SUSAN P STEIGERWALT: So what I'm going to be talking about today is really mostly about resistant hypertension, which we all groan and roll our eyes when the patients walk in and they have blood pressures of 180 over 110. And they're on four medicines. And this is a very pragmatic, in-the-trenches talk, but I'm going to give you enough references, that if you're interested in looking them up, you certainly can do so. And I would encourage you to do so.

And now, if I can figure out what I'm doing here, we'll be on our way. I have one disclosure to make, which is I am an investigator for the SPIRAL trial, which is a trial of renal denervation through Medtronics. And that's done at Providence Hospital. I receive no direct funding for myself from that, but that's, of course, an important disclosure.

I'm also involved in the CRIC study with Dr. Jamerson, who's also in the audience, and others, which is a study, 'an epidemiologic studying, of patients with chronic kidney disease. And Dr. Pandu Rao, he is here, is the principal investigator. And I'm one of the co-investigators now with that.

So there was a great editorial recently by Ray Townsend and Epstein, Murray Epstein, in hypertension. I'm going to start with definitions, because in resistant hypertension, it is important to understand the definition. It's defined as a failure to achieve goal blood pressure despite three different antihypertensive medications at full doses, not super-physiologic doses, but full doses, one of which is a diuretic. That's one definition.

The pathogenesis of true resistant hypertension, that means you've proved it with an ambulatory blood pressure monitor, hint, hint, is multi-factorial. but there are two pivotal factors. One is volume excess, volume excess, volume excess. The second is the myriad effects of aldosterone and MR signaling at the level of the vasculature to vasoconstrict and enhance vasculary activity, and with the kidney, to hold on to salt and water.

So mineralocorticoid antagonists, particularly spironolactone, have been demonstrated to be the most effective add-on drug for the treatment of resistant hypertension. The concern, and the problem, and the challenge we face is that the risk of MRA-induced hyperkalemia is increased in many of the patients that we want to use this drug on, specifically those with chronic kidney disease-- but we're going to talk about that in a bit more detail later-- diabetes, and older folks, because despite normal creatins, they often have, of course, decreased estimated GFRs.

And at this point in time, despite their early promise, mechanical methods for dealing with resistant hypertension are not quite ready for prime time. They include baroreceptor stimulation, catheter-based renal denervation, some of the research I'm involved in, and iliac fistulae. They're not yet ready. And there are a couple of other types, some of which are going to be investigated here at the University of Michigan, so you can stay tuned for desperate announcements looking for patients.

So those are the most important key pieces of my talk. There's going to be detail. If you get paged-out now or fall asleep, you've gotten the high points. So this is my first case. And this is a patient I saw about a month ago-- well, actually, no, about eight weeks ago.

He's an 80-year-old individual with longstanding diabetes, low renin hypertension, CKD stage 3b to 4, depending on his level of hydration and his level cardiac function, and marked hyperkalemia with even low doses of either spironolactone or eplerenone, another PEARL, as occasionally, when we have people with refractory hyperkalemia with spironolactone, we'll switch them to eplerenone, because it's shorter acting, doesn't have metabolites that accumulate it as much. But again, if you've got an estimated GFR below 30, you are skating on thin ice when it comes to the lawyers. And I'd recommend doing it very, very carefully with reliable patients, but again, we'll talk about that more later.

This patient has recurrent fluid overload, systolic blood pressures of 190 over 90, pedal edema, complaints of dyspnea with exertion, and presented on the following medications-- torsemide 30 milligrams daily, hydralazine 100 three times a day-- and I gasped, because the ceiling dose for someone with CKD should be a maximum of 200 milligrams a day-- isosorbide mononitrate 30 TID, clonidine 0.2 twice daily, and nifedipine ER 90. So we're going to think about this gentlemen as we go through this talk. And at the end, I'm going to tell you what I did and what happened. And I will-- full disclosure, he wasn't cured.

So in terms of, when we talk about resistant hypertension, I like this cartoon. And if I can figure out how to use the pointer, I'll be in great shape here, but I'm not sure I can. So someone's going to be to assist me again. Let's see if that-- oh, that didn't work. Well all right, we'll start at the bottom and move to the top. You guys can read.

So in the middle are the numbers of medications the patient is purportedly ingesting. And they said purportedly. We'll talk about that in a moment. So you have patients, if you look at the green stuff, initially with one, two, or three medications. You have controlled patients with controlled blood pressure.

When you get into four medications but the blood pressure is controlled, we call that controlled-resistant hypertension. And all of controlled-- resisted hypertension and anyone who meets the criteria of resistant hypertension in the clinic, according to some studies, is at significantly increased cardiovascular risk. So if you have patients on four medicines controlled in the clinic, they still have enhanced cardiovascular risk.

And then on the right are the people who aren't controlled, so one or two meds, uncontrolled hypertension. It's considered resistant when you're taking full doses of three medications and not controlled, or four. And five or more medications, not controlled, is new classification we have which is refractory hypertension, which in fact represents a very small percentage of patients, about 3% overall, so not a common problem, but a frustrating one.

So what I can't read but you can is that, in terms of controlling patients, drugs we're going to use, a RAS control such as beta blockers, RAS blockers, alpha-2 agonists, and vasodilators, calcium channel alpha blocker, vasodilators, and last, volume control. In terms of minimizing your patients' pill count, combination of an ACE and a CCB, which was originally elaborated in the ACCOMPLISH trial, the major investigator of whom sits in this auditorium with us and is one of my colleagues. So you start with an ACE and a CCB. And then you add a diuretic, chlorthalidone or indapamide, and then you go on to your fourth drug, obviously with variations depending on individual's allergies and intolerances.

So when we look at all US adults with hypertension, and a year ago, I would've said 68 million. Now we're to 70 million. And it keeps going up, because everybody's getting heavier and less active. And we have more high fructose corn syrup in our diet.

Within that group, about 21%, depending on the studies you read, have what we call apparent treatment-resistant hypertension. Of that apparent treatment-resistant hypertension, fully, at least, depending on the study you read, almost 65% will actually have controlled hypertension. That's variable. And you're left with about 32%.

You're going to show me. Thank you. Got it, thank you, thank you. I do fine without it, but that helps a lot.

But then a very small percentage-- we'll use it-- in fact, yeah, there we go. Woo, it works. A very small percentage have what we call refractory hypertension, which is only 0.5% to 1% of all hypertensives, and truly, only about 3% of people who we consider are resistant. So this is a small group, but it's real. It exists, and very difficult to deal with. So when we look at less than 50% of patients have true resistant hypertension, because many of them have-- and of those, they have occult fluid retention and inappropriate mineralocorticoids, as we've already discussed about.

So in the REGARDS study, it suggested that patients who actually were controlled out of office did not have increased cardiovascular events, which is people that you've shown an ambulatory blood pressure monitoring are controlled despite elevated office readings. And part of those of course are white coats. However, in patients with resistant hypertension that's confirmed, you have a very high enhanced cardiovascular risk. That's from the ALLHAT trial in people with normal renal function. And the CRIC trial, some of the data of which was collected at this university, also shows enhanced cardiovascular events in CKD patients with resistant hypertension.

So going backwards just slightly, so the first thing you want to know is, is this truly resistant hypertension or not? Just to focus briefly on the refractory, which is the very small number of patients who are on five medicines and, not to try to get even more business, but if you've got people like that in your clinic, I'd really recommend a referral to the hypertension clinic so we can help you worry about the patient. So if you're truly uncontrolled, most of the data suggests this is excess sympathetic nervous system activity.

And these patients often respond to evil dreaded drugs like clonidine. But clonidine should be the sixth drug that you reach for, not the second or third. I know none of you would ever do that, but we sometimes see patients in clinic. And they come to us with a diuretic and clonidine. And they can gradually-- it's difficult for them to drag themselves to work in the morning, so we try to reserve the use of drugs like that for people with really severe hypertension like this.

So there are some problems with our conventional definition of resistant hypertension, number one, it uses clinic blood pressure data. And we really believe out-of-office readings are key. I might add that many of the studies that we've done up until very recently did not use the optimum way of measuring blood pressures in the clinic. It was casual office blood pressure, or reasonably careful research blood pressures, like those were done in ALLHAT or the CRIC study, but they were still not the best way to measure blood pressure.

24-hour ambulatory data shows up to one third of patients are controlled out of office, suggesting that 24-hour ambulatory blood pressure monitoring, which is currently available at Domino's Farms, but will soon be available through multiple cardiology clinics here, should be performed before a patient is truly considered to have resistant hypertension. This is a test that is utterly under utilized, gives us a lot of valuable information, and is absolutely critical to managing your patient with resistant hypertension appropriately. I'd like to say, and I believe, it's critical to managing every patient with hypertension, but we have to work on the cost, work on the aggravation factor before we can quite say this. But this is one group that really needs an ambulatory blood pressure monitor.

OK, so my favorite hypertension doctor is Norman Kaplan, who is still clinically active at the age of 88, not unlike Dr. Stevo Julius, who introduced the speaker last week, Dr. Brook, who is the head of my division. The measurement of blood pressure is likely the clinical procedure of greatest importance that is performed in the sloppiest manner-- true that.

So make sure first that a blood pressure is accurate, OK? And there are at least three things that are happening in this picture that are incorrect, horrible, not to be done, OK? I'm told I'm not supposed to call on people in grand rounds, so I'll tell the answer for you.

First of all, you've got a doctor, we presume, taking the blood pressure of a patient-- no. Second of all, she's seated on the table. Her back is not supported. Her feet are not on the floor, although her arm is at the level of the heart.

And lastly, he's using a mercury manometer, which was outlawed many years ago. And he will be taken away by the PC police, in addition to which the level of the manometer is not at his eye level, so he's going to be inaccurate about recording the reading. Then we don't know if he has had his hearing checked. And we don't know further if he's been re-educated once a year, which anyone that uses manual readings in the clinic, your staff have got to have another re-education once a year or you're going to have the dreaded digit preference, et cetera, et cetera.

So what you can read, and again, I can't, is that inaccurate office readings probably are present-- that that's probably the cause in about 33% of patients. Ha, ha, ha, now you have a cartoon. You can laugh at it.

So the issue is, again, with current office blood-- thank you guys, you are being so nice to me. This is my first grand rounds in Michigan, although I've given many elsewhere, and I was a little nervous. And you guys are even nicer than most of my audiences, so thank you very, very much. So office blood pressures-- poor technique, inaccurate instruments-- did we say inaccurate instruments-- measurements without allowing the patient to rest, and failure to average multiple readings, and then of course white-coat hypertension.

So we have a cure for that. And it's called automated blood pressure devices, or, finally, let's start measuring blood pressure correctly. We have two automated devices. How many of you use automated devices to measure-- automated devices with the patients unobserved in your clinic to measure blood pressures? OK, Dr. Margolis, you do that in [INAUDIBLE]. Don't you use the BpTRU?

AUDIENCE: We have it, but--

SUSAN P STEIGERWALT: Oh, oh no! It's sitting on the shelf. All right, that makes me really sad. So the BpTRU, this is the first used-- first automated unobserved blood pressure reading. It measures five readings and chucks the first. It's used in 40% of primary care offices in Canada. And Canada, of course, is fortunate enough to have single payer, so there-- medical bankruptcies aren't the second leading cause of bankruptcies in their country as they are here, but we can talk about that another time.

It's $900, but that's with a five-year service agreement. It correlates with daytime ambulatory blood pressure, also correlates well with target organ damage. This was the first of the unobserved automated cuffs. I might add, as you all, I hope, are aware, is casual office readings correlate with absolutely nothing-- no target organ damage, no patient outcomes. If we are measuring the blood pressure ourselves, it's to diagnose orthostatic hypotension or a hypertensive urgency, probably brought on by our white coats, but it really doesn't tell us anything about what's going on with the patient other than that.

The second device, which is slightly more reasonable in price, is the OMRON 907XL. It measures three readings after five minute rest. You wrap the cuff. The nursing assistant wraps the cuff around the patient appropriately, not the neck, the arm, sits them back supported, feet on the floor, arm at the level of the heart, pushes a button, walks out of the room. It times five minutes rest and then measures three readings in a row.

Why is this such an amazing device? It's amazing because it was the device that was used in the SPRINT trial. And there are hard outcomes related to readings in the SPRINT trial. And this is the first time we've had careful research readings being done with a device that we can take home and use ourselves in our clinics, so this is really important.

Office blood pressures measured in your clinics can now truly mean something if we have the political will to get involved in this process. The other important thing to know is these readings are lower. So those of you that direct clinics, this is going to immediately raise your HIDA score and increase the percentage of patients with control in your clinics, so it's a win-win-win.

Leaving the patient alone with automated devices minimizes the white coat effect. This was how blood pressure was measured in SPRINT. And it's lower than casual office readings by about seven to 15 millimeters. But there isn't some sort of fudge factor, you really have to see, it varies by individual.

But this means a couple of things also when you look at the SPRINT data that we're not going to talk about much more today, just really mainly about the measurement. When you look at people who have a goal of 120 and achieve it in Sprint, and have lower outcomes, this isn't a 120 systolic in your clinic unless this is the way you measure blood pressure. So blood pressure measurement is key to interpreting the results of SPRINT, but I would add, blood pressure measurement is key to accurately classifying and treating your patients-- end of lecture, no, not kidding.

OK, there we go. All right, so an algorithm that was developed in 2012 using automated devices, which is basically, you measure a automated unobserved blood pressure. If it's less than 130 over 80, patient's fine, continue to follow. If it's between 130 to 139 over 80 89, again, this is with the OMRON or what the BpTRU, you've got an abnormal reading. You need an ambulatory blood pressure monitor or home readings. If it's more than 140 over 90, they are clearly hypertensive. And actually, with both BpTRU and the OMRON, the readings probably need to be a little lower than that to be considered normal, probably 130 to 135 systolic in the office.

OK, so first thing we've got to figure out with our resistant hypertensives-- I'm back to talking about them again, not proselytizing-- rule out white-coat hypertension. And patients who in fact have controlled blood pressure on ambulatories have lower cardiovascular risk than those with true resistant hypertension.

So this is just an example. This was with ambulatory blood pressure monitoring. This is a Spanish registry. They don't mess around in Spain. They do a lot of ambulatory blood pressure monitors. They're way ahead of us.

So they had 68,000 people who'd had the ambulatory blood pressure monitors. 12% of these patients had resistant hypertension based on office readings. When they went ahead and did monitors on these patients, 8,000 monitors, again, not a trivial number, 37% were controlled. No treatment intensification was necessary. 62% were uncontrolled, so still a lot, but you've immediately lopped off one third of your intensification of therapy and worrying about secondary hypertension.

OK, so just to review, and I'm sure you're all aware of this already, but we have suggested values for daytime, nighttime, and 24-hour reading. We actually think the nighttime reading should be a little bit lower than this. It should be less than 120 over 70. But optimum daytime is 130-- I'm sorry, that's correct, nighttime is 115, sorry. 24-hour is 125 over 75.

And what we call clearly abnormal with daytime readings with an ambulatory, 135 over 85, nighttime, more than 120 over 70, normal, less than 130 over 80. So you're going to get blood pressure monitors back that are going to say controlled or uncontrolled based on 24-hour ambulatory monitor, and you'll know. We're almost through talking about measurement.

OK, so let's talk for a moment though about home blood pressure monitoring. At this point, OMRONs are preferred, although there are expensive A&D monitors that actually sync with EPIC. So if your patient has over $200 to drop on a monitor, we can get the readings right into EPIC. We're working on making that better.

So OMRON is currently what we recommend. Most patients need large adult cuffs, $70 or so at Costco or Sam's Club, Extra large OMRON cuffs are available on the internet. If you have a Brand X cuff that the patient brings into clinic to show you, you can go to a website, dableducational.org, to check whether the cuff's been validated-- that type of cuff has been validated.

And frankly, we're not validating cuffs when we bring-- have people bring their cuffs to clinic. We're making sure they know how to measure their blood pressure appropriately. And we're comparing it to our automated device to make sure it's sort of close. We have a protocol, but that's the truth.

So home readings tend to be lower. They're more reproducible. The American Heart Association-- and these are still the recommendations, but they're being regrooved-- is recommending that an average of 12 readings taken morning and evening over several days be used to make clinical decisions, which is what we do.

So let's talk for a moment-- ah, we're finally getting to causes-- of treatment resistant hypertension. Well, we're going to talk about this a little more. I think this is the worst news ever, which is treatment non-adherence is present in about 50%. 50% of patients with resistant hypertension are either partially or completely non-adherent. Completely non-adherent, they're not taking any of their pills.

So the way this has been shown-- and this will be referenced-- is with measurements of high-performance liquid chromatography looking at the drugs. We can do-- and we don't have that readily available in this country yet. It is available in Europe. For a couple of trials that I'm involved in, we're sending our blood and urine over to Europe for evaluation. Clearly we're not going to be doing that forever. And it will be available in this country soon.

There's a couple of issues with this. Number one, we're still not sure how to counsel people so that we don't turn them off. But we can just say, when we did this we noticed that not all the medications-- you're not taking all the medications, lots of eye messages. I'm concerned. I'm worried about you.

So we're not quite clear about how to handle this correctly, but it's always important to ask your patient whether they're taking the medicines. Check the pharmacy. A lot of the, sort of, scales, like, I think there's a Morisky scale for adherence to therapy, those don't work so well, those were very discordant with actual measurements.

So your best bet is, you can have the patients bring their blood pressure cuffs in, which we always do. You can talk to them. And just be aware, that sometimes, this is a problem. And we're just, sort of, stuck with that at the moment.

White-coat hypertension, associated factors are very important. Sleep disorders and sleep deprivation are huge problems. It's always important to ask about sleep duration, less than 6.5 hours, you risk increased risk of heart attack, stroke, and uncontrolled blood pressure. Sleep apnea, although the amount that it lowers blood pressure is totally underwhelming in most patients, but there are other reasons to treat sleep apnea-- obesity.

Shift work is also associated with enhanced cardiovascular risk. That hasn't been carefully studied as to why. It's probably something to do with our circadian variation.

Then we come to medications. Weight loss medications, stimulants, venlafaxine and other SSRIs, SSNIs are big deals. They're big deals. MAO inhibitors, which are being used more frequently, calcineurin, VEGF, erythropoietin-- we know about this. You can look it up.

I want to emphasize herbal medications, including stimulants, bitter orange, and licorice-- so everybody goes, nobody eats enough European black licorice to cause hypertension. Well, sometimes they do. And sometimes they chew tobacco that has European black licorice in. And sometimes, they take the energy-inducing health food supplements that also have European black licorice.

The problem with herbal medications, as you also know, is, half the time, we don't know what's in them. If the patients get supplements that have the USP label on it, it means, at some point, somebody has checked the drug. And it has what it says it has in it.

But we don't know when that was. Was that a year? Was that two years? So really, patients are on their own when they're taking herbal medications.

Excessive alcohol consumption-- CKD is a big one. I put it down towards the bottom, because it's a problem. It's a problem to control the blood pressure. And it's not like we can cure it yet. I guess we're working on that too, And then secondary hypertension.

Most commonly and most importantly, primary aldosteronism, other endocrine. Renal artery stenosis is there, but it's way down the list. And most of the time you're going to manage it clinically, so please don't order that CTA and spend hundreds of dollars before you do blood tests and aldosterone-renin ratio to screen your patients for low renin, excessive aldosterone, which is the problem most of the time.

So when we look at serum and urine drug levels in resistant hypertensives, 25% to 55% total or partial adherence. So there are other things you can do. You can actually have the patient take their pills in clinic, which most people are angry about, so that's probably not the best plan, but it works. There's a very nice position paper from the American Society of Hypertension that talks about this.

I want to emphasize, again, adherence is a two-way street. Our job is to mitigate barriers. We don't want to be another barrier.

The patient comes in. We're frowning. We're telling them how bad they are. Then they're never going to come back, OK? Just like you've got to ask about sexual function in all of your patients and make sure the medicines you're giving them are not making things worse, because that's a great reason that middle-aged men will typically stop their blood pressure medicine. And who could blame them?

So again, we talked about-- this is a little bit of a fuller list. NSAIDs, estrogen oral contraceptives, alcohol, and high-dose steroids are all causes of resistant hypertension-- Decongestants, migraine medications, beta agonists, and then the chemo that we talked about. I think just about everything is on here. I don't know why someone would be on florinef, except for hyperkalemia, but that's like bathing your body in aldosterone. And then plus-minus caffeine, couple millimeters then you get used to it, tobacco plus-minus recreational stimulant, and then we go through all the herbs again that can cause-- worsen hypertension. And there was a comprehensive list in the *American Journal of Medicine* in 2012.

So when we think about middle-aged people, I'm not talking about the young ones. Maybe there are some med-peds residents in here. I apologize. That's another story. But most of it is obesity. A lot of it is obesity in terms of resistant hypertension, medications, CKD, primary aldosteronism, way too much salt, energy drinks, alcohol, and cocaine, and sleep deprivation. In older folks, people above 65, getting close here, renovascular hypertension, aldosterone, alcohol, lots occult alcohol overuse, CKD, sleep disorders, so I use the acronym, REARS.

In terms of a clinical evaluation of your resistant hypertension patients, duration of hypertension, control or previous evaluation-- were they well-controlled and they suddenly popped up? Then you got to think about an acquired secondary cause, a new supplement, whatever. Medication side effects, over-the-counters and supplements, you have to ask always, VEGF, inhibitors, et cetera.

Sleep apnea, you want to do an Epworth sleepiness scale or STOP-Bang, which you should be doing on all your patients anyway. Menstrual history-- younger women with resistant hypertension may have PCOS. That's going to contribute to uncontrolled hypertension. And don't forget pseudopheochromocytoma. How many people here have heard of pseudopheochromocytoma? OK, good, there are some. That is excellent.

So severe emotional stress can cause marked labile hypertension, but not anxiety to go with it overtly. People talk about this as a calm panic disorder. It was first described by Dr. Samuel Mann in concentration camp survivors.

We see it in people who've had severe emotional stress in the past, and have gotten through it by just moving through and not dwelling on it. This is people who've been rape victims, incest victims, watched a family member commit suicide, anything that would be considered a really severe stress. And the patient doesn't appear overly anxious, so it's important when you're doing your social history to gently probe for childhood trauma, young-adult trauma, because that may be the explanation.

And if it is, these patients are much better managed by a combination of a beta blocker and alpha blocker to basically block the paroxysms, and therapy, if they're interested in getting it, then pouring on all the rest of the meds. And I would commend any articles, including the one in *UpToDate* on labile hypertension by Dr. Samuel Mann if you're interested in learning more about this. But it's not that uncommon.

OK, so this is just a picture, right? You all have your patients open their mouths to see whether you can see the uvula or not, but this is a very easy clinical clue, in addition to excessive daytime sleepiness, to the possibility of resistant hypertension. It predicts, particularly Mallampati four, predicts the prevalence of sleep apnea. I might add that patients with advanced CKD, CKD stage 4 and 5, 20% of those patients will have significant amounts of sleep apnea. so particular you CKD patients, look for it.

So while you are evaluating the patient, lifestyle, walking, DASH diet, walking 30 minutes daily, and the blood pressure monitors we already talked about. I'm going to skip through these slides. But weight loss does reduce blood pressure, not by huge amounts, but some. And it's very important to note that high potassium intake basically fights a battle and wins with sodium intake, so that is very important-- and this is from the PURE study from the *New England Journal.* Be aware that if you can get your patients to DASH, their blood pressures really will be improved.

And obviously, if their potassiums are skirting six, they may have advanced CKD. This may not be a good idea. But if you've got fairly normal renal function, CKD 3 and above, no hyperkalemia, do put them on the DASH diet. It makes a difference, as just 30 minutes of exercise, as does structured weight loss, and sleep.

So are we using an adequate anti-hypertensive regime? OK, how many of you-- and I don't know your names, so there's no grades attached. How many of you use hydrochlorothiazide in your hypertensive patients? Oh my god, only a few, great. How many use indapamide? How many of you treat hypertension?

[LAUGHTER]

OK, there's a few. How many use chlorthalidone? OK, so there's a few. All right, so basically, chlorthalidone, if you're dealing with a resistant hypertensive, chlorthalidone is really the drug to use. When big studies are done, it's grossly underutilized.

The other problem we see, just looking at this, and they're not things any of you would ever do, but sometimes people combine ACEs and ARBs. We don't do that anymore. And in a large study of uncontrolled patients in another health care system whose name shall remain nameless, only about 15% of people were on appropriate therapy before they were called resistant.

So why you should use chlorthalidone, is superior blood pressure control. And that's compared to hydrochlorothiazide. It's longer acting, improves blood pressure control, greater blood pressure reduction, and superior outcome data in MRFIT and in other studies. Admittedly, some are smaller. And some are meta-analyses. But we believe the duration of therapy makes a huge difference.

The other drug that has also been shown to have enhanced cardiovascular benefits, particularly for stroke, is indapamide or Lozol. It's an older drug. Now all these drugs have the same problems, is all thiazides and chlorthalidone has a particular problem with hyperkalemia or hyperuricemia, so you may need to use it with a potassium-sparing drug like spiro. Nevertheless, it works. It also works down to an estimated GFR of about 20-- very, very helpful.

So I just wanted to mention Pathway 3. I'm really going to be emphasizing Pathway 2, but Pathway 3 was a combination of hydrochlorothiazide plus amiloride versus hydrochlorothiazide. And in patients with normal renal function, addition of amiloride is also very helpful in improving blood pressure control.

So when you look at chlorthalidone versus loop diuretics, small studies have shown that it's effective down into an estimated GFR of around 20. This was from Rajiv Agarwal. It needs to be duplicated, but it's important to remember that furosemide does not lower blood pressure. If you're going to use a loop diuretic, use a long-acting one like torsemide or BID Bumex, because those are the drugs that have been shown to reduce blood pressure. And the other thing to do is use a loop with chlorthalidone. And that may also improve diuresis and lower blood pressure.

Mineralocorticoid blockade is the next. And most people, we want combination pills and then intensifying their diabetic regimen. After you've done all of those things, you want something that's going to target the sympathetic nervous system, either an alpha blocker or guanfacine, or clonidine, if you have to use it, and then a strong vasodilator like minoxidil. And then in old folks you can use long-acting nitrates. They improve central blood pressure. And they improve systolic blood pressure a bit.

The other important thing to do is, if a drugs not working, get rid of it, OK? People that come to you with low-renin hypertension on atenolol, if they're not on it for rate control, taper it off, get rid of It-- no reason for people to have to be on more meds than they have to be on.

So Pathway 2-- and I commend you to read this-- was in the November 2015*Lancet.* Pathway 2 showed-- was a very carefully done trial, where individual patients with resistant hypertension were cycled through spironolactone, placebo-- they're taking their ACE, CCB, and diuretic. Then they are cycled through spironolactone, bisoprolol, doxazosin, and placebo.

This study took them eight years to complete. They got about a 270 patients through it. And it's very important because of what they were able to show. So when they looked at all these patients across the board, and they measured renin and aldo, and even up to very high renin levels, like renin levels of, say what our equivalent would be 10, still very responsive.

So placebo group fell from 148 to 143. Spiral fell further to 133. Doxazosin 48 milligrams, which is a heroic dose, or bisoprolol 10 milligrams, also a heroic dose, again, you got improvement, but not nearly what you got with spiro, 25 to 50. So again, your fourth drug, after you've started to think about secondary hypertension is spironolactone.

And 58% of the patients on spironolactone came to blood pressures less than 135 over 85. It was the most effective drug. And only 5% of the patients that-- where spiro was added had systolic blood pressures above 150 at home. So I just want to emphasize, this is also under-utilized.

There are definitely side effects. I'm not minimizing those. But when you start with 25 milligrams, you have a relatively low [INAUDIBLE] incidence of gynecomastia, sexual dysfunction, abdominal pain, et cetera, so start with the low dose and see where you go. But one other thing about spiro is it takes a long time to see the full effect, average six weeks to three months. So please, when you're titrating, that's one drug you need to titrate slowly.

So what are you going to do in the clinic? Oh, I forgot. None of you treat-- well, some of you treat hypertension. So I want to thank Dr. Rob Brook for this slide and some of the others. He put this together. It's awesome.

What are you going to do? Are you going to do a serum aldo-renin to look for primary aldo. Free plasma metanephrines exclude a pheochromocytoma, which, again, is vanishingly rare. Make sure you know their kidney function.

You could do a calcium and PTH. We usually detect our hyperparathyriodism because we put people on chlorthalidone and their calcium goes to 11. And we go, oops, there's a problem here. TSH will largely-- hyperthyroidism will largely cause diastolic hypertension.

And then sleep questionnaires or a sleep apnea study-- I want to emphasize, 60% to 80% of patients with resistant hypertension also have sleep apnea. Please, please remember this. The patient will thank you.

So after it's confirmed, as I said, 20% have inappropriate aldo secretion, often primary aldo. If they're a surgical candidate, proceed to salt load, confirmatory adrenal venous sampling, and removal of the offending gland. Most cases don't have hypokalemia. If they're not a surgical candidate, you do a low-radiation CT to make sure they don't have an adrenal cancer. And then you toss them on spironolactone.

I actually use the aldosterone-renin ratio in a little bit more expansive way. I find it helps me figure out, partially, what the heck is going on with the patient. It's helpful in terms of treating them of course.

But when you see people with low renin and low aldo, you think about low-renin hypertension. You think about anything that might be suppressing aldosterone, DOC-secreting tumors, Liddle syndrome, Cushing syndrome, licorice ingestion, mineralocorticoid receptor activation or abnormalities in apparent, let's see, pseudohypoaldosteronism type II, et cetera. Primary aldo, low renin, high aldo, and then secondary diuretics, renovascular hypertension, renin-secreting tumors, coarctation of the aorta, but you will have figure that out already because your young patient will have had a thigh blood pressure cuff done.

So what about renal artery stenosis? I'm ignoring it. Oh my god. And I'm in the cardiology division. What's wrong with me? Well basically, both ASTRAL and CORAL show positive results in a very limited fashion. It appears from very recent studies that if you have no microalbumin at all, that you tend to respond better, if you have a significant renal artery stenosis, to stenting, than if you have any degree of proteinuria.

However, there is a group of patients that CORAL really didn't talk about. Those are people who have-- or they're very intolerant to ACE inhibitors or have a with improved blood pressure, have a big bump in creatinine, more than 3%, or patients with loud abdominal bruit can't take the ACE inhibitor, because their potassium goes up, because their kidneys are doing so well. People that present with recurrent pulmonary edema, you have to think about bilateral renal artery stenosis.

Younger folks with fibromuscular disease and then individual patients where they have severe new onset of very high blood pressures or acute worsening in GFR with no other explanation, image their kidneys and think about it. But again, this is clinical judgment. This is not guideline-induced. And this is something where you want someone who's interested in hypertension working with you. So beyond--

What do we do? We're almost done. We're going to be done with time for about four minutes time for questions, but we started late. So what else do you do? Device-guided slow breathing, the RESPeRATE. That helps a little. Transcendental meditation helps a little. Isometric hand grip helps a little. And we're about to do research on that.

Other things, if you have health food nuts for patients, or people who just hate pills, two tablespoons of ground flax seed daily is the equivalent of one medicine. One cup of beetroot juice daily, which I find a little overwhelming. One cup of beetroot juice daily will also lower your blood pressure, the equivalent of one medicine. But you have to persist with all of this.

So then we come to other things, renal sympathetic nerve ablation. It seems to work in Europe. We haven't figured out how to make it work in this country yet. But the idea is you basically burn the renal nerves, both afferent and efferent, going to the CNS, going to the kidneys, results in natriuresis, diuresis, and vasodilation.

However, the randomized controlled trial that we've done in this country is negative, so we don't have any positive data yet. We have positive from a single-blind well-performed study in Europe that suggests, in that study, that blood pressures were improved. And that's called the DENERHTN. And it was published in *The Lancet* in 2015, but still not ready for prime time.

Baroreceptor stimulation is also being reworked. The four other things we have, one of which, the eCoin, is going to be investigated here at the University of Michigan, we hope. Deep-brain stimulation, [INAUDIBLE] uncoupling, which is an external iliac AV fistula is created. And that does lower-- there's a proof of concept. There are studies ongoing.

Carotid body ablation, and then decompression of one of the arteries in your brain, which again, is done in Germany. We don't do it in this country. But these are really all things we are looking at in people with truly refractory hypertension.

I think there's one more side. Takeaway points, first, you want to make sure you have true resistant hypertension, right? Second, optimize the diuretic regimen and evaluate for primary aldo. Next, add spiro. Finally, refer to a hypertension specialist.

I might add one-- two things, right? You don't have to just refer to a hypertension specialist. You can become one. The American Society of Hypertension has a test you can take and become one. Learn about it if it's something you're interested in.

But don't wait 10 years to refer your patient, because target organ damage is ongoing, OK? So if you're stuck, it's a year out, and you're still scratching your head, please refer the patient to someone with an interest in hypertension so we can get the patient evaluated and better controlled, whatever degree you want to stop the evaluation yourself.

OK, so what did I do for this patient? Long story short, I added chlorthalidone 25 milligrams daily, he diuresed 10 pounds over three weeks-- resolution of dyspnea and edema. Now his systolic blood pressure is down to 164, not 190, 158 standing.

Now I'm really trying to figure out whether I can do things any better or not with this guy. I'm not sure. So again, it's not perfect, but I believe I have decreased his risk, and certainly increased his quality of life by lowering his blood pressure by 30 points systolic.

All right, I'm finally done. Thank you very much.

[APPLAUSE]

OK, we have three minutes for questions for those of you who don't have 1 o'clock clinic.

SPEAKER 1: Questions? Yes, question in the back?

AUDIENCE: [INAUDIBLE]

SUSAN P STEIGERWALT: I can't even-- I--

SPEAKER 1: So the question was a nutritional approach to hypertension.

SUSAN P STEIGERWALT: OK, nutritional approach to hypertension, that includes the DASH diet, which in hypertensives, when it was a feeding study, decreased systolic blood pressure by 8 to 11 millimeters of mercury. Those results haven't entirely been duplicated in the real world, but there is an improvement with that. In addition, flax seed, two tablespoons taken daily, will lower systolic blood pressure by about 5 millimeters of mercury. Beetroot juice one cup daily, again, lowers blood pressure 5 to 8 millimeters of mercury. Then if you exercise, brisk walking, 30 minutes five days a week, statistically significant lowering in blood pressure based on ambulatory monitoring results in resistant hypertension, about 3 to 4 millimeters by ambulatory, which is a bit more-- probably a bit more in the clinic.

SPEAKER 1: Yes, question?

AUDIENCE: What do you do for your older patients [INAUDIBLE] false pressure, isolated systolic hypertension, lower diastolic blood pressure, already on [INAUDIBLE]. Is there anything to add, or--

SUSAN P STEIGERWALT: Well, are they already on a calcium channel blocker?

SPEAKER 1: Yes.

SUSAN P STEIGERWALT: OK, and they're-- are they able to tolerate a diuretic like indapamide?

AUDIENCE: They're already on it.

SUSAN P STEIGERWALT: OK, have you done an ambulatory blood pressure monitor to find out how bad it really is?

AUDIENCE: No, we haven't done that.

SUSAN P STEIGERWALT: OK, I would do that before you do anything else. The other drugs that will tend to help lower-- if your true-- probably the first thing I do is make sure you really are volume-- really, patient's blood volume is really controlled, calcium channel blockers, both because they decrease your blood pressure variability and also because they tend to lower systolic a bit more. Your nitrates are good. Then you're, sort of-- are they on spiro already?

AUDIENCE: No.

SUSAN P STEIGERWALT: OK, so spiro is very effective at lowering systolic blood pressure, but if you look at the SHEP trial, you look at [INAUDIBLE], most of those trials used chlorthalidone and then additional medications. HYVET used indapamide plus perindopril, both long-acting. But I think when you're talking about the add-ons, the next, I would absolutely put spiro on if the patient can tolerate it. But I'd still do an ambulatory and see how bad it is. Because, particularly if they're older, the little old ladies tend have a lot of white-coat hypertension.

AUDIENCE: OK, so you would keep pushing, assuming that ambulatory blood pressure--

SUSAN P STEIGERWALT: If the blood pressure-- yeah, if it's still really high, I would. But you're going to balance risk-benefit. If they're 90 years old, would I push so hard? Probably not. If they're 75, I would.

AUDIENCE: Lower than 150?

SUSAN P STEIGERWALT: Oh yeah, absolutely. And actually the SPRINT trial suggests in maybe even lower than that. But absolutely, try to get the patient below 150, probably-- in my clinic I like to try to get them to at least 135. But sometimes, it's impossible when you start at 210 systolic. You just make the patient too sick.

SPEAKER 1: In the interest of time, if any additional questions, perhaps I'll have you stay and speak with Susan. Thank you again, Susan, for a wonderful talk.

SUSAN P STEIGERWALT: Thank you.