Hypertension

EDITORIAL

Endothelin Antagonism: A New Era for Resistant Hypertension?

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Hypertension, defined as a blood pressure (BP) above which treatment provides more benefit than harm, is the leading cause of morbidity and mortality worldwide and is strongly associated with the development of a range of diseases, including cerebrovascular, chronic kidney, and coronary disease. Between 1990 and 2019, the global prevalence of hypertension doubled, and it is now estimated to affect ≈1 in 4 adults worldwide.[1] Despite an extensive therapeutic armamentarium, only 1 in 5 individuals with hypertension achieve adequate BP control.[2] The reasons for this are multifactorial and include therapeutic inertia partly as a consequence of physicians doubting the accuracy of office BP measures[3] and poor medication adherence.[4] However, there is a particularly high-risk group of patients with treatment-resistant hypertension (TRH) who, despite lifestyle measures and adherence to maximally tolerated doses of ≥3 different classes of antihypertensive including a diuretic, continue to have uncontrolled BP.

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ET-1 (endothelin-1) is the most potent endogenous vasoconstrictor acting via 2 receptors, ET_A (endothelin-A) and ET_B (endothelin-B).[5] Although long recognized that the ET system plays an important role in hypertension,[6] it was only last year that the first drug targeting the system was approved by the Food and Drug Administration for the treatment of hypertension. Aprocitentan, a dual $ET_{A/B}$ antagonist, was evaluated in the Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION).[7] The trial involved 3 parts: in part one (duration 4 weeks), patients were randomized in a double-blind manner to aprocitentan 12.5 mg daily, 25 mg daily, or placebo; in part 2 (duration 32 weeks), all patients received aprocitentan 25 mg; and in part 3 (12 weeks), patients were randomized to aprocitentan 25 mg or placebo. The PRECISION study demonstrated a significant reduction in office systolic BP with aprocitentan (≈4 mm Hg for both low- and high-dose) compared with placebo, findings confirmed by 24-hour BP monitoring. Surprisingly, despite the placebo phase of the trial being only 4 weeks duration, the Food and Drug Administration licensed aprocitentan at a dose of 12.5 mg for the treatment of uncontrolled hypertension, rather than TRH, thereby substantially widening its potential use.

In this edition of *Hypertension*, Flack et al[8] present a substudy of the PRECISION trial, examining the efficacy and safety of aprocitentan in Black and African-American patients. These patients comprised only 11% (82 patients; mean age, 61 years; 51% male; baseline office BP 156/88 mm Hg) of the original study population even though TRH is more common in these groups. Despite the small numbers, and based on 24-hour monitoring, aprocitentan dose-dependently reduced BP (reduction in systolic BP of ≈3 and ≈8 mm Hg with low- and high-dose aprocitentan, respectively, compared with placebo). Notably, aprocitentan and placebo did not differ on office readings where placebo reduced systolic BP by ≈12 mm Hg—similar to the reduction with placebo in the original trial. Although, in part 3 of the study, the placebo group showed a rise in both office and ambulatory systolic BP (≈10 and ≈8 mm Hg, respectively) compared with the group maintained on aprocitentan. It is important to recognize that as a substudy of the original trial, the groups were not matched. For example, in the placebo group, 35% had chronic kidney disease, a condition where BP is particularly difficult to control,[9] compared with 25% and 11% in the low- and high-dose

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aprocitentan groups, respectively. Conversely, those randomized to aprocitentan had a higher frequency of severe obesity (36% in high-dose aprocitentan versus 15% in the placebo group).

In the present study, 52% of patients had albuminuria, a major, independent risk factor for cardiovascular disease, and aprocitentan dose-dependently reduced this (by 38% and 65% for low- and high-dose, respectively, versus a 13% reduction with placebo). As the patients in this substudy were at high-risk (80% were obese or severely obese; 68% had diabetes; 53% had chronic kidney disease), this finding is encouraging. Given selective ET_A receptor antagonism has been shown to improve a range of cardiovascular risk factors—including circulating lipids,[10] high-sensitivity troponin,[11] and serum urate[12]—in high-risk patients, it would be interesting to know whether the same effects are seen with a dual endothelin-blocking approach. This would certainly make aprocitentan a more appealing antihypertensive than others that reduce BP alone.

Fluid retention is the commonest dose-dependent and treatment-limiting side effect of all ET receptor antagonists.[5] During part one of the present study, no patients randomized to low-dose aprocitentan developed

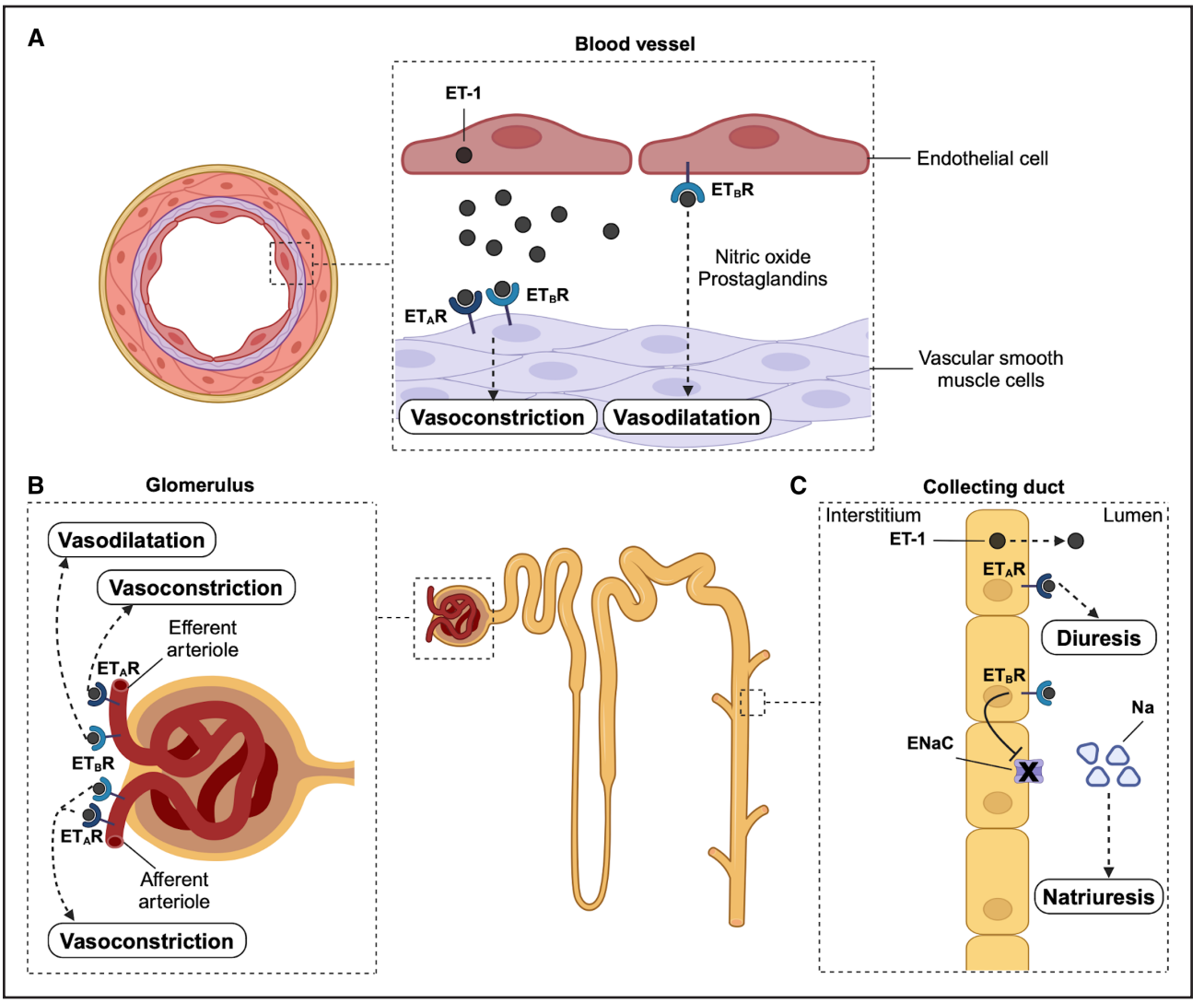

Figure. Effects of ET-1 (endothelin-1).
A, Role of ET-1 in the systemic vasculature. ET-1 is constantly generated in the vascular endothelium where it maintains vascular tone and blood pressure. ET-1 acts on ET_AR (endothelin-A receptors), predominantly expressed on vascular smooth muscle cells, to cause vasoconstriction. The role of ET_BR (endothelin-B receptors) is more complex. On vascular smooth muscle, ET-1 activation of ET_BR promotes vasoconstriction. This effect is attenuated by ET-1 activation of ET_BR on endothelial cells which stimulates local nitric oxide and prostaglandin release and consequently leads to vasodilatation. **B**, Role of ET-1 in the glomerulus. In the kidney, ET-1 activation of both ET_A and ET_B receptors on the afferent arteriole causes vasoconstriction. However, in the efferent arteriole, ET_A and ET_B stimulation have opposing effects; ET_A causes vasoconstriction while ET_B stimulates vasodilatation. Through these actions, ET-1 can regulate glomerular blood flow and it is likely that the reduction in albuminuria seen with both selective ET_A and dual $ET_{A/B}$ receptor antagonism is partly due to this. **C**, Role of ET-1 in the collecting duct. ET-1 has a prominent role in salt and water regulation here. Activation of ET_BR inhibits epithelial sodium channels (ENaC) resulting in natriuresis. Animal studies have shown deletion of the ET_AR in the collecting duct protects against ET_AR antagonist-induced fluid retention.

fluid retention (compared with ≈10% on low-dose in the main trial).[7] Importantly, given both the short duration (4 weeks) and small sample size of this substudy (only 28 patients were on low-dose aprocitentan), adverse events may be underestimated. During the 32-week part 2 period when all patients were on the higher dose of aprocitentan, 1 in 5 developed peripheral edema. The minority required increased diuretic therapy, and none required treatment discontinuation. Although reassuring, patients with more severe heart failure and those with elevated circulating BNP (B-type natriuretic peptide) concentrations—an indirect marker of left ventricular stretch identifying those most likely to develop fluid overload—were excluded from the trial. BNP is not routinely measured in patients with TRH, and so aprocitentan use requires judicious monitoring for fluid retention.

The authors suggest that dual $ET_{A/B}$ receptor antagonism may have a more favorable safety profile compared with selective ET_A blockade. However, there remains no head-to-head trial comparing these approaches for any indication, and the existing data do not support this.[11] For example, in the recent randomized, double-blind, placebo-controlled Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) study, which evaluated the efficacy of the highly ET_A selective antagonist, zibotentan, in patients with microvascular angina, zibotentan resulted in a comparable reduction in systolic BP and a similar rate of peripheral edema (11%) to that seen with the Food and Drug Administration–approved dose of aprocitentan in PRECISION.[13] These findings are also consistent with other studies of zibotentan in patients with chronic kidney disease, a population at high-risk of fluid retention.[14] Intriguingly, in this patient group, concomitant prescription of a SGLT2 (sodium-glucose cotransporter 2) inhibitor alongside zibotentan has been shown to reduce BP and albuminuria more so than an SGLT2 inhibitor alone and without excess fluid retention, perhaps attributable to the natriuretic effects of SGLT2 inhibition.[14] Given the broad cardioprotection offered by SGLT2 inhibition, this combined approach might be appealing in those with TRH and should be explored in future trials.

An ET blocking approach may be particularly attractive in Black and African-American patients who are recognized to have salt-sensitive low-renin hypertension, and elevated plasma and vascular ET-1 concentrations compared with White patients.[6] ET-1 has a range of deleterious effects mediated mainly through vascular smooth muscle ET_A receptors (Figure), whereas ET_B activation promotes local nitric oxide production and also provides the key clearance mechanism for ET-1 from the circulation. Consequently, plasma ET-1 concentration was previously considered to reflect ET_B receptor activity (with rises after ET antagonist administration suggesting functional ET_B blockade).[5] However, this paradigm has been challenged recently as treatment with highly selective ET_A antagonists led to rises in plasma ET-1 in different disease states,[13,15] perhaps suggesting disease-specific ET receptor function. Currently, it is unclear whether plasma ET-1 concentrations associate with outcomes in patients receiving ET receptor antagonists, or if plasma ET-1 could identify those patients most likely to benefit from these drugs. These are important questions that might be answered if industry were willing to share these data from clinical trials such as PRECISION and PRIZE.

The licensing of aprocitentan represents the first new antihypertensive to be approved in over 2 decades and the first via a new pathway in almost 4 decades. This substudy has demonstrated efficacy and safety of aprocitentan in Black and African-American patients, a group who are often underrepresented in clinical trials and in whom TRH is a major problem. Aprocitentan, given its long half-life (≈44 hours), may have particular utility in TRH in the real-world setting where poor adherence is a major issue, although future work should compare the efficacy and safety of aprocitentan against existing fourth-line antihypertensive agents. Currently, data demonstrating that the BP-lowering effects of ET receptor antagonism result in improved cardiovascular outcomes are lacking. Similarly, other novel antihypertensive agents are under development and showing promise, including aldosterone synthase inhibitors and nonsteroidal mineralocorticoid inhibitors.[1] However, given the broad beneficial effects ET receptor antagonism has on a range of cardiovascular risk factors, it may not be long before clinicians reach for these drugs above other, more established antihypertensive medications.

ARTICLE INFORMATION

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