Cytomegalovirus Seropositivity and C-Reactive Protein Have Independent and Combined Predictive Value for Mortality in Patients With Angiographically Demonstrated Coronary Artery Disease

To the Editor:

In the recent article by Muhlestein et al., there are internal inconsistencies in serum C-reactive protein (CRP) levels that make interpreting the study difficult. CRP levels in Figure 1, Table 1, Methods, and the Abstract are given in mg/dL. The median CRP concentration in this patient population with angiographically documented coronary disease was between 1.2 and 1.7 mg/dL (Methods). The first tertile cut point of CRP level for the significant difference found in survival curves (Figure 2) was 1.2 mg/dL (which is equal to 12 mg/L). In the Results section, however, mean CRP concentration was given as 1.5 mg/L in survivors and 3.1 mg/L in those who died. These levels in the Results section are one-tenth of those noted elsewhere in the article, and they are more likely to be correct, because median CRP concentrations between 1 and 4 mg/L have been reported in studies of similar patients with nonacute manifestations of coronary artery disease. Patients with acute coronary syndromes have much higher CRP levels than either patients with stable coronary disease or subjects in population studies, with medians ranging from 3 to 7 mg/L and cut points for separation of those at risk from adverse events during follow-up ranging from 3 to 16 mg/L. The actual CRP concentration may be quite significant from a pathophysiological standpoint; my colleagues and I recently showed a marked synergism between interferon and CRP on tissue factor expression by monocytes at CRP concentrations >5 μg/mL (or 5 mg/L). Thus, the higher serum CRP concentrations above the cut points for adverse events (>3 to 16 mg/L) seen in studies of acute coronary syndromes could be a potential link between inflammation and thrombosis. Therefore, it is important to ascertain whether the cut point in Muhlestein et al.’s study was 1.2 mg/dL or 1.2 mg/L.

Confusion of units to report serum CRP concentrations is unfortunate but not unknown in communications about the prognostic role of this acute phase reactant.1

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Response

We thank Dr Freedman for his insightful review of our recently published article.1 We apologize for the proof-reading error that resulted in confusion regarding the units used in reporting C-reactive protein (CRP) concentrations. In actuality, all measurements of CRP throughout the paper were made in mg/dL, not mg/L, and the numbers reported are correct if interpreted as such. As noted by Dr Freedman, the median levels of CRP from patients in our study, therefore, are significantly higher than those reported in some other studies of patients with coronary artery disease.3 Despite this difference, however, these higher CRP levels, when broken into tertiles, remain highly predictive of future mortality. The exact explanation for the higher median CRP level found in our study population compared with other reported series of patients with coronary artery disease is unknown. However, some thoughts may be offered.

One explanation may be that different clinical CRP assays were used. The Abbot Diagnostics CRP kit was used in our study, and it may not have correlated exactly with other assays that have been used. Therefore, something related to the assay methodologies used in the different laboratories may have resulted in a shift of the median CRP concentrations to higher or lower levels, while retaining internal consistency in all the results. This emphasizes the need for standardizing all clinically available CRP assays. However, although differences between assays may exist, it is our opinion that they are unlikely to be of a great enough magnitude to explain all the differences noted.

A more likely explanation is that our study population has essential differences from populations in other, similar studies. For example, compared with the Cholesterol And Recurrent Events (CARE) study, which required all patients to be stabilized before enrollment, 33% of our population presented with unstable angina, 23% presented with acute myocardial infarction, and all patients were undergoing angiographic evaluation due to at least modestly urgent symptoms. These patients with more acute presentations are likely to have generally higher CRP concentrations. In addition, the majority of patients in our study were from the Intermountain West and had been living at a significantly higher (>4000 feet) elevation than sea level. Recent studies have demonstrated at least some effect of altitude on markers of inflammation, including CRP.2 Other unknown clinical differences in the study population might also contribute to the variance in median CRP concentrations. However, whatever the reason for these differences, it is important to note that the stratification of patients into tertiles based on their CRP concentrations was very predictive of future mortality. As Dr Freedman has noted, many of the patients in our study had CRP concen-
trations that were potentially high enough to produce an interaction between inflammation and thrombosis.

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