JACC Vol. 31, No. 7
June 1998:1460–5

C-Reactive Protein Is a Potent Predictor of Mortality Independently of and in Combination With Troponin T in Acute Coronary Syndromes: A TIMI 11A Substudy

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Objectives. **We evaluated C-reactive protein (CRP) alone and in conjunction with a rapid qualitative assay for cardiac-specific troponin T (cTnT) for predicting 14-day mortality in patients with unstable angina or non-Q wave myocardial infarction (NQMI).**

Background. **Elevated CRP has been found to correlate with higher risk for cardiac events in patients with coronary disease.**

Methods. **At enrollment into the Thrombolysis in Myocardial Infarction (TIMI) 11A trial, a dose-ranging trial of enoxaparin for unstable angina and NQMI, serum was obtained for CRP measurement and rapid cTnT assay.**

Results. **Quantitative CRP and rapid cTnT assays were performed in all patients. CRP was higher among patients who died than in survivors (7.2 vs. 1.3 mg/dl, $p = 0.0038$). The probability of a positive rapid cTnT assay rose with increasing CRP concentration ($p < 0.0001$). Among patients with a negative rapid cTnT assay, the mortality rate was higher among patients with CRP ≥1.55 mg/dl (5.80% vs. 0.36%, $p = 0.006$). Patients with both an early positive rapid cTnT assay (≤10 min until assay positive) and CRP ≥1.55 mg/dl had the highest mortality, followed by those with either CRP ≥1.55 mg/dl or an early positive rapid cTnT assay, whereas patients with both a negative rapid cTnT assay and CRP <1.55 mg/dl were at very low risk (9.10% vs. 4.65% vs. 0.36%, $p = 0.0003$).**

Conclusions. **Elevated CRP at presentation in patients with unstable angina or NQMI is correlated with increased 14-day mortality, even in patients with a negative rapid cTnT assay. Quantitative CRP and a rapid cTnT assay provide complementary information for stratifying patients with regard to mortality risk.**

(J Am Coll Cardiol 1998;31:1460–5)

As our understanding of the pathogenesis of atherosclerotic heart disease has evolved, the contribution of inflammation to this process has attained increasing recognition (1–5). Several of the acute-phase proteins, which serve as nonspecific markers of the human inflammatory response, have been found to be elevated across the clinical spectrum of atherosclerotic coronary artery disease (6–14). Furthermore, increased concentrations of the acute-phase reactant C-reactive protein (CRP) appear to be predictive of higher risk for long-term cardiovascular morbidity/mortality in patients with both stable and unstable angina, as well as in asymptomatic patients at risk for coronary artery disease (CAD) (15–18). This potential predictive capacity of CRP warrants further evaluation alone and in conjunction with established serum cardiac markers.

Cardiac-specific troponin T (cTnT), a subunit of the troponin regulatory complex in cardiac myocytes, is now well recognized as a more sensitive and specific marker of myocardial necrosis than creatine kinase and its MB isoenzyme. Elevation of serum cTnT has been shown (19–23) to identify patients with acute coronary syndromes at increased risk for adverse clinical outcomes. Previous investigations of cTnT (19–23) have demonstrated the prognostic value to be most evident when specimens are collected >6 h after the onset of ischemic symptoms. In a study of patients with severe unstable angina with no increase in cTnT, Liuzzi et al. (24) observed that an elevation of CRP above a threshold value of 0.3 mg/dl was associated with a trend toward increased adverse clinical outcomes, including major cardiac events, recurrent ischemia and a prolonged hospital stay. A more recent analysis of data collected in a large prospective European study of patients with angina (18) has corroborated the predictive value of CRP for major cardiac events; however, no data on cTnT were provided in that report. In a recent report of a substudy in the Thrombolysis in Myocardial Infarction (TIMI) 11A trial (25), we demonstrated that a positive rapid bedside assay for cTnT identifies those patients with unstable angina and non-Q wave myocardial infarction (NQMI) at higher risk for adverse clinical events. Furthermore, stratification of patients by time

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Manuscript received October 31, 1997; revised manuscript received February 24, 1998, accepted March 4, 1998.

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0735-1097/98/$19.00
PII S0735-1097(98)00136-3

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CI = confidence interval
MI = myocardial infarction
NQMI = non-Q wave myocardial infarction
TIMI = Thrombolysis in Myocardial Infarction

to development of a positive rapid assay identifies those patients at highest risk of death (25). We now extend our analysis of the patients enrolled in TIMI 11A. To define further the prognostic information offered by CRP in acute coronary syndromes, we evaluated the ability of CRP alone and in conjunction with a rapid bedside assay for cTnT, performed from simultaneous samples drawn at least 6 h after symptom onset, to predict 14-day mortality in a cohort of patients admitted to the hospital with unstable angina or NQMI.

Methods

Patients. Men and women admitted with unstable angina or NQMI and enrolled in the TIMI 11A trial at any one of the 45 participating centers were eligible for this serum marker substudy. The TIMI 11A trial 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 previous week, defined as one of the following: rest angina of at least 5 min in duration; new-onset angina of at least Canadian Cardiovascular Class III severity, with onset within 2 months of presentation; or previously diagnosed angina that became distinctly more frequent, longer in duration or lower in threshold. To support the presence of ischemic heart disease, patients must have met at least one of the following criteria: a history of typical myocardial ischemic-type discomfort; electrocardiographic changes (ST segment deviation or T wave inversion, or both) in association with ischemic discomfort; a history of previous myocardial infarction (MI); a previous positive exercise tolerance test; previous coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty or a previous coronary angiogram showing 50% stenosis of a major epicardial coronary vessel (26). Patients with an evolving Q wave MI or thrombolytic therapy within 24 h before randomization, CABG within the previous 2 months or other serious illness (active cancer, significant hepatic or renal dysfunction) were excluded. Other exclusion criteria included contraindications to anticoagulation; ongoing indication for long-term, continuous anticoagulation; or history of heparin-induced thrombocytopenia. 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 receiving a fixed dose of subcutaneous enoxaparin every 12 h, for a total treatment period of 2 weeks, after which each patient's clinical status was ascertained (26).

Blood sampling and measurement of serum markers. The serum marker protocol specified that a serum specimen be drawn at enrollment for the quantitative assessment of CRP. The serum specimens 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 (D.L.W.) in blinded manner as to patient treatment and outcome. Quantitative serum CRP (N Latex CRP mono) determination was performed with the Behring BN II Nephelometer (Behring Diagnostics). In this assay, polystyrene beads coated with mouse monoclonal antibodies bind CRP present in the serum sample, and form aggregates. The intensity of scattered light is proportional to the size of the aggregates and thus reflects the concentration of CRP present in the sample. The sensitivity of the assay is 0.01 mg/dl, and reproducibility around concentrations of 0.05, 5.5 and 13.8 mg/dl is 5.5, 2.9 and 3.6%, respectively. Performance of this assay in the core laboratory in serum obtained from 104 healthy adult blood donors demonstrated a mean CRP of 0.215 mg/dl and a 99th percentile value of 1.55 mg/dl. The value for the 99th percentile for control serum was determined with the same instrument/assay used for serum CRP measurement in each of the patient samples analyzed in the study and was subsequently used as the CRP threshold for the outcomes analysis.

In addition, a rapid bedside qualitative assay for cTnT was performed at enrollment at each site by placing 150 μl of whole blood in a specimen well where cTnT reacts with two monoclonal antibodies. The cTnT in the patient's blood binds to the two antibodies and forms a sandwich that flows along a glass-fiber fleece toward the read zone. The immune complexes are immobilized in the read zone by an interaction between streptavadin and the biotinylated antibody, leading to production of a purplish-red line in the read zone (27,28). The intensity of the color and speed with which it develops correlate with the concentration of cTnT in the patient's blood (27). The detection limit of this version of the assay is 0.2 ng/ml of cTnT. 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 within $\leq$10 or $>$10 min, with an early positive result (i.e., at $\leq$10 min) reflecting higher concentrations of cTnT (25).

Statistical analysis. The CRP and cTnT data were merged with the main TIMI 11A clinical database, and analyses were performed at COVANCE. To adequately assess the performance of CRP and the rapid cTnT assay simultaneously, it was required that patients included in the analysis have complete information regarding both CRP and rapid cTnT status, including the time to positivity of the rapid assay. In addition, on the basis of previous experience with cardiac-specific troponins, which has shown diminished sensitivity in patients presenting $<$6 h after the onset of ischemic symptoms, patients who had serum markers drawn $<$6 h after symptom onset were not included. Statistical comparison of baseline characteristics

and clinical outcomes was performed using the chi-square or Fisher exact test for dichotomous variables and either the Wilcoxon rank sum or the two-tailed *t* test for continuous variables. Rapid assay results across patient groups distributed by quintile of CRP concentration were compared by a one-way analysis of variance. In an effort to identify those patients at highest mortality risk, thresholds for the primary outcomes analysis were set toward the extremes of CRP and cTnT elevation (the 99th percentile of normal range for CRP and early positive rapid cTnT assay results). A series of two-by-two contingency tables for each test category (CRP ≥1.55 mg/dl, rapid cTnT assay early positive and both conditions positive) for the outcome of death at 14 days were constructed and the sensitivity, specificity and likelihood ratio for each test determined. All statistical comparisons were two-tailed, and p values <0.05 considered statistically significant.

Results

Baseline characteristics. Of the 630 patients enrolled in the TIMI 11A trial between July 1995 and January 1996, 437 (70%) had both a rapid cTnT assay and quantitative CRP determined at least 6 h after symptom onset. Those who did not have the requisite samples drawn and data reported for this serum marker substudy did not differ significantly from participants with respect to any of the baseline characteristics collected, except that there were fewer patients reporting a previous history of angina (62% vs. 74%, p = 0.003) with a concomitant decrease in the use of aspirin and intravenous nitrates before enrollment.

CRP values ranged from 0.01 to 19.80 mg/dl (median 0.58; 25th and 75th percentiles 0.24 and 1.48 mg/dl, respectively). Twenty-five percent of patients had a markedly elevated CRP ≥1.55 mg/dl (99th percentile of healthy control values from the core laboratory). These patients had baseline characteristics similar to the remainder of the cohort, with few exceptions (Table 1). Of note, previous examination of CRP in a large patient group demonstrated no association between CRP concentration and diabetes (18). Higher rates of intravenous heparin and nitrate use may reflect the more serious clinical condition consistent with the higher risk profile of the group with elevated CRP.

Correlation with rapid troponin T. Of the 437 patients included in the present substudy, 346 had a negative rapid cTnT assay, and 43 of the remaining 91 patients had a positive rapid cTnT assay with an early positive result. The probability of a positive rapid cTnT assay increased with rising concentrations of CRP (Fig. 1). However, even among those patients with a negative rapid cTnT assay, a wide range of CRP concentrations were observed, with a median of 0.51 mg/dl and 25th and 75th percentiles of 0.21 and 1.21 mg/dl, respectively. Twenty percent of patients with a negative rapid cTnT assay had CRP levels ≥1.55 mg/dl.

Correlation of serum markers with mortality at 14 days. Mean CRP concentration at enrollment was elevated at 7.21 mg/dl in patients who subsequently died during the 14-day follow-up period versus 1.29 mg/dl in survivors (p = 0.0038). The all-cause 14-day mortality rate for the study cohort was 1.6%. Mortality was significantly higher among patients with CRP ≥1.55 mg/dl than in all others, and notably, this increase in mortality was evident even among those with a negative rapid cTnT assay (Fig. 2). Furthermore, among patients with a positive rapid cTnT assay, the mortality rate in the group with CRP <1.55 mg/dl was 0% compared with 5.1% in those with CRP above threshold. Stratifying by both CRP and rapid cTnT, we found that patients with both an early positive rapid cTnT assay (≤10 min until assay positive) and CRP ≥1.55 mg/dl had the highest mortality, followed by those with either CRP ≥1.55 mg/dl or an early positive rapid cTnT assay. Patients with both a negative rapid cTnT assay and CRP <1.55 mg/dl were at very low risk (p = 0.0007) (Fig. 3).

A CRP level elevated to ≥1.55 mg/dl was a more sensitive marker for increased mortality than was early positive cTnT assay positivity (86% vs. 29%) while maintaining moderate specificity (76% vs. 91%) (Fig. 4). Analysis of all positive rapid cTnT assays shows a mortality rate of 2.2% for patients with a positive test compared with 1.5% in those with a negative result, with a corresponding sensitivity and specificity of 29% and 79%, respectively. The combination of CRP and an early positive rapid cTnT assay was the most specific indicator of mortality at 95% and was associated with the highest likelihood ratio for mortality at 6.1.

Table 1. Baseline Characteristics

Baseline Characteristic	CRP <1.55 mg/dl (n = 329)	CRP ≥1.55 mg/dl (n = 108)
Mean age (yr)	62.1	62.9
Gender		
Male	220 (67%)	60 (56%)*
Female	109	48
Race		
White	264 (80%)	85 (79%)
Other	65	23
Diabetes	99 (30%)	47 (44%)*
Current smoker	89 (27%)	27 (25%)
Hypertension	196 (60%)	69 (64%)
Previous cardiac history		
Angina	247 (75%)	78 (72%)
Previous angiogram with stenosis ≥50%	194 (59%)	58 (54%)
PTCA	57 (17%)	14 (13%)
CABG	27 (8%)	17 (16%)*
MI	5 (2%)	2 (2%)
Medications before enrollment		
ASA	274 (83%)	95 (88%)
IV nitrates	82 (25%)	43 (40%)*
Beta-blockers	164 (50%)	52 (48%)
IV heparin	168 (51%)	70 (65%)*

*Denotes categories for which p ≤ 0.05. For continuous variables, the values shown indicate the median; for dichotomous variables, the values indicate the number (percent) of patients with a given finding. ASA = aspirin; CABG = coronary artery bypass graft surgery; IV = intravenous; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

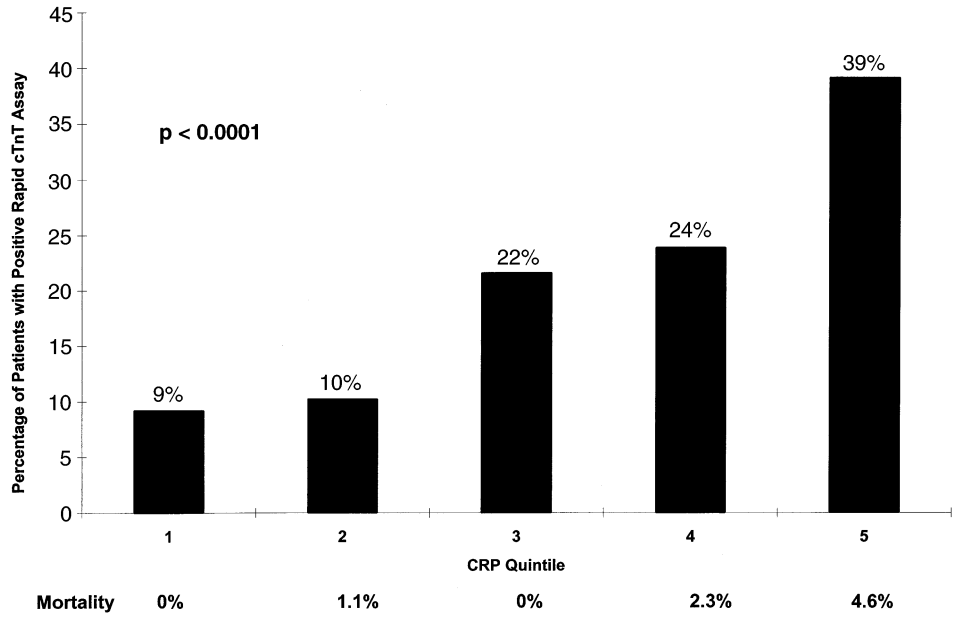


Figure 1. Correlation of rapid cTnT assay results and CRP concentration expressed as the percentage of cTnT assay results reading positive by quintiles of CRP concentration. Trend was evaluated by chi-square test. Mortality at 14 days is displayed by CRP quintile.

Discussion

The present analysis of serum markers drawn at enrollment of patients with unstable angina and NQMI in the TIMI 11A trial strongly suggests a prognostic role for CRP with respect to short-term mortality in this cohort. In addition, the present report demonstrates the combined prognostic value of an assay for cTnT and CRP in stratifying patients for mortality risk. Notably, among patients with a negative rapid bedside cTnT assay, a markedly elevated CRP (≥99th percentile for normal control values in the core laboratory) identifies patients who remain at significantly increased risk for death in the first 14 days and thus confers additional prognostic information above cTnT results alone. Furthermore, we observed that using the rapid cTnT assay and CRP in combination provided a more comprehensive risk assessment with respect to mortality. Patients with unstable angina and NQMI compose a diverse population with a broad range of risk for adverse clinical outcomes (29,30). Thus, the ability to effectively risk stratify patients at presentation should prove useful in triaging patients to the appropriate level of hospital care as well as potentially guiding clinical interventions.

Inflammation in coronary artery disease. Multiple lines of investigation have converged to suggest a prominent role of inflammation in acute coronary syndromes. Histologically, atheromatous plaques obtained at autopsy have demonstrated (31–33) the presence of inflammatory mononuclear cells with foci of monocytes, macrophages and T lymphocytes in the arterial wall. Anatomically, the most common site of plaque rupture in acute coronary syndromes appears to occur in the shoulder region, where inflammatory cells are most prominent and might serve to compromise the integrity of the surround-

Figure 2. Mortality rate at 14 days by CRP concentration (**open bars** = <1.55 mg/dl; **solid bars** = >1.55 mg/dl) in all patients and in those with negative (neg) and positive (pos) rapid cTnT assays. Statistical comparison made by Fisher exact test.

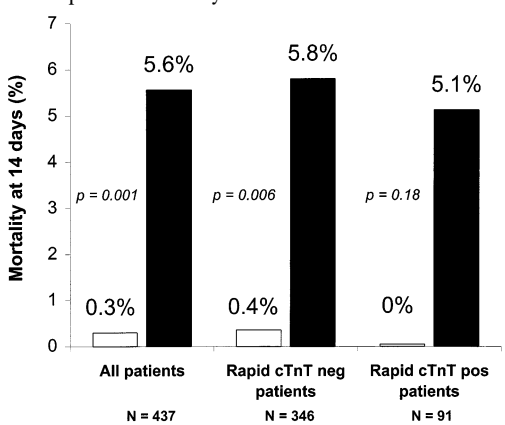
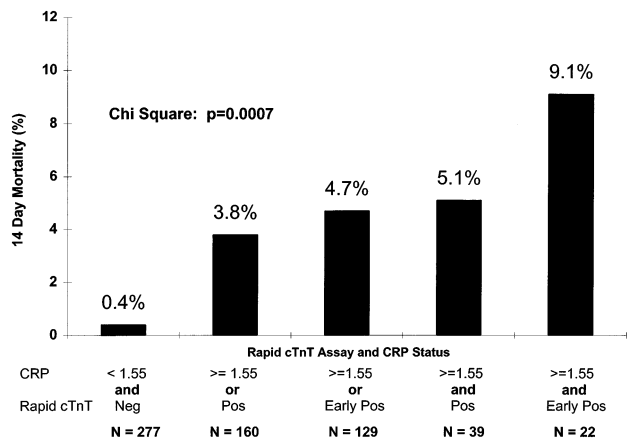
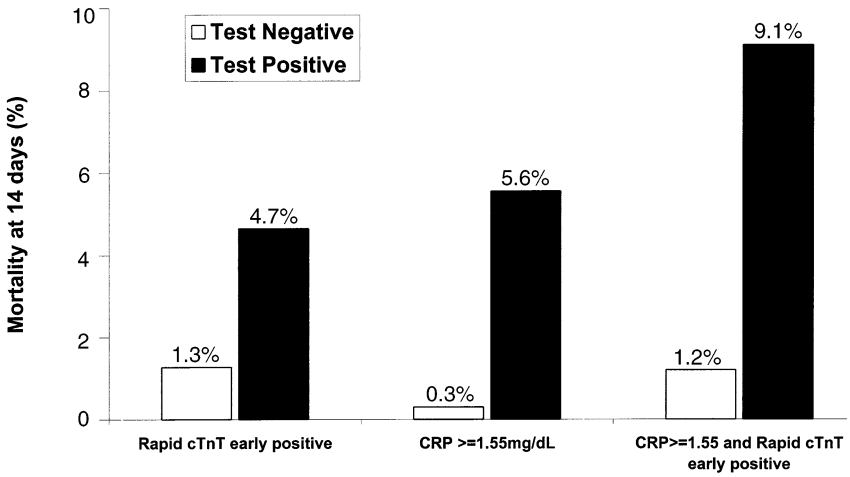


Figure 3. Risk stratification by CRP (mg/dl) and rapid assay status expressed as 14-day mortality rate by CRP and rapid cTnT result. Early positive rapid assays are those that could be read positive by ≤10 min. Trend evaluated by chi-square test. Neg = negative; Pos = positive.





Sensitivity	**29%**	**86%**	**29%**
Specificity	**91%**	**76%**	**95%**
Likelihood Ratio	**3.0**	**3.6**	**6.1**

Figure 4. Mortality rate at 14 days by CRP and rapid cTnT assay status. Early positive rapid assays for cTnT are those for which the red line appeared by ≤10 min, with a "negative" test in this category including both negative and late positive rapid cTnT results. CRP ≥1.55 mg/dl is considered a positive test for CRP. "Test Positive" in the category "CRP ≥1.55 mg/dl and Rapid cTnT early positive" requires both tests to be positive, with a "negative" test in this category representing all other combinations.

ing connective tissue (34). Release of key cytokines, such as interleukin-6, with resultant stimulation of hepatic production of acute-phase reactants, has been shown (35,36) to occur in acute coronary syndromes, even in the absence of evidence of myocardial necrosis. Thus, the acute-phase reactants have been proposed as potential indicators of underlying atherosclerotic disease and "unstable" atheromatous lesions (9,37). The fact that there are reliable, widely available assays to determine the serum concentration of CRP, and that this concentration is essentially entirely dependent on the rate of primary production, renders CRP a particularly attractive candidate serum marker for this purpose (38–41). With a view toward widespread clinical applicability, the assay used for this protocol is a highly sensitive, fully automated, commercially available assay.

CRP and prognosis. Studies of both cross-sectional and case-control design have supported the association between CRP and symptomatic CAD, as well as demonstrating an increased risk of cardiovascular morbidity and mortality with higher concentrations of CRP. Mendall et al. (10) examined 388 men between 50 and 69 years of age recruited from general practice registers in Great Britain and showed an odds ratio for CAD of 1.55 (95% confidence interval [CI] 1.25 to 1.92) per doubling of CRP concentration. The MRFIT Research Group (16) documented an association between CRP and coronary heart disease mortality over 17 years of follow-up in asymptomatic persons with multiple risk factors with a relative risk of 2.8 (95% CI 1.4 to 5.4) between the fourth and first quartiles of CRP concentration. In a recent study by Ridker et al. (15), CRP was shown to be a predictor of increased risk for subsequent major cardiac events for patients with no known CAD. In addition, at least two prospective studies reflecting a spectrum of patients with symptomatic CAD have been completed. In the first study to suggest the prognostic value of CRP for short-term outcome, Liuzzo et al. (24) showed that in a subgroup of 31 patients with severe unstable angina and no evidence of myocardial necrosis by admission quantitative cTnT, a serum CRP concentration >0.3 mg/dl (90th percentile of normal distribution) was predictive of more frequent recurrent angina and exhibited associated trends toward higher rates of revascularization, MI and death. Subsequently, the European Concerted Action on Thrombosis and Disabilities Study Group (18) reported a correlation between elevated CRP and nonfatal MI or sudden cardiac death in >2,000 outpatients with stable and unstable angina followed prospectively for an average of 2 years, with an odds ratio for these events of 1.81 for patients in the highest quintile of CRP relative to those in the first to fourth quintiles.

Conclusions. Our report extends these observations on the prognostic value of CRP to short-term mortality in the acute hospital setting and supports using a combination of CRP and cTnT for a more comprehensive risk assessment in patients with unstable angina and NQMI. In addition, these data demonstrate CRP to perform with superior sensitivity and comparable specificity to an assay for cTnT in the identification of patients at risk for early mortality in acute coronary syndromes. We recognize the potential limitations of examining this risk relation in a single cohort with relatively few events. However, the present study offers provocative data that suggest a powerful role for mortality risk stratification combining information from measurement of both CRP and cTnT.

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