Serum Amyloid A Predicts Early Mortality in Acute Coronary Syndromes: A TIMI 11A Substudy
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OBJECTIVES
We evaluated the ability of serum amyloid A (SAA), alone and in combination with a rapid qualitative assay for cardiac-specific troponin T (cTnT), to predict 14-day mortality in patients with unstable angina or non-Q-wave myocardial infarction (NQMI).

BACKGROUND
Elevated C-reactive protein (CRP) has been associated with adverse outcomes in unstable coronary syndromes but data regarding its acute phase counterpart, SAA, are conflicting.

METHODS
Serum amyloid A measurement and a rapid cTnT assay were performed on blood obtained at enrollment into Thrombolysis in Myocardial Infarction 11A, a dose-ranging trial of enoxaparin for unstable angina and NQMI.

RESULTS
Serum amyloid A was higher in patients who died compared with survivors (6.28 vs. 0.75 mg/dL, p = 0.002). Among patients with a negative rapid cTnT, mortality was higher for those in the top quintile of SAA (6.1 vs. 0.7%, p = 0.003). Patients with both an early positive rapid cTnT (≤10 min until assay positive) and SAA in the fifth quintile had the highest mortality followed by those with either markedly elevated SAA or an early positive rapid cTnT, while patients with both a negative rapid cTnT and SAA in quintiles 1–4 were at very low risk, (9.1 vs. 3.6 vs. 0.7%, p < 0.002).

CONCLUSIONS
Similar to CRP, baseline elevation of SAA identifies patients hospitalized with unstable angina and NQMI at higher risk for early mortality, even among those with a negative rapid assay for cTnT. These data support further investigation of inflammatory markers used alone and in combination with cardiac troponins for risk assessment in unstable coronary syndromes. (J Am Coll Cardiol 2000;35:358–62) © 2000 by the American College of Cardiology

 Serum cardiac markers provide diagnostic and prognostic information that may refine our ability to manage the heterogeneous population presenting with acute coronary syndromes. Candidate markers reflect critical elements involved in the evolution of an acute coronary syndrome (1). With inflammation now recognized as contributing to atherogenesis (2,3), inflammatory proteins have been investigated as potential indicators of underlying atherosclerosis (4,5) as well as “unstable” atheromatous lesions (6–8). Elevated levels of C-reactive protein (CRP), the prototypical acute phase protein, are associated with adverse cardiovascular outcomes in patients with stable (9) and unstable ischemic heart disease (7–9), as well as healthy men without clinical vascular disease (5). However, the specific mechanism(s) underlying these associations between CRP and prognosis are unclear, and thus researchers continue to evaluate other inflammatory markers which might provide consistent evidence of a correlation between systemic inflammation and cardiovascular risk (10,11).

 Serum amyloid A (SAA), also an important acute phase protein, has an expanded dynamic range with different kinetics compared with CRP (12–14) and is reported to be a more sensitive indicator of inflammation in some noncardiovascular inflammatory conditions (14,15). However, SAA has not been examined as extensively in ischemic heart disease (7,9,16) and prospective studies have shown conflicting results regarding prognosis (7,9,17). We have previously demonstrated the ability of CRP, alone and in conjunction with a rapid bedside assay for cardiac-specific troponin T (cTnT), to predict 14-day mortality in a cohort of patients hospitalized with unstable angina or non-Q-wave...
myocardial infarction (NQMI) (8). In this analysis, we now evaluate whether a similar relationship exists between SAA and clinical outcome in this population of patients presenting with non-ST elevation acute coronary syndromes.

METHODS

Patients. Men and women admitted with unstable angina or NQMI and enrolled in Thrombolysis In Myocardial Infarction (TIMI) 11A at any of the 45 participating centers were eligible for the serum marker substudy. TIMI 11A was an open-label dose ranging study of the low molecular weight heparin, enoxaparin, in patients with evidence of ischemic heart disease presenting with unstable angina or NQMI within the prior week. Further details of the inclusion criteria have been outlined previously (18). Patients with an evolving Q-wave myocardial infarction (MI) or thrombolytic therapy within 24 h before randomization, coronary artery bypass surgery (CABG) within the previous two months or other serious illness (active cancer, significant hepatic or renal dysfunction) were excluded. Patients received one of two weight-based doses of subcutaneous enoxaparin plus aspirin administered in hospital for a minimum of 48 h and then continued on a fixed dose of enoxaparin subcutaneous Q12 h for a total treatment period of two weeks, after which each patient’s clinical status was ascertained (18).

Blood sampling and measurement of serum markers. The serum marker protocol specified that a blood specimen be drawn at enrollment for the determination of baseline cardiac markers. The sera were stored at −20°C or colder until shipped to a core laboratory (Clinical Chemistry Laboratory, Children’s Hospital, Boston, Massachusetts) where all samples were assayed by a single operator blinded to patient treatment and outcome. Quantitative serum SAA (N Latex SAA, Dade Behring, Newark, Delaware) determination was performed on the BN II Nephelometer (Dade Behring, Newark, Delaware). The sensitivity of the assay is 0.08 mg/dL with variability at concentrations of 1.15 and 8.16 mg/dL of less than 7.3%. Quantitative CRP has been previously measured using the N Latex CRP monoassay (Dade Behring).

A rapid qualitative assay for cTnT was performed at enrollment at each site. The intensity of the color and speed with which a positive assay result develops correlates with the concentration of cTnT in the patient’s blood (19). The detection limit of this assay version is 0.2 ng/ml. The test was read as either positive (red line appeared within 20 min) or negative. Positive results were further categorized as to whether the red line appeared in ≤10 min or >10 min with an early positive result reflecting higher concentrations of cTnT (20).

Statistical analysis. The SAA and cTnT data were merged with the TIMI 11A clinical database and analyses performed at COVANCE (Princeton, New Jersey). Complete information regarding SAA and rapid cTnT status, including the time to positivity of the rapid assay, were required for inclusion in this substudy. Since prior data with cardiac troponins have shown diminished sensitivity in patients presenting less than 6 h after onset of ischemic symptoms, patients who had enrollment specimens drawn earlier than 6 h after symptom onset were excluded. Statistical comparison of baseline characteristics and clinical outcomes were performed using the chi-square or Fisher exact test for dichotomous variables and either the Wilcoxon rank sum or two sample t test for continuous variables. Correlation between baseline CRP and SAA was evaluated with a Spearman rank test. All statistical comparisons were two-tailed and p values of <0.05 were considered to indicate statistical significance.

RESULTS

Baseline characteristics. Of the 630 patients enrolled in TIMI 11A, 435 (69%) had the requisite serum marker information for this substudy. Those who did not have the required data had lower rates of previously diagnosed coronary artery disease (CAD) (63 vs. 74%) but did not differ with respect to any traditional cardiovascular risk factors including age, gender, smoking, cholesterol, hypertension or diabetes.

Serum amyloid A values ranged from 0.09 to 80.9 mg/dL with a median of 0.768 mg/dL and 25th and 75th percentiles of 0.44 and 1.86 mg/dL, respectively. All patients with baseline SAA concentrations in the fifth quintile had SAA levels exceeding the 99th percentile of normal controls (1.2 mg/dL) as previously established in the core laboratory (21). A strong correlation between SAA and CRP levels at baseline was observed (r = 0.71, p = 0.0001). Baseline characteristics for the patients with markedly elevated SAA were similar to those for the remainder of the population with few exceptions as detailed in Table 1. It is not expected that higher rates of intravenous heparin and nitroglycerin use would have adversely affected mortality in this group.

Serum markers and mortality. All cause 14-day mortality for the study population was 1.6%. Median SAA concentration at enrollment was significantly elevated at 6.28 mg/dL among those patients who subsequently died during the 14-day follow-up period versus 0.746 mg/dL among survivors (p = 0.002). Those with the highest levels of baseline...
SAA were at significantly increased mortality risk (Fig. 1). Moreover, this relationship persisted among the 346 patients with negative rapid assays for cTnT (Fig. 1). In a risk stratification scheme employing both SAA and rapid cTnT, we found that patients with both an early positive rapid cTnT assay (≥10 min) and SAA in the fifth quintile were at highest mortality risk. Whereas, those with either markedly elevated SAA or an early positive rapid cTnT assay were at intermediate risk compared with patients with both a negative rapid cTnT assay and SAA in quintiles 1–4 who were at very low mortality risk (p < 0.002; Fig. 2).

A markedly elevated SAA (Quintile 5) at baseline was a more sensitive predictor of early mortality than either an early positive cTnT assay or any positive rapid troponin result (71% vs. 29% vs. 29%) while maintaining comparable specificity (81% vs. 91% vs. 79%). The combination of a markedly elevated SAA and an early positive rapid cTnT assay was the most specific marker combination at 95% and was associated with the highest likelihood ratio for mortality at 5.6.

In an analysis of mortality stratified by CRP results previously reported for this population (8), SAA did not offer further prognostic information among those with positive (mortality of 3.3% vs. 6.5% in SAA Q1–4 vs. Q5, p = 0.52) or negative CRP results. A positive CRP identified a single patient in SAA Q1–4 who subsequently died by 14 days, but the difference was not statistically important with respect to mortality prediction (p = 0.17). The combination of a positive SAA and CRP was slightly more specific for mortality prediction than SAA or CRP alone (83% vs. 81% vs. 76%, respectively).

### DISCUSSION

This analysis of serum markers drawn at enrollment of patients with unstable angina and NQMI in TIMI 11A suggests that, like its acute phase counterpart CRP, SAA may provide important prognostic information with respect to short term mortality among patients presenting with an acute coronary syndrome without ST elevation. We found that a markedly elevated SAA at enrollment is predictive of increased mortality at 14 days even among those with a negative assay for troponin. Further, we observed that the combination this alternative marker of inflammation and cardiac specific troponin data again yielded a comprehensive approach to risk assessment.

#### Previous clinical studies.

While a prognostic role for CRP in unstable ischemic heart disease has now been demonstrated in at least six prospective studies (7–9,22–24), the data regarding a similar capacity of SAA are fewer and conflicting (7,9,24). In a study of 31 patients presenting with unstable angina without evidence of myocardial necrosis, those subjects with elevated SAA on admission had more frequent recurrent angina and exhibited associated trends toward higher rates of revascularization, MI and death (7). In contrast, the European Concerted Action on Thrombosis and Disabilities Study Group found that SAA was not predictive of more frequent nonfatal MI or cardiac death among 2,121 patients with angina followed prospectively for two years (9). However, the population studied in this long-term European study was recruited from outpatient clinics and included patients with stable angina as well as atypical chest pain and, thus, was very different from the hospitalized population examined by Liuzzo and colleagues. The prognostic capacity of SAA in patients with severe unstable angina has been additionally supported by recent data demonstrating an association between elevation of SAA at discharge and higher rates of admission for recurrent unstable angina or MI by one year (24).

#### Potential implications.

Our report extends prior observations for SAA to short term mortality in the acute hospital setting and demonstrates the prognostic capacity of this additional inflammatory marker used in combination with cTnT. Further, we find that the sensitivity and specificity of SAA as a predictor of early mortality compare favorably with that observed previously in this population for CRP (71 vs. 86% and 81 vs. 76%, respectively) (8). Though we

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>SAA Quintiles 1–4</th>
<th>SAA Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>348</td>
<td>87</td>
</tr>
<tr>
<td>Mean</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>228 (66)</td>
<td>51 (59)</td>
</tr>
<tr>
<td>Female</td>
<td>120</td>
<td>36</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>277 (80)</td>
<td>70 (80)</td>
</tr>
<tr>
<td>Other</td>
<td>71</td>
<td>17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>114 (33)</td>
<td>31 (36)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>94 (27)</td>
<td>22 (25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>212 (61)</td>
<td>52 (60)</td>
</tr>
<tr>
<td>Prior cardiac history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>260 (75)</td>
<td>62 (71)</td>
</tr>
<tr>
<td>Prior angiogram with stenosis ≥50%</td>
<td>203 (60)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>PTCA</td>
<td>61 (18)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>CABG</td>
<td>33 (10)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>MI</td>
<td>5 (1)</td>
<td>2 (2)</td>
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<tr>
<td>Medications before enrollment</td>
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</tr>
<tr>
<td>ASA</td>
<td>287 (83)</td>
<td>79 (91)</td>
</tr>
<tr>
<td>Intravenous nitrates</td>
<td>83 (24)</td>
<td>41 (47)*</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>165 (47)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>Intravenous heparin</td>
<td>177 (51)</td>
<td>58 (67)*</td>
</tr>
</tbody>
</table>

*Denotes categories for which p ≤ 0.05. For continuous variables, values shown indicate the median; for dichotomous variables, values indicate the number (percent) of patients with a given finding.

ASA = aspirin; CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SAA = serum amyloid A.
must recognize the limitations that stem from examining this relationship in a single cohort with relatively few events, our current analysis corroborates prior observations correlating elevated SAA with adverse cardiovascular outcome and supports further investigation of other inflammatory markers in addition to CRP.

As the pathophysiologic relationship between elevation of CRP and adverse clinical outcomes has remained undefined, possible direct effects of CRP on coagulation and intracellular adhesion have been raised (25,26). While the current data demonstrating the predictive capacity of a second inflammatory marker do not exclude the possibility of such direct interactions of CRP or SAA, they suggest that the observed prognostic associations may be more likely due to a primary inflammatory process than to direct effects of CRP or SAA. In addition, investigators have observed an advantage of combined use of SAA and CRP to identify individuals with consistent evidence of systemic inflamma-

![Figure 1](image1.png)

**Figure 1.** Mortality at 14 days by SAA concentration in all patients and those with negative (neg) rapid cTnT assays. SAA = serum amyloid A. SAA concentrations: open square = quintiles 1–4; closed square = quintile 5.

![Figure 2](image2.png)

**Figure 2.** Risk stratification by SAA and rapid assay status expressed as 14-day mortality by SAA and rapid cTnT result. Early positive rapid assays could be read positive by ≤10 minutes. cTnT = cardiac specific troponin T; Neg = negative; Pos = positive; Q = quintile; SAA = serum amyloid A.
tion in the prognostic evaluation of patients with stable ischemic heart disease (17). Further investigation evaluating the relative contributions of SAA and CRP, as well as the combination of these acute phase proteins, in cardiovascular risk assessment appears warranted.

Conclusions. This report supports the prognostic value of baseline SAA measurement with respect to short term mortality among patients presenting with non-ST elevation acute coronary syndromes. Similar to CRP, SAA is found to identify a population of patients without elevation of cTnT who remain at increased mortality risk and thus confers additional prognostic information beyond that provided by troponin alone. The results of this study support further investigation of markers of inflammation alone and in combination with specific indicators of myocardial necrosis for cardiovascular risk assessment in unstable ischemic heart disease.

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19. Crea F, Gallimore JR, Tennent GA, et al. Impact of inflammation and risk factors on mortality among patients presenting with non-ST elevation acute coronary syndromes. Similar to CRP, SAA is found to identify a population of patients without elevation of cTnT who remain at increased mortality risk and thus confers additional prognostic information beyond that provided by troponin alone. The results of this study support further investigation of markers of inflammation alone and in combination with specific indicators of myocardial necrosis for cardiovascular risk assessment in unstable ischemic heart disease.


