The risk of death or recurrent myocardial infarction (MI) in patients with chest pain and baseline isolated troponin elevation is unclear. To determine the early and short-term risk of death or MI associated with isolated troponin elevation across a spectrum of chest pain syndromes, we used baseline creatine kinase (CK)-MB and troponin data from the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) B troponin substudy, the Global Utilization of Strategies To Open Occluded Coronary Arteries (GUSTO) IIA troponin substudy, and the Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) study. Patients were grouped into 1 of 4 categories based on marker status (troponin-positive/CK-MB-positive, troponin-positive/CK-MB-negative, troponin-negative/CK-MB-positive, or troponin-negative/CK-MB-negative). The adjusted odds of death or MI occurring at 24 hours and 30 days was assessed by baseline marker status using multivariable logistic regression, with the group negative for both markers used as the reference. Patients who were positive for both markers had the highest odds of the 24-hour and 30-day end point. The adjusted odds of the 30-day end point for patients with isolated troponin elevation were 1.3 (95% confidence interval 0.7 to 2.3) and 4.8 (95% confidence interval 1.4 to 16.0) for high- and low-risk patients, respectively. The risk for 24-hour and 30-day death or MI with isolated positive CK-MB results was lower than with isolated positive troponin results, and it was not significantly greater than if the 2 markers were negative. For patients with high- and low-risk chest pain, baseline troponin elevation without CK-MB elevation was associated with increased risk for early and short-term adverse outcomes. This suggests that these patients should be admitted to the hospital and monitored in either an intensive care or step-down unit.

METHODS

Study population: Eligible patients were from the trial populations of the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) B troponin substudy (n = 1,160), the Global Utilization of Strategies To Open Occluded Coronary Arteries (GUSTO) IIA troponin substudy (n = 855), and the Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) study (n = 1,006). The details of these trials has been published previously.1-3

PARAGON B randomized patients presenting with a suspected non–ST-segment elevation acute coronary syndrome who had symptoms in the preceding 12 hours to the intravenous glycoprotein IIb/IIIa inhibitor lamifiban, or placebo. GUSTO IIA randomized patients with a presumed acute coronary syndrome who had symptoms within the preceding 12 hours to receive either intravenous unfractionated heparin or...
hirudin. The acute coronary syndrome populations of PARAGON B and GUSTO IIa were considered to be moderate- to high-risk based on their clinical characteristics, and data from the trials were evaluated together (referred to as “combined population”).

CHECKMATE prospectively evaluated 2 different multimarker strategies (CK-MB/troponin I or CK-MB/troponin I/myoglobin) for risk stratification of patients observed in chest pain units who had chest pain that was possibly ischemic in origin. Patients were excluded if the initial electrocardiogram demonstrated ST-segment elevation or left bundle branch block that led to the consideration of acute reperfusion therapy. Patients in the CHECKMATE study were considered low-risk based on their clinical characteristics, and these data were evaluated separately from the combined population.

Our analyses included only patients for whom clinical and serum marker data were complete. We excluded patients with ST-segment elevation on the admission electrocardiogram.

**Measurement of cardiac markers:** Troponin T levels in PARAGON B were determined from samples collected at enrollment, 24 to 72 hours after randomization. Only the enrollment values were used for the purpose of this analysis. Samples were frozen and sent to the core laboratory at the University of Maryland. Troponin T levels were assayed using the third generation TnT STAT electrochemiluminescence immunoassay on the Elecsys 2010 system (Roche Diagnostics Corp., Indianapolis, Indiana). The minimum detectable concentration of this system is 0.01 ng/ml. The prespecified positive threshold used in this study was a troponin T level ≥0.1 ng/ml.

Troponin T levels in GUSTO IIa were drawn as soon as possible after admission and at 8 and 16 hours; they were measured at the University of Maryland core laboratory by an enzyme-linked immunosorbent assay with an ES 300 automated analyzer with streptavidin-coated tubes (Boehringer Mannheim, Indianapolis, Indiana). The lower limit of detection for this assay was 0.04 ng/ml, respectively.

CK-MB values in the PARAGON B study were measured at the laboratories of the participating centers. Positive values were defined on the basis of the upper limit of normal for the respective center. In GUSTO IIa, CK-MB mass was measured at the core laboratory using the Stratus II instrument (Baxter Diagnostics, Miami, Florida). The lower limit of detection was 0.4 ng/ml; the upper limit of the reference range was 7.0 ng/ml.

Troponin I and CK-MB levels in the CHECKMATE study were measured using a near-patient instrument as part of a multimarker strategy at enrollment, 3 hours, 6 hours, 12 hours, and 24 hours. The Dade-Behring Stratus CS STAT (Dade-Behring, Deerfield, Illinois) near-patient instrument was used for analysis. The lower limit of detection and the upper range of normal for troponin I were 0.03 and 0.1 ng/ml, respectively. The lower limit of detection and the upper range of normal for CK-MB were 0.3 and 4.0 ng/ml, respectively. Only the troponin I and CK-MB values at the time of presentation were used for this analysis.

**End points and definitions:** The primary end point for our study was death or MI at 30 days (excluding MI occurring at enrollment), but we also examined the rates of death or MI occurring in the 24 hours after admission. The occurrence of the MI end point for our analyses was as determined for each study’s primary analysis.

For PARAGON B and GUSTO IIa, a central Clinical Events Classification Committee determined the occurrence of MI using prespecified definitions. The diagnosis of MI in the CHECKMATE study was determined by computer algorithm using CK-MB (or troponin if CK-MB was unavailable) levels reported from sites’ local laboratories, core laboratory electrocardiogram readings, and investigator classification.

**Statistical analysis:** For each population (combined and CHECKMATE), patients were assigned to 1 of 4 categories based on the status of 2 admission cardiac markers: troponin (T or I)-positive/CK-MB-positive, troponin-positive/CK-MB-negative, troponin-negative/CK-MB-positive, and troponin-negative/CK-MB-negative. Descriptive statistics, medians with interquartile ranges or percentages, were generated for baseline characteristics and outcomes.

For PARAGON B, GUSTO IIa, and CHECKMATE, we generated unadjusted odds ratios with 95% confidence intervals for the risk of death or MI in each marker category relative to the troponin T-negative/CK-MB-negative category. For PARAGON B and GUSTO IIa, we used the variables in a previously validated model for death or MI to adjust these comparisons for differences in baseline characteristics that were predictive of the death or MI end point. These variables included age, heart rate, the presence of rales or congestive heart failure during admission, and the presence of ST-segment depression on the admission electrocardiogram. Similarly, for the CHECKMATE model, adjusted odds ratios were generated for each comparison using the variables gender, previous MI, diabetes mellitus, and abnormal admission electrocardiogram from a model previously developed to predict death or MI in this population.

To generate odds ratios for each marker category in the combined population, we used FastPro software (Academic Press, Kent, United Kingdom) and an empirical Bayes random-effects meta-analytic model to pool the odds ratios (for unadjusted and adjusted comparisons) generated separately in PARAGON B and GUSTO IIa for death or MI in each category. The extent of heterogeneity in these trials was examined using DerSimonian and Laird’s Q statistic.

**Ethics of protocol:** The Institutional Review Board of all participating institutions reviewed and approved the protocols of the GUSTO IIa, PARAGON B, and CHECKMATE studies. All patients enrolled in these studies gave written informed consent.
RESULTS

Baseline characteristics: After excluding patients with ST-segment elevation and those without complete clinical and cardiac marker data, 797 patients from PARAGON B, 232 patients from GUSTO IIa, and 823 patients from CHECKMATE remained. Baseline characteristics for the patients in the 3 trials are presented in Tables 1 to 3. Overall, the CHECKMATE population had lower-risk clinical characteristics than either the PARAGON B or GUSTO IIa populations, regardless of marker category. In the PARAGON B population, the group with isolated positive troponin results had more high-risk clinical characteristics than patients in the other categories of marker status; in the GUSTO IIa population, the group with positive results for both markers had more high-risk clinical characteristics. In the lower-risk CHECKMATE population, there was an age gradient among the 4 categories of marker-positive results. The group with isolated positive troponin results had more risk factors for coronary artery disease.

24-hour outcomes: In the combined population at 24 hours, the group with isolated troponin elevation had more early events (Table 4). In the CHECK-
MATE population, the group with positive results for both markers had the highest number of events at 24 hours.

The group with positive results for both markers in the combined population had the highest 24-hour odds of death or MI in the unadjusted analysis (odds ratio 5.3, 95% confidence interval [CI] 0.8 to 37.8). The group with isolated troponin elevation had similar unadjusted odds of the 24-hour end point (odds ratio 5.2, 95% CI 2.2 to 11.9). Patients with isolated CK-MB elevation had lower unadjusted odds of the early end point (odds ratio 1.7, 95% CI 0.3 to 8.9). Of the CHECKMATE patients, those with CK-MB and troponin elevation were at the highest risk for 24-hour events (unadjusted odds ratio 24.0, 95% CI 4.5 to 115.2). Those with isolated positive troponin results had unadjusted odds of 3.7 (95% CI 0.2 to 25.3). There were no 24-hour events in patients with isolated CK-MB elevation.

30-day outcomes: At 30 days, the group with CK-MB and troponin elevations had the highest number of events for both the combined and CHECKMATE populations, followed by the group with isolated troponin elevation (Table 4). For 30-day death or MI in the combined population, the group with positive results for both markers had the highest odds in the unadjusted analysis (odds ratio 2.5, 95% CI 1.6 to 3.8). The group with isolated positive troponin results had similar odds of the primary end point (odds ratio 2.1, 95% CI 1.4 to 3.0). In contrast, patients with isolated positive CK-MB results had a 30-day risk similar to that of the reference group (odds ratio 1.0, 95% CI 0.6 to 1.6). After adjustment, the patterns of risk remained similar but were no longer statistically significant for the group with isolated positive troponin results (Figure 1).

In the CHECKMATE population, the unadjusted 30-day odds of death or MI followed the same pattern as that for the combined population. Patients with positive results for both markers had the highest unadjusted odds of death or MI (odds ratio 9.5, 95% CI 2.0 to 33.7). The group with isolated positive troponin results also had significantly higher unadjusted odds of the primary end point (odds ratio 7.9, 95% CI 2.4 to 23.3). Patients with isolated CK-MB elevation were not at significantly higher risk (odds ratio 1.7, 95% CI 0.1 to 9.2). The increased risk with isolated positive troponin results remained statistically significant after multivariable adjustment (Figure 2).

DISCUSSION

Our results show that baseline troponin elevation in the absence of CK-MB elevation is associated with an increased risk of 24-hour and 30-day death or MI. Furthermore, this increased risk was evident in pa-
patients with high- and low-risk clinical features. The low-risk patients in the CHECKMATE study were observed in chest pain units on the basis of their overall clinical findings, but those with isolated troponin elevation had increased odds of the 30-day end point even after adjusting for high-risk electrocardiographic findings such as ST-segment depression. This provides further evidence for the value of troponin alone as a marker for short-term risk in patients with acute chest pain, and it suggests that patients with baseline troponin elevation in the absence of other high-risk features should be monitored closely in either an intensive care or step-down unit setting.

Although other studies have demonstrated the prognostic value of troponin in ST-elevation MI and non–ST-elevation acute coronary syndromes, few studies have included patients with low-risk clinical features or in whom an ischemic etiology for chest pain was unclear. Hamm et al found that elevated troponin T or I was predictive of death or MI at 30 days in 773 emergency department patients with chest pain and no ST-segment elevation. No patient with CK-MB elevation and undetectable troponin on presentation was confirmed to have had a cardiac ischemic event during follow-up. In 414 consecutive patients admitted to a chest pain unit, defilippi et al found that in this group, which was anticipated to have a low prevalence of coronary disease and a good long-term prognosis, patients with elevated troponin T had extensive and complex coronary disease by coronary angiography and a significantly higher incidence of adverse cardiac events. Similarly, in 383 patients admitted to the chest pain unit at a university hospital, elevated troponin levels predicted short-term nonfatal end points and long-term mortality in this low-risk population. None of these studies focused specifically on the value of troponin elevation in the absence of CK-MB elevation. Our results extend previous observations by demonstrating that baseline troponin elevation, regardless of the CK-MB result, is predictive of early and late adverse events across the spectrum of patients with chest pain. In addition, our findings support the hypothesis that troponin is a superior marker of risk compared with CK-MB.