For heart failure markers, what looks hopeful?

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November 2015—Cardiologist James Januzzi Jr., MD, sounds like he could be running for political office. *Are you going to settle for something different? Or is it time to demand something better?*

Those questions aren't aimed at voters; rather, he issued that challenge to his audience at an AACC session during the group's annual meeting this summer. When it comes to novel biomarkers for heart failure, being new is not enough. How do they perform relative to the natriuretic peptides? Do they add prognostic as well as diagnostic information? Are they useful for treating and monitoring patients?

Dr. Januzzi

Those are high bars, Dr. Januzzi concedes. But there's no shortage of candidates trying to make the leap. "When you start talking about novel biomarkers, it's like drinking from a fire hose," he says. He should know. As an associate editor at the *Journal of the American College of Cardiology: Heart Failure,* he sees a steady parade of markers aiming for coverage. "There are hundreds of possible choices," says Dr. Januzzi, the Hutter Family professor of medicine, Harvard Medical School, and senior faculty at the Harvard Clinical Research Institute. Indeed, he credits his editorial position to the fact that 50 percent of the submissions are about biomarkers in heart failure, some of which have never been looked at before. Someone has to help sort through the many first-in-human analyses. "It's up to us to try to identify which markers may have some legs, so to speak, and have some clinical value."

The clinical need is strong. Dr. Januzzi has seen his specialty's future, and it's troubling. "This is the battlefield for the next decade," he says. Heart failure is the only diagnosis in cardiology that is rising in incidence, he says, whether it's a primary or a secondary diagnosis in men or women. And with its five-year, 50 percent mortality rate in some patients, and a one-year 30 to 35 percent mortality risk after hospitalization, the burden on the health care system—let alone patients—is significant.

If ever there were a disease in which laboratory medicine and internal medicine/cardiology could team up to improve matters, heart failure is it, he says. It's "definitely one of those areas where precision medicine is going to be the future," says Dr. Januzzi, who also spoke to CAP TODAY in a follow-up interview.

And yet he's a bit of a doubting Thomas about new markers. "We may have gotten to the point where the science has outstripped our ability to understand how biomarkers in heart failure might be used," he says, noting that his lab had sent out a 200-µL aliquot, from which it planned to measure 65 biomarkers. "There needs to be a strong distinction between biomarkers that are biological curiosities versus biomarkers that may actually help us better care for patients." Driving the point home, he adds, "The natriuretic peptides are the gold standard and will remain so." (See story, page 66.)

Galectin-3 appears to be prognostic, for example, but doesn't seem to identify situations where a currently available therapy might improve outcome. "To me as a clinician, that's not going to be useful," Dr. Januzzi says. ST2, on the other hand, might be not only more powerful than the natriuretic peptides for prognosis, but also a predictive biomarker, allowing clinicians to choose from available or emerging therapies.

Clinicians will have their favorite markers, of course, and vendors aren't hesitant to tout their own entrants. Without careful vetting, menus of HF markers could start to resemble a gerrymandered voting district.

To avoid such a disjointed approach, Dr. Januzzi posits that heart failure markers should reflect process as well as presence. To bring a new marker to the bedside—to look beyond the natriuretic peptides and their diagnostic excellence—physicians need to understand what it says about the biology of the heart. What makes a marker abnormal in a patient?

As with the natriuretic peptides, it's important to kick the tires of any new marker. "How do we interpret it?" Dr. Januzzi asks. "What's abnormal? What is our goal with respect to therapy adjustments? For prognostic markers especially, can therapies improve the risk that these markers are telling us?"

Dr. Januzzi suggests prognostic can morph into predictive. By definition, a marker that is prognostic means higher event rates in patients with elevated values, he says. But prognostic doesn't necessarily mean that a therapy will retrieve that risk. What clinicians need are predictive markers—those that identify a risk that can be changed.

With all that in mind, he offers several ways of considering novel biomarkers that might be useful, particularly as they pertain to myocardial stretch, injury, and remodeling—the three primary mechanisms by which heart failure progresses.

Cardiac remodeling, Dr. Januzzi explains, is a process in which the myocardium is injured via fibrosis, cardiomyocyte hypertrophy, and apoptosis, ultimately leading to geometric change in left ventricular chamber size. "As the heart remodels, [it] increases in size, and the squeezing strength weakens. The problem with remodeling, which is the sine qua non of heart failure, is that it is not felt, generally, until a person is remodeled to the point where their cardiovascular performance worsens," he says. Physical exam tools won't detect it, and imaging isn't necessarily useful in identifying remodeling until it has already occurred.

That's where newer biomarkers may have their greatest potential. Dr. Januzzi notes that several biomarkers besides the natriuretic peptides can identify active remodeling. These are the so-called fibrosis markers such as galectin-3 and ST2, which are already incorporated in the 2013 ACCF/AHA Guideline for the Management of Heart Failure.

Galectin-3 is a macrophage lectin, secreted in the context of tissue injury. While not cardiac specific, it's useful as a heart marker, given that tissue injury is quite prevalent in the myocardium of heart failure patients. It sits at a pivotal position proximal to multiple changes that lead to the deposition of fibrosis in tissue. Showing one example in his talk, Dr. Januzzi notes,"Galectin-3 stains quite intensely in the interstitium next to the cardiomyocytes."

Dr. Januzzi traces matters back to the PRIDE study (van Kimmenade RR, et al. *J Am Coll Cardiol.*

2006;48:1217–1224—Dr. Januzzi is a coauthor), which involved the first in-human use of galactin-3 for heart failure evaluation and showed that concentrations could indeed be found in the circulation of HF patients. Though it had scant diagnostic value, initially the marker was seen as working well for short-term prognosis, he says. Later studies showed that in four years of follow-up, “we see in patients with acutely decompensated heart failure that galectin is measurable and appears prognostic.”

In chronic heart failure, as demonstrated in the PROTECT study—with which Dr. Januzzi is also involved—baseline values appear to be valuable, and serial measurements even more so. Most reassuring was the group of patients whose low measurements stayed low during the entire trial. The threshold for high and low in the study was 20 ng/mL, which is a bit higher than the FDA-approved threshold of 17.6 ng/mL. Dr. Januzzi and his colleagues chose the higher cutoff because, he says, “We wanted to use the strongest threshold that we could to examine the merit of galectin from a prognostic point of view.”

Galectin can also be measured in the general population, Dr. Januzzi says, since it’s present in nearly everyone’s circulation. Data from the Framingham Heart Study show that elevated galectin-3 predicts onset of heart failure in apparent normals.

The marker “seems great. What could possibly go wrong?” Dr. Januzzi asks, before delivering his cautionary tale about letting enthusiasm drive a new marker into clinical use. Galectin, as he notes, was prognostic in their initial studies, but he and his colleagues recognized early on—as others have since—that its value becomes “a little more shaky” once physicians use it as more than a univariable predictor. (In other words, “The moment you start folding in other important aspects of patient demographics, like age, renal function, and natriuretic peptides.”) Cautions Dr. Januzzi, returning to his initial point: “If we’re going to bring a new marker to the bedside, it has to add to what we already know about the patient and provide robust information about therapy decision-making.”

That latter point is critical, he says. “The therapeutic meaning of galectin-3 values remains unclear. I know of no data showing that in a patient with an elevated value that therapies can reduce the risk predicted by galectin-3 when it is above that threshold of 17-and-a-half or so.”

It’s not an abstract concern. Plenty of scientific pondering went into thinking about galectin’s ability to predict fibrosis, and whether spironolactone or eplerenone, which are mineralocorticoid receptor antagonists, had an antifibrotic effect. So rampant was this speculation, he recalls, that “Lecturers were getting up in front of large rooms at national meetings saying, ‘If your [patient’s] galectin is high, start them on spironolactone’—with no clinical data to support that argument.” In fact, data from several trials (HF-ACTION, COACH, PROTECT) show that galectin-3 levels do not predict benefit from this therapy, he says. “In our hands it actually predicted potential harm,” with more renal dysfunction in patients whose elevated levels were treated with mineralocorticoid blockers. (He adds, however, that direct galectin inhibitors are being evaluated in current trials.)

What about ST2? It has cardiac and extracardiac roles, including in allergic and immunologic diseases. It was first described, Dr. Januzzi says, during the search “for another BNP.”

It also interacts with interleukin-33, which has the favorable effect of blocking cardiomyocyte hypertrophy and fibrosis. But it’s a long way—and a lot of mice studies—from that fact to understanding the clinical meaning of ST2 concentrations. Dr. Januzzi says it adds to the natriuretic peptides for prognostication. When both NT-proBNP and ST2 are low, risk is lower; when both are high, risk goes up, according to data from the PRIDE study.

ST2 is also dynamic, which sets it apart from a number of other markers, including galectin-3 and highly sensitive troponins. Serial changes—at admission for heart failure and then postdischarge—are prognostically meaningful, he says, with those patients who have a robust change in their ST2 value having the best prognosis, compared with those without a significant delta in their ST2 value.

The marker has an apparent interaction with therapies, as do the natriuretic peptides (but unlike other markers). Data from Linz, Austria, show that patients with elevated ST2 levels who are treated with beta blockade in their

acute hospitalization for heart failure had significant attenuation in their risk. This is something that Dr. Januzzi and his research colleagues have also noted. Patients in the PROTECT study who had elevated ST2 concentrations and who were titrated to high-dose beta blockers profited the most from the intervention. Others have shown possible benefit from angiotensin receptor blockers and from mineralocorticoid receptor antagonists. Dr. Januzzi also points to evidence suggesting ST2 may predict onset of systolic hypertension in addition to the onset of clinical heart failure. Moreover, ST2 may be involved in remodeling not only in the myocardium but also in the vascular system. "Much like other biomarkers that are referred to as 'cardiovascular stress markers,' I think that's the best way to frame ST2."

No discussion of heart failure would be complete without the critical but maddening mention (they're still awaiting approval for use in this country) of highly sensitive cardiac troponins.

While their primary role will continue to be in diagnosing acute myocardial infarction, there could be a number of mechanistic reasons why troponins might elevate in patients with heart failure and, frequently, in patients without coronary artery disease, Dr. Januzzi says. "More and more when I lecture, I try to disabuse clinicians of the notion that troponins are a heart attack biomarker. They are a biomarker of myocardial necrosis." Since highly sensitive troponins can measure concentrations well below the lower measuring range of conventional troponins, he says, "We're picking up a lot of signals in patients with nonischemic cardiovascular disease that are quite prognostic but are independent of the presence of an ischemic event."

Physicians will need to figure out what elevations mean and how to act on the predicted risk. Preliminary data, at least, suggest that depending on the assay that's used, there may be value to serial measurements with highly sensitive troponins. There's also evidence to suggest that highly sensitive troponins, relative to the natriuretic peptides and soluble ST2, appear to be additive with respect to their prognostic meaning.

Says Dr. Januzzi: "With highly sensitive troponins, we now recognize that myocardial injury, even in the absence of a heart attack, is very common in patients with heart failure," with an elevated troponin level identifying high risk for an adverse outcome, including worsening heart function. "Unfortunately, we don't know if there are any therapies to rescue this picture. At present, it appears that troponins are prognostic but not necessarily predictive for therapy response."

Renal markers are intriguing to think about as well, and Dr. Januzzi urges physicians to start considering them in the context of heart failure. "Cardiorenal syndrome is a term that we throw around describing the interaction between heart dysfunction and kidney dysfunction." Creatinine is a biomarker, of course, as is estimated GFR and blood urea nitrogen. NGAL is another. Dr. Januzzi calls it reasonably good, and while other, better markers may emerge, it offers an example of how it might work alongside a traditional heart failure model. Used in conjunction, NGAL and a natriuretic peptide allow physicians to identify patients who are more likely to worsen their renal function in the context of acutely decompensated heart failure, compared with patients who have neither marker elevated.

Dr. Januzzi makes the important distinction between markers of kidney dysfunction and kidney injury. A person can have a fairly substantial amount of injury without loss of function, he explains; likewise, worsening function can occur without much injury. A troponin of the kidney, so to speak, would identify injury. To capture loss of function, markers such as cystatin C and beta-trace protein might be useful to guide physicians in making therapy decisions for heart failure.

As for other comorbidities in heart failure, Dr. Januzzi refers to neurohormonal derangements. Vasopressin, a hormone involved in salt and water handling, is, predictably, deranged in the physiology of heart failure, he says. Perhaps elevations in a biomarker reflective of vasopressin concentrations—specifically C-terminal provasopressin—might be useful for heart failure prognostication. "Sure enough, elevations in this marker, copeptin, appear to be quite prognostic," although it doesn't appear to be linked to sodium concentrations, he says. Nonetheless, patients with elevated copeptin, with a low sodium, have the worst prognosis. And vasopressin

receptor antagonist drugs are now clinically available.

“In short, we’re really encouraging drug developers to start thinking about how they can use biomarkers in a more targeted way—the so-called precision medicine approach to drug development,” he says. “This is the future.”

Heart failure specialists are eyeing the future from another perspective as well: They’re adopting the idea that the ultimate way to beat the disease is not to respond to its presence, but to prevent its occurrence.

Excellent data show that biomarkers may identify patients at high risk for developing heart failure, and that that risk may be improved with specific intervention, he says. Perhaps these patients can be identified early, at a biochemical level, before symptoms emerge, much like wildlife that sense an impending earthquake and flee the area long before the china starts bouncing out of cabinets.

And if that sounds more like hypothesis than strategy, says Dr. Januzzi, consider this: Two trials—Stop-HF and PONTIAC, each using a natriuretic peptide—have shown that higher-risk patients who have not yet developed prevalent heart failure “can be identified, targeted, and incident heart failure can be prevented,” he says. “This seems to provide proof of concept that we can start thinking about using markers in the primary care setting to prevent heart failure onset.”
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