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REVIEW ARTICLE

Systematic Review Article: New Drug Strategies for Treating Resistant Hypertension—the Importance of a Mechanistic, Personalized Approach

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Abstract

Resistant hypertension (RHT) is characterized by persistently high blood pressure (BP) levels above the widely recommended therapeutic targets of less than 140/90 mmHg office BP, despite life-style measures and optimal medical therapies, including at least three antihypertensive drug classes at maximum tolerated dose (one should be a diuretic). This condition is strongly related to hypertension-mediated organ damage and, mostly, high risk of hospitalization due to hypertension emergencies or acute cardiovascular events. Hypertension guidelines proposed a triple combination therapy based on renin angiotensin system blocking agent, a thiazide or thiazide-like diuretic, and a dihydropyridinic calcium-channel blocker, to almost all patients with RHT, who should also receive either a beta-blocker or a mineralocorticoid receptor antagonist, or both, depending on concomitant conditions and contraindications. Several other drugs may be attempted, when elevated BP levels persist in these RHT patients, although their added efficacy in lowering BP levels on top of optimal medical therapy is uncertain. Also, renal denervation has demonstrated to be a valid therapeutic alternative in RHT patients. More recently, novel drug classes and molecules have been tested in phase 2 randomised controlled clinical trials in patients with RHT on top of optimal medical therapy with at least 2–3 antihypertensive drugs. These novel drugs, which are orally administered and are able to antagonize different pathophysiological pathways, are represented by non-steroid mineralocorticorticoid receptor antagonists, selective aldosterone synthase inhibitors, and dual endothelin receptor antagonists, all of which have proven to reduce seated office and 24-h ambulatory systolic/diastolic BP levels. The main findings of randomized clinical trials performed with these drugs as well as their potential indications for the clinical management of RHT patients are summarised in this systematic review article.

Keywords Resistant hypertension · Renin-angiotensin system · Aldosterone synthase inhibitors · Finerenone · Baxdrostat · Lorundrostat · Endothelin receptor antagonists · Aprocitentan

1 Introduction

Uncontrolled hypertension still represents today a major clinical challenge at world level, being largely responsible for most of the global burden of cardiovascular diseases. Clinical observational studies have demonstrated that among treated hypertensive outpatients only 30–35% achieved the recommended therapeutic blood pressure (BP) targets of less than 140/90 mmHg in office or less than 130/80 mmHg during 24-h ambulatory BP monitoring [1–5]. Several factors have been proposed for explaining the unsatisfactory rate of BP control. Among these, complex therapeutic regimen, preferred use of monotherapies or free combination therapies, poor adherence to prescribed antihypertensive medications, drug-related side effects and high rate of discontinuations

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represent the most frequent causes of uncontrolled hypertension in daily clinical practice [6, 7]. Besides, one has to consider the complexity of the pathophysiological background of hypertension, which is only partially covered by the currently available drug strategies.

In the effort of improving overall rates of BP control, international guidelines have promoted several recommendations for drug treatment of hypertension, beyond the adoption of healthy lifestyles and balanced low sodium diet [8–10]. In particular, the assumption of dual or triple combination therapies (preferably in fixed single-pill formulations) in patients with hypertension has been recognised as the key strategy to reduce BP levels and achieve the recommended therapeutic BP targets [11, 12]. Accordingly, the first-line antihypertensive therapy recommended by both 2017 AHA/ACC [9] and 2018 ESH/ESC [10] hypertension guidelines should be based on an agent blocking the renin-angiotensin-aldosterone system (RAS), including either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), along with a calcium-channel blocker (CCB) and a thiazide or thiazide-like diuretic at maximally tolerated doses. If dual antihypertensive therapy does not allow effective and sustained BP control, then triple combination therapies with these drug classes should be prescribed to achieve the recommended therapeutic BP goals. The same approach has been recently confirmed also by 2023 ESH hypertension guidelines [13].

If uncontrolled hypertension persists despite this therapeutic regimen, a condition of resistant hypertension (RHT) should be considered and the addition of a mineralocorticoid receptor antagonist (MRA), such as spironolactone or eplerenone, is advised. Alternatively, other classes of antihypertensive drugs may be considered, including loop diuretics, beta-blockers, or alpha-blockers, depending on the compelling indications and potential contra-indications [9, 10, 13]. These drugs have demonstrated to promote further systolic/diastolic BP reductions and achievement of office and 24-h ambulatory BP therapeutics targets in patients with difficult-to-treat or resistant hypertension [14, 15]. Also, renal denervation has demonstrated to be effective and safe in providing further BP reductions on top of medical therapies in patients with RHT [16–18].

In the recent years, novel antihypertensive drug classes have been developed and tested for reducing systolic/diastolic BP levels in patients with uncontrolled hypertension, on top of antihypertensive drug therapy with three or more BP lowering agents. These novel drugs, that can be orally administered, are represented by non-steroid mineralocorticorticoid receptor antagonists (MRA), selective aldosterone synthase inhibitors (ASI, and dual endothelin receptor antagonists (ERA), all of which have proven to reduce seated office and 24-h ambulatory systolic/diastolic BP levels. The aim of this systematic review is to discuss the currently available evidence suporting these novel drugs for the clinical management of uncontrolled hypertension and RHT, and their potential indications in the clinical practice.

2 Resistant vs Pseudo-Resistant Hypertension

Resistant hypertension is a condition defined by the failure of achieving the recommended therapeutic office BP targets of less than 140 mmHg for the systolic and/or less than 90 mmHg for the diastolic office BP, respectively, in the presence of at least three antihypertensive agents at maximum tolerated dosages (one of which should be a diuretic) [9, 10, 13]. Inadequate BP control should be documented also with out-of-office BP assessment by 24-h ambulatory (ABPM) or home (HBPM) measurements in patients whose adherence to prescribed antihypertensive therapy has been confirmed and any other potential causes of secondary forms of hypertension have been excluded [7, 19–21]. Thus, true RHT is a diagnosis of exclusion after pseudo-RHT has been excluded.

Several possible causes of pseudo-RHT should be ruled out, before confirming the diagnosis of true RHT. These include white-coat hypertension, inadequate office BP measurements, and poor adherence to prescribed medications. Furthermore, many other factors can contribute to apparent RHT, such as excessive alcohol consumption, high intake of sodium, vasopressor or other sodium-retaining substances, including some herbal remedies, abuse of illegal drugs (cocaine, anabolic steroids, etc), along with obesity, obstructive sleep apnoea syndrome, and psychological stress. Even after considering all these factors, prevalence of apparent treatment or pseudo RHT is relatively high in real world practice [22–25].

Reported prevalence of RHT largely varies in the scientific literature, largely depending on the adopted diagnostic criteria, the number of antihypertensive drugs, the methods of BP measurements and reference populations (e.g. general populations, hypertensive cohorts, treated uncontrolled hypertensive outpatients, ethnic groups). It is generally accepted that RHT has an average estimated prevalence of 5-10% among treated uncontrolled hypertensive adult outpatients [26].

In patients with true RHT, the recommended treatment strategy should include the prescription of appropriate and strict lifestyle measures, optimization of the antihypertensive therapies (triple fixed combination strategy should be preferred), and the addiction of mineralocorticoid receptor antagonists, mostly spironolactone [9, 10, 13]. Other drug classes of antihypertensive agents [14, 15] or renal denervation [16–18] may be also introduced to further reduce BP levels in these patients. More recently, novel molecules based on new or more selective mechanisms of interaction have been developed and investigated for their potential therapeutic use in hypertension. These new drugs have been tested in phase 2 randomised controlled clinical trials in patients with stage 2 hypertension or RHT on top of combination therapies with at least 3–4 antihypertensive drugs. The main pathophysiological mechanisms of these compounds and their interactions with key enzymatic steps involved in BP regulation are schematically illustrated in Fig. 1.

3 Materials and Methods

3.1 Literature Search, Eligibility Criteria and Study Selection

In adherence with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework for systematic review and meta-analysis reporting [27, 28], a systematic review was conducted. The review encompassed searches within the Medline, Cochrane, EMBASE, OVID, and PROSPERO databases, spanning the period from January 2000 to January 2024. The Systematic review was registered on the International prospective register of systematic reviews (CRD42023467540).

To effectively identify essential study concepts and facilitate the search procedure, we employed the Population, Interventions, Comparisons, Outcomes (PICO) framework in alignment with recommended practices [29]. The integration of the PICO framework within the field of health education is becoming increasingly essential, as it ensures comprehensive literature exploration and maintains relevance to the improvement of the health outcomes under investigation. Literature search strategy involved the utilization of Medical Subject Heading (MeSH) terms and free-text terms designed to refine the selection of relevant trials, specifically targeting the following items: “resistant hypertension”, and “aldosterone synthase inhibitors”, and “endothelin receptor antagonists”. As outcomes, we considered the “reduction of office (clinic) systolic/diastolic blood pressure” or “reduction of 24-h ambulatory systolic/diastolic blood pressure reduction”. Additionally, we conducted a review of the references cited in the articles identified during our search, to ensure the inclusion of comprehensive data.

For this study, stringent eligibility criteria were established to ensure the selection of relevant research material while maintaining scientific integrity. The study considered individuals of both sexes, aged 18 years or older, who had been diagnosed with resistant hypertension as eligible candidates for inclusion in the analysis. The primary focus of our analysis was centered on randomized clinical trials (RCTs) conducted specifically on patients undergoing optimal medical treatment for resistant hypertension. It is important to note that we specifically sought phase 2–3 RCTs, as these trials provide valuable insights on the effectiveness and tolerability of therapies when added to optimal medical treatment for resistant hypertension.

To ensure the precision and reliability of our research, certain types of articles were excluded. The excluded categories encompassed conference proceedings, abstracts, commentaries, reviews, observational studies, and case reports. The exclusion of these article types was imperative to ensure

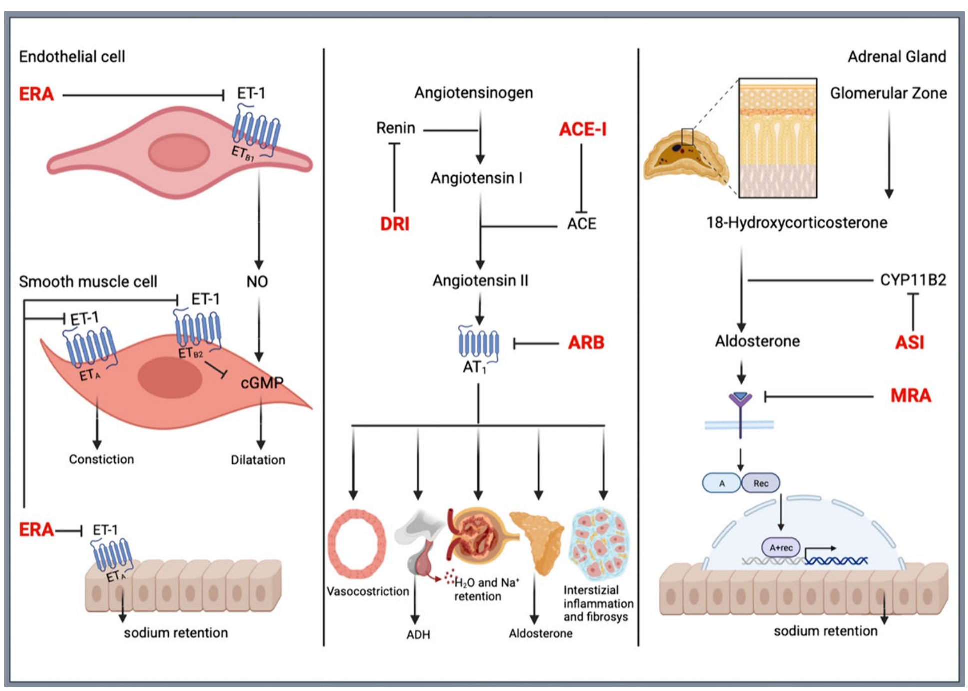

Fig. 1 Schematic representation of key molecular pathways involved in the pathogenesis of high blood pressure and sites of therapeutic interactions with different classes of antihypertensive agents. In figure: ERA, endothelin receptor antagonists; ET-1, endothelin-1; NO, nitric oxide; DRI, direct renin inhibitors; ACE, angiotensin-converting enzyme; ACE-I, ACE inhibitors; ARB, angiotensin receptor blockers; ASI, aldosterone synthase inhibitors; MRA, mineralocorticoid receptor antagonists. Created with BioRender.com (agreement number: QS26EZQUTU).

that the analysis primarily relied on phase 2–3 RCTs, thereby upholding the study's scientific rigor, reducing bias, and ensuring the originality of the research findings.

Specifically, a total of 138,234 records was initially identified. After the removal of duplicates and initial screening, 127,879 records were excluded, as our inclusion criteria were limited to RCT exclusively and substantial portion of the initially retrieved articles did not align with the predefined research goals. Furthermore, 4277 additional records were excluded, as selection criteria were limited to studies conducted between 2011 and 2024. Several of the initially included articles, despite being filtered for RCT, were found to be non-pertinent to the purposes of our study. This discrepancy occurred as a result of the items utilized in the PICO format, which led to the selection of numerous trials unrelated to our research focus. Ultimately, our comprehensive review incorporated only five full-text articles.

A summary of the literature selection and screening process is presented in Fig. 2, adhering to the PRISMA guidelines. The key characteristics of selected randomized controlled clinical trials have been concisely summarized in Table 1.

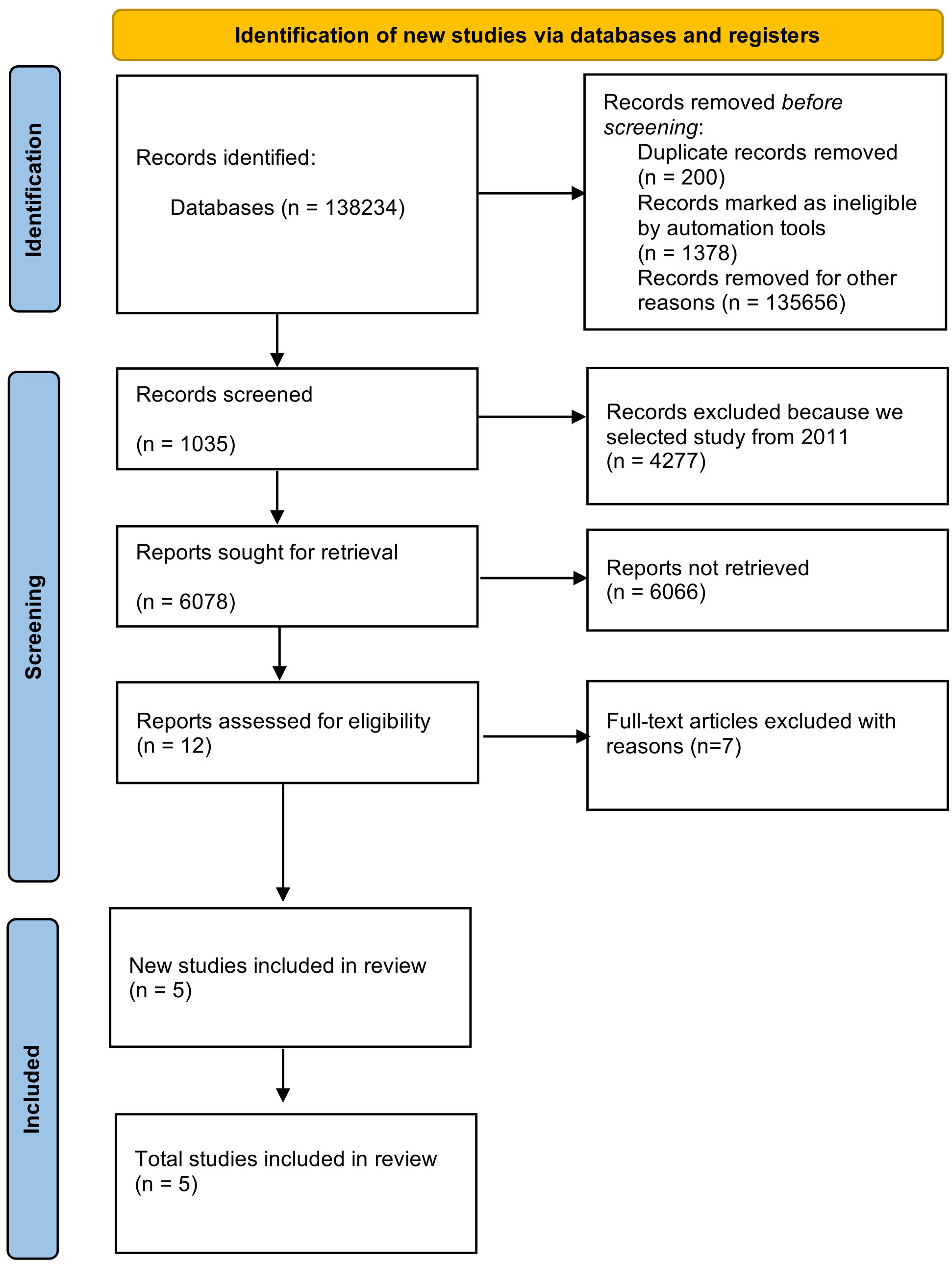

Fig. 2 PRISMA 2020 flow diagram for updated systematic reviews, which included searches of databases and registers only.

Table 1 General characteristic of the study included in the systematic review

Trial	Sample Size (num)	BP measurement	Treatment (mg/day)	Baseline Mean Seated Office SBP/DBP (mmHg)	Reduction in Mean Seated Office SBP/DBP (mmHg)	Baseline Mean 24-h SBP/DBP (mmHg)	Reduction in Mean 24-h SBP/DBP (mmHg)	Follow up
NCT00758524, 2011	N=**524**	Attended						8 weeks
	92		Osilo 0.25 mg OD	157.7/100.4	−9.7/−5.2	140.6/89.4	−7.2/−4.0	
	87		Osilo 0.5 mg OD	157.0/99.9	−8.7/−4.7	139.8/88.8	−4.9/−2.4	
	86		Osilo 1.0 mg OD	159.2/100.0	−12.6/−7.1	142.6/90.4	−7.7/−5.0	
	96		Osilo 0.5 mg BID	158.5/100.2	−9.7/−4.7	142.0/91.2	−6.2/−2.8	
	84		Epl 50 mg BID	158.2/100.4	−13.8/−7.9	143.1/90.8	−10.5/−6.0	
	77		PL	156.7/100.5	−2.6/−2.6	141.6/89.5	1.1/1.0	
NCT04519658, 2023 (BRIGHT-HTN)	N=275	Attended				NA	NA	12 weeks
	69		Baxdro 0,5 mg OD	147.6/87.6	−12.1/−8.6			
	69		Baxdro 1 mg ID	147.7/87.7	−17.5 /−11.8			
	67		Baxdro 2 mg OD	147.3/88.2	−20.3/−14.3			
	69		PL	148.9/88.2	−9.4/−9.2			
NCT05001945, 2023 (TARGET-HTN)	**Cohort 1** n=163	Attended				NA	NA	8 weeks
	30		Lorundro 100 mg OD	142.2/78.5	−11.9/−5.8			
	28		Lorundro 50 mg OD	140/84.7	−13.7/−7.1			
	30		Lorundro 25 mg BID	142.8/80.1	−11.1/−4.1			
	22		Lorundro 12.5 mg BID	142.6/81.6	−11.3/−5.5			
	23		Lorundro 12.5 mg OD	142.9/80.3	−5.6/−3.8			
	30		PL	142.9/83.8	−4.1/−1.6			
	Cohort 2 n=37				−11.4/−5.6			
	31		Lorundro 100 mg OD	139.8/78.6				
	6		PL	135.3/81.5				
NCT02603809, 2020	N=**490**	Unattended				NA	NA	8 weeks
	82		PL	149.0/97.9	−7.7/−4.9			
	82		Aprocit 5 mg OD	148.2/97.4	−10.3/−6.3			
	82		Aprocit 10 mg OD	150.5/97.8	−15/−9.9			
	82		Aprocit 25 mg OD	152.0/98.4	−18.5/−12			
	81		Aprocit 50 mg OD	149.3/98.4	−15.1/−10			
	81		Lisinopril 20 mg OD	149.7/96.8	−12.8/−8.4			

Table 1 (continued)

Trial	Sample Size (num)	BP measurement	Treatment (mg/day)	Baseline Mean Seated Office SBP/DBP (mmHg)	Reduction in Mean Seated Office SBP/DBP (mmHg)	Baseline Mean 24-h SBP/DBP (mmHg)	Reduction in Mean 24-h SBP/DBP (mmHg)	Follow up
NCT03541174, 2022	**Part 1** n=730	Unattended						4 weeks
PRECISION	243		Aprocit 12,5 mg OD	153.2/87.9	− 3.8/− 3.9	137.7//83.5	− 4.2/− 4.3	
	245		Aprocit 25 mg OD	153.3/87.7	− 3.7/− 4.5	137.6/82.5	− 5.9/− 5.8	
	242		PL	153.3/87.1	(placebo corrected)	137.1/82.5	(placebo corrected)	
	Part 3 n=614							12 weeks
	307		Aprocit 25 mg OD		(Aprocit corrected)		(Aprocit corrected)	
	307		PL		5.8/5.2		6.5/6.8	

3.2 Bias Risk Assessment and Quality of Evidence

When incorporating RCT into the analysis, it is essential to adopt the endorsed evaluation instrument, namely the updated iteration of the Cochrane tool, denoted as RoB 2 tool [30]. RoB 2 presents a structured framework for appraising the potential bias associated with a single outcome estimate derived from diverse types of randomized trials. RoB 2 is organized into distinct domains that encompass potential sources of bias impacting the outcome. The identification of these domains draws from a synthesis of empirical data and theoretical insights, enhancing its effectiveness as a bias assessment tool.

All the studies included in our analysis have consistently shown a low risk of bias, as indicated in Fig. 3 (online available), minimizing potential sources of systematic error or distortion in the results. A low risk of bias is a crucial aspect in ensuring the reliability and credibility of our findings, as it suggests that the data collected and analyzed in these studies are more likely to accurately represent the true relationships and effects under investigation. This strengthens the overall robustness and validity of our research.

3.2.1 Aldosterone Synthase Inhibitors (ASI)

Aldosterone is a key hormonal component of the renin-angiotensin-aldosterone system (RAAS). It is produced in the zona glomerulosa of the adrenal cortex and its production is enhanced by angiotensin II, high extracellular potassium concentration, and adreno- corticotropic hormone (ACTH). Aldosterone is involved in the regulation of fluid and electrolyte homeostasis via activation of the mineralocorticoid receptor, producing vasoconstriction of vascular smooth muscle and increased water and sodium retention by the kidneys at the distal tubule level. High levels of aldosterone can lead to hypokalemia, sodium reabsorption, and fluid retention, resulting in sustained BP elevation. The rate-limiting enzyme in the synthetic pathway from 18-hydroxycorticosterone to aldosterone is aldosterone synthase (also known as CYB11B2), as shown in Fig. 1.

According to guidelines, the preferred drugs for treating hyperaldosteronism and RHT are MRAs (spironolactone and eplerenone) [9, 10, 13]. More recently, ASI has been proposed as an alternative therapeutic strategy for reducing aldosterone production in the adrenal glands and aldosterone-related BP elevation [31, 32]. Some ASI agents have been developed and tested over the las few years. The results of clinic and 24-hour ambulatory BP reductions produced by these drugs at different dosages are summarised on Table 1.

A first agent in the ASI class was (LCI699, osilodrostat), which demonstrated to effectively correct hypokalemia in patients with primary aldosteronism in a proof-of-concept study [33] and to dose- dependently lower BP in patients with essential hypertension [34]. In this latter study, LCI699 was tested in a double-blind, randomized trial, performed in patients with primary hypertension [34]. After a 2-week of wash-out period and a 2-week single-blind placebo-controlled run-in period, eligible patients were randomly assigned to 1 of 6 treatment groups of double-blind treatment: LCI699 0.25 mg once daily, LCI699 0.5 mg once daily, LCI699 1.0 mg once daily, LCI699 0.5 mg twice daily, eplerenone 50 mg twice daily, or placebo for 8 weeks. Higher doses of LCI699 were not adopted, since preliminary studies indicated that these doses had the potential to inhibit 11--hydroxylase and to reduce cortisol synthesis [33]. The primary endpoint was changes in mean sitting diastolic BP compared to baseline values. Secondary endpoints included changes in mean sitting systolic BP and 24-h ambulatory systolic and diastolic BP changes from baseline.

From September 2008 to April 2009, 903 subjects were screened, 105 patients were excluded after the wash-out period, 274 during the single-blind period, 524 were randomly assigned to double-blind treatment, and 474 completed the 8-week double-blind period. At the end of the treatment period, LCI699 was associated with dose-dependent reductions in systolic BP levels of −9.7 mmHg, −8.7 mmHg, –12.6 mmHg, and –9.7 mmHg at the 0.25 mg, 0.5 mg, and 1.0 mg daily, and 0.5 mg twice daily, respectively, compared with placebo. However, eplerenone 50 mg twice per day produced lager and significant systolic BP reduction –13.8 mmHg) compared with placebo. With regard to the secondary endpoints, LCI699 1.0 mg daily (–7.1 mmHg; P=0.0012) and eplerenone 50 mg twice daily (–7.9 mmHg; P=0.0001) produced diastolic BP reductions compared with placebo (–2.6 mmHg); however, other doses of LCI699 did not provide significant changes in diastolic BP levels. Significant reductions in clinic systolic blood pressure were observed with all doses of LCI699 (P=0.005 or better) and eplerenone (P<0.0001). All doses of LCI699 significantly reduced systolic and diastolic 24-h ambulatory BP levels compared with placebo, though also in this case eplerenone 50 mg twice per day produced lager and significant systolic and diastolic 24-h ambulatory BP levels compared to placebo. Morning cortisol levels remained unchanged regardless of the dose of LCI699; however, ACTH stimulation of cortisol was suppressed in about 20% of patients receiving the higher doses.

In a subsequent randomized, double-blind, parallel-group, multicenter, dose-ranging study, the safety and efficacy of LCI699 was tested in RHT patients compared with either eplerenone or placebo [35]. After a 2-week single-blind placebo run-in, eligible patients were randomized (1:1:1:1:1) to receive placebo, eplerenone 50 mg twice daily or 1 of 3 doses of LCI699 (0.25 mg twice daily, 1 mg once daily, 0.5 mg then titrated to 1 mg twice daily after 4 weeks). All patients were treated for 8 weeks (any treatment discontinuation occurred) and a further follow-up safety visit was conducted 2 weeks after completing the study treatment. A total of 155 patients were randomized for the study and treated with study medication, and at the end of the treatment period, all LCI699 groups provided systolic and diastolic, clinic and 24-h ambulatory BP reductions, though none achieved statistical significance compared to placebo [35].

LY3045697 was the next ASI to be developed. This drug was tested in two small, placebo-controlled, crossover-designed clinical studies, which evaluated safety, pharmacodynamics, and pharmacokinetics under single and repeated dose conditions in otherwise healthy subjects, aged 18-65 years [36]. LY3045697 caused rapid dose and concentration-dependent reduction of SA levels, but it was not tested for BP lowering efficacy in humans [36].

Another drug in the ASI class is represented by CIN-107 (baxdrostat), which demonstrated high selectivity for the CYB11B2 enzyme inhibition, and lower affinity for 11b-hydroxylase compared to previous ASI agents, thus resulting in no relevant changes in plasma cortisol levels [37–39]. This drug was tested in preclinical and first-in-human clinical studies [40, 41] and more recently in phase 1, randomized, double-blind, multiple ascending dose study, which involved healthy volunteers [37]. This study aimed to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of baxdrostat at different dosages (0.25, 0.5, 1, 2 mg once daily) for 10 days in subjects with a normal- or low-salt diet [37]. The low-salt diet cohorts were included to stimulate aldosterone production. The study demonstrated that baxdrostat produces a dose-dependent decrease in SA levels compared to baseline and placebo, while having no meaningful impact on serum cortisol levels [37]. The clinical effectiveness and safety of this drug in hypertension has been tested in a subsequent trial.

The BrigHTN trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial, comparing the safety and efficacy of baxdrostat at different dosages with that of placebo [42]. The trial enrolled adult outpatients aged 18 years or more, with uncontrolled hypertension taking three or more antihypertensive drugs at maximally tolerated doses (one of which was a diuretic). Among these, about 45% were women, 70% were Caucasians, about half had obesity and 28% had diabetes. Baseline systolic/diastolic BP levels were 147/87 mmHg on average.

After a screening period of 8 weeks, and a subsequent 2-week, single-blind run-in period (during which medication adherence was assessed), eligible patients were randomly assigned to receive either 0.5 mg, 1 mg, or 2 mg of baxdrostat or placebo. The primary efficacy endpoint was the change in the mean seated systolic BP from baseline to the end of the 12-week treatment period in each baxdrostat group as compared with the placebo group. The secondary endpoints were the change from baseline in the mean seated diastolic BP and the percentage of patients with a seated BP of less than 130/80 mmHg at the end of the 12-week treatment period.

From July 2020 to June 2022 a total of 779 patients were screened, 360 entered in the run-in period and 275 patients were randomized. The main reasons for being excluded from the study were not reported. After the prespecified interim analysis, the trial was early stopped because the independent data monitoring committee concluded that the criteria for overwhelming efficacy were achieved. After 12 weeks of treatment, baxdrostat was associated with dose-dependent changes in systolic BP levels of −20.3 mmHg, −17.5±2.0 mmHg, and −12.1 mmHg at the 2-mg, 1-mg, and 0.5-mg doses, respectively. Compared to that observed in the placebo group (−9.4 mmHg), dosages of 2 mg daily (−11.0 mmHg; P<0.001) and 1 mg daily (−8.1 mmHg; P=0.003) induced significant systolic BP reductions, whereas the dose of 0.5 mg did not produce significantly different systolic BP changes. With regard to the secondary endpoint, baxdrostat 2 mg daily reduced diastolic BP by 14.3 mmHg, corresponding to −5.2 mmHg with that obtained in the placebo group.

Dose-dependent reductions in systolic BP levels were paralleled by reductions in serum aldosterone (SA) levels and compensatory increases in plasma renin activity (PRA), but not relevant effects on serum cortisol levels. Few adverse events were recorded (none serious).

Finally, lorundrostat is another agent in the ASI class to be tested in RHT patients. The Target-HTN trial was a multicenter, prospective, randomized, placebo-controlled, dose-ranging clinical trial, aimed at comparing the safety and efficacy of lorundrostat at different dosages with that of placebo [43]. The trial included adult outpatients aged 18 years or more, with uncontrolled hypertension taking two or more antihypertensive drugs at maximally tolerated doses. Among these, 60% were women, 36% were Afro-Americans and 48% were Hispanics; of note, about half had obesity, and 40% had diabetes. Baseline systolic/diastolic BP levels were 142/80 mmHg on average.

After 2–4 weeks of pre-screening and 2 weeks of placebo run-in period, eligible patients were stratified into two groups: cohort 1 enrolled participants with suppressed PRA ≤1.0 ng/mL/h and SA levels of 1.0 ng/dL, while cohort 2 enrolled participants with PRA greater than 1.0 ng/mL/h. Then, patients in cohort 1 were randomized to placebo or 1 of 5 dosages of lorundrostat (12.5 mg, 50 mg, or 100 mg once daily); in a subsequent group, patients were randomised to receive 12.5 mg or 25 mg of lorundrostat twice daily. Patients in the cohort 2 were randomized to receive placebo or 100 mg lorundrostat once daily. The primary efficacy end point was change in systolic attended office BP from baseline to the end of study week 8. Secondary efficacy endpoints included changes in diastolic attended office BP, and changes in 24-h ambulatory BP levels.

From July 2021 to June 2022, a total of 380 patients were screened and 200 were randomized (n=163 in cohort 1 and n=37 in cohort 2). The main reasons for being excluded from the study were inadequate PRA assessment. After 8 weeks of treatment in cohort 1, office systolic BP levels were reduced by 11.9, 13.7, and 5.6 mmHg with 100 mg, 50 mg, and 12.5 mg once daily of lorundrostat, respectively, and by 11.1 and 11.3 mmHg with 50 mg or 12.5 mg of lorundrostat twice daily, respectively. The corresponding differences from placebo in systolic BP change were –7.8, –9.6, –5.6 mmHg for once daily dosages and –7.0 and –7.2 mmHg for twice daily dosages. In cohort 2, lorudonstrat 100 mg reduced office systolic BP levels by 11.4 mmHg compared to placebo. With regard of secondary endpoint, lorundrostat 50-mg once-daily dose reduce diastolic attended office diastolic BP levels by 5.5mm Hg compared with placebo (P=0.02), whilst other doses did not provide statistically significant diastolic BP reductions compared with placebo. Also in this trial, few adverse events were recorded (none serious), mostly related to changes in serum potassium levels from baseline.

3.2.2 Endothelin A/Endothelin B Receptor Antagonists

Endothelin-1 (ET-1) is a vasoconstrictor peptide, produced in many different tissues, particularly in the endothelium of blood vessels. Endothelin-1 may act in a paracrine or autocrine way on blood vessels, by interacting with either ETA or ETB receptors on smooth muscle to stimulate contraction or on ETB receptors on endothelial cells to induce the release of vasorelaxants (nitric oxide and prostacyclin), thus contributing to regulate BP homeostasis [44]. Endothelin-1 production is increased in the presence of endothelial dysfunction and hypertension, and ERA has recently emerged as a novel target for high BP management and control. Indeed, preclinical studies demonstrated the efficacy of ERA in lowering BP [45], particularly in low-renin condition [46]. In these experimental models of hypertension, dual blockade of ETA/ETB receptors appeared to have a lower risk of fluid retention and vascular leakage than ETA-selective blockade. Aprocitentan is a potent, orally active, dual endothelin A/endothelin B (ETA/ETB) receptor antagonist, with long half-life (44 h).

The clinical effectiveness and safety of aprocitentan in hypertension has been tested in one dose-finding study [47] and in one phase 3 trial [48], both showing positive results in terms of systolic/diastolic BP reduction with good tolerability and safety profile [49]. It should be noted, however, that both these studies adopted unattended office systolic/diastolic BP measurements for efficacy and safety assessments; this may at least, in part, contribute to explain the high rate of screening failure reported in both studies [47, 48]. The results of clinic and 24-hour ambulatory BP reductions produced by this drug at different dosages are also reported on Table 1.

In a randomized, double-blind, multicenter, the efficacy and safety of aprocitentanat different dosages of 5, 10, 25, and 50 mg once-daily were evaluated in patients with grade 1–2 essential hypertension compared to that of either placebo or lisinopril 20 mg once daily [47]. After initial screening, patients entered in a single-blind, placebo run-in period for 4–6-weeks, then eligible patients were randomized to receive either placebo, or aprocitentan, or lisinopril at predefined doses. After 8 weeks of double-blind treatment, all patients entered a 2-week single-blind, placebo withdrawal period. Among 1,659 initially screened patients, 996 were enrolled in the placebo-run-in period, 490 were randomized and 430 patients completed the 8-week treatment period. At the end of the treatment period, significant dose-response changes in mean seated diastolic BP from baseline to week 8 were observed (P<0.001 for all 6 prespecified dose-response models) [47]. In those patients with valid ABPM at baseline and at week 8 (n=281), 10, 25, and 50 mg aprocitentan produced significant reductions in mean 24-hour systolic/diastolic BP levels from baseline by 3.99/4.04, 4.83/5.89, and 3.67/4.45 mmHg, respectively [47].

In the subsequent multicentre, double-blinded, randomised, parallel-group, phase 3 trial, the PRECISION trial [48], included adult outpatients with RHT, as defined by seated systolic BP of 140 mmHg or higher despite taking standardised background therapy with three antihypertensive drugs, including a diuretic. The study consisted of three sequential parts: (a) part 1 was a 4-week double-blind, randomised, and placebo-controlled period, during which patients received aprocitentan 12.5-25 mg, or placebo in a 1:1:1 ratio; (b) part 2 was a 32-week single-blind period, during which all patients received aprocitentan 25 mg; (c) part 3 was a 12-week double-blind, randomised, and placebo-controlled withdrawal period, during which patients were again randomised to either aprocitentan 25 mg or placebo in a 1:1 ratio; (d) part 4 was a 30-day safety follow-up period, during which all patients continued standardised background therapy. The primary endpoints were defined as changes from baseline to week 4 (part 1), and from withdrawal baseline (week 36) to week 40 (part 3), in mean sitting office systolic BP levels. Secondary endpoints included changes at week 4 and week 40 in mean sitting office diastolic BP and in 24-h ambulatory systolic and diastolic BP levels.

Overall, 1965 individuals were screened, 730 were randomised, 704 (96%) completed part 1; of these, 613 (87%) completed part 2 and, of these 577 (94%) completed part 3 of the study. In part 1, at 4 weeks, office systolic BP levels were reduced by –15,3 mmHg for aprocitentan 12,5 mg, –15,2 mmHg for aprocitentan 25 mg, and –11,5 mmHg for placebo; placebo-mediated differences were –3,8 mmHg (p=0·0042) and –3,7 mmHg (p=0·0046), respectively. Office diastolic BP levels also decreased with both aprocitentan doses compared with placebo (–3·9 and –4·5 mm Hg, respectively). During part 2, both systolic and diastolic office BP levels were maintained in patients previously receiving aprocitentan and decreased within the first 2 weeks of part 2 before stabilising in those previously receiving placebo. In part 3, after 4 weeks of withdrawal from the study drug, office systolic (5.8 mmHg, p<0·0001) and diastolic (5.2 mmHg, p<0·0001) BP significantly increased with placebo compared with aprocitentan.

Similar trends were observed in those patients who had valid 24-h ABPM. At the end of part 1 (week 4), aprocitentan decreased both the 24-h ambulatory systolic (–4.2 mmHg for the 12·5 mg dose and –5.9 mmHg for the 25 mg dose) and diastolic (–4.3 mmHg for the 12.5 mg dose and –5·8 mmHg, for the 25 mg dose) BP levels. At the end of part 3, after 4 weeks of withdrawal (week 40), both the 24-h ambulatory systolic and diastolic BP increased with placebo compared with aprocitentan (6.5 mmHg and 6.8 mmHg, respectively).

3.2.3 Non-steroidal Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA), mostly spironolactone, have demonstrated to be effective in reducing BP in RHT patients [14]. These drugs are able to antagonize the binding of aldosterone to mineralocorticoid receptors, which are expressed in many tissues, including kidneys, thus reducing sodium retention, as schematically shown in Fig. 1. The use of these drugs, however, may be limited by the presence of renal impairment, chronic kidney disease (CKD) or dialysis. In addition, MRAs, particularly spironolactone, may be associated with adverse systemic effects, such as gynecomastia and sexual disorders. Current guidelines now recommend the use of MRAs for treating RHT patients only in the presence of an estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m2 and a serum potassium concentration ≤4.5 mmol/L [9, 10, 13]. The most recent ESH 2023 hypertension guidelines [13] give preference to spironolactone as compared to other MRA for the treatment of RHT patients, mostly in view of the results of recent studies [14, 15, 50, 51] and meta-analyses [52–54].

Finerenone, a nonsteroidal MRA, has demonstrated to provide kidney protection in patients with advanced CKD and markedly elevated albuminuria included in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial [55], as well as in patients with type 2 diabetes and moderate-to-severe CKD with moderately elevated albuminuria or mild CKD with severely elevated albuminuria included in the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial [56]. These trials [30, 31] were not planned to test efficacy of finerenone in RHT patients. Nevertheless, in a *post-hoc* analysis, RHT patients with advanced CKD and type 2 diabetes mellitus from FIDELITY (pooled population from the FIDELIO-DKD and FIGARO-DKD trials) was selected to evaluate BP lowering effects of this drug. Definition of RHT was based on the eligibility criteria adopted in the Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease (AMBER) trial [57], a phase 2, multicenter, randomized, double-blind, placebo-controlled trial. In the FIDELITY-TRH *post-hoc* analysis [58], which included RHT patients with an eGFR of 25–45 mL/min/1.73 m^2 and baseline serum potassium between 4.3

and 5.1 mmol/L. From baseline to week 17 office systolic BP was reduced −7.1 mmHg by finerenone and by −1.3 mmHg with placebo (between-group difference −5.74 mmHg, P<0.0001) [58]. In the AMBER cohort study, from baseline to week 12 office systolic BP was reduced by −11.7 mmHg by spironolactone + patiromer and −10.8 mmHg by spironolactone and placebo (between-group difference −1.0 mmHg; P=0,58) [58].

The mechanistic strategy underlying the potential use of finerenone in RHT cannot be identified with a novel therapeutic approach. However, the features of this compound, and namely the lack of the classical adverse effects of steroids, which are of clinical concern, and the demonstrated safety in a population with advanced CKD and diabetes, provide solid basis to further test the potential clinical advantages of finerenone in RHT.

4 Discussion

To the best of our knowledge, this is the first systematic review focused on the efficacy of novel classes of antihypertensive agents, including ASI, and ERA, in lowering seated office (clinic) and 24-h ambulatory BP levels on top of optimal medical therapies in RHT patients enrolled in randomized, controlled, phase 2–3 clinical trials.

The main results of these trials demonstrated that all these classes of drugs provided beneficial effects in reducing systolic and diastolic BP levels, compared to placebo or conventional treatment, on top of optimal BP lowering therapy, in RHT patients aged 18 years or more and without overt cardiovascular diseases. These beneficial effects on systolic and diastolic BP levels were observed both at office and at 24-h ambulatory BP measurements, and without clinically relevant adverse reactions or side effects. Indeed, these trials confirmed the efficacy of the ASI baxdrostat [42] and lorundrostat [43], as well as of the ERA aprocitentan [48], by tackling key molecular pathways involved in the development and persistence of sustained BP elevation in RHT patients.

Despite similarities in reference population (RHT patients), study design (phase 2–3 randomized controlled clinical trials) and outcomes (reductions in office systolic/diastolic BP levels), these trials also presented several differences, including screening procedures, type of BP measurements (attended vs. unattended), follow-up periods (32 weeks or longer), comparators (active treatment or placebo), sample sizes, which might be relevant from a clinical point of view, that should be considered when interpreting the observed results.

First of all, in the PRECISION trial [48], aprocitentan has been administered on top of triple combination therapy, which included valsartan 160 mg, hydrocholorothiazide 25 mg and amlodipine 5–10 mg, depending on physicians' judgment. This background therapy was in line with the recommendations provided by current hypertension guidelines, which suggested to use triple combination therapies, possibly in fixed formulations and at maximum tolerated doses, to achieve the recommended therapeutic targets of office systolic/diastolic BP levels below 140/90 mmHg or 24-hour ambulatory BP levels below 135/85 mmHg [9, 10, 13],. Indeed, the use of such combination therapy allowed to properly identify RHT patients during the run-in period of the trials and to exclude those patients with apparently resistant or pseudo-resistant hypertension. In addition, the adoption of unattended BP measurement allowed to further exclude those patients with white-coat hypertension or white-coat phenomenon, thus further selecting those with true RHT. The rigorous selection procedures based on accurate BP assessment and pre-defined run-in periods (during which antihypertensive medications should be titrated at maximum tolerated dosages) may at least, in part, explain the relatively high proportions of screening failure reported in these trials (about 60% during the screening period) [48].

In the BrigHTN trial [42] all patients received a diuretic, about 93% a RAS blocking agent, about 70% a calcium-channel blocker and about 60% a beta-blocker. In the Target-HTN trial [43], all patients were on dual or triple combination therapies, though diuretics were used in less than 60% and ACE inhibitors or ARBs in about 70% (no data available for calcium-channel blockers and beta-blockers). Also, in the FIDELITY-TRH subgroup, all patients received a RAS blocking agent and a diuretic, but only about 70% of patients received a calcium-channel blocker, and 65–70% a beta-blocker [58]. Although the definition of RHT is substantially uniform across these trials, the differences reported on background therapies should be always considered, when interpreting the baseline BP values (either office or 24-h ambulatory) and the subsequent BP reductions during active treatment periods.

Selected trials excluded those patients with secondary forms of hypertension, since all patients underwent complete diagnostic screening before randomization. In particular, patients with hyperaldosteronism have been excluded from these trials, and baseline and ongoing assessments of PRA, SA and cortisol levels were performed in both ASI [42, 43] and ERA [48] trials for safety and tolerability outcomes. However, in the Target-HTN trial [43], patients were stratified into two groups, depending on the presence of either suppressed PRA (≤1.0 ng/mL/h) and SA level of 1.0 ng/dL or greater (cohort 1) or normal PRA (>1.0 ng/mL/h) (cohort 2). The conclusions of this trial reported no relevant differences in BP lowering effects between the two cohorts of RHT patients [43], although it might be assumed that lorundrostat can be effectively and safely used in those patients with aldosterone-related forms of RHT. There was no clear mention on this specific exclusion criterion (secondary hypertension) in the Fidelity-TRH trial [58]. However, it was also stated that patients with abnormal serum potassium levels were not included in the analysis, according to the AMBER trial criteria [57].

Finerenone is the only drug that has been tested in the FIDELITY-TRH [58] in RHT patients with diabetes and different degrees of CKD, a condition that has been systematically excluded in those trials performed with ASI [42, 43] and ERA [48]. Although no absolute contraindication exists, lorundtrat, baxdrostat and aprocitentan should not be used in the presence of an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 and a serum potassium concentration >4.5 mmol/L.

The lack of direct comparisons within the same class or between different classes of novel antihypertensive agents, as well as the absence of long-term randomized controlled clinical trials on major cardiovascular endpoints (cardiovascular morbidity and mortality) do not allow any speculation on which drug or class of drug should be preferred in RHT patients, beyond optimal medical therapy. Nevertheless, some practical considerations might be derived from the results of the selected trials.

As stated, in RHT patients with moderate-to-severe CKD and diabetes, ASI and ERA should be avoided. In those with normal renal function and evidence of RAS activation (as demonstrated by high PRA or SA levels), the ASI baxdrostat or lorundrostat might be preferred, particularly in obese individuals; on the other hand, in those with normal RAS activity and no evidence of fluid retention or congestion (low levels of NT-terminal brain natriuretic peptide), the ERA aprocitentan might be adopted. Indeed, during the part 1 of the PRECISION trial [48], aprocitentan modestly decreased haemoglobin concentration and increased plasma volume, thus potentially favoring fluid retention or oedema [59]. Alternatively, renal denervation may represent a valid therapeutic option in RHT patients, as also stated by 2023 ESH guidelines [13]. It should be noted, however, that these drugs are currently under evaluation for being approved for the clinical treatment of hypertension, thus nowadays they are not approved for prescription in daily management of hypertension.

In our systematic review we did not discuss the clinical efficacy of zilebesiran, since this drug was tested in a multicenter, phase 1 clinical trial, performed in adult outpatients with treated or untreated hypertension and seated office systolic BP between 130 and 165 mmHg [60]. Zilebesiran is a small interfering RNA [siRNA] covalently linked to an N-acetyl-galactosamine [GalNAc] ligand) that binds with high affinity to the hepatic asialoglycoprotein receptor, thus reducing the hepatic angiotensinogen messenger RNA (mRNA) levels and the production of angiotensinogen. Aliskiren, a direct renin inhibitor, has proven to lower systolic and diastolic office and 24-h ambulatory BP levels, alone or in combination therapies with other classes of antihypertensive agents, including ACE inhibitors [61], ARBs [62], calcium-antagonists [63], and beta-blockers [64], in adult outpatients with different degrees of hypertension. Its administration is currently limited to those hypertensive patients without diabetes and renal impairment [65], or heart failure [66] and not assuming other RAS blocking agents. However, we did not discuss this drug, since it does not fit with the definition of "novel" antihypertensive therapy. Finally, we did not discuss the clinical efficacy of the fixed combination therapy based on sacubitril/valsartan in lowering systolic/diastolic seated office BP levels [67], for the same reasons.

5 Conclusions

Control of hypertension represents a key element for reducing the risk of major cardiovascular events and complications and the risk of hypertension-related hospitalizations. Given the high prevalence of the disease, effective antihypertensive strategies aimed at providing sustained (office and 24-h ambulatory) BP reductions with favorable tolerability profile should be adopted in all patients with diagnosed hypertension. Indeed, international guidelines recommend the use of dual or triple fixed combination therapies to achieve the recommended therapeutic BP targets in almost all treated hypertensive outpatients [9, 10, 13]. Guidelines also recommended additional drugs to be used in RHT patients, mostly including beta-blockers or spironolactone, depending on concomitant conditions and comorbidities [9, 10, 13]. It is a matter of fact, however, that most of the treated hypertensive outpatients present a condition of uncontrolled hypertension or RHT, being responsible for most of the global burden of CV diseases.

In these patients with uncontrolled hypertension or RHT, novel drugs, including the ASI baxdrostat [42] and lorundrostat [43], as well as of the ERA aprocitentan [48], may be considered as valid, effective and safe therapeutic options for treating RHT on top of optimal background therapy. Available evidence from phase II or III randomized controlled clinical trials discussed in this systematic review, demonstrated that these drugs significantly and persistently reduced both systolic and diastolic, both seated office and 24-h ambulatory BP levels in RHT patients, with favorable tolerability profile and low risk of drug-related side effects or adverse reactions. Long-term clinical trials are needed to confirm these positive results and to support indications for treating essential uncomplicated hypertension.

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Declarations

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Ethical Approval No request to local Ethic Committee has been made, given the descriptive nature of the manuscript (systematic review).

Availability of Data and Materials The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards This article does not contain any studies involving human participants performed by any of the authors. All procedures performed in clinical trials discussed in this manuscript and involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the clinical trials, according to the study protocols.

References

1. Volpe M, Tocci G, Trimarco B, Rosei EA, Borghi C, Ambrosioni E, et al. Blood pressure control in Italy: results of recent surveys on hypertension. J Hypertens. 2007;25(7):1491–8.
2. Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, et al. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: results from the EURIKA study. Int J Cardiol. 2016;218:83–8.
3. (NCD-RisC) NRFC. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet. 2019;394(10199):639–51.
4. Torlasco C, Faini A, Makil E, Bilo G, Pengo M, Beaney T, et al. Nation-wide hypertension screening in Italy: data from May Measurements Month 2017-Europe. Eur Heart J Suppl. 2019;21(Suppl D):D66–70.
5. Geldsetzer P, Manne-Goehler J, Marcus ME, Ebert C, Zhumadilov Z, Wesseh CS, et al. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1·1 million adults. Lancet. 2019;394(10199):652–62.
6. Bunker J, Chang CL, Chapman N, Poulter N, Thom S, Thornton-Jones L, et al. True resistant hypertension following observed drug ingestion: a systematic evaluation. J Clin Hypertens (Greenwich). 2017;19(3):250–5.
7. Hameed MA, Dasgupta I. Medication adherence and treatment-resistant hypertension: a review. Drugs Context. 2019;8: 212560.
8. Volpe M, Rosei EA, Ambrosioni E, Cottone S, Cuspidi C, Borghi C, et al. 2012 consensus document of the Italian Society of Hypertension (SIIA): strategies to improve blood pressure control in Italy: from global cardiovascular risk stratification to combination therapy. High Blood Press Cardiovasc Prev. 2013;20(1):45–52.
9. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13–115.
10. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
11. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–28.
12. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906.
13. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. 2023;41(12):1874–2071. https://doi.org/10.1097/HJH.0000000000003480. Epub 2023 Sep 26.
14. Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007;49(4):839–45.
15. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–68.
16. Volpe M, Rosei EA, Ambrosioni E, Cottone S, Cuspidi C, Borghi C, et al. Renal artery denervation for treating resistant hypertension : definition of the disease, patient selection and description of the procedure. High Blood Press Cardiovasc Prev. 2012;19(4):237–44.
17. Bruno RM, Taddei S, Borghi C, Colivicchi F, Desideri G, Grassi G, et al. Italian Society of Arterial Hypertension (SIIA) position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient. High Blood Press Cardiovasc Prev. 2020;27(2):109–17.
18. Barbato E, Azizi M, Schmieder RE, Lauder L, Böhm M, Brouwers S, et al. Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2023;44(15):1313–30.

19. Volpe M, Tocci G. Challenging hypertension: how to diagnose and treat resistant hypertension in daily clinical practice. Expert Rev Cardiovasc Ther. 2010;8(6):811–20.
20. Volpe M, Gallo G. The enigma of resistant hypertension: from lifestyle changes and pharmacological treatment to renal denervation. Eur Heart J Suppl. 2022;24(Suppl I):I197–200.
21. Chan RJ, Helmeczi W, Hiremath SS. Revisiting resistant hypertension: a comprehensive review. Intern Med J. 2023;53(10):1739–51.
22. Chiu N, Lauffenburger JC, Franklin JM, Choudhry NK. Prevalence, predictors, and outcomes of both true- and pseudoresistant hypertension in the action to control cardiovascular risk in diabetes trial: a cohort study. Hypertens Res. 2021;44(11):1471–82.
23. Chun KH, Lee CJ, Oh J, Lee SH, Kang SM, Kario K, et al. Prevalence and prognosis of the 2018 vs 2008 AHA definitions of apparent treatment-resistant hypertension in high-risk hypertension patients. J Clin Hypertens (Greenwich). 2020;22(11):2093–102.
24. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of apparent treatment-resistant hypertension in the United States. Hypertension. 2019;73(2):424–31.
25. Wu C, Wang Y, Zhang W, Li X, Wang L, Hui R. Prevalence and characteristics of apparent treatment-resistant hypertension in older people in China: a cross-sectional study. Clin Exp Hypertens. 2019;41(8):753–8.
26. Matanes F, Khan MB, Siddiqui M, Dudenbostel T, Calhoun D, Oparil S. An update on refractory hypertension. Curr Hypertens Rep. 2022;24(7):225–34.
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
28. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372: n160.
29. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16.
30. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane, editor2023.
31. Volpe M, Galiuto L. More on aldosterone biosynthesis inhibition and resistant hypertension: a Phase-2 study with lorundrostat. Eur Heart J. 2024;45(2):87–8.
32. Volpe M, Patrono C. The promise of selective aldosterone synthase inhibition for the management of resistant hypertension. Eur Heart J. 2023;44(8):641–2.
33. Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. Hypertension. 2010;56(5):831–8.
34. Calhoun DA, White WB, Krum H, Guo W, Bermann G, Trapani A, et al. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. Circulation. 2011;124(18):1945–55.
35. Karns AD, Bral JM, Hartman D, Peppard T, Schumacher C. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. J Clin Hypertens (Greenwich). 2013;15(3):186–92.
36. Sloan-Lancaster J, Raddad E, Flynt A, Jin Y, Voelker J, Miller JW. LY3045697: Results from two randomized clinical trials of a novel inhibitor of aldosterone synthase. J Renin Angiotensin Aldosterone Syst. 2017;18(3):1470320317717883.
37. Freeman MW, Bond M, Murphy B, Hui J, Isaacsohn J. Results from a phase 1, randomized, double-blind, multiple ascending dose study characterizing the pharmacokinetics and demonstrating the safety and selectivity of the aldosterone synthase inhibitor baxdrostat in healthy volunteers. Hypertens Res. 2023;46(1):108–18.
38. Feldman RD, Sanjanwala R, Padwal R, Leung AA. Revising the roles of aldosterone in vascular physiology and pathophysiology: from electocortin to baxdrostat. Can J Cardiol. 2023;39(12):1808–15.
39. Dogra S, Shah S, Gitzel L, Pusukur B, Sood A, Vyas AV, et al. Baxdrostat: a novel aldosterone synthase inhibitor for treatment resistant hypertension. Curr Probl Cardiol. 2023;48(11): 101918.
40. Martin RE, Aebi JD, Hornsperger B, Krebs HJ, Kuhn B, Kuglstatter A, et al. Discovery of 4-aryl-5,6,7,8-tetrahydroisoquinolines as potent, selective, and orally active aldosterone synthase (CYP11B2) inhibitors: in vivo evaluation in rodents and Cynomolgus monkeys. J Med Chem. 2015;58(20):8054–65.
41. Bogman K, Schwab D, Delporte ML, Palermo G, Amrein K, Mohr S, et al. Preclinical and early clinical profile of a highly selective and potent oral inhibitor of aldosterone synthase (CYP11B2). Hypertension. 2017;69(1):189–96.
42. Freeman MW, Halvorsen YD, Marshall W, Pater M, Isaacsohn J, Pearce C, et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med. 2023;388(5):395–405.
43. Laffin LJ, Rodman D, Luther JM, Vaidya A, Weir MR, Rajicic N, et al. Aldosterone synthase inhibition with lorundrostat for uncontrolled hypertension: the target-HTN randomized clinical trial. JAMA. 2023;330(12):1140–50.
44. Schiffrin EL. Endothelin and endothelin antagonists in hypertension. J Hypertens. 1998;16(12 Pt 2):1891–5.
45. Trensz F, Bortolamiol C, Kramberg M, Wanner D, Hadana H, Rey M, et al. Pharmacological characterization of aprocitentan, a dual endothelin receptor antagonist, alone and in combination with blockers of the renin angiotensin system, in two models of experimental hypertension. J Pharmacol Exp Ther. 2019;368(3):462–73.
46. Chamorro V, Wangensteen R, Sainz J, Duarte J, O'Valle F, Osuna A, et al. Protective effects of the angiotensin II type 1 (AT1) receptor blockade in low-renin deoxycorticosterone acetate (DOCA)-treated spontaneously hypertensive rats. Clin Sci (Lond). 2004;106(3):251–9.
47. Verweij P, Danaietash P, Flamion B, Ménard J, Bellet M. Randomized dose-response study of the new dual endothelin receptor antagonist aprocitentan in hypertension. Hypertension. 2020;75(4):956–65.
48. Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022;400(10367):1927–37.
49. Mahfooz K, Najeed S, Tun HN, Khamosh M, Grewal D, Hussain A, et al. New dual endothelin receptor antagonist aprocitentan in hypertension: a systematic review and meta-analysis. Curr Probl Cardiol. 2023;48(7): 101686.
50. Václavík J, Sedlák R, Jarkovský J, Kociánová E, Táborský M. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). Medicine (Baltimore). 2014;93(27): e162.
51. Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57(6):1069–75.
52. Liu L, Xu B, Ju Y. Addition of spironolactone in patients with resistant hypertension: a meta-analysis of randomized controlled trials. Clin Exp Hypertens. 2017;39(3):257–63.
53. Zhao D, Liu H, Dong P, Zhao J. A meta-analysis of add-on use of spironolactone in patients with resistant hypertension. Int J Cardiol. 2017;233:113–7.

54. Guo H, Xiao Q. Clinical efficacy of spironolactone for resistant hypertension: a meta analysis from randomized controlled clinical trials. Int J Clin Exp Med. 2015;8(5):7270–8.
55. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–29.
56. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385(24):2252–63.
57. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10208):1540–50.
58. Agarwal R, Pitt B, Palmer BF, Kovesdy CP, Burgess E, Filippatos G, et al. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. Clin Kidney J. 2023;16(2):293–302.
59. Kohan DE, Heerspink HJL. Fluid retention and heart failure in the PRECISION trial. Lancet. 2023;401(10385):1335.
60. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Engl J Med. 2023;389(3):228–38.
61. Uresin Y, Taylor AA, Kilo C, Tschöpe D, Santonastaso M, Ibram G, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. J Renin Angiotensin Aldosterone Syst. 2007;8(4):190–8.
62. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007;370(9583):221–9.
63. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 2011;377(9762):312–20.
64. Dietz R, Dechend R, Yu CM, Bheda M, Ford J, Prescott MF, et al. Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension. J Renin Angiotensin Aldosterone Syst. 2008;9(3):163–75.
65. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204–13.
66. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in heart failure. N Engl J Med. 2016;374(16):1521–32.
67. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375(9722):1255–66.