Clinical Predictors of Left Main Coronary Artery Disease in High-Risk Patients With a First Episode of Non-ST-Segment Elevation Acute Coronary Syndrome

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Introduction and objectives. Risk stratification in non-ST-elevation acute coronary syndrome makes use of clinical variables that can identify patients at an increased risk of complications. Our objective was to identify clinical variables that predict significant stenosis (i.e., >50%) of the left main coronary artery in high-risk patients who have had a first episode of non-ST-elevation acute coronary syndrome but who do not have a history of coronary artery disease.

Methods. The study included 102 high-risk patients with no history of coronary artery disease who were admitted because of non-ST-elevation acute coronary syndrome. All underwent coronary angiography. Patients were divided into 2 groups: those with significant left main coronary artery stenosis (n=14) and those without (n=88).

Results. Univariate analysis showed that the variables significantly associated with left main coronary artery stenosis were age >65 years (57.1% vs 15.9%; P=0.002), diabetes mellitus (71.4% vs 33.0%; P=0.006), chronic renal failure (28.6% vs 5.7%; P=0.019), left heart failure (71.4% vs 6.8%; P<0.0001), cardiogenic shock (21.4% vs 1.1%; P=0.008), and a low left ventricular ejection fraction at admission (49.9% [14.7%] vs 58.8% [9.9%]; P=0.044). In the multivariate analysis, the only significant independent predictor of left main coronary artery disease was left heart failure.

Conclusions. The presence of left heart failure at initial assessment of high-risk patients with non-ST-elevation acute coronary syndrome but without a history of coronary artery disease could be a useful predictor of significant left main coronary artery disease.


Variables clínicas predictoras de enfermedad del tronco común en pacientes de alto riesgo con un primer episodio de síndrome coronario agudo sin elevación del segmento ST

Introducción y objetivos. En la estratificación del síndrome coronario agudo disponemos de variables clínicas para identificar a los pacientes con alto riesgo de presentar complicaciones. Analizamos si los pacientes de alto riesgo, sin antecedentes de cardiopatía isquémica, que presentan un primer episodio de síndrome coronario agudo sin elevación del segmento ST presentan variables clínicas predictoras de estenosis significativa (> 50%) del tronco común.

Métodos. Se analizó a 102 pacientes de alto riesgo sin antecedentes de cardiopatía isquémica con síndrome coronario agudo sin elevación del segmento ST, a los que se les practicó coronariografía. Establecemos 2 grupos: con estenosis significativa del tronco común (n = 14) y el resto (n = 88).

Resultados. Variables relacionadas con la estenosis del tronco común en el análisis univariado: edad > 65 años (el 57.1 frente al 15.9%; p = 0.002), diabetes mellitus (el 71.4 frente al 33.0%; p = 0.006), insuficiencia renal crónica (el 28.6 frente al 5.7%; p = 0.019), insuficiencia cardíaca izquierda (el 71.4 frente al 6.8%; p < 0.0001), shock cardiogénico (el 21.4 frente al 1.1%; p = 0.008) y fracción de eyecisión más reducida en el momento del ingreso (49.9 ± 14.7 frente a 58.8 ± 9.9%; p = 0.044). La única variable con valor predictivo significativo independiente de enfermedad del tronco común en el análisis multivariable fue la insuficiencia cardíaca izquierda.

Conclusiones. La presencia de insuficiencia cardíaca izquierda en la evaluación inicial del síndrome coronario agudo sin elevación del ST, en pacientes de alto riesgo sin antecedentes de cardiopatía isquémica, puede ser un predictor útil de enfermedad del tronco común.

ABBRévIATIONS
RCA: right coronary artery.
CX: circumflex artery.
LAD: left anterior descending artery.
NSTE-ACS: non-ST-segment elevation acute coronary syndrome.
LMCA: left main coronary artery.

INTRODUCTION
A set of clinical, electrocardiographic, and biochemical variables is available in daily clinical practice to allow risk stratification of patients presenting with a non-ST-segment elevation acute coronary syndrome (NSTE-ACS). These variables are virtually the same as those appearing in the most widely used clinical guidelines for NSTE-ACS, with only minimal, inconsequential variations between them. These variables are the cornerstone of the initial work-up in these patients. In effect, depending on their presence or absence, it is possible to estimate the patient’s short-term risk of presenting major cardiovascular events (death, myocardial infarction) and to establish patient groups according to whether the risk is low, intermediate or high. In addition, NSTE-ACS stratification allows optimization of treatment for these patients. Thus, in the high-risk group, in addition to conventional therapy, perfusion of glycoprotein IIb/IIIa inhibitors and urgent coronary revascularization would be indicated, with the aim of improving their prognosis.

The natural history of significant stenosis of the left main coronary artery (LMCA) without revascularization treatment is associated with elevated mortality of patients with stable coronary disease (50% at 3 years) as well as those with acute coronary syndrome (ACS) (78.6% in patients with acute myocardial infarction [AMI] complicated by cardiogenic shock). Stenosis of the LMCA is more frequent in high-risk patients with NSTE-ACS, hence, the possibility of predicting its presence is of maximum interest. The aim of this study, performed in patients with NSTE-ACS, no known history of ischemic heart disease, and classified as at high risk, was to analyze whether any of the clinical, electrocardiographic, or biochemical parameters we use to stratify risk in NSTE-ACS at hospital admittance is related with significant LMCA stenosis in the coronary angiography undertaken later.

METHODS
Patients
Between June 2000 and December 2004, 833 patients with NSTE-ACS were admitted to our hospital coronary care unit. Their data were analyzed retrospectively and the following cases were excluded: patients with a history of ischemic heart disease, defined as those who had been hospitalized previously for myocardial infarction or unstable angina, patients treated with percutaneous or surgical coronary revascularization prior to the current event, and patients with significant valvular disease who had been diagnosed previously or during hospitalization. Patients presenting exertional angina who did not require hospital admittance with onset during the 2 months prior to the current hospitalization were, however, included. Among the total, 319 patients (38.3%) had none of the above-mentioned exclusion criteria. Of these, 102 were considered at short-term high-risk following the initial clinical assessment and comprised the study group.

Patients who presented the following factors were considered at high-risk: a) typical pain at rest that persisted despite medical treatment and involved a severe ST-segment decrease or signs of left heart failure (crepitant rales, third heart sound, or indicative features on the chest x-ray), hypotension, severe mitral regurgitation or sustained ventricular tachycardia; b) recurrent angina at rest despite optimal medical treatment, including intravenous nitroglycerin; c) angina at rest of less than 24 hours’ evolution and more than 30 minutes’ duration with ST segment decrease ≥2 mm in the anterior territory, or transient ST segment elevation; and d) angina of less than 24 hours’ evolution with ST segment decrease <2 mm or with a pronounced negative T-wave in the anterior territory, with positive biochemical necrosis markers (creatinine kinase MB isoenzyme [CK-MB] and/or troponin I), age ≥65 years or diabetes, and at least one of the following variables on the initial work-up: ejection fraction known to be ≤40% or peripheral vascular disease (defined as peripheral vascular murmur, intermittent claudication of the lower limbs, or history of peripheral vascular surgery).

The presence of chronic renal failure is not formally contemplated for risk stratification in the NSTE-ACS guidelines. Nevertheless, because of the growing evidence linking this condition with a poorer prognosis in patients presenting an ischemic event,2,9 we have included this factor in the present study as a clinical variable that should be taken into consideration in the initial assessment of these patients.

Experimental Methods
The first electrocardiogram performed in each patient following hospital admission was taken as a reference. The anterior territory was defined as the electrocardiographic tracings obtained with the V1, V2, V3, and V4, leads, the lateral territory

Claver E et al. Clinical Predictors of Left Main Coronary Artery Disease.
corresponded to the I, aVL, V5, and V6 tracings and the inferior territory, to the II, III, and aVF tracings. Myocardial necrosis markers were considered pathological when the troponin I value was >0.5 ng/mL (Dade Behring, United Kingdom) and/or CK-MB was >5 ng/mL (Dade Behring, United Kingdom), provided the fraction represented more than 5% of the total CK. Plasma determinations of the myocardial necrosis markers were performed on three occasions, every 8 hours from the time of onset of the chest pain that led to the patient’s hospitalization.

The drugs commonly used for NSTE-ACS, administered during the interval between hospital admission and the coronary angiography examination, were recorded to compare the homogeneity of the medical treatment between patients with and without LMCA disease.

Coronary angiography was done within the first 48 hours after hospitalization in all selected high-risk patients with NSTE-ACS, according to the aforementioned criteria. Depending on the result obtained, 2 patient groups were established: those with significant LMCA stenosis and the remaining patients. A lesion was considered to be angiographically significant when ≥50% of the diameter of the vessel lumen was compromised on at least 2 different views in the case of the LMCA and ≥70% for the remaining coronary arteries, using as a reference the adjacent segment of the vessel without angiographic lesions. The criteria most frequently used to establish the percentage of stenosis was the subjective assessment of any of the 3 experienced interventional radiologists who performed the coronary cardiologist. In 15 patients (14.7%), intracoronary ultrasonography was also used. In this case a lesion was considered significant when the lumen area of the stenotic vessel segment was <6 mm² in the LMCA or <4 mm² in the remaining vessels.12,13

The analyses (univariate and multivariate) include the quantitative results of the first left ventricular ejection fraction in each patient, as measured by contrast ventriculography in the catheterization laboratory or by echocardiography in certain patients with renal failure who could not undergo this method.

**Statistical Analysis**

The results are expressed as the mean ± standard deviation for quantitative variables and as percentages with the 95% confidence interval (CI), obtained with the exact binomial method, for qualitative variables. Student’s t test was used for comparisons between qualitative variables and the χ² test for comparisons between quantitative variables. To assess their independence, variables attaining statistical significance in the univariate analysis were introduced in the multivariate logistic regression model by the forward stepwise method, with the criterion of 0.05 for entrance and 0.10 for elimination from the model. SPSS for Windows, version 11.0 (SPSS, Chicago, USA) was used for the analyses. Statistical significance was set at P<.05.

**RESULTS**

**Demographic Characteristics**

Among the total of 102 high-risk patients with NSTE-ACS and no known history of ischemic heart disease, 83 were men. The mean age was 57.1±10.1 years. It is noteworthy that nearly all the patients (94%) showed alterations indicative of ischemia on the electrocardiogram and the majority had prolonged chest pain (72%) that appeared at rest (80%) and was associated with elevated myocardial necrosis markers (61%). The percentages at which the various drugs were administered in the 2 patient groups (with and without LMCA disease) are shown in Table 1.

**Results of Coronary Angiography**

Fourteen patients had significant LMCA stenosis and constituted the study group (Table 2). Among these patients, 2 had no other angiographically significant lesions, 7 had additional lesions in 3 coronary arteries (left anterior descending artery [LAD], circumflex artery [CX], and right coronary artery [RCA]), 4 had lesions in 2 vessels (1 CX and RCA and 3 LAD and CX), and 1 patient had a lesion in 1 vessel (CX). The remaining patients comprised the group without LMCA disease (n=88, 86.3%).

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**TABLE I. Percentage of Drugs Administered in High-Risk Patients With NSTE-ACS With and Without Significant Left Main Coronary Artery Disease, During the Interval Between Hospital Admission and the Coronary Angiography Study*\(^a\)**

<table>
<thead>
<tr>
<th>Drug Administered</th>
<th>LMCA Disease</th>
<th>No LMCA Disease</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, %</td>
<td>100.0</td>
<td>97.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>64.3</td>
<td>50.0</td>
<td>.32</td>
</tr>
<tr>
<td>Nitroglycerin, %</td>
<td>100.0</td>
<td>98.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta blockers, %</td>
<td>50.0</td>
<td>73.3</td>
<td>.08</td>
</tr>
<tr>
<td>Calcium-channel blockers, %</td>
<td>7.1</td>
<td>16.3</td>
<td>.38</td>
</tr>
<tr>
<td>Heparin, %</td>
<td>92.9</td>
<td>91.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa receptor antagonists/ inhibitors, %</td>
<td>21.4</td>
<td>13.6</td>
<td>.43</td>
</tr>
<tr>
<td>Duretics, %</td>
<td>57.1</td>
<td>9.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inotropic agents (dopamine or dobutamine), %</td>
<td>21.4</td>
<td>1.2</td>
<td>.008</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>18.2</td>
<td>15.3</td>
<td>.68</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin-converting enzyme; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; LMCA, left main coronary artery.
TABLE 2. Results of Coronary Angiography in High-Risk Patients With NSTE-ACS and No Known History of Ischemic Heart Disease (n=102)

<table>
<thead>
<tr>
<th>Coronary Angiography Result</th>
<th>Patients (n=102)</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without significant angiographic lesion</td>
<td>4</td>
<td>3.9</td>
<td>1-8</td>
</tr>
<tr>
<td>Single-vascular coronary disease†</td>
<td>38</td>
<td>37.3</td>
<td>29-48</td>
</tr>
<tr>
<td>Two-vascular disease‡</td>
<td>20</td>
<td>19.6</td>
<td>12-28</td>
</tr>
<tr>
<td>Three-vascular disease‡</td>
<td>26</td>
<td>25.6</td>
<td>18-35</td>
</tr>
<tr>
<td>Left main coronary artery disease‡</td>
<td>14</td>
<td>13.7</td>
<td>8-21</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; NSTE-ACS, non-ST-segment elevation acute coronary syndrome.
†Stenosis >70%.
‡Stenosis >50%.

Among the patients with single-vessel disease (n=38, 37.3%), 21 had a lesion in the LAD, 10 in the CX and 7 in the RCA. Among the patients with 2-vessel disease (n=20, 19.6%), 8 had lesions in the RCA and LAD, 7 in the LAD and CX, and 5 in the RCA and CX.

**Relationship Between the High-Risk Variables and Left Main Coronary Artery Disease**

In the univariate analysis, the following clinical variables used in the initial risk stratification showed a statistically significant association with the presence of LMCA: age >65 years at the time of the event, history of diabetes mellitus, chronic kidney failure, signs of left heart failure detected at the time of hospital admittance, appearance of pain while at rest, recurrence of pain despite intravenous nitroglycerin administration, or presence of ventricular arrhythmia in the first 24 hours of the ischemic event. None of the electrocardiographic alterations analyzed were associated with the presence of LMCA disease, although patients with this condition showed a non-significant trend toward presenting a more highly depressed ST segment. None of the territories showing electrocardiographic signs of ischemia were associated with the group having LMCA disease. Maximum plasma concentrations of myocardial necrosis markers were not higher in patients with LMCA disease (Table 3).

In the logistic regression analysis of variables that were statistically significant in the univariate analysis, the only variable with a significant independent predictive value for LMCA disease was the presence of left heart failure at the time of hospitalization (odds ratio [OR]=32.5; 95% CI 7.8-135.3; P<.0001).

**DISCUSSION**

In this study, involving 102 high-risk patients with NSTE-ACS and no history of ischemic heart disease as defined above, 13.7% presented significant LMCA stenosis, a percentage similar to the 16% of LMCA involvement encountered in a recently published study performed in 103 patients with NSTE-ACS at high risk according to the TIMI scale. In the same study, patients considered to be at low or intermediate risk presented 3% and 7%, respectively, of significant LMCA disease. In the PRISM-PLUS study, the proportion of patients with significant LMCA disease was 10% in the group with highest values on the TIMI scale, and 4% in the groups with lower scores.

Age >65, one of the parameters used in the TIMI risk scale, was related with LMCA disease in the univariate analysis in our series. The results of the classic CASS study have already shown an association between advanced age and the presence of LMCA disease. Chronic renal failure and diabetes mellitus were also significantly associated with disease of the LMCA. The association between these risk factors and the presence of severe coronary disease is well recognized.

With regard to the prognostic importance of heart failure in NSTE-ACS, the GRACE registry disclosed a significant association between signs of left heart failure at the time of hospitalization and in-hospital and out-of-hospital mortality. In addition, the prognostic value of the Killip classification was well-established for NSTE-ACS in a recent, extensive meta-analysis in which it was an independent predictor of short- and long-term mortality, with greater prognostic value than electrocardiographic alterations or elevated myocardial necrosis markers. Thus, the search for signs of left heart failure in the initial work-up of patients with NSTE-ACS is important. Moreover, it is well recognized that because of the poor short- and medium-term prognosis of patients with NSTE-ACS and left heart failure, an early revascularization strategy is clearly beneficial for these individuals.

We found no relationship between ST-segment elevation in the aVR lead and LMCA disease. A relationship between these factors was reported in a study containing a larger number of patients. The presence of signs of left heart disease in subjects with non-Q-wave myocardial infarction was associated with the grade of ST-segment elevation in the aVR lead, and this, in turn, was related with the presence of severe coronary disease (3-vessel or LMCA disease).

In our series, signs of left heart failure in the initial work-up of high-risk patients presenting NSTE-ACS were predictive of LMCA disease. Nevertheless, it should be taken into account (as stated in the Limitations section) that these results must be interpreted in the light of the small size of the sample.
The patients analyzed herein had no known history or echocardiographic signs of having presented prior episodes of myocardial infarction. Thus, it is reasonable to believe that they had no previous areas of myocardial necrosis that could have independently contributed to the left ventricular dysfunction, apart from the current process.

Myocardial ischemia is initially accompanied by diastolic ventricular dysfunction due to decreased ventricular relaxation, with a left displacement of the diastolic pressure-volume curve, such that the ventricular diastolic pressure is greater for any given diastolic volume. When the ischemia persists, the myocardial contractile capacity decreases and systolic dysfunction develops. In an ischemic event able to alter left ventricular functionality and trigger left heart failure, there must be a considerable proportion of dysfunctional left ventricular myocardium caused by the ischemia. It has been estimated that clinical manifestations of left heart failure appear when about 25% of the left ventricular myocardium is compromised, and if the compromise reaches 40%, cardiogenic shock usually develops. The LMCA irrigates a high percentage of at-risk myocardium. In fact, the severe, acute left ventricular contractile deficit that causes the development of cardiogenic shock or acute pulmonary edema is virtually the norm in ST-segment elevation AMI when the LMCA is the culprit vessel.

According to data from the SHOCK study, hospital mortality is 78.6% in patients with AMI caused by an LMCA lesion and complicated by cardiogenic shock. A decrease in hospital mortality to 55%-58% has been reported when percutaneous revascularization is applied in patients with AMI due to a LMCA lesion, the majority complicated by cardiogenic shock. In 2 recently published studies in our setting involving patients with unstable angina or AMI who were treated with a percutaneous LMCA procedure either because they were not candidates for surgery or because they required emergency interventional procedures, the documented mortality was between 45.4% and 55%. Nevertheless, the literature shows a generalized underuse of revascularization procedures in patients with an ischemic event complicated by left heart failure or cardiogenic shock.

### TABLE 3. High-Risk Patients With NSTE-ACS and No History of Ischemic Heart Disease (n=102)

<table>
<thead>
<tr>
<th>LMCA Disease (n=14)</th>
<th>No LMCA Disease (n=88)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, %</td>
<td>64.3</td>
<td>84.1</td>
</tr>
<tr>
<td>Age &gt;65 years, %</td>
<td>57.1</td>
<td>15.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>71.4</td>
<td>33.0</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>42.9</td>
<td>18.3</td>
</tr>
<tr>
<td>Dialysis, %</td>
<td>14.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Chronic renal failure, %</td>
<td>28.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Chest pain &gt;30 min, %</td>
<td>78.6</td>
<td>70.5</td>
</tr>
<tr>
<td>Chest pain appearing at rest, %</td>
<td>92.9</td>
<td>78.4</td>
</tr>
<tr>
<td>Left heart failure, %</td>
<td>71.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Recurrent chest pain, %</td>
<td>21.4</td>
<td>44.3</td>
</tr>
<tr>
<td>Recurrent chest pain with ECG signs of ischemia, %</td>
<td>14.3</td>
<td>35.2</td>
</tr>
<tr>
<td>Cardiogenic shock, %</td>
<td>21.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Ventricular arrhythmia, %</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>49.9</td>
<td>58.8</td>
</tr>
<tr>
<td><strong>Electrocardiographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-wave changes, %</td>
<td>7.1</td>
<td>19.3</td>
</tr>
<tr>
<td>Depression ST-segment elevation, %</td>
<td>7.1</td>
<td>23.9</td>
</tr>
<tr>
<td>Grade of ST-segment depression, %</td>
<td>64.3</td>
<td>45.5</td>
</tr>
<tr>
<td>ECG inferior wall changes, %</td>
<td>35.7</td>
<td>21.6</td>
</tr>
<tr>
<td>ECG lateral wall changes, %</td>
<td>57.1</td>
<td>54.6</td>
</tr>
<tr>
<td>ECG anterior wall changes, %</td>
<td>50.0</td>
<td>56.8</td>
</tr>
<tr>
<td><strong>Biochemical variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum troponin I peak, ng/mL</td>
<td>36.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Maximum CK-MB peak, U/L</td>
<td>40.3</td>
<td>22.6</td>
</tr>
</tbody>
</table>

*CK-MB indicates creatinine kinase MB isoenzyme; ECG, electrocardiogram; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; LMCA, left main coronary artery.
Generally, the artery causing acute myocardial ischemia in NSTE-ACS does not present complete lumen occlusion and the clinical manifestations tend to be less severe than those seen in ST-segment elevation infarction. For example, in the GUSTO-IIb study, patients presenting ACS with ST-segment elevation at the time of hospitalization developed cardiogenic shock more frequently (4.2%) than those without ST-segment elevation (2.5%).

Lastly, it should be pointed out that the medical treatment given was similar between the 2 groups studied (with and without significant LMCA involvement), except in the use of diuretics and inotropic drugs (dopamine and dobutamine), which were administered more frequently in the group of patients with LMCA disease (Table 1).

CONCLUSIONS

In high-risk patients with no history of ischemic heart disease presenting with NSTE-ACS, the presence of signs of left heart disease in the initial work-up was a useful predictor of LMCA disease. In the light of these results, we believe it is worthwhile to perform emergency coronary angiography in these patients, given their poor prognosis and the possibility for improvement with therapeutic procedures such as surgical or percutaneous revascularization.

Limitations of the Study

This study has the limitations inherent to a retrospective analysis of the clinical data obtained in a single center and a small sample size. This latter aspect is a quantitative limitation, but it is also an accurate reflection of our patient population and the diagnostic and therapeutic interventions we use.

REFERENCES


Claver E et al. Clinical Predictors of Left Main Coronary Artery Disease.


