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What New Therapies (drugs and devices) Are on the Horizon for Resistant Hypertension?

Announcer:

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Dr. Vemulapalli:

Hi, everybody. My name's Sreek Vemulapalli. I'm an Assistant Professor of Medicine and a cardiologist at Duke University Medical Center, and today, we're going to be talking about therapies on the horizon for resistant hypertension. I have two distinguished guests with me today. Dr. Ferdinand, would you mind introducing yourself, sir?

Dr. Ferdinand:

Hi, I'm Dr. Keith C. Ferdinand, Professor of Medicine, Gerald S. Berenson Endowed Chair in Preventive Cardiology at Tulane in New Orleans, Louisiana.

Dr. Vemulapalli:

Right, thank you, Dr. Ferdinand, and Dr. Shah, would you introduce yourself, please?

Dr. Shah:

Absolutely. Hello, everyone. My name is Nishant Shah. I'm an Assistant Professor of Medicine here at Duke University Medical Center. I work in cardiometabolic prevention. I'm happy to be here.

Dr. Vemulapalli:

Right. Thank you both for being here. I wanted to start off our conversation, Dr. Ferdinand, with you. Where do you see the real holes are right now in terms of available therapies for patients with true resistant hypertension?

Dr. Ferdinand:

Well, first of all, resistant hypertension is anywhere from 10 to 15% of the population. These are persons on three or more medicines, one of which could be a diuretic at maximum tolerated doses, don't have their blood pressures controlled to the new goal of less than 130 over 80, so it's a growing problem as the population ages. The medicines we have are really excellent if you're using a long-acting thiazide-type diuretic calcium blocker and a RAS-blocking agent, then you add a mineral corticosteroid receptor antagonist, that goes a long way, but still, there are other classes of agents that are looking at different ways of approaching that. We know endothelin plays a part of that. There's an endothelin receptor antagonist that's on the works. There's some central RAS agents, one called Firibastat that works in the brain, and even the SGLT2 inhibitors, which were first approved for diabetes, and we now know are cardiovascular medicines, may have a part in resistant hypertension.

Dr. Vemulapalli:

Thank you. Dr. Shah, you know, Dr. Ferdinand talked a little bit about the endothelial receptor antagonist. Can you tell us a little bit about that and what we might expect here in the next few months to year in developments in those areas?

Dr. Shah:

Yes, absolutely, and it's a great question and a really exciting area of research. As Dr. Ferdinand mentioned, you know, there's so many classes of drugs that we have available at the moment, and you know, we know that they work well when used together with different mechanisms of action. However, as Dr. Ferdinand mentioned, resistant hypertension, even refractory hypertension, is still very prevalent, and so looking exactly at the endothelium is a very exciting area. We've seen endothelin receptor antagonists work really well in other settings in terms of dropping pressures in the pulmonary vasculature, for instance, in the heart failure space, and so knowing that data, knowing how much it's worked before, we're hoping to see this have a big impact in the blood pressure space in general. The endothelin receptor antagonists work along the different cyclooxygenase pathways as well as well as nitric oxide, and so there's a lotta downstream effects of these therapies that should be very helpful.

Dr. Vemulapalli:

Perfect. Thank you. So you know, given that this is a new mechanism of action, obviously, there's ongoing clinical trials here. We don't actually have an indication yet for an endothelin receptor antagonist for resistant hypertension, so you know, I think we want to focus in a little bit here on what might be coming in the future. So obviously, there's the precision trial that's ongoing right now with apocritentan. Dr. Ferdinand, can you talk a little bit about what the timing might be where we might expect those results? Is that later 2022, something like that?

Dr. Ferdinand:

Well, we really never know when the FDA is going to approve apocritentan, but the high-lying results, which means this is not peer-reviewed, it's not been finalized, suggests that it will reduce blood pressure in those patients with true resistant hypertension without any bad side effects. Previously, we had the difficulty with endothelin receptor antagonists with fluid retention, but this one blocking ETA and B doesn't appear to have that problem, so don't know, but I would suggest perhaps by the end of 2022, we may hear the final results and maybe even FDA approval this year.

Dr. Vemulapalli:

Yeah, that would be, I think, really exciting, given, you know, the difficulty, despite having multiple drugs, as you mention, and mineralocorticoids for some patients. You know, I also want to spend a few minutes and talk a little bit about other therapies, so we've mentioned a couple of drug therapies. What about device therapies on the horizon? Dr. Shah, any thoughts there, especially around renal denervation?

Dr. Shah:

Absolutely. You know, renal denervation is evolving. We've had a lot of sham controlled randomized trials just to see, you know, what the impact is, and there certainly been mixed results, to say the least, but I do think this is, you know, an area that needs more exploration and evolution, and just like all device therapies, you know, over the history and cardiology, and so looking at technologies to better denervate, how we do the ablations, things like that, I think will evolve. One of the limitations as well in the early denervation trials has been the fact that many patients may have not been on medical therapies or may have not been, you know, appropriately increased in a stepwise approach to medical therapy.

We know that in defer hypertension, they did use that approach and did see a little bit longer term benefit, but we also don't know what the outcomes are like, and so these are questions that hopefully trials will be able to provide us in the denervation space to see if there is truly a benefit. In terms of other devices, you know, the baroreflex device therapies are also something that is evolving. We've not seen too much in the way of conclusive evidence just yet because it's quite new, but that is something else that we should look for, where we look at devices that essentially work on our carotid baroreflexes to help reduce blood pressure, so definitely keep a lookout for that.

Dr. Vemulapalli:

Dr. Ferdinand, you know, ACC this past year, SPYRAL ON MED, which has been going on for quite some time, actually, presented results from their first about 80 or 100 patients, and I think we're expecting the sort of rest of the couple hundred patients later on this year. You know, Dr. Shah mentioned this long evolution, especially with renal denervation going back, you know, all the way to SYMPLICITY 3 hypertension. How do you think about renal denervation given some of the failings that have happened several years back, and now more promising data that seems to be coming forth?

Dr. Ferdinand:

Well, hypertension is perhaps the most potent and prevalent cardiovascular risk factor. It's difficult to control in many patients, and the new device is appearing better than the simple unipolar device that we'd use in SYMPLICITY 3. Another unknown fact about SYMPLICITY 3 is that the African American cohort actually did better on the placebo because they started taking their medicine. So here's the bottom line: make sure the patients are taking conventional medicines. There's no magic bullet such that renal denervation is

going to overcome nonadherence. The outcomes with the Spyral catheter, which is an improvement from the original unipolar catheter, may actually suggest that this will be a safe and effective therapy, but it won't obliterate the need to take medicines and take them appropriately.

Dr. Vemulapalli:

I think that's a really key point there, and it sort of brings me to the question I want to conclude with, which is if, let's say, we fast-forward a year from now, and we have at least one endothelin receptor antagonist that's been approved for resistant hypertension with some efficacy there, and one or perhaps even multiple device-based therapies for resistant hypertension, where does all this fit? Like if I'm a simple cardiologist or a primary care doctor, and I've got my at least five or six other medications that I might use in these patients, and now, I've got these devices, and I've got endothelin receptor antagonists, what do I do with all this? Dr. Shah, you want to start with that?

Dr. Shah:

Yeah, I think that's a really great question, and it's a, you know, question we're seeing a lot of in so many different spaces in cardiology: lipids, diabetes, et cetera, and so what I would say, and then I think this is the art of medicine, right. Everything is very patient-specific, and we need to identify the right patient that these therapies will help. I think it adds more tools in our pocket to be able to help patients, particularly those that are, you know, adherent, are using the lifestyle modifications we talk about, don't have any other secondary causes of hypertension, aren't on any medicines that could be causing their hypertension. You know, we know that there's a subset of patients with resistant hypertension just based on genetics that tend to just mount high blood pressures, and maybe these therapies are better for those people, and so I think this certainly fits, but we do need to be very directed at the patient-specific needs.

Dr. Vemulapalli:

Dr. Ferdinand, your thoughts on that, and especially how we integrate that with hypertension specialists?

Dr. Ferdinand:

I certainly agree with the comments. I think the future potential is going to be to recognize the potent and prevalent risk factor that hypertension really is, but you know, a lot about interventions and a lot about lipids, hypertension is right up there. The benefit will be using the conventional medicines and ensuring adherence using text messaging and other novel means, including self-monitored blood pressure, to communicate with the patient and share decision-making. Once you've done all the right things, I think the addition of endothelin receptor antagonists and even in some cases renal denervation will greatly lower those patients who have resistant hypertension, true resistant hypertension: taking their medicines, trying to control the blood pressure, and cannot effectively get the blood pressure less than 130 over 80.

Dr. Vemulapalli:

Well, thank you both through really a great discussion today about some of the new therapies on the horizon for resistant hypertension and really just the beginning of an exciting time for the treatment and control of hypertension, so thank you.

Dr. Ferdinand:

Thank you.

Dr. Shah:

Thank you.

Announcer:

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