**EDITORIAL COMMENT**

**The Skinny on Fatty Acid-Binding Protein**

James A. de Lemos, MD, FACC,†
Michelle O’Donoghue, MD‡

*Dallas, Texas; and Boston, Massachusetts*

Biomarkers have come to play an increasingly important role in the evaluation and management of patients with suspected acute coronary syndromes (ACS). To date, cardiac troponins T and I remain the best established biomarkers in ACS for both diagnosis and risk assessment. In addition to providing high sensitivity and specificity for detecting myocardial necrosis, troponins provide assessment of the risk of adverse outcomes in patients with ACS and help to identify patients who benefit most from particular treatment strategies, including glycoprotein IIb/IIIa inhibitors, low molecular-weight heparins, and routine coronary angiography (1).

*Editors published in the Journal of American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.*

Advances in methodologies for protein identification and a greater understanding of the inflammatory pathophysiology of atherothrombosis have contributed to a proliferation of candidate biomarkers in ACS over the past several years. Many of these novel markers reflect pathways that are distinct from myocardial necrosis, because it is largely believed that high-quality troponin assays allow little room for other markers of necrosis. Recent guidelines, in fact, recommend that troponins are the only necrosis markers that should be measured routinely for diagnosis and risk stratification in ACS (1).

However, despite a robust evidence base supporting their routine measurement in ACS, troponins have several important limitations. In particular, because of troponins’ relative large size and location bound within the contractile apparatus of the cardiomyocyte, troponin release is typically delayed for several hours after the onset of ischemic injury. Thus, blood must be sampled at least 6 h after the onset of ischemic discomfort in order to achieve adequate sensitivity. As such, for a large number of patients without classic symptomatology or electrocardiographic changes, significant irreversible myocardial injury might occur before a definitive therapeutic plan is implemented. In addition, troponin levels might remain elevated for 7 to 14 days after the initial ischemic insult, thereby limiting sensitivity for detecting recurrent myocardial injury. Importantly, because current troponin assays are unable to detect ischemia in the absence of necrosis, troponins are unable to identify patients with unstable angina who are at increased risk of adverse outcomes and who might benefit from specific treatment strategies. Finally, it is increasingly recognized that, among hospitalized patients, a substantial proportion of elevated troponin levels are caused by conditions other than ACS (2). Troponins, although specific for myocardial necrosis, are by no means specific for acute plaque rupture leading to ischemic injury.

In the current issue of the Journal, Kilcullen et al. (3) report on the prognostic utility of heart-type fatty acid-binding protein (H-FABP) in patients with ACS. Heart-type fatty acid-binding protein is a biomarker of myocardial necrosis and injury that offers several theoretical advantages over troponin. Heart-type fatty acid-binding protein is smaller in size (14 to 15 kDa) than troponin I or T (21 to 37 kDa) and is concentrated in the cytoplasm of cardiomyocytes. Owing to its small size, H-FABP is released quickly into the circulation when membrane integrity is compromised in response to myocardial injury. Levels of H-FABP are detectable as early as 2 to 3 h and typically return to baseline levels within 12 to 24 h of the initial insult (4,5). Consistent with these findings, a growing number of studies have shown that H-FABP is a sensitive marker for the diagnosis of myocardial infarction (MI) (4,6–8) and might be more sensitive than older-generation troponin assays when measured in the early hours after symptom onset (8,9). Moreover, because of its rapid release kinetics, H-FABP might be useful for the detection of reperfusion after ST-segment elevation MI (10). These properties theoretically make H-FABP an attractive marker both for the detection of myocardial ischemia in the absence of necrosis and possibly for the early detection of recurrent myocardial injury. To date, however, there is no definitive evidence to show that ischemic injury below the threshold for necrosis can lead to H-FABP release.

We recently reported that elevated levels of H-FABP measured in the first few days after an ACS event were associated with an increased risk of death, heart failure, and early recurrent ischemic events (11). Moreover, H-FABP seemed to provide incremental information for risk stratification that was independent of established risk factors and biomarkers, including troponin I, B-type natriuretic peptide, and myoglobin. Because H-FABP is released and cleared rapidly from the circulation, we hypothesized that elevation in serum H-FABP at this later time point (41 ±
20 h) might help to identify patients with either ongoing or recurrent myocardial injury who are at particular risk of adverse outcomes (11). However an important limitation to our report was the use of an older generation troponin assay, which precluded definitive evaluation of the incremental utility of H-FABP beyond that which is provided by newer high-sensitivity troponin assays (12).

In the current study, Kilcullen et al. (3) evaluated the prognostic utility of H-FABP in a registry of 1,448 patients with ACS from West Yorkshire, United Kingdom. Heart-type fatty acid-binding protein was powerfully and independently associated with the risk of death when measured within 12 to 24 h of symptom onset after ACS. Moreover, H-FABP identified subjects at increased risk of death even when troponin levels were normal. This study provides important confirmatory information to substantiate the prognostic utility of this emerging marker and addresses the most important limitations of our prior study. In particular, the current analysis employed the use of higher-sensitivity assays for the assessment of both troponin (Accu TnI, Beckman Coulter, Fullerton, California) and H-FABP (Dainippon Pharmaceutical, Osaka, Japan). In the presence of a negative troponin I (<0.06 ng/ml), an elevation in H-FABP (>5.8 µg/l) was associated with a significant increase in the risk of death after adjusting for variables in the GRACE (Global Registry of Acute Coronary Events) prediction model and for levels of C-reactive protein.

Several limitations to the current study merit consideration. Few subjects with unstable angina were included, and therefore it will be important to further delineate the role of H-FABP in a well-defined population of patients with unstable angina in the future. In addition, the authors did not measure myoglobin in the present study. Although myoglobin has a molecular weight and kinetic profile similar to H-FABP, a much higher proportion of H-FABP is concentrated in myocardial tissue (vs. skeletal muscle) relative to myoglobin. Thus, H-FABP might offer improved specificity and sensitivity over myoglobin, owing to its relative predominance in myocardial tissue and lower normal reference range (7,8,13). Nevertheless, elevated levels of myoglobin have also been associated with an increased risk of death and heart failure after ACS (14), and additional direct comparisons are needed to fully establish the superiority of H-FABP over myoglobin for risk stratification.

These are “early days” in the lifespan of H-FABP, and many important clinical, logistical, and scientific questions remain to be answered. Because the present study measured H-FABP 12 to 24 h from symptom onset, the relative diagnostic and prognostic value of the marker in the earliest hours from symptom onset (when it should be most useful) remains unclear. Earlier reports suggest that H-FABP is indeed useful for risk stratification when measured <6 h from symptom onset (15,16). Because only mortality data were collected in the current analysis, future studies are needed to determine whether H-FABP is useful for predicting the risk of heart failure or early recurrent myocardial injury. Moreover, it remains unknown whether H-FABP might help to guide selection of specific treatment strategies in ACS.

Perhaps the most intriguing question that remains is why H-FABP might provide prognostic information for death and heart failure that is independent of and superior to troponin. The answer to this question will teach us as much or more about troponin as it does about H-FABP. It is of interest that the association of H-FABP (as well as myoglobin and creatine kinase-myocardial band) with infarct size seems to follow a straightforward single compartmental model, whereas the association between troponin and infarct size is considerably more complex. Although it is tempting to speculate that H-FABP elevation might identify ischemic injury below the threshold of detection with troponin, mortality was considerably higher among patients in this subgroup in the present study than one would expect for patients with ACS who have normal troponin levels. Future studies correlating H-FABP levels with necropsy findings among patients with normal troponin levels would be particularly helpful for characterizing the mechanistic links between H-FABP elevation and mortality. Alternatively, delayed-enhancement magnetic resonance imaging studies might allow delineation of differences in the relationships between various biomarkers of necrosis and myocardial injury. At present, it seems the most plausible hypothesis is that elevated levels of H-FABP at later time points might identify patients with either ongoing or recurrent myocardial injury who are at increased risk of death.

Although much further investigation will be required before the clinical use of H-FABP can be considered, the current study provides early confirmatory evidence to suggest that this biomarker might help to identify high-risk patients who are troponin negative. Although troponins remain the benchmark for ACS biomarkers, they have important limitations, and investigators should continue to evaluate other biomarkers in the necrosis class, provided their incremental utility relative to state-of-the-art troponin assays can be definitively established.

Reprint requests and correspondence: Dr. James A. de Lemos, University of Texas Southwestern Medical Center, 5909 Harry Hines Boulevard, HA 9.133, Dallas, Texas 75390. E-mail: James.deLemos@UTSouthwestern.edu.

REFERENCES


