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REVIEW

Aldosterone synthase inhibitors in cardio-renal diseases: a state-of-the-art review

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Abstract

Aldosterone plays a pivotal role in the progression of cardio-renal diseases by driving myocardial fibrosis, vascular dysfunction, and renal injury through both genomic and non-genomic mechanisms. While mineralocorticoid receptor antagonists have long served as the cornerstone of pharmacologic intervention, their use is limited by adverse effects such as hyperkalemia, gynecomastia, and incomplete suppression of aldosterone-mediated pathology. Aldosterone synthase inhibitors, a novel class of therapeutics, offer a promising alternative by targeting the enzymatic production of aldosterone at its source, thereby circumventing receptor-level limitations. This narrative review comprehensively explores the physiological role of aldosterone, critiques existing RAAS-targeted therapies, and provides an in-depth evaluation of the pharmacology, efficacy, and safety of emerging ASIs including baxdrostat, lorundrostat, and osilodrostat. Evidence from recent clinical trials such as BrigHTN, HALO, Target-HTN, and FIONE is synthesized to assess their clinical potential. In addition, the review highlights novel mechanistic frontiers including the role of ASIs in overcoming aldosterone escape, attenuating cardio-renal fibrosis, modulating neurohormonal dysregulation, and enabling precision therapy through pharmacogenomic stratification. Future directions emphasize drug design innovations such as adrenal-specific prodrugs and nanoparticle-based formulations. Overall, ASIs represent a mechanistically robust and clinically promising advancement in the treatment of heart failure, chronic kidney disease, and primary aldosteronism. Their integration into multidrug regimens and personalized treatment frameworks may redefine the therapeutic landscape of cardio-renal-metabolic disease.

Key words: aldosterone synthase inhibitors, mineralocorticoid receptor, cardio-renal disease, hypertension, aldosterone pathophysiology, renin-angiotensin-aldosterone system (RAAS).

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Introduction

The renin–angiotensin–aldosterone system (RAAS) is fundamental to cardiovascular and renal homeostasis, and while its modulation has been central to the management of hypertension, heart failure, and chronic kidney disease (CKD),[1] growing evidence implicates aldosterone as a key driver of inflammation, fibrosis, and maladaptive remodeling in these conditions.[2-4] Beyond its classical role in fluid and electrolyte balance, aldosterone exerts deleterious genomic and non-genomic effects, promoting vascular stiffening, myocardial fibrosis, and renal injury.[2,5-6] Although mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone have demonstrated clinical benefit, their use is limited by adverse effects including hyperkalemia, gynecomastia, and renal dysfunction as well as by the phenomenon of aldosterone escape.[7] Moreover, MRAs may inadequately address aldosterone's receptor-independent actions.[8] Targeting aldosterone synthase (CYP11B2), the enzyme responsible for the final steps of aldosterone biosynthesis, offers a novel strategy to suppress aldosterone production at its source while potentially avoiding the drawbacks of MR blockade.[9-10] Aldosterone synthase inhibitors (ASIs) thus represent an emerging class of therapeutic agents with the potential to reshape the treatment paradigm for cardio-renal diseases.[11] This review explores the pathophysiological rationale for aldosterone suppression, the pharmacologic development of ASIs, emerging clinical trial evidence, and future directions, aiming to assess the readiness of this novel therapeutic class for clinical integration.

Physiological and pathophysiological role of aldosterone

Aldosterone biosynthesis is a tightly regulated enzymatic process that predominantly occurs in the zona glomerulosa of the adrenal cortex.[12] The key rate-limiting step involves the conversion of 11-deoxycorticosterone to aldosterone, a reaction catalyzed by aldosterone synthase (AS), a mitochondrial cytochrome P450 enzyme encoded by the *CYP11B2* gene.[13] AS contains a heme prosthetic group that facilitates the hydroxylation and oxidation reactions essential for aldosterone production. Structurally, aldosterone synthase shares over 95% sequence homology in its coding region with 11β-hydroxylase (*CYP11B1*), the enzyme responsible for cortisol synthesis.[14] Both genes are located on chromosome 8q21.[15] Despite their high degree of sequence similarity, they exhibit distinct zonal expression patterns within the adrenal cortex: *CYP11B2* is selectively expressed in the zona glomerulosa, while *CYP11B1* is primarily confined to the zona fasciculata and zona reticularis.[16-17] Aldosterone synthesis is modulated by a variety of physiological stimuli. Angiotensin II, generated in response to hypovolemia or hyponatremia, activates the angiotensin II type 1 receptor (AT1R), triggering intracellular signaling pathways that upregulate AS activity and promote aldosterone secretion.[18] Elevated serum potassium levels similarly stimulate *CYP11B2* expression, enhancing aldosterone production.[19] Additionally, adrenocorticotropic hormone (ACTH) exerts an acute stimulatory effect via its binding to the melanocortin 2 receptor (MC2R) in the adrenal cortex.[20] In contrast, several inhibitory mechanisms act to restrain aldosterone output. Notably, nitric oxide (NO) signaling and the ACE2/angiotensin-(1-7)/Mas receptor axis have been shown to suppress aldosterone synthesis, suggesting a complex and finely tuned interplay between stimulatory and inhibitory pathways (Figure 1).[21-23] Dysregulation of this tightly controlled system, predominantly characterized by aldosterone excess, has been implicated in the pathophysiology of various cardiovascular and renal disorders through the activation of molecular mechanisms that extend beyond its classical role in electrolyte balance and contribute to disease initiation and progression,[24] through both genomic and non-genomic pathways. At the genomic level, aldosterone binds to the intracellular mineralocorticoid receptor (MR), forming a complex that translocates to the nucleus and acts as a transcription factor to upregulate genes involved in sodium reabsorption, inflammation, fibrosis, and oxidative stress.[25,26] In cardiac tissue, this transcriptional activity contributes to cardiomyocyte hypertrophy and the development of myocardial fibrosis.[27] In vascular endothelial cells, MR activation impairs nitric oxide bioavailability, resulting in endothelial dysfunction and increased vascular stiffness.[28-30] In the renal system, aldosterone induces glomerulosclerosis and tubulointerstitial fibrosis through the upregulation of pro-inflammatory and pro-fibrotic mediators.[2,31] Aldosterone also induces rapid non-genomic effects, independent of gene transcription, via extracellular signal-regulated kinases 1/2 (ERK1/2), protein kinase C (PKC), calcium influx, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase,[32] leading to reactive oxygen species (ROS) generation that amplifies inflammatory and fibrotic responses.[33] Non-genomic pathways may also be initiated through non-classical receptors, including the G-protein-coupled estrogen receptor (GPER) and the insulin-like growth factor-1 receptor (IGF-1R), further expanding aldosterone's spectrum of action.[34] Collectively, these genomic and non-genomic actions of aldosterone contribute to maladaptive remodeling, laying the molecular foundation for organ-specific dysfunction in cardiovascular and renal diseases (Table 1).

Limitations of conventional aldosterone modulation: a rationale for upstream innovation

Pharmacologic modulation of the RAAS is central to the management of hypertension, heart failure, and CKD.[35,36] Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), and MRAs represent the cornerstone of current RAAS-targeted therapies.[37] Despite substantial improvements in cardiorenal outcomes, these agents exhibit no-

Table 1. Multisystem pathogenic effects of aldosterone: mechanistic insights and clinical implications.

System	Mechanism	Pathologic effect
Heart	Activation of MR receptors, induction of TGF-β, increased NOX mediated oxidative stress.	Myocardial fibrosis, LVH, electrical remodeling, increased risk of arrhythmias.
Kidney	MR activation in tubular and glomerular cells, upregulation of SGK-1, ROS production.	Proteinuria due to podocyte injury, glomerulosclerosis, tubulointerstitial fibrosis, progression of CKD.
Vasculature	Endothelial dysfunction through ROS accumulation, NF-κB activation, increased expression of ICAM-1.	Pro-inflammatory state, vascular inflammation, endothelial barrier disruption, vascular smooth muscle proliferation and remodeling
CNS	Enhanced sympathetic outflow via central MR activation, altered autonomic regulation.	Sustained elevation in BP, impaired baroreceptor reflex sensitivity, sympathetic overactivity.
Immune system	Activation of the NLRP3 inflammasome, pro-inflammatory cytokine release, immune cell recruitment.	Chronic low-grade inflammation, increased macrophage infiltration into target organs, amplification of tissue injury and fibrosis.

MR, Mineralocorticoid receptors; TGF-β, transforming growth factor-beta; NOX, NADPH oxidase; LVH, left ventricular hypertrophy; SGK-1, serum/glucocorticoid-regulated kinase 1; ROS, reactive oxygen species; CKD, chronic kidney disease; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; ICAM-1, intercellular adhesion molecule-1; CNS, central nervous system; BP, blood pressure; NLRP3, nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3.

table limitations in suppressing aldosterone-mediated pathophysiology, thus driving efforts to identify more comprehensive upstream strategies. While ACEi and ARBs reduce aldosterone synthesis indirectly by inhibiting angiotensin II formation or action, this effect is often transient. A well-documented phenomenon, referred to as "aldosterone escape" or "aldosterone breakthrough," occurs in up to 50% of patients undergoing chronic RAAS inhibition,[38] potentially due to alternative angiotensin II-generating enzymes or compensatory hyperkalemia.[39] This incomplete suppression permits continued aldosterone-driven injury to cardiovascular and renal tissues, undermining long-term efficacy. To circumvent upstream escape, MRAs such as spironolactone and eplerenone were developed to directly block mineralocorticoid receptor activation. Spironolactone demonstrated a 30% mortality reduction in patients with heart failure with reduced ejection fraction (HFrEF) in the RALES trial, while eplerenone yielded similar benefits in the EPHESUS and EMPHASIS-HF trials among post-myocardial infarction and mildly symptomatic heart failure populations, respectively.[40,41] However, spironolactone's non-selectivity confers

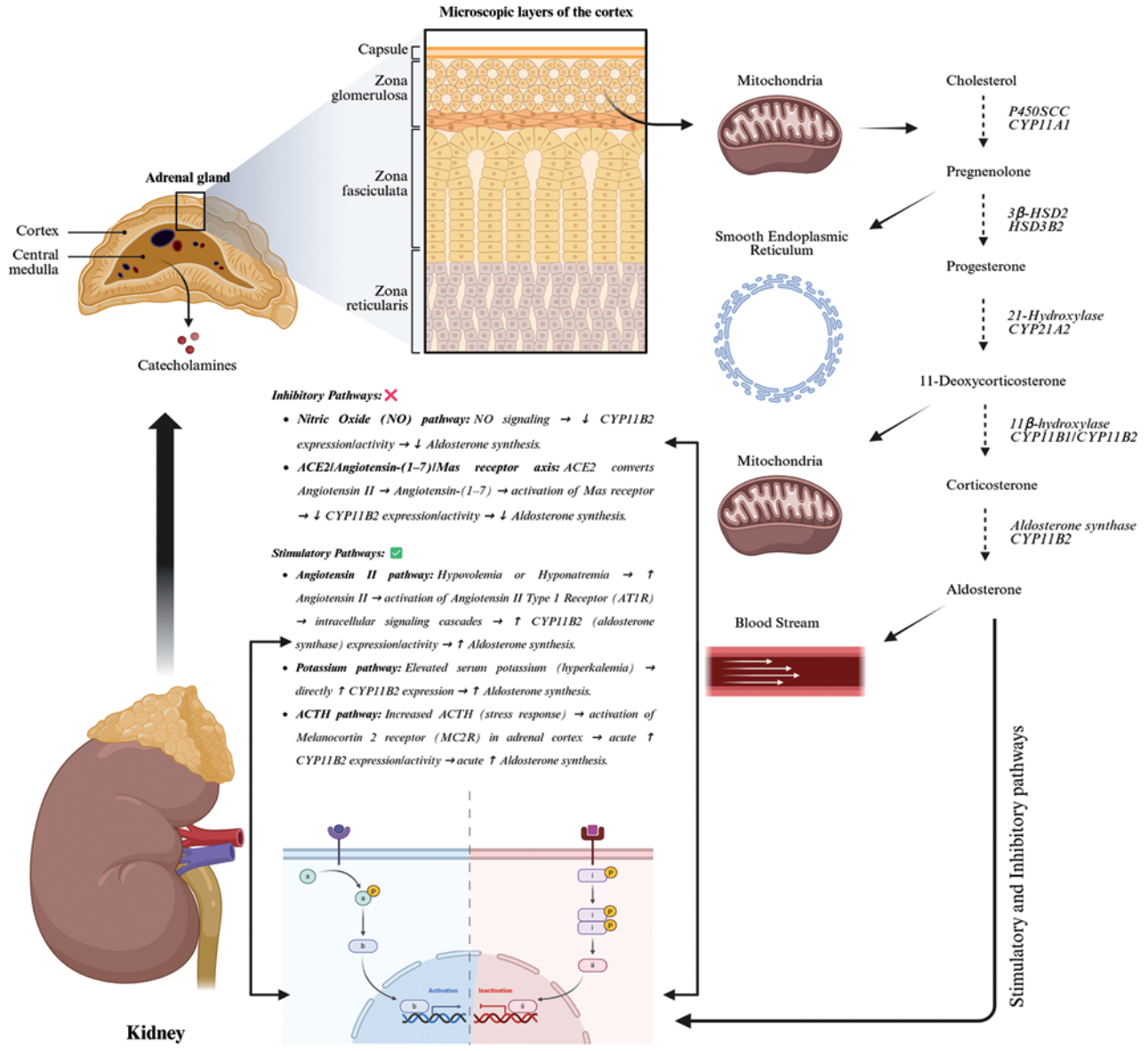

Figure 1. Dynamic regulation of aldosterone: interplay of stimulatory and inhibitory signals. Aldosterone is synthesised in the zona glomerulosa of the adrenal cortex via a multistep steroidogenic pathway involving key enzymes such as CYP11B2 (aldosterone synthase). In cardiorenal disease, overstimulation of the renin–angiotensin–aldosterone system (RAAS), hyperkalaemia, and elevated ACTH levels enhance CYP11B2 expression, driving excessive aldosterone production. This contributes to sodium retention, hypertension, left ventricular hypertrophy, and progressive renal dysfunction. In contrast, inhibitory signals such as nitric oxide and activation of the ACE2–angiotensin-(1–7)–Mas receptor axis suppress CYP11B2 transcription and reduce aldosterone synthesis. The balance between these regulatory mechanisms underlies both disease progression and emerging therapeutic strategies targeting mineralocorticoid excess in cardiorenal syndromes.

adverse endocrine effects, most notably gynecomastia, menstrual irregularities, and sexual dysfunction.[42] Moreover, both agents increase the risk of hyperkalemia, particularly in patients with CKD, diabetes, or those receiving concurrent RAAS blockade,[43] with adverse effects frequently compromising long-term adherence.[44] Furthermore, MRAs neither suppress aldosterone synthesis nor effectively inhibit its rapid, non-genomic actions, which are implicated in inflammation, fibrosis, and vascular dysfunction.[45] These mechanistic shortcomings have spurred the development of non-steroidal MRAs, such as finerenone and esaxerenone, which exhibit greater receptor selectivity and improved safety profiles. Finerenone, in particular, has demonstrated cardiorenal benefits in patients with diabetic kidney disease in the landmark FIDELIO-DKD and FIGARO-DKD trials.[46,47] Nonetheless, hyperkalemia remains a clinically relevant limitation, and these agents continue to act downstream of aldosterone biosynthesis. In light of these persistent challenges, there is growing interest in a more proximal therapeutic strategy: direct inhibition of aldosterone production. ASIs offer a mechanistically novel approach by selectively targeting *CYP11B2*, the enzyme responsible for converting 11-deoxycorticosterone into aldosterone.[48] By reducing aldosterone at its source, ASIs have the potential to attenuate both its genomic and non-genomic effects while avoiding receptor-related adverse effects and potentially lowering the risk of hyperkalemia.[11] Importantly, upstream blockade may also eliminate the phenomenon of aldosterone escape, offering a paradigm shift in RAAS-targeted therapy.[49] In summary, while ACE inhibitors, ARBs, and MRAs have markedly improved cardio-renal outcomes, their inability to achieve sustained aldosterone suppression underscores the need for upstream intervention positioning ASIs as a promising next-generation strategy in RAAS-targeted therapy (Table 2).

ASIs: mechanisms and therapeutic advancements

ASIs represent a novel pharmacologic class that selectively targets the key enzyme CYP11B2 to directly suppress aldosterone

Table 2. Comparative evaluation of RAAS-targeting and cardio-renal therapeutic classes in cardio-renal disease.

Therapy class	Primary site of action	Effect on aldosterone	Mechanistic strengths	Key limitations	Clinical implications
ACEi	Inhibit ACE, preventing AT I → AT II conversion.	Indirect suppression (temporary).	Reduces vasoconstriction, preload, afterload; proven mortality benefit in HF and CKD.	Aldosterone escape in 30-50% of patients; no direct impact on aldosterone synthesis or receptor signaling.	First-line therapy, but insufficient as monotherapy in aldosterone-driven conditions.
ARBs	Block AT1 receptor, downstream of AT II.	Indirect suppression (temporary).	Favorable safety profile; good for patients intolerant to ACEi.	Does not block non-AT1-mediated aldosterone release; aldosterone escape still occurs.	Often used in combination with other RAAS inhibitors; limited aldosterone suppression.
Steroidal MRAs	Competitive inhibition at the MR.	No suppression; aldosterone levels may rise.	Blocks genomic MR-mediated sodium retention, fibrosis, inflammation.	Hyperkalemia (esp. in CKD/diabetes), gynecomastia, menstrual irregularities, impotence; aldosterone escape.	Effective in HFrEF; poor tolerability limits long-term use in high-risk patients.
Non-steroidal MRAs	Selective MR blockade.	No suppression.	Improved MR selectivity; fewer sex hormone-related side effects.	Hyperkalemia risk persists; limited long-term data; does not target upstream aldosterone production.	Promising option in DKD and HF; not suitable in advanced CKD or combination settings.
SGLT2 Inhibitors	Reduce sodium-glucose reabsorption in proximal tubule; indirectly modulate RAAS.	No suppression.	Improves CV and renal outcomes; reduces intraglomerular pressure; lowers HF hospitalizations.	Not RAAS-specific; aldosterone levels unchanged; limited benefit in severe hyperaldosteronism.	Used adjunctively; insufficient in aldosterone-mediated pathologies.
ASIs	Inhibit CYP11B2 (aldosterone synthase).	Direct suppression at source.	Block both genomic and non-genomic effects; prevent aldosterone escape; MR-independent.	Selectivity challenge (CYP11B2 *vs* CYP11B1); adrenal suppression potential; long-term safety still emerging.	Novel therapeutic class; potential to replace or complement MRAs in resistant disease.

RAAS, Renin-angiotensin-aldosterone system; ACE, angiotensin-converting enzyme; AT I, angiotensin I; AT II, angiotensin II; ACEi, ACE inhibitors; ARBs, angiotensin receptor blockers; AT1, angiotensin 1 receptor; MR, mineralocorticoid receptor; MRAs, mineralocorticoid receptor antagonists; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; DKD, diabetic kidney disease; SGLT2, sodium-glucose cotransporter 2; ASIs, aldosterone synthase inhibitors; CYP11B2, cytochrome P450 family 11 subfamily B member 2; CYP11B1, cytochrome P450 family 11 subfamily B Member 1; CV, cardiovascular; HF, heart failure.

Note: while ACE inhibitors, ARBs, MRAs, and aldosterone synthase inhibitors directly target components of the RAAS, other therapies listed -such as SGLT2 inhibitors- primarily influence renal and cardio-renal physiology, with indirect downstream effects on RAAS activity.

biosynthesis at its source, offering a theoretical advantage over conventional receptor antagonists that act downstream by blocking aldosterone's effects (Figure 2).[39,48] However, a major pharmacological challenge arises from the substantial structural similarity between CYP11B2 and CYP11B1 enzymes that share approximately 95% amino acid sequence homology and are encoded in close proximity on chromosome 8q21, which limited the selective inhibition of aldosterone synthase, leading to unintended inhibition of CYP11B1, the enzyme responsible for cortisol synthesis.[14,15] Early or first-generation ASIs, such as osilodrostat (LCI699), exhibited limited selectivity for *CYP11B2* and substantial off-target inhibition of *CYP11B1*, leading to un-

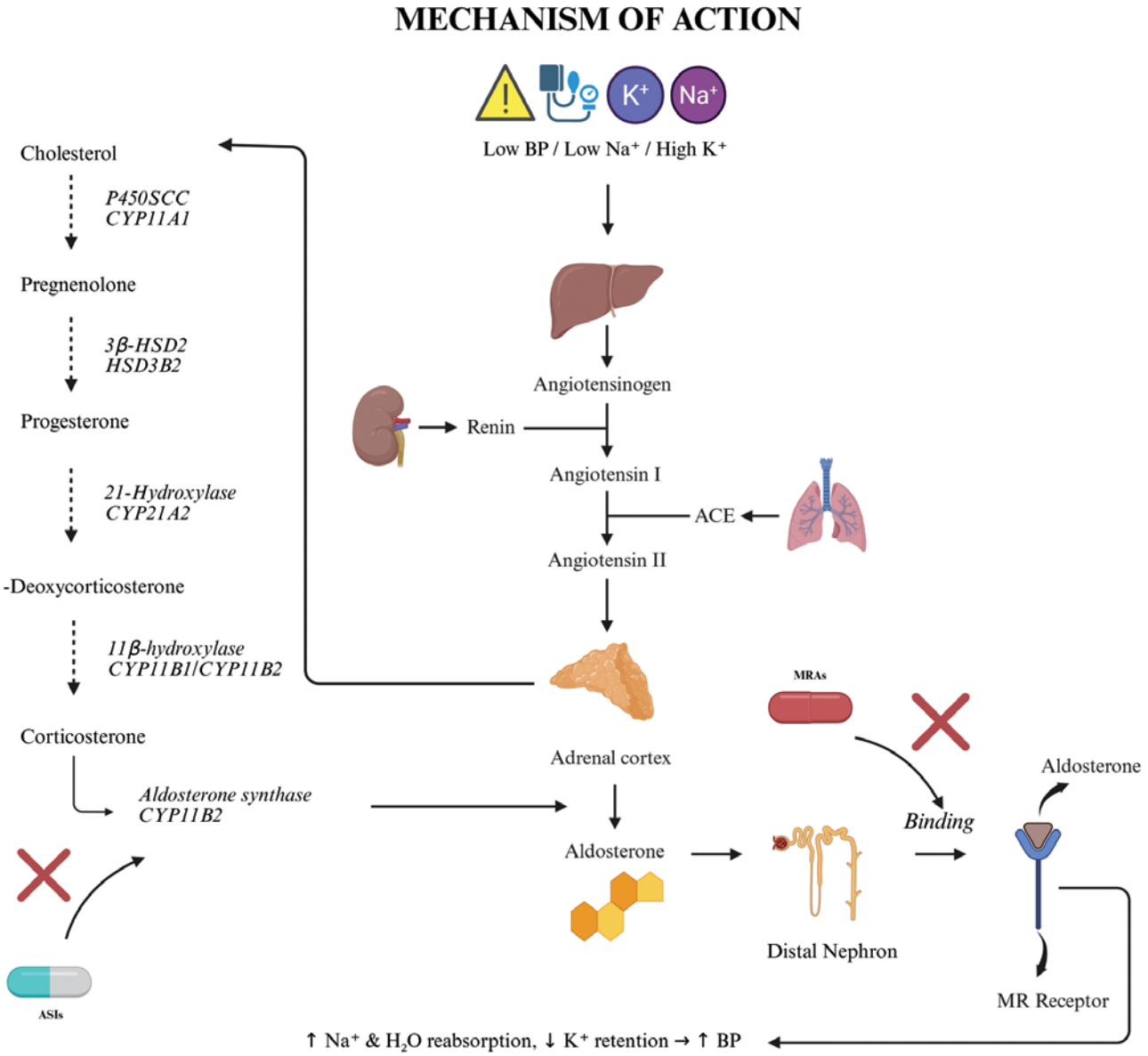

Figure 2. Comparative mechanism of action: aldosterone synthase inhibitors vs mineralocorticoid receptor antagonists. Aldosterone is synthesised in the zona glomerulosa of the adrenal cortex via a multistep steroidogenic pathway involving key enzymes such as CYP11B2 (aldosterone synthase). In cardiorenal disease, overstimulation of the renin–angiotensin–aldosterone system (RAAS), hyperkalaemia, and elevated ACTH levels enhance CYP11B2 expression, driving excessive aldosterone production. This contributes to sodium retention, hypertension, left ventricular hypertrophy, and progressive renal dysfunction. In contrast, inhibitory signals such as nitric oxide and activation of the ACE2–angiotensin-(1–7)–Mas receptor axis suppress CYP11B2 transcription and reduce aldosterone synthesis. The balance between these regulatory mechanisms underlies both disease progression and emerging therapeutic strategies targeting mineralocorticoid excess in cardiorenal syndromes. Aldosterone synthase inhibitors (ASIs) suppress aldosterone production at its source by blocking the conversion of corticosterone to aldosterone via inhibition of aldosterone synthase (CYP11B2). In contrast, mineralocorticoid receptor antagonists (MRAs) act downstream by preventing aldosterone from binding to mineralocorticoid receptors (MR) in the distal nephron. While both approaches lead to decreased sodium and water reabsorption, increased potassium excretion, and reduced blood pressure, they differ in their site of action within the renin-angiotensin-aldosterone system (RAAS) and may have distinct effects on hormonal feedback and systemic regulation.

intended unintended cortisol suppression.[50-54] This reduction in cortisol triggered compensatory activation of the hypothalamic-pituitary-adrenal (HPA) axis, characterized by elevated adrenocorticotropic hormone (ACTH) levels and accumulation of steroid precursors such as deoxycorticosterone (DOC), which possesses intrinsic mineralocorticoid activity and may attenuate the desired antihypertensive effects of ASI therapy.[52] These maladaptive endocrine alterations may also contribute to systemic consequences, reminiscent of cardiac wasting syndromes observed in advanced cancer, where catabolic processes drive heart failure-like states.[53]

Across multiple phase II trials, osilodrostat demonstrated only modest reductions in systolic blood pressure (SBP) -ranging from 4.1 to 8.7 mmHg- depending on dose and population studied, with a concomitant rise in serum potassium levels (0.01–0.4 mmol/L).[54-61] These modest antihypertensive effects, in conjunction with cortisol suppression and endocrine-related adverse events, led to the discontinuation of osilodrostat's development for hypertension; however, its cortisol-lowering properties facilitated its successful repurposing and subsequent approval for the treatment of Cushing's disease, wherein cortisol suppression provides therapeutic efficacy.[62-63] Acknowledging these limitations, the newer-generation of ASIs emphasize on achieving high selectivity for *CYP11B2* over *CYP11B1* to preserve cortisol synthesis and maintain HPA axis integrity.[39,48] Several investigational agents have since advanced into early-phase clinical development, demonstrating improved pharmacologic profiles and promising clinical efficacy. Among next-generation ASIs, baxdrostat (CIN-107) has demonstrated the most robust evidence of clinical efficacy and hormonal selectivity to date. In the BrigHTN trial (Phase II, n=275), conducted in patients with treatment-resistant hypertension, baxdrostat achieved dose-dependent reductions in systolic blood pressure (SBP) ranging from 8.1 to 11.0 mmHg, without suppressing cortisol levels or elevating ACTH -highlighting its high selectivity for CYP11B2. Mild increases in serum potassium (0.19-0.36 mEq/L) were observed, but overall tolerability was favorable.[64,65] The subsequent HALO trial (n=248), which enrolled patients with uncontrolled but less severe hypertension, reported more modest BP reductions (SBP ↓ 3.2 mmHg; not statistically significant), although consistent aldosterone suppression was maintained, further supporting the agent's mechanism of action.[66] Baxdrostat is also being evaluated in chronic kidney disease (CKD) populations through the FIGHTN-CKD trial (n=300), which aims to assess renal outcomes and combination strategies with SGLT2 inhibitors,[67] which have consistently demonstrated improvements in health status, symptom burden, and quality of life among patients with heart failure, further supporting their synergistic potential in cardio-renal disease management.[68] Additionally, in a small pre-post study in primary aldosteronism (PA) (n=18), preliminary data suggest effective aldosterone suppression and BP reduction after dose titration, although cortisol data were not reported.[69] Another next-generation agent, lorundrostat (MLS-101), showed particular efficacy in obesity-related hypertension, a population often exhibiting hyperaldosteronism. In the Target-HTN trial (n=196), lorundrostat at 50 mg/day achieved a mean SBP reduction of 9.7 mmHg, with no observed suppression of cortisol and only mild potassium elevations (0.25-0.29 mmol/L), reinforcing both its clinical efficacy and endocrine safety in a metabolically vulnerable subgroup.[70]

Further expanding the ASI landscape, DP13 is under investigation in patients with primary aldosteronism (n=36), where early results indicate aldosterone suppression, although full BP and safety data remain pending.[71] Meanwhile, BI 690517 is being studied in the large FIONE trial (n=714) targeting both diabetic and non-diabetic CKD patients. Preliminary findings suggest a reduction in urinary albumin-to-creatinine ratio (UACR), especially when combined with empagliflozin, indicating potential synergistic renoprotection through RAAS-SGLT2 modulation (Table 3).[72] This progress marks a paradigm shift in RAAS modulation from downstream receptor blockade to direct aldosterone synthase inhibition enabling more precise and effective treatment strategies for aldosterone-mediated disorders. The transition is further supported by the mortality-reducing benefits of adjunctive therapies such as SGLT2 inhibitors in high-risk populations, emphasizing the importance of integrated, mechanism-based approaches in cardio-renal therapeutics.[73]

Safety considerations OF ASIs

Although ASIs represent a mechanistically distinct and promising alternative to MRAs, their broad clinical implementation will ultimately hinge on the robust demonstration of long-term safety, tolerability, and an acceptable benefit-risk profile. Like all pharmacologic agents that modulate the RAAS and steroidogenesis pathways, ASIs present specific safety considerations some of which overlap with those associated with MRAs, while others are attributable to their upstream site of action.[37] A notable shared adverse effect is the potential for hyperkalemia, particularly among patients with compromised renal function or concomitant diabetes mellitus.[37,49,74] ASIs lower aldosterone concentrations, thereby reducing activation of epithelial sodium channels (ENaC) in the distal nephron, which in turn diminishes potassium excretion.[75] Nonetheless, preliminary clinical data suggest that the incidence of hyperkalemia with ASIs -such as baxdrostat and lorundrostat- may be lower than that observed with MRAs.[11,37] This reduction may stem from the preservation of glucocorticoid-mediated mineralocorticoid receptor activation in tissues lacking 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), or from a more tempered modulation of the RAAS axis.[76,77]

In the BrigHTN and HALO trials, hyperkalemia was reported in fewer than 5% of participants, with most episodes being mild and reversible.[64-66] Similarly, lorundrostat demonstrated a hyperkalemia incidence ranging from 2% to 5%, suggesting that ASIs may offer improved tolerability profiles in high-risk populations, including individuals with CKD or those receiving concurrent RAAS inhibitors.[78] Another critical issue in ASI development is the off-target inhibition of cortisol synthesis due to the structural similarity between CYP11B2 and CYP11B1, as seen with early non-selective agents like osilodrostat, which suppressed both aldosterone and cortisol production, leading to compensatory HPA axis activation, elevated ACTH levels, and accumulation of steroid precursors such as DOC.[51,79] These precursors have mineralocorticoid activity that may counteract an-

tihypertensive effects, as seen with osilodrostat, which despite lowering aldosterone led to cortisol deficiency symptoms and limited its use in hypertension.[80,81] In contrast, next-generation ASIs like baxdrostat and lorundrostat exhibit greater selectivity for *CYP11B2* over *CYP11B1*, showing minimal effects on cortisol synthesis, with clinical trials reporting stable cortisol, ACTH, and 11-DOC levels and no signs of adrenal insufficiency.[11,82,83] Nevertheless, long-term studies are required to evaluate chronic HPA axis stability, particularly in older adults or those with pre-existing adrenal disorders. An additional theoretical concern is the accumulation of steroid intermediates such as DOC with incomplete CYP11B2 inhibition, as DOC can activate mineralocorticoid receptors and potentially contribute to hypertension—though this has not been clinically significant in trials of selective ASIs, it remains a mechanistic consideration for less selective or subtherapeutically dosed agents.[10,11] From a pharmacologic perspective, drug–drug interactions are a relevant concern, as ASIs may alter the metabolism of steroidogenic compounds, CYP3A4 substrates, or potassium-altering medications;[84,85] while no serious interactions have been reported in phase II trials, continued vigilance is essential as these agents advance to broader clinical use amid polypharmacy. Finally, a key limitation of most investigational ASIs is the lack of long-term outcome data, as existing trials are short in duration (8-12 weeks) and focus on surrogate endpoints[86] rather than definitive cardiovascular or renal outcomes, leaving unanswered questions about the durability of blood pressure control, real-world effectiveness in comorbid populations, and impact on heart failure, CKD progression, or mortality. In summary, next-generation ASIs show promise, but long-term safety remains

Table 3. Pharmacologic properties and clinical outcomes of aldosterone synthase inhibitors in completed and ongoing phase II-III trials.

Drug (trial)	Target enzyme	CYP11B2 Selectivity	Study design and population	Cortisol axis effect	BP/UACR outcome	Potassium effect	Key findings/comments
Baxdrostat (BrigHTN)	CYP11B2	High	Phase II RCT; resistant HTN (n=275)	No suppression; ACTH stable	SBP ↓ 8.1–11.0 mmHg (dose-dependent)	Mild ↑K^+ (0.19–0.36 mEq/L)	Strong BP and hormonal efficacy with good tolerability
Baxdrostat (HALO)	CYP11B2	High	Phase II RCT; uncontrolled HTN (n=248)	Not assessed	SBP ↓ 3.2 mmHg (NS); aldosterone ↓	↑K^+ 1.6–5%	Hormonal suppression consistent; modest BP effect
Baxdrostat (FIGHTN-CKD)	CYP11B2	High	Phase II RCT; CKD + HTN (n=300)	Pending	Outcome pending	Pending	Ongoing study assessing renal outcomes and combo strategies
Baxdrostat (PA cohort)	CYP11B2	High	Phase II pre-post; primary aldosteronism (n=18)	Not reported	BP ↓ after titration (up to 8 mg)	Not reported	Aldosterone suppression evident; limited sample size
Lorundrostat (Target-HTN)	CYP11B2	Moderate–High	Phase II RCT; uncontrolled HTN, obesity subgroup (n=196)	No cortisol suppression	SBP ↓ 9.7 mmHg (50 mg/day)	Mild ↑K^+ (0.25–0.29 mmol/L)	Notably effective in obese HTN; favorable safety
DP13 (DP13-PA)	CYP11B2	Unknown	Phase II pre-post; PA (n=36)	Not reported	Aldosterone ↓; BP pending	Not reported	Early data show hormonal effect; full results awaited
BI 690517 (FIONE)	CYP11B2	Unknown	Phase II RCT; diabetic & non-diabetic CKD (n=714)	Not reported	↓ UACR (combo w/ empagliflozin)	Not reported	Investigating renoprotection and synergistic RAAS-SGLT2 blockade
Osilodrostat (PA study)	CYP11B2 and CYP11B1	Low	Phase II; PA (n=14)	↓ Cortisol; ↑ACTH	PAC ↓ 75%; SBP ↓ 4.1 mmHg	↑K^+ (3.27 → 3.89 mmol/L)	Cortisol suppression limits long-term BP use
Osilodrostat (Essential HTN)	CYP11B2 and CYP11B1	Low	Phase II RCT; essential HTN (n=524)	↓ Cortisol post-ACTH stim	DBP ↓ 7.1 mmHg	↑K^+ (0.01–0.28 mmol/L)	Comparable to eplerenone in BP reduction
Osilodrostat (Add-on HTN)	CYP11B2 and CYP11B1	Low	Phase II RCT; resistant HTN (n=155)	Minimal suppression at 1 mg	SBP ↓ 4.3 mmHg	↑K^+ (0.1-0.4 mmol/L)	Modest BP benefit; mild endocrine effect
Osilodrostat (LINC-3/ LINC-4)	CYP11B2 and CYP11B1	Low	Phase III RCT; Cushing's (n=137, 73)	Hypocortisolism in 14–51% disease	UFC normalized in 77-86%	Hypokalemia, not hyperkalemia	Approved for Cushing's; not applicable to HTN/CKD

CYP11B2, Cytochrome P450 family 11 subfamily B member 2; CYP11B1, cytochrome P450 family 11 subfamily B member 1; RCT, randomized controlled trial; HTN, hypertension; CKD, chronic kidney disease; ACTH, adrenocorticotropic hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; K^+, potassium; PA, primary aldosteronism; UACR, urinary albumin-to-creatinine ratio; PAC, plasma aldosterone concentration; UFC, urinary free cortisol; NS, not significant; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter 2.

uncertain; continued monitoring is essential to establish their role in cardio-renal therapy.

Limitations of ASIs

In the evolving landscape of cardio-renal therapeutics, ASIs represent a mechanistically distinct and promising intervention. However, several critical limitations within the current evidence base must be acknowledged to contextualize their clinical potential. Firstly, the absence of direct head-to-head comparative trials between ASIs and established standard-of-care agents such as mineralocorticoid receptor antagonists (MRAs), finerenone, or other antihypertensive therapies commonly employed in resistant hypertension hampers a definitive evaluation of their relative efficacy and safety.[49,87] This gap is particularly significant in complex patient cohorts where polypharmacy with multiple RAAS-modulating agents is frequently employed. Secondly, although ASIs exert a targeted effect on aldosterone biosynthesis, existing clinical trials have not integrated biomarker-based or pharmacogenomic stratification frameworks.[88,89] Considering the interindividual variability in RAAS activity and aldosterone physiology, the absence of precision-guided methodologies limits the ability to tailor ASI therapy and optimize therapeutic outcomes.[90] Thirdly, the purported mechanistic benefits of ASIs such as the attenuation of myocardial and renal fibrosis, modulation of neurohormonal activity, and mitigation of aldosterone breakthrough remain insufficiently validated by mechanistic endpoints.[3] Most studies have yet to incorporate advanced imaging modalities for fibrosis quantification, serial measurements of RAAS intermediates, or comprehensive panels of inflammatory and fibrotic biomarkers. Moreover, the generalizability of current phase II trial findings is limited due to the underrepresentation of high-risk populations including older adults, individuals with advanced chronic kidney disease, postmenopausal women, and racially diverse groups with heterogeneous hypertension phenotypes given the predominance of middle-aged participants with relatively controlled comorbidities.[91,92] Furthermore, the long-term neuropsychological and autonomic consequences of sustained aldosterone suppression remain insufficiently studied, with potential implications for mood, cognition, and sympathetic regulation particularly in vulnerable or elderly populations while the safety and physiological impact of abrupt ASI discontinuation also remain unclear, posing concerns about rebound hypertension, adrenal dysregulation, and hormonal instability.[93-95] From a translational perspective, significant implementation challenges remain, including the lack of standardized dosing regimens, titration protocols, and evidence-based combination strategies with other RAAS-targeted therapies, which may hinder clinical integration; moreover, uncertainties regarding the long-term cost-effectiveness of ASIs relative to generic MRAs, alongside regulatory, reimbursement, and access barriers, may further constrain their adoption, particularly in resource-limited healthcare settings.[39,49,96] Addressing these limitations through rigorous late-phase trials, inclusive study designs, and translational research will be essential to fully define the therapeutic role of ASIs in cardio-renal disease management.

Clinical integration and future mechanistic horizons of ASIs in cardio-renal diseases

The advent of ASIs signifies a pivotal advancement in RAAS-targeted therapy, with implications extending well beyond hypertension into broader cardio-renal-metabolic disease domains. While initial trials have centered on resistant hypertension, aldosterone's pathogenic role in myocardial fibrosis, oxidative stress, and renal fibrosis positions ASIs as promising candidates across multiple conditions.[11,83,97] In heart failure, particularly with preserved ejection fraction (HFpEF), ASIs may overcome limitations of MRAs by targeting aldosterone synthesis without engaging sex hormone receptors, thus potentially reducing endocrine side effects and expanding applicability in phenotypes with obesity, diabetes, or mineralocorticoid excess.[98-101] In CKD, where MRAs are restricted by hyperkalemia risk, ASIs offer upstream inhibition of aldosterone with early evidence suggesting renal protection and favorable electrolyte profiles;[11] the ongoing FIONE trial may further establish synergy with SGLT2 inhibitors in diabetic kidney disease.[102] ASIs also represent a direct and potentially superior therapeutic approach for primary aldosteronism (PA), offering improved hormonal suppression and organ protection over MRAs.[103] Importantly, ASIs align with precision medicine, with potential for genotype-guided strategies involving CYP11B2 variants and biomarker-guided dosing using aldosterone-renin ratio, 11-deoxycorticosterone, and urinary aldosterone.[104-106] ASIs may also serve as integral components in multidrug regimens for cardio-renal optimization, including combinations with SGLT2 inhibitors for dual renal-hemodynamic effects, ACE inhibitors or ARBs to prevent aldosterone escape, and non-steroidal MRAs for layered RAAS blockade.[107,108] Mechanistically, ASIs provide a durable solution to aldosterone breakthrough by directly inhibiting CYP11B2, circumventing non-ACE escape pathways.[48] Their upstream modulation of pro-fibrotic and pro-inflammatory mediators such as TGF-β, NADPH oxidase, and NLRP3 inflammasome highlights anti-fibrotic and anti-inflammatory potential, which may be explored further through cardiac/renal MRI, biomarker profiling (e.g., galectin-3), and longitudinal omics studies.[109,110] Looking forward, innovations in ASI formulation such as adrenal-specific prodrugs, nanoparticle or sustained-release systems, and AI-guided CYP11B2-selective designs aim to improve safety, target engagement, and tolerability in high-risk populations, including the elderly and those with advanced CKD or polypharmacy.[11,111] Thus, ASIs are poised to transform cardio-renal care through multifaceted clinical integration and evolving mechanistic insights.

Conclusions

In conclusion, ASIs represent not just a new class of antihypertensive agents but a paradigm shift in how aldosterone-mediated pathology is conceptualized and treated. Unlike MRAs, which block the downstream effects of aldosterone, ASIs inhibit its production at the source offering upstream intervention that targets both classical and emerging pathogenic pathways. This includes modulation of fibrosis, inflammation, oxidative stress,

and sympathetic overactivation across the cardiovascular and renal axes. By incorporating pharmacogenomics, targeting neuro-cardiometabolic pathways, addressing aldosterone escape, and leveraging innovations in drug design, ASIs provide a novel and mechanistically elegant solution to longstanding therapeutic challenges in cardio-renal medicine. Their compatibility with personalized dosing frameworks and multidrug regimens further enhances their clinical utility, particularly in patients with resistant hypertension, chronic kidney disease, and heart failure phenotypes such as HFpEF. As the therapeutic paradigm shifts toward more precise and pathophysiology-driven interventions, aldosterone synthase inhibitors stand poised as more than just another RAAS-targeting agent. Their ability to disrupt the aldosterone axis at its origin combined with favorable tolerability, potential for real-world integration, and synergy with existing therapies positions them as a keystone of next-generation cardio-renal-metabolic care. Future clinical trials must focus on long-term outcomes, safety in diverse populations, and real-world implementation strategies. If successful, ASIs may not only complement but potentially redefine the foundational treatment landscape for patients across the cardio-renal continuum.

Contributions

All authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflict of interest, and all authors confirm accuracy.

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