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When GDMT Isn't Enough: Understanding Residual Risk in Patients with HFrEF

Announcer:
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Dr. Butler:
Hello, this is CE on ReachMD, and I'm Dr. Javed Butler. In this brief lecture, I will discuss the residual risk in patients with heart failure and reduced ejection fraction on quadruple guideline-directed medical therapy, or GDMT, and device therapy.

Granted that over the past couple of decades we have had a lot of success that we should really celebrate in the management of patients with heart failure and reduced ejection fraction. I remember when I started my career, we had no therapies for these patients. We basically gave patients diuretics and digoxin, which was primarily for symptom improvement. Neither of the 2 therapies improved patient survival, and the mortality rates for these patients exceeded many forms of cancer.

Then we had a glorious era of neurohormonal modulation in patients with heart failure and reduced ejection fraction: ACE inhibitors, ARB, ARNI, beta-blockers, MRA. All of them subsequently showed more and more reduction in the risk of mortality, the risk of hospitalization for these patients. The outcomes continue to improve.

Then we hit a little bit of a ceiling that further neurohormonal modulation did not tend to improve the outcome for those patients. We tried endothelin blockers, we tried vasopressin antagonists—did not improve outcomes. So then we started looking for therapeutic targets outside of neurohormonal modulation, and that's where the SGLT2 inhibitors came in.

And again, further improvement in the risk of mortality and hospitalization. So now we have 4 pillars of a therapy for heart failure with reduced ejection fraction or 4 foundational therapies that are recommended by the guidelines: ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors. However, the downside is that there is a little bit of a narrative out there that now that we have these 4 therapies—and of course in a sub-select group of population, we also have defibrillator or cardiac resynchronization therapy—do we need more therapies for heart failure, or do we have enough? So the question is how do you answer this question? How do you think about do we have enough therapies? Well, the answer simply cannot be numerical, right? We cannot say that 4 drugs are too many and 2 drugs are too few, so the right number is 3.

The answer is, well, is there any further need? So now let's look on the device side. CRT, or cardiac resynchronization therapy, is applicable to a distinct minority of patients with heart failure with reduced ejection fraction: ejection fraction less than 35%, a preferably normal sinus rhythm, and a wide QRS, preferably in the left bundle branch block pattern. So that's a really minority of the patients that qualify. Defibrillator therapy is obviously not therapy for heart failure. It is when you run into trouble with arrhythmias, it can shock you

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out, and that also is not perfect.

So the question is how are you going to improve the outcomes of patients with heart failure? So the glass half full, or maybe even more than half full, is that these 4 foundational therapies have substantially improved outcomes. The issue here is what is the residual risk? So let's look at what we saw with SGLT2 inhibitors, right? So these trials, when they were done, the patients were on excellent background medical therapy, 90+% RAAS inhibitor, 90+% beta-blocker, 70+% MRA use, and 100% SGLT2 inhibitor use in the SGLT2 inhibitor arm.

In those trials with that background therapy, all patients were outpatient, not hospitalized, sick patients. All patients were outpatients. 70% were NYHA Class II. The annualized event rate with the trial in DAPA HF was about 12%, and the annualized event rate exceeded 15% in EMPEROR-Reduced trial. In other words, about 1 in 6 patients died or got hospitalized within 1 year. Despite of all these characteristics that I'm saying—GFR less than 30, excluded from DAPA HF, as I said, NYHA Class II, greater than 70% of those people, excellent background therapy, and yet.

Now if you move on to the VICTORIA trial that took patients who were hospitalized within the past 6 months or required outpatient IV diuretic within the past 3 months—again, not cardiogenic shock, not in the ICU within the past 6 months, hospitalized or not even hospitalized, outpatient IV diuretic within the past 3—those patients had an annualized event rate, hospitalization or mortality, exceeding 30%. More than 1 in 3 patients.

And now finally, let's look at the latest trial that we have, which is the VICTOR trial with vericiguat. These patients were the opposite. These patients were not hospitalized within the past 6 months or requiring outpatient IV diuretic. In fact, 85% of the patients were either never hospitalized or hospitalized remotely, over a year ago. 80% of the patients had NYHA Class II. These patients, about 60% or so, were on ARNI. About 60% or so were on an SGLT2 inhibitor. 95% were on beta-blocker; 95% were on any RAAS inhibitor therapy. Even in this group of patients, the annualized event rate was over 11%. Over 11%. So I don't know when the risk is low enough that perhaps doing further is not needed. Maybe when your risk of dying or getting hospitalized is 1%, maybe it's not worth going to 0.5%. But when your risk exceeds 10%, there is substantial residual risk that we need more therapies to improve the outcome for these patients.

Remember, when we do trials in atherosclerotic cardiovascular disease, like high-dose statin therapy, for instance, 5% annualized event rate is considered high risk, and 7% is considered very high risk. And in heart failure, that does not even come into the radar screen, for our lowest-risk patients that we saw in the VICTOR trial exceeded 10%.

So to summarize, we should really celebrate all the successes we have had in heart failure and how the outcomes have improved, but we are not done with our work. I haven't even discussed the issues related to quality of life and symptoms as well. So we have some more ways to go and further new therapies, hopefully, will improve the outcome for these patients further.

I hope this short, brief introduction to the topic of residual risk was of help to you and your patients.

Announcer:
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