Defining a Role for Novel Biomarkers in Acute Coronary Syndromes

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BACKGROUND: Biomarkers play a pivotal role in the diagnosis and treatment of patients with cardiovascular disease. Active investigation has brought forward an increasingly large number of novel candidate markers; however, few of these markers have yet to be incorporated into routine clinical use.

CONTENT: This review discusses biomarkers currently used in the setting of acute coronary syndromes. In this context, we assess the contemporary unmet needs for novel biomarkers in acute ischemic heart disease and the related challenges faced in developing new biomarkers to the point of integration into clinical practice. In particular, we address the impact of the availability of increasingly sensitive biomarkers of myocardial necrosis on the potential roles for novel biomarkers of inflammation, thrombosis, and ischemia.

SUMMARY: Although active investigation has produced a growing list of candidate novel biomarkers for the care of patients with cardiovascular disease, it has become increasingly challenging to find appreciable incremental clinical benefit for their addition to existing markers, in particular newer, more analytically sensitive cardiac troponin assays. A major challenge for researchers and clinicians will be to demonstrate whether candidate novel markers are useful in improving diagnosis and guiding clinical treatment.

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Biomarkers are integral to the care of patients with cardiovascular disease, in particular those presenting with acute syndromes of chest discomfort or shortness of breath, for whom biomarkers are central to establishing a diagnosis and guiding evidence-based therapy (1). Since the detection of circulating serum proteins as a tool for the diagnosis of acute coronary disease was first proposed 50 years ago (2), there has been a virtual explosion of investigation of novel candidate biomarkers. Despite the intensive effort at evaluation and despite the multitude of putative cardiovascular biomarkers studied, the cadre of biomarkers that have been recommended for routine use in the care of patients with cardiovascular disease remains quite small (1). Why have these intensive efforts at biomarker discovery failed to dramatically expand the use of novel cardiovascular biomarkers in clinical practice? This review assesses the contemporary unmet needs for novel biomarkers in acute ischemic heart disease and the related challenges faced in developing new biomarkers to the point of integration into clinical practice. In particular, we address the impact of the availability of increasingly sensitive biomarkers of myocardial necrosis on the potential roles for novel biomarkers of inflammation, thrombosis, and ischemia.

Current Role of Biomarkers in Clinical Care

Several well-studied biomarkers have withstood the test of time and become integrated into contemporary clinical care because of their readily apparent diagnostic, prognostic, and/or therapeutic utility. Cardiac troponin (cTn)2 established a paradigm for the modern clinical use of a biomarker for identifying high-risk patients for whom specific therapeutic interventions could be implemented to modify the associated risk. The natriuretic peptides have since been widely adopted to aid in the diagnosis of the patient with shortness of breath and, to a lesser extent, to optimize the care of patients with heart failure and improve risk stratification in acute coronary syndromes (ACSs). A brief summary of the contemporary use of these 2 biomarkers serves to set a foundation for understanding the potential incremental value of novel biomarkers.

Cardiac Troponin

cTn, the most diagnostically sensitive and specific biomarker of myocardial injury available, is a cornerstone for the accurate and timely diagnosis of patients with suspected ACS. The superior value of cTn over creatine kinase MB and other biomarkers of myocardial necrosis, such as myoglobin, derives from the tissue specific-
ity of its cardiac isoforms. Because of this specificity for cardiac tissue, it has now become possible to interpret any reliably detected concentration of cTn in the peripheral circulation as abnormal and indicative of myocardial injury (3). The resulting diagnostic sensitivity enables the clinician to detect myocardial injury in 30%–50% of patients presenting with suspected ACS and a creatine kinase MB concentration below the upper limit of normal (4). In the appropriate clinical context, an increase in the cTn concentration greater than the 99th percentile of a reference population is considered diagnostic for acute myocardial infarction (MI) (5). Thus, using cTn in conjunction with the contemporary decision limit at the 99th percentile has substantially improved the clinician’s ability to identify patients with MI. For example, in a study of 1719 patients with possible ACS, the diagnostic sensitivity for detecting MI with cTnI at the 99th percentile was increased nearly 50% compared with that using creatine kinase MB (6).

Although this superior diagnostic sensitivity is clinically meaningful by itself, the strong relationship between cTn and prognosis, along with the established value of cTn for guiding therapy, has been the primary force driving its integration into clinical practice. The availability of data evaluating the interaction of cTn results with clinical benefit in adequately powered, well-designed, randomized clinical trials of glycoprotein IIb/IIIa receptor antagonists, low molecular weight heparins, and early invasive vs conservative invasive evaluation have provided the foundation for evidence-based professional guidelines recommending these treatments in patients with increased cTn values (7).

Even now, more than 20 years after its first introduction as a biomarker, the clinical use of cTn continues to evolve. Steady improvements in the analytical performance of commercially available assays, in conjunction with an expanding number of studies confirming the clinical relevance of low concentrations of cTn (8, 9), have supported consistent professional recommendations for the use of lower decision limits (the 99th percentile) (1, 5) at the same time as improved precision has caused this level to move toward increasingly lower concentrations (Fig. 1). Consequently, newer assays that use contemporary cutoff points, in addition to identifying substantially more patients with suspected ACS who have myocardial injury, have also been shown to facilitate detection earlier after presentation. In one study, for example, samples from 103 patients with definite myocardial injury but with an initially negative cTnI result according to a current-generation assay were analyzed with a newer, more analytically sensitive assay, which revealed detectable injury in the first samples in 64% of the cases (10).

This substantially increased overall clinical sensitivity of cTn has been recognized as an important advance by experts and professional societies (1, 5) but has not been uniformly embraced by the clinical community. The application of assays with improved limits of detection and lower cutoff points has also produced large increases in the proportions of patients evaluated in the emergency setting who have detectable concentrations of cTn in the absence of a strong clinical suspicion for ACS (10, 11). Indeed, release of cTn has been described in a large number of acute and some chronic medical conditions in which myocardial injury occurs in quantities that were not previously detectable with other biomarkers and older assays. Thus, diagnostic interpretation requires integration of the specific clinical context and other available data (1, 5). From a prognostic perspective, it is noteworthy that in almost every setting studied to date, patients presenting with an increased cTn concentration have been found to have a poorer prognosis compared with those without detectable troponin (12). Nevertheless, in the absence of well-defined therapeutic algorithms, these findings of increased troponin under such varied conditions as uncontrolled infection or severe exacerbations of pulmonary disease have at times led to frustration by clinicians who are faced with having to grapple with the results. These observations underscore the need for an updated clinical approach to the use of cTn— one that both recognizes cTn as a biomarker of myocardial injury rather than as synonymous with MI and focuses on the need to deduce the mechanism of injury and associated therapeutic implications without committing a patient to an overly simplistic algorithm of antithrombotic therapy or all patients with increased cTn to an invasive evaluation.

**Natriuretic Peptides**

The cardiac neurohormone B-type natriuretic peptide (BNP) and the cleavage product of its prohormone [N-terminal pro-BNP (NT-proBNP)] are released predominantly in response to ventricular strain (13). These natriuretic peptides have filled a strongly perceived need in clinical practice as an aid to the often challenging diagnosis of heart failure in patients presenting to the clinic or emergency department with shortness of breath (14). Similarly to cTn, the concentrations of natriuretic peptides may be increased in a variety of circumstances that produce increased ventricular wall stress without overt or primary cardiac failure. Nevertheless, measurement of the natriuretic peptides has consistently been shown to improve on the clinician’s initial diagnostic impression, as well as to correlate with prognosis across the variety of patho-
logic conditions in which increased concentrations may be detected (14).

In patients with ACS, more than 10 studies have shown a strong association between BNP or NT-proBNP and outcome (1). In this group of patients, higher concentrations of BNP and NT-proBNP are associated with a higher risk of death or heart failure independently of other prognostic variables, including the left ventricular ejection fraction. For example, among a cohort of approximately 1600 ACS patients, the death rate increased from <1% for patients with BNP concentrations in the lowest quartile to 15% in those with a BNP concentration in the highest quartile (P < 0.0001) when BNP was measured at a median of 40 h after presentation (15). Importantly, BNP and NT-proBNP identify patients without systolic dysfunction or signs of heart failure who are at higher risk of death and heart failure and provide prognostic information that is complementary to cTn (16).

The clinical use of natriuretic peptides in the context of this evidence illustrates the physician’s perceived needs for biomarkers in patients with suspected ACS. Despite these consistent data demonstrating a robust relationship between BNP and NT-proBNP on the one hand and the risk of death and worsening heart failure in patients presenting with ACS on the other, the predominant clinical application of these natriuretic peptides is as a diagnostic tool to identify heart failure in the patient with undifferentiated chest symptoms. In contrast, the clinical application of natriuretic peptides for prognostication, although supported as reasonable (class IIa) for enhanced risk assessment in ACS (1), has seen limited use for this purpose because the appropriate therapeutic response to increased natriuretic peptide concentrations in ACS patients is not as clear as in patients with heart failure (17). This lesson regarding the importance of a link to therapeutic interventions is a valuable one. We now turn to con-
sider the potential for newer biomarkers to contribute to clinical care.

**Biomarker Discovery—Understanding the Potential of Novel Candidates**

Growing hand in hand with our contemporary fascination with the promises of personalized medicine, the discovery of novel biomarkers in cardiovascular disease has been embraced as a major objective of government-, private-, and industry-supported research initiatives. More than a decade of advances in our understanding of the complex mechanisms underlying the initiation and progression of atherothrombosis and its complications has stimulated efforts to identify and characterize new markers associated with these processes. In addition, newer screening-based discovery techniques such as metabolomics and proteomics have revealed large numbers of candidate metabolites and proteins associated with underlying disease for which the function or role in pathophysiology has yet to be explained.

On an a priori basis, it makes sense that noninvasive indicators of separate pathobiologically diverse contributors to the progression of cardiovascular disease, such as inflammation and thrombosis, could add complementary information (18). Indeed, novel biomarkers of inflammation, such as C-reactive protein (CRP) and myeloperoxidase, and of pathways for thrombosis, such as soluble CD40 ligand and von Willebrand factor, have been shown to add independent prognostic information in a variety of clinical settings, including those involving stable and unstable ischemic heart disease (19–23). Nevertheless, as gauged by such biomarkers’ limited integration into clinical practice, the incremental clinical benefit of their addition to existing markers and clinical tools has not been convincing to many practitioners. Let us therefore consider the present unmet needs for cardiovascular biomarkers in ACS and the resulting criteria for evaluating novel biomarkers.

**Unmet Needs for Cardiovascular Biomarkers**

**DIAGNOSTIC NEEDS**

There are 3 basic needs for the diagnostic application of a biomarker in any acute cardiovascular condition. In addition to desirable analytical and logistical properties, a diagnostic biomarker should be able to detect patients with or at risk of the disease with maximal diagnostic sensitivity, as early as possible, and with acceptable diagnostic accuracy. Because the optimal treatment of many acute cardiovascular conditions, such as acute MI, relies more on early recognition and early initiation of therapy than many noncardiac conditions, a greater premium is placed on the rapidity and sensitivity of diagnosis. For example, for medical and legal reasons our society is not permissive of a missed or delayed diagnosis of MI.

Although cTn is a robust diagnostic and prognostic marker in the setting of suspected ACS, an interest in testing newer biomarkers of ischemia and necrosis has persisted because of perceived limitations of cTn. First, because of the kinetics of cTn release from the disrupted cellular cytoskeleton, early diagnostic studies of troponin indicated that a delay of at least 6 h from symptom onset was necessary to support an acceptable assay sensitivity. Second, the expert consensus remains that detectable quantities of cTn are released only in the setting of irreversible myocardial injury, i.e., myocardial necrosis, thereby leaving the patients with unstable angina, which by definition indicates myocardial ischemia without necrosis, undiagnosed with cTn. If these limitations are accepted, there may be a role both for biomarkers designed for earlier detection of MI, such as myoglobin and heart-type fatty acid–binding protein, and for biomarkers of myocardial ischemia that do not require myocardial necrosis to be detectable in the peripheral circulation (24). As discussed earlier in this review, however, data for contemporary analytically improved assays for cTn suggest that these limitations are no longer substantial. In addition, the newer generations of cTn assays that are undergoing evaluation in research settings appear to decrease the limit of detection by an additional 10- to 100-fold compared with current-generation assays (25).

At the same time that analytically more sensitive cTn assays have diminished the need for early diagnostic biomarkers, they have also contributed to the necessity for clinicians to consider complementary diagnostic information to aid in determining the etiology of myocardial injury in patients with detectable troponin. At present, a skillfully obtained clinical history and ancillary diagnostic testing, such as electrocardiography and occasionally cardiac imaging, are most helpful in establishing whether an observed increase in cTn concentration is related to myocardial ischemia or to some other cause, such as heart failure, myocarditis, pulmonary embolism, or sepsis (5). It is possible, however, that this need may also be met in the future by novel biomarkers. For example, if the intense interest in biomarkers of plaque rupture were realized with the discovery of a biomarker with sufficient specificity to accurately indicate a compromise of underlying atherovascular plaque, then the paired use of such a biomarker with cTn could be exceedingly valuable to establishing the diagnosis of ACS during an emergency room assessment of chest pain. At this time, however, inflammatory biomarkers with such biological specificity have not clearly emerged. Some investigators...
have proposed that cTn subtypes and cTn-modification products also may eventually fulfill this need to define the specific mechanism of myocardial injury (26, 27).

**PROGNOSTIC NEEDS**
The clinical objective that novel biomarkers have most clearly addressed is that of improving risk assessment among the broadly heterogeneous population of patients who present with suspected ACS. Specifically, multimarker approaches to risk profiling that integrate multiple pathobiologically distinct biomarkers, such as CRP, BNP, and cTn, enhance the differentiation of risk among patients presenting with suspected ACS and complement the use of cTn alone (28, 29). A central tenet of current guidelines for ACS management is that knowledge of a patient’s absolute risk for death and major complications due to ACS should guide triage decisions and determine the aggressiveness of care (7). Therefore, improved risk stratification holds some clinical value by itself and has led to support for the selective clinical use of some novel biomarkers, such as the natriuretic peptides and CRP (1); however, this clinical application has been constrained by the absence of clear therapeutic guidelines based on results of such biomarker testing.

CRP perhaps best exemplifies the challenges involved in the development of novel biomarkers. CRP is widely available for testing via convenient and analytically well-validated commercial assays that can be performed at a reasonable cost. CRP has been shown to be associated with short- and long-term morality risk in no less than 15 prospectively conducted clinical studies, not only for patients with acute and chronic ischemic heart disease but also for those at risk for atherosclerosis (30). Although estimates of the magnitude of the risk relationship have been reduced somewhat over time (31), the observation of an independent relationship between CRP and cardiovascular risk has remained remarkably consistent across multiple study populations. Lastly, decision limits have been relatively well defined and validated for acute and chronic disease (30). Despite the depth of this epidemiologic evidence, recommendations for the routine use of CRP in the assessment of patients with suspected acute or chronic ischemic heart disease have not emerged. This is because firm guidelines regarding the therapeutic response to an increased CRP concentration cannot yet be made (1), a constraint that has been mirrored in the clinical setting. Simply put, clinicians are not likely to use a biomarker unless they know exactly what to do with the result with respect to patient care. Information regarding patient risk, albeit meaningful, is generally viewed by clinicians as limited in its practical clinical application.

**THERAPEUTIC NEEDS**
The preceding discussion arrives at the conclusion that the primary action that drives the potential clinical use of a novel biomarker is that it substantially alter the manner in which the patient should be treated. This need for therapeutic guidance can be met either by substantially improving diagnostic performance, such as has been achieved with natriuretic peptides for heart failure, or by identifying candidates for specific, often more aggressive therapies among patients with an established diagnosis. cTn is the paradigm for such use of a biomarker for therapeutic decision making. Among patients with a clinical syndrome consistent with ACS, those with increased cTn are at higher risk for both early and late adverse events than patients without increased cTn values.

More aggressive antithrombotic and antiplatelet therapies including low molecular weight heparins and glycoprotein Ib/IIa antagonists have been shown to have increased benefit in this higher-risk subgroup of ACS patients. Among patients presenting with non–ST segment MI, those who had increased cTn concentrations showed an increased benefit of enoxaparin use compared with similar patients without increased cTn values (4). Similarly, the use of glycoprotein Ib/IIa antagonists has been shown to produce approximately 50%–75% relative reductions in the risk of death and ischemic events in ACS patients who have increased cTn concentrations (32, 33). Troponin results are also important for predicting which ACS patients will derive the most benefit from an early invasive strategy. Even minor cTn increases are associated with an appreciable clinical benefit in high-risk patients presenting with ACS and thus can help clinicians in early therapeutic decision making (8).

Because the discovery of novel biomarkers has largely been based on the detection of pathobiological processes distinct from myocardial necrosis, such markers have the potential to direct treatment aimed at newer therapeutic targets, such as underlying inflammation (18). Although such novel applications have an exciting potential to add to current management algorithms in ways that complement rather than duplicate available treatment options, they are also the farthest from clinical application, because most antiinflammatory pharmacotherapeutics are only in the early stages of development. Nevertheless, the documented interaction between CRP and the antiinflammatory actions of statins supports the hope that this approach may eventually be integrated into clinical practice. Statins lower CRP concentrations by 13%–50% compared with placebo, depending on the dose (34–38). Moreover, intensive statin therapy has been shown to produce even greater decreases than moderate statin therapy. Three nested prospective analyses from clinical
trials of statins suggest that these changes in CRP are associated with improved outcomes. In a randomized trial of lovastatin in candidates for primary prevention, patients who had an LDL concentration below the median but an increased CRP concentration derived a benefit from statin therapy similar to that of patients with a high LDL concentration (38). We subsequently found in the PROVE-IT (Pravastatin or AtorvastatinEvaluation and Infection Therapy) trial that the CRP concentration achieved with statin therapy was a strong indicator of subsequent outcome; that is, patients who achieved lower CRP concentrations had outcomes superior to those with CRP concentrations >2 mg/L, regardless of the LDL concentration achieved (37). A highly consistent finding was also observed with another statin (Fig. 2) (39). Although the full results are forthcoming, the recent announcement that the first prospective randomized trial of statin therapy in patients with increased CRP and below-average LDL concentrations had to be stopped prematurely because of the overwhelming efficacy of the therapy indicates that definitive evidence establishing the usefulness of CRP for directing statin therapy may soon become available. These data may mark an important transition of CRP from a prognostic marker only to one with direct therapeutic implications. This type of transition appears to be necessary for novel biomarkers in development to achieve an integrated role in clinical care.

Conclusions

To be clinically useful, a biomarker must provide incremental information that both adds to existing clinical findings and is useful in the clinical care of the patient. The guidelines-based application of cTn for therapeutic decision making serves as a standard against which newer biomarkers have informally and formally been assessed. New methodologies that include genetic studies, transcriptional profiling, metabolomics, and proteomics are likely to lead to more potential novel biomarkers (40). As illustrated in the experience with CRP, this pathway of biomarker development toward its integration into routine practice is a long one and requires an accumulation of convincing epidemiologic and interventional data. To date, however, most proposed novel markers have only a moderate incremental benefit when used with existing markers. Even the most promising biomarkers will need assessment and validation similar to those for cTns and natriuretic peptides. In addition, the evolution of cTn assays has narrowed the need for newer biomarkers in some areas, such as the early detection and diagnosis of unstable angina. Finally, the major challenge for researchers and clinicians is to demonstrate whether newer and future biomarkers are useful for guiding specific treatment algorithms.

Grant/Funding Support: The TIMI Study Group has received appreciable research grant support from Accumetrics, Amgen, AstraZeneca, Bayer HealthCare, Beckman Coulter, Biosite, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapeutics, Merck, Merck/Schering-Plough Joint Venture, Millennium Pharmaceuticals, Novartis Pharmaceuticals, Nuvelo, Ortho Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, Sanofi-Synthelabo, and Schering-Plough.
Financial Disclosures: D. A. Morrow has received honoraria for educational presentations from Bayer Diagnostics, Beckman Coulter, Dade Behring, Sanofi-Aventis, and Roche Diagnostics. He has received fees as a consultant for GlaxoSmithKline and Sanofi-Aventis and is on advisory boards for Critical Diagnostics, Beckman Coulter, and Siemens Medical Solutions.

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