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Should We Be Resistant to Newer Therapies on the Horizon?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Ferdinand:
One of the interesting things about being a researcher and a physician is that you always are learning something different, and we have new therapies down the horizon. I would also caution that many of these are not FDA-approved and that some of them are available, but not approved for the treatment of hypertension.

Atrial natriuretic peptides, there's a novel one that stimulates guanylyl cyclase B, and it goes on to cause some of the benefits that we see with natriuretic peptides. It has to be done perennially and it's in phase two studies. There's an endothelial receptor antagonist, a dual receptor antagonist. You just heard about aprocitentan, and we're going to hit more data about that soon. The centrally acting aminopeptidase inhibitors, we thought was going to be a really great pathway. We don't know. There's another trial which will be a late-breaker on Monday, we'll see whether or not they will maintain themselves as a means of effectively treating difficult patients. And the non-steroidal mineralocorticoid receptor antagonist, finerenone, has been approved. There are others that are on the way. Finerenone doesn't appear to be a very potent anti-hypertensive agent, but it has a very good effect in patients with type 2 diabetes and kidney disease. And not just CKD three and four, but even one and two, decreasing progression of renal disease and cardiovascular disease. The ARNIs are now Class 1A evidence for HFrEF. The rest of the story is that they also have a blood pressure effect from PARAGON which was for HFpEF. There was a benefit with patients with higher blood pressures. So perhaps a patient with HFpEF, high blood pressure, the ARNI will be beneficial. Not in terms of outcomes but I'm talking here about the blood pressure effect. Sodium-glucose co-transporter 2 inhibitors, the SGLT2 inhibitors. Boy, they're being used for everything now, HFpEF, HFrEF, mid-rEF. There's some data that they lower blood pressure. I did a study and 150 African-Americans were able to lower blood pressure significantly, but George has pointed out that it's not going to be an anti-hypertensive drug class. And I would agree with that, but a person who has diabetes and has elevated blood pressure, perhaps that's an additional benefit.

This cartoon looks at some of the pathways. We're not going to look at every part of the pathway in detail, but it points out where some of the newer agents may come into play. In the RAS inhibition, there's angiotensinogen, siRNA, which may actually block the RAS. It will add to what we have seen with the ACE inhibitors and the ARBs, in terms of their effect in vasoconstriction, sodium retention, and aldosterone secretion. We talked about the ARNIs. It has valsartan, and ARB, and it has sacubitril. So that combination may be beneficial for patients who have hypertension. We know they're beneficial for HFrEF. They have some benefit for hospitalization, not cardiovascular death with HFpEF, but perhaps in those patients who have HFpEF, there's the additional bonus of lowering blood pressure. In the AT1 receptor antagonist, now the big question is, George and I have been doing this long enough. This particular approach failed in the past because of sodium and water retention. And as Shariq has mentioned, we have to be careful in patients who perhaps have heart failure because volume may be something that may be a side effect, but perhaps it's not going to be as much in effect when we dually block ATA and ATB. It remains to be seen. I've not yet seen the data but if it effectively lowers blood pressure and

does not cause significant edema volume retention, it may be an additional means of approaching these patients.

In terms of the natriuretic peptides, the atrial natriuretic peptide has now been formulated in phase two study. It's a novel approach. It simulates guanylyl cyclase A and cyclic GMP. It causes a combination of factors; vasodilatation, natriuresis, and aldosterone inhibition. This is still phase two. It's far away from phase three. It's not yet a prime time, but let's look out for something in the atrial natriuretic peptide family.

The dual endothelin receptor antagonist, aprocitentan, has not been approved by the FDA. It's still an investigational but we're going to hear data at this Congress, that perhaps by blocking endothelin A and B that we can have an effect on blood pressure.

I mentioned the non-steroidal mineralocorticoid receptor antagonist, finerenone, it is available. Doesn't really appear to be as potent of blood pressure effect as spironolactone, has less off-target, and has now been approved by the FDA for protection of progression of renal disease and cardiovascular disease in patients with type 2 diabetes. And remember, it's not just severe CKD, it's patients with CKD one and two. All of this is in the label. The rest of the story is that there are other agents in this particular class. George does a lot in this particular area since he's a nephrologist, and he suggests that perhaps there will be others that have a more potent blood pressure-lowering effect.

This is sacubitril/ valsartan, the ARNI. It has benefit in terms of the neprilysin effect, the vasodilation effect, and the ARB effect. So, these drugs are good for HFrEF, have been shown to decrease hospitalization, not cardiovascular death with HFpEF. But additionally, may be beneficial in patients who have elevated blood pressure.

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