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Aldosterone synthesis inhibitors in resistant hypertension: the BaxHTN trial

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Inhibitors of the renin–angiotensin–aldosterone system remain foundational therapies for arterial hypertension across major international guidelines. Their effectiveness, however, may be partially attenuated by the phenomenon of aldosterone escape, characterized by chronic elevation of adrenal aldosterone due to activation of alternative enzymatic pathways. Mineralocorticoid receptor antagonists are recommended as first-line therapy for resistant hypertension, yet their clinical utility is limited by poor adherence and high discontinuation rates, driven largely by hyperkalaemia and sex hormone–related adverse effects such as gynaecomastia, impotence, and menstrual irregularities. Recent pharmacologic research has focused on alternative strategies for suppressing aldosterone activity, particularly through the development of selective aldosterone synthase inhibitors (ASIs). This approach has led to the emergence of highly selective agents such as baxdrostat and lorundrostat. Clinical studies have demonstrated meaningful reductions in blood pressure among patients with resistant or uncontrolled hypertension, with favourable tolerability and without clinically significant adverse events. Further studies are required to determine the impact of ASIs on hypertensive-mediated organ damage, major cardiovascular events, nephrovascular outcomes, and long-term safety.

Introduction

Renin–angiotensin–aldosterone system (RAAS) inhibitors—specifically angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB)—represent the principal pharmacologic approach for treating hypertension.[1-3] Their efficacy, however, may be diminished by aldosterone escape, a process whereby aldosterone levels rise chronically through alternative enzymatic cascades involving chymase and cathepsin G, which stimulate transcription of CYP11B2, the enzyme responsible for converting 18-hydroxycorticosterone into aldosterone.[4]

Persistent aldosterone excess plays a central role in the pathophysiology of resistant hypertension (defined as blood pressure >140/90 mmHg despite triple therapy including a diuretic), contributing to sodium and water retention in the distal nephron, increased vascular resistance, and hypertension-mediated organ damage.[4]

Mineralocorticoid receptor antagonists are therefore considered first-line therapy for resistant hypertension, even when combination therapy with ACE inhibitors or ARBs, diuretics, and calcium-channel blockers is already in use.[1-3,5] Nevertheless, their tolerability remains a major limitation, with high rates of hyperkalaemia and

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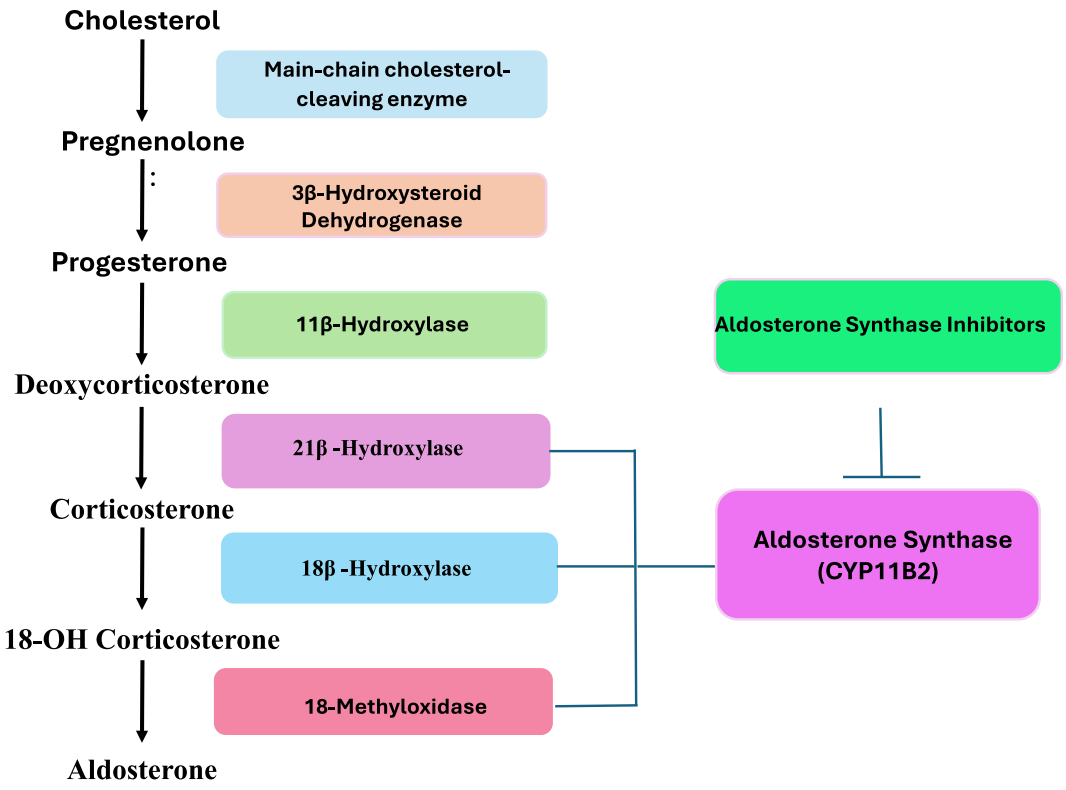

Figure 1 Mechanism of action of aldosterone synthase inhibitors.

adverse effects linked to off-target binding at sex hormone receptors, including gynaecomastia, erectile dysfunction, and menstrual disturbances.[6]

To address these limitations, recent pharmacologic development has concentrated on aldosterone synthase inhibitors (ASIs), which act by selectively suppressing CYP11B2 (*Figure 1*). Early challenges stemmed from the high structural and genetic similarity between aldosterone synthase and 11β-hydroxylase (CYP11B1), the enzyme responsible for cortisol synthesis, raising concern for potential adrenal insufficiency.[7]

Advances in molecular design have yielded highly selective ASIs—most notably baxdrostat and lorundrostat—which may represent future therapeutic options for resistant hypertension (*Figure 2*).

Baxdrostat

Phase 2 evidence

Several studies have investigated the efficacy and safety of baxdrostat in resistant or uncontrolled hypertension.

In the Phase 2 BrigHTN trial,[8] 248 individuals were randomized to baxdrostat 2, 1, 0.5 mg, or placebo. At 12 weeks, reductions in systolic blood pressure (SBP) were:

- −20.3 mmHg (2 mg),
- −17.5 mmHg (1 mg),
- −12.1 mmHg (0.5 mg), and
- −9.4 mmHg (placebo).

Significant placebo-adjusted reductions were observed with 2 mg (−11 mmHg) and 1 mg (−8.1 mmHg). Baxdrostat was not associated with adrenal insufficiency, and hyperkalaemia >6.0 mmol/L occurred in only two participants, resolving after temporary drug withdrawal without clinically relevant sequelae.

Phase 3 evidence: BaxHTN

The Phase 3 BaxHTN trial enrolled 794 patients with resistant or uncontrolled hypertension despite two antihypertensive agents.[9] The study was conducted in four sequential phases:

(1) Randomization to baxdrostat 1, 2 mg, or placebo for 12 weeks.
(2) Re-randomization of patients previously assigned to 1 mg or placebo to 2 mg or usual care (Weeks 12–24).
(3) Withdrawal phase (Weeks 24–32), evaluating persistence of drug effect.
(4) Long-term safety follow-up of baxdrostat 2 mg (Weeks 32–52).

At 12 weeks, reductions in SBP were:

- −14.5 mmHg (1 mg),
- −15.7 mmHg (2 mg), and
- −5.8 mmHg (placebo).

The corresponding placebo-adjusted differences were −8.7 and −9.8 mmHg. During withdrawal, a residual reduction of −3.7 mmHg persisted in the 2 mg group, whereas SBP increased by 1.4 mmHg in the placebo group—suggesting a prolonged biological effect, potentially via sustained inhibition of aldosterone

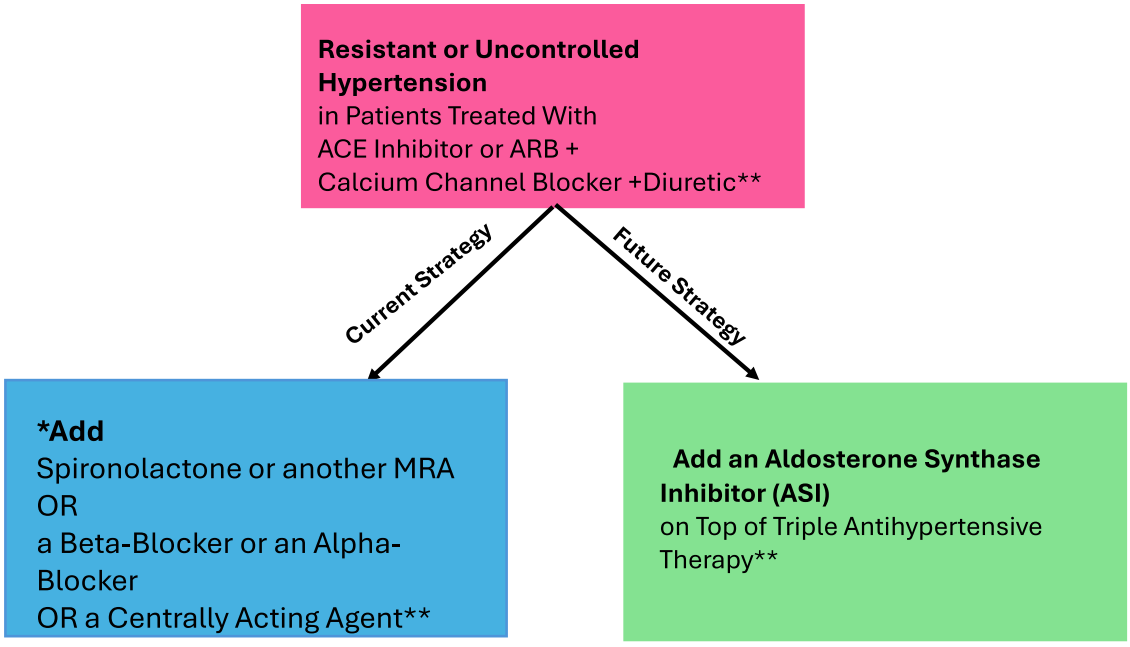

Figure 2 Potential role of aldosterone synthase inhibitors in resistant hypertension.

synthesis with implications for cardiac and vascular remodelling.[10]

Adverse events occurred in 41–47% of patients across groups and were predominantly mild, including electrolyte abnormalities (hyperkalaemia, hyponatremia), hypotension, and dizziness. Hyperkalaemia >6.0 mmol/L was infrequent, and no cases of adrenal insufficiency were reported.

A modest decline in estimated glomerular filtration rate (eGFR) (~7 mL/min/1.73 m^2), similar to that observed with RAAS inhibition, was noted with both baxdrostat doses, with subsequent stabilization. Reductions >30% occurred in 12.6 and 15.6% of patients receiving 1 and 2 mg, respectively; however, participants had preserved renal function at baseline (mean eGFR 85 mL/min/1.73 m^2). Safety in moderate chronic kidney disease remains to be established.

Moreover, enrolled patients were relatively young (mean age 61 years), and the study did not exclude pseudoresistant hypertension or confirm resistant hypertension via ambulatory blood pressure monitoring, as recommended in contemporary guidelines. Exclusion of secondary hypertension, including primary aldosteronism, was not clearly documented.[11]

Ambulatory blood pressure evidence: Bax24

In the Bax24 trial, baxdrostat reduced 24 h mean SBP by −14 mmHg, and 71% of patients achieved a 24 h SBP <130 mmHg compared with 17% on placebo.[12]

Lorundrostat

Phase 2 TargetHTN Trial

The TargetHTN trial evaluated lorundrostat in 163 patients with suppressed plasma renin activity (≤1.0 ng/mL/h) and elevated aldosterone (>1.0 ng/dL), plus a secondary cohort of 37 patients with non-suppressed renin. Patients with eGFR <60 mL/min/1.73 m^2 were excluded.[13]

Participants were randomized to placebo or one of five lorundrostat regimens. After 8 weeks, in the suppressed-renin cohort, reductions in SBP were:

- −14.1 mmHg (100 mg once daily),
- −13.2 mmHg (50 mg once daily),
- −6.9 mmHg (12.5 mg once daily),
- −10.1 mmHg (25 mg twice daily),
- −13.8 mmHg (12.5 mg twice daily), and
- −4.1 mmHg (placebo).

Significant placebo-adjusted reductions were observed with 50 mg (−9.6 mmHg) and 100 mg (−7.8 mmHg). In the non-suppressed renin cohort, lorundrostat 100 mg reduced SBP by −11.4 mmHg.

Phase 3 Advance-HTN trial

The Advance-HTN trial randomized 285 patients with resistant hypertension to placebo, lorundrostat 50 mg daily, or lorundrostat titrated to 100 mg if 24 h SBP remained >130 mmHg after 4 weeks.[14]

After 12 weeks:

- −15.4 mmHg (50 mg),
- −13.9 mmHg (titrated to 100 mg), and
- −7.9 mmHg (placebo).

Both studies demonstrated a favourable safety profile, with low rates of hyperkalaemia >6.0 mmol/L and no adrenal insufficiency.

Meta-analysis

A meta-analysis including 1426 patients across three trials confirmed a significant pooled SBP reduction of −9.8 mmHg, although with higher incidences of hypotension, hyponatremia, and hyperkalaemia.[15]

Conclusions

Further research is needed to validate the efficacy and safety of ASIs in patients at elevated cardiovascular risk and to determine their impact on hypertensive-mediated organ damage, major cardiovascular events such as myocardial infarction, stroke, and heart failure, and long-term cardiorenal protection.

Emerging therapeutic strategies may include combining ASIs with pharmacologic classes offering cardio-renal-metabolic protection, such as type 2 sodium glucose transporter inhibitors or glucagon like peptide-1 receptor agonists, particularly in hypertensive patients with comorbid diabetes or heart failure.

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Data availability

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

Disclaimer

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