Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/emerging-data-on-new-therapy-combinations-for-hfref-raising-clinician-awareness/12691/

Released: 06/30/2021
Valid until: 06/30/2022
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Emerging Data on New Therapy Combinations for HFrEF: Raising Clinician Awareness

Announcer:
Welcome to CME on ReachMD. This activity, entitled "*Emerging Data on New Therapy Combinations for HFrEF: Raising Clinician Awareness*" is provided by Merck.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Armstrong:
Good day, and welcome to this second and final program in the series on worsening heart failure, where we are exploring emerging data on some new therapies and combinations in patients with heart failure and reduced ejection fraction. I'm Paul Armstrong, from the University of Alberta, cardiologist and professor of medicine, and I'm delighted to welcome Justin Ezekowitz, a friend and colleague, who is also a cardiologist and professor at that university, and co-director of the Canadian VIGOUR Centre. We're here to talk about some of the new evidence that were recently presented at the American College of Cardiology meeting and how it might reflect on our understanding and care of patients with worsening heart failure.

Justin, great to have you with us and thanks for joining.

Dr. Ezekowitz:
Thank you, Paul. It's really a pleasure to be here today.

Dr. Armstrong:
This issue of worsening heart failure has taken on a new profile and perhaps expanded understanding. Why is this relevant to the care of patients with heart failure? How big of a problem is it, and how should we address it? What have we learned that is important as we move forward?

Dr. Ezekowitz:
So we really need to focus in on this group where they have great morbidity and mortality risk, they are coming back to hospitals and are being rehospitalized, and we need to prevent that with whatever therapies that are in front of us, including medications or other nonpharmacologic therapies.

So, Paul, the risk of a patient is really amplified after each hospitalization, such that when they are hospitalized once, there's some risk. But then there's risk after every subsequent hospitalization, so when they're coming back again and again, the risk is amplified over time. So this is a group of patients who we really need to focus in on and really understand how do we treat these patients better. Now we've had huge advances in pharmacotherapy, and I want to just tweak your brain there, Paul, about what do you think are the most exciting, new developments in HFREF, or heart failure with a reduced ejection fraction, and where do you think the newer kind of molecules – such as soluble guanylate cyclase stimulators – where do they fit? Is vericiguat going to lead the way, or is it one of many other molecules out there?

Dr. Armstrong:

So, Justin, thanks. The new molecule, soluble guanylate cyclase stimulator vericiguat, has really, I think, broadened the landscape for heart failure therapy. And it's been my privilege to work with you and others in the VICTORIA trial to investigate whether a once-a-day stimulator of soluble guanylate cyclase, that not only turns the amplifier on for GMP and protein kinase G, which we know is critically important for both myocardial and vascular function, but also in an environment where nitric oxide is diminished, this new therapy and pathway really provides a new avenue for therapy.

Our primary endpoint in VICTORIA was the composite of cardiovascular death and heart failure hospitalization, and we did achieve a significant reduction. Ten percent relative seems modest, but when you look at the extraordinary event rate in this population, with over a 37% annual impact on cardiovascular death or heart failure hospitalization, this absolutely translated into a reduction of 4.2 on the primary endpoint per 100 patient years. We saw a trend, but not a significant reduction in cardiovascular death, and a significant reduction in heart failure hospitalization in this population. When we examined some of the prespecified subgroups, a few things were of particular interest. One, irrespective of the functional class – remember I said over 40% were in the advanced functional class – vericiguat's efficacy was equally effective in the class 1-2 and the 3-4s. Importantly, we were able to get at least 14% of patients on sacubitril/valsartan, which was just coming in as baseline therapy at that point in time, and the efficacy again was equal, whether or not patients were on baseline sacubitril/valsartan. Patients had a low GFR in many instances, and we allowed patients down to less than 30, above 15, of a GFR, and efficacy was equal across GFR groups. And the story of natriuretic peptide we want to come back to because this is of particular, I think, interest in this study.

Importantly as we think about context, across the PARADIGM, DAPA-HF, and more recently, the GALACTIC trial, which studied the myosin activator omecamtiv mecarbil, we think about how do the endpoints compare since the endpoint of cardiovascular death and heart failure hospitalization was common across all 4 trials. So in the PARADIGM situation, the comparator endpoint was 13.2%, about one-third of VICTORIA's 37.8. In DAPA-HF, it was about a half or less, and in GALACTIC-HF, the comparator arm was 26%, which is about 50% less than VICTORIA.

So if we set that across our scale of comparisons and then say, "Well, what about the rate reduction, the number of patients that were actually – per hundred patient-years benefited?" And it was 2.7 in PARADIGM, 4.0 in DAPA-HF, 4.2, respectable, in VICTORIA, and 2.1 in GALACTIC-HF. Again, when we look at cardiovascular death, 1.5 in PARADIGM, 1.4 in DAPA-HF, and 1 in VICTORIA, and no change in GALACTIC. So the absolute rate reduction on first hospitalization was also meaningful – 1.6 in PARADIGM, 2.9 in DAPA-HF, 3.2 in VICTORIA and 1.6 in GALACTIC.

So I think this perspective really does provide an understanding that on a background of evidence-based therapy the new soluble guanylate cyclase stimulator has some traction and something to offer.

But what I'd like to do now is return to the story of natriuretic peptide and, in particular, the work that you've undertaken. So, Justin, please give us your insights on the story of natriuretic peptide.

Dr. Ezekowitz:
Thanks, Paul. It's quite remarkable to put this overall VICTORIA trial in context of the other trials, and one of the things that really helps us understand the differences is some of the biomarkers we measure in practice, with NT-proBNP being, of course, the one that we really do focus on in heart failure trials and also in clinical practice. Now the VICTORIA trial was relatively unique in the population it enrolled but also in how it did the analyses around the natriuretic peptides, so I'm going to come back to this point of how we did the analysis. You know, in the main paper of VICTORIA and in the main analysis, we looked at NT-proBNP at the very baseline, when patients were enrolled into the trial using the quartiles of NT-proBNP. And even by the first glance of that, we can see that the patients enrolled had very high natriuretic peptides compared to some of the other populations in other clinical trials such that the median NT-proBNP is in the 2800s, and the top quartile is 5,314 pg/mL, so a pretty high NT-proBNP level. And it looked like there was some statistical heterogeneity in the efficacy of vericiguat based on those quartiles of NT-proBNP. Now that's really important to look at, and it's a rough guide as to something we wanted to look at. These were FDA mandated as part of the clinical trial, but what if we took some advanced data analytics and really looked at this overall question about NT-proBNP, the relationship to clinical outcomes, and then the relationship to the efficacy of vericiguat? And this is really striking as to what we found.

The first part about it is that we used the continuous value of NT-proBNP and looked over the spectrum of all the patients and found that the bulk of patients are really clustered under 5,000 or even 8,000 pg/mL, and such that the data told us where those cut points were at 4,000 and 8,000. And so when we looked using those data-derived cut points, we identified that vericiguat had a greater efficacy in the lower ranges of NT-proBNP, such that for patients less than 4,000 pg/mL for the primary endpoint, the hazard ratio was 0.77, so a 23% reduction in the primary outcome and a very striking difference across those ranges of NT-proBNP.

We further took this out to 8,000, so a 15% relative risk reduction in the primary endpoint, and then we broke it down into the components of that primary outcome – cardiovascular death, heart failure hospitalization, and so a very similar finding. And so when we

look at this across the spectrum, it's a much more sophisticated method and gives us much more deeper insight into how we apply this.

We also can look across the spectrum of different clinical trials. PARADIGM and DAPA are the two in which we can compare to, and they really do show that in PARADIGM, for example, an NT-proBNP at the median value was around 1,600 pg/mL, and DAPA was about 1,400 pg/mL, so a full thousand pg/mL less. Then we really have to put this in context to where these trials would fit. And in fact, those populations really fit under the 4,000 pg/mL bar, and in fact we have very similar results when we look at both the endpoints of cardiovascular death, heart failure hospitalization, and the combined cardiovascular death and heart failure hospitalization.

Now fast forward to thinking about, what do we do with this information? It really does tell us that there is an overall trial efficacy of vericiguat, but even in a group with a lower NT-proBNP value, they are likely to derive even greater efficacy from being on vericiguat compared to placebo in our case. So from a clinical practice standpoint, that may be a sweet spot where we want to offer this up to our patients early on and consider it for other patients down the road depending on other clinical scenarios.

Dr. Armstrong:
So really neat data, Justin, and I know that you've explored and thought about what kinds of patients might be in this rather high-risk group beyond 8,000. What have you learned about who's there? What are the clinical profiles that the audience might be interested in learning about?

Dr. Ezekowitz:
Right. Well, we first thought, well, anybody with a high NT-proBNP might just be much sicker or some other variable, but it is a mixed group, and it's not as clear as we initially thought. There are patients with slightly lower or slightly worse renal function, somewhat slightly higher NYHA class, but some of the typical variables weren't showing up as the risk. Now they do have overall higher risk from a MAGGIC risk score perspective, and so we are having to explore that, but there's no one factor that determines that level, so that just tells us that this is a multifactorial peptide that we need to look at in context with other factors of that patient.

Dr. Armstrong:
For those just joining us, this is CME on ReachMD. I'm Dr. Paul Armstrong, and I'm here today with Dr. Justin Ezekowitz. We're discussing worsening heart failure and emerging data on heart failure with reduced ejection fraction and soluble guanylate cyclase stimulators, recently presented at the ACC scientific sessions.

Dr. Ezekowitz:
So, Paul, maybe we can move on from my favorite, NT-proBNP, and on to other biomarkers that are out there, the troponin value. We're all very used to seeing troponin, especially in the emergency department, hospitalization around acute coronary syndromes, but in heart failure, it's also quite important. And one of the abstracts that was presented from VICTORIA looked at troponin T and looked at it in the same population of VICTORIA. I wonder if you could really speak to what was found in that troponin T analysis and how it really will play a role in HFrEF when we think about therapies.

Dr. Armstrong:
So thanks, Justin. Our friends and colleagues at Inova, and Chris DeFilippi working with Chris O'Connor, have helped us understand that these patients with worsening heart failure also have high ambient troponin levels. So when we looked at troponin T, we found that the median value, irrespective of coronary disease, will come to was 30 ng/mL, and because of the insights that you've just provided on natriuretic peptide, we then asked ourselves, well, if we've got a biomarker that is already helping us understand potentially the windows of opportunity of therapy, is there another one based on troponin that reflects myocardial injury that might be useful?

And indeed, when we look at the treatment effect on the primary outcome, there did appear to be a trend towards a greater benefit at lower values of troponin all the way up to perhaps 80% or 90% of patients. But of particular interest was when we looked at cardiovascular death as opposed to heart failure hospitalization. There, we saw a statistically interactive effect of vericiguat in patients with troponins all the way up to, again, about 80% or 90% of the values that these patients had. So now we have a second biomarker that potentially provides additional insight, and as you might expect, the higher the troponin, the higher the risk of the outcome.

So I think now we've got another window to look through relative to that marker, and obviously we look forward, given the exciting learning opportunities from VICTORIA, to come back and explore with you and others whether the relationship between NT-proBNP and cardiac troponin will yield further insights into not only risk, but treatment efficacy.

Dr. Ezekowitz:
Thanks, Paul. I mean, this is fascinating as they may predict different outcomes but be quite important for the same patient. And those are levels that people are walking around with, in terms of the troponin T values. So it's very different from the emergency department troponins we look at.

Now if we turn our attention from troponin and heart failure to thinking about coronary artery disease, there was another abstract that was really looking at the history of CAD or looking at prior PCI, prior bypass. Just talk me through what was found there in terms of coronary disease and the VICTORIA trial.

Dr. Armstrong:
There were about 53% of patients with coronary disease, and we strictly defined that as patients with prior MI or PCI or CABG, and we found that indeed if you had coronary disease – and understandably, that goes with some comorbidities, more male sex, more diabetes, diminished renal function – they had a significantly more, about a 23% more relative risk of their effect on heart failure and cardiovascular death. Interestingly, when we saw cardiovascular death as opposed to heart failure hospitalization, it did appear that there was a greater impact on cardiovascular death than heart failure hospitalization in the presence of coronary disease. And this was true even though devices were more commonly used with coronary disease.

So I think the take-home message here is that because the majority of our patients do have coronary disease, we recognize that they bring special risk to the problem. But importantly, vericiguat's efficacy is unimpaired. It works equally well in those patients with and without coronary disease, which is a great take-home message.

So I would like to conclude this podcast by simply asking, where in the context of all that we've learned and new foundational therapies does vericiguat fit? I think the exciting thing is that we have a new arrow for the clinical quiver for patients with worsening heart failure that is not going away, and the residual risk, as you've heard during this podcast, is very substantial. In patients who are unable to tolerate standards of therapy, vericiguat is very safe and well tolerated as it relates to blood pressure, heart rate, renal function, and potassium. No need for laboratory monitoring. It seems to be particularly effective in patients below a natriuretic peptide level of 8,000, and I think it offers, then, an additional option for clinicians to care for their patients.

So I want to thank you, Justin, for this conversation. It's been a pleasure to converse and discuss these new data, and we look forward to future opportunities to learn about best care for patients with worsening heart failure.

Dr. Ezekowitz:
Thank you, Paul. Great participating in this with you.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Merck.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.