Clin Hypertens. 2025 Dec 1;31:e42
https://doi.org/10.5646/ch.2025.31.e42
eISSN 2056-5909

Clinical Hypertension

Review

Check for updates

Amiloride: revisiting an old drug for resistant hypertension

Chan Joo Lee, and Sungha Park*

Division of Cardiology, Severance Cardiovascular Hospital, Integrative Research Center for Cerebrovascular and Cardiovascular Diseases, Yonsei University College of Medicine, Seoul, Republic of Korea

OPEN ACCESS

Received: Sep 21, 2025
Revised: Oct 12, 2025
Accepted: Oct 20, 2025
Published online: Dec 1, 2025

***Correspondence:**
Sungha Park
Division of Cardiology, Severance Cardiovascular Hospital, Integrative Research Center for Cerebrovascular and Cardiovascular Diseases, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
Email: shpark0530@yuhs.ac

ORCID iDs
Chan Joo Lee
https://orcid.org/0000-0002-8756-409X
Sungha Park
https://orcid.org/0000-0001-5362-478X

Abbreviations
AR ratio, aldosterone/renin ratio; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CI, confidence interval; ENaC, epithelial sodium channel; HF, heart failure; MR, mineralocorticoid receptor; RAS, renin-angiotensin system; RALES, Randomized Aldactone Evaluation Study; RCT, randomized clinical trial; RH, resistant hypertension; SBP, systolic blood pressure; SD, standard

ABSTRACT

Resistant hypertension (RH) remains a major clinical challenge, defined as uncontrolled blood pressure (BP) despite the use of 3 antihypertensive agents, including a renin-angiotensin system inhibitor, a calcium channel blocker, and a diuretic, or the need for 4 or more agents. Spironolactone has been considered the most effective fourth-line therapy, supported by the PATHWAY-2 trial, but its real-world use is limited by adverse effects such as gynecomastia, menstrual irregularities, and hyperkalemia. Therefore, there was a clinical need for alternative agents, and thus the use of amiloride, an epithelial sodium channel (ENaC) inhibitor and potassium-sparing diuretic, has been proposed. Data from PATHWAY-2 suggested amiloride's comparable BP-lowering efficacy, though based only on an open-label extension. Recently, the SPironolactone versus Amiloride for REsistant hypertension (SPARE) trial provided the first randomized evidence directly comparing the 2 agents. In 118 patients with RH inadequately controlled on fixed-dose triple therapy, participants were randomized to spironolactone 12–25 mg or amiloride 5–10 mg for 12 weeks. Mean reductions in home systolic blood pressure (SBP) were −14.7 mmHg with spironolactone and −13.6 mmHg with amiloride, meeting the prespecified non-inferiority margin. Safety profiles were favorable, with only one discontinuation due to hyperkalemia in the amiloride group and no reports of gynecomastia. Subgroup analyses suggested greater efficacy of amiloride in patients with higher body mass index and lower aldosterone–renin ratios, highlighting a potentially distinct mechanism of action. Unlike spironolactone, whose efficacy correlated with aldosterone activity, amiloride showed consistent SBP reduction across renin and aldosterone levels. Beyond its renal ENaC inhibition, amiloride may also modulate vascular biology. In addition to its inhibition of renal ENaCs, amiloride may also have an impact on vascular biology. Experimental studies indicate that ENaC is present in endothelial cells, where its activation can lead to reduced nitric oxide release, increased oxidative stress, endothelial stiffness, and vascular fibrosis. Amiloride may consistently lower BP across a wide range of renin-aldosterone activity by improving endothelial function through the inhibition of ENaC, as well as by decreasing intravascular volume. The findings from the SPARE trial suggest that amiloride may be a viable alternative to spironolactone for RH, particularly in patients who are intolerant to mineralocorticoid receptor antagonists. While spironolactone remains the preferred option due to its established role in blocking systemic aldosterone activation and proven cardiovascular benefits, amiloride can provide a practical and well-tolerated alternative.

Keywords: Resistant hypertension; Amiloride; Spironolactone; Hyperkalemia; Aldosterone; Epithelial sodium channel

deviation; SPARE, SPironolactone versus Amiloride for REsistant hypertension; PRA, plasma renin activity.

Funding

This research was supported by the Korea National Institute of Health research project 2024-ER0901-01.

Competing interest

Chan Joo Lee reported receipt of personal fees from Novartis, Hanmi Pharmaceutical, Yuhan, Boryung Pharmaceutical, and Daiichi Sankyo, and receipt of grant from Chong Kun Dang, and stock options from Mediwhale. Sungha Park reported receipt of personal fees from Viatris, Organon, Boryung, Handok, Hanmi, Daewoong, Donga, Celltrion, Servier, Daiichi Sankyo, and Skylabs and has stocks from Mediwhale.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

Conceptualization: Lee CJ, Park S; Funding acquisition: Park S; Investigation: Lee CJ; Supervision: Park S; Validation: Park S; Writing - original draft: Lee CJ, Park S; Writing - review & editing: Lee CJ, Park S.

INTRODUCTION

Resistant hypertension (RH) is defined as the failure to lower blood pressure (BP) below the target BP despite the use of ≥ 3 antihypertensive drugs, usually including dihydropyridine calcium channel blockers (CCBs), renin-angiotensin system (RAS) inhibitors, and diuretics, or the need for treatment with ≥ 4 antihypertensive medications to achieve the target BP [1,2]. The prevalence of RH varies according to different reports. In a pooled analysis of 3,207,911 hypertensive patients, the prevalence was 10.3% for true RH and 14.7% for apparent treatment-RH [3]. In Korea, analysis of the National Health Insurance Service database reported a prevalence of RH of 7.4% [4]. When BP is not controlled by the maximally tolerated triple combination of RAS inhibitors, CCBs, and diuretics, spironolactone is considered the drug of choice [1,5,6]. However, spironolactone has side effects such as gynecomastia, decreased libido, menstrual irregularity, and hyperkalemia that limit its usage [7]. Therefore, while several guidelines, including the 2024 European Society of Cardiology hypertension guideline, suggest that amiloride may be considered as an alternative to spironolactone, the evidence supporting this was somewhat weak [6,8,9]. Recently, a randomized trial comparing the efficacy of spironolactone and amiloride in patients with RH was reported, which demonstrated non-inferiority of amiloride when compared with spironolactone for home BP lowering efficacy [10]. In this review, based on the latest evidence, we will discuss the possible new role of amiloride as a treatment option in patients with RH.

THE ROLE OF SPIRONOLACTONE IN THE TREATMENT OF RH

In the PATHWAY 2 trial, spironolactone demonstrated superior efficacy compared to doxazosin (−4.03 mmHg [95% confidence interval {CI}, −5.04 to −3.02], $P < 0.0001$] and bisoprolol (−4.48 mmHg [95% CI, −5.50 to −3.46], $P < 0.0001$] in reducing home systolic BP in patients with RH [5]. Based on this study, major guidelines have recommended spironolactone as the drug of choice in RH. However, spironolactone has an antiandrogenic effect that results in side effects such as gynecomastia, a decrease in libido, and menstrual irregularity [7]. In an analysis of the US Food and Drug Administration Adverse Event Reporting System, the reported odds ratio of spironolactone for gynecomastia was 15.8 (13.99 to 17.83) [11]. In a meta-analysis of randomized clinical trials, the odds ratio for the development of gynecomastia with the use of spironolactone was 8.39 (95% CI, 5.03 to 13.99). Also, spironolactone can cause hyperkalemia, which is an important limiting factor for its usage, especially in patients with RH in whom chronic kidney disease is highly prevalent and combination treatment with RAS inhibitors is usually required [12]. These factors are likely the primary reasons for the low usage of spironolactone in real-world settings. In the aforementioned analysis of RH patients in Korea using the National Health Insurance Service database, only 5.1% of patients with RH were being prescribed potassium-sparing diuretics [4]. Spironolactone is recommended as a fourth-line agent for RH. However, analysis of a RH cohort with over 1,400 patients registered across 15 tertiary hospitals in Korea revealed a significantly higher rate of beta-blocker use compared to spironolactone [13]. This finding may demonstrate that spironolactone is a medication that physicians are reluctant to prescribe in actual clinical practice for various reasons. In cases where spironolactone is not tolerated, major guidelines have suggested that potassium-sparing diuretics, such as amiloride, may be considered. But this was based on findings from a substudy of the aforementioned PATHWAY-2 trial, which assessed the efficacy of amiloride

10–20 mg on clinic systolic blood pressure (SBP) during an optional 6–12 week open-label runout phase. In the substudy, amiloride 10 mg reduced clinic SBP by 20.4 mmHg (95% CI, 18.3 to 22.5) compared to 18.3 mmHg (16.2 to 20.5) for 25 mg of spironolactone [9]. However, no randomized clinical trials have compared the efficacy of spironolactone and amiloride in patients with RH.

THE BP-LOWERING EFFICACY OF AMILORIDE IN RH

In the recently published SPironolactone versus Amiloride for REsistant hypertension (SPARE) trial, 118 RH patients with home SBP greater than 130 mmHg after 4 week run in with fixed-dose triple combination of olmesartan, amlodipine and hydrochlorothiazide were randomized spironolactone 12–25 mg and amiloride 5–10 mg in an open-label, blinded end-point trial with the primary endpoint being reduction of home SBP at week 12 with the objective being to demonstrate non inferiority of amiloride (baseline mean home SBP 141.5 mmHg) compared to spironolactone (baseline mean home SBP 142.3 mmHg). At week 12, the reduction of home SBP was –13.6 mmHg (standard deviation [SD], 8.6 mmHg) and –14.7 mmHg (SD, 11.0 mmHg) by amiloride and spironolactone, respectively (between-group difference in change, –0.68 mmHg, 90% CI, –3.50 to 2.14 mmHg) with amiloride demonstrating non-inferiority to spironolactone (**Fig. 1**). Both drugs were relatively safe in this study, with one case of drug discontinuation due to hyperkalemia with amiloride and no cases of gynecomastia [10]. In the subgroup analysis, there was significant interaction for body mass index (BMI, *P* for interaction = 0.03) and aldosterone/renin ratio (AR ratio, *P* for interaction = 0.04) with amiloride showing better home SBP lowering efficacy in participants with higher BMI and lower AR ratio than spironolactone [10]. An interesting finding from this study was that while the BP-lowering efficacy of spironolactone increased with decreasing plasma renin activity (PRA) and increasing AR ratio, the efficacy of amiloride remained consistent regardless of PRA and AR ratio (**Fig. 2**) [10]. Because amiloride is a diuretic and because the main pathophysiologic mechanism of RH is volume excess, one would expect that amiloride would be more efficacious in those with lower PRA and higher AR ratio. What could be the explanation for the unexpected findings?

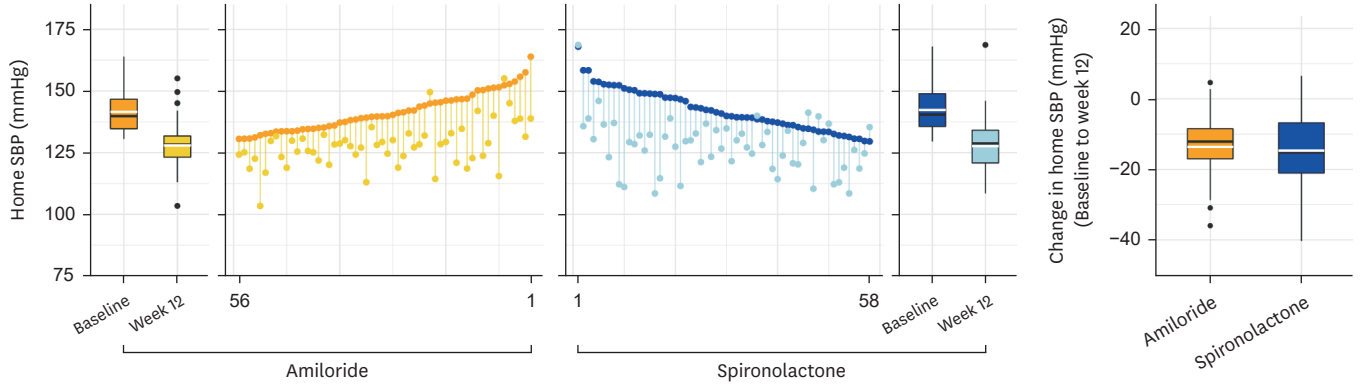

Fig. 1. Change in home SBP in patients treated with amiloride vs. spironolactone. A parallel dot chart on the right displays one vertical line per patient, extending from the baseline home SBP measurement to the home SBP at 12 weeks. A downward line indicates a decrease in home SBP over time, while an upward line indicates an increase. Baseline home SBP is displayed in ascending order for the amiloride group and in descending order for the spironolactone group. The box plot on the right shows the change in blood pressure from baseline to 12 weeks for each group. Adapted with permission Lee et al. JAMA. 2025;333:2073-82 [10], with permission from the American Medical Association.
SBP, systolic blood pressure.

https://doi.org/10.5646/ch.2025.31.e42

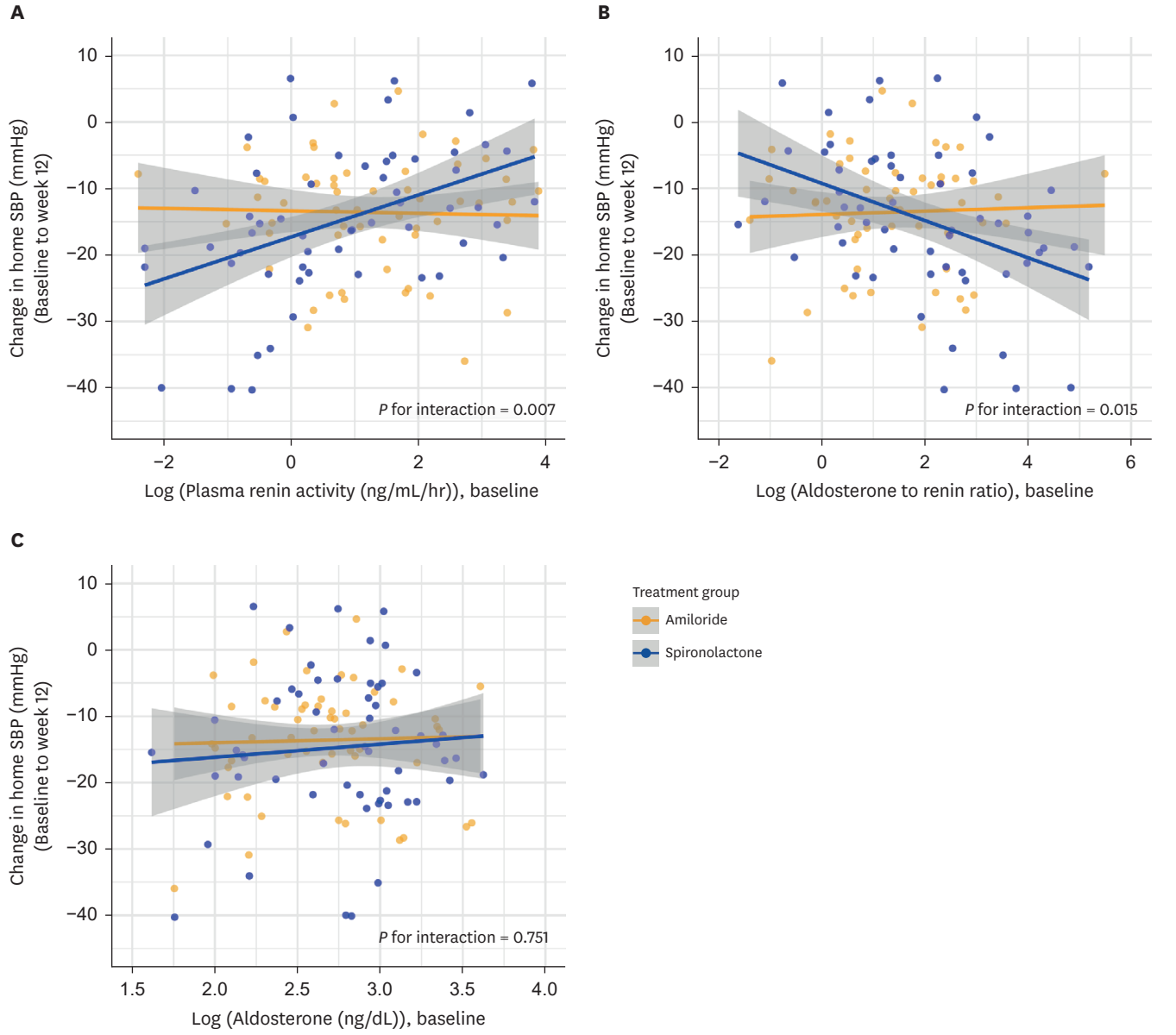

Fig. 2. Change of home SBP according to baseline plasma renin activity (A), aldosterone to renin ratio (B), and serum aldosterone level (C). The x-axis represents the log-transformed baseline biomarker values, while the y-axis shows the change in home SBP from baseline to week 12. The orange dots indicate the amiloride group, and the orange line represents the regression line between baseline biomarker values and changes in home SBP in the amiloride group. Blue dots indicate the spironolactone group, and the blue line represents the regression line between baseline biomarker values and changes in home SBP in the spironolactone group. Adapted with permission from Lee et al. JAMA. 2025;333:2073-82 [10], with permission from the American Medical Association.
SBP, systolic blood pressure.

Amiloride is a pyrazine-carbonyl-guanidine derivative first developed in the 1960s. It is an inhibitor of the epithelial sodium channel (ENaC) and acts as a potassium-sparing diuretic [14]. **Table 1** summarizes the differences between amiloride and spironolactone. Recent studies have shown that amiloride-sensitive sodium channels are not only located in the kidneys but are also expressed in endothelial cells and are important mediators of vascular endothelial function [16]. Increased activation of ENaCs is associated with impaired endothelial NO release, increased oxidative stress-mediated NO destruction, increased vascular permeability resulting in increased vascular tone and fibrosis [16]. ENaC is important in mediating endothelial stiffness and endothelial dysfunction in obesity, and

https://doi.org/10.5646/ch.2025.31.e42

Table 1. Comparison of spironolactone and amiloride

Domain	Spironolactone	Amiloride
Mechanism of action	Competitive mineralocorticoid (aldosterone) receptor antagonist in distal nephron → ↓ ENaC expression, ↓ Na^+ reabsorption, K^+-sparing diuresis; additional antifibrotic/antiremodeling effects via MR blockade.	Direct ENaC blocker in the late distal tubule/collecting duct → ↓ Na^+ reabsorption, K^+-sparing natriuresis.
BP-lowering efficacy (particularly in resistant hypertension)	PATHWAY-2 [5]: most effective add-on; −12.8 mmHg from baseline home SBP; −8.7 mmHg vs. placebo; −4.3 mmHg vs. bisoprolol/doxazosin. PATHWAY-2 substudy [9]: −18.3 mmHg from baseline office SBP. SPARE [10]: −14.7 mmHg from baseline home SBP.	PATHWAY-2 substudy [9]: −20.4 mmHg from baseline office SBP. SPARE [10]: −13.6 mmHg from baseline home SBP (noninferior to spironolactone).
Hyperkalemia risk	Present; rises with CKD, RAS inhibitors, and higher doses.	Present (ENaC blockade) and potentiated by RAS inhibitors.
Gynecomastia	Well-recognized, dose- and duration-dependent (anti-androgenic). RALES [15]: ~10% of men reported gynecomastia/breast pain; reports up to ~50% at very high doses.	Rare/none (no anti-androgen effect).
Expected CV outcomes	HF with reduced ejection fraction: RALES [17] showed ~30% relative mortality reduction and fewer HF hospitalizations. Disease-modifying via mineralocorticoid receptor blockade. Hypertension: no dedicated outcomes RCTs; benefits are inferred from BP lowering.	No definitive CV outcomes RCTs as monotherapy or add-on for hypertension/HF. Risk reduction is expected with BP lowering.

ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; BP, blood pressure; SBP, systolic blood pressure; SPARE, SPironolactone versus Amiloride for REsistant hypertension; CKD, chronic kidney disease; RAS, renin-angiotensin system; RALES, Randomized Aldactone Evaluation Study; HF, heart failure; RCT, randomized clinical trial; CV, cardiovascular.

hyperinsulinemia is associated with increased activation of ENaC [17]. This connection may help explain why amiloride consistently demonstrates efficacy across a range of AR ratios and why it is more effective than spironolactone in participants with a higher BMI.

Relatively, spironolactone works by mechanistically blocking aldosterone from binding to its receptor, so theoretically, it is expected to be more effective at lowering BP in patients with relative aldosterone excess. On the other hand, amiloride inhibits ENaC to produce a diuretic effect, so it can be presumed to exhibit a consistent BP-lowering effect independent of aldosterone levels.

POSITION OF AMILORIDE AFTER THE SPARE TRIAL

In the SPARE trial, amiloride was shown to be non-inferior to spironolactone for BP lowering in patients with RH. Although spironolactone should still be the preferred drug in RH, considering its effect in blocking systemic aldosterone activation and proven efficacy in reducing cardiovascular outcomes [6,8,15]. Also, in patients with an elevated AR ratio, spironolactone should be the drug of choice. However, in patients with adverse side effects to spironolactone, amiloride could be an effective alternative for treating RH. Based on these findings, we propose a new algorithm for managing RH, as illustrated in **Fig. 3**. It recommends amiloride as an alternative to spironolactone in cases of intolerance. This algorithm slightly modifies the management strategy outlined in the Korean Society of Hypertension's consensus document on RH published in 2023 [1]. Also in the SPARE trial, good BP-lowering efficacy was observed with low-dose spironolactone and low-dose amiloride with minimal side effects and good tolerability. Therefore, future trials to demonstrate the efficacy of a combination of low-dose spironolactone and low-dose amiloride may be of interest, as suggested by a recent editorial [18].

Although evidence remains relatively scarce regarding whether amiloride reduces cardiovascular outcomes to date, it is clear that BP control in hypertensive patients reduces

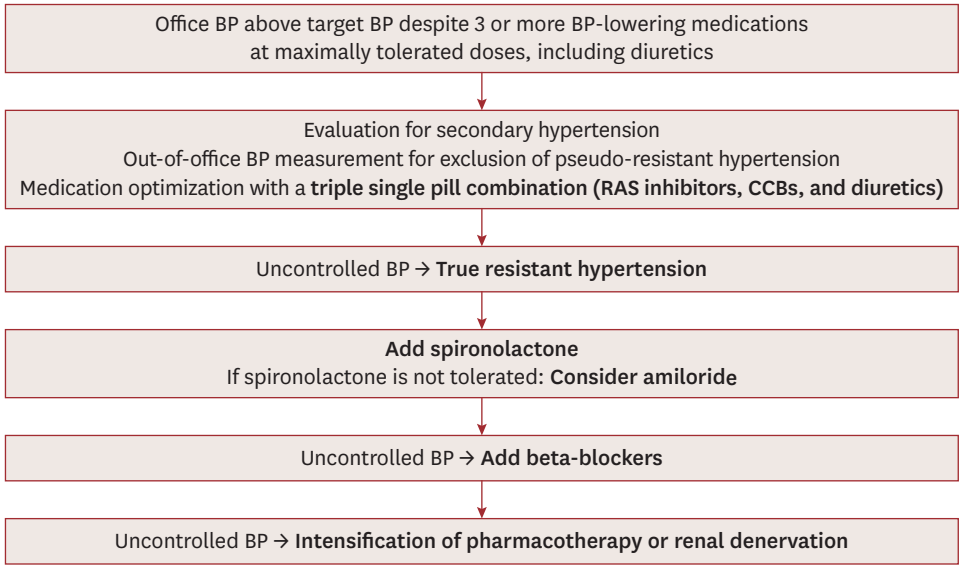

Fig. 3. Newly proposed stepwise management algorithm for resistant hypertension. Apparent resistant hypertension is defined as office BP above target despite treatment with ≥ 3 antihypertensive agents at maximally tolerated doses, including diuretics. An evaluation for secondary hypertension and confirmation with out-of-office BP monitoring is required to exclude pseudo-resistance. Optimizing medication with a triple single-pill combination of RAS inhibitors, calcium channel blockers and diuretics may improve adherence. If BP remains uncontrolled, spironolactone is the preferred fourth-line agent, with amiloride being an alternative if spironolactone is not tolerated. If BP remains uncontrolled despite these steps, the addition of a β-blocker is warranted, followed by further pharmacologic intensification or renal denervation if BP remains uncontrolled. BP, blood pressure; RAS, renin-angiotensin system; CCB, calcium channel blocker.

the incidence of cardiovascular events. Therefore, it is reasonable to expect that BP control using amiloride in patients with RH, while not an aldosterone antagonist, will be beneficial in the long term.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to all investigators and collaborators of the Korean Resistant Hypertension Cohort for their invaluable contributions to patient enrollment, data collection, and clinical insights that have greatly enriched this review.

REFERENCES

1. Park S, Shin J, Ihm SH, Kim KI, Kim HL, Kim HC, et al. Resistant hypertension: consensus document from the Korean Society of Hypertension. Clin Hypertens. 2023;29:30. PUBMED | CROSSREF
2. 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:e53-90. PUBMED | CROSSREF
3. 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;105:98-105. PUBMED | CROSSREF
4. Lee CJ, Lee H, Seo J, Hwang J, Kang D, Park SH, et al. Prognosis of apparent treatment-resistant hypertension and poor adherence: a nationwide cohort study. Hypertens Res. 2025;48:49-59. PUBMED | CROSSREF
5. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. 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;386:2059-68. PUBMED | CROSSREF

6. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912-4018. PUBMED | CROSSREF
7. Lainscak M, Pelliccia F, Rosano G, Vitale C, Schiariti M, Greco C, et al. Safety profile of mineralocorticoid receptor antagonists: spironolactone and eplerenone. Int J Cardiol. 2015;200:25-9. PUBMED | CROSSREF
8. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. 2023;41:1874-2071. PUBMED | CROSSREF
9. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. Lancet Diabetes Endocrinol. 2018;6:464-75. PUBMED | CROSSREF
10. Lee CJ, Ihm SH, Shin DH, Jeong JO, Kim JH, Chun KH, et al. Spironolactone vs amiloride for resistant hypertension: a randomized clinical trial. JAMA. 2025;333:2073-82. PUBMED | CROSSREF
11. Yang X, Zheng X, Zhang M, Huang J, Huang P, Wang J. Drug-induced gynecomastia: data mining and analysis of the FDA Adverse Event Reporting System database. Clin Epidemiol. 2024;16:617-30. PUBMED | CROSSREF
12. Yoon M, You SC, Oh J, Lee CJ, Lee SH, Kang SM, et al. Prevalence and prognosis of refractory hypertension diagnosed using ambulatory blood pressure measurements. Hypertens Res. 2022;45:1353-62. PUBMED | CROSSREF
13. Seo J, Lee CJ, Kim DH, Kim SY, Moon JY, Park JH, et al. Discrepancies between home blood pressure and ambulatory blood pressure monitoring in apparent treatment-resistant hypertension: analysis from the Korean resistant hypertension cohort. Hypertens Res. 2025;48:37-48. PUBMED | CROSSREF
14. Sun Q, Sever P. Amiloride: a review. J Renin Angiotensin Aldosterone Syst. 2020;21:1470320320975893. PUBMED | CROSSREF
15. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709-17. PUBMED | CROSSREF
16. Hill MA, Jaisser F, Sowers JR. Role of the vascular endothelial sodium channel activation in the genesis of pathologically increased cardiovascular stiffness. Cardiovasc Res. 2022;118:130-40. PUBMED | CROSSREF
17. Sowers JR, Habibi J, Aroor AR, Yang Y, Lastra G, Hill MA, et al. Epithelial sodium channels in endothelial cells mediate diet-induced endothelium stiffness and impaired vascular relaxation in obese female mice. Metabolism. 2019;99:57-66. PUBMED | CROSSREF
18. Brook RD, Cohen JB, Rajagopalan S. New support for old medications in resistant hypertension. JAMA. 2025;333:2058-60. PUBMED | CROSSREF