COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

A New Class of Drugs Approved in the United States for Hypertension: Endothelin Antagonists

Globally, hypertension is estimated to affect 1.28 billion adults aged 30-79 years, the majority of whom have uncontrolled hypertension.[1] In the United States, almost half of adults have blood pressure (BP) >130/80 mmHg or are taking an antihypertensive medicine; hypertension is estimated to have caused or contributed to 691,095 deaths in 2021.[2] Systemic hypertension results from a mosaic of interdigitating pathophysiological mechanisms, hence a combination of antihypertensive drugs is necessary to lower BP levels.[3] Despite optimal adherence and therapy, approximately 5% of hypertensive patients have a BP >140/90 mmHg (ie, true-resistant hypertension), equating to approximately 6 million people in the United States.[2,3] It was therefore with cautious optimism that on March 19, 2024, the US Federal Drug Administration (FDA) approved aprocitentan (TRYVIO^{TM}) an endothelin (ET) receptor antagonist (ETRA) for resistant hypertension. This is the first new class of oral antihypertensive medicines to be approved by the FDA in almost 40 years.

THE ENDOTHELIN SYSTEM

The ET system plays a critical role in increasing peripheral vascular resistance, the ultimate pathway in the causation of hypertension. Endothelin-1 (ET-1) is predominantly an ET-derived compound that exerts a variety of hemodynamic and structural alterations in the cardiovascular and pulmonary circuits (Figure 1).[4,5] The effects of ET-1 are mediated by 2 types of transmembrane G protein-coupled receptors: ET_A and ET_B, which are widely distributed in the cardiovascular system.[4,6] The biophysical effects mediated by these 2 receptor types dictate the therapeutic implications, that is, selective (ET_A) vs dual (ET_A/ET_B) receptor antagonism (Figure 2).[4]

Funding: None.

Conflict of Interest: None.

Authorship: The author is solely responsible for the content of this manuscript. CVSR: Conceptualization, Writing − original draft, Writing − review & editing.

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The mechanisms responsible for BP elevation are multiple and complex: however, ET-mediated effects (directly or via the sympathetic nervous system and renin-angiotensin-aldosterone activation) are detrimental to cardiovascular homeostasis. Overexpression of ET-1 causes adverse vascular remodelling.[7] Patients with hypertension have exaggerated vascular ET activity which triggers intense vasoconstriction that can be reversed by the nonselective blockade of ET_A and ET_B receptors.[8] This dual blockade, in addition to causing vasodilation, may exert anti-inflammatory and anti-fibrotic effects and promote reversal of cardiac hypertrophy.[9,10]

Overall, ET receptor antagonists (ETRAs) are associated with some side effects such as headaches, flushing, edema, and anemia.[6] Endothelin receptor antagonists are also classified as pregnancy category X because studies in knockout mice have demonstrated the potential for teratogenic effects.[11]

APROCITENTAN AND THE PRECISION TRIAL

Aprocitentan is a dual ETRA that blocks both the ET_A and ET_B receptors.[12] Aprocitentan has a half-life of 44 hours, and its BP-lowering ability is dose-dependent and appears to be synergistic with renin-angiotensin-system blockers.[13,14] It is not known to have any significant drug-to-drug interactions and can be safely taken with other common cardiovascular medications.[12,13] Aprocitentan was approved by the FDA for the treatment of hypertension in combination with other antihypertensive drugs, to lower BP in adults not adequately controlled with other medicines. This approval appears to be based on the pivotal phase III PRECISION trial.[15]

The PRECISION investigators recruited patients with a sitting systolic blood pressure (SBP) ≥ 140 mmHg despite the use of 3 antihypertensive therapies (including a diuretic) for ≥ 1 year.[15] The mean body mass index of patients was 33-34 kg/m^2. Diabetes was present in 52%-56% and 30%-32% had ischemic heart disease. The design of PRECISION was ingenious, as pseudo-resistant hypertension was excluded by switching patients to a combination triple-therapy pill to achieve a maximally tolerated background dose that continued throughout the study (Figure 3).[15] The

https://doi.org/10.1016/j.amjmed.2024.04.044

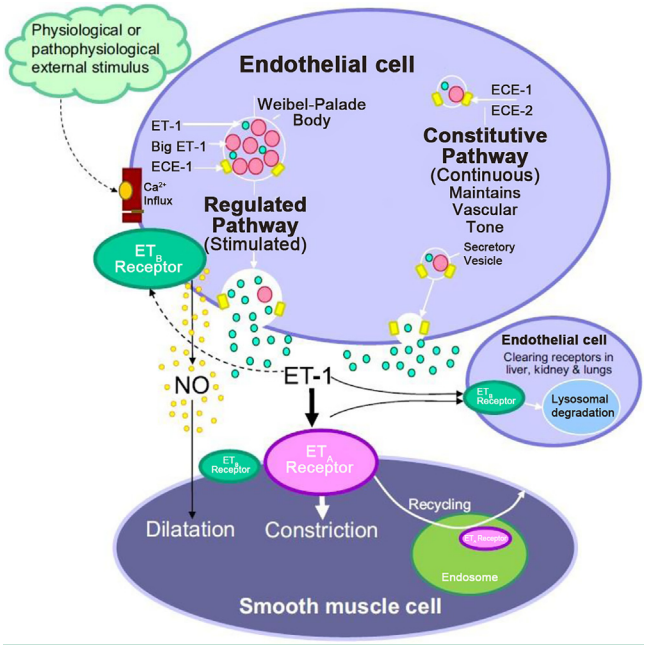

Figure 1 Schematic representation of Endothelin-1 signalling. Adapted from Macguire and Davenport et al (2015).[5]

primary endpoint of change in mean trough sitting office SBP from baseline to week 4 (Part 1) provided a dose-response and placebo-controlled comparison. The single-blind 32-week use of aprocitentan 25 mg (Part 2) satisfied any ethical concerns that high-risk patients might be denied potentially beneficial treatment. Finally, the key secondary endpoint of change in office SBP from withdrawal baseline at week 36 to week 40 (Part 3) provided insights into the sustainability and reversibility of any change in BP.

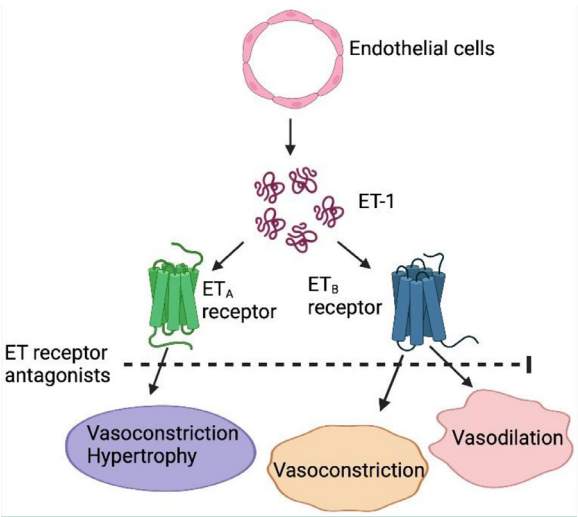

Figure 2 The endothelin system and action of endothelin receptor antagonists. Created in BioRender.com.

From 730 patients who were enrolled in PRECISION, the mean change in office SBP after 4 weeks of aprocitentan 12.5 mg was -15.3 mmHg, -15.2 mmHg for aprocitentan 25 mg and -11.5 mmHg for placebo.[15] This equated to a respective difference vs placebo of -3.8 mmHg (P = .0042) and -3.7 mm Hg (P = .0046). Office diastolic BP was also similarly decreased compared with placebo. In Part 3, after 4 weeks of withdrawal, the SBP of patients treated with placebo increased significantly compared with aprocitentan (5.8 mmHg, $P < .0001$) and persisted to week 48. These results were confirmed by ambulatory BP monitoring, and a pronounced reduction in nocturnal BP was observed. Interestingly, following Part 1, a respective reduction of -28% and -31% was seen in urine albumin-creatinine ratio of the aprocitentan 12.5 mg and 25 mg arms, compared with a 5% increase in the placebo arm. The most common adverse event in PRECISION was edema in 9%, 18%, and 2% of the aprocitentan 12.5 mg, 25 mg, and placebo arms, respectively.[15]

PLACE IN THERAPY

Due to concerns about possible teratogenic effects, aprocitentan can only be prescribed at present via a restricted distribution program that requires prescribers to be trained and dispensing pharmacies to be certified. The use of aprocitentan is contraindicated during pregnancy.

In summary, dual ET_A and ET_B receptor antagonism is a novel approach to treat hypertension that can be utilized in combination with other classes of anti-hypertensive drugs,

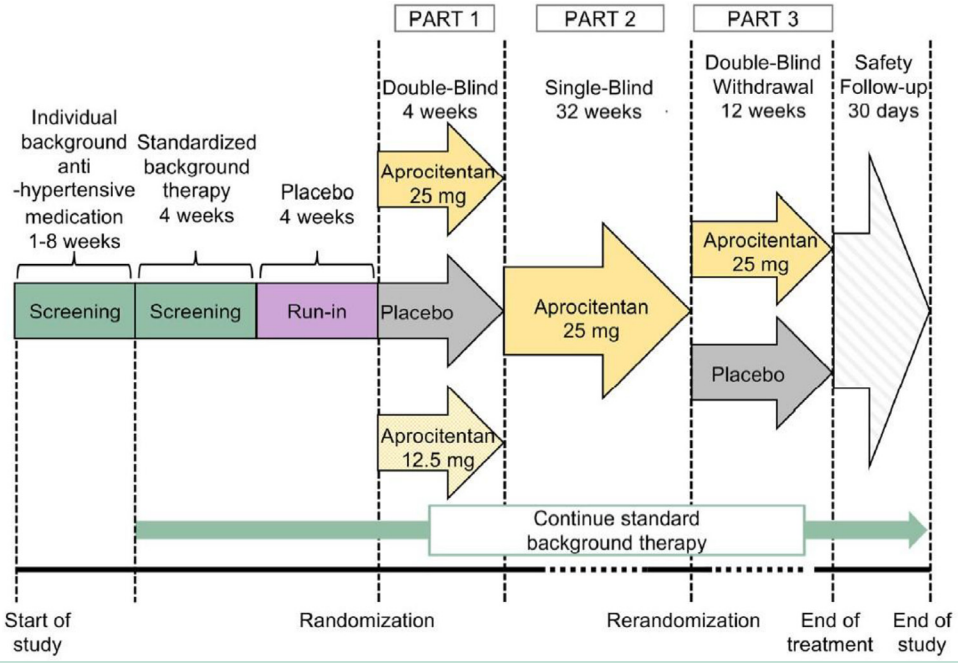

Figure 3 The PRECISION study design. Adapted from Danaietash et al (2022).[16]

with once-daily dosing likely to optimize treatment adherence. Although the FDA has approved aprocitentan for resistant hypertension, its ultimate place in the antihypertensive armamentarium can only be revealed when the drug is available for all grades of hypertension. Further studies are also required to determine whether aprocitentan-induced ankle edema is a local cosmetic (benign) phenomenon or mediated by the cardio-renal axis. Certainly, the improvement in urine albumin-creatinine ratio compared with placebo is intriguing, and the possibility that aprocitentan is synergistic with renin-angiotensin-system inhibitors suggests an additional benefit may be possible for patients with hypertension and kidney disease who require careful monitoring if they are prescribed spironolactone. Endothelin receptor antagonists are therefore a welcome novel option to improve hypertension control rates; however, this optimistic premise awaits evidence from prospective clinical experience and additional studies.

ACKNOWLEDGMENTS

The author appreciates the professional editorial assistance and verification of references provided by Mr. Mark Caswell.

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