Serial NT-proBNP found to identify risk for adverse CV outcomes

Anne Paxton

August 2018—For diabetes type 2 patients with cardiovascular disease, findings of a new study support clinicians' use of serial measures of NT-proBNP concentrations to make critical treatment decisions easier by basing them on risk of major cardiovascular events, including heart failure.

Researchers analyzed differences between baseline and later NT-proBNP (N-terminal B-type natriuretic peptide) test results along with outcomes in the population with diabetes type 2 who were enrolled in the EXAMINE trial. They found a "strong graded relationship" between increasing baseline and six-month NT-proBNP concentration and the incidence of future major cardiovascular events.

NT-proBNP at baseline was independently associated with development of major cardiovascular events—in particular, hospitalization for heart failure (Jarolim P, et al. *Diabetes Care.* 2018;41[7]:1510–1515).

In a cohort of patients singled out by the study, "the risk of heart failure was really dramatic," says lead author Petr Jarolim, MD, PhD, director of clinical laboratories at Dana-Farber Cancer Institute and medical director of clinical chemistry and director of the biomarker research and clinical trials laboratory at Brigham and Women's Hospital. Dr. Jarolim presented the study at the Heart Failure 2018 conference in Vienna, Austria, in May. The study was also featured in the closing session highlights of the meeting.

"When we teased out high-risk patients" (those with persistently high NT-proBNP or newly high NT-proBNP at six months) from the quartiles in which patients were stratified according to their NT-proBNP results, "we showed that the risk of heart failure for them is very significant. For this group of patients—about 10 percent of the population of type 2 diabetes patients—the risk we identified is very high," Dr. Jarolim says.

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—Petr Jarolim, MD, PhD

Evidencing the strong correlation with risk, the hazard ratios shown in the study—the ratio of the hazard rates corresponding to the conditions described by two levels of a variable—"were on the order of five to 10 in those patients seen by a clinician and marked as abnormal," he says. This signifies that the high-risk group was five to 10 times as likely as the others (those with persistently low NT-proBNP or an NT-proBNP that declined to a low level over six months) to be hospitalized for heart failure.

The model used for this study adjusted for important potential confounders, including age, sex, BMI, type of qualifying acute coronary syndrome event and time since the event, history of heart failure, hypertension, and estimated glomerular filtration rate.

The study is another in a string of recent papers on serial changes in biomarkers such as troponin relating to treatment of cardiovascular disease. “It didn’t come out of the blue,” says Dr. Jarolim, whose research laboratory worked on several earlier studies. Troponin and NT-proBNP have solid predictive value, he says. “The reason we focused here on NT-proBNP is that there is a lot of discussion about the potential benefits of new antidiabetic medications for cardiovascular disease.”

The FDA mandated about a decade ago that each new antidiabetic medication have sizable post-marketing studies addressing the safety of the drug, he notes. “Although no studies show there is a risk in using these new medications, one of the initial concerns was possible increased hospitalizations for heart failure and whether they could be predicted.”

Use of the high-risk patients in the EXAMINE trial (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care), who were enrolled after a clinical presentation of acute coronary syndrome, was one of the limitations of the study. The rate of major cardiovascular events in a stable diabetic patient population is relatively low, so the size of any study has to be large if patients are not high-risk patients. “However, we believe our findings can be applied to lower-risk patient populations,” Dr. Jarolim says.

“What may eventually be needed is actually a similar study to ours in patients who are not pre-selected as high-risk patients, who are just your standard type 2 diabetes patients without active CV disease yet. That’s important to show this effect is the same or similar in the general population with type 2.”

But this study, the authors say, indicates the potentially heightened clinical relevance of strategies for biomarker-based CV risk stratification in patients with type 2 diabetes. As examples of such strategies, they cite the emerging data demonstrating the efficacy of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide 1 agonists in modifying the risk for heart failure in type 2 diabetes patients.

For the laboratory, the clinical implications of the study should also be of interest. “If you read most papers, there is one way to evaluate data which is really proper and statistically correct. And we have it in our paper. Our study is statistically sound. We didn’t introduce any bias. When you just look at the distribution of test results, you either get or you don’t get a statistical association of the biomarker level to outcomes.”

There is a problem with this approach, however. “All of the graphs are fine and helpful,” Dr. Jarolim says. “But then you have to transfer this knowledge to clinical practice. You have to decide what the clinically useful cutoff should be.”
“Once you want to transfer the findings into clinical use, you obviously cannot just tell clinicians that patients in the highest quartile are at the highest risk. They don’t know when one quartile ends and another starts. They need a really defined cutoff, which typically doesn’t coincide with any quartile or quintile. You have to give them numbers.”

Therefore, in many studies, “we try to not only use statistically correct stratification, but also to come up with a number that will be clinically useful. In this particular study, we explored various cut points and found that NT-proBNP concentration of 400 pg/mL as the point between so-called high and low NT-proBNP worked very well.” It’s not a magic number, he says. “It could be adjusted or optimized once we study an average type 2 diabetes patient population, not just those at high risk.” But here, the 400 pg/mL cutoff showed a clear discrimination of risk and may be most practical for clinical practice.

Dr. Jarolim describes a paradox that arises with the drugs that protect the natriuretic peptides. “Natriuretic peptides are established biomarkers of both BNP, which is the biologically active part of the precursor molecule proBNP, and NT-proBNP, which is the inactive N-terminal portion of the molecule that hangs in the circulation and is more stable and somewhat easier to measure.”

Both BNP and NT-proBNP are elevated in patients with heart failure, Dr. Jarolim notes. “BNP is generally good for you. So why would the patient be doing worse with a higher BNP? It was discovered some years ago that only a small fraction of BNP molecules in patients are the full-size molecule that is biologically active, and most BNP measured by current clinical assays are the less active or inactive fragments of BNP.” The other part of the precursor molecule that is measured, proBNP, just goes down, as expected, because it’s not cleaved; it’s not protected, he explains. BNP, however, does not go down.

Alogliptin, the dipeptidyl peptidase 4 (DPP-4) inhibitor studied in the EXAMINE trial, is one of the molecules that should protect full-size BNP cleaved by DPP-4. But in this study, the researchers found that treatment with a DPP-4 inhibitor did not meaningfully alter either NT-proBNP or BNP concentrations. “We didn’t see any differences between alogliptin patients and patients getting a placebo.”

A new medication heavily advertised in the past two years that combines neprilysin inhibitor sacubitril and angiotensin receptor blocker valsartan to treat heart failure patients is not mentioned by name in the study. This medication, marketed as Entresto, works as a treatment by inhibiting protease, which cleaves BNP, he says. “When you start treating patients with a neprilysin inhibitor, they get clinically better and you would expect they should have lower BNP levels. But, paradoxically, they don’t show lower levels. They have higher levels of BNP.”

“It seems obvious that the more of the good, full-size BNP your patients have, the better,” Dr. Jarolim says. “But that can be confusing to clinicians since favorable response to heart failure treatment is typically associated with lower BNP levels. In contrast, NT-proBNP responds to this therapy as one would expect, that is, we see its levels decline.”
When Entresto came on the market, “it created a bit of a panic among laboratories that didn’t have the NT-proBNP assay available or that had only BNP.” Some diagnostic companies offer only the BNP assay, he says, while other companies offer the NT-proBNP assay.

Further research on how biomarkers may help to predict and stratify possible side effects of selected treatments is underway. “We are definitely addressing the cardiovascular safety of certain medications. As an example, we are evaluating biomarkers that may predict the risk of bleeding in patients with atrial fibrillation treated by anticoagulants.”
“Clinicians should welcome this study’s support for use of serial NT-proBNP results to assess—and potentially to aggressively treat—diabetes and ischemic heart disease patients at highest risk of heart failure,” Dr. Jarolim says. “You can be more aggressive in various approaches with antidiabetic medications, blood pressure medications, and so on, so it’s very important to identify those patients at high risk.”

Dr. Jarolim doesn’t wish to oversell the study, however. “But it would be a logical outcome of these findings that there may be a recommendation to conduct monitoring of CV patients every several months,” he says.

Anne Paxton is a writer and attorney in Seattle.