Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/aldosterone-targeted-therapies-for-uncontrolled-hypertension-in-chronic-kidney-disease/56405/

Released: 05/15/2026
Valid until: 05/15/2027
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Aldosterone-Targeted Therapies for Uncontrolled Hypertension in Chronic Kidney Disease

Announcer:
Welcome to CME on ReachMD. This activity, titled Aldosterone-Targeted Therapies for Uncontrolled Hypertension in Chronic Kidney Disease, is provided by Vox Media. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Luther:
All right. Thank you very much. So I'm going to introduce the role of aldosterone in the pathophysiology of kidney disease. I've consulted with aldo synthase inhibitors, which I'm not actually going to talk about in my presentation, but others will in their presentation.

So aldosterone regulates sodium and chloride transport in the kidney, and this is done classically under the regulation or stimulation by angiotensin II. So angiotensin II, in the setting of low sodium intake, appropriately stimulates the angiotensin I receptor, which then, in turn, in the adrenal produces aldosterone, which signals through the mineralocorticoid receptor in the kidney and other epithelial tissues, where it produces sodium retention, potassium excretion. And this results in volume expansion and restores, ideally, plasma volume and maintains blood pressure. But when it's inappropriate, will produce hypertension.

It can also signal in non-epithelial tissues such as the heart, where it can cause cardiac fibrosis, perivascular inflammation, and glomerular injury. So that's what we'll talk about here today.

Aldosterone can also be produced autonomously by the adrenal gland, oftentimes by either an aldosterone-producing adenoma or 50% of the time by both adrenal glands. So this is done without the stimulation of angiotensin II, so it's produced autonomously, where it, in an unregulated fashion, stimulates this pathway. And in that setting, it can produce hypertension, hypokalemia, through volume expansion, through these classically mediated pathways.

Other non-aldosterone mineralocorticoids can also activate the mineralocorticoid, such as deoxycorticosterone, corticosterone. These are more minor steroids, but cortisol can also do this. So when cortisol is extremely high or dysregulated, it can also activate the mineralocorticoid receptor.

So we think of primary aldosteronism—and we'll talk about that today—in relation to renin status. That's the hormone that's most easily measured in humans clinically.

So I've got the slide. This is in a *Hypertension Secrets* book, which is available, but if you measure aldosterone and renin, you can classify people as either high aldosterone and high renin. So this would be also a high angiotensin state. So renin stimulates the production of angiotensin II, which then stimulates aldosterone. So this would be appropriate or secondary aldosteronism, and this is often caused by a lot of different medical conditions. Oftentimes, or most often, it's due to medication. So diuretics will do this.

We're talking about unregulated or autonomous aldosterone production today. So aldosterone is often high or high-normal or inappropriately normal, and renin is either low or undetectable in those conditions. So this is called primary aldosteronism. This can be due to an adrenal aldosterone-producing adenoma. It can be idiopathic or bilateral. And it can be due to bilateral adrenal hyperplasia. There are some rare familial syndromes that cause this. I'm not going to go through those today. And there's other mineralocorticoid

excess that are classified by low aldo/low renin. And these are interesting to me, but I'm not going to go through this today, in this lecture today.

So resistant hypertension is the state where we often find aldosterone excess. So resistant hypertension is when a patient has uncontrolled hypertension on either three or more medications, including a diuretic. So most patients with hypertension are controlled, but in those people, about 12 to 15% of hypertensives that are uncontrolled or have resistant hypertension, a lot of these are just not taking their medicines. So if you really do a study, give them medicines, and properly determine this. A lot of them are controlled if you just observe them taking their medicines and do proper ambulatory blood pressure or characterizing them.

So a significant number of people, though, are uncontrolled on these medicines. So these people that have resistant hypertension have a higher cardiovascular risk. And as we'll go through in some of the other slides, they have a higher incidence of primary aldosteronism.

So primary aldosteronism is, if you take all these people that are referred to a hypertension clinic, so most but not all the people referred to this clinic would have resistant hypertension. And Gian Paulo Rossi in Italy characterized all these people, and he put them all through this phenotyping protocol to determine if they had primary aldosteronism. So 85% of them had essential hypertension, and about 11% of all the people that were referred to his clinic had primary aldosteronism. So they had elevated aldosterone, they had low renin, and if you take the ratio of those two—so if you do it for a renin activity, so this is the way that he did it, the ratio above 40, or if they're given captopril and the ratio is above 30, then the likelihood that they have PA is very high.

So of those people, it's about 50/50 roughly. I'm not going to go into the details, but 1/2 of those people have an aldosterone-producing adenoma, and 1/2 of them, roughly 57%, actually have idiopathic or bilateral primary aldosteronism.

So these people would benefit from adrenalectomy and surgery. These people here that have idiopathic hyperaldosteronism, or IHA, would benefit from just medical treatment.

But we don't really do a very good job of it. If we look across the best institutions across the US or VA institutions, the screening rate is very low. So the height of this is just the number of patients. This is the percent. The black line here on the bottom is the number or percentage of people that are actually screened for primary aldosteronism. So it's a very low percentage, around about 2 to 5%, so very low screening rates. We don't do a very good job.

And if you follow that trend over time, it hasn't improved or changed, even though we have increasingly recognized this condition as being something important that we should target. And we even think it's probably present in even more people than resistant hypertension. So if you just look at the general population that just have normal blood pressure, some of them have inappropriate aldosterone. If you measure in the 24-hour urine the excretion rate for the day, all these people have suppressed renin or low renin on a high sodium diet, and they still excrete a lot of aldosterone, suggesting that they have unregulated or dysregulated aldosterone production. And this percentage increases in the people with stage 1/stage 2 hypertension, and it becomes fairly common in the people with resistant hypertension.

So primary aldosteronism is very common. It correlates with the stage or severity of hypertension, and we don't do a good job of picking this up and treating it.

So onto the part about the pathophysiology of aldosterone, or just the evidence that it promotes kidney injury. If you just take rats and you treat them with aldosterone—and you have to give them salt, by the way; if you give them just aldosterone, it's not enough.—if you give them excess sodium in their diet where they're given it in their drinking water, it promotes cardiac fibrosis, and this is osteopontin staining, so evidence of damage here. And you can block this just by giving an MR antagonist, such as either eplerenone in this study. Other studies use spironolactone. Newer drugs use finerenone or other newer nonsteroidal MR antagonists. So aldosterone plus salt, which reflects the sodium intake in the US population. It's very high. It's inappropriate. So you don't really have to think of people's intake as being extra salt. It's very hard to get a low sodium intake in our modern culture.

So aldosterone produces inflammation, fibrosis through a number of injuries. It also produces hyperfiltration. So it can also signal in increasing vascular resistance in the efferent arteriole in the glomerulus. This increases the pressure in the glomerulus and results in hyperfiltration. So this is just one mechanism by which aldosterone produces kidney injury. It also brings in inflammatory cells and drives hypertension as well that produces kidney injury that can be prevented and improve kidney outcomes.

So just some of the clinical evidence that is emerging showing that aldosterone is associated with worsening kidney function in patients that we're treating. So the classical way that you measure, or should measure, for primary aldosteronism is an aldosterone renin ratio. Pay attention to whether your institution measures renin activity or renin concentration.

So in this example, in this study here by Dr. Hundemer, they measured renin concentration, because you can tell by it's a concentration of the renin instead of in activity units, but the Y axis here is a decline in eGFR. So the more negative it is, the steeper the slope and the

more rapid the decline in GFR.

So aldosterone itself, if you just look at aldosterone, does not really correlate very well with the rate of kidney decline. If you look at renin, you can see that the group here that's the lower renin has actually worse outcomes. So that's a significant finding.

If you combine the two and you're looking at the ratio, you can see that as the ratio of the aldosterone to renin increases, it's associated with bad outcomes. So these people have inappropriate—you can think of this as having inappropriate aldosterone excretion or production that's associated with worse kidney decline over time.

Other studies have also started to show this. This is a more recent study as well. So on the top here is this classifying people with rapid kidney decline. So the aldo-renin ratio here, the higher the aldo-renin ratio here is associated with higher hazard ratio of kidney function decline. So as opposed to the prior study, just if you look at aldosterone, it also is associated with it. But the people that have the highest rate here—if you just look at renin, you can see it's the low renin category here. And as you approach higher renin, it's more equal to 1.

So this goes along with the prior slide as well, showing that inappropriate or excess aldosterone production is associated with kidney injury.

And just shown on the bottom part here is similar to the previous slide, is the eGFR decline or kidney failure. The same study is looking if you put them on a heat map and you think of this conceptually, the renin here is shown on the X axis, the aldosterone concentration on the Y axis, and the color—so red is the highest incidence of kidney function decline—you can see it clusters here in this group that is a low renin. So pretty much everybody. The rate here is the highest in low renin, and it tends to be people with higher aldosterone. And that's basically what we were seeing in that other slide, just shown in a different way.

So not just aldosterone, but low renin, so it's inappropriate aldosterone production or dysregulated aldosterone production. So hopefully that concept is getting through.

And if you treat patients with an MR antagonist, you should increase renin. And this was one of the studies that was a paradigm shifting study that showed that if you look at patients who were treated with primary aldosteronism and they achieved a renin activity, their incidence—so this is unsuccessful treatment. If their renin activity remains suppressed or less than 1, their incidence of cardiovascular events is higher than those people who are treated and achieve non-suppressed renin activity. And that's similar to the rates in essential hypertension.

So this was a paradigm shifting thing that was cardiovascular outcomes. Now we're seeing that in people, if you look at the rate of kidney function decline, patients that have primary aldosteronism and are treated with surgery here, their rate of decline is similar to the patients with essential hypertension, as opposed to if they're treated with MR antagonists and don't have as successful treatment.

Shown better in this slide is that this group from Japan looked at the patient's response by the plasma renin activity. So if you treat and you achieve again a renin activity greater than 1, then you mitigate this rate of eGFR decline, as opposed to the people with suppressed—potentially continually suppressed—plasma renin activity, there is ongoing kidney injury and ongoing decline in eGFR.

And the last section here, I'll introduce and Dr. Bhalla will carry on this about treatment with MR antagonists. So not just in primary aldosteronism, but this extends to other kidney disease. So this first example is people with diabetic nephropathy. We've known for a long time that if you treat patients with an ACE inhibitor, it should decrease aldosterone, so it blocks the angiotensin II, that blocks the stimulus for aldosterone production. But some patients don't achieve suppression of aldosterone, and they actually, over time, their aldosterone increases. So some people used to refer to that as aldosterone escape. I think a better term is aldosterone breakthrough to treatment. And they have a higher aldosterone concentration, obviously, and they also have a higher urine albumin excretion, so they have worse outcomes. And if you treat them with spironolactone, they showed in this initial pilot study that you saw a decrease in albumin production.

Other studies have come along—and I'm going to skip over this—but it also works in other proteinuric diseases. And in other studies, if you follow them long enough, and these people have fairly high proteinuria from various kidney disease treated properly on an ACE inhibitor, treat them with spironolactone and it decreases. And then as soon as you stop the spironolactone at 8 weeks, you can see that the proteinuria increases in these patients.

This was associated with aldosterone, so the patients that had the higher aldosterone production, they were treated with spironolactone actually had more of a benefit from this treatment.

And over time, these initial studies were not randomized, but they have now done randomized trials with spironolactone, and Dr. Bhalla is going to talk further about other drugs. If you take them and treat patients with diabetic nephropathy and albuminuria with persistent

proteinuria, you can see a nice decline in proteinuria. So you can decline in proteinuria much more than if you just continue to treat them with standard of care. So this is regardless of the kidney function status.

So that ends this introduction part of the talk. And I've given these conclusions, and I'll hand it over to Dr. Bhalla after this.

Dr. Bhalla:
The title of my talk is *Aldosterone-Targeted Therapies for Hypertension*, looking specifically at mineralocorticoid receptor antagonists. Let's make sure that this works here. Thank you.

These are my disclosures of relevance to this talk. I do consulting for AstraZeneca, which makes one of the aldosterone synthase inhibitors. But I won't be talking about that today.

The outline for what I'm going to cover in the next 15 minutes is we're going to talk about the role of mineralocorticoid receptor antagonists in hypertension. We're going to cover both steroidal MRAs and then a newer class, which are nonsteroidal MRAs, talk about efficacy and adverse effects and compare them, and then get into the trial data for mineralocorticoid receptor antagonists in chronic kidney disease and look at efficacy and adverse effects as well. And then going to talk a little bit about the tradeoff between those components as we move forward, it's particularly looking at hypertension in CKD and CKD progression.

So just as a perspective, this is a chart looking at the advent of different antihypertensives over time from the last 100 years. Highlighted in red here, I've just shown where spironolactone came up in the early 1950s, and eplerenone, I think, was introduced right around 1988, 1989. And then what's not on here is finerenone, because it's not a classic antihypertensive treatment. But the steroidal MRAs, at least, have been around now for quite some time, and they're getting increasing recognition, particularly in our field of chronic kidney disease progression.

So just to introduce this concept of steroidal versus nonsteroidal mineralocorticoid receptor antagonists, I've created this table, which is, for the most part, generally correct, and I'll point out a couple of specific exceptions as we go through.

So what I've shown here is a listing of a couple of different steroidal MRAs, both spironolactone and eplerenone. And on the right are nonsteroidal MRAs, both that are available in the United States or elsewhere, as well as including a medication that is no longer being used due to some treatment failure in trials.

And so these are the different compounds for steroidal and nonsteroidal MRAs. Most of these have been—and finerenone is the one I'm going to talk about the most, but most of them have come up much more recently after the chemistry to derive a nonsteroidal MRA was in place.

I'll talk about MR affinity. So this is affinity for the mineralocorticoid receptor. You see there that the nonsteroidal mineralocorticoid receptor antagonists, for the most part, have a higher affinity than the steroidal MRAs. And of the steroidal MRAs, eplerenone classically has the lowest affinity.

The tissue distribution is a big difference. So steroidal MRAs can target particularly the collecting duct much better than nonsteroidal MRAs. That's one of the reasons they're used in hypertension and have more hyperkalemia. And the opposite is true in general for the nonsteroidal MRAs. Their tissue distribution is more equal between kidney and, for example, in other end organ like cardiomyocytes in the heart. And again, one of the reasons that they're not as good for hypertension, but they also suffer from less hyperkalemia.

One of the exceptions to this rule is ocedurenone. Ocedurenone had a much higher drop in blood pressure compared to one of its cousins, the finerenone, in prior studies. The phase 3 trial was discontinued due to a lack of difference in blood pressure, and I believe that company is no longer pursuing it in trial data. But for the most part, the nonsteroidal MRAs do not work as well for hypertension for the chemistry and distribution reasons that I'm showing here.

In terms of the structure, these generally share a similar structure compared to a more bulky structure for the nonsteroidal MRAs, and this is part of the reason that you see a difference in chemistry.

So I've created a couple different symbols to pictorialize this difference, and I'll just walk you through this.

So if we have a mineralocorticoid receptor here, and we have a classic ligand like aldosterone shown in A here, it can work in a couple of different ways. I'm going to talk about its MR dependent function, and Dr. Luther talked about that as well. Dr. Dwyer is going to talk about other ways to target this whole system with aldo synthase inhibitors.

But if we think about one of the prime differences between a steroidal and nonsteroidal MRA when it comes up practically, is that a steroidal MRA blocks the effect of the ligand. So it can block the effect of aldosterone or, in non-epithelial tissues, also cortisol from activating mineralocorticoid receptors. The difference for nonsteroidal MRAs is they also inhibit the receptor, but based on their

chemistry and based on how they inhibit the receptor, they are more ligand independent. In other words, they can also block these ligands and cause changes in gene transcription that is more or less independent of the aldosterone.

And so that's a classic difference between these two. And so they're not all from the same types of chemistry. And an important thing to think of going forward as we look at the CKD trials and the blood pressure trials, and we see distinct differences between these different subclasses of steroidal versus nonsteroidal MRAs.

In terms of breaking them down into the ones I'm going to cover, spironolactone, eplerenone, and finerenone are the ones on this trial on this stage on this table that I wanted to cover. Aldosterone synthase inhibitors as a comparison is shown here, where we're actually getting rid of the aldosterone. But spironolactone is classically a high potency, and has high potency for the mineralocorticoid receptor antagonism. Eplerenone, on the other hand, is much lower. Finerenone has a higher potency for MR, particularly outside of the nephron, and lower for hypertension. The dosing frequency you can see there.

And for the most part, steroidal MRAs, primarily spironolactone, suffer from endocrine side effects due to antagonism or agonism of other steroid receptors, such as the progesterone receptor, the estrogen receptor, or the androgen receptor. Eplerenone much less so, but it's also less potent. And finerenone has virtually no endocrine side effects. All three suffer from hyperkalemia, but because finerenone has a lower kidney tissue distribution and it does not work as well for hypertension, it also does not cause as much hyperkalemia. So those are the classic differences.

So as we get into trials for spironolactone in hypertension, the classic one that I wanted to cover is the PATHWAY-2 trial. This came out more than 10 years ago now. This is 230 patients, all with resistant hypertension based on the definition that you heard from Dr. Luther. It was a randomized crossover trial, and it was compared to two other classes of agents.

Many of you might be familiar with this data. What's shown on the right is simply the placebo-controlled drop in blood pressure, and spironolactone had a larger drop in blood pressure for resistant hypertensive patients compared to a beta blocker or compared to an alpha-1 antagonist like doxazosin.

Similarly to spironolactone, amiloride at a high dose had a similar drop in blood pressure. And the curve on the left shown here is essentially the difference in blood pressure with spironolactone at 25 to 50 versus 10 BID of amiloride. And you can see that there's some unity in this curve. So that's why the title of my slide is *It's All About ENaC*, because it's likely showing us that blockade of the epithelial sodium channel in the kidney is responsible for these changes in blood pressure, and these two drugs have a shared mechanism of action to do that.

It's also been shown that we have a very good biomarker for looking at spironolactone response. In our field, as you know, we've been looking for renal troponin for CKD and AKI for a really long time. We've been looking at biomarkers for hypertension for a really long time. The news flash is 10 years ago we had one. We don't use it as much as we should, but we have one, and that's the aldo-renin ratio.

So what's shown on this curve up here is you're looking at the change in blood pressure with spironolactone. And this is a negative deflection, so the lower the number, the larger drop in blood pressure with spironolactone.

And then on this curve is renin, aldosterone, and aldosterone renin ratio. And very similar to what Dr. Luther said about kidney disease outcomes—I'll skip over to the aldo-renin ratio—the higher the aldo-renin ratio, mostly driven by the low renin, the larger drop in blood pressure. If you look at a low aldo-renin ratio or conversely a high renin, that the drop in blood pressure with spironolactone, which is this magic fourth drug that we have, was virtually similar to placebo. It really wasn't that good. But the patients with a large aldo-renin ratio was a biomarker for spironolactone response.

How does spironolactone compare for resistant hypertension to other agents in this field? This is a table simply lining up spironolactone versus other recent trials. So aprocitentan is an endothelin receptor antagonist, and then there have been two recent renal denervation trials looking at resistant hypertension. And you can see here with spironolactone at the placebo or sham control reduction in blood pressure, it's about 10.2, significantly different than placebo, and a very large drop in blood pressure. This you will be able to compare when we look at Dr. Dwyer's slides on the aldo synthase inhibitors. It's similar, but these are all larger drops in blood pressure compared to renal denervation or compared to aprocitentan when you look at all comers.

Keep in mind, though, that this 10.2 is mixing all the patients with a low renin and a high renin and a low aldo-renin ratio and a high aldo-renin ratio, so the drop in blood pressure can be significantly more than 10.2 or significantly less, again based on a biomarker that we probably should be using more.

This data has made it into guidelines. I've just shown the guideline here. I'm not going to read these through, but basically both KDIGO and the *AJACC* hypertension guidelines have espoused the idea that for resistant hypertension we should be using spironolactone as

the next agent before using an alpha-1 antagonist or before using a beta blocker, basically echoing the results of the PATHWAY-2 trial that I went over earlier.

However, if you look at a resistant hypertension population, and this is from the REGARDS study, which was about 2,500 people in this part of the country in the southeast United States, the percentage of people that were on spironolactone or eplerenone having had resistant hypertension—and granted, this came out before the results of the PATHWAY-2 trial but it's no better now if you look at a more recent study—The number of patients who the indication would be 100% of these people should be on an MRA, it was about 10%, 9.8%. This group also had a low rate of chlorthalidone usage historically too. So take it for what it's worth. In clinical practice, these guideline recommendations for using a mineralocorticoid receptor antagonist in the setting of resistant hypertension is not as common as guidelines would want it to be.

So I'm going to transition now from mineralocorticoid receptor antagonists and their role in hypertension, and I'm still going to stick with the steroidal MRAs for a moment and then move over to CKD. I will come back to the nonsteroidal MRAs to look at both hypertension and CKD after covering this.

So what's shown here is data from the BARACK study. So the BARACK-D study was a phase 3 open blinded endpoint probe trial that looked essentially at kidney progression with spironolactone versus placebo in a group of patients that had stage 3b CKD. So the idea here was to look at a placebo-controlled trial to look at whether steroidal MRAs could help improve kidney progression. You saw data from Dr. Luther looking at its role in proteinuria production. We all know that that's not an acceptable hard outcome to look at CKD progression. So this study was designed to look at that.

And they looked at a primary outcome, which was mortality and CV disease combined, and then they had secondary outcomes on the things that you would imagine: eGFR decline, change in blood pressure, and hyperkalemia. I apologize that this should be bigger, but right over here on the bottom right of this slide is the overall data in the trial for who was recruited for this trial. It shows a urine ACR, an eGFR, the potassium level, and the serum creatinine.

Basically the eGFR was fine. The eGFR was about 43.5 for this group, but the amount of proteinuria that these patients had was 8 mg/g if you convert it into American units, and the serum creatinine on average was about 1.4. These people had stage 3b CKD, but it was considered a milder population of patients with CKD. About 25% were diabetic in total. So the earlier data that we saw on the role of spironolactone to reduce proteinuria and to improve outcome were probably done in much sicker patients than those who were enrolled in the BARACK-D study.

Not surprisingly, there was no difference in outcome with spironolactone versus placebo in this study. So I think one of the things we can take away from that is that if you look at a less sick population, if you look at a population that is less likely to progress, you're essentially asking for a tradeoff of hyperkalemia without much hard outcome benefit.

I'm now going to shift over to nonsteroidal mineralocorticoid receptor antagonists, and these were studied with an indication for major adverse kidney events. So there's never been a true trial, a phase 3 trial of a nonsteroidal MRA for blood pressure. So the entry criteria for the FIDELIO study was, it was about 6,000 patients. They were looking at patients with diabetes and looking at a GFR that was about CKD 3 to 4 with proteinuria. So urine ACR of 30 to 300. You could have a higher GFR, but you had to have more proteinuria. So it was a group that was more likely to progress than the BARACK-D study that I just showed.

And the primary outcome was a composite kidney outcome. It was death from a renal cause, decrease in eGFR more than 40%, or the need for dialysis. And you can see here that there was a significant benefit of finerenone versus placebo. This study came out in 2020. Many of you might be familiar with this. The hazard ratio was 0.82. A very small proportion of these patients were on SGLT2 inhibitors, but that same hazard ratio persisted in that group, and there was a small but discernible significant amount of hyperkalemia compared to placebo, but a very low discontinuation rate. So essentially what you might think is that if you can get somebody who is progressing on an MRA, and in this case it was a nonsteroidal MRA, and if you could keep them on it, then they might do better than if they're not on that medicine alone for CKD.

This study came out last week, and I wanted to share it with you guys because I think it's really interesting. This is by the finerenone investigators, where they combined the data from the two studies. So they combined FIDELIO and FIGARO, and this is all the patients from these two type 2 diabetic CKD studies. It was about 13,000 patients. They had a discontinuation rate of about 20% on drug in both studies. So those who got placebo, about 20% discontinued it for the reasons that clinical trial placebo patients do. And in the finerenone study, the discontinuation rate was also that. And in the initial FIDELIO study that I showed, the discontinuation rate specifically for hyperkalemia was not that high. The rate of hyperkalemia was high, but the discontinuation rate wasn't that high. So most of this discontinuation is for reasons that are found in clinical trials.

But what they did show, which I think is really interesting to point out, is that the hazard ratio differed for those that discontinued versus continued. If you see here that the outcome rate for those who discontinued was similar to the overall hazard ratio if you combine it with that. That's what that number is here. But then if you separate out those that stayed on drug for the entirety of the trial, the hazard ratio was 0.65 both for the composite kidney outcome and also for CV outcomes, arguing that if you're able to keep a patient on the drug for the entirety of this study, then the difference between placebo and the drug is therefore more.

And so I think that that's a really important caveat that we probably didn't appreciate as much from the initial study, which did have significantly low hazard ratio that didn't cross 1, but didn't get the highest feedback from the community, such as the SGLT2 inhibitors and certainly the GLP-1 agonists have gotten. But a hazard ratio of 0.65 is pretty good for CKD.

So then now I want to compare hypertension and CKD between these two agents. So we have spironolactone, really good for blood pressure in patients with resistant hypertension, and finerenone, which I've said up to this point is not very good for blood pressure but is really good for CKD progression, and that compares favorably compared to spironolactone, which in a not very sick population didn't do as well.

So what's shown here is sort of a composite historical comparison. So in a trial for resistant hypertension and CKD—that was a trial to look at a K binder. So this is the patiromer trial—everybody was essentially resistant hypertension and CKD, and they gave patients either spironolactone or spironolactone plus K binder, the idea being that the K binder would allow patients to stay on spironolactone, and we'd be able to actually look at the change in blood pressure with spironolactone in a patient population with CKD, which tells you already that hyperkalemia is a significant issue.

And then the FIDELIO investigators or the FIDELITY investigators pulled out the patients from FIGARO and FIDELIO that had resistant hypertension, and they compared about 620 patients in the combined FIDELITY study with 295 in this patiromer study, which was called AMBER. And what's shown on the graph here is the difference in blood pressure compared to placebo. So finerenone reduced blood pressure by 7.1 compared to its placebo, which was about 1.3, so placebo corrected that's about 6 mmHg.

Spironolactone, on the other hand, dropped blood pressure significantly more, very similar to the non-CKD population of the PATHWAY-2 trial. It was 10 to 12 mmHg, so nearly double what finerenone, echoing that same biochemistry that I talked about at the beginning, that spironolactone is better for blood pressure than a nonsteroidal MRA.

But the rub comes here. Look at the rates of hyperkalemia in this study. So these are patients with CKD. You see here that the rate of hyperkalemia with FIDELITY is about 11%, and hyperkalemia in this study is defined as having a blood test that showed a K above 5.5. The rate of discontinuation was significantly less than that, but 5.5 happened in 10% of the time compared to placebo, which was virtually nil. But if you look at spironolactone, the rates of hyperkalemia are astounding. It was 35% for the group that got patiromer specifically designed to be able to stay on spironolactone, and it was 64% in spironolactone alone.

So when we think about other side effects of these medications, I think hyponatremia is an important one to bring up. For those of you who prescribe MRAs quite a bit, you'll see this. I used to think of this as a very theoretical thing that was dwarfed compared to thiazide-induced hyponatremia. But spironolactone or eplerenone compared to placebo can drop your serum sodium about 1-2 mmHg. In patients with heart failure, it can probably drop it more. And in patients who have thiazide-induced hyponatremia, it's a more reliable thing that can happen.

And the incidence in this overall study with finerenone is about 1.2%. It's slightly lower, again arguing that it doesn't do as much in the collecting duct as spironolactone or other steroidal MRAs do.

And so I came up with this kind of scale to think about steroidal MRAs versus nonsteroidal MRAs. Some of the benefits that we would get from either one of them may be BP control, and I just went over how steroidal MRAs are probably better for that. Then another potential benefit is risk reduction of CV events, which we know from spironolactone was good for heart failure events from the last 30 years, but for kidney events has not been proven to be that good compared to a nonsteroidal MRA. And then there's cost savings. Spironolactone is very, very cheap compared to finerenone for the next few years.

If we then put that up against the risks of these different agents, we have hyperkalemia, we also have hyponatremia, and then we have hormonal side effects, in particular with spironolactone, compared to virtually nil with eplerenone or finerenone.

And then the cost of eplerenone for some patients now, although it's quite a bit less expensive than it was 20 years ago. And then really the cost of finerenone is much higher.

So in looking at a patient with CKD, and particularly one with resistant hypertension and CKD, the tradeoff will be, do I want to fix their CKD and maybe not fix their blood pressure as much? Or do I really want to fix their blood pressure and not have the data to back me up

for their CKD? And I might have to contend with the hyperkalemia a bit more if I choose to go that route.

So just in summary, MRAs work very well for resistant hypertension. They're truly first line for resistant hypertension after triple therapy. They do have side effects, and those side effects are probably more in CKD, in particular the hyperkalemia, as I showed you. And they do have benefit for GDMT. In particular, the nonsteroidal MRAs have been proven to show that. We've seen that in diabetes for CKD outcomes, diabetes for CVD outcomes, and then I think Bayer just announced recently that the non-diabetic CKD and CVD outcomes were positive, but that data has not been released yet.

And so I think for future directions in this field, sort of answering this question of which type of MRA chemistry do you want? Do you want CKD progression, or do you want blood pressure and suffer the side effects of either one? And then another thing I think that comes up, which I think is part of answering that debate, is whether we're going to screen patients with CKD before we give them either a steroidal or a nonsteroidal MRA, or maybe even very soon.

And I'll leave it with that. So I just want to thank a number of people at Stanford and also collaborators of mine on the research side and the opportunity to give this talk. So thank you.

Dr. Dwyer:
Thanks. So I'm going to be talking about aldosterone synthase inhibitors, as was discussed earlier, and in their role as an emerging therapy for hypertension and chronic kidney disease. My disclosures are that I do work with AstraZeneca on baxdrostat, and so that is a relevant disclosure. I've also worked with Boehringer Ingelheim on other projects independent.

So this is what I intend to cover. I want to evaluate the scientific rationale to target aldosterone directly and interpret the results of the ASI studies in uncontrolled hypertension in particular. I want to start by reviewing the risk that is residual despite guideline-directed medical therapy. We're now at the point where we can begin to use that term like the cardiologists have to talk about what the guidelines ask us to do to treat our patients, and then quickly review a large amount of data. So I'm going to hit some high points on a series of clinical trials and then discuss some upcoming studies that are actually ongoing as outcome trials in chronic kidney disease, and then reflect on the implications.

There we go. All right, so bottom line up front, aldosterone dysregulation contributes to residual risk, as you have been hearing about, and we'll show you some of those data. Aldosterone synthase inhibitors suppress aldosterone production upstream of places where we are normally accustomed to thinking about intervening on the renin angiotensin system.

And then there are a number of trials right now that demonstrate meaningful reductions in blood pressure in a variety of populations, and we're going to talk through some of those. And those ongoing outcomes trials that I mentioned are really around kidney and cardiovascular events.

So this is really the residual risk. This risk is the area under the curve in treated here with dapagliflozin in DAPA-CKD or empagliflozin in the EMPA-KIDNEY trial. And that is the risk of progression to hard renal outcomes that our patients with advanced kidney disease experience.

The development of the aldosterone synthase inhibitor drug class has actually been ongoing for quite a while. Importantly though, the original compound had much more B1—CYP11B1 activity, and the goal here is to have more B2 than B1, so I'm going to show you that later. And the reason is, is that that allows the compounds to not interfere along the cortisol axis. And we'll summarize some of those trials about their effect on the cortisol axis.

Now if you go down this list, osilodrostat is the one that is now approved for Cushing's because of its basically equipotent effect on B1 and B2. The current drugs that we're going to be talking about today, baxdrostat, lorundrostat, and vicadrostat, have significantly more B2 activity, on the order of 100 to, say, 250 times more potent for B2, so they're very much selective aldosterone synthase inhibitors.

So I want to very quickly go through these trials, and I'll start with lorundrostat. The Advance-Hypertension trial was a trial of lorundrostat to evaluate the efficacy and safety in participants with uncontrolled hypertension. And you can see here that participants underwent a single blind run-in, which is often done in many of these hypertension trials to help with issues such as compliance or adherence to the medication regimen. And then they were randomized to either lorundrostat 50, placebo, or 50 that then got uptitrated to 100 mg.

And the primary efficacy outcome was the change in 24-hour ambulatory blood pressure monitors, systolic blood pressure, so averaging all the systolic blood pressures at the end of the 12 weeks, so week 0 to week 12. And you can see here in the left bar, the difference here is about -15 mmHg, but placebo corrected gets us to about -8 mmHg. And that's the magnitude that you would anticipate, and I think you're going to see a recurring theme of that magnitude.

There are key laboratory results shown here. As you would expect, changes in serum potassium—potassium went up—and then also

changes in serum sodium. And then the other thing to remember is that these are drugs which acutely reduce GFR. It is hypothesized that that is beneficial, but the magnitude of those changes in GFR, I think is we are awaiting the results of much larger trials to understand what that magnitude implies and how that relates to kidney protection.

The Launch-HTN trial was in participants with uncontrolled hypertension and also treatment-resistant hypertension. So similar here, this is placebo, 50 mg, or 50 uptitrated to 100 mg, and that dose escalation occurred at the midpoint if their blood pressure was still elevated.

So I'm going to show you those results here. This is busy. We wanted you to have all of these data. But if you look in the first row, the primary outcome, systolic blood pressure baseline to 6 weeks, lorundrostat versus placebo, a 9 mmHg reduction in baseline to 6 weeks. Importantly, this is ambulatory seated blood pressure. This is not ABPM, so this is more akin to AOBP or in office.

Now the adverse events here, you know, in short studies like this, you wouldn't anticipate that there would be any deaths. These are patients who are on a lot of blood pressure medicine, so adverse event rates will still exist. There'll still be patients who have AEs. But if you draw your attention to the adverse events of special interest, severely elevated blood pressure, there are more patients in placebo than in treated with lorundrostat. That makes a lot of sense. I think hypotension is also interesting. These are some of the most difficult to control patients, and their blood pressure is too low. It's actually a refreshing problem.

And then hyperkalemia and hyponatremia, as Dr. Bhalla mentioned, these are things that we're going to be seeing more of. Importantly, no adverse events related to the glucocorticoid axis.

Now, Explore-CKD was a phase 2 trial that looked at blood pressure and UACR reduction in lorundrostat added to a background treatment that included an SGLT2 and an ACE or an ARB, and these patients had to have a GFR of greater than 30 and a UACR of above 200. That's important as we compare this to, say, FigHTN in a minute. So the change in systolic blood pressure here, placebo adjusted, is -7.5 mmHg. Again, on that magnitude of 7.5 to 9 that we're seeing with these drugs. More hyperkalemia in participants treated with lorundrostat. But importantly, the change in the UACR is -25%. And you'll recall that this is very close to the threshold amount that is likely to predict a protective effect on the kidney in harder renal outcomes.

There are a couple of other trials with lorundrostat of interest, the sleep apnea study. So the primary endpoint was around the apnea hypopnea index, which was not met, but there were substantial blood pressure reductions. I think this is valuable information for us to remember that in patients in whom we believe blood pressure is being mediated by, in part, their sleep apnea.

And then the lorundrostat NDA has already been filed, and we anticipate, if it is accepted by the FDA, that we'll be able to prescribe this drug for our patients sometime in early 2027.

So now I want to turn to baxdrostat across a range of trials, and I want to talk about FigHTN first. When I presented the results of FigHTN a couple of months ago, someone called it FIG hypertension, and I realized that that's actually a better name than FigHTN. FigHTN is a phase 2 trial of baxdrostat in participants with CKD and uncontrolled hypertension. The entry criteria were modeled after DAPA-CKD, and participants were randomized to strategies of baxdrostat, a low-dose or a high-dose strategy, and also to placebo. And the primary outcome was change in blood pressure, and UACR was considered an exploratory outcome.

The placebo corrected change in blood pressure after 26 weeks of treatment with baxdrostat was -8.1 mmHg, again right in the middle of what you would anticipate. And then other consistent changes across various secondary outcomes, the two strategies compared to placebo independently, etc.

Now, the safety data here are also very similar to what we've reviewed before, and I'll just draw your attention to the bottom around hyperkalemia events and changes in kidney function. Again, acute declines in eGFR, as one of our colleagues says, “Buy the dip.” We think that this is going to happen, and we anticipate this to be a key problem that ultimately is hypothesized to be renoprotective.

And then I'll just very briefly mention that in the exploratory endpoint, the UACR reduction was 55%, which is much larger than the 27% which is hypothesized to reliably predict changes in protective effects for the kidney.

And this is really the study that allows us to conduct Arctic and Pacific, which I'll talk about in a minute. The pivotal hypertension program is called BaxHTN, and it consists of three clinical trials, BaxHTN, Bax24, and BaxAsia. BaxHTN and Bax24 have both been read out and published, and BaxAsia is in process of being reported. Altogether, there are about 1,200 participants on doses of baxdrostat from 1-2 mg in complex designs that assess the efficacy as an antihypertensive in a variety of ways: the acute effect, the durability of effect, and then things like what happens when you take it away to see if there's a washout or a durability of effect without the drug.

The primary outcomes are often systolic blood pressure, and of course in the Bax24, things like changes in the ambulatory blood

pressure monitoring are the point. So here you can see the magnitude of the reduction in blood pressure for BaxHTN in a seated blood pressure during the pivotal part of the study, right in the middle before the washout, is about the exact same that we've been seeing before.

Importantly, the potassium that is of a level that I think nephrologists are worried about is quite low. These are confirmed potassium levels greater than 6. You know, you send the patient back to get the lab checked a second time, and this is a low proportion of participants where this is occurring. Obviously, I think in the real world, when this gets able to be prescribed, I think it'll be a little bit higher, if not much higher.

You can see here across a range of prespecified subgroups, but most importantly, in participants whose baseline hypertension was either uncontrolled or resistant, the magnitude of the treatment effect is very similar and favors baxdrostat all the way down the row.

Now, Bax24 is the ambulatory blood pressure monitor, and I'm only just very briefly going to state that the placebo corrected systolic blood pressure was 14 mmHg, so significantly higher than the other trials, and something that you would probably anticipate with an ambulatory blood pressure trial.

Again, here, more hyperkalemia and acute changes in eGFR as a reduction, which again we hypothesize is renoprotective.

Now, there are a couple of other trials ongoing, Arctic, which is an eGFR slope study which is fully recruited and will probably read out in the next 18 months, and then Pacific which is a hard renal outcome study and is still recruiting.

There's also a specific trial for BaxPA, and then there's a heart failure study called PreventHF, which is ongoing as well. It's anticipated that the FDA is going to act on the NDA quite soon, and our expectation is that this will be able to be prescribed sometime maybe by early July or August in the United States.

So I just want to briefly cover vicadrostat as well. So this is a phase 1 study that evaluated the safety, tolerability, PK, and PD, but also the early albuminuric efficacy of vicadrostat. And here you can see—now this is a phase 1 study, so as you blenderize all these data, you might see that there is a difference in the blood pressure changes. And here you can see that those placebo corrected changes are slightly smaller than they had been. But again, I'm not sure that that's necessarily a key takeaway.

This is a phase 2 study that looked at participants with a GFR of 30 to 90 and a UACR very similar to the early lorundrostat trials, and they were first randomized to empa versus placebo. And you can see here again changes in blood pressure as well as the changes in serum potassium in patients by varying levels of potassium.

Now, the phase 3 trial that's ongoing is a very large 11,000 participant, more like a pragmatic RCT called EASY-Kidney, empagliflozin plus aldosterone synthase inhibition for kidney outcomes. And again, 11,000 participants with GFR quite wide, 20 to 90. And people are trying to exclude participants who already have proven to have hyperkalemia. And the composite primary outcome here is CKD progression, CV death or hospitalization for heart failure, so a combined cardiorenal composite outcome.

So this is a very recent Bayesian meta-analysis about the current trials. About 2,500 patients have been treated with ASIs versus about 900 with placebo. And all of those findings put us at about a -7 mmHg change in systolic blood pressure. I haven't really talked about diastolic pressure on purpose because the primary outcome for essentially all of these trials is around systolic blood pressure.

And then serious adverse events are about the same, and severe hyperkalemia in this meta-analysis was about 2%, so that's probably going to be the floor that we'll see in the real world.

There's a lot of hypothesis around potential synergy between aldo synthase inhibitors and SGLT2 inhibitors. There's a mechanistic idea there, but also there is potentially a protective effect against hyperkalemia because SGLT2 inhibitors blunt the hyperkalemic effect of aldo synthase inhibitors. And this is being tested very specifically in Arctic, Pacific, and EASY-Kidney. As I mentioned, those three trials, and those trials are around cardio and kidney outcomes and really is going to move us beyond blood pressure control directly into more organ protection.

And the way I think we should be hypothesizing and thinking about these studies today is really around what is the population that's being studied, as Dr. Luther talked about the definition of resistant hypertension and comparing that to other things like uncontrolled and refractory. The background therapies—many of these trials require the use of a potent thiazide to get in, and so that is a very important background in order to get that beneficial effect. And then of course the safety are the things that we would anticipate: hyperkalemia, hyponatremia, and no real cortisol effects.

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

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Vox Media. To receive your free CME credit or to download this activity, go to reachmd.com/cme. Thank you for listening.