Aldosterone-Targeted Therapies for Uncontrolled Hypertension in Chronic Kidney Disease
Audience Q&A from the Live Symposium

Dr. Luther:
So I presented the administration of aldosterone plus salt to animals, and this is in multiple studies; I just showed one study. If you give aldosterone, and I never showed this, but if you just give aldosterone without sodium, you don't get the end-organ damage—so kidney fibrosis or heart damage. But if you add salt to the drinking water, or if you give excess sodium, you get end-organ damage. So the question is, is it the sodium retention or the sodium chloride that has the effect? Or is it in a secondary part—is it blood pressure-related or just renal damage?

So in that study I showed, those rats did not actually develop hypertension. Their blood pressure did go up slightly, so I won't say that it didn't increase blood pressure, but they didn't have severe hypertension, and they still had that injury. So the combination of salt and aldosterone—I would say we don't fully understand why that occurs or why the sodium chloride is essential. But this is well known to researchers that do these animal studies; you have to give salt in combination to aldosterone, and it's not a blood pressure effect per se.

And let's see. The second part is, is it for the blood pressure too, or just the renal damage? And I think the more salt you give with excess aldosterone, there are additive or synergistic even effects on blood pressure. So I do think it does contribute to the severity of blood pressure.

Vivek, do you want to comment on how sodium chloride plus aldosterone contributes?

Dr. Bhalla:
It's a good question. I don't think we totally know, but this phenomenon of salt plus ligand or salt plus activated mineralocorticoid receptor is mirrored in cardiology studies, in preclinical models, as well as in kidney. So it's the same phenomenon that if you have activated mineralocorticoid receptor plus salt, that's when you get the damage compared to salt alone or the mineralocorticoid overexpression or aldo treatment alone. So I don't think we know exactly why, but that's what's been shown.

Dr. Luther:
And if you think you're eating a low-sodium diet in the US, you're not. When we do these studies—and I've done some of these studies in our Clinical Research Center—we have to special order foods, bread especially, that basically has elemental sodium in it to get a sodium down to what we consider to be low salt, which is 10 mEq a day. It's almost impossible with food that you can buy off the shelf. So nobody in the US is eating low-sodium diet. The average is about 160 mmol a day in the Southeast, and that's way higher than is necessary to achieve the end-organ damage with aldosterone.

Dr. Dwyer:
And the trials for kidney stones were 50 mEq per day, and you're talking 10 mEq per day. So think about that as it relates to regular diet, kidney-stone diet, ultra-low-sodium diet in these trials.

Vivek, you have a question?

Dr. Bhalla:
Yeah, this was a question for anybody, but I'll go ahead and take it. It's noted to be more of a curiosity

than a question. How sure are we that the effects that we've been talking about are high aldosterone, or is it the low renin? And could it be the low renin itself that's causing kidney or other tissue damage? Or is it really, you know, the aldo-renin ratio?

And to that, I would say that I think some of the analysis that's been shown shows that it's probably a combination of the two, particularly because when you look at the groups and you look at outcome data and the classifications of those groups, those that have the highest events are those that have a low renin but also have a normal or high aldosterone, and exclude those that have a low aldosterone. So the low-renin, low-aldo group is not classified as the one that gets the higher event rate. And so it's probably a combination of both.

In some respects, the low renin is a sign that the aldosterone or the aldosterone action is sufficient to drive the renin down. You know, combined with a high-salt diet, it's sufficient to drive the renin down, but I think it's a combination of both. And in the low renin is more of a biomarker than anything else. It's a good biomarker. But if you have a normal to high aldosterone, then that's considered inappropriately high as far as this is when we're looking at classifiers of subclinical aldosterone or sub-aldo dysregulation and the outcome data.

That's what I would say. Unless you guys—

Dr. Luther:
I would say the interpreting the aldo-renin ratio is something that everybody should think about a lot, because I think we should send it more. So if you see a high aldosterone and a high renin, you also have to think about what medicines they're on and what their blood pressure is. So if they're hypertensive and they have a high aldo/high renin, you know, it could be due to the medications. I see a lot of people with malignant hypertension where this system is just spiraled out of control. They have high aldo/high renin.

In the patients with primary aldo, they've already got high blood pressure and often or occasionally low potassium. So we're looking for what's driving that. So high aldo is often what's driving it. And, as Vivek mentioned, the low renin is kind of a readout of the effect of aldosterone.

And conversely, if somebody has low blood pressure and you measure their aldosterone and renin, this might be something you're doing in a patient with Gitelman if you're a nephrologist—Gitelman or Bartter syndrome—they have the highest aldosterone and renin measurements that you're going to find. So they're going to have aldosterone in the hundreds, renins that are extremely high. And that's appropriate. It's reflective of their low blood pressure. They're not reabsorbing sodium chloride like they should. And that's appropriate for the system to do that.

We're focusing in on high aldosterone and low renin as being a marker of dysregulated or autonomous aldosterone production. So it's inappropriate.

Dr. Bhalla:
I think the corollary to that point is also really important, which is that medicines like diuretics and medicines like ACE inhibitors and ARBs are known to raise the renin. And oftentimes you will see a patient, and whether it's because they have independent aldosterone secretion or an additional concomitant high-salt diet, they will have a low renin on those medicines. You don't need to remove the medicines to see it. You see it when you just do a random screen, and that can tell you something, that if

you're seeing a low renin in the setting of medicines that are supposed to raise the renin, you know it's truly, really, really low. You can be confident in that measure.

Dr. Luther:
That's exactly what I'm doing. Yeah, if you draw it on a thiazide plus an ARB, yes, it's like a confirmatory test.

Dr. Dwyer:
Thanks again to AstraZeneca for providing the educational grant for this session and to Vox Media for sponsoring this symposium. Thank you all.