

Point-of-care Testing for Cardiac Markers at the Bedside

a report by

Alan H B Wu, PhD, DABCC

Director, Clinical Chemistry and Toxicology, San Francisco General Hospital and Professor of Laboratory Medicine, University of California, San Francisco

Alan H B Wu, PhD, DABCC, is Director of Clinical Chemistry and Toxicology at San Francisco General Hospital, and Professor of Laboratory Medicine, University of California, San Francisco. He completed a clinical chemistry fellowship in at Hartford Hospital and is certified by the American Board of Clinical Chemistry. Dr Wu has been the co-editor-in-chief of *Clinica Chimica Acta* since 1999. He is the author of *Cardiac Markers*, Human Press, Totowa, NJ, which is in its second edition. Dr Wu has published over 250 articles, book chapters, and abstracts in the field of cardiac markers. He has traveled throughout the world lecturing on this topic. He received BS degrees in chemistry at Purdue University and a PhD degree in analytical chemistry at the University of Illinois.

Heart Disease in America

Acute cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in the US and throughout the Western world. According to the American Heart Association (AHA), 64 million Americans have CVD. Each year, roughly eight million Americans present to the emergency department (ED) with chest pain. The annual total of new and recurrent heart attacks (acute myocardial infarction (AMI)) is 1.2 million. Many of these patients die suddenly due to arrhythmias before they are able to seek help. In the majority of cases, an AMI is caused by the rupture of a coronary artery plaque. The exposure of the lipid-rich core of the plaque to circulating blood leads to a clot caused by the formation of a thrombus and the aggregation of platelets. These events lead to blockage of blood through coronary artery circulation.

The diagnosis of myocardial infarction (MI) is predicated on criteria established by the European Society of Cardiology (ESC) and American College of Cardiology (ACC). In the clinical context of myocardial ischemia, AMI occurs when there is a typical rise and fall in the concentration of serum biomarkers. Ischemia can be defined by a presentation of acute chest pain, and electrocardiographic, angiographic, and/or pathologic evidence indicative of ischemia. The most commonly used laboratory tests for the diagnosis of AMI are cardiac troponins T or I, the creatine kinase (CK)-MB isoenzyme, and myoglobin. These biomarkers are released into the blood from irreversibly damaged myocytes caused by plaque rupture and coronary artery occlusion.

In addition to AMI, there are approximately five million Americans who have heart failure. MI is the leading cause of heart failure because structural damage of the heart produces functional impairment. Other causes of heart failure include hypertension, valve and infectious diseases, and idiopathic etiologies. The incidence of heart failure is expected to increase in the next few years due to the aging of the 'baby boomer' generation. The diagnosis of heart failure is made on the basis of clinical presentation, electrocardiographic (ECG) and echocardiographic data, and serum biomarkers such as B-type natriuretic peptide

(BNP) and NT-proBNP. BNP is a neurohormone that regulates blood pressure, fluid volume and electrolyte concentrations. BNP and NT-proBNP, an inactive peptide, both originate from proBNP produced by the left ventricle of the heart. In heart failure, there is an overstimulation of the renin-angiotensin-aldosterone axis resulting in vasoconstriction, and water and sodium retention. This condition stimulates the production of proBNP, which causes the increased release of BNP and NT-proBNP into the general circulation. Increased concentrations of these markers are useful for diagnosis, staging, and prognosis of heart failure. Clinical trials are currently underway to determine whether BNP and NT-proBNP can be used for monitoring the success of drug therapy to heart failure as well.

Stroke is the third leading cause of death among Americans. There are roughly 700,000 new or recurrent cases of stroke, and 300,000 annual deaths. Stroke is caused by blockage of a cerebral artery or bleeding in the brain. Currently, there are no biomarkers routinely used in the ED. However, this is an area of active biomedical research.

The Need for Rapid Diagnosis of Cardiovascular Disease

Roughly 10% to 20% of patients who present to the ED with chest pain have MI. Patients who present with ST-segment elevations on the ECG have a heart attack and should be immediately treated, ideally with percutaneous coronary intervention and balloon angioplasty. Although routinely ordered and tested, serum biomarkers are unnecessary in ST-elevation MIs. Laboratory tests for cardiac biomarkers play a critical major role for non-ST-elevation MIs, and those who rule out for AMI. A disadvantage for laboratory tests such as cardiac troponin or CK-MB is that they are not abnormal during the initial three to six hours after the onset of chest pain. For patients with a high likelihood of disease, ED physicians must wait a sufficient amount of time before sending the patient home if negative for AMI, or treat and triage the patient to the appropriate level of care if positive for AMI. For patients with a low likelihood of disease, an ED physician may send the patient home without waiting for biomarkers to

increase in order to save hospital resources. In this case, there is a risk for medical malpractice should a diagnosis of AMI be missed. Obtaining rapid results for serum biomarkers is very helpful in maximizing the efficiency of decisions made on these cases. Numerous professional groups such as the ACC, ESC, AHA, Heart Attack Alert Program, and the National Academy of Clinical Biochemistry (NACB) have made recommendations as to the optimum turnaround time for reporting laboratory results. Defined as the time the blood is collected to the reporting of results to the attending physicians, the maximum turnaround time for troponin, CK-MB, and myoglobin if applicable, is 60 minutes, with an ideal time of 30 minutes.

A similar situation for laboratory testing exists for heart failure. Patients presenting to the ED with symptoms of shortness of breath should be quickly evaluated to determine the etiology of the symptoms so that the proper management decisions can be made. Patients with pulmonary diseases will be treated with a different care pathway to those with congestive heart failure. BNP and NT-proBNP can be used to determine which cause is most likely so that patients can be triaged to the appropriate level of care and therapy given as soon as possible. The NACB has recommended a turnaround time of 60 minutes for testing of heart failure biomarkers from the ED. Thus, either central laboratory or testing at the point of care can be used to meet these goals. There is an additional need for rapid turnaround times if BNP and NT-proBNP prove to be useful in adjusting therapy for heart failure patients. The ability of testing and reporting BNP results from a physician office laboratory will enable dosing adjustments to be made while the patient is still in the office. Sending specimens to an off-site reference laboratory will result in delays.

Clinical Laboratory Testing Models

There are several approaches that the clinical laboratory can take regarding cardiac biomarker testing. Most tests are conducted within the central laboratory using highly trained laboratory personnel on automated instruments. This testing requires time to delivery to the laboratory (one to 15 minutes) and centrifugation of the sample (five to 10 minutes) to obtain serum or plasma for testing. Some hospitals have a pneumatic tube that connects the ED to the laboratory thereby minimizing transportation time. Other hospitals have an ED laboratory and the availability of smaller laboratory instruments to perform testing. While this also reduces the time required to deliver the sample, this situation is less efficient from the personnel utilization standpoint, as technologists from the ED laboratory are not likely available when assistance is needed from the central laboratory. The actual on-instrument time for testing of a sample range is 15–20 minutes, while the reporting of results takes an additional

Table 1: Commercial Point-of-Care Testing for Cardiac Markers

Name	Platform	Type	Cardiovascular disease menu
Status (Spectral)	Strip test	Qualitative	cTnI, CK-MB
Triage (Biosite)	Reader	Quantitative	cTnI, CK-MB, myoglobin, BNP, d-dimer, stroke*
CardiacT (Roche)	Strip & reader	Qual/Quant	cTnT, myoglobin, d-dimer
iSTAT (Abbott)	Reader	Quantitative	cTnI, CK-MB*, BNP*
Ramp (Response)	Reader	Quantitative	cTnI, CK-MB, myoglobin
Stratus CS (Dade)	Small analyzer	Quantitative	cTnI, CK-MB, myoglobin, NT-proBNP, d-dimer
Inverness Medical	TBD	Quantitative	NT-proBNP*

*In development. TBD=to be determined.

one to five minutes. Given these steps, it is not likely that a central laboratory can meet the ideal turnaround time recommended by professional groups.

Point-of-care testing (POCT) is the fastest and most efficient means of generating clinical laboratory reports. POCT devices are very inexpensive and sufficiently simple in operation whereby testing can be conducted by the care-givers, e.g. nursing staff. Moreover, anticoagulated blood samples can be directly tested, obviating the need to centrifuge the sample. The unit cost for POCT testing is higher than automated analyzers. Moreover, the analytical performance of the tests, such as precision, is lower. However, the gain in turnaround time for obtaining results may justify using POCT.

POCT Platforms

POCT platforms have evolved over the past 10 years since the introduction of the first assays. Table 1 summarizes the current menu of commercial assays for cardiac markers. Tests for d-dimer are included in this list, as it provides a means to assess venous thrombotic diseases such as deep vein thrombosis and pulmonary embolism. The initial tests were qualitative, using a strip device that had a visual end-point, either positive or negative. Although these devices are rapid and did not require any additional equipment, they cannot be used to determine whether the concentration of the marker is increasing or decreasing. Strip device readers were soon developed that enabled quantification of results. Soon, quantitative multimarker devices became available for POCT of cardiac markers. One instrument is listed as a point-of-care device but in reality is a small bench-top clinical chemistry analyzer.

In addition to the panel of markers for heart disease, a panel of markers for detection of stroke has been developed. This assay has not yet been cleared by the US Food and Drug Administration (FDA). Therefore, the utility of this test and the need for POCT in the ED remains to be determined. ■