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Aprocitentan in the treatment of resistant arterial hypertension: promising possibilities of endothelin-oriented therapy. Review

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Resistant arterial hypertension (RAH) remains one of the most challenging clinical problems in modern cardiology, especially among patients with concomitant type 2 diabetes mellitus, obesity, and chronic kidney disease (CKD). Despite the use of standard combination treatment regimens, a significant proportion of patients fail to achieve target blood pressure (BP) levels, thereby elevating cardiovascular and nephrological risk. Excessive activation of the endothelin system, particularly endothelin-1, plays a crucial role in the pathogenesis of RAH by promoting vasoconstriction, sodium retention, vascular remodelling, and progression of target organ damage.

Aprocitentan, the first dual endothelin receptor (ETA and ETB) antagonist approved for the treatment of RAH, introduces new opportunities for targeted pathogenetic therapy. This article summarises current data on the mechanisms of action, pharmacological properties, clinical efficacy, and safety of aprocitentan based on findings from the multicenter PRECISION trial. Aprocitentan has been shown to provide a sustained and clinically significant reduction in BP, including in elderly patients and those with CKD, with an acceptable safety profile. Thus, aprocitentan is considered a promising alternative or adjunct to standard treatment strategies for RAH, with potential cardio- and nephroprotective properties, paving the way for personalised antihypertensive therapy. Further long-term real-world studies are warranted to confirm its impact on cardiovascular risk and renal disease progression. Incorporation of endothelin receptor antagonism into contemporary treatment algorithms may significantly enhance risk stratification and optimisation of therapy in patients with true resistant hypertension, particularly in high-risk multimorbid populations.

Keywords:
resistant arterial hypertension, endothelin-1, endothelin receptor antagonists, aprocitentan, dual ETA/ETB receptor blockade, chronic kidney disease, type 2 diabetes mellitus.

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Resistant arterial hypertension (RAH) remains one of the most complex and clinically significant issues in modern cardiology and internal medicine. Despite the availability of a broad spectrum of antihypertensive drugs and clearly defined therapeutic algorithms, a substantial proportion of patients fail to achieve target blood pressure (BP) levels even with combination therapy. According to epidemiological studies, the prevalence of true resistant hypertension among treated patients with hypertension is approximately 10—15 %, whereas in the population of patients with chronic kidney disease (CKD), this rate is two to three times higher [15, 24, 38].

Particularly unfavourable prognoses are observed in patients with a combination of RAH and metabolic comorbidities, notably type 2 diabetes mellitus (T2DM) and obesity [6, 23, 36, 37]. Such patients are characterised by pronounced insulin resistance, chronic low-grade inflammation, activation of neurohumoral systems, and progressive target organ damage. The presence of CKD further complicates the selection of antihypertensive therapy by limiting the use of mineralocorticoid receptor antagonists due to the risk

of hyperkalemia and a decline in glomerular filtration rate (GFR), thereby necessitating alternative therapeutic approaches [8, 17, 22].

Endothelial dysfunction plays a key role in the pathogenesis of RAH, accompanied by excessive production of vasoconstrictive and proliferative mediators. Among these, endothelin-1 is particularly important as one of the most potent endogenous vasoconstrictors. It contributes to increased peripheral vascular resistance, sodium retention, vascular wall remodelling, and the progression of cardio-renal damage [4, 25, 43]. Activation of the endothelin system is associated with more severe hypertension, reduced responsiveness to standard antihypertensive therapy, and increased risk of cardiovascular events [29, 34].

In this context, aprocitentan, a first-in-class dual endothelin receptor antagonist specifically approved for the treatment of RAH, has attracted considerable attention [9, 13]. Unlike selective antagonists, aprocitentan blocks both endothelin ETA and ETB receptors, providing a more comprehensive modulation of endothelin-mediated mechanisms of vasoconstriction and organ damage [21, 27, 32]. Clinical studies have demonstrated its ability to achieve sustained reductions in blood pressure in patients at high cardiovascular and renal risk, including those with CKD and T2DM.

Therefore, investigating the role of aprocitentan in the treatment of RAH is a relevant area of current research, offering new perspectives for personalised antihypertensive therapy in complex clinical patient populations.

Pathophysiological role of endothelin-1 in resistant hypertension

Endothelin-1 (ET-1) is one of the most potent endogenous vasoconstrictors. It exerts its effects via ETA and ETB receptors located on vascular smooth muscle cells, endothelium, cardiomyocytes, and renal tissue cells [20, 43]. Excessive activation of ETA receptors promotes vasoconstriction, sodium retention, myocardial hypertrophy, progression of nephropathy, and the development of resistance to standard antihypertensive therapy (Fig. 1) [42].

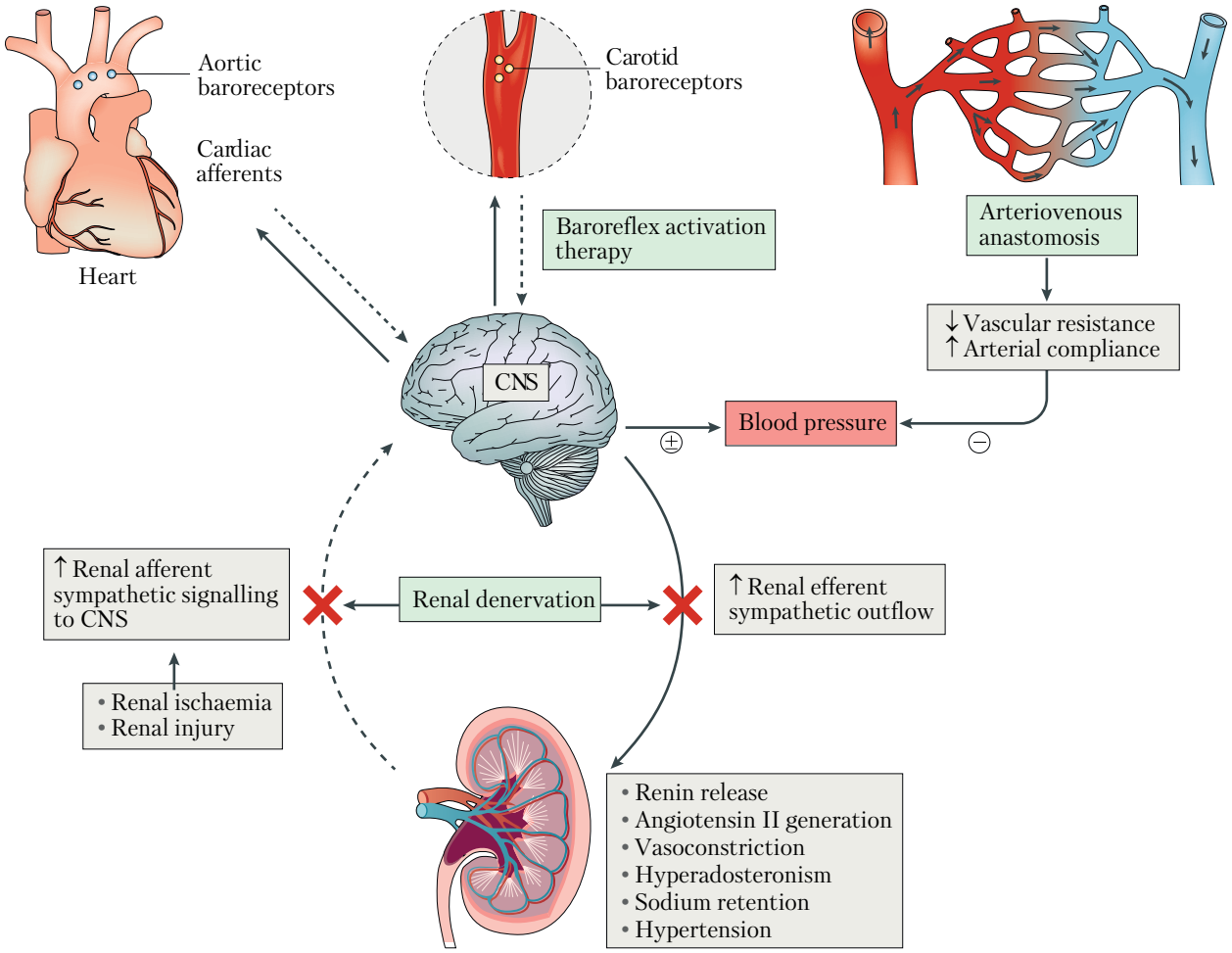


Figure 1. Pathophysiological mechanisms of blood pressure regulation in resistant hypertension: the role of the sympathetic nervous system, renal afferent and efferent pathways, and the central nervous system [22]

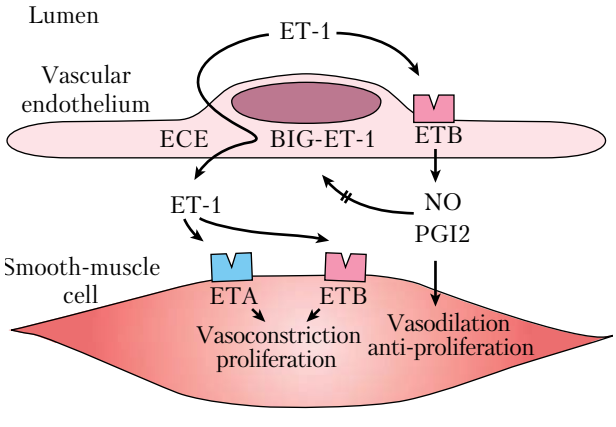
Dual blockade of ETA and ETB receptors not only reduces vasoconstriction but also partially preserves endothelium-dependent vasodilation, which is a key pharmacological advantage of aprocitentan over selective endothelin receptor antagonists [20, 27].

Pharmacological characteristics of aprocitentan

Aprocitentan is an active metabolite of macitentan and belongs to the class of dual endothelin receptor antagonists (ERAs), blocking both ETA and ETB receptors [14, 16, 44]. The drug was initially developed by Idorsia Pharmaceuticals and subsequently licensed to Janssen. In March 2024, aprocitentan received FDA approval in the United States for the treatment of arterial hypertension in adult patients with inadequate blood pressure control despite combination antihypertensive therapy [10]. The recommended dose is 12.5 mg once daily, with or without food, in combination with other antihypertensive agents. Contraindications include pregnancy and hypersensitivity. As of the date of this article, aprocitentan is not registered in Ukraine and is not available on the national pharmaceutical market [1].

The pharmacodynamic effects of aprocitentan are driven by dual blockade of ETA and ETB endothelin receptors. Endothelin-1, a potent vasoconstrictor, plays a central role in the pathogenesis of resistant hypertension by increasing systemic vascular resistance, promoting sodium and water retention, remodelling vascular walls, and contributing to target organ damage [5, 30, 31].

Blockade of ETA receptors reduces vasoconstriction and vascular smooth muscle cell proliferation, whereas modulation of ETB receptors affects both vascular and renal endothelin-mediated effects, including natriuresis and vascular tone. This dual mechanism provides more comprehensive inhibition of endothelin-mediated pathological processes than selective receptor antagonists [11] (Fig. 2).



ET-1 — endothelin-1; BIG-ET-1 — proendothelin-1; ECE — endothelin-converting enzyme; NO — nitric oxide; PGI2 — prostacyclin

Figure 2. Endothelin-1-dependent mechanisms of regulation of vascular tone and cell proliferation: the role of ETA- and ETB-receptors in vascular smooth muscle cells and endothelium and pharmacological targets of dual blockade of endothelin receptors [32]

Clinically, aprocitentan demonstrates a sustained, dose-dependent reduction in both systolic and diastolic BP, maintenance of antihypertensive effects with long-term use, and reversibility upon drug discontinuation. In addition, potential nephroprotective effects have been reported, including a reduction in albuminuria in patients with CKD, which is particularly important for individuals at high cardiorenal risk [28, 33].

Aprocitentan has favourable pharmacokinetic properties allowing once-daily dosing. It is well absorbed after oral administration, with peak plasma concentrations reached within several hours. Its bioavailability is not significantly affected by food intake.

The drug exhibits high plasma protein binding, ensuring a stable systemic effect. It is primarily metabolised in the liver into pharmacologically active metabolites, and its half-life is sufficiently long to maintain therapeutic levels over 24 hours [26, 45].

Aprocitentan is excreted via both bile and urine. Its pharmacokinetic profile remains relatively stable in patients with mild to moderate renal impairment, which is especially important given the high prevalence of CKD among patients with RAH. Clinical trial data indicate that routine dose adjustment is not necessary in elderly patients or those with moderately reduced GFR [19].

Clinical efficacy: the PRECISION study

The pivotal evidence supporting the clinical efficacy of aprocitentan comes from the multicenter, randomised, double-blind, Phase III PRECISION trial (NCT03541174) in patients with RAH. The study enrolled 730 adult patients with a systolic BP ≥ 140 mm Hg despite receiving at least three antihypertensive agents, including a renin-angiotensin system blocker, a calcium channel blocker, and a diuretic. More than half of the participants were taking four or more antihypertensive medications, confirming the severe and truly resistant nature of hypertension in the study population [35].

The study design included multiple sequential phases, allowing assessment of both short-term and long-term efficacy, as well as the durability of the antihypertensive effect following treatment discontinuation. The primary endpoint was the change in seated systolic BP, measured by automated office BP monitoring, after 4 weeks of treatment compared with baseline [7].

Results demonstrated that after only 4 weeks of therapy, aprocitentan at a 12.5 mg dose provided an additional reduction in office systolic BP of approximately 15 mm Hg, which was statistically significantly greater than placebo. A similar trend was observed for diastolic BP, with a clinically meaningful decrease. These findings indicate the rapid onset of antihypertensive action of aprocitentan, even in patients with longstanding and drug-resistant hypertension.

During the 32-week extension phase, the antihypertensive effect of aprocitentan was maintained without signs of tachyphylaxis or diminishing efficacy. Patients initially receiving placebo who were later switched to active treatment showed a gradual, sustained BP reduction, confirming the reproducibility and consistency of the effect. In the randomised withdrawal phase, BP increased in the placebo group but remained controlled in the aprocitentan group, providing strong evidence of a causal relationship between the drug and BP control.

Subgroup analysis revealed particularly pronounced antihypertensive effects in elderly patients (≥ 75 years) and in those with stage 3–4 CKD and macroalbuminuria

· groups traditionally associated with high cardiovascular and renal risk, as well as limited treatment options. These findings support the potential benefit of aprocitentan in complex clinical scenarios where efficacy and safety are paramount [39].

Safety and tolerability

The safety profile of aprocitentan was comprehensively evaluated in the multicenter PRECISION trial and demonstrated an acceptable benefit–to–risk ratio in patients with resistant hypertension and elevated cardiovascular and renal risk [35].

The most common adverse event was dose-dependent fluid retention, clinically manifesting as peripheral oedema. The incidence of this complication was approximately 9 % in the 12.5 mg group and exceeded 18 % with the 25 mg dose, significantly higher than in the placebo group. In most cases, the oedema was mild to moderate and was successfully managed by optimising diuretic therapy without requiring discontinuation of treatment.

It should be noted that fluid retention occurred more frequently in patients with pre-existing heart failure, CKD, and T2DM — populations inherently at higher risk of fluid-electrolyte imbalance. This underscores the importance of close clinical monitoring, particularly during the early stages of therapy, including assessment of body weight, peripheral oedema, and urine output [8].

A key advantage of aprocitentan is the absence of clinically significant hepatotoxicity, distinguishing it from earlier members of the endothelin receptor antagonist class. No notable elevations in liver transaminases or cases of drug-induced liver injury were observed, which is especially important in patients with comorbidities and polypharmacy.

Transient, moderate increases in natriuretic peptide levels (notably NT-proBNP and MR-proANP) were observed during early therapy, which later stabilised and returned to baseline after drug discontinuation. This suggests a compensatory response to changes in volume status rather than impaired myocardial function.

Serious adverse events, including hospitalisations for decompensated heart failure, were mainly observed in patients with a history of severe cardiovascular disease and were more common at higher doses. Consequently, the 25 mg dose was not approved for clinical use due to the increased risk of fluid retention without additional antihypertensive benefit. The 12.5 mg dose demonstrated an optimal balance of efficacy and safety.

Place of aprocitentan in current guidelines

According to the 2023 European Society of Hypertension (ESH) guidelines, the foundation of RAH management remains a stepwise intensification of therapy with mandatory use of combination regimens that include a renin-angiotensin system blocker, a calcium channel blocker, and a diuretic. If target BP is not achieved, mineralocorticoid receptor antagonists (MRAs), particularly spironolactone, are recommended as fourth-line agents [2].

However, clinical practice shows that a significant proportion of patients with RAH cannot tolerate therapeutic doses of spironolactone due to hyperkalemia, declining GFR, or hormone-related adverse effects such as gynecomastia and erectile dysfunction. These limitations are especially relevant for patients with CKD, T2DM, and the elderly, who represent the primary population with true resistant hypertension.

In this context, aprocitentan is viewed as a promising therapeutic alternative or adjunct to standard treatment regimens. Unlike MRAs, aprocitentan targets a distinct key pathogenic mechanism of RAH — the endothelin system — thereby enabling BP reduction independently of aldosterone-mediated pathways [36].

Aprocitentan may be particularly valuable in patients with stage 3–4 CKD, where spironolactone is limited or contraindicated. Clinical trial data indicate that, in this patient subgroup, aprocitentan not only provides a clinically meaningful BP reduction but also reduces albuminuria, positioning it as a potential component of a cardionephroprotective strategy.

Furthermore, aprocitentan may benefit elderly patients, who are more sensitive to the adverse effects of conventional antihypertensive drugs and are frequently subject to polypharmacy. Its pharmacokinetic profile and once–daily dosing support improved adherence and easier integration into complex treatment regimens.

Nephroprotective potential and combination therapy

An increasing body of experimental and clinical data supports the role of endothelin receptor antagonists not only in BP control but also in slowing the progression of CKD. Endothelin-1 is a key mediator of intrarenal vasoconstriction, glomerular hypertension, inflammation, and fibrosis. Its overactivation is associated with progressive albuminuria and a decline in GFR. Therefore, blockade of endothelin receptors represents a pathogenetically justified nephroprotective strategy [34].

Clinical trials with ERAs have demonstrated significant reductions in proteinuria in patients with CKD of various etiologies, including diabetic nephropathy. Decreased albuminuria carries independent prognostic value, as proteinuria is a well-established predictor of renal disease progression and cardiovascular complications. In this context, aprocitentan is particularly noteworthy, as studies in patients with RAH and CKD revealed more pronounced BP reductions in subgroups with macroalbuminuria and reduced GFR [40].

Dual ETA and ETB receptor blockade may reduce intraglomerular pressure, suppress inflammatory activity, and slow tubulointerstitial fibrosis. These effects extend beyond BP control and position aprocitentan as a promising component of comprehensive cardiorenal protection in patients with RAH, T2DM, and CKD.

An auspicious direction is combination therapy with sodium-glucose co-transporter 2 inhibitors (SGLT2i). These agents have been shown to reduce the risk of CKD progression, cardiovascular mortality, and heart failure hospitalisation, regardless of diabetes status. Their mechanisms include reducing intraglomerular hypertension, inducing natriuresis, exerting anti-inflammatory effects, and exerting metabolic effects.

Combining aprocitentan with SGLT2 inhibitors may yield synergistic benefits by targeting different but complementary pathways: endothelin-mediated vasoconstriction and proximal tubular sodium-glucose reabsorption. Moreover, SGLT2i may partially offset the risk of fluid retention associated with ERAs, improving the safety profile of such combination regimens [3, 18, 41].

Thus, available evidence supports the role of aprocitentan not only as an effective antihypertensive agent for RAH but also as a potential component of multifaceted cardiorenal protection. Further clinical studies of ERA and SGLT2i co-administration may expand treatment options for high-risk patients.

Conclusions

Resistant arterial hypertension remains one of the most challenging clinical problems, particularly in patients with comorbid T2DM, obesity, and CKD, where achieving target BP is often hindered by complex pathophysiology and limited tolerance to standard treatment regimens.

Dysregulation of the endothelin system plays a pivotal role in the development and maintenance of RAH, justifying the use of targeted therapy via endothelin receptor blockade.

Aprocitentan, as a dual ETA/ETB receptor antagonist, has demonstrated clinically significant and sustained BP reduction in patients with RAH, including those at high cardiorenal risk.

Current clinical data support aprocitentan's manageable safety profile and its consideration as an effective alternative or adjunct to mineralocorticoid receptor antagonists in patients with contraindications or intolerance to standard therapies, while its nephroprotective potential warrants further investigation.

Conflicts of interest: none.

Authorship contributions: conception and design, critical revision of the article — I.P.D., P.P.K., O.V.K.; acquisition of data, analysis and interpretation of data, drafting the article — I.P.D., O.I.P., O.M.D.

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Апроцитентан у лікуванні резистентної артеріальної гіпертензії: перспективні можливості ендотелін-орієнтованої терапії. Огляд

Резистентна артеріальна гіпертензія (РАГ) залишається однією з найскладніших клінічних проблем сучасної кардіології, особливо в пацієнтів із супутнім цукровим діабетом 2 типу, ожирінням і хронічною хворобою нирок. Незважаючи на застосування стандартних комбінованих схем лікування, значна частина хворих не досягає цільових рівнів артеріального тиску, що зумовлює високий серцево-судинний та нефрологічний ризик. Важливу роль у патогенезі РАГ відіграє надмірна активація ендотелінової системи, зокрема ендотеліну-1, який спричиняє вазоконстрикцію, затримку натрію, судинне ремоделювання та прогресування ураження органів-мішеней.

Апроцитентан — перший подвійний антагоніст рецепторів ендотеліну (ЕТА та ЕТВ), схвалений для лікування РАГ, демонструє нові можливості таргетної патогенетичної терапії. У статті узагальнено сучасні дані щодо механізмів дії апроцитентану, його фармакологічних властивостей, клінічної ефективності та безпечності на підставі результатів багатоцентрового дослідження PRECISION. Показано, що апроцитентан забезпечує стійке та клінічно значуще зниження артеріального тиску, зокрема в пацієнтів похилого віку та хворих із хронічною хворобою нирок, із прийнятним профілем переносності. Таким чином, апроцитентан розглядають як перспективну альтернативу або доповнення до стандартних схем лікування РАГ із потенційними кардіопротекторними та нефропротекторними властивостями, що відкриває нові можливості для персоналізованої антигіпертензивної терапії. Для підтвердження його впливу на серцево-судинний ризик та прогресування захворювань нирок необхідні подальші довгострокові дослідження в реальних умовах. Включення антагоністу рецепторів ендотеліну до сучасних алгоритмів лікування може значно покращити стратифікацію ризику та оптимізацію терапії у пацієнтів з істинно резистентною гіпертензією, особливо у популяціях з високим ризиком поліморбідних захворювань.

Ключові слова: резистентна артеріальна гіпертензія, ендотелін-1, антагоністи рецепторів ендотеліну, апроцитентан, подвійна блокада ЕТА/ЕТВ-рецепторів, хронічна хвороба нирок, цукровий діабет 2 типу.

ДЛЯ ЦИТУВАННЯ

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