ROCHE DIAGNOSTICS' ELECSYS® PROBNP IMMUNOASSAY FOR ACCURATE DIAGNOSIS AND PROGNOSIS OF HEART FAILURE

Fast, Reliable, and Fully Automated

The **Elecsys® proBNP Immunoassay** was cleared by the FDA in 2002 for use as an aid in the diagnosis of individuals suspected of having congestive heart failure (CHF). Developed by **Roche Diagnostics** (Indianapolis, IN), the Elecsys proBNP is the first fully automated assay for fast, reliable, and accurate quantification of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in serum and plasma. By measuring the level of NT-proBNP, a protein secreted almost exclusively by the heart, physicians can collect important information regarding diagnosis and prognosis of heart failure in symptomatic patients. With such accurate information, physicians are able to assess the severity of a patient's condition, allowing them to fine-tune and optimize treatment. Although NT-proBNP is an outstanding diagnostic marker for congestive heart failure, it adds vital prognostic information for patients with ischemic heart disease as well. The Elecsys proBNP assay has made it possible for physicians to rule out heart failure in symptomatic patients efficiently while also enabling them to stratify those who are at high risk for developing heart failure. The test is fully automated, so laboratories can run a higher volume of samples, making the test more readily available to the patients who need it.

BNP is synthesized and stored in myocytes as a prohormone. Upon stress or stretch of the myocyte, the prohormone is released and cleaved to result in the N-terminal portion, NT-proBNP and the C-terminal portion, cBNP.

NT-proBNP does not cross react with Nesiritide (Natrecor®).

ProBNP is secreted mainly by the left ventricle of the heart when the heart is unable to pump blood efficiently, in response to volume expansion in the peripheral circulation, pressure overload, or increased wall tension. During the process of secretion, it is cleaved to yield the active hormone, brain natriuretic peptide (BNP), and the N-terminal fragment, NT-proBNP, which is biologically inactive. In subjects with left ventricular dysfunction, serum and plasma

concentrations of NT-proBNP have been shown to be increased. A high amount of NT-proBNP in the blood indicates the presence of ventricular remodeling. The higher the blood level of NT-proBNP, the more serious is the condition.

Leslie Parker, PhD, Chief Biochemist, Washington Hospital (Washington, PA), has used the Roche Elecsys proBNP assay since it was first introduced in December 2002. Dr. Parker states, "I believe the proBNP assay has a number of advantages over the BNP assays. ProBNP has been proven to be very sensitive in picking up NYHA stages I and II of CHF, where BNP assays are not quite as sensitive. And, as with any disease, the earlier you pick it up, the earlier you can treat the patient, and the better the patient outcome can be. Recently, proBNP has also been approved to predict outcomes in patients with CHF—the higher the proBNP levels, the less well a CHF patient will do. Additionally, proBNP has been recently certified by the FDA as being useful as a predictor of patient outcome in ACS [Acute Coronary Syndrome] as well, while BNP assays have not been approved for the same use. It has been shown that the higher the proBNP levels, the less well an ACS patient will do. As for stability, we find that a blood sample for a BNP assay is only stable for 3-5 hours. With the proBNP assay, the samples remain good for 24 hours and for as long as 2-3 days if they are refrigerated. Because of the usefulness of the proBNP assay, I believe there will be more use of it in physicians' offices, rather than just in intensive care units or emergency departments."

The automated Elecsys proBNP has a host of benefits, including the ability to accommodate the testing of large numbers of clinical samples. Using serum or
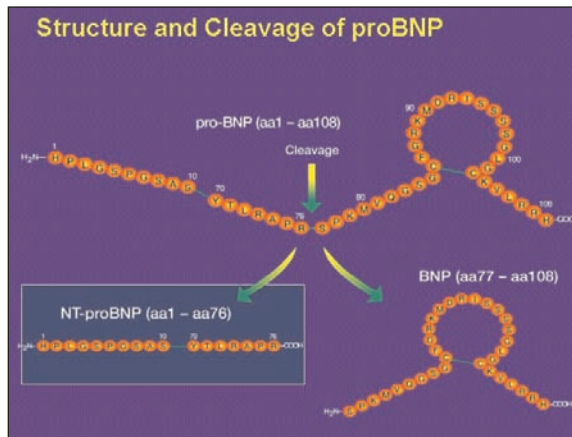
plasma samples, laboratories can provide rapid results to physicians in as little as 18 minutes. While reducing technologist time, it also minimizes human error. The Elecsys proBNP assay provides quantification of NT-proBNP without interference from certain drug therapies. The test helps identify patients requiring further cardiac assessment, leading to more cost-effective use of echocardiography. Additionally, the Elecsys proBNP assay provides improvement of patient management by helping to optimize or tailor a patient's therapy to avoid over- or under-treatment.

A recent study set out to show that certain biochemical markers are helpful for prediction of cardiac events in non-ST-segment-elevation ACS patients. The study evaluated the associations between NT-proBNP and other biochemical risk indicators, as well as their prognostic significance relating to the individual endpoints of death and cardiac morbidity over 1 year in a large group of ACS patients. The trial included 7,800 patients from 458 centers in 24 countries during 1999 and 2000. The results of the study showed that the use of NT-proBNP appears to add critical prognostic insight in the assessment of this patient population (*1*).

Another multicenter evaluation compared the performance of the automated Elecsys NT-proBNP assay with the Biosite Triage BNP assay and revealed that the Elecsys NT-proBNP method is precise (CV≤6.1%), has a wide dynamic measuring range (30-35,000 ng/L), is free from common interferences, and does not cross-react with BNP. Comparison studies showed a reasonable correlation between NT-proBNP and BNP assays, with a substantially higher slope bias of 6-20 for the NT-proBNP assay. The study concluded that the Roche NT-proBNP assay has good analytical performance and better precision than the Biosite Triage™ BNP assay (*2*).

Venu Menon, MD, Director of the Coronary Care Unit, University of North

Carolina, Chapel Hill, utilizes the Roche proBNP assay in three main areas: "In the emergency department, the measurement of NT-proBNP level is important in that it has a very good negative predictive value. If a patient presents with acute shortness of breath and has normal NT-proBNP levels, we can be quite confident in predicting that the shortness of breath is unlikely to be coming from a heart condition. A measurement of NT-proBNP also allows us to establish a baseline in CHF patients, which enables us to evaluate and manage each individual patient's condition continually and put objectivity into a subjective diagnosis. Further, NT-proBNP levels have been shown to be strong prognostic markers for
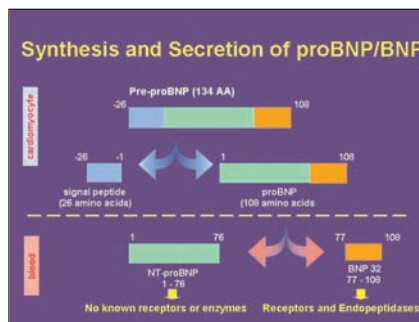
After cleavage, NT-proBNP is primarily cleared by the kidneys. BNP, active hormone has multiple modes of clearance including receptor-mediated, degradation by circulating neutral endopeptidases and renal clearance. The differences in clearance rates results in different in vivo circulating half-lives.

mortality (long-term) in patients with ACS who present with a heart attack."

Christopher deFilippi, MD, Associate Professor of Medicine, Division of Cardiology, University of Maryland (Baltimore, MD), says, "My interest in the Elecsys proBNP immunoassay is with patients who have some element of kidney disease who may be at a high risk for cardiovascular disease, and to what extent proBNP can predict left ventricular dysfunction or underlying disease that can lead to heart failure. We conducted a study that looked at 207 asymptomatic patients who had kidney disease but did not require dialysis. We found that by measuring the proBNP level in these patients, we were able to predict those

patients who ultimately had a diagnosis of coronary artery disease in the presence of renal disease. The prediction was accurate when we did a statistical adjustment for the extent of renal dysfunction, presence of diabetes, and age. We divided the population into quartiles based on levels of proBNP and found that those who had higher levels of proBNP (2 groups with higher levels) were 3-4 times more likely to have coronary artery disease than those who had the lower levels. We think that the proBNP marker may in fact have a very useful role for predicting left ventricular hypertrophy in patients who have ischemic heart disease and concomitant renal dysfunction."

Heart failure is a growing and costly problem, affecting 2%-3% of the U.S. population. Cardiovascular diseases are expected to continue to rise, due to the aging population and increase in acute coronary syndrome survival. The need for developing new and more specific diagnostic approaches to cardiovascular diseases is widely recognized. The Elecsys proBNP assay has helped revolutionize the way we approach the diagnosis and management of heart failure in a simple and seemingly accurate way, allowing physicians to differentiate disease states and individualize therapy.

For more information concerning the Elecsys proBNP Immunoassay or other Roche Diagnostics products, call 1-877-762-4366 or visit the company Web site at www.probnp.com.

References:

1. James, SK, *et al*. N-Terminal Pro-Brain Natriuretic Peptide and Other Risk Markers for the Separate Prediction of Mortality and Subsequent Myocardial Infarction in Patients with Unstable Coronary Disease, A Global Utilization of Strategies to Open occluded arteries (GUSTO)-IV Substudy, 2003;108:275-281.
2. Yeo, KT, *et al*. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay, *Clin Chim Acta*. 2003 Dec; 338(1-2):107-15.