Resistant Hypertension

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Resistant HTN Section

DR. BAKRIS: Hello, I'm George Bakris, Professor of Medicine and Director of the American Heart Association, Comprehensive Hypertension Center at the University of Chicago Medicine. I'm here today to talk to you about approaches to true resistant hypertension and you'll see why I call it true resistant hypertension in a second. These are my dualities of interest.

Let's talk about definitions. Apparent resistant hypertension is a blood pressure of less than 130 despite adhering the full doses of appropriate three drug anti-hypertensive combinations including an appropriate diuretic for kidney function, a CCB and a RAS blocker maximally dosed. True resistant hypertension is the same definition except now you actually know that the patient is taking the medication. That's the difference. The major difference is exactly what I'm telling you right here. Instead of trusting the patient, you actually document if that the patient is taking the drug.

Now two most common non-disease causes of apparent resistant hypertension, white coat or anxiety and poor medication adherence. Now by the way before I go on, we're talking about true resistant hypertension. The way you do this is the way they did it in the SPRINT trial. You do what's called a DOT ABPM or DOT BP measurement. DOT stands for direct observed treatment. You tell the patient to bring their medicines in the morning. You watch them take it. And then you can either hook them up if you have the ability to an ambulatory blood pressure monitor or you can give them instructions for home blood pressures over that day to take pressures over three or four times a day, write them down and send them to you and then see what those numbers are compared to the other numbers. I think that's an appropriate distinction.

One of the following needs to be present before diagnosing with true resistant hypertension. Number one, they're truly adherent on a low sodium diet. And you can do this. Most patients can easily do this for a week. Number two, their sleep quality is good. Six to seven hours non-interrupted sleep at night. No question, that's good enough. Substitution of drugs in the same class, for example, I'm going to show you this in a minute, you have a patient that's on hydrochlorothiazide and they're on good doses of a CCB and they're on good doses of an ARB and their pressure is 148 but you want to get it better. You can substitute chlortalidone and you get a much better blood pressure control. You can substitute some ARBs and we talked about that. You got to rule out secondary causes especially primary hyperaldosteronism. And that's what you've got to do. I just want to remind you about primary hyperaldosteronism, you've got to rule that out before you accuse somebody of any true resistant hypertension, so very important point.

You're going to see this multiple times in these presentations. This is another thing of the non-pharmacologic approach to blood pressure. Sodium here is critically important and the others are equally important but sodium is going to screw you up more than anything else. This is something that you really want to make sure that you deal with and you can

mix and match. The kidney function is good. DASH diet, etc. Very, very important observations and people discount them but they're very important and can reduce blood pressure meds by at least one if not two if patients actually follow this.

I just want to show you again the importance of sleep. It's very important. We're not talking about sleep apnea now. We're talking about insomnia. And five hours of sleep, if you're not getting minimum of six to seven, but five hours of sleep or less is going to increase your cardiovascular risk dramatically. And this is data from The Nurses Health Study that show this very clearly. Take a look at 6 hours of sleep, 30% increased risk over 10 years for coronary heart disease. This is 71,000 women that are nurses. Five hours of sleep, you're almost doubling the risk. This is critically important.

I just want to show you a pilot study of data that we did looking at people with kidney disease, stage IIIB and IV kidney disease that had hypertension that also had sleeping difficulties. These people did not have, some of them, 50% has sleep apnea but they are being treated. The rest just couldn't sleep or couldn't stay asleep. What we did is put them on different medications, gave them various techniques, work with their sleep people and basically got their blood pressures controlled over the next couple of months. And we actually reduced the medications in many of them so that we can keep their blood pressures at reasonable level. And you can see it maintained itself at going out over six months.

The combos you need to use, I've already told you this. And the adherence is very important. These are two studies where they actually measured metabolites. One didn't tell the patient, the other one did tell the patient. At the end of the day, the amount of adherence was similar, 45%. It doesn't matter what you're doing. Patient adherence is critical and they're only going to do it if they see it's important. And that really requires a discussion.

This is data from all the different clinical trials in hypertension, diabetes, kidney disease. The bottom line is look at the blood pressures that they've achieved and look at the number of medications needed. They need at least two, in fact they need an average of 2.6 medications to get the blood pressure to the goals in those studies. Start with one drug, maximize the dose. That was stuff that I learned in medical school in the 70s. We need to start with initial combination therapy as recommended in the guidelines for these types of people. And again more evidence to support this. Bottom line, if you start with monotherapy and double the dose, you're going to be less likely to get the goal blood pressure than starting with one drug and adding a second drug at a medium dose. And that's what this shows you here, different classes of drugs were started. In the blue, they doubled the dose. The pink, they added a second drug and you can see who got the blood pressure goal with fewer side effects.

Again, the recommendation for first-line therapy right here from the guidelines, the ACC/AHA. Very important to keep in mind that this is not just something I'm telling you. But it's something that the guidelines are telling. In fact, this has been in the guidelines since the JNC-6, but really magnified the JNC-7. Europeans are ahead of us. They're saying, forget it, start with single pill combination because bottom line, adherence is going to be an issue. You're not going to fix it. This is the best way to deal with it.

They'll be on two meds. They're likely to get there. They'll have fewer side effects, so very important point.

Let's talk a little bit about different classes of agents. Not all thiazides are the same. And not all ARBs are the same. Let's just take a look at this in terms of treatment. This is a study that looked at all these BP. They also looked at the 24-hour ABPM. This looks at hydrochlorothiazide 25 versus chlorthalidone 25. And you can see here, a very nice additional blood pressure reduction with chlorthalidone that persists. This is a study that we did in our office. These are all referral patients. They're coming on triple therapy. Hydrochlorothiazide, ACE-R arm, CCB and their blood pressure to start were 152. All we did is switch the chlorthalidone at the same dose, if they were in 12 ½, they got 12 ½ of chlorthalidone. That's all we did. Then you can see the difference in the blood pressure. You don't necessarily need to add drugs. You need to understand the drugs within the class that you're looking at.

Now, there's a very famous trial that just got published in The New England Journal, the CLICK trial from our friends at Indiana University with Rajiv Agarwal. And this is important because this looks at people with advance stage kidney disease. These are people with stage IV CKD, GFR less than 30. We all think loop diuretics in these people, thiazides don't work. Not true. This study looked specifically at people with GFRs in the low 20s, that's the mean, and with profound albuminuria. Guess what? Chlorthalidone worked beautifully here. Obviously there weren't other agents. But when you add a chlorthalidone versus placebo, they get very nice blood pressure reduction here. And even after discontinuation, it persists. Remember, chlorthalidone has not had chlorothiazide. It has a very different chemistry, a very different pharmacology. And so, keep in mind, in advanced disease, don't be switching to loop diuretics because those only last for about six hours or less. These agents give you more sustained effect than it does work.

Now what about ARBs, are they all created equal? Well, no, they're not. They have different indications. It depends on the company, what studies they did, etc. But let's take a look at a comparison between valsartan and azilsartan. Azilsartan is the most recent ARB. It's still under patent. And you can see here these are ABPMs, 984 ABPMs, these are means. And basically what you have here is starting at 146/86, clear difference in maximal dose valsartan and maximal dose azilsartan in red, much, much better blood pressure reduction.

Now what against Ramipril. Well, azilsartan against Ramipril, you can see here very clearly at the bottom, you're getting an additional almost 10 mm reduction or 8 mm reduction in blood pressure when you use azilsartan over Ramipril, again substitution not having to do more than that.

This is a pooled analysis looking at azilsartan at the top against olmesartan and azilsartan against valsartan. Now at the top, you can see there's normal glycemic prediabetes, type 2 diabetes. There's not a big difference between azilsartan and olmesartan. There's about a 2-3 mm difference. And in many cases, olmesartan works quite well. But I just wanted to show you, but against valsartan, again you can see especially in the normal glycemic and pre-diabetic patient significant differences.

Now why is this the case? Is there something special here? Well, yeah, it has to do with half-life from binding. Just so you know, the binding of losartan is about 55% of the AP1 receptors. The binding of azilsartan is about 85%. And here you can see in black is when they're taking the drug. You've got in addition across the board. But here is when they stop the drug. And you can see very quickly here that valsartan and telmisartan are fading quickly and even olmesartan. Well, it's not fading as fast as its fading. Azilsartan persists. And that's one of the major reasons why the affinity for the receptors would distinguish this.

Now what about CCBs? Did you know that you can combine dihydropyridine and non-dihydropyridine CCBs. This is a very nice study published again back in 1996 but it shows low dose nifedipine in 30 mg with low dose diltiazem 240 mg versus 240 mg of rampiril gives you additive blood pressure reductions. And with diltiazem it persists for long period of time. Someone as many patients where you can't use beta blockers, this is a nice way to move forward.

Now for resistant hypertension in normal kidney function patients, no question about spironolactone is the way to go. This is a PATHWAY 2 trial. And you can see here compared to alpha blockers or beta blockers, spironolactone worked as the drug to get blood pressure control. I think that's really important information. And I want to thank you for that. And I want to move ahead to future drug development in resistant hypertension because this is not relatively hot area and it's moving quickly with new agents that are going to be looked at.

One of the classes that's on the forefront are the nonsteroidal mineral corticoid receptor antagonist as you can here on the bottom. We know about fineronone. But the one to watch for is the KBP-5074. Of the class, this is the one that seems to have so far the greatest blood pressure lowering ability where in one study that was published last year by us, 11 mm placebo subtracted drop in blood pressure at the highest dose. And this isn't people with stage IV CKD. It's very important to keep in mind that there are other things coming down the pipe.

This is a preclinical data looking a eplerenone here in red. And this is the KBP compound down here, very important, blood pressure reduction information here. The BLOCK-CKD study which is the one we published, you can see here the group that was studied in terms of kidney disease, it was a simple blood pressure study, so we had 162 patients and there was placebo, low dose and high dose. And they were followed up, that was 12 weeks and then there was a 4-week follow up. You can see the blood pressures here very clearly. And you can see that 89-90% of the patients were taking three or more drugs. This was the fourth drug. Instead of spironolactone, this was added. And you can see here basically on the right placebo subtracted, a significant reduction in blood pressure at both doses, but the 0.5 mg dose really gave you the most.

What about AEs? What about hyperkalemia? Well, you can see here, there's not a lot of AEs. There was hyperkalemia. But I want you to know if there was hyperkalemia in the placebo group as well. And it didn't require premature discontinuation.

Another class of drugs that's being developed are combined endothelin A and endothelin

B receptor antagonist. This is data looking at endothelin A receptor antagonist and there's no question, there is a clear benefit with blood pressure reduction. The problem with these agents is 24-hour ABPM data. The problem with these agents is edema, more edema than what you're going to get with amlodipine at high dose. And so now we have a combination of ETA and ETB receptors. And you have the balance of, here you don't get the edema that you do with blocking on endothelin A and you get profound vasodilation.

This is a list of endothelin receptor antagonist. The one that's really being studied for resistant hypertension is here. This is coming. These studies are on their way. They're in phase II. They're not ready yet for prime time. But the PRECISION trial is the trial that's being looked at and the primary outcome is basically sitting blood pressure at four weeks. It's a double-blind study. And we'll see what the results are.

Again, going to management of resistant hypertension, we've got a fairly good arm of material but we need to know how to use it. I showed you some tricks on how to use it. If you're going for minoxidil, that's kind of last resort. That renal denervation and barrier receptor activation, these are not quite ready for prime time. Renal denervation is approved in Europe. If you're dying, then have a patient do a renal denervation. You could send them to Germany. No problem. It's about $12,000. But you can do it. And then barrier receptor activation is approved for heart failure. They started looking at hypertension here and we were one of the centers, very effective. Unfortunately, it's a surgical procedure that's required to implant the receptor on the carotid and they perfected the procedure now and now they're going to come back and look at blood pressure. That's not ready either.

But I just want to show you, this is data on the renal renovation. It works. There's no question that it works. I don't want people thinking it doesn't work. In fact, you get every bit of 7-8 mm reductions in blood pressure, placebo subtracted. It works, however again not approved, so it's limited.

Let me summarize by saying that the updated guidelines continue to emphasize combo therapy and adherence with drugs and lifestyle. Those are really the key. You need to think of spiro for now as a fourth drug after appropriate diuretics. CCBs and RAS blockers, for people that have GFR with above 45 because the risk for hyperkalemia is going to be low and that's really where the data is coming from for resistant hypertension. Remember, there's a range of efficacy for certain drugs. And that doesn't mean that in that class, there may not be another drug. They may not be beneficial. I'm going to finish with that. Thank you for your time and hope you got something out of this.

HTN Patient Case

DR. BAKRIS: Hello again, this is George Bakris and we're going to present a challenging case now and we'll see how you do. This is a 63-year-old black man that comes in with a blood pressure of 168/88 and a heart rate of 84. And he's got new onset dyspnea on exertion. He also says that he's gained 15 pounds in the last few months. His past medical history is positive for hypertension for 15 years. He does have type 2 diabetes for 10 years. And

he's got hyperlipidemia for 10 years. He's got a positive family history for MI, coronary artery disease, hypertension and diabetes. And his father was on dialysis, so clearly CKD.

Social history: he denies smoking, has occasional alcohol or alcoholic drink. And he's a manager at a local store. His physical exam shows that he's got a positive S4. He's obese. He's got 1+ pedal edema. His labs are normal except his Ks 4.9. He's got a GFR of 48. Hemoglobin A1c is 7.2. He's got a fasting sugar of 155. And his LDLs are 109. HE does have 624 mg/g albuminuria. And an echo two years ago and that showed EF of 50%. He had a negative stress test three years earlier. He's on 100 of losartan. He's on 25 of hydrochlorothiazide. He's on amlodipine 10 mg. He's on atorvastatin 80 mg. He's on a gram of bid metformin. He's on a 100 daily of sitagliptin. And he's on 10 mg of - -.

They get a repeat echo, showed that his EF is now 40. He's got evidence of half REF. He's getting educated enough, 1500 mg sodium diet and they made some changes. His losartan went to candesartan 32 mg daily. Hydrochlorothiazide was changed to chlorthalidone 12 ½ daily. And they continued the amlodipine and he was getting spironolactone added at 25 mg daily.

The patient returned in one month and stated that his dyspnea on exertion was gone and he felt better. His BP now is 132/78, markedly improved from the 160/80. His potassium was 4.8. His GFR was 40. His albuminuria dropped substantially down to 125 from 629. And his hemoglobin A1c was essentially unchanged 7.2, 7.4.

Given these findings, what would be the next steps in managing the patient's risk factors? Would you stop the ARB and spironolactone and start hydralazine and nitrates? Would you stop spiro and give a loop diuretic and educate the patient about low K diet? Would you continue treatment but chance chlorthalidone to torsemide and educate the patient about the low K diet? Continue treatment and add a potassium binding agent and educate the patient about low K diet or add finerenone to reduce cardio-renal risk further? You can answer that.

Well, I'm not sure what you answered, but we added finerenone 10 mg daily and we repeated the labs in one month. The K was 4.9. The blood pressure was 130/76. Finerenone was increased to 20 mg per day and the patient was followed up in one month. Coming back in a month, his dyspnea on exertion was better. But his labs now, his blood pressure was 142/82. His K is 5.2. His GFR is still 48. His UACR is still 125. And his hemoglobin A1c is now 8.2. Given these findings, what would be the next steps in managing the patient's risk? Stop the ARB and spiro and start hydralazine and nitrate. Stop spiro and give a loop diuretic and educate the patient about low K diet. Continue treatment but change chlorthalidone to torsemide and educate the patient about low K diet and then add potassium binding agent. Add semaglutide, reduce the dose of spironolactone to 12 ½ and add carvedilol 12.5 mg bid. Add finerenone to reduce cardiovascular risk for.

Well, you want to add semaglutide and reduce the dose to spiro to 12 ½ and carvedilol 12.5 mg bid. Semaglutide is being given to reduce weight. It's a weight loss drug. It improves diabetes control but it also improves cardiovascular risk. Carvedilol is added because he has had REF and a high BP. And we're reducing spironolactone because the K

increased.