# More clarity over time for heart failure biomarkers

## Karen Lusky

**June 2016—Robert Christenson, PhD, a professor of pathology** and of medical and research technology at the University of Maryland School of Medicine, likens the U.S. mortality rate for myocardial infarction to three or four jumbo jets crashing daily. For heart failure, it's about half that many deaths, "so maybe one and one-half jumbo jets," Dr. Christenson said in a session on cardiac biomarkers at the CAP annual meeting last year.

Dr. Christenson

With more people living longer in general but surviving acute MI, said co-presenter and cardiologist Christopher deFilippi, MD, "we are seeing a marked increase in the number of hospitalizations and the incidence of heart failure in the population."

Heart failure has moved front and center, too, because of its high readmission rate—about 25 percent within 30 days of discharge as of a couple of years ago, said Dr. deFilippi, vice chair of academic affairs at Inova Heart and Vascular Institute in Fairfax, Va. Yet only about a third of those readmissions are due to heart failure. "These patients have a huge number of comorbidities that can influence a variety of biomarkers," he noted.

The 2015 approval of the Novartis drug Entresto has brought more attention. Dr. Christenson, Dr. deFilippi, and others talked with CAP TODAY recently about the questions Entresto has raised, and about the conventional and less conventional heart failure biomarkers.

Dr. deFilippi

Entresto, approved for patients with heart failure and reduced ejection fraction, is a chemically bound compound of valsartan, which is a well-known angiotensin receptor blocker, and sacubitril, a neprilysin inhibitor that blocks the breakdown of BNP.

Brian Lund, MT(ASCP), of Alere, which manufactures BNP and NT-proBNP assays (the latter not sold in the U.S.), says that in Novartis' clinical trial for Entresto, called PARADIGM-HF, the natriuretic peptides showed an "interesting pattern" over the three time points when they were measured. Initially, a small rise in BNP was seen followed by a steady decrease over the next eight months, he says. "In contrast, NT-proBNP showed a small decline initially and a continued decline at the remaining time points similar to that observed for BNP. There are theories on why this pattern emerges, but more work needs to be done," says Lund, who is global product director in the cardiometabolic business unit in the Waltham, Mass.-based company. (Alere's assays were not used in PARADIGM-HF.)

Entresto hasn't had a major uptake in the United States because of its cost and insurance companies' reluctance to cover it, says cardiologist Allan Jaffe, MD, a professor of medicine and cardiology and of laboratory medicine and pathology at Mayo Clinic in Rochester, Minn. "We do use that particular agent, and given the data in regard to outcomes, its use should increase."

Dr. Jaffe

"The simplistic view," he says, "is that the sacubitril portion of the [drug], which is converted in the liver into a neprilysin inhibitor, is responsible for degrading BNP. Thus, BNP is higher due to the drug." But it's complicated because at least in most experiments, he says, "neprilysin itself does very little to BNP in humans as opposed to in rats and cats. So first of all, it's not clear that BNP at all is part of the mechanism." It's likely that other peptides are predominantly affected, he adds.

Dr. Jaffe has written several editorials suggesting that the mechanisms by which the changes occur are unclear. "We also do not know how sustainable the changes are or whether or not we can significantly equate changes in one or the other natriuretic peptides to the effects of the drug." For example, he says, changes in glycosylation could explain all of the changes independent of changes in protein concentration.

"The one thing that does appear to be correct, however, is that the idea that the lower the NT-proBNP, the better for heart failure patients is probably still correct, but that may be less true for BNP," says Dr. Jaffe. It may turn out that different approaches will be required if one uses natriuretic peptides to monitor sacubitril/valsartan therapy.

Dr. Apple

Fred Apple, PhD, medical director of clinical laboratories at Hennepin County Medical Center and a professor of laboratory medicine and pathology at the University of Minnesota, says it could be that both BNP and NT-proBNP, as well as possibly proBNP, have a role in terms of how biomarkers change up or down following therapy. "Multiple biomarkers might provide very useful information. It's too early to tell, and the evidence-based literature over time will tell the story."

Clyde Yancy, MD, MSc, chair of the writing committee for the 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure guideline, says that as a clinician he has had at least a moderate amount of experience with Entresto. He has opted to omit serial BNP or NT-proBNP assessment during dose titration or clinical follow-up. "This avoids the inevitable confusion that is likely with both assays available in clinical practice. Rather, I rely on clinical experience to make bedside assessments," he says. "In this scenario, if a tool was needed, the use of other newer biomarkers might be an option, including ST2 and galectin-3." Dr. Yancy is a professor of medicine and of medical social sciences, chief of cardiology, and associate director of the Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine.

In the acute care setting, it's likely, says Dr. deFilippi, that it will not matter whether BNP is used for Entresto

patients because you're looking at large variations. "And the change in BNP is not going to be subtle."

Dr. Christenson says many experts in the field think there will be a wholesale switch to NT-proBNP based in part on the potential interference from neprilysin. "We'll have to wait and see how widely the drug is used. As an aid in the diagnosis of acute decompensated heart failure, BNP or NT-proBNP will remain essentially equivalent as stated in 2013 ACCF/AHA heart failure guidelines. However, for use in prognosis and treatment monitoring of chronic heart failure patients who are administered Entresto, lower NT-proBNP values will continue to reflect a better prognosis whereas for BNP levels this relationship does not appear to hold." Laboratories will not offer both BNP and NT-proBNP, he adds, so the latter will likely win out if use of Entresto becomes widespread for heart failure management.

**Of the natriuretic peptides in general, Dr. Christenson** said in the CAP session, they "aren't specific for heart failure by a long shot, but they are released in a setting of hemodynamic stress." As of today, for diagnosis of heart failure, the differences between BNP and NT-proBNP are "dwarfed by the similarities."

"Biological variability is quite substantial," he says, noting there can be about a 100 percent difference in the natriuretic peptides from day to day. "In order to notice a real change, you have to see a doubling or halving of the BNP or NT-proBNP." Both are about the same in that respect.

The natriuretic peptide value at hospital discharge, or the change between the admission and discharge values, is more prognostic than the admission value alone for a patient who presents with acute decompensated heart failure, Dr. deFilippi says. "For people with chronic heart failure who are stable, a baseline BNP or NT-proBNP level is typically the summation of the severity of underlying comorbidities such as diabetes and hypertension." When they become acutely ill, "their BNP or NT-proBNP rises because of volume/pressure overload. This component is important with respect to diagnosis," he says, "but is reversible over the course of in-hospital treatment and appears to be of less importance for prognosis."

Therefore, if the natriuretic peptide level remains high and relatively unchanged over the course of hospitalization despite an improvement in symptoms and diuresis and associated weight loss, the prognosis remains poor, "not so much due to this episode of decompensation but due to the impact and severity of the underlying comorbidities that have resulted in heart failure," Dr. deFilippi says. With the emphasis on preventing readmission, cardiologists are increasingly recognizing the importance of the pre-discharge natriuretic peptide level for outpatient follow-up.

Using the natriuretic peptides for more than diagnosis or prognosis is gaining traction, Dr. deFilippi said in the session last year. "Registry studies have shown that people who should be on optimal medical management, with respect to ACE inhibitors, beta blockers, aldosterone antagonists, spironolactone being the prototype, generally aren't. And the thinking may be that a natriuretic peptide can perform like a hemoglobin A1C and get us all to work a little bit harder if we get feedback through numbers, and perhaps make patients more compliant too."

Use of BNP or NT-proBNP to guide therapy remains of interest "but the data to date are mixed and don't yet support this in a well-defined way," says Rick San George, PhD, Alere's vice president of clinical affairs. "There are no BNP or NT-proBNP assays with an FDA clearance for guiding therapy."

Dr. deFilippi reported that an ongoing study of about 42 centers funded by the National Heart, Lung and Blood Institute, called GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure), will look at whether titrating medical therapy based on minimizing NT-proBNP levels will be superior to usual care.

The study, which involves patients in the clinician office setting rather than the emergency department (and does not include patients on Entresto), will probably be completed in about two to three years, says Dr. Christenson, who adds that no such BNP trial is ongoing. NT-proBNP is "reasonably well harmonized between platforms because all users must currently obtain a license from a single manufacturer," he says.

**Dr. deFilippi calls ST2 "a very** powerful predictor of mortality." A high NT-proBNP and ST2 indicate people who have an extremely high risk of dying over the next several years, he says.
Neither ST2 nor galectin-3 are cardiospecific biomarkers, Dr. deFilippi cautions. There are a lot of comorbidities that may also result in elevation of ST2 or galectin-3, particularly in older adults.

ST2 and galectin-3 likely have different mechanisms, says Dr. Jaffe, but both appear to target mechanisms related to fibrosis. "And we think fibrosis is important in patients with heart failure. The question has been, however, that even though there are lots of interesting, exciting, mechanistically relevant data about these markers, there is no well-defined indication for [their routine use]." Currently, they are in "a niche position" with potential uses in small groups of patients.

"For example, we often see patients in whom the severity of shortness of breath seems modest and the natriuretic peptide values don't look too bad." In that case, if the patient's ST2 or galectin-3 is very high, Dr. Jaffe says he would follow that patient more closely. "What would be better would be to say because of these elevations, we should give this specific drug or increase therapy in one way or the other. That's the missing link with ST2 and with galectin-3."

As for troponin, "What we know," Dr. deFilippi says, "is once you start looking at a high-sensitive troponin, you go from about 10 percent detection of troponin in stable heart failure [patients] toward 90 percent" who will have detectable levels. "The higher that level, the poorer the outcome with respect to mortality or subsequent hospitalizations."

Dr. Christenson says that a study (in which he was one of the researchers) of a cohort of elderly subjects without symptoms of heart failure found that those in the upper strata of high-sensitivity troponin values versus the lower values were at higher risk for heart failure (deFilippi CR, et al. *JAMA*. 2010;304[22]:2494–2502).

"It's just a matter of time," says Dr. deFilippi, "that if you want to look at your overall cardiovascular risk, you'll get a high-sensitive troponin done" during an office visit. The marker ultimately is a better predictor of a person's future heart failure risk than atherosclerotic cardiovascular disease events, he adds. And "it's typically superior to a generalized inflammatory marker, such as CRP," for predicting risk of heart failure.

Dr. deFilippi reports that he, Dr. Christenson, and colleagues have shown in observational studies that people who exercise more were less apt to have an increase in cardiac troponin and less likely to develop heart failure. "We even saw in a small study of several hundred previously sedentary adults 75 years or older randomized to moderate physical activity versus usual care for a year that those newly engaging in moderate activity had less of a rise in their troponin level. Ultimately, whether that translates into reduction of heart failure, we will have to wait to see."

Dr. deFilippi said they were planning to study an intervention, such as an ARB or ACE inhibitor, for older individuals who have high troponin T levels to lower the risk of developing renin-angiotensin-aldosterone system heart failure with reduced ejection fraction, which troponin appears to be effective at predicting.

"Potentially, biomarkers may overall both guide outpatient therapy for symptomatic heart failure and identify at-risk asymptomatic individuals who could benefit from preventive therapy," Dr. deFilippi says.

"New heart failure therapies may challenge the accuracy [of natriuretic peptides], particularly of BNP, and that waits to be seen."
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