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RESISTANT HYPERTENSION: EFFICACY OF SPIRONOLACTONE AND EMERGING PHARMACOLOGICAL THERAPIES IN CURRENT MANAGEMENT

HIPERTENSÃO ARTERIAL RESISTENTE: EFICÁCIA DA ESPIRONOLACTONA E TERAPIAS ATUAIS EMERGENTES NO MANEJO FARMACOLÓGICO

HIPERTENSIÓN ARTERIAL RESISTENTE: EFICACIA DE LA ESPIRONOLACTONA Y TERAPIAS EMERGENTES ACTUALES EN EL MANEJO FARMACOLÓGICO

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ABSTRACT

Resistant hypertension (RH) is a multifactorial condition associated with high cardiovascular morbidity and mortality and remains a major therapeutic challenge. This study aimed to critically review the available scientific evidence on the efficacy of spironolactone and the role

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of emerging pharmacological therapies in the management of RH. An integrative literature review was conducted, including publications indexed in PubMed, Scopus, Web of Science, SciELO, and the Cochrane Library between 2015 and 2025. Randomized clinical trials, systematic reviews, meta-analyses, and clinical guidelines evaluating pharmacological interventions for RH were included. The final sample comprised 27 high-quality studies. The findings demonstrated that spironolactone remains the most effective fourth-line drug, achieving an average systolic blood pressure reduction of 8 to 13 mmHg and significant improvement in resistant blood pressure control. Nonsteroidal mineralocorticoid receptor antagonists, such as finerenone and eplerenone, showed comparable efficacy with fewer adverse effects. Moreover, emerging therapies—including SGLT2 inhibitors, angiotensin receptor–neprilysin inhibitors (ARNIs), and renal denervation—showed complementary potential in blood pressure control and cardiovascular protection. It is concluded that spironolactone remains the gold-standard pharmacological treatment for RH, while novel therapies broaden the possibilities for personalized and integrated management, reinforcing the importance of multidisciplinary approaches and long-term comparative studies.

Keywords: Resistant Hypertension. Spironolactone. Mineralocorticoid Receptor Antagonists. Finerenone. Renal Denervation. SGLT2 Inhibitors.

RESUMO

A hipertensão arterial resistente (HAR) é uma condição multifatorial de difícil controle clínico, associada a elevada morbimortalidade cardiovascular e desafios terapêuticos persistentes. Este estudo teve como objetivo revisar criticamente as evidências científicas disponíveis sobre a eficácia da espironolactona e o papel das terapias farmacológicas emergentes no manejo da HAR. Foi realizada uma revisão integrativa da literatura, abrangendo publicações indexadas nas bases PubMed, Scopus, Web of Science, SciELO e Cochrane Library, no período de 2015 a 2025. Foram incluídos ensaios clínicos randomizados, revisões sistemáticas, metanálises e diretrizes clínicas que avaliaram intervenções farmacológicas aplicadas ao tratamento da HAR. A amostra final foi composta por 27 estudos de alta qualidade metodológica. Os resultados demonstraram que a espironolactona permanece como o fármaco de quarta linha mais eficaz, com redução média de 8 a 13 mmHg na pressão sistólica e benefícios significativos no controle pressórico refratário. Os antagonistas não esteroidais do receptor de mineralocorticoide, como a finerenona e a eplerenona, apresentaram eficácia comparável e melhor perfil de segurança. Além disso, terapias emergentes, como os inibidores de SGLT2, bloqueadores duplos de receptores de angiotensina e neprilisina (ARNIs) e a denervação renal, mostraram potencial complementar no controle pressórico e na proteção cardiovascular. Conclui-se que a espironolactona mantém-se como o tratamento farmacológico de referência para HAR, enquanto novas terapias ampliam as perspectivas de manejo personalizado e integrado, reforçando a necessidade de abordagens multidisciplinares e de estudos comparativos de longo prazo.

Palavras-chave: Hipertensão Resistente. Espironolactona. Antagonistas de Mineralocorticoide. Finerenona. Denervação Renal. Inibidores de SGLT2.

RESUMEN

La hipertensión resistente (HRH) es una enfermedad multifactorial de difícil control clínico, asociada a una alta morbilidad y mortalidad cardiovascular y a desafíos terapéuticos persistentes. Este estudio tuvo como objetivo revisar críticamente la evidencia científica disponible sobre la eficacia de la espironolactona y el papel de las terapias farmacológicas

emergentes en el manejo de la HRH. Se realizó una revisión bibliográfica integradora, que abarcó publicaciones indexadas en PubMed, Scopus, Web of Science, SciELO y la Biblioteca Cochrane, entre 2015 y 2025. Se incluyeron ensayos controlados aleatorizados, revisiones sistemáticas, metaanálisis y guías clínicas que evaluaron intervenciones farmacológicas aplicadas al tratamiento de la HRH. La muestra final consistió en 27 estudios de alta calidad metodológica. Los resultados demostraron que la espironolactona sigue siendo el fármaco de cuarta línea más eficaz, con una reducción promedio de 8 a 13 mmHg en la presión arterial sistólica y beneficios significativos en el control de la presión arterial refractaria. Los antagonistas de los receptores de mineralocorticoides no esteroideos, como la finerenona y la eplerenona, han demostrado una eficacia comparable y un mejor perfil de seguridad. Además, terapias emergentes, como los inhibidores de SGLT2, los antagonistas duales de los receptores de angiotensina-neprilisina (ARNI) y la denervación renal, han demostrado un potencial complementario para el control de la presión arterial y la protección cardiovascular. Concluimos que la espironolactona sigue siendo el tratamiento farmacológico estándar para la hipertensión resistente, mientras que las nuevas terapias amplían las perspectivas de un manejo personalizado e integrado, lo que refuerza la necesidad de enfoques multidisciplinarios y estudios comparativos a largo plazo.

Palabras clave: Hipertensión Resistente. Espironolactona. Antagonistas de Mineralocorticoides. Finerenona. Denervación Renal. Inhibidores de SGLT2.

1 INTRODUCTION

Resistant arterial hypertension (RH) represents one of the greatest contemporary clinical challenges in cardiology and internal medicine, accounting for a significant portion of global cardiovascular morbidity and mortality. It is defined as the persistence of blood pressure levels above the recommended target, despite the concomitant use of three distinct classes of antihypertensive drugs at appropriate therapeutic doses, including a diuretic, or when blood pressure control requires four or more pharmacological agents (Carey et al., 2023; Whelton et al., 2018). The overall prevalence of RH varies between 10% and 20% of treated hypertensive patients, with a higher incidence in individuals with obesity, type 2 diabetes mellitus, and chronic kidney disease, configuring a condition that is difficult to manage and has an unfavorable prognosis (Dudenbostel; Calhoun, 2017; Judd et al., 2020).

From the pathophysiological point of view, RH is a multifactorial condition, resulting from the interaction between genetic, neurohormonal and hemodynamic factors. The role of the renin-angiotensin-aldosterone system (RAAS) is central in the perpetuation of blood pressure elevation, mediating sodium retention, vascular remodeling, and increased peripheral resistance. Excess aldosterone promotes extracellular volume expansion and activation of the sympathetic nervous system, in addition to contributing to vascular inflammation and myocardial fibrosis (Williams et al., 2024; Schiffrin, 2022). This mechanism explains the limited response to conventional triple therapy (ACE inhibitor or angiotensin II receptor blocker, calcium channel blocker, and thiazide diuretic), justifying the need for additional pharmacological strategies.

Among these strategies, spironolactone, a steroidal antagonist of the mineralocorticoid receptor, has established itself as the most effective option in fourth-line therapy. The PATHWAY-2 trial, conducted by Williams et al. (2015), demonstrated that the addition of spironolactone to patients with RH significantly reduced systolic blood pressure compared to other booster drugs such as bisoprolol and doxazosin. These results were confirmed in subsequent meta-analyses, establishing spironolactone as the gold standard in the pharmacological treatment of resistant hypertension (de Souza et al., 2020; Parthasarathy et al., 2022).

Despite its proven efficacy, the use of spironolactone is limited by dose-dependent adverse effects such as hyperkalemia and gynecomastia, especially in patients with reduced glomerular filtration rate. This limitation has driven the development of non-steroidal mineralocorticoid receptor antagonists, such as eplerenone and finerenone, which have

greater selectivity and a lower incidence of endocrine side effects (Pitt et al., 2021; Agarwal et al., 2021). In parallel, other pharmacological and interventional approaches have been investigated, including sodium-glucose cotransporter type 2 (SGLT2) inhibitors, combined angiotensin II and neprilysin receptor blockers (NIRAs), and renal denervation, a minimally invasive technique aimed at the sustained reduction of sympathetic activity (Bakris et al., 2020; Mahfoud et al., 2022; Ruilope et al., 2022).

The advancement of these emerging therapies reflects a paradigm shift in the management of RH, guiding treatment towards a personalized approach that considers the patient's hemodynamic, metabolic, and renal profile. In this context, integrative literature reviews are essential to synthesize the current evidence on the comparative efficacy of spironolactone and new therapeutic options, enabling a critical analysis of the clinical applicability, safety, and prognostic impact of each intervention.

Thus, the present study aims to **review the efficacy of spironolactone in the treatment of resistant hypertension in an integrative manner**, as well as **to analyze the emerging pharmacological therapies that have shown promise in the management of this condition**, in light of the scientific evidence published between 2015 and 2025 in the main international biomedical databases.

2 METHODOLOGY

The present study was designed as an **integrative review of the literature**, based on the theoretical model of Whittemore and Knafl (2005) and on the recommendations adapted by Souza, Silva and Carvalho (2010). The integrative review was chosen because it allows the **critical and comparative synthesis of empirical and theoretical evidence** from different methodological designs, randomized controlled trials, systematic reviews, meta-analyses, and clinical guidelines, promoting a broad and interdisciplinary understanding of the efficacy of spironolactone and the role of emerging pharmacological therapies in the management of resistant hypertension (RH).

2.1 SEARCH STRATEGY AND DATABASES

The bibliographic search was conducted in a systematic and reproducible manner between **February and October 2025**, covering the **PubMed/MEDLINE**, **Scopus**, **Web of Science**, **SciELO,** and **Cochrane Library** databases. These databases were selected for their representativeness in the indexing of high-impact studies and international coverage.

The search strategy used **controlled descriptors MeSH (Medical Subject Headings)** and **DeCS (Health Sciences Descriptors),** combined by the Boolean operators **AND** and **OR**, ensuring sensitivity and specificity in the retrieval of the studies. The following combinations were applied: ("Resistant Hypertension" OR "Refractory Hypertension") AND ("Spironolactone" OR "Mineralocorticoid Receptor Antagonists") AND ("Finerenone" OR "Eplerenone") AND ("SGLT2 Inhibitors" OR "Renal Denervation" OR "Antihypertensive Therapy").

In addition, a manual search was performed in the reference lists of the included articles (*snowball sampling*), in order to identify relevant studies not detected in the electronic search. The publication period was delimited between **January 1, 2015 and August 31, 2025**, ensuring the inclusion of contemporary post-trial evidence PATHWAY-2 and AMBER, fundamental for the current understanding of RH therapy.

2.2 INCLUSION AND EXCLUSION CRITERIA

The selection criteria were previously defined to ensure **transparency, reproducibility, and methodological quality**, in accordance with the recommendations of PRISMA 2020 (Page et al., 2021).

Inclusion Criteria:

1. randomized controlled trials, systematic reviews, meta-analyses, or published clinical guidelines;
2. Articles available in full, in English, Portuguese or Spanish;
3. Studies conducted in **an adult population (≥ 18 years old)** with a confirmed diagnosis of resistant hypertension, according to the criteria of the AHA (2018) and ESC/ESH (2024);
4. Pharmacologic interventions involving **spironolactone, eplerenone, finerenone, SGLT2 inhibitors, ARNI, or renal denervation**;
5. Evaluation of relevant clinical outcomes: **blood pressure reduction, systolic/diastolic blood pressure control, renal function, cardiovascular events, or mortality**.

Exclusion Criteria:

1. Preclinical studies in animal models or *in vitro*;
2. Case reports, editorials, narrative reviews or expert comments;
3. Duplicate publications between different databases;

4. Studies that addressed only secondary hypertension or hypertension of specific causes (e.g., primary hyperaldosteronism without associated HAL).

These criteria aimed to concentrate the sample on studies **with high external validity**, maximizing the clinical applicability of the findings.

2.3 SCREENING PROCESS AND SELECTION OF STUDIES

The screening process followed the model of the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020),** contemplating four sequential phases: identification, screening, eligibility, and final inclusion.

1. **Identification:** Initially, 1,042 records **were retrieved** from the databases consulted. All results were exported in RIS format and imported into the **Rayyan QCRI software (2024 version),** used for reference management and automatic duplicate detection.
2. **Screening:** After exclusion of 214 duplicates, **828 records** were screened by two independent reviewers. Titles and abstracts were evaluated based on the eligibility criteria.
3. **Eligibility:** 64 articles **were selected** for full reading, with evaluation of thematic and methodological relevance.
4. **Final inclusion:** After complete analysis, **27 studies** were included in the final sample, comprising **12 randomized controlled trials, 8 systematic reviews, 3 meta-analyses, and 4 international guidelines.**

Disagreements between reviewers were resolved by consensus, and a third reviewer was consulted in cases of doubt about eligibility.

2.4 DATA EXTRACTION AND SYNTHESIS

Data extraction was performed manually using a **structured spreadsheet in Microsoft Excel 2021**, containing the following fields: author, year, country, design, sample, intervention, comparator, duration of follow-up, primary outcomes, and main outcomes.

The **synthesis of the data** followed a **thematic and comparative** approach, grouping the evidence into three central axes:

1. **Efficacy of spironolactone in controlling RH blood pressure**, including data from multicenter assays such as PATHWAY-2 and AMBER;
2. **Comparison between steroidal and non-steroidal mineralocorticoid receptor antagonists**, with emphasis on renal efficacy, safety, and impact;

3. **Emerging therapies**, SGLT2 inhibitors, ARNI, and renal denervation, evaluated for their complementary contribution to standard pharmacotherapy.

The results were presented in a **narrative and interpretative** way, respecting the heterogeneity of the designs and outcome measures.

2.5 EVALUATION OF METHODOLOGICAL QUALITY

The quality of the included studies was assessed using the GRADE (**Grading of Recommendations Assessment, Development and Evaluation) system**, which classifies the level of evidence as **high, moderate, low or very low**, considering risk of bias, consistency, accuracy and applicability (Guyatt et al., 2011). Randomized trials received an initial score of "high" and could be downgraded according to detected limitations; systematic reviews and meta-analyses were evaluated using the **AMSTAR 2 protocol** (Shea et al., 2017).

In addition, the review ensured **cross-validation of data** and **inter-rater quality control**, with a Kappa of agreement > 0.85, ensuring reproducibility and methodological reliability.

2.6 INTERPRETATIVE SYNTHESIS AND TREATMENT OF EVIDENCE

The final stage consisted of the elaboration of an **integrative synthesis**, articulating the findings in a critical manner. For each thematic axis, the evidence was interpreted according to:

- magnitude of blood pressure reduction (in mmHg);
- effect on renal function and albuminuria;
- impact on cardiovascular mortality;
- frequency of adverse events (hyperkalemia, gynecomastia, hypotension);
- and applicability in special subgroups (diabetics, CKD patients, and the elderly).

Quantitative data from meta-analyses were described in terms of weighted mean difference and *odds ratio* with a 95% confidence interval. This approach gave the study **statistical consistency and analytical density**, even while maintaining an integrative and non-meta-analytic character.

3 RESULT AND DISCUSSION

After applying the eligibility criteria and methodological screening, **27 studies** were included in the final sample, comprising **12 randomized controlled trials**, **8 systematic reviews**, **3 meta-analyses,** and **4 international guidelines** published between 2015 and 2025.

The results were organized into **three main thematic axes** , with emphasis on the efficacy, safety, and clinical applicability of the different pharmacological interventions used in the management of resistant hypertension (RH).

3.1 EFFICACY OF SPIRONOLACTONE AS FOURTH-LINE THERAPY

Spironolactone remains the reference drug in the pharmacological treatment of RH, due to its proven efficacy in high-impact clinical trials. The **PATHWAY-2 study**, conducted by Williams et al. (2015) with 314 patients, demonstrated that the addition of spironolactone (25–50 mg/day) to the standard therapy regimen reduced mean systolic blood pressure by **8.7 mmHg** more than placebo and **4.3 mmHg** more than the beta-blocker bisoprolol. The reduction was particularly significant in patients with elevated suppressed plasma renin levels, indicating the central role of sodium retention and mineralocorticoid hyperactivity (Williams et al., 2015).

Later studies confirmed these results in different populations. The meta-analysis by **de Souza et al. (2020),** which evaluated 1,208 patients, reported a mean reduction of **13.3 mmHg** in systolic pressure and **6.4 mmHg** in diastolic pressure with the use of spironolactone, with the effect being more pronounced in individuals with mild to moderate renal dysfunction.

Another relevant finding was the positive impact on arterial stiffness and pressure variability, suggesting an additional beneficial effect on vascular remodeling (Judd; Calhoun, 2020).

From a safety standpoint, the main limitation of spironolactone is the risk of **hyperkalemia**, especially in patients with a glomerular filtration rate < 45 mL/min/1.73 m² or concomitant use of RAAS inhibitors. In the **AMBER trial** (Agarwal et al., 2019), the associated use of **patiromer**, potassium chelator, allowed the maintenance of spironolactone without a significant increase in hyperkalemia, suggesting a viable alternative to optimize treatment in high-risk patients.

Thus, the body of evidence reinforces spironolactone as the **most effective fourth-line drug** for RH, with a strong level of recommendation (Class I, Level A) in **the AHA (2023)** and **ESC/ESH (2024) guidelines**.

3.2 NONSTEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS: EPLERENONE AND FINERENONE

The need to reduce the adverse effects of spironolactone has led to the development of **non-steroidal mineralocorticoid receptor antagonists (ANERMs),** such as **eplerenone** and **finerenone**, characterized by higher selectivity and improved metabolic profile.

Eplerenone showed similar pressure efficacy to spironolactone, but with a lower incidence of gynecomastia and erectile dysfunction (Pitt et al., 2014). However, its antihypertensive potency is lower, requiring higher doses (50–100 mg/day) and presenting a higher cost (Calhoun; Dudenbostel, 2020).

Finerenone, in turn, represents a pharmacological innovation with greater affinity for the mineralocorticoid receptor and less tissue penetration, reducing myocardial fibrosis and oxidative stress. The **FIDELIO-DKD trial** (Pitt et al., 2021) and the **FIGARO-DKD trial** (Bakris et al., 2022) demonstrated that finerenone significantly reduced cardiovascular and renal events in diabetic patients with chronic kidney disease, with a modest reduction in mean arterial pressure (**–6 mmHg**), but significant prognostic benefit.

Recent experimental studies indicate that finerenone may have a synergistic effect with SGLT2 inhibitors, expanding its therapeutic potential in refractory RH (Agarwal et al., 2021). The review by Parthasarathy et al. (2022) highlights that, although data on HAR are still limited, preliminary results suggest an efficacy profile equivalent to spironolactone, but with **a lower incidence of hyperkalemia and better tolerability**.

Thus, ANERMs are second-generation **alternatives** for inhibiting the mineralocorticoid axis, especially indicated in patients with intolerance or contraindication to prolonged use of spironolactone.

3.3 EMERGING THERAPIES IN THE PHARMACOLOGICAL MANAGEMENT OF RESISTANT HYPERTENSION

In recent years, the management of RH has expanded beyond the modulation of RAAS, incorporating new pharmacological classes and interventional strategies. Among

them, **SGLT2 inhibitors**, **dual angiotensin and neprilysin receptor blockers (NIRAs),** and **renal denervation** stand out.

3.3.1 SGLT2 Inhibitors

Clinical trials such as **EMPA-REG OUTCOME (Zinman et al., 2015)** and **DAPA-HF (McMurray et al., 2019)** revealed that the use of empagliflozin and dapagliflozin promoted mean blood pressure reductions of **3–6 mmHg** in SBP and **1–3 mmHg** in DBP, regardless of the presence of diabetes. Proposed mechanisms include osmotic natriuresis, plasma volume reduction, and improved vascular compliance (Ruilope et al., 2022). Recent systematic reviews highlight that, in patients with RH, the association of spironolactone with SGLT2 inhibitors enhances blood pressure control and decreases the risk of hyperkalemia (Bakris et al., 2023).

3.3.2 Dual Blockers (ARNIs)

NIRAs, such as sacubitril/valsartan, showed a modest blood pressure lowering effect (–5 to –8 mmHg), but significant hemodynamic and antifibrotic benefit. The **PARAGON-HF trial** (Solomon et al., 2020) suggested that the association between angiotensin II receptor blockade and neprilysin inhibition improves vascular function and cardiac remodeling, and may play a future role in refractory RH.

3.3.3 Renal denervation

Renal **denervation** has re-emerged as a promising interventional approach. In the **RADIANCE-HTN TRIO trial** (Azizi et al., 2021), a mean reduction of **8.0 mmHg** in ambulatory SBP was observed in 24 hours compared to the sham control. The **Global SYMPLICITY Registry** (Mahfoud et al., 2022) confirmed sustained efficacy for up to three years, with a high safety profile. Although not yet a substitute for pharmacotherapy, denervation is recommended as an add-on therapy for patients with true RH refractory to optimal drug treatment.

3.4 CRITICAL SYNTHESIS AND FUTURE PERSPECTIVES

The findings of this integrative review indicate that **spironolactone** remains the most effective therapeutic standard for reducing blood pressure in RH, presenting robust evidence and support in international guidelines.

However, pharmacological developments have expanded the therapeutic possibilities with the introduction of **selective antagonists, SGLT2 inhibitors, and combination therapies**, which promise a better safety profile and additional cardiovascular benefits.

The integration between pharmacotherapy and nonpharmacological interventions, such as renal denervation, represents a **multimodal and personalized approach** to the control of RH. Future studies should focus on **the direct comparison between spironolactone, finerenone, and SGLT2 inhibitors**, as well as explore **predictive models based on biomarkers and artificial intelligence**, aiming to optimize individualized management and reduce the global burden of resistant hypertension.

4 CONCLUSION

Resistant arterial hypertension represents a condition of high clinical and pathophysiological complexity, whose therapeutic approach requires integration between pharmacological rationale, control of comorbidities, and continuous therapeutic adherence. Among the available options, spironolactone remains the drug with the highest proven efficacy, acting directly on the mineralocorticoid axis and promoting significant pressure reductions, even in patients refractory to multiple combinations of antihypertensive agents.

However, the therapeutic evolution of the last decade shows a transition from the paradigm exclusively focused on the suppression of aldosterone to a multifactorial model, which includes new strategies of neurohormonal, metabolic and renal modulation. The introduction of nonsteroidal mineralocorticoid receptor antagonists, SGLT2 inhibitors, and dual blockers of the renin-angiotensin-neprilysin system demonstrates concrete advances in the control of resistant hypertension, with additional benefits in preserving renal function and reducing overall cardiovascular risk.

This evidence reinforces the importance of a personalized therapeutic approach, based on the integrated evaluation of the patient's clinical, metabolic, and renal profile. The optimal management of resistant hypertension should combine the rational use of highly effective drugs with the implementation of continuous monitoring strategies and therapeutic adherence, recognizing that the pharmacological response is influenced by multiple biological and behavioral determinants.

Finally, future perspectives indicate that the combination of innovative pharmacological therapies with interventional approaches, such as renal denervation, may represent a new frontier in the control of refractory blood pressure. The consolidation of long-term comparative

studies and the incorporation of predictive biomarkers and artificial intelligence algorithms in risk stratification will be essential for the development of more effective and individualized therapeutic protocols.

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