

TRANSCRIPT
AMERICAN HEART ASSOCIATION 2023

SERIES: Unmet Needs in Hypertension Treatment Options

Title: Drugs or Devices for the Resistant Hypertensive Patient (Podcast 6 of 6)

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Guests: Jordana Cohen, MD and Atul Pathak, MD

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Dr. Hiremath: Welcome to the American Heart Association, hypertension Treatment Options podcast. This podcast series is part of a larger program addressing the unmet needs in hypertension treatment options. In addition to the podcast, this PR program includes webinars Spotlight Series, which are speakers presenting grand rounds type presentations, and an update to the comprehensive guide on hypertension, which will be, which was released in January of 2023. The overall goal of this program is to improve systems of care and understanding the unmet blood pressure needs along the hypertension patient journey.

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My name is Swapnil Hiremath, I'm an nephrologist and epidemiologist from the City of Ottawa, Canada. Today's episode is entitled Drugs or Devices for the Resistant Hypertensive Patient. We review renal denervation from a patient perspective, and I'll be your host for today's podcast. I do serve on the Hypertension Canada guidelines for health behavior change, but otherwise, have no disclosures for today's episode.

Joining me today are two special guests, Dr. Jordana Cohen, and Dr. Atul Pathak. First, Dr. Cohen, please introduce yourself to the listening audience.

Dr. Cohen: Hi, my name Jordana (I usually go by Jordy) Cohen. I'm a nephrologist and epidemiologist at the University of Pennsylvania, where I see patients in a complex hypertension clinic. And I lead and contribute to a series of observational studies and trials that evaluate the best way to manage patients, hypertension, depending on their elevated risk factors and their comorbidities. In terms of disclosures, I don't have any actual disclosures for today. I am coach or vice chair of the Hypertension Science Committee for the American Heart Association, which is part of the relevance of my interest in today's talk.

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Dr. Hiremath: Perfect. Thanks for coming on tonight Dr. Cohen. Next, Dr. Pathak, please give us a brief intro as well.

Dr. Pathak: Yes, I'm a cardiologist and a pharmacologist. I'm the head of department here, the cardiovascular medicine Institute in Monaco, also president of Society of Hypertension, and, have been involved for many years, in the field of renal denervation, and I've also served as consultant for different companies marketing devices in the field. My background basically is autonomic neuroscience and when I started working in the field, my mentor or my friends would always say, well, we have beta blockers, we have alpha blockers, the story is we don't need to work in the field. But renal denervation was really a nice episode putting back on the front scene, autonomic neuroscience and more generally how to cope with hypertension in a different way. So happy to be part of this educational program.

Dr. Hiremath: Exactly. And, and as you said, renal denervation has brought the role of the sympathetic nervous system in hypertension back into play. We are living in exciting times. Um, before we get started on the interviewing and the Q&A, let's review the learning objectives specific to today's podcast, and they are to (1) recognize treatment and management options for resistant hypertension patients, (2) Identify the rationale for candidate selection for renal denervation, (3) discuss some recent studies illustrating patient preferences. (4) We'll also look at the Global Innovation registry and (5) illustrate how shared decision making can better engage patients in their healthcare, and how to make decisions to improve health equity.

For regular listeners of our podcast, we did discuss the *science* of renal denervation, how is it done, how does it work, and what is the data on efficacy in the previous episode (Episode 5). If you haven't listened already, I would recommend having a listen to the excellent discussion between Dr. Ajay Kirtane and Dr. Raymond Townsend during the last episode. The podcast themselves can be found on learn.heart.org or any podcast network under the term AHA.

So, before we dive into renal denervation itself, I do want to explore the other options, right? We are talking about drugs or devices for resistant hypertension. Dr. Cohen, you mentioned that you take care of patients with difficult to control hypertension, including resistant hypertension. What are the common issues you face and common changes you make to successfully control blood pressure in these patients?

Dr. Cohen: Yeah, there's a diverse range of challenges in managing resistant hypertension, of course. I think first and foremost are the fundamentals. A lot of people come, uh, refer to my clinic who aren't optimized on first line antihypertensive therapies. So that's the first and most basic and important step we can take is just making sure, is somebody actually having an elevated blood pressure on three first line anti-hypertensive therapies, or does it take four medications to actually control their blood pressure? Uh, and so those first line anti-hypertensive therapies as folks on the podcast are aware would be people being on an ACE inhibitor or an A R B calcium channel blocker and a thiazide or a thiazide like diuretic. And it's incredibly common that people come to me

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that are on, uh, other agents that are our nth line or, or fifth six line agents, and not necessarily on these.

Dr. Cohen: And that can be for a variety of reasons. If it was medication intolerance or the inability to be able to take these due to adverse effects of the medications, that's one issue. But many patients, it's that their regimen never got built in the right way. Uh, and we can take a step back and make sure that they're on appropriate treatment. Then we have to ask ourselves if they are optimized on optimally tolerated doses of three first line agents and their blood pressures are still elevated. Are they truly elevated? Is their blood pressure being measured correctly? Is the clinic that's measuring them using automated office blood pressure for standardized blood pressure measurement? Has this, has this been confirmed out of office blood pressure measurement? Ideally with 24-hour ambulatory blood pressure monitoring and supplemented with home blood pressure monitoring for titration of their medications long term; to make sure that they don't just have white coat effect.

Dr. Cohen: That's confounding our diagnosis for them. Since we know that once people are already on antihypertensive medication therapy, white coat effect, that elevated office blood pressure, but well controlled blood pressure outside the office is not associated with elevated risk. It is just associated with an increased risk of, of transitioning to sustained hypertension. So they just require ongoing out of office monitoring to make sure that doesn't happen. So that's the first and foremost, do we actually trust the numbers. Next, of course, which we can talk about a little bit more throughout the period is, do we actually trust that they're taking their medication? And do we have a good rapport with our patient to really dig down and understand if they're having concerns or issues of taking them, or if there are any barriers to them getting their medications. And then we think about, well, what else can we do for the regimen?

Dr. Cohen: They're on these three first line agents. What are our best tolerated and most effective, effective fourth agents and onward? And first and foremost people should be getting treated a after we've gone through the all of those first line therapies with a mineralocorticoid receptor antagonist. And this should be really ubiquitous across almost all patients, unless they have risk for elevated potassium levels, for instance, due to advanced chronic kidney disease. But there are many patients that I see as a nephrologist with advanced chronic kidney disease whose potassium levels run less than 4.5, and these patients are quite primed to be treated with mineral mineralocorticoid receptor antagonists, but often aren't because people are afraid to. And I think that that's unfortunately a missed opportunity in many of these individuals, who are often quite volume expanded and can benefit a lot. And we have really high-quality data to support why we should be using mineralocorticoid receptor antagonists in these folks.

Dr. Cohen: Uh, there are many randomized control trials and meta-analysis of randomized control trials that have shown up to a 20mm mercury over a nine mm mercury improvement in blood pressure once we add a mineral corticoid receptor antagonist as a fourth agent. So lots and lots of reasons to do this. Of course, though, with the understanding that there are adverse effects that come with, uh, these agents, the risk of hyperkalemia, as I mentioned, because they're diuretics, there's the risk of increasing of creatinine with

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some, with some of the volume depletion that you see. So it's important to monitor labs after we start them. Very occasionally we might see hyponatremia in some patients with these agents. And in spironolactone specifically, we have elevated risk of gynecomastia. So often with my male patients, I will initiate, off the bat eplerenone instead of spironolactone. But I think that that's up to providers to determine what the best fit is for them.

Dr. Cohen: Both our excellent agents, spironolactone, is just a bit more potent than eplerenone then if patients still have uncontrolled hypertension on these four agents, and we're pretty confident that their blood pressure is truly uncontrolled, we start looking at subsequent agents that have more adverse effects, are often more poorly tolerated and often aren't quite as effective in terms of blood pressure lowering for each additional agent. And this is when we start thinking about central alpha agonists, alpha blockers, beta blockers as potential options, loop diuretics, particularly in patients who have chronic kidney disease or, or heart failure with resort rejection fraction. And when we start thinking about, more potent vasodilators, I really hate using some of those medications because they can cause edema and other adverse effects, um, such as pericardial fusions, even in some of them. Uh, but that is, that's typically what our next step is, such as hydralazine, or in last case scenario. Minoxidil, though I I'm very proud that I've never actually had to use Minoxidil to manage a patient's blood pressure. I've only ever had to discontinue it. Uh, so I think that that's really my overview of my approach to these difficult patients. There are a lot of challenges in terms of adverse medication effects and drug intolerances, in particular in these groups of patients and polypharmacy in general, remembering to take these complex drug regimens, it can be really tough.

Dr. Hiremath: Excellent. That's a great overview. You know, especially talking about proper drug choices, there is so many times we get people who are on hydralazine but are not on good doses of the first line drugs. Um, is there anything you would like to add to that, uh, Dr. Pathak

Dr. Pathak: Yeah, I think, uh, it's a nice academic approach and I think, uh, your step-by-step approach really, uh, uh, I think, um, uh, is not missing at all what we are supposed to do according to guidelines and best medical practice. But from a patient perspective, I think that, uh, when you see these uncontrolled hypertensive patient, I consider this as a very nice opportunity and I look at them in a different way. I, I see this as an opportunity sometime to ask them if they really take their drugs, because we know that one out of two patient who is prescribed three or more drugs is indeed not taking them. So it's a good way to reassess sometimes where do they stand according to their disease. Second, it's also a nice opportunity to go back to some basic things. You are sometimes surprised that these hypertensive patient treated for so many years do not know anything about the impact of alcohol or salt, or the need to regularly exercise because we have been focusing so much on their treatment, their disease, their cardiovascular, ways that we have forgotten to talk about basics.

Dr. Pathak: And finally, I also think sometimes it's a nice opportunity to, and by that I would like also to add some more, uh, academic, uh, input, uh, to just be sure that we didn't miss the

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opportunity to exclude the secondary cause. Cause we treat them, we add drugs, we build up a nice regimen, but we sometimes discover that we miss first cover secondary hypertension, primary hyperaldosteronism, sometimes also drugs, which are increasing the level of blood pressure. So I think it's also a nice way to reassess basics to dig with the patient into his psychology, try to understand if he's taking not his drugs, and to help him sometimes with other aspect, uh, regarding lifestyle changes or sometimes more complicated aspect, being sure that we didn't miss, uh, uh, to exclude the secondary course.

Dr. Hiremath: Fabulous. So regular listeners of the podcast, you know, Dr. Pathak covered adherence and, and lifestyle measures, which we have, you know, gone into more, if you really want to know more you can listen to the first few episodes where we dig deeper into these issues, which are really way more common than, you know, the exotic causes of hypertension that people often reach for in these populations. So after drugs, and, you know, the other aspects of blood pressure control, let's now move on to renal denervation. Listeners should note that renal denervation is yet to be approved in North America, though it is expected that with the pivotal trials having all been completed under the FDA guidance that they will be likely be approved sometime this year. Now, Dr. Pathak you have been lucky in, in Europe and I'm, I'm somewhat envious that you have had access to these interventions for quite a while. What has your personal experience overall been with the renal denervation?

Dr. Pathak: I think to summarize maybe our situation in Europe a couple of days ago a consensus paper has been released by the European Society of Cardiology and also the European Association for PCI. A very important document, because as you know, there was a kind of a discrepancy between data we collected until 2015 and the last seven years. But to make the story very short, we have learned that at least two types of devices are able to reduce blood pressure in patient without, or with drugs. So maybe uncontrolled patient without, or with drugs, that the therapy is safe, that the treatment is able to reduce blood pressure during day, but also during line, there is a long-lasting effect without any side effects related to target organ or to the procedure. So this has changed the way we use the therapy.

Dr. Pathak: So, you know, Europe is a very complex geographical area because every country is having its own approach. But let's say that globally in which type of patient would use this therapy first, uncontrolled hypertensive patient despite three drugs as, uh, nicely described by Jordy. So the three appropriate drugs, the optimal treatment, if your patient is uncontrolled by this drug, he could be a nice candidate to optimize it. Blood pressure control, this is really strong evidence. Then according to the situation, sometimes this patient who are drug intolerant or sometimes patient with elevated cardiovascular risk, target organ damage, or patient who experience event because of their uncontrolled blood pressure, are also suitable candidates. So what we do in clinical practice is uncontrolled hypertensive patient with three drugs, sometime discussing patients who are intolerant of drugs, and sometimes patients who are uncontrolled and who experience event, but also to make it very clear up to now, 90% of these patients were included in clinical trial and probably less than 10% where patient were part of clinical practice. But this is now changing fast in France, we had, the news that the

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therapy will be reimbursed in hypertensive patient, but more severe treatment with four drugs. And in other countries, probably these three phenotype of patient will be, uh, patient where renal denervation will be available for them.

Dr. Hiremath: Excellent. Again, from your experience, if I can ask a little bit more, have you had any safety issues or safety concerns at all?

Dr. Pathak: Yeah, I think it, it's really important because it's a procedure. We are talking about interventional cardiology, so you're doing something in the renal arteries. So first, and I'm talking now to the nephrologist, you fear renal artery stenosis, dissection, any type of local complication. And we know now, after so many years that the therapy is safe regarding procedural complication, whether in the renal artery or also at the level of the femoral artery. So no risk or excessive risk of hematoma, pseudoaneurysm, I mean, nothing new for an interventional cardiologist. The therapy is safe. Second, we started treating the origin of the renal artery, and we learned from physiologists that finally the accessories arteries, but also the bifurcation were important sites where innovation was sometimes more important than at the pa at the main part of the, of the ostium. And so we started treating more distally.

Dr. Pathak: And again, there was a razor or there was a concern that are you doing something in this tiny artery arteries, which could lead to tiny stenosis, increasing resistance in the, in the renal parenchyma. But again, nothing to worry about that. So I think from a safety point of view, I really feel that this therapy is safe. We have now also a lot of cohorts, the longest follow up is now of nine or 10 years, small cohort, but we have now evidence with more important cohort with 2- 3000 patients showing that finally what you have done is safe and is not increasing the risk for the patient.

Dr. Hiremath: Thank you. That's really good to know. In terms of the longer term experience, Dr. Cohen, do you have any comments or thoughts about renal denervation so far?

Dr. Cohen: So, our site does renal denervation at Penn, but I haven't really been directly involved in the studies. I think I was a sub-I on one, but didn't actually do anything. So I really have had limited experience other than a couple of patients who've done the studies. And I just, to me, the main question is...it seems that really only very, that the previous results, the studies, there was some discussion that they'd been poorer results in the past based off of the variety of sites doing it that didn't have as much experience. And that with growing experience, the results have gotten better as more providers have been doing this more. Dr. Pathak, can you tell us a little bit about your experience with that, because I think it almost seems like only certain centers are going to be able to do this initially until lots of folks get more experience. Is that what you're thinking?

Dr. Pathak: It's a good point, Jordy. I think there is a learning curve, like for any type of intervention, and we have seen that, I mean, you need still to be experienced in the field. This procedure is perceived as being easy. It's not TAVI (transfemoral aortic valve implantation). It's not just replacing a mitral valve. You're not doing a complex coronary case. So when you talk about renal denervation with interventional cardiologist, it's not necessarily the procedure, which is the most exciting for them, but you still need to do it

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in a proper way. You need to assess the arteries. You need to know where you are going to treat the patient, the accessories are you going to go, et cetera. So there is a need to learn how to do, uh, the best procedure. Second, what we have also learned from trials is that, what you are referring the trial from the past had a, a couple of pitfalls, blood pressure while measured in office.

Dr. Pathak: Now all studies are looking at a DPM (drug level measurement), the drug adherence was not measured. Now there's a toxicological assessment for this patient to be sure that they're taking or not taking the drug. And finally, you, the very important part of the trials is that all the recent trials are sham control, which is in the field of cardiology or in the field of device medicine, something new where you are offering a placebo, a sham control trial for a device, which was in this case most of the time, a renal angiogram, which is again, I think putting the bar very high. And the data you have now are really taking into account all these confounders, addition to the treatment correct measurement, learning curve of the proceduralist, and, having a real sham control trial. And this is really making now the difference.

Dr. Hiremath: It, it's true. You're absolutely right, the quality of trials and the design is very sophisticated. And the kind of results we have gotten are pretty robust. Uh, and you made a really good point about, you know, it may not seem like a technically challenging procedure, but it still has to be done very, very meticulously to ensure you get, uh, complete denervation. Uh, but let's now talk about it from the patient perspective. And I know Dr. Pathak has done some research on it from the patient preferences. Can you tell us a little bit about what you did and what your findings were?

Dr. Pathak: Yeah, you know, it's a very interesting story because in the field you have believer and non-believers, okay? So believer will tell, well, I'm sure any patient would like to go for renal denervation. Okay? Non-believers will say, I'm sure no patient would go, want to go for, for intervention in the field of hypertension. So the story of patient preferences started initially with the paper we did with Roland Schmieder, a German colleague who just simply, you know, asked patient. So patients who were not taking anti-hypertensive medication, but also patient who were prescribed anti-hypertensive medication. It was a questionnaire, very simple cross-sectional survey in patient with elevated blood pressure in Germany, more than a thousand patient, what would you like to go for if your blood pressure has not controlled drug therapy or renal denervation? And more or less, only 25 to 35% of the patient were ready to go for renal denervation, while the rest of the cohort would ask, would answer and say, I rather go for drug therapy if my blood pressure has not controlled.

Dr. Pathak: But there was a major limitation in this type of study because this approach, you know, the survey approach is, you know, not the best way to do a quantitative and a qualitative assessment of what really is patient preference. So we moved the step forward, and with the help of colleagues and, and especially David Kandzari and Michael Weber, we use a new type of approach, which, which is called, uh, Discrete Choice Experiment. So basically it's a type of statistical method which is used to compare respondent preference for two or more alternative, okay? And it has been used in the field of economy, and even it earned Daniel McFadden the Nobel Prize in the year 2000,

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because it's a way to mimic realistic choice. If I have to give an example, when you want to buy an iPhone or, or a Samsung phone, whatever, um, you go in a shop and you say, okay, I want to buy a phone. But then you start thinking, do I want a big screen or a short screen? Do I want a big memory, a short memory? Do I want a red one or a blue one? Uh, and, and, and in fact, the way you process your decision is not based on yes or no. In fact, you are ranking things in your mind and you are giving importance to the mind. And that's what we did in this study where basically we try to mimic the way people decide for something. How? By identifying what we call attributes, for example, reduction in blood pressure, uh, uh, the, the risk of drug side effects and the level of these attributes. So when you talk about reduction blood pressure, what is meaningful? Five point reduction, 3 point reduction, 10 point reduction? When you talk about the risk of side effect, what is important? Uh, 12% of bruising, 15% of bruising, okay.

Dr. Pathak: And this allowed us to build scenario. So we were able to submit these questions to a cohort of 400 patient, hypertensive patients, uncontrolled, who never experienced renal denervation, and we offered them treatment alternatives. So, uh, what would you go for a treatment A where your blood pressure will go down by this amount? The risk of side effect is of that, uh, the, the, the follow up has shown that the therapy is safe OR this treatment? And the treatment could be a drug or device. And this really help us to quantify and qualify what will be patient preferences for these attribute level associated with hypertension treatment, with medication or intervention. Now, the cohort I'm talking about are really patients you are used to say in your clinical practice, nothing special. Uh, mainly female male, uh, gender ratio was the same. Mostly 60 years old history of hypertension for more than five years, and let's say mild to moderate hypertension in this case.

Dr. Pathak: And you will not be surprised what was finally driving the choice. What was the strongest factor influencing treatment choice? Well, the capacity to reduce blood pressure. So if any therapy was able to reduce blood pressure, whether it's a treatment, a drug, or a device, well, definitely this will lead the, the decision process to what you are offer offering. So first, the capacity to reduce office systolic blood pressure. Second, the duration of the effect. But then you could also start playing with this data. So we could, for example, calculate what was patient openness towards a hypertension procedure. And okay, the higher you were able to reduce the blood pressure, the higher the number of patients were willing to go for a procedure. And then you could even see, and you could even calculate the benefit/risk ratio, what was a patient ready to accept as risk for this level of blood pressure decrease.

Dr. Pathak: So for example, in exchange for a treatment benefit patients were ready to accept a certain level of risk. And surprisingly, we found that this is a survey that for a very tiny blood pressure reduction of, let's say 2.5 millimeters of mercury, the maximum acceptable risk for the patient was of 20%. So very high. So, and this is really something very interesting required to make a summary of our findings. So let's say that you could reach almost 76% of patient willing to go to consider an interventional approach if blood pressure was able to be reduced almost at the amount of what, what we are able to see in clinical trials, that patient were willing to tolerate risk if you are able to offer them a solution which was associated with a significant blood pressure reduction. And finally,

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uh, this goes in line what we, what we know about patient preferences, where when you offer the patient a choice, you have to explain him what to expect, and according to that it will make the best choice for him.

Dr. Hiremath: Fascinating. That's, that's really, and the discrete choice experiment is, you know, way better I agree than just doing a yes or no survey. But these are very interesting results Dr. Cohen, do these results, you know, do they go along with what your expectations are or do you find them somewhat surprising?

Dr. Cohen: I mean, based on conversations with patients in my clinic, this seems like so much higher of a proportion of patients who would be willing to go for a renal denervation. But I think it all comes down to your framing and which patients you have in front of you, and asking the questions the right way. And so I think when it comes down to the fact that it's actually available in front of them, we may see something very similar to what's described, because these were sort of created scenarios meant to simulate reality, whereas when I'm talking more hypothetically with a patient, it's much more vague. So I'm very curious to see what ends up happening. My experience has been much more skepticism, but I think a lot of that's also driven by the provider skepticism that's much higher in the US than it is in Europe.

Dr. Pathak: That's a good point, Jordy, because we always talk about patient preferences, but we don't talk about physician preferences. And I think that you're absolutely right. You need to match these two things. And I would say if we look at the same patient through the eye of Jordy or through my eye, and the way you will talk and present or interact about devices or drugs will definitely be different, because I've been in the field for years. So I think the way I would present, I would be able to present these data regarding devices are totally different for somebody who I never experienced the procedural approach. And it's funny because even in my department, when I listen to fellows or when I look at what my colleagues are doing, I think that those who are not used to the procedure tend not to talk about it. You know, this is really very interesting. We never do this with drugs, you know? So when you, when you start prescribing a drug, you rarely ask a patient, would you rather go, for example, an ACE inhibitors or the ARB, you decide for the patient, okay? You never ask him, uh, when you, when you start him on a diuretic, you don't ask him, would you like to go for a thiazide or a thiazide-like diuretic? You just prescribe it. But when you're talking about procedure, then you start thinking, okay, uh, and this is where you see the difference, uh, between what you do. For example, in the management of coronary stenosis, you see a patient who's having ischemia, you need to offer him angioplasty or a stent, you never ask him, you want to be treated with drugs, or you want to go for a procedure. You say, okay, you're going to be admitted. I'll do a I'll do a procedure on you. So I think this is something new we are facing in the field of hypertension also, because those who are taking care of these patients are totally different. You're talking about a cardiologist, a nephrologist, an endocrinologist, an internal medicine guy, GP, and sometimes even a neurologist. And the way they see the management of blood pressure is totally different.

Dr. Hiremath: These are really good points, you know, and it brings back the whole drugs or devices title of this podcast episode. Um, when, when renal denervation does become available

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(in the US) this is a hypothetical question, Dr. Cohen, but when it does become available, what kind of patients are you really excited to offer this to? We have, here two extremes, right? There are patients who have truly uncontrolled hypertension, the kind of patients in whom you are, you know, perhaps reaching for those drugs that you mentioned have side effects, or and patients who are adherent, of course at the same time, there may be some patients who are on one or two drugs, and if you do denervation, they might completely come off those medications completely, you know, so as was seen in the SPYRAL hypertension OFF MED trial or in RADIANCE SOLO trial what about patients who are non-adherent and, and you know, they're non-adherent because they're not taking pills, but maybe renal denervation will bring their blood pressure down a little bit. Again, I have absolutely no idea what indication it'll be approved for and what the access will be for us in North America. But, you know, what kind of patients are you excited about where you may think this will be a good option?

Dr. Cohen: Yeah, I mean, assuming it's available to everybody, not knowing what the outcome will be, I, I think there are a few situations where I see it as a good option and a few where I'm a little concerned. The ones where I think it will be a great option, I have people referred to me, for instance, who have anaphylaxis to several anti-hypertensive therapies who have almost no options. Oh gosh, this is going to be a lifesaver. We've been trying to get it approved for experimental use in people in those situations and haven't had success. So I think that, that, that is a no-brainer. And then there's the patient where it's not necessarily true, like anaphylactic type allergy, but drug intolerances, people who have multiple drug intolerances who come to my clinic saying, Dr. Cohen, I will do anything to not add another drug because I don't want, I, I think that they're dealing with a lot of anxieties of just anticipating adverse effects for medications, whether or not some of those adverse effects are quite as severe from our perspective, it's from this person's perspective, they are not survivable, not livable, they don't want another day with dealing with those effects. And I think that those are the appropriate patients to be offering something like this. Um, I also, with ad non-adherent patients, it's plus or minus. I think all of it comes down to setting expectations appropriately. If I'm offering this to non-adherent patient, I worry about the fact that this may to them give them an opportunity to be allowed to stop their medications. And I just want to make sure that they have truly a realistic understanding of how much blood pressure lowering they can expect from this, and how much blood pressure lowering they need to actually achieve like actual cardiovascular benefit. So I often see patients with blood pressures when they come into the clinic and the 180 s over 100 s and I just want those patients to really understand that adding renal denervation needs to be an adjunctive to many other therapies, and that that renal denervation alone isn't going to reduce their risk sufficiently. But that, of course, we can offer it to help reduce their medication load. Um, so those are the people in my mind who I think will benefit most. I am sure that there are folks who are not on anti-hypertensive therapies yet who will come to us looking for this. Will I be reticent to offer it potentially? But will I offer it if it's the right fit for them? Sure. I think it really requires a patient by patient discussion of like, what really is most important to you not being on any medications for some young folks who really take it as a hit to their, like, mortality assessment and like their ability to continue living their lives. I do have patients like that who come to me, Dr. Cohen I will do anything to not have to start medication. It makes me feel like I'm old.

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Yeah. I could see those folks wanting to do it. It reminds me almost of folks who go for LASIK under at a young age understanding that they're probably gonna end up need glasses later. And I, I think it's a really similar correlation that those are folks that of course we can benefit them because it will reduce their long-term cardiovascular risk to get them started. I worry about them getting lost in the system, especially in the US the way that our healthcare system works, that many of those folks will go for renal denervation, have benefit initially, but then get lost to follow up, not be monitoring their blood pressure regularly and suddenly be surprised that they've now developed worse hypertension a few years later. Not that the, that the renal denervation didn't do its job more just that they already had hypertension and it's going to progress with time as, as it's likely to. So that's really, I, I think there will be lots of folks who are looking for it more so that American providers are willing to admit. But all of us who don't have experience with it will continue to be reticent about it until we see more.

Dr. Hiremath: Yeah, yeah, exactly. So some of those indications are pretty clear, like you said, they're no-brainers, right. But, but I'm more curious about the people with milder hypertension. So if I can be a little bit provocative, I know Dr. Pathak, you mentioned that it's been approved in France for the, you know, the people who are on four drugs or who are uncontrolled hypertension, where the indications are clearer. But what if this in this area where it's some milder hypertension where you, you've got a potential for a, you know, "a cure". What are your thoughts about using renal denervation in that area?

Dr. Pathak: Well, I think, you know, in the frame of clinical trials, there is a huge range of patients, so when you focus on this trial, we call SPYRAL OFF MED, where mild to moderate hypertensive patient we weaned off the drugs or, or RADIANCE SOLO or RADIANCE 2 similar patient, mild to moderate hypertensive patient without any drugs. Again, the therapy is able to reduce blood pressure by, let's say 8-10 millimeters of mercury, so it's basically what a single drug is able to do. We're not talking about something which is reducing blood pressure by 40 millimeters of mercury, though there is a huge variability. You have these super responders who have a significant drop. But I think, you know, maybe I will help you to see the future in a different way. Uh, there is again, an opportunity for us who are taking care of these hypertensive patients to define who is the correct or who is the right candidate, because the risk is if you put this therapy in the hands of interventional cardiologists who get, who see tons of hypertensive patients or who get referral, you know, so you will have a GP will call and say my patients on controlled, can you do renal denervation? If we are not offering the right way to select the patient, the technique is out there, and then it will be very difficult to control who is going to be treated or not with the therapy. So I think we need to do the way we do up to now with drugs to define selection criteria, do the assessment, take care of the patient, but you have to imagine that for the first time, we're not talking about, uh, mineralocorticoid receptor antagonists where everybody fears prescribed with them. We are talking about something which is easy. I mean, in, in half an hour, 40 minutes, your patient has been treated and it, it can be done ambulatory, and tomorrow you will have radial catheter so people will enter in hypertension clinic in the morning and get out in the afternoon having, having. So I think that it's our job to be there to say, what is the level of evidence? What is the appropriate candidate? And I think that really what matters also is to sit down with the patient and share with him your thoughts and try to

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understand what his expectations are. I agree, you cannot treat a patient and then think that your job is done because you're talking about, for example, management of cardiovascular risk. So if your patient is not willing to take an antihypertensive drugs, he might not also be willing to take a statin. So what are you going to offer him now? Well, you can offer him PCSK-9 injection. So the, the management of cardiovascular risk in the, in the future could be renal denervation on one side, PCSK-9 on the other side, and the job is done.

Dr. Pathak: But that's not the way you want to manage cardiovascular risk. So we need to be very cautious. You, we shouldn't stop the therapy. We shouldn't be too selective, but we should also be there to try to offer the best medical practice according to evidence, you will never have a morbidity mortality trial with renal denervation. And this is something I understand Jordy was saying. I mean, the level of evidence is very high regarding the quality of the data and the blood pressure reduction, but there are things which are missing and you, there are things you have with drugs and you don't have with the device. So it's up to us to find the right way.

Dr. Hiremath: Exactly right. So, you know, we have to walk the right balance. And you're right that it is, once it's approved, you know, it's out there and, and there's nothing to stop people from doing this procedure in the inappropriate way. So it's up to us to kind of, you know, make sure we, we at least we, uh, set useful guidelines to use that responsibly.

Dr. Pathak: If I may just add something, sorry about patient selection because, uh, up to now we don't have a single predictor of response. Okay? Yeah. You cannot, you cannot predict who is going to be a good responder or bad responders. We have some slight information. For example, a hypertensive patient with elevated heart rate above 73 beats per minute could be a good candidate. At least his, his rate of response will be higher. The, the sympathetic profile could be the right candidate but whenever you measure sympathetic activity with very fancy techniques like microneurography or, or catecholamine spillover, unable to predict the response. So this is also the tricky part. You need to finally to define a patient population, which is not based on physiology, which is not based on outcome trial, but which is based on these evidence, which are, it's reducing the pressure in, in trials which have been correctly done.

Dr. Hiremath: Exactly right. So, you know, these techniques are, are research techniques, and they still haven't been, you know, useful for us to predict. But, you know, we have talked about it from the provider aspect, and both of you did sort of mention this before, but I wanted to explore this a little bit more explicitly to talk about it from the patient perspective. You know, how much should we factor in patient choice? And we talk about shared decision making, but what would it mean in this context. Now ignoring cost and access issues and coverage, if renal denervation was widely available, it was easily accessible, should we be gatekeepers? You know, or not? So it's not an easy question. So I'll let each of you describe it, but maybe I'll let Dr. Pathak go first about how he would approach this kind of a question. If you have a patient that you are not really sure, but they come in demanding, you know, I want to have a renal denervation, how would you approach that issue?

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Dr. Pathak: Yeah, I think it's, it's a very important question. My understanding would be to look first at what is defining the patient's preference? And finally, what is triggering his situation and what is part of his personal history? Has he experienced, for example, side effect with blood pressure medication which have negatively impacted his life? What is his perception of high blood pressure? Does he understand the concept of elevated risk? And is he ready to go for any type of intervention? But also, what is his personal experience, including comorbidities, that have made, I would say high blood pressure consequences. Real, I mean, a patient who suffered from stroke has a different perception of the risk of blood pressure, elevated blood pressure, in comparison with a patient with a silent chronic disease who is not complaining of anything. So this is one part I want to understand what is driving my patient choice? What is his understanding of the disease? What is his personal history?

On the other side, you have the physician choice. And what we have learned also from our studies is that those patients with elevated blood pressure, those patient with a higher number of blood pressure medication, are those where the physician tends to drive the patient for renal denervation instead of, instead of drugs. We know that. And if, especially if the doctor was an interventional cardiologist, when an interventional cardiologist see a patient with elevated blood pressure and high number of drugs, I have the solution for you, you'll go for renal denervation, and you have to put these two, I would say, assessment together in front of the patient and then discuss with him, you know, and somehow in the way we did in our DCE (Discrete Choice Experiment) approach, you know, so what is really affecting his choice? We know that if you say, okay, this therapy is able to reduce blood pressure by seven millimeters of mercury, but let's be honest, adding a drug would do exactly the same thing. You know, that blood pressure reduction is driving his choice, but you have to offer him the right balance, you know, between the therapy and the drug. But on the other side, you need to take a drug every day. The therapy, the intervention is once, okay, you know, that the drug is reducing morbidity and mortality. There are some question marks about renal derivation, but renal denervation is reducing blood pressure, and we know that the strongest driver for reducing morbidity and mortality is blood pressure reduction. So I think really, but this needs a lot of time. I'm not sure this is something you could do in a regular clinic. You need to have documents, you need to have time.

Dr. Pathak: I have a double screen, a screen for my patient, screen for me. We go to the data. I have small cartoons, I write down things, I draw things, and it takes at least an hour just to go to all the options available. So this is, I think, another part of our job, which is new, taking the time. So we started doing this, for example, for oral anticoagulant, when the, the, the direct oral anticoagulant appeared on the market and you had the choice between VKA (vitamin K antagonist) any type of newer oral anticoagulant, we started doing this. Okay, you have the antidote. You don't have the antidote, you have the trials, but they are non-inferior trials. You have here, if you have a valve, you can do this. You know. So we started doing this, and I think it will be more and more common, but it's almost a situation where you need time and maybe also new type of jobs. You need to maybe involve behavioralist, maybe you need to involve psychologists. You need to involve specialists who are used to deal with, with, with patient preferences and shared

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medical decision process. So the two balance are easy, the patient, the physician, but at the end, I think it's more complex.

Dr. Hiremath: It, it is indeed more complex. I love your description of, you know, the cartoons and two screens. I'll have to see how we can incorporate that. So to you, Jordy, uh, Dr. Cohen, what do you think about, you know, uh, patient preferences and how would you incorporate that, especially if someone comes in asking for this procedure?

Dr. Cohen: Well, I love Dr. Pathak's image that he describes in general of this multidisciplinary approach, because that's just like this idyllic world. It reminds me of what was meant to happen with bariatric surgeries, but often doesn't in terms of this appropriate screening of the right patient to ensure optimal outcomes. Yes, in a perfect world, I'd love to see that happen. I think that that would be the best way for the direction of things to go in. I think right now there are probably many physicians listening who think to themselves, oh my gosh, you spend over an hour talking to a patient about this. I get 20 minutes for a new patient visit, 10 minutes for a follow up. When does this happen? And in the reality where we might not be able to change that, especially not in the short term, my thinking is that sort of more pragmatically as a provider, seeing these patients in front of me that I should not be, frankly, a gatekeeper. I agree with shared decision making, but perhaps my role can be to be a harbinger of expectations, balancing expectations versus reality. Making it crystal clear to patients that this is not going to fix everything, that it is a procedure that has risks, but that it can benefit them in a similar way to a single anti-hypertensive drug, would be able to (maybe two depending on the patient). And to think about it that way, and to help them balance the pros and cons, understanding some very simple information, just from what time I have to be able to talk to my patient, to go through that with them. In a perfect world, they deserve, and I think we should be able to eventually provide more information that Dr. Pathak's describing to really help people make a more complicated decision that this deserves. I don't think we're going to be there by the time this ends up getting approved.

Dr. Hiremath: Fantastic. I like it. The harbinger of expectations. Uh, that's the physician. So the provider's role. Uh, so to wrap up, you know this has been a fantastic discussion. We may be going over time, but this is really, really, fascinating conversation we have had. Are there any take home messages after this conversation, Dr. Pathak first...

Dr. Pathak: I see your nice picture behind you of Star Wars, and so my take home message will be, may the force be with you. May the force be with you because we are living in a wonderful time with new drugs coming up in the field of hypertension, endothelin antagonist, aldosterone synthase inhibitors, new devices. So I think this is, I think, a fantastic time for us managing these hypertensive patients. We are having new options. So may the force be with us to cope with new options. May the force be with us to select the right patient, and may the force be with us to start shifting the way we practice medicine, try to find time or new strategies to take into account patient preferences and try to set up the whole concept of shared medical decision.

Dr. Hiremath: Fabulous. <laugh> Dr. Cohen?

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Dr. Cohen: I don't have much else to add. I agree. I think this has been a fascinating learning experience for me. And I think my balance to that is, I have a LEGO globe behind me, <laugh>, and thinking more globally. I think as Americans, we have a very different view of, and it just North Americans have a very different view of renal denervation than Europeans do, that in general, most folks are more skeptical and concerned of really, we're just looking at these often single digit blood pressure benefits from a whole procedure. Whereas in Europe, people are thinking, oh my gosh, I can get benefit from a procedure and take one less medication. This is incredible. And so I think it's going to be ongoing conversations to that flavor of really balancing these different worldviews and really thinking about the patient and getting the perspectives of the patients here to really make sure that we're doing best for, for them either way, whichever direction it goes in. And that we're not just making these paternalistic decisions as physicians opposed to something that we, that we really question the reality of. But that we also continue to use a little bit of our healthy cynicism too.

Dr. Hiremath: Exactly. So helping patients, you know, do what's best for them. Exactly. I love that. So, uh, you know, thank you again, uh, Dr. Pathak and Dr. Cohen for spending the hour with us on this, on this fabulous discussion. I had a lot of fun and I think I learned a lot.

For listeners, this concludes the six series podcast series on the unmet needs in hypertension from the American Heart Association. You can find all six podcasts on learn.heart.org, as well as on most podcast networks if you search for the American Heart Association. Just a reminder again that the views and opinions in this podcast are, those of the speakers and reflect the synthesis of science and expertise, and the content should not be considered as official policy of the American Heart Association.

So on behalf of the American Heart Association, thank you and I hope you had a good listen today and have a good evening.

Thank you.