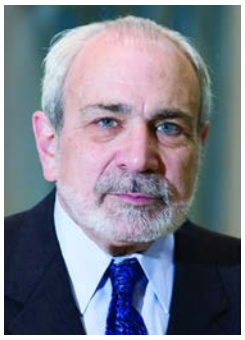
Clinical Chemistry

Role of BNP vs NT-proBNP Testing in the Age of New Drug Therapies: Sacubitril-Valsartan



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Guest: Dr. Allan Jaffe is Professor of Medicine in the Department of Cardiovascular Medicine and Professor and Chair of the Division of Core Clinical Laboratory Services in the Department of Laboratory Medicine and Pathology at the Mayo Clinic.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Sacubitril/Valsartan, known as Entresto, is a new dual drug therapy that includes an angiotensin receptor inhibitor and is indicated to reduce the risk of cardiovascular death and hospitalization in patients with chronic heart failure. Since its approval for the treatment of chronic heart failure with reduced injection fraction, a commonly raised question is whether treatment with this drug challenges the use of B-type natriuretic peptide, or BNP, testing compared to the N terminal proBNP assay because Sacubitril may interfere with BNP clearance. The clinical and analytical studies addressing this issue are limited, along with the fact the diversity of both BNP and NT-proBNP assays used in clinical laboratory practice have not been adequately evaluated in clinical trials or studies to provide an evidenced-based on final decision as to what assay or assays should be used or eliminated from use when a patient is on Entresto.

In the September 2019 issue of *Clinical Chemistry*, a Q&A feature titled, "Role of BNP vs NT-proBNP Testing in the Age of New Drug Therapies" asked five experts with different roles in this field to discuss this issue. The moderator for this Q&A feature is Dr. Fred Apple, and one of the experts participating is Dr. Allan Jaffe, who is professor of medicine in the Department of Cardiovascular Medicine and professor and chair of the Division of Core Clinical Laboratory Services in the Department of Laboratory Medicine and Pathology at the Mayo Clinic. Dr. Jaffe is our guest in this podcast.

So, Dr. Jaffe, do you think the difference between BNP and NT-proBNP measurements in patients receiving Entresto are only an early phenomenon because they both seem to be reduced over time?

Dr. Allan Jaffe: Well, part of that true and they do seem to be reduced over time, but I think the implication that has been drawn from the fact that BNP seems not to go down and if anything

goes up a little bit initially, has been to suggest that the mechanism of action of the drug is really through BNP. And in point of fact, there's recent data to suggest that the increases in BNP that are seen has to do with increases and glycosylation of the proteins which make them difficult to detect by some of the BNP assays compared to the NT-pro assay, and that's why those minor changes occur. So, I don't think those changes say anything about mechanism. They do provide a little bit of a confound when one starts the drug, if one wants to use natriuretic peptides to follow one's response to the drug, but it's short term and relatively modest.

Bob Barrett: So, do you believe that those differences between BNP and NT-proBNP measurements will lead to diagnostic confusion in patients taking Entresto if only BNP were to be used, and if so, in what clinical situations?

Dr. Allan Jaffe: I think it shouldn't as long as clinicians understand that initially there may be a relatively sluggish response for BNP. Over time that seems to change, and one can subsequently, once one has a new baseline, again use BNP because the dynamic range of the assay is fairly large. So if there's decompensation of congestive heart failure, there should be a big signal, and similarly if there's marked therapeutic change, there ought to be a marked reduction. And that's one of the advantages of natriuretic peptides, and in point of fact, the clinical data provided from the PARADIGM-HF Trials suggested if one eventually looks, one can use both prognostically. So, I think if one is careful, one can avoid confusion.

Bob Barrett: Tell us, do the results of GUIDE-IT influence how you feel about the differences between BNP and NT-proBNP in the patients on Entresto?

Dr. Allan Jaffe: Not at all. The trial was a trial that attempted to look and whether or not one could use natriuretic peptides in general, and NT-proBNP in specific, to monitor therapy and decide how much more aggressive one needed to be. In point of fact, largely the data seemed to suggest because the clinicians who were not using the NT-pro guided therapy were very aggressive with their uptitration medications, the trial was null. That simply says that using natriuretic peptides to monitor therapy doesn't work in sophisticated centers where one is willing to push high doses of drug from clinicians who are used to dealing with heart failure patients. That would include Entresto in my opinion.

Bob Barrett: Well, given the lack of harmonization of BNP assays in general, do you think that knowing the specific NT fragments that are influenced by Entresto would help clarify

how to best use assays to monitor the use of this medication?

Dr. Allan Jaffe: Well, in the long run if we could understand them, they would likely be very helpful. As of right now, the problem with looking at the fragments is that it appears that everyone has a relatively unique individual pattern. And in addition, our ability to separate them is not sufficiently sensitive, so that we don't detect all the fragments in all patients. My suspicion would be that if we could look at this entire panoply of fragments that there would be diagnostic and therapeutic information in it, but it's certainly not there now. My suspicion also is that the insights that occur are likely to be important biologically and might well lead to new therapy if we could understand how to change one fragment to another.

Bob Barrett: Well, finally Dr. Jaffe, are there other commercial or novel biomarkers that would be clinically useful to measure in patients on Entresto therapy?

Dr. Allan Jaffe: Well, there are several. The first is ANP and there's a nice assay for proANP. It appears that Entresto, Sacubitril/Valsartan, actually has a much greater effect on ANP than BNP. In addition, there are assays that had been developed for neprilysin which is thought to be one of the important mechanistic proteins that's affected. These drugs, Sacubitril in particular, is a neprilysin inhibitor and it's the enzyme that breaks down a lot for vasoactive peptides. So, measuring neprilysin might well be helpful as well. There are some other compounds that are affected by neprilysin and therefore by neprilysin inhibitors, both substance P and adrenomedullin. And they would be interesting to look at, and they've been looked at only very preliminarily. Finally, there are a paucity of data about ST2 and galectin-3 that are sort of have become more commonly used markers nowadays. It's not clear how well they could be used. Galectin-3 doesn't change tremendously. ST2 tends to change more, so one might have a better signal with ST2, but the data are yet to be developed.

Bob Barrett: That was Dr. Allan Jaffe, Professor of Medicine in the Department Cardiovascular Medicine and Professor and Chair of the Division of Core Clinical Laboratory Services of the Department of Laboratory Medicine and Pathology at the Mayo Clinic. He's been our guest in this podcast from *Clinical Chemistry* on the role of BNP vs NT-proBNP testing in the age of new drug therapies. That Q&A feature appears in the September 2019 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.