tients with STEMI are excluded from the analyses, the additional value of copeptin seems to be limited.

In summary, although our study was small, it did provide excellent data regarding the absence of associations between copeptin and cardiac structure and function in a population with a low to intermediate likelihood of acute coronary syndrome, in which biomarkers may add an important incremental value to clinical evaluations for risk assessment, triage decisions, and further test selection. Our results echo data from the majority of available subsequent studies, which demonstrate that although copeptin findings may support the results of conventional non–high-sensitivity troponin methods for chest pain evaluation, the data do not seem to support the use of copeptin in situations in which high-sensitivity troponin assays are available.

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High-Sensitivity Cardiac Troponin Assays—Change Is Important

To the Editor:

The recent publication by Aldous and colleagues in *Clinical Chemistry (1)* starts an important discussion concerning the optimal change criteria that should be used with high-sensitivity (hs)[1] cardiac troponin assays. This report suggests that an optimal relative change (i.e., percent δ) in hs cardiac troponin T (hs-cTnT) for predicting a major adverse cardiovascular event over a 1-year period is 3%. This relative difference was not significant, however, with respect to risk stratification (hazard ratio, 1.6; $P = 0.052$) and would not be considered an analytically robust change, because 3% is within the imprecision of the assay at concentrations measured with the low- and high-quality control materials provided by Roche Diagnostics for this assay. From the data presented, it appears that the percent δ values for hs-cTnT concentrations over 2 h

[1] hs, high-sensitivity; hs-cTnT, high-sensitivity cardiac troponin T (assay); MI, myocardial infarction; FAST II, Fast Assessment of Thoracic Pain II (study); FASTER I, Fast Assessment of Thoracic Pain by Neural Networks I (study); APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation (trial).

were not important for long-term risk stratification; however, relative changes (e.g., 10% as determined by ROC curve analysis) did improve the detection of the index diagnosis of myocardial infarction (MI) in patients presenting with symptoms suggestive of acute coronary syndrome *(1)*. The authors provide data for using the lower relative change values observed in their study, as opposed to other reports in the literature that used ROC curve analyses for the diagnosis of MI *(1)*. These authors also note that another study indicated that long-term prognostication using change criteria might not be beneficial; however; the proper citation for this finding should be the study by Kavsak et al. *(2)*. Furthermore, the δ (as expressed as ratios) in the Kavsak et al. study, which failed to manifest prognostic significance over 4 years, was assessed only in the patients with documented myocardial injury detected with either the fourth-generation cTnT assay (n = 85) or the second-generation cTnI assay (n = 81), and not hs cardiac troponin assays *(2)*. In a larger analysis from the FAST II (Fast Assessment of Thoracic Pain II) and FASTER I (Fast Assessment Of Thoracic Pain By Neural Networks I) studies, however, Eggers and colleagues *(3)* demonstrated that cTnI concentrations that exceeded the 99th percentile with at least a 20% change in concentrations identified patients at higher risk for death and myocardial infarction at 6 months and death at a median follow-up of 5.8 years. Interestingly, in this analysis the magnitude of change with this guideline-acceptable assay (i.e., Stratus CS) did not translate into higher event rates *(3)*.

These studies highlight the fact that δ is important, with the interpretation of δ being reliant on both the cardiac troponin assay characteristic and the indication for its use (i.e., diagnostic or prognostic). With respect to prognosis, measuring with an hs-cTnI assay and assessing change in a larger chest pain population (cohort n = 223) revealed that δ expressed as either an absolute concentration or a percentage difference was useful for predicting death and/or MI at 1 year *(4)*. Interestingly, absolute δ appeared to be superior to percent δ, because the area under the ROC curve for absolute δ was higher than the area under the curve for percent δ, with only absolute δ providing important information for earlier risk stratification (e.g., at 30 days and 6 months) *(4)*. Aldous and colleagues *(1)* did not assess absolute δ in their study for either MI diagnosis or subsequent prognosis. A recent publication from the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) trial, however, demonstrated the superiority of absolute δ over percent δ for the diagnosis of MI *(5)*. The findings from the studies of Kavsak et al. and Reichlin et al. *(4, 5)* suggest that change is also important for hs cardiac troponin assays, with absolute δ possibly providing important diagnostic and prognostic information. Future studies that assess either absolute δ or possibly a combination of both absolute δ and percent δ are required to determine the optimal change for predicting a serious cardiac outcome in patients presenting with chest pain to the emergency department.

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In Reply

P. Kavsak and A. Jaffe raise some important issues regarding the diagnostic and prognostic utility of change criteria with high-sensitivity troponin assays in patients with acute coronary syndromes *(1)*.

Our recently published study *(2)* evaluated a cohort of 939 patients presenting with chest pain, with an acute myocardial infarction (AMI)[1] rate of 21.3%. In patients with a peak concentration (at 0–2 h) in the Roche high-sensitivity cardiac troponin T (hs-cTnT) assay ≥99th percentile, use of the relative change between 0 h and 2 h after presentation significantly improved the specificity but reduced the sensitivity for the diagnosis of AMI. The authors refer to a recent publication that demonstrated that absolute changes in troponin outperform relative changes between 0 h and 1 h or 2 h after presentation for the diagnosis of AMI *(3)*. The area under the ROC curve (AUC) was 0.95 for absolute changes and 0.76 for relative changes. The AUCs for absolute values (irrespective of the change) were reported for baseline concentrations (0.94 and 0.95 for hs-cTnT and hs-cTnI, respectively) but not peak concentrations for comparison. The ROC curve–determined optimum for absolute change was 0.007 μg/L. An analysis of our study showed that the use of relative changes in the hs-cTnT assay was inferior to the use of absolute changes [AUC, 0.78 (95% CI, 0.75–0.81) vs 0.92 (95% CI, 0.90–0.94); $P < 0.001$]. The use of absolute changes was inferior to absolute peak values irrespective of change [AUC, 0.95 (95% CI, 0.93–0.97); $P = 0.003$]. The ROC curve–determined optimum for relative change was 10% and was 0.002 μg/L for absolute change. The respective sensitivities and specificities for AMI for the peak hs-cTnT value ≥99th percentile were: (*a*) 94.4% (95% CI, 90.7%–96.9%) and 79.8% (95% CI, 78.8%–80.5%) irrespective of change; (*b*) 69.0% (95% CI, 63.7%–73.8%) and 89.7% (95% CI, 88.3%–91.0%) with a 10% relative change; and (*c*) 82.0% (95% CI, 77.0%–86.2%) and 91.2% (95% CI, 89.9%–92.3%) with an absolute change of 0.002 μg/L.

We also showed that absolute peak hs-cTnT values irrespective of change outperformed the relative change in hs-cTnT values for predicting adverse events after discharge (death, nonfatal AMI, or revascularization), which were incurred by 11.8% of the patients by 1 year. In the study of Kavsak et al. of patients with confirmed AMI, there was no difference between quartiles of relative change seen between a median of 2 h and 9 h after presentation for adverse events (death, nonfatal AMI, or heart failure) by 4 years *(4)*. We confirm such findings in our study. The AUC in the 200 AMI patients was 0.49 (95% CI, 0.39–0.59) for relative changes in hs-cTnT values and 0.47 (95% CI, 0.36–0.57) for absolute changes for adverse events occurring within 1 year.

The study of Eggers et al. *(5)* of 454 patients with an AMI rate of 31.3% demonstrated rates of 6-month outcomes (AMI or death) and 5.8-year mortality that were significantly higher in patients with higher relative changes in the Stratus troponin I assay than in those with lower relative changes. The AUC for 5.8-year mortality using relative changes did not show prognostic utility, however [AUC, 0.53 (95% CI, 0.44–0.62)]. A comparison with absolute values irrespective of change was not made. Another study by Kavsak et al. *(6)* measured multiple samples with a Beckman Coulter hs-cTnI assay over a 48-h period in 223 patients with chest pain, with a median time from presentation to peak hs-cTnI concentration of 9 h. They demonstrated that absolute changes outperformed relative changes for predicting adverse events at 10 years (hazard ratio, 2.95 vs 1.89) and events at 1 year [AUC, 0.70 (95% CI, 0.61–0.78) vs 0.63 (95% CI, 0.53–0.72)]. Again, the performance of absolute values irrespective of change was not reported. In our study, the use of relative changes in the hs-cTnT assay was inferior to the use of absolute changes [AUC, 0.60 (95% CI, 0.55–0.67) vs 0.64 (95% CI, 0.59–0.69); $P = 0.028$]. Absolute changes were inferior to absolute peak values irrespective of change [AUC, 0.67 (95% CI, 0.60–0.72); $P = 0.046$]. The ROC curve–determined optimum was 3% for relative change and 0.001 μg/L for absolute change. These ROC curve optimums are within the imprecision of the assay.

In summary, our data confirm that absolute changes outperform relative changes for both diagnostic and prognostic purposes. More studies are needed to ascertain the optimum absolute change and timing of samples to make a diagnosis of AMI and for risk stratification. In clinical practice, neither absolute change nor absolute peak concentration is used to the exclu-

[1] Nonstandard abbreviations: AMI, acute myocardial infarction; hs-cTnT, high-sensitivity cardiac troponin T (assay); AUC, area under the ROC curve.