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New Modalities and MOAs for Resistant Hypertension?

Announcer:
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Dr. Vemulapalli:
So, we're going to move forward to our next session, and I'm going to talk a little bit about some of the specialized treatment options and newer modalities for treatment of resistant hypertension.

So, you know, we did talk about the general approach in terms of three drug regimens and spironolactone, but of course, approach can be tailored by comorbidities as well. And I'll just highlight a few of them here, especially since we're at a cardiology conference. So certainly, in patients with heart failure with reduced ejection fraction, Sacubitril valsartan, which has substantial blood pressure effect, MRAs have an indication, SGLT-2s, which you'll hear more about later on in the talks as well as hydralazine and nitrates in African Americans would all be indicated for the heart failure and would be appropriate for hypertension as well. And we've seen a real change in the management of heart failure with preserved ejection fraction over the last couple of years as well. There are now indications for MRAs such as spironolactone or eplerenone, SGLT-2s, and of course Sacubitril valsartan in those groups as well. And I don't think we should forget about, and I think we're appreciating more at the American Heart Association, the interplay between the kidney and the heart. So, in patients with CKD and diabetes with albuminuria, certainly ACE or ARBs are indicated there. We're seeing, and there'll be more data on SGLT-2s in that particular group. And for those that don't know about the drug finerenone is emerging in this place as well, and we'll talk a little bit more about that in subsequent sessions.

So, in terms of the fourth-line hypertensive agent, we've heard a bit about spironolactone, and I wanted to go through the trial data for this. So, this is the pathway to trial, and this was patients who were on multidrug regimens with resistant hypertension who were then randomized essentially sequentially to either placebo, spironolactone, doxazosin, or bisoprolol. And what you can see here, the bar in the red, is the blood pressure reduction with systolic being at the top and diastolic being at the bottom for spironolactone was the greatest, about eight points greater than placebo and about four points or so greater than doxazosin or bisoprolol in terms of the systolic blood pressures. And this really forms much of the basis for the recommendation about spironolactone as a fourth-line agent.

Now, you may have caught on some of the earlier slides, one of the issues to take into account once you're in this fourth, fifth, sixth line agent area is heart rate. So, if you have a patient who remains with an elevated heart rate despite being on multiple medications in the course of their anti-hypertensive therapy there is rationale to actually try to add agents, such as beta-blockers, to decrease their heart rate. And much of this comes from secondary analyses, and I've presented them here. The first one here is the life study. You can see the graph on the right, essentially for risk of onset heart failure for those patients with a heart rate above 84 while on treatment versus patients below, a heart rate below 84. Additionally, heart rate either change or increase of 10 mil, 10 beats per minute, or just persistence of elevated heart rate were major predictors of adverse outcome in that study. And then of course the value study which is Valsartan anti-hypertensive use a similar sort of thing where they actually looked at quintiles of heart rate while on therapy, and the highest quintile of heart rate had the highest risk for the composite adverse outcome of CV death, heart failure hospitalization, nonfatal

MI, and emergency revascularization. So again, thinking about heart rate once you're into that fourth or fifth or sixth-line therapy area is important.

And how about fifth and sixth-line therapy options? We've heard a little bit earlier about direct vasodilators. I'll just point out hydralazine, especially with nitrates in heart failure with reduced ejection fraction in African Americans has a lot of data in the heart failure space. And then I'll mention here as a sixth line agent, or as a last option as Dr. Bakris would say, minoxidil. This is mentioned in the guidelines and can be very effective, but I will say it needs to be monitored very carefully. There's certainly a reflex tachycardia that comes with this. So, use with the beta blocker is very important. There's volume overload, which often manifests itself as pericardial effusion and certainly there's hair growth. And so, it's not always wanted hair growth, especially in our female patients.

So, moving forward, I want to talk a little bit about device-based therapies for resistant hypertension. And much of the pathophysiologic basis for this is based on the fact that there's substantial CNS input or sympathetic activation within the pathophysiology of resistant hypertension.

And I'll highlight a few trials in this area. So DENERHTN was published back in 2015 in the Lancet, and this was about 50 patients in each arm so randomized to renal denervation versus blood pressure control medication. And you can see that there's a substantial decrease in terms of systolic blood pressure between the two arms with it favoring renal denervation. So, this was kind of one of the first large studies that was published in this area. And then we'll move forward a few years, just in the last year or so, the SPYRAL ON-MED data, the three-year data was published, and again this was around 50-ish patients in both arms. This is patients on anywhere between one and three anti-hypertensive medications, still uncontrolled, with blood pressures generally in the 150-plus range. And what you can see on the graphs there are the 24 months in the top row and then the 36 months in the bottom row blood pressures with the first column being the 24-hour systolic blood pressure. And then I'll point you towards the last column being the clinic blood pressures. And again, a substantial difference in favor of device therapy here for these patients with drug-resistant or partially drug-resistant blood pressure.

And then I'll finish with the Radiance Trio study. This was about 130 patients with uncontrolled hypertension despite the use of three medications. And this was actually kind of prescribed three medications, including a diuretic. And what I'm showing you here on the panel on the left is the renal denervation group. You can see there just under 70 patients. The panel on the right is the sham control group here. And what you're looking at is 24-hour blood pressures. And the first part of each panel is the daytime blood pressure. And the second part is the nighttime blood pressure. And you can see that the change, so the blue line is pre and the red line is couple months post. The change in blood pressure is greater in the renal denervation arm than in the sham arm.

So, I think you'll see more in terms of on Monday, there will be further data about the SPYRAL ON-MED study that's presented as a late-breaker. But I also want to point towards newer pharmacotherapy that's in development here. So, you'll see baxdrostat, and that's a non-steroidal inhibitor of the mineralocorticoid receptor, has been shown to reduce proteinuria in CKD patients, and there's a phase two study that's going to be presented here at AHA, which is randomized double blind placebo-controlled, so be on the lookout for that. And then of course, aprocitentan, which is a dual endothelial receptor antagonist, and the PRECISION trial, which we've heard a little bit about and we'll talk more about in a few minutes, is going to be presented with nearly 2000 patients here at AHA as well.

So, the key messages, spironolactone is recommended of course as a fourth-line agent in resistant hypertension, and that's based on the pathway 2 trial. Direct vasodilators such as hydralazine and minoxidil can be used as fifth and sixth-line agents, certainly need to watch out for side effects, especially with minoxidil. And there are therapies, device-based therapies on the way that are targeting the impact of the sympathetic nervous system on resistant hypertension. And then, of course, endothelin receptor antagonism is being presented here at AHA 2022 and may be on the horizon depending on the results.

Announcer:
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