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THE ROLE OF NEXT-GENERATION ANTIHYPERTENSIVE AGENTS IN THE TREATMENT OF ARTERIAL HYPERTENSION: CURRENT EVIDENCE AND CLINICAL PERSPECTIVES

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ABSTRACT

Arterial hypertension is a leading modifiable determinant of cardiovascular and renal morbidity, yet suboptimal blood pressure (BP) control persists despite the availability of effective conventional therapies. This narrative review critically examines the clinical efficacy, safety, and potential therapeutic positioning of next-generation antihypertensive strategies, including endothelin-receptor antagonism, aldosterone-synthase inhibition, RNA interference, and innovative single-pill combinations. International clinical guidelines, randomized controlled trials, and official United States regulatory documents available through 10 November 2026 were analyzed. In the PRECISION trial, aprocitentan 12.5 mg achieved a placebo-adjusted reduction of 3.8 mmHg in office systolic BP (SBP) at 4 weeks. In BaxHTN, baxdrostat 1 and 2 mg reduced office SBP by an additional 8.7 and 9.8 mmHg, respectively, at 12 weeks, whereas lorundrostat 50 mg achieved a 9.1-mmHg placebo-adjusted reduction at 6 weeks in Launch-HTN. The investigational RNA-interference agent zilebesiran demonstrated sustained reductions in ambulatory BP, with effects varying according to background therapy in KARDIA-2. Novel triple and quadruple single-pill combinations also yielded clinically relevant improvements in BP control. These findings suggest that newer therapies may expand treatment options for appropriately selected patients with uncontrolled or resistant hypertension. Nevertheless, their clinical incorporation should follow confirmation of genuine treatment resistance and optimization of standard therapy, with careful consideration of regulatory status, adverse effects, renal function, electrolyte disturbances, affordability, and the limited availability of drug-specific cardiovascular outcome data.

Keywords: arterial hypertension; resistant hypertension; novel antihypertensive drugs; aprocitentan; baxdrostat; lorundrostat; zilebesiran; aldosterone synthase inhibitor; RNA interference; single-pill combination.

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INTRODUCTION

Arterial hypertension is a major determinant of stroke, ischemic heart disease, heart failure, and chronic kidney disease. The NCD Risk Factor Collaboration has documented persistent global disparities in hypertension detection, treatment, and control, indicating that effective management depends not only on pharmacological innovation but also on treatment accessibility, adherence, and timely therapeutic intensification [1]. Evidence from a large meta-analysis further confirms that lowering BP reduces major cardiovascular events, thereby establishing sustained BP control as a cornerstone of cardiovascular prevention [2]. Consistent with this evidence, European and American guidelines continue to prioritize established therapeutic classes, particularly renin–angiotensin system inhibitors, long-acting calcium-channel blockers, and thiazide or thiazide-like diuretics [3,4]. Combination therapy, preferably administered as a single-pill regimen when clinically appropriate, is frequently required to achieve treatment targets. Nevertheless, persistent hypertension despite multidrug therapy, together with the contribution of aldosterone-mediated sodium retention and alternative vasoconstrictor pathways, has prompted the investigation of treatments that extend beyond conventional pharmacological mechanisms [3–5].

A clear distinction between uncontrolled and genuinely resistant hypertension is essential before treatment escalation. Apparent resistance may result from nonadherence, inaccurate BP measurement, a white-coat effect, excessive dietary sodium, interfering medications, or inadequately investigated secondary causes. True resistance is generally considered when BP remains above the recommended target despite a properly selected and tolerated three-drug regimen that includes a diuretic, after relevant sources of pseudoresistance have been addressed. Because spironolactone remains an evidence-supported add-on treatment, newer and potentially more expensive agents should be considered in relation to, rather than as automatic replacements for, optimized conventional therapy [5,6].

Recent advances in antihypertensive pharmacotherapy involve four complementary approaches: blockade of endothelin-mediated vasoconstriction with aprocitentan; inhibition of aldosterone synthesis with baxdrostat and the investigational agent lorundrostat; suppression of hepatic angiotensinogen production using the small-interfering RNA (siRNA) agent zilebesiran; and the simplification of multidrug treatment through low-dose triple or four-component single-pill combinations. Although these approaches may address different barriers to BP control, they vary substantially in their degree of clinical validation, regulatory approval, monitoring requirements, and safety profiles [7–17]. Against this background, the present review synthesizes trial-level evidence and contemporary clinical recommendations to propose an evidence-informed approach to the selection, safety monitoring, and practical integration of next-generation therapies in adults with uncontrolled or resistant arterial hypertension.

MATERIALS AND METHODS

This study was designed as a targeted narrative clinical review and methodological synthesis, rather than a prospective or retrospective patient study, registered systematic

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review, or meta-analysis. The evidence base comprised European Society of Cardiology recommendations issued in 2024, American Heart Association/American College of Cardiology guidance published in 2025, the 2026 American College of Cardiology expert consensus pathway, peer-reviewed randomized controlled trials and major evidence syntheses, and official US Food and Drug Administration prescribing information available through 10 November 2026 [1–18]. Literature identification focused on the terms “resistant hypertension,” “aprocitentan,” “baxdrostat,” “lorundrostat,” “aldosterone synthase inhibitor,” “zilebesiran,” “RNA interference,” “KARDIA,” “PRECISION,” “BaxHTN,” “Launch-HTN,” “single-pill combination,” and “hypertension guideline.” Priority was given to original randomized trials, authoritative recommendations, and regulatory documentation. For each relevant study, information was extracted on the clinical population, design, interventions and comparators, BP endpoints, follow-up duration, reported between-group effects, major safety findings, and regulatory status. Bibliographic details and numerical estimates were checked against the original publications or official product labeling where accessible.

The selected evidence was organized according to pharmacological mechanism and potential clinical application. When available, efficacy was expressed as the published placebo-adjusted mean difference in SBP change, while office and ambulatory BP measurements were considered separately. No new patient-level data, pooled effect estimates, formal cross-trial statistical comparisons, or independently measured clinical outcomes were generated. The figures display individual published estimates for explanatory purposes and should not be interpreted as comparative efficacy rankings, given differences in eligibility criteria, background treatment, endpoints, and follow-up periods. Similarly, the proposed management pathway is a conceptual framework rather than a validated decision rule. Because this review involved neither recruitment nor intervention, and no identifiable patient information was processed, institutional ethics approval and individual informed consent were not required.

RESULTS

The analysis identified three principal forms of therapeutic innovation: newly authorized agents acting through additional molecular pathways, agents undergoing clinical investigation, and more efficient delivery of existing antihypertensive classes. Aprocitentan received US Food and Drug Administration approval in March 2024, followed by the initial US approval of baxdrostat in May 2026; lorundrostat and zilebesiran remained investigational within the evidence and guidance considered in this review [5,8,10]. Importantly, US regulatory authorization should not be interpreted as confirmation of registration, reimbursement, or commercial availability in Uzbekistan or any other jurisdiction. The mechanisms, evidence base, and principal clinical limitations of these approaches are summarized in Table 1.

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Table 1. Mechanism, clinical role, development status and key limitations of selected next-generation strategies

Agent / approach	Mechanistic target	Evidence / role	Main limitation
Aprocitentan	Dual endothelin A/B receptor antagonism	US-approved adjunct for adults uncontrolled on other drugs; PRECISION	Fluid retention; anemia; hepatic monitoring; embryo–fetal toxicity
Baxdrostat	Selective aldosterone synthase (CYP11B2) inhibition	US-approved adjunct for insufficient control; BaxHTN	Hyperkalemia, hyponatremia; renal-function monitoring
Lorundrostat	Selective aldosterone synthase inhibition	Investigational; phase 3 BP reduction	Electrolytes, renal effects; long-term outcomes unknown
Zilebesiran	Hepatic angiotensinogen silencing by siRNA	Investigational; prolonged BP control in KARDIA studies	Long duration complicates rapid reversal; safety/outcomes follow-up
Triple/quadruple single-pill regimens	Complementary established classes with simplified dosing	Clinical implementation and adherence strategy; GMRx2, QUADRO	Not a new molecular class; individualized contraindications

The endothelin pathway contributes to vascular tone, endothelial dysfunction, and sodium homeostasis, providing a mechanistically distinct therapeutic target in patients whose BP remains elevated despite multidrug treatment. By antagonizing both endothelin receptor subtypes, aprocitentan offers an additional approach to BP reduction. In the phase 3 PRECISION trial involving 730 participants, aprocitentan 12.5 mg reduced unattended office SBP by a placebo-adjusted 3.8 mmHg at week 4 (97.5% confidence interval [CI], −6.8 to −0.8); the corresponding additional reduction in 24-hour ambulatory SBP was 4.2 mmHg. The randomized-withdrawal phase supported persistence of its antihypertensive effect [7]. These benefits must, however, be interpreted alongside its safety profile. During the short blinded phase, edema or fluid retention was reported in 9% of patients receiving aprocitentan 12.5 mg compared with 2% receiving placebo, and reductions in hemoglobin were also observed. The US prescribing information includes a boxed warning regarding embryo–fetal toxicity and precautions concerning fluid retention, anemia, and potential hepatic injury, together with pregnancy-related safeguards where applicable [8]. Aprocitentan should therefore be considered a selectively prescribed add-on therapy rather

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than a routine alternative to appropriately optimized diuretic treatment and mineralocorticoid receptor antagonism.

Aldosterone contributes to sodium retention and cardiovascular and renal remodeling. Unlike mineralocorticoid receptor antagonists, which inhibit downstream receptor activation, aldosterone-synthase inhibitors suppress hormone production at its source. Although this mechanism may provide more selective endocrine modulation, it also necessitates vigilance for hyperkalemia, hyponatremia, and changes in renal function, particularly in patients with chronic kidney disease or those receiving concomitant renin–angiotensin system inhibitors [6,9–12]. In the phase 3 BaxHTN trial, 796 patients with uncontrolled or resistant hypertension were randomized, of whom 794 received study treatment. At 12 weeks, baxdrostat 1 and 2 mg produced placebo-adjusted reductions in seated office SBP of 8.7 mmHg (95% CI, −11.5 to −5.8) and 9.8 mmHg (95% CI, −12.6 to −7.0), respectively. Serum potassium concentrations exceeding 6.0 mmol/L occurred in 2.3% and 3.0% of participants in the respective active-treatment groups, compared with 0.4% in the placebo group [9]. US prescribing information authorizes baxdrostat as adjunctive therapy for adults with insufficient BP control despite other antihypertensive medications and specifies assessment of serum potassium and sodium before and during treatment [10]. Despite these favorable short-term BP findings, dedicated evidence establishing a baxdrostat-specific reduction in stroke, myocardial infarction, or other major cardiovascular outcomes is not yet available in the reviewed sources.

The selective aldosterone-synthase inhibitor lorundrostat has also demonstrated clinically relevant BP reductions, although its regulatory development differs from that of baxdrostat. In the phase 3 Launch-HTN study, lorundrostat 50 mg once daily reduced automated office SBP by 16.9 mmHg, compared with 7.9 mmHg in the placebo group at 6 weeks, yielding an adjusted between-group difference of −9.1 mmHg (95% CI, −13.3 to −4.9) [11]. The Advance-HTN trial additionally evaluated treatment under a standardized background regimen with ambulatory BP assessment [12]. From a safety perspective, hyperkalemia, hyponatremia, and changes in kidney function warrant attention. Although these results support the potential clinical utility of selective aldosterone suppression, favorable surrogate BP endpoints cannot be equated with proven long-term cardiovascular benefit or therapeutic equivalence to approved agents. Selected randomized trial findings are presented in Table 2.

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Table 2. Selected published randomized trial results (effect estimates reproduced, not pooled)

Trial; population	Active intervention / comparator	Primary endpoint / time	Published between-group finding
PRECISION; resistant HTN, n = 730	Aprocitentan 12.5 mg vs placebo	Unattended office SBP; week 4	−3.8 mmHg (97.5% CI −6.8 to −0.8) [7]
BaxHTN; uncontrolled/resistant HTN, n = 796 randomized	Baxdrostat 1 or 2 mg vs placebo	Seated office SBP; week 12	−8.7 and −9.8 mmHg, respectively [9]
Launch-HTN; uncontrolled/resistant HTN, n = 1083	Lorundrostat 50 mg vs placebo	Automated office SBP; week 6	−9.1 mmHg (95% CI −13.3 to −4.9) [11]
KARDIA-2; inadequately controlled HTN	Zilebesiran 600 mg vs placebo added to oral background drug	24-hour ambulatory SBP; month 3	−12.1 with indapamide; −9.7 with amlodipine; −4.5 with olmesartan (mmHg) [15]
QUADRO; resistant HTN, n = 183	Quadruple vs triple single-pill regimen	Office SBP; week 8	−8.0 mmHg versus active triple therapy [17]

Note. Effect estimates correspond to the original study populations and specified endpoints; they must not be compared as if derived from a head-to-head trial. The QUADRO result uses an active triple-drug comparator, whereas the other listed estimates are placebo-adjusted.

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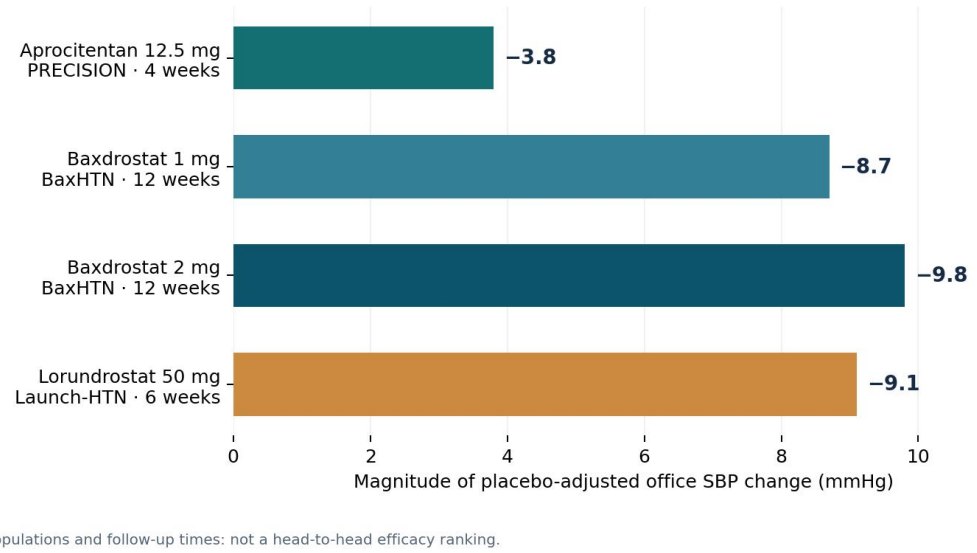


Figure 1. Placebo-adjusted office SBP reductions reported in individual phase 3 trials [7,9,11]. Different follow-up durations and clinical populations prohibit ranking these agents by bar length.

Zilebesiran represents a different molecular strategy based on RNA interference. By using siRNA to suppress hepatic angiotensinogen synthesis, it attenuates activity upstream of angiotensin I and II. An early clinical investigation demonstrated sustained pharmacodynamic effects and BP lowering after subcutaneous administration [13], while the randomized KARDIA-1 study documented placebo-adjusted reductions of up to 16.7 mmHg in 24-hour ambulatory SBP at 3 months, with effects maintained to 6 months at selected doses [14]. Subsequently, the phase 2 KARDIA-2 study assessed a single 600-mg injection as adjunctive treatment to standardized oral monotherapy. At 3 months, the additional reductions in 24-hour ambulatory SBP compared with placebo were 12.1 mmHg in the indapamide cohort, 9.7 mmHg in the amlodipine cohort, and 4.5 mmHg in the olmesartan cohort [15]. Variation across background-treatment groups highlights the importance of regimen-specific interpretation and precludes simplistic comparisons between treatment combinations. The prolonged pharmacodynamic effect may reduce daily pill burden, but it could also complicate the management of hypotension, dehydration, acute kidney injury, and pregnancy-related risks. Accordingly, prolonged follow-up and dedicated cardiovascular outcome studies remain necessary before routine clinical use can be justified.

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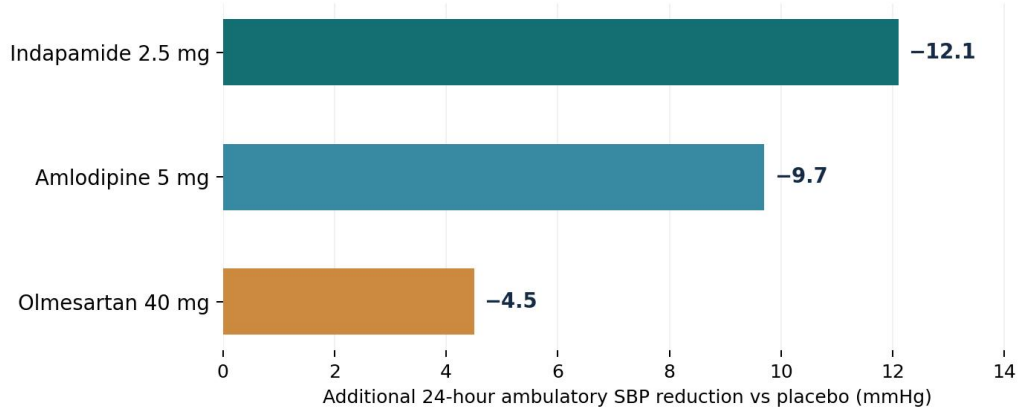


Figure 2. KARDIA-2: placebo-adjusted reduction in 24-hour ambulatory SBP 3 months after zilebesiran 600 mg, stratified by the randomized background-treatment cohort [15].

Pharmacological innovation is not restricted to the development of new molecules; improved delivery of established agents may also address clinically important barriers to effective treatment. The 2024 GMRx2 randomized study compared a low-dose triple single-pill combination containing telmisartan, amlodipine, and indapamide with dual-component regimens [16]. More recently, the 2026 QUADRO phase 3 trial randomized 183 patients with resistant hypertension following a triple-therapy run-in and showed that a single-pill quadruple combination of perindopril, indapamide, amlodipine, and bisoprolol reduced office SBP by an additional 8 mmHg at 8 weeks compared with continued triple treatment [17]. These findings suggest that regimen simplification may reduce pill burden while retaining complementary pharmacological mechanisms; nevertheless, fixed combinations must be selected with regard to contraindications, dose suitability, and the confirmation of genuine treatment resistance. Importantly, current guidelines continue to emphasize accurate BP assessment, adherence, evaluation for secondary causes, and optimization of established first-line combinations before newer agents are introduced [3–5]. The evidence supporting spironolactone as a fourth-line option remains substantial [6]. Although finerenone has demonstrated cardiorenal benefits in patients with type 2 diabetes and chronic kidney disease, these findings should not be interpreted as a general indication for its use in uncomplicated hypertension [18]. Table 3 outlines the monitoring requirements and principal safety considerations associated with the reviewed strategies.

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Table 3. Selected adverse effects, monitoring priorities and practical precautions

Option	Principal concerns	Monitoring / selection safeguards
Aprocitentan	Edema, volume overload, anemia, liver injury risk; embryo–fetal toxicity	Review heart failure and volume status, hemoglobin, liver enzymes, pregnancy status and contraception as indicated; avoid use in pregnancy [8].
Baxdrostat	Hyperkalemia, hyponatremia; changes in kidney function	Potassium, sodium, creatinine/eGFR before treatment and periodically; increased frequency in CKD, diabetes, older age or with K+-raising drugs [10].
Lorundrostat (investigational)	Hyperkalemia, hyponatremia, renal effects	Within research protocols monitor electrolytes, renal function, BP and symptoms; avoid assuming regulatory approval [11,12].
Zilebesiran (investigational)	Hypotension, hyperkalemia, acute kidney events; prolonged pharmacodynamic effect	Trial protocol monitoring of renal function, potassium, pregnancy-related risks and intercurrent illnesses [13–15].
Single-pill multi-agent therapy	Component-dependent: bradycardia, electrolyte changes, edema or renal effects	Select components and doses based on comorbidity, heart rate, renal function and tolerability; monitor after intensification [3–5,16,17].

On the basis of these findings, a sequential clinical approach can be proposed. The initial assessment should establish the BP phenotype through validated office measurements and, when indicated, home or ambulatory monitoring to identify possible pseudoresistance. Subsequently, adherence, sodium intake, interacting medications, lifestyle-related factors, and secondary causes should be assessed and addressed. Standard treatment should then be optimized using an appropriate renin–angiotensin system blocker, a long-acting dihydropyridine calcium-channel blocker, and a thiazide-like diuretic, with spironolactone considered where indicated and tolerated. Patients with persistent, confirmed treatment resistance may require specialist assessment to determine whether an approved add-on mechanism is appropriate in view of renal function, electrolytes, comorbidities, pregnancy-related risks, and local regulatory authorization. Finally, BP response and treatment safety must be reassessed following intensification rather than inferred from isolated measurements [3–6]. Figure 3 depicts this conceptual sequence, while Table 4 relates common clinical scenarios to evidence-based management considerations.

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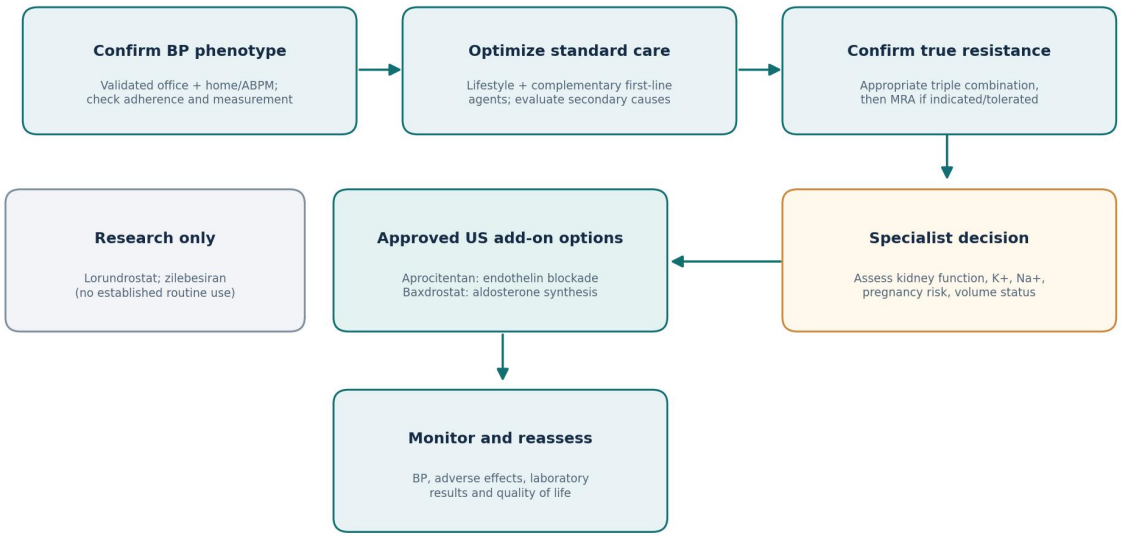


Figure 3. Evidence-informed pathway proposed for assessing and introducing next-generation antihypertensive agents. This is an original conceptual synthesis, not a validated clinical decision rule [3–5].

Table 4. Practical evidence-to-decision matrix for clinical and research use

Clinical situation	Preferred consideration	Evidence-based caution
Newly diagnosed / conventional hypertension	Lifestyle intervention and guideline-recommended first-line therapy, often in a single pill	Novel add-on agents generally not the starting point [3,4].
Uncontrolled BP on 2–3 agents	Confirm measurement, adherence and drug optimization; consider single-pill regimen	Pseudo-resistance and undertreatment must be excluded [3–5].
True resistant hypertension after optimal 3–4-drug regimen	Specialist assessment; consider FDA-approved aprocitentan or baxdrostat when appropriate	Safety checks, local licensing and patient preference; no head-to-head outcome proof [5,7–10].
CKD / diabetes / potassium-related risk	Individualize renin–angiotensin and mineralocorticoid pathway choices	Baxdrostat/MRA hyperkalemia risk; finerenone evidence relates to cardiorenal phenotype [10,18].
Research candidate needing extended dosing	Consider zilebesiran or lorundrostat only within authorized trial settings	No routine clinical indication established in cited guidance [5,11–15].

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DISCUSSION

The expanding portfolio of antihypertensive therapies reflects a shift toward interventions directed at endothelin signaling, aldosterone biosynthesis, and hepatic angiotensinogen expression. Nevertheless, molecular novelty does not in itself demonstrate clinical superiority. The therapeutic sequence must begin with accurate BP phenotyping, confirmation of adherence, and appropriate use of effective and affordable conventional combination therapy. European recommendations issued in 2024, American guidelines published in 2025, and the 2026 ACC expert pathway consistently emphasize these principles, with newer add-on mechanisms reserved for selected patients after standard approaches have been optimized [3–5]. Within this framework, aprocitentan and baxdrostat occupy distinct pharmacological and regulatory positions. Aprocitentan provides endothelin-receptor antagonism but has shown a relatively modest additional office SBP reduction in PRECISION and is limited by risks including fluid retention, anemia, hepatic adverse effects, and embryo–fetal toxicity. Baxdrostat demonstrated greater placebo-adjusted BP reduction in a separate trial but introduces clinically relevant requirements for electrolyte and renal monitoring. Because the trials differed in participant characteristics, background regimens, endpoints, and treatment duration, their reported estimates do not permit a valid conclusion that one drug is superior to the other [7–10].

The investigational agents lorundrostat and zilebesiran further illustrate the opportunities and unresolved questions associated with emerging treatment pathways. Lorundrostat targets aldosterone synthesis, whereas zilebesiran provides prolonged suppression of angiotensinogen expression that could potentially reduce dependence on daily dosing. However, prolonged drug action may also reduce flexibility when rapid treatment modification is required because of intolerance or intercurrent illness. This balance reinforces the need for carefully designed safety studies, including investigations in clinically vulnerable populations. Moreover, neither reductions in surrogate BP measurements nor prolonged pharmacodynamic activity can substitute for evidence of lower cardiovascular event rates, improved kidney outcomes, long-term tolerability, or meaningful patient-reported benefits [11–15]. In parallel, triple and quadruple single-pill regimens demonstrate that reducing treatment complexity may itself improve the feasibility of evidence-based care. Their value is particularly relevant where therapeutic inertia and missed doses compromise BP control, although fixed-dose combinations remain unsuitable when individual component doses or contraindications do not match the patient's clinical profile [4,5,16,17].

The translation of these findings into routine practice in Central Asia, including Uzbekistan, will depend on national marketing authorization, procurement systems, access to laboratory monitoring, affordability, and specialist referral pathways. Because this review draws on international trials and US regulatory information, it does not establish registration, reimbursement, or prescribing eligibility for any specific product in Uzbekistan. Future research should therefore evaluate real-world implementation, pharmacoeconomic value, treatment discontinuation, older adults, patients with chronic kidney disease, and the comparative benefits of novel add-on agents versus optimized generic combinations. Several methodological limitations must also be acknowledged. The

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review was narrative rather than systematic and did not employ preregistration, independent screening by two reviewers, formal risk-of-bias assessment, or an exhaustive search for unpublished studies. Furthermore, trial results should not be pooled informally because office and ambulatory endpoints, baseline BP, concurrent treatment, doses, and follow-up durations differed. The regulatory status and prescribing information of individual drugs may change after the evidence cut-off of 10 November 2026 and may vary across countries. No new patient-level analyses or cardiovascular outcome estimates were generated; consequently, the proposed pathway should be interpreted as an educational synthesis requiring adaptation to local practice and specialist clinical judgment.

CONCLUSION

Next-generation antihypertensive agents broaden the range of available and emerging strategies for BP reduction, particularly in patients whose hypertension remains uncontrolled despite optimized evidence-based therapy. Aprocitentan and baxdrostat are approved in the United States for specified add-on use and offer distinct mechanisms of action accompanied by different monitoring and safety requirements. Lorundrostat and zilebesiran remain investigational within the evidence evaluated, whereas newer single-pill combinations represent an important means of improving treatment implementation without introducing additional molecular targets. The clinical value of these approaches is likely to be greatest when true treatment resistance has been established through appropriate BP measurement, assessment of adherence, exclusion of relevant secondary causes, and optimization of conventional multidrug treatment. Decisions concerning newer therapies should additionally reflect renal function, serum potassium and sodium, fluid status, reproductive safety, medication burden, affordability, and local regulatory approval. Direct comparative trials and long-term cardiovascular and renal outcome studies are required to determine whether favorable short-term BP effects translate into sustained reductions in clinically meaningful events.

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