CKJ REVIEW

New trials in resistant hypertension: mixed blessing stories

Carmine Zoccali [1], Francesca Mallamaci[2,3], Luca De Nicola [4] and Roberto Minutolo [4]

[1]Renal Research Institute, New York, NY, USA, [2]Unità Operativa di Nefrologia, Dialisi e Trapianto Renale, Grande Ospedale Metropolitano di Reggio Calabria, Reggio Calabria, Italy, [3]Institute of Clinical Physiology-Reggio Cal Unit, National Research Council of Italy, Reggio Calabria, Italy and [4]Division of Nephrology, Department of Scienze Mediche e Chirurgiche Avanzate, University of Campania "Luigi Vanvitelli", Naples, Italy

Correspondence to: Carmine Zoccali; E-mail: carmine.zoccali@icloud.com

ABSTRACT

Resistant hypertension (RH) is linked to an increased risk of cardiovascular and renal complications. Treatment options include non-pharmacological interventions, such as lifestyle modifications, and the use of specific antihypertensive drug combinations, including diuretics. Renal denervation is another option for treatment-resistant hypertension. New compounds targeting different pathways involved in RH—including inhibitors of aminopeptidase A, endothelin antagonists and selective aldosterone synthase inhibitors—have been tested in clinical trials in this condition. The centrally acting drug firibastat, targeting the brain renin–angiotensin system, failed to demonstrate significant effectiveness in reducing blood pressure (BP) in patients with difficult-to-treat and RH in the Firibistat in Resistant Hypertension (FRESH) trial. Aprocitentan, a dual endothelin A and B receptor antagonist, showed a moderate but statistically significant decrease in BP in patients with RH in the Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION) trial. However, concerns remain about potential adverse events, such as fluid retention. The use of baxdrostat, a selective aldosterone synthase inhibitor, showed promising results in reducing BP in patients with treatment-resistant hypertension in the Baxdrostat in Resistant Hypertension (BrigHTN) trial. However, a subsequent trial, HALO, failed to meet its primary endpoint. The unexpected results may be influenced by factors such as patient adherence and white-coat hypertension. Despite the disappointing results from HALO, the potential benefits of inhibiting aldosterone synthesis remain to be fully understood. In conclusion, managing RH remains challenging, and new compounds like firibastat, aprocitentan and baxdrostat have shown varied effectiveness. Further research is needed to improve our understanding and treatment of this condition.

Keywords: aprocicentan, baxdrostat, cardiovascular risk, firibistat, resistant hypertension

INTRODUCTION

In 2018, the American Heart Association defined resistant hypertension (RH) as a condition where blood pressure (BP) remains above the target range despite the use of three or more antihypertensive drugs, including a diuretic, at their maximum tolerated doses [1]. It should be noted that patients who achieve their BP goal while taking four or more antihypertensive
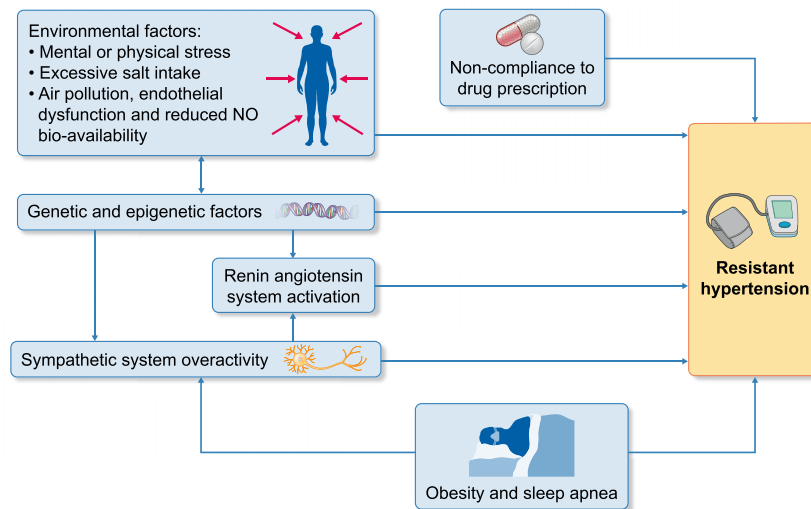
Figure 1: Mechanisms of RH (reviewed in ref. [5]) Resistant hypertension is a multifactorial problem. Noncompliance to drug prescription, environmental factors spanning from excessive salt intake and endothelial dysfunction secondary to various environmental factors, genetic and epigenetic factors, renin–angiotensin and sympathetic system activation and obesity and sleep apnoea all concur to determine RH. These factors (sleep apnoea, obesity, sympathetic overactivity and renin–angiotensin system activation) interact in determining RH.

medications are also considered to have controlled RH. The diagnosis of RH is often associated with secondary causes of hypertension, such as obstructive sleep apnoea, chronic kidney disease (CKD), renal artery stenosis and primary hyperaldosteronism. However, other endocrine diseases like pheochromocytoma, Cushing syndrome and hyperthyroidism less commonly contribute to RH [1]. To accurately diagnose RH, excluding the influence of illicit substances and medications that can raise BP (e.g. nonsteroidal anti-inflammatory drugs, corticosteroids, oral contraceptives) is mandatory [1].

The prevalence of RH varies depending on the population studied. A meta-analysis involving 3.2 million patients with essential hypertension from 91 studies conducted between 1991 and 2017 reported a prevalence of 10.3% [2]. The estimates were higher in the elderly (12.3%), CKD patients (22.9%) and renal transplant recipients (56.0%). The definition of RH is more closely related to the number of antihypertensive medications used rather than the presence of hypertension itself, as it can be diagnosed in uncontrolled and controlled BP. However, it is important to recognize that factors such as incorrect BP measurement, white-coat effect (elevated BP only in a clinical setting) and poor adherence to treatment can lead to misdiagnosis of RH. Therefore, accurate office BP measurement following standardized protocols and out-of-office monitoring are necessary to confirm the diagnosis. Non-adherence to medication is prevalent among hypertensive patients, affecting between 27% and 40% globally [3]. Factors such as the complexity of multiple drug regimens, pill burden, cost, adverse reactions and clinician inertia contribute to non-adherence, potentially impacting the diagnosis of RH. In the absence of information on medication dose, adherence or out-of-office BP readings (which can lead to pseudo-resistance), patients may be classified as having apparent RH (aRH). Data from the National Health and Nutrition Examination Survey showed that the prevalence of aRH increased from 16% to 28% from 1988 to 2008 [4]. The pathophysiology of RH, recently reviewed by Champaneria *et al.* [5], is summarized in Fig. 1.

RH is associated with an increased risk of adverse outcomes and represents a significant public health concern. Large retrospective studies involving hundreds of thousands of hypertensive patients have shown that RH is linked to a higher risk of ischemic heart disease, heart failure, stroke, end-stage kidney disease and all-cause mortality [6]. RH in CKD patients is of particular concern for its high prevalence and risk of death and adverse cardiovascular outcomes [7, 8].

When treating RH, it is important to exclude any identifiable secondary causes of hypertension and implement non-pharmacological interventions as the first step. These interventions may include exercise, weight loss and a healthy diet, emphasizing a low-sodium diet. Sodium restriction is crucial because volume expansion contributes to RH, and excessive salt intake can lead to resistance to antihypertensive therapy [1]. The choice of diuretic becomes important when non-pharmacological interventions alone are insufficient. Chlorthalidone and spironolactone are commonly recommended diuretic agents. The PATHWAY-2 study, which included patients with RH and normal kidney function, showed that spironolactone was the most effective add-on drug in reducing BP compared with other medications [9]. However, spironolactone can cause hyperkalemia, particularly in patients with CKD, limiting its long-term use even with the availability of new potassium binders. A recent secondary analysis of the chlorthalidone in chronic kidney disease (CLICK) study focused on CKD patients with RH and found that chlorthalidone had a rapid and sustained lowering effect on 24-h ambulatory BP and albuminuria compared with placebo. However, chlorthalidone was associated with a higher incidence of side effects such as hypokalemia, hyperglycemia, dizziness, orthostatic hypotension and hyperuricemia, and a reversible increase in serum creatinine [10]. Renal denervation (RDN) is a therapeutic option for RH included in the European Society of Cardiology/European Society of Hypertension guidelines [11]. The two best-studied platforms for RDN include radiofrequency RDN (rRDN) and ultrasound RDN (uRDN). rRDN is currently

performed with the Symplicity Spyral™ RDN system (Medtronic Inc.), emitting radiofrequency waves from four radiopaque electrodes on the Spyral™ catheter's helical-shaped tip. uRDN is performed with the Paradise Renal Denervation System (ReCor Medical), which contains a balloon at its distal tip surrounding an ultrasound-emitting core [12]. Other device-based approaches are baroreflex activation therapy and endovascular baroreflex amplification—which is a less invasive approach targeting the carotid sinus-, iliac artero-venous anastomosis created by a catheter-based device and stimulation of the median nerve, an intervention that mitigates sympathetic nervous system activity [13]. However, these approaches are at an early stage of development and should be regarded at an experimental stage. Some of these devices are being tested in ongoing clinical trials [13].

Treatment approaches to RH involve non-pharmacological interventions and the use of specific antihypertensive medications, such as diuretics like spironolactone or chlorthalidone. However, the choice of medication should consider potential side effects and individual patient characteristics, especially in the presence of CKD. Regular monitoring and treatment adjustment are necessary to manage RH and effectively reduce the risk of complications. Importantly, pharmacological research on the treatment of hypertension remains an unmet clinical need because a not trivial proportion of patients with treatment-resistant hypertension remain hypertensive while on treatment with combinations of three or more drugs, including a diuretic (about 10%–20%) and after renal denervation (about 50% of patients with true treatment-resistant hypertension, i.e. patients already on three or more drugs including a diuretic). Finally, the problem of higher adherence to therapy in the trial's placebo arm (the Hawthorn effect) should be carefully considered in trials testing new treatments in RH.

RECENT PHARMACOLOGICAL RESEARCH IN RH

After years of pharmacologic research silence on this high-risk condition, three recent trials tested new compounds targeting three critical pathophysiology pathways in treatment-resistant hypertension, namely firibistat [an inhibitor of aminopeptidase A (APA) that lowers the conversion of angiotensin II into angiotensin III in the brain, down-regulating vasopressin release and sympathetic nerve activity while increasing baroreflex], aprocitentan (an endothelin antagonist) and baxodrostat (a selective aldosterone synthase inhibitor).

The disappointing firibistat story

Firibastat is a centrally acting drug developed by Quantum Genomics to treat high BP and prevent cardiovascular disease risks. Unlike other antihypertensive treatments targeting the systemic renin–angiotensin–aldosterone system, this compound targets the brain renin–angiotensin system [14] (Fig. 2). Firibastat, a prodrug, is converted into two active (3S)-3-amino-4-sulfanyl-butane-1-sulfonic acid (EC33) molecules after crossing the blood–brain barrier. EC33 binds to the active site of APA. This enzyme hydrolyses the terminal aspartate residue of angiotensin II, leading to angiotensin III formation, which is *per se* a vasoconstrictor like angiotensin II. In the brain, angiotensin III is the primary ligand for angiotensin receptor type 1 and 2 because APA rapidly converts brain angiotensin II into angiotensin III. Therefore, reduced formation of angiotensin III secondary to APA inhibition results in BP reduc-

tion. Furthermore, under brain APA blockade, alternative pathways of angiotensin II metabolism may be activated, such as via angiotensin-converting enzyme 2 (ACE2). This enzyme gives rise to angiotensin VII, a vasodilatory peptide, while aminopeptidases and endopeptidases transform angiotensin II into inactive fragments. For these reasons, inhibition of the conversion of angiotensin II to angiotensin III results in a BP-lowering effect [14]. Preliminary phase 2 studies with firibastat showed that firibistat is safe and well-tolerated in hypertensive patients [15].
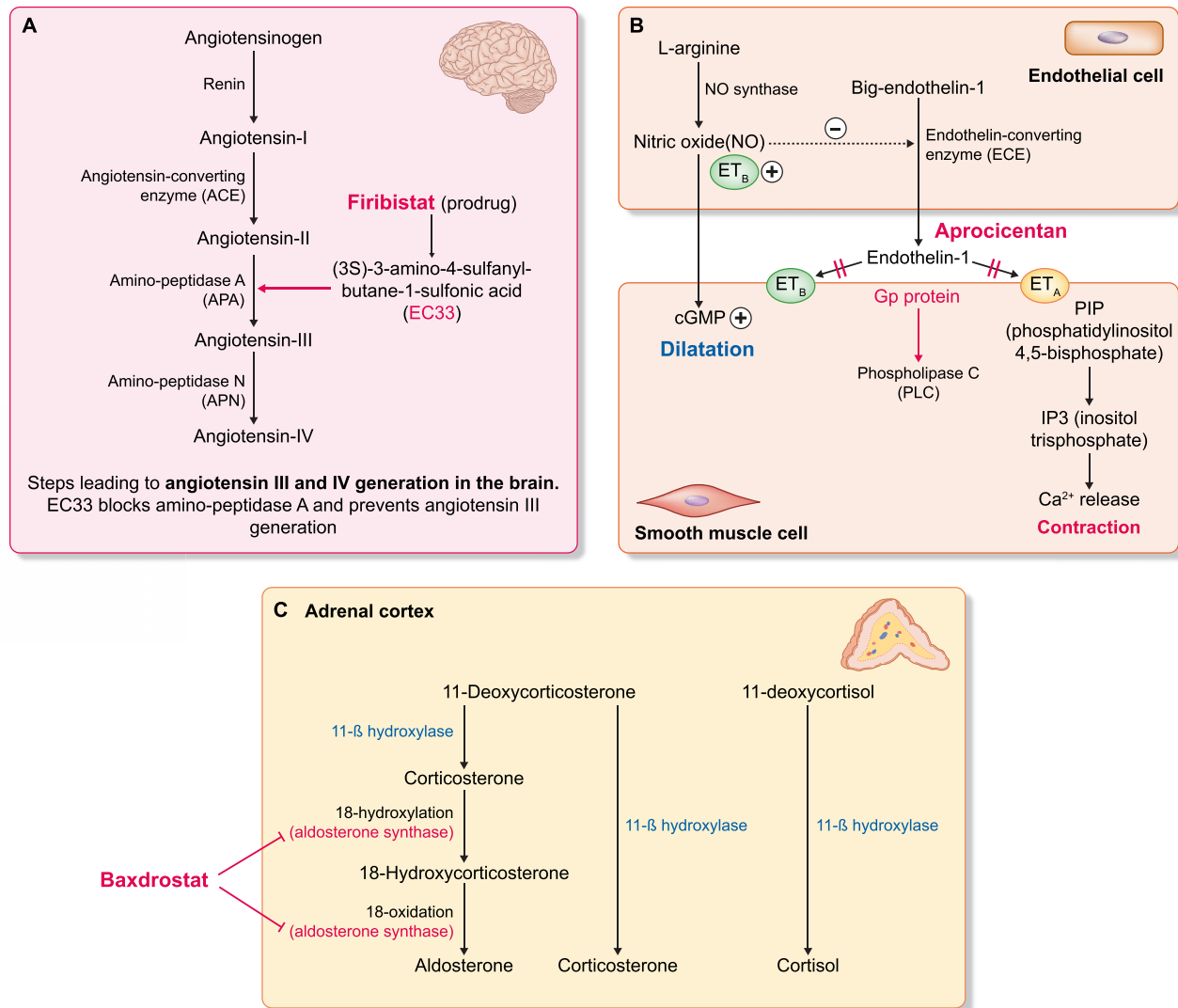
Based on these studies, an international phase 3 trial of firibastat, a first-in-class inhibitor of APA in the brain (Fig. 2A), the Firibistat in Resistant Hypertension (FRESH) trial, was performed. The results of this trial presented at the 2022 Congress of the American Heart Association failed to demonstrate a significant reduction in patients with difficult-to-treat and RH [16]. The lack of effect was consistent across all subgroups analysed and all secondary endpoints. The trial randomized 514 patients at 75 sites in 11 countries with unattended office systolic BP (SBP) of 140–180 mmHg despite treatment with at least two classes of antihypertensive agents (difficult-to-treat) or at least three classes, including a diuretic (resistant). Patients were randomized to firibastat 500 mg twice daily (255 patients) or placebo (259 patients) for 12 weeks and followed for an additional 4 weeks. The primary endpoint was the change in unattended office SBP from baseline to Week 12. The median age was 63 years, 58.4% were male, 81.2% were Caucasian and 13.6% Black patients, 73% had resistant hypertension with a mean SBP of 146.15 mmHg. At the end of Week 12, SBP in the firibastat arm had fallen by 7.82 mmHg compared with –7.85 mmHg for the placebo arm, a difference of 0.03 mmHg ($P = .98$) (Table 1). Secondary endpoints, including 24-h ambulatory BP monitoring (ABPM), daytime ABPM and nighttime ABPM, similarly failed to show significant differences between active and placebo groups.

There were no serious adverse events. Allergic skin reactions were seen in 5.1% of the firibastat arm but in just one patient in the placebo group (Table 1). Firibastat failed to show efficacy in this trial. Thus, FRESH is a disappointing trial, and Quantum Genomics announced that another larger trial testing the same drug, the Randomized Study of Extended Treatment With Firibastat in Treatment-Resistant Hypertension (REFRESH) trial, was prematurely interrupted and dropped.

Aprocicentan, a dual endothelin A and B inhibitor

Blocking the endothelin pathway could be a novel approach to reducing BP in individuals with RH. Initial studies with endothelin receptor antagonists like bosentan and darusentan have demonstrated a BP-lowering effect in patients with essential hypertension and RH, without causing reflex neurohormonal activation. However, while darusentan showed promising results as an add-on therapy for RH in an initial phase 3 study, these findings were not replicated in a subsequent study.

Aprocitentan, a once-daily orally active drug, acts as a dual endothelin A and B receptor antagonist (Fig. 2B). It has a half-life of 44 h and low potential for drug interactions. In a phase 2 dose-finding study involving hypertensive patients, aprocitentan demonstrated the most favourable profile when administered as monotherapy in the 10–25 mg range. It effectively lowered BP while maintaining low rates of fluid retention. Based on these findings, the doses of 12.5 mg and 25 mg were selected for further investigation to simplify the treatment approach. To further explore the short-term antihypertensive effect of aprocitentan and its sustainability in patients with RH, the Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant

A

Angiotensinogen

↓ Renin

Angiotensin-I

Angiotensin-converting
enzyme (ACE) ↓   **Firibistat** (prodrug)

Angiotensin-II   ↓

Amino-peptidase A ←── (3S)-3-amino-4-sulfanyl-
(APA)   butane-1-sulfonic acid
↓   (EC33)

Angiotensin-III

Amino-peptidase N
(APN) ↓

Angiotensin-IV

Steps leading to **angiotensin III and IV generation in the brain.**
EC33 blocks amino-peptidase A and prevents angiotensin III
generation

B   **Endothelial cell**

L-arginine   Big-endothelin-1

NO synthase ↓   ↓

Nitric oxide(NO)········(−)········ Endothelin-converting
enzyme (ECE)

ET_B (+)

                                              Aprocicentan

                    Endothelin-1

ET_B ←//──   ──//→ ET_A

cGMP (+)   Gp protein   PIP
                                        (phosphatidylinositol
Dilatation   4,5-bisphosphate)

                    Phospholipase C   ↓
                    (PLC)   IP3 (inositol
                                            trisphosphate)
                                                ↓
Smooth muscle cell Ca^{2+} release

                                          Contraction

C   Adrenal cortex

11-Deoxycorticosterone   11-deoxycortisol

11-ß hydroxylase ↓

Corticosterone

18-hydroxylation
(aldosterone synthase) ↓   11-ß hydroxylase ↓   11-ß hydroxylase ↓

18-Hydroxycorticosterone

Baxdrostat ──┤
18-oxidation
(aldosterone synthase) ↓

Aldosterone   Corticosterone   Cortisol

Figure 2: Mechanism of action of firibistat, aprocicentan and baxdrostat. (**A**) Firibistat is a pro-drug that generates two molecules of EC33, a compound that blocks APA in the brain and therefore reduces the generation of angiotensin III in the brain. Angiotensin III exerts central stimulatory effects on BP through several proposed mechanisms. Reduced angiotensin III generation safely mitigates hypertension in experimental models. (**B**) Aprocicentan blocks endothelin A and B (ETA and ETB) receptors in the smooth muscle cell. This effect, via the Gp protein, inhibits phospholipase C, the enzyme that catalyses the phosphatidylinositol 4,5-bisphosphate (PIP) transformation into inositol trisphosphate (IP3), a compound that releases intracellular calcium and causes muscle cell contraction. This leaves unopposed the vasodilatory effect of nitric oxide released by the endothelial cells via cGMP generation. (**C**) Aldosterone synthase catalyses the conversion of the precursor hormone, corticosterone, into aldosterone through a series of enzymatic reactions starting with 11-β hydroxylation (aldosterone synthase has a 93% structural homology with 11-β hydroxylase). This conversion involves the addition of a hydroxyl group at the 18th carbon atom and the subsequent oxidation of this carbon atom. Baxodrostat blocks aldosterone synthase but has a minimal influence on 11-β hydroxylase. Therefore the synthesis of corticosterone and cortisol is not altered by baxdrostat.

Hypertension (PRECISION) was conducted [17] (Table 1). This study supports the idea of targeting the endothelin pathway as a potential treatment strategy for RH.

Participants with uncontrolled SBP $\geq$140 mmHg despite three or more antihypertensive agents were switched from their current antihypertensive regimen to a triple fixed-dose combination of amlodipine, valsartan and hydrochlorothiazide for 4 weeks, then moved to a blinded placebo run-in for 4 weeks. Those with continuing hypertension were randomized to placebo or one of two doses of aprocitentan, 12.5 mg or 25 mg, daily for 4 weeks. Subsequently, all patients were moved to aprocitentan 25 mg for 32 weeks, followed by a 12-week double-blind aprocitentan 25 mg or placebo withdrawal

period. The trial population included 730 individuals with rHTN across 22 countries. At baseline, 69.2% were obese, 54.1% had diabetes, 22.2% had stage 3–4 CKD and 19.6% had congestive heart failure. At screening, 63.0% of randomized patients were on four or more antihypertensive agents. After 4 weeks of treatment, there was a clinically and statistically significant decline in in-office SBP from baseline for both the 12.5 mg and 25 mg dose of aprocitentan versus placebo ($P = .0042$ and $P = .0046$, respectively) (Fig. 3 and Table 1). Findings were confirmed by 24-h ambulatory SBP measurements. SBP reductions remained consistent during 32 weeks of single-blind use of aprocitentan 25 mg. A 12-week double-blind withdrawal phase of aprocitentan 25 mg versus placebo showed a significant increase in SBP

Table 1: Clinical trials.

| Trial	Target population	Drug and comparator (and number of patients)	Duration of the trial	Main endpoint	Results	Limitations/side effects
Firibistat in Resistant Hypertension (FRESH) phase 3 trial [16]	RH	Firibastat (500 mg twice daily, N = 255) vs placebo (N = 259)	12 weeks	Office SBP change	Firibistat –7.82 mmHg; placebo –7.85 mmHg	Skin allergic reactions; firibistat 5.1%; placebo 0.004%
Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION) [17]	RH	Placebo N = 244; aprocicentan 12.5 mg (N = 243) or 25 (N = 243) ×4 weeks → 25 mg ×32 weeks	36 weeks	Office SBP change	Aprocicentan –3.7 (SE 1.3) mmHg (97.5% CI –6.8 to –0.8, P = .0042) vs placebo both at the 12.5 mg and 25 mg doses	Mild–moderate fluid retention in the aprocicentan 25 mg arm leading seven patients to discontinue treatment
Baxdrostat in Resistant Hypertension (BrigHTN) phase 2 trial [18]	RH	Baxdrostat 0.5 mg (N = 69); baxdrostat 1 mg (N = 70); baxdrostat 2 mg (N = 67); placebo (N = 69)	12 weeks	Office SBP change	Baxdrostat 0.5 mg 12.1 mmHg; baxdrostat 1.0 mg, –17.5 mmHg; baxdrostat 2 mg, –20.3 mmHg; placebo, –9.4 mmHg	Hyperkaliemia in 2 patients on baxdrostat (it did not recur after stopping/restarting the drug)

SE, standard error.
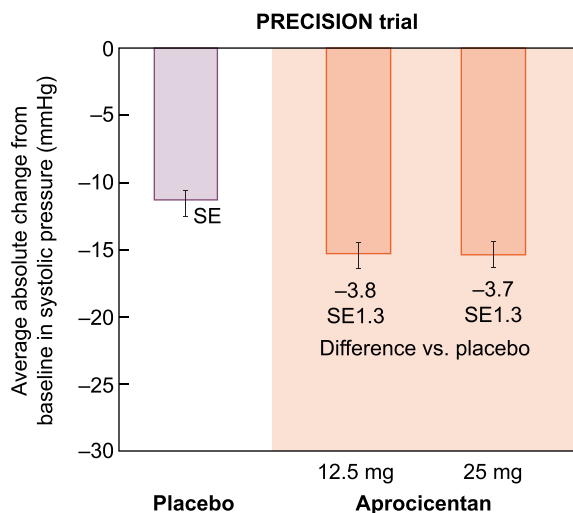
Figure 3: Average absolute change (and standard error of the mean) in SBP from baseline in the placebo, 12.5 and 25 mg aprocicentan arms of the PRECISION trial.

for the placebo arm but not the aprocitentan arm, P < .0001 for consistent SBP lower effect over 48 weeks. The most frequent adverse event was mild–moderate fluid retention in the aprocitentan 25 mg arm leading seven patients to discontinue treatment.

This study showed a statistically significant but moderate decrease in BP. The reduction in systolic pressure was only –3.7 (standard error 1.3) mmHg [97.5% confidence interval (CI) –6.8 to –0.8, P = .0042] both at the 12.5 mg and 25 mg aprocitentan doses compared with placebo after 4 weeks and ABPM confirmed the results. However, whether this decrease is clinically relevant is yet to be determined. While small changes in BP can significantly affect population health, it can be challenging to communicate the significance of a few millimetres of mercury difference to patients who have had experiences with seemingly ineffective treatments and hope for more substantial effects. Of note, the study also found a significant BP-lowering effect in the placebo group, indicating that there might be more to RH than just physiological and pharmacological factors. It suggests that psychological and contextual factors may also play a role in the treatment of RH. Furthermore, treatment with aprocitentan is not without risks. The most reported serious adverse event was fluid retention, affecting up to 18% of patients. This raises concerns, especially for patients with early stages of heart failure or subclinical kidney disease, as they may experience adverse events that could have life-threatening consequences. Close monitoring of patients is recommended until more data on the drug's safety are available.

Good news with baxdrostat but it is too early for a clear 'yes'

Countering aldosterone pharmacologically is complex with currently available drugs because aldosterone synthase inhibitors also inhibit cortisol synthesis, which can lead to adverse effects such as hyperkalemia and hypotension. The third trial [18] focused on the use of baxdrostat, a selective aldosterone synthase inhibitor, as a potential treatment for hypertension. Aldosterone synthase is an enzyme that controls the synthesis of aldosterone, a hormone that regulates BP by promoting sodium retention and potassium excretion in the kidneys. Inhibiting aldosterone synthase in a selective way is difficult because it shares 93% sequence similarity with another enzyme that catalyses cortisol synthesis (11-β hydroxylase) (Fig. 2C). In preclinical and phase 1 studies, baxdrostat demonstrated high selectivity for aldosterone synthase inhibition (100:1) compared with cortisol synthesis. It also reduced plasma aldosterone levels without affecting cortisol levels, a property lacking in other unselective mineralocorticoid receptor antagonists like spinolactone. Based on these promising results, the Baxdrostat in Resistant Hypertension (BrigHTN) trial, a multicentre, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial, was performed [18] (Table 1). The trial enrolled men and women who were 18 years of age or older, were receiving stable doses of at least three antihypertensive medications (one of which
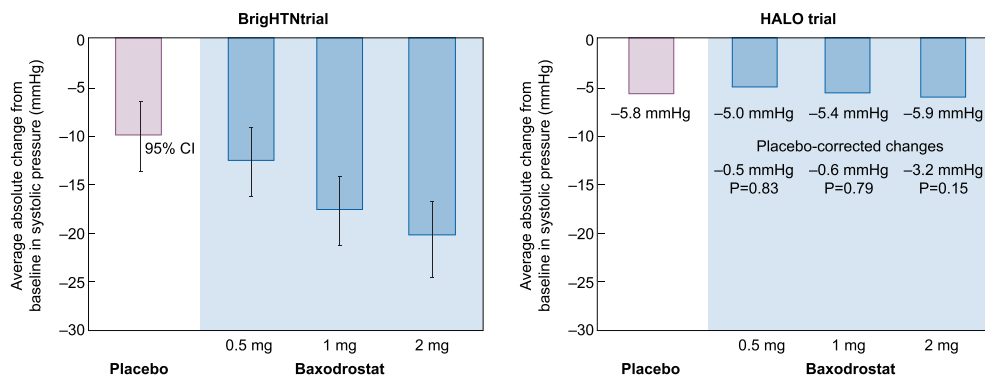
Figure 4: Left panel: average absolute change in SBP (and 95% CI) in the placebo, 0.5, 1 and 2 mg arms of the BrigHTN trial. Right panel: average absolute change in SBP and placebo corrected changes of the same variable in the placebo, 0.5, 1 and 2 mg arms of the HALO trial.

was a diuretic) and had a mean BP of at least 130/80 mmHg while seated. A total of 248 patients completed the trial. Changes in SBP with the 2 mg, 1 mg and 0.5 mg baxdrostat doses were –20.3, –17.5 and –12.1 mmHg, and –9.4 mmHg with the placebo. The difference in the change in SBP between the 2-mg baxdrostat group and the placebo group was –11.0 mmHg (95% CI –16.4 to –5.5; P < .001), and the difference was progressively smaller in the other two doses groups but still highly significant (Fig. 4). As expected, baxdrostat reduced serum and urine aldosterone levels by >50% with a reciprocal increase in plasma renin activity up to 3-fold without reducing serum cortisol levels. The drug was quite safe with no deaths and no serious adverse events, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level (≥6.0 mmol/L) occurred in only two patients, but these increases did not recur after stopping and restarting the drug. Due to these quite positive results, the independent data review committee halted the trial early due to overwhelming benefit in treatment-resistant hypertension.

Inhibition of aldosterone synthesis with baxdrostat may expand the possible choices of therapeutic agents for treatment-resistant hypertension. The benefits of inhibiting aldosterone synthesis may extend beyond treatment-resistant hypertension because elevated aldosterone levels have been implicated in the pathobiology of pulmonary hypertension, obesity, and insulin resistance and metabolic syndrome.

However, a subsequent trial of the same drug, the phase 2 HALO trial in patients with uncontrolled hypertension, which was presented on 8 March 2023 at the American College of Cardiology congress [19], failed to meet its primary endpoint. Patients receiving baxdrostat at the same doses tested in BrigHTN there were reductions in seated SBP ranging from 16.0 to 19.8 mmHg through 8 weeks; there were no significant differences compared with placebo-treated patients, who saw an average decline in BP of 16.6 mmHg. The results were unexpected because baxdrostat demonstrated significant placebo-corrected reductions in BP in the phase 2 BrigHTN trial. What happened in HALO is a reminder of the experience with the SYMPLICITY trial of renal denervation [2]. In HALO, there was indeed a Hawthorne effect such that the patients were more adherent to their background therapy than they normally were. Therefore, patients in the placebo group also experienced remarkably reduced SBP. Furthermore, there could have been some white-coat hypertension–dependent effect because this alteration was evident in some enrolled patients. To sort out this issue, a fully fledged phase 3 trial is needed, which is underway.

HALO enrolled a different group of patients with uncontrolled hypertension as compared with BrigHTN, i.e. mean seated SBP ≥140 mmHg, on a stable antihypertensive regimen consisting of: an ACE inhibitor or angiotensin-receptor blocker (ARB); an ACE inhibitor/ARB plus a thiazide diuretic; or an ACE inhibitor/ARB plus a calcium channel blocker.

After a run-in period lasting 2–4 weeks to assess adherence, 249 patients (mean age 60 years; 47% women) were randomized 1:1:1:1 to placebo or one of three doses of baxdrostat (0.5, 1 or 2 mg), on top of their background regimens. Most patients (73%) were white and 24% were Black; slightly more than half (53%) reported Hispanic ethnicity.

At baseline, mean seated SBP was 146–148 mmHg across groups, and mean seated diastolic BP was 82–84 mmHg. The proportion of patients who achieved a SBP of <130 mmHg at 8 weeks was 56.3% in the placebo group and 57.1%, 53.2% and 71.7% across the three baxdrostat dose groups; there were no significant differences compared with placebo. Like in BrigHTN, all three doses of baxdrostat were associated with a significant reduction in serum aldosterone compared with placebo. Plasma renin activity tended to increase with the two highest doses, but the difference achieved statistical significance only for the 1-mg dose. These changes in aldosterone excretion and in plasma renin were less than in the BrigHTN trial, suggesting worse adherence to the study drug in HALO. The problem of non-adherence in this trial was supported by the finding that 36% of patients in the 2 mg arm had plasma levels of baxdrostat at 8 weeks <0.2 ng/mL, a level <1% of that expected in full compliers. In a *post hoc* analysis focused on patients with baxdrostat plasma levels indicative of adherence, the 2-mg dose of baxdrostat was associated with a placebo-corrected decline in SBP or 7.9 mmHg (P < .01).

Despite the disappointing results from HALO, the effectiveness of baxdrostat seems much likely, an issue that will be definitively solved by the ongoing phase 3 trial.

The story of HALO is reminiscent of the SYMPLICITY HTN-3 [20] and other RH trials, where patients with uncontrolled BP become much more controlled in the placebo arm with conservative management, making it difficult to show a difference with active treatment.

In conclusion, managing RH is crucial to reducing cardiovascular and renal complications risk. While some new compounds targeting different pathways have shown promise in clinical trials, such as aprocitentan as a dual endothelin receptor antagonist, the results have been mixed. The centrally acting drug firibastat targeting the brain renin–angiotensin system did not

demonstrate significant effectiveness. Similarly, the selective aldosterone synthase inhibitor baxdrostat showed promise in one trial but failed to meet its primary endpoint in another. These findings highlight the complexity of treating RH and the need for further research and exploration of treatment options to manage this condition effectively.

PERSPECTIVES

Lifestyle modifications, improving adherence to drug therapy and the development of new anti-hypertensive drugs should be more vigorously pursued to reduce the burden of a multifactorial, high-risk condition like RH. New approaches to patient education using smartphone applications, telemonitoring and greater involvement of healthcare professionals to enhance patient adherence are being tested.

As for novel compounds that are of peculiar interest for RH treatment, a non-steroidal mineralocorticoid receptor antagonist, ocedurenone (KBP-5074), improved 24 h ambulatory BP with minimal risk of hyperkalemia in a phase 2b trial in patients with stage G3b–4 CKD already receiving background antihypertensive medication [21]. Baxdrostat apart, other aldosterone synthase inhibitors, like lorundrostat, are presently investigated (ClinicalTrials.gov NCT05769608). A recent phase 1 trial [22] tested zilebesiran, a small interfering RNA (siRNA) covalently linked to an N-acetylgalactosamine (GalNAc) ligand, that binds with high affinity to the hepatic asialoglycoprotein receptor. This siRNA lowers hepatic angiotensinogen messenger RNA levels leading to reduced production of angiotensinogen. Single doses of zilebesiran ($\geq$200 mg) decreased SBP ($>$10 mmHg) and diastolic BP ($>$5 mmHg) by Week 8 and these changes were sustained at 24 weeks.

Tailoring treatment strategies based on individual patient characteristics, such as genetic and molecular profiles, to optimize therapeutic outcomes is paramount in modern medicine. Given the public health implications of RH, precision medicine approaches need to be explored in this condition.

CONFLICT OF INTEREST STATEMENT

C.Z. is member of the *CKJ* Editorial Board.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

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