

# PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

## The PRECISION Trial: A new endothelin antagonist and new lessons for hypertension trials

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Those of us in the field of hypertension are only too well aware that blood pressure control rates are disappointingly low, even in high income countries. Much of this stems from the dual problems of inadequate prescribing by practitioners and poor medication adherence by patients. Even so, many patients have hypertension that remains uncontrolled despite standard triple therapy, usually a RAS-blocker, amlodipine and a diuretic. To satisfy this need, exciting new drugs as well as device therapy such as renal denervation are in development and soon likely to be available for patients with hard-to-control hypertension.

### Endothelin

While we have focused attention in recent years on the pressor effects of the sympathetic nervous system and the renin-angiotensin system, endothelin also possesses powerful blood pressure-raising properties and so is a relevant new target for therapeutic intervention. Studies with endothelin antagonists like bosentan in the 1990s and darusentan about 20 years later were performed in patients inadequately responsive to treatment with 3 or 4 drugs. Promising blood pressure reductions were observed. But, concern over excessive fluid retention, which is an inevitable consequence of blocking endothelin receptors, as well as some inconsistency in blood pressure effects, resulted in the darusentan's commercial sponsor discontinuing its development, to the disappointment of the academic investigators.

Aprocitan is a new endothelin antagonist with dual ETA/ET<sub>b</sub> actions. It is believed that its dual action can reduce fluid-retaining effects. A phase-2 study with this agent showed that daily doses of 12.5 and 25mg provided useful blood pressure lowering effectiveness together with an acceptable safety profile. Accordingly, the well-powered phase-3 PRECISION trial was undertaken to confirm and expand those findings.

### The PRECISION Trial

This study, published recently in *The Lancet* (Nov 7, 2022) was focused on patients with true resistant hypertension, with the expectation that Aprocitan will be used predominantly (though not necessarily always) as a fourth line drug. Strong attempts were made to ensure that only study subjects taking optimal triple therapy with true resistant hypertension were randomized. After study consent, all previous medications were discontinued during a 4-8 week initial screening period and replaced with a single-pill combination of amlodipine 5 or 10mg, valsartan 160mg and hydrochlorothiazide 25mg for an additional 4 week screening period. And, as a further precaution, placebo was added to the combination therapy to all patients for an additional 4-week single blind run-in period to confirm eligibility.

Double-blind randomization allocated patients equally to placebo, aprocitentan 12.5mg daily, and aprocitentan 25mg daily for the 4-week period to the primary study endpoint. The result, measured by automated office blood pressures, was positive. Aprocitentan 12.5mg was significantly superior to placebo by 3.8/3.0 mmHg and Aprocitentan 25mg by 3.7/4.5 mmHg.

What was entirely unexpected, however, was that despite all the pre-randomization precautions, systolic blood pressure fell by 11 mmHg in the placebo group. Obviously, it fell by even more in the aprocitentan patients, but it's still likely that the real effects of the investigational drug were at least partly diluted by so many patients exhibiting an excessive placebo effect. 24-hour ambulatory blood pressure monitoring provided a somewhat clearer picture of the drug's effect: aprocitentan 12.5mg beat placebo by 4.2/4.3mmHg and 25mg beat placebo by 5.9/5.8mmHg.

After reaching that endpoint, all patients were switched into a single large group, all receiving the same aprocitentan 25mg dose, for a 32 week period to measure the drug's durability and safety.

And then came the highlight of the trial: with all patients now stable, there was a re-randomization, with half remaining on aprocitentan 25mg and half switched to placebo. The endpoint for this comparison was after 4 weeks: the patients remaining on aprocitentan experienced virtually no change in blood pressure; whereas those now on placebo had a significant increase compared with the aprocitentan group of 5.5/5.2mmHg by automated office measurement, and by 6.5/6.7mmHg for 24h ambulatory blood pressure.

### Fluid Issues

As expected, oedema/fluid retention was the most common adverse event. Overall, 184 patients on the active drug had fluid retention, but only 8 on placebo (although duration of exposure to the active drug was greater than to placebo). Fluid retention occurred most often in the first few weeks of treatment; 40% of these patients received intensification of diuretic therapy, though only 7 patients discontinued aprocitentan because

of fluid retention. This adverse effect was most common in patients with chronic kidney disease.

Of note, the trial allowed patients with uncontrolled hypertension being treated for heart failure to be enrolled, including some whose loop diuretic therapy was replaced with hydrochlorothiazide! Ten patient required hospitalization for fluid issues (all with backgrounds of heart failure, kidney disease or diabetes.) Remarkably, all these patients remained in the study on their assigned treatment after discharge.

### What we have learned

Although this trial was designed primarily to study aprocitentan, it also brought to light other interesting issues.

1. Aprocitentan: This drug significantly reduced blood pressure when added to single pill triple therapy in patients with uncontrolled hypertension. An excessive placebo response signaled that too many patients did not have resistant hypertension and so diluted the drug's effectiveness. The main safety issue was fluid retention despite all patients receiving a modest thiazide dose. The study's findings would strongly suggest that replacing hydrochlorothiazide with a more powerful and longer acting agent like chlorthalidone or indapamide would more effectively reduce fluid retention and also enhance efficacy. In fact, it could be recommended, or even mandated, that one of these more powerful diuretics be administered routinely with aprocitentan; perhaps a single pill combination could be considered.

2. Hypertension study design: This trial emphasized the clarity of measuring a drug's antihypertensive efficacy by introducing a randomized placebo comparison after all patients are established on the drug. This approach has been endorsed by the FDA and used in previous trials, and should be considered in forthcoming studies of blood pressure-lowering drugs.

3. We start and end with the prevalent issue of uncontrolled hypertension. This trial, carefully designed to exclude patients with pseudo-treatment resistant hypertension, enrolled 1,965 potential candidates whose blood pressure

and prescriptions indicated treatment resistant hypertension. But 872 of these candidates during the sustained pre-randomization period were excluded for failing to maintain an elevated systolic blood pressure. Even so, these precautions were not sufficient. At baseline 730 patients were randomized, but the drop in systolic blood pressure of 11 mmHg in the placebo group makes it obvious that a large proportion of patients had withheld their medications in order to enter the trial and did not, in fact, have treatment resistant hypertension. This phenomenon of randomizing inappropriate patients has adversely affected several other recently performed studies of blood pressure treatments.

4. One lesson is clear: in an era when patients often measure their own blood pressures and adjust their medications accordingly, we will need to consider measurement of plasma and urine drug levels to determine adherence with protocol medications to maintain the integrity of our clinical trials.<sup>1</sup>

#### Reference

1. Schlaich MP, Bellet M, Weber MA et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. *Lancet*. 2022; 400: 1927-1937

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