medicine? The answer: focused, gender-specific, cardiovascular clinical research.

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REFERENCE

REPLY
In the gender subgroup analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial data, we observed that fewer women across all Thrombolysis In Myocardial Infarction (TIMI) risk strata underwent coronary angiography compared to men (1). However, among women who did have significant coronary artery disease (CAD), an equal proportion went on to have coronary revascularization compared to men. We also noted, however, that women in the high-risk acute coronary syndromes (ACS) group were significantly more likely to have refractory angina or be readmitted to a hospital with recurrent angina as compared to men. Dr. Kessler is correct that the differences in revascularization rates could not account for the difference in refractory ischemia/rehospitalization rates we observed. However, if women were equally as likely to have coronary angiograms as men, then more women with significant CAD may have been identified. Subsequent revascularization in this high-risk group may have equalized the rates of refractory ischemia between women and men.

However, we recognize that our association represents a subgroup analysis, which at best can raise a hypothesis but cannot confirm whether it is true. Like Dr. Kessler, we also advocate sex- and gender-based research in cardiovascular disease using sufficient sample sizes and methodology to be confirmatory.

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Troponin Trumps Common Sense
The state-of-the-art review of biomarkers in acute cardiac disease by Drs. Jaffe, Babuin, and Apple is thoughtful and timely (1). My concern, shared by many cardiologists, is that troponin testing has gotten out of hand. Most cardiologists have been asked to see a patient (often urgently) found to have a mildly elevated troponin when the test was ordered reflexively—regardless of the patient’s presenting complaints or past history. Cardiologists on hospital services are tripping over troponin every day. The most challenging situation is when a patient presents with a serious (even life-threatening) noncardiac condition, and one or more doctors involved in their care gets distracted by an incidental mild troponin elevation. Occasionally, this leads to a sudden obsession over one test result, a phenomenon I call “troponin trumps common sense.” Several problems are associated with the uninformed use of this sensitive assay. The authors present information about the appropriate use of troponin testing that should be actively diffused into practice. They write, “Because of the sensitivity of cTn [cardiac troponin], elevations are common in patients with a large number of acute and chronic cardiovascular diseases. It is up to the clinician to decide whether the presentation is one of acute ischemia.”(1) Table 2 (1) lists about two dozen situations where “elevations of troponin in the absence of overt ischemic heart disease” occur. Admittedly, most patients presenting with an acute coronary syndrome (ACS) also have one or more of the conditions listed. This is where clinical judgment counts. The patients I am describing do not present with chest pain, dyspnea, or other symptoms and signs, or an electrocardiogram suggesting an acute cardiovascular problem.

Consider the cost of all the unnecessary stress tests ordered, coronary angiograms performed, and anti-platelet agents prescribed for mild troponin elevations when the clinical situation makes an acute cardiovascular problem very unlikely. The casual use of the phrase non–ST-segment elevation myocardial infarction (NSTEMI) when the mild troponin elevation is not, in fact, due to atherosclerotic coronary artery disease, creates its own legacy. Think twice before attaching the NSTEMI label to a patient with a mild troponin elevation much more likely to be due to one or more of the conditions outlined by the authors in Table 2 (1).

It is useful to draw an analogy between mild troponin elevations and nonspecific ST-T changes on an electrocardiogram. I suggest using the descriptive phrase “nonspecific mild troponin elevation” if there is no compelling evidence to support a diagnosis of an ACS and in patients with chronic cardiovascular disease or noncardiac diseases. Doctors do not feel compelled to request an urgent cardiology consult on every patient with nonspecific ST-T changes on an electrocardiogram in the absence of any cardiac symptoms or history of cardiac disease. Rather than allowing troponin to trump common sense, we should inject more common sense into the process of ordering a troponin level in the first place.
Biomarkers in Acute Cardiac Disease

In their state-of-the-art paper on biomarkers in acute cardiac disease (1), Dr. Jaffe and colleagues list creatine kinase-MB (CK-MB) as a “potentially outdated marker.” However, CK-MB has a specific utility in the diagnosis of reinfarction (2), and it cannot be replaced by the cardiac troponins for this purpose. By following up the time course of rise and fall of CK-MB, an interruption in the progressive decline in the level of the biomarker (to levels below upper reference limit) can be detected (2–4). Re-elevations in CK-MB by more than 50%, can be used to diagnose re-infarctions as early as 18 h after the index event (2). Both cardiac troponin T (cTnT) and cardiac troponin I (cTnI) on the other hand are continuously released from degenerating contractile apparatus in necrotic cardiomyocytes and may show persistent elevations, 7 to 10 days in the case of cTnI and up to 10 to 14 days in the case of cTnT, after the index event (2). The protracted time course of kinetic release of cTnI and cTnT limit their ability to diagnose reinfarction even several days after the index ST-segment elevation myocardial infarction (STEMI) because the cardiac troponin levels will still be on the rise during this period as a result of their normal kinetics, and it is not possible to be sure whether the rise is due to a re-infarction or not. It is because of this important difference in the kinetics between CK-MB, which shows a rapid rise and fall, and the troponins, the American College of Cardiology/American Heart Association Practice guidelines for STEMI specifically state that CK-MB is superior for diagnosing reinfarction (2). This is very relevant as the state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same. The state of the art and guidelines are not the same.

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REPLY

Drs. Fye, Nagajothi, and Trivedi raise important issues that we are pleased to address.

One that many of us have tried to reinforce for years is that elevations of biomarkers of cardiac injury are not synonymous with myocardial infarction (1). This is especially important for cardiac troponin which, because it is more sensitive than creatine kinase MB (CKMB), detects cardiac injury in many situations which are not due to primary coronary abnormalities. Thus, many patients with elevations do not require the extensive workups Dr. Fye correctly indicates can occur if one obviates common sense. Some may need an evaluation for pulmonary embolism or myocarditis and some only watchful waiting. Some of this can occur in the outpatient setting in our view, but we often see cardiologists assume that once the patient is discharged that they can forget about elevations. Neglecting such a potent risk factor for mortality is not good common sense either. Regardless of the etiology, elevations of troponin are indicative of significant cardiovascular disease and usually are associated with an adverse prognosis in the short term (2) and over time once recovery occurs (3) and in those who are more compensated (4). When such elevations occur in critically ill individuals, first efforts should be focused on the primary disease process which very often is the stimulus for the cardiac injury. Additional work is necessary to distinguish when we as cardiologists should address cardiac issues acutely or and above treating the underlying disease state. Many of us are actively involved in trying to define such subsets at present. Whether or not acute intervention is needed, it is clear from most studies that elevations of troponin also predict adverse long term events (3,4). Thus, those who were critically ill and recover and those in whom “incidental” elevations of troponin were detected, require careful evaluation. That could mean an evaluation for ischemic heart disease but as Dr. Fye suggests, it is prudent to consider other etiologies for elevations as well.

It is also good common sense to upgrade our clinical judgment periodically. It is thus prudent in considering the possibility in a given patient of ischemic heart disease to take note of information concerning the lack of perfection of the angiogram, (5) differences in the way in which women present with infarction, (6) and the recent article in the Journal of the American College of Cardiology suggesting the high frequency of unrecognized myocardial infarctions detected in older individuals by MRI (7).

The issue of reinfarction is one where we have used common sense. The state of the art and guidelines are not the same. The later are often much more conservative. It was presumed in the initial studies, that increases in CKMB post-infarction were indicative of reinfarction. There was no independent validation of that. There has been no validation of the use of increases on the