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High-Risk HFrEF: Who Will Benefit Most from Novel Therapies?

Announcer:
Welcome to CME on ReachMD. This activity, entitled "High-Risk HFrEF: Who Will Benefit Most from Novel Therapies?" is provided by Medtelligence.

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Dr. Butler:
New data and approval of novel therapies have changed the game for patients with heart failure with reduced ejection fraction, or HFrEF. Have you started implementing these therapies with your patients? And are you ready to get with the guidelines?

This is CME on ReachMD, and I'm Dr. Javed Butler.

Dr. Zieroth:
And I'm Dr. Shelley Zieroth.

Dr. Butler:
So, Shelley, good to be with you. We have a ton of things to discuss, so let's dive right in. To start our conversation, can you briefly discuss the challenges we face managing our patients with HFrEF?

Dr. Zieroth:
Well, it's great to be here with you today, Javed. And, well, let's start with diagnosing HFrEF. In some areas, there's poor access to diagnostic tests such as echocardiograms to assess left ventricular ejection fraction, and even natriuretic peptide blood test availability can hinder the diagnosis of heart failure. And I think, furthermore, in a lot of areas, specialist care may also be limited. And given the increasing numbers of patients with HFrEF, it's really upon all of us to provide patient-centered care and attempt to reduce the risk of future hospitalizations and mortality by prescribing guideline-directed medical therapy.

And, you know, you ask exactly how are we doing at this? And I think you and I both know that the contemporary clinical registries like CHAMP-HF have shown us that we're not really doing a great job at this, both in prescribing guideline-directed medical therapy for HFrEF or achieving target doses. And as clinicians, it really is our job and our responsibility to inform our patients as to the benefits of these therapies in order for them to participate in shared decision-making with regards to their medications.

Dr. Butler:
You know, I completely agree with you. And there is really no suboptimal time to initiate these therapies that we have so much good data with in terms of improving their outcomes. The whole idea of practice of medicine is to start the therapy early so that we can prevent worsening of the disease. But also, when somebody does develop worsening heart failure, have high-risk features, just realize that they are at such an extraordinary high risk that unless and until we optimize medical therapy and reverse the trajectory of their disease, they are heading towards a further worsening and need for advanced treatments or, unfortunately, palliative care.

Now, you know, SGLT2 [sodium-glucose transport protein 2] inhibitors and the new sGC [soluble guanylate cyclase] stimulators have

shown some dramatic results in clinical trials, and also real-world data has come in as well. What differentiates these 2 classes of treatment?

Dr. Zieroth:
Well, let's start with the SGLT2 inhibitors. First of all, I'm not sure we know the exact mechanism of action with this class of foundational therapy. There's evidence for some modest and early diuresis. There's improved kidney function and cardiorenal physiology. There's changes in hemodynamics that occur. There's improvements in cardiac remodeling and bioenergetics.

But the SGLT2 clinical trials, they were published first, before the soluble guanylate cyclase stimulator trials. So they were DAPA-HF and EMPEROR-Reduced, and they resulted in significant changes to international heart failure guidelines for patients with HFrEF. DAPA-HF was the first one out. And in that study of nearly 5,000 patients, with patients randomized to dapagliflozin and standard of care, the trial demonstrated – it was a 26% relative risk reduction in the primary composite endpoint of cardiovascular death or hospitalization for heart failure or an urgent heart failure visit. And this was statistically significant and occurred as early as 28 days in those HFrEF patients who received dapagliflozin. And in addition, the rate of decline of slope of eGFR [estimated glomerular filtration rate] was slowed, and there were also improvements in quality of life.

And about a year later, EMPEROR-Reduced came out, and that added to the totality of evidence for this class of drug and achieved a very similar favorable result when empagliflozin was evaluated in a very similar population: symptomatic HFrEF patients on standard of care therapy. And again, we saw those patients randomized to empagliflozin demonstrated a very similar 25% relative risk reduction in the composite endpoint of cardiovascular death and the hospitalization for heart failure. And in addition, the study confirmed the renal benefits of SGLT2 inhibitors in a HFrEF population.

Before we get into vericiguat, let's take a look at the following video.

[ANIMATION PLAYS.]

Dr. Zieroth:
Vericiguat increases soluble guanylate cyclase activity, which improves both myocardial and vascular function. And I'm excited about it because it really introduces another opportunity and a novel pathway for us to modify the pathophysiology of HFrEF.

And vericiguat was recently investigated in the VICTORIA trial. And this trial studied a group of patients who are at higher heart failure risk than those enrolled in the SGLT2 inhibitors that we just discussed. The VICTORIA trial enrolled patients with chronic symptomatic HFrEF with New York Heart Association class 2 to 4 symptoms and an ejection fraction less than or equal to 45%. And those patients randomized to vericiguat, they benefited from a significant reduction in the primary composite endpoint of cardiovascular death or heart failure hospitalization. The statistically significant 10% relative risk reduction, that equated to an absolute event rate reduction of 4.2 events per 100 patient-years. And the VICTORIA study also included patients with an eGFR down to 15, which is the lowest of any ambulatory clinical heart failure trial to date.

So I believe that vericiguat will be an important consideration in those patients on foundational therapies and with worsening heart failure, including those with a recent heart failure hospitalization or those with a need for outpatient IV diuretics.

Dr. Butler:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Javed Butler. And here with me today is Dr. Shelley Zieroth. We are discussing the use of novel agents to manage high-risk patients with heart failure and reduced ejection fraction.

So, you know, this is really fascinating. So can you tell us a little bit about this concept of worsening heart failure? Is it the same as just somebody getting into the hospital with decompensated heart failure?

Dr. Zieroth:
Well, worsening heart failure is defined by those who've had a recent heart failure hospitalization, those who required IV diuretic as an outpatient, but I think it actually expands beyond that. You know, in my mind, I consider worsening heart failure, as well, those in whom the foundational drugs are having to be reduced or discontinued or not tolerated. And in addition, I would identify those patients with escalating doses of diuretic or diuretic resistance as well.

I mean, we all recognize that when we're treating patients with HFrEF when they're hospitalized, in the absence of a clear exacerbating factor, essentially, it's a failure of their current therapy. We know that the first 30 days post heart failure hospitalization has been deemed the vulnerable period for rehospitalization, but that may actually extend to a longer interval, 60 or 90 days.

Regardless, time is of the essence. Early post-discharge follow-up is important, review of existing therapies, and looking for opportunities to optimize them with newer agents including SGLT2 inhibitors and vericiguat is important.

And I should also point out that international guidelines, including the European Society of Cardiology Heart Failure Guidelines and the Canadian Heart Failure Guidelines, they've incorporated formal recommendations for the use of vericiguat in those patients recognized as having worsening heart failure as defined in the VICTORIA trial.

Dr. Butler:
Well, that's a fantastic overview. How do we know what is the right therapy for the high-risk patients sitting in front of us? Especially that we are so focused right now on preventing hospitalization, which is both a marker of high risk for mortalities, of prevention of hospitalization. And rehospitalization is important but also has major economic concerns for the society and the healthcare systems as well.

Dr. Zieroth:
Yeah, it's really important for us to look at the patient in front of us. Not all patients are going to tolerate all 4 foundational therapies. And, you know, there was a really great article out recently about the various patient profiles in HFrEF, and it identified 11 different profiles based on the presence or absence of chronic kidney disease, the blood pressure, the presence or absence of atrial fibrillation. And so, you know, all of these factors need to be taken into consideration.

I think we have to individualize what therapies we initiate with our patient and, certainly, in those patients who have had a hospitalization or IV diuretics, you have to look for opportunities to prevent those hospitalizations and really recognize that worsening heart failure profile when you see it.

Dr. Butler:
So today we are discussing these 2 classes of drugs, SGLT2 inhibitors and soluble guanylate cyclase stimulator. So what is the safety tolerability profile of these 2 classes of agent for those things that traditionally made it difficult to optimize therapy?

Dr. Zieroth:
I think that, having had some experience in the VICTORIA trial with vericiguat, I thought it was a very well tolerated drug. There are no concerns with hyperkalemia. Again, it can be used in patients with chronic kidney disease as well. In patients with a softer blood pressure, you may have to be a little bit more cautious. But again, I use it across a broad spectrum of patients, and it was very well tolerated, and my patients did have symptomatic benefit with it. Again, no impact with heart rate, and so a lot of opportunity to use vericiguat in the worsening heart failure population.

SGLT2 inhibitors, again, minimal blood pressure-lowering effect. It can go down to typically an eGFR, depending on the agent, down to 20. No concerns with hyperkalemia either, no impact on heart rate.

So overall implementation of both of these therapies is quite easy, very well tolerated from a safety perspective as well.

Dr. Butler:
Well, this certainly has been a fascinating conversation. And you have given us a wealth of information in a relatively small period of time. But before we wrap up, can you share with us and audience members one take-home message?

Dr. Zieroth:
Okay. I think I'll even use some of my – you'll like this – my favorite Twitter hashtags. So I would say not only do we have 4 foundational therapies for HFrEF, but we have additional opportunities to reduce risk of hospitalizations in those with worsening heart failure. So my hashtag number one is guideline-directed medical therapy works. #GDMTworks. And then, using our guideline-directed medical therapy and personalizing therapies, we can turn heart failure into – here's hashtag number two – it's #heartsuccess.

Dr. Butler:
Well, I don't think I can top that one. So completely agree with you. I would just urge our audience members to listen to your words of wisdom carefully because there is really no bad time to optimize therapy. But once somebody develops worsening heart failure, please realize that these patients are at an extraordinarily high risk and that optimization of therapy and to use any tools that we might have to prevent recurrent rehospitalization is really, really important.

Well, unfortunately, that's all the time we have today, so I want to thank our audience members for listening in and thank you, Dr. Zieroth, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

Dr. Zieroth:
It was great speaking with you too today, Javed. Have a great day.

Dr. Butler:
Thank you.

Announcer:
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