue evaluar el pronóstico de este grupo de pacientes y averiguar si hay factores clínicos y derivados de la prueba de esfuerzo que permitan predecir su evolución.

Pacientes y método. La población estaba constituida por 449 pacientes hospitalizados por dolor torácico de posible origen isquémico, sin criterios de alto riesgo (sin alteraciones isquémicas en el electrocardiograma ni elevación de la troponina), a los que se realizó una prueba de esfuerzo previa al alta, tras un período de observación de al menos 12 h. La mediana de seguimiento fue 479 días. Se consideraron acontecimientos adversos la muerte cardíaca o el reingreso por infarto agudo de miocardio (IAM) no mortal o angina inestable.

Resultados. De los 449 pacientes, 44 (10%) presentaron algún suceso. En el análisis de regresión de Cox se identificaron como predictores independientes de evolución desfavorable cuatro variables clínicas (edad ≥ 65 años, diabetes, IAM previo y carácter típico del dolor torácico) y una prueba de esfuerzo positiva.

Conclusiones. Los pacientes hospitalizados por dolor torácico sin criterios de alto riesgo tras su evaluación inicial, a los que se efectúa una prueba de esfuerzo, no están exentos de sucesos adversos tras el alta. El perfil clínico contribuye, junto con el resultado de la ergometría, a la valoración del riesgo de estos pacientes.

Palabras clave: *Electrocardiograma. Ejercicio. Angina inestable. Infarto de miocardio. Pronóstico.*

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INTRODUCTION

Information on the prognosis of patients with suspected non-ST segment elevation acute coronary syndrome (NSTEMI ACS) and on the use of risk evaluation tools has been obtained in selected patients (often those enrolled in clinical trials) from objective data such as ischemic electrocardiogram (ECG) changes or elevation of cardiac markers.^{1,2} From these data, protocols have been devised to attend patients presenting at emergency rooms (ER) for chest pain.³⁻⁷ In patients not presenting high-risk characteristics during initial observation, the probability of unfavorable evolution is assumed to be low,⁸ meaning early discharge is possible.

In Spain, however, little is known about the evolution of patients hospitalized with possible ischemic chest pain and presenting no high-risk criteria during initial observation. We consider this population to be poorly represented by reports on low-risk patients included in registers or NSTEMI ACS clinical trials, or patients evaluated in the exclusive context of specific emergency service chest pain units. Despite this, the proposed management of these patients is the same.^{1,9} After excluding those who present recurrent chest pain, hemodynamic abnormalities, ischemic ECG changes and cardiac marker elevation, decisions are based on results of noninvasive ischemia testing. Clinical practice guidelines accord noninvasive testing a homogeneous predictive value that could detract from the importance of previous clinical evaluation when interpreting results.

Consequently, our objective was to establish the prognosis of patients hospitalized with suspected NSTEMI ACS, without high-risk criteria and undergoing

exercise testing (ET) prior to discharge, and determine whether clinical factors or ET enable us to predict their evolution.

PATIENTS AND METHODS

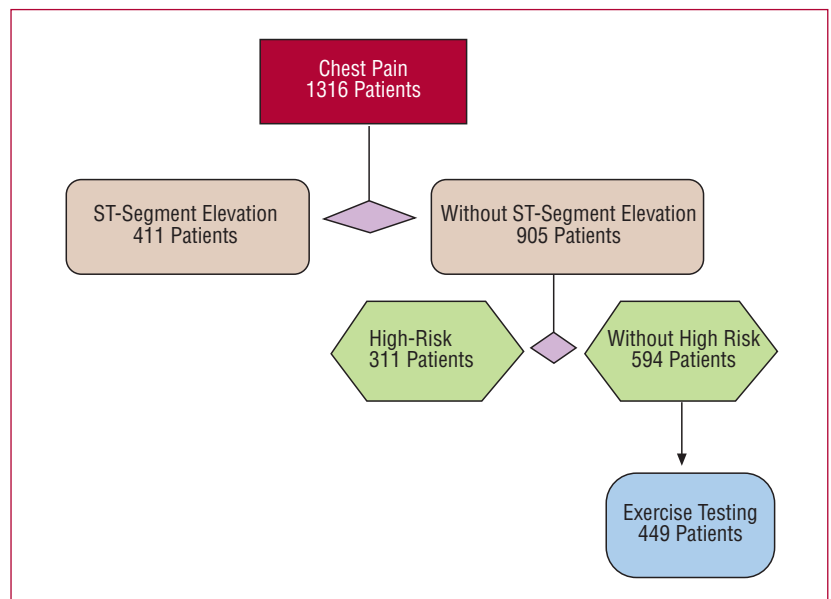
Study Population

We designed a prospective study of a consecutive series of patients hospitalized in the cardiology service of our hospital with suspected NSTEMI ACS. The study population was made up of low-risk patients referred to the noninvasive diagnosis unit to undergo ET prior to discharge from June 2001 thru December 2002 (Figure 1). This population represents 49% of the 920 hospitalized patients undergoing ET before discharge.

No chest pain observation unit was available in our center during the study period. Consequently, patients with suspected NSTEMI ACS were hospitalized in the conventional way in the cardiology service as indicated by ER physicians. The study design meant all patients underwent ECG and troponin level evaluation on hospitalization with ≥ 12 hours in-hospital observation before ET and at least 1 new ECG and a second troponin test at 6-12 hours observation. Exercise testing took place >12 hours after arrival at ER, on the indication of the clinical cardiologist and according to the availability of test facilities.

Only patients without evidence of recurrent episodes of chest pain, ischemic ECG changes or elevated troponin T concentrations during observation were included. Patients with suspected post-acute myocardial infarction (AMI) angina (≥ 30 days), surgical or percutaneous revascularization during the

Figure 1. Selection of the 449 patients who constitute the study population, based on patients hospitalized in the cardiology service for chest pain.



previous 6 months, hemodynamic instability or severe ventricular arrhythmias were excluded. Patients with suspected left ventricular systolic dysfunction underwent echocardiography. We excluded patients with left ventricular ejection fraction (LVEF) $\leq 40\%$.

We also excluded patients with baseline ECG changes associated with electric responses that could not be interpreted as ischemia in ET⁵ (left bundle-branch block, pacemaker rhythm, preexcitation, ST-segment depression of ≥ 1 mm, or less in presence of digoxin treatment or other criteria of left ventricular hypertrophy).

Nature of Chest Pain, ECG, and Troponin Levels

We prospectively recorded the variable nature of chest pain in all patients. Clinical cardiologists subjectively defined chest pain as typical or atypical when clinical characteristics indicated it was of probable or improbable ischemic origin, respectively. To determine interobserver agreement on nature of chest pain thus defined, prior to ET a second cardiologist performed a new anamnesis in a random sample of 100 patients ($\kappa=0.81$).

Ischemic ECG changes were defined as observable reversible ST-segment depression ≥ 0.5 mm in at least 2 contiguous leads or evolution of changes in T-wave polarity or persistent T-wave inversion ≥ 0.2 mV, of ischemic nature.

To quantify troponin T (TnT) we used electrochemiluminiscent enzyme immunoassay (Elecsys 2010; Roche Diagnostics Corporation, Indianapolis, US). The manufacturer reports a lowest detection limit concentration of 0.01 ng/mL. The imprecision of the trial is characterized by a 4.2% variation coefficient of a 0.1 ng/mL concentration. Elevated troponin concentration was defined as >0.01 ng/mL.

Exercise testing

Treadmill ET limited by symptoms was performed using the standard Bruce protocol with a commercially available computerized electrocardiography stress system. In all patients drug regimens prescribed by the clinical cardiologist responsible were maintained. Criteria for terminating ET were: *a*) exhaustion of physical capacity to achieve the age-predicted maximum heart rate (220-age); *b*) systolic blood pressure depression (SBP) or a hypertensive response (SBP ≥ 230 mm Hg or diastolic blood pressure [DBP] ≥ 130 mm Hg); *c*) dizziness, intense dyspnea, severe claudication or evidence of peripheral hypoperfusion; *d*) ventricular arrhythmias (frequent ventricular extrasystoles, polymorphic complexes or 3-beat runs); *e*) technical difficulty monitoring ECG or blood pressure; *f*) intense angina pectoris; *g*) ST-segment depression ≥ 3 mm; and *h*) at the patient's request.

Positive ET criteria were: *a*) presence of angina (positive clinical test), or *b*) ≥ 1 mm ST-segment depression or ≥ 1 mm ST-segment elevation in leads without pathologic Q-wave (not in lead aVR), measured at 80 ms from J-point (positive electric test). We accepted computerized electrocardiography stress system readings of ST-segment deviation confirmed by an experienced cardiologist.

Follow-Up of Patients

Telephone interview follow-up was conducted by medical staff for all patients at ≥ 6 months after the inclusion of the last patient. Mean follow-up was 436 days (median, 479 days); lower quartile 342 and top quartile 540 days. The single combined endpoint was defined as time to cardiac death or first new hospitalization for nonfatal AMI or unstable angina. Definite or possible adverse events were confirmed from in-hospital clinical reports or clinical history review except in the case of 1 (sudden, out-of-hospital) death. Myocardial infarction was defined as typical elevation of biochemical markers of myocardial necrosis (MB isoenzyme of creatin kinase [CK-MB] and/or troponin) and at least one of the following: symptoms of acute myocardial ischemia, development of pathologic Q-waves in the ECG and/or ischemic changes of ST-segment or T-wave, following myocardial revascularization. Unstable angina was recorded when clinical signs and symptoms coincided with at least one of the following: ischemic ECG changes, known coronary heart disease, or positive noninvasive exploration.

Statistical Analysis

Quantitative variables are expressed as mean $\pm$ standard deviation. Groups of continuous variables were compared using Student's *t* test for unrelated samples or the Mann-Whitney U test for data that did not present a normal distribution. Qualitative variables are expressed as percentages and bivariate comparison was by χ^2 and the Fisher test when necessary. Multivariate analysis of event-free survival was by Cox logistic regression. Values of $P < .05$ were considered significant. All calculations were performed with SPSS (SPSS Inc., Chicago, Illinois).

RESULTS

Characteristics of the Population

Distributions of principal demographic characteristics, cardiovascular risk factors and personal antecedents are in Table 1. Echocardiograms were performed on 278 patients (62%). We observed alterations in left ventricular regional contractility in 52 patients (18.7%),

all of whom had previous myocardial infarction but in none was this associated with LVEF $\leq 40\%$.

Results of Exercise Testing and In-Hospital Management

At ET, 155 patients (34.5%) were receiving beta-blockers. Hemodynamic characteristics and ET results appear in Table 2. Exercise testing was positive in 79 patients (17.59%): clinically positive in 11, electrically positive in 38, and clinically and electrically positive in 30. Exercise testing was negative in 370 patients: 195 (52.7%) failed to achieve 85% of the theoretical age-predicted maximum heart rate.

During hospitalization, coronary angiography was performed on 61 (77%) of the 79 patients with positive ET, 57 of whom had coronary heart disease (93%). Subsequently, 43 underwent revascularization procedures: 35 percutaneous and 8 surgical. In contrast, coronary angiography was performed on only 32 patients (9%) with negative ET and coronary heart disease was found in 24 (75%), 17 of whom underwent revascularization procedures: 15 percutaneous and 2 surgical.

Evolution

During follow-up, 44 patients (10%) presented events: cardiac death, 2; nonfatal myocardial infarction, 13; unstable angina, 30. One patient had 2 events: rehospitalization for unstable angina and subsequently for nonfatal myocardial infarction. Revascularization procedures were performed on 24 patients (percutaneous, 20; surgical, 4). More than half of the events ($n=26$; 59%) occurred during the first 6 months. The greater concentration of events ($n=7$; 16%) was in the first month. Adverse events took place following revascularization in 1 patient with negative ET and 11 patients with positive ET. The distribution of clinical variables and of ET in patients with and without adverse events is in Table 3. Exercise testing was negative in 16 of the 44 patients with events (36%) and in 179 of the 405 patients without events (44%; $P=NS$) who failed to achieve 85% of the age-predicted maximum heart rate. There were no significant differences between the groups with and without adverse events with regard to proportions of patients receiving angiotensin converting enzyme inhibitors (27% vs 26%; $P=NS$), antiplatelet drugs (64% vs 58%; $P=NS$), and statins (39% vs 33%; $P=NS$), respectively.

Variables Predicting Evolution

The Cox model included those variables that had proved significant in bivariate analysis: gender, age ≥ 65 , diabetes, previous infarction, typical pain, positive ET,

TABLE 1. Clinical Characteristics*

	N=449 n (%)
Men	312 (69)
Age ≥ 65	181 (40)
Smoking	143 (32)
AHT	222 (49)
Hypercholesterolemia	235 (52)
Diabetes	126 (28)
Family history	18 (4)
Previous infarction	83 (18)
Previous revascularization	64 (14)
PAD or CVD	30 (7)
Antiplatelet agents	104 (23)
Typical pain	307 (68)

*Antiplatelet agents indicates treatment with antiplatelet drugs during the week prior to hospitalization; PAD, peripheral arterial disease; CVD, cerebral vascular disease; AHT, arterial hypertension.

TABLE 2. Characteristics of Exercise Testing*

	N=449 Mean $\pm$ SD
Duration, min	7.5 $\pm$ 3
MHR	128 $\pm$ 23
% TMHR	80 $\pm$ 13
SBP	172 $\pm$ 28
Double product (HR $\times$ BP)	22 314 $\pm$ 14 100
Duke score	5.37 $\pm$ 5.6

*SD indicates standard deviation; HR, heart rate; MHR, maximum heart rate; TMHR, theoretical age-predicted maximum heart rate by; BP, blood pressure; SBP, systolic blood pressure.

and maximum double product. Four clinical variables: age ≥ 65 , diabetes, previous infarction, and typical pain, were associated, together with a positive ET result, with greater incidence of events (Table 4). The Cox regression model equation is:

$$h(t;X) = h_0(t) \cdot \exp [0.35 \times \text{man} + 0.75 \times \text{age} \geq 65 + 0.78 \times \text{diabetes} + 0.90 \times \text{previous AMI} + 1.79 \times \text{typical pain} + (-0.0003 \times \text{double product}) + 1.6 \times \text{Positive ET}]$$

Adverse events occurred following revascularization, so analysis was repeated after adjusting patient data at the time of revascularization. In this second analysis, the 5 variables (age ≥ 65 , $P=.007$; diabetes, $P=.03$; previous infarction, $P=.03$; typical pain, $P=.02$, and positive ET, $P=.01$) maintained their predictive value. Of 79 patients with positive ET, 23 had an event (positive predictive value 29.11%); 349 of the 370 patients with negative ET had no event (negative predictive value 94.32%). Table 5 shows incidence of events by number of clinical variables present (age ≥ 65 , diabetes, previous infarction, typical chest pain), and ET results. Patients were grouped by number of clinical variables presented: <2 ,

TABLE 3. Clinical Characteristics and Characteristics of Exercise Testing in Patients With and Without Events. Bivariate Analysis*

	With Events (n=44), n (%)	Without Events (n=405) n (%)	P
Men	37 (84)	275 (68)	.026
Age ≥65	27 (61)	154 (38)	.0027
Smoking	15 (34)	128 (32)	.73
AHT	25 (57)	197 (49)	.3
Hypercholesterolemia	29 (66)	206 (51)	.057
Diabetes	22 (50)	104 (26)	.0006
Family history	2 (5)	16 (4)	.84
Previous infarction	19 (43)	64 (16)	<.0001
Previous revascularization	8 (18)	56 (14)	.43
PAD or CVD	5 (11)	25 (6)	.19
Antiplatelet agents	14 (32)	90 (22)	.15
Typical pain	42 (95)	265 (65)	<.0001
Double product	19 746±6100	22 593±6303	.0045
Positive ET	23 (52)	56 (14)	<.0001

*Antiplatelet agents indicates treatment with antiplatelet drugs during the week prior to hospitalization; PAD, peripheral arterial disease; CVD, cerebral vascular disease; AHT, arterial hypertension; ET, exercise testing.

TABLE 4. Predictors of Events. Multivariate Analysis*

	HR (95% CI)	P
Man	1.42 (0.6-3.3)	.41
Age ≥65	2.12 (1.13-3.96)	.01
Diabetes	2.18 (1.2-3.9)	.01
Previous AMI	2.47 (1.3-4.6)	.005
Typical pain	5.8 (1.6-23.2)	.01
Double product	1.12 (0.9-1.3)	.24
Positive ET	4.9 (2.6-9.1)	.00001

*HR indicates hazard ratio; AMI, acute myocardial infarction; CI, confidence interval; ET, exercise testing.

2, or >2. In these groups, positive predictive value of ET was 8.6%, 28.5%, and 52.3% and negative predictive value was 99.5%, 91.7%, and 79.6%, respectively (Figure 2).

DISCUSSION

Prognosis of Low-Risk NSTEMI ACS

The prognosis of patients with suspected NSTEMI ACS considered low-risk is not homogeneous in the series reported. Patients with ACS as defined, such as those included in registers or clinical trials, present a noteworthy rate of events. For example, the TACTICS-TIMI trial¹⁸ reported a 15.7% incidence of death, infarction or rehospitalization for ACS at 6-month follow-up¹⁰ in patients with TnT<0.01; a FRISC II sub-study reported that patients without ST-segment depression in the ECG and TnT<0.03 had a 7.45% incidence of death or AMI at 1 year¹¹; the TIMI III register reports a 19.5% rate of death, AMI or recurrent ischemia at 1 year follow-up¹² among patients considered low-risk due to their 0-2 TIMI risk score. In contrast, the rate of complications described in series enrolling patients with low-risk chest pain evaluated in chest pain units is significantly lower.³⁻⁸

Little, therefore, is known about the prognosis of patients with suspected NSTEMI ACS considered low risk after initial evaluation, and even this is contradictory. This may be due to the different clinical profiles of the populations studied arising from the fact that although many criteria indicating high-risk of early complication referred to in clinical practice guidelines are unequivocal, others are more or less controversial and, therefore, risk factors differ from one scientific society publication to another. This implies limitations in defining homogeneous groups of patients in which to determine prognosis, evaluate possible predictive factors and design appropriate management guidelines. The present study was designed with these limitations in mind.

Clinical Risk Factors

The proposed management of patients with suspected NSTEMI ACS considered low-risk is uniform and is based on noninvasive ischemia testing. This may underestimate the importance of the clinical context in which noninvasive test results have been

TABLE 5. Incidence of Events, According to Number of Clinical Risk Predictors and Exercise Testing Results*

Clinical Variables	n	Positive ET (n=79)		Negative ET (n=370)	
		Events (n=23)	Without Events (n=56)	Events (n=21)	Without Events (n=349)
0	57	1 (1.7%)	0	0	56 (98.2%)
1	166	1 (0.6%)	21 (12.6%)	1 (0.6%)	143 (86.1%)
2	156	10 (6.4%)	25 (16%)	10 (6.4%)	111 (71.1%)
3	61	8 (13.1%)	8 (13.1%)	8 (13.1%)	37 (60.6%)
4	9	3 (33.3%)	2 (22.2%)	2 (22.2%)	2 (22.2%)

*Clinical variables: age ≥65, diabetes, previous infarction, and typical nature of chest pain. ET indicates exercise testing.

interpreted. We hypothesized that in low-risk patients hospitalized with suspected NSTEMI ACS, ET results and clinical evaluation contribute to prognosis stratification. We thought it opportune to include the variable nature of chest pain as principal indicator of probability of myocardial ischemia secondary to coronary heart disease. Our study confirmed its independent prognostic value, together with that of 3 other clinical variables (age, diabetes, and previous infarction),^{13,14} already known to be of use in patients with NSTEMI ACS.

Predictive Value of Exercise Testing

Having demonstrated the usefulness of clinical evaluation and ET results, patients were allocated to 1 of 3 groups depending on whether they had presented <2, 2, or >2 of the clinical variables that in the Cox analysis had proven significant, to illustrate simply and graphically (Figure 2) how ET predictive value is modified by the number of variables present. The result is not surprising, since the clinical variables associate with greater probability of presenting coronary heart disease and greater risk. Bayes theorem states that the greater the probability of illness or adverse events prior to ET, the greater the positive predictive value and the lower the negative predictive value.¹⁵ The importance of clinical diagnosis in the evaluation of ET results has already been demonstrated. Thus, it has been proved that in patients with low-risk ET, the evolution of those who present recently stabilized unstable angina is not always favorable¹⁶ and, in any case, is worse than that of patients with chronic stable angina.¹⁷

Comparison With Previous Studies

Several Spanish research teams have recently reported series of patients attending emergency services for chest pain of possible coronary origin who, following initial observation, were considered low-risk. Pastor Torres et al¹⁸ described a series of 179 patients undergoing early ET in 27 of whom results were positive (15%). At 1-year follow-up, 89% of the patients with negative ET were event-free. Events (rehospitalization for unstable angina) were recorded in 22% of the patients with positive ET. Age, presence of coronary risk factors and positive ET predicted unfavorable evolution.

Zarauza et al¹⁹ described a series of 147 patients who underwent early ET with positive results in 50 (34%). Of the 147 patients, 125 were discharged after negative, inconclusive or positive-at-high-load ET results. Incidence of events (death, AMI, rehospitalization for unstable angina, or revascularization) in this group was 6.4%, somewhat lower than the present study. The lower incidence of events reported by Zarauza et al¹⁹ may well

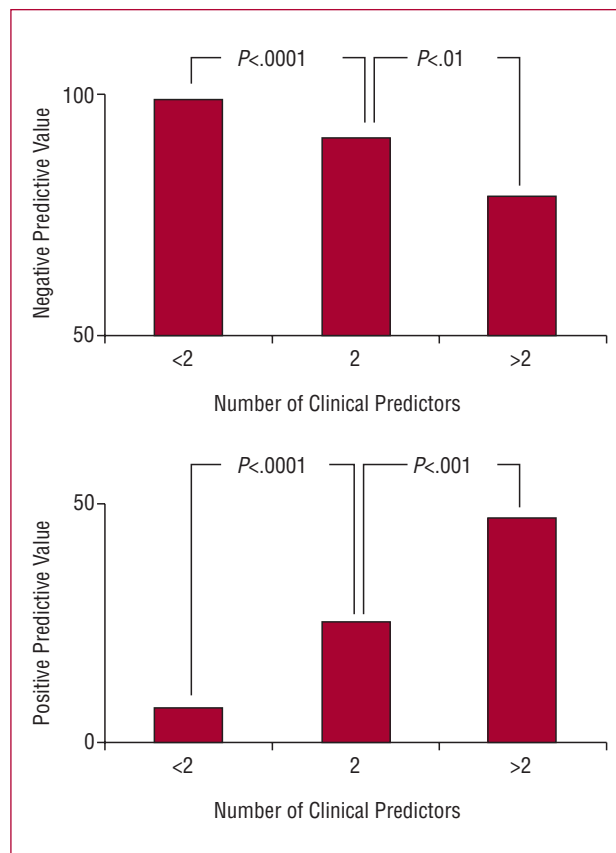


Figure 2. Above: negative predictive value of exercise testing, according to the number of clinical variables (age ≥ 65 , diabetes, previous acute myocardial infarction, typical nature of chest pain). Below: positive predictive value of exercise testing, according to the number of clinical variables present

be due to the fact their follow-up excluded low-risk patients indicated for standard hospitalization (most of whom had positive ET). This study did not analyze predictive factors.

Sanchís et al²⁰ reported an interesting series of 609 consecutive patients attended in emergency service for chest pain and with normal levels of troponin. Early ET was undergone by 283 patients considered low-risk and results were positive in 60 (21%). None of the patients with negative ET had had a serious event (cardiac death or AMI) at 6-month follow-up. Incidence of severe events in the remainder was 6.9%. In consonance with our results, nature of chest pain and diabetes were independent predictors of adverse events, together with variables such as previous coronary surgery and ST-segment depression. The reduced size of the sample prevented Sanchís et al from analyzing the subgroup of patients undergoing ET and incorporating the variables derived from this in the Cox regression model.

Finally, Martínez Sellés et al²¹ reported a study of a population of 365 patients hospitalized in a chest pain

unit. Four clinical variables (typical pain, use of aspirin, diabetes and age >64) associated independently with presence of coronary heart disease. With these variables, they constructed a risk index associated with the appearance of ACS during follow-up. Three of the predictive variables coincide with the present study (typical pain, diabetes, and age >64 years).

Clinical Implications

The management of patients with chest pain, without high-risk criteria and undergoing ET should be individualized with reference to the presence of clinical characteristics such as nature of chest pain, age, diabetes, or antecedents of infarction. Patients with low clinical risk and negative ET have an excellent prognosis, which does not justify aggressive management. When there is a discrepancy between clinical risk and ET results (low clinical risk and positive ET or high clinical risk and negative ET) the indication for coronary angiography should be on an individual basis and should not be conditioned exclusively to ET results. In this group of patients, we need to further our knowledge of factors such as the additional prognostic value of other complementary noninvasive tests or the potential benefit of aggressive management.

CONCLUSIONS

Currently, patients hospitalized for chest pain with suspected NSTEMI ACS, who after an initial period of observation do not show high-risk criteria, present a noteworthy incidence of events following discharge. Clinical evaluation contributes, together with ET results, to the stratification of prognosis in these patients.

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