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Sustained Blood Pressure Lowering Effect With the Dual Endothelin Receptor Antagonist Aprocitentan in Resistant Hypertension: Results From a Randomized, Controlled Study Including a Withdrawal Phase

Announcer:
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Dr. Bakris:
Hello, I'm Dr. George Bakris, professor of medicine and director of the American Heart Association Comprehensive Hypertension Center at the University of Chicago Medicine. I'm presenting to you one of the late-breaking trials at the American Heart entitled, "Sustained Blood Pressure Lowering Effect of the Dual Endothelin Receptor Antagonist Aprocitentan in Resistant Hypertension: The Results From a Randomized, Controlled Study Including a Withdrawal Phase." So, the background is very important here. Failure to control blood pressure with currently available drugs suggest that relevant pathophysiologic pathways remain unopposed. You can see very clearly the renal angiotensin system in the diagram has a lot of inhibitors already available, including ACE inhibitors, angiotensin receptor blockers, and mineral corticoid receptor antagonists. But endothelin is a much more potent vasoconstrictor and has been implicated in the pathogenesis of hypertension. And you can see now visualized the endothelin system and its blockade. They're endothelin A and endothelin B receptors, and they both have respective duties in monitoring cellular behavior. And this is a combined endothelin A endothelin B receptor antagonist, aprocitentan, and this is what was used in the precision study.

Now, the design is kind of a unique design cause one of the things we wanted to make sure about was that everybody was on the maximal therapy that could be given to make sure blood pressure was controlled. So, we could really say they had resistant hypertension. So, everybody got Valsartan 160 milligrams. They started with amlodipine 5, gone up to 10, and everybody was on hydrochlorothiazide. Why? Because this was a single-triple therapy combination. So that's what's very important about this. So, people were maintained on this, and then there was a four-week placebo run, and then people were randomized to either continuing the placebo, 12.5 or 25 of aprocitentan, and they were followed out for a period of four weeks, and that's one of the primary endpoints. They then were switched, everybody, to 25 milligrams of aprocitentan and followed for a period of 36 weeks. And then they were flipped to continuing the 25 of aprocitentan or back to placebo. And then there was a wash out period at the end of the study. So clearly, a number of changes that occurred and observations that happen on blood pressure over this time.

The study population, you can see here the inclusion criteria, were people with uncontrolled office blood pressures on three or more antihypertensive medications and unattended sitting office blood pressure greater than or equal to 140 milligrams systolic. The exclusion criteria are there, and you could read them for yourself. And these are the baseline characteristics that you see in the study. And so you can see these are people in their early 60s, mostly men, but really, not a bad mix there because it's just barely over 50%. And you can see that there were 12% African Americans in the study and about 5 to 6% Asians. These were people that were obese without any question. And these are people whose baseline eGFR in terms of percentage of people under 60, in other words, stage three or stage four, was about a quarter of the study. You can also see that in terms of albuminuria, that about 30% had micro or macro albuminuria.

So clearly, a sicker population than what you'd normally expect. And about 2/3 of the people were on four or more drugs.

So, these are the unattended office blood pressure results. And you can see, in the first part, at one month, that there was a clear reduction in blood pressure by both doses of aprocitentan, and then the switch to 25 milligrams maintained that over the 36-week period. And then the flip to placebo blood pressure went back up, and then the aprocitentan continued. So very important, and you can see there the change from starting at baselines of around 154 and coming down with aprocitentan down to around 136 as a blood pressure in the first four weeks. This is the 24-hour ambulatory blood pressure monitoring that you can see here at the different doses of aprocitentan. And you can see very nicely, these people dipped, and the dipping was continued and potentiated to a certain extent. And so there's a very nice monitor, and you can see the changes below in terms of the delta changes in blood pressure. So clearly, the 25-milligram dose of aprocitentan gave you significant blood pressure lowering that was maintained over this entire period. Now, here you can see, that was part one, the initial four-week period. Now you can see the double-blind withdrawal period, that's the last period that I just showed you. And you can see here that aprocitentan's blood pressure effect maintains and continues. And very importantly, if you look below, not totally appreciated on the ABPM, that there was a significant change in nighttime blood pressure with an increase back to where baseline was when you stopped the aprocitentan and the aprocitentan maintained the lowering of pressure at night. So very important observation.

Now, there were a number of subgroup analyses that you can see, and fundamentally the effects are pretty clear across the board favoring aprocitentan. If you look at the line of identity, and the line of identity is the dotted line that you see there, not the solid line. And here you can see albuminuria. Very important as a nephrologist, I certainly would look at this. Clearly, in the initial period with aprocitentan, you're getting very nice reductions with both doses. But again, importantly, in the double-blind withdrawal period, you're getting maintenance of lowering of albuminuria, whereas there's complete reversal in the group that got placebo. So clearly, an effect that that is sustaining.

So, if we look at treatment-emergent adverse events, the bottom line here, just to summarize the slide, is there really were not significant adverse events that were occurring here except for, as you would expect, a little bit of volume overload, and about twice as many people had a volume overload than the placebo group. But I think importantly here, if you look at the aprocitentan 25 group and compare that to the placebo group, if you look at discontinuation of the steady treatment, there was one person that discontinued it. Additional diuretics were needed in three people in the aprocitentan group. But there were additional diuretics needed in the placebo group. So, I think, again, an important point to consider there. And so, I think bottom line is, if you compare that to the aprocitentan where everybody was on aprocitentan, clearly there was a discontinuation of greater numbers of people there by two, five people. But edema is real with these agents. And anybody that knows about endothelium blockade knows that this is going to be something that you're going to have to monitor and deal with. And so lastly, if you look at this and you look at hospitalizations for heart failure, cause that's actually what you want to avoid, there were two cases in that first period in the aprocitentan group, none in the placebo group. And when you look at the double-blind withdrawal period at the end, in that last 12 weeks, there were two people that were hospitalized in the aprocitentan group, one in the placebo group. So again, something that you need to be aware of.

So, the conclusions are as follows. Aprocitentan lowered both standardized automated office and 24-hour ambulatory BP compared to placebo after four weeks. The BP-lowering effect was maintained over 48 weeks. Edema/fluid retention was most common AE reported with aprocitentan within the first four weeks of treatment. Events were clinically manageable with the addition of up-titration of diuretic therapy. So dual endothelial antagonism with aprocitentan may represent a new alternative pharmacologic approach to treat resistant hypertension. Thank you very much for your time.

Announcer:
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