

Cystatin C Provides More information Than Other Renal Function Parameters for Stratifying Risk in Patients With Acute Coronary Syndrome

José M. García Acuña, Eva González-Babarro, Lilian Grigorian Shamaqian, Carlos Peña-Gil, Rafael Vidal Pérez, Ana M. López-Lago, Mario Gutiérrez Feijóo, and José R. González-Juanatey

Servicio de Cardiología y Unidad Coronaria, Departamento de Medicina, Hospital Clínico Universitario de Santiago, Santiago de Compostela, A Coruña, Spain

Introduction and objectives. The protein cystatin C has a stable plasma concentration and is eliminated exclusively by the kidneys. The aim of this study was to determine the prognostic value of cystatin C in patients with acute coronary syndrome (ACS).

Methods. The prospective study included 203 hospitalized ACS patients. Clinical evaluation during the first 24 hours of hospitalization included a hemogram and measurement of creatinine, cystatin C, total and fractionated cholesterol, and markers of myocardial necrosis. The glomerular filtration rate (GFR) was estimated using the MDRD (Modification of Diet in Renal Disease) equation. A comparison was made between 2 groups of patients divided according to a serum cystatin-C level above or below 0.95 mg/L. The mean follow-up period was 151 days.

Results. In total, 90 patients (44.3%) had a cystatin-C level ≤ 0.95 mg/L and 113 (55.7%) had a level > 0.95 mg/L. Those with a cystatin-C level > 0.95 mg/L had poorer in-hospital outcomes, including more frequent heart failure (51.3% vs 13.3%; $P = .001$) and higher in-hospital mortality (17.6% vs 3.3%; $P = .001$), as well as higher mortality throughout follow-up (22.0% vs 5.6%; $P = .001$). Multivariate analysis adjusted for age, ejection fraction and troponin-I, and high-sensitivity C-reactive protein concentrations showed that cystatin C was the most powerful independent predictor of a cardiovascular event (relative risk = 1.91; 95% confidence interval, 1.03-3.53). Patients with a GFR > 60 mL/1.73 m² and a cystatin-C level > 0.95 mg/L had higher in-hospital mortality (10.2% vs 3.9%; $P = .001$).

Conclusions. Measurement of cystatin C in high-risk ACS patients may be clinically useful for risk stratification during hospitalization, particularly in those with a normal GFR.

Key words: Cystatin C. Acute coronary syndrome. Heart failure. C-reactive protein.

Correspondence: Dr. J.M. García Acuña.
Servicio de Cardiología y Unidad Coronaria.
Travesía da Choupana, s/n. 15706 Santiago de Compostela. A Coruña.
España.
E-mail: jose.maria.garcia.acuna@sergas.es

Received April 14, 2008.

Accepted for publication February 10, 2009.

La cistatina C aporta más información que otros parámetros de función renal en la estratificación del riesgo de los pacientes con síndrome coronario agudo

Introducción y objetivos. La cistatina C es una proteína con una concentración plasmática estable y eliminación exclusivamente renal. El objetivo del presente estudio es evaluar el valor pronóstico de la cistatina C en pacientes con síndrome coronario agudo.

Métodos. Estudiamos prospectivamente a 203 pacientes ingresados por síndrome coronario agudo. Se realizó una determinación analítica a las 24 h del ingreso que incluía creatinina, cistatina C, hemograma, colesterol total y fraccionado y marcadores de necrosis miocárdica. Se estimó la tasa de filtrado glomerular mediante la ecuación MDRD. Se compararon 2 grupos según las concentraciones séricas de cistatina C ($> 0,95$ y $< 0,95$ mg/l). Se llevó a cabo un seguimiento medio de 151 días.

Resultados. Noventa (44,3%) pacientes tenían cistatina C $\leq 0,95$ mg/l y 113 (55,7%) $> 0,95$ mg/l. Aquellos con cistatina C $> 0,95$ mg/l presentaron peor evolución hospitalaria con más insuficiencia cardíaca (el 51,3 frente al 13,3%; $p = 0,001$), mayor mortalidad hospitalaria (el 17,6 frente al 3,3%; $p = 0,001$) y durante el seguimiento (el 22 frente al 5,6%; $p = 0,001$). En un modelo multivariable ajustado por edad, fracción de eyección, troponina I y proteína C reactiva ultrasensible, la cistatina C demostró ser el predictor independiente más potente de complicaciones cardiovasculares (RR = 1,91; intervalo de confianza del 95%, 1,03-3,53). Los pacientes con cistatina C $> 0,95$ y tasa de filtración > 60 /ml/1,73 m² presentaron mayor mortalidad hospitalaria (el 10,2 frente al 3,9%; $p = 0,001$).

Conclusiones. La determinación de cistatina C en el síndrome coronario agudo de alto riesgo podría ser un buen elemento clínico en la estratificación de su riesgo durante la hospitalización, en particular en pacientes con filtrado glomerular normal.

Palabras clave: Cistatina C. Síndrome coronario agudo. Insuficiencia cardíaca. Proteína C reactiva.

ABBREVIATIONS

ACS: acute coronary syndrome
MDRD: Modification of Diet in Renal Disease
TpI: troponin I

INTRODUCTION

Basic and clinical research carried out in recent years has established a direct, 2-way relationship between chronic kidney disease and cardiovascular disease.^{1,2} In daily clinical practice, serum creatinine concentrations and the glomerular filtration rate estimated with the Cockcroft-Gault³ formula or Modification of Diet in Renal Disease (MDRD)⁴ equation are commonly used to estimate renal function. However, plasma creatinine concentrations can be influenced by a number of factors, such as patient age, sex, muscle mass, physical activity, diet, and medication.⁵

Cystatin C is a protein inhibitor of cysteine protease that is synthesized at a stable rate by all nucleated cells. Because of its low molecular weight and high isoelectric point, it can be eliminated almost exclusively by glomerular filtration. Cystatin C concentrations are not influenced by age, sex, or protein ingestion, and they are sensitive to small changes in glomerular filtration. Because of these characteristics, plasma cystatin C concentration is considered among the best markers of glomerular filtration status.⁶⁻⁹ Recently, several studies have reported an association between elevated cystatin C values and the development of cardiovascular complications in patients with coronary disease. It is currently not known whether this relationship is due to the fact that cystatin C is a better marker of renal function than serum creatinine or whether there are factors apart from glomerular filtration that affect the concentration of this protein and are additionally related to cardiovascular risk.¹⁰

The aim of this study was to assess the prognostic value of plasma cystatin C concentration in patients hospitalized for high-risk acute coronary syndrome (ACS), and to investigate the relationship between cystatin C and other markers of renal function and inflammation.

METHODS

This is a prospective, observational study performed between May 2006 and July 2007. A total of 203 patients older than 18 and consecutively

hospitalized in the cardiac intensive care unit (ICU) of our center with a diagnosis of high-risk ACS were included.

The diagnostic criteria for high-risk ACS included at least 2 of the following factors: pain with ischemic characteristics, electrocardiographic alterations consistent with ischemia, and/or elevated myocardial necrosis markers. The treatment provided and additional tests performed during the patient's hospital stay were based on the clinical decisions of the attending physician. In most patients, an invasive strategy was used, involving urgent coronary angiography (for myocardial infarction with ST segment elevation or left bundle branch block) or early scheduled coronary angiography during the first 24 to 72 hours following hospital admission.

Clinical Characteristics

The following data were recorded from the patients' clinical records: demographic information, presence of classic cardiovascular risk factors (diabetes mellitus, systemic hypertension, dyslipidemia, and smoking), and history of known vascular disease (ischemic heart disease, cerebrovascular disease, peripheral arterial disease, and prior myocardial revascularization treatment). The other clinical variables analyzed included the type of ACS, Killip class at the time of hospitalization, systolic and diastolic pressure values, pulse pressure (estimated as the difference between systolic and diastolic arterial pressure), and heart rate.

All patients underwent echocardiography, in which the left ventricular ejection fraction was estimated with the Simpson method using a 4-chamber approach; the mean of 3 determinations was calculated in patients with sinus rhythm, and the mean of 5 determinations in those with atrial fibrillation.

In 95% of patients, coronary angiography was performed, and the severity of coronary lesions was evaluated with a score based on the number of affected epicardial coronary arteries.

Analytical Data

Baseline hemoglobin, hematocrit, leukocytes, glucose, and creatinine values were recorded in the first laboratory analyses performed at our center at the time of hospitalization. Concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, high-sensitivity C-reactive protein, and cystatin C were recorded in the first 24 hours, together with the peak troponin I (TpI) level.

Cystatin C was measured with an automated homogeneous immunoassay using a Dade-Behring BN ProSpec nephelometer. The reagent for the analysis consisted of polystyrene particles coated with antibodies against the protein that agglutinate when mixed with samples containing cystatin C and disperse light at an intensity proportional to the concentration of the analyte.

The reference interval for serum cystatin C concentration in adults with the nephelometric method used is 0.51 to 0.95 mg/L. Concentrations of high-sensitivity C-reactive protein were also determined by immunoassay. The glomerular filtration rate was estimated with the MDRD equation.

Episodes Analyzed

The cardiovascular complications analyzed included in-hospital mortality, all-cause mortality during follow-up, development of a new myocardial infarction, defined as chest pain or equivalent anginal pain with ECG changes, or elevated tumor necrosis markers during the first 24 hours following hospitalization (patients with elevated markers after coronary interventional procedures were excluded), and development of heart failure during hospitalization or follow-up.

Clinical Follow-up

Mean follow-up was 186 (SD, 110; median, 156) days, during which time all the patients' clinical events were recorded. Follow-up was performed by telephone contact, in outpatient clinics, and by review of the patients' hospital medical records.

Statistical Analysis

All information was prospectively recorded in a database created with Microsoft Office Access 2003 SP2. The statistical analyses were performed with SPSS (Statistical Package for the Social Sciences), version 12.0. The categorical or dichotomous variables are expressed as absolute values and percentages, and were compared with the Pearson χ^2 test. The continuous variables with a normal distribution are described as the mean (SD), and the Student *t* test was used for the comparisons between groups. Variables that did not present a Gaussian distribution were compared with the Mann-Whitney *U* test.

Spearman's correlation coefficient was used to evaluate the correlations of cystatin C concentration with high-sensitivity C-reactive protein and glomerular filtration rate. A logistic regression analysis was used to assess the independent role of clinical and laboratory factors with respect to cystatin

C for predicting the development of cardiovascular complications during hospitalization, including the significant variables in the univariate analysis. The adjusted odds ratios and 95% confidence intervals (CI) are presented. Kaplan-Meier survival curves during follow-up were constructed and compared using the long-rank test.

To carry out a descriptive analysis of the population studied, some quantitative variables were categorized into intervals: the glomerular filtration rate (>90, 90-60, <60 mL/min), the number of affected vessels on coronary angiography into 3 intervals, and the ejection fraction (>55% and <55%). Cystatin C was categorized into 2 groups (>0.95 and <0.95 mg/L) for the univariate analysis.

A *P* value less than .05 was considered statistically significant.

RESULTS

From May 2006 to July 2007, 203 patients hospitalized with a diagnosis of high-risk ACS were included in the study. The mean age was 66.6 (13.16) years. Among the total, 62.1% of patients (n=126) presented non-ST-segment elevation ACS and 37.9% (n=77), ST-segment elevation ACS. The baseline characteristics of the study population are described Table 1.

The median cystatin C concentration was 1.01 (range, 0.83-1.35) mg/L, plasma creatinine at the first analysis performed was 1 (0.9-1.3) mg/L, glomerular filtration rate was 72.4 (49.12-93.73) mL/min/1.73 m², and high-sensitivity C-reactive protein was 1.37 (0.46-5.02) mg/L. Glomerular filtration at the time of hospitalization was <60 mL/min/1.73 m² in 32.5% of patients and serum cystatin C was >0.95 mg/L in 113 (55.7%) patients.

Patients with higher cystatin C values presented a poorer clinical profile, were older, had a high prevalence of hypertension, worse Killip class at the time of hospitalization, more severe coronary disease on coronary angiography, and higher plasma creatinine and C-reactive protein values (Table 2).

There were no significant differences between the 2 cystatin C groups regarding the coronary intervention performed; the final angiographic result yielded a similar success rate and no significant complications (3.27% for patients with cystatin C \leq 0.95 and 4.09% in the other group). Analysis of the pharmacological treatment showed a substantially higher use of beta-blockers and aspirin in the group with cystatin C \leq 0.95 (Table 2).

Serum cystatin C values showed a higher correlation with estimated glomerular filtration rate ($r=-0.655$; $P=.001$) (Figure 1) than with microalbuminuria ($r=0.302$, $P=.01$) and a lower correlation with C-reactive protein ($r=0.29$; $P=.01$).

TABLE 1. Baseline Characteristics of the Study Population

Age, y	66.6 (13.16)
Male sex	157 (77.3)
Hypertension	120 (59.1)
Diabetes mellitus	71 (35)
Hyperlipidemia	108 (53.2)
Prior ischemic heart disease	65 (32)
Smoking	106 (52.2)
NSTE-ACS	126 (62.1)
STEMI	77 (37.9)
SP at admission, mm Hg	134 (27)
Heart rate, bpm	80 (25)
Killip	
I	153 (75.3)
II	25 (12.3)
III	21 (10.3)
IV	4 (2)
Ejection fraction	
>55%	114 (56.2)
55%-30%	81 (39.9)
<30%	8 (3.9)
Coronary angiography	191 (94.1)
No lesions	8 (3.9)
1-Vessel disease	66 (32.5)
2-Vessel disease	43 (21.2)
3-Vessel disease and/or mainstem	74 (36.5)
GFR <60 mL/min/1.73 m ²	66 (32.5)
GFR 60-90 mL/min/1.73 m ²	78 (38.4)
GFR >90 mL/min/1.73 m ²	59 (29.1)
Myocardial revascularization surgery	23 (11.3)
Percutaneous coronary intervention (PCI)	127 (62.6)
Medical treatment	50 (26.1)
Aspirin	181 (89.2)
Clopidogrel	146 (71.9)
Beta-blockers	133 (65.5)
ACE inhibitors/ARA-II	125 (61.5)
Statins	172 (84.7)

ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; GFR, glomerular filtration rate; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SP, systolic pressure; STEMI, ST-segment acute myocardial infarction.

Data are expressed as n (%) or mean (SD).

In the group of patients with cystatin C values >0.95, 6.5% presented normal glomerular filtration rates and 46%, glomerular filtration rates between 60 and 90 mL/min/1.73 m². In addition, 10% of the patients who had renal dysfunction with a filtration rate of <60 mL/min/1.73 m² had cystatin C values <0.95. In our sample, the cut-off point selected by our laboratory as the upper normal limit for cystatin C (0.95 mg/L) predicted cardiovascular complications during follow-up with a sensitivity of 89% and a specificity of 80.26% (Figure 2). Receiver operating characteristic (ROC) curves were performed to determine the diagnostic performance of creatinine,

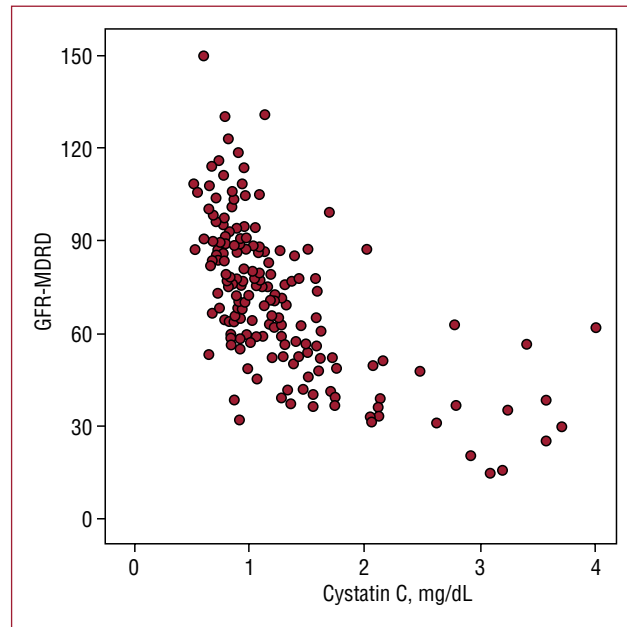


Figure 1. Correlation between cystatin C values and glomerular filtration rate estimated with the MDRD formula (GFR-MDRD).

glomerular filtration rate estimated by MDRD, and cystatin C to identify the subgroup of patients who would present cardiovascular complications. Cystatin C showed a slightly larger area under the curve than the glomerular filtration rate; serum creatinine was the parameter with the smallest area under the curve (Figure 2, Table 3).

Hospital stay lasted a median of 9 (6-19) days. From the time of admission to the completion of the study follow-up, 56 (27.58%) patients from the overall sample had developed heart failure, most of them in the group with elevated cystatin C values (45 [38.5%] patients). In-hospital mortality was significantly higher in the group with elevated cystatin C values (17.6% vs 3.3%; $P=.001$), and these differences persisted during follow-up (Figure 3, Table 4).

In the univariate analysis, no association was observed between cardiovascular complications and the type of ACS, hyperlipidemia, or peak T_{PI} concentration, but an association was found with the remaining cardiovascular risk factors: number of affected vessels, ejection fraction, renal function markers, cystatin C, and high-sensitivity C-reactive protein. When results from patients with a glomerular filtration rate of >60 mL/min/1.73 m² were analyzed, we found that patients with cystatin C >0.95 mg/L presented a significantly higher rate of cardiovascular complications than patients with glomerular filtration >60 and cystatin C <0.95 mg/L (Table 5). Despite the fact that the former patients had slightly lower

TABLE 2. Baseline Patient Characteristics According to Cystatin C Concentration

	Cystatin ≤ 0.95 mg/L	Cystatin >0.95 mg/L	P
Patients	90 (44.3)	113 (55.7)	
Age, mean (SD), y	59.21 (12.26)	72.49 (10.69)	.002
Male sex	75 (83.3)	82 (72.5)	.069
Diabetes	29 (32.2)	43 (38.05)	.385
HT	38 (42.22)	79 (69.9)	.001
Hyperlipidemia	45 (50)	59 (52.2)	.745
History of ischemic heart disease	25 (27.7)	39 (34.5)	.305
Smoking	53 (28.8)	53 (46.9)	.089
Creatinine, mg/dL	0.9 (0.8-1.1)	1.2 (1-1.4)	.01
Killip III-IV	7 (7.7)	18 (15.9)	.001
LVEF (%)	56	51	.01
3-Vessel and/or trunk disease	27 (30)	47 (41.6)	.009
Troponin I, ng/mL	13.51 (3.6-72.5)	15.49 (3.4-39.3)	.52
hsCRP, mg/L	1.07 (0.3-2.2)	2.45 (0.5-9.3)	.001
GFR <60 mL/min	9 (10)	54 (47.8)	.001
GFR 60-90 mL/min	45 (50)	52 (46)	.1
GFR >90	36 (40)	7 (6.2)	.001
MRS	0 (11.1)	13 (11.5)	.6
PCI	60 (66.7)	67 (59.3)	.5
Aspirin	85 (94.4)	96 (85)	.07
Clopidogrel	68 (75.6)	78 (69)	.2
Beta-blockers	67 (74.4)	66 (58.4)	.03
ACE inhibitors/ARA-II	62 (68.8)	80 (70.7)	.2
Statins	79 (87.8)	93 (82.3)	.5

ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; GFR, glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; HT, hypertension; LVEF, left ventricular ejection fraction; MRS, myocardial revascularization surgery; PCI, percutaneous coronary intervention. Data are expressed as n (%) or median (range).

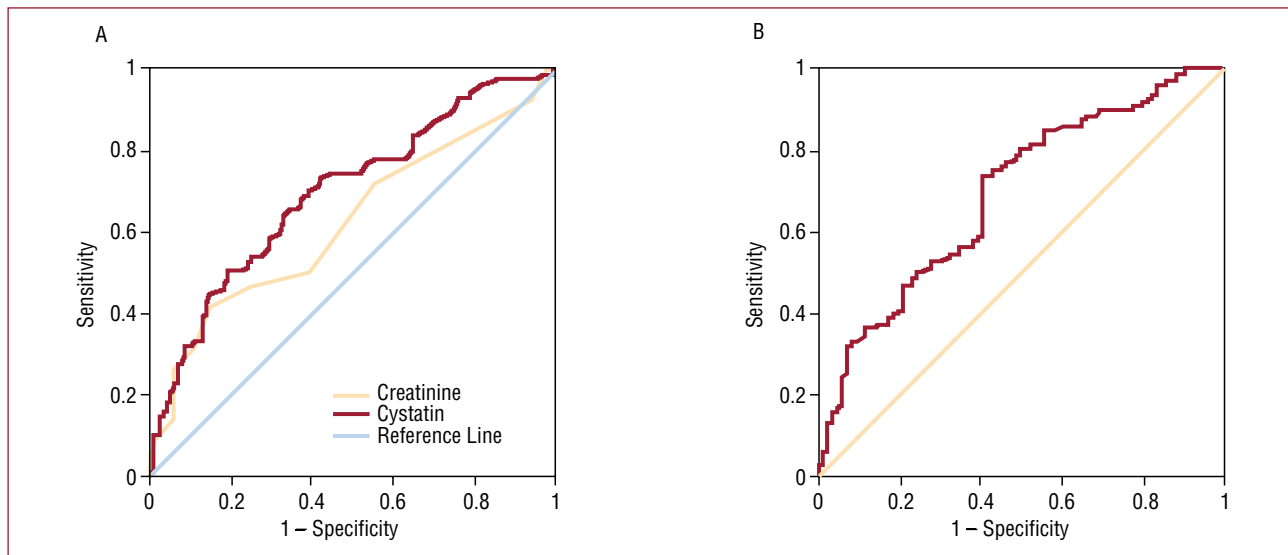


Figure 2. A, ROCs of cystatin C and creatinine in relation to the development of cardiovascular complications (heart failure, infarction, and cardiovascular death). B, ROC curve of the glomerular filtration rate estimated with the MDRD in relation to the development of cardiovascular complications (heart failure, infarction, and cardiovascular death).

or normal glomerular filtration, they presented a significantly higher percentage of cardiovascular events (heart failure, infarction, and deaths due to a cardiovascular cause) than those with a glomerular filtration rate >60 and cystatin C <0.95 mg/L.

Estimated event-free survival (ie, no heart failure, myocardial infarction, or death) following a mean follow-up of 186 days was significantly higher in the group of patients with cystatin values ≤ 0.95 mg/L: 75% versus 44% ($P=.02$) (Figure 4).

TABLE 3. Estimated Area Under the Curve of Renal Function Parameters for Predicting Major Cardiovascular Events

	AUC	P	95% CI
Cystatin C	0.695	.038	0.626-0.758
Creatinine	0.620	.040	0.549-0.688
GFR-MDRD	0.685	.037	0.615-0.748

AUC indicates area under the curve; CI, confidence interval; GFR-MDRD, glomerular filtration rate estimated with the MDRD method; MDRD, Modification of Diet in Renal Disease.

The multivariate analysis identified age, ejection fraction, and cystatin C concentration as independent predictive factors of cardiovascular complications during hospitalization (Table 6).

DISCUSSION

The results of the present study indicate that elevated cystatin C values predict the development of in-hospital heart failure, myocardial infarction,

and cardiovascular death in patients with high-risk ACS, independently of other classic risk factors. In addition, plasma cystatin C value may have a greater capacity to stratify patients at a high risk of cardiovascular complications during hospitalization than other methods of assessing renal function. We found that elevated cystatin C was associated with a poorer cardiovascular prognosis even in the group of patients with normal glomerular filtration. To our knowledge, this is the first report of this association, which we believe could have implications for risk stratification in this patient population.

In recent years, several articles have described a close association between renal dysfunction and cardiovascular complications during follow-up of patients with acute and chronic ischemic heart disease, as well as other clinical presentations of cardiovascular disease, in particular, heart failure.^{1,10-12} A reduction in glomerular filtration below 60 mL/min is related to a significant increase in the risk of death, myocardial infarction, and stroke, both in patients with or without prior cardiovascular disease.¹³ Specifically, this relationship has been

TABLE 4. Description of Cardiovascular Events According to Serum Cystatin C Concentration

	Cystatin ≤0.95 mg/L	Cystatin >0.95 mg/L	P
Patients	90 (44.3)	113 (55.7)	
Heart failure	11 (12.8)	45 (38.5)	.001
Acute myocardial infarction	7 (8)	9 (8)	.6
In-hospital mortality	3 (3.3)	20 (17.6)	.001
Mortality during follow-up	5 (5.6)	25 (22)	.001

Data are expressed as n (%).

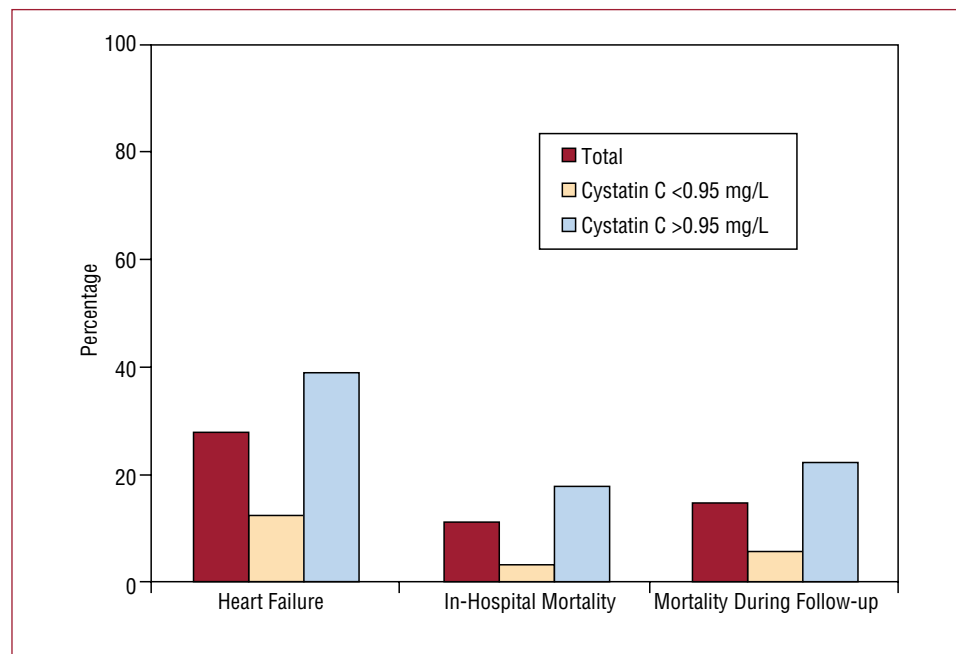


Figure 3. Association between cystatin C <0.95 mg/L and >0.95 mg/L and the development of in-hospital cardiovascular events.

TABLE 5. Comparative Analysis of Cardiovascular Events According to Determination of Glomerular Filtration Rate and Cystatin C

	GFR ≥60 mL/min/m ² and Cystatin C ≤0,95 mg/L	GFR <60 mL/min/m ² and Cystatin C ≤0,95 mg/L	GFR ≥60 mL/min/m ² and Cystatin C >0,95 mg/L	GFR <60 mL/min/m ² and Cystatin C >0,95 mg/L	P
Patients	76 (37)	10 (5)	63 (31)	54 (27)	
Heart Failure	6 (7.5)	5 (50)	23 (39)	22 (40.7)	.01
In-hospital mortality	3 (3.9)	0	6 (10.2)	14 (25.9)	.01
Mortality during follow-up	3 (3.9)	0	10 (16.9)	17 (31.5)	.001

GFR indicates glomerular filtration rate.
Data are expressed as n (%).

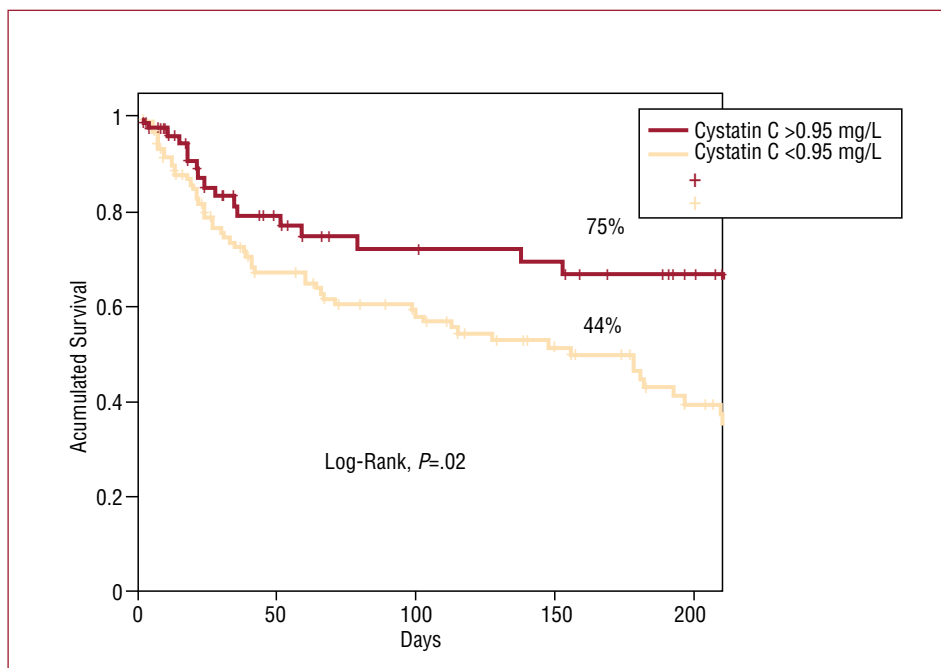


Figure 4. Kaplan-Meier curves to estimate the probability of survival free from major cardiovascular events, according to cystatin C value.

TABLE 6. Multivariate Analysis for the Development of Major Cardiovascular Events (Heart Failure, Myocardial Infarction, Cardiovascular Death) Using Cystatin C and Glomerular Filtration Rate Estimated With the MDRD Method

	OR (95% CI)	P
Measured with cystatin C		
Age	1.05 (1.01-1.08)	.002
Ejection fraction	0.92 (0.90-0.96)	.001
Cystatin C	1.91 (1.03-3.53)	.03
hs-CRP	1.04 (0.97-1.11)	.18
Measured with GFR-MDRD		
Age	1.04 (1.01-1.08)	.005
Ejection fraction	0.93 (0.90-0.96)	.001
MDRD	0.98 (0.96-0.99)	.04
hs-CRP	1.05 (0.98-1.12)	.15

CI indicates confidence interval; GFR-MDRD, glomerular filtration rate estimated by the MDRD equation; hs-CRP, high-sensitivity C-reactive protein; MDRD, Modification of Diet in Renal Disease; OR, odds ratio.

described in ACS patients with ST-segment elevation and those without.^{10,13-15} In the VALIANT study¹⁶ (patients with ventricular dysfunction and heart failure following ST-segment-elevation myocardial infarction), deterioration of renal function (assessed with the glomerular filtration rate) was associated with an increase in mortality and cardiovascular complications during follow-up. Similar results have been reported for the patient populations included in the SAVE (postinfarction ventricular dysfunction), HOPE (patients with a high cardiovascular risk, the majority with chronic ischemic heart disease), and PEACE (patients with chronic ischemic heart disease) studies. In these studies, the relationship between renal dysfunction and the prognosis was observed for decreased glomerular filtration rates as well as for urinary albumin excretion.¹⁶⁻¹⁹

As mentioned above, a direct 2-way relationship has been described between renal dysfunction and

cardiovascular disease. Chronic renal failure favors the development of hypertension and dyslipidemia, and promotes activation of the renin-angiotensin-aldosterone system. These factors, together with the increase in inflammatory mediators, seem to contribute to higher production of free radicals, which intervene in the atherosclerotic process and cardiovascular injury. In addition, mineral metabolism alterations (increase of the promoters and decrease of the inhibitors of calcification) favor calcium deposits in the coronary vessels.^{20,21} Lastly, less intensive use of therapeutic interventions of recognized clinical and prognostic benefit has been described in patients with renal dysfunction. Specifically, in those with ACS, less aggressive treatment and longer delays in performing interventional coronary procedures, as well as lower use of IIb/IIIa, blockers of the renin-angiotensin-aldosterone axis, beta blockers, statins, and antiplatelet agents, may contribute to the poorer prognosis described in this patient population.²²

In daily clinical practice, assessment of renal function is usually based on serum creatinine determinations and estimates of the glomerular filtration rate using the Cockcroft-Gault or MDRD formulas. Both these methods present several limitations, many of which are derived from factors that affect creatinine production, such as age, female sex, race-related characteristics, diet, and the course of chronic diseases.

These equations were recently evaluated in patients with heart failure and compared with NT-proBNP, a prognostic marker. The prognostic information provided by NT-proBNP was found to be superior to that of renal function estimated by the MDRD formula.²³

Cystatin C possesses molecular and metabolic characteristics that make plasma concentrations of this protein a good biological marker for estimating renal function; small functional alterations are detected with a higher sensitivity than the conventional parameters used for this purpose.²⁴ This may justify the fact that in the group of patients with serum cystatin C concentrations above the upper normal limit, 15% presented a normal glomerular filtration rate; determination of statin C may be useful for identifying patients with a preclinical state of renal disease.⁶

The results obtained in the present study are, to a certain degree, in keeping with the reported findings indicating that cystatin C is an independent predictor of cardiovascular complications in patients with coronary disease.²⁵⁻²⁷ Moreover, our data can extend this concept to include patients with a normal glomerular filtration rate. Jernberg et al²⁶ analyzed the relationship between plasma cystatin C values and prognosis in a group of patients hospitalized for non-ST-segment-elevation ACS, and reported

a significant association between cystatin C values and mortality. It has also been described that elevated cystatin C concentrations are associated with an increased risk of death, cardiovascular complications, and the incidence of heart failure in outpatients with chronic coronary disease.²⁴ In older persons without manifest renal disease, cystatin C is a risk marker for death, cardiovascular disease, and chronic renal disease.⁶ In the current study, we found that patients with elevated cystatin C levels had a poorer risk profile; however, the relatively low C-reactive protein level was surprising. We believe this can be explained by the kinetics of the protein, which has a specific, characterized spectrum in which its value depends on the time point when the sample is drawn (the peak occurs at 49 hours following the onset of symptoms, and a more delayed peak is seen in ST-segment-elevation acute myocardial infarction); in our study, samples were taken within the first 24 hours following hospitalization.²⁸ The cardiovascular complications affecting the patients in our study differ from those published in recent registries,²⁹ and this may be because patients at very high risk and with a higher incidence of complications were included. In the recently published MASCARA registry, only 50% of the patients included had been initially admitted to an ICU or cardiac ICU, whereas all our patients came from a cardiac ICU, a fact that undoubtedly implies some selection bias. Nevertheless, the patient group with elevated cystatin C comprised a population with a significantly higher-risk profile and number of cardiovascular complications than the remaining patients. The present study contributes to establish greater precision in these associations by providing the first report that elevated cystatin C levels in the first hours of hospitalization for high-risk ACS are an independent predictor of in-hospital cardiovascular complications. Moreover, the association between cystatin C and a risk of cardiovascular complications is higher than that of other widely used parameters for estimating renal function, and is maintained even in the group of patients with normal glomerular filtration. Currently, it is not precisely known whether the capability of predicting a higher risk of complications stems from the fact that cystatin C is a better marker of renal function than other common parameters (serum creatinine and glomerular filtration rate), or that there are other factors apart from glomerular filtration that affect the cystatin C concentration and could be directly related to cardiovascular risk. In this line, a positive correlation of plasma C-reactive protein values and fibrinogen with elevated cystatin C concentrations and the presence of cardiovascular disease has been described.³⁰ In the PRIME study (Prospective Epidemiological Study of Myocardial Infarction),

the association between cystatin C and development of acute myocardial infarction cardiac death and angina was investigated in patients without coronary disease. After adjusting for the common cardiovascular risk factors, plasma cystatin C level was significantly associated with development of the first coronary complication of ischemic origin. In the opinion of the authors, the decreased glomerular filtration rate would not justify the higher cystatin C values presented by the cases with respect to the controls, and they proposed that inflammation could be at the origin of the relationship between cystatin C and the risk of cardiovascular disease.^{31,32} In keeping with these data, our results showed a positive correlation between cystatin C and high-sensitivity C-reactive protein ($r=0.2$), which is also an independent predictor of cardiovascular complications, and provide further evidence to justify the presence of direct relationships between renal disease, inflammation, and cardiovascular disease.

Among the main limitations of the study presented, we should point out that the results refer only to patients with high-risk ACS hospitalized in a cardiac ICU, the majority aggressively treated with early coronary angiography. On the other hand, these characteristics should be highlighted, because there is little information on this specific population, in whom cystatin C was measured at hospital admission. In almost all the published studies, the time point of the determinations is not indicated, and, at least in patients with ACS, plasma cystatin C concentrations can be influenced by the length of time since the event and the diagnostic and therapeutic interventions performed. The limitation of a short follow-up impedes extending our observations to the medium- or long-term. Nonetheless, our findings offer a possibility to improve risk stratification in patients hospitalized for high-risk ACS, which will be useful for deciding therapy as well as establishing the diagnosis.

CONCLUSIONS

Cystatin C determination at the time of hospitalization in patients with high-risk ACS may be a good clinical tool for stratification of cardiovascular risk. Determination of this protein would complement the information provided by other methods of assessing renal function and, in addition to the diagnostic implications, could be useful for identifying the group at highest risk. It may be necessary to pay special attention to fulfilling the recommendations contained in clinical practice guidelines in this population. Moreover, cystatin C could contribute important information for stratifying patients with high-risk ACS and

preserved renal function. Additional studies with a longer follow-up may be needed to define the role of cystatin C in ACS with greater precision.

REFERENCES

1. Carda R, de Agustín JA, Manzano MC, García-Rubira JC, Fernández-Ortiz A, Vilacosta I, et al. Valor pronóstico intrahospitalario del filtrado glomerular en pacientes con síndrome coronario agudo y creatinina normal. *Rev Esp Cardiol.* 2007;60:714-9.
2. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furger CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol.* 2001;38:705-11.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999;130:461-70.
5. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function —measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354:2473-83.
6. Shlipak MG, Katz R, Sarnak MJ, Fried LM, Newman AB, Stehman-Breen C, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med.* 2006;145:237-46.
7. Singh D, Whooley MA, Ix JH, Ali S, Shlipak MG. Association of cystatin C and estimated GFR with inflammatory biomarkers: the Heart and Soul Study. *Nephrol Dial Transplant.* 2007;22:1087-92.
8. Christensson AG, Grubb AO, Nilsson JA, Norrgren K, Sterner G, Sundkvist G. Serum cystatin C advantageous compared with serum creatinine in the detection of mild but no severe diabetic nephropathy. *J Intern Med.* 2004;256:510-8.
9. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med.* 2005;352:2049-60.
10. Fácila L, Núñez J, Bodí V, Sanchos J, Bertomeu-González V, Consuegra L, et al. Valor pronóstico de la creatinina sérica en el síndrome coronario agudo sin elevación del segmento ST. *Rev Esp Cardiol.* 2006;59:209-16.
11. Gibson M, Pinto D, Murphy S, Morrow DA, Hobbach H-P, Wiviott SD, et al. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol.* 2003;42:1535-43.
12. Grigorian L, Varela A, Pedreira M, Gómez I, Virgós A, González-Juanatey JR. La insuficiencia renal es un predictor independiente de la mortalidad en pacientes hospitalizados por insuficiencia cardíaca y se asocia con un peor perfil de riesgo cardiovascular. *Rev Esp Cardiol.* 2006;59:99-108.
13. Mueller C, Neumann F-J, Perruchoud A, Buettner HJ. Renal function and long term mortality after unstable angina/non-ST segment elevation myocardial infarction treated very early and predominantly with percutaneous coronary intervention. *Heart.* 2004;90:902-7.
14. Wison S, Foo K, Cunningham J, Cooper J, Deaner A, Knight C, et al. Renal function and risk stratification in acute coronary syndromes. *Am J Cardiol.* 2003;91:1051-4.
15. Wiener DE, Tighiouart H, Amin MG. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol.* 2004;15:1307-15.
16. Verma A, Anavekar NS, Meris A, Thune JJ, Arnold JM, Ghali JK, et al. The relationship between renal function and cardiac

- structure, function, and prognosis after myocardial infarction: the VALIANT Echo Study. *J Am Coll Cardiol.* 2007;50:1238-45.
17. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol.* 2006;17:2886-91.
 18. Gerstein HC, Bosch J, Pogue J, Taylor DW, Zinman B, Yusuf S. Rationale and design of a large study to evaluate the renal and cardiovascular effects of an ACE inhibitor and vitamin E in high-risk patients with diabetes. The MICRO-HOPE Study. Microalbuminuria, cardiovascular, and renal outcomes. *Heart Outcomes Prevention Evaluation. Diabetes Care.* 1996;9:1225-8.
 19. Solomon SD, Rice MM, Jablonski K, Jose P, Domanski M, Sabatine M, et al. Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation.* 2006;114:26-31.
 20. Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction. *Circulation.* 2004;110:3667-73.
 21. Schiffrin W, Lipman ML, Mann JF. Chronic kidney disease effects on the cardiovascular system. *Circulation.* 2007;116:85-97.
 22. Brugts JJ, Boersma E, Chonchol M, Deckers JW, Bertrand M, Remme WJ, et al. The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial. *J Am Coll Cardiol.* 2007;50:2148-55.
 23. Gardner RS, Chong KS, O'Meara E, Jardine A, Ford I, McDonagh TA. Renal dysfunction, as measure by modification of diet in renal disease equations, and outcome with advance heart failure. *Eur Heart J.* 2007;28:3027-33.
 24. Ix JH, Shlipak MG, Chertow GM, Whooley MA. Association of Cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: data from the Heart and Soul study. *Circulation.* 2007;115:173-9.
 25. Koenig W, Twardella D, Brenner H, Rothenbacher D. Plasma concentrations of cystatin C in patients with coronary heart disease and risk for secondary cardiovascular events: more than simply a marker of glomerular filtration rate. *Clin Chem.* 2005;51:321-7.
 26. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST- elevation acute coronary syndrome. *Circulation.* 2004;110:2342-8.
 27. Chew JCS, Saleem M, Florkowski C, George PM. Cystatin C. A paradigm of evidence based laboratory medicine. *Clin Biochem Rev.* 2008;29:47-62.
 28. Sánchez PL, Rodríguez MV, Villacorta E, Albarrán 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.
 29. Ferreira-González I, Permayr-Miralda C, Marrugat J, Heras M, Cuñat J, Civeira E, et al. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. *Rev Esp Cardiol.* 2008;61:803-16.
 30. Loew M, Hoffmann MM, Koenig W, Brenner H, Rothenbacher D. Genotype and plasma concentration of cystatin C in patients with coronary heart disease and risk for secondary cardiovascular events. *Arterioscler Thromb Vasc Biol.* 2005;25:1470-4.
 31. Luc G, Bard JM, Lesueur C, Arveiler D, Evans A, Amouyel P, et al. Plasma cystatin-C and development or coronary heart disease: the PRIME study. *Atherosclerosis.* 2006;185:375-80.
 32. Levin A. Cystatin C, serum creatinine and estimates of kidney function: searching for better measures of kidney function and cardiovascular risk. *Ann Intern Med.* 2005;142:586-8.