STATE-OF-THE-ART PAPER

Biomarkers in Acute Cardiac Disease
The Present and the Future
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The use of biomarkers to aid diagnosis and treatment is increasing rapidly as genomics and proteomics help us expand the number of markers we can use and as an improved understanding of the pathophysiology of cardiac disease guides their use. However, as with all rapidly expanding fields, there is the risk of excessive enthusiasm unless we are circumspect about the data that guide the clinical use of these new tools. This review focuses first on how to use troponin, which at present is the best validated of the new markers, and will hopefully provide insight into how to use this biomarker more productively by distinguishing subsets of patients and by providing an understanding of the meaning of elevations in various clinical situations. The review then discusses the use as well as the knowledge gaps associated with emerging biomarkers such as B-type natriuretic peptide and C-reactive protein, which are increasingly moving toward more productive clinical use. Finally, it reflects on some of the large number of markers that are still in development. (J Am Coll Cardiol 2006;48:1–11)

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An improved understanding of pathophysiology and improvements in the ability to identify potentially important biomarkers via genomics and proteomics (1,2) has led to a proliferation in the number of biomarkers available to clinicians. Many of these improve our understanding of pathophysiology (3,4). However, the bias in favor of positive reports combined with the fact that analyses often focus on prognostic value allows for the possibility of not capturing the entire picture when evaluating a new analyte. In addition, there are concerns regarding the analysis of data published about these markers, including the use of inappropriately low cutoff concentrations for standard biomarkers such as cardiac troponin (cTn) and C-reactive protein (CRP), the use of insensitive analytical methods for analytes used for comparison or as covariates, the use of single samples when serial samples would be most useful, the lack of information relating the timing of patient presentation and sampling, the use of specimens without data showing that they have been appropriately preserved, and the technique of using one biomarker at a predetermined concentration and then performing receiver-operating curve analysis to determine the optimal level for the new biomarker being studied (5). At times, populations of patients are admixed to show that a given biomarker does well when compared with another when the marker used as a comparator would never be abnormal in some of the populations included. An example of how much difference these issues can induce is shown in Figure 1 from the FRISC (FRagmin and Fast Revascularization during InStability in coronary artery disease) database (6). Note that even at a value 20 times the upper limit of normal (0.2 ng/ml) for cTnT, only 60% of the values with the less sensitive assay were detected. Rather than troponin identifying 139 of the 154 patients who eventually died, the point of care troponin I assay identified only 98. Thus, a new marker might look very different depending on which troponin assay was used as a comparator. These issues, if not handled carefully, can exaggerate the importance of new markers. Many of the new biomarkers will overlap substantially, and their use likely will not be synergistic but duplicative. It will take some time to sort out which biomarkers are of clinical diagnostic and/or prognostic value. Accordingly, this review will: 1) define the use of the present state-of-the-art biomarkers for the diagnosis of patients with acute cardiovascular disease; 2) touch on markers of historical interest whose use should be diminished or eliminated; and 3) identify emerging markers, and 4) identify biomarkers in the developmental stage.

ESTABLISHED BIOMARKERS
cTn. There is one biomarker that has been established for diagnosis (7,8) and that also provides robust prognostic information (9–11) and that is cTn. The cTn biomarkers, assuming high-quality analytic methods, whether for cTnI or cTnT, are highly specific and sensitive for cardiac injury (12). With the exception of renal dysfunction (see later text), cTnI and cTnT provide equivalent clinical information.
ASSAY-RELATED ISSUES. The cTn are regulatory proteins with both cytosolic and structural pools. Best data suggest that they are released because of necrosis (7,8). Early release is thought to be attributable to the cytosolic pool, and later release to the structural pool (7,8). There are now a multiplicity of assays for cTnI (13), which makes standardization problematic (14). All have different analytical sensitivities. It is essential for clinicians to understand whether they use a highly sensitive assay or one that lacks sensitivity at the cutoff concentrations used for clinical decisions. The International Federation for Clinical Chemistry has provided a comparison of analytical imprecision (sensitivity) for cTnI assays (13). There is substantial heterogeneity of assay sensitivities (Fig. 2). Different assays measure different epitopes and different fragments of cTnI. Thus, there are differences in the responses of specific assays to the various troponin forms (15), and assays probably detect slightly different groups of patients, depending on the nature and timing of cTn release. A list of assays and their cut off values is included in Table 1. Recent data suggest that a subset of patients may have antibodies to parts of cTnI that can result in occasional false-negative results (16). The heterogeneity of assays is not a problem for cTnT because there is only one assay. There is a need to improve the rapidity with which assay results are available. Clinicians expect values in 30 to 40 min, laboratorians in 60 min, whereas in reality results are often available only after 100 min or more (17).

USE OF THE MARKER. The basic science substrate for use of cTn has been elucidated elsewhere (12,18). For clinical use, several principles are important.

The cTn elevations begin 2 to 4 h after onset of symptoms (Fig. 3). With the use of precise highly sensitive assays and the use of the 99th percentile reference cutoff recommended, cTn provides all the information needed for the evaluation of patients who present with possible acute ischemic heart disease. Other “rapidly increasing biomarkers” have little or no utility if this approach is used (Fig. 4) (19).

Elevations of cTn persist for days (cTn 5 to 10, cTnT 5 to 14). There are emerging data suggesting that re-elevations and an increasing pattern are the best way to determine whether a given event is acute or whether the elevation is one from a previous event or is chronic. This concept is important when there is an elevation in the initial sample, when reinfarction is suspected (20), and in patients with end-stage renal disease (ESRD), who can have chronic elevations.

The number of patients identified with cTn in patients with possible acute ischemic heart disease depends on the subset of patients being evaluated. Patients with ST-segment elevation infarction are different from those with high-risk acute coronary syndrome (ACS) presentations and from those who manifest moderate-risk and/or low-risk presentations (21).

Because of the sensitivity of cTn, 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. If so, elevations can make the diagnosis of acute myocardial infarction, as defined by the European Society of Cardiology/
If acute ischemia is not present, alternative etiologies should be sought and different diagnoses made. A partial listing of situations in which cTn can be elevated in the absence of acute ischemic heart disease is included in Table 2.

Patients with acute ST-segment elevation myocardial infarction do not need biomarker measurements before therapy. Patients with elevated cTn on presentation have a lower rate of coronary recanalization, whether with thrombolysis (10) or direct percutaneous coronary intervention (PCI) (22) and an adverse short-term and long-term prognosis (23,24). Part of this effect is related to the fact that it takes time for cTn to become elevated in the blood, and patients who come in late do less well than patients who come in early. However, even when one corrects for time of onset, the same prognostic effect is found (25). In one study of patients with inferior infarctions, stenting seemed to improve the prognosis of this group (26).

Infarct size can be estimated from the 72-h troponin value. The data are stronger for this approach with cTnT than with cTnI (27,28). For cTnI, peak levels work better (29,30), but the data vary depending on whether or not there has been acute reperfusion (29).

High-risk patients with ACS. This group has been extensively studied. Patients often are elderly, and have chest pain at rest, transient electrocardiogram (ECG) changes, increasing symptoms or signs of ischemia, evidence of hemodynamic instability, and/or arrhythmias. They have a high incidence of elevated cTn when one uses the 99th percentile reference range (31,32). They meet criteria for non–ST-segment elevation myocardial infarction (7,8,12). The elevated cTn defines a high-risk subset and provides guidance in regard to therapy. Patients with elevated cTn have more procoagulant activity and an adverse coronary anatomy as judged by the degree and extent of angiographic stenosis, the Thrombolysis In Myocardial Infarction (TIMI) grade of perfusion, and the complexity of the coronary lesions (33). As such, these patients do better with the use of low-molecular-weight heparin (34), IIb/IIIa anti-platelet agents (35), and an early invasive interventional strategy (36). Most of the trials of IIb/IIIa agents were done before the routine use of clopidogrel. Recent data suggest that these agents may be synergistic (37). Clopidogrel is the one agent that accures benefit to patients whether or not cTn values are elevated (38). These more aggressive therapies not only are not beneficial but in some studies seem to even be detri-

Table 1. Presently Available Assays for Cardiac Troponin and Key Values

<table>
<thead>
<tr>
<th>Assay</th>
<th>LLD</th>
<th>99th Percentile</th>
<th>ROC Cutoff</th>
</tr>
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<tbody>
<tr>
<td>Abbott ARCH</td>
<td>0.009</td>
<td>0.012</td>
<td>0.3</td>
</tr>
<tr>
<td>Abbott i-STAT*</td>
<td>0.02</td>
<td>0.08 (WB)</td>
<td>ND</td>
</tr>
<tr>
<td>Bayer Centaur</td>
<td>0.02</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Beckman Accu</td>
<td>0.01</td>
<td>0.04</td>
<td>0.5</td>
</tr>
<tr>
<td>Biosite Triage*</td>
<td>0.19</td>
<td>&lt;0.19</td>
<td>0.4</td>
</tr>
<tr>
<td>Dade RxL</td>
<td>0.04</td>
<td>0.07</td>
<td>0.6–1.5</td>
</tr>
<tr>
<td>Dade CS*I</td>
<td>0.03</td>
<td>0.07</td>
<td>0.6–1.5</td>
</tr>
<tr>
<td>DPC Immulite</td>
<td>0.1</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Orthos Vitros</td>
<td>0.02</td>
<td>0.08</td>
<td>0.4</td>
</tr>
<tr>
<td>Response*</td>
<td>0.03</td>
<td>&lt;0.03</td>
<td>ND</td>
</tr>
<tr>
<td>Roche Elecsys (cTnT)</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Roche Reader*</td>
<td>0.05</td>
<td>&lt;0.05</td>
<td>0.1</td>
</tr>
<tr>
<td>Tosoh AIA</td>
<td>0.06</td>
<td>&lt;0.06</td>
<td>0.31–0.64</td>
</tr>
</tbody>
</table>

*Point-of-care assay. †Cleared by the U.S. Food and Drug Administration as high-sensitivity assay, 2004.

99th = upper limit of normal and the ROC value equates cardiac troponin values in general with creatine kinase-MB elevations; cTnT = cardiac troponin T; LLD = lower limit of detection; ND = not done; ROC = receiver-operating curve; WB = whole blood.
mental if applied to patients without cTn elevations. The one area where there is some question comes from the TACTICS–TIMI-18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conserva-
tive Strategy–Thrombolysis in Myocardial Infarction-18) study, in which based on one admission sample for cTn, it was claimed that female patients with elevations in B-type natriuretic peptide (BNP) and/or CRP benefited from an early invasive strategy even if cTn were normal (39).

Indeterminate- and low-risk patients. This patient group is hard to triage clinically. They may not have rest pain or ongoing pain, may have normal ECGs, and depending on the specifics, may be at intermediate or low risk. The frequency of elevated cTn is lower, nonetheless, these patients benefit optimally from triage with cTn. The most robust trial was one by Hamm et al. (40) in 733 patients. Almost every patient at short-term risk (30 days) was identified by elevations in cTn. Two caveats are important. First, cTn value had to have been obtained at least 6 h after the onset of symptoms. This may be less necessary now with more sensitive assays. The second caveat is related to sensitivity. Detectability was considered abnormal. We now have more sensitive assays, which should make for even greater predictive accuracy. Even for patients at low risk, the finding of an elevated cTn is prognostic. Some studies showing this prognostic effect were not done with contemporary assays, which now allow for lower clinical cutoffs. One would suspect that the data would be even more

Figure 3. Time course of the appearance of various markers in the blood after acute myocardial infarction (AMI). Shown are the time concentrations/activity curves for myoglobin and creatine kinase (CK) isoforms, troponin after large and small infarctions, and CK-MB. Note that with cardiac troponin some patients have a second peak in addition. CV = coefficient of variation.

Figure 4. Sensitivity of cardiac troponin (cTnI) compared with myoglobin and creatine kinase (CK)-MB for the detection of myocardial injury. Note the use of the 10% coefficient of variation (0.1 ng/ml) were superior to the use of myoglobin. Reprinted, with permission, from Eggers et al. (19).
impressive with this approach. Nonetheless, in a cohort at low risk (a 5% to 7% incidence of acute myocardial infarction) whose ECGs are mostly normal, an elevated cTn is associated with nearly a 90% frequency of coronary artery disease by angiography (41). This was compared with a frequency of 23% in the group without elevations. It is likely that the additional patients who had angiographic disease may have been detected had the more sensitive cTn assays and low cutoffs been used. During 1-year follow-up, patients with elevated cTn values, two-thirds of whom had two- or three-vessel disease, had an increased frequency of events. These data are similar to those from emergency room studies of patients who had “minor elevations” of cTn (Fig. 5) (42). Some degree of caution is necessary in all of these situations. A normal troponin value is not an imprimatur against disease, especially if the assay in use is either insensitive or is used at a high cutoff value.

**Patients with chronic renal disease.** The most common cause of death in chronic renal failure is cardiovascular, and coronary artery disease is common. The cTn values, especially with cTnT, are often abnormal (43,44). Initially, this was presumed to be because cTnT was less tissue specific. However, extensive studies have now been done to show that this is not the case (45). Nonetheless, the frequent cTnT elevations (30% to 70% of ESRD patients compared with <5% in similar patients for cTnI) are problematic to clinicians (43,44). Several suggestions may be helpful.

In patients with an ACS, an elevated cTn, whether cTnI or cTnT, should be treated as if renal failure (chronic or acute) were not present (46). These patients are at increased risk. Although all of the therapeutic caveats cannot be applied from all of the studies, many of which had only limited numbers of patients with ESRD, it seems likely that these individuals also would benefit from an aggressive antithrombotic (47) and interventional approach (48).

For patients with ESRD who do not have ACS but have elevated cTn, several approaches are helpful; cTnI is now approved for prognostication in patients with ESRD. Thus, baseline values can and should be obtained. The prognosis (all-cause death) of patients with ESRD and even minor elevations of cTnT is two to five times higher than those with undetectable values (49,50). C-reactive protein may further improve prognostication (50,51). Having a baseline value allows not only for prognostication but also for an evaluation of whether or not values are changing over time. Increasing values suggest an acute problem. In the absence of increasing values, when a clinician does not find evidence of an acute process known to cause elevations of cTn, one is probably safe to consider these more chronic elevations.

**Table 2. Elevations of Troponin in the Absence of Overt Ischemic Heart Disease**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Trauma (including contusion, ablation, pacing, implantable cardioverter-defibrillator firings including atrial defibrillators, cardioversion, endomyocardial biopsy, cardiac surgery, after interventional closure of atrial septal defects)</td>
</tr>
<tr>
<td>Congestive heart failure—acute and chronic</td>
</tr>
<tr>
<td>Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypotension, often with arrhythmias</td>
</tr>
<tr>
<td>Postoperative noncardiac surgery patients who seem to do well</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Critically ill patients, especially with diabetes, respiratory failure</td>
</tr>
<tr>
<td>Drug toxicity, e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Apical ballooning syndrome</td>
</tr>
<tr>
<td>Coronary vasospasm</td>
</tr>
<tr>
<td>Inflammatory diseases, e.g., myocarditis, e.g., Parvovirus B19, Kawasaki disease, sarcoid, smallpox vaccination, or myocardial extension of bacterial endocarditis</td>
</tr>
<tr>
<td>Post-percutaneous coronary intervention patients who seem to have no complications</td>
</tr>
<tr>
<td>Pulmonary embolism, severe pulmonary hypertension</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Burns, especially if total body surface area is &gt;30%</td>
</tr>
<tr>
<td>Infiltrative diseases including amyloidosis, hemachromatosis, sarcoidosis, and scleroderma</td>
</tr>
<tr>
<td>Acute neurological disease, including cerebrovascular accident, subarachnoid bleeds</td>
</tr>
<tr>
<td>Rhabdomyolysis with cardiac injury</td>
</tr>
<tr>
<td>Transplant vasculopathy</td>
</tr>
<tr>
<td>Vital exhaustion</td>
</tr>
</tbody>
</table>

**Figure 5.** Cardiac events after emergency department discharge based on levels of cardiac troponin T. Reprinted, with permission, from Henrikson et al. (42).
These patients may require alteration in a variety of therapies to improve their prognosis, but may not require acute treatment. The putative mechanisms for these chronic elevations, which are invariably associated with pathologic abnormalities at autopsy (52), include endothelial dysfunction, acute cardiac stretch, intradialysis hypotension and hypertension, the use of iron sucrose, and left ventricular hypertrophy. All are potentially benefited by altering the frequency of dialysis, the weight gain (fluid control), and the blood pressure control. Given the high incidence of coronary disease, some of these patients may have occult underlying coronary artery disease. Elevations of cTn in patients with renal dysfunction but without ESRD are common but likely attributable to the association of other comorbidities and probably cannot be considered the same as those seen in ESRD patients.

Patients after PCI. Elevations of creatine kinase (CK)-MB after PCI presage adverse outcomes (53). The greater the elevation, the more adverse the prognosis. This has not consistently been the case with cTn. However, one would suspect that it should be. There should, for each cTn assay, be values that correlate with the CK-MB values. However, this relationship may need to be confirmed with each assay for each biomarker (CK-MB and troponin) in use locally. Recent data suggest that many of the elevations observed after PCI both for cTn and CK-MB are presaged by elevations in cTn when sensitive assays and lower cutoff values are used (54). Thus, they could reflect ongoing myocardial damage that has little to do with the procedure itself or identify patients with a high likelihood or post-PCI marker elevation. Patients who present with ACS who have cTn elevations manifest worse angiographic disease and an adverse prognosis. It may be that CK-MB not being elevated, because it is less sensitive compared with cTn, is seductive to clinicians who believe it can be used as a baseline; however, the effect may be the same. Thus, it is unclear how to use either biomarker in patients who present acutely or have an elevated cTn pre-procedure. If the baseline cTn is normal pre-PCI and the patient has not presented acutely, cTn and CK-MB values after PCI will likely be informative about the procedure itself and elevations are associated with early major adverse cardiac events (54).

Patients after coronary artery bypass grafting. Patients who undergo cardiac surgery have some amount of cTn and CK-MB release (55). The higher the value, the worse the associated injury, and high values presage subsequent events, including death. Elevations have been related to the surgical approach, the extent of cross-clamp and bypass time, the nature of cardioplegia, and the nature of the procedure (valves and coronaries vs. coronary artery bypass grafting alone). Magnetic resonance imaging studies suggest that most of the injury is subendocardial and apical (56). Graft occlusion (57) as a cause of the injury does not seem to be common.

Patients who present with chest pain who have normal angiograms. One needs to be cautious in evaluating patients with elevated cTn even if an angiogram does not show significant coronary disease. The coronary angiogram is not perfect (58). In the TACTICS–TIMI-18 trial, individuals with an elevated cTn despite angiographically normal coronary arteries had an adverse prognosis (59). This may reflect the inadequacies of the angiogram or may be related to the late angiography in some patients (60). In some data sets, elevated cTn has been associated with asymmetric lesions that tend to be vasoactive (61). Thus, the finding of angiographically “normal” coronary arteries needs to be interpreted within the context of patient care. If the patient does not have an ACS but appears acutely ill, there are a variety of other etiologies, such as pulmonary embolism and congestive heart failure, in which even in the absence of coronary artery disease elevated cTn can be observed (these elevations may be related to wall stress); patients who may have subendocardial ischemia/injury related to left ventricular hypertrophy with diseases such as aortic stenosis or hypertrophic cardiomyopathy or perhaps even severe hypertension; myocarditis; and/or toxic insults such as seen with sepsis, in which tumor necrosis factor alpha and heat shock protein have been impugned as potential cardiac toxins.

Potentially Outdated Markers

CK-MB. Creatine kinase-MB (18) is a cytosolic carrier protein for high-energy phosphates. As clinicians become more comfortable with cTn, it will have a diminishing role. Some would argue that it still could be used to define infarct timing or after PCI.

Myoglobin and CK isoforms. Myoglobin, a ubiquitous heme-related protein, and CK isoforms (18) have been used with the hope of shortening the time to a more definitive diagnosis in patients with chest pain. They have been relied on particularly for their negative predictive value. Recent data suggest that with modern contemporary sensitive assays and sensitive cutoffs for cTn, cTn can assume this role (19).

In the emergency room, where patients at low risk for cardiovascular disease are still screened with cardiac biomarkers, it has been suggested that myoglobin may identify additional patients at risk. This is likely because of detection of serious noncardiovascular disease (62).

Emerging Markers

For a marker to be useful, it needs to make a diagnosis or to define prognosis in such a way that it guides therapy. In this regard, there are two emerging markers, CRP and the natriuretic peptides BNP and NT-proBNP.

CRP. Assay-related issues. C-reactive protein is an acute-phase reactant protein made in the liver. Its most proximate stimulator is interleukin 6. A specific receptor for CRP has recently been reported (63). There is controversy regarding the variability of CRP levels (64,65). Some argue that in the absence of acute illness, including myocardial
injury, levels of CRP are stable. Others argue that levels fluctuate and vary by gender and ethnicity (66). If one has an elevation and is acutely ill or has evolving infarction, the test should be repeated at least 2 weeks later (64). Values above 10 mg/l are likely caused by acute disease (67). Values >3 mg/l are associated with higher risk, and values <1 mg/l are associated with low risk (64). Those between 1 and 3 mg/l are considered intermediate (64). Multiple assays exist for CRP (designated high-sensitive CRP or hsCRP), and most give comparable results.

USE OF THE MARKER. Recent data from the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial (68), which are consistent with those from the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid-lowering Therapy) trial (69,70), suggest that the titration of statin therapy predicated on CRP values would result in fewer events and regression of atherosclerosis. They probably explain why in prior studies an elevated CRP level was found to be prognostic for late events after presentation with ACS (71). In those studies, the changes in prognosis and extent of disease associated with differences in CRP were not associated with the effects observed with low-density lipoprotein lowering (Fig. 6) (68). Differences in events started early after presentation. It seems that using CRP values as early as 30 days after infarction to avoid the effects of myonecrosis on CRP may be a reasonable approach. These trials did not titrate therapy based on CRP, which make the data provocative and suggestive but not definitive. Elevations of CRP often are related to numerous other clinical issues, such as obesity, diabetes, estrogen therapy, hypertension, smoking, etc. Thus, an argument could be made that one should attempt to control these risk factors before resorting to pharmacology.

The use of CRP for primary prevention is more controversial. There are abundant data concerning its prognostic efficacy, but limited data showing that interventions are of benefit save a suggestion in regard to aspirin (72) and statins (73). Given the large numbers of patients at risk, it is difficult to show the cost effectiveness of this approach. Recent guidelines have suggested the use of CRP in patients who are at intermediate risk for coronary artery disease to assist in defining the level of aggression of risk factor intervention (74).

BNP. Assay-related issues. B-type natriuretic peptide is a 32-amino-acid counterregulatory peptide released in response to cardiac stretch. It is synthesized as a propeptide and then cleaved to the active moiety by a protease called corin (75,76). There are multiple immunoassays (75,76). In general, they have similar diagnostic cutoff values of 100 ng/ml for congestive heart failure, because this has been the value developed in early diagnostic studies. Above and below that value, they correlate less well (76). In addition, there is an immunoassay for NT-proBNP (75,76), which detects the 76 amino acid carrier protein, which with the active 32 amino acid compound is called proBNP. This protein is thought to be cleaved when BNP is secreted. However, it seems that some proBNP circulates, and it is likely that many assays detect it. In addition, for both of these analytes, women and older individuals have higher values (69) and obese individuals have lower values (77) (Fig. 7). Patients with renal failure often have substantially higher values (78). This increase is more accentuated for NT-proBNP. Both BNP and NT-proBNP manifest substantial biological variability (79). If formal values are relied on, values have to either double or half to be sure that a “real” change has occurred.

USE OF THE MARKER. The BNP and/or NT-proBNP values are helpful for the detection of congestive heart failure in patients in whom one is unsure of the cause of dyspnea (80). This is not the same as advocating its routine use (81). For BNP, values <100 ng/l make heart failure unlikely with a negative predictive value of 90%. If the value is >500, heart failure is highly likely with a positive predictive value of 90% (82). For NT-proBNP, levels >450 ng/l for patients <50 years of age and >900 ng/l for patients ≥50 years of age are sensitive and specific for heart failure (83). If the value is

Figure 6. Synergistic prognostic value of C-reactive protein (CRP) and low-density lipoprotein (LDL) in PROVE-IT study. Reprinted, with permission, from Ridker et al. (68). MI = myocardial infarction.
<300 ng/l, heart failure is highly unlikely with a negative predictive value of 99% (83). However, in the middle ranges, the predictive accuracy is less and that is likely where many of the less typical patients’ values will reside. Patients with right-sided heart failure, sepsis, volume overload, stroke, and left ventricular hypertrophy also have higher values. In patients with acute pulmonary edema and acute mitral regurgitation, values may not be elevated initially (82).

There is prognostic value of BNP and NT-proBNP as well in patients with heart failure (84,85). Patients with higher values on admission and/or discharge to hospital generally do worse. Those with marked reductions during treatment do better. However, the percentage changes with therapy are less than anticipated and often less than biological variability, suggesting that the natriuretic peptide system may require some time to upregulate and downregulate (86). In addition, in critically ill heart failure patients, low values are predictive of an adverse survival (87). The BNP and NT-proBNP do not go down nearly as rapidly in response to therapy as one would expect from the short (20 min for BNP and 2 h for NT-proBNP) half-lives (86). This may relate to the time needed for the system itself to autoregulate.

In ACS patients, BNP and NT-proBNP elevations are prognostic for death in all studies, but the data are not consistent for recurrent myocardial infarction. When one has a conjoint end point such as death, one can be confounded in evaluating myocardial infarction, however. Because so many studies have used optimized cutoff values for their own data sets, there is no consensus on the proper cutoff values. In addition, what actions should be predicated on elevated values are unclear (88,89). The only trial in which it seemed that there was therapeutic guidance associated with elevated values was the TACTICS-TIMI-18 study, in which women with elevated BNP or CRP values seemed to benefit from early PCI even if they had normal cTn values (39). If a strategy to treat such cTn-negative patients could be developed, this could prove to be an important adjunct to the evaluation of patients who present with ACS.

Higher BNP values identify patients with ACS who are at higher risk, but what to do in response is unclear. Elevated values also predict an adverse outcome in stroke, obstructive sleep apnea, diabetes, left ventricular hypertrophy, and stable coronary artery disease.

Thus, the questions regarding what are the appropriate cutoffs in the varied situations in which BNP and NT-proBNP might be used and what one does when one exceeds those cutoffs is unclear. Until these issues are better defined, enthusiasm for the routine use of BNP or NT-proBNP will be blunted.

DEVELOPING MARKERS

sCD40 ligand. sCD40 (90) is a signaling protein that reflects both inflammatory and platelet interactions with the plaque. Increased sCD40 ligand has been shown in patients with ACS. Moreover, articles have suggested that is has prognostic significance in these patients. Several of the studies have used high cutoff values for cTn or insensitive assays. A multiplicity of analytic issues remain.

Myeloperoxidase. Myeloperoxidase (90), a degranulation product, comes from white cells. Elevations occur even when values are obtained from the coronary effluent draining a nonculprit coronary vessel. Systemic levels have been said to aid in prognostication in patients presenting to the emergency department with chest pain, but comparisons have often used high cTn cutoff values or only the admission troponin level. Recently, a commercial assay has been made available.

Ischemia-modified albumin. Ischemia-modified albumin (90) has been touted as a way to detect ischemia even if necrosis is not present. The theory is that the metal
binding site on the amino terminus of albumin is damaged by ischemia. It is marketed for its “negative predictive value.” It has been difficult to validate ischemia-modified albumin because of the lack of a gold standard for ischemia. In addition, the assay is cumbersome to use.

**Pregnancy-associated plasma protein-A.** A member of the insulin–like growth factor family of proteins, pregnancy-associated plasma protein-A (90) is thought to be released when neovascularization occurs and thus may be a marker of incipient plaque rupture. It does not correlate with any of the presently available markers of cardiac injury. It has in some studies seemed to identify patients at risk for subsequent events. There is no available standardized assay.

**Choline.** Choline (90) is a biomarker that is released when phospholipids are cleaved, which suggests that perhaps it could be a marker of ischemia and/or necrosis. Several studies suggest that the marker might improve prognostication in patients with ACS, but high cutoff values for cTn have generally been used.

**Placental growth factor.** Placental growth factor (90) is a member of the vascular endothelial growth factor family that has been touted by some but not others to be prognostic in patients with ACS. Some of the positive studies have not used appropriate cTn cutoff values. There is no standard assay for placental growth factor.

**Cystatin C.** This biomarker is a low-molecular-weight basic protein (13 kDa) that is freely filtered and metabolized after tubular reabsorption. It seems that it is less influenced by age, gender, and muscle mass than serum creatinine. There is a U.S. Food and Drug Administration-cleared assay that is analytically robust. Some studies suggest that the marker might improve prognostication in patients with ACS, but high cutoff values for cTn could be a marker of ischemia and/or necrosis. Several studies suggest that the marker might improve prognostication in patients with ACS, but high cutoff values for cTn have generally been used.

**Fatty acid binding protein.** Fatty acid binding protein is an alternative to myoglobin. It has been reported to perform better (94), but it still lacks cardiac specificity. There are no U.S. Food and Drug Administration-approved assays.

**Conclusions.** The present and future for cardiac biomarkers is exciting. In the near future, many of these biomarkers will provide important new insights into pathophysiology and aid in the diagnosis and management of cardiovascular patients. We are likely to be able to multiplex assays, personalizing biomarker strategies and providing large numbers of values quickly and cheaply. There is great enthusiasm for such a multimarker approach. However, before we implement such a strategy, we must overcome poorly done yet enthusiastic limited reports (5), so that what is eventually recommended will work optimally clinically. In the interim, to provide optimal clinical care, clinicians need to learn more about the biomarkers that they rely on in current clinical practice, i.e., cTn, natriuretic peptides, and CRP, both analytically and clinically.

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Because of limitations to the number of citations in this review, we apologize to those whose work could not be cited or could only be cited indirectly.

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