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Primary aldosteronism in patients with resistant hypertension – diagnostic challenges and clinical implications

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ABSTRACT

Primary aldosteronism (PA) has become increasingly recognised as a frequent and clinically important cause of resistant hypertension. In the past, the importance of PA was marginalised, but the newest research indicates that it may be present in a significant number of patients with persistently uncontrolled hypertension, despite the use of multiple antihypertensive drugs. The main reason for treatment resistance is aldosterone excess. It leads to volume expansion, vascular remodelling, endothelial dysfunction, and direct organ damage, which limit the effectiveness of standard antihypertensive therapies. Diagnostic evaluation in patients with resistant hypertension is challenging. One main reason is the interference from medications during hormonal testing, along with variations in aldosterone-renin ratio (ARR) results. The limitations of confirmatory procedures and the common occurrence of normokalemic disease must also be considered during diagnosis. Relying only on ARR and strict diagnostic guidelines can slow the diagnosis of primary aldosteronism (PA). This leads to a longer exposure to excess aldosterone, which raises the chances of heart, kidney, and metabolic problems. Treatment options include mineralocorticoid receptor antagonists or adrenalectomy. These treatments help control blood pressure and lower overall cardiovascular risk. Furthermore, adrenalectomy can completely cure some cases. This review brings together current evidence on the prevalence, underlying causes, diagnostic challenges, and treatment implications of primary aldosteronism in patients with resistant hypertension. The key point is the need for individualised and clinically focused diagnostic approaches that combine biochemical data with clinical evaluation and suitable imaging.

Keywords: primary aldosteronism, resistant hypertension, aldosterone–renin ratio; secondary hypertension; mineralocorticoid receptor antagonists

1. INTRODUCTION

Resistant hypertension refers to a clinical condition in which target blood pressure cannot be achieved despite treatment with three different classes of

antihypertensive drugs, including a diuretic, or in which blood pressure control is possible only with the use of four or more medications (Carey et al., 2018). Although resistant hypertension has a multifactorial etiology, a growing number of cases previously classified as essential hypertension are now recognised to have an identifiable secondary cause. One such case is primary aldosteronism (PA), whose clinical importance and prevalence are increasingly recognised (Rossi et al., 2006; Monticone et al., 2017).

According to researchers, like Professor John Funder from Hudson Institute of Medical Research, primary aldosteronism involves autonomous aldosterone secretion, inadequately suppressed by the renin–angiotensin–aldosterone system (Funder et al., 2008). Hypokalemia has traditionally been considered a hallmark of primary aldosteronism. However, a number of the latest studies show that early diagnosis is especially challenging among patients with normal potassium levels (Burrello et al., 2020; Asbach et al., 2022). Since primary aldosteronism affects up to 20–30% of patients with resistant hypertension, PA plays an imperative role in clinical evaluation (Douma et al., 2008; Parasiliti-Caprino et al., 2020).

To this day, PA remains a significantly underdiagnosed disease, especially among patients with resistant hypertension. In recent years, despite PA gaining more popularity and research papers dedicated to its study, this phenomenon has not changed.

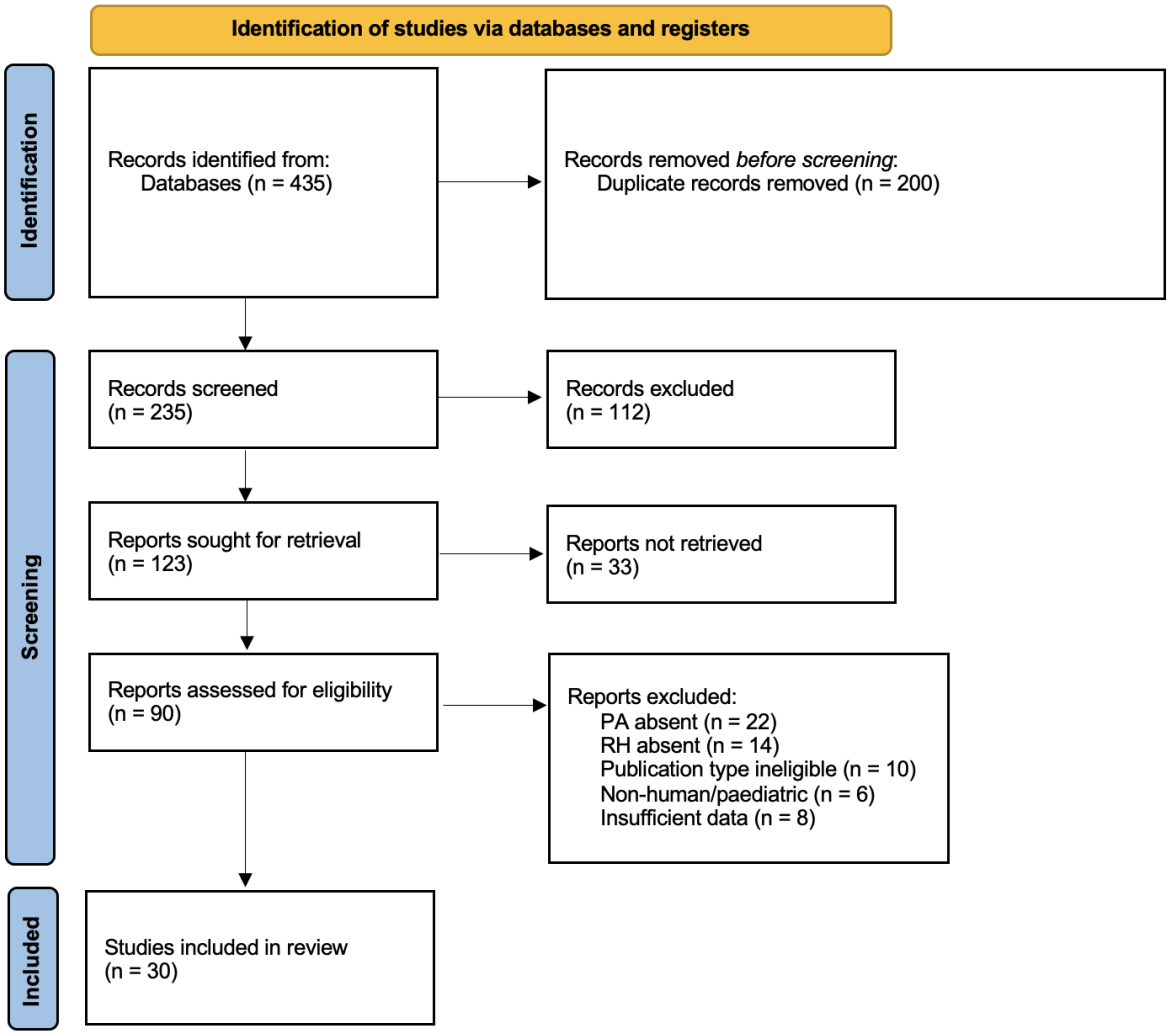

Figure 1. PRISMA flow diagram.

2. REVIEW METHODS

This review aims to gather and evaluate the data on primary aldosteronism in patients with resistant hypertension. The literature search took place in the PubMed database. It included publications from 1990 to August 2025. Previous studies were examined to understand how diagnostic concepts and medical terms have changed.

A detailed literature search was conducted using Medical Subject Headings (MeSH) and related free text terms. These search terms included aldosteronism, Conn's syndrome, resistant hypertension, secondary hypertension, aldosterone-renin ratio, confirmatory testing, mineralocorticoid receptor antagonists, and adrenalectomy. Additional studies were identified manually by the review of the reference lists of key articles.

Adult patients with primary aldosteronism were the subject of this study, which included original research, systematic reviews, meta-analyses, and clinical practice guidelines concerning either treatment or diagnosis. Studies consisting of case reports on fewer than five individuals were deliberately not included in the paper. In addition, the analysis discarded all research conducted on animals, articles unavailable in full text, and conference reports without direct clinical relevance.

Appropriate studies were first checked by looking at titles and abstracts to see if they were suitable for further review. The flow of study selection is shown in the PRISMA flow diagram (Figure 1). After finding relevant sources, the authors performed a thorough analysis. In order to limit any irregularities in study design and outcomes, the results were synthesised in a narrative review. The sources included only published data, which does not require ethical approval and informed consent.

3. RESULTS & DISCUSSION

3.1. Primary Aldosteronism in Patients with Resistant Hypertension - Definition and Prevalence

Primary aldosteronism (PA) is also known as Conn's syndrome. It is a disorder in which aldosterone is secreted from the adrenal glands in excessive amounts. Hormone production is independent from the renin–angiotensin–aldosterone system (RAAS) regulation (Funder et al., 2008). Observed arterial hypertension is the consequence of sodium retention, potassium excretion, and inhibition of plasma renin activity. As the disease progresses, cardiovascular and renal damage may occur.

The most common causes of PA are adenomas producing aldosterone and unilateral or bilateral adrenal hyperplasia. On the contrary, inherited glucocorticoid-remediable aldosteronism is considered a rare cause of PA (Funder et al., 2008).

In the past, primary aldosteronism was regarded as an uncommon cause of hypertension. Reported historical prevalence is below 1% among hypertensive patients (Sinclair et al., 1987). Over the past two decades, the diagnosis process advanced, changing this perception. Nowadays, studies indicate that PA is present in approximately 5–10% of patients with hypertension (Rossi et al., 2006). Among the patients with resistant hypertension, up to 20% of them may be affected (Douma et al., 2008).

However, recent studies reported an even higher prevalence. Parasiliti-Caprino identified primary aldosteronism in nearly one-third of cases in a cohort of patients with confirmed resistant hypertension (Parasiliti-Caprino et al., 2020).

3.2. Pathophysiological Mechanisms of Treatment Resistance

Patients with elevated aldosterone levels are at risk of numerous clinical complications. However, the present review focuses on mechanisms that directly contribute to resistance to antihypertensive treatment. A well-known mechanism of action of aldosterone is its effect on sodium–potassium balance. It causes retention of sodium ions and increased urinary excretion of potassium ions. This causes more water to be reabsorbed and creates an increase in extracellular fluid volume. Consequently, patients with hyperaldosteronism may not respond to standard antihypertensive drugs, as these medications do not affect the root of the problem - aldosterone excess (Funder et al., 2008; Williams et al., 2015). It has also been observed that vascular endothelial damage occurs, whereas under normal conditions, the endothelium produces vasodilatory substances. Impairment of this mechanism may lead to a weaker response to antihypertensive treatment (Nishizaka et al., 2004).

Previous observations suggest that standard antihypertensive treatment may be ineffective, particularly when it does not address the harmful effects of excess aldosterone.

3.3. Diagnostic Challenges in Patients with Resistant Hypertension

3.3.1. Who Should Be Screened for Primary Aldosteronism?

Over the past few years, recommendations for screening for primary aldosteronism have grown. The "Endocrine Society Clinical Practice Guideline," published in 2016, suggests screening specific high-risk groups. This includes patients with resistant hypertension, which happens even when they are on antihypertensive medications. It also includes those with hypertension along with other conditions such as low potassium levels, sleep apnea, or a family history of primary aldosteronism (Funder et al., 2016).

In contrast, the "European Society of Cardiology Guidelines," released in 2024, supports a broader, more active approach to screening for secondary causes of hypertension, such as primary aldosteronism. These guidelines recommend lowering the clinical threshold for diagnostic assessment in patients with hypertension (McEvoy et al., 2024).

Research by Dissanayake shows that screening criteria lack sufficient sensitivity. This claim can be additionally supported by the finding that approximately 30% of patients treated with either one, two, or three antihypertensive medications have primary aldosteronism (Dissanayake et al., 2025).

This hypothesis is slowly gaining regard among the scientific community. Published in 2025, the Endocrine Society Clinical Practice Guideline included the latest research by recommending screening for primary aldosteronism in all patients with hypertension (Adler et al., 2025).

Despite extending the recommendations, not enough time has passed to note any significant changes in the diagnosis of primary aldosteronism. According to a new study conducted on a group of nearly 19,000 patients with resistant hypertension, only a handful of them (4.2%) had undergone screening for primary aldosteronism in any form. This data is especially concerning, since a large number of those patients (16.9%) were later diagnosed with PA (Cohen et al., 2021). The analysis leads to a straightforward conclusion: there is an urgent need to raise awareness of primary aldosteronism and implement screening in patients with hypertension.

3.3.2. Aldosterone–Renin Ratio (ARR) - Limitations in Patients with Resistant Hypertension

The aldosterone–renin ratio (ARR) is used as a screening test for patients at risk of primary aldosteronism. One of the characteristics of arterial hypertension that prompts the determination of the ARR is resistance to antihypertensive treatment. On the other hand, this indication itself implies a significant interpretative problem, because patients with resistant hypertension are initially treated with multidrug therapy that significantly affects renin and aldosterone concentrations. Commonly used antihypertensive drugs affect the renin-angiotensin-aldosterone system. This may cause inaccurate aldosterone-to-renin ratio (ARR) measurements. One example is β-blockers. They block β_1 receptors in the juxtaglomerular apparatus of the kidney, which reduces renin secretion. This process can lead to false-positive results. Patients undergoing treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are at a higher risk of false-negative results due to lower aldosterone levels caused by these medications (Mulatero et al., 2002). The combined effect of these medications on the ARR may be challenging to predict. Simultaneously, due to their minimal impact on the RAAS, calcium channel blockers and α-adrenolytics may represent a viable therapeutic option during the diagnostic evaluation of primary aldosteronism. Another factor influencing the ARR result is potassium concentration. Hypokalemia is a well-known mechanism that reduces aldosterone secretion by the zona glomerulosa of the adrenal cortex. In milder forms of primary aldosteronism, hypokalemia alone may lead to a false-negative result (Morkos et al., 2018). Moreover, in patients with resistant hypertension, hypokalemia may be exacerbated by the use of antihypertensive medications, particularly diuretics. Therefore, it is recommended to normalise the potassium level before testing.

As described above, many factors may influence the ARR result. Its interpretation, particularly in borderline values, should be conducted with caution. The ARR result should not be considered in isolation, as it is not a stable value even in patients without primary aldosteronism (Veldhuizen et al., 2022). Hence, when reviewing the ARR results, scientists should consider the patient's broader clinical picture and look for additional confirmatory testing.

3.3.3. Confirmatory Testing - Practical Limitations

When a patient is suspected of suffering from PA by an elevated aldosterone–renin ratio (ARR), it is vital to conduct confirmatory testing. In his work, Funder described a broad catalogue of procedures viable for this testing. These include various examinations, like oral sodium loading, saline infusion, or suppression with fludrocortisone. The methods are especially beneficial when examining elevated ARR in patients unresponsive to inhibition by the renin–angiotensin–aldosterone system (Funder et al., 2016).

The advantages and disadvantages of various confirmatory tests are considerably different. For example, the fludrocortisone suppression is time-consuming and may often require admission to the hospital. Nevertheless, it is considered highly reliable. Oral sodium-loading and saline-infusion tests are simpler to perform but are limited by the need for careful patient preparation and standardised conditions. To date, there is no consensus on which confirmatory test is superior.

Fischer conducted a detailed study of patients suffering from resistant hypertension. According to his research, this subject group carries a high risk of suffering from comorbidities and is more prone to treatment with antihypertensive drugs, like beta-blockers, ACE inhibitors, and diuretics. Fischer claims that these therapies may influence the RAA system, which complicates the interpretation of

diagnostic tests. On the other hand, Fischer claims that resigning from these therapies can carry a significant risk of worsening hypertension and fluid overload (Fischer et al., 2011). Fischer's findings lead to the conclusion that medical practitioners often conduct confirmatory testing in suboptimal conditions.

A high risk of false-negative results is one of the key flaws of confirmatory testing. Across the studies, one can note different test protocols and results interpretation. According to Leung, systematic review and meta-analysis showed that many diagnostic studies have a high risk of bias and that confirmatory tests may miss cases identified by other reference standards (Leung et al., 2022). If the pre-test probability of primary aldosteronism is already high, confirmatory testing does not add any significant diagnostic value.

3.3.4. Normokalemic Primary Aldosteronism

Primary aldosteronism is not necessarily present with hypokalemia. Clinical data indicate that the normokalemic form of the disease is significantly more common (Burrello et al., 2020). Patients suffering from early stages of primary aldosteronism may exhibit normokalemia, which may be rooted in compensatory mechanisms of potassium homeostasis. It proves that measuring potassium levels does not belong in the catalogue of reliable screening methods for PA. Further diagnosis of PA is mainly indicated by the presence of arterial hypertension or dysfunction with the RAA system (Asbach et al., 2022).

The normokalemic course of primary aldosteronism may result in the misclassification of patients in the essential hypertension group. As a result, treatment of hypertension depends on escalation of antihypertensive therapy, which may lead to ineffective blood pressure control and the development of apparent treatment resistance. At the same time, untreated aldosterone excess may continue to exert adverse effects on target organs.

3.3.5. Pitfalls in differential diagnosis

As previous analysis showed, primary aldosteronism is still hard to diagnose, especially in patients with resistant hypertension. The main reasons this problem persists are the low plasma renin activity in these patients and their use of several antihypertensive medications. Both factors make it much harder to interpret biochemical results.

One of the scholars who has extensively studied the differential diagnosis of primary aldosteronism is the well-regarded endocrinologist Dr Victor Montori. According to his work, when differentiating PA from similar conditions, one should consider low-renin hypertension and secondary causes of hypertension. In both PA and low-renin essential hypertension, the ARR may be elevated, but through different mechanisms. On the one hand, an elevated level of ARR featured in PA is caused by autonomous aldosterone secretion. On the other hand, its primary source in essential hypertension is marked renin suppression. After detailed analysis, Montori et al., (2001) argues that the interpretation of ARR should always consider the absolute aldosterone and renin concentrations, rather than relying on the ratio alone.

Although agreeing with Dr Montori's claims, other scholars stress that the diagnostic process may be further complicated by other secondary causes of hypertension. In the works of both Omura and Rossi, disorders such as Cushing syndrome, pheochromocytoma, and renovascular hypertension may present with overlapping clinical or biochemical features, even though they are less frequent than primary aldosteronism. These renowned scientists are among the key proponents of additional targeted investigations. They thoroughly describe the group of possible procedures, which include cortisol assessment, measurement of plasma or urinary metanephrines, and appropriate imaging studies in cases when renovascular disease is suspected (Omura et al., 2004; Rossi et al., 2020).

Careful consideration of the aforementioned analyses leads to the conclusion that relying on the ARR alone may create false results, making it imperative to conduct a broader differential diagnosis.

3.4. Consequences of Missed or Delayed Diagnosis of Primary Aldosteronism

The harmful effects of aldosterone on target organs are not limited to pathologies resulting from elevated blood pressure values. Evidence for this is its effect on the heart, which, regardless of blood pressure levels, is characterised in affected individuals by left ventricular hypertrophy, impaired diastolic function, and myocardial fibrosis (Wu et al., 2021).

Elevated aldosterone levels cause blood pressure–independent albuminuria because aldosterone damages the glomerular filtration barrier (Sechi et al., 2006). Patients with primary aldosteronism who have not received etiological treatment have a higher risk of developing chronic kidney disease than patients with hypertension (Hundemer et al., 2018). The risk of diabetes mellitus and metabolic syndrome in these patients is also higher than in those with hypertension (Monticone et al., 2018). The above data indicate that patients with primary aldosteronism belong to a high-risk group for cardiovascular events as well as renal and metabolic complications,

independently of blood pressure values. Additionally, unrecognised primary aldosteronism leads to the need for intensification of antihypertensive therapy and may be associated with adverse events related to the concomitant use of multiple antihypertensive agents.

3.5. Therapeutic Implications in Patients with Resistant Hypertension

3.5.1. Pharmacological treatment

Recent studies show that pharmacological therapy has remained the main treatment for patients with PA to this day. This relates especially to patients diagnosed with bilateral adrenal disease or those ineligible for surgical intervention. Professor John Funder from Hudson Institute of Medical Research is a leading expert in the pharmacological treatment of PA. According to his work, the most efficient therapy consists of mineralocorticoid receptor antagonists (MRAs) - primarily spironolactone and eplerenone, which directly block the pathophysiological actions of aldosterone (Funder et al., 2016).

There are multiple observational studies and randomised trials that back Professor Funder's views. One of them, conducted in 2015, showed MRA therapy as a leading cause of improvement in blood pressure control (Williams et al., 2015). Still, many of the studies highlight that MRA therapies can have varying results and depend on disease severity, adherence, and aldosterone excess (Monticone et al., 2017). The analysis of available studies leads to the conclusion that pharmacological treatment serves only as symptomatic therapy and does not eliminate autonomous aldosterone production. Therefore, the higher cardiovascular risk linked to PA may not be completely reversed.

Another drawback of MRA therapy is its side effects, which include high potassium levels, kidney problems, and anti-androgen effects like gynecomastia. These issues can impact how well patients tolerate the treatment and how likely they are to stick with it (Funder et al., 2016; Hundemer et al., 2018). For these reasons, doctors often view pharmacological therapy as a lifelong treatment. It is regarded as an alternative rather than a curative approach, in contrast to adrenalectomy in a selected group of patients with unilateral disease.

3.5.2. Surgical treatment

A prerequisite for qualification for adrenalectomy is a confirmed diagnosis of primary aldosteronism. The diagnostic standard consists of a positive screening test in the form of an increased aldosterone–renin ratio (ARR) and at least one positive confirmatory test, the purpose of which is to demonstrate the lack of appropriate suppression of aldosterone secretion. These tests are intended to confirm autonomous aldosterone production, independent of the renin–angiotensin–aldosterone system. They include the saline infusion test, the oral sodium loading test, and tests used in routine clinical practice. Authors like Quencer et al., (2023) suggest that confirmatory testing can sometimes be skipped when the diagnosis of PA is clear, such as in cases of spontaneous hypokalemia, suppressed renin levels, and elevated plasma aldosterone concentration.

Before surgical treatment, primary aldosteronism should be assessed with respect to the lateralisation of aldosterone secretion, as only confirmation of unilateral aldosterone excess qualifies a patient for adrenalectomy. Assessment of lateralisation is performed using adrenal vein sampling (AVS) and computed tomography (Adler et al., 2025). An additional prerequisite is the patient's informed consent and the absence of contraindications to surgical treatment.

In the group of patients with resistant hypertension, surgical treatment is of particular importance, as in individuals with unilateral primary aldosteronism, it allows elimination of the underlying cause of arterial hypertension and often leads to a significant improvement in blood pressure control, and in some cases to its remission (Iacobone et al., 2015).

3.6. Future Research Directions and Knowledge Gaps

Although current guidelines suggest a step-by-step diagnostic approach that includes the ARR and confirmatory tests, the traditional diagnostic process for primary aldosteronism is often hard to carry out. Changing antihypertensive treatment to conduct these tests can be risky. Their feasibility is limited in this patient population (Yuan et al., 2025).

The research shows that today there are no universally approved diagnostic methods that would decisively identify an aldosterone-dependent mechanism of resistant hypertension. This is despite intensive research efforts, which grow stronger every year. The majority of available data derive from studies conducted in selected populations of patients with confirmed primary aldosteronism. Only to a limited extent do they address the needs of patients with resistant hypertension, in whom classical diagnostic algorithms are often difficult to apply. In this context, the use of simplified clinico-biochemical methods integrating phenotypic and laboratory data

may be considered; however, such approaches require further evaluation and validation in prospective studies. The key findings of the Results section are summarised in Table 1.

Table 1. Summary of Key Findings.

Domain	Findings
1. Primary Aldosteronism in Patients with Resistant Hypertension - Definition and Prevalence	Primary aldosteronism is a disorder with excessive aldosterone production in the adrenal glands. The prevalence can reach up to 30% among patients with resistant hypertension.
2. Pathophysiological Mechanisms of Treatment Resistance	Aldosterone excess causes retention of sodium ions and an increase in extracellular fluid volume. The damage to the vascular endothelium impairs the production of vasodilatory substances. Both mechanisms lead to resistance to antihypertensive treatment.
3. Diagnostic Challenges in Patients with Resistant Hypertension	PA should gain greater recognition, and all patients with hypertension should undergo screening. The aldosterone–renin ratio (ARR) is used as a screening test. The results should be interpreted in the context of the overall clinical picture. As PA can be normokalemic, measuring potassium levels should not be used as a reliable screening method. Additional confirmatory testing does not add any significant diagnostic value if the pre-test probability of primary aldosteronism is already high. Broader differential diagnosis enables the exclusion of other causes of secondary hypertension.
4. Consequences of Missed or Delayed Diagnosis of Primary Aldosteronism	Missed or delayed diagnosis of PA may lead to heart damage (left ventricular hypertrophy, impaired diastolic function, and myocardial fibrosis) and renal damage (development of chronic kidney disease). Patients have a higher risk of diabetes mellitus and metabolic syndrome.
5. Therapeutic Implications in Patients with Resistant Hypertension	Pharmacological therapy has remained the main treatment for patients with PA. The most efficient therapy consists of mineralocorticoid receptor antagonists (MRAs) - primarily spironolactone and eplerenone, which directly block the pathophysiological actions of aldosterone. Adrenalectomy can be a cure in individuals with unilateral primary aldosteronism.
6. Future Research Directions and Knowledge Gaps	There are no universally approved diagnostic methods that would decisively identify an aldosterone-dependent mechanism of resistant hypertension. Approach to integrating clinical and biochemical methods requires further evaluation and validation in prospective studies.

The findings summarised in this review suggest that diagnostic difficulties in primary aldosteronism among patients with resistant hypertension are of significant clinical importance, as they may lead to delayed diagnosis and prolonged exposure to excess aldosterone. These difficulties result from the intensive pharmacotherapy used in this patient population, which affects factors such as the results of hormonal tests, the ARR, or potassium homeostasis. The presented research shows that strict adherence to standard diagnostic methods is not always viable in this group of patients. This may result in delayed diagnosis and long-term exposure to aldosterone excess. As a consequence, the risk of cardiovascular, renal, and metabolic complications is increased, independently of blood pressure values.

The available clinical and observational data suggest that, in a selected group of high-risk patients, a more individualised diagnostic approach may be justified. Integration of biochemical test results with the patient's clinical presentation may be more appropriate than

reliance solely on individual screening or confirmatory tests, while simultaneously reducing the risk of modifying antihypertensive therapy.

From a therapeutic perspective, both pharmacological treatment with mineralocorticoid receptor antagonists and adrenalectomy provide significant clinical benefits. However, etiological treatment should be implemented whenever it is feasible. Implications for clinical practice are presented in Table 2.

Table 2. Clinical implications.

Implication	Rationale	Clinical impact
Standard diagnostic methods may be suboptimal in resistant hypertension	Multidrug therapy affects results in hormonal tests; confirmatory tests are difficult to conduct	Risk of delayed diagnosis and prolonged exposure to aldosterone
A more individualised approach in high-risk patients may be required	Integration of biochemical test results with clinical presentation may be more efficient than reliance solely on individual screening or confirmatory tests	Earlier identification of PA and reduced risk associated with modification of antihypertensive therapy
Etiological treatment should be implemented whenever it is feasible	Adrenalectomy cures unilateral PA; MRAs provide symptomatic treatment but not etiological cure	Reduction in cardiovascular risk, renal and metabolic complications
Reliance on ARR alone may be insufficient	The results should be interpreted in the context of the overall clinical picture and absolute hormone levels	Reduced diagnostic misclassification
Broader screening strategies may be justified	PA is more prevalent than historically assumed (especially among patients with resistant hypertension)	Greater detection and appropriate treatment
Evidence gaps persist	Lack of prospective studies in resistant hypertension	Need for validation of simplified diagnostic pathways

4. CONCLUSION

The diagnosis of patients with hyperaldosteronism among those with resistant hypertension is still a major clinical challenge. These patients might benefit from a more personalised diagnostic approach that considers both the general clinical presentation and biochemical findings. It is especially important to identify early which patients are eligible for causal treatment. It will result in better long-term clinical outcomes.

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Data and materials availability
All data associated with this study will be available based on reasonable request to the corresponding author.

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