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Released: 10/06/2023
Valid until: 03/27/2024
Time needed to complete: 15 minutes

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Updated Heart Failure Treatment Recommendations – Across the Spectrum

Announcer:
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Dr. Goldberg:
Hello, and welcome to Medical Minute 2, Updated Heart Failure Treatment Recommendations Across the Spectrum. This is the second in a 3-part series called Expert Insights on Navigating and Implementing the 2022 Heart Failure Guidelines. I'm Dr. Lee Goldberg, Section Chief of Advanced Heart Failure and Cardiac Transplant, and Vice Chair of Medicine for Informatics at the University of Pennsylvania.

Here are my disclosures.

Our learning objective for today is to summarize the updated pharmacologic treatment recommendations across the spectrum of heart failure. So, let's begin, we can look at various degrees of left ventricular ejection fraction that helped to drive some of our pharmacotherapy. So, we have some new definitions. Heart failure with reduced ejection fraction is defined as an ejection fraction less than or equal to 40%. Heart failure with mildly reduced ejection fraction is an ejection fraction of 41 to 49%. Heart failure with preserved ejection fraction is defined as an ejection fraction of greater than or equal to 50%. And then we have a unique group of patients who start with an ejection fraction less than or equal to 40% but have an increase in their ejection fraction of greater than 10 points with a second ejection fraction greater than 40%. And those patients are considered heart failure with improved ejection fraction.

So here's what our latest 2022 ACCHA guidelines say about pharmacotherapy in patients with Stage B through D, and New York Heart Association Classes I to IV. The mainstay therapies really fall into 4 categories. They are an ACE inhibitor, or an ARB, or an ARNI kind of classed together, with ARNI being preferred in most patient populations, a beta blocker, and SGLT-2 inhibitor and aldosterone antagonist. And then there's a series of other medications, which we'll consider add-on therapy. These are drugs that are added on in addition to the 4 main therapies for selected patients based on symptoms, demographics, or response to therapy.

Now, if we look across the severity of heart failure, as well as the staging of heart failure, you can see that in Stage B, there's medical therapy that's recommended. And in Stage D, they would get all the therapies of Stage C, but also some additional therapies for patients with refractory or end-stage disease.

So, here's our treatment algorithm. The first step is to establish the diagnosis of heart failure with reduced ejection fraction to address congestion with diuretics and then initiate as rapidly as possible guideline-directed medical therapy. And there are 4 main pillars for guideline-directed medical therapy, as we already mentioned. An ARNI, or an ACE or ARB if not tolerated, a beta blocker, mineralocorticoid antagonists, and an SGLT-2 inhibitor. And recent data has shown us that if we add all 4 of the evidence-based therapies as quickly as possible, we have a significant reduction in risk; the relative risk reduction 72.9%, but an absolute risk reduction of 25.5%. And you would need to treat about 4 patients over 24 months to prevent 1 death from heart failure, which is a really good

return on investment.

So if we start to think about the standard guideline-directed medical therapy, we have the ACEs and the ARBs, and they were the mainstays of therapy for many years, leading to about a 20% reduction in mortality. We know the improved cardiac function and remodeling, I only have to monitor for hypotension, renal dysfunction, and hyperkalemia. Beta blockers have even a bigger impact in reduction in mortality of about 35%, also improve cardiac function and remodeling. But you have to monitor for bradycardia and hypotension. And then lastly, mineralocorticoid antagonists, another 30% reduction in mortality, again, promote positive remodeling, and you have to monitor renal function as well as potassium.

So what about some of the core data for beta blockers? Here's an example of one of the beta blocker trials, MERIT-HF, that was looking at metoprolol succinate. And in this trial, you can see by 3 months, the curves are separating with a statistically significant reduction in mortality in the patients getting the beta blocker as compared to placebo. And this was on top of an ACE inhibitor in this particular trial.

What about the mineralocorticoid antagonists? Well, here's some data from eplerenone from EMPHASIS-HF. Even in patients with relatively mild symptoms, you can see that there is a reduction in mortality in the patients that received eplerenone on top of an ACE inhibitor and a beta blocker as compared to those that were on placebo.

Now, what about the newest agents in the angiotensin renin blockade area? That is sacubitril/valsartan. And this drug was so exciting because instead of being against a placebo, like we saw on the other clinical trials, this agent was tested against another active therapy, enalapril. So a head-to-head trial between enalapril and sacubitril/valsartan. And in over 30 years, no drug had ever really been superior to enalapril in reducing mortality or cardiac or heart failure hospitalization. And in this case, the sacubitril/valsartan was superior. There was about a 20% reduction in sudden death, cardiovascular death, and heart failure hospitalizations when compared against an active therapy, in this case the ACE inhibitor, and there were lower rates of discontinuation with the sacubitril/valsartan, although there was more hypotension. And for this reason, the guidelines now suggest that an ARNI, the sacubitril/valsartan, is really preferred over an ACE or an ARB due to this modest incremental benefit.

Now, what about the SGLT-2 inhibitors? Well, we have two drugs that have significant data, empagliflozin and dapagliflozin, and you can see here that in patients with diabetes, there was a significant reduction in heart failure hospitalization or cardiovascular death in patients with reduced ejection fraction. Importantly, however, the bottom half of this slide shows that even in the absence of diabetes, in the patients that did not have diabetes at baseline, there is an equal benefit to the use of an SGLT-2 inhibitor in reducing cardiovascular hospitalizations or death. So, what this tells us is that the mechanism of action and how the SGLT-2s are improving outcomes is independent to their glucose lowering or diabetes effects.

So now back to our algorithm; we've gone through and titrated our various medications. What can we do once we've gotten patients on those 4 drugs? Well, we want to implement additional guideline-directed medical therapy in appropriate patients, as well as device therapy as indicated.

So what about the role of isosorbide dinitrate and hydralazine in the management of heart failure? Well, this is a very old trial from the early 1990s. And it was looking at the use of enalapril, hydralazine and isosorbide dinitrate, and actually placebo. I show just the data of the enalapril and isosorbide dinitrate and hydralazine here, because I want to make the point that although the hydralazine and isosorbide dinitrate was better than placebo in reducing mortality, it was not better than enalapril. So when you take your patient off an ACE or an ARB or an ARNI, for whatever reason, and transition them to hydralazine and isosorbide dinitrate, you are giving up a small amount of mortality benefit. And so, it's important to be sure that they're not tolerating the ACE or the ARB.

Now, in African American patients, we do know that add-on therapy with hydralazine and isosorbide dinitrate is effective in reducing mortality, but alone, it's not as good as enalapril.

What about ivabradine? This is a compound that actually inhibits the funny channel in the SA node and reduces heart rate. In this clinical trial called SHIFT, they were comparing patients who had ejection fractions 35% or less, and a heart rate greater than 70, despite being on maximally tolerated beta blocker, as well as an ACE inhibitor and other therapies. And they were randomized to have ivabradine, which controls heart rate or placebo. And interestingly, in this trial too at about 3 months, the curve separated and there was a statistically significant reduction in cardiovascular death or hospital admission for worsening heart failure with ivabradine. Remember that ivabradine can be associated with more atrial fibrillation, and is not indicated in patients who have a pacemaker and are using the pacemaker regularly.

But what about vericiguat, one of the newer drugs that had been added to our armamentarium? This is the VICTORIA trial. This was a trial that was looking at patients with symptomatic heart failure with reduced ejection fraction who had recently been hospitalized for heart failure or had received outpatient IV diuretics. And all of these patients were receiving, as well as tolerated, guideline-directed medical therapy. And in this trial, you can see that again, the vericiguat reduced the primary outcome, which was the risk of

cardiovascular death, or first hospitalization for heart failure. And you can see that the serious adverse events were slightly lower in the vericiguat group as compared to the placebo group.

And then lastly, for those patients that had heart failure with improved ejection fraction, the TRED-HF trial shows us clearly here that in those patients that were in the withdrawal group, meaning their medications were discontinued, they had a much higher rate of developing symptomatic heart failure, or a drop in their ejection fraction to the point where the trial actually had to be terminated early, and reinforced the concept that patients that even who have normalized their ejection fraction, should remain on the neurohormonal blockade indefinitely.

Now what about patients who have heart failure with that mid-range ejection fraction of 41 to 49%? Well, now our newest data suggests that these patients may actually do well if they're treated as if they had heart failure with reduced ejection fraction. And so, they would also be candidates for SGLT-2 inhibitors, and ACE, ARB, or ARNI, a mineralocorticoid antagonist, and then one of the 3 evidence-based beta blockers, metoprolol succinate, carvedilol, or bisoprolol.

What about patients who have heart failure with preserved ejection fraction, a group where we really didn't have a lot of trials that were positive in the past? Well, now we do have some data, which I'll show you in just a moment, around SGLT-2 inhibitors, as well as angiotensin receptor blockers and mineralocorticoid antagonists. And so, these drugs now are indicated for patients who have HFpEF. In addition, we want to focus on treating underlying comorbidities, including iron deficiency anemia, atrial fibrillation, hypertension, and ischemic heart disease. And there may be some data that regular cardiac rehab is helpful, although clinical trials in this regard are currently ongoing.

So here's the data on SGLT-2 inhibitors in heart failure with preserved ejection fraction, again, looking at empagliflozin and dapagliflozin, and in both clinical trials, there was a statistically significant improvement as compared to placebo. Now remember, dapagliflozin is not currently FDA approved for the treatment of HFpEF, and our guidelines are still being updated in terms of how to incorporate these medicines. But it's very clear they're going to have a very important role in the treatment with heart failure with preserved ejection fraction going on into the future.

So here's the summary of management of heart failure. For heart failure with reduced ejection fraction, ejection fraction is less than 40%, you see the 4 core medicines that we know reduce morbidity and mortality, as well as positively remodel the ventricle. For heart failure with mid-range ejection fraction, ejection fraction is 41 to 49%, we have good data for the SGLT-2 inhibitors, as well as some data for the addition of ARNI, beta blocker, and mineralocorticoid antagonists as well as an ACE or an ARB. And then lastly, and probably the most exciting since we now have approved therapies, would be heart failure with preserved ejection fraction, where we would add an SGLT-2 inhibitor where we have clear data from the 2 clinical trials, as well as some data for the use of ARNI and an ARB as well as a mineralocorticoid antagonist.

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