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SYSTEMATIC REVIEW

Aldosterone Synthase Inhibitors for Resistant Hypertension: Pharmacological Insights – A Systematic Review

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Abstract

Background Resistant hypertension (RHT) is a challenging clinical condition characterized by persistently elevated blood pressure despite adherence to lifestyle modifications and the use of at least three antihypertensive agents, including a high-dose diuretic. RHT is a heterogeneous condition, influenced by multiple pathophysiological mechanisms such as sodium retention, sympathetic overactivity, and vascular dysfunction. Among these, hyperaldosteronism plays a pivotal role in a subset of patients.

Methods This systematic review examines in depth the pharmacokinetic properties of aldosterone synthase inhibitors (ASIs), with a focus on their therapeutic potential in patients with RHT. A comprehensive literature search was conducted to identify clinical trials and pharmacological studies investigating ASIs, including baxdrostat, dexfadrostat, lorundrostat, LY3045697, and osilodrostat (LCI699).

Results ASIs have shown compelling efficacy in lowering both office-based and 24-h ambulatory blood pressure, particularly in patients with elevated aldosterone levels. These findings underscore the critical role of aldosterone-mediated mechanisms in the pathophysiology of RHT. The inhibitors differ substantially in their metabolic pathways, selectivity profiles, and pharmacokinetic characteristics.

Conclusions Emerging data support the potential of ASIs as a therapeutic option for RHT, particularly when treatment is individualized based on renal function, dietary sodium intake, and comorbidities. Personalized treatment strategies may enhance efficacy, improve tolerability, and support durable blood pressure control in this difficult-to-treat population.

Registration PROSPERO identifier number CRD42024522918

[Graphical abstract available]

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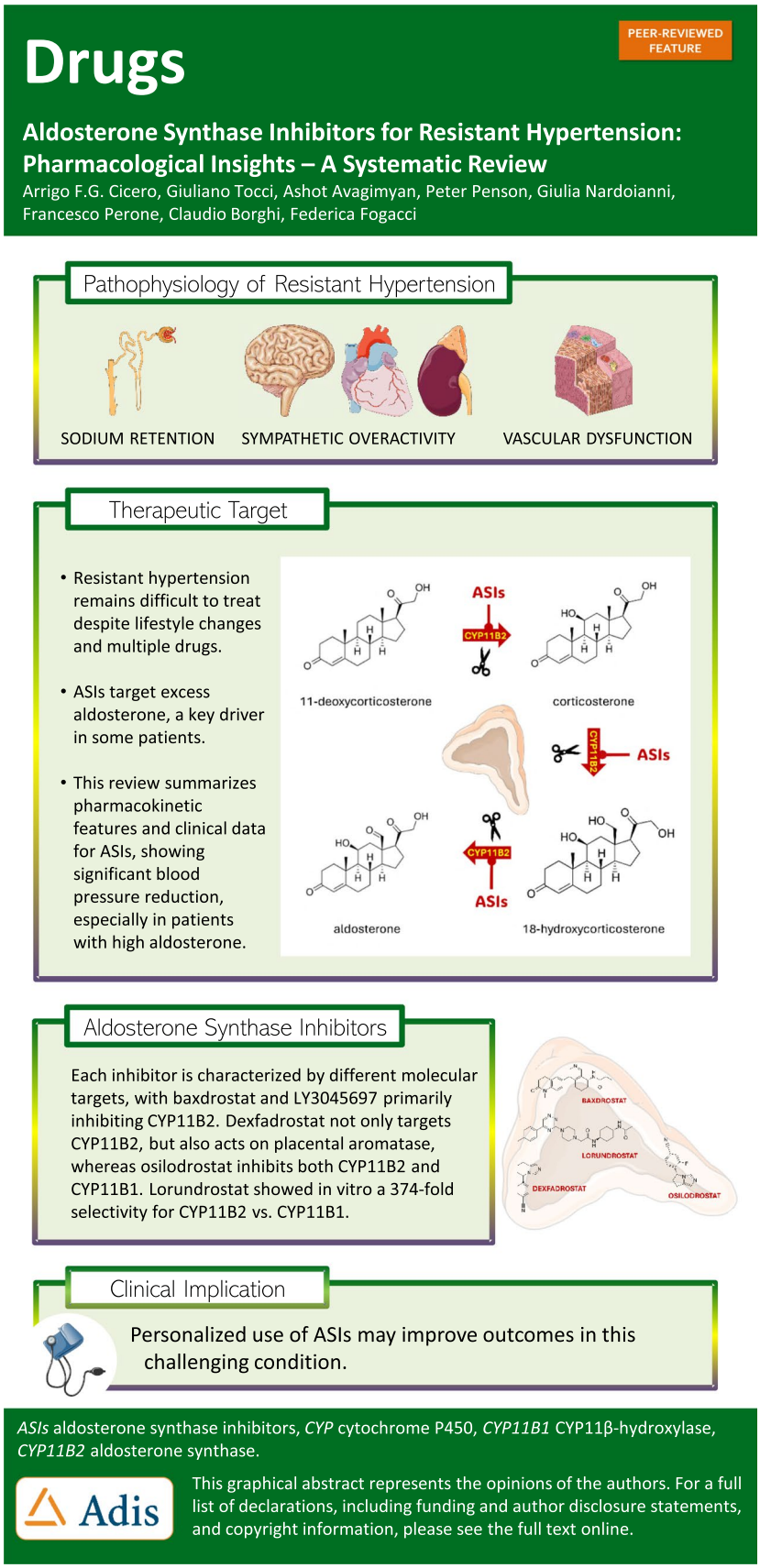
Graphical Abstract



Key Points

Aldosterone synthase inhibitors (ASIs), including baxdrostat, lorundrostat, and dexfadrostat, have demonstrated promising efficacy in lowering blood pressure in patients with resistant hypertension, particularly among those with elevated plasma aldosterone levels.

The degree of selectivity of ASIs for cytochrome P450 (CYP)-11B2 over CYP11B1 is a key determinant in reducing cortisol-related adverse effects, making highly selective ASIs preferable therapeutic options for resistant hypertension compared with less selective compounds such as osilodrostat.

Further long-term, well-designed randomized controlled trials are warranted to assess the durability of blood pressure reduction, long-term safety, and the potential integration of ASIs into treatment algorithms for resistant hypertension.

1 Introduction

Resistant hypertension (RHT) is defined as persistently elevated blood pressure (BP) despite treatment with at least three antihypertensive agents from different classes, administered at the maximum tolerated doses, including at least one diuretic [1]. The prevalence of RHT varies, but a meta-analysis of 91 studies, involving over 3 million patients estimated that true RHT affects approximately 10.3% (95% confidence interval [CI] 7.6–13.2) of treated outpatients with hypertension without secondary hypertension or major comorbidities [2]. This finding underscores a persistent therapeutic gap, whereby a considerable proportion of patients have uncontrolled disease despite adherence to evidence-based treatment algorithms. Given this scenario, it is essential to screen for secondary causes of hypertension, such as primary aldosteronism, renal artery stenosis, and pheochromocytoma, to implement appropriate and individualized therapeutic strategies. Current guidelines recommend referring patients with suspected RHT to specialized hypertension centers after optimizing antihypertensive regimens and addressing common contributors to poor BP control, including medication non-adherence, recreational drug use, and sleep disorders [3, 4]. Once these confounding factors have been excluded, more intensive treatment strategies may be warranted. First-line pharmacological management of RHT typically includes a triple combination of agents such as a renin-angiotensin system blocker, a dihydropyridine calcium channel blocker, and a thiazide or thiazide-like diuretic, preferably in fixed-dose combinations [3, 4]. If needed, beta-blockers or alpha-blockers can be added. This strategy has been shown to improve 24-h BP control, enhance treatment adherence, and reduce discontinuation rates, while maintaining an acceptable side effect profile [3, 4]. Beyond these three agents, international guidelines recommend spironolactone as the fourth-line therapy of choice for RHT, based on findings from the PATHWAY-2 trial [5]. This pivotal study demonstrated that spironolactone significantly outperformed bisoprolol and doxazosin in reducing BP in patients with RHT, thereby justifying its inclusion in current treatment algorithms. Spironolactone and eplerenone, both steroidal mineralocorticoid receptor antagonists (MRAs), are effective but often limited by side effects such as hyperkalemia and hormonal disturbances. Eplerenone is associated with a more favorable side effect profile due to its higher receptor specificity and lower affinity and potency than spironolactone [6]. Notably, non-steroidal MRAs such as finerenone have emerged as potential alternatives to ASIs, with a potentially superior safety profile. Although initial concerns were raised regarding its risk of inducing hyperkalemia, recent meta-analyses have shown that this risk is comparable to that observed with finerenone and eplerenone in patients with heart failure [7]. Despite these advances, 8–10% of patients treated for hypertension continue to exhibit BP values above 140/90 mmHg [3, 4], reinforcing the need for novel interventions. In this context, two alternative therapeutic strategies are under investigation. The first is renal artery denervation (RDN), which has shown some efficacy and good safety in lowering BP, although its BP-lowering effect appears modest and its application remains limited to experienced centers. The second strategy targets non-conventional pathways within the renin-angiotensin system, particularly elevated aldosterone levels – frequently observed in RHT. Although direct renin inhibitors such as aliskiren, and dual endothelin receptor antagonists such as aprocitentan, are currently not recommended for routine use in essential hypertension [8, 9], pharmacological suppression of aldosterone synthesis has emerged as a promising direction. Aldosterone contributes to BP elevation through enhanced sodium retention and vasoconstriction [10]. Recently, aldosterone synthase inhibitors (ASIs), which selectively block aldosterone biosynthesis at the enzymatic level (Fig. 1), have been developed and are under clinical investigation for the treatment of RHT.

These drugs have shown promising potential in lowering BP in patients with RHT. This review critically evaluates the pharmacokinetic properties of ASIs and explores their role as a targeted therapeutic strategy to improve BP control in patients with uncontrolled hypertension (i.e., those

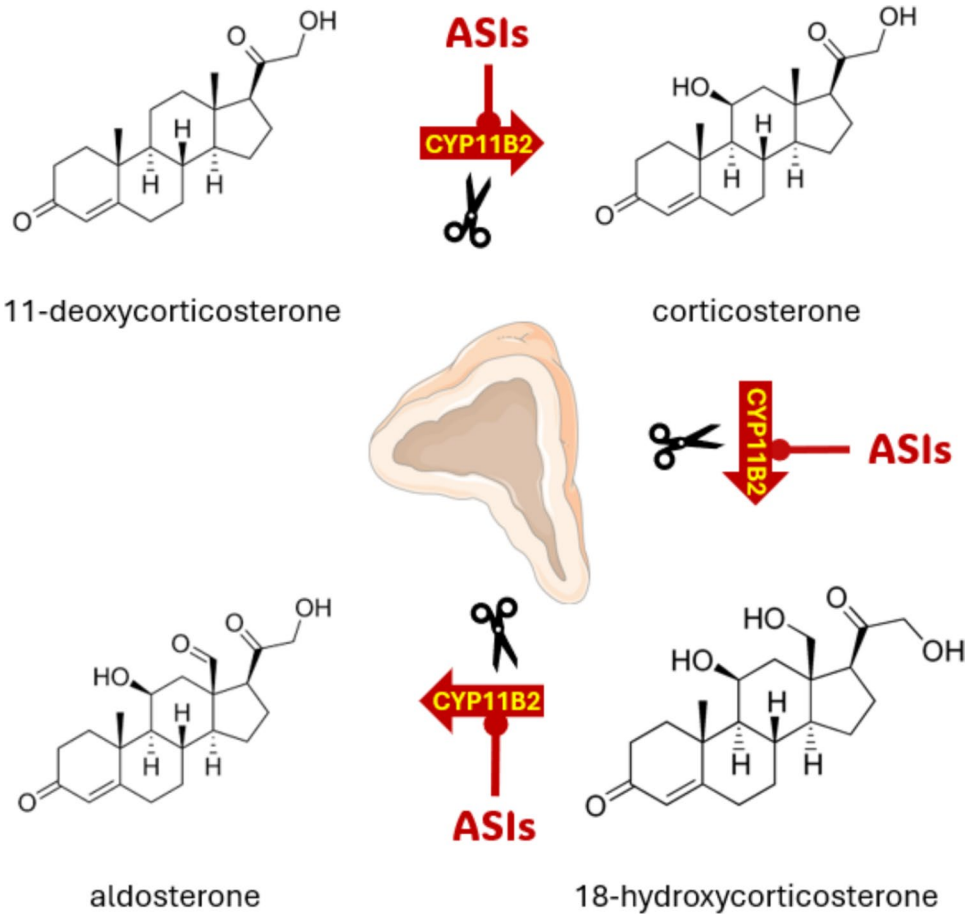


Fig. 1 Overview of the adrenal steroidogenesis pathway affected by aldosterone synthase inhibitors (ASIs). ASIs block the activity of cytochrome P450 (CYP)-11B2, the enzyme responsible for the conversion of 11-deoxycorticosterone to corticosterone, corticosterone to 18-hydroxycorticosterone, and ultimately to aldosterone. By inhibiting CYP11B2, ASIs reduce the biosynthesis of aldosterone and its precursors

receiving one or two antihypertensive agents) as well as in individuals with RHT (i.e., those receiving at least three or four antihypertensive medications without achieving guideline-recommended office BP targets).

2 Methods

This systematic review was designed according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [11]. The protocol of the study was prospectively registered in the PROSPERO database (CRD42024522918). No ethical approval was required as no new participants were recruited and existing published data were exclusively used.

2.1 Search Strategy

Web of Science, PubMed-MEDLINE, Google Scholar, Scopus and Clinicaltrial.gov were systematically searched without applying any filters (e.g. without any language or date restriction), from inception to January 1, 2025. The terms "hypertension," "baxdrostat," "dexfadrostat," "lorundrostat," "LY3045697," "osilodrostat," "LCI699," "BI 690517," and "aldosterone synthase inhibitors" were utilized in various combinations and in conjunction with the truncation and Boolean operators "AND," "OR," and "*" to increase the sensitivity of the search strategy. The resulting reference list was manually checked for additional relevant articles. All paper abstracts were screened by two authors to remove ineligible articles; the full texts of eligible articles were obtained and again assessed by the same authors, who also extracted the data and conducted a quality assessment. Disagreements were discussed with the principal investigator (AFGC).

2.2 Criteria for Eligibility of Studies

The comprehensive population, intervention, comparison, outcomes, and study (PICOS) selection criteria are presented in Table 1.

2.3 Data Extraction

Data extracted from the eligible articles were as follows: (1) first author's name; (2) year of publication; (3) study location; (4) follow-up; (5) main inclusion criteria and underlying disease; (6) tested intervention; (7) study groups; (8) number of participants in the active and control groups; (9)

Table 1 The PICOS framework summarizing the rationale behind the systematic review, outlining the criteria for the included clinical studies

Category	Inclusion criteria	Exclusion criteria
Population	Adult participants (aged ≥18 years)	Patients with Cushing disease
Intervention	Aldosterone synthase inhibitors	
Comparison	Placebo/control treatment	
Outcome measure	Pharmacological properties and clinical efficacy	
Study type	Randomized controlled studies or their open-label extensions Trials conducted in accordance with the Helsinki Declaration and its amendments	

pharmacological properties of drugs; (10) parameters of clinical efficacy.

2.4 Risk-of-Bias Assessment

The risk of bias in the included randomized controlled clinical studies was systematically assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2 tool), which considered the following domains: randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results [12]. Two authors independently performed the risk-of-bias assessment [13]. Disagreements were resolved by discussion and consensus.

3 Results

3.1 Flow of Literature and Characteristics of the Included Studies

The selection process is shown in Fig. 2. The main pharmacokinetic characteristics of ASIs are included in Table 2.

Each inhibitor is characterized by a defined molecular formula, with dexfadrostat ($C_{14}H_{13}N_3$) being the simplest and lorundrostat ($C_{24}H_{33}N_7O_2$) the most complex (Fig. 3). The molecular targets differ, with baxdrostat and LY3045697 primarily inhibiting aldosterone synthase (cytochrome P450 [CYP]-11B2). Dexfadrostat not only targets CYP11B2 but also acts on placental aromatase, whereas osilodrostat inhibits both aldosterone synthase (CYP11B2) and 11β-hydroxylase (CYP11B1). Lorundrostat showed highly selective inhibition of CYP11B2 in vitro, with 374-fold selectivity for CYP11B2 versus CYP11B1 [14].

Regarding metabolism, baxdrostat undergoes various pathways, including oxidation and N-dealkylation, whereas osilodrostat is metabolized by multiple CYP enzymes and UDP-glucuronosyltransferases, with no single enzyme responsible for more than 25% of its clearance. The area under the concentration–time curve (AUC), a measure of drug exposure over time, increases proportionally with the dose across all drugs. This is especially evident in patients with renal impairment, in whom the AUC of baxdrostat is notably higher than in individuals with healthy renal function.

The maximum plasma concentration (C_{max}) also rises with dose escalation for all ASIs. However, renal function affects C_{max} values, particularly for baxdrostat, which exhibits lower C_{max} levels in patients with kidney failure. The time to reach maximal plasma concentration varies between 1 and 4 h across the drugs within the class, depending on the specific dose and patient characteristics. For LY3045697, plasma concentrations peak rapidly, sometimes within 30 minutes when administered after a meal.

The plasma elimination half-life is significantly different among ASIs. Baxdrostat demonstrates a relatively long half-life of approximately 26–31 h, depending on renal function, whereas the half-life of osilodrostat is shorter, around 4–5 h. Lorundrostat shows a more consistent half-life of approximately 9–10 h, regardless of dosage.

Clearance rates also vary: baxdrostat displays a clearance rate influenced by dietary salt intake, ranging from 3 to 5 L/h. Volume of distribution for baxdrostat ranges between 135 and 150 L, indicating extensive distribution in body tissues. The proportion of unmodified drug excreted varies; for baxdrostat, it is about 12% in patients with healthy renal function but significantly lower in those with kidney failure.

The pharmacokinetics of these inhibitors are dose dependent, as evidenced by proportional increases in both AUC and C_{max}. LY3045697 demonstrates strong selectivity for CYP11B2 over CYP11B1, with a 39-fold difference, establishing it as a highly specific ASI. Notably, the pharmacokinetics of LY3045697 remain consistent between single- and multiple-dose administrations, with minimal drug accumulation. Patient variability is evident, particularly in the coefficient of variation for several pharmacokinetic

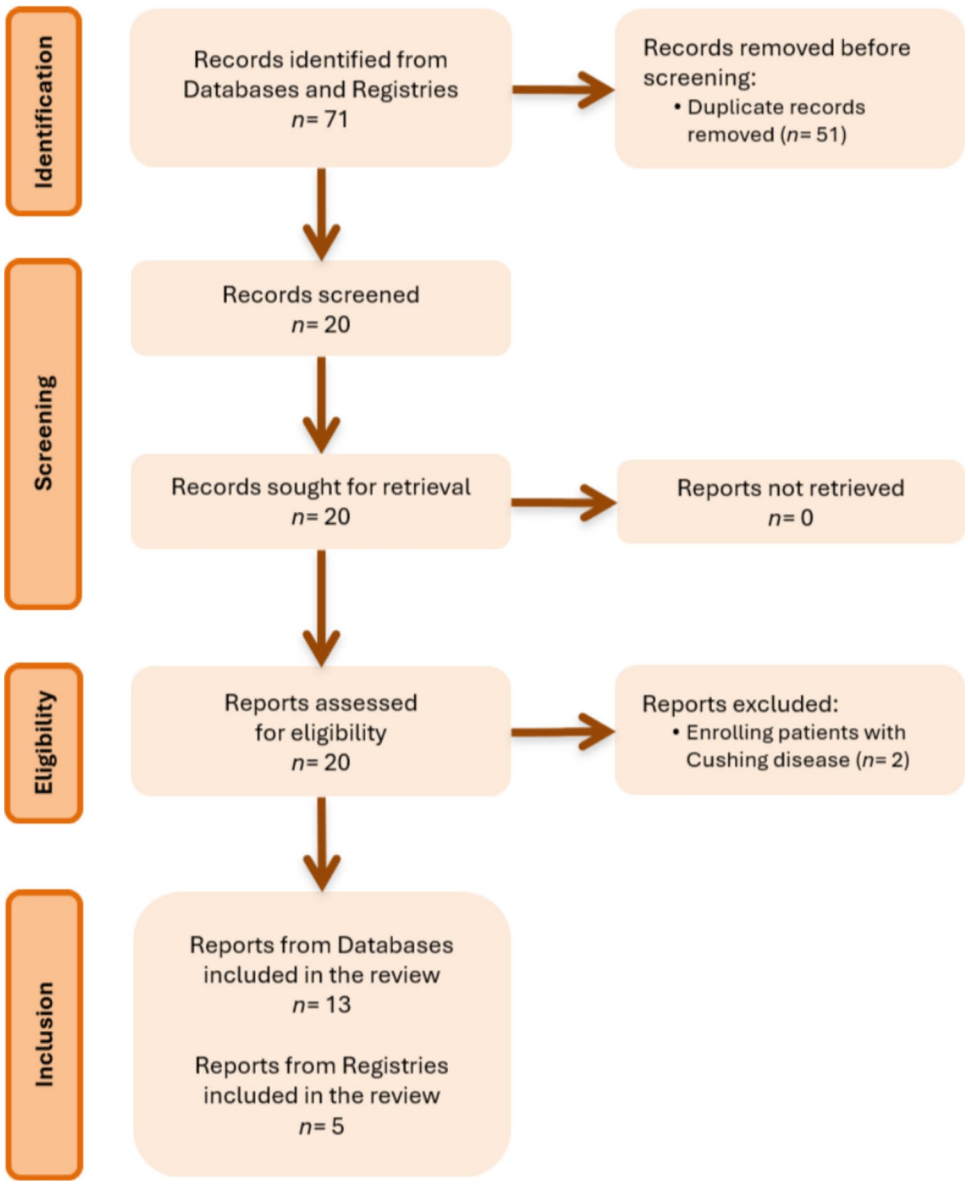


Fig. 2 Flow chart of the number of studies identified and included in the systematic review

parameters, reflecting individual differences in metabolism and drug clearance. Additionally, pharmacokinetic data for BI 690517 and lorundrostat have not yet been published.

Table 3 summarizes the characteristics of clinical trials investigating ASIs, highlighting both differences and commonalities in terms of study design, scope, and objectives.

These agents, including baxdrostat, BI 690517, dexfadrostat, lorundrostat, LY3045697, and osilodrostat, have been tested primarily in phase I and II randomized controlled trials, with notable variations in dosing strategies, treatment durations, and participant populations.

Baxdrostat and BI 690517 are notable for their extensive dose-ranging investigations. Both drugs were tested across multiple dosages, with baxdrostat evaluated in studies ranging from 0.5 mg to 10 mg, whereas BI 690517 trials included doses as high as 40 mg. However, BI 690517 was also incorporated in combination with empagliflozin in phase II trials, reflecting a broader focus on synergistic treatments than with the primarily standalone testing of baxdrostat [19, 20].

Trials of dexfadrostat and lorundrostat similarly emphasized dose escalation, but their approaches differed. Studies of dexfadrostat included both single- and multiple-dose designs, with shorter treatment durations (1–8 days in phase I and 8 weeks in phase II trials). In contrast, the Target-HTN trial, performed with lorundrostat, spanned 8 weeks and specifically stratified participants by plasma renin activity, offering a more targeted exploration of treatment efficacy in distinct patient subgroups [23].

Trials of LY3045697 and osilodrostat provide insight into earlier stages of development. LY3045697 was tested across a wide dose range (0.1–300 mg) in early phase I trials,

Table 2 Main pharmacokinetic characteristics of the aldosterone synthase inhibitors

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
Molecular formula	$C_{22}H_{25}N_3O_2$	$C_{14}H_{13}N_3$	$C_{24}H_{33}N_7O_2$	Unknown	$C_{13}H_{10}FN_3$
Molecular target	AS (CYP11B2)	DEX is a potent nonsteroidal inhibitor. It also inhibits human placental aromatase and aldosterone biosynthesis	AS (CYP11B2)	AS (CYP11B2)	11β-hydroxylase (CYP11B1) and orally AS (CYP11B2)
Metabolic pathway	BAX metabolism is predominately mediated by oxidation, and, to a lesser extent, N-dealkylation, amide hydrolysis, N-demethylation, and N-acetylglucosaminidation. Notable secondary biotransformation pathways include reduction, glucuronidation, and oxidation	Daily DEX phosphate treatment results in a dose-dependent increase of the CYP11B2 (11β-hydroxylation) substrate THDOC and an increase of the CYP11B2 (18-hydroxylation) substrates THA, THB, and 5αTHB. At the highest doses (8–16 mg), DEX causes a decrease of the CYP11B2 (18-oxidase) product THALDO. Moreover, DEX phosphate dose-dependently increases blood levels of 11-deoxycortisol, even if its CYP11B1 inhibitory activity is not potent enough to affect basal cortisol levels. There is no effect of DEX phosphate on CYP19A1 (aromatase)	Metabolic enzyme/protease; vitamin D-related/nuclear receptor	LY3045697 inhibits human AS (in vitro CYP11B2 IC_{50} = 4.5 nM) with a 39-fold selectivity over cortisol synthase (in vitro CYP11B1 IC_{50} = 176 nM). Cortisol and 11-deoxycortisol results after IV ACTH challenge suggest an inhibitory effect of LY3045697 on CYP11B1 occurring between a daily dose of 10 and 100 mg	Multiple CYP enzymes (i.e. CYP3A4, CYP2B6, and CYP2D6) and UGTs contribute to OLI metabolism. No single enzyme contributes >25% to the total clearance
$AUC_{0\text{-last}}$	Proportionally increased with increasing dosages After a single daily dose of BAX 10 mg: in pts with eGFR ≥60 mL/min, 3377 ± 917 h * ng/mL in pts with moderate to severe renal impairment (eGFR 59–15 mL/min), 4013 ± 1193 h * ng/mL; in pts with kidney failure (eGFR <15 mL/min), 2567 ± 1363 h * ng/mL	Range: 1.15–1.21 (geometric mean accumulation ratio) across doses	After a single dose of LOR: 5 mg, 229 ± 25 ng * h/mL 10 mg, 450 ± 47 ng * h/mL 20 mg, 764 ± 183 ng * h/mL 50 mg, 2153 ± 260 ng * h/mL 100 mg, 5366 ± 493 ng * h/mL 200 mg, 10,645 ± 3486 ng * h/mL 400 mg, 17,257 ± 2907 ng * h/mL 800 mg, 29,331 ± 3623 ng * h/mL	Generally increases in proportion to dose After multiple daily dosing of LY3045697 in the fed state: 1 mg, 19.2 h * ng/mL (CV 29%) 10 mg, 195 h * ng/mL (CV 22%) 100 mg, 1818 h * ng/mL (CV 28%)	After multiple daily dosing of OLI: 0.5 mg OD, 9.23 h * ng/mL (CV 50%) 1 mg OD, 3.79 h * ng/mL (CV 43%) 1 mg BID, 5.52 h * ng/mL (CV 33%) 2 mg OD, 4.9 h * ng/mL (CV 17%)

Table 2 (continued)

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
$AUC_{0-\infty}$	After a single daily dose of BAX 10 mg: in pts with eGFR ≥60 mL/min, 3531 ± 1033 h * ng/mL in pts with moderate to severe renal impairment (eGFR range: 59–15 mL/min), 4341 ± 1487 h * ng/mL in pts with kidney failure (eGFR <15 mL/min), 2662 ± 1462 h * ng/mL	Range: 43.6–65.9 (dose-normalized geometric mean)	After a single dose of LOR: 5 mg, 232 ± 25 ng * h/mL 10 mg, 452 ± 46 ng * h/mL 20 mg, 770 ± 183 ng * h/mL 50 mg, 2457 ± 259 ng * h/mL 100 mg, 5376 ± 495 ng * h/mL 200 mg, 40,660 ± 3483 ng * h/mL 400 mg, 17,275 ± 2906 ng * h/mL 800 mg, 29,385 ± 3623 ng * h/mL After multiple doses of LOR: 40 mg OD, 1954 ± 366 ng * h/mL (at day 7) 120 mg OD, 6468 ± 1481 ng * h/mL (at day 7) 360 mg OD, 23,668 ± 4457 ng * h/mL (at day 7)	Generally increases in proportion to dose After single daily dosing of LY3045697 in the fed state: 1 mg, 12.1 h * ng/mL (CV 51%) 3 mg, 49.1 h * ng/mL (CV 31%) 10 mg, 138 h * ng/mL (CV 19%) 30 mg, 482 h * ng/mL (CV 32%) 100 mg, 1726 h * ng/mL (CV 15%) 300 mg, 6226 h * ng/mL (CV 19%)	Unpublished data
AUC_{0-24}	BAX 0.5 mg, 212.13 ± 65.54 ng * h/mL BAX 1 mg, 376.58 ± 144.72 ng * h/mL BAX 2 mg, 745.4 ± 203.38 ng * h/mL	Range: 1310–2350 (geometric mean) after multiple oral doses (dose-dependent parameter)	After a single dose of LOR: 5 mg, 212 ± 24 ng * h/mL 10 mg, 420 ± 44 ng * h/mL 20 mg, 709 ± 185 ng * h/mL 50 mg, 2053 ± 245 ng * h/mL 100 mg, 5093 ± 458 ng * h/mL 200 mg, 10,288 ± 3446 ng * h/mL 400 mg, 16,617 ± 2724 ng * h/mL 800 mg, 28,290 ± 3546 ng * h/mL After multiple doses of LOR: 40 mg OD, 1795 ± 312 ng * h/mL (at day 7) 120 mg OD, 5816 ± 1315 ng * h/mL (at day 7) 360 mg OD, 21,825 ± 3955 ng * h/mL (at day 7)	Generally increases in proportion to dose	Unpublished data

Table 2 (continued)

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
C_{max}	C_{max} proportionally increases with ascending doses of BAX In the BrigHTN trial: 0.5 mg, 11.08 ± 3.43 ng /mL 1 mg, 21.76 ± 7.1 ng/mL 2 mg, 2.64 ± 1.69 ng/mL After a single daily dose of BAX 10 mg: in pts with eGFR ≥60 mL/min, 108 ± 26 ng/mL in pts with moderate to severe renal impairment (eGFR 59–15 mL/min), 110 ± 23 ng/mL in pts with kidney failure (eGFR <15 mL/min), 96 ± 27 ng/mL	Range: 4.61–61.9 ng/mL across doses and following a single oral dose	After a single dose of LOR: 5 mg, 36.69 ± 6.71 ng/mL 10 mg, 76.26 ± 20.38 ng /mL 20 mg, 140.6 ± 76.14 ng /mL 50 mg, 572.78 ± 205.74 ng / mL 100 mg, 1211 ± 248.34 ng / mL 200 mg, 2847.5 ± 1015.24 ng /mL 400 mg, 4454.83 ± 862.39 ng /mL 800 mg, 7708.5 ± 1617.12 ng /mL After multiple doses of LOR: 40 mg OD, 365.14 ± 46.48 ng/mL (at day 7) 120 mg OD, 1038.74 ± 342.81 ng/mL (at day 7) 360 mg OD, 3812.13 ± 1282.32 ng/mL (at day 7)	Generally increases in proportion to dose After single daily dosing of LY3045697 in the fed state: 0.1 mg, 0.32 ng/mL (CV 28%) 0.3 mg, 1.10 ng/mL (CV 33%) 1 mg, 1.96 ng/mL (CV 49%) 3 mg, 9.95 ng/mL (CV 97%) 10 mg, 27.9 ng/mL (CV 24%) 30 mg, 83.7 ng/mL (CV 25%) 100 mg, 458 ng/mL (CV 27%) 300 mg, 951 ng/mL (CV 20%) After multiple daily dosing of LY3045697 in the fed state: 0.1 mg, 0.37 ng/mL (CV 30%) 1 mg, 3.45 ng/mL (CV 36%) 10 mg, 37.4 ng/mL (CV 29%) 100 mg, 371 ng/mL (CV 37%)	After multiple daily dosing of OLI: 0.5 mg OD, 1.42 ng/mL (CV 36%) 1 mg OD, 2.94 ng/mL (CV 35%) 1 mg BID, 4.62 ng/mL (CV 35%) 2 mg OD, 8.86 ng/mL (CV 21%)

Table 2 (continued)

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
t_{max}	Median t_{max} reached within 4 h of dosing of BAX: 0.5 mg, 2.25 ± 1.71 h 1 mg, 2.71 ± 2.43 h 2 mg, 2.64 ± 1.69 h After a single daily dose of BAX 10 mg: in pts with eGFR ≥60 mL/min, 2.1 ± 1.6 h; in pts with moderate to severe renal impairment (eGFR 59–15 mL/min), 1.82 ± 1 h; in pts with kidney failure (eGFR <15 mL/min), 1.63 ± 0.8 h	Approximately 2 h (range: 1.25–4 h across doses)	Median t_{max} after a single dose of LOR: 5 mg, 1.5 h (range: 1–3 h) 10 mg, 1.25 h (range: 0.98–1.5 h) 20 mg, 1.5 h (range: 1–3.02 h) 50 mg, 1 h (range: 0.5–3 h) 100 mg, 1.51 h (range: 0.52–3 h) 200 mg, 1.25 h (range: 1–3.02 h) 400 mg, 1.25 h (range: 0.5–3 h) 800 mg, 1.5 h (range: 0.52–4.02 h) Median t_{max} after multiple doses: 40 mg OD, 2 h (range: 1–3 h at day 7) 120 mg OD, 1.52 h (range: 0.52–5 h at day 7) 360 mg OD, 2.5 h (range: 1–4 h at day 7)	Following administration after a standard breakfast, LY3045697 plasma concentrations rapidly increase and reach the peak typically as early as 0.5 h Median t_{max} after single daily dosing of LY3045697 in the fed state: 0.1 mg, 0.75 h (range: 0.5–1 h) 0.3 mg , 0.5 h (range: 0.5–1 h) 1 mg, 1 h (range: 0.5–2 h) 3 mg, 0.5 h (range: 0.5–0.5 h) 10 mg, 0.75 h (range: 0.50–2 h) 30 mg, 1 h (range: 0.5–2 h) 100 mg, 0.5 h (range: 0.5–1 h) 300 mg, 0.5 h (range: 0.5–1 h) After multiple-daily dosing of OLI in the fed state: 0.1 mg, 0.95 h (range: 0.5–3 h) 1 mg, 0.95 h (range: 0.5–3 h) 10 mg, 0.95 h (range: 0.5–2 h) 100 mg, 0.95 h (range: 0.5–0.95 h)	t_{max} reached approximately within 1 h post dosing Median t_{max} after multiple daily dosing of OLI: 0.5 mg OD, 2.21 h (range: 1–4 h) 1 mg OD, 1 h (range: 1–4 h) 1 mg BID, 1 h (range: 0.5–4 h) 2 mg OD, 1 h (range: 1–3 h)

Table 2 (continued)

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
$t_{½}$	Approximately 26–31 h (plasma drug concentrations decline in an apparent biphasic manner after reaching t_{max}) After a single daily dose of BAX 10 mg: in pts with eGFR ≥60 mL/min, 35.63 ± 12.1 h in pts with moderate to severe renal impairment (eGFR: 59–15 mL/min), 42.14 ± 16.5 h in pts with kidney failure (eGFR <15 mL/min), 29.7 ± 10.5 h	Range: 9.5–11.1 h across doses (plasma drug concentrations decline in a monophasic manner after reaching t_{max})	After a single dose of LOR: 5 mg, 8.26 ± 0.74 h 10 mg, 7.92 ± 0.92 h 20 mg, 10.03 ± 1.87 h 50 mg, 9.13 ± 1.87 h 100 mg, 9.95 ± 0.9 h 200 mg, 9.92 ± 3.61 h 400 mg, 9.7 ± 2.28 h 800 mg, 10.54 ± 2.09 h After multiple doses of LOR: 40 mg OD, 9.1 ± 1.79 h (at day 7) 120 mg OD, 11.94 ± 2.46 h (at day 7) 360 mg OD, 9.24 ± 2.45 h (at day 7)	Approximately 10 h (plasma drug concentration–time profiles exhibit a mostly biphasic decline after reaching t_{max}) Appears to be dose independent and consistent between single- and multiple-dose administration After single daily dosing of LY3045697 in the fed state: 1 mg, 9.11 h (CV 43%) 3 mg, 8.73 h (CV 32%) 10 mg, 9.99 h (CV 20%) 30 mg, 9.57 h (CV 20%) 100 mg, 9.62 h (CV 28%) 300 mg, 10.8 h (CV 30%) After multiple-daily dosing of LY3045697 in the fed state: 10 mg, 9.84 h (CV 18%) 100 mg, 10.8 h (CV 26%)	Range: 3.8–5.5 h across the studied dose range After multiple daily dosing of OLI in the fed state: 0.5 mg OD, 4.67 h (CV 37%) 1 mg OD, 3.79 h (CV 43%) 1 mg BID, 5.52 h (CV 33%) 2 mg OD, 4.9 h (CV 17%)
Cl/F	On a low-salt diet, dose of BAX: 2.5 mg, 3.28 ± 0.53 L/h 5 mg, 3.21 ± 0.84 L/h On a normal-salt diet, dose of BAX: 0.5 mg, 3.42 ± 0.01 L/h 1.5 mg, 3.35 ± 0.92 L/h 2.5 mg, 4.32 ± 1.59 L/h After a single daily dose of 10 mg BAX: in pts with eGFR ≥60 mL/min, 3.06 ± 0.9 L/h in pts with moderate to severe renal impairment (eGFR: 59–15 mL/min), 2.6 ± 1 L/h in pts with kidney failure (eGFR <15 mL/min), 5.07 ± 2.9 L/h	Range: 253–382 mL/min (dose-independent parameter)	Unpublished data	Unpublished data	Unpublished data

Table 2 (continued)

Characteristic	BAX	DEX	LOR	LY3045697	OLI (LCI699)
Vz/F	On a low-salt diet, dose of BAX: 2.5 mg, 134.7 ± 36.7 L 5 mg, 134.27 ± 41.98 L On a normal-salt diet, dose of BAX: 0.5 mg, 151.58 ± 44.5 L 1.5 mg, 136.87 ± 15.77 L 2.5 mg, 150.38 ± 42.42 L	Range: 235–345 L (dose-independent parameter)	Unpublished data	Unpublished data	Unpublished data
Unmodified excretion (%)	After a single daily dose of 10 mg BAX: in pts with eGFR ≥60 mL/min, 12.53 ± 38.1% in pts with moderate to severe renal impairment (eGFR: 59–15 mL/min), 11.81 ± 26% in pts with kidney failure (eGFR <15 mL/min), 0.91 ± 60.7%	Unpublished data	Unpublished data	Unpublished data	Unpublished data

AS aldosterone synthase, *AUC* area under the concentration–time curve, $AUC_{0\text{-}24}$ AUC from time 0 to 24 h, $AUC_{0\text{-}\infty}$ AUC from time 0 extrapolated to infinity, $AUC_{0\text{-}last}$ AUC from time 0 to time of last quantifiable concentration, *BAX* baxdrostat, *BID* twice daily, *CL/F* total plasma clearance, C_{max} maximal plasma concentration, C_{max} maximum plasma concentration, *CV* coefficient of variation, *CYP* cytochrome P450, *DEX* dexfadrostat, *eGFR* estimated glomerular filtration rate, *h* hour(s), *IC50* half-maximal inhibitory concentration, *IV* intravenous, *LOR* lorundrostat, *OD* once daily, *OSI* osilodrostat, *pts* patients, $t_{½}$ plasma terminal elimination half-life, t_{max} time to $C_{max,}$ *UGTs* UDP-glucuronosyltransferases, *Vz/F* volume of distribution during terminal phase.

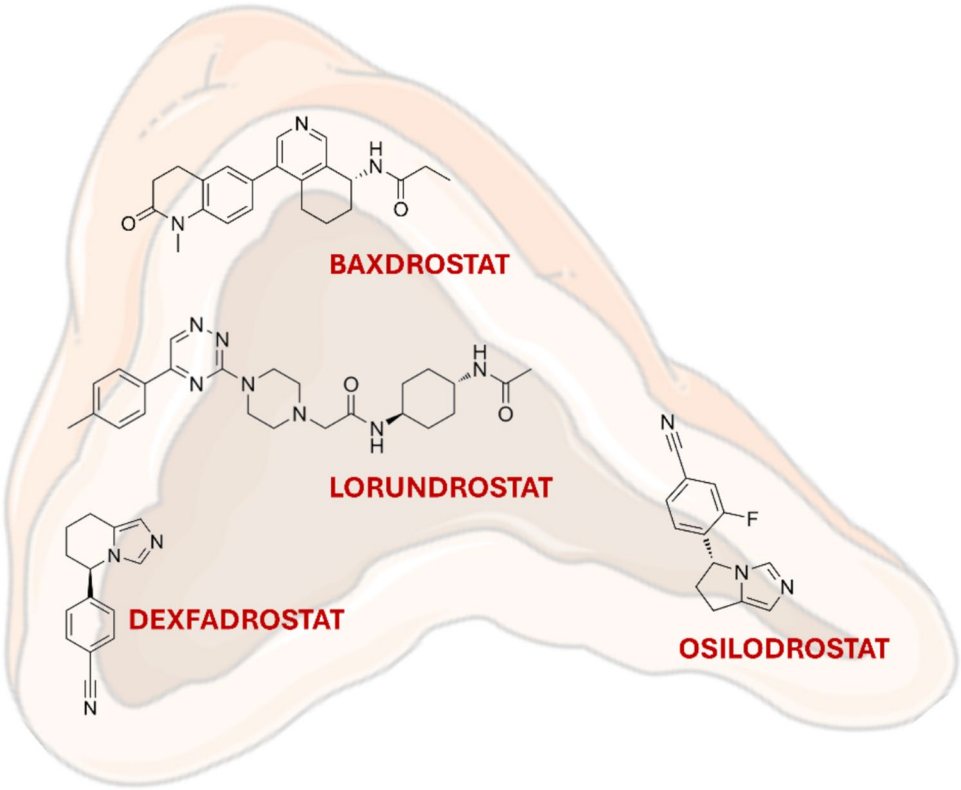


Fig. 3 Molecular formulas of the main aldosterone synthase inhibitors in development for the treatment of resistant hypertension

focusing on safety and tolerability [25]. Similarly, trials of osilodrostat evaluated a variety of doses but extended into phase II, where it was compared both with placebo and with active controls such as eplerenone, setting it apart from the others in terms of study design complexity [26].

Although the drugs share a common focus on hypertension or related conditions, their clinical trajectories reveal diverse strategies. Baxdrostat and BI 690517 have undergone comprehensive dose-ranging studies, whereas dexfadrostat and lorundrostat trials have focused more on participant stratification and escalation schedules. LY3045697 and osilodrostat reflect early-phase exploratory efforts, with osilodrostat further distinguished by its inclusion of active comparators. These differences illustrate varying priorities in optimizing dosage, exploring combination therapies, and tailoring interventions to specific patient populations.

Additional information about the ongoing clinical studies testing ASIs for the treatment of RHT is provided in Table 4.

These trials vary significantly in terms of study phases, designs, inclusion criteria, and expected BP outcomes.

Baxdrostat is being evaluated in three distinct phase III clinical trials. These trials focus on participants with RHT, characterized by elevated systolic BP despite being on a stable regimen of at least three antihypertensive medications, including a diuretic. The studies include large-scale enrolments, with one trial planning to recruit up to 2500 participants (NCT06268873), making it notably broader in scope than other studies. The inclusion criteria for baxdrostat trials also emphasize the need for controlled serum potassium levels and adequate kidney function, with an estimated glomerular filtration rate of ≥45 mL/min/1.73 m^2. Additionally, one study (NCT06034743) differentiates between subpopulations with uncontrolled hypertension versus RHT, further refining its approach to patient selection. In line with the importance of appropriate patient stratification, baseline renin-angiotensin-aldosterone system activity, and dosing considerations, the recent HALO study investigating CIN-107 (baxdrostat) in patients with uncontrolled hypertension did not demonstrate significant BP reductions at dose of 0.5–2 mg/day compared with placebo. This finding underscores the relevance of careful selection and trial design in assessing the efficacy of ASIs.

In contrast, lorundrostat is being tested across multiple phase II and III studies, reflecting a slightly earlier stage of development than baxdrostat. The trials target patients with varying degrees of hypertension and kidney function. For example, phase II studies (such as NCT06150924) incorporated patients with albuminuria and estimated glomerular filtration rate as low as 30 mL/min/1.73 m^2, indicating a focus on individuals with coexisting renal impairments. Lorundrostat trials also explored unique study designs, such as a dose-escalation open-label arm (Part B of NCT06150924) and an open-label extension study (NCT05968430) for patients completing previous trials.

Table 3 Characteristics of the available clinical studies testing aldosterone synthase inhibitors

Drug	Study phase	Study code	Study design	Treatment length	Treatment groups		Participants (n)
Baxdrostat	I	NCT05500820 (CIN-107-111) [15]	Single-center, randomized, double-blind, placebo-controlled, dose-ranging study	10 days	Low-salt diet	2.5 mg baxdrostat	9
						5 mg baxdrostat	9
						Placebo	6
					Normal-salt diet	0.5 mg baxdrostat	9
						1.5 mg baxdrostat	9
						2.5 mg baxdrostat	6
						Placebo	8
	I	NCT05470725 (CIN-107-113) [16]	Single-center, open-label study	1 day	10 mg baxdrostat		33
	II	NCT04519658 (BrigHTN trial, CIN-107-121) [17]	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study with an adaptive design	12 weeks	0.5 mg baxdrostat		69
					1 mg baxdrostat		70
					2 mg baxdrostat		67
					Placebo		69
BI 690517	I	NCT03165240 [18]	Multicenter, randomized, double-blind, placebo-controlled study	28 days	3 mg BI 690517		18
					10 mg BI 690517		13
					40 mg BI 690517		14
					25–50 mg eplerenone		4
					Placebo		9
	II	NCT05182840 [19, 20]	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study	14 weeks	3 mg BI 690517 + placebo		71
					10 mg BI 690517 + placebo		72
					20 mg BI 690517 + placebo		72
					BI 690517 placebo + placebo		73
					3 mg BI 690517 + empagliflozin		76
					10 mg BI 690517 + empagliflozin		74
					20 mg BI 690517 + empagliflozin		74
					BI 690517 placebo + empagliflozin		74

Table 3 (continued)

Drug	Study phase	Study code	Study design	Treatment length	Treatment groups		Participants (n)
Dexfadrostat	I	NCT03046589 (DP13C101) [21]	Single-center, randomized, double-blind, placebo-controlled study conducted in two parts	1 day	Part A (single ascending-dose escalation)	1–16 mg dexfadrostat	16
						Placebo	12
				8 days	Part B (multiple ascending-dose escalation)	4 mg dexfadrostat	8
						8 mg dexfadrostat	8
						16 mg dexfadrostat	8
						Placebo	8
	II	NCT04007406 [22]	Multicenter, randomized study consisting of a single-blind 2-week placebo run-in period, a double-blind 8-week treatment period, and a single-blind 2-week withdrawal period during which participants received placebo	8 weeks	4 mg dexfadrostat		10
					8 mg dexfadrostat		12
					12 mg dexfadrostat		13
Lorundrostat	II	NCT05001945 (Target-HTN trial, MLS-101-201) [23]	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study	8 weeks	Cohort 1 (PRA ≤1 ng/mL/h)	12.5 mg lorundrostat OD	19
						12.5 mg lorundrostat BID	19
						25 mg lorundrostat BID	28
						50 mg lorundrostat OD	28
						100 mg Lorundrostat OD	25
						Placebo	29
					Exploratory cohort (PRA >1 mg/mL/h)	100 mg lorundrostat OD	31
						Placebo	6
	III	NCT06153693 (Launch-HTN trial, MLS-101-301) [24]	Multicenter, randomized, double-blind, placebo-controlled study	12 weeks	50 mg lorundrostat OD for 6 weeks, followed by 100 mg lorundrostat OD for 6 additional weeks		270
					50 mg lorundrostat OD		541
					Placebo		272

Table 3 (continued)

Drug	Study phase	Study code	Study design	Treatment length	Treatment groups	Participants (n)
LY3045697	I	NCT01750853 (ASEA, I6S-MC-ASEA) [25]	First-in-human, incomplete, single ascending dose study	1 day	0.1–300 mg LY3045697	27
	I	NCT01821703 (ASEB, I6S-MC-ASEB) [25]	Incomplete, randomized, double-blind, placebo- and positive-controlled, crossover designed, dose-ranging study	8 days	0.1–300 mg LY3045697 OD	24
					25 mg spironolactone OD	
					Placebo	
Osilodrostat (LCI699)	II	NCT00817414 (CLCI699A2215) [26]	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study	6 weeks	0.5 mg osilodrostat OD	12
					1 mg osilodrostat OD	12
					1 mg osilodrostat BID	13
					2 mg osilodrostat OD	13
					Placebo	13
	II	NCT00758524 (CLCI699A2201) [27]	Multicenter, randomized, double-blind, placebo- and active-controlled, dose-ranging study	8 weeks	0.25 mg osilodrostat OD	92
					0.5 mg osilodrostat OD	87
					1 mg osilodrostat OD	86
					0.5 mg osilodrostat BID	96
					50 mg eplerenone BID	84
					Placebo	77

BID twice daily, *OD* once daily, *PRA* plasma renin activity

Table 4 Ongoing clinical studies testing aldosterone synthase inhibitors (ASIs) for the treatment of resistant hypertension (RHT)

Drug	Study phase	Study code	Study design	Main inclusion criteria	Estimated enrolment	Study group	Study start date (actual)	Estimated primary completion date	Estimated study completion date
Baxdrostat	III	NCT06268873 (D6972C00003)	Multicenter, randomized, double-blind, active-controlled study	RHT defined as seated SBP ≥140 mmHg at screening and mean AOBPM ≥130 mmHg at randomization, despite a stable regimen of ≥3 AHTs, with at least a diuretic	2500	Baxdrostat/dapagliflozin OD	29 Mar 2024	10 Dec 2027	10 Dec 2027
				Serum potassium level ≥3.5 and <5.0 mmol/L at screening		Dapagliflozin/placebo OD			
				eGFR ≥45 mL/min/1.73 m^2 at screening					
	III	NCT06034743 (D6970C00002)	Multicenter, randomized, double-blind, placebo-controlled study	Mean seated SBP on AOBPM ≥140 mmHg and <170 mmHg at screening	720	1 mg or 2 mg baxdrostat OD orally	22 Nov 2022	13 Oct 2025	13 Oct 2025
				Mean seated SBP on attended AOBPM of ≥135 mmHg at randomization		Placebo			
				Fulfil at least 1 of the following 2 criteria:					
				Subpopulation with uncontrolled hypertension: have a stable regimen of 2 AHTs, from different therapeutic classes (with at least a diuretic), at maximum tolerated dose					

Table 4 (continued)

Drug	Study phase	Study code	Study design	Main inclusion criteria	Estimated enrolment	Study group	Study start date (actual)	Estimated primary completion date	Estimated study completion date
				Subpopulation with RHT: have a stable regimen of ≥3 antihypertensive medications, from different therapeutic classes (with at least a diuretic), at maximum tolerated dose Serum potassium level ≥3.5 and <5.0 mmol/L at screening eGFR ≥45 mL/min/1.73 m^2 at screening					
	III	NCT06168409 (D6970C00009)	Multicenter, randomized, double-blind, placebo-controlled study	Mean seated SBP on AOBPM ≥140 mmHg and <170 mmHg at screening Mean ambulatory SBP ≥130 mmHg at randomization Stable regimen of ≥3 antihypertensive medications, from different therapeutic classes (with at least a diuretic), at maximum tolerated dose for at least 4 weeks before screening Serum potassium level ≥3.5 and <5.0 mmol/L at screening eGFR ≥45 mL/min/1.73 m^2 at screening	212	2 mg baxdrostat OD orally	15 Mar 2024	25 Apr 2025	25 Apr 2025

Table 4 (continued)

Drug	Study phase	Study code	Study design	Main inclusion criteria	Estimated enrolment	Study group	Study start date (actual)	Estimated primary completion date	Estimated study completion date
						Placebo			
Lorundrostat	II	NCT06150924 (MLS-101-206)	Part A Multicenter, randomized, double-blind, placebo-controlled study	UACR 300–3500 mg/g at screening	80	Lorundrostat/dapagliflozin OD	14 Dec 2023	Oct 2024	Jan 2025
				eGFR 45–89 mL/min/1.73 m^2 at screening		Lorundrostat OD			
				AOBP SBP 135–180 mmHg at screening		Placebo			
				AOBP SBP 135–160 mmHg at randomization					
				Stable treatment with an ACEi or ARB for ≥2 months before screening					
				BMI 18–45 kg/m^2 at screening					
			Part B Open-label, single arm, dose escalation	UACR 300–3500 mg/g at screening		Lorundrostat OD orally			
				eGFR 30–44 mL/min/1.73 m^2 at screening					
				AOBP SBP 135–180 mmHg at screening					
				AOBP SBP 135–160 mmHg at week 0					
				Stable treatment with an ACEi or ARB for ≥2 months before screening					
				BMI 18–45 kg/m^2 at screening					

Table 4 (continued)

Drug	Study phase	Study code	Study design	Main inclusion criteria	Estimated enrolment	Study group	Study start date (actual)	Estimated primary completion date	Estimated study completion date
	II - III	NCT05968430 (MLS-101-901)	Multicenter, open-label extension study	Completing the double-blind treatment phase of a respective parent study (including, but not limited to MLS-101-202 and MLS-101-301) and agreeing to transition immediately to this OLE study	900	Lorundrostat	14 Jul 2023	Dec 2025	Dec 2025
	II	NCT05769608 (MLS-101-202)	Multicenter, randomized, double-blind, placebo-controlled study	AOBP SBP 140–180 mmHg and AOBP DBP 65–110 mmHg or 90–110 mmHg at screening	261	Lorundrostat	13 Mar 2023	Jan 2025	Feb 2025
				24-h mean ABPM SBP 130–180 mmHg or 24-h mean ABPM DBP >80 mmHg		Lorundrostat			
				Taking 2–5 AHT medications at screening		Placebo			
				BMI 18–40 kg/m^2 at screening					

ACEi angiotensin-converting enzyme inhibitor, *AHT* antihypertensive, *AOBPM* automated office blood pressure measurement, *ARB* angiotensin receptor blocker, *BMI* body mass index, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *OD* once daily, *OLE* open-label extension, *RHT* resistant hypertension, *SBP* systolic blood pressure, *UACR* urine albumin-to-creatinine ratio

Both drugs share similarities in terms of their reliance on rigorous randomized, double-blind, placebo-controlled designs. However, they diverge in their patient focus, with baxdrostat trials targeting those with RHT on higher medication regimens and lorundrostat trials exploring broader patient profiles, including those with renal dysfunction and proteinuria. Additionally, lorundrostat trials incorporate those with fewer participants in earlier phases but compensate with long-term extension trials.

In summary, although both baxdrostat and lorundrostat demonstrate potential in addressing RHT, their ongoing trials reflect distinct strategies: baxdrostat trials lean toward large-scale, late-phase studies, whereas lorundrostat trials adopt a more exploratory and flexible approach, emphasizing kidney-related comorbidities and patient subpopulations. These complementary approaches may ultimately offer diverse therapeutic options for RHT.

3.2 Risk-of-Bias Assessment

The evidence regarding ASIs was thoroughly supported by multiple studies that provided sufficient and reliable information concerning critical methodological aspects. Specifically, these studies reported robust details about the allocation concealment process, the sequence generation procedures, and the measures taken for personal assessments and outcome evaluations. These methodological rigor elements were crucial in ensuring the reliability and validity of the findings and are detailed in Table 5, which summarizes the specific results and quality of the included studies.

4 Discussion

Pharmacokinetic analyses and available clinical data suggest that ASIs represent a promising therapeutic option for improving BP control in patients with RHT. However, several critical questions remain regarding their safety and long-term clinical applicability. The studies included in this systematic review show that ASIs significantly reduce both systolic and diastolic BP in patients with RHT. Specifically, baxdrostat, lorundrostat, and dexfadrostat have demonstrated dose-dependent BP reductions, with particularly notable efficacy in individuals with elevated plasma aldosterone concentrations. Moreover, the enzyme selectivity of certain ASIs, such as lorundrostat and LY3045697, for the CYP11B2 enzyme (responsible for aldosterone synthesis) over CYP11B1 (involved in cortisol synthesis), presents a compelling advantage in terms of minimizing off-target hormonal effects [28]. In contrast, osilodrostat (LCI699) lacks this selectivity and inhibits both enzymes, leading to cortisol suppression. This pharmacological profile has led to its primary approval for the treatment of Cushing's syndrome rather than RHT [29]. Although osilodrostat has shown BP-lowering effects in selected populations, including patients with type 1 familial hyperaldosteronism [30], its impact on the hypothalamic-pituitary-adrenal axis limits its clinical applicability in RHT compared with more selective ASIs such as baxdrostat and lorundrostat [31]. This is clinically relevant, as inhibition of CYP11B1 can interfere with cortisol production, potentially resulting in hypothalamic-pituitary-adrenal axis suppression and other adverse hormonal effects [32]. Therefore, ASIs with greater selectivity for CYP11B2 are expected to provide a more favorable safety profile, minimizing risks related to cortisol biosynthesis [33]. This distinction is especially important in the context of long-term therapy, since chronic cortisol suppression may lead to adrenal insufficiency and associated complications [34].

A pivotal consideration in the clinical use of ASIs for RHT is their electrolyte safety, particularly regarding the risk of hyperkalemia [35]. Although baxdrostat and lorundrostat appear to exhibit a relatively benign electrolyte profile, with a lower incidence of clinically significant hyperkalemia than less selective agents such as osilodrostat [36], available evidence suggests that the incidence of hyperkalemia is dose-dependent, with higher doses associated with a greater likelihood of electrolyte imbalances [37]. Moreover, in patients with RHT, particularly those with chronic kidney disease (CKD) or other comorbidities that affect potassium balance, the risk of hyperkalemia may be further exacerbated [37]. This presents a significant concern, as hyperkalemia can lead to serious complications, including arrhythmias, muscle weakness, and even life-threatening cardiovascular

Table 5 Outcomes of the risk-of-bias evaluation of the included studies using version 2 of the Cochrane risk-of-bias tool for randomized trials

Drugs	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results
Baxdrostat	Low risk	Low risk	Low risk	Low risk	Low risk
Dexfadrostat	Low risk	Low risk	Low risk	Low risk	Low risk
Lorundrostat	Low risk	Low risk	Low risk	Low risk	Low risk
LY3045697	Low risk	Low risk	Low risk	Low risk	Low risk
Osilodrostat (LCI699)	Low risk	Low risk	Low risk	Low risk	Low risk

events [38]. Consequently, careful monitoring of potassium levels is essential, especially during the initiation and titration phases of therapy, to ensure that patients do not experience dangerous electrolyte disturbances. Pharmacokinetics also play a crucial role in the clinical application of ASIs. For instance, baxdrostat has a long half-life (26–31 h), which allows for once-daily administration, thus improving patient adherence to treatment. In contrast, ASIs with shorter half-lives, such as osilodrostat (4–5 h), require more frequent dosing, which may contribute to fluctuations in BP and increase the risk of adverse effects. The pharmacokinetic properties of these drugs are important not only for determining their dosing schedules but also for understanding their potential for accumulation in the body, particularly in patients with renal insufficiency. In patients with impaired renal function, the clearance of ASIs may be reduced, leading to drug accumulation and a higher risk of adverse effects, such as hyperkalemia and hypotension.

Another important consideration is whether ASIs could be a suitable option for RHT in facilities capable of performing RDN. RDN has emerged as a potential treatment for patients with RHT, particularly those with sympathetic overactivity. Given that ASIs target aldosterone synthesis whereas RDN modulates renal sympathetic nerve activity, there is potential for these approaches to be complementary. Future investigations should explore the therapeutic interplay between ASIs and RDN or assess ASIs as viable alternatives in patients with disease refractory to interventional approaches. Head-to-head comparative studies evaluating ASIs versus RDN in the management of RHT could yield valuable insights into their relative efficacy, safety, and long-term clinical utility. Despite the promising efficacy and safety profile demonstrated thus far, significant knowledge gaps remain, particularly concerning long-term cardiovascular outcomes and the use of ASIs in clinically complex, high-risk subpopulations. One of the most urgent priorities is the conduct of well-powered, long-duration trials that evaluate the sustained effectiveness and safety of ASIs across diverse patient cohorts, as most of the current evidence derives from short-term studies with narrow inclusion criteria.

In particular, future studies should enroll patients with prevalent comorbidities such as diabetes, CKD, and cardiovascular disease, as these conditions may alter the pharmacokinetics and safety profiles of ASIs [20]. In CKD, elevated aldosterone may also contribute to disease progression via pro-inflammatory and fibrotic mechanisms independent of BP control [39]. Importantly, patients with coexisting RHT and CKD have limited therapeutic options, particularly due to the electrolyte-related constraints of many antihypertensive agents. In this context, vicadrostat (BI 690517), a novel, potent, selective ASI, is under development for the treatment of CKD with or without concurrent diabetes. Early phase studies have demonstrated a favorable benefit–risk evaluation in healthy volunteers [40], and a phase III randomized controlled trial is ongoing [41]. As research progresses, long-term data will also be crucial for evaluating the durability of BP reduction with ASI therapy and assessing the long-term cardiovascular outcomes of patients treated with these agents.

Beyond RHT, ASIs may also offer benefit in patients with uncontrolled essential hypertension, particularly those with evidence of aldosterone excess. In patients with primary aldosteronism, especially those with bilateral adrenal hyperplasia or who are non-surgical candidates, ASIs have demonstrated significant BP-lowering effects, potentially offering a mechanistically superior approach over receptor blockade alone [42]. ASIs may also prove beneficial in other aldosterone-driven phenotypes, such as obesity, type 2 diabetes mellitus, and CKD, where inappropriate renin-angiotensin-aldosterone system activation is often present despite normovolemia. To explore this potential, well-designed randomized controlled trials are required to identify subgroups most likely to benefit.

Randomized controlled trials comparing ASIs with standard antihypertensive therapies, in both uncontrolled hypertension and RHT, are needed to fully define their therapeutic positioning. In this regard, the recently published lorundrostat HTN trial [24] provides compelling evidence supporting the clinical utility of ASIs in patients with uncontrolled hypertension or RHT. Participants were randomized to receive lorundrostat 50 mg/day for 6 weeks followed by 100 mg/d for 6 weeks, lorundrostat 50 mg/d for 12 weeks, or placebo for 12 weeks. The results reinforce the therapeutic potential of lorundrostat in these populations. In the pooled cohort, 6 weeks of treatment with lorundrostat 50 mg/day led to a significant reduction in office systolic BP compared with placebo (−8.8 mmHg; $P<0.001$). In the RHT subgroup (i.e. patients receiving three or more antihypertensive agents), lorundrostat 50 mg/day produced an even greater reduction in office systolic BP (−9.0 mmHg; $P<0.001$) relative to placebo. In addition, prospective cohort studies and real-world observational data could offer valuable insights into the long-term safety and effectiveness of ASIs across a broader spectrum of patients with hypertension. Such research will be critical to establishing the definitive clinical role of ASIs and to optimizing their integration into hypertension treatment algorithms. Finally, head-to-head comparative trials between ASIs and other fourth-line treatments for RHT, such as MRAs, are warranted. Although MRAs have proven efficacy in BP reduction in patients with hyperaldosteronism, they are frequently associated with undesirable side effects, including hyperkalemia, sexual dysfunction,

and gynecomastia. If ASIs demonstrate comparable antihypertensive efficacy but with an improved safety and tolerability profile, they could emerge as a preferred alternative, particularly for patients who are intolerant to MRAs or experience significant adverse effects.

5 Conclusions

ASIs represent a promising therapeutic strategy for managing RHT, supported by encouraging pharmacological and clinical evidence. Data provide valuable insights into their mechanisms of action, pharmacokinetic properties, and potential therapeutic applications.

Evidence suggests that baxdrostat, lorundrostat, and dexfadrostat may provide effective BP control with an acceptable safety profile in patients with uncontrolled hypertension or RHT. In addition, given that ASIs target aldosterone synthesis and RDN modulates renal sympathetic nerve activity, there is potential for these approaches to be complementary in patients with difficult-to-treat hypertension.

Further investigations are needed to clarify the role of ASIs in clinical practice, optimize treatment protocols, and evaluate their long-term efficacy and safety. Research should also explore the potential application of ASIs in patients with hypertension without RHT and assess their role in settings where RDN is available.

Well-designed randomized controlled trials and real-world observational studies will be essential to define the optimal integration of ASIs into hypertension management across diverse patient populations.

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Consent for Publication Not applicable.

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