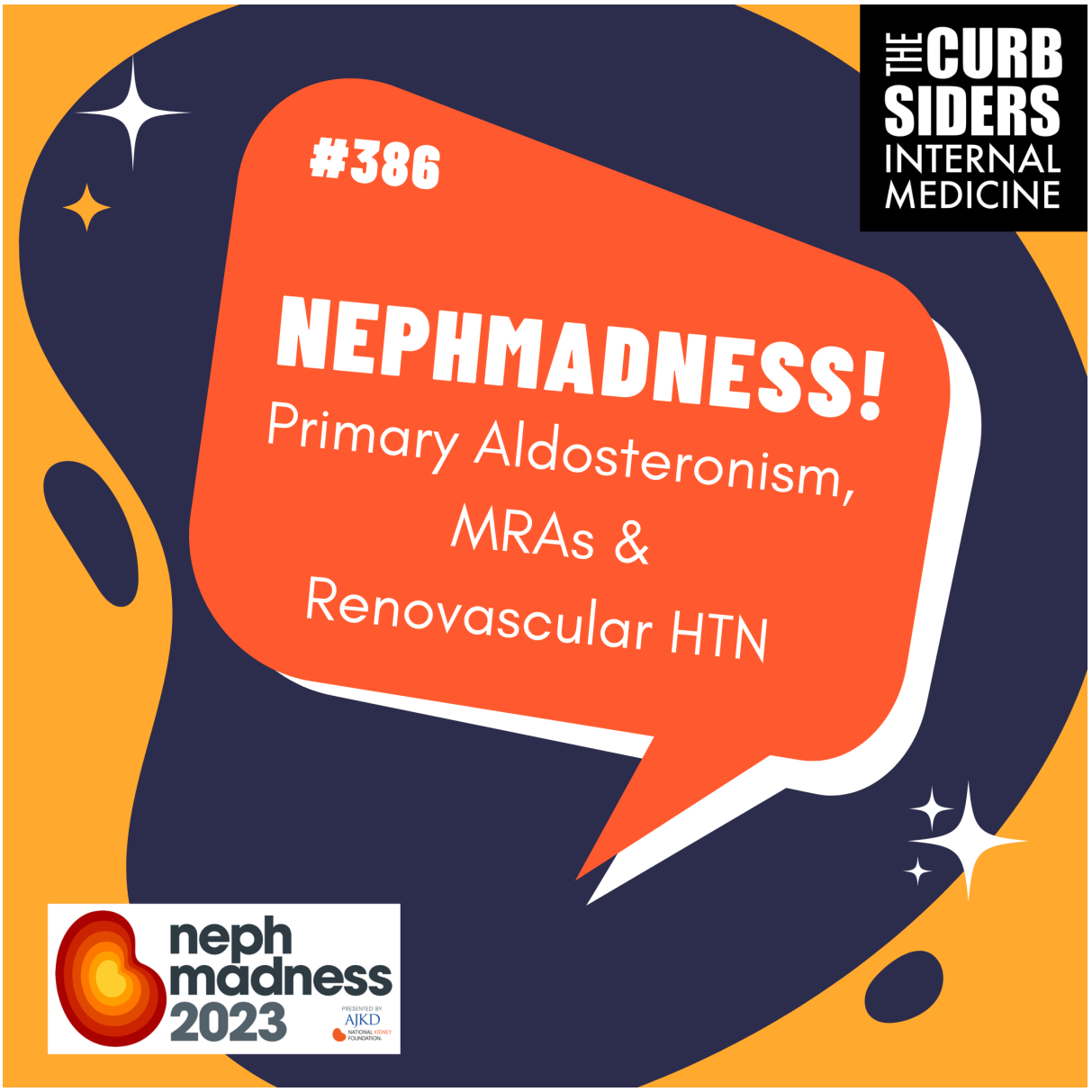
#386 Primary Aldosteronism, MRAs, and Renovascular Hypertension: NephMadness Pod Crawl 2023



Matt: Welcome to the NephMadness PodCrawl. The idea behind this PodCrawl, which we participated in last year, is to get a bunch of medical podcasts together to cover all eight regions in NephMadness. So, we're doing that again this year. If you check out the description in the show notes, you can see all eight podcasts, or you can go to *nephmadness.com/podcrawl* to get the links to all of the shows. And, of course, don't forget to fill out your brackets for this year's NephMadness Tournament.

Paul, I went to my doctor this week and I was pretty ill, but he told me I should rub salt over my entire body and, Paul, now I'm cured.

Paul: That's actually not bad.

[Disclaimer]

[Curbsiders theme]

Matt: Welcome back to The Curbsiders. I'm Dr. Matthew Watto here with my great friend, Dr. Paul Nelson Williams. Paul tonight to NephMadness episode we're talking about primary aldosteronism and renovascular hypertension. Are you excited?

Paul: I am. It's an amazing episode. I was crosschecking a lot of what we learned against patients that I'm currently taking care of and thinking I need to do some other stuff now. So, this was jampacked with useful stuff.

Matt: Yeah. We recently did primary aldosteronism with Dr. William Young, Bill Young. We immediately had people, like, that was great. We want more on that topic. And so, with this guest, we just couldn't resist talking about this. We also, of course, give our picks for the MRA category in NephMadness. This is part of the NephMadness PodCrawl for this year. There're a bunch of other podcasts, too many to name, but they will be in the show description here. So, please make sure you check out some of those. A lot of great NephMadness podcasts going on. Paul, will you remind the audience what is it that we do on The Curbsiders on this show?

Paul: On this show in particular, we are *the* Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice changing knowledge. We had the good pleasure of talking to Dr. Matt Luther about all things MRAE and renovascular hypertension specifically. I will actually let you tell us more about who we talk to and what we talked about.

Matt: So, Dr. Matt Luther. He is an associate professor at Vanderbilt Medical Center. He is director of the Vanderbilt Comprehensive Hypertension Center, where he evaluates and treats resistant and secondary causes of hypertension such as primary aldosteronism and renovascular hypertension. He is board certified in internal medicine and nephrology and is a certified hypertension specialist. He is co-editor of the recent *Hypertension Secrets, 2nd Edition* and serves as an education editor for the journal Hypertension.

A reminder to the audience that this episode and most episodes are available for CME through VCU Health at *curbsiders.vcuhealth.org*. And our disclosures for this episode, Dr. Luther has consulted for Mineralys and for Bayer. Bayer is the maker of finerenone, which we discussed briefly on this episode. However, he has no financial interest in that product and our discussion tonight was fair and balanced. We talked about a balanced range of therapeutic options. So, with all that, enjoy the show.

Matt, we've been talking for a while. I'm very excited for the audience to meet you. Thank you so much for coming on the show.

Dr. Luther: Thank you. I'm glad to be here. Thank you for having me.

Matt: The topics we're going to get into tonight are stuff that I don't understand as well as I would like to. We're just going to get right into some cases here. We're going to talk about primary aldosteronism, we're going to talk about renovascular hypertension. Paul, would you start us off with a case from Kashlak.

Paul: Sure, I'd be thrilled to. Matt, we're going to talk about CJ at least to start, CJ is a 55-year-old male with a diagnosis of hypertension, actually diagnosed at age 25, class 1 obesity, type 2 diabetes with the most recent A1c being 7.5% with mild albuminuria, CKD 3b with an eGFR of 35 who is coming in for follow up with his hypertension. He takes, brace yourself, hydrochlorothiazide 25 milligrams, telmisartan 80 milligrams, amlodipine at 10 milligrams. Despite being on these, blood pressure is still consistently elevated. The systolic is 150s to 160s. The diastolic is 90s to 100s. He does not have, as far as our lab review can tell, any history of spontaneous hypokalemia. He's been tolerating his thiaizide just fine, does not have sleep apnea, does not use NSAIDs with any consistency or any other culprit medications that we can think about.

No one's feeding him any steroids, does not drink alcohol, and had a prior renal artery ultrasound that was normal. He's tried many different combinations of blood pressure regimens over the years. So, to be a little more definitive, we decide to check an early morning renin and an aldosterone level. The renin is suppressed. The aldosterone is 13 and he's had a non-con CT scan that we review that actually shows he has bilateral adrenal hyperplasia. We've got a lot of information here for this patient and a lot of things to dig into. I guess before we get into treatments, I would ask you is there anything else that we miss or that we should do in terms of working this patient up?

Dr. Luther: Well, I would say this is a pretty typical patient for who I see in the Resistant Hypertension Clinic or most nephrologists see in a Nephrology Clinic, CKD Clinic. The main thing I would do is review what has already been done to look at the trend for protein in the urine, so proteinuria trend, albuminuria trend, how he's responded to treatment. So, that's the first thing. Also, just to check off the hypertension checklist to look at the EKG, because I risk stratify people based on if they have LVH or repolarization abnormalities, you might be a little more aggressive or do echo testing if they have significant abnormalities on that.

And also, the important thing is the creatinine trend, is it rapidly changing, has it recently gotten worse, what is the trend for both proteinuria and creatinine trends based on the treatments there. This is not someone who-- it's very suggestive of primary aldo already, just based on the aldosterone at 13 with a suppressed renin on the medicines that this patient is taking. Especially a thiazide and an ARB so with telmisartan, that renin should not be suppressed on those medicines. So, that's abnormal right there and highly suggestive of primary aldo.

Although, with their medical conditions, this is not necessarily somebody that I'm enthusiastic about working up for surgery. They've got bilateral appearance of disease on their adrenal CT. I would look at that, see if they look like they have a large nodule that's not really commented on in the CT report, because often the radiologists, they gloss over adrenal nodules quite often. So, I'm in the habit of looking at that myself to see and I'm surprised that they mentioned bilateral hyperplasia or nodularity. Oftentimes, I'll look at the CT and it looks nodular, hyperplastic and it's mentioned within normal limits, which some nodules are within normal limits, so they just say within normal limits.

I think the other question besides primary aldo is there any contribution of cortisol. So, I would probably consider doing a milligram dexamethasone suppression test in this patient,

learned from Bill Young on your podcast, also about doing a DHEAS first and using that to kind of guide the workup. So, that would be another way to screen for hypercortisolism but really, this patient sounds like they may have primary aldo and need treatment for that.

Matt: I just wanted to point out because you mentioned us talking to Dr. Young. Since then, I've had a couple of patients where I'm looking at adrenal nodules and a lot of the times they'll just say a nodule and they won't give you the Hounsfield units, they won't say if it's fatty.

Dr. Luther: They don't.

Matt: So, you are having to call the radiologist and prompt them with okay, clinically, this person has hypertension and hypokalemia or whatever could this be this or this, and what are the Hounsfield units. I'm finding that that's just not always there.

Dr. Luther: It's not. It's never in my reports. I've gotten in the habit of just learning to do it myself. I usually consult with our adrenal surgeons. If I have somebody that I think is headed their way, I'll give them a heads up and look at the CT scan with them.

Matt: Okay. Yeah. What you mentioned here is, even if someone did say there's bilateral hyperplasia, you still look to see if there's a nodule because I think even with bilateral hyperplasia, one side could be still where most of the aldosterone is coming from. It sounded like so still they do.

Dr. Luther: There are rare cases where we do refer people to surgery that have bilateral hyperplasia. Those situations and we're kind of getting ahead, maybe in this case, but this is the only time I would consider in this particular patient of referring this patient to surgery, is if they just have refractory hypertension. It's just uncontrollable. We've got them on maximal medications and they clearly have an aldosterone excess, renin suppressed. You keep pushing up an MRA like spironolactone or they don't tolerate spironolactone or eplerenone or amiloride or anything you're doing to treat their hypertension, and their potassium is still on the lower side. So, there's evidence that you're just not able to give them enough spironolactone. That is the case in the rare patient. It does happen occasionally.

And then those people we would take to adrenal vein sampling and if they have a predominance on one, if they lateralize to one side, then you may still get some benefit of doing adrenalectomy as like a debulking-type procedure. That's like a last ditch off option for a lot of these patients. I think I've only done that a couple of times, but places that have really high-volume adrenal centers, they probably do that a lot more.

Matt: So, Paul, this is my true fashion. I'm just jumping us way ahead. [crosstalk] I'm sure you love that. You want to ground us, bring us back to earth with more of a linear progression here.

Paul: Sure, yeah, no I'll do the Paul thing right. Just go back to very basics and actually let's say, so you have a lot of evidence for PA here. I mean, we have adrenal hyperplasia. You have sort of some correlating evidence. Say you're explaining this to a patient. We would love to hear what your spiel looks like when you're trying to explain to patients why their blood pressure is the way it is and what you're trying to work them up for. How do you counsel patients about this in plain language?

Dr. Luther: So, I basically tell them that primary aldo is the most common reason that we see resistant hypertension in patients. It's about in my clinic, which is a specialty referral clinic for resistant hypertension, about 15 to even 20% of the patients that I see new in my clinic have primary aldo. So, that is a pretty high percentage of people. It's inappropriate

aldosterone production by the adrenal gland. And I don't go into all the genetics and all the stuff that we do know about this to the patients, but we've learned an incredible amount over the past 10 to 20 years. I would say I think about 15 years.

We basically understand the genetics of all these nodules, the aldo-producing adenomas and even the hereditary forms. I think we understand about 95% of the cases as far as the genetic cause of it. We still don't understand why it's so common. It's just very common. But it's inappropriate aldosterone production that talks to the kidneys and makes your kidneys reabsorb salt and excrete potassium and that drives hypertension. So, about 50% of the time it's due to a nodule that we can remove surgically and the other 50% of the time it needs to be treated with medicines. That is the suspicion in this case just based on the adrenal hyperplasia on CT. Although that may be misleading too.

Matt: You mentioned trending the proteinuria, albuminuria. I hadn't really associated-- I usually think of doing that for people with diabetic kidney disease. But what about with primary aldosteronism? Are patients more likely to have hypertension that also has proteinuria with the CKD, is that part of the progression like, say it goes untreated?

Dr. Luther: I see a lot of people with severe hypertension that's just been going on for years. Even though hypertension shouldn't have massive proteinuria, you can have quite a bit of proteinuria even with severe hypertensive disease that's just gone on for a long time. I want to see what direction they're headed. If they're treated aggressively, their blood pressure has recently been improving, and then I also see that their proteinuria is improving. That's reassuring to me. The real thing I want to make sure is that I'm not missing another kidney disease, so I'm not missing a glomerulonephritis.

Occasionally somebody comes to my clinic that has a glomerulonephritis. If they've got a lot of blood in their urine, I'll make sure that I'm paying attention to that and there's not some other urologic explanation for it. If they have glomerulonephritis, though, they may need a kidney biopsy, especially if it's brand-new AKI, a brand-new kidney disease, proteinuria, or hematuria, obviously take that much more seriously and don't just blame that. Primary aldo does not cause hematuria and proteinuria. It doesn't cause like a full-blown glomerulonephritis. So that would be something totally different.

Matt: Paul's initial question. So, what else would we do. It sounds like you're looking for end organ damage, so the EKG, is there LVH, early repolarization that might lead to an echo, as we just talked about sort of looking how bad is their kidney disease, how much proteinuria do they have if any, what's the trend of the creatinine. And then you said also, just looking at the scans yourself, kind of the Hounsfield units, are there any nodules there that weren't commented on. And then you said also maybe looking for excess cortisol secretion. So, thinking about that work up there with a dexamethasone suppression test.

And so, now let's say that stuff they don't have, this patient CJ, a 55-year-old man doesn't have hypercortisol. Let's just say the creatinine has been stable. Let's say we see some LVH, echo doesn't look too bad, like grade 1 diastolic dysfunction, which [crosstalk] the old joke that everyone has it. What else would you do next to confirm PA in this person, primary aldosteronism?

Dr. Luther: So, in this particular patient, I'm not sure that I would do a whole lot more testing. I would probably opt to go straight to treatment for this person and I think they have a lot of things that kind of indicate that they're high risk. They've got uncontrolled hypertension, their diabetes is marginally controlled, not too uncontrolled, but they've got CKD. Those are pretty high cardiovascular risk factors right there along with the LVH would add to it. So, I would push pretty hard to reduce blood pressure, maybe not necessarily to 120 or below, but close

to as close as I can. My approach to that is I try to get everybody to less than 120, but you do run into problems and sometimes that makes you stop or pull back just little bit.

Matt: So, to remind the audience, this person is on hydrochlorothiazide 25, telmisartan 80, amlodipine 10, how might you tweak this regimen off the bat and what else might you add or change?

Dr. Luther: The first change I probably would make off the bat is switch to chlorthalidone 25 milligrams. It's milligram per milligram. It's more potent. I know the study recently showed no cardiovascular differences, but 25 milligrams of chlorthalidone is more potent than 25 of HCTZ. There's pretty good evidence now in CKD that chlorthalidone at that dose is going to beneficial. So, that also may make a difference. So, I would do that. It would also lower potassium a little bit more than just HCTZ alone, so that may actually be a benefit and help us get this patient to tolerate an MR antagonist. I think an SGLT2 inhibitor is indicated for this patient too. They've got CKD, proteinuria, so an SGLT2 inhibitor also would help lower potassium a little bit or at least constrain it if you did add an MR antagonist. So, I think all those things probably need to be done here given that their blood pressure is pretty far away from being in the goal range.

Paul: Right. This is a case-by-case basis. I would think once you know putatively what's causing the hypertension, I wonder why you wouldn't prioritize an MRA as opposed to-- I mean, obviously the SGLT2 makes sense, just to get rid of the background diabetes and all the known protections with that. Let me ask the question a different way. How likely are we able to get this patient controlled without an MRA sort of tweaking the medications that we have in place already. Is that a realistic expectation?

Dr. Luther: Yeah, honestly, I would probably do that. At the same time, I would probably if potassium allows, add spironolactone as well as change to chlorthalidone.

Paul: Got you.

Dr. Luther: So, it does depend on what the potassium is and whether they have hyponatremia, which is always a confounding factor, and also how stable their creatinine is. This patient's creatinine is pretty stable. So, it's a little bit risky whenever their creatinine is, you know they've got CKD 3. I do use quite a bit of spironolactone in these patients and watch really closely and creatinine will go up when you initiate all these treatments and lower blood pressure as well. So, we will have to counsel them and warn them. Creatinine is going to go up when we lower blood pressure no matter what we use, but we know that it's going to go up when we start spironolactone especially.

Matt: Yeah, you were mentioning this to me when we did sort of our pre-interview. You were saying that these people, are they hyperfiltrating because they have unopposed aldosterone and they're hyperfiltrating and then once you relieve that, we expect the GFR. Is that because aldosterone is clamping the outflow from the glomerulus, so it's clamping that down, so they're hyperfiltrating, and then when you relieve that, all of a sudden there's less pressure, so their GFR goes down. That's my, we are talking about simplistic explanations before, but how does that work?

Dr. Luther: Simplistically aldo excess causes glomerular hyperfiltration. So, that is going to make their GFR look better than it truly is. So, there's probably some underlying kidney damage even more pronounced than what we suspect based on the labs. So, if you start them on an MRA, creatinine is going to go up because you're going to prevent that hyperfiltration. In the long run it's a good thing just like it is when we prevent that with an ACE inhibitor. Now also with an SGLT2 inhibitor, we think it does the same thing. We know that people with primary aldo have the same hyperfiltration. In fact, if you send patients to

adrenalectomy and cure their primary aldosteronism, creatinine, it can go up significantly because a lot of those patients are completely inadequately treated until they get adrenalectomy. So, creatinine can go up significantly after adrenalectomy. I've seen that a few times and been surprised myself even though I know it can happen.

Matt: Yeah, Paul, this seems like this would make me scared because you're like putting them on the right medication. Once you get the dose right, their creatinine is going to get worse.

Paul: Yup. [laughs]

Matt: I'm not sure how I'm going to handle this practically.

Paul: [crosstalk] -all just by my side.

Dr. Luther: Yeah, I haven't done this. I haven't seen a huge increase in creatinine. And I'm a nephrologist and so I'm a little more comfortable with creatinine going up to 3 from 1.5 to up to 3 and as long as it is stable, I've got patients that had severe hypertension. You get them on all these right medicines, you bring their blood pressure down. I've seen two people within the past week that I started treating 10 years ago, and when I brought their blood pressure down, put them on MR antagonist, creatinine did go up to about 3. And I've got quite a few patients whose creatinine went up to 3 and it stayed there over 10 years, it hasn't gotten any worse. But you take the biggest hit when you first lower blood pressure, when you first put these people on the appropriate medicines. But long term, as we've always seen in the trials, it stays there and it has a slower decline.

Just anecdotally, I see that in these patients that I'm seeing that have stable CKD 3 kind of people that I've been telling for 10 years, we're going to have to think about dialysis at some point that it stayed stable. Now, that's not everybody. There are people that progress to end stage renal disease. The biggest thing I worry about in these patients is that their biggest risk is cardiovascular risk. By far their biggest risk is not necessarily developing kidney failure and needing dialysis. Their biggest risk is developing a stroke, heart failure, and dying. That's much more likely than them going on to end stage renal disease.

Matt: Yeah. I was reading about that. It makes intuitive sense, but just for people with the same risk factors, with just essential hypertension versus primary aldosteronism, there's increased adverse cardiac and kidney events. MACE and MAKE, Paul, your favorite acronyms. [crosstalk] MACE and MAKE with primary aldosteronism, even if everything else was the same, which kind of makes sense, but it just wasn't on my radar, I guess. So, we're expecting this creatinine bump, probably you should have a friendly neighborhood nephrologist following along as well, especially if they're a CKD 3 or CKD 4.

Dr. Luther: Yes, in this patient, yes.

Matt: And then you mentioned starting spironolactone. So, I was reading that the dose may need to go as high as up into the 100s. Normally we start at 12.5 or 25 and then we go up to 50. I'm not usually going much higher than that. So, what's a typical dose for somebody with bilateral-- because I think I read maybe there's of a different clinical phenotype if someone has an aldosterone-producing adenoma versus bilateral hyperplasia but what are typical doses?

Dr. Luther: Yeah, I would be cautious in starting it just like you're describing. I would start 12.5 once a day, monitor, check potassium, creatinine within one to two weeks, and then I would push that up based on potassium, blood pressure. And I'll also monitor renin or renin activity. Kashlak Memorial does renin concentration I presume. Renin concentration to make

sure that that's-- if you treat appropriately that should increase and it should no longer be suppressed. That's when you know that you've really treated them successfully. It's really hard and I would predict this patient's-- you're going to have a hard time pushing the dose up high enough to achieve that. In patients with bilateral hyperplasia, it's more difficult. I have to push the dose up higher.

Even in all the patients that I see that are similar to this, this is the patient that I might get up to 100 milligrams. I don't usually push up a whole lot further than that. If I'm in that range, this patient probably you're going to be limited by potassium because of their CKD, so you're probably not going to be able to push up the dose any higher than that. So, practically speaking that's where this is. But if they didn't have CKD, they had bilateral hyperplasia, this might be somebody that you would push the dose up to 100, 200 milligrams.

In the 1970s, they used 400 milligrams of spironolactone. So, that's a lot. You're going to get gynecomastia in men, almost guaranteed. At that high dose, you actually inhibit aldo synthase and so you actually block the aldosterone production, which in these patients might be a benefit, but we don't really do that. I have never done that.

Matt: Eplerenone is a little bit more selective, so less side effects. I read it has to be dosed twice a day. What does the dosing and titration-- What's it like for that one?

Dr. Luther: Yeah, ideally twice a day, I'd basically double the dose of spironolactone. If I'm switching from spironolactone to eplerenone, first of all, spironolactone takes a while to wash out of the system. You got to be a little careful if you're switching to either eplerenone or amiloride, especially if potassium has been borderline, you want to probably give spironolactone a little bit of time to washout and then start the other agent. So, eplerenone, I use twice the dose of spironolactone daily and then gradually go up. The biggest issue I've had with eplerenone is when you start getting up to 50 milligrams twice a day or 100 milligrams twice a day, I just have trouble getting the pharmacist to fill it, even though it's the right thing for the patient and insurance to pay for it. They definitely need it at those doses, but you start getting just incredible pushback from pharmacy and people paying for the medicine.

Matt: Is amiloride something you're using as an adjunct to the MRAs or is it just sometimes as monotherapy if they don't tolerate because of side effects.

Dr. Luther: Typically, I use it as an alternative. You almost never should be using spironolactone plus amiloride. I would say most people should never be using those two together, that definitely carries a huge risk of hyperkalemia. The patients that have severe bilateral hyperplasia that's just really refractory and they continue to have severe hypokalemia and resistant hypertension, there might be a patient or two in my career where I've talked to other hypertension specialists, adrenal specialists that actually do use the two together, but it's really in a rare patient. You really probably shouldn't be doing that.

Matt: Paul, we probably won't be doing that.

Paul: There's a 0% chance of doing that.

Dr. Luther: Yeah. You got to be really careful with these things and also the other ones to look out for, like Bactrim.

Paul: Oh, sure.

Dr. Luther: Bactrim raises the risk of hyperkalemia tremendously when you're giving spironolactone, amiloride, any of the case-bearing diuretics and it's ubiquitous and I have a

hard time preventing it even in my patients because they have a UTI and that's what they get.

Paul: Matt, I feel like we're possibly I can never tell, but possibly on the cusp of wild enthusiasm for the nonsteroidal MRAs, I know with FIDELIO we're looking at finerenone and actually for this particular patient who has diabetes and some challenging blood pressure and a little bit of albuminuria that might even be indicated. I guess my question for you is that a class of medications we're seeing used for PA specifically.

Dr. Luther: I wouldn't say specifically finerenone wouldn't necessarily be great for this patient for the treatment of PA, but this person also has CKD with albuminuria, so it'd be a good treatment for that. So, this patient has two indications. One is spironolactone for resistant hypertension, the other is finerenone because of the CKD and albuminuria. So, I would base my decision on whether they can tolerate spironolactone with the rise in creatinine or potassium. And if they have issues with that, I would probably use finerenone. But the blood pressure effects of finerenone are a little bit less proven, although there is some data coming out that it may have some benefit in people that have severe hypertension.

Matt: Do you think they're going to go for an approval for primary aldosteronism with finerenone?

Dr. Luther: I'm not sure if they are or not. That's really a small piece of the pie, so I'm not sure that it's going to be easy to do a clinical study in that group and get a specific approval. It would also probably be difficult for finerenone to beat spironolactone in that category, so I think it serves probably as a good alternative agent if you have issues with spironolactone, amiloride, eplerenone and there're plenty of those patients. I have patients that have difficulty tolerating a bunch of those different medicines. Obviously, spironolactone has its side effects due to the off-target effects, eplerenone more well tolerated, but amiloride, people have GI side effects with that and sometimes can't tolerate it. I'm in the camp that I think it's always good to have a number of options for my patients. Whatever works for them is what I'm trying to get.

Matt: With finerenone, what we talked about with Joel was that for patients with CKD and diabetes, it just made it recently into the KDIGO guideline. It seems like especially if they're on RAS blockade and they're already on an SGLT2 inhibitor and they still have residual proteinuria then that maybe a reason to go to it but we'll see. As Paul and I were joking the other day, I'm seeing commercials for it pop up on TV, which I was surprised. I'm like, “Oh, my gosh, it seems like such a niche medication," but I guess a lot of patients have diabetes and CKD. [crosstalk]

Dr. Luther: I think as much as I hate direct to consumer advertising, it's really great to see it for a condition like CKD because we've not had those treatments in the past that have been proven well enough to advertise on TV.

Matt: Yeah. I guess helping patients connect that diabetes can cause CKD. Well, I guess, Paul, at this point, maybe we can do quickly our picks for NephMadness. So. the NephMadness region is MRAs. And so, it's like, is this new kid the nonsteroidal MRA. Is that the bigger story or is spironolactone still, is that going to be your pick? Well, Matt, you're our guest. Let's go to you first. Which one of these two would you pick to win in NephMadness this year?

Dr. Luther: Spironolactone or nonsteroidal or is it just steroidal versus nonsteroidal?

Matt: I think it's steroidal versus nonsteroidal MRAs.

Dr. Luther: I've used spironolactone for such a long time. It is very hard to beat spironolactone. I give a lot of props to finerenone for doing the study and proving that MR antagonists are beneficial in CKD not just for cardiovascular events but for kidney disease for multiple indications. I'm still going to go with steroidal because they are such a good tool that I use every day and I'm a resistant hypertension specialist. So, I've got to go with steroidal.

Matt: Paul?

Paul: Yeah. We've talked about this on prior NephMadness. I do comically bad. I wash out immediately. My first instinct is always the wrong instinct. Probably done better than I have. I've never finished in the top 50%. No, I wash out like putting my name in for the-- it's not great. Having said that, I feel like people like a new toy. I'm going to go with the nonsteroidals just because it is the new kid. We do have some studies that are creating some buzz knowing I'm going to fail. But I think I'm just going with that trying to play the game. What do you think man?

Matt: Well, I'm going to go with the steroidal like the tried and true, the MRAs. I'm always skeptical, Paul, these new trials, highly selected patients, nonsteroidal MRAs. I still want to hear some more about it, but I would go with spironolactone and eplerenone, the older MRAs for my bracket there. Like both you guys, I have done terrible in NephMadness as far as brackets go. As far as podcasting goes, Paul, we've killed it [crosstalk] for many years now.

All right, Paul. Well, with the rest of our time here, we do want to talk about another topic that we have never covered on the show before, Paul, so let's do a case here.

Paul: BB is a 62-year-old female with a diagnosis of hypertension diagnosed at age 55, she has pure hypercholesterolemia. She is in the overweight category for the BMI, her BMI being 29, she has CKD 3a with an eGFR of 48 and a creatinine of 1.3. Former history of tobacco use. She quit 10 years ago after a 30-pack-year history. She also has a family history of premature CAD with a father who had a heart attack at age 45, who's coming to your clinic with uncontrolled hypertension. She was recently admitted for an episode of flash pulmonary edema. Today, in your office, her blood pressure is 165/95 and this is fairly consistent with prior readings. She is currently on valsartan and hydrochlorothiazide, the combo of 320 and 25, respectively, nifedipine XL 90 milligrams, which she's been on for the past two weeks. For many years, she was actually controlled on HCTZ 25 milligrams and nifedipine XL 60 milligrams.

This has been a little bit of a change for her. She does not have adrenal adenoma or hyperplasia according to our expertly read CT. She does not have sleep apnea. She does not have history of alcohol use. She's not taking NSAIDs. We are not filling her full of steroids. She does have a recent echocardiogram because who in this world does not with an EF of approximately 55% to 60% with impaired relaxation of the left ventricle. We're trying to paint a picture here, I think, is actually perhaps a patient with renovascular hypertension. So, I'm wondering if you talk us through what that even means I think to start and then we'll start to talk about what the workup looks like and where to go from here.

Dr. Luther: All right, so the renovascular hypertension in this patient, the big clue is the flash pulmonary edema and that was before she was started on the valsartan, I think. And then her blood pressure is controlled after that or actually it's not controlled. Renovascular hypertension is something that can provoke flash pulmonary edema. That would be an indication to pursue maybe a workup or intervention especially if it occurs when they're on an ARB already.

So, I've seen a few cases of that where they're on losartan or maybe a lower dose ineffective ARB, and they still have severe episodes of hypertension that can just come on episodically, that can happen with renovascular hypertension and cause pulmonary edema especially if they have a little LV dysfunction. Renovascular hypertension is not just a blockage in the kidney artery. It usually has to be pretty severe enough to cause an ischemic insult to the kidney that provokes renin release and that provokes these episodes of hypertension.

I see a lot of cases that have a little bit of stenosis on either angiogram or renal duplex ultrasound. Not everything that you see there is causing renovascular hypertension. I've sent plenty of people to an intervention and they don't improve after having that stenosis relieved. So, resistant hypertension is just super common and you have to be really selective in those patients that you really work up for this or send to an intervention especially.

Paul: Can you explain to me-- I feel like I'm missing something obvious here, but the sort of paroxysms, hypertension or so these patients sort of crashing the flash pulmonary edema. I guess mechanistically it makes sense if you had started someone on an ACE or ARB and then their blood pressure would go up like that or their creatinine would go up that I can kind of track. Why are they having these episodes? Like, what's the periodicity and what's the mechanism behind that?

Dr. Luther: It's not super common and I'm not sure that I can explain why it happens episodically like that but it does. That's not an unusual story. Part of it may just be that their ARB is not an adequate dose or it's not long acting enough or they periodically forget to take it. I try to use the highest dose of a longer acting ARB as I can. I tend to use olmesartan in those patients that I'm trying to get the longest activity of an ARB. So that's typically what I'm using nowadays. Although, like everybody else, we evolve in practice. I've seen plenty of people and those people that do present with flash pulmonary edema that is due to the renovascular hypertension, they do tend to respond pretty well to an intervention, so an angioplasty or stent, a stent would have to be done if they've got atherosclerotic disease.

Matt: Yeah. In this patient, we gave you all the risk factors for atherosclerotic disease plus the age. I know when you read about this topic, they always mention like fibromuscular dysplasia. So, what does that patient look like? How would that patient look different from this patient?

Dr. Luther: You can present later in life with fibromuscular dysplasia, so don't discount it in a 55, 65-year-old woman because they can present later in life. I've seen that but typically classically it is a younger woman. The fibromuscular dysplasia is more of a developmental disease. It's like a web, like interference with the blood flow. So, the way that the vascular people have described it to me is like a spiraling or like a web like blockage of blood flow. And to really know for sure, you have to go do angiogram, put a wire across and measure the pressure because sometimes it can look pretty bad on angiogram, but there's actually no pressure drop across the lesion. So, to know for certain that you're doing something that's going to benefit the patient, you need to do a pressure gradient measurement and then do the angioplasty.

The good thing about FMD is that these patients are typically younger, 95% female, so it's pretty unusual for a male to have this but can happen. But it usually just needs angioplasty and not a stent unless there's like a complication, which can happen when you try to angioplasty, you can have a dissection or spontaneous dissection can occur with FMD. And then the other thing is they have disease elsewhere in their body, so they have carotid, vertebral disease. You have to listen everywhere. Listen over their brachial arteries, femoral, listen over any artery you can think of. I've heard it over the brachial artery, you know different arteries across the body. I typically don't deal with a carotid and vertebral. We've got

a vascular team that also kind of helps do that evaluation, but they can also have coronary artery dissections as well. That's not a totally benign disease, but it's usually the patients that I'm seeing are focused on just the kidney artery. I try to intervene when we can.

Matt: Before I forget to do this, you were involved in writing, it was in 2022 or at least it was released in 2022, the AHA put out a statement about renovascular disease and hypertension and I found it very useful to read through. It's very readable. There're figures and tables in there that are really useful. There's an algorithm in there, kind of how to think about this, so just a shout out to that. This is a condition where I feel like when we see resistant hypertension, as you mentioned, that's pretty common. We see that all the time and everyone's like, “Oh yeah, we're going to get the renal artery ultrasound,” and make it seem like A, we would know what to do if we found something and then B, if we find something, all these people are going to benefit from doing something about it. So, can you just comment on sort of the work up identifying people that have it from either atherosclerosis or FMD. I imagine they're not going to jump right to angiography.

Dr. Luther: Yeah. My initial approach is I don't do a work up for it, even [crosstalk] if I suspect that they have renovascular hypertension, I will try to treat them medically with an ACE or an ARB, maximize that. If it is a case where I think it's FMD and it's the right situation, I am more inclined to send those patients to intervention. If it's a young woman that wants to become pregnant that's beneficial because they don't have to deal with the ACE or an ARB. So, there're some reasons to do an intervention. It's also lower risk. Hopefully, they can just do angioplasty in that case, so that FMD is one of the cases where I do think it's reasonable to go ahead and do the evaluation and sometimes do an intervention. Now, the higher risk patients that have likely atherosclerotic disease, I don't go for an evaluation for those patients unless I really think that they have an indication for surgery.

So, the patients that present with hypertensive encephalopathy, which is a condition that is pretty rare, but I almost always find a secondary cause of hypertension in those patients in the hospital. I work those patients up to the hilt including some sort of renal imaging for renal artery stenosis. I've at least found a few renal artery stenosis that we angioplasty it in that case and that's a severe presentation.

Other conditions, if they have bilateral renal artery stenosis and they're failing in some way, so resistant hypertension is not improving or the classical cycle that I describe of bilateral stenosis is, you treat with any medicine, it doesn't matter if it's an ACE or an ARB, you lower the blood pressure and then you see creatinine go up. And then shortly after that, blood pressure goes up. So, then you intensify the medicines, again get the blood pressure down, creatinine goes up again. So, you get in this vicious cycle where you're chasing your tail to improve blood pressure and no matter what you do creatinine worsens.

That patient, make sure that they don't have bilateral renal artery stenosis. That's not a condition, that's unilateral stenosis, just one blockage in one artery is not going to do that. That patient might have bilateral stenosis and that's somebody that needs possibly an intervention. Those are the people with severe disease and they would benefit from an intervention. They're not people that fit into the criteria for ASTRAL or CORAL. Those studies really enrolled people with pretty mild renovascular hypertension that was often unilateral. And doing an intervention in that case doesn't really help those people prevent progression of their kidney disease. What I'm describing are people that fall outside of the criteria for that, so they're people that their hypertension specialist or kidney disease doctor would have done an intervention on and they never would have been enrolled in those studies.

I've got several of those patients too that I described to you earlier that I've got successes and I've got failures in those patients. You don't always help people by doing an intervention.

Some of the worst cases I've seen have been pretty advanced bilateral stenosis. You try to do an intervention, open up the kidney artery, and they have pretty rapid decline in their kidney function. So, I've seen that and I've also like I said had successes where we've done an angioplasty or stent and preserved their kidney function. The people that I've seen that I have the most long-standing success with have had an open intervention. So, they've had a bypass like a splenorenal bypass or a graft bypass. You don't necessarily want to do that and usually that's because they've got some anatomical reason they can't do a stent.

So, one patient I had had a huge coral reef aorta, had a blockage that was so big you couldn't get to the arteries to do an intervention, so they had to do a bypass. The other thing to emphasize, those patients have a huge cardiovascular risk, probably the highest cardiovascular risk of any patient you take care of and you've got to make sure that everything is intensified. So, statin, aspirin maybe Plavix. I'm not really a hot prescriber of Plavix, but usually a cardiologist or another vascular specialist involved, and they're optimizing that.

Paul: Or clopidogrel.

Matt: You're saying the highest risk group is that bilateral renal artery stenosis, the ones where they're having that, you lower their blood pressure, their creatinine goes up, the blood pressure goes up. You lower the blood pressure again, creatinine goes up. That group is the highest risk.

Dr. Luther: Well, any patient with renovascular hypertension, actually, because it's a risk equivalent, so it's a PAD risk equivalent.

Matt: Got it.

Dr. Luther: But the people with bilateral stenosis are extremely high risk and if they're in that cycle that I'm describing, they're at a pretty significant risk of their kidneys going on to fail no matter what you're doing, because that's kind of rapidly declining, like I said. Those people you're usually doing an intervention to try to salvage kidney function and it does work sometimes, not all the time.

Matt: It sounds like bilateral because the paradox here for me and Paul, I don't know if you noticed this too. We're always taught, like, okay, if you start an ACE or an ARB and they're creatinine bumps more than 30%, they might have bilateral renal artery stenosis.

Paul: Yeah.

Matt: I always thought the answer would be, “Okay, then they should not be on an ACE or an ARB.” But it sounds like the medical therapy is you still have to try to treat them medically. How do we reconcile those things because I would be like, “Uh-oh, creatinine went way up. I got to stop.”

Dr. Luther: Yeah. Some of the people I've seen at least a couple of cases where they just have profound-- you start of lisinopril 10 milligrams and they go into renal failure. I've seen a couple of people required dialysis from it. One of the first patients I found with it was on dialysis for a month and I met him when he was kind of recovering and actually came off of dialysis. I said, “Okay, this is clearly suspicious for bilateral stenosis.” MRI, I think we did, they called me the next day and said not only does he have bilateral stenosis, it's because he has a type A aortic dissection, which has probably been there for months. That's just an anecdote but you should evaluate those patients.

Matt: So, the question is, if you put someone on ACE or an ARB and they're creatinine

bumps, what do we do? Do you keep going or you do the evaluation, you're like, okay, let's say you do an ultrasound or you do a CTA or MRA, you prove that they have bilateral stenosis and then you're like, okay, so they have it. I know why they're creatinine bumped. I'm going to keep going with that blockade.

Dr. Luther: Yes. If it's a unilateral stenosis, I always try to treat medically and a little bit of a creatinine bump I'm going to push through. Especially if you're going from severe hypertension to controlled, you'd expect a little bit of a rising creatinine there. So, I'm personally tolerating that. I understand that people get really nervous about that. If they have bilateral stenosis and they've got a severe increase, like I described, it really doesn't matter if it's an ACE or an ARB. It's anything you throw at them to control blood pressure is going to worsen their creatinine. Nonspecific vasodilator therapy, if that is worsening renal function when you control blood pressure that's a huge red flag for bilateral stenosis and somebody that needs an intervention.

Paul: There's going to be a couple of Paul Williams classics moves in here. I'm going to actually take us a step back, if that's okay, and ask a fundamental question. Also, it'll be a multi-part question just to confuse the issue. But I would like, could you talk us through your approach to imaging, I feel like if you suspect renovascular hypertension, I feel like often what I see is starting with an ultrasound and then using that. If that doesn't serve anything, then escalating, which feels kind of inefficient, and so, I guess what is your approach to imaging and then second question is, does it differ if you suspect fibromuscular dysplasia versus atherosclerotic renovascular stenosis?

Dr. Luther: Yes, definitely. So, I use whatever imaging they have already had done, look at the images. If there's a huge discrepancy in renal size, no matter if it's CT, ultrasound or whatever imaging, that's a huge indication to me that I should suspect renovascular hypertension. I don't necessarily do further work up. I treat medically. Then once I've decided we need to do more imaging, probably it's going to be driven mainly by their renal function. So, if they have advanced CKD, MRI is probably out with the gadolinium. My number one approach is to do a CT angiogram because I think that gives you the best definition. You can be misled if you have FMD. So, FMD is difficult really. If you have a huge suspicion for FMD, you may be better off to go straight to angiogram and just put it to rest, especially if it's a young patient, low risk, they don't have a lot of atherosclerosis. It's a low-risk procedure in that patient. Now, I don't want to make everybody go out and order a bunch of angiograms for that.

Matt: Can I read from the guidelines that the AHA wrote. They wrote suspected FMD because there's a line. It says, “Particularly women with early onset accelerated, malignant, or resistant hypertension, a small kidney without any uropathy or arterial bruit in the abdomen flank or neck or FMD in another vascular territory.” I don't think people are going to be sending too many people to angiograms if they look for that description.

Dr. Luther: Yeah. The other option, obviously, is renal duplex ultrasound. And I feel like I've been misled a lot of times by either regular ultrasound or duplex ultrasound. I do find it useful and I have a specific group that I send patients to to do this that I trust and I feel it gives me the best result. And every different institution is going to have a specific either vascular radiology or specific group that may give more reliable results.

I've specifically been misled on some ultrasounds that showed normal size kidneys and then by the time they were referred to my clinic and I said, “Okay, you're correct. This sounds like bilateral stenosis, but there's no difference in kidney size.” I repeat the imaging. If you have a high suspicion for bilateral stenosis, the key is repeat the imaging, because I've seen this at least a couple of times. If their kidney is truly ischemic, it can really shrink rapidly.

The patient that I saw from an outside location, nephrologist was appropriately concerned about it, did an ultrasound, kidneys were normal size, sent them to me, and I said, “You're right. This sounds like bilateral stenosis.” By the time I repeated the imaging, even within a couple of months, the kidney had really shrunken to basically a nonfunctional size. It was very clear that they had a vascular insult to that kidney, and they did have eventually bilateral stenosis and intervened on that patient. But if you do suspect it, you might need to follow up imaging.

Matt: Yeah. One of the things I thought was interesting in just reading about the pathophys and just the natural course of this was that if you are going to intervene, according to this paper I keep referencing, you guys have that figure where it says, like, okay, you want to get to it before the fibro-- it's ischemic, but it hasn't been ischemic for so long that it's shrunken and all fibrotic and there's nothing to salvage. Which seems like what you're describing there, maybe this could even happen over the course of months. So, maybe that's why it's been so hard to prove.

Paul: It's hard.

Matt: [crosstalk] that benefit.

Dr. Luther: Yeah, it's really hard. The patients that I've described, I've been surprised at how rapidly the kidney size has atrophied. So, those are patients I'm taking care of, and I'm trying to intervene and salvage kidney. I think the key is you're not necessarily trying to salvage one kidney. You're trying to salvage probably the other kidney. So, you're probably not trying to salvage that atrophied kidney. You're trying to treat the other one that still has a pretty good kidney mass and if they've got bilateral stenosis, that's the one to go after.

Matt: So, we've talked a lot about this renovascular disease. I think it's very useful. We talked about how to recognize people with FMD, like what that would look like. We talked about the patients that maybe they're just on a little bit of lisinopril and they can't tolerate it. That might be somebody that has bilateral renal artery stenosis and how to recognize that. What about if we're just, as you said, looking at prior imaging for people, and we see, oh, this person has, like, a one kidney smaller and if we suspect somebody or if we just suspect somebody has renal artery stenosis because we saw it was commented incidentally on imaging. Do we have to do anything different as a primary care that's treating this person for high blood pressure?

Dr. Luther: Right. Not all small kidneys are due to renovascular disease, especially for younger patients it's fairly common that they've either got a congenital urologic abnormality, maybe they've had kidney infections in childhood that's affected one side more than the other that led to atrophy. That alone can be a cause of hypertension. It's pretty rare that FMD is the cause of renal atrophy. That's not very common although it can occur. I'm not going to say it can never occur, but the real clue is do they have other either systemic disease from FMD in their carotid, their vertebral artery is somewhere else, or have peripheral artery disease due to atherosclerotic disease with all the risk factors. Usually, you can identify other vascular disease. A good screening test for that group might be an ABI. So, an ankle-brachial blood pressure, and they're high risk, and you're going to treat them as a high cardiovascular risk patient. Again, I treat medically and then pursue the renovascular work up if they're not behaving like they should or there's an indication for an intervention.

Matt: Okay. That's well within our primary care wheelhouse. Treat all their cardiovascular risk factors, try to get their blood pressure to go. Probably, until I get a couple of cases of this under my belt, I'm probably going to be or maybe even after I get a couple of cases under

my belt, I'm going to be calling for services from people like yourself to make sure I'm doing the right thing. Paul, any last questions or should we go to take-home points?

Paul: I am ready for some take-home points.

Matt: Okay, so, Matt, this has been fantastic. As we said, up top of the show, this is part of our NephMadness PodCrawl. So, people should check out the other NephMadness podcasts. They can look for them, links in the show notes or in the show description of this episode. But, Matt, what are your take-home points for the audience from these two cases we gave you tonight?

Dr. Luther: So, for the primary aldosterone workup, number one, you don't have to stop all the medicines to screen for PA. In fact, if you're on an ACE or an ARB and you have findings that are suggestive, that's almost more specific. Number two is you don't have to have hypokalemia. I didn't emphasize that in the first case, but resistant hypertension on three or four medicines is an indication to look for primary aldo. So, send the renin aldo in that setting and you don't have to do the full work up for PA. For our case, I wasn't probably going to send that patient to surgery eventually, but just having the aldo and the renin helps me understand what might be a best treatment for that patient. So, just knowing that they've got suppressed renin, their aldo is 13, which is not super high, but it's also not low either. They would benefit from probably an MR antagonist as well.

Matt: And then for the second case, renovascular disease that we talked about, what about a take-home point or two from that one?

Dr. Luther: So, for renovascular hypertension, treat medically and then look when you have an indication that you think might be pushing you to do an intervention, they're not behaving correctly. Or if they've got one of those high-risk situations which you want to prevent in the future, like hypertensive encephalopathy or admission with uncontrolled hypertension, flash pulmonary edema already on an ACE or an ARB, then those are patients that I would probably do the intervention for. And the bigger kind of, not enough people see this, so I think it needs to be driven home, that people with bilateral renal artery stenosis, their renal function is going to worsen with any blood pressure control, it doesn't matter if it's an ACE or an ARB and then you get in a cyclical situation. Those are the people you need to do the work up then and do the evaluation, do the intervention when you can.

Matt: Oh, I wonder how many people are going to be like, “Wait a minute, I think I've seen that, now that I know it exists.”

Paul: Yup, I'm taking previous notes.

Matt: [crosstalk] caveat.

Dr. Luther: Yeah, the caveat is that severe hypertension, once you bring it under control, creatinine does go up. Like, let's say creatinine goes from 1.5 to 2.5 with control of blood pressure from 240 down to 140 to 150. That's pretty common too. But the thing is with bilateral renal artery stenosis, it just keeps recurring, so then creatinine goes up and then blood pressure worsens, and then you get the blood pressure under control and the creatinine goes up even further. So, it becomes a cycle. When you're in that situation, look for renal artery bilateral stenosis.

Matt: So, the last thing I wanted to do was we're talking off air about this, give the audience a plug about the book that you've done on high blood pressure.

Dr. Luther: Yeah. So, Swapnil Hiremath, Edgar Lerma, and myself, we edited the

Hypertension Secrets book. It's a small book. It's pretty concise, our goal is to keep it relatively concise, surface level-ish although enough detail to fill in and hopefully prompt people to go look for more. It's for anybody that takes care of resistant hypertension, nephrologist, primary care, anybody that's interested in taking the hypertension certification exam, it's a good book as well as it's in that same group as the *Nephrology Secrets* book, which is also a great book that Joel Topf does.

[music]

Matt: All right, thank you so much for all your time. This has been fantastic.

Dr. Luther: All right, thank you for having me. I enjoyed talking about this stuff. You can tell.

Paul: This has been another episode of The Curbsiders bringing you a little knowledge food for your brain hole.

Matt: Yummy.

Paul: Always with a little bit of a question. Get your show notes at *thecurbsiders.com* and while you're there, sign up for our mailing list to get our weekly show notes in your inbox plus twice each month, you'll get our Curbsiders Digest recapping the latest practice-changing articles, guidelines, and news in internal medicine.

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And I wanted to give a special thanks to Joel Topf and the whole crew at NephMadness for inviting us to be part of this, again this PodCrawl. The Curbsiders is produced and edited by the team at Pod Paste, Elizabeth Proto runs our social media, and Stuart Brigham composed our theme music. With all that, Paul, until next time, I've been Dr. Matthew Frank Watto.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

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