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*Original Article*

# Review on: Aprocitentan Unveiled: A New Horizon in Anti-Hypertensive Therapy

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## ABSTRACT

Aprocitentan is an oral once-daily dual endothelin-1 receptor antagonist preventing ET-1 binding quite effectively to ETA and ETB receptors.It is a derivative of macitentan somewhat oddly used in treating pulmonary arterial hypertension with orphan drug status. Aprocitentan gets eliminated slowly in urine and faeces after being highly bound to proteins. Aprocitentan is tolerable at doses up to 600 milligrams and possesses a half-life (t1/2) of 44 hours with daily dosing. Dosages as low as 25 mg show significant ET receptor antagonism, with minimal differences in plasma exposure between genders and age groups. Preclinical and clinical research suggests that Aprocitentan effectively reduces blood pressure (BP), with noticeable decreases within 14 days of use. It also enhances the effects of other anti-hypertensive medications, such as renin-angiotensin system blockers. In individuals with resistant hypertension, Aprocitentan may improve cardiovascular outcomes by further lowering BP and providing broader cardiovascular protection. The findings support its potential as a new treatment option for resistant hypertension.

**Keywords:** Aprocitentan; Endothelin; Blood pressure; Treatment; Resistant Hypertension

## INTRODUCTION

Hypertension: The World Health Organization (WHO) defines hypertension (excessive blood stress), as a circumstance wherein the stress with inside the blood vessels is 140/90 mmHg or above.

**Table 1: Categories of hypertension.**

| Category | Systole | Diastole |
|---|---|---|
| Optimal | <120 | <80 |
| Normal | <130 | <85 |
| Level1 (Mild-hypertension) | 140-159 | 90-99 |
| Level2 (Moderate hypertension) | 160-179 | 100-109 |
| Level3 (Severe hypertension) | ≥ 180 | ≥ 110 |

Endothelin-1plays a role in the pathophysiology of hypertension and controls blood pressure (BP) and vascular tone. It is a strong vasoconstrictor peptide that induces endothelial dysfunction, fibrosis, hypertensive damage to the end organs (including vascular hypertrophy and remodelling), neurohormonal and sympathetic stimulation and enhanced aldosterone production and secretion. Studies using human and animal models have demonstrated that hypertension increases the expression of vascular ET-1[1-3].

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.


**Figure 1: Aprocitentan's chemical structure.**

A potent oral-active dual ET receptor antagonist, Aprocitentan (As Figure 1) blocks the binding of ET-1 with a ratio of inhibitory potency of 1:16 of both ETA/ETB receptors [5]. A 5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl) oxy] ethoxy} pyrimidin-4-yl replaces one of the amino groups of sulphonamides in this class member [6]. An orphan medication used to treat pulmonary arterial hypertension, Macitentan (derived by oxidative depropylation) has an active metabolite called Aprocitentan [7]. Aprocitentan lowers blood pressure in a dose-dependent manner & has been demonstrated to work in concert with RAS blockers. Therefore, when existing medications are insufficient to control high blood pressure, it may be a new treatment option. Our review's primary objectives were toprovide mechanism of action, contraindication, adverse effect, and drug interaction [4]. Resistant hypertension, as described through Judd and Calhoun (2014), is out of control blood stress regardless of triple therapy, that's created from renin-angiotensin device blockers at suitable dosages, wonderful compliance with medicine administration, and the shortage of secondary hypertension.It is also commonly linked to an increase in intravascular volume and an excess of aldosterone. At every stage, the most often prescribed therapies for hypertension are based on RAS blockage and the resulting salt depletion. It would beanticipated that a new antihypertensive medication with an innovative mode of action would further reduce BP [8]. When it is provided in patients with uncontrolled hypertension in conjunction with current therapies and as a result, ought to show further clinical advantages [30]. Aprocitentan, a dual $ET_A/ET_B$ antagonist, should be tested in conjunction with current treatments, especially RAS blockers, because it targets a distinct route. Use of the combination of RAS blockade plus a mineralocorticoid receptor antagonist (such as Spironolactone) is unlikely to be effective or safer compared to a combination of Aprocitentan with a RAS blocker. Since the occurrences of hyperkalemia and renal dysfunction are frequent unwanted side effects from pronounced pharmacologic inhibition of the renin-angiotensin-aldosterone axis, use of this regimen in conjunction with Aprocitentan could improve safety [9]. Endothelial cells predominately generate the 21-amino acid peptide known as endothelin-1. A number of triggers, such as a lack of oxygen shear stress, Angiotensin-II, hyperglycaemia and inflammatory cytokines, cause these endothelial cells to produce more of it [10–12]. It has exceptionally long-lasting effects and operates in a paracrine fashion, causing a potent vasoconstrictor effect [13–16]. Besides inducing endothelial dysfunction and cardiac and vascular remodelling, ET-1 is also involved in the kidney's regulation of water and sodium ET-1 expression in the endothelium is upregulated in patients with severe hypertension and it is involved in the pathophysiology of vascular hypertrophy and blood pressure increase. Diabetic, obese, chronic renal disease and salt-sensitive hypertensive patients also have increased ET system activity [13-19]. According to experimental models, ET receptor antagonists can prevent as well as reversibly alter tissue changes in an organ-specific manner which may prove beneficial in the long run [21]. Additionally, it has been suggested that these benefits might not be related to the therapy's effect on hemodynamic [20-21]. Therefore, what is missing is the exact impact of the ET system on volume-dependent hypertension along with other end-organ dysfunctions, or coexisting intra related conditions of hypertension. Of particular note is the application of ET-1 receptor antagonists as a novel pharmacological approach to treat resistant hypertension [19-21]. Moreover, some data suggest that

selective and mixed antagonists, regardless of ET receptor's limitations, which stem from a poor cumulative side effect profile of sodium retention causing increased total body sodium, enhance forearm vasodilation and lower blood pressure in hypertensive patients [22, 23].

## MECHANISM OF ACTION:

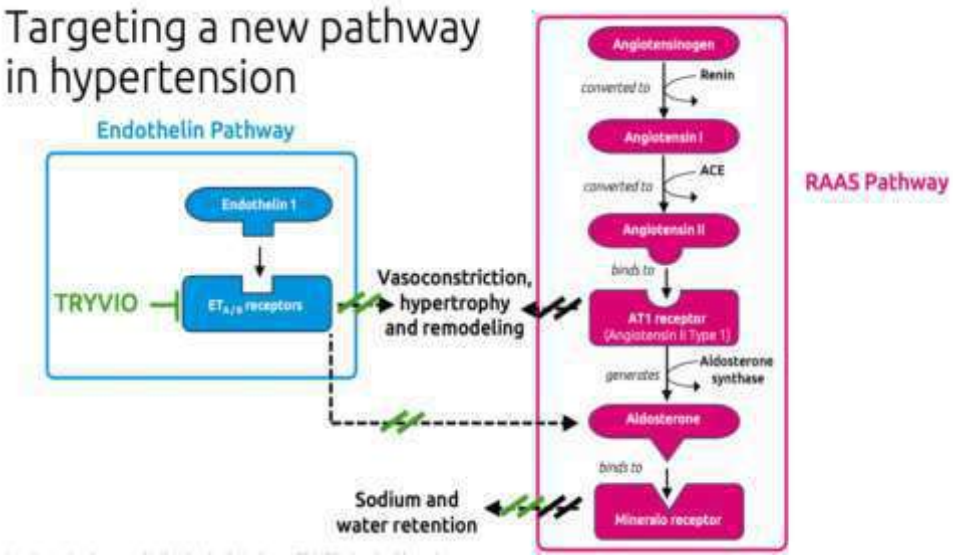


**Figure 2: MOA of Aprocitentan.**

The most common isoform of endothelin in the human body's circulatory system is endothelin-1 (ET-1). It is synthesized continuously by vascular endothelial cells to maintain vascular tone and exists in numerous other cells, including cardiomyocytes, fibroblasts, macrophages, neurons, vascular smooth muscle cells and kidney and lung epithelial cells [29]. By causing vasoconstriction or vasodilation, ET-1 exerts its action on two receptors, $ET_A$ and $ET_B$, present on vascular smooth muscle cells as well as endothelial cells. They regulate blood pressure. A potent vasoconstrictor, ET-1 primarily works through its action on the $ET_A$ receptor. Under pathological conditions, it also acts on $ET_B$-2 to induce vasoconstriction. Overexpression of both ET-1 and $ET_A$, $ET_B$ receptors has been demonstrated in numerous pathologies, such as essential hypertension, pulmonary arterial hypertension, chronic kidney disease and diabetes mellitus.

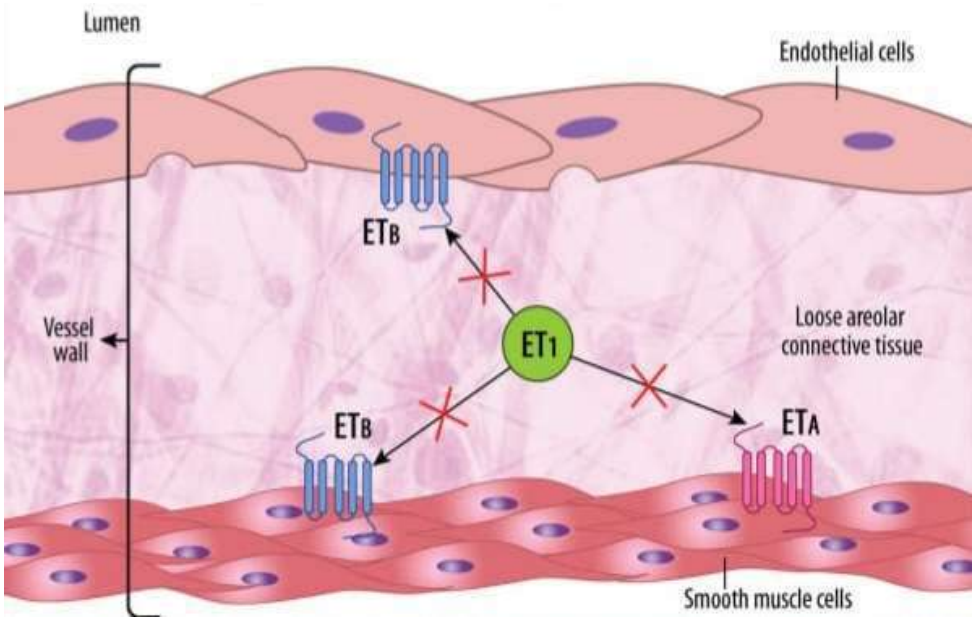


**Figure 3: Inhibiting binding of ET-1.**

Aprocitentan is a dual endothelin receptor antagonist (ERA) that specifically targets the endothelin-A ($ET_A$) and endothelin-B ($ET_B$) receptors. It was mainly created to treat resistant hypertension, particularly in people whose levels of control are inadequate while using traditional antihypertensive medication.

**1. Endothelin System Overview**

Endothelial cells create peptides called endothelins, which are essential for controlling blood pressure and vascular tone. With two G-protein coupled receptors (GPCRs), they exert their influence: Mostly found on smooth muscle cells, the endothelin-A ($ET_A$) receptor causes vasoconstriction and elevated blood pressure when it is activated. Endothelin-B ($ET_B$) receptor present on smooth muscle and endothelial cells. $ET_B$ receptors can cause vasoconstriction when they are activated on smooth muscle cells, but they can also cause the release of vasodilatory chemicals (such as prostacyclin and nitric oxide) when they are active on endothelial cells.

**2. Aprocitentan's Action on Endothelin Receptors**

Although it preferentially binds to $ET_A$ receptors, Aprocitentan is made to block both of these receptors ($ET_A$ and $ET_B$). This activity has the following effects on blood pressure regulation and vascular function.

**i. Blockade of $ET_A$ Receptor**

- **Vasoconstriction Reduction**: Vasoconstriction and elevated systemic vascular resistance (SVR) are the results of endothelin-1's (ET-1) typical binding to $ET_A$ receptors upon vascular smooth muscle. Aprocitentan decreases this vasoconstrictor action by inhibiting $ET_A$ receptors, which lowers blood pressure and causes vasodilation.

- **Reduction in Peripheral Resistance**: Because the main function of $ET_A$ receptors is vasoconstriction, blocking them lowers peripheral vascular resistance and this in turn lowers blood pressure.

**ii. Action on $ET_B$ Receptor**

Aprocitetan blocks both $ET_A$ and $ET_B$ receptors on smooth muscle cells, leading to endothelial vasodilation. Vasodilators like prostacyclin and nitric oxide (NO) tend to be released when ET-$_B$ receptors on endothelial cells are stimulated. Aprocitentan may reduce some of this advantageous vasodilatory action by blocking $ET_B$ receptors. This impact is regarded as secondary to the primary action on $ET_A$; however, it is less noticeable than the inhibition of $ET_A$ receptors.

**3. Effect on Blood Pressure**

By blocking both $ET_A$ and $ET_B$ receptors, Aprocitentan:

- **Reduces Systemic Vascular Resistance (SVR)**: $ET_A$ receptor antagonism reduces vasoconstriction, which in turn reduces SVR, a major factor in blood pressure.

- **May Improve Endothelial Function**: Although $ET_B$ blockage decreases vasodilation, over time enhanced endothelial function may result from the overall decrease in vasoconstriction, which may enhance blood flow and lower blood pressure.

**4. Therapeutic Implications**

Aprocitentan works particularly well for resistant hypertension, a condition in which repeated antihypertensive therapy is insufficient to manage high blood pressure. The special mechanism of action of Aprocitentan, dual receptor blockage, provides an extra strategy for controlling hypertension by targeting the role of the endothelin system in regulating blood pressure and vascular tone.

**Pharmacokinetics &Pharmacodynamics**

Aprocitentan is excreted in both urine and faeces and is strongly bound to plasma proteins [25]. Aprocitentan's safety, pharmacokinetics, cardio Pharmacodynamics, and tolerability at single and multiple doses have been studied in healthy male and female individuals up to 600 milligrams for single doses and 100 milligramonce daily for repeated doses [7]. All doses of Aprocitentan were generally well tolerated. With a half-life ($t_{1/2}$) of 44 hours, its pharmacokinetic profile fits a once-daily dosage schedule with plasma ET-1 concentrations rise noticeably with dosages of ≥ 25 milligrams. By day 8,

accumulation at steady state had tripled. Only small differences were found in the exposure of healthy males and females, healthy elderly and adult participants, fed and fasted situations and renal function.

**1. Absorption:**

Oral bioavailability of Aprocitentan is unknown. It takes four to five hours after administering 25 milligrams of Aprocitentan (double the recommended dosage) to reach $C_{max}$.

**2. Effect of Food:**

After giving healthy volunteers a high-fat, high-calorie, no clinically significant changes in Aprocitentan pharmacokinetics were noted.

**3. Distribution:**

About 20 L is the apparent volume of distribution of Aprocitentan. More than 99 percent of Aprocitentan is bonded to plasma proteins, mostly albumin. Hepatic or renal dysfunction has no effect on protein binding. The blood to plasma ratio of Aprocitentan is 0.63.

**4. Elimination:**

The apparent clearance of Aprocitentan is approximately 0.3 L/h, and its effective half-life ($t_{1/2}$) is approximately 44 hours.

**5. Metabolism:**

Aprocitentan is mainly metabolized by UGT1A1- and UGT2B7-catalyzed N-glucosidation and non-enzymatic hydrolysis.

**6. Excretion:**

About 52% of the dose of radio labelled Aprocitentan was removed through urine (0.2% intact) and 25% through faeces (6.8% unaffected) following a single administration.

**Drug Interactions:**

Aprocitentan has been evaluated for interactions with Midazolam, Rosuvastatin, and RAS blockers [26]. There have been no reports of serious drug-to-drug interactions. Trensz and colleagues took a closer look at how Aprocitentan affects blood pressure and kidney function in two different models of hypertension: one with low renin and the other with normal renin. They specifically investigated how Aprocitentan works in combination with RAS blockers like Valsartan and Enalapril, as well as with the mineralocorticoid receptor antagonist Spironolactone alongside the same RAS blockers. In both models, Aprocitentan teamed up effectively with the RAS blockers to lower blood pressure. In a study involving sodium-restricted hypertensive rats, the combination of Enalapril and Aprocitentan was found to further reduce blood pressure without harming the kidneys, which was a notable difference compared to Spironolactone [4]. In another part of the research, nineteen healthy male participants were given a single dose of 8 milligrams of Midazolam. After that, they started treatment with Aprocitentan, beginning with a loading dose of 150 milligrams followed by 50 milligrams daily. They also received an additional dose of Midazolam while on a steady regimen of Aprocitentan. The study looked at the pharmacokinetics and tolerability of Midazolam and its metabolite, 1-Hydroxy Midazolam, 24 hours after each dose [27]. Additionally, an open-label, single-sequence, single-centre study explored the interaction between Rosuvastatin and Aprocitentan. Twenty healthy male volunteers took a single dose of 10 milligrams of Rosuvastatin on days 1 and 13, with their pharmacokinetics and tolerability monitored for up to 120 hours. From days 5 to 17, they received 25 milligrams of Aprocitentan daily. Throughout the steady state, Aprocitentan did not impact the pharmacokinetics of Rosuvastatin, and the combination of the two drugs was well tolerated [26].

**Adverse Reactions:**

**1. Embryo-Foetal Toxicity:**

TRYVIO is contraindicated for usage in pregnant individuals and can harm the foetus when given during pregnancy, based on outcomes of animal reproduction experiments using endothelin receptor antagonists (ERAs). Prior to initiation of TRYVIO medication, exclude pregnancy and ensure proper contraception methods are employed. Advice patients who are capable of getting pregnant on the risk to a foetus. Before beginning TRYVIO treatment, during treatment as well as one month following the last dosage of TRYVIO, patients should use appropriate contraceptive methods to prevent pregnancy. They

should also check for pregnancy every month during medication & one month after stopping it. If pregnancy is found, stop taking TRYVIO.

**2. Tryvio Rems:**

Because embryo-foetal toxicity is possible, TRYVIO is available only through a limited program under REMS called the TRYVIO REMS.

Key requirements of the TRYVIO REMS are as follows:

- Prescribers must participate in and finish training in order to become certified through TRYVIO REMS.
- TRYVIO REMS certification is required for pharmacies that dispense TRYVIO.

**3. Hepatotoxicity:**

ERAs such as TRYVIO have been associated with elevated levels of aminotransferases and hepatotoxicity. Increases in the alanine transaminase or AST (aspartate aminotransferase) above 5-fold the upper limit of normal (ULN) have been seen in very few patients receiving Aprocitentan in the clinical trial, including patients who were positive for recalling. To limit the possibility of potential significant hepatotoxicity, monitor blood levels of aminotransferase and total bilirubin previous to therapy commencement and monitor during treatment occasionally and as clinically necessary.

**4. Fluid Retention:**

Peripheral edema& fluid retention are known side effects of ERAs, such as TRYVIO.

TRYVIO can cause edema and fluid retention in elderly patients with chronic renal disease.

There is no yet experience with TRYVIO in patients with heart failure (NYHA class III-IV), unstable cardiovascular condition, or NTproBNP ≥ 500 pg/ml. TRYVIO is not recommended in some conditions. Treat adequately and consider withdrawing TRYVIO if fluid accumulation occurs.

**5. Haemoglobin decrease:**

There have been drops in the hematocrit and haemoglobin concentration. It is not advised to start TRYVIO in people who have severe anaemia.

**6. Decreased Sperm Counts:**

Similar to other ERAs, TRYVIO may negatively impact spermatogenesis. Men should be advised about possible impacts on fertility.

## CONTRAINDICATIONS:

**1. Pregnancy:**

It is not recommended to use TRYVIO when pregnant. Patients who are capable of becoming pregnant should utilize an appropriate method of contraception before starting TRYVIO treatment, through treatment and for a month following treatment termination in order to avoid getting pregnant.

**2. Hypersensitivity:**

Patients with a history of Aprocitentan as well as any of its excipient hypersensitivity should not take TRYVIO.

## INDICATIONS:

Along with other antihypertensive medications, TRYVIO, an endothelin receptor antagonist, is prescribed to treat hypertension in adults whose blood pressure is not sufficiently regulated on additional substances. Bringing blood pressure down lowers thechanceof cardiovascular events, both deadly and non-lethal, generally strokes and fatal heart attacks.

## RESULT:

**Table 2: Drug Profile: Aprocitentan.**

| Feature | Description |
|---|---|
| Drug Name | Aprocitentan |
| Brand Name | Tryvio |
| Class | Endothelin Receptor Antagonist (ERA) |
| Mechanism of Action | Inhibits the binding of endothelin-1 to $ET_A$& $ET_B$ receptors, leading to vasodilation and reduced blood pressure. |

| | |
|---|---|
| Indication | Treatment of hypertension in adults whose blood pressure is not adequately controlled on other medications. |
| Administration | Oral |
| Approval Date | March 2024 (USA) |
| Manufacturer | Idorsia Pharmaceuticals |
| Common Side Effects | Headache, dizziness, fatigue, nausea, diarrhoea, and upper respiratory tract infection. |
| Adverse Effects | Liver injury, fluid retention, and low red blood cell count. |
| Contraindications | Pregnancy, severe hepatic impairment, and hypersensitivity to Aprocitentan or related compounds. |
| Pharmacokinetics | Aprocitentan is an oral drug for resistant hypertension with a peak concentration reached in 2-6 hours and a half-life of around 44 hours, enabling once-daily dosing. It is mainly metabolized in the liver by $CYP_3A_4$ and is excreted through bile. |
| Drug Interactions | May interact with strong $CYP_3A_4$ inhibitors and inducers, affecting its metabolism and efficacy. Monitoring Regular monitoring of liver function tests and blood pressure is recommended. |

**Clinical Studies:**

Aprocitentan was created to treat resistant hypertension and other disorders associated with malfunction of the endothelin system. Here is a quick rundown of the stages of its clinical trial.

**Phase 1:**

**Objective:** Examine the pharmacokinetics, Pharmacodynamics, safety, and tolerability of healthy volunteers.

**Findings:** Aprocitentan had dose dependent impacts on endothelin receptor blockage and was generally well tolerated. Mild stomach issues and headaches were among the most frequent adverse effects. Once-daily dose was supported by the pharmacokinetic characteristics.

**Phase 2:**

**Objective:** Assess safety and effectiveness in people with diseases such as hypertension.

**Findings:** In individuals who had resistant hypertension, Aprocitentan dramatically lowered blood pressure. For several weeks, the medication remained effective, indicating long-term blood pressure control. As is common with medications in this class, edema and moderate fluid retention were among the side effects.

**Phase 3:**

**Objective:** Verify long-term safety and effectiveness in a greater patient base.Patients having resistant hypertension was included in order to compare Aprocitentan to standard therapy and a placebo.

**Findings:** Over an extended period of time, Aprocitentan showed a clinically significant drop in blood pressure. Even among patients who responded poorly to other treatments, it demonstrated advantages. No unexpected safety issues surfaced, and side effects were in line with previous stages.

**Overall:**

With steady efficacy and a controllable safety profile across all trial stages, Aprocitentan has generally demonstrated promise as a therapy for resistant hypertension.

## CONCLUSION:

Aprocitentan is a promising dual endothelin receptor antagonist that effectively reduces blood pressure in patients with resistant hypertension by blocking both $ET_A$ and $ET_B$ receptors, which decreases vasoconstriction. Clinical studies demonstrate its efficacy, particularly in patients who do not respond to conventional therapies. The drugdose-dependent blood pressure-lowering effects provide flexible dosing options, though adverse effects such as fluid retention and edema may require monitoring and dose adjustments. While Aprocitentan has been generally well tolerated, potential liver enzyme elevations and drug interactions, especially with $CYP_3A_4$ inhibitors, call for caution and patient monitoring. Its

combination use with other anti-hypertensive may enhance blood pressure reduction but also increases hypotension risk. Overall, Aprocitentan stands out as a new and effective option for managing resistant hypertension, with additional research needed to explore its potential in pulmonary arterial hypertension (PAH) and other cardiovascular conditions

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