

ORIGINAL ARTICLES

Oxidized LDL, Lipoprotein (a), and Other Emergent Risk Factors in Acute Myocardial Infarction (FORTIAM Study)

Miquel Gómez,^a Vicente Valle,^b Fernando Arós,^c Ginés Sanz,^d Joan Sala,^e Miquel Fiol,^f Jordi Bruguera,^a Roberto Elosua,^g Lluís Molina,^a Helena Martí,^g M. Isabel Covas,^h Andrés Rodríguez-Llorián,ⁱ Montserrat Fitó,^h Miguel A. Suárez-Pinilla,ⁱ Rocío Amezaga,^j and Jaume Marrugat^g, on behalf of the FORTIAM group of researchers

^aServicio de Cardiología, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain

^bServicio de Cardiología, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

^cServicio de Cardiología, Hospital Txagorritxu, Vitoria, Spain

^dServicio de Cardiología, Hospital Clínic y CNIC, Barcelona, Spain

^eServicio de Cardiología, Hospital Josep Trueta, Girona, Spain

^fServicio de Cardiología, Hospital Son Dureta, Palma de Mallorca, Spain

^gPrograma de Investigación en Procesos Inflamatorios y Cardiovasculares, Grupo de Epidemiología y Genética Cardiovascular, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain

^hPrograma de Investigación en Procesos Inflamatorios y Cardiovasculares, Grupo de Riesgo Cardiovascular y Nutrición, CIBER de Fisiopatología de Obesidad y Nutrición, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain

ⁱServicio de Cardiología, Hospital de Asturias, Oviedo, Asturias, Spain

^jServicio de Cardiología, Hospital Clínico Universitario, Zaragoza, Spain

Introduction and objectives. To determine the prevalence of acute myocardial infarction (AMI) without classical risk factors, and to ascertain whether affected patients exhibit a higher prevalence of emergent risk factors and whether the presence of specific emergent risk factors influence prognosis at 6 months.

Methods. The FORTIAM (Factores Ocultos de Riesgo Tras un Infarto Agudo de Miocardio) study is a multicenter cohort study that includes 1371 AMI patients who were admitted within 24 hours of symptom onset. Strict definitions were used for classical risk factors and the concentrations of the following markers were determined: lipoprotein (a) [Lp(a)], oxidized low-density lipoprotein (oxLDL), high-sensitivity C-reactive protein, fibrinogen, homocysteine, and antibody to *Chlamydia*. The end-points observed during the 6-month follow-up were death, angina, and re-infarction.

Results. The prevalence of AMI without classical risk factors was 8.0%. The absence of classical risk factors

did not affect the 6-month prognosis. The only emergent risk factors independently associated with a poorer prognosis were the Lp(a) and oxLDL concentrations. Cut-points were determined using smoothing splines: 60 mg/dL for Lp(a) and 74 U/L for oxLDL. The associated hazard ratios, adjusted for age, sex, and classical risk factors, were 1.40 (95% confidence interval, 1.06-1.84) and 1.48 (95% confidence interval, 1.06-2.06), respectively.

Conclusions. The proportion of AMI patients without classical risk factors was low and their prognosis was similar to that in other AMI patients. Both oxLDL and Lp(a) concentrations were independently associated with a poorer 6-month prognosis, irrespective of the presence of classical risk factors.

Key words: Prognosis. Myocardial infarction. Lipoproteins. LDL cholesterol.

LDL oxidada, lipoproteína(a) y otros factores de riesgo emergentes en el infarto agudo de miocardio (estudio FORTIAM)

Introducción y objetivos. Determinar la prevalencia de pacientes que sufren un infarto agudo de miocardio (IAM) sin factores de riesgo (FR) clásicos, si presentan una mayor prevalencia de FR emergentes y si algún FR emergente modifica el pronóstico a los 6 meses.

Métodos. FORTIAM (Factores Ocultos de Riesgo Tras un Infarto Agudo de Miocardio) es un estudio multicéntrico de cohortes de 1.371 pacientes que sufrieron un IAM e ingresaron en las primeras 24 h. Se utilizaron definiciones estrictas para los FR clásicos y se determinaron: lipoproteína (a) [Lp(a)], lipoproteína de baja densidad oxidada (LDLox), proteína C reactiva ultrasensible, fibrinógeno, homocisteína y anticuerpos anticlamidia. Los

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Correspondence: Dr. J. Marrugat.
REPICA-ULEC-EGEC-IMIM.
Dr. Aiguader, 88. 08003 Barcelona. España.
E-mail: jmarrugat@imim.es

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acontecimientos de interés a los 6 meses fueron: muerte, angina o reIAM.

Resultados. La prevalencia de pacientes con IAM sin FR clásicos fue del 8%. La ausencia de FR clásicos no afectó al pronóstico a los 6 meses. Lp(a) y LDLox fueron los únicos FR emergentes que de forma independiente se asociaron a un peor pronóstico. Puntos de corte (suavización con *splines*): 60 mg/dl para Lp(a) y 74 U/l para LDLox. La *hazard ratio* ajustada por edad, sexo y FR clásicos, 1,40 (intervalo de confianza [IC] del 95%, 1,06-1,84) y 1,48 (IC del 95%, 1,06-2,06), respectivamente.

Conclusiones. La proporción de pacientes con un IAM sin FR clásicos es baja y su pronóstico es similar al resto de pacientes con IAM. LDLox y Lp(a) se asociaron a un peor pronóstico a los 6 meses de forma independientemente de los FR clásicos.

Palabras clave: Pronóstico. Infarto de miocardio. Lipoproteínas. Colesterol ligado a las LDL

ABBREVIATIONS

AMI: acute myocardial infarction
CI: confidence interval
CRP: C-reactive protein
LDL: low-density lipoprotein
Lp(a): lipoprotein (a)
oxLDL: oxidized LDL
RF: risk factors

INTRODUCTION

Although the number of patients who suffer an acute myocardial infarction (AMI) without having a previous history of classical risk factors (RF) is low, these patients are an interesting group for studying other determinants of coronary heart disease. A meta-analysis including 14 clinical studies found that 15.4% of women and 19.4% of men with coronary heart disease did not have any of the classical RF.^{1,2} Likewise, the IBERICA registry showed that 15% of the patients between 25 and 74 years of age did not have these factors, and furthermore, these patients might prove to have a poorer prognosis.³ Data such as those presented in the INTERHEART study have established the crucial role of classical RF in the development of heart disease, independently of geographical region⁴; even so, the collection of data obtained from the clinical history reported by the patient in the acute phase of AMI is not always sufficiently precise.

In recent years several emergent RF have been proposed as markers of atherosclerosis and the onset

of clinical events, such as C-reactive protein (CRP), lipoprotein (a) [Lp(a)], fibrinogen, homocysteine, or *Chlamydia pneumoniae*, among others, often with controversial results.⁵⁻⁷ More recently, oxidized low-density lipoprotein (oxLDL), which is directly involved in the formation of atheromatous plaques, has been associated with the process of instability and extent of coronary atherosclerosis.⁸⁻¹¹ However, few clinical data exist that associate oxLDL with the prognosis after an acute coronary syndrome.¹²

The aims of the present study were to determine the prevalence of patients with AMI who did not have classical RF, analyze whether they present a higher prevalence of emergent RF, ascertain whether a specific emergent RF adds prognostic information for patients who suffer an AMI, and if so, establish cut-points.

METHODS

Study Design

FORTIAM (Factores Ocultos de Riesgo Tras un Infarto Agudo de Miocardio) is a multicenter cohort study with a 6-month follow-up. The patients were recruited from the coronary care units of 15 Spanish hospitals.

The study included a total of 1371 patients between the ages of 25 and 74 years who were admitted to a coronary care unit within 24 hours of the onset of symptoms of a first AMI. For inclusion, AMI was defined according to the criteria jointly accepted by the European and Spanish Cardiology Societies (ESC-ACC clinical guidelines).¹³ Only patients who survived the first 24 hours after admission were included. Clinical management was carried out at the discretion of each center. With the objective of specifically determining the prevalence of AMI without classical RF, in 6 centers the inclusion was strictly consecutive (n=949). In the remaining coronary care units inclusion was done randomly to assure a sufficient sample size.

Definition of Classical RF

The following standardized definitions of classical RF were applied: dyslipidemia (a diagnosis or previous lipid-lowering treatment, low-density lipoprotein cholesterol [LDL-C] >160 mg/dL, high-density lipoprotein cholesterol [HDL-C] <35 mg/dL in men or <45 mg/dL in women); diabetes mellitus (a diagnosis or previous treatment, glycemia during admission \geq 200 mg/dL, 2 fasting glycemia measurements during hospitalization >125 mg/dL); hypertension (a diagnosis or previous hypotensive drug treatment or systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mm Hg, measured

48 h before discharge in a stable hemodynamic state); and active smoker (a mean of 1 or more cigarettes per day); or ex-smoker for less than 1 year. Data were collected within 24 h of admission.

Laboratory Analysis

Blood samples were obtained within 24 h of admission and were centralized in the same laboratory. Plasma fibrinogen levels were measured using the coagulometric Clauss assay (Izasa, Barcelona, Spain). Serum glucose, total cholesterol, HDL-C, and triglycerides were measured using enzymatic methods (Roche, Basle, Switzerland). LDL-C was calculated using the Friedewald formula when triglycerides were <300 mg/dL. Serum Lp(a) was analyzed using immunoturbidimetry. Determination of oxLDL in EDTA-plasma was by sandwich ELISA (murine monoclonal antibody mAB-4E6—capture—and peroxidase-conjugated antibody against oxidized apolipoprotein B in the solid-phase [Mercodia, Uppsala, Sweden]). High sensitivity CRP in serum was determined using immunoturbidimetry (Horiba ABX, Montpellier, France). The serum homocysteine concentration was obtained using fluorescence polarization immunoanalysis (Abbott, IL). Serum IgG anti-Chlamydia pneumoniae antibodies were measured using ELISA (Vircell, Granada, Spain).

Measurements

Physical activity: measured with the Minnesota Leisure Time Physical Activity questionnaire, validated for use in both sexes in Spain.^{14,15} Waist circumference was measured at the midpoint between the last rib and the iliac crest. The height and weight were measured with subjects wearing only undergarments. The blood pressure was obtained using a calibrated sphygmomanometer, after 10 min resting in a seated position. The mean of 2 measurements was calculated. A coronary angiography was performed in a randomized sample of 435 patients to determine the number of vessels with angiographically significant lesions (>70% stenosis). The ejection fraction (EF) was measured indiscriminately using either echocardiography, catheterization or isotopic ventriculography.

Follow-up and Endpoints

The combined endpoint included cardiovascular death, unstable angina, or infarction at the 6-month follow-up. Cardiovascular death was defined as unequivocal cardiovascular death according to medical registry or autopsy. Unstable angina included post-infarction angina (first 28 days after

infarction) or readmission for unstable angina (need for hospitalization due to coronary pain with ischemic electrocardiographic changes without elevation of necrosis markers). Infarction was defined as readmission for coronary pain accompanied by an elevation in myocardial necrosis markers or reinfarction during the acute phase (28 days); periprocedural revascularization AMIs were not included. Clinical events after discharge were recorded in telephone interviews or personally and, in both the hospitalization phase as well as after discharge, were verified from the clinical registries. The study was approved by an ethics committee and all patients signed an informed consent.

Statistical Analysis

The Student *t* test or the Mann-Whitney *U* test was used for comparison of means between groups with and without RF and with and without each emergent RF, and the χ^2 test for categorical variables. To analyze the relationship between the emergent RF and the event of interest 2 approaches were used: categorizing the emergent RF in tertiles and smoothing using 3-node splines in a Cox linear regression model to define the best cut-points. All the analyses were adjusted for possible confounding variables. The effect of each emergent RF was adjusted for classical RF (hypertension, diabetes, dyslipidemia, and smoking). The oxLDL was also adjusted for the use of statins. An adjustment was made for each hospital to confirm the consistency of the observed effects. The relationship between oxLDL and total LDL and between Lp(a) and oxLDL was studied using bivariate analysis, as was its correlation. The analyses were performed using the statistical package R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

The prevalence of patients who suffered a first AMI with no classical RF was 13.2% when just the clinical history as reported by the patient was taken into account and 8.0% (95% confidence interval [CI], 6.3-9.7) when an active measurement of classical RF was made. Of all the patients, 981 (77.1%) had an ST-elevation AMI and 293 (22.9%), a non ST-elevation AMI. Of the patients with a non ST-elevation AMI, 44.0% underwent coronary angiography, and 30.0% of these underwent revascularization. Of the patients with an ST-elevation AMI, 643 (65.5%) received fibrinolysis; 182 (18.5%) primary angioplasty; and 156 (16.0%) did not receive reperfusion.

Of the whole sample of 1371 patients, 126 had a first AMI with no classical RF. Of all the patients,

TABLE 1. Clinical Characteristics of Patients Admitted to Hospital for a First Acute Myocardial Infarction According to the Presence of at Least 1 Classical Risk Factor

	With N Classical RF (n=26)	With Classical RF (n=1245)	P
Age, mean (SD), y	61.3 (9.9)	57.0 (10.7)	<.001
Age >65 years, %	45.2	27.2	<.001
Women, %	16.7	16.1	.886
BMI, kg/m ²	26.9 (3.7)	27.5 (4.3)	.136
Obesity (BMI>30), %	14.8	18.8	.314
Waist (men, >102 cm; women, >88 cm), %	7.2	13.8	.123
Glycemia on admission, mg/dL	119 (31)	139 (61)	<.001
Triglycerides, mg/dL	119 (59)	162 (101)	<.001
Total cholesterol, mg/dL	196 (36)	212 (44)	<.001
LDL-C, mg/dL	128 (31)	139 (39)	.003
HDL-C, mg/dL	45 (12)	41 (12)	.002
SBP, mm Hg	110 (14)	113 (16)	.043
DBP, mm Hg	65 (10)	67 (10)	.163
History of dyslipidemia, %	0	49.0	
History of diabetes, %	0	23.4	
History of hypertension, %	0	48.0	
History of smoking, %	0	62.1	
Physical activity, median (interquartile range), kcal/day	203 (68-460)	210 (45-436)	.874
Clinical characteristics/management			
Killip III-IV on admission, %	1.7	3.2	.575
EF >45%, %	77.7	80.5	.4
Treatments on discharge			
Antiplatelet drugs, %	96.7	96.9	.787
Beta-blockers, %	71.9	73.6	.684
ACE inhibitors/ARA II, %	47.2	48.3	.801
Statins, %	57.7	74.4	<.001

ACE indicates angiotensin-converting enzyme; ARA II, angiotensin II receptor antagonist; BMI, body mass index; DBP, diastolic blood pressure; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factors; SBP, systolic blood pressure.

21.8% had a cardiovascular event in the 6-month follow-up period (18.8% of those who did not present classical RF, with no statistically significant differences [NS]). Mortality was 3.1%, a new AMI in 4.3%, and unstable angina in 14.4%. Table 1 shows the characteristics and the classical RF profile in the patients who had at least 1 classical RF. The patients with no classical RF were a mean of 4.3 years older. Smoking was the most frequent classical RF noted, followed by hypercholesterolemia, hypertension, and diabetes. The clinical characteristics, energy expenditure, and EF were similar in both groups. The percentage of patients with main trunk or multivessel disease, in the patients who received coronary angiography, did not differ between the 2 groups: 43.2% of the patients with no classical RF as compared with 48.9% in the remainder (NS).

Emergent Risk Factors

Table 2 shows the characteristics of the emergent RF for the groups of patients with and without classical RF. Of note was the high percentage of

positivity for *anti-Chlamydia*, with no significant differences between groups. Nor did the mean values of Lp(a), fibrinogen, homocysteine, or CRP differ between groups. The oxLDL values were seen to be higher in the group of patients who presented at least 1 classical RF. The AMI patients with no classical RF did not present more emergent RF.

Six-Month Follow-up

Follow-up was completed in 93% of the patients. The 6-month prognosis in patients with and without classical RF was similar (Table 3). The patients in the group with events during the follow-up were somewhat older and included more women. Low systolic and diastolic blood pressures on admission (greater hemodynamic instability), as well as a Killip III-IV were associated with a worse prognosis. The EF and the proportion of patients with multivessel or main trunk disease (in the subgroup who underwent angiography) were marginally superior in the group that suffered an event (51.5% as opposed to 47.1%; $P=.285$). The prevalence of classical RF was similar

TABLE 2. Emergent Risk Factors and Cardiovascular Events According to the Presence or Absence of Classical Risk Factors

	Emergent RF	With N Classical RF (n=126)	With Classical RF (n=1245)	P
oxLDL, U/L	<48.1	45.3%	32.1%	.01
	48.1-68.6	28.2%	34.0%	
	>68.6	26.5%	33.9%	
Lp(a), mg/dL	10.1-14.6	41.5%	32.3%	.076
	14.6-47.7	29.3%	33.8%	
	>47.7	29.3%	33.8%	
hsCRP, mg/dL	<0.3	38.2%	32.9%	.494
	0.3-0.8	28.5%	33.7%	
	>0.8	33.3%	33.4%	
Anti-Chlamydia, % positivity		83.8%	83.9%	.971
Fibrinogen, mg/dL	<275	35.4%	33.3%	.453
	275-365	35.4%	32.9%	
	>365	29.3%	33.8%	
Homocysteine, μ mol/L	<9.2	35.0%	33.5%	.698
	9.2-12.4	33.3%	33.3%	
	>12.4	31.6%	33.2%	
Cardiovascular events at 28 days				
Death		0	2.2%	.167
Postinfarction angina		12.1%	11.3%	.781
Reinfarction		0.8%	2.2%	.507
Cardiovascular events from 28 days to 6 months				
Death		0	1.3%	.216
Readmission for unstable angina		7.1%	5.6%	.551
Readmission for AMI		1.5%	2.3%	.999
Any cardiovascular event		18.8%	22.1%	.408

AMI indicates acute myocardial infarction; *anti-Chlamydia*, antibodies against *Chlamydia pneumoniae*; Lp(a), lipoprotein(a); oxLDL, oxidized low-density lipoprotein; RF, risk factors; hsCRP, high-sensitivity C-reactive protein.

in both groups. No differences were observed in global or abdominal obesity. In relation to the emergent RF studied, higher levels of Lp(a) were found in the patients who suffered an event during the follow-up (Table 3).

Emergent RF and 6-Month Prognosis

Table 4 presents the hazard ratios (HR) of emergent RF in relation to the 6-month prognosis, divided into tertiles in a Cox model adjusted for classical RF, age, sex (and use of statins for oxLDL, which 14.7% of the patients received). A second model included the hospital as an adjustment variable and a third model analyzed the relationship between oxLDL and LDL, as well as Lp(a) and oxLDL.

Concerning the Lp(a) and oxLDL, the patients in the top tertile had an increased risk of developing events at 6 months. No significant differences were observed in the remaining emergent RF analyzed.

The association between CRP, Lp(a), oxLDL, and homocysteine with the combined end-point of cardiovascular morbidity and mortality is shown in Figure. Similar to the relationship seen in the tertile analysis of Lp(a) and oxLDL (Table 4),

the values of the top tertile were associated with higher cardiovascular morbidity and mortality. The optimum cut-points were established using smoothing spline analysis: 60 mg/dL for Lp(a) and 74 U/L for oxLDL (Figure). The HR for the patients with values above these cut-points were 1.40 (95% CI, 1.06-1.84) for Lp(a) and 1.48 (95% CI, 1.06-2.06) for oxLDL. The number of events for patients with Lp(a) values >60 mg/dL was 87 (26.9%) and 69 (23.5%) for oxLDL values >74 U/L.

The effect of oxLDL and Lp(a) was mutually independent ($R^2=0.001$; $P=.31$). OxLDL correlated considerably with total LDL ($R^2=0.103$; $P<.001$). Table 4 shows that, in spite of this, the magnitude of the effect of the variable oxLDL adjusted for LDL (model 3) did not change appreciably.

DISCUSSION

Prevalence of Classical and Emergent RF in the Patients Who Had an AMI

The results obtained in the present study show that the prevalence of patients with AMI but no classical RF out of all the AMI patients, when a

TABLE 3. Characteristics of Risk Factors According to Prognosis at 6 Months

	With no Events (n=1004)	With Events (n=270)	P
Age	57.3 (10.6)	59.1 (10.6)	.009
Women, %	15.3%	21.8%	.011
Patients with no classical RF	9.8%	8.1%	.409
BMI, kg/m ²	27.5 (4.0)	27.5 (5.0)	.877
Obesity (BMI>30)	22.9%	23.2%	.919
Waist (men >102 cm; women >88 cm)	40.5%	42.9%	.578
Glycemia on admission, mg/dL	137 (59)	139 (59)	.674
Triglycerides, mg/dL	160 (100)	148 (83)	.090
Total cholesterol, mg/dL	212 (45)	209 (43)	.414
LDL-C, mg/dL	138 (38)	137 (40)	.830
HDL-C, mg/dL	42 (12)	42 (12)	.698
SBP, mm Hg	114 (16)	111 (16)	.010
DBP, mm Hg	67 (11)	65 (10)	.003
History of dyslipidemia	45.1%	45.8%	.857
History of diabetes	21.8%	20.3%	.616
History of hypertension	43.1%	50.2%	.047
Smoking	56.2%	52.4%	.268
Physical activity, median (interquartile range), kcal/day	210 (54-452)	210 (46-436)	.608
Clinical characteristics and management			
Killip III-IV on admission	2.5%	5.2%	.023
EF >45%	81.4%	76.8%	.130
STEMI	78.4%	73.3%	.077
NSTEMI	21.6%	26.7%	.077
Emergent RF			
Oxidized LDL, U/L			
<48.1	33.7%	30.5%	.177
48.1-68.6	33.9%	32.2%	
>68.6	32.4%	37.3%	
Lipoprotein (a), mg/dL			
10.1-14.6	35.2%	26.8%	.007
14.6-47.7	33.7%	35%	
>47.7	31.2%	38.1%	
hsCRP, mg/dL			
<0.3	33.2%	35.3%	.953
0.3-0.8	33.9%	30.2%	
>0.8	32.9%	34.5%	
<i>Anti-Chlamydia</i> positivity, %	84.2%	83.0%	.641
Fibrinogen, mg/dL			
<275	34.7%	29.9%	.319
275-365	32.9%	35.8%	
>365	32.4%	34.2%	
Homocysteine, μ mol/L			
<9.2	33.4%	37.7%	.406
9.2-12.4	33.6%	29.8%	
>12.4	33%	32.5%	

BMI indicates body mass index; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non ST-elevation myocardial infarction; RF, risk factors; STEMI, ST-elevation myocardial infarction; hsCRP, high-sensitivity C-reactive protein.

strict measurement of these RF was performed in addition to asking about the history, was just 8%. The prevalence would have been 13.2% if only the history as reported by the patients were taken into account. This fact is surely a consequence of unawareness on the part of the patient or

because no accurate measurement of classical RF was carried out prior to admission. This value is similar to that found in a meta-analysis² and in the INTERHEART study,⁴ where between 15%-20% of the patients did not present classical RF. These data confirm that the true proportion of

TABLE 4. Distribution by Tertiles of Emergent Risk Factors. Hazard Ratio Adjusted for Morbidity and Mortality at 6 Months

		Model 1	Model 2	Model 3	Number of Events
Oxidized LDL, U/L	<48.1	1	1	1	74
	48.1-68.6	1.18 (0.78-1.79) (n=761)	1.18 (0.78-1.80) (n=761)	1.21 (0.78-1.86) (n=732)	77
	>68.6	1.61 (1.08-2.42) (n=761)	1.65 (1.09-2.49) (n=761)	1.66 (1.07-2.57) (n=732)	87
Lipoprotein (a), mg/dL	10.1-14.6	1	1	1	74
	14.6-47.7	1.32 (0.92-1.90) (n=987)	1.30 (0.90-1.88) (n=987)	1.48 (0.99-2.21) (n=874)	91
	>47.7	1.68 (1.18-2.39) (n=987)	1.65 (1.15-2.35) (n=987)	1.82 (1.23-2.68) (n=874)	100
hsCRP, mg/dL	<0.3	1	1		91
	0.3-0.8	0.91 (0.65-1.28) (n=983)	0.90 (0.64-1.27) (n=983)		80
	>0.8	0.98 (0.70-1.38) (n=983)	1.02 (0.72-1.44) (n=983)		92
Anti- <i>Chlamydia</i> (positivity)	No	1	1		43
	Yes	0.91 (0.61-1.36) (n=900)	0.91 (0.61-1.36) (n=900)		206
Homocysteine, μ mol/L	<9.2	1	1		96
	9.2-12.4	0.87 (0.62-1.21) (n=970)	0.86 (0.61-1.21) (n=970)		76
	>12.4	0.84 (0.60-1.19) (n=970)	0.85 (0.60-1.21) (n=970)		87

LDL indicates low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein. Model 1: adjusted for age, sex, history of hypercholesterolemia, history of diabetes, history of hypertension, and smoking. For oxLDL, also use of statins; model 2: adjusted for variables of model 1 and hospital (as random effects factor); model 3: oxLDL adjusted for LDL and lipoprotein (a) adjusted for oxLDL.

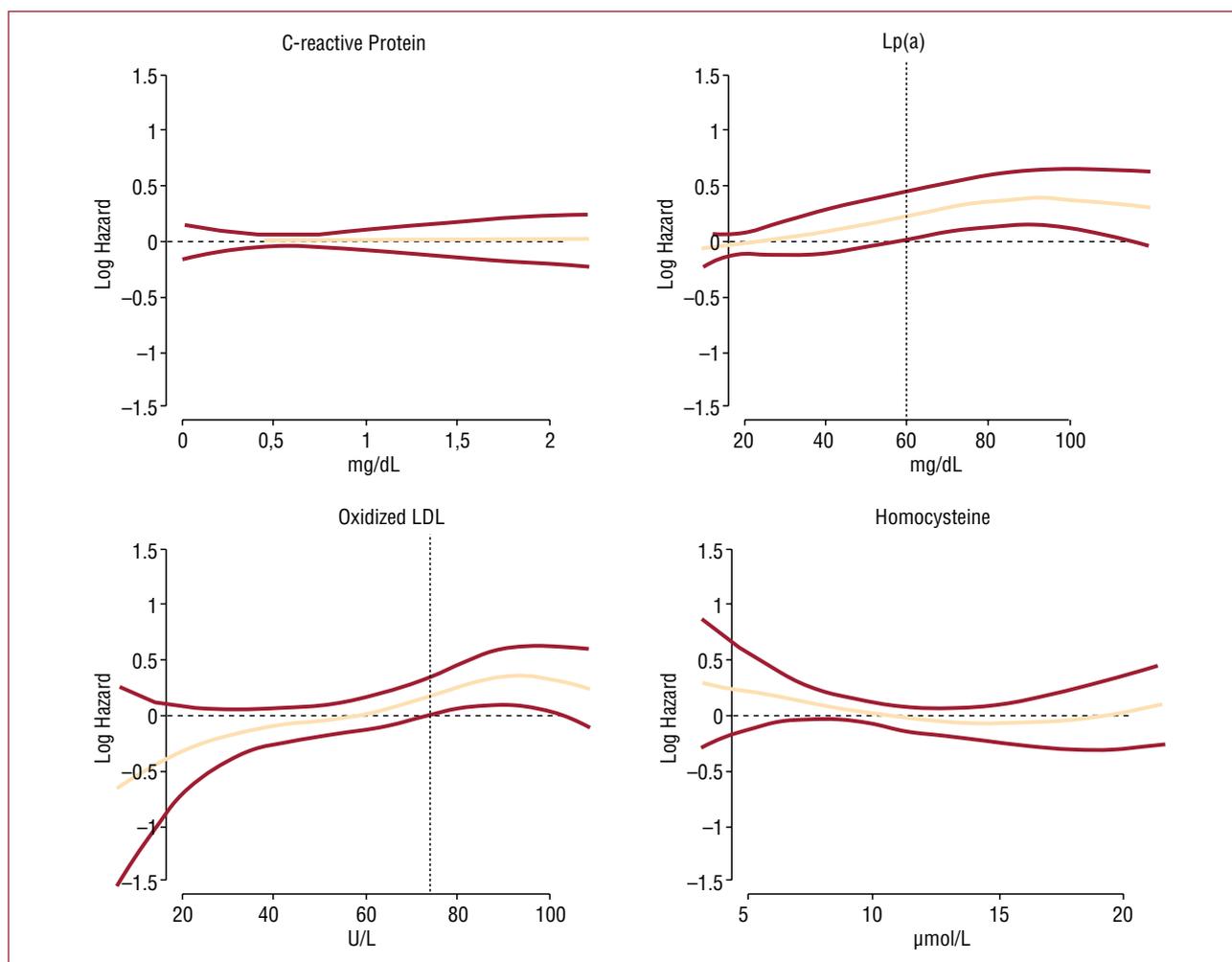


Figure 1. Relationship of emergent risk factors with prognosis at 6 months in patients with a first infarction. Spline analysis (adjusted for classical risk factors, age, and sex. OxLDL also adjusted for use of statins on admission).

AMI patients who lack classical RF is, in fact, low and somewhat lower than has been published in some studies.¹⁶ The patients with no classical RF were older, which is in agreement with previous studies where, in women over 75 years and in men over 65 years, the absence of classical RF was above 20%.¹ This fact can be explained by the decrease in the number of smokers in older patients. Indeed, in men who suffered an AMI who were under 55 years of age or in women under 65 years, an absence of classical RF was observed in only 10%.¹ Among the classical RF, smoking was the most common in young patients, as occurs in other studies where more than 70% of patients who suffered an AMI before reaching 45 years of age were active smokers.^{5,6}

In our study it was hypothesized that AMI patients with no classical RF could be more exposed to emergent RF, an aspect that has not been confirmed. The high proportion of positive *Chlamydia pneumoniae* serologies in both groups stands out, a fact also observed in other studies that identified the bacteria in atheromatous plaques.^{17,18} Even so, the usefulness of antibiotic treatment in slowing the progression of coronary heart disease has not been demonstrated.¹⁸ The association found with Lp(a) is in agreement with various publications, among these a meta-analysis where this relationship was established independently of other lipid fractions.^{6,19}

Emergent RF and 6-Month Prognosis

The prognostic value of emergent RF is generally controversial, though the value of oxLDL has recently taken on special interest.¹² In our study only oxLDL and Lp(a) were independently related to the 6-month prognosis in patients with a low-risk AMI. OxLDL is one of the factors required for the formation of coronary plaque through the action of macrophages in the subendothelial space.^{8,10} Various studies have shown that patients with ischemic cardiopathy present higher concentrations of oxLDL than healthy individuals,²⁰ and their serum concentrations are associated with extent and severity.^{11,21} In middle-aged men, oxLDL values have shown the capacity to predict cardiovascular events¹¹; nevertheless, until now no data were available on the prognostic value of measurement of this marker of oxidative stress in patients who have had an AMI.¹² The use of statins markedly decreases the concentration of phospholipids associated with apolipoprotein B-100 in patients with coronary heart disease²² and various studies suggest these drugs show antioxidant capacity.²³ For this reason, oxLDL levels were adjusted for lipid-lowering therapy in our Cox model.

Lp(a), due to its chemotactic and thrombolysis inhibitory activity in damaged vascular zones,²⁰ has been associated with the presence and extent of coronary heart disease¹⁰ and has demonstrated its power to predict cardiovascular events, especially in diabetic patients.²⁴

In our study, CRP concentrations were similar in patients who had an AMI with or without classical RF. Furthermore, we observed no added prognostic value for CRP after adjusting for classical RF. Some publications have reported an increase in risk associated with elevated CRP values,²⁵⁻²⁸ especially >3 mg/L. However, other studies found that CRP was a moderate or null risk predictor.²⁹ The lack of predictive power of CRP in our relatively low-risk cohort might have been influenced by the exclusion of patients who died within 24 h of admission.

Fibrinogen, a possible risk indicator both of coronary heart disease as well as cerebrovascular disease,⁵ was not elevated in our patients with no classical RF nor was a prognostic role seen. Patients treated with fibrinolytic drugs (in whom the fibrinogen concentration can drop abruptly) were excluded from the analysis. No differences were found in homocysteine concentrations between groups (with or without classical RF). Although studies exist that attribute a prognostic value due to their role in plaque activation, oxidative stress, endothelial dysfunction, hypercoagulability, or cell proliferation,⁷ no association with prognosis was observed in our study.

Limitations and Clinical Implications

The present study included patients who survived the first 24 h after infarction. This selection, necessary to obtain fasting blood samples as well as an active measurement of RF, might have influenced the evaluation of the prognostic capacity of RF. The selection of first infarctions reduces the possible confounding influence of a history of prior coronary events in the prognosis and in the management of RF. We highlight the fact that patients older than 74 years of age were excluded from our study, as their co-morbidity could lead to difficulties in the interpretation of oxidative stress.

Our results regarding oxLDL and Lp(a) may have clinical implications for the prognosis of patients who have had an AMI, particularly in those who do not present classical RF. Considering the pleiotropic effect as an antioxidant agent,²³ intensifying statin treatment may be justified in patients presenting an increase of one of these 2 risk indicators.

The absence of statistically significant differences in the 6-month prognosis with relation to EF and the extent of coronary heart disease reflects the low risk of our cohort of first AMI patients under

75 years of age and who survived the first 24 h. This meant that the number of events in each category was small, which could lead to extreme and unstable results. The fact that the study was centered on those patients who survived the first 24 h. from admission for an AMI means that the results cannot be extrapolated to all patients with an AMI, such as those that are not admitted to a hospital. The study did not include AMI related to percutaneous procedures.

The association of oxLDL and Lp(a) with the prognosis was significant and independent, as the analysis was adjusted for confounding variables; even so, the strength of this was modest (HR=1.40 and HR=1.48). Future studies should therefore attempt to replicate these findings.

CONCLUSIONS

The recording of RF in a patient with AMI based not only on the information provided by the patient but also on active measurement of the RF results in the proportion of AMI patients with no observed classical RF being, in reality, very low. These patients have a similar 6-month prognosis to those that do present classical RF. None of the emergent RF analyzed was more prevalent in the AMI patients with no classical RF, although the prognosis was worse in patients who presented with elevated levels of Lp(a) and oxLDL on hospital admission, independent of the presence of classical RF.

REFERENCES

- Khot U, Khot M, Bajzer C, Sapp S, Ohman E, Brener S, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290:898-904.
- Greenland P, Knoll M, Stamler J, Neaton J, Dyer A, Garside D, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290:891-7.
- Fiol M, Cabades A, Sala J, Marrugat J, Elosua R, Vega G, et al. Variabilidad en el manejo hospitalario del infarto agudo de miocardio en España. Estudio IBERICA (Investigación, Búsqueda Específica y Registro de Isquemia Coronaria Aguda). *Rev Esp Cardiol*. 2001;54:443-52.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study). *Lancet*. 2004;64:937-52.
- Hackam D, Anand S. Emerging risk factors for atherosclerotic vascular disease. *JAMA*. 2003;290:932-40.
- Rosengren A, Wilhelmsen L, Eriksson E, Risberg B. Lipoprotein (a) and coronary heart disease: a prospective case-control study in a general population sample of middle aged men. *BMJ*. 1990;301:1248-51.
- Braunwald E. Cardiovascular medicine at the turn of the millennium: triumphs, concerns and opportunities. *N Engl J Med*. 1997;337:1360-9.
- Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet*. 1994;344:793-5.
- Tsimikas S, Lau HK, Han KR, Shortal B, Miller ER, Segev A, et al. Percutaneous coronary intervention results in acute increases in oxidized phospholipids and lipoprotein(a): Short-term and long-term immunologic responses to oxidized low-density lipoprotein. *Circulation*. 2004;109:3164-70.
- Tsimikas S, Brilakis E, Miller E, McConnell J, Lennon R, Kornman K, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005;353:46-57.
- Meisinger C, Baumert J, Khuseynova N, Loewel H, Koenig W. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. *Circulation*. 2005;112:651-7.
- Armstrong E, Morrow D, Sabatine M. Inflammatory biomarkers in acute coronary syndromes. Part III. Biomarkers of oxidative stress and angiogenic growth factors. *Circulation*. 2006;113:289-92.
- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959-69.
- Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. *Am J Epidemiol*. 1994;139:1197-209.
- Elosua R, Garcia M, Aguilar A, Molina L, Covas M, Marrugat J. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish women. *MARATHOM Group. Med Sci Sports Exerc*. 2000;32:1431-7.
- Futerman LG, Lemberg L. Fifty percent of patients with coronary artery disease do not have any of the conventional risk factors. *Am J Crit Care*. 1998;7:240-4.
- Dahlen G, Boman J, Birgander L, Lindblom B. Lp(a) lipoprotein, IgG, IgA and IgM antibodies to *Chlamydia pneumoniae* and HLA class II genotype in early coronary artery disease. *Atherosclerosis*. 1995;114:165-74.
- Cannon CP, Braunwald E, McCabe CH, Grayston JT, Muhlestein B, Giugliano RP, et al. Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome. *N Engl J Med*. 2005;352:1646-54.
- Maier VMG, Brown BG. Lipoprotein(a) and coronary heart disease. *Curr Opin Lipidol*. 1995;6:229-35.
- Weinbrenner T, Cladellas M, Covas MI, Fito M, Tomas M, Senti M, et al. High oxidative stress in patients with stable coronary heart disease. *Atherosclerosis*. 2003;168:99-106.
- Ehara S, Ueda M, Naruko T. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. *Circulation*. 2001;103:1955-60.
- Tsimikas S, Witztum J, Miller E, Sasiela W, Szarek M, Olsson A, et al. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. *Circulation*. 2004;110:1406-12.
- Rosenson RS. Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities. *Atherosclerosis*. 2004;173:1-12.
- Saeely CH, Koch L, Schmid F, Marte T, Aczel S, Langer P, et al. Lipoprotein(a), type 2 diabetes and vascular risk in coronary patients. *Eur J Clin Invest*. 2006;36:91-7.
- Sánchez P, Rodríguez M, Villacorta E, Albarran C, Cruz I, Moreiras JM, et al. Cinética de la proteína C reactiva en las distintas manifestaciones clínicas del síndrome coronario agudo. *Rev Esp Cardiol*. 2006;59:441-7.
- Fournier JA, Delgado-Pellecin C, Cayuela A, Cabezón S, Mendoza MD. La PCRas al mes de implantar un stent clínicos tardíos. *Rev Esp Cardiol*. 2008;61:313-6.

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27. Acevedo M, Arnáiz P, Barja S, Bambs C, Berríos X, Guzmán B, et al. Proteína C reactiva y su relación con adiposidad, factores de riesgo cardiovascular y aterosclerosis subclínica en niños sanos. *Rev Esp Cardiol.* 2007;60:1051-8.
28. Huelmos A, Jiménez J, Guijarro C, Belinchón J, Puras E, Sánchez C, et al. Enfermedad arterial periférica desconocida en pacientes con síndrome coronario agudo: prevalencia y patrón diferencial de los factores de riesgo cardiovascular tradicionales y emergentes. *Rev Esp Cardiol.* 2005;58:1403-10.
29. Danesh J, Wheeler J, Hirschfield G, Eda S, Eiriksdottir G, Rumley A, et al. C-Reactive Protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Eng J Med.* 2004;350:1387-97.