New hope in the quest for a novel add-on therapy for uncontrolled hypertension

- Resistant hypertension is a condition observed in 10–15% of hypertensive patients and is associated with an increased risk of disability and death.
- Professor Markus Schlaich at The University of Western Australia, together with colleagues from other centres worldwide, undertook the PRECISION clinical trial to assess whether the novel drug aprocitentan, targeting the endothelin system, could improve blood pressure control in these patients.
- The trial demonstrated that aprocitentan safely reduced systolic and diastolic blood pressure.
- The drug may present a new treatment for those whose blood pressure is difficult to control with traditional medications.

Elevated blood pressure, called hypertension, is the leading risk factor for death and disability worldwide. It is estimated to affect 1.3 billion people, or one in four adults, and is responsible for around 11 million deaths per year worldwide.

Hypertension is a leading risk factor for stroke, coronary heart disease (myocardial infarction), heart failure, and kidney damage. For the majority of those affected by hypertension, adequate control of blood pressure to within recommended target ranges can be achieved via a healthy lifestyle and blood-pressure-lowering medications. This can prevent serious cardiovascular conditions and reduce the risk of death and disability, particularly for patients with a high risk of developing cardiovascular disease and hypertension-related comorbidities.

However, for 10–15% of patients, it is not possible to achieve office blood pressure control to below 140/90 mmHg despite taking three or more blood-pressure-lowering medications, a condition referred to as resistant hypertension. In comparison to those patients whose hypertension is well-controlled, these patients are at a much greater risk of heart attack, stroke, end-stage renal (kidney) disease, and death. Failure to control blood pressure suggests that, in part, the drugs that are currently available are not targeting relevant pathways involved in blood pressure control.

One such pathway implicated in the pathogenesis of hypertension is the endothelin (ET) pathway. Endothelin is a protein produced primarily by vascular endothelial cells, which constitute the lining of arteries, veins, and capillaries. It is known to play a role in blood pressure control by binding to its receptors on smooth muscle cells to cause constriction (tightening) of blood vessels, thereby raising blood pressure. This pathway is currently not targeted by existing anti-hypertensive therapies.

Aprocitentan is a first-in-class endothelin receptor antagonist developed to treat patients whose high blood pressure is uncontrolled despite receiving other anti-hypertensive medications.

Professor Markus Schlaich, renal physician and a European Society of Hypertension accredited hypertension specialist from The University of Western Australia, together with other researchers worldwide, tested whether the novel drug aprocitentan, which blocks the effects of endothelin, could be effective in treating resistant hypertension.

The first new treatment in over 30 years

Aprocitentan is a first-in-class endothelin receptor antagonist developed to treat patients whose high blood pressure is uncontrolled despite receiving other anti-hypertensive medications. The oral drug prevents the binding of endothelin to its receptors, thereby reducing the

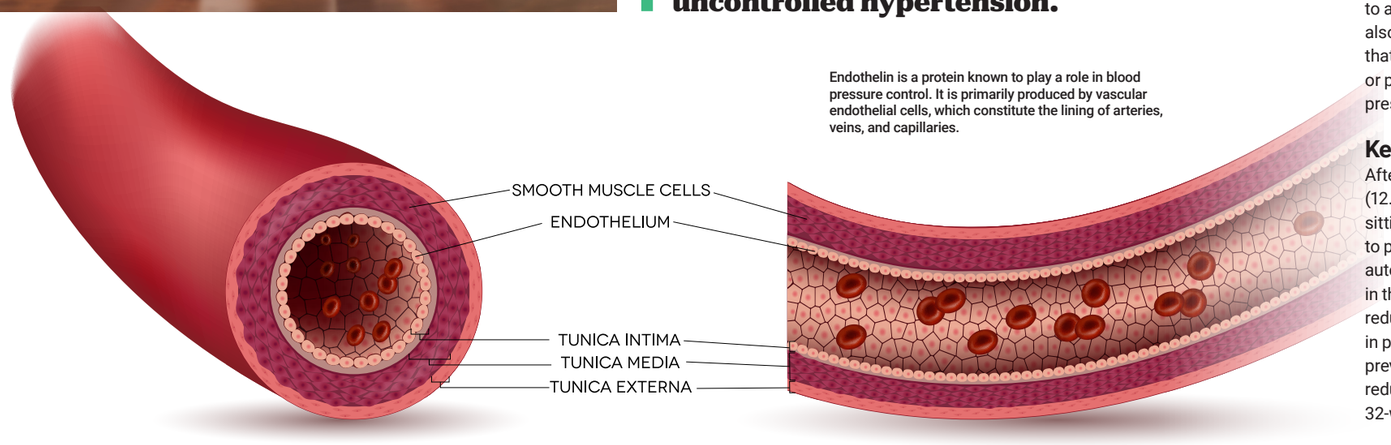
Aprocitentan can be taken once daily and has low potential for drug–drug interaction.

To reduce white-coat blood pressure elevation, blood pressure was also measured via an automated method.

constriction of blood vessels. It is the first anti-hypertensive medication to be developed in over 30 years that specifically targets this yet unopposed pathway. Importantly, aprocitentan can be taken once daily, thereby increasing the likelihood of patient adherence to the medication, and it has a low potential for drug–drug interaction, which is essential as it is intended to be used in addition to other medications.

Schlaich and a team of investigators conducted the PRECISION trial – an international, multicentre, blinded, randomised, phase 3 clinical trial that aimed to assess the safety and efficacy of aprocitentan for treating patients with resistant hypertension. Initially, the researchers screened all adults who had a history of uncontrolled hypertension, with sitting systolic blood pressure (siSBP) in the office of at least 140 mmHg after taking at least three different classes of anti-hypertensive medications for a minimum of four weeks. Subsequently, all eligible patients were transitioned to a standardised background therapy (SBT) for four weeks, a run-in period in which to stabilise their blood pressure on background anti-hypertensive medications. Only patients who maintained a sitting blood pressure above 140/90 mmHg made it into the trial.

The findings offer hope as a novel, effective and well-tolerated treatment for patients with uncontrolled hypertension.



Endothelin is a protein known to play a role in blood pressure control. It is primarily produced by vascular endothelial cells, which constitute the lining of arteries, veins, and capillaries.

The PRECISION study consisted of three major parts. Part 1 was a four-week double-blind phase in which patients with resistant hypertension were randomised to receive aprocitentan at 12.5 mg (n=243) or 25 mg (n=243), or a placebo (n=244), on the background of a stable regimen of at least three anti-hypertensive medications. Subsequently, all patients received aprocitentan at 25 mg for 32 weeks, followed by a 12-week double-blind withdrawal phase in which patients were re-randomised to aprocitentan 25 mg (n=307) or placebo (n=307). At baseline, week 4 and week 40, participants' blood pressure was also assessed by ambulatory blood pressure monitoring, a method which measures and tracks blood pressure at regular intervals over 24 hours using a blood pressure cuff attached to a portable device. Blood pressure was also measured via an automated method that did not require the attendance of a nurse or physician to reduce any white-coat blood pressure elevation.

Key PRECISION findings

After four weeks, both aprocitentan doses (12.5 mg and 25 mg) significantly reduced sitting systolic blood pressure compared to placebo, as measured by unattended automated office blood pressure. Furthermore, in the second part of the study, a continued reduction in blood pressure was seen in patients on aprocitentan, and those previously on a placebo experienced a further reduction in blood pressure throughout the 32-week phase. As expected, once patients were re-randomised after 36 weeks, blood pressure was maintained in patients receiving aprocitentan while there was a significant rise in blood pressure in the placebo group.

The results from ambulatory blood pressure monitoring supported the office blood pressure readings and provided an accurate indication across 24 hours. A significant decline in blood pressure levels during the night was observed in patients who received the higher dose of aprocitentan. Blood pressure level during the night is known to be more accurate in predicting death due to disease of the heart or blood vessels compared to other blood pressure indices; therefore, reducing nighttime blood pressure is likely to have significant additional benefits. The blood-pressure-lowering effect of aprocitentan was evident across the entire 24-hour period with once-daily dosing, and this effect was sustained for the entire 40-week period of the study. Aprocitentan was similarly effective in patient populations including the elderly and those with chronic kidney disease, who frequently present with difficult-to-treat hypertension. Importantly, aprocitentan was well-tolerated, and side effects such as fluid retention were easily managed.

In summary, the PRECISION clinical trial successfully demonstrated the safety and efficacy of a novel therapeutic approach to treat resistant hypertension by targeting the endothelin pathway with a dual endothelin antagonist aprocitentan. The findings offer hope as a novel, effective, and well-tolerated treatment for patients with high blood pressure despite receiving multiple anti-hypertensive medications.

Personal response

What are the next steps following the outcome of the PRECISION trial?

Given this was a pivotal trial, regulatory approval is now sought by the Food and Drug Administration for the USA, the European Medicines Agency for the EU, and other countries. Once obtained, educational activities to assist practitioners in the appropriate clinical use of the drug will be important.

What level of evidence will be needed for aprocitentan to be added to standardised anti-hypertensive regimen in the setting of resistant hypertension?

Given that PRECISION was the pivotal phase 3 trial and pending regulatory approval, aprocitentan could and should be implemented as soon as possible as an additional therapeutic option in patients with resistant hypertension.

Will aprocitentan be tested against spironolactone, a currently recommended add-on therapy for patients with resistant hypertension?

To my knowledge, there are currently no studies planned, but it would be pertinent to compare the two head-to-head to explore a) which drug is safer and better tolerated and b) which one is more effective. On the other hand, spironolactone should be avoided in patients with an eGFR below 35-40ml/min/1.73m^2 for safety reasons (eGFR reduction, risk of hyperkalemia), whereas aprocitentan appears to be safe and effective in this cohort with moderate to severe chronic renal impairment.

What is next for you and your team?

In future studies, we aim to explore the effect of aprocitentan in specific populations with high unmet medical needs.

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Bio

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Competing interest statement

Markus Schlaich has received research and travel support from Idorsia.

Further reading

Schlaich, MP, et al, (2022) Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial, *The Lancet*, 400(10367), 1927–1937.

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