Prognostic value of ischaemia-modified albumin in patients with non-ST-segment elevation acute coronary syndromes

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KEYWORDS
Acute coronary syndrome; Ischaemia-modified albumin; Prognostic value

Summary
Background. — Ischaemia-modified albumin (IMA) is a new sensitive diagnostic biochemical marker of myocardial ischaemia. The purpose of the study was to analyse the prognostic value of IMA in patients admitted for non-ST-segment elevation acute coronary syndromes (NSTE ACS).
Methods. — Consecutive patients admitted for NSTE ACS in our institution were prospectively included. IMA, cardiac troponin I (TnI) and C-reactive protein (CRP) were measured in all patients within 3 h of last chest pain. The clinical combined endpoint was major adverse cardiac events (MACE) including cardiac death, nonfatal myocardial infarction (MI) and recurrent ischaemia leading to urgent revascularization. The independent prognostic impact of IMA on occurrence of the combined endpoint during hospitalization and at 1 year was tested by a logistic regression model and was systematically adjusted for other known clinical and biological predictors.
Results. — Seventy-nine patients were enrolled. Nine (11.4%) patients experienced the combined endpoint during hospitalization and 16 (20.2%) during 1-year follow-up. Median IMA level
Background

Several cardiac biomarkers, now routinely available to clinicians, have emerged as strong predictors of risk in patients presenting with non-ST-elevation acute coronary syndromes (NSTE ACS). Elevated levels of troponin I (TnI) [1], C-reactive protein (CRP) [2] and B-type natriuretic peptide (BNP) [3,4] are associated with higher rates of death and recurrent ischaemic events after NSTE ACS. Several recent studies have shown that ischaemia-modified albumin (IMA), as measured by the albumin cobalt binding (ACB) test, can be a potential novel marker of transient myocardial [5–7] or peripheral ischaemia [8]. The ACB test measures the binding capacity of exogenous cobalt to the N-terminus of human albumin. In the presence of ischaemia, structural changes take place in the N-terminus of albumin that rapidly reduces its binding capacity for transition metal ions. Recent studies have shown that IMA is highly sensitive for identifying ACS, with a good negative predictive value in patients with a normal electrocardiogram and negative troponin [6,7]. IMA has also been shown to be elevated in patients after percutaneous coronary intervention (PCI) as a result of periprocedural ischaemia [9–11]. However, the prognostic value of IMA has only been tested in studies of patients with end-stage renal disease [12], presenting with chest pain [13] and after elective PCI [14], but no data are available about the prognostic value of IMA after NSTE ACS. We therefore designed a prospective study to assess the additional prognostic value of IMA over conventional clinical and biochemical markers of cardiovascular (CV) risk in patients with NSTE ACS.

Methods

Patient population

Consecutive patients admitted for NSTE ACS within 3 h of last chest pain between June 2006 and December 2006 were eligible for this prospective study. Patients were required to have crescendo, prolonged (≥ 20 min) or recurrent (≥ two episodes lasting at least 5 min) anginal pain at rest or with minimal effort within the prior 24 h that was...
accompanied by objective evidence of ischaemic heart disease. The latter consisted of electrocardiographic (ECG) changes (ST depressions greater than or equal to 0.05 mV, transient ST elevations greater than or equal to 0.10 mV or T-wave inversions greater than or equal to 0.3 mV in at least two leads), elevated cardiac biomarkers of necrosis or a documented history of coronary artery disease. The exclusion criteria were age below 18 years, persistent ST-segment elevation acute coronary syndrome (ACS), New York Heart Association class IV, coronary artery bypass graft (CABG) surgery within the previous 3 months, creatinine clearance below 30 mL/min, total serum albumin extremely low (< 30 g/L) or extremely high (> 55 g/L), patient samples that appeared grossly lipaemic or icteric, severe peripheral or cerebral vascular disease or refusal of the patients to participate. Patients were treated according to current guidelines [15–17]. The initial strategy was either invasive (PCI) or medical (including patients with a culprit lesion not suitable for PCI after coronary angiography).

Clinical data

Clinical data were collected on admission including history of coronary artery disease (defined as previous CABG or PCI), diabetes mellitus, ECG changes (as defined above) and ejection fraction (by echocardiography). All patients had baseline blood samples collected on admission and within 3 h of the last ischaemic episode.

Measurement of biochemical markers

Blood samples for testing cardiac biomarkers (TnI, CRP and IMA) were drawn in the coronary care unit. TnI was measured using the ADVIA centaur® TnI (Siemens medical solution diagnostics SAS, 95613 Cergy-Pontoise cedex, France, cut-off value: 0.3 ng/mL). CRP was measured on a Synchron® LX 20 analyzer (Beckman Coulter, 95942 Villepinte—Roissy-CDG, France). IMA was evaluated as described previously [18]. Briefly, the ACB test is a quantitative in vitro diagnostic test that detects IMA by measuring the cobalt binding capacity of albumin in human serum (Ischemia Technologies, Denver, CO). Human serum, including that collected in serum separator tubes, is the only specimen type for the ACB-test version, CO). Human serum, including that collected in serum of albumin in human serum (Ischemia Technologies, Den-

France). IMA was evaluated as described previously [18]. Optimal discrimination limits were identified at the cut point value below 0.05 were considered statistically significant. To assess the best predictive value of IMA, receiver operating characteristic (ROC) curves were generated, and the area under the curves (AUC) was calculated. Optimal discrimination limits were identified at the cut point that maximizes sensitivity and specificity to predict hospital and 1-year outcomes. The sensitivity and specificity for group distinction were determined according to sensitivity, i.e.: true positives/true positives + false negative) × 100% and specificity, i.e.: (true negatives/true negatives + false positives) × 100%.

Results

A total of 79 patients with NSTE ACS who fulfilled the enrolment criteria were included in our study. Demographic data are summarized in Table 1. The mean age was 68.8 ± 14 years and 73.4% were men. Fifty-three (67%) patients had significant ECG changes. Sixteen (20.2%) patients presented with troponin elevation at admission above the cut-off defined by the laboratory, with a median value of 0.03 ng/mL (range: 0–32.4). The median value for
Table 1 Clinical characteristics of the population.

| Characteristic | N = 79 | Men, N (%) | 58 (73.4) | Women, N (%) | 21 (26.6) | Age (years)a | 64.8 ± 14 | History of revascularization (CABG or PCI), N (%) | 36 (45.5) | Previous CABG, N (%) | 10 (12.7) | Previous PCI, N (%) | 26 (32.9) | Diabetes mellitus, N (%) | 19 (24.1) | Current smoker, N (%) | 46 (58.2) | Hypertension, N (%) | 60 (75.9) | Family history of CAD, N (%) | 9 (11.4) | Dystipidaemia, N (%) | 55 (69.6) | Body mass index (kg/m²)a | 25.6 ± 2.9 | ECG changes: ST depression or T-wave inversion, N (%) | 53 (67) | Troponin I (ng/mL)b | 0.03 (0–32.4) | Positive troponin at admission | 16 (20.2) | C-reactive protein (mg/L)b | 10 (1–159) | Ischaemia modified albumin (U/mL)b | 102 (42–138) | Glycoprotein IIb/IIIa antagonists, N (%) | 21 (26.6) | Initial invasive strategy, N (%) | 33 (41.7) | Ejection fraction ≤ 40%, N (%) | 11 (14) | Ejection fraction (%)b | 49.6 ± 8 |

a Mean ± standard deviation.
b Median (range).

CABG: coronary artery bypass graft; CAD: coronary artery disease; ECG: electrocardiographic; PCI: percutaneous coronary intervention.

CRP was 10 mg/L (range: 1–159). Results for IMA analysis showed a normal distribution from 42 to 138 U/mL, with a median value of 102 U/mL (mean: 100 ± 18).

Predictors of in-hospital events

During hospitalization, nine (11.4%) MACE occurred, including two CV deaths, five nonfatal MI (including one failed PCI and one acute stent thrombosis) and two recurrent ischaemias leading to urgent revascularization (one after previous PCI on another segment and one after the initial medical strategy). Median IMA and TnI values were significantly higher in patients with MACE during hospitalization (Table 2). There was no statistically significant difference in median CRP in patients with MACE, as well as TnI and CRP (Table 4).

Table 2 Predictors of in-hospital major adverse cardiovascular events (MACE): univariate analysis.

<table>
<thead>
<tr>
<th>Biomarkers, median (range)</th>
<th>MACE</th>
<th>No MACE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia-modified albumin (U/mL)</td>
<td>115 (93–126)</td>
<td>100 (42–138)</td>
<td>0.007</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>1.13 (0.03–32.4)</td>
<td>0.03 (0.03–25.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>12 (5–159)</td>
<td>10 (1–60)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 3 Predictors of in-hospital major adverse cardiovascular events (MACE): multivariable analysis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive proteina</td>
<td>1.00</td>
<td>0.97–1.04</td>
<td>0.81</td>
</tr>
<tr>
<td>Troponin Ia</td>
<td>1.06</td>
<td>0.93–1.22</td>
<td>0.34</td>
</tr>
<tr>
<td>Agea</td>
<td>1.07</td>
<td>0.98–1.18</td>
<td>0.12</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.53</td>
<td>0.14–17.28</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.90</td>
<td>0.16–22.82</td>
<td>0.61</td>
</tr>
<tr>
<td>Ejection fractiona</td>
<td>0.90</td>
<td>0.81–1.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Invasive strategy (PCI)</td>
<td>0.47</td>
<td>0.06–3.71</td>
<td>0.47</td>
</tr>
</tbody>
</table>

a Continuous variables.

Figure 1. Major adverse cardiovascular event (MACE)-free survival during the first year after diagnosis according to initial value of ischaemia modified albumin (cut-off: 109). IMA: ischaemia-modified albumin.

MAE remained an independent predictor of MACE during hospitalization (Table 3).

Predictors of 1-year follow-up

MACE reported at 1 year included in-hospital events. Sixteen (20.2%) MACE were reported, including four (5%) CV deaths, eight (10.1%) nonfatal MI and four (5%) recurrent ischaemias leading to urgent revascularization. IMA level was significantly higher in patients with MACE, as was TnI and CRP (Table 4).
Table 4  Predictors of 1-year follow-up major adverse cardiovascular events (MACE): univariate analysis.

<table>
<thead>
<tr>
<th>Biomarker, median (range)</th>
<th>MACE</th>
<th>No MACE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia-modified albumin (U/mL)</td>
<td>114 (93–126)</td>
<td>97 (42–138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>0.33 (0.03–32.4)</td>
<td>0.03 (0.03–25.81)</td>
<td>0.015</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>12 (5–159)</td>
<td>9 (1–60)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Fig. 1 shows MACE-free survival during the first year after diagnosis. After adjustment for clinical characteristics (age, sex, diabetes mellitus and left ventricular ejection fraction), biological data (CRP and TnI) and initial treatment strategy (invasive or medical), IMA remained an independent predictor of MACE at 1 year as was ejection fraction (Table 5). The prognostic accuracy of this Cox model was relatively good (C-index: 0.82). There was no correlation between different biomarkers (maximal indct between CRP, cTnI and IMA: 0.23).

Determination of predictive cut-off value of IMA for 1-year prognosis

Using ROC analysis we determined the most predictive value of IMA for 1-year prognosis. The cut-off was found to be 109 U/mL (area under ROC curve: 0.79), predicting MACE with positive and negative predictive values of 44.4 and 91.7%, respectively (odds ratio [OR]: 8.8; CI 95%: 2.46–31.48) (Fig. 2). Fifty (63.3%) patients had an IMA value below 109 U/mL with four (8%) events, and 29 (36.7%) patients had an IMA value greater than or equal to 109 U/mL with 12 events (41.4%) (OR: 8.8; CI 95%: 2.46–31.48; p=0.008) (Fig. 3).

Discussion

This study showed the potential in-hospital and 1-year prognostic value of IMA in patients with NSTE ACS. In multivariable analysis, we demonstrated that IMA is an independent predictor of in-hospital and 1-year follow-up events. In addition, we have demonstrated that a cut-off value of 109 U/mL might be a reliable threshold to predict increased risk of events in patients with NSTE ACS.

CV disease is the principal cause of mortality in industrialized countries [16,17,19,20]. It is responsible, each year, for 100,000 deaths in Europe [19,20] and 500,000 deaths in the United States [16,21,22]. According to the European Society of Cardiology guidelines, markers indicating a high-risk patient include recurrent ischaemia, recurrent chest pain, elevated troponin levels, diabetes mellitus, haemodynamic instability, early postinfarction unstable angina and dynamic ST-segment changes (ST-segment depression or transient segment elevation) [16,17]. Biomarkers of MI (TnI, CK), systemic inflammation (CRP) and haemodynamic stress (BNP and NTproBNP) have already been shown to be accurate prognostic markers in NSTE ACS [1—4]. It is currently standard that patients presenting with chest pain to an emergency department (ED) are evaluated not only by ECG but also by determination of cardiac biomarkers of myonecrosis, including CK and TnI. However, these markers

Table 5  Predictors of 1-year follow-up major adverse cardiovascular events (MACE) in multivariable analysis.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia-modified albumin (U/mL)a</td>
<td>1.07</td>
<td>1.03–1.12</td>
<td>0.003</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)a</td>
<td>0.99</td>
<td>0.98–1.02</td>
<td>0.95</td>
</tr>
<tr>
<td>Troponin I (ng/mL)a</td>
<td>1.02</td>
<td>0.95–1.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Agea</td>
<td>1.05</td>
<td>0.99–1.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.37</td>
<td>0.47–12.05</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.65</td>
<td>0.36–7.54</td>
<td>0.52</td>
</tr>
<tr>
<td>Ejection fractiona</td>
<td>0.91</td>
<td>0.86–0.97</td>
<td>0.004</td>
</tr>
<tr>
<td>Invasive strategy (PCI)</td>
<td>0.97</td>
<td>0.31–3.04</td>
<td>0.96</td>
</tr>
</tbody>
</table>

C-index: 0.82.  
a Continuous variables.
neous coronary angioplasty and/or antithrombotic therapy remains difficult. The additive value of IMA could be helpful in identifying these patients. The pathophysiology of ACS is complex; therefore, it is unlikely that a single biomarker could evaluate global CV risk. Thus, it is of interest to propose that multimarker scores using several biomarkers could potentially be used to predict CV risk and patient prognosis. Several studies support the concept of a multimarker strategy for risk stratification in patients with ACS [23,24]. IMA, with its excellent negative predictive value, could be integrated into a risk score associated with TnI, BNP and CRP [25]. In addition, IMA could be used in primary prevention to detect asymptomatic ischaemia and/or hypoxic stress in high-risk CV patients. The potential mechanisms responsible for the strong association between IMA elevations and short- and long-term major CV events cannot be ascertained in the present study. IMA is a sensitive but unspecified marker of myocardial ischaemia, whose level is also elevated in nonmyocardial ischaemia. Thus, IMA—a like cardiac TnI—should be integrated with the clinical context for prognostic assessment.

Study limitations

The main limitations of our study were the small sample size and occurrence of events. The results should be confirmed in larger studies. Nevertheless, the baseline characteristics of the population correspond to epidemiological registries published on NSTE ACS [19—22] and the prognostic value of TnI and CRP [1,2,25]. Moreover, additional research is required to understand the physiopathological link between elevated levels of IMA and increased risk of MACE in patients with NSTE ACS.

Conclusions

In this study, baseline IMA level was associated with both short- and long-term recurrent ischaemic events in patients admitted to hospital for NSTE ACS. In addition, a cut-off of 109 U/mL had a good predictive negative value, which is potentially usable in daily clinical practice. These data suggest that IMA—a diagnostic biochemical marker of NSTE ACS—is also of prognostic value in this clinical setting.

Conflict of interest

None.

Financial disclosure

None.

References


