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Understanding the Mechanisms Behind Resistant Hypertension

Announcer:
You're listening to *Heart Matters* on ReachMD, and this episode is sponsored by Mineralys Therapeutics Inc. Medical Affairs. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *Heart Matters* on ReachMD. I'm Dr. Steve Jackson, and today we're taking a closer look at the key drivers of resistant hypertension and how we can address them. Joining me in this conversation are Drs. Jan Basile and Michael Bloch.

Dr. Basile is a Professor in the Division of Cardiology at the Medical University of South Carolina in Charleston. Dr. Basile, thanks for being here today.

Dr. Basile:
Nice to be with you.

Dr. Jackson:
And Dr. Bloch is a Clinical Associate Professor in the Department of Internal Medicine at the University of Nevada School of Medicine. He's also the Medical Director of Vascular Medicine and Anticoagulation Services at the Renown Institute for Heart and Vascular Health in Reno. Dr. Bloch, it's great to have you with us as well.

Dr. Bloch:
Thank you so much. Looking forward to our conversation.

Dr. Jackson:
To get us started, Dr. Basile, how do you define resistant hypertension, and what factors help you distinguish true resistance from pseudo-resistance or secondary hypertension?

Dr. Basile:
That's a very good question, and a controversial one, because some are using less than 140 over 90, but with the ACC and AHA, we're now using less than 130 over less than 80 as our target. So it's three classes of antihypertensive agents, one of which is a diuretic, that do not enable the patient to get to the target blood pressure of less than 130 over less than 80.

My concern with that is I'd see patients referred to me who would be on a beta blocker and a diuretic. And those classes of drugs don't make pathophysiologic sense to me. In my mind, the definition should be—and in the white paper in 2018 in hypertension, it was embellished by saying that it was including—a renin-angiotensin system inhibitor, a calcium channel blocker, and a thiazide diuretic.

Now, there are times you have to use a loop, but they are venodilators, and I would only use them when the GFR was low and very low and they had edema. So I think the best definition is on a RAS blocker, a calcium channel blocker, and a diuretic.

Dr. Jackson:
And in your experience, Dr. Bloch, where do you see clinicians most often running into challenges when trying to determine whether a patient truly has resistant hypertension?

Dr. Bloch:
It's a great question. We run a resistant hypertension clinic at my office, and many of the patients that we get referred meet that definition of resistant hypertension. But oftentimes, patients don't. And there's a number of reasons why that might be—why a clinician

might think a patient has resistant hypertension, but in fact they don't really have resistant hypertension, and they perhaps have what we call pseudo-resistance, which is blood pressure that looks resistant but is not necessarily meeting that definition.

The first is, as Jan alluded to, inappropriate regimen. The second thing, though, is adherence. It's a really big issue in the management of hypertension. And many times, we have patients who we think are resistant, but it's just simply that they're not taking their medications.

And then the third, and also a very important concept, is how we're measuring blood pressure. Blood pressure measurement seems simple, but it's actually quite complex. Just getting a good measurement in the office can be difficult. And our guidelines talk about making the definition of resistant hypertension out of the office, so using home blood pressure monitoring and ambulatory blood pressure monitoring to confirm that diagnosis. And that leads to all sorts of potential constraints in terms of determining what a patient's blood pressure actually is. It's a really fundamental issue, but one that we face every day in the office: is what is my patient's blood pressure?

Dr. Jackson:
So if we zero in on the underlying biological drivers here, Dr. Basile, what mechanisms are most important to consider in these patients, and where does aldosterone play a role?

Dr. Basile:
The mechanisms in hypertension, which clearly are part of the patient that presents with resistant hypertension, has to do with volume excess, salt and water retention, renin-angiotensin-aldosterone activation, and sympathetic nervous system activation. And it's the interplay of these three main pathophysiologic systems that contribute to hypertension.

Many times, these drug classes that are used in patients as the first three do not appropriately antagonize these systems, and often that is not including a diuretic. That leads to volume excess or inappropriate volume reduction, and no matter what you do, the patient continues to have resistant hypertension.

The other thing is lifestyle management. Patients may be having canned foods, frozen foods, and foods that are high in sodium. And depending on their renal function, they may not be able to get rid of that sodium load appropriately. And that leads to volume excess as well. So these are the three main pathophysiologic mechanisms.

The role of aldosterone clearly is important. And we're anticipating the release of the first aldosterone synthase inhibitor, which do not block the receptor where aldosterone interacts to cause hypertension but actually blocks the synthesis of aldosterone.

Dr. Jackson:
For those just tuning in, this is *Heart Matters* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Drs. Jan Basile and Michael Bloch about underlying drivers of resistant hypertension that may go unrecognized in routine care.

Now, when we haven't fully identified these underlying mechanisms, we often find ourselves escalating therapy. So Dr. Bloch, how can stacking antihypertensive meds influence outcomes, and where might that approach fall short in addressing what's truly behind resistant hypertension?

Dr. Bloch:
I think we need to take a little bit more thought in terms of how we stack these pharmacologic agents and maybe take a bit more of an individualized approach. Taking just a step back to that initial foundational treatment of high blood pressure before you even make the diagnosis of resistant hypertension, that ACD therapy that Jan described—something that blocks the renin-angiotensin system, a calcium channel blocker, and a diuretic—really should be the first attempt in the vast majority of patients. Our guidelines say to start with two of those medicines in a low-dose fixed combination and then add a third and increase the dose. And that should happen over months. Three to six months should be enough to get that initial foundational therapy on board in a patient, or at least attempt it, as long as it is tolerated. And oftentimes, it takes much longer than that in our current delivery system.

So then getting more to your question, what about a patient who's already on those medicines? We have to really think about the pathophysiology of resistant hypertension. Why is it that despite this therapy, our patient's blood pressure is not well controlled? As Jan mentioned, aldosterone is one of the key drivers of that. We know that the longer patients have high blood pressure, the more likely it is that their aldosterone levels are going to rise despite activation of the renin-angiotensin system. So this aldosterone escape becomes very important in resistant hypertension, but it's not the only driver. We're also not blocking the endothelin system, which is a very powerful vasoconstrictor. We're not blocking sympathetic tone very well.

And so I think we haven't really had a lot of drugs or other interventions to block those systems for a while. But now, we have these interventions that are going to take care of some of that pathophysiology that's been unaddressed previously.

Dr. Jackson:
In day-to-day practice, identifying these underlying drivers isn't always straightforward. So from your perspective, Dr. Basile, how do real-world factors like access to care, follow-up, or available diagnostics affect your ability to fully evaluate and manage these patients?

Dr. Basile:
Adherence is really a major problem. For the many years that I've been in practice, I've had patients bring me their last filled bottle of any medication that anyone writes for them, and I want to see everything that they're on. I want to make sure that they don't have any interfering substances or any drugs that are going to cause excess weight, which may contribute to their blood pressure being elevated.

Patients often will tell me, "Well, Dr. Basile, you know what I'm on," or, "Here's my list." Well, the reality is I e-script and hope that the patient will go and pick it up, but they don't, and the medicine is restocked on the shelf. My office is never called. As Michael said, the follow-up is in three to six months or even longer. I think they're on the medicine; they've never been on the medicine. They then bring me a list, and they're not on the medicine, and that's why maybe they're not being controlled.

In fact, in one of the studies that Michael and I were involved in, when we took patients on three or more medicines and we gave them a triple antihypertensive medication that had a RAS blocker, a CCB, and a diuretic in it, and then we studied them to see if they were still eligible to get into the trial, 42 percent were no longer eligible. We reduced their pill burden. We gave them one pill instead of three, and it was once a day, and now they were much better controlled. So you can see adherence is a big thing to do.

Now, we didn't really mention home blood pressure. White coat was mentioned in the 2018 white paper that we had on resistant hypertension. And now, in our 2025 ACC/AHA guideline, where there is a small part but not a separate white paper to resistant hypertension, they are talking about home blood pressures being the most important blood pressure to make decisions on treatment, uptitration, and effectiveness of blood pressure control. It turns out that home or self-measurement of blood pressure correlates better with target organ disease and vascular effects than office blood pressure. So that's another thing that's important.

Dr. Jackson:
And finally, Dr. Bloch, as we look ahead, how can clinicians better align treatment decisions with drivers of hypertension rather than relying primarily on stepwise escalation?

Dr. Bloch:
First of all, it's important to make a distinction between the early treatment of run-of-the-mill, mild-to-moderate hypertension and the treatment of resistant hypertension. When we're talking about the initial management of people with blood pressure, I think we can take an algorithmic approach. And many systems have done that with a good deal of success. ACD therapy really should be the foundation of care in the vast majority of patients, and this can be uptitrated with an approved pathway by a pharmacist or even MAs who work with patients with remote monitoring. So I do think the algorithmic treatment of high blood pressure in its early stages makes a lot of sense given the population health issues.

But once you get to a patient who appears to be resistant, who either is on ACD therapy or can't tolerate ACD therapy, that's when I think we have to stop treating these patients like they are all the same. There are probably twenty million people in the US who are treated but not controlled, and there are probably different drivers of hypertension, different socioeconomic factors, and other health issues going on with each of these patients.

I think taking a personalized approach makes a lot of sense. For example, we may have patients where adherence really seems to be an issue. In those patients, we may want to approach an adherence-independent therapy like renal denervation. Another example is potentially a patient with advanced kidney disease, where we're a little bit concerned about adding more diuretic therapy, particularly an MRA. In those patients, an endothelin receptor antagonist may make more sense.

So I think we're really entering an era where we need to move towards an algorithmic approach to treating most patients' blood pressure, and then a thoughtful, individualized approach to patients who appear to have resistant hypertension.

Dr. Jackson:
That is a great way to round out our discussion. And I want to thank my guests, Drs. Jan Basile and Michael Bloch, for joining me to explore underrecognized drivers of resistant hypertension and how we can address them.

Dr. Basile, Dr. Bloch, it was great having you both on the program.

Dr. Basile:
Thank you for having us.

Dr. Bloch:
Thank you so much.

Announcer:
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