In diabetes patients, biomarker use for early-stage HF

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March 2024—For patients with type 2 diabetes, the cardiac biomarkers are a better predictor of early-stage heart failure than conventional risk prediction scores. “We need to use biomarkers,” says Petr Jarolim, MD, PhD, medical director of clinical chemistry, Brigham and Women’s Hospital, and medical director of clinical laboratories, Dana-Farber Cancer Institute.

The supporting evidence is clear: In a session at the ADLM meeting last year, Dr. Jarolim, who is also director of the hospital’s biomarker research and clinical trials laboratory and professor of pathology at Harvard Medical School, pointed to a study that found that NT-proBNP was the strongest independent predictor of future cardiovascular events in patients with type 2 diabetes, outperforming echocardiography, albuminuria, and electrocardiography (Busch N, et al. *J Diabetes.* 2021;13[9]:754–763). And the expert consensus concurs. In a 2022 report, the American Diabetes Association and American College of Cardiology recommended a natriuretic peptide or high-sensitivity cardiac troponin measurement at least yearly in patients with type 2 diabetes (Pop-Busui R, et al. *Diabetes Care*. 2022;45[7]:1670–1690).

But practically speaking, there are details to be ironed out, starting with the proposed biomarker thresholds, says Dr. Jarolim, who discussed the report in his ADLM presentation and in a recent interview with CAP TODAY. “The recommendations are important,” he says. “But I can’t completely agree with the cutoffs proposed in the recommendations.”

Those cutoffs are 50 pg/mL for BNP, 125 pg/mL for NT-proBNP, and a value greater than the 99th percentile for a healthy patient population for high-sensitivity cardiac troponin. For NT-proBNP, Dr. Jarolim says, “125 is a fairly low reading. It is predictive, and if you go even lower you identify more patients and may be able to identify them earlier, at the expense of a further decrease in specificity. But it would be important to optimize it.”

Dr. Jarolim

Women, he says, have roughly twice the levels of natriuretic peptides as men of the same age group, and concentrations increase with age in both sexes. “So, all that suggests that it should be more granular and more specific. And it should be able to predict the early onset of heart failure with higher certainty.”

“It’s a simplistic solution, at this point, to use this cutoff,” he adds.

The first study to propose the 125 pg/mL cutoff had “surprisingly limited data,” he says, with a population of 631 patients with diabetes and a one-year follow-up (Huelsmann M, et al. *Eur Heart J*. 2008; 29[18]:2259–2264). At 125 pg/mL, the NT-proBNP assay had a sensitivity of 0.795 and a negative predictive value of 97.6 percent for hospitalization or death within the observation period. “The assay has high sensitivity and high negative predictive value,” Dr. Jarolim says. “You can’t argue with that. The lower you go, the higher the sensitivity—that’s how our testing works.” The positive predictive value was 12.9 percent. “But if you look at real numbers, or the real prevalence, that’s an overestimate,” he says. “If it were a tumor marker you probably wouldn’t use it for screening with a positive predictive value of 13 percent. Yet based on this paper, numerous studies have published that NT-proBNP of greater than 125 is associated with higher risk of progression to heart failure, seemingly suggesting that this is the optimal cutoff.”

Some experts admit that a positive predictive value of 13 percent isn't optimal, he says, but they don't see it as a critical issue because "by the time we get optimal cutoffs for positive predictive value, we are in a zone that includes people with already established heart failure, and the goal of this approach is to aim for people in transition."

But the low positive predictive value could result in overdiagnosis or overtreatment with sodium-glucose cotransporter-2 inhibitors, he says. "And it's not an inexpensive therapy."

Some laboratories, such as Mayo Clinic, use age- and sex-stratified reference ranges for NT-proBNP. At Mayo Clinic, he says, the lowest upper reference limit for women is still above 125 pg/mL. "The lowest is in the 45- to 54-year-old group, and it's 141." For women 65 and older it's less than 540 pg/mL. "And these are all apparently healthy women."

In contrast, the package insert for one NT-proBNP assay puts the cutoff at 125 pg/mL for patients under 75, and 450 pg/mL for patients over 75. "Here, if you have 250 and you are 74 years old, you are at risk of heart failure and should be treated. If you have 250 and you are 76 years old, you are well within the reference range. So we need to look carefully at these cutoffs."

"That said, we know that BNP and NT-proBNP perform better than established diabetes markers," he says. Zelniker, et al., showed that patients with higher NT-proBNP quartiles had increased rates of cardiovascular death and hospitalization for heart failure (13.7 percent [Q4, >165 pg/mL] versus 1.0 percent [Q1, ≤35 pg/mL]) (Zelniker TA, et al. *Eur J Heart Fail*. 2021; 23[6]:1026–1036). They also found that the incidence of cardiovascular death and hospitalization in patients without a history of heart failure but with biomarker levels of 450 pg/mL or higher was similar to the incidence in the overall subgroup of patients with a history of heart failure—18.3 percent versus 19.9 percent.

As a measure of risk for heart failure, the difference between BNP and NT-proBNP is negligible, Dr. Jarolim says. NT-proBNP is approved for multiple sample types, unlike BNP, which is approved for EDTA plasma only. "NT-proBNP also is slightly more sensitive because it's more stable and therefore has a longer half-life and circulates in higher concentrations," he says. "But as far as predictive value goes, they are comparable."

Dr. Jarolim and others studied serial NT-proBNP monitoring in a study of 5,380 patients with type 2 diabetes (Jarolim P, et al. *Diabetes Care.* 2018;41[7]:1510–1515). Outcomes were stratified by change in NT-proBNP between the baseline measurement and six months. "We divided patients into two categories: high, when the NT-proBNP was greater than 400 [pg/mL], and low, when NT-proBNP levels were less than 400," he says. Patients who had persistently high NT-proBNP or developed high NT-proBNP at six months were at significantly higher risk for cardiovascular death or heart failure than those in whom NT-proBNP remained low at both time points or who had a high NT-proBNP baseline measurement that subsequently declined to the low category. "Their outcomes are almost the same as those who started low and continued low," he says. "So it is worth doing these repeat measurements" and attempting to lower NT-proBNP levels through therapy.

Body mass index affects the natriuretic peptides. "It's known that levels are lower in patients with higher BMI, so this affects the cutoff," Dr. Jarolim says. "Initially we thought this was because adipose tissue has receptors for BNP, so it would make sense that in overweight people BNP would be lower." But NT-proBNP levels also are lower in those with higher BMI, he says. "So that suggests that obese people produce fewer natriuretic peptides." The Heart Failure Association of the European Society of Cardiology recommends cutoff concentrations 50 percent lower in obese patients in its practical guidance on the use of natriuretic peptides (Mueller C, et al. *Eur J Heart Fail*. 2019;21[6]:715–731).

Dr. Jarolim and others investigated the interaction between NT-proBNP and body mass index and its effects on heart failure risk in a study of 24,455 overweight or obese patients (Patel SM, et al. *Eur J Heart Fail*. Published online Dec. 22, 2023. doi:10.1002/ejhf.3118). They found a significant inverse association between NT-proBNP and BMI that persisted after adjustment for all clinical variables. Higher NT-proBNP and higher BMI were each associated with greater probability of hospitalization for heart failure. In patients with an NT-proBNP of less than

125 pg/mL, risk of hospitalization was low irrespective of BMI. But in those with an NT-proBNP of more than 125 pg/mL, risk of hospitalization for any given NT-proBNP value was significantly higher among those with obesity. In particular, the authors write, clinicians should recognize the meaningful risk of hospitalization for heart failure in patients with severe obesity with low-level elevations in NT-proBNP between 125 and 450 pg/mL.

“So we definitely should adjust for BMI,” Dr. Jarolim says.

In the emergency setting, if a patient has shortness of breath with or without chest pain, congestion, and other symptoms, a natriuretic peptide test is the test to order, Dr. Jarolim says.

“The natriuretic peptides are a prototypical marker of heart failure.” Cardiac troponin is a more generic marker of myocardial damage that can signify a number of conditions. But elevated cardiac troponin is associated with the onset of heart failure, he says. In his own research, he’s demonstrated that troponin levels increase significantly with the increasing severity of heart failure (Jarolim P, et al. *Clin Chem*. 2015;61[10]:1283–1291). “So clearly troponin is associated with heart failure and has solid predictive value.” Using both markers in tandem may be an asset in some scenarios, he says. In patients with higher BMI, for example, “troponin as an adjunct to the natriuretic peptides may be helpful.”

In a study that examined the national prevalence of subclinical CVD—assessed by elevated NT-proBNP or cardiac troponin and using stored serum samples—in 10,304 U.S. adults without a history of CVD, Fang, et al., found that in patients with diabetes, the risk of mortality was highest when both markers were simultaneously elevated (Fang M, et al. *J Am Heart Assoc*. 2023;12[11]:e029083). The authors looked at cardiovascular disease, Dr. Jarolim notes, rather than incident heart failure, and they used the cutoffs recommended in the ADA report (NT-proBNP ≥125 pg/mL and high-sensitivity cardiac troponin T ≥14 ng/L, which is the 99th percentile used in Europe). They found that the crude prevalence of subclinical CVD was about twice as high in adults with diabetes versus those without. About one in three adults with diabetes had subclinical CVD: hs-cTnT was elevated in 19 percent, NT-proBNP was elevated in 23 percent, and both biomarkers were elevated in nine percent. Among adults with diabetes, the cumulative incidence of all-cause and CVD mortality was substantially higher in those with elevated high-sensitivity cardiac troponin T or NT-proBNP.

For high-sensitivity cardiac troponin assays, “we don’t have a gold standard that would allow us to say this amount or standard should be detected,” Dr. Jarolim says, “so we use the 99th percentile.” When it comes to the high-sensitivity cardiac troponin T assay, the FDA in 2017 approved cutoffs of 14 ng/L in women and 22 ng/L in men. “At Mass General Brigham we decided to be more conservative,” he says. “We’re using 10 nanograms per liter for women and 15 nanograms per liter for men for the diagnosis of acute myocardial infarction.” But some situations call for a more lenient approach, he says. At Dana-Farber, where cardiac troponin is used to monitor patients on immune checkpoint inhibitors, the FDA-approved cutoffs are used. “It would be too restrictive to use the low cutoffs we use for MI [at Brigham],” he says. “It would exclude half the patients from cancer trials, which are potentially lifesaving.”

For patients with type 2 diabetes, there’s evidence to support the more cautious approach. Pandey, et al., he notes, use the FDA-approved troponin T assay’s limit of quantitation of ≥6 ng/L in their biomarker-based risk score to identify individuals with dysglycemia who are at a five-year risk for incident heart failure (Pandey A, et al. *JACC Heart Fail*. 2021;9[3]:215–223). As a marker of long-term risk, Dr. Jarolim says, “it makes sense to go lower than the 99th percentile.”

Grinstein, et al., found in their study of 4,160 patients with acute coronary syndrome that those with baseline high-sensitivity cardiac troponin T of 14 ng/L or more had a higher 30-day risk of cardiovascular death or myocardial infarction than those below 14 ng/L (9.1 percent versus 1.9 percent). But even patients who had levels between 14 ng/L and the limit of detection of 3 ng/L used in Europe—that is, within the reference range—had a two percent risk. Patients with undetectable troponin had zero percent risk (Grinstein J, et al. *Clin Cardiol*. 2015;38[4]:230–235).

Cavender, et al., studied the incidence of cardiovascular disease or hospitalization for heart failure in 3,808 patients with type 2 diabetes using a high-sensitivity cardiac troponin assay. They found that patients who had troponin I levels greater than 26 ng/L after six months had a two-year incidence of 17.5 percent. But patients who measured between 10 and 26 ng/L after six months had almost the same two-year incidence, at 15.1 percent (Cavender MA, et al. *Circulation*. 2017;135[20]:1911–1921). “So it isn’t enough to be in the so-called reference range,” Dr. Jarolim says. “You need to be lower.”

A large study of the general population, which proposed specific high-sensitivity cardiac troponin I cutoffs for cardiovascular risk stratification in asymptomatic patients, found that “levels greater than 12 [ng/L] for men and greater than 10 [ng/L] for women are associated with significant elevated long-term risk of adverse outcomes,” Dr. Jarolim says (Blankenberg S, et al. *Eur Heart J*. 2016;37[30]:2428–2437). “So again, you want to be in the low single digits.”

Whether C-reactive protein, too, could improve clinical risk scores has come up. “Brigham and Women’s Hospital advocated the use of high-sensitivity CRP as a cardiac risk factor, based on several studies,” he says. “But many follow-up studies, including some by our group, have shown that its predictive value is lower than that of the natriuretic peptide or high-sensitivity cardiac troponin assays. It’s also a finicky marker, in that it responds to any inflammation you might have. So I don’t think CRP would add much.”

Dr. Jarolim doesn’t expect the biomarker testing to have an outsize effect on laboratory operations, even after more institutions begin to follow the ADA recommendation.

Test volumes will increase, “but it won’t happen overnight,” he says. “And compared to the clinical chemistry lab at Brigham, where we run eight million tests per year, this will be thousands or tens of thousands of tests, added gradually. So that’s a relatively minor impact.”

And because the testing will be performed in the outpatient setting, “turnaround time is not a critical issue,” he says, and “theoretically it should be reimbursed, especially if payers appreciate that this approach should postpone or even prevent the onset of heart failure.” Still, he adds, “Screening is a dirty word in the reimbursement world.”

At Brigham, troponin orders in the outpatient setting for symptomatic patients are discouraged, he says. The lab runs 150 cardiac troponin tests daily, of which about two-thirds are elevated, and it isn’t possible to notify every clinician whose patient has an abnormal result. “So we ask clinicians to send symptomatic patients to the emergency department. But if cardiac troponin becomes a standard risk prediction test, we will need to change this approach.”

The need for new diagnostic cutoffs and age- and sex-specific ranges and BMI adjustments may mean that “our resulting screens get a little more complex,” Dr. Jarolim says. One solution would be to create a new test in the laboratory information system—cardiac troponin as a risk predictor, for example, with a different cutoff. There’s precedent for it, he says. “For C-reactive protein, we use the same assay as two different markers—inflammation marker versus cardiac risk factor.” For cardiac risk prediction the cutoff is 3 mg/L, and for inflammation it’s 10 mg/L. The two tests use the same reagent but have different order and charge codes. “So it wouldn’t be unheard of.”

Implementing the biomarker testing in clinical practice won’t be easy, he concedes. “An overwhelmed primary care physician may have a problem ordering NT-proBNP. It’s not an inexpensive assay.” Internist Jennifer Zreloff, MD, of Emory University, a co-presenter in the ADLM session, says that it wouldn’t be difficult to add to the checklist another laboratory test. “But it hasn’t gotten to our radar yet. We’re focusing already on a lot of cardiovascular issues. If we can’t get the blood pressure of our patients controlled, if we can’t convince them to take a statin . . . where is screening for the early stages of heart failure on that to-do list?”

In some countries, Dr. Jarolim notes, the natriuretic peptides are not part of the diagnostic toolkit. “Many hospitals

in Spain, for instance, use CA-125, the ovarian cancer marker, as a marker of congestion for monitoring heart failure. And we see patients previously treated for ovarian cancer who don't have a relapse, yet their CA-125 is increasing." A physician may incorrectly conclude a patient has a cancer relapse when they're exhibiting signs of heart failure. "So it's difficult to implement these tests in primary care," he says.

As Mass General Brigham undergoes consolidation and a transition to Epic Beaker, a push for standardization across the hospital system is being made. But the cardiac troponin reference ranges at Dana-Farber will remain distinct from those at Brigham, Dr. Jarolim says. "It would be counterproductive to use the low cutoffs. And it may be reasonable to use these higher cutoffs for monitoring cancer patients on potentially cardiotoxic therapies in other institutions, including Mass General Brigham."

With high-sensitivity cardiac troponin becoming more established in clinical practice, Dr. Jarolim envisions different cutoffs for various indications—a specific cutoff for monitoring cardiovascular safety of potential cardiotoxic therapies, for example, or for myocardial injury during noncardiac surgery. The latter in particular is needed, he says, because troponin elevations often occur in surgery, with some patients developing myocardial injury. "Among other factors, it's underdiagnosed because of the use of anesthesia. Patients have an MI and don't know it. So again, in this case, a different cutoff may be warranted."

In summing up, Dr. Jarolim said the "jury is out" on whether a single marker or risk scores should be used. "I would say one [biomarker] for now," he says. Whether that's NT-proBNP, BNP, or high-sensitivity cardiac troponin is unknown, as are the optimal cutoffs.

"However, we know that NT-proBNP and troponin go up with age significantly, and we know that women have less troponin but more NT-proBNP and BNP than men." That and having to adjust for BMI point to perhaps using troponin with the natriuretic peptides in some situations.

"We can create even larger risk scores" with additional markers, "which may have slightly better C-statistics, but I don't think that's a viable approach," he says.

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