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New Therapies Offer Improved Outcomes in HFrEF Management

Announcer:
Welcome to CME on ReachMD. This activity, entitled "*New Therapies Offer Improved Outcomes in Management of Heart Failure with Reduced Ejection Fraction"* is provided by Medtelligence and is supported by an independent educational grant from Merck.

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Here is Dr. Javed Butler

Dr. Butler:
Finding the optimal treatment strategy for patients with chronic heart failure with reduced ejection fraction can be challenging. However, novel mechanism of action and recent therapy approvals are offering new opportunities for these patients.

Welcome to our discussion entitled, "New Therapies Offer Improved Outcomes and HFrEF Management." I am Dr. Javed Butler, and I am joined today by Dr. Paul Armstrong. Welcome to the program, Paul.

Dr. Armstrong:
Good to be with you, Javed, on a subject that we both have been concerned about for a long time.

Dr. Butler:
Yes, so these patients with heart failure and reduced ejection fraction, I mean, they are a really challenging group of patients. What makes this patient group such a high-risk patient group, and what are the unmet needs in this patient population?

Dr. Armstrong:
So maybe we can start with reflecting on the commonality of heart failure and the incredible increase in this population with the advances in other therapeutic endeavors. We know that there's a period of stabilization on good medical therapy, but we also recognize that as many as 1 in 5 of these patients have a worsening event where increased dyspnea, fluid accumulation, and fatigue require either outpatient administration of IV diuretic or rehospitalization. And once that occurs, there's an extraordinary price that's paid as it relates to morbidity, recurrent hospitalization – in as many as half within a month or 2 – and mortality, such that at 5 years, half of these people have died. So this is a huge problem, and it has occurred even in the space of good medical therapy, and thus I think there is an extraordinary need, an unmet need to address this growing population and the implications for patient care, quality of life, and the healthcare system and the costs that ensue.

Dr. Butler:
So what's exciting in this respect is that, one, obviously we have a high-risk patient population and that that we need to do some targeted research and find some therapeutic options for this high-risk group of patients, but we have had a long run, about 2 or 3 decades of, sort of, traditional neurohormonal modulation for improving outcomes for patients with heart failure with reduced ejection fraction, but now we are moving into some really novel pathways.

Dr. Armstrong:
Exactly. The neurohumoral blockade, the vasodilators, the inotropes that we've had are now – I think there's an opportunity to explore a

new mechanism and a new pathway, and I'd like you to define what we've learned together on that subject over the last while.

Dr. Butler:
We will be talking a lot about this medication called vericiguat, which works on the soluble guanylate cyclase pathway so let's look at a video describing how this mechanism of action works.

[Animation plays.]

So that was an interesting video. So, Paul, let's move on with our discussion.

So basically, nitric oxide has literally ubiquitous signaling all over the body, whether it's your heart, lungs, kidneys, the skeletal muscles, nitric oxide binds with guanylate cyclase and have multiple protein – protein kinases, phosphodiesterases, ion channels through which many of the normal physiologic functioning occurs. In patients with high oxidative stress, like heart failure, the nitric oxide is not very bioavailable, and it's actually shunted. So, one, nitrates tend to – you develop tolerance over time, but also, the nitrate which is available is then converted in the cases of oxidative stress, and it does not become available for soluble guanylate cyclase activation.

The beauty of this molecule, vericiguat, is that it binds with the soluble guanylate cyclase in the cytoplasm, and it has dual function. One, it can directly stimulate the soluble guanylate cyclase irrespective of the need of nitric oxide. But whatever little nitric oxide you may have bioavailable, it increases the sensitivity of the soluble guanylate cyclase for that nitric oxide, which then enhances the downstream signaling convergence of GTP to cGMP and subsequent PKG-signaling pathway, and as I said, there is a lot of cardiovascular potential beneficial effect with this pathway.

So now that we know that this pathway is important biologically and we actually have an agent that can modulate this pathway which is adversely affected in cases like heart failure or other oxidative stress states, can you tell me a little bit about the study that that was done with vericiguat, VICTORIA trial? What were the patient population that was studied? What were the results? Can you expand on that a little bit, Paul?

Dr. Armstrong:
What we did in the VICTORIA trial was we identified this population of heart failure with worsening events and reduced ejection fraction. Two-thirds of them were within 3 months of a hospitalization. Another third, another sixth with 3 to 6 months and another sixth with IV diuretics. They were patients that were on good medical therapy, and what we did was, in fact, choose patients who had a natriuretic peptide that was elevated disproportionate to many other studies. So they needed a natriuretic peptide, NT pro-BMP of over 1,000 in sinus rhythm or over 1,600 in atrial fibrillation. And we accepted patients with blood pressures above 100, and we also accepted patients who had lowered GFRs, so renal function down to 15 mL per minute, and we randomized them then to patients with vericiguat or placebo. There were 5,050 patients in the trial to achieve our primary objective of either a recurrent hospitalization or cardiovascular mortality. We quickly up-titrated them over 12 weeks to the target dose of 10 mg of vericiguat and we also measured natriuretic peptide with baseline. And as we discussed with the FDA, it was required that we prespecify that we would look at the outcomes according to quartiles of baseline natriuretic peptide.

And we achieved our objectives within 10.8 months, sooner than expected because of the very high rate of morbidity and mortality in this study. And I'm pleased to report that we achieved our primary objective, which was a statistically significant reduction in the time to first cardiovascular death or heart failure hospitalization. The hazard ratio, modest, was 0.90, but because the event rate was in excess of 38% at 12 months, it turned out to be a very efficient form of therapy. We achieved a risk reduction of 4.2% per year and were able to then translate this into a number needed to treat of 24. The cardiovascular death did not achieve statistical significance, but was concordant, hazard ratio of 0.93, and as you would expect, the heart failure hospitalization was significant with an absolute risk reduction of 3.2 per 100 patient-years.

Naturally, Javed, we looked across a variety of subgroups, prespecified subgroups, and I'll really just focus on 3 of these. One, to say that irrespective of functional class 3/4 or 1/2, the treatment was effective. And that's important because it sets it apart from some other trials. Secondly, irrespective of whether patients were on sacubitril-valsartan or not, they achieved benefits, so that was an important signal in relationship to the novel pathway that you've just reminded us of, through which vericiguat works.

And then, importantly, as we looked across the quartiles of natriuretic peptide, the first 3 showed highly significant effects on the outcomes. But the fourth quartile did not achieve therapeutic benefit. That, in turn, led us to pursue this question in much more detail. And we've gotten a continuous look at the natriuretic peptide and, lo and behold, at a level of 4,000, a natural cut point in the continuous analysis, we see event rates, reductions in both death and in heart failure hospitalization that are equal to or even better than PARADIGM and DAPA-HF, whose patients also, for large part, were within this range of 4,000 where two-thirds of our patients were. And the treatment benefit went all the way up to 8,000. We're comfortable now that we've got, I think, a nice range of natriuretic peptide to understand how best to use this therapy.

Just to underscore, this is a therapy that was well tolerated, very few in the way of adverse effects, minimal effect on symptomatic hypotension and syncope, and a mild effect in 2% of the people with anemia that was not troublesome beyond 16 weeks and we think was not related to blood loss or hemolysis. So I think it's a safe therapy; it's easy to use once a day, a 10-mg dose, so no worries there about the dose. And of course, because of the freedom from hyperkalemia and impaired renal function, it circumvents the need for frequent laboratory monitoring, and as we've underscored, it can be added to evidence-based therapy.

And so the obvious question is, with this new arrow in the quiver, where does it fit in your mind as we think about guidelines emerging and future therapies?

Dr. Butler:
Yeah, we are in a good place in heart failure with reduced ejection fraction because there's a lot of trials that have come out. But I want to actually highlight something that you said, and that is that all of the other trials, barring one that was done, were actually in patients with heart failure not targeting worsening heart failures.

Yeah, I mean, one thing that you mentioned that, again, I really want our colleagues listening to this program to realize is that we in this trial, went down to GFR of 15, really other than empagliflozin, we have no, not much data where we have studied patients with heart failure with GFR less than 30, so going down to the GFR of 15, that's unusual, and that also opens up a vulnerable population where we don't have much evidence.

So your question to me was, where do I think this fits into the management of patients with heart failure with reduced ejection fraction? So I think the straightforward answer is – so first of all, I don't want to sort of bypass the guidelines, and I'm sure that the guidelines will come out and we'll see what our professional society colleagues are saying, and I am sort of looking forward to those guidelines. But in the meantime, I think a straightforward answer is, what the indication is given to this therapy by the regulators which is patients with worsening heart failure, ejection fraction less than 45% for a cardiovascular death or heart failure hospitalization reduction, so that's pretty straightforward. But couple of, sort of, other interesting questions that come up. One is that with a BNP levels or NT-proBNP levels less than 8,000, there was more benefit, also cardiovascular mortality benefit at lower levels. That becomes a pretty attractive option so that if you actually have a patient who does not have worsening heart failure, but because of potassium, because of blood pressure, because of kidney function, for whatever reason, is unable to tolerate standard medical therapy, and you have this option available and it is well tolerated, should this drug be used? So I don't know. Perhaps we need to do more research in that patient population, but that really opens up another opportunity. But I would say for worsening heart failure, patients with low ejection fraction, this is the next step in that patient's journey.

So that's it. We are out of time. I want to thank our audience and offer a special thank you to my colleague, Dr. Paul Armstrong, for sharing his thoughts with us today. It was great speaking with you.

Dr. Armstrong:
Indeed. Enjoyed it. Good to be with you.

Announcer:
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