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Missing the Window in Ambulatory Patients With HFrEF on GDMT: Strategies for CV Risk Reduction

Announcer:
Welcome to CE on ReachMD. This activity, titled "Missing the Window in Ambulatory Patients With HFrEF on GDMT: Strategies for Cardio Vascular Risk Reduction" is provided by Medcon International.

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Dr. Greene:
What is the optimal timing for adding evidence-based therapies beyond our foundational quad therapy in patients with heart failure with reduced ejection fraction? Stay with us to find out.

This is CE on ReachMD and I'm Dr. Stephen Greene, and it's my pleasure to be joined by my good friend and colleague, Dr. Gianluigi Savarese.

Dr. Savarese:
Hi, Steve. Nice to see you.

Dr. Greene:
Great to see you, my friend.

So really looking forward to this discussion today. And let's just start with a case to set the context. So this is a case that I might see in my clinic pretty routinely. So let's take, for example, a 60-year-old gentleman with heart failure with reduced ejection fraction. He's been doing, quote/unquote, relatively well for at least a year or so now. He was hospitalized for heart failure last year, but it's been really a solid 12 months of staying out of the hospital and still has some symptomatic limitations. But again, he's not really complaining much and he's overall pretty happy.

When we look at his medical therapy, he's prescribed quadruple medical therapy with metoprolol, sacubitril valsartan, spironolactone, and empagliflozin. He's on target doses of the SGLT2 inhibitor and MRA. The medium doses of beta-blocker and ARNI—we had tried to go higher, but he had symptomatic hypotension. He's kind of been at these maximally tolerated doses.

So he comes to your clinic, and I check labs pretty routinely on these patients, including NT-proBNP. And I'm always, in the back of my mind, saying, you know, he's feeling really well, but NT-proBNP seems to be stubborn around like 2,000 or so. And again, not really forwardly volume overloaded, looks relatively euvolemic on exam, but I'm trying to think about what else can I offer or what else should I be thinking about in a patient like this?

Dr. Savarese:
Yeah, I mean, these are patients we are very used to seeing in our clinics, I think, Steve. It's the case of those patients where you are there and you think they are doing quite well, but still, is there anything else I could do before they might have later worsening heart failure events or not? So this is a scenario which is, I think, extremely frequent, in particular since we see patients at follow-up every 6

months and so on. So we are used to seeing and receiving the same patients very often. And here, I think we see some features indicating that there is actually high risk, although the patient is not at the moment worsening. We see the high NT-proBNP levels. We see that the patient, as in any case, being hospitalized during the last year. We see that the patient is actually on many medications and at high doses. And in our daily clinical practice, we really need to push for that. But sometimes there is some clinical inertia. So if you really see that the patient is on top of all the 4 pillars at target doses, it also means that, actually, the doctors really felt it was really needed to do the best to take care of this patient. And sometimes the patient is also younger, and so you really need a team that you need to do something more for this patient.

Dr. Greene:
Yeah, no, I completely agree. And when I'm working with trainees on a patient like this, taking care of them, I constantly remind them there's no such thing as a low-risk HFrEF patient. There's no such thing. And patients like this you see in clinic are almost like traps for us to just say, oh, yeah, they're doing fine. They must be low risk because they look okay today, and they feel fine and not complaining of anything. But just when you look at the absolute risk for someone like this, even without a recent hospitalization, with reasonable NYHA functional class 2 symptoms, we're still talking about a 1-year risk of CV death or heart failure hospitalization, upwards of about 10% per year, in that we don't get risk in HFrEF lower than that. And it's still much higher than the average patient with, quote, very-high-risk ASCVD in terms of absolute terms. So we really need to be taking these patients seriously.

Dr. Savarese:
It's important to speak about residual risk. I completely agree. And indeed, that's really highlighted. There is still room to do something to improve prognosis in these patients.

Dr. Greene:
Yep, I absolutely agree. And with that context, trying to view this kind of patient population as a real, still unmet need, even though they're not recently in a hospital, NYHA class 2 symptoms.

We recently had the presentation of the VICTOR trial with vericiguat. And, Gianluigi, why don't you walk us through what vericiguat is and some of the high-level results from VICTOR.

Dr. Savarese:
Yeah, I mean, definitely in a patient as the one you are describing, of course, I mean, the one you were describing was on the the 4 pillars, target doses, so there is not much work to do in terms of up-titration, of optimization of the foundational therapy. Still, I think it's important to consider whether there is an indication for a device. And I don't think this was the case. So really here we need something new to reduce the residual risk in this patient. And I think the VICTOR trial actually is providing that evidence that we were missing.

So the VICTOR trial is providing, I think, very high-level evidence regarding the use of vericiguat in these patients with actually stable HFrEF, those we do see in our outpatient clinic quite often. And in this trial, vericiguat, which was the drug which was indeed tested against placebo, which is an sGC stimulator, which has a completely different mechanism of action as compared to the other foundational therapies. So we might think it has kind of synergetic effect together with the other medication. Actually, the drug was shown, although could not meet the primary outcome of cardiovascular mortality or heart failure hospitalization, to significantly reduce the risk of cardiovascular death by 17%, so quite high relative risk reduction. The risk of the sudden cardiac death by 25%, and the risk of all-cause mortality by 16%. So very important risk reduction in terms of mortality. And we should not forget that the trial was actually powered to assess cardiovascular mortality, which is very, very important, I think, to remember.

Then the VICTOR trial was also pooled together with the VICTORIA trial in a pooled analysis, which was indeed assessing the efficacy and safety of vericiguat across the disease spectrum in terms of disease severity spectrum in these patients with HFrEF, showing that there was no heterogeneity. So basically a very important reduction in risk of cardiovascular mortality or heart failure hospitalization and mortality across the spectrum of disease severity.

Dr. Greene:
Yeah, I mean, that’s a perfect summary. And I think when VICTOR was presented, I think on one hand, there are 2 different views that kind of emerged with how to look at the data. And one was a very purist statistical view.

And the purist statistical view said, well, as you mentioned, the primary endpoint of CV death or heart failure hospitalization was neutral, so therefore I don't need to take any points from VICTOR and we can try again in the future on another trial.

But I think you mentioned one of the key things here is about the significant reduction in cardiovascular death and also all causes of death. And you mentioned very importantly, the trial, even though, yes, you had a primary endpoint that was the composite, the trial was power for cardiovascular death. And there were more than 600 cardiovascular deaths in VICTOR, so you had a very—just by common

sense, a lot of reliability in terms of really getting granularity in the estimate, in the truth on the cardiovascular death effect in VICTOR. And again, it was nominally statistically significant.

The other thing that I bring up too is that this cardiovascular death benefit in VICTOR didn't come out of thin air. I mean, the way VICTOR was designed, it was based on a post hoc analysis from the prior VICTORIA trial where they saw that the benefit in VICTORIA, and that was a patient population of recent worsening heart failure patients, but vericiguat in that patient population did not reduce cardiovascular death overall, but it did reduce cardiovascular death in those with an NT-proBNP less than 6,000. So it kind of generated the hypothesis from VICTORIA that that would be a patient population that might have mortality benefit with vericiguat.

And then, what did VICTOR do? Well, VICTOR was designed with an upper cap of NT-proBNP of 6,000. So the way I kind of view this is that essentially was a validation of that hypothesis that VICTORIA generated. And we also, again, in VICTOR, saw this cardiovascular death benefit and a lot of cardiovascular deaths to really get that estimate, of again, over 600.

Dr. Savarese:
Definitely. Steve, this is a very good point, and I think there are also other important points for discussion. So first of all, the primary outcome was a composite of cardiovascular death or heart failure hospitalization. And the way we handled patients in daily clinical practice has completely changed over time. And nowadays, we are more and more used, in particular after COVID-19 pandemics, to handle worsening heart failure events in the outpatient clinic. And actually, this was not really considered in the primary outcome of the trial. Indeed, there are also some post hoc analyses showing that whether also worsening heart failure events managed in the outpatient clinic, such as using intravenous diuretics in the outpatient setting because the patient gets worsening in symptoms or dose escalation of diuretic therapy, whether these were considering the primary outcome as well, the trial would have met the goal.

So I think this trial is teaching us a lot. It's also teaching us how we should design the next trials, which is also an important point, and that we are doing quite well, actually, managing these patients in the outpatient setting, which also leads to a reduction in the costs.

We should not forget that, in fact, in one of the post hoc analyses of this trial, worsening heart failure events when considered also as dose escalation of diuretics or intravenous use of diuretics, was related to mortality. And in the trial, it was seen a consistent reduction in all-cause cardiovascular mortality and sudden cardiac death with vericiguat, which I think also the consistency in the reduction of all these different causes of death, actually, is important and really highlights that this is not a result by chance.

Dr. Greene:
Yeah, no, I completely agree. And when you put VICTOR and VICTORIA together, we have over 11,000 patients randomized to vericiguat versus placebo. And again, the totality of evidence in my mind clearly shows a benefit with vericiguat versus placebo. And again, also pointing out in VICTOR, again, CV death and all-cause death benefit. And now you cannot ignore those endpoints, which really, in the heart failure landscape have historically been the endpoint of all endpoints. Cardiovascular death and all-cause death also highlight the relative safety of vericiguat versus placebo as well. The thing is some of our therapies in the HFrEF landscape are more or less difficult for patients to tolerate. But generally speaking, vericiguat, whether you were talking about the VICTOR trial patient population or VICTORIA, again, total serious adverse events, very similar to placebo.

Relatively blood pressure neutral is a very important thing, I think, practically speaking for our practice. And also, enrolled patients with an eGFR as low as 15. So, many of those patients with stage 4 CKD in clinical practice, we kind of are scratching our heads with what can we offer these patients from a safety perspective that might be helpful? Well, again, this is kind of a niche that vericiguat has been studied in and we have reassuring evidence there.

Dr. Savarese:
Yeah, I think this data highlight how, actually, it's easy to use this drug. There are no particular tolerability issues. It's easy to use also in those patients where we have a little bit of troubles with RAASI, MRA because of the impact on renal function. No impact on potassium levels, which is another common barrier to the implementation of GDMT. So really, the safety profile of the drug also allows a good implementation of use of the medication in daily clinical practice. But when it comes to that, probably, Steve, it would be interesting to discuss the dosing, how we should initiate this treatment, also, because I mean you are the best person here to explain also, so what you showed in the VELOCITY trial.

Dr. Greene:
Yeah, well, thanks so much now, Luigi. And I think you're talking about the user-friendliness of vericiguat based on the side effect profile or relatively lack thereof in the clinical trials. But from a practical perspective, one of the key things of being a user-friendly GDMT is if you have a lot of doses versus a few doses. Because titration, as we've seen in clinical practice, is such a barrier. And many patients, they stay on the same dose over and over and over again. And if you have simplified dosing strategies, you get your patients a much higher chance of getting to target doses.

So in VICTOR and VICTORIA, the starting dose of vericiguat was 2.5 mg/day. And because of that, the regulatory labels initially started with recommendation of 2.5 mg daily as a starting dose. What we wanted to see is, well, given how, again, relatively blood pressure neutral, say, from a kidney perspective, could we get away with being more aggressive, with starting vericiguat at 5 mg and have patients still tolerate the drug well? And if so, would that increase the chances of them eventually getting to 10 mg? Because again, only a one-step titration versus 2 would be a very, again, user-friendly clinical practice.

And in VELOCITY, and this was a single-arm study of about 100 patients, we gave 5 mg of vericiguat right away to patients with HFrEF. And again, the key take-home message is more than 9 out of 10 of them tolerated the drug very well without any discontinuation concerns or moderate to severe symptomatic hypotension. And because the 5 mg starting dose was so well tolerated, very recently in the EU, they've actually changed the label for vericiguat to say that you can consider starting at 5 mg in select patients, and you don't necessarily automatically need to be starting at the 2.5 mg.

So, yeah, again, I think it just adds to vericiguat being relatively user-friendly in our own clinical practice.

Dr. Savarese:
Very, very nice point. No, I completely agree with you. I mean, you are providing very, very good advice also on how to initiate and work on the up-titration of this drug. I think that if we consider our discussion today, one point that might rise is that actually the data we have available is really highlighting probably starting vericiguat earlier is better.

I think VICTOR trial and the pooled data are really pointing out in that direction. I think it's important to consider important risk markers such as the one our patient reported, so elevated NT-proBNP, that there was a prior heart failure hospitalization around 1 year before and so on. And actually treating the patient before a new worsening event emerged actually is what leads to reduced risk of mortality. I think that's a very important take-home message that we have today.

So we also somehow are highlighting important risk markers that we need to consider in our clinical practice. So not to wait for a worsening heart failure event, but trying to use the drug to prevent a worsening heart failure event. So I think this is a take-home message we could consider, right?

Dr. Greene:
I totally agree. And also, I'll say that one of the things that VICTOR showed us is that vericiguat was incremental to whatever background therapy the patient was on in terms of reducing the risk of cardiovascular mortality and all-cause mortality. So, for example, like the patient case that I presented. Some clinicians might say, well there's quad therapy. I mean, well, is adding anything else on top of quad therapy really going to make that much of a difference? But VICTOR showed that it did. And there was about 44% of the patient population were on quad therapy at baseline, so it was a very, very well-treated patient population in VICTOR. And even if you were on quad therapy, vericiguat got an incremental reduction in cardiovascular death and incremental reduction in all-cause death.

And again, going back to my teaching point, there's no such thing as a low-risk HFrEF patient. That, especially when you have a drug that's safe and well-tolerated, I just say, why would you not want to use every possible tool in your tool kit when you're dealing with a prognosis that in many cases is comparable to a cancer? Even if the patient is feeling well at that given day and time. We talk about risks of sudden death for these, quote/unquote, stable HFrEF patients. vericiguat also reduced the risk of sudden death in VICTOR. So, again, it’s just one of those things to keep in mind that we're dealing with such an extreme-risk patient population; regardless if they're very symptomatic or less symptomatic, they are not low risk.

Dr. Savarese:
Definitely, Steve, I completely agree. And I think, overall, this is a call to action. Of course, we need to wait for the next guidelines when it comes to recommendation for treatment. But I think the data we have been discussing today together very much align that preventing is better than treating, so we should prevent a worsening heart failure event and not just treat it when it's too late

Dr. Greene:
Yeah, I completely agree. Essentially, take-home point is treat HFrEF with the sense of urgency that it deserves.

Well, my friend, I think that's all the time we have for today. So I of course want to thank our audience for listening in. Thank you, Dr. Gianluigi Savarese, for joining me and sharing all of your valuable insights and expertise. And so, again, we’ll see you next time.

Dr. Savarese:
Thank you, bye.

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