REPLY

We appreciate the interest by Jarai and colleagues in our recent paper (1). Unfortunately, from the FRISC-II data we cannot answer the questions raised. Further subgrouping of the data makes the groups small and estimates unreliable.

A number of problems arise when trying to define optimal decision limits in patients with non-ST-segment elevation acute coronary syndrome. One problem is that the level of N-terminal pro-brain natriuretic peptide (NT-proBNP) changes over time after presentation. Previous studies have shown that the level of NT-proBNP increases during the first 14 to 48 h after a myocardial infarction (2), and thereby gradually decreases at least for six months (3). Therefore, the timing in relation to the acute event will be important when defining optimal decision limits for NT-proBNP in patients with non-ST-segment elevation acute coronary syndromes. Thus, NT-proBNP levels measured after a median time of 9 h from the last episode of symptoms in the GUSTO-IV trial (4) does not correspond to levels measured after a median time of 39 h in the FRISC-II trial (1).

Another important issue is whether decision limits should be related to gender. It is well known that NT-proBNP levels are higher in women (5). The reason for this gender-related difference is still unclear. The fact that the age-related mortality is lower in women than in men suggests that the reason for this gender difference does not cause increased mortality. Therefore, we believe gender differences should be considered when determining suitable decision limits. Evidently, further studies regarding the best time point for analysis and the most appropriate decision limit are needed.

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**Troponin and Outcomes**

We read with interest the report of Kontos et al. (1), which showed that any detectable troponin I in the serum of patients admitted with chest pain was associated with worse outcomes. We recently reported the results of a similar study involving troponin T levels (2), and we found that among 428 patients admitted with ongoing chest pain, troponin T levels that were detectable but within the range reported as normal were markers of an increased risk of death/subsequent myocardial infarction/vascularization during the four-month follow-up.

We would like to comment on two aspects of the Kontos et al. (1) study: 1) the conclusion that most of the tests with detectable cardiac troponin I in the normal range “represent analytical false positive results due to the assays themselves” and 2) what to call detectable troponin values within the normal range. Troponin assays are exquisitely sensitive and, conceptually, a minor event, that cannot be detected clinically, can lead to a detectable level of troponin in the serum. Instead of thinking of detectable levels of troponin in patients with a negative subsequent workup as “false positive,” we believe that the patients should be thought of as having suffered a minor event, be it transient vascular occlusion, blood pressure changes, short runs of ventricular arrhythmias, or any number of other conditions (3). Whereas most patients suffer no testable harm from such events, some do, and hence the observed higher risk of poor outcomes.

Finally, in our report we referred to detectable troponin within the normal range as “marginal” troponin, indicative of “minor myocardial injury.” We believe these terms aid in thinking about these patients, and we would advocate their continued use.

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REPLY

We appreciate the interest by Drs. Henrikson and Chandra-Strobos in our recent study (1). They disagree with the conclusion that lower levels of troponin are likely analytical false positives and are more likely related to necrosis. This is based on the results of their recent study (2), in which patients with minor troponin T (TnT) elevations had a higher event than those without detectable levels, and were closer to those with clearly elevated levels (2).

However, the two studies are not directly comparable. The range of TnT levels, which they called “marginal” (defined as levels between 0.01 ng/ml and 0.09 ng/ml), was fairly broad. The TnT levels from 0.01 to 0.03 ng/ml (between the lower limit of detectability and 10% coefficient of variation [CV]) (3) are equivalent to our low troponin I values, whereas those from 0.03 to 0.09 ng/ml (from the 10% CV to the prior myocardial infarction [MI] diagnostic criteria) would be equivalent to our intermediate TnI levels. The fact that their marginal TnT values are a combination of low and intermediate TnT values likely explains the higher event rate that was found. For example, the proportion of patients who had elevated creatine kinase-MB fraction (CK-MB) was 15% in our TnI intermediate group, comparable to 14% in their marginal TnT group; in contrast, only 1.1% of patients in our TnI low group had increased CK-MB.

In addition, we did not call patients with detectable TnI values “normal.” We made the distinction between low elevations, in which some represent necrosis; this is seen by the higher event rate. However, as we and others have noted (4), this is a mixture of a small number of patients who truly have necrosis and a much higher number who have analytical false positives. As we noted, labeling a patient who has atypical chest pain, no-ischemic electrocardiographic changes, low levels of CK-MB not near the diagnostic cut-off, and with minor troponin elevations as having an myocardial infarction has significant implications for the patient’s long-term health care, and we believe this is inappropriate. As none of the currently available assays conform to recommended standards (5), our data, as well as other recommendations (6), are that these values may be indicative of necrosis, and therefore should be further evaluated. This evaluation should be dependent on the clinical scenario. Rather than routinely performing coronary angiography as recommended by the American College of Cardiology/American Heart Association guidelines for patients who have troponin elevations, we believe that stress testing would be an appropriate evaluation, for many of these patients.

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The Diet–Heart Hypothesis: An Evolutionary Support

Nothing in biology makes sense except in the light of evolution.
Theodosius Dobzhansky, 1973

Considering that humankind and its metabolic physiology are biological products of evolution, one might well ask why Weinberg’s report (1) not only ignores the evolutionary arguments supporting the diet–heart hypothesis, but also advances the evolutionarily untenable thesis that the low-fat, high-carbohydrate diet is responsible for the current epidemics of obesity, type II diabetes, and the metabolic syndrome.

Weinberg seems to forget that the low-fat, high-carbohydrate diet represents the diet “for which human beings are in essence genetically programmed” (2), because their metabolic physiology has been evolutionarily molded by a nutritional environment in which, for millions of years, that diet was practically the sole one available to our ancestors (3). For 99% of its evolution, humankind indeed lived mainly on fruits and vegetables, which consist essentially of carbohydrates, and consumed little fat, because game was very lean and cattle-breeding, chicken farming, butter, dairy products, margarines, and oils did not exist (2).