Hypertension

REVIEW

Emerging Medical Therapies for Primary Aldosteronism

Peeradon Vibhatavata, Adina F. Turcu

ABSTRACT: Medical therapy for primary aldosteronism has been stagnant for decades, relying on mineralocorticoid receptor antagonists, which block downstream signaling of aldosterone rather than aldosterone production. This approach typically leads to reactive elevation of aldosterone production, and possible implications of its nongenomic effects. In addition, steroidal mineralocorticoid receptor antagonist use is limited by cross-reactivity with other nuclear receptors and concern for hyperkalemia, particularly in kidney insufficiency. These limitations have propelled a rising interest in therapies that suppress aldosterone production. Aldosterone synthase inhibitors directly target aldosterone synthase overexpression and aldosterone excess. This review presents the evolving landscape of primary aldosteronism therapies, including emerging aldosterone synthase inhibitors and nonsteroidal mineralocorticoid receptor antagonists, and it presents a perspective on expected benefits and limitations of these emerging classes.

Key Words: adrenal ■ aldosterone ■ Cytochrome P-450 CYP11B2 ■ hyperaldosteronism ■ hypertension ■ mineralcorticoids

Primary aldosteronism (PA) is gaining recognition as a common cause of secondary hypertension, affecting at least 10% of individuals with hypertension and over 20% of those with treatment-resistant hypertension.[1,2] PA disproportionately enhances the risk of cardiovascular and renal morbidity and mortality compared with primary hypertension of similar severity.[3,4] Recently updated clinical practice guidelines emphasize the importance of early detection and targeted therapy of PA, and broaden recommendations for PA screening to all[5,6] or most individuals with hypertension.[7] While PA is potentially curable with unilateral adrenalectomy in select cases with single gland involvement, medications remain the mainstay of targeted therapy in majority of patients, including those with bilateral PA, and those with residual or recurrent disease following surgery.[8,9] Moreover, in contrast with the complex resources and expertise required for PA subtyping and identification of surgical candidates, medical management is readily accessible and can be promptly initiated in primary care clinics following a simple screening test, or even empirically.

Mineralocorticoid receptor (MR) antagonists (MRAs) have served as the backbone of PA medical therapy since the introduction of spironolactone in 1960, and of eplerenone 4 decades later[10] (Figure 1). By blocking the effects of aldosterone at receptor level, MRAs effectively lower blood pressure and help restore electrolyte balance.[11,12] Beyond blood pressure control, MRAs confer significant cardiovascular benefits, including regression of left ventricular hypertrophy, reduction in proteinuria, and decreased risk of cardiovascular events, particularly when used at doses that overcome renin suppression.[13–16] Nonetheless, steroidal MRAs have been underutilized, in part due to concerns for potential dose-dependent adverse effects, such as hyperkalemia, glomerular filtration rate decline, and antiandrogenic effects with spironolactone—which can compromise tolerability and adherence. By interfering with sodium reabsorption in the distal nephron, where urinary dilution occurs, MRAs can occasionally promote hyponatremia, particularly when associated with dysregulation of the antidiuretic hormone, as in heart failure or other settings in which free water excretion is impaired,[17] although this phenomenon is uncommon in PA. As such, even when considered for hypertension treatment, MRAs are often prescribed at low dosages,[11,12] which permit partial MR activation and sustained renin suppression. Consequently, overall,

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Nonstandard Abbreviations and Acronyms

11-DOC	11-deoxycorticosterone
ASI	aldosterone synthase inhibitor
CKD	chronic kidney disease
CYP11B1	11β hydroxylase
CYP11B2	aldosterone synthase
DBP	diastolic blood pressure
HSD11B2	11β-hydroxysteroid dehydrogenase type 2
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
ns-MRA	nonsteroidal mineralocorticoid receptor antagonist
PA	primary aldosteronism
PRA	plasma renin activity
SBP	systolic blood pressure

MRA therapy is inferior to surgery in mitigating cardiovascular and renal morbidity.[4,18,19] These limitations have fueled interest in improved therapies for PA, including more selective and better tolerated MRAs, and in aldosterone-targeted therapies that directly suppress aldosterone excess.

NONSTEROIDAL MRAs

Steroidal MRAs mimic aldosterone structurally and are built on the classic cyclopentanoperhydrophenanthrene steroid nucleus. These compounds induce an MR conformation that may still allow partial coactivator recruitment; in the case of spironolactone, the steroid-like structure facilitates its cross-reactivity with other nuclear hormone receptors, including androgen and progesterone receptors, resulting in off-target effects. To overcome these limitations, nonsteroidal MRAs (ns-MRAs) were developed using novel heterocyclic scaffolds that bind MR in a distinct, highly selective manner, and stabilize an inactive receptor conformation.[20,21] An additional benefit of ns-MRAs is a more neutral polarity, which contrasts with the highly lipophilic steroidal MRAs; this ensures a more balanced cardiac-renal tissue distribution of ns-MRAs, and a decreased risk of hyperkalemia. This advantageous pharmacological profile has renewed interest in MR blockade for prevention of albuminuria and cardiovascular morbidity in populations at risk, such as individuals with type 2 diabetes and chronic kidney disease (CKD). Nevertheless, to date, data in PA have been limited.

Finerenone

Finerenone is a dihydropyridine-based ns-MRA with high selectivity and strong MR antagonistic potency. Its balanced tissue distribution, which reduces renal accumulation, and lack of active metabolites lower the risk of hyperkalemia, particularly in advanced CKD.[22] In the phase III trials FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease)[23] and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kindney Disease),[24] finerenone reduced kidney disease progression and major cardiovascular events (including hospitalization for heart failure and cardiovascular death). The placebo-controlled FINEARTS-HF (Finerenone trial to investigate Efficacy and Safety Superior to placebo in Patients with Heart Failure) clinical trial enrolled patients with heart failure and a left ventricular ejection fraction of at least 40% and showed that finerenone, titrated to a maximum

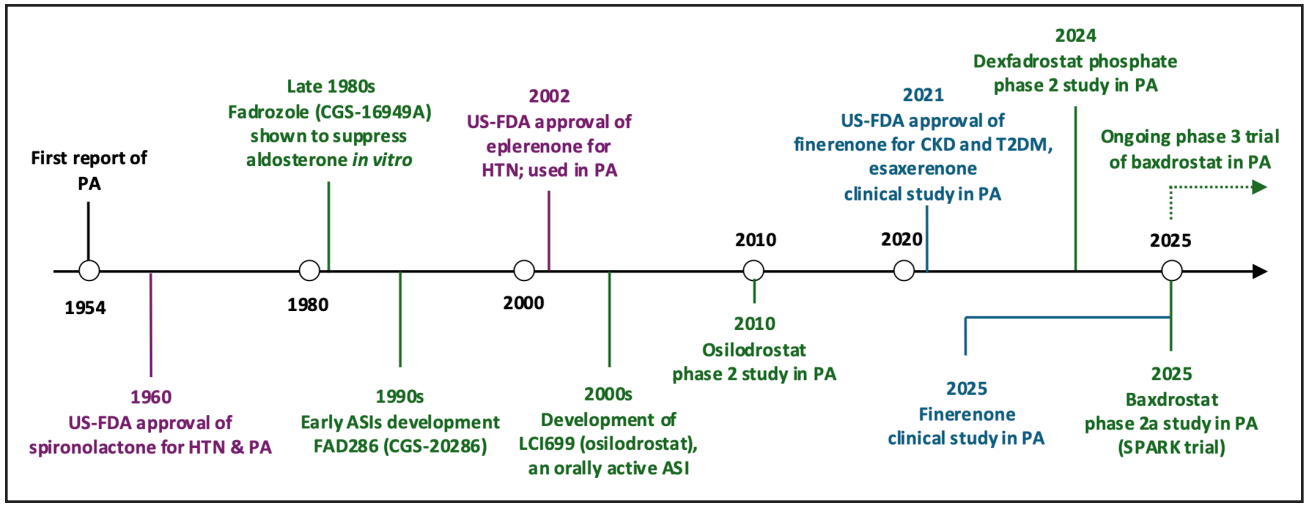


Figure 1. Milestones in medical therapy for primary aldosteronism (PA).
ASI indicates aldosterone synthase inhibitor; CKD, chronic kidney disease; HTN, hypertension; T2D, type 2 diabetes; and U.S. Food and Drug Administration, United States Food and Drug Administration.

dose of 40 mg daily, reduced the incidence of death from cardiovascular causes and total heart failure events.[25] These studies supported the U.S. Food and Drug Administration approval of finerenone in 2021 for CKD associated with type 2 diabetes (Figure 1). However, at the doses tested in these populations, the blood pressure reduction observed with finerenone was modest.[23,24]

Real-world data in 25 patients with PA showed that switching from eplerenone (median 100 mg/day) to finerenone (median 20 mg/day) reduced the proportion of patients with normal blood pressure and complete biochemical response, as renin levels declined to suppressed levels.[26] In a randomized trial of 70 patients with PA, finerenone at a mean dose of 22 mg/day lowered systolic blood pressure (SBP) and increased renin to a similar extent to low-dose spironolactone (mean 23 mg/day).[27] Finerenone was well tolerated, without notable side effects, while 20.7% of patients treated with spironolactone experienced antiandrogenic side effects or hyperkalemia. A prospective multicenter single-arm study of 57 patients with PA evaluated the efficacy of finerenone over 12 weeks of therapy.[28] Treatment was initiated at 20 mg/day and up-titrated to 40 mg/day in divided doses in 60% of patients, due to uncontrolled hypertension. This therapy led to reductions in mean daytime ambulatory SBP and diastolic blood pressure (DBP) of 6.7 and 4.6 mm Hg, respectively, and larger declines in office SBP and DBP of 15.6 and 8.6 mm Hg, respectively. Hypokalemia was corrected in most patients and renin suppression was reversed in 32.7% at study completion.

Esaxerenone

Esaxerenone is a ns-MRA with high MR-binding specificity and a long elimination half-life (20–24 hours).[29,30] Esaxerenone showed antihypertensive efficacy comparable to that of steroidal MRAs and was approved for the treatment of hypertension in Japan in 2019.[31] Esaxerenone also confers renal benefit in diabetic kidney disease through significant reductions in albuminuria.[32]

In a multicenter prospective study from Japan that enrolled 44 patients with PA, daily esaxerenone doses of 2.5 to 5 mg over 12 weeks lowered SBP and DBP by ≈18 mm Hg and 9 mm Hg, respectively. Blood pressure control (<140/90 mm Hg) was achieved in only 48% of participants, and 59% continued to have suppressed renin at study completion.[33] A retrospective cohort study reported similarly small increases in renin with esaxerenone.[34] A randomized trial of 74 Japanese patients showed that spironolactone achieved greater reductions in SBP and larger increases in serum potassium and renin than esaxerenone.[35] Although well tolerated, esaxerenone showed inferior antihypertensive and biochemical efficacy in PA.

Apararenone

Apararenone, a ns-MRA with extended half-life (≈280 hours), was well tolerated in healthy volunteers across studied doses.[36] In a randomized, placebo-controlled phase II study of patients with stage 2 diabetic nephropathy, daily doses of apararenone (2.5–10 mg) for 24 weeks significantly reduced urinary albumin-to-creatinine ratio compared with placebo: ≈37% to 50% mean reduction in urinary albumin-to-creatinine ratio at 24 weeks across active doses versus an increase with placebo (113.7%). Longer term (52-week) extension data showed sustained urinary albumin-to-creatinine ratio reduction with continued apararenone treatment.[37]

ALDOSTERONE SYNTHASE INHIBITORS

Aldosterone synthase inhibitors (ASIs) directly target aldosterone production by inhibiting the key and rate-limiting enzyme in its synthesis, CYP11B2 (aldosterone synthase). CYP11B2 performs the final 3 enzymatic steps in aldosterone synthesis: 11 -hydroxylation of 11-deoxycorticosterone (11-DOC) to corticosterone, followed by its 18-hydroxylation to 18-hydroxycorticosterone, and then 18-oxidation to aldosterone (Figure 2). While ASIs share a common mechanism of action, currently available agents differ in several pharmacological and clinical aspects, as summarized in Table 1.

The major challenge in developing ASIs has been the 93% structural homology between CYP11B2 and CYP11B1 (11β-hydroxylase), which results in cross-inhibition of cortisol synthesis.[38] Fadrozole (CGS-16949A), an imidazole-based aromatase inhibitor, provided the first proof of aldosterone suppression via CYP11B2 inhibition, but it also inhibited CYP11B1 and caused cortisol suppression.[39] Its dextro-enantiomer, FAD286, lowered aldosterone in angiotensin II-infused rats,[5] although its selectivity for CYP11B2 over CYP11B1 was only about 6-fold.[40,41]

Osilodrostat (LCI699) is a first-generation, orally active ASI derived from the FAD286 scaffold, but with markedly higher potency.[42] In patients with PA, osilodrostat lowered 24-hour SBP by 4 mm Hg and DBP by 2 mm Hg, and it reduced plasma aldosterone by up to 75%, with a corresponding dose-dependent rise in 11-DOC of up to 17-fold from baseline, consistent with marked CYP11B2 blockade. Osilodrostat, however, also led to adrenocorticotropic hormone elevation, accompanied by a blunted cortisol response, indicating CYP11B1 inhibition.[43] This agent was subsequently repurposed for Cushing syndrome.[44] Osilodrostat might have a role in patients with PA and cortisol excess. In a patient with bilateral macronodular adrenal hyperplasia and PA, osilodrostat improved blood pressure, and effectively suppressed both aldosterone and cortisol excess.[45]

 Hypertension. 2026;83:e26229. DOI: 10.1161/HYPERTENSIONAHA.126.26229

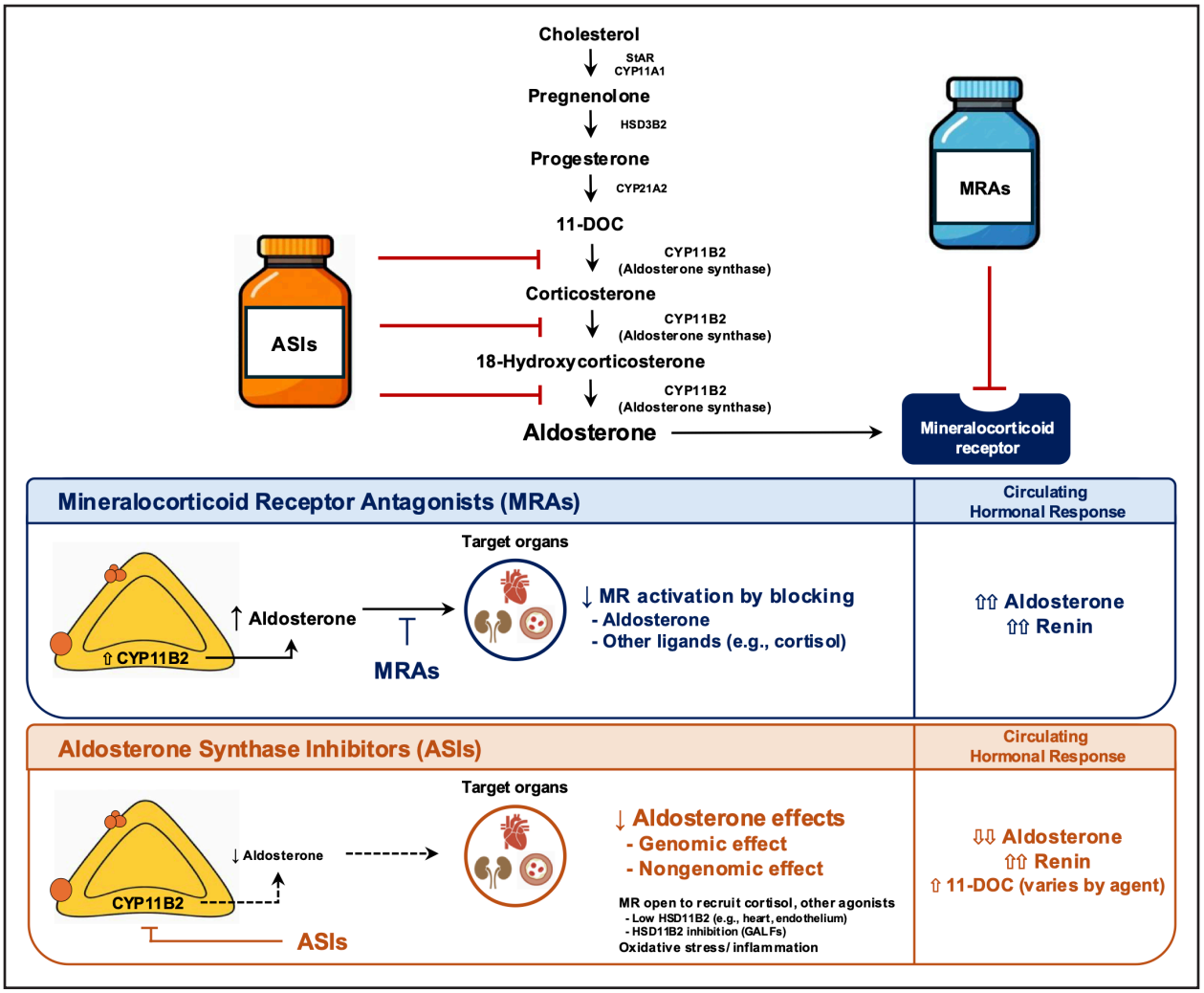


Figure 2. Mechanisms of action of mineralocorticoid receptor antagonists (MRAs) and aldosterone synthase inhibitors (ASIs). 11-DOC indicates 11-deoxycorticosterone; CYP11B2, aldosterone synthase; GALF, glycyrrhetinic acid-like factor; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; and MR, mineralocorticoid receptor.

Dexfadrostat Phosphate

Dexfadrostat phosphate, an FAD286-derived second-generation ASI designed to enhance structural selectivity for CYP11B2, was evaluated in a phase II study of 35 patients with PA who received 4, 8, or 12 mg once daily for 8 weeks.[46] Dexfadrostat phosphate lowered mean 24-hour SBP and DBP by 10.7 mm Hg and 5.7 mm Hg, respectively. The drug reduced the median aldosterone-renin ratio from 15.3 (ng/dL)/(mIU/L) to 0.6 (ng/dL)/(mIU/L). A marked reduction in 24-hour urinary tetrahydroaldosterone, the major aldosterone metabolite, was also observed in all dose groups, accompanied by a fall in plasma aldosterone in both lateralized and bilateral PA. Cortisol concentrations remained stable throughout treatment.

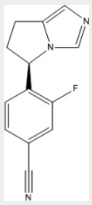
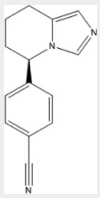
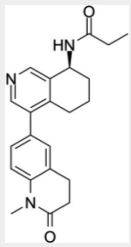
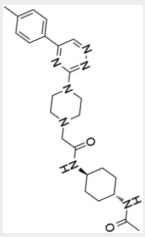
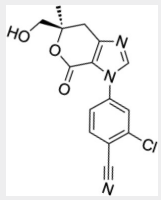
Hypokalemia persisted in 9% of participants at study completion. As with osilodrostat, 11-DOC progressively accumulated in all dose groups throughout the treatment period, reaching a 20-fold increase with the highest dose tested.

Baxdrostat

Baxdrostat is an oral second-generation nonimidazole ASI characterized by high potency and more than 100-fold selectivity for CYP11B2 over CYP11B1.[47] Baxdrostat is rapidly absorbed and has a half-life of 30 to 42 hours, allowing once daily dosing. Baxdrostat undergoes extensive hepatic metabolism, and only 12% is excreted unchanged in urine. Hence, renal impairment does not meaningfully alter its pharmacokinetics.[48]

In a study of patients with treatment-resistant hypertension, 1 mg and 2 mg of baxdrostat daily significantly lowered SBP compared with placebo, and it reduced aldosterone concentrations in a dose-dependent manner, with reciprocal renin elevation, while cortisol levels remained stable.[49] In a subsequent phase III clinical trial, the 2 mg dose of baxdrostat lowered SBP by 15.7 mm Hg, corresponding to a placebo-corrected reduction of 9.8 mm Hg at 12 weeks.[50] Serum aldosterone fell by more than half, and renin rose within the first 4

Table 1. Characteristics of Aldosterone Synthase Inhibitors

Characteristic	Osilodrostat	Dexfadrostat phosphate	Baxdrostat	Lorundrostat	Vicadrostat
Structure					
Selectivity for CYP11B2 vs CYP11B1	8:1	38:1*	100:1	374:1	250:1
Half-life	≈4 h	≈8-10 h	≈30-42 h	≈10-12 h	≈4-6 h
Effect on cortisol levels	↓	↔	↔	↔	↔
Studies in HTN	Approved for Cushing syndrome (US and EU)	_	Phase II/III in HTN, Phase II in CKD	Phase II/III in HTN	Phase II in CKD
Studies in PA	Phase II	Phase II	Phase II, Ongoing phase III	_	_

*Dexfadrostat data assumed from (R)-Fadrozole data. CKD indicates chronic kidney disease; EU, European Union; HTN, hypertension; PA, primary aldosteronism; and US, United States.

weeks of treatment. No cases of adrenal insufficiency were reported; severe hyperkalemia occurred in 3% of participants.[50]

In a phase II randomized trial of 195 patients with CKD and uncontrolled hypertension receiving background renin-angiotensin system blockade, baxdrostat was administered at 0.5 to 1 mg or 2 to 4 mg once daily. At week 26, baxdrostat led to a placebo-corrected reduction in SBP of 8.1 mm Hg, and in albuminuria of about 55%. Hyperkalemia was more frequent with baxdrostat, but most events were mild and transient.[51]

Specifically in PA, baxdrostat has been studied in 15 patients who underwent a phase IIa proof-of-concept, dose-escalation study.[52] Participants received initially 2 mg of baxdrostat daily, with up-titration to 4 or 8 mg daily, based on blood pressure response and tolerability. Mean SBP was reduced by 25 mm Hg and mean DBP by 11 mm Hg at week 12, a magnitude of reduction similar to that achieved with high-dose spironolactone.[53] Hypokalemia normalized in all affected patients, and serum and urinary aldosterone concentrations decreased rapidly after treatment initiation and were suppressed by >90% at week 12. Plasma renin activity (PRA) rose to ≈1.8-fold from baseline. The aldosterone-renin ratio fell below the diagnostic threshold for PA in 93% of patients, a degree of biochemical normalization that exceeds the long-term proportion of biochemical cure after adrenalectomy[9] and compares favorably with the proportions achieving reversal of renin suppression with MRAs.[11] In extended follow-up of the same cohort, patients who continued treatment to week 72 had further reductions in SBP and progressive increases in PRA. Levels of 11-DOC rose early during treatment to ≈11.5-fold from baseline and declined thereafter, to roughly half of peak values by week 36. This pattern coincided with a steady rise in PRA during prolonged enzyme blockade. Baxdrostat was well tolerated in patients with PA, with no discontinuations during the initial 12-week period. During the extension phase, baxdrostat was stopped in 1 patient who developed transient acute kidney injury and severe hyperkalemia, and 3 other cases of reversible decline in kidney function. Cortisol remained stable throughout the study.

An ongoing phase III placebo-controlled trial of baxdrostat in PA (BaxPA; REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT07007793) will expand on long-term safety and efficacy data in this population.

LORUNDROSTAT

Lorundrostat is a second-generation ASI achieving >300-fold selectivity for CYP11B2 over CYP11B1.[54] In a phase II dose-ranging study of 200 patients with uncontrolled hypertension, >80% of participants exhibited suppressed PRA at baseline. Lorundrostat was administered once or twice daily at doses ranging from 12.5 to 100 mg for 8 weeks. Placebo-corrected reductions in SBP of ≈8 to 10 mm Hg were observed with doses of lorundrostat ≥50 mg once daily. Blood pressure lowering appeared similar across renin strata. Lorundrostat was well tolerated, with preserved cortisol responses to cosyntropin stimulation.[55]

In a randomized, placebo-controlled study of 285 patients with uncontrolled or treatment-resistant hypertension, participants were assigned to placebo, lorundrostat at a stable dose of 50 mg once daily, or a

dose-adjusted regimen starting at 50 mg and titrated to 100 mg at week 4. At 12 weeks, lorundrostat produced comparable placebo-adjusted reductions in 24-hour ambulatory SBP of 7 to 8 mm Hg across regimens, accompanied by >50% reductions in circulating aldosterone and >2-fold increases in PRA. Hyperkalemia was more frequent at the higher dose (7% versus 5%), and no cases of adrenal insufficiency were observed.[56]

In the multicenter phase III Launch-HTN trial of 1083 patients with uncontrolled or treatment-resistant hypertension, lorundrostat 50 mg once daily lowered office SBP by 16.9 mm Hg at week 6, for a placebo-corrected reduction of 9.1 mm Hg, while DBP fell by 8.6 mm Hg compared with 5.2 mm Hg with placebo. Treatment discontinuation due to electrolyte or renal events occurred in <1% of participants, and no cases of glucocorticoid deficiency were identified.[57] Studies of lorundrostat in individuals with PA have not yet been conducted.

Given that PA accounts for ≈25% of treatment-resistant hypertension cases,[58] inclusion of patients with undiagnosed or mild PA may have contributed to the blood pressure responses observed with ASI therapy in this population. Nevertheless, although a subset of participants had suppressed renin at study entry,[49,50,55] blood pressure reduction was also observed in patients without suppressed renin, suggesting a role of dysregulated aldosterone production in hypertension pathology, regardless if primary or secondary.

Vicadrostat

In a phase II trial of 586 patients with albuminuric CKD receiving maximally tolerated renin-angiotensin system blockade, 14 weeks of vicadrostat treatment reduced albuminuria by up to 39% and by 46% when combined with empagliflozin.[59] Small SBP reduction was observed, given the relatively well-controlled baseline blood pressure and once-daily dosing despite the short half-life. Hyperkalemia and adrenal insufficiency were more frequent with vicadrostat than with placebo.[59]

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This second-generation ASI with >300-fold selectivity for CYP11B2 over CYP11B1 has been studied in primates, where it achieved up to 98% suppression of basal aldosterone, without notable changes in cortisol, 11-deoxycortisol, or 11-DOC.[60] Further investigations in humans are needed to define its safety profile and therapeutic potential.

ASIs VERSUS MRAs: THERAPEUTIC TRADE-OFFS AND FUTURE DIRECTIONS

Key pharmacological characteristics of ASIs and MRAs in PA therapy are summarized in Table 2, and their mechanisms of action are illustrated in Figure 2. Pathological aldosterone excess drives hypertension, hypokalemia, and tissue injury primarily via MR activation and downstream transcription-dependent (genomic) actions, which promote renal sodium retention and promote inflammatory and fibrotic remodeling in cardiovascular and renal tissues. In addition, aldosterone has nongenomic effects arising from rapid, membrane-associated signaling pathways within epithelial tissues (kidney, colon) and nonepithelial tissues (heart, vasculature, adipose tissue). These rapid nongenomic aldosterone signaling pathways have

Table 2. Comparison of Steroidal MRAs, Nonsteroidal MRAs, and ASIs in PA Therapy

	Steroidal MRAs	Nonsteroidal MRAs	ASIs
Mode of action	Competitive MR antagonists, variable androgen and progesterone receptor blockade	Highly selective MR antagonists, reverse agonists in low-aldosterone states	Inhibit aldosterone synthase
Nongenomic (MR-independent) aldosterone effects	Not inhibited	Not inhibited	Reduced
Blood pressure reduction	+++	+	+++
Correction of hypokalemia	+++	++	+++
Effect on aldosterone levels during chronic use	↑	↑	↓
Biochemical efficacy	+++ (↑ renin)	+ (↑ renin)	+++ (↓ aldosterone-renin ratio)
Key strengths	Long established use, widely available, affordable, proven outcome benefits, ligand-independent MR blockade	High MR selectivity, proven outcome benefits, no off-target steroid receptor effects, lower risk of hyperkalemia, ligand-independent MR blockade	Directly target aldosterone excess, mitigate both genomic and nongenomic signaling
Key limitations	Inhibition of androgen and progesterone receptors, hyperkalemia in advanced renal failure, limited effect on nongenomic signaling	Limited data in PA, modest blood pressure reduction and renin impact at studied doses, limited effect on nongenomic signaling	Variable CYP11B1 cross-inhibition, ↑ 11-DOC, limited data in PA, need for long-term outcomes data

11-DOC indicates 11-deoxycorticosterone; ASI, aldosterone synthase inhibitor; CYP11B1, 11β-hydroxylase; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; and PA, primary aldosteronism.

been linked to vasoconstriction through increased intracellular calcium and activation of the sodium-hydrogen exchanger (NHE1), oxidative stress, inflammation, and fibrotic tissue remodeling.[61,62] By suppressing aldosterone production, ASIs counteract both genomic and nongenomic aldosterone effects, whereas MRAs act downstream and only inhibit genomic MR signaling. Nevertheless, the clinical relevance of such effects remains incompletely understood, and MRAs have well-established benefits across a variety of cardiovascular pathologies.[15,63]

Pathological MR activation is not exclusively driven by aldosterone. Cortisol is a potent MR agonist, with affinity comparable to aldosterone, and its physiological concentrations are routinely 100- to 1000-fold higher compared with aldosterone,[10,61] far exceeding even aldosterone levels of most patients with PA. Although HSD11B2 (11β-hydroxysteroid dehydrogenase type 2) normally limits cortisol access to MR by converting it to cortisone, HSD11B2 expression is low in the myocardium and vascular endothelium, permitting cortisol-mediated MR activation in these tissues.[64] Furthermore, HSD11B2 activity is inhibited by licorice and by a number of exogenous and endogenous glycyrrhetinic acid-like factors, including 5α-reduced corticosterone and 11β-hydroxyprogesterone derivatives. Such compounds enable MR activation by cortisol and have been linked with low-renin hypertension.[65] In addition, oxidative stress and inflammation in pathological cardiac states can contribute to MR activation.[66,67] In this context, MRAs may confer benefit by broadly inhibiting MR activation arising from both aldosterone and nonaldosterone mediated mechanisms, and have consistently shown cardiovascular benefits across a broad range of populations, including hypertension, heart failure, and postmyocardial infarction.[25,68–70]

Accumulation of 11-DOC, a biologically active MR agonist, represents a class-level limitation of ASIs in PA treatment. Sustained elevations of 11-DOC during osilodrostat[43] (≈2.6 nmol/L) and dexfadrostat phosphate[46] (≈4.1 nmol/L) therapy reach concentrations ≈10 to 15-fold higher than those required for MR activation,[71] resulting in more modest blood pressure reduction and incomplete correction of hypokalemia. During treatment with baxdrostat, 11-DOC levels peaked around week 8 of therapy, and subsequently declined to steady-state levels of ≈0.6 nmol/L, accompanied by robust blood pressure reduction and reversal of renin suppression, supportive of negligible MR activation.[54] In contrast with the sharp rise of 11-DOC observed with all ASIs in PA studies, 11-DOC increased only modestly in healthy or hypertensive individuals,[72–75] possibly due to 11-DOC conversion to corticosterone via CYP11B1 within normal adrenal glands. In PA, CYP11B1, which is expressed in zona fasciculata and inner zona reticularis, might not have direct access to nodular 11-DOC, although this remains speculative. In addition, prolonged cytoreductive effects of ASIs have been suggested by sustained aldosterone suppression for many months following cessation of baxdrostat in some SPARK participants.[52] Similarly, cortisol suppression for up to 2 years has been reported following cessation of osilodrostat therapy for Cushing syndrome.[76–79] Recent reports of adrenal gland shrinkage in patients with adrenocorticotropic hormone-dependent Cushing syndrome treated with osilodrostat, despite sustained adrenocorticotropic hormone elevations[80] further support the hypothesis that CYP11B1/2 inhibitors might contribute to cell death or involution, specific to cells expressing these enzymes, although such effects were not observed in vitro or in animal studies. For ns-MRAs, currently available data using doses largely extrapolated from CKD populations suggest more modest clinical and biochemical control in PA, particularly with respect to reversal of renin suppression, a biomarker associated with cardiovascular risk reduction.[81] Higher and divided doses of finerenone improved blood pressure control in PA, but renin rise remained incomplete and less pronounced than with ASIs. Although ns-MRAs offer improved safety in advanced CKD and avoid off-target nuclear receptor effects, potential drug–drug interactions via cytochrome P450 pathways warrant careful consideration.[82,83]

Randomized head-to-head trials are needed to directly compare the effects of ASIs versus MRAs on blood pressure, biochemical control, and long-term cardiovascular and renal outcomes. Combined ASI-MRA therapy could be considered for the added benefit of aldosterone suppression while blocking residual MR activation driven by cortisol, 11-DOC, or MR overexpression in cardiovascular and renal pathology, although this approach requires further investigation and careful consideration of overlapping adverse effects, such as hyperkalemia.

CONCLUSIONS

Novel medical therapies for PA are reshaping the treatment landscape by moving beyond traditional MR blockade. ASIs target the core biochemical abnormality of the disease by suppressing aldosterone production and restoring its upstream regulatory signals, in contrast to the compensatory rise in aldosterone seen with MRAs. Early data indicate that ASIs may offer an effective treatment option for patients with PA. As clinical experience grows, these emerging therapies may broaden treatment strategies and align management more closely with the underlying biology of PA, across its subtypes.

ARTICLE INFORMATION

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Sources of Fundings

AFT was supported by grants: R01HL155834 from the National Heart, Lung, and Blood Institute, and 1R01AG080516 from the National Institute of Aging.

Disclosures

A.F. Turcu served as advisor for AstraZeneca and as local PI for an AstraZeneca-sponsored clinical trial. The other author report no conflicts.

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