GEORGE BAKRIS: Hello. I'm Dr. George Bakris, professor of medicine and director of the ASH Comprehensive Hypertension Center at the University of Chicago Medicine. Today, I'm going to give you a brief overview of resistant hypertension. What is it? What do we do about it? And what do certified hypertension experts think is the best way to approach it?

So I'd like to start off by really giving you a definition. And while this is a busy slide, I would invite you to go to the far right, because that is the true definition of resistant hypertension. And you can see there that it's basically someone who has a blood pressure above 140 over 90 who is already on three adequately dosed complimentary mechanistic drugs, meaning simply a diuretic, a calcium antagonist, and a blocker of the Renin angiotensin system. If they are on those three drugs and their blood pressure's still above 140 over 90 and they're on a low sodium diet and they're following everything that they're supposed to be following in terms of lifestyle, that is defined as resistant hypertension. So we have a perspective.

There are other forms of hypertension, however. And you can see those other forms there. And they can be confused with resistant hypertension, especially white coat hypertension, which is a marked elevated blood pressure in the office with a normal blood pressure outside of the office. So again, very important, and these are the types of blood pressure that you want to screen out before you make a diagnosis of resistant hypertension. It is a diagnosis of exclusion.

Now, if we look at global estimates, it depends where you go well. It depends how it was done. It's very diverse. Here's some data from Spain, looking at ambulatory blood pressure monitoring data, very good data. It talks about 7.6% of patients with hypertension being resistant.

Then we have a study coming from Italy. Here they're talking about 18% of people with resistant hypertension, same definition. And then we have US data, which is a little humbling, from the Kaiser Permanente out in California. And this gives us very low numbers-- 1.9% of the patients with resistant hypertension. So it depends on, not the definition, but it depends on adherence to low sodium diets. It depends on the type of medications being used and the dosage of the medication being used and the adherence of the medication by the patient.

And, in fact, when you look at patient characteristics of people that have resistant hypertension, what you find are two key things. One, many of them do not follow a low sodium diet. That is 2,400 milligrams a day or less, one level teaspoon.

Or they're simply not taking their drugs. They're taking some of them. They may not be taking any of them. And then that's a problem. So these are things you have to think about, and these are other predictors as well that relate to this.

The salt is a big deal, because there's a big controversy now and people say, ah, you don't have to restrict salt. Well, here's the reality. The reality is that if you don't have hypertension, if you don't have a family history of hypertension, then it's fine. You don't need to restrict salt that much. On the other hand, if you have hypertension and especially if you have kidney disease as in the study that I'm showing you here, you absolutely have to restrict salt, because if you don't, you will pay for it.

Many people want to not take drugs. So here you go. Here's a study that was done in the UK. These are people that have low kidney function. They've lost 70% of their kidney function. They've put everybody on a 3,000 milligram or 3 gram sodium diet. That's a little bit above the normal, the recommendation. And then they measure 24-hour urinary sodium and how many drugs it took to keep their blood pressure below 140.

So you can see at 3,000 milligrams, either there were drugs are no drugs. They just increased it by 300 to 500 milligrams. That's not very much. That's about a quarter of a teaspoon of salt. And now they need an additional drug.

They increased it again, now by half a teaspoon. Now they need a third drug. And then they increased it again to what most Americans are eating, about 4,000 milligrams a day. And now they're on four drugs or more.

So many patients don't understand, you want to stop your drugs, stop the salt. And I've had many cases like this of people referred to me for resistant hypertension, because we are the center that deals with this, both from a research and a clinical perspective. And I can tell you two cases where I was able to stop all the drugs by the patient really being adherent with lifestyle. They had normal kidney function. They were very compliant. And so things can happen in a positive way, but it's up to the patient.

This is not the physician's problem. This is the patient's problem. And the patient has to take ownership of this, and you'll get good results.

Here's an example of people not taking meds. This is a study done in Germany, and it was a study where patients were given a questionnaire to answer-- if they're taking drugs, what drugs they're taking-- and see if they're knowledgeable. And then urine was collected to actually measure the metabolites of the drugs they were taking, and the patients knew this. There wasn't a big surprise.

When they did that, it turns out that angiotensin receptor blockers-- the sartans, the losartans and those drugs-- were the ones that were taken the most. And that's been shown in every study, because they have a very low side effect profile. And then in Germany, they really love beta blockers, not in the US but in Germany. And so there, they actually did pretty well there.

Other drugs faded away. And so it's very important. There's another study like this that was published from the UK, and the patients were not told that their urine was going to be measured for this. And they got similar results.

45%, only 45%, of the people that were actually taking drugs were taking the drugs the way they were supposed to. That means the majority were either taking some of drugs or none of the drugs. And this was true in the UK, as well. So I think one has to be very cautious about making a diagnosis of resistant hypertension unless they really know the patient's taking the drugs.

And this is what I was referring to earlier, the Holy Trinity here of therapies of agents and at maximal tolerated doses. Now, there is fixed dose combination therapies that are available, and these are single pill doses of combinations. This is the guidelines from the American Society of Hypertension on how to use combinations. And what you see here are what most people already know. ACE inhibitors or angiotensin receptor blockers married to either diuretics or calcium antagonists are the best single-pill combination out there for blood pressure control.

There are other combinations that a lot of physicians use that really are much less effective. For example, if you go to the bottom of the slide, you can see that clonidine combined with a beta blocker is not very effective. In fact, it's a nice way to cause heart block.

Combinations of ACE inhibitors and ARBs-- not very effective and, in fact, in advance kidney disease are now contraindicated. And beta blockers with ACE inhibitors-- cardiologists love that combination. Very good for heart failure, very little help in blood pressure. So again, important to keep that in mind.

Within the class, there are differences in drugs. This is a study that was done comparing a very common angiotensin receptor blocker, valsartan, with a newer one called azilsartan. And you can see here dramatic, better blood pressure control on 24-hour ABPM within the same class at maximal doses. So just because you're within a class doesn't mean there are drugs in the class that aren't better. Very important.

What you marry them with is important. Now, this is a study that we published a couple years ago with azilsartan and two different diuretics-- hydrochlorothiazide and chlorthalidone, chlorthalidone being the recommended preferred, many physicians still using hydrochlorothiazide. And you can see an average of about five to six millimeters better blood pressure control. And if you look to the right, that's 24-hour blood pressure monitoring. And you can see very clearly there that there is an advantage to what is combined with the agent from a class, even within the class.

Now, let's say you did all this and you failed. Now you have two options. You have bare receptor activation therapy, and you have renal denervation. Both of these require some procedure. They're not drugs. This is if you've truly failed and truly have problems with resistant hypertension, and we are a center doing both these studies here. And, in fact, I'm the principal investigator on both these studies.

And so you can see here bare receptor activation requires a vascular surgeon to place a small electrode just on top of the carotid bifurcation. There's a wire that's floated through. A battery's implanted in the chest just like a pacemaker. And then there's a magnet, and turn on the battery, and you can actually see the response in terms of blood pressure. And you'll know immediately if it's going to work or not, because you're right there when you're seeing it.

Here are the results of a trial we published a few years ago in the journal American College of Cardiology, and you can see very nice blood pressure control going out over one year. We now have data going out five years, and it's sustained. And you can see a dramatic improvement in the people that were resistant in red to the people that are still resistant. So definitely something to look forward to.

The catheter denervation studies, the simplicity trials, the renal denervations studies, which are very prominent in the literature, have been out there-- clearly in the early data, and this is early data I'm showing you here, that does work too if it's done properly. And you can see here the hormonal changes in sympathetic tone that occurred over time. And basically, you can see that there is an effect without any question within one month.

And this is a different procedure, because this goes up, just like a cardiac cath, except it goes into the arteries of both kidneys and basically causes, using ultrasonic frequency, a burning of the lining of the renal artery, and that denervates the kidney. And the renal nerves clearly have a role in controlling blood pressure.

And so there were a number of studies done. The early studies were very promising. Unfortunately, the early studies didn't do a lot of what needed to be done. They were more pilot studies. And, in fact, you can see here data from the first study that goes out for three years, and you can see very nice blood pressure control.

However, there was no control group. They did not ensure that everybody was taking the maximal doses of meds. They did not do ambulatory blood pressure monitoring before and after. And there were a number of other problems with these studies. And so, as a result, it looked phenomenal.

But then, unfortunately, we were contracted out. I was asked to be a co-PI. And we designed the study to really be foolproof. If you could survive the study, you clearly had an effect. No question about it.

And so we did this trial. It was just published in the *New England Journal*. And we basically looked at people that had the same criteria as the previous studies, but it was multi-center. This time we had a lot more people, not 100 or 75, but 535 people. 88 centers around the country.

It was a single blind study, so the only person that knew the treatment was the cardiologist that did it. The investigator did not know, the nurse did not know, and the patient really didn't know. So nobody really knew who got what until the very end. It was a six-month. It was only focused on blood pressure.

And you can see that it was a randomization. More people got the procedure than didn't. If you've got randomized to sham for ethical reasons, at the end of six months, you were told you got sham. And if you wanted the procedure, you could get the procedure. So that was an option given to the patient.

We looked for a difference in blood pressure at six months between the groups. And we also looked at a change in ambulatory blood pressure between the groups. And it was a five-year follow up which we're still doing. This is the data from the study, and this is the baseline data.

So you can see that if you go down here, these are pretty fat people with BMIs in the mid 30s. These are a fairly well-represented African American group at about 26%, 27%. And you can see that they are pretty sick, because they've got a variety of diseases that you can see on the slide.

You can also see that when the study was done, it was a pretty safe study. There were no significant differences and major adverse events. And if you look at the primary endpoint, which is this is what the story was about, there really was no difference.

So when you compare sham to the regular control, we were looking for five millimeters. We got half that. So not good enough.

And then when you look at ambulatory blood pressure monitoring and look at the differences, there we really for two, didn't make it. Got 1.96 but a big variation. And so didn't quite make it.

So the question is, what happened? What went wrong? Well, it's unclear. Argument is, well, if you really take all your drugs, this doesn't offer that much. That's one option. The other option is that maybe the procedure, because of so many centers, was not done correctly and properly with careful technique at all centers. And that's a very viable answer as well.

So this is being looked at with a little more careful finesse. Maybe there were some subgroups that did better than others. Well, you can see here in the analysis of the main paper that actually that was not true. There was no group that clearly did better or clearly did worse. So not a good thing.

So what are the conclusions? The conclusions are that resistant hypertension is probably realistically about 5% to 6% of all hypertensive people. In the US, that's about 75 million people. So about 5% have this.

The good news is that there is hope and there are nonpharmacologic options, but they're not ready for prime time just yet. And my hope is that, in the next two to three years, there will definitely be something, because the bare receptor stimulation that I talked about is still being investigated. The renal denervation is not dead. They've gone back to the drawing board, and they're looking a little more carefully at the regional and nerve anatomy to see if they can finesse a little bit.

So with that, I thank you very much. Thank you for listening. And have a great day.