SVOA Medical Research

e-ISSN 2977-3644

ScienceVolks Open Access

Review Article

Aldosterone Synthase Inhibitors in Resistant Hypertension

Guido Damianich, MD[1*], Noelia Roldán, MD[2]

[1]Cardiologist specialising in hypertension; Director, Hypertension Unit, and Attending Physician, Cardiometabolic Diseases Unit, Canning Health Institute, Canning, Buenos Aires, Argentina; Former Director and current Advisor, Hypertension Council, Argentine Society of Cardiology.

[2]Cardiologist specialising in hypertension; Attending Physician, Hypertension Unit and Echocardiography Department, Canning Health Institute, Canning, Buenos Aires, Argentina.

***Corresponding Author:** Guido Damianich, Director, Hypertension Unit, and Attending Physician, Cardiometabolic Diseases Unit, Canning Health Institute, Canning, Buenos Aires, Argentina; Former Director and current Advisor, Hypertension Council, Argentine Society of Cardiology.

https://doi.org/10.58624/SVOAMR.2026.04.001

Received: December 26, 2025

Published: January 09, 2026

Citation: Damianich G, Roldán N. Aldosterone Synthase Inhibitors in Resistant Hypertension. *SVOA Medical Research* 2026, 4:1, 01-10. doi: 10.58624/SVOAMR.2026.04.001

Abstract

Resistant hypertension is a high-risk clinical phenotype characterised by persistent blood pressure elevation despite optimised combination therapy and is associated with an increased burden of cardiovascular and renal complications. Aldosterone excess and dysregulated sodium handling play a central role in the pathophysiology of treatment resistance. Current international guidelines recommend mineralocorticoid receptor antagonists as fourth-line therapy, supported by robust clinical evidence. However, their use is limited by adverse effects, incomplete blood pressure control in a substantial proportion of patients, and persistent aldosterone exposure, prompting interest in alternative therapeutic strategies. Highly selective, novel aldosterone synthase inhibitors have recently demonstrated consistent blood pressure–lowering effects in patients with uncontrolled and resistant hypertension, without clinically relevant interference with cortisol synthesis. Emerging phase II and III data support their potential role as a novel and complementary treatment option, offering a more mechanism-based and individualised approach to the management of resistant hypertension.

Keywords: *Resistant hypertension, Aldosterone, Mineralocorticoid receptor antagonists, Aldosterone synthase inhibitors, Renin–angiotensin–aldosterone system, Cardio–renal–metabolic syndrome*

Introduction

Hypertension, which affects approximately one third of the adult population worldwide, is a leading contributor to the burden of cardiovascular disease [1]. Poor control of this condition leads to progressive damage to multiple target organs and is associated with a marked increase in cardiovascular events and mortality [2,3].

Despite major advances in pharmacological treatment and clear guideline recommendations, achieving and maintaining adequate blood pressure (BP) control in everyday clinical practice remains challenging [4]. Within this context, a subset of patients continues to exhibit elevated BP despite lifestyle modification and treatment with multiple antihypertensive agents. This group, commonly referred to as resistant hypertension (RH), is associated with particularly high cardiovascular and renal risk and often requires complex, individualised management [5].

Given the central role of aldosterone dysregulation in hard-to-control hypertension, emerging therapies that inhibit aldosterone synthesis have the potential to significantly transform the management of patients with RH.

In this article, we summarise the current definitions and epidemiology of RH, its impact on target-organ damage and its principal pathophysiological mechanisms, with a particular focus on aldosterone. We also review current treatment strategies, including the role and limitations of mineralocorticoid receptor antagonists. Finally, we discuss the pharmacology and available clinical evidence for aldosterone synthase inhibitors and consider how these agents may be integrated into the future management of RH.

Definitions and epidemiology

According to the European Society of Cardiology (ESC) and the International Society of Hypertension (ISH), RH is defined when an appropriate treatment strategy, including lifestyle measures and maximally tolerated doses of a thiazide or thiazide-like diuretic, a renin–angiotensin system blocker and a calcium-channel blocker, fails to reduce office systolic and diastolic blood pressure (BP) values to <140 mmHg and <90 mmHg, respectively [6,7]. Lower office BP thresholds for RH have also been proposed in contemporary American Heart Association /American College of Cardiology (AHA/ACC) scientific guidelines [5,8].

Before establishing a diagnosis of RH, pseudoresistance must be carefully excluded. The most common contributing factors include poor adherence, one of the most frequent and often overlooked causes, suboptimal or inappropriate treatment regimens, drug or substance interactions, and inaccuracies in office BP measurement. In addition, uncontrolled BP values should be confirmed by out-of-office measurements, either through home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM), in order to exclude the white-coat effect. Secondary causes of hypertension should also be systematically investigated, particularly in patients with persistent grade-2 hypertension, abrupt onset or rapid worsening of BP levels, or accelerated progression of target-organ damage [5–8].

Estimates of RH prevalence vary across populations and diagnostic criteria but generally range between 5% and 15% of treated hypertensive patients. Higher prevalence has consistently been reported in older individuals, in patients with obesity, chronic kidney disease (CKD) or diabetes, and in those managed in secondary or tertiary care settings [9,10]. In a large meta-analysis including data from 91 studies and more than three million patients published between 1991 and 2017, the prevalence of true RH was estimated at 10.3%, whereas apparently RH accounted for 14.7% of cases, underscoring the clinical relevance of systematically excluding pseudoresistance before confirming the diagnosis [11].

Prognosis

RH is associated with a poorer prognosis, largely driven by sustained BP elevation over time and by pathophysiological mechanisms that tend to confer a more aggressive disease course. As a consequence, target-organ damage is more common and develops earlier, including left ventricular hypertrophy, impaired renal function, and markers of vascular damage such as subclinical atherosclerosis and increased arterial stiffness, when compared with non-resistant hypertension [12,13].

Consistent with these observations, patients with RH have an approximately twofold higher risk of major adverse cardiovascular events [14,15].

In a large cohort study including more than 400,000 individuals, RH was associated with a 24% higher risk of ischaemic heart disease (IHD), a 46% higher risk of heart failure (HF), a 14% higher risk of stroke, a 32% higher risk of advanced CKD and a 6% increase in all-cause mortality [16].

Taken together, these findings underscore the need for more effective therapeutic strategies that not only improve BP control but also target the underlying mechanisms driving disease progression.

Pathophysiology of Resistant Hypertension

RH is a heterogeneous condition resulting from the interplay of haemodynamic, neurohormonal and renal mechanisms [17,18] (Figure 1). Central to its pathophysiology is inappropriate sodium retention and volume expansion, frequently driven by dysregulation of the renin–angiotensin–aldosterone system (RAAS), even in the absence of biochemically overt hyperaldosteronism [19,20]. Altered renal sodium handling represents a key feature of resistant hypertension, characterised by increased salt sensitivity, impaired pressure–natriuresis and reduced renal sodium excretion, which together promote a sodium-dependent phenotype with sustained BP elevation and impaired BP regulation.

Beyond volume expansion, RH is commonly characterised by heightened sympathetic nervous system (SNS) activity, endothelial dysfunction, vascular remodelling and increased arterial stiffness, which further perpetuate BP elevation [21–23]. These mechanisms are particularly relevant in patients with long-standing hypertension, obesity and CKD, in whom haemodynamic and neurohormonal abnormalities tend to coexist and reinforce each other.

Within this complex pathophysiological framework, aldosterone occupies a pivotal position not only through its renal effects on sodium and water balance, but also via direct non-epithelial actions on the cardiovascular system. Experimental and clinical data indicate that excess or inappropriate aldosterone signalling promotes vascular inflammation, fibrosis and adverse cardiac remodelling, thereby accelerating target-organ damage and sustaining the resistant hypertensive state [24–26].

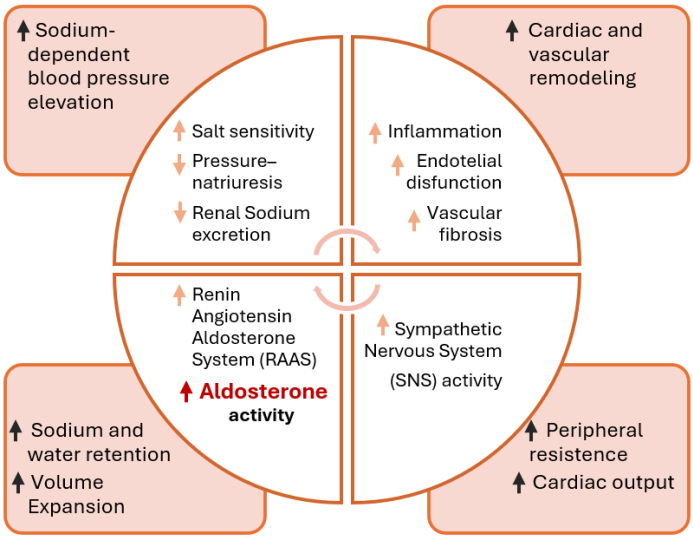

Figure 1. Pathophysiological mechanisms underlying resistant hypertension.

Schematic representation of the major interacting mechanisms contributing to resistant hypertension. Altered renal sodium handling with increased salt sensitivity and impaired pressure–natriuresis, activation of the renin–angiotensin–aldosterone system with heightened aldosterone activity, sympathetic nervous system activation, and vascular inflammation and fibrosis interact to promote sodium- and volume-dependent blood pressure elevation, increased peripheral resistance and adverse cardiac and vascular remodelling.

Current treatment strategies in resistant hypertension

Current international guidelines recommend that antihypertensive treatment be initiated with blockade of the renin–angiotensin system, most commonly using an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, combined, preferably as a fixed-dose regimen, with a calcium-channel blocker and/or a thiazide or thiazide-like diuretic [6-8]. This stepwise approach aims to address complementary pathophysiological mechanisms while improving adherence through regimen simplification.

When BP remains uncontrolled despite maximally tolerated doses of this triple therapy and after confirmation of adherence and out-of-office BP measurements, the addition of a fourth agent is recommended. Over the last decade, mineralocorticoid receptor antagonists (MRAs) have become firmly established as the preferred fourth-line treatment in RH [5-8].

Role of mineralocorticoid receptor antagonists

The pivotal role of MRAs in RH was convincingly demonstrated in the PATHWAY-2 trial. This double-blind, randomized, placebo-controlled crossover study enrolled 335 patients with RH and compared spironolactone (25–50 mg once daily) with bisoprolol, doxazosin modified release and placebo. Spironolactone was superior to all comparators, achieving the greatest reduction in mean systolic blood pressure (SBP), with an average decrease of approximately 13 mmHg from baseline and a significant advantage over placebo and the active comparators [27].These findings provided strong clinical confirmation that inappropriate sodium retention and volume expansion are key drivers of treatment resistance, even in patients already receiving combination therapy targeting the renin–angiotensin system and vascular tone.

Limitations of steroidal MRAs

Despite its proven efficacy, the use of spironolactone may be limited by adverse effects related to its interaction with androgen and progesterone receptors, including gynaecomastia and sexual dysfunction. In patients who develop such intolerance, eplerenone represents a reasonable alternative due to its greater receptor selectivity and more favourable endocrine profile, although its antihypertensive potency is generally lower [28].

Another clinically relevant limitation of MRAs is the risk of hyperkalaemia, particularly in patients with chronic kidney disease and those receiving concomitant RAAS inhibitors. This concern often leads to underuse or premature discontinuation of therapy in high-risk populations. The AMBER trial demonstrated that the potassium-binding agent patiromer significantly reduced discontinuation of spironolactone due to hyperkalaemia, enabling more sustained MRA therapy in patients with RH and impaired renal function [29].

Non-steroidal mineralocorticoid receptor antagonists

Finerenone, a non-steroidal and highly selective mineralocorticoid receptor antagonist, has been shown to provide significant cardiorenal protection in patients with diabetic kidney disease [30]. In this population, finerenone produces modest but sustained reductions in ambulatory BP over 24 hours [31]. Indirect comparisons in patients with RH and CKD suggest that finerenone is associated with smaller reductions in SBP than spironolactone, but with a lower incidence of hyperkalaemia and treatment discontinuation [32].

Rationale for novel therapeutic approaches

Although MRAs have substantially improved the management of RH, their use is limited by adverse effects and by incomplete blood pressure control in a substantial proportion of patients. Importantly, mineralocorticoid receptor antagonism does not suppress aldosterone synthesis and may be accompanied by compensatory increases in circulating aldosterone levels, allowing persistent hormone exposure and continued cardiovascular and renal injury [20]. Together, these limitations provide a strong rationale for alternative therapeutic strategies aimed at selectively reducing aldosterone excess at its source.

Aldosterone synthase inhibitors in resistant hypertension

Direct inhibition of aldosterone synthesis has long been considered an attractive therapeutic strategy in resistant hypertension. By targeting aldosterone production upstream, aldosterone synthase inhibitors (ASIs) have the potential to reduce mineralocorticoid receptor activation without directly antagonising the receptor itself. Early attempts at this approach were limited by insufficient selectivity, as aldosterone synthase (CYP11B2) shares significant structural homology with cortisol synthase (CYP11B1), raising concerns regarding cortisol suppression and adrenal insufficiency [33].

Recent advances in medicinal chemistry have enabled the development of highly selective ASIs that effectively suppress aldosterone production while preserving cortisol synthesis, thereby renewing interest in this therapeutic class [34] (Figure 2).

Key mechanistic and clinical differences between mineralocorticoid receptor antagonists and aldosterone synthase inhibitors are summarised in Table 1, providing essential context for the emerging clinical evidence with aldosterone synthase inhibitors

Table 1. Comparison between mineralocorticoid receptor antagonists and aldosterone synthase inhibitors in resistant hypertension.

Feature	Mineralocorticoid receptor antagonists (MRAs)	Aldosterone synthase inhibitors (ASIs)
Primary mechanism of action	Competitive antagonism of the mineralocorticoid receptor, blocking aldosterone-mediated effects at the tissue level	Direct inhibition of aldosterone synthesis through selective blockade of aldosterone synthase (CYP11B2)
Site of action	Distal nephron and extra-renal mineralocorticoid receptors (heart, vasculature)	Adrenal zona glomerulosa (upstream inhibition of aldosterone production)

Table 1 continued....

Effect on circulating aldosterone levels	Aldosterone levels often remain elevated or increase due to feedback stimulation	Reduction of circulating aldosterone concentrations
Antihypertensive efficacy	Strong blood pressure–lowering effect in resistant hypertension (established fourth-line therapy)	Consistent blood pressure reduction demonstrated in phase II–III trials in uncontrolled and resistant hypertension
Impact on sodium and volume balance	Reduces sodium retention and volume expansion by blocking aldosterone action	Reduces sodium retention and volume expansion by limiting aldosterone production
Effects on potassium homeostasis	Increased risk of hyperkalaemia, particularly in patients with CKD or concomitant RAAS blockade	Lower incidence of hyperkalaemia observed in clinical trials to date, though monitoring remains required
Cardiovascular and renal effects	Well-established cardiovascular and renal protective benefits, particularly in heart failure and CKD	Potential cardiorenal protective effects under investigation in large outcome-driven trials
Endocrine selectivity	Steroidal MRAs may interact with androgen and progesterone receptors (spironolactone)	High enzymatic selectivity for CYP11B2 with minimal interference with cortisol synthesis
Main limitations	Endocrine adverse effects, hyperkalaemia, incomplete BP control in some patients	Long-term safety and outcome data still emerging
Potential role in clinical practice	Established fourth-line therapy in resistant hypertension	Emerging and potentially complementary or sequential therapy tailored to patient phenotype

Clinical evidence with baxdrostat

Baxdrostat is a highly selective aldosterone synthase inhibitor (100:1 selectivity for the enzyme in preclinical studies) that has demonstrated consistent BP–lowering effects in patients with uncontrolled hypertension and RH. In the phase II brigHTN trial, baxdrostat was evaluated in patients with RH receiving stable background antihypertensive therapy. Over 12 weeks, baxdrostat produced dose-dependent reductions in systolic blood pressure, with mean changes from baseline of −20.3 mmHg for the 2 mg dose, −17.5 mmHg for the 1 mg dose and −12.1 mmHg for the 0.5 mg dose, compared with −9.4 mmHg in the placebo group. Placebo-adjusted reductions were −11.0 mmHg (95% CI −16.4 to −5.5; $p<0.001$) and −8.1 mmHg (95% CI −13.5 to −2.8; $p=0.003$) for the 2 mg and 1 mg doses, respectively [35].

Importantly, baxdrostat did not significantly affect cortisol levels, and no cases of adrenal insufficiency were reported, confirming the high selectivity of aldosterone synthase inhibition. Rates of hyperkalaemia were low and manageable, supporting a favourable safety profile.

These findings were subsequently confirmed in the phase III BaxHTN programme. This was a multinational, double-blind, randomized, placebo-controlled trial which enrolled 796 patients with a seated SBP of between 140 mm Hg and less than 170 mm Hg despite stable treatment with two antihypertensive medications (uncontrolled hypertension) or three or more such medications (RH), including a diuretic. After a 2-week placebo run-in period, patients with a seated SBP of 135 mm Hg or more were randomly assigned in a 1:1:1 ratio to receive baxdrostat at a dose of 1 mg, baxdrostat at a dose of 2 mg, or placebo once daily for 12 weeks. The primary end point was the change in seated SBP from baseline to week 12.

At 12 weeks, baxdrostat 2 mg achieved an absolute reduction in SBP of −15.7 mmHg (95% CI −17.6 to −13.7), corresponding to a placebo-adjusted reduction of −9.8 mmHg (95% CI −12.6 to −7.0; p<0.001). Baxdrostat 1 mg resulted in a placebo-adjusted reduction of −8.7 mmHg (95% CI −11.5 to −5.8; p<0.001). Reductions were consistent across office and ambulatory BP measurements, including nighttime values, suggesting sustained 24-hour efficacy [36].

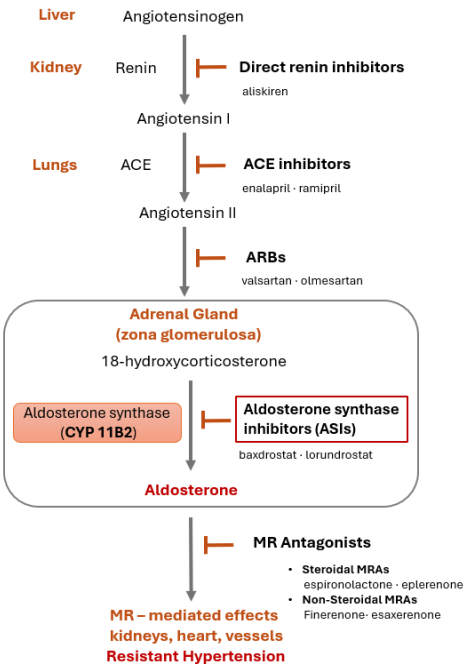

Figure 2. Renin–angiotensin–aldosterone system and pharmacological targets in resistant hypertension.

Schematic overview of the renin–angiotensin–aldosterone system (RAAS) and key pharmacological targets involved in resistant hypertension. Renin converts angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE). This cascade can be modulated by direct renin inhibitors, ACE inhibitors and angiotensin receptor blockers (ARBs).

In the adrenal zona glomerulosa, angiotensin II stimulates aldosterone synthesis via aldosterone synthase (CYP11B2), with 18-hydroxycorticosterone as an intermediate precursor. Aldosterone synthase inhibitors act upstream by reducing aldosterone production, while mineralocorticoid receptor antagonists block aldosterone-mediated effects in target organs, highlighting complementary therapeutic approaches in resistant hypertension.

Clinical evidence with lorundostrat

Lorundrostat is another highly selective, second-generation aldosterone synthase inhibitor that has shown significant BP–lowering effects in patients with uncontrolled hypertension and RH.

In the TARGET-HTN trial, a randomised, double-blind, placebo-controlled study including 200 patients with uncontrolled hypertension despite stable treatment with two or more background antihypertensive agents, lorundrostat administered at doses of 50 mg or 100 mg once daily for 12 weeks achieved placebo-adjusted reductions in office SBP of approximately 8–11 mmHg, depending on dose. Treatment was associated with marked suppression of plasma aldosterone concentrations, while cortisol levels remained largely unchanged, supporting adequate enzymatic selectivity, and overall tolerability was acceptable, with a low incidence of clinically relevant hyperkalaemia [37].

More recently, the antihypertensive efficacy of lorundrostat has been confirmed in a larger and more diverse population in the phase III LAUNCH-HTN clinical trial. This randomised, double-blind, placebo-controlled, parallel-group, multicentre study enrolled 1,083 patients with uncontrolled or RH receiving background antihypertensive therapy. Lorundrostat 50 mg once daily reduced automated office SBP by a least-squares mean of 16.9 mmHg at 6 weeks, compared with 7.9 mmHg with placebo, corresponding to a placebo-adjusted reduction of −9.1 mmHg ($p<0.001$); this effect was sustained through 12 weeks. Treatment discontinuation attributable to hyperkalaemia, hyponatraemia or deterioration in renal function occurred in <1% of participants, supporting a favourable tolerability profile in this higher-risk population [38].

Other aldosterone synthase inhibitors and future directions

Increasingly, RH is being recognised as frequently occurring within a broader cardio–reno–metabolic context, particularly in patients with obesity, diabetes or CKD, rather than as an isolated haemodynamic disorder. This evolving conceptual framework has important therapeutic implications, shifting the focus from BP control alone towards integrated strategies targeting shared pathophysiological pathways involved in sodium handling, intrarenal haemodynamics, inflammation and fibrosis [39,40].

Consistent with this approach, current and planned studies are evaluating ASIs in combination with sodium–glucose cotransporter-2 inhibitors (SGLT2i), particularly in patients with CKD and other cardio–reno–metabolic comorbidities. Ongoing clinical programmes include studies exploring the combination of baxdrostat or lorundrostat with SGLT2 inhibitors such as dapagliflozin or empagliflozin, reflecting a broader strategy aimed at targeting complementary mechanisms beyond BP lowering alone [41,42].

In this context, another highly selective aldosterone synthase inhibitor under advanced clinical development is vicadrostat, which is being explored primarily within a cardio–renal protection framework rather than as monotherapy for BP control. Building on encouraging signals from earlier phase II studies demonstrating effective aldosterone suppression, reductions in albuminuria and acceptable tolerability, particularly when combined with sodium–glucose cotransporter-2 inhibition, vicadrostat has progressed to large-scale outcome-driven clinical evaluation [43]. The multicentre, international, randomised, double-blind, placebo-controlled phase III EASi-KIDNEY trial (NCT06531824) will enrol approximately 11,000 patients with chronic kidney disease to assess whether vicadrostat, when added to standard care including SGLT2 inhibitors, can reduce kidney disease progression, heart failure hospitalisations and cardiovascular mortality [44]. Together, these programmes exemplify an expanding role for aldosterone synthase inhibition beyond BP reduction alone.

Importantly, the emergence of ASIs does not necessarily imply therapeutic competition with MRAs. While MRAs exert their effects at the receptor level and have well-established cardiovascular and renal protective benefits, aldosterone synthase inhibition acts upstream by reducing hormone production itself and may offer advantages in terms of hormonal selectivity and tolerability. These therapeutic classes may therefore be deployed in a complementary or sequential manner, tailored to individual patient phenotypes, comorbidities and risk of adverse effects [45].

As longer-term data become available, future studies will need to determine whether sustained aldosterone suppression translates into meaningful reductions in target-organ damage and cardiovascular events. Within an evolving cardio–reno–metabolic framework, aldosterone synthase inhibitors may ultimately contribute—alongside established therapies—to a more integrated, pathophysiology-driven and individualised approach to the management of RH.

Conclusions

RH remains a prevalent and clinically challenging condition, associated with a high burden of cardiovascular and renal complications despite the widespread use of combination antihypertensive therapy. Accumulating evidence highlights the central role of aldosterone-mediated sodium retention, volume expansion and tissue injury in sustaining BP elevation and target-organ damage in these patients.

Mineralocorticoid receptor antagonists have substantially improved blood pressure control in resistant hypertension and remain the recommended fourth-line therapy. However, their use is limited by adverse effects, incomplete efficacy in a significant proportion of patients, and persistent aldosterone exposure. These limitations provide a strong rationale for therapeutic strategies that directly target aldosterone excess at its source.

Recent clinical trials with highly selective, second-generation aldosterone synthase inhibitors have demonstrated consistent and clinically meaningful reductions in BP, with favourable tolerability profiles. Together with ongoing studies exploring their use in broader cardio–reno–metabolic contexts and in combination with established therapies, aldosterone synthase inhibition represents a promising and pathophysiology-driven approach that may further refine the management of RH.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, Regional, and National Burden of Cardiovascular Diseases and Risk Factors in 204 Countries and Territories, 1990-2023. J Am Coll Cardiol. 2025;86(22):2167-2243
2. Kario K, Okura A, Hoshide S, Mogi M. The WHO Global report 2023 on hypertension warning the emerging hypertension burden in globe and its treatment strategy. Hypertens Res. 2024;47(5):1099-1102
3. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. Sci Rep. 2018;8(1):9418
4. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957-980.
5. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018;72(5):e53-e90
6. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45(38):3912-4018
7. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-1357
8. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension. 2025;82(10):e212-e316
9. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation. 2012;125(13):1594-1596
10. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of Apparent Treatment-Resistant Hypertension in the United States. Hypertension. 2019;73(2):424-431
11. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. Heart. 2019;105(2):98-105
12. Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, et al. Resistant hypertension and target organ damage. Hypertens Res. 2013;36(6):485-91
13. Rubattu S, Pagliaro B, Pierelli G, Santolamazza C, Castro SD, Mennuni S, et al. Pathogenesis of target organ damage in hypertension: role of mitochondrial oxidative stress. Int J Mol Sci. 2014;16(1):823-39.

14. Tsioufis C, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, et al. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study.J Hypertens. 2014;32:415–422

15. De la Sierra A, Ruilope LM, Staplin N, Gorostidi M, Vinyoles E, Segura J, et al. Resistant Hypertension and Mortality: An Observational Cohort Study. Hypertension. 2024;81(11):2350-2356.

16. Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension.Kidney Int. 2015; 88:622–632

17. Judd EK, Calhoun DA, Warnock DG. Pathophysiology and treatment of resistant hypertension: the role of aldosterone and amiloride-sensitive sodium channels. Semin Nephrol. 2014;34(5):532–539.

18. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: mechanisms and treatment. Curr Hypertens Rep. 2017;19(7):56.

19. Bioletto F, Bollati M, Lopez C, et al. Primary aldosteronism and resistant hypertension: a pathophysiological insight. Int J Mol Sci. 2022;23(9):4803.

20. Gaddam KK, Pimenta E, Husain S, et al. Aldosterone and cardiovascular disease. Curr Probl Cardiol. 2009;34(2):51–84.

21. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003;139(9):761–776.

22. Hering D, Schlaich M. The role of central nervous system mechanisms in resistant hypertension. Curr Hypertens Rep. 2015;17(8):58.

23. Bansal S. Revisiting resistant hypertension in kidney disease. Curr Opin Nephrol Hypertens. 2024;33(5):465–473.

24. Duprez DA. Aldosterone and the vasculature: mechanisms mediating resistant hypertension. J Clin Hypertens (Greenwich). 2007;9(1 Suppl 1):13–18.

25. Connell JMC, Freel EM. Aldosterone and cardiovascular disease. Clin Sci (Lond).

26. Pitt B, Zannad F, Remme WJ, et al. Aldosterone blockade in patients with left ventricular dysfunction. N Engl J Med. 1999;341(10):709–717.

27. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059-2068

28. Manolis AA, Manolis TA, Melita H, Manolis AS. Eplerenone Versus Spironolactone in Resistant Hypertension: an Efficacy and/or Cost or Just a Men's Issue? Curr Hypertens Rep. 2019;21(3):2

29. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, Ma J, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10208):1540-1550.

30. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022;43(6):474-484

31. Agarwal R, Ruilope LM, Ruiz-Hurtado G, Haller H, Schmieder RE, Anker SD, et al. Effect of finerenone on ambulatory blood pressure in chronic kidney disease in type 2 diabetes. J Hypertens. 2023;41(2):295-302

32. Agarwal R, Pitt B, Palmer BF, Kovesdy CP, Burgess E, Filippatos G, et al. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. Clin Kidney J. 2022;16(2):293-302.

33. Strushkevich N, Gilep AA, Shen L, Arrowsmith CH, Edwards AM, Usanov SA, Park HW. Structural insights into aldosterone synthase substrate specificity and targeted inhibition. Mol Endocrinol. 2013 Feb;27(2):315-32

34. Weldon SM, Brown NF. Inhibitors of Aldosterone Synthase. Vitam Horm. 2019;109:211-239

35. Freeman MW, Halvorsen YD, Marshall W, Pater M, Isaacsohn J, Pearce C, et al; BrigHTN Investigators. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. N Engl J Med. 2023 Feb 2;388(5):395-405.

36. Flack JM, Azizi M, Brown JM, Dwyer JP, Fronczek J, Jones ESW et al; BaxHTN Investigators. Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension. N Engl J Med. 2025;393(14):1363-1374

37. Laffin LJ, Rodman D, Luther JM, Vaidya A, Weir MR, Rajicic N, et al; Target-HTN Investigators. Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension: The Target-HTN Randomized Clinical Trial. JAMA. 2023;330(12):1140-1150

38. Saxena M, Laffin L, Borghi C, Fernandez Fernandez B, Ghali JK, Kopjar B, et al; Launch-HTN Investigators. Lorundrostat in Participants With Uncontrolled Hypertension and Treatment-Resistant Hypertension: The Launch-HTN Randomized Clinical Trial. JAMA. 2025;334(5):409-418

39. Ruilope LM, Pitt B, de la Sierra A, Ruiz-Hurtado G. Towards a better prevention in cardio-kidney metabolic syndrome: Role of aldosterone and albuminuria. Nefrologia (Engl Ed). 2025;45(9):501399.

40. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al; American Heart Association. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023 Nov 14;148(20):1606-1635

41. https://www.clinicaltrials.gov/study/NCT06268873

42. https://clinicaltrials.gov/study/NCT06150924?term=NCT06150924&rank=1

43. Tuttle KR, Hauske SJ, Canziani ME, Caramori ML, Cherney D, Cronin L, et al; ASi in CKD group. Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial. Lancet. 2024;403(10424):379-390

44. Judge PK, Tuttle KR, Staplin N, Hauske SJ, Zhu D, Sardell R, et al. The potential for improving cardio-renal outcomes in chronic kidney disease with the aldosterone synthase inhibitor vicadrostat (BI 690517): a rationale for the EASi-KIDNEY trial. Nephrol Dial Transplant. 2025;40(6):1175-1186.

45. Ferreira JP, Marques P, Leite AR, Neves JS, Zannad F, Pitt B. Mineralocorticoid Receptor Antagonists and Aldosterone Synthase Inhibitors: Agent Comparison With Implications for Clinical Practice and Trial Design. J Card Fail. 2025:S1071-9164(25)00203-9