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Ready, Set, Act! Opportunities to Address Persistent Unmet Needs in Patients With HFrEF: A Case-Based Discussion

Announcer:
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Dr. Greene:
For patients with heart failure with reduced ejection fraction, quadruple medical therapy has been a tremendous advance and proven to substantially reduce the risk of death and hospitalization. Yet HFrEF is an extreme-risk condition, and even with quadruple medical therapy, there is a very high residual risk of poor outcomes. Remember, we're talking about a condition with a prognosis comparable to many forms of cancer. Moreover, when we think about quad therapy, many patients cannot tolerate one or more components of the quad therapy, and discontinuation rates for these drugs in clinical practice unfortunately remain high.

However, fortunately, there's also established evidence and emerging evidence supporting the use of additional therapies beyond the traditional pillars of HFrEF care, and that list includes soluble guanylate cyclase stimulators like vericiguat. But these treatments remain underutilized in our patients with HFrEF.

Today, we will review how to develop patient-centered plans to maximize cardiovascular protection for our patients with HFrEF, and in doing so, keep our patients at optimal health for as long as we can.

This is CE with GLC, and I'm Dr. Stephen Greene.

Dr. Lam:
And I'm Dr. Carolyn Lam.

See, Steve, this is great, but let's make it real. Let's use a case. I heard that you've got a recent case that you'd like to share. Let's discuss it.

Dr. Greene:
So this was a 70-year-old gentleman who just moved to my area, now establishing care for his longstanding chronic HFrEF diagnosis. So he has an ischemic cardiomyopathy, EF at 30%, had an MI several years ago, and has had residual LV dysfunction since that time. Has an ICD in place, and I see that he is on quad medical therapy. He's on metoprolol 200 mg once a day. He's on spironolactone 25 mg a day. He's on a medium dose of sacubitril/valsartan, the 49/51 dose, and he's also on dapagliflozin 10 mg daily.

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I see that he's got a blood pressure which I would say is marginal, 105 systolic. He has a heart rate of 65, and again, that's in the context of the medical therapy that I mentioned. I see his recent lab values. He's got an NT-proBNP of 1200, and it's been about 1200 for the last few times it's been checked as an outpatient.

He was hospitalized for heart failure about a year ago, but has been doing relatively well since then, and is just here because he knows he needs a heart doctor and doesn't really have any major complaints today. I would call him probably about NYHA class II.

So I don't know, Carolyn, does this kind of resonate with you, some of these people that we're seeing in with chronic HFrEF in our clinic?

Dr. Lam:
Absolutely, and that just shows what a global problem HFrEF is. I mean, I practice in Asia, but that kind of patient could have moved to my area of the town.

So elderly gentleman, ischemic HFrEF. One thing I would say may be a bit unusual: his therapy is, frankly, pretty darn good for real world. I mean, he's already on quad with an ICD. I have to tell you, and this is with a little bit of my eyes lowered in shame, that if we look at the epidemiology of HFrEF, and we've done that across Asia, very few patients are actually receiving triple or quad therapy, and even fewer have ICD, and even fewer have the doses that you already mentioned.

So I think all of this really points to a couple of things that you'd already said. First of all, there's GDMT, and then there's what we ought to be doing. Okay? And we're not reaching guideline-directed medical therapy. We look at any real-world series, and you realize—I think part of it is a patient reason, like you said, there are reasons we can't start or up-titrate. Part of it, unfortunately, we have to recognize, is physician reason, and it's this kind of patient that's particularly dangerous—I'll say this carefully—because we get complacent.

Now, if we really, really are honest with ourselves, though, there's room to improve, right? I mean, we can see in this patient, he says he's okay, but you yourself admitted New York Heart Association class II. That's without pushing. But if you were to actually push, do a 6-minute walk, ask him, hey, can you actually do everything that you want to do? You realize that we kind of underestimate the patient's functional status, and they actually restrict their activity because they can't keep up. So I now realize, and so have the guidelines, that we cannot think of a patient with HFrEF as stable.

Just as we are always on the lookout in a patient with cancer for them getting worse or going to a worse stage, we need to view our patients with HFrEF the same way—not complacent—that even when they're not complaining yet, be sure to give them everything we can, urgently.

Steve, I don't think you mentioned his creatinine, and I'd love to know what you did.

Dr. Greene:
Yes. So yes, I should have mentioned some of his other lab work.

So we repeated his NT-proBNP, and it was also again around 1100 or so, so roughly where it had been previously. His creatinine and eGFR in the 50s, so I mean that's typical, what we see. He's 70 years old and definitely has some chronic kidney disease, but fortunately not so, so bad there, and his potassium was not an issue, in the mid 4s.

So what do we do for this guy? So I'm meeting him for the first time, and I'm trying to establish a relationship. And he's, of course, not really expecting to do anything different. He's like, "I've been fine. You're a new guy. Why would you want to rock the boat on anything?" So this is what I told him. I was like, well, I'm very happy that your symptoms are relatively minor and that he was not on a standing loop diuretic. That's a good thing. But I told him let's just look at this NT-proBNP, for example: 1100. I mean, that, to me, I use that as a messaging tool with my patients, for example, when I'm trying to just establish how serious we need to take this. Even though you're feeling fine today, we cannot misconstrue clinical stability today with meaning you're at low risk. And it kind of ignores this whole idea that sudden death is the leading cause of death among chronic ambulatory HFrEF patients, and sudden death by definition is people who die really without warning, that are feeling fine.

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So we talked about things, and he's like, "Well, what else can we do besides—these are the 4 key drugs. My doctor told me these are the 4 important drugs." And I said, "Yes, those drugs are important, but there's other things that we can do to even lower your risk further. And again, this NT-proBNP, to me, is telling me it's a wake-up call. We need to try to do as much as we can."

So with that, we initiated vericiguat. It's a soluble guanylate cyclase stimulator I know you're familiar with, Carolyn. But we did this because, again, there's evidence that shows that incremental to quad therapy, incremental to being on an ICD, a patient just like this can derive benefit on mortality reduction and hospitalization reduction or worsening heart failure reduction.

So we did that.

For those just tuning in, I'm Dr. Stephen Greene, and here with me today is Dr. Carolyn Lam. We're discussing how to optimize outcomes for ambulatory patients with heart failure with reduced ejection fraction.

And, Carolyn, why don't you tell our audience a little bit about soluble guanylate cyclase stimulators, and then we can review some of the data.

Dr. Lam:
I really feel passionate about this topic because if we look at all the other pillars, the 4 that we know about, they all inhibit kind of bad stuff, and the soluble guanylate cyclase is really complementary because it stimulates the good stuff. That's how I like to think about it, and it works perfectly with the others, and now we even have the data, the clinical outcome data, to completely stand on firmly to say it should be the fifth therapy. I mean, you and I have looked through the data, and I can say with a hand on heart, if I were that patient, I would want it.

The data, if you combined VICTORIA and VICTOR. VICTORIA was done in more patients who were recently worsened and unstable. And together, the results show clearly that vericiguat compared to placebo on top of standard of care actually reduces heart failure hospitalizations and death.

So for me, why not initiate it, especially when the pill burden is so low? This is something that's an oral once a day, very, very well tolerated. It's not like I need to bring him in many, many times to check potassium and worry about creatinine and things like that.

Could you review for us exactly how you initiated vericiguat, like the dose and what you need to watch out for?

Dr. Greene:
Yeah, absolutely. So in our patient, what we did was we initiated vericiguat at 5 mg once daily. Now, historically, we've always been taught to think about 2.5 mg as the starting dose of vericiguat. And to be fair, that was the starting dose in VICTORIA, and it was the starting dose in VICTOR. And you up-titrate to 5 mg in 2 weeks, and then target dose 10 mg 2 weeks after that.

But now we have a new study called VELOCITY, which I'll talk about in a second. But also, I'll note that the results of VELOCITY now make it regulatory approved in the US, Europe, and maybe other parts of the world to have 5 mg really be the default starting dose for vericiguat.

So VELOCITY was a small study of around 100 patients. It was single arm, and it's pretty simple. We took patients who were VICTORIA-like—HFrEF with a recent worsening heart failure event—and also some that were VICTOR-like—HFrEF without a recent worsening heart failure event—and we just pretty much gave them 5 mg of vericiguat and watched for safety and tolerability signals.

And we really didn't see anything when we compared historically to what patients did in the first couple weeks after starting 2.5 mg in VICTORIA. Notably, really no significant difference in blood pressure compared to the 2.5-mg starting dose, the historical control, and again, we already know that this is a very safe drug from a safety from a kidney and potassium and all those traditional things.

But I don't know, Carolyn. What do you think about the dosing with vericiguat in your practice?

Dr. Lam:
So, so, so helpful, Steve, because 5 to 10, and the target dose is 10 mg once a day, is really just a 2-step thing, and I really appreciate

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the simplicity because that was the major thing also that holds up GDMT optimization where I come from, right? Bringing the patient back, titrating, you get complacent again, blah blah blah. So this really simplifies.

And the reassuring stuff about blood pressure and tolerability is extremely important in Asia, where we tend to feel like our patients may be a bit more vulnerable to hypotension. Well, guess what? I can chuck that away now with the vast experience that we've seen.

So 5 to 10 mg in a 2-step up-titration, and no need to monitor creatinine or be limited by potassium is really an advantage with adding this medication.

Dr. Greene:
Yeah, I mean, I remember when we were back at the ESC when VICTOR was presented and everything, and there's a long-awaited trial. We already had the VICTORIA trial results that gave us regulatory approval, but that was in the post-worsening phase. Now we're talking about these, quote/unquote—I know the word is not a nice word to say—stable HFrEF patients with NYHA class II, but the results of VICTOR, you see vericiguat versus placebo. Initially the primary endpoint, CV death or heart failure hospitalization, neutral, and I think that surprised a lot of folks. And there was initially like a sigh in the room and everything as we thought, okay, nothing else to see here and everything.

But then those secondary endpoints started coming out, and I think you're hinting at this, Carolyn. So the secondary endpoint of CV death, 17% relative risk reduction. All-cause death, the endpoint of all endpoints in a heart failure trial, 16% relative risk reduction. And then not to mention a 25% reduction in sudden death and a 29% reduction in heart failure death.

But if people are not impressed with this heart failure hospitalization endpoint in VICTOR, I mean, I think what further gives me reassurance is the NT-proBNP biomarker data, right? We know that NT-proBNP going up, that's on the road to hospitalization. And what we saw in VICTOR is patients randomized to vericiguat had a relatively flat NT-proBNP. It stayed stable. People randomized to placebo, much higher chance of their NT-proBNP going up over time.

So and then when you put the 2 trials together, VICTOR and VICTORIA, again the same drug, vericiguat, across a spectrum of HFrEF, here you get statistically significant benefits on death and good old-fashioned heart failure hospitalization, not to mention all the outpatient worsening events that we saw in VICTOR as well.

So with that, before we wrap up, let's each take a final take-home message. So, Carolyn, I'm going to put you on the spot first. What do you hope our listeners will leave with today?

Dr. Lam:
HFrEF is an urgent condition to treat urgently. We must optimize therapy and use everything in our armamentarium. Let's not get complacent. So there is a quad therapy, yes, but there's more, and I strongly believe that vericiguat is that fifth consideration. And you know what? Don't even say 5 because then we pull it up only after everything else. But it is something that should be considered up front.

Dr. Greene:
And when we're talking about doing everything possible, that's where a drug like vericiguat comes in, which, again, I think about as an evidence-based way to further reduce mortality and risk of downstream heart failure.

And that's all the time we have today. So I want to thank our audience, and I also want to send a special thank you to Dr. Carolyn Lam, who's always a pleasure to speak with, and I appreciate all of her valuable insights and expertise. So, Carolyn, it was a pleasure working with you.

Dr. Lam:
Likewise. Thank you so much, Steve.

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