Cystatin C
A Novel Predictor of Outcome in Suspected or Confirmed Non–ST-Elevation Acute Coronary Syndrome

Tomas Jernberg, MD, PhD; Bertil Lindahl, MD, PhD; Stefan James, MD, PhD; Anders Larsson, MD, PhD; Lars-Olof Hansson, MD, PhD; Lars Wallentin, MD, PhD

Background—Patients with suspected or confirmed non–ST-elevation acute coronary syndrome (ACS) constitute a large and heterogeneous group. Measurements of renal function such as serum creatinine and estimation of creatinine clearance carry independent prognostic information in this population. Cystatin C is a new and better marker of renal function than creatinine. The aim was therefore to evaluate the prognostic value of cystatin C in this population.

Methods and Results—Cystatin C was analyzed on admission in 726 patients admitted because of symptoms suggestive of an acute coronary syndrome and no ST-segment elevations. Patients were followed up with regard to death and myocardial infarction for a median of 40 and 6 months, respectively. The median cystatin C level was 1.00 mg/L (25th to 75th percentile, 0.83 to 1.24 mg/L). The risk of death during follow-up increased with increasing levels of cystatin C. In the group with non–ST-elevation ACS, patients in the second, third, and fourth quartiles had a relative risk of subsequent death of 1.8 (95% CI, 0.6 to 5.3), 3.2 (95% CI, 1.2 to 8.5), and 11.7 (95% CI, 4.7 to 29.3) compared with the lowest quartile. In Cox regression models including well-known predictors of outcome, cystatin C level was independently associated with mortality but not with the risk of subsequent myocardial infarction. In a comparison of the markers of renal function in receiver-operating curve analyses, cystatin C had the best ability to discriminate between survivors and nonsurvivors.

Conclusions—A single measurement of cystatin C will substantially improve the early risk stratification of patients with suspected or confirmed non–ST-elevation ACS.

Key Words: angina • cystatins • kidney • myocardial infarction • prognosis

Early risk stratification is essential in the management of patients with suspected or confirmed non–ST-elevation acute coronary syndrome (ACS). Traditionally, this stratification is performed by the use of medical history, ECG, and biochemical markers of myocardial damage. In addition, other biochemical indicators such as markers of inflammation and cardiac performance are useful.1

Recently, measurements of renal function such as serum or plasma creatinine and estimation of creatinine clearance by the Cockcroft-Gault equation have been shown to carry independent prognostic information in this population.1–5 However, creatinine concentration is an unreliable estimate of the glomerular filtration rate (GFR). The level of creatinine is influenced by factors such as age, gender, muscle mass, physical activity, and diet.6 Because of the nonlinear relationship between creatinine concentration and GFR, it is also insensitive to detect small decreases in GFR and mild renal dysfunction.7

Cystatin C is a cysteine protease inhibitor involved in the catabolism of proteins. It is produced in all nucleated cells at a constant rate and is freely filtered by the glomerulus without secretion or subsequent reabsorption to the blood flow.8 Cystatin C has been shown to be a better endogenous marker of GFR than creatinine.8,9 With the introduction of rapid, sensitive, and precise immunoassays, it is now possible to use cystatin C as a marker of renal function routinely in the clinic. Therefore, the aims of the present study were to evaluate the prognostic value of cystatin C in patients with symptoms suggestive of an non–ST-elevation ACS and to compare it with that of creatinine and other biochemical indicators of increased risk.

Methods

Patient Selection
Patients admitted to the coronary care unit at the Uppsala University Hospital between March 1997 and February 1998 were eligible for participation. Inclusion criteria were a history of chest pain or other symptoms suggestive of an ACS. Exclusion criteria were prehospital thrombolysis, presence of ST-segment elevation on admission ECG,
and previous enrollment in the study. After a run-in period of 2 months, consecutive patients were included.

Of the 1194 eligible patients, 131 were excluded because of prehospital thrombolysis or ST-segment elevation on admission ECG and 170 because of previous enrollment in the study. Frozen plasma samples from 167 randomly selected patients were used for other purposes. Thus, 726 patients had an admission sample available for analysis of cystatin C.

All clinical data were prospectively collected and entered into the local database of the Swedish Register of Cardiac Intensive Care. The treatment of individual patients was left to the discretion of the individual physician. The local ethics committee approved the study.

**Laboratory Analysis**

Blood samples were collected in EDTA-containing tubes. The samples were then centrifuged, and plasma was stored frozen in aliquots at −70°C within 30 minutes. Plasma cardiac troponin T (cTnT) was determined by the third-generation cTnT assay, and plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) was determined from Elecsys proBNP sandwich immunosassay, both with an Elecsys 2010 (Roche Diagnostics). High-sensitivity C-reactive protein (CRP) measurements were performed by latex-enhanced reagent (N Latex CRP, Dade Behring) with a Behring BN ProSpec analyzer (Dade Behring). Plasma cystatin C measurements were performed by latex-enhanced reagent (N Latex Cystatin C, Dade Behring) with the same instrument. The total analytical imprecision for cystatin C was 4.8% at 0.56 mg/L and 3.7% at 2.85 mg/L. The upper reference level, defined as the 97.5th percentile value in an apparently healthy population, is 1.22 mg/L for those ≤65 years of age and 1.21 mg/L for those who are older.10 From the cystatin C level, GFR was calculated by the following formula: 

\[
GFR = \frac{172.4}{\text{cystatin C}^{1.203}}
\]

Plasma creatinine was assayed by means of the modified kinetic Jaffe reaction with a Hitachi 911 analyzer (Roche Diagnostics). Creatinine clearance rate was calculated with the Cockcroft-Gault equation.11

**Follow-Up**

The end points were death and myocardial infarction (MI). All in-hospital events were registered in the local database of the Swedish Register of Cardiac Intensive Care. Only new MIs occurring >24 hours after admission were considered new events. Out-of-hospital information about death was obtained from the National Registry on Mortality, with a median follow-up time of 40 months (range, 35 to 47 months). With regard to MI outside hospital, the median follow-up time was 6 months (range, 1 to 13 months). Information was obtained from the hospital diagnosis registry and patient records. This information contains complete data on all admissions to the only hospital providing hospital care for acute diseases for the present patient population. For the diagnosis of acute MI, both index and recurrent events, one of the following should be fulfilled: (1) pathological Q waves developing in ≥2 leads, (2) symptoms suggestive of acute MI and typical elevated levels of biochemical markers with creatine kinase-MB ≥10 µg/L (and a creatine kinase-MB rise of ≥50% from previous level in case of an MI occurring soon after the index event), and (3) signs of acute MI at autopsy.

**Statistical Analysis**

All data analysis was performed with the Statistical Package for Social Sciences (SPSS 11.5) software (SPSS Inc). Differences in proportions were judged by χ² analysis. If not stated otherwise, continuous data are given as median value (25th to 75th percentile). The Kruskal-Wallis test was used to test the equality of distributions in the 4 cystatin C groups. To evaluate the correlation between the level of cystatin C and levels of cTnT, NT-proBNP, CRP, and creatinine, Spearman’s rank correlation coefficient was calculated. The Kaplan-Meier method was used to analyze the timing of events during follow-up. Statistical assessment was performed with the log-rank test, with values of P<0.05 considered significant. To compare the prognostic value of cystatin C and creatinine, receiver-operating characteristic (ROC) curves were generated, and the area under the curves was calculated. For the ROC analysis, death at 35 months was used as an end point. To identify predictors of death and MI, univariate Cox regression analyses were used. All variables with a value of P<0.10 were then tested in a multivariate Cox regression analysis using backward stepwise selection. Variables were removed if values of P>0.10.

**Results**

**General Findings**

Baseline characteristics, findings on admission ECG, and diagnoses within 24 hours of admission are listed in Table 1. Of 380 patients with non–ST-elevation ACS, 61 (16%) and 88 (23%) were revascularized during the hospital stay and during 30 days after admission, respectively. During follow-up, there were 161 deaths (22%).

**Cystatin C**

The median value of cystatin C was 1.00 mg/L (25th to 75th percentile, 0.83 to 1.24 mg/L) (cystatin C–derived GFR, 77 mL/min [25th to 75th percentile, 59 to 98 mL/min]). A total of 212 patients (29%) had a cystatin C level above the upper reference level, defined as the 97.5th percentile value in an apparently healthy population (age ≤65 years, 1.12 mg/L; age >65 years, 1.21 mg/L).10 The relationship between cystatin C level and clinical background factors is shown in Table 1. Patients with elevated levels of cystatin C were older and more likely to have adverse baseline characteristics.

The group with a cTnT <0.01 µg/L on admission had a median level of cystatin C of 0.95 mg/L (25th to 75th percentile, 0.81 to 1.16 mg/L) (cystatin C–derived GFR, 82 mL/min [25th to 75th percentile, 64 to 101 mL/min]). In patients with cTnT ≥0.01 µg/L, the median level was 1.12 mg/L (25th to 75th percentile, 0.92 to 1.54 mg/L) (cystatin C–derived GFR, 67 mL/min [25th to 75th percentile, 47 to 86 mL/min]). In the latter group, there was a weak correlation between level of cTnT and level of cystatin C (r=0.25, P<0.001). The cystatin C level also correlated weakly to the CRP level (r=0.31, P<0.001) and moderately to the levels of NT-proBNP (r=0.59, P<0.001) and creatinine (r=0.61, P<0.001).

**Cystatin C and Mortality**

The risk of death during follow-up increased with increasing levels of cystatin C (Figure 1). In the group with non–ST-elevation ACS, patients in the second, third, and fourth quartiles had a relative risk of subsequent death of 1.8 (95% CI, 0.6 to 5.3), 3.2 (95% CI, 1.2 to 8.5), and 11.7 (95% CI, 4.7 to 29.3) compared with the lowest quartile (Figure 2A). In the group, with noncardiac or unknown causes to their symptoms, there was a similar association between cystatin C level and mortality (Figure 2B). In a Cox regression model including variables significantly associated with mortality in the univariable analyses, the cystatin C level was independently associated with mortality (Table 2). The level of cystatin C remained an independent predictor of mortality when the same model was tested in patients with non–ST-elevation ACS. Also, when revascularization within 30 days was added to the final model in patients with non–ST-elevation ACS, the
The association between cystatin C and mortality remained unchanged.

When the upper reference level (age ≥65 years, 1.12 mg/L; age >65 years, 1.21 mg/L) was used as cutoff value, the 35-month mortality was 44% in the group with elevated cystatin C compared with 10% (P <0.001) in the group with lower cystatin C levels (sensitivity, 64%; specificity, 80%). When the cutoff value with the highest sensitivity and specificity according to ROC analysis (Figure 3) was used, a cystatin C level >1.06 mg/L (cystatin C–derived GFR, <72 mL/min) identified 299 patients (41%) with a 35-month mortality of 37% compared with 8% in those with lower cystatin C levels. (sensitivity, 76%; specificity, 68%).

**Comparison Between Cystatin C and Creatinine**

In a comparison of the markers of renal function in ROC analyses, cystatin C had the best ability to discriminate between survivors and nonsurvivors (Figure 3). The area
under curve was 0.79 (95% CI, 0.74 to 0.83) for cystatin C, 0.72 (95% CI, 0.68 to 0.77) for creatinine clearance, and 0.66 (95% CI, 0.61 to 0.72) for creatinine. When patients were divided into quartiles according to levels of creatinine, creatinine clearance, and cystatin C, the cystatin C level was the best marker to separate low- from high-risk patients (Figure 4). In a Cox regression model including the 3 markers of renal function (either as continuous variables or as variables categorized into quartiles), the cystatin C level remained independently associated with mortality.

Cystatin C and MI

With regard to the rate of MI, the patients were followed up for a median time of 6 months (range, 1 to 13 months). In the univariable analysis, there was a significant association between cystatin C level and risk of subsequent MI. The cumulative probability of MI at 12 months was 4.4%, 5.3%, 12.3%, and 20.3% (log-rank \(P=0.02\)) for the respective quartiles. However, when adjusted for other variables associated with outcome, cystatin C was not an independent predictor of future MI.

Discussion

It has been known for several years that patients with end-stage renal disease have a high prevalence of cardiovascular disease and excessive cardiovascular mortality. More recently, mild to moderate renal impairment has also been shown to be strongly associated with cardiovascular morbidity and mortality in patients with atherosclerotic disease and in the general population.

The important prognostic value of renal function in patients with ACS has been demonstrated in substudies of clinical trials and in studies including more unselected patients. Measurement of renal function has therefore emerged as one of several risk markers to be included in the early assessment of these patients. In most previous studies, renal function has been measured as serum or plasma level of creatinine or by an estimation of GFR by the Cockcroft-Gault equation. The level of creatinine, however, is an unreliable indicator of renal function and is influenced by several other factors. Although the Cockcroft-Gault equation improves the estimation, there is a nonlinear relationship between creatinine concentration and GFR, which leads to overestimation of GFR at high levels of creatinine and underestimation of GFR at low values of creatinine.

Recently, assays have been introduced to measure cystatin C, which has been shown to be a better marker of GFR than creatinine.

The present study is the first to demonstrate that measurement of cystatin C substantially improves the early risk stratification of the large population of patients with suspected or confirmed non–ST-elevation ACS. When patients were divided according to final diagnosis into those with non–ST-elevation ACS, those with other cardiac causes, and those with other noncardiac or unknown causes, the prognostic value of cystatin C was evident in all groups. When adjusted for other well-known predictors of outcome, the cystatin C level remained an independent predictor of mortality.

During follow-up, there was a stepwise increase in mortality with increasing levels of cystatin C. The cumulative probability of death was 55.6% in the highest quartile (cystatin C ≥1.25 mg/L; cystatin C–derived GFR <58 mL/min) compared with 6.8% in the lowest quartile (cystatin C <0.83 mg/L; cystatin C–derived GFR >98 mL/min). In

![Figure 1](http://circ.ahajournals.org/)

*Figure 1. Cumulative probability of death in patients with cystatin C <0.83 mg/L (n=183; group 1), 0.83 to 0.99 mg/L (n=182; group 2), 1.00 to 1.24 mg/L (n=182; group 3), and ≥1.25 mg/L (n=179; group 4). Group 1 vs 2, log-rank \(P=0.07\); group 2 vs 3, log-rank \(P=0.002\); group 3 vs 4: log-rank \(P<0.001\). Curves are terminated when <10 remain at risk. GFR was calculated as \(77.24 \times \text{cystatin C}^{-1.263}\).*

![Figure 2](http://circ.ahajournals.org/)

*Figure 2. Cumulative probability of death in patients with (A) non–ST-elevation ACS (n=76, 92, 106, 106) (pooled log-rank \(P<0.001\)) and (B) other noncardiac or unknown causes (n=92, 76, 53, 32) (pooled log-rank \(P<0.001\)). Curves are terminated when <10 remain at risk.*
clinical practice and in decision algorithms, a single cutoff value can be convenient. The present findings suggest that the upper reference level, defined as the 97.5th percentile value in apparently healthy individuals, could be a suitable decision limit. The upper reference level (age < 65 years, 1.12 mg/L; age ≥ 65 years, 1.21 mg/L) divided patients into low- and high-risk groups with a 35-month mortality of 10% and 44%, respectively. Cystatin C levels even below the upper reference limit were associated with increased mortality (Figures 1 and 2). However, a cutoff value below the upper reference value would lead to an unacceptably low specificity.

When the prognostic value of cystatin C was compared with that of plasma creatinine and creatinine clearance calculated from the Cockcroft-Gault equation, cystatin C was a better marker to discriminate between survivors and nonsurvivors. When patients were categorized into quartiles for each marker, cystatin C was best for separating high- and low-risk patients. For cystatin C, the fourth quartile had a 12-times-higher mortality compared with the first quartile. For creatinine clearance and creatinine, the highest quartiles had a 6- and 3-times-higher mortality, respectively, compared with the lowest quartiles. Thus, an improved estimate of GFR will improve the ability to predict outcome in patients with symptoms suggestive of non–ST-elevation ACS.

The strong association between renal function and mortality probably is explained by several cooperating mechanisms. One reason seems to be that renal dysfunction indicates a generalized atherosclerosis and vascular damage.18 In accor-

### TABLE 2. Cox Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.06–1.09)</td>
<td>&lt;0.001</td>
<td>1.04 (1.02–1.07)</td>
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<td>Male</td>
<td>1.01 (0.73–1.38)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.17 (1.54–3.06)</td>
<td>&lt;0.001</td>
<td>1.81 (1.18–2.79)</td>
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<tr>
<td>Hypertension</td>
<td>1.32 (0.97–1.80)</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.24 (0.84–1.84)</td>
<td>0.273</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.89 (1.39–2.58)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>0.72 (0.46–1.13)</td>
<td>0.154</td>
<td></td>
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<tr>
<td>Previous congestive heart failure</td>
<td>2.50 (1.82–3.42)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ECG on admission</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No ST depression</td>
<td>1</td>
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<td></td>
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<tr>
<td>ST depression ≥0.05 mV</td>
<td>3.29 (2.32–4.66)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>LBBB</td>
<td>5.95 (3.75–9.42)</td>
<td>&lt;0.001</td>
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<tr>
<td>cTnT, μg/L</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>&lt;0.01–0.04</td>
<td>2.82 (1.80–4.41)</td>
<td></td>
<td>1.29 (0.74–2.26)</td>
</tr>
<tr>
<td>0.05–0.23</td>
<td>2.55 (1.63–3.99)</td>
<td></td>
<td>1.23 (0.69–2.22)</td>
</tr>
<tr>
<td>≥0.24</td>
<td>4.59 (3.06–6.88)</td>
<td></td>
<td>2.21 (1.29–3.79)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤113</td>
<td>1</td>
<td></td>
<td>1</td>
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<tr>
<td>113–400</td>
<td>3.07 (1.22–7.74)</td>
<td>0.017</td>
<td>1.40 (0.37–5.33)</td>
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<td>401–1653</td>
<td>8.34 (3.55–19.6)</td>
<td>&lt;0.001</td>
<td>2.92 (0.82–10.4)</td>
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<td>≥1654</td>
<td>21.6 (9.46–49.5)</td>
<td>&lt;0.001</td>
<td>3.19 (0.85–11.9)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤1.11</td>
<td>1</td>
<td></td>
<td>1</td>
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<tr>
<td>1.11–2.76</td>
<td>0.85 (0.34–1.84)</td>
<td>0.680</td>
<td>0.77 (0.35–1.68)</td>
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<tr>
<td>2.77–7.32</td>
<td>1.69 (0.87–3.28)</td>
<td>0.122</td>
<td>0.89 (0.45–1.76)</td>
</tr>
<tr>
<td>≥7.33</td>
<td>5.61 (3.13–10.0)</td>
<td>&lt;0.001</td>
<td>2.06 (1.09–3.88)</td>
</tr>
<tr>
<td>Cystatin C, mg/L (GFR, mL/min)</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>&lt;0.83 (&gt;98)</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0.83–0.99 (78–98)</td>
<td>2.07 (0.93–4.60)</td>
<td>0.075</td>
<td>1.44 (0.48–4.26)</td>
</tr>
<tr>
<td>1.00–1.24 (59–77)</td>
<td>4.98 (2.41–10.3)</td>
<td>&lt;0.001</td>
<td>2.13 (0.79–5.75)</td>
</tr>
<tr>
<td>≥1.25 (58)</td>
<td>15.0 (7.56–19.7)</td>
<td>&lt;0.001</td>
<td>4.28 (1.64–11.2)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; LBBB, left bundle-branch block. GFR was calculated as 77.24 × cystatin C exponent -2.346. For troponin T, patients were categorized into those with a value <0.01 μg/L and 3 equally sized groups with a value ≥0.01 μg/L. For other biomarkers, patients were categorized into quartiles.
Patients are divided into quartiles with the following cutoff values: for creatinine, 86, 98, and 115 μmol/L; for creatinine clearance, 41.8, 57.4, and 79.1 mL/min; and for cystatin C, 0.83, 1.00, and 1.25 mg/L.

Figure 3. ROC curve with regard to death at 35 months for creatinine, creatinine clearance, and cystatin C with area under curve of 0.66 (95% CI, 0.61 to 0.72), 0.72 (95% CI, 0.68 to 0.77), and 0.79 (95% CI, 0.74 to 0.83), respectively.

A trend with earlier reports, patients with renal dysfunction, as reflected by high levels of cystatin C in our study, were older and had more often diabetes, hypertension, and history of prior MI. They also presented more often with high-risk features such as ST-segment depression and elevated levels of troponin T, CRP, and NT-proBNP, reflecting more severe coronary artery disease. In addition to being a marker of increased risk, renal dysfunction may directly promote atherosclerosis by causing changes in parameters such as blood pressure, lipids, lipoproteins, homocysteine, and CRP. Another reason for the poor prognosis may be that patients with ACS and renal dysfunction are less likely to receive adequate treatment compared with those without renal dysfunction.

In the present study, the level of cystatin C was independently associated with mortality in patients without cardiac causes for their symptoms (Figure 2B). This may indicate that the association between renal function and atherosclerotic processes is not the only reason for the increased mortality seen at higher cystatin C levels. Also, the lack of independent association between cystatin C and the risk of future MI in our study may imply that there are also other reasons for the association between cystatin C and mortality. However, the power to detect an independent association between cystatin C level and risk of future MI was low. A previous larger study has found measurements of renal function to be independently associated with the risk of subsequent MI in ACS patients.

In this study, almost one third of the patients had a cystatin C level above the upper reference level in healthy control subjects. This finding is well in line with previous findings of a high prevalence of renal insufficiency in the present population and emphasizes the importance of considering renal function when evaluating patients with ACS. However, to be useful, a clinical risk indicator should not only identify patients with increased risk but also help the clinician to select the appropriate treatment. So far, studies have demonstrated that patients with mild to moderate renal impairment seem to benefit to a similar extent from fibrinogen receptor blockers, early revascularization, and long-term ACE inhibitors. These studies carry important messages because patients with mild to moderate impairment are less likely to receive such treatment. Still, further studies are needed to examine whether patients with ACS and mild to moderate renal dysfunction should be treated differently than ACS patients with normal renal function.

Conclusions

Early risk stratification of patients with suspected or confirmed non–ST-elevation ACS is essential. Estimation of renal function by measuring creatinine and calculating creatinine clearance has emerged as an important part in this process. The present study strongly suggests that measuring plasma cystatin C not only is more practical at bedside by making complicated calculations unnecessary but also will substantially improve the early assessment of these patients.

Acknowledgment

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References

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