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The PROVE-HF Study: Additional Proof for the Inclusion of the Manufacturer's Name When Reporting B-Type Natriuretic Peptide Results

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Guest: Dr. Peter Kavsak from the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario, Canada.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Both the high-sensitivity cardiac troponins and the natriuretic peptides have taken a prominent role in the clinical definitions and laboratory recommendations related to myocardial infarction and heart failure. However, noticeable differences persist in the test interpretation between these biomarkers.

The November 2022 issue of *Clinical Chemistry* published a paper where the investigators measured B-type natriuretic peptide in a subset of patients from a biomarker study with three different BNP assays and found that BNP measurements may modestly differ depending on the assay method used, particularly after a few months of treatment. The same issue had an accompanying editorial that noted these data provide additional proof for the inclusion of the manufacturer's name when reporting B-type natriuretic peptide results.

The author of that editorial is Dr. Peter Kavsak. He is a Professor in the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario, Canada. He is also a Fellow of the Canadian and American Academies of Clinical Biochemistry and Clinical Chemistry. We are pleased to have Dr. Kavsak as our guest in this podcast.

So, first of all doctor, is there a difference in how clinicians interpret the natriuretic peptide and high-sensitivity cardiac troponin?

Peter Kavsak: That's an excellent question, and the fact is that they do represent different etiologies in the fact that troponin is usually a marker of myocardial injury, whereas the natriuretic peptides are more of dysfunction. But in the heart of the matter is the fact is that interpretation for high-sensitivity troponin assays have really rested on the upper limit of normal as designated by the upper 99th percentile of a healthy population, and that's stratified by sex, male versus female.

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Whereas the different approach has been applied for the natriuretic peptides insofar that they don't use sex-specific cut offs per se using the upper limit of normal that clinicians would use to aid in the diagnosis, but they've used cutoffs that have been used from clinical studies. So for example, the universal heart definition has proposed 2 cutoffs in the hospitalized setting to help make a diagnosis of heart failure. Typically, the universal heart definition has proposed a cutoff as 100 nanograms per liter for the B-type natriuretic peptide, or the BNP, and for NT-proBNP, or amino-terminal part of proBNP, it's 300.

That's really in contrast with what clinicians are using high-sensitivity troponin assays to help identify myocardial injury and also for the diagnosis of myocardial infarction. So, there's a little bit of a dichotomy here in that both very important biomarkers that come from the heart, but how they are interpreted clinically is a little bit different based upon concentration cutoffs.

Bob Barrett: Okay, but for the natriuretic peptides, are they reported and interpreted the same way?

Peter Kavsak: Yes. So it was alluded to, there are real subtle differences and the fact is that the universal definition is trying to come up with a more simple common ground. But in actual fact, if you look at the clinical studies, the NT-proBNP assays actually use cutoffs to maximize the positive predictive value as well as negative predictive value, but more so for the positive predictive value, or the positive likelihood ratio for ruling in heart failure. And in doing so, what studies have demonstrated, at least for the NT-proBNP assays, that different cutoffs based upon age of the individuals presenting to the hospital acutely with possible acute heart failure will actually are helpful in ruling in patients.

That is in contrast to BNP, where there is no age specific cutoffs that have been demonstrated through clinical trials to be helpful to rule in. So, even though when we think of BNP and NT-proBNP, and they come from the same precursor protein proBNP, one would think that they should be interpreted the same way and data would have demonstrated the same type of utility, but in actual point in case if you look at the studies, what they've demonstrated is that using age specific cutoffs for NT-proBNP has actually been beneficial to rule in patients with heart failure. So even though they're from the same precursor protein, even clinically, they are used somewhat differently.

Bob Barrett: Your editorial implies that laboratories should report both the manufacturer, the B-type natriuretic peptide, and diagnostic test name along with the results. Why is that?

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Peter Kavsak: Yeah, well, part of that has to do with the PROVE-HF study. So that study, as published in *Clinical Chemistry*, looked at the utility of NT-proBNP initially to see if a decrease in NT-proBNP would be useful for patients that are being treated with sacubitril–valsartan. Now, that's a drug that is kind of a combination drug. The first aspect is sacubitril, which is a neprilysin inhibitor, and valsartan is an angiotensin receptor inhibitor. So these ARNI, or this type of drug, has been shown to improve patients with heart failure. And what the PROVE-HF study started to do at first was to show that a reduction in NT-proBNP correlated with improvements of cardiac function and volume at over 12 months of patients being treated with this drug. So very powerful information. And part of that is the fact is that NT-proBNP is not a substrate for neprilysin.

So, what has been shown is that BNP actually, as soon as it's released and it's the active protein that does the beneficial effects, it starts to get degraded. And there are several proteases that do that, but one of them is neprilysin. So this drug stops breakdown of BNP, and so what the PROVE-HF investigators now did is to look at the effect of patients on this drug, sacubitril–valsartan, and looked at longitudinal measurements of BNP with different BNP assays. And what they found was very striking, and the fact is that within the first 12 weeks, there was no change in BNP, which is very different from what we have observed with NT-proBNP, that they saw a nice drop with NT-proBNP and that correlated with improving function. But the first 12 weeks, there's really no differences between the different assays, the BNP assays.

Subsequently, after that, a couple of the assays actually started to see lower values as they're monitoring the patients' BNP value started to get lower and lower and lower, whereas one assay, there was no change in BNP assayed. This is an important information. The fact is, in one monitoring patients on long term treatment for heart failure, one doesn't want to be misled by misinterpreting BNP values if they're performed by different BNP assays. So the investigators of the PROVE-HF study even commented that the assays, even though they're reliable for monitoring, there should be some careful consideration when one wants to measure this with different assays. And in fact, this actually supports what the International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Biomarkers has recommended: to not use different natriuretic peptide assays in clinical practice, and further recommended that for monitoring purposes to use the same manufacturer's test.

This point is now solidified in the fact is what we see with the PROVE-HF study is that different BNP assays will give you different results and the interpretation may change to say if the treatments working versus not working if one is to mix and match different BNP assays.

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Bob Barrett: Okay, well finally, Dr. Kavsak, in your opinion, will it be important to also report the manufacturer name of the NT-proBNP assays?

Peter Kavsak: Yes, I do think in the future it probably will be, for a couple of reasons. One is the fact that there will be different companies now producing NT-proBNP assays. So that is on the horizon. The second thing about it is the fact is that much of our focus on the natriuretic peptides has been on higher concentrations, in trying to understand how to best optimize higher concentrations to say, rule in, for specificity, or to improve the positive predictive value or the positive likelihood ratio for ruling in heart failure.

So a lot of our focus for natriuretic peptide, especially NT-proBNP assays, have been on that end. But what we've also realized through recent studies in the literature is that lower concentrations are very important to a), identify low risk individuals, and here the cutoffs are well below what is used in the realm of heart failure to rule in and rule out, and so well below the 300 nanograms per liter cutoff. So at the lower concentrations, differences between the natriuretic peptide assays, especially the NT-proBNP assays, may exist.

And more importantly, as we start to probe more the biology of the natriuretic peptides, specifically that low, low concentrations may not always be so protective in different patient populations such as pregnancy and etcetera. There's an emerging area in that field. One has to start to consider that, if we were reporting perhaps the manufacturer name with the BNP assays, we ought to start to do the same for the NT-proBNP assays.

Right now, I think where the field is and how people are using natriuretic peptides, looking at the higher concentrations for ruling in and a little bit lower concentrations for ruling out, the differences for the BNP and NT-proBNP may not be so drastic. But when we get into monitoring patients and specific therapies and especially probing lower concentrations and regarding health outcomes, I really think that we'll probably start to see important differences and in this manner probably stating the BNP, the type of natriuretic peptide assay, the company that's providing it with that type of test, similar to what we do for the serum tumor markers, I think will be a beneficial step for improving patient care.

Bob Barrett: That was Dr. Peter Kavsak from the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario, Canada. He has been our guest in this podcast on using natriuretic peptide measurements in cardiovascular disease. His editorial, as well as an original scientific paper on B-type natriuretic peptide levels measured by three

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different assays appear in the November 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.

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