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A Procitentan, A New Novel Drug to Treat Resistant Hypertension

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Abstract. *Resistant hypertension (RH) is defined as the failure to attain a controlled blood pressure in spite of the use of a triple combination therapy comprising a renin-angiotensin system inhibitor (RAS-i), a calcium antagonist, and a diuretic.Endothelin has been identified as a potential therapeutic agent target in the treatment of resistant hypertension. In hypertension and end-organ damage, endothelin plays a key role as a vasoconstrictor, comitogenic agent, and mediator of aldosterone and catecholamine release. ET inhibitors (receptor antagonist), currently approved by FDA in 2024 for the treatment of resistant and pulmonary hypertension. Aprocitentan seem to be also very useful for both essential hypertension and RH as well and could be used in combination of other hypertension drugs to get the best blood pressure control. Aprocitentan (Tryvio) is a novel new drug that administrated orally and showed well tolerated dual ET receptor antagonist, which has been inspected in numerous scientific studies and many clinical trials that showed hopeful results for RH control. As a result, that has been approved and optimistically it will help patients and prevent further cardiovascular disease and other organs damages. This article discusses several research that studied Aprocitentan from all aspects.*

Keywords: *Aprocitentan, Dual Endothelin Receptor Antagonist, Endothelin System, Endothelin, Resistant Hypertension.*

1. INTRODUCTION

Hypertension is the most popular chronic heart disease through the globally and characterises a chief risk factor for other cardiovascular disease and other death condtion. Numerous clinical studies in the past have showed the important of reducing blood pressure, (BP) within normal limits to avoid many other health problems in patients (Cushman and Basile, 2006).

In recent periods, a resistant hypertension become recognized widely with an growing rate as a considerable factor producing inadequate BP control among hypertensives patients ,creating an significant public health concern (Arvanitis et al., 2025, Parodi et al., 2024).

According to the World Health Organization (WHO), hypertension affects over a billion people globally and is one of the primary contributors to premature death worldwide (Kario et al., 2024). While lifestyle factors—such as an unhealthy diet, physical inactivity, and excessive alcohol consumption—play a substantial role, genetic predisposition, age, and underlying health conditions also contribute to the risk of developing high blood pressure (Booth III et al., 2017).

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The endothelin pathway, particularly involving endothelin-1 (ET-1), has gained attention for its role in vascular regulation. ET-1 is a potent vasoconstrictor that contributes to vascular tone and blood pressure regulation. Dysregulation of ET-1 signaling has been implicated in resistant hypertension—a form of hypertension that does not respond well to standard antihypertensive therapies) Motte et al., 2006 (. This pathway's involvement in vascular remodeling and inflammation makes it a promising target for new treatments like aprocitentan, a dual endothelin receptor antagonist designed to block ET-1's effects, thereby reducing vascular resistance and lowering blood pressure (Angeli et al., 2021).

The aim of this review is to present latest results about the development of novel dual ET inhibitors especially aprocitentan and their important role in the management of RH, through summarizing current experimental scientific studies and many clinical trials, emphasizing the importance of early recognition and effective controlling of RH.

2. INTRODUCTION TO HYPERTENSION

High blood pressure or hypertension is a chronic disease that occurs when the arterial blood vessels are constantly under high traps pressure. Blood pressure, the strength of blood pushing against the walls of arteries, moves up and down throughout a day depending on activity your diet (high sodium), stress, or health status (Staessen et al., 2003). High blood pressure becomes hypertension when this pressure stays too high, making it a major risk factor for diseases of the heart and circulatory system including stroke, myocardial infarction and chronic kidney damage (Rabi et al., 2011).

Types of Hypertension

Hypertension has two main types: primary (essential), which accounts for most hypertension cases, and secondary. Although primary hypertension — the most common type — does not have an identifiable cause, it is often attributed to a variety of lifestyle choices combined with genetic predisposition. In contrast, secondary hypertension is due to an underlying medical condition, such as kidney disease or certain endocrine disorders, and/or the use of particular medicines (Tousoulis et al., 2012).

Clinical Measurement and Diagnosis

Hypertension diagnosis relies on measuring blood pressure accurately. Blood pressure readings are two numbers: systolic pressure (the force during a heartbeat) and diastolic pressure (the force between heartbeats). Health organizations like the American Heart Association (AHA) define hypertensive blood pressure readings as those that remain at or above 130/80 mmHg. We assume monitoring is in the clinical, ambulatory or home and accurate across settings (Carretero and Oparil, 2000).

Mechanisms and Pathophysiology

Hypertension is known as the "silent killer" because it can be asymptomatic for many years and cause silent organ damage over time. This is derived from intertwined mechanisms including the role of central and peripheral nervous system, kidney, vascular function and impairment as well as hormone signaling principally through renin-angiotensin-aldosterone system (RAAS) inhibition, but also endothelin-1 signaling (Takahashi et al., 2011). Recurrent activation of these pathways drive vasoconstriction, fluid retention, and structural vascular remodeling increasing arterial resistance and blood pressure (Oparil et al., 2003).

Resistant Hypertension (RH)

Resistant hypertension become more interesting and scientist issued an important guideline about is in 2018 by the American Heart Association (AHA). RH is defined as blood pressure that remains raised above the normal patient's target pressure even after use of three or more antihypertensive agents from different classes and different mechanism of action containing administration of maximum therapeutic dose of a diuretic, plus taking angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and beta-blockers (Carey et al., 2018).

With all hypertension drugs, about 10% to 20% of hypertension patients are still resistant to these treatment, representing that high blood pressure of these patients unable to respond to the existing drugs and the medications cannot resolve and treat all the underlying pathological causes of their hypertension (Carey et al., 2019).

The progression of resistant hypertension is faster and more dangerous in comparing with the controlled hypertension, thus increase significantly the risk of damaging other organs as well as induce cardiovascular morbidity and mortality (Trial, 2014).

Recent studies showed that lifestyle interventions that decrease oxidative stress through dietary changes, exercise, and smoking cessation are recommended to maintain endothelial function. Statins are well-known for their cholesterol-lowering properties and have been used in hypertension via increased eNOS activity-induced NO production that counter acts vasoconstriction (Schiffrin and Fisher, 2024, Flack et al., 2024). Endothelin receptor antagonism, such as with aprocitentan represents a more specific targeting of the ET-1 pathway for resistant hypertension patients, whereby this class preferentially blocks the action of ET-1 in bringing about blood pressure reduction, even amongst those poorly responsive to conventional agents (Clozel, 2022).

3. ENDOTHELIAL SYSTEM FUNCTIONS IN CARDIOVASCULAR HEALTH

The endothelial system is the largest organ in human body which appears as a single layer of endothelial cells that line blood and lymphatic vessels, essential for proper cardiovascular health. These cells modulate vascular tone, regulate perfusion, and respond to biochemical stimuli in order to maintain a homeostatic vascular milieu. Endothelial dysfunction is one of the major drivers of hypertension (i.e., persistent high blood pressure), and an important mechanism for developing and resistant to it (Jankowich and Choudhary, 2020).

One of the endothelium's primary roles is regulating vascular tone through the release of vasoactive substances, notably nitric oxide (NO) and endothelin-1 (ET-1). NO, produced by endothelial nitric oxide synthase (eNOS), relaxes vascular smooth muscle, thereby inducing vasodilation, reducing blood pressure, and preventing platelet aggregation. Conversely, ET-1 is a potent vasoconstrictor, modulating blood flow and vascular resistance when released under specific stimulation. The balance of NO versus ET-1 is an essential pathophysiologic determinant for cardiovascular health and has a critical role in adaptation to physiological stressors (Boesen, 2015, Genovesi et al., 2022).

Interestingly, the pathogenesis in hypertension is augmented by endothelial dysfunction. Chronic excessive release of ET-1 and low supply of NO causes sustained vasoconstriction, vascular remodeling (increased myogenic tone), which leads to increased blood pressure. The synthesis and release of ET-1 is mostly performed by endothelial cells after stimulation with shear stress, hypoxia or pro-inflammatory cytokines (A Khalil, 2011).

Dual Endothelin Receptor Antagonists (ERAs) in Hypertension

Dual endothelin receptor antagonists (ERAs) are a new class of pharmacological agents with potential clinical benefit in the management of essential hypertension, especially among patients showing resistance to the conventional antihypertensive armamentarium. Dual ERAs focus specifically on the endothelin (ET) system, which is of great importance in the regulation of vascular tone and blood pressure due to the activity of its potent vasoconstrictor, endothelin-1 (ET-1) (Heidari Nejad et al., 2023, Boutari and Siskos, 2023).

Several peptides are included in the endothelin system, mainly ET-1, et-2 and et-3, that work through two receptors, ET_A and ET_B (endothelin) .The synthesis and release of ET-1 is mostly performed by endothelial cells after stimulation with shear stress, hypoxia or pro-inflammatory cytokine s (Russell and Molenaar, 2000). Of the two major theoretical pathways of angiotensin II, the ET_A receptors that mediate vasoconstriction and sodium retention are localized mainly to vascular smooth muscle cells which lead directly to an increase in blood

pressure. Endothelial ET_B receptors trigger vasodilation and clearance of ET-1 from the circulation (Iglarz and Clozel, 2007). It is important to note that the ET_B receptor can also mediate vasoconstriction and inflammation under pathological conditions, particularly in the kidney and lungs (Kuiper et al., 2008).

Aprocitentan's effectiveness in clinical trials highlights the importance of targeting the endothelin pathway to address underlying endothelial dysfunction in resistant hypertension (Clozel, 2022).

4. APROCITENTAN

Aprocitentan is a new drug approved on 2024 to manage hypertension. It belongs to group of medications that lower blood pressure by acting as dual endothelin receptor antagonist (ERA). Aprocitentan control hypertension by blocking both endothelin-A (ET-A) and endothelin-B (ET-B) receptors, so prevent the action of endothelin-1 (ET-1) that mange vasoconstriction and sodium balance (Dhillon, 2024). Key sites for the action of endothelin-1 (ET-1), a potent vasoconstrictor that plays a significant role in vascular tone regulation, sodium balance, and blood pressure management (Ji et al., 2023).

By blocking both receptor types, aprocitentan reduces the vasoconstrictive and inflammatory effects of ET-1 across the vascular system. This dual antagonism has been shown to lower blood pressure effectively by reducing peripheral resistance and vascular stiffness, mechanisms that are often heightened in patients with resistant hypertension (Varzideh et al., 2024). On addition, aprocitentan inhibits both receptor types and the ET_B extensive distribution ensures modulation in ET-1 levels in circulation, enhancing the therapeutic response. This balanced reduction of blood pressure is critical for keeping vascular tissue EEA1 homeostasis stable (Angeli et al., 2021).

Clinical Development of Aprocitentan

Pharmacokinetics

Aprocitentan has a high protein binding affinity and it eliminated by kidney and liver (Sidharta et al., 2019b). Aprocitentan administrated up to 600 mg as a single doses or 100 mg as multiple doses have been examined in healthy individuals subjects (Sidharta et al., 2019a). The pharmacokinetic studies have showed that aprocitentan half-life about 44 h, which make it suitable for once per day dosing (Sidharta and Dingemanse, 2020).

Preclinical Studies

In preclinical studies, aprocitentan was shown to significantly lower blood pressure and revert the changes that happen in vessels due to hypertension. In animal rats studies, aprocitentan had a greater reduction in blood pressure and the synergistic dual receptor

blockade improved oxidative stress and inflammatory markers related to endothelial dysfunction. Two models of hypertension rats include spontaneously hypertensive rats group and in the hypertension rat induced by administration of deoxycorticosterone acetate (DOCA)-salt showed excellent results regarding reduce blood pressure without any kidney damaged signs (Trensz et al., 2019). These preclinical results confirmed the hypothetical efficacy of aprocitentan in blood pressure control at different, potentially interacting mechanisms state in every particular patient with complicated hypertension characteristics.

Phase I Clinical Trials

Early Phase I trials of aprocitentan were performed to evaluate safety, tolerability and pharmacokinetics in healthy subjects. All doses of aprocitentan were generally well tolerated and only few AEs were reported. With optimal absorption and half-life properties fit for once-daily dosing, the pharmacokinetic profile promotes patient adherence. Due to these positive outcomes, aprocitentan can move forward into the latter stages of clinical trials (Sidharta and Dingemanse, 2020).

Phase II and III Clinical Trials

The clinical trials Phase II and III for aprocitentan were focused on hypertensive patients, specifically those who were resistant to hypertension. A potent oral dual endothelin receptor antagonist, aprocitentan decreased systolic and diastolic blood pressure compared with placebo in a 48-week Phase III study among patients with resistant hypertension published as an early view article in The Lancet. The study design for the trial included an initial randomized controlled phase followed by a long-term open-label phase which enabled data to be obtained on both immediate and long-term effects. These effects were associated with overall good safety profile (most common side effect mild to moderate edema) and reductions in blood pressure (Danaietash et al., 2022).

In the open-label extension period, aprocitentan consistently reduced blood pressure, suggesting that this dual receptor antagonism strategy could provide lasting cardiovascular advantages. This durability of blood pressure lowering is notable given that many resistants often fail to achieve stable control with conventional antihypertensive regimens (Danaietash et al., 2022).

Comparative Effectiveness of Aprocitentan

Aprocitentan comparative effectiveness was also assessed versus other antihypertensive therapies. Dual ERAs such as aprocitentan attained a more optimal blood pressure lowering effect in studies with patients who only partially responded to other drug classes, including ACE inhibitors, calcium channel blockers, and beta-blockers. In contrast to

these conventional antihypertensive agents, aprocitentan represents a novel mechanism of action with this particularly challenging patient population already on multiple standard therapies) Trensz et al., 2019, Phillips et al., 2024(.

Aprocitentan has showed higher endothelial function, which was clinically associated with decreased oxidative stress and markers of vascular inflammation. These benefits imply that aside from lowering the blood pressure aprocitentan can interfere with pathophysiological process involved in vascular health, thus decreasing risk of cardiovascular events in patients with resistant hypertension (Yao et al., 2023).

Safety Profile and Side Effects

The dual receptor blockade with aprocitentan has been linked to particular adverse effects, mainly fluid retention and mild–moderate peripheral edema due to inhibition of the ET_B receptor that influences renal sodium and water excretion (Phillips et al., 2024). In clinical trials, this risk of fluid retention was managed either by adjusting the dose or administering a diuretic (in some cases), as shown in. Fluid retention is a common side effect of dual ERA therapy; however, in the initial and long-term studies with aprocitentan, there was an overall favorable safety profile (Gueneau de Mussy et al., 2021).

Safety data is early but remains minimal, and longer-term safety assessments are still underway particularly to assess potential hepatic or renal effects from the drug-associated liver enzyme elevations that were reported with some ERA therapies. Still, data thus far suggest a reasonably safe and well-tolerated profile for aprocitentan, making it an option to at least consider in patients with otherwise resistant hypertension (Fontes et al., 2022).

5. CONCLUSION

Endothelin-receptor antagonism with dual receptor blockade is a novel mechanism for resistant hypertension, exemplified by Aprocitentan. Particularly in the case of patients with resistant hypertension where current therapies have failed, its mechanism, clinical benefit and effect on blood pressure control over time fill an unmet need in the management of hypertension. Further investigations on the long-term safety of and combination treatments with this medication will define its position in hypertension management and possibly broaden its application to other cardiovascular disorders.

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