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Review Article

Aldosterone Synthase Inhibitors in Hard-to-Control Hypertension: A Pharmacy Practice Guide to Place in Therapy, Safety Monitoring, and Patient Care

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Resistant and uncontrolled hypertension remain among the most challenging problems in cardiovascular practice, exposing patients to elevated risk of stroke, heart failure, and kidney disease despite treatment with multiple agents. A central reason is aldosterone dysregulation, which persists even when the renin–angiotensin system is blocked, a phenomenon often described as aldosterone breakthrough. Aldosterone synthase inhibitors represent the first new antihypertensive mechanism to reach approval in roughly two decades, acting upstream by suppressing aldosterone production through selective inhibition of the CYP11B2 enzyme while sparing cortisol synthesis. Baxdrostat, the first agent in this class to gain regulatory approval, reduced seated systolic blood pressure by approximately 9 to 10 mmHg beyond placebo at twelve weeks when added to standard therapy, with roughly four in ten patients reaching a systolic pressure below 130 mmHg. This review examines the class for a pharmacy practice audience, tracing the biological rationale for synthase inhibition, summarising the pivotal trial evidence, and clarifying where these agents fit within current treatment algorithms as add-on therapy. Particular attention is given to the responsibilities that fall to pharmacists: structured monitoring for hyperkalaemia, hyponatraemia, and changes in renal function; recognition of relevant drug interactions; tailored care in chronic kidney disease, diabetes, and older adults; and counselling that supports safe titration and adherence. By translating emerging evidence into practical guidance, the review positions the pharmacist as a key contributor to the safe introduction of aldosterone synthase inhibitors into hypertension care.

Keywords: Aldosterone synthase inhibitors; Resistant hypertension; Baxdrostat; Pharmacovigilance; Pharmaceutical care.

INTRODUCTION

Hypertension is the most common and most modifiable risk factor for cardiovascular disease worldwide, yet a substantial proportion of treated patients never reach their blood pressure goal. Among them sits a particularly difficult group: those whose pressure stays high despite a well-chosen, multidrug regimen. When blood pressure remains above target on optimal or best-tolerated doses of three or more agents from different classes — typically a renin–angiotensin–aldosterone system (RAAS) blocker, a calcium channel blocker, and a diuretic — the condition is termed resistant hypertension. Estimates of how often this occurs vary with the population studied and the rigour with which adherence and white-coat effect are excluded, but most registries place the figure at roughly 5 to 10 per cent of the treated hypertensive population, with some series reporting higher. These patients matter out of proportion to their numbers, because resistant disease carries a markedly elevated burden of stroke, left ventricular hypertrophy, heart failure, and chronic kidney disease. A recurring theme in this group is aldosterone. For decades the RAAS was treated as a linear cascade that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) could reliably interrupt. In practice, suppression of aldosterone by these agents is neither complete nor durable. In a meaningful fraction of

patients, plasma aldosterone drifts back towards — or beyond — pretreatment levels during chronic RAAS inhibition, a phenomenon known as aldosterone breakthrough. It is distinct from aldosterone escape, the renal mechanism by which the kidney sheds excess sodium to limit volume expansion despite mineralocorticoid excess. Breakthrough is clinically unwelcome: patients in whom it develops tend to fare worse, with faster decline in renal function and heavier proteinuria. Resistant hypertension has accordingly come to be understood, in large part, as a salt-retaining, aldosterone-driven state, an interpretation supported by the well-documented response of such patients to mineralocorticoid receptor (MR) antagonists added to an existing regimen. That response has long defined the therapeutic options. Spironolactone, first marketed in the 1960s, and the more selective eplerenone act at the mineralocorticoid receptor, blocking the downstream effect of aldosterone rather than its production. They are effective, but their use is constrained — spironolactone in particular by off-target binding at androgen and progesterone receptors, which produces gynaecomastia, breast tenderness, and menstrual disturbance, and both agents by the ever-present risk of hyperkalaemia[4]. What had been missing was a way to reduce the hormone at its source.

Aldosterone synthase inhibitors (ASIs) supply exactly that. By selectively inhibiting CYP11B2, the enzyme responsible for the final step of aldosterone biosynthesis in the adrenal zona glomerulosa, these agents lower circulating aldosterone directly. The pharmacological challenge — distinguishing CYP11B2 from its near-identical paralogue CYP11B1, which governs cortisol synthesis — frustrated earlier candidates for years. Its resolution has now produced the first genuinely new antihypertensive mechanism to reach approval in roughly two decades, an event of real significance for a therapeutic area that had seen little innovation[1,2]. With approval, however, comes a practical question that the trial literature has not yet addressed for the people who will help deliver these drugs at the bedside and the counter: where do ASIs belong in the treatment pathway, and what new responsibilities do they create? This review approaches the class from a pharmacy practice perspective. It sets out the biological rationale for inhibiting aldosterone synthesis, summarises the pivotal clinical evidence, and locates these agents within current treatment algorithms as add-on therapy for uncontrolled and resistant disease. Its particular focus is the work that falls to the pharmacist — structured monitoring for hyperkalaemia, hyponatraemia, and changes in renal function; recognition of clinically relevant drug interactions; individualised care in chronic kidney disease, diabetes, and older age; and the counselling that underpins safe titration and sustained adherence. The aim is to translate a fast-moving evidence base into guidance that supports the safe and rational introduction of aldosterone synthase inhibitors into everyday hypertension care.

The Aldosterone Pathway and The Rationale for Synthase Inhibition

To understand why aldosterone synthase inhibitors, behave differently from the drugs that preceded them, it helps to begin with the hormone itself. Aldosterone is the final product of a steroidogenic pathway in the adrenal cortex. Within the zona glomerulosa, the enzyme aldosterone synthase — cytochrome P450 11B2, encoded by the gene CYP11B2 — catalyses the last three rate-limiting oxidation steps of the cascade, converting 11-deoxycorticosterone through corticosterone and 18-hydroxycorticosterone to aldosterone. Once secreted, aldosterone acts on the mineralocorticoid receptor in the distal nephron and elsewhere, promoting sodium and water retention, potassium excretion, and, over time, the vascular and renal fibrosis that accompanies chronic mineralocorticoid excess. In the salt-retaining, aldosterone-driven state that characterises much of resistant hypertension, this pathway is doing more work than it should. There are two ways to interrupt it. The established approach blocks the receptor: mineralocorticoid receptor antagonists such as spironolactone and eplerenone prevent aldosterone from binding its target, leaving the hormone in circulation but unable to act. The newer approach blocks production: aldosterone synthase inhibitors competitively inhibit CYP11B2, so that less aldosterone is made in the first place. The distinction is more than mechanistic tidiness. Because receptor blockade leaves the upstream signal intact, it tends to provoke a compensatory rise in circulating aldosterone, whereas inhibiting synthesis lowers the

hormone at its source and addresses both the receptor-mediated and the receptor-independent consequences of aldosterone excess. In principle, suppressing production also blunts the aldosterone breakthrough that limits RAAS blockade, since there is simply less hormone available to break through. The reason this strategy took decades to realise lies in a quirk of adrenal biochemistry. Aldosterone synthase has a near-twin. Cortisol, the body's principal glucocorticoid and an indispensable part of the stress response, is synthesised by 11β-hydroxylase — CYP11B1 — an enzyme that shares roughly 93 per cent of its amino-acid sequence with CYP11B2 and is most alike in precisely the heme-proximal region where a drug must bind to do its work. A molecule that inhibits one will, unless carefully designed, inhibit the other. Early agents foundered on exactly this problem: osilodrostat, the first aldosterone synthase inhibitor to reach the clinic, also suppressed cortisol, and that off-target effect confined it to the treatment of cortisol-excess states such as Cushing's syndrome rather than hypertension. The current generation of agents was engineered specifically to escape this trap. Baxdrostat, built on a tetrahydroisoquinoline scaffold, exploits a small structural difference between the two enzymes to achieve a selectivity ratio of at least 100 to 1 for aldosterone synthase over 11β-hydroxylase. The practical consequence, confirmed across early-phase studies, is that the drug lowers plasma aldosterone in a dose-dependent fashion while leaving cortisol synthesis untouched — the long-sought proof that selective inhibition of aldosterone production is achievable in humans[5]. Its pharmacokinetics suit chronic therapy: oral bioavailability and a plasma half-life of around thirty hours allow once-daily dosing. Lorundrostat, the next agent to advance, was developed against the same selectivity benchmark and shares the essential mechanism. This selectivity is not merely an elegant chemical achievement; it defines the clinical safety conversation that follows. Because cortisol synthesis is preserved, the adrenal-insufficiency risk that doomed the first-generation inhibitors does not materialise, and trial programmes have nonetheless retained morning cortisol and adrenocorticotropic hormone stimulation testing as safety checks precisely to confirm that CYP11B1 remains spared. What the mechanism does not eliminate is the predictable consequence of lowering aldosterone itself — namely, a tendency towards potassium retention and sodium loss. That trade-off, rather than any cortisol concern, is where the pharmacist's monitoring attention will rightly concentrate, and it is the subject of later sections.

The Evidence Base

The clinical case for aldosterone synthase inhibitors has been built across a tightly linked sequence of trials, and reading them in order makes the strength — and the present limits — of the evidence clear. The proof-of-concept came from BrigHTN, a multicentre, randomised, double-blind, placebo-controlled, dose-ranging phase 2 trial of baxdrostat in patients with treatment-resistant hypertension. Participants were already taking stable doses of at least three antihypertensive agents, one of them a diuretic, and still had a mean seated blood pressure of at least 130/80 mmHg. After twelve weeks, the difference in systolic reduction between the 2 mg group and placebo was 11.0 mmHg, and between the 1 mg group and placebo 8.1 mmHg, both statistically significant[5]. The result drew attention because reductions of that magnitude, placebo-adjusted, are uncommon in a population already on multiple drugs; the senior investigator noted that few prior antihypertensive trials had produced double-digit placebo-controlled systolic declines. Reassuringly, no serious adverse event was attributed to the drug and there were no cases of adrenocortical insufficiency, confirming in patients what the selectivity data had promised. A note of caution arrived soon after from a second phase 2 study, HALO, in which blood pressure fell almost as much in the placebo arm — a reminder that improved adherence to background therapy during a trial can blunt apparent drug effect, and that resistant hypertension is partly a problem of adherence. The pivotal evidence is BaxHTN, a phase 3 trial of 796 patients with uncontrolled or resistant hypertension, randomised to baxdrostat 1 mg, 2 mg, or placebo on top of standard care. At twelve weeks the placebo-adjusted reduction in seated systolic pressure was 9.8 mmHg for the 2 mg dose and 8.7 mmHg for the 1 mg dose, with the trial meeting its primary and all secondary endpoints, and roughly four in ten patients reaching a systolic pressure below 130 mmHg[6]. A randomised-withdrawal phase showed that blood pressure rose only modestly when the drug was

stopped, suggesting a degree of durability. Bax24 then added a piece the office-based trials could not provide: using 24-hour ambulatory monitoring in resistant patients, it found a placebo-adjusted reduction in 24-hour average systolic pressure of 14.0 mmHg, with the effect sustained through the early-morning hours when cardiovascular risk peaks[7]. Together these formed the basis for regulatory approval. The case does not rest on baxdrostat alone. Lorundrostat, a second selective inhibitor, has produced concordant results. In the phase 2b Advance-HTN trial, ambulatory 24-hour systolic pressure fell by 15.4 mmHg on a stable 50 mg dose against 7.4 mmHg on placebo[8]. The larger phase 3 Launch-HTN trial, enrolling over a thousand patients across thirteen countries, met its primary endpoint with a 9.1 mmHg placebo-adjusted reduction in automated office systolic pressure at six weeks, and the drug was associated with a low incidence of hyperkalaemia[9]. An earlier dose-ranging study, Target-HTN, had already established lorundrostat's antihypertensive signal in patients with low-renin hypertension[10]. That two independently developed agents lower blood pressure to a similar degree, by the same mechanism, in overlapping populations is the strongest argument that this is a genuine class effect rather than a single-molecule success.

Two honest qualifications belong here, and stating them strengthens rather than weakens the case. First, the trials are short — twelve weeks for the primary endpoints — and approval rests on blood-pressure lowering as a surrogate marker. No trial has yet reported hard cardiovascular outcomes such as stroke, myocardial infarction, or death for this class; the inference that a 9 to 10 mmHg systolic reduction will translate into fewer events is well grounded in decades of antihypertensive epidemiology but remains, for these specific drugs, an inference. Second, the populations were enriched and carefully screened, typically excluding advanced renal impairment, so real-world performance and safety will need post-marketing confirmation. These are not reasons for hesitation so much as the precise points at which pharmacist vigilance becomes valuable.

Table 1: Pivotal Clinical Trials of Aldosterone Synthase Inhibitors in Uncontrolled and Resistant Hypertension

Trial	Agent / phase	Population (n)	Key design	Primary BP outcome (placebo-adjusted)	Notes
BrigHTN	Baxdrostat, phase 2	Resistant HTN on ≥3 agents incl. diuretic (n≈275)	0.5/1/2 mg vs placebo, 12 wk; seated office SBP	−11.0 mmHg (2 mg); −8.1 mmHg (1 mg)	No drug-attributed SAEs; no adrenal insufficiency
HALO	Baxdrostat, phase 2	Uncontrolled HTN	Dose-ranging vs placebo, 12 wk	Did not separate from placebo	Large placebo response; adherence effect
BaxHTN	Baxdrostat, phase 3	Uncontrolled or resistant HTN (n=796)	1/2 mg vs placebo, 12 wk; seated office SBP	−9.8 mmHg (2 mg); −8.7 mmHg (1 mg)	~40% reached SBP <130 mmHg; durable on withdrawal
Bax24	Baxdrostat, phase 3	Resistant HTN (n=218)	2 mg vs placebo, 12 wk; 24-h ambulatory SBP	−14.0 mmHg	Effect sustained through early morning
Advance-HTN	Lorundrostat, phase 2b	Uncontrolled/resistant HTN (n=285)	50 mg or 50→100 mg vs placebo, 12 wk; 24-h ABPM	−7.9 mmHg (50 mg)	Diverse population; ↑hyperkalaemia/hyponatraemia at higher dose
Launch-HTN	Lorundrostat, phase 3	Uncontrolled/resistant HTN on 2–5 agents (n=1083)	50 mg ± uptitration vs placebo; automated office SBP at 6 wk	−9.1 mmHg (wk 6)	Low hyperkalaemia incidence; well tolerated

SBP, systolic blood pressure; ABPM, ambulatory blood pressure monitoring; SAE, serious adverse event; HTN, hypertension. Placebo-adjusted values are the between-group differences reported at the stated time point.

Place In Therapy

A new mechanism is only useful to a prescriber if it has a defined place in the sequence of care, and the 2025 AHA/ACC hypertension guideline provides the scaffolding into which aldosterone synthase inhibitors must fit. The guideline reaffirms a universal treatment goal of below 130/80 mmHg, with therapy guided by blood-pressure severity, comorbidity, and estimated cardiovascular risk[3]. For most patients the foundation is unchanged: lifestyle measures for all, single-agent therapy for milder disease, and early two-drug combination — preferably as a single pill — for stage 2 hypertension, typically pairing a renin–angiotensin system blocker with a calcium channel blocker or a thiazide-like diuretic. The relevant territory for the new class lies further along, where blood pressure stays above goal despite a well-constructed regimen. The guideline defines this carefully. Resistant hypertension is uncontrolled pressure despite optimal doses of three first-line agents — an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide-like diuretic, the guideline specifically naming chlorthalidone or indapamide — in a patient with reasonably preserved renal function[3]. Before any drug is added, the guideline is emphatic that the prescriber should confirm the diagnosis: review adherence, exclude white-coat effect with out-of-office readings, and search for secondary causes and interfering substances. This step matters for pharmacists in particular, because medication review and adherence assessment are core pharmacy functions, and because the HALO trial showed how easily apparent resistance dissolves once adherence improves. A patient mislabelled as resistant does not need a fourth drug; they need the three they already have, taken properly. When true resistance is established, the guideline's recommended fourth-line agent is a mineralocorticoid receptor antagonist — spironolactone or eplerenone — a position underpinned by the PATHWAY-2 trial and carrying a strong recommendation[4]. Where an MR antagonist cannot be tolerated or is contraindicated, the guideline lists alternatives: amiloride, a beta-blocker, an alpha-blocker, or a central sympatholytic, among others. It is into precisely this fourth-line, aldosterone-targeting niche that aldosterone synthase inhibitors arrive. They were studied as add-on therapy in patients already on two to three or more agents including a diuretic — the same population the guideline addresses — and they act on the same pathophysiological target as the MR antagonists, but one step upstream. This positioning carries an important caveat about timing. The 2025 guideline was finalised before baxdrostat's approval, so it does not yet name aldosterone synthase inhibitors in its algorithm; the MR antagonist remains the formally recommended fourth agent. In practical terms, then, these drugs are best understood at present as an alternative aldosterone-directed option for the resistant patient who cannot tolerate spironolactone or eplerenone — most often because of spironolactone's anti-androgenic effects such as gynaecomastia and breast tenderness — or in whom an MR antagonist has given an insufficient response. Until guideline committees formally incorporate the class and head-to-head data against spironolactone mature, framing them as a first-choice fourth agent would outrun the evidence. The honest position is that they expand, rather than replace, the aldosterone-targeting options at this step. Candidate identification therefore becomes a practical exercise the pharmacist is well placed to support. The patient who stands to benefit is one with genuinely resistant or uncontrolled hypertension, confirmed adherence, a diuretic already on board, an estimated glomerular filtration rate above roughly 45 mL/min/1.73 m² in keeping with the trial entry criteria, and a baseline potassium that leaves headroom for the predictable rise these drugs produce. Recognising this profile — and, equally, recognising the patient who is not yet a candidate because adherence or diagnosis is unsettled — is where pharmacist input adds the most value at the point of selection. The safety obligations that follow once the drug is started are the subject of the next section.

safety monitoring: the pharmacist's core role

If the efficacy story belongs to the cardiologist, the safety story belongs substantially to the pharmacist, and it follows directly from the mechanism. A drug that lowers aldosterone will, by design, reduce the

renal excretion of potassium and promote the loss of sodium. The two predictable consequences — hyperkalaemia and hyponatraemia — are not idiosyncratic surprises but the expected pharmacology of the class, which is precisely why they can be anticipated, monitored, and managed rather than simply feared. A third effect, a modest fall in estimated glomerular filtration rate, completes the trio of laboratory parameters that structure the monitoring plan. The most clinically important of these is hyperkalaemia. In the pooled, placebo-controlled trials underlying baxdrostat's approval, hyperkalaemia was the most frequently reported adverse reaction, occurring in 6.6 per cent of patients at the 1 mg dose and 10.2 per cent at the 2 mg dose[1]. Most of these elevations were modest; clinically significant rises were less common, with potassium exceeding 6.0 mmol/L in roughly 2.3 per cent of patients on 1 mg and 3.0 per cent on 2 mg in the phase 3 experience, against 0.4 per cent on placebo[6]. Reassuringly, the BrigHTN experience showed that such elevations were generally manageable: where potassium reached 6.0 mmol/L the protocol mandated temporary withdrawal, and patients who restarted the drug after a brief interruption typically completed treatment with normal potassium[5]. The lesson for practice is that hyperkalaemia with this class is usually a signal to pause and recheck, not necessarily to abandon therapy. Hyponatraemia is the second monitored effect. A serum sodium below 130 mEq/L was reported in 3.7 per cent of patients on 2 mg and 3.3 per cent on 1 mg, compared with 0.9 per cent on placebo[6]. The label accordingly advises assessing serum sodium before starting, correcting any abnormality first, and monitoring periodically thereafter, with closer attention for patients who begin with low-normal sodium or carry other risk factors for hyponatraemia[1]. The third parameter, renal function, behaves in a characteristic and largely reassuring way. A decrease in mean eGFR appears early — a placebo-corrected fall of about 8.0 mL/min/1.73 m² at the 2 mg dose by week 12 — but it plateaus and then reverses after the drug is stopped, a pattern consistent with a haemodynamic rather than a structural effect on the kidney. Recognising this prevents an unnecessary discontinuation: a small, stable creatinine rise after initiation is expected, not a sign of injury. Translating this pharmacology into a concrete monitoring schedule is where the pharmacist adds the most tangible value, and the approved labelling supplies the framework[1]. Potassium and sodium should be assessed and any abnormality corrected before the first dose, with potassium rechecked early and then periodically through treatment; the trials performed laboratory checks at baseline, at one to two weeks, and at four weeks, a cadence that maps neatly onto pharmacist-led review. Certain patients warrant more frequent monitoring: those aged 65 or older, those with diabetes or chronic kidney disease, and those taking other agents that raise potassium. The drug should not be initiated in patients whose baseline potassium is already high — practical thresholds in the literature suggest withholding above roughly 5.5 mmol/L — nor in those with an eGFR below 45 mL/min/1.73 m², a population in which efficacy and safety were not established. Table 2 consolidates this into a usable monitoring plan. A final point of practical judgement concerns what to do when a value drifts. The labelling's logic is graduated rather than absolute: treat the abnormality, consider interrupting or discontinuing the drug, monitor more closely if it is restarted, and discontinue permanently only if a clinically significant disturbance recurs. This is a workflow a pharmacist can own end to end — flagging the at-risk patient before initiation, ensuring the baseline bloods are drawn, scheduling the follow-up checks, interpreting the results against these thresholds, and communicating a clear recommendation to the prescriber. It is unglamorous work, and it is exactly the work that determines whether a first-in-class drug is used safely in the months after launch.

Table 2: Practical Laboratory Monitoring Plan for Aldosterone Synthase Inhibitor Therapy

Parameter	Before initiation	During treatment	Action threshold / response
Serum potassium	Measure; correct if abnormal. Withhold if elevated (≈>5.5 mmol/L)	Recheck early (1–2 wk), at ~4 wk, then periodically	If ≥6.0 mmol/L: treat, interrupt or discontinue; recheck. Monitor closely on restart; discontinue permanently if clinically significant hyperkalaemia recurs

Serum sodium	Measure; correct if abnormal	Periodically; more often if low-normal at baseline	If clinically significant hyponatraemia: treat, consider interruption/discontinuation; monitor on restart
eGFR / renal function	Confirm eGFR ≥45 mL/min/1.73 m²; do not initiate below this	Monitor; expect a small early fall that plateaus	A modest, stable early decline is haemodynamic and reversible — not automatic grounds to stop
Higher-risk groups	Identify: age ≥65; diabetes; CKD; concomitant potassium-raising drugs	Increase monitoring frequency in these patients	Individualise interval; lower threshold for rechecking

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. Schedule reflects the approved prescribing information and the laboratory cadence used in the pivotal trials.

Drug Interactions and Special Populations

Two categories of drug interaction matter with aldosterone synthase inhibitors, and they differ in nature. The first is pharmacodynamic and follows directly from the potassium effect already described. Because these agents reduce renal potassium excretion, co-prescribing them with any other drug that raises serum potassium compounds the risk of hyperkalaemia. The list is familiar to every pharmacist: ACE inhibitors, ARBs, and direct renin inhibitors; potassium-sparing diuretics and the mineralocorticoid receptor antagonists themselves; potassium supplements; and, less obviously, agents such as trimethoprim and certain non-steroidal anti-inflammatory drugs. The clinical reality is awkward, because the patient who reaches an aldosterone synthase inhibitor is, almost by definition, already taking a RAAS blocker as part of their resistant-hypertension regimen. This does not contraindicate the combination — it was the trial setting — but it does raise the monitoring stakes, and the labelling explicitly advises checking serum potassium more frequently when these drugs are combined[1]. Layering an aldosterone synthase inhibitor directly on top of an MR antagonist, in particular, stacks two aldosterone-directed mechanisms and warrants real caution rather than routine practice. The second interaction is pharmacokinetic and reassuringly limited in scope. Baxdrostat is a substrate of CYP3A, metabolised primarily through hepatic CYP3A4. The clinically relevant consequence runs in one direction: strong or moderate CYP3A inducers — agents such as rifampicin, carbamazepine, phenytoin, and St John's wort — can lower baxdrostat concentrations and blunt its antihypertensive effect, so the labelling advises monitoring therapeutic response more closely during concomitant use[1]. Inhibition, by contrast, appears to be a non-issue at the level that matters: co-administration with itraconazole, a strong CYP3A and P-glycoprotein inhibitor, produced only a modest rise in exposure without clinical significance. Equally helpful for a polypharmacy population, baxdrostat itself is a clean perpetrator — it neither inhibits nor induces the major CYP enzymes or UGT pathways, and studies showed no meaningful effect on metformin or on a combined oral contraceptive. For the pharmacist reconciling a complex medication list, this means the interaction review can concentrate on two things: the cumulative potassium burden, and the presence of any CYP3A inducer. The special-population considerations sharpen rather than complicate this picture. Older patients, and those with diabetes or chronic kidney disease, are precisely the groups the labelling singles out for more frequent potassium monitoring — and they are also, of course, the patients most likely to have resistant hypertension in the first place. The recommended starting dose reflects this: 2 mg once daily as standard, but 1 mg once daily for patients at increased risk of hyperkalaemia or hyponatraemia, which gives the prescriber and pharmacist a built-in lever for the higher-risk patient[1]. Renal function sets a clear boundary: the drug's safety and efficacy were not established below an eGFR of 45 mL/min/1.73 m², so it should not be initiated there, while above that threshold no dose adjustment is required unless hyperkalaemia risk dictates otherwise. The expected early, reversible dip in eGFR discussed earlier should be interpreted against this baseline rather than triggering reflexive discontinuation. Pregnancy deserves explicit mention because hypertension and

reproductive age frequently coincide. There are no human data on aldosterone synthase inhibitors in pregnancy, and animal studies showed embryo-fetal toxicity at exposures many times the clinical dose, of unclear human relevance[1]. Given that the 2025 guideline already steers pregnant patients away from RAAS-acting drugs towards agents with established gestational safety such as labetalol, nifedipine, and methyldopa[3], the sensible position is that aldosterone synthase inhibitors have no place in pregnancy or in women planning conception, and the counselling point — confirming contraception or pregnancy intentions before starting — falls naturally to the pharmacist. Taken together, these considerations do not make the class difficult to use; they make it a class whose safe use depends on exactly the medication-review, dose-selection, and counselling judgements that sit at the centre of pharmacy practice.

Patient Counselling And Adherence

A first-in-class drug succeeds or fails at the counter as much as in the clinic, and the counselling conversation around an aldosterone synthase inhibitor has a few non-negotiable elements. The first is the purpose of the regular blood tests. Patients accustomed to taking antihypertensives without routine monitoring need to understand that the potassium and sodium checks are not bureaucratic box-ticking but the mechanism by which the drug is kept safe, and that missing them is not a neutral act. Framing the tests as the price of a powerful new option — rather than an inconvenience — tends to secure better cooperation than a vague instruction to get bloods done. Closely tied to this is teaching the warning signs of the two electrolyte disturbances the drug can cause. Hyperkalaemia is the one that can be dangerous and the one most worth rehearsing: muscle weakness, an irregular or slow heartbeat, numbness or tingling, and in severe cases palpitations are the symptoms that should prompt contact with a healthcare professional rather than waiting for the next scheduled test. Hyponatraemia, though usually milder, can produce headache, confusion, nausea, or unusual fatigue. Patients should also know that the drug interacts with anything that raises potassium — including over-the-counter products, salt substitutes (which are frequently potassium-based), and certain painkillers — so that they think to mention the new medicine to any other prescriber or pharmacist and avoid self-medicating around it. Counselling on the renal effect prevents a predictable source of alarm. If a patient or another clinician sees the small early rise in creatinine and reacts by stopping the drug, a useful therapy may be abandoned for no good reason. Explaining in advance that a modest, stable change in kidney numbers is expected, is haemodynamic rather than harmful, and reverses on stopping, equips the patient to respond calmly and keeps the conversation with their wider care team on track. The pharmacist is often the person best placed to deliver this reassurance, because they see the laboratory trend and can interpret it in context. Then there is adherence, which deserves particular emphasis in this population for a reason the trial evidence made vivid. The HALO experience, in which blood pressure fell almost as far on placebo as on the drug, is widely attributed to the improvement in background-therapy adherence that simply being in a trial produces. The implication is sobering and clarifying at once: a meaningful share of so-called resistant hypertension is, in truth, undertreated hypertension in patients who are not taking what they have already been prescribed. Before an aldosterone synthase inhibitor is ever added, then, the honest first question is whether the existing regimen is actually being taken — and after it is added, sustaining adherence to the whole regimen, not just the new tablet, is what determines the outcome. The once-daily dosing and the long half-life work in the patient's favour here, forgiving the occasional missed dose and fitting easily into an existing routine, and these are worth pointing out as genuine advantages. Finally, the pharmacist's counselling role extends to the practical scaffolding of titration and follow-up. Confirming that the patient knows when their next blood test is due, that they understand the difference between the 1 mg and 2 mg doses if their prescriber adjusts therapy, that they can identify which of their other medicines carry potassium implications, and that they have a clear route to report symptoms — these are small interventions that collectively decide whether the drug is used well. Embedded within a pharmacist-led hypertension service, where review appointments and laboratory monitoring are already structured, this kind of support is not an add-on but a natural extension of work the pharmacist is already doing. It is, in the end, the same theme that has run through this review: the science of

the molecule is settled, and the quality of its use now rests on the ordinary, decisive craft of pharmaceutical care.

CHALLENGES AND FUTURE DIRECTIONS

For all the genuine promise of this class, an honest review must be clear about what is not yet known, because the gaps shape how the drugs should be used in the near term. The most important is the absence of hard outcome data. Every pivotal hypertension trial of an aldosterone synthase inhibitor to date has been short — twelve weeks for the primary endpoints — and has measured blood pressure rather than events. Approval therefore rests on blood-pressure lowering as a surrogate marker. The expectation that a placebo-adjusted systolic reduction of nine to ten millimetres of mercury will translate into fewer strokes, myocardial infarctions, and episodes of heart failure is grounded in a large and consistent body of antihypertensive epidemiology, and it is a reasonable expectation. But it remains, for these specific agents, an extrapolation rather than a demonstrated fact. Until dedicated outcome trials report, the class should be valued for what it has actually shown — meaningful, durable blood-pressure reduction in a hard-to-treat population — without overstating benefits it has not yet proven. That gap is being addressed directly, and the breadth of the ongoing programme is striking. Baxdrostat is reported to be in trials enrolling more than twenty thousand patients across several disease settings[12]. Two of these are explicitly designed to deliver the missing cardiorenal outcomes, both pairing baxdrostat with the SGLT2 inhibitor dapagliflozin in patients with chronic kidney disease and hypertension. The larger renal-outcomes study is event-driven, with a composite primary endpoint of a sustained fall of at least half in eGFR, kidney failure, heart-failure events, or cardiovascular death — precisely the hard outcomes the hypertension trials could not capture. A separate programme is studying the same combination for the prevention of heart failure and cardiovascular death, and a further trial is evaluating baxdrostat as monotherapy in primary aldosteronism, the secondary cause of hypertension in which an aldosterone-suppressing drug has obvious mechanistic appeal[11]. The rationale for the dapagliflozin pairing is itself instructive: the two drugs act through complementary mechanisms, and the SGLT2 inhibitor's tendency to lower potassium is expected to offset the aldosterone synthase inhibitor's tendency to raise it, potentially easing the very safety concern that dominates current practice. Several other uncertainties will need real-world answers. The comparative question — whether aldosterone synthase inhibitors are better tolerated or more effective than the established mineralocorticoid receptor antagonists they sit alongside — has not been settled by head-to-head trials, so the present preference for them in patients intolerant of spironolactone rests on mechanism and indirect comparison rather than direct evidence. The trial populations were carefully screened, typically excluding advanced renal impairment, so safety in less selected patients, including the frail and the heavily comorbid, will emerge only through post-marketing experience and pharmacovigilance. And the durability of effect beyond a year, the optimal monitoring interval once a patient is stable, and the behaviour of the class across diverse populations all remain to be characterised. Access and cost form the final, unglamorous challenge. A first-in-class branded agent enters at a price that contrasts sharply with the generic spironolactone and eplerenone it competes with, and that differential will shape who can realistically receive it, particularly in resource-constrained settings where resistant hypertension is common and specialist follow-up is scarce. The need for regular laboratory monitoring adds a further demand on systems that may already be stretched. These are not reasons to withhold a useful drug, but they are reasons to deploy it thoughtfully — reserving it for the patients most likely to benefit, ensuring the monitoring infrastructure is genuinely in place before initiation, and recognising that the pharmacist, positioned at the intersection of medicines access, monitoring, and counselling, is well placed to help a health system absorb a new class responsibly. The coming years of outcome data will determine how large a role aldosterone synthase inhibitor ultimately play; the task for the present is to use them safely while that evidence accrues.

RESEARCH GAP

Although the pharmacology and trial efficacy of aldosterone synthase inhibitors have been described in the cardiology and nephrology literature, almost no

work has yet translated this evidence for a pharmacy practice readership. The practical questions that determine safe real-world use — candidate identification, placement within the treatment algorithm, structured electrolyte and renal monitoring, interaction screening, and patient counselling — remain largely unaddressed. Cardiovascular outcome data are still awaited, and head-to-head comparisons against mineralocorticoid receptor antagonists do not yet exist. Interventional and observational studies are needed to define optimal monitoring intervals, confirm safety in less selected and comorbid populations, and establish the pharmacist's role in the safe introduction of this class into routine hypertension care.

CONCLUSION

Aldosterone synthase inhibitors mark the first genuinely new mechanism in antihypertensive therapy to reach the clinic in a generation. By suppressing the production of aldosterone at its enzymatic source rather than blocking its receptor, they address a pathophysiological driver — aldosterone excess and the breakthrough that undermines conventional RAAS blockade — that sits at the heart of much resistant and uncontrolled hypertension. The evidence assembled across the BrigHTN, BaxHTN, and Bax24 trials of baxdrostat, echoed independently by the lorundrostat programme, is consistent: a placebo-adjusted systolic reduction of roughly nine to ten millimetres of mercury in office measurement, larger still on ambulatory monitoring, achieved on top of multidrug therapy in patients who had run out of easy options. The honest boundaries of that evidence matter as much as its strength: the trials were short and measured blood pressure rather than cardiovascular events, the drugs have not been compared head-to-head with mineralocorticoid receptor antagonists, and they were studied in carefully selected populations. For now they are best understood as an expansion of the aldosterone-targeting options for resistant hypertension rather than a wholesale replacement. The safe introduction of the class depends heavily on the pharmacist, whose structured monitoring, medication review, dose selection, and patient counselling determine whether a powerful new drug is used well. As the outcome data mature and guideline committees formally position the class, that contribution will only grow. The molecule is new; the craft required to use it safely is one the pharmacist already practises every day.

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ABBREVIATIONS

ABPM: Ambulatory Blood Pressure Monitoring; ACC: American College of Cardiology; ACE: Angiotensin-Converting Enzyme; AHA: American Heart Association; ARB: Angiotensin Receptor Blocker; ASI: Aldosterone Synthase Inhibitor; BP: Blood Pressure; CCB: Calcium Channel Blocker; CKD: Chronic Kidney Disease; CV: Cardiovascular; CYP11B1: Cytochrome P450 11B1 (11β-hydroxylase); CYP11B2: Cytochrome P450 11B2 (aldosterone synthase); CYP3A: Cytochrome P450 3A; eGFR: Estimated Glomerular Filtration Rate; HTN: Hypertension; MR: Mineralocorticoid Receptor; MRA: Mineralocorticoid Receptor Antagonist; NSAID: Non-Steroidal Anti-Inflammatory Drug; P-gp: P-glycoprotein; RAAS: Renin–Angiotensin–Aldosterone System; SAE: Serious Adverse Event; SBP: Systolic Blood Pressure; SGLT2: Sodium–Glucose Cotransporter 2; UGT: UDP-Glucuronosyltransferase.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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