



## **Comparing NT-proBNP Risk Stratification Strategies for Heart Failure**

*Serial Determinations May Offer a Superior Strategy for Risk Classification*

By John R. Bell

---

The Valsartan Heart Failure Trial (Val-HeFT), a large-scale randomized, multinational clinical study of the angiotensin receptor blocker valsartan, assessed therapeutic options for patients with heart failure. Now researchers have gone back and analyzed NT-proBNP levels in 1,742 of those patients with chronic, stable heart failure who were enrolled in the placebo arm of the Val-HeFT trial (*J. Am. Coll. Cardiol.* 2008;52;997-1003). Their purpose was to evaluate the association between changes over time of NT-proBNP and outcome.

To do so, the investigators examined the relationship between mortality in this cohort and the level of plasma NT-proBNP measured at randomization and at 4 months using three statistical methods: absolute change from baseline, percent relative change from baseline, and categorical changes. Using the categorical changes, each patient was allocated to a category of NT-proBNP status in relation to a threshold of 1,078 pg/mL at baseline and 4 months: low-low, high-high, high-low, and low-high.

The research team then compared these methods' ability to predict patient mortality. Using quartiles of absolute change between baseline to 4 months, the investigators found a U-shaped curve, in that patients in the category with the largest decrease or the category with the largest increase in NT-proBNP had the highest mortality rates—approximately 15% for the former group and 26% for the latter group. Likewise, patients' levels assessed across quartiles of percent change also showed an independent association with mortality, from roughly 9% in quartile 1 to 21.5% in quartile 4. Unlike the rates for absolute change, however, those for relative change increased in a stepwise fashion. Analysis via categorical changes, the third method, was less clear, showing a mortality rate of 8.9% of patients with less than 1,078 pg/mL at baseline and 4 months, who constituted more than half of the cohort. Patients whose NT-proBNP went from more than to less than that level within 4 months had a mortality rate of 7.2%. For those whose levels went from less than 1,078 pg/mL to more than this threshold, mortality was 21.1%. Patients whose NT-proBNP levels began higher than this level and remained so had a mortality rate of 25.7%.

These findings led the investigators to conclude that "serial determinations of natriuretic peptide (BNP or NT-proBNP) concentration and classification into few categories of changes according to threshold levels may be a superior strategy for risk stratification of patients with chronic and stable HF."

The study's lead author, Serge Masson, PhD, says that the study's global sample—302 centers in 16 countries— makes the results widely applicable. "These unique features make the conclusions

robust and generalizable, within the well-accepted limitations of post-hoc analyses," said Masson of the Mario Negri Institute for Pharmacological Research in Milan, Italy. Masson cautioned, however, that natriuretic peptide levels are influenced by factors such as age, sex, body mass index, renal function, and prescribed pharmacological therapy. These confounding factors should be accounted for by physicians when interpreting single concentrations and their evolution over time, he said.

### **The Mortality-Risk Question**

But do these findings settle the question of how to measure HF mortality risk? "Measurement of natriuretic peptides is one very powerful way to assess mortality and morbidity risk in heart failure," said James L. Januzzi Jr., MD, a cardiologist and associate professor of medicine at Harvard University Medical School, who was not affiliated with the study. "It is inherently attractive, as it is considerably easier than using other, more expensive adjunctive tests, or much more complicated risk scores, although I would suggest that these other testing options or risk scores do show additive value to natriuretic peptides," he said. "So it may be in the future that we use 'all of the above' to objectively evaluate our patients with heart failure. We just need to figure out how to operationalize this approach."

Januzzi noted that as a lab test, the natriuretic peptides are "a remarkable advance" in the ability of the physician to rapidly, accurately, and serially follow patients with a tool that provides objectively powerful prognostic data." However, he cautioned, "The million dollar question is whether we should take the results of NT-proBNP or BNP testing, and intervene appropriately if a pattern is seen that is predictive of risk--and do something about that risk."

He suggested two scenarios: "On the one hand, in the context of a low NT-proBNP or BNP, we are reassured that the risk to our patient with heart failure is generally low, and after re-assessing medication use and adherence to salt and water restriction, we may be able to harness the excellent negative predictive value for adverse outcome, and not worry too much about imaging, or other testing."

On the other hand, in the context of a rising natriuretic peptide value, should the cardiologist intervene? And if so, how? "We now know that therapies with proven benefit for heart failure such as diuretics, as well as ACE inhibitors, ARBs, beta-blockers, spironolactone, and biventricular pacing, all lower natriuretic peptides in parallel with improvements in outcomes. So should we titrate therapies in response to a rising value? This remains speculative, but the data are promising in regards to this approach," said Januzzi, who is also associate director of the Coronary Care Unit at Massachusetts General Hospital, Boston.

### **Biological Variability Debated**

Another researcher, who has published studies on BNP, noted that the attempt to define what constitutes a normal level of either BNP or NT-proBNP should be adjusted for age, sex, and renal function. Wayne L. Miller, MD, PhD, professor of medicine at the Mayo Clinic, Rochester, noted that BNP has large biologic variability and significant molecular heterogeneity, which confounds the interpretations of BNP levels. "Because of the large biologic variability, it takes considerable change--perhaps more than 80%--to be considered a clinically meaningful change, and this is not commonly observed in clinical studies. So it would seem that if BNP values are all normal, then the value of measuring serial values is to determine if or when BNP becomes elevated, thereby suggesting increased risk that requires intervention. However, if BNP values are at least modestly elevated, then there is probably no benefit in serial measurements; risk is already established." Januzzi disagrees with this point: "While it is true that the biological variability is high at lower concentrations of BNP or NT-proBNP, studies have conclusively shown that at higher natriuretic

peptide values—such as those seen among patients with established heart failure—the biological variability is much lower, in the range of 25%. This firmly puts both BNP and NT-proBNP in a position to be used as a monitoring tool, at least in the heart failure population.

Should clinicians monitor natriuretic peptides serially over time? Januzzi thinks so. “At present, the preponderance of data would argue that serial measurement of NT-proBNP is the gold standard for biomarker prediction of risk in heart failure,” he said, noting that the goal is to get NT-proBNP preferably below approximately 1000 pg/mL, where the risk drops dramatically, he said.

But an editorial accompanying the report questioned whether “changes in peptide levels offer significant practical advantages over single measurements,” wrote A. Mark Richards, MD, of the Christchurch (New Zealand) School of Medicine and Health Sciences (*J. Am. Coll. Cardiol.* 2008;52:1004-5). However, he encouraged investigators undertaking cohort studies or therapeutic trials in HF to incorporate serial measurements in their study designs.

Dr. Januzzi disclosed relationships with Roche Diagnostics, Siemens, Ortho-Clinical Diagnostics, Inverness, BG Medicine, and Critical Diagnostics.