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Rethinking Heart Failure: The ACC-ECDP Recommendations on the Role of ARNIs

Announcer:
You're listening to *Heart Matters* on ReachMD, and this episode is sponsored by Novartis. Here's your host, Dr. Javed Butler.

Dr. Butler:
Based on the 2021 American College of Cardiology Expert Consensus Decision Pathway recommendations, it might be time to rethink our approach to heart failure. But what exactly do the latest recommendations say regarding the role of angiotensin receptor-neprilysin inhibitors, or ARNis, for short?

Welcome to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and here to help answer that key question is Dr. Nancy Albert, Associate Chief Nursing Officer for the Cleveland Clinic's Office of Nursing Research and Innovation within the Zielony Nursing Institute. She's also a clinical nurse specialist in Cleveland Clinic's George M. and Linda H. Kaufman Center for Heart Failure Treatment and Recovery in the Heart, Vascular, and Thoracic Institute.

Dr. Albert, welcome to the program.

Dr. Albert:
Thanks. Happy to be here.

Dr. Butler:
So, let's just start. First, with this whole thing about the pillars of heart failure therapy; there's a lot of chatter about the four pillars of heart failure therapy and how we are thinking about the management of heart failure with reduced ejection fraction differently. Can you expand on that a little bit?

Dr. Albert:
Sure. Managing heart failure has become more complex in recent years, and when we think about the four pillars, those are the four classes of medications that all of our patients should have as core medications. And so the first class is a renin angiotensin system agent. We ideally would like it to be an ARNi, but it may also be an ACE inhibitor, and if the patient cannot tolerate an ACE inhibitor, it can be an angiotensin receptor blocker. So those three make up the first of the four pillars.

The second pillar is an evidence-based beta blocker. So we know we have three evidence-based beta blockers available to us in the United States today. The third class is a mineralocorticoid receptor antagonist. And the fourth class is our newest pillar and that is a sodium-glucose cotransporter-2 inhibitor, or an SGLT2 inhibitor. And then what's not discussed in those four pillars is that if a patient has hypervolemia or congestion, they probably also will need a loop diuretic and that would be I guess you could say a fifth pillar. But the four pillars are the pillars that can actually decrease morbidity and improve survival in our patients with heart failure.

Dr. Butler:
So I guess this is great news for the patients. That sounds like there are more therapeutic options, but certainly increases some complexity in terms of the management of these patients. So now let's focus on the American College of Cardiology Expert Consensus Decision Pathway. What do they say about the role of angiotensin receptor-neprilysin inhibitor in the management of patients with HFrEF?

Dr. Albert:
So that document came out in 2021, and I think part of the reason for the document was because our United States or American Heart

Association, American College of Cardiology, and Heart Failure Society of America guidelines had not been updated yet. And I think the whole emphasis in that pathway was to increase awareness and use of ARNi as a first line agent in that pillar that we just talked about. And so ARNi should be the clear first drug of choice when patients need to be started on a renin angiotensin system agent and then of course they should be up-titrated every two weeks to get to target dose. So the pathway really helps us to recognize what we should be doing and helps providers understand the newer drug class. It's not new anymore, remember it was FDA-approved in 2015, so we just need to keep in mind we've got one agent available, and that agent should be the first drug of choice in that renin angiotensin pathway.

Dr. Butler:
So if I get what you're saying correctly, you're saying that the pathway now specifically recommends ARNi as a preferred RAS inhibitor or other RAS inhibitors like ACE inhibitors and ARB. Is that correct? And why was that recommendation made?

Dr. Albert:
The recommendation was made because in PARADIGM heart failure, which was one of our research studies, patients received ARNi versus receiving an ACE inhibitor. And it turned out in the patients who received the ARNi, they had a 4.7% absolute risk reduction for cardiovascular death and first hospitalization and a 20% relative risk reduction for those same two composite outcomes, cardiovascular death and heart failure hospitalization. And it turned out you only needed to treat patients for 24 months and you would reduce this composite outcome in 21 patients. And so it's important to understand I think that the trial did not compare an active drug with placebo. It compared an active drug with another active or another class of agent. And because of that, we saw this beautiful benefit that we hadn't seen before, and an important benefit because we have a very high re-hospitalization rate and a cardiovascular death rate in our patients with heart failure and reduced ejection fraction.

So by considering an ARNi as the first line of treatment, we have the benefit of a 20% relative risk reduction that's on top of an ACE inhibitor, which was our go-to agent of choice before an ARNi was available. So that was a very important research study.

Dr. Butler:
But then what do you do if somebody is unable to take or tolerate an ARNi?

Dr. Albert:
So when patients cannot tolerate an ARNi and the number one and two reason for not tolerating it is generally a low systolic blood pressure and moderate-to-severe renal dysfunction, then the next drug of choice is to use an ACE inhibitor. So the ARNi is the first drug of choice in that renin angiotensin system class and ACE inhibitor is the next drug of choice, and if somebody cannot tolerate an ACE inhibitor because of side effect profile or other adverse events, then we go to the angiotensin receptor blocker as our drug of choice. And hopefully one of those three will be able to be used in that renin angiotensin system pillar.

Dr. Butler:
For those just tuning in, you're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Dr. Nancy Albert about the 2021 American College of Cardiology Expert Consensus Decision Pathway recommendations on the role of angiotensin receptor-neprilysin inhibitors in treatment of heart failure with reduced ejection fraction.

Now, what about de novo heart failure? So, if somebody comes into the hospital, has nuance of heart failure, do you start ARNi as de novo therapy as well?

Dr. Albert:
So when we think about patients coming in with de novo heart failure and newly diagnosed and they may not have been on a RAS or renin angiotensin system agent previously, it is OK now to start the patient on an ARNi. They do not need to be started on an ACE inhibitor or an ARB and then if they're tolerating it, work their way up to an ARNi. So in newer research, patients were started on ARNi as de novo therapy and they actually tolerated it very similar to the tolerability of an ACE inhibitor or an angiotensin receptor blocker and they were able to have the medication up-titrated and then get that benefit early on. So we do want to use an ARNi in our chronic heart failure patients and also our patients who have acute decompensating heart failure, even though they were chronic previously, and also in our de novo patients, our patients that are ACE inhibitor or ARB naïve and have never been on one of those two agents.

Dr. Butler:
So that actually makes the management a little bit easier because you start the better drug right up front and hopefully have incremental benefit.

But now let's look at the opposite scenario, which is the more common scenario that the patients are already on an ACE inhibitor or an angiotensin receptor blocker, whether it's for chronic heart failure or even de novo heart failure, they may be on these medications for some other indications like hypertension or something else. What are the considerations on switching somebody from an ACE or an ARB to an ARNi?

Dr. Albert:
Yeah, so we do need to think about switching. And so the first thought is, was the patient on an angiotensin receptor blocker, an ARB? If they were, then the switch is pretty easy because remember that our ARNi contains both an angiotensin receptor blocker and a neprilysin inhibitor. So switching from an ARB to ARNi just means to look at the dose the patient was on and to put them on a relatively similar dose. So if they were on a low dose of an ARB, they're going to start off at low dose of ARNi. If they were on what we would call the target dose of an ARB, then they could start at the mid-range dose of ARNi and within two weeks be up-titrated to the target dose.

But with ACE inhibitors, it's a little bit different. So when somebody is on an ACE inhibitor, they must have that ACE inhibitor discontinued for 36 hours before we initiate the ARNi. And so patients need to be aware of that. We need to give them notes and signs and reminders to stop all drugs for 36 hours. Often time if somebody's on their medicine at night, I'll just tell them not to take their night dose tonight or the next day and then just to start the following day. And that is because there is a risk of angioedema in somebody who is on an ACE inhibitor and then also starts the ARNi at the same time. So we want to reduce the risk of angioedema occurring because it could be fatal in some patients, very few, but it could be fatal. And so, we want to reduce that risk as much as possible and hold off for 36 hours before we start the ARNi.

Dr. Butler:
Well, that's a lot of really very, very valuable information. Are there any final messages you want our listeners to take with them?

Dr. Albert:
I would say when I think about final messages, there are some key insights. One is that ARNi has been available in the United States since 2015 and the uptake in the United States is really not where it ought to be knowing that we're on our seventh year, we'll be at seven years in July. And so we really need providers around the country to look at their patients, and often times providers will say something like, well, you know, my patient's stable, I don't need to make any change. But we need to remember that in the PARADIGM heart failure study, the ARNi was predominantly used in patients in functional class 2. These are patients with mild symptoms of heart failure, not moderate or severe, and yet, we saw this huge 20% relative risk reduction. And so we need to remember that for people that use the term stable in relation to their patients with heart failure, that even patients that they may be considering stable may not be as stable as they thought. They're still at risk for cardiovascular death and for hospitalization, and we just need to remember that the benefits of using guideline-directed medication therapies that have been spelled out for us in the guidelines and in the care pathway from 2021 are really important for all of us to consider and use whenever we can.

Dr. Butler:
Well with those wise words, I would like to thank my guest, Dr. Nancy Albert, for sharing her deep insights into the use of angiotensin receptor-neprilysin inhibitor and what ACC Expert Consensus Decision Pathway is recommending for its use.

Nancy, it was an absolute pleasure talking with you.

Dr. Albert:
Thanks, Javed. Enjoyed it, as well.

Announcer:
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