

Introduction

An important outcome of research in the field of biomarkers and clinical proteomics has been the realization that with organ damage or dysfunction, peptides may be released into the circulation that have diagnostic and prognostic significance.

This *Clinical Cornerstone* supplement contains 3 articles on the use of cardiac biomarkers in myocardial infarction (MI) and acute coronary ischemia and in the syndrome of congestive heart failure (CHF). These articles are founded on the basic concept that when the heart is injured, with an alteration in structure or function due to myocardial ischemia or other processes, it releases peptides into the circulation that provide specificity in diagnosis and prognosis and may also guide clinical management.

In the first article, Maisel and Mehra provide a comprehensive review of the role of B-type natriuretic peptide (BNP), which is activated during heart failure (HF), in the diagnosis and monitoring of CHF. These authors note the challenge of diagnosing acute CHF in the emergency care setting due to the nonspecific signs and symptoms of HF, the difficulty of obtaining a comprehensive history in the acutely ill patient, the nonspecificity of dyspnea, and the lack of accuracy of routine tests such as the chest radiograph and electrocardiogram (ECG).¹ The review describes the utility of BNP in diagnosing this acute syndrome of decompensated HF. The authors also discuss the prognostic significance of elevated BNP in patients with HF and provide a balanced view of how the BNP level can be used to guide therapy in both acutely ill patients and those in the ambulatory setting.

Since the discovery in 1981 by de Bold et al² that the heart synthesizes and releases natriuretic peptides that not only enhance renal function but also have autocrine and paracrine actions in the heart, the use of atrial natriuretic peptide and BNP as diagnostic markers in CHF has continued to grow.³ The US Food and Drug Administration has approved BNP for the treatment of acute decompensated HF, as well as to aid in the diagnosis of HF. It is well understood that as pro-BNP is synthesized and released into the circulation from the

heart, it is cleaved into the mature biologically active peptide, BNP, and the longer, linear, nonbiologically active form, *N*-terminal pro-BNP (NT-pro-BNP).⁴ The importance of screening for early HF is based on compelling data that those with this condition are at high risk for increased mortality.⁵ However, detecting these individuals is difficult in the absence of symptoms. Tang et al discuss the use of BNP and NT-pro-BNP in the detection of early, asymptomatic left ventricular dysfunction. They describe a comparison of 2 BNP methods between patients with New York Heart Association (NYHA) class I–IV HF and a control group with no signs or symptoms of HF. The authors tested a point-of-care (POC), single-use fluorescence immunoassay, as well as a laboratory-based, microparticle enzyme immunoassay (MEIA).

Although these authors found the overall between-assay concordance in diagnostic accuracy acceptable, their main finding was that the BNP cutoff values used for screening purposes must be assay specific for optimal test sensitivity. Despite the fact that all commercially available BNP assays use the same cutoff value for the detection of acute HF (100 pg/mL), there are considerable differences in assay sensitivity. Although the sensitivity of the 2 assays was similar in patients presenting with more symptoms and a higher NYHA classification, the MEIA had higher sensitivity compared with that of the POC assay in patients with minimally symptomatic HF (NYHA class I). These findings underscore the need for further studies, particularly trials that prospectively characterize the general population with and without ventricular dysfunction but lacking symptoms of HF.

This is most important as one goes beyond HF, as we now know that even in those without ventricular dysfunction but with cardiovascular risk factors, BNP and NT-pro-BNP (which may be modestly increased but still below the cutoff value for HF) are predictive of increased risk for HF and death.^{6,7}

Finally, Apple and Murakami present a comprehensive discussion of the use of cardiac biomarkers to aid in the accurate diagnosis of MI and provide infor-

mation on the prognosis. These authors give a detailed analysis of cardiac troponin (I or T) as the preferred biomarker for detection of MI. Their discussion is built on the rationale that the heart releases a protein from cardiac myocytes during myocardial injury, particularly in the setting of MI and acute coronary ischemia. Recent guidelines from cardiovascular societies are discussed,⁸ along with the need to improve the accuracy of new assay technology, particularly to reduce the coefficient of variation (CV) in troponin assays. This review indicates that troponin measurements aid in establishing the diagnosis in patients who present with nonspecific symptoms or who have nondiagnostic ECG findings but are undergoing active myocardial ischemia. Specifically, troponin measurements have prognostic value and are useful in risk stratification and therapeutic decisions.

The authors offer new data on a recently developed chemiluminescent microparticle immunoassay (CMIA) that is used in an automated immunoassay instrument system, which is analytically sensitive at low concentrations and approaches the recommended $\leq 10\%$ CV at the 99th percentile reference point, suggesting that it may be sensitive and accurate as a diagnostic and risk-stratification tool in patients presenting with symptoms of acute coronary syndrome (ACS).

The use of cardiac biomarkers shows great promise, both for the diagnosis of syndromes such as ACS and MI and in the diagnosis and management of CHF. These markers will undoubtedly be the focus of intense investigation in the coming years.

John C. Burnett, Jr, MD
Guest Editor

REFERENCES

1. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002; 347:161–167.
2. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci.* 1981;28:89–94.
3. Burnett JC, Jr, Kao PC, Hu DC, et al. Atrial natriuretic peptide elevation in congestive heart failure in the human. *Science.* 1986;231:1145–1147.
4. Luchner A, Stevens TL, Borgeson DD, et al. Differential atrial and ventricular expression of myocardial BNP during evolution of heart failure. *Am J Physiol.* 1998;274:H1684–H1689.
5. Wang TJ, Evans JC, Benjamin EJ, et al. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation.* 2003;108:977–982.
6. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* 2004;350:655–663.
7. Kragelund C, Gronning B, Kober L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med.* 2005; 352:666–675.
8. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol.* 2000;36:959–969.