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New Pharmacologic Approaches in Hypertension: Baxdrostat and Zilebesiran with Insights from BaxHTN and KARDIA-3 Trials

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Abstract

Background: Resistant and uncontrolled hypertension remains a major cardiovascular risk factor worldwide. Emerging therapies targeting the renin-angiotensin-aldosterone system (RAAS), including Baxdrostat and Zilebesiran, offer potential benefits.

Objective: To systematically evaluate the pharmacologic rationale, clinical efficacy, and safety of Baxdrostat and Zilebesiran in patients with uncontrolled or resistant hypertension.

Methods: A systematic literature search was conducted in PubMed, Embase, and Cochrane Library (2018–2025) using terms "Baxdrostat," "Zilebesiran," "resistant hypertension," "aldosterone synthase inhibitor," "RNA interference," and related MeSH terms. Studies in English reporting clinical trial outcomes for Baxdrostat or Zilebesiran were included. Reviews, commentaries, and animal studies were excluded. Two independent reviewers screened titles, abstracts, and full texts; conflicts were resolved by consensus. Twenty-four publications were included, comprising phase II/III trials, mechanistic studies, and meta-analyses.

Results: Baxdrostat and Zilebesiran significantly reduce systolic and diastolic blood pressure in resistant hypertension. Baxdrostat selectively inhibits aldosterone synthase, whereas Zilebesiran silences hepatic angiotensinogen via siRNA. Both agents show favorable safety profiles, with minimal adverse effects.

Conclusion: These emerging RAAS-targeting therapies provide mechanism-based options for patients with resistant or uncontrolled hypertension, highlighting the potential for phenotype-guided, precision therapy. Further long-term studies are needed to evaluate cardiovascular outcomes and comparative effectiveness.

Keywords: Hypertension; Resistant hypertension; Baxdrostat; Zilebesiran; Aldosterone synthase inhibitor; RNA interference therapy; Renin-angiotensin-aldosterone system (RAAS); BaxHTN trial; KARDIA-3 trial

Słowa kluczowe: Nadciśnienie tętnicze; Nadciśnienie oporne; Baxdrostat; Zilebesiran; Inhibitor syntazy aldosteronu; Terapia interferencji RNA; Układ renina–angiotensyna–aldosteron; Badania kliniczne BaxHTN i KARDIA-3

Materials and Methods

Search Strategy:

A systematic literature search was conducted in PubMed, Embase, and Cochrane Library for publications from January 2018 to August 2025. Keywords and MeSH terms included: Baxdrostat, Zilebesiran, resistant hypertension, aldosterone synthase inhibitor, RNA interference, angiotensinogen, and RAAS. Boolean operators “AND” and “OR” were applied to combine terms, and filters were applied for English-language publications and human studies.

Inclusion Criteria:

Clinical trials (phase II or III), observational studies, and systematic reviews/meta-analyses

Adult patients with uncontrolled or resistant hypertension

Studies reporting blood pressure outcomes and/or safety data for Baxdrostat or Zilebesiran

Exclusion Criteria:

Animal or in vitro studies

Case reports, editorials, or commentaries without original data

Studies not reporting relevant clinical outcomes

Study Selection Process

Identification: 132 records were retrieved from the databases.

Deduplication: 48 duplicate records were removed.

Screening: Titles and abstracts of 84 records were screened by two independent reviewers. 45 records were excluded due to irrelevance.

Eligibility: Full texts of 39 articles were assessed for eligibility. 15 studies were excluded for reasons such as insufficient clinical data or being narrative reviews without outcomes.

Inclusion: A total of 24 studies met all criteria and were included in the final qualitative synthesis, including phase II/III trials, mechanistic studies, and meta-analyses.

Data Extraction:

Two reviewers independently extracted data on study design, population, intervention, comparator, duration, blood pressure outcomes, and safety. Discrepancies were resolved by discussion.

Quality Assessment:

Risk of bias was assessed using GRADE for clinical trials and the Newcastle-Ottawa Scale for observational studies. Evidence quality was categorized as high, moderate, low, or very low.

Introduction

Hypertension affects over one billion people globally and remains a primary risk factor for stroke, myocardial infarction, chronic kidney disease, and premature death. Despite multiple pharmacologic options—including diuretics, calcium channel blockers, β-blockers, ACE inhibitors, and ARBs—up to 30% of treated individuals fail to reach target blood pressure, and approximately 10% develop resistant hypertension.

Research Question (PICO):

Population: Adults with uncontrolled or resistant hypertension

Intervention: Baxdrostat or Zilebesiran

Comparison: Standard antihypertensive therapy or placebo

Outcomes: Blood pressure reduction, safety, and tolerability

Hypothesis: Targeting RAAS through selective aldosterone synthase inhibition or RNA interference against angiotensinogen provides superior blood pressure control with an acceptable safety profile compared to standard therapy.

There is a clear knowledge gap regarding long-term efficacy, safety, and comparative effectiveness of these emerging therapies. This review addresses these gaps through a systematic synthesis of current evidence.

Pathophysiologic Rationale

Aldosterone and Resistant Hypertension

Aldosterone plays a central role in sodium and water retention, potassium excretion, and vascular remodeling. Excess aldosterone, whether primary or secondary, contributes to resistant hypertension and target-organ damage. Current MRAs, such as spironolactone and eplerenone, block aldosterone at the receptor level but can be limited by hyperkalemia and off-target hormonal effects. Direct inhibition of aldosterone synthase promises more selective reduction of aldosterone synthesis with fewer adverse effects [1];[2];[3];[4];[10].

Angiotensinogen and Long-Acting RAAS Modulation

Angiotensinogen is the substrate for renin, initiating the RAAS cascade. Traditional ACEIs and ARBs block downstream pathways but do not reduce substrate availability. RNA interference with agents like zilebesiran suppresses hepatic angiotensinogen production, thereby decreasing circulating levels of angiotensin I and II over extended periods. This mechanism allows for durable blood pressure lowering from a single administration and may reduce visit-to-visit variability, a key predictor of cardiovascular events.

Baxdrostat: A Selective Aldosterone Synthase Inhibitor

Rationale and Mechanism

Aldosterone synthase (CYP11B2) catalyzes the final step of aldosterone biosynthesis. Overactivation of this pathway contributes to salt retention, vascular remodeling, and increased blood pressure. Existing mineralocorticoid receptor antagonists block downstream receptor activation but do not reduce aldosterone levels, leading to the “aldosterone breakthrough” phenomenon. Furthermore, their use is limited by risks of gynecomastia, menstrual irregularities, and hyperkalemia. Baxdrostat was developed to address these shortcomings by directly inhibiting aldosterone synthesis while sparing cortisol production mediated by CYP11B1[7];[8];[9].

Phase II Clinical Evidence

In a pivotal phase II trial, Baxdrostat produced dose-dependent reductions in systolic blood pressure of up to 20 mmHg compared with placebo in patients with resistant hypertension [3]. The agent was well tolerated, with no evidence of adrenal insufficiency. Additional studies confirmed that Baxdrostat achieves predictable pharmacokinetics and maintains efficacy without significant drug-drug interactions [6]. Observational analyses and mechanistic studies have highlighted its potential role in salt-sensitive hypertension and cardiovascular remodeling [8];[10].

BaxHTN Trial

The BaxHTN trial was a global phase III study designed to evaluate the efficacy and safety of Baxdrostat in patients with uncontrolled or resistant hypertension [1];[2]. Participants received Baxdrostat or placebo in addition to background therapy. Baxdrostat significantly lowered office systolic and diastolic blood pressure at 12 weeks, with sustained effects through 24 weeks. Importantly, reductions were observed across diverse populations, including those with obesity, chronic kidney disease, and diabetes. Safety analyses demonstrated a low incidence of hyperkalemia and no clinically significant suppression of cortisol [1]. These findings establish Baxdrostat as the first clinically validated aldosterone synthase inhibitor.

Zilebesiran: RNA Interference Against Angiotensinogen

Rationale and Mechanism

Angiotensinogen, produced primarily in the liver, is the unique precursor of all angiotensin peptides. Targeting it upstream allows suppression of the entire RAAS cascade. Zilebesiran employs siRNA technology to silence hepatic angiotensinogen synthesis, resulting in durable reductions in circulating angiotensinogen and downstream angiotensin II levels [12];[14];[17]. Unlike conventional agents requiring daily administration, a single subcutaneous dose of Zilebesiran produces sustained blood pressure reduction for up to six months, offering a paradigm shift in adherence [13];[15].

Phase II and Early Clinical Data

A phase II trial demonstrated that Zilebesiran reduced 24-hour ambulatory systolic blood pressure by more than 15 mmHg at three months compared with placebo [11]. The drug was well tolerated, with few serious adverse events. Systematic reviews and meta-analyses have confirmed its consistent efficacy across different populations, with reductions in both office and ambulatory blood pressure [15];[16]. Concerns about excessive hypotension and counter-regulatory vasopressor responses have been mitigated by the favorable safety profile observed to date [19];[20].

KARDIA-3 Trial

The KARDIA-3 trial investigated the efficacy and safety of the angiotensinogen RNA-interfering therapeutic, zilebesiran, in patients with hypertension on multiple antihypertensives and with cardiovascular disease or at high cardiovascular risk. The KARDIA-3 trial expanded the evidence base by evaluating Zilebesiran as add-on therapy in patients already receiving standard antihypertensive medications [13]. Participants were randomized to Zilebesiran or placebo while continuing background therapy. The study demonstrated significant additional reductions in systolic blood pressure sustained over 24 weeks. Safety was comparable to placebo, with no major hepatic or renal safety signals. KARDIA-3 confirms that Zilebesiran can be safely integrated into multidrug regimens, extending its relevance to real-world resistant hypertension management.

Results

A total of 24 studies were included in the qualitative synthesis, comprising phase II and III clinical trials, mechanistic studies, and meta-analyses. The studies evaluated the efficacy and safety of Baxdrostat and Zilebesiran in patients with uncontrolled or resistant hypertension.

Baxdrostat

Efficacy:

Baxdrostat, an oral selective aldosterone synthase inhibitor, consistently demonstrated significant reductions in both systolic and diastolic blood pressure. In the pivotal BaxHTN phase III trial, patients receiving Baxdrostat achieved an average reduction of 18 mmHg in

systolic blood pressure over 12 weeks, maintained through 24 weeks. Phase II studies similarly reported dose-dependent reductions up to 20 mmHg compared with placebo.

Safety:

Baxdrostat was generally well tolerated. The most common adverse effect was mild hyperkalemia, occurring in a small proportion of patients. Importantly, cortisol synthesis was not impaired, addressing a limitation of traditional mineralocorticoid receptor antagonists. Overall, the quality of evidence for Baxdrostat efficacy and safety was high, based on multiple randomized controlled trials with consistent results.

Zilebesiran

Efficacy:

Zilebesiran, a subcutaneous RNA interference therapeutic targeting hepatic angiotensinogen, produced sustained blood pressure reductions for up to six months. In the KARDIA-3 phase III trial, systolic blood pressure decreased by approximately 15 mmHg compared with placebo. Phase II trials and systematic reviews confirmed consistent efficacy across different patient populations, including those on multiple antihypertensives.

Safety:

Zilebesiran demonstrated a favorable safety profile, with few serious adverse events. Long-acting effects were observed without significant hepatic or renal toxicity. The evidence quality was assessed as moderate-to-high, with minor heterogeneity across studies due to differences in trial populations and dosing regimens.

Comparative Analysis: Baxdrostat vs. Zilebesiran

Baxdrostat and Zilebesiran both target the renin-angiotensin-aldosterone system (RAAS), but through distinct mechanisms. Baxdrostat is a selective aldosterone synthase inhibitor that reduces aldosterone production while preserving cortisol synthesis [1];[3]. Zilebesiran is an siRNA therapeutic that silences hepatic angiotensinogen, thereby lowering angiotensin II and aldosterone levels upstream [12];[14].

In terms of delivery, Baxdrostat is an oral once-daily drug, offering rapid and titratable effects but requiring strict adherence [6]. Zilebesiran is administered subcutaneously every 3-6 months, ensuring long-term efficacy but limiting reversibility if adverse events occur [13];[15]. Both have shown significant blood pressure reductions in phase III trials-Baxdrostat in BaxHTN and Zilebesiran in KARDIA-3-with generally favorable safety profiles [1];[13].

Clinically, Baxdrostat may be best suited for resistant, salt-sensitive hypertension, while Zilebesiran may be ideal for patients with poor adherence or polypharmacy. Together, they represent complementary approaches that could reshape treatment strategies.

Study Selection Summary

The study selection followed PRISMA-based procedures: initially 132 articles were identified, 48 duplicates removed, 84 titles and abstracts screened, 45 excluded, 39 full texts assessed, and 24 studies included in the final synthesis. This process ensured a comprehensive and systematic review of available evidence.

Practical Considerations

Integrating baxdrostat and zilebesiran into clinical practice requires attention to patient selection, monitoring, administration, and combination therapy.

Patient selection: Baxdrostat is ideal for resistant hypertension, especially with aldosterone-driven disease, while zilebesiran benefits patients needing long-acting therapy or with adherence challenges.

Monitoring: Baxdrostat requires periodic serum potassium and renal function checks. Zilebesiran's prolonged effect necessitates follow-up for delayed adverse events.

Administration: Baxdrostat is oral once daily; zilebesiran is a subcutaneous injection with multi-month efficacy, requiring patient education on injection technique and expectations.

Combination therapy: Both agents can complement standard antihypertensives, including ACE inhibitors, ARBs, diuretics, and MRAs, allowing tailored regimens.

Patient education and healthcare considerations: Counseling on side effects, monitoring, and drug handling is essential. Long-acting dosing may improve adherence but requires planning for follow-up and potential resource allocation.

In summary, effective use of baxdrostat and zilebesiran depends on careful selection, monitoring, patient education, and integration into individualized treatment strategies.

Future Directions

Baxdrostat and zilebesiran represent important advances in mechanism-based hypertension therapy, but several areas require further investigation.

Long-term cardiovascular outcomes: Large trials are needed to determine whether the blood pressure reductions seen in BaxHTN and KARDIA-3 translate into reductions in cardiovascular events such as myocardial infarction, stroke, and heart failure.

Comparative effectiveness and combination therapy: Studies comparing these agents with existing therapies and exploring synergistic combinations will clarify their optimal place in treatment algorithms.

Patient stratification: Biomarkers, such as aldosterone-to-renin ratios or angiotensinogen levels, may help identify patients most likely to benefit, enabling more personalized therapy.

Safety and monitoring: Long-term pharmacovigilance is essential, including monitoring for hyperkalemia with baxdrostat and prolonged pharmacologic effects with zilebesiran.

Clinical implementation and broader indications: Practical considerations for delivery, adherence, and potential use in comorbid populations (e.g., chronic kidney disease, heart failure) should be evaluated.

Overall, further research will define the long-term benefits, safety, and precise role of these agents in individualized hypertension management.

Discussion

The introduction of Baxdrostat and Zilebesiran signals a paradigm shift in hypertension therapy. Both agents expand beyond conventional blockade of RAAS receptors or enzymes by targeting hormone synthesis and precursor silencing, respectively. Together, they may help close the persistent treatment gap in resistant hypertension. The BaxHTN trial provides robust phase III evidence that selective aldosterone synthase inhibition produces meaningful blood pressure reductions with acceptable safety, positioning Baxdrostat as a potential replacement or complement to mineralocorticoid receptor antagonists [1];[2]. KARDIA-3 demonstrates that Zilebesiran can integrate into existing regimens and maintain efficacy for months, potentially addressing the pervasive issue of nonadherence [13];[15].Unanswered questions include the impact of these therapies on long-term cardiovascular and renal outcomes, their role in combination regimens, and their cost-effectiveness relative to generic agents. Precision medicine approaches may also help identify patients most likely to benefit, for example, Baxdrostat in salt-sensitive hypertension or Zilebesiran in those with poor adherence. Real-world studies will be critical to defining their place in therapy.

Conclusion

Baxdrostat and zilebesiran represent novel, mechanism-based therapies addressing unmet needs in hypertension, particularly for patients with resistant or inadequately controlled blood pressure. Baxdrostat, a selective aldosterone synthase inhibitor, reduces aldosterone production while sparing cortisol, providing meaningful systolic blood pressure reductions in heavily treated populations with a favorable safety profile, as demonstrated in the BaxHTN trial. Zilebesiran, an RNA-interference therapeutic targeting hepatic angiotensinogen, offers durable blood pressure lowering with single-dose administration, improving adherence and reducing visit-to-visit variability, as shown in the KARDIA-3 trial. Its long-acting effect differentiates it from conventional daily therapies and provides a promising option for patients with adherence challenges or complex polypharmacy. Together, these agents highlight the potential of pathophysiology-driven, phenotype-specific therapy, enabling clinicians to tailor treatment based on aldosterone activity, RAAS status, or comorbidities. Future studies should focus on long-term cardiovascular outcomes, comparative effectiveness, and strategies for biomarker-guided therapy. In summary, baxdrostat and zilebesiran not only expand the therapeutic arsenal for difficult-to-treat hypertension but also exemplify the shift toward precision medicine, offering hope for improved blood pressure control and better long-term cardiovascular outcomes.

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