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A PARADIGM SHIFT IN HYPERTENSION MANAGEMENT: THE EMERGENCE OF FIRST-IN-CLASS BAXDROSTAT

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ABSTRACT

Hypertension remains the leading modifiable risk factor for cardiovascular morbidity and mortality worldwide, affecting more than 1.3 billion individuals. Despite the availability of multiple antihypertensive drug classes, nearly half of treated patients fail to achieve optimal blood pressure control, with resistant hypertension representing a major unmet clinical challenge. Excessive aldosterone production is increasingly recognized as an important driver of resistant hypertension, cardiovascular remodeling, chronic kidney disease, and heart failure. Conventional mineralocorticoid receptor antagonists effectively block aldosterone signaling but are frequently limited by hyperkalemia, endocrine adverse effects, and poor tolerability. Baxdrostat, a highly selective aldosterone synthase inhibitor (ASI), represents the first-in-class therapeutic strategy that directly inhibits aldosterone biosynthesis while preserving cortisol synthesis through selective inhibition of CYP11B2.

KEYWORDS: Baxdrostat; Aldosterone synthase inhibitor; Resistant hypertension; CYP11B2; Blood pressure; Cardiovascular disease; Precision medicine; Novel antihypertensive therapy.

1. INTRODUCTION

Hypertension is the most prevalent chronic cardiovascular disorder and remains the leading contributor to ischemic heart disease, stroke, chronic kidney disease, heart failure, and premature mortality. According to global estimates, over 1.3 billion adults are affected, yet only a minority achieve recommended blood pressure targets despite the availability of multiple antihypertensive drug classes.

Current treatment strategies primarily include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics, β-blockers, and mineralocorticoid receptor antagonists. Although these therapies substantially reduce cardiovascular risk, resistant

hypertension—defined as blood pressure remaining above target despite treatment with at least three antihypertensive agents including a diuretic—continues to pose a major therapeutic challenge.

Recent advances in hypertension research have identified inappropriate aldosterone production as a central mechanism underlying resistant hypertension. This has stimulated the development of aldosterone synthase inhibitors that suppress aldosterone production at its source rather than blocking receptor activation.

Baxdrostat is the first highly selective aldosterone synthase inhibitor to successfully demonstrate clinically meaningful blood pressure reduction in Phase III clinical trials, marking one of the most significant advances in hypertension therapeutics in recent decades.

2. GLOBAL BURDEN Of HYPERTENSION

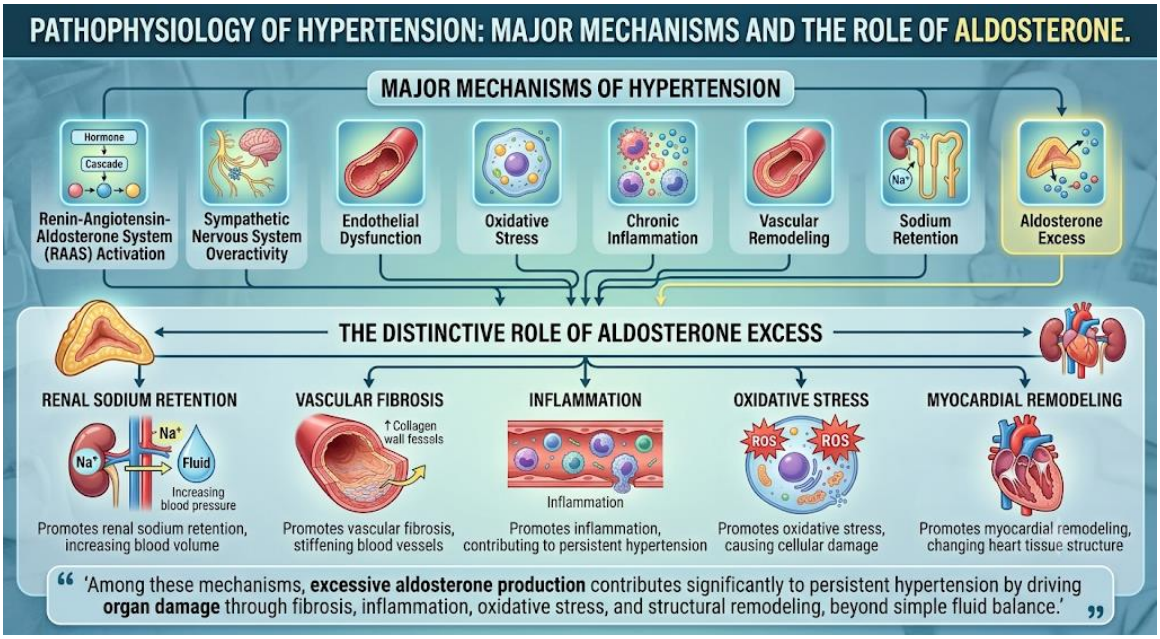
- Over 1.3 billion adults worldwide have hypertension.
- Approximately 10 million deaths annually are attributable to elevated blood pressure.
- Resistant hypertension affects 10–20% of treated patients.
- Uncontrolled hypertension markedly increases the risk of myocardial infarction, stroke, heart failure, atrial fibrillation, chronic kidney disease, dementia, and premature death.

3. PATHOPHYSIOLOGY Of HYPERTENSION

Major Mechanisms

- Renin–angiotensin–aldosterone system (RAAS) activation
- Sympathetic nervous system overactivity
- Endothelial dysfunction
- Oxidative stress
- Chronic inflammation
- Vascular remodeling
- Sodium retention
- Aldosterone excess

Among these, excessive aldosterone production contributes significantly to persistent hypertension by promoting renal sodium retention, vascular fibrosis, inflammation, oxidative stress, and myocardial remodeling.

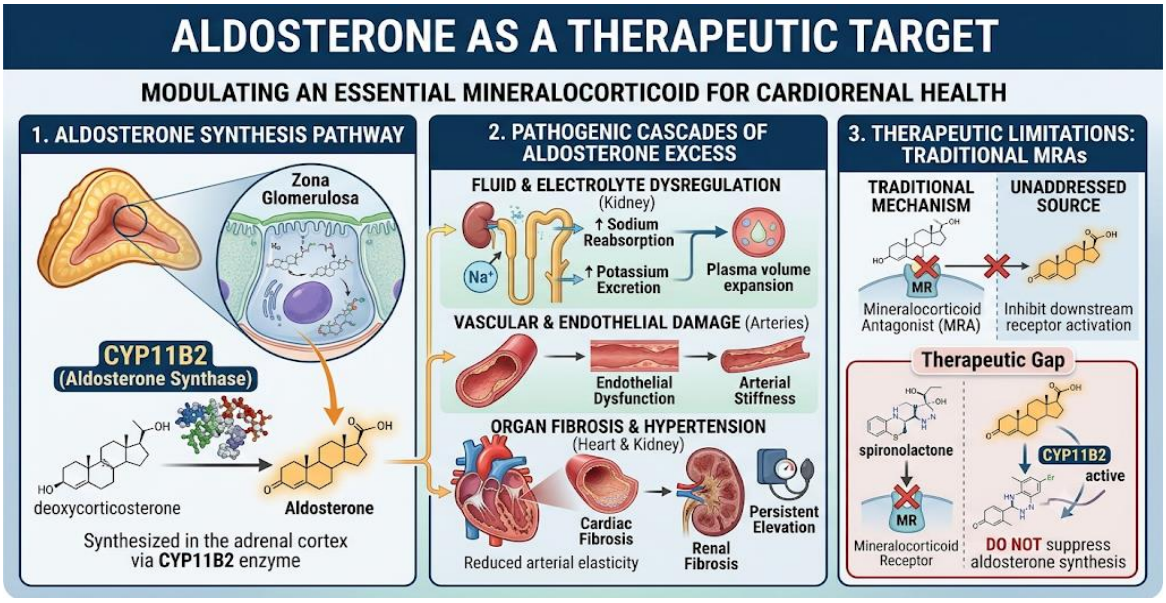


4. ALDOSTERONE AS A THERAPEUTIC TARGET

Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex via the enzyme aldosterone synthase (CYP11B2). Excess aldosterone causes:

- Increased sodium reabsorption
- Potassium excretion
- Plasma volume expansion
- Arterial stiffness
- Endothelial dysfunction
- Cardiac fibrosis
- Renal fibrosis
- Persistent elevation of blood pressure

Traditional mineralocorticoid receptor antagonists inhibit receptor activation but do not suppress aldosterone synthesis.



5. BAXDROSTAT: A FIRST-IN-CLASS ALDOSTERONE SYNTHASE INHIBITOR

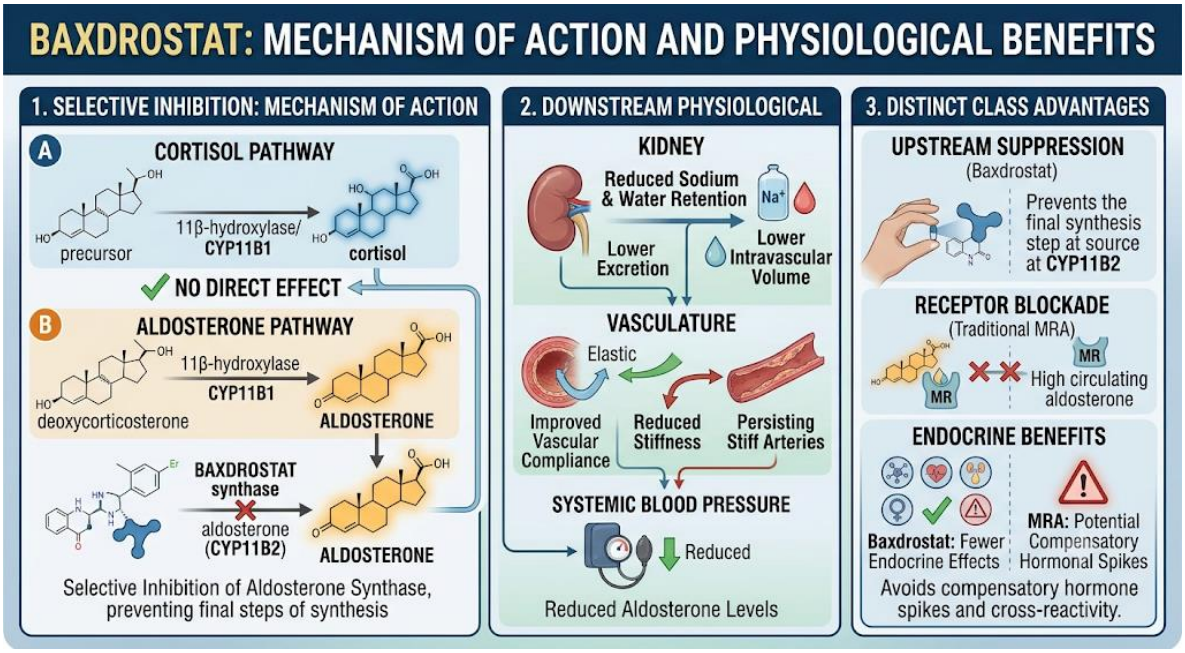
Drug Profile

- Drug class: Selective Aldosterone Synthase Inhibitor
- Molecular target: CYP11B2
- Administration: Oral, once daily
- Developer: AstraZeneca
- Indication under investigation: Uncontrolled and resistant hypertension

Unlike earlier compounds, baxdrostat selectively inhibits CYP11B2 while sparing CYP11B1, thereby minimizing cortisol suppression.

6. MECHANISM Of ACTION

Baxdrostat selectively inhibits aldosterone synthase, preventing the final steps of aldosterone biosynthesis. Reduced aldosterone levels decrease sodium and water retention, lower intravascular volume, improve vascular compliance, and reduce systemic blood pressure without directly affecting cortisol production. This mechanism differentiates baxdrostat from mineralocorticoid receptor antagonists and may reduce endocrine-related adverse effects.



7. CLINICAL DEVELOPMENT

Phase II – BrigHTN

- Demonstrated clinically meaningful reductions in systolic blood pressure.
- Established dose-dependent efficacy.
- Supported progression to Phase III.

Phase III – BaxHTN

The multinational BaxHTN trial enrolled patients with uncontrolled or resistant hypertension receiving standard antihypertensive therapy.

Key findings included:

- Significant reductions in seated systolic blood pressure versus placebo.
- Consistent efficacy across patient subgroups.
- Acceptable safety profile.
- Positive primary and secondary endpoint achievement.

8. SAFETY PROFILE

Most adverse events were mild to moderate.

Common findings:

- Hyperkalemia
- Mild reduction in aldosterone
- Stable cortisol concentrations
- Good overall tolerability

Routine monitoring of serum potassium and renal function remains advisable during therapy.

9. COMPARISON WITH CURRENT ANTIHYPERTENSIVE AGENTS

Drug Class	**Primary Target**	**Major Limitation**
ACE inhibitors	ACE enzyme	Cough, angioedema
ARBs	AT1 receptor	Incomplete aldosterone suppression
MRAs	Mineralocorticoid receptor	Hyperkalemia, endocrine effects
Baxdrostat	CYP11B2 (aldosterone synthase)	Hyperkalemia monitoring

10. FUTURE PERSPECTIVES

Potential future applications include:

- Resistant hypertension
- Primary aldosteronism
- Chronic kidney disease
- Heart failure prevention
- Precision medicine based on aldosterone biomarkers
- Combination therapy with SGLT2 inhibitors and RAAS blockers

11. CONCLUSION

Baxdrostat represents a major breakthrough in hypertension management by directly inhibiting aldosterone synthesis rather than antagonizing mineralocorticoid receptors. Clinical evidence indicates substantial reductions in systolic blood pressure with a favorable safety profile in patients with uncontrolled and resistant hypertension. If long-term cardiovascular outcome studies confirm reductions in major adverse cardiovascular and renal events, baxdrostat may become a foundational therapy for aldosterone-mediated hypertension and a key component of future precision cardiovascular medicine.

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