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Does the PRECISION Trial Change the Landscape of Resistant Hypertension?

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Dr. Vemulapalli:
So, we'll move to our next panel discussion and talk a little bit about the PRECISION trial. So, Raven, can you take us through a little bit of the nuts and bolts of the PRECISION trial?

Dr. Voora:
Yeah, happy to. So just to remind everybody, as you were saying before, aprocitentan is a dual endothelin receptor antagonist. So, it prevents the binding of endothelin to two receptors. The reason why this is important is cause endothelin is a powerful vasoconstrictor. So, the PRECISION trial, like as you said, the results will be revealed at the concurrent AHA conference. The goal of it was to evaluate the safety and efficacy of aprocitentan when combined to standard of care antihypertensive therapy in patients with resistant hypertension. So, this is a multicenter randomized Phase 3 study mostly involving study sites from North America and from Europe. And here's the study design, and there are a couple things that I want to point out about the trial design. And one of the first things I really want to point out, and the really nice strength of this study is that the investigators had a really long screening and run-in period prior to randomization. And this was really important because it was during this time that the investigators identified patients with true resistant hypertension and excluded pseudoresistance. So, how did they do this? So patients to be eligible for the study, you know, had to have uncontrolled hypertension despite three medications. But what the investigators did is they placed all patients on standardized antihypertensive therapy, including three antihypertensive agents of different classes, including a diuretic. And the three agents that they chose were amlodipine, valsartan, and hydrochlorothiazide. So, they put them on a pretty good regimen. In addition, not only that, in order to maximize adherence, they gave all these patients these three medications in a single pill and that was to maximize adherence. So, all patients were put on standardized antihypertensive therapy, a single pill that was triple combination. And the two strengths are shown there on the previous slide of what was available. And moreover, to be randomized in trial, you had to be on the triple therapy, but you had to have a systolic blood pressure of at least 140, as measured by unattended automated office blood pressure monitoring. As I mentioned before, automated office blood pressure monitoring really can help maximize the accuracy and reliability of measurements and when unattended, can minimize white coat effect. And here, listed here is the exclusion criteria which I think is pretty standard. Patients with severe hypertension, patients with advanced heart failure and advanced CKD were excluded from this study. So, they identified patients with true resistant hypertension and then they could be randomized. And there are three parts to the intervention. And during the intervention patients could receive aprocitentan or placebo while on the standardized antihypertensive therapy, the combination medication. And as you can see the intervention phase was pretty quite long. So, they took 48 weeks to study the safety and efficacy. So again, a nice long time and another strength of this study. And then following the study after the last treatment dose, patients were followed up for additional 30 days for safety. As you can see here what the study endpoints here, the primary study endpoint was changed in blood pressure, systolic blood pressure from baseline to week 4 as measured by unattended AOBP, automated office blood pressure monitoring. And there were several secondary endpoints. The key one was really again, change of

systolic blood pressure from week 36 to week 40. Again, as measured by unattended automated office blood pressure monitoring. I will point out another nice secondary endpoint is that they assess blood pressure by 24-hour ambulatory blood pressure monitoring.

Dr. Vemulapalli:
So, thanks, Raven. You know, obviously, we don't know the results of the study yet, we got to wait a couple days for that. But George, I wanted to ask you, let's say this is positive in some way, that aprocitentan actually lowers blood pressure effectively. Where might you think about using this in your practice? What kind of population?

Dr. Bakris:
So, excellent question. I think as you've heard so far, the reason spiro is number four is because it worked in that study. It has truckloads of side effects as you all know. So really the competition now is to find something as or more effective in spiro, that doesn't have all the baggage. The only side effect of this class, and this goes back into the early 2000s, is edema. And so that's a limiting factor. However, a little hint data from the SONAR trial which we published a few years ago, which was a renal trial, but edema again there was a limiting factor, and it was a non-hypotensive dose and yet it was still protective of the kidney. Remember endothelin is three times more vasoconstrictive than angiotensin II. So, this is a very powerful thing that you're working on. If you can screen patients, make sure that their NT-proBNP is fine. There's no reason this drug can't work and can't help. The way I would use this is a substitute for spironolactone because I'm confident based on what I know that the effect is going to be the same if not slightly better and better tolerated overall.

Dr. Vemulapalli:
Thanks George. Keith, what are, what are your thoughts here?

Dr. Ferdinand:
Well, of course, we don't know until a drug is approved and available. I still like to use frontal lactone if the GFR is over 45 and the baseline potassium is less than 4.5. George has actually had studies that shown that it can be fairly safe in that particular setting. The off-target effects, estrogen stimulation, gynecomastia, breast tenderness is limiting in men even at lower doses. That's where eplerenone was used in the Los Angeles barbershop study. So perhaps in those patients where we don't want to have either the off-target effects and we are concerned with some of the effects with hyperclemia. Other than volume, I think this may be a good added medication in our armamentarium with difficult-to-treat and resistant hypertension. I would also suggest that remember this is a clinical trial, so people were probably taking their medicines, getting paid for their time and travel. The big thing that we have in usual clinical practices, people do not take their medicines. About 50% have non-adherence after two years. So, we need to make sure that first of all, the patient is on effective regimen but more importantly they're taking it.

Dr. Bakris:
And I just want to quickly add. The reason they were on this triple combo, you noticed the dose of losartan was stuck at 160. This was an international trial, and in many places around the world, you can't get 320. You can in the US but you can't outside. And hydrochlorothiazide, you're stuck, that's what's in the combos, they didn't put chlorthalidone on it. So, there are some limitations and that needs to be recognized as well.

Dr. Ferdinand:
Yeah, it wasn't a bad triple combination, George, but I agree with you. I probably have used a higher doses of an ARB or even an alternative ARB irbesartan or olmesartan, which has a longer half-life than valsartan. And I probably would've tried the person on chlorthalidone and indapamide. Many of you don't use indapamide, it's used mainly in Europe, but it is available in United States as a generic, and it's similar to perhaps not as good as chlorthalidone but it has the benefit of a very low dose of 1.25 that's available. And so, you can get some of the benefits of chlorthalidone and see how the patient can tolerate it.

Dr. Vemulapalli:
This is great. So, I think what I've heard in terms of thinking about aprocitentan if it turns out to be positive is a couple things. One, certainly off-target effects with spironolactone can be limiting and some of them can occur even with eplerenone. So, this might be an option there instead of MRAs. We need to be concerned potentially about edema and excluding patients with heart failure perhaps in that setting. And then in terms of applying this to clinical practice, of course, in the trial they're using hydrochlorothiazide as opposed to chlorthalidone. There will be a late-breaker in a few hours addressing that question here at AHA. And certainly, dosing in terms of valsartan and whether irbesartan potentially could have been used instead.

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