Chest pain is the presenting complaint in approximately 5% of all emergency department visits, making chest pain the second most common reason for seeking acute medical care (1). The prevalence of acute myocardial infarction (AMI) in this emergency department population with chest pain ranges from 5% to 15%. Reliable exclusion or confirmation of AMI within the first few hours after presentation still constitutes a diagnostic challenge. Earlier confirmation (rule-in) than is obtainable currently would permit earlier start of appropriate treatment, and earlier exclusion (rule-out) would facilitate early discharge of patients for whom further in-hospital evaluation or treatment is unnecessary.

Myocardial infarction is defined as myocardial necrosis of ischemic origin (2). AMI is not a homogenous condition, however. It ranges from minor infarctions with necrosis of less than 1 g of the myocardium to large infarctions of more than one-third of the left ventricular mass. Furthermore, although by definition the cause of the necrosis is ischemia, the causes of the ischemia can range from plaque rupture with an overlaying coronary-flow–obstructing thrombosis (type I infarction) to supply/demand imbalance without a thrombotic component (type II, secondary infarction) to iatrogenic causes, e.g., associated with percutaneous coronary intervention or coronary artery bypass grafting procedures (type IV and V infarctions). Thus, the challenge to find biochemical markers useful for diagnosis of AMI remains fundamentally important.

Presently, the only biochemical markers used for diagnosis of AMI are markers of myocardial necrosis. According to current international guidelines, the diagnosis of AMI requires demonstration of an increase of a specific marker of myocardial injury, e.g., cardiac troponin I or T. Although an increase of cardiac troponin is highly specific for myocardial injury, it tells nothing about the origin of the injury and is thus not sufficient on its own for the diagnosis of AMI. Evidence of an ischemic origin of the injury also is needed (2). Another limitation of the use of troponin for early diagnosis of AMI is the time lag of up to 6 h from the start of the infarction to the appearance of increased concentrations of cardiac troponins in the blood that can be detected by use of current troponin assays, although there is evidence that troponin fragments may appear in the circulation within the first hour of onset (3).

Therefore, other biochemical markers have been sought that reflect important, upstream processes in the pathophysiology of AMI and might give an earlier signal of an ongoing AMI. Alternatively, markers that provide a signal of an atherothrombotic origin of the myocardial injury might increase the diagnostic specificity.

In this issue of Clinical Chemistry, Apple and coworkers report an evaluation of a multimarker approach for early diagnosis of AMI (4). They tested the hypothesis that adding the measurement of different nonnecrosis biochemical markers to troponin I would increase diagnostic accuracy, a hypothesis that, surprisingly, has been tested in only a few previous studies (5, 6). The results of Apple and coworkers showed convincingly and in accord with previous experience (6) that compared with the use of troponin I alone, none of the tested markers [myeloperoxidase, soluble CD40 ligand, placental growth factor, matrix metalloproteinase 9 (MMP-9), C-reactive protein, N-terminal pro-B natriuretic peptide, or creatinine (as determined by estimated glomerular filtration rate)] provided any clinically significant additional diagnostic value when measured in addition to troponin I.

Because most of these markers have been shown to provide independent prognostic information in patients with acute coronary syndrome (7–11), it is reasonable to ask why they failed to provide additive diagnostic information in the present study. First, it is important to note that cardiac troponin I alone already has a high diagnostic accuracy, as reflected in its high specificity of 89% on admission, making it difficult to further improve on the diagnostic accuracy of this test. Second, the tested nonnecrosis markers demonstrated very poor diagnostic accuracy on their own; none of the 7 markers had an area under the ROC of more than 0.60, and 4 of the markers, CD40L, placental growth factor, myeloperoxidase, and estimated glomerular filtration rate, provided no significant diagnostic information whatsoever. The low specificity of several of the markers was not surprising given that they respond to nonspecific inflammatory stimuli (e.g., high-sensitivity C-reactive protein and myeloperoxidase) or other stimuli that can be present in the absence of AMI (e.g., N-terminal pro-B natriuretic peptide). However, the poor sensitivity seen with these markers was more surprising and disappointing. Myeloperoxidase, in partic-
ular, has been promoted as an early marker of AMI (12).

To be useful in a rule-out situation, a marker must have very high sensitivity, and for a rule-in the marker must have very high specificity. All the tested nonnecrosis markers had specificities far from the level needed to be useful for rule-in. Only 1 marker, MMP-9, had a sensitivity (96%) that was high enough to be potentially useful for rule-out. Of the total 25 patients with AMI, all 7 patients who had falsely negative troponin I on admission had increased admission concentrations of MMP-9. Hence, a negative troponin I together with a negative MMP-9 had a negative predictive value of 100% in this cohort. However, only 69 (16%) of the 432 non-AMI patients had both a negative troponin I and a negative MMP-9 on admission, making the clinical usefulness and positive cost/benefit ratio of this diagnostic strategy very doubtful.

The question can be raised as to whether upstream, prenecrosis markers have the potential to improve the diagnosis of AMI. The requirements of such markers are not trivial. For instance, a specific marker of plaque rupture, if such a marker indeed exists, must be detectable at very low concentrations in the blood, given the tiny amount of tissue damage that occurs during a plaque rupture. Furthermore, the small increase of the marker caused by the plaque rupture of the culprit lesion in the coronary artery has to be detectable against the background of concurrent plaque ruptures throughout the arterial tree, which might occur frequently, especially in an atherosclerotic aorta. In addition, this marker would not be useful for detecting the AMIs that are not caused by plaque rupture (type II, secondary AMI). A marker of thrombus formation (i.e., a marker of activation of the platelets or of the coagulation system) presents similar difficulties. A specific marker of myocardial ischemia, which always precedes the development of AMI, is an attractive possibility. Methods to detect ischemia-modified albumin are available commercially, and ischemia-modified albumin may be an early marker of cardiac ischemia. The early sensitivity of ischemia-modified albumin for AMI has been evaluated in several studies, however, and found to be well below 100% (13). Likewise, elevations of ischemia-modified albumin have not proven specific for cardiac ischemia (14).

Another approach that has been tested is to add an earlier necrosis marker to troponin (15). However, the currently available early markers, myoglobin and heart fatty acid binding protein, have relatively poor specificity (especially myoglobin). Furthermore, the introduction of more sensitive troponin assays has raised serious questions about whether these markers appear any earlier in the circulation than troponin (16). Indeed, the next generation of high-sensitivity troponin assays enable the high-precision measurement of the low concentrations of troponin circulating in healthy people. The increased analytical sensitivity and improved imprecision of these new assays make it possible to detect increasing troponin concentrations much earlier than with the current assays and will likely facilitate detection of all AMIs by the simple examination of an initial concentration and change in concentrations between 2 samples measured 1 or 2 hours apart. However, there is a possibility that earlier necrosis markers than troponin exist. In an interesting, recently reported study that used a proteomic approach, several potential very early necrosis markers were identified (17). The clinical feasibility and diagnostic value of these markers remain to be investigated.

Another approach that has been tested is to combine measurement of a necrosis marker with other noninvasive nonbiochemical methods, e.g., different electrocardiogram techniques (18) or imaging techniques such as point-of-care myocardial scintigraphy (19). The rapid development of cardiac imaging techniques, especially cardiac MRI and computed tomographic angiography, might make the combination of high-sensitivity troponin determination with noninvasive cardiac imaging an attractive future solution to the diagnostic challenge of rapidly assessing patients for possible myocardial infarction.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: B. Lindahl, Beckman Coulter and Siemens.
Stock Ownership: None declared.
Honoraria: B. Lindahl, Siemens, Beckman Coulter, and Roche Diagnostics.
Research Funding: None declared.
Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation or approval of manuscript.

-- Bertil Lindahl
Uppsala Clinical Research Center and
Department of Cardiology
University Hospital
Uppsala, Sweden
Address correspondence to the author at:
References


DOI: 10.1373/clinchem.2008.117572