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PREVALENCE, MANAGEMENT, AND OUTCOME OF RESISTANT HYPERTENSION IN PEOPLE WITH CKD : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Patients with chronic kidney disease (CKD) are susceptible to resistant hypertension, which is a serious problem. Patients should take into account reversible causes as the prevalence of this ailment is difficult to ascertain. Its development is influenced by the renin-angiotensin-aldosterone system and the sympathetic nervous system. The efficacy of current hypertension treatments, such as medication and lifestyle modifications, in treating resistant hypertension is low. Recent studies have shown a reduction in blood pressure equivalent to that of a single antihypertensive drug in less severe cases of hypertension.*

Methods: *Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. The literature was assembled using a variety of online databases, including ScienceDirect, PubMed, and SagePub.*

Result: *The study screened about 3.000 publications using reputable sources including Science Direct, SagePub, and PubMed. Five papers were found to be pertinent for systematic investigation, after which the entire material was examined in more detail.*

Conclusion: *It has been demonstrated that patiromer, a K1-binding drug, improves cardiovascular outcomes in patients with hypertension and chronic kidney disease (CKD). Phase II trial results demonstrated that patiromer can safely permit spironolactone use and prevent hyperkalemia, hence reducing renin-angiotensin-aldosterone system inhibitor non-use in patients with heart failure refractory to exercise. Long-term findings regarding the effects on the kidneys and heart are nevertheless required. Treatment for renal denervation has demonstrated encouraging outcomes in lowering blood pressure without side effects.*

Keyword: *CKD, resistant hypertension, outcomes, patiromer*

INTRODUCTION

According to Calhoun, resistant hypertension is either regulated blood pressure with the use of four or more antihypertensive drugs, or blood pressure that remains above goal despite the present use of three antihypertensive medications of different classes, one of which is a diuretic, at their maximum tolerable doses.[1] It is challenging to determine the prevalence of real resistant hypertension, thus patients who may be at risk should carefully consider any reversible reasons.[2] Patients with chronic kidney disease (CKD) frequently have arterial hypertension, which is a major factor in the progression of CKD and has a bidirectional interaction with CKD.[3] It has been demonstrated that persistent resistant hypertension damages the smaller renal arteries, setting off a vicious cycle that eventually results in a loss of kidney function.[4] On the other hand, poor blood pressure regulation may result from the CKD's increasing loss of kidney function.[5] The sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) are involved in the development of resistant hypertension and are also linked to the onset, course, and long-term consequences of chronic kidney disease.[6]

Rigidity in the course of renal disease is perpetuated by increased systemic blood pressure (BP) in conjunction with impaired autoregulation of glomerular pressure. This combination results in intra-glomerular hypertension, glomerulosclerosis, and a progressive decline in the glomerular filtration rate (GFR).[7] The general guidelines for managing chronic kidney disease include controlling blood pressure, which is essential for preventing the development of end-stage kidney disease (ESKD) and lowering the cohort's comparatively high cardiovascular risk.[5,8] The research has addressed certain issues related to the use of pharmaceutical and lifestyle therapies as current therapy methods for hypertension. The primary drawback of these regimens is their low efficacy in treating resistant hypertension, which is common in this population.[9] The shortcomings in the current treatment standards have also been linked to issues with patient adherence to treatment prescriptions and their capacity to tolerate anti-hypertensive medicine.[10] There is a correlation between uncontrolled hypertension and a higher risk of significant cardiovascular events. The majority of patients with chronic kidney disease die from cardiovascular disease since the risk of dying from this condition exceeds the chance of dying from end-stage renal disease. As a result, cardiovascular disease accounts for a large portion of the patient group's premature mortality.[7] For this reason, nephrologists treating hypertension patients with CKD need to be knowledgeable about available treatments.[11]

Numerous experimental findings have established the involvement of renal sympathetic hyperactivity in the development of arterial hypertension and associated conditions, such as chronic kidney disease.[12] Radiation-frequency catheter ablation of the renal afferent and efferent nerves is the minimally invasive percutaneous procedure known as sympathetic renal denervation (RDN). Large sections of the nerve fibers inside the renal artery adventitia can be effectively disrupted by the heat increase produced by applying low-dose radiofrequency energy. Recent randomized, sham-controlled trials have demonstrated a drop in blood pressure in less severe cases of hypertension comparable to what would be expected from a single antihypertensive medication.[11] Understanding the relationship between the prevalence and treatment of resistant hypertension in individuals with CKD is essential to improving the efficacy of care for these patients. This study aims to provide a comprehensive overview of the research on resistant hypertension in individuals with chronic kidney disease (CKD) that has been published within the past 10 years.

METHODS

Protocol

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were scrupulously followed by the work's author. This was done to make sure the study complied with all rules. The method of choice was laboriously created to guarantee the precision and coherence of the research outcomes.

Criteria for Eligibility

This work offers an extensive analysis of research conducted in the last ten years on the prevalence, management and outcome of resistant hypertension in patients with chronic kidney disease. Through thorough data analysis, this study aims to clarify and enhance patient care procedures. This thesis' main goal is to highlight important topics that may be found throughout a range of literary works.

To ensure that the data used in this investigation was accurate, strict inclusion and exclusion criteria were put in place. An item must have been published in English between 2014 and 2024 in order to be eligible for inclusion. Among the exclusion criteria are editorials, submissions without a DOI, reviews that have already been published, and duplicate journal entries.

Search Strategy

The study's keywords include "resistant hypertension, chronic kidney disease, CKD, prevalence, management, outcomes, therapy, incidence, prognosis". For this research, the following Boolean MeSH keywords were entered into the databases:

((("resistant hypertension"[MeSH Terms] OR "resistant hypertension "[All Fields] AND "chronic kidney disease"[All Fields]) OR ("resistant hypertension"[MeSH Terms] OR "resistant hypertension"[All Fields] AND "CKD"[All Fields]) AND ("prevalence"[MeSH Terms] OR "management"[All Fields] OR "outcomes"[All Fields] OR "therapy"[MeSH Subheading] OR "incidence"[All Fields] OR "prognosis"[All Fields]))).

Data retrieval

The writers carefully read the title and abstract of each article to determine its significance before starting this arduous examination. Greater weight was only assigned to studies that met the inclusion criteria and bolstered the goals of the article. A recurring pattern produced a definitive answer after several searches. Full-text entries were only accepted in the English language. Content that satisfied all predetermined inclusion criteria and had a clear connection to the study's topic matter was produced through the strictest screening procedure. Studies that deviated from these trends were typically disregarded and their conclusions were not given much weight. During the evaluation, a great deal of information was located and looked over, including factors, titles, authors, publication dates, places, and study methodologies.

Quality Assessment and Data Synthesis

The authors separately assessed the research cited in the titles and abstracts of each article in order to determine whether papers require additional investigation. Examining every document that complied with the prerequisites in advance for review inclusion was the next step. The selection of the papers for the review is based on the evaluation findings. This criterion expedited the selection of publications for additional investigation, enabling a comprehensive appraisal of previous work and the circumstances that qualified it for assessment.

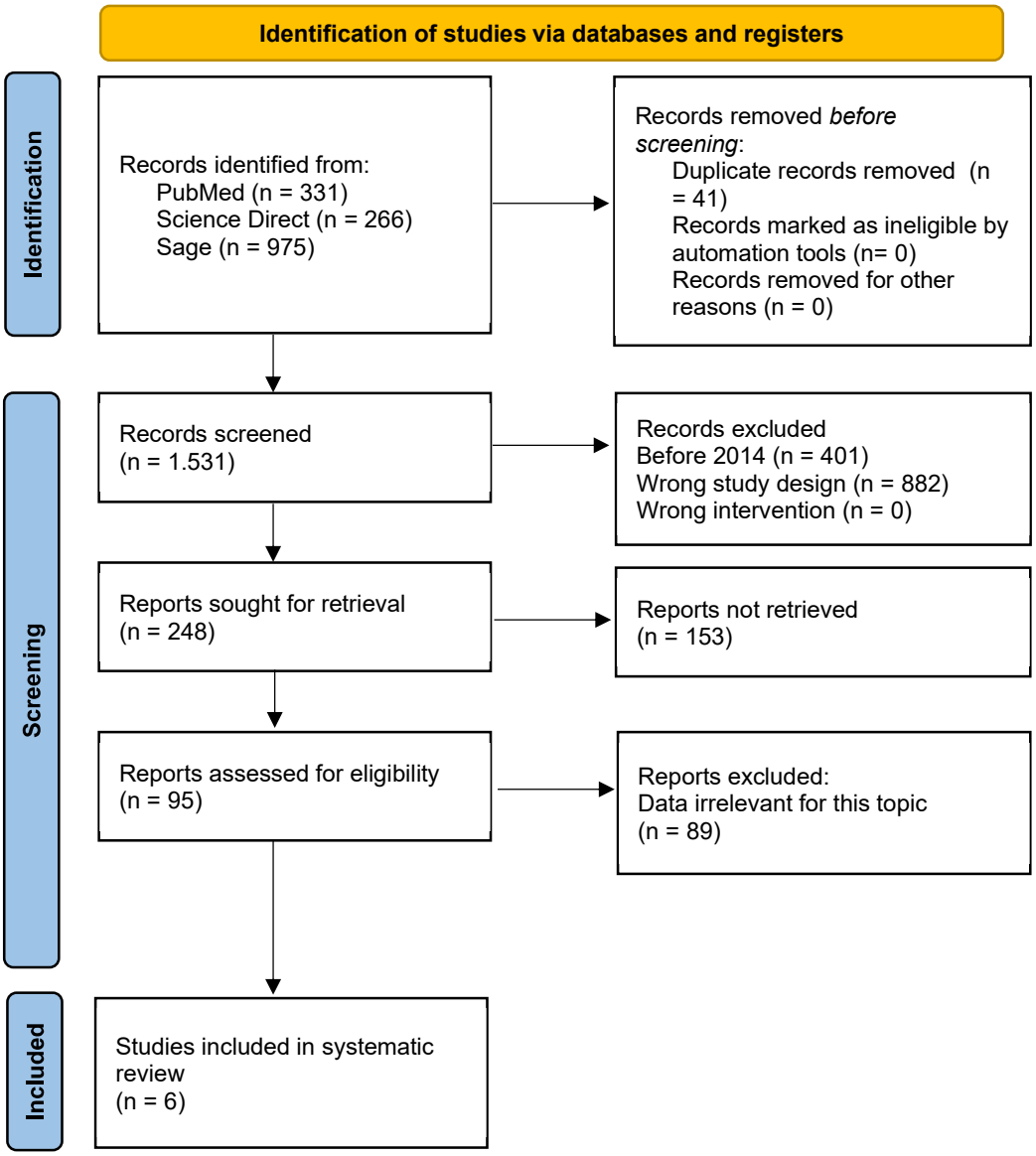

Figure 1. Article search flow chart

RESULT

Our research team first collected almost three thousand publications from reliable sources like PubMed, Science Direct, and SagePub. After a comprehensive three-tier screening procedure, only six papers were judged to be immediately related to our continuing systematic inquiry. After that, a few passages were chosen for further study and a thorough examination of the whole document. For convenience of viewing, the content that was evaluated for this analysis has been condensed into Table 1.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Rossignol et al.[13] (2020)	Multicenter	RCT	295 patients	This pre-specified subgroup analysis in patients with HF, resistant hypertension, and advanced chronic renal disease showed that patiromer facilitated more persistent use of spironolactone by lowering the risk of hyperkalemia, which is consistent with the overall outcomes of the AMBER trial.
Agarwal et al.[14] (2021)	USA	RCT	295 patients	The patiromer group showed a significant reduction in spironolactone use compared to the placebo group, with a 29% difference (P,0.03). In the eGFR 30-45 subgroup, a 69% reduction was observed in the placebo group, while 86% in the patiromer group. There was no significant interaction between eGFR subgroups, and similar proportions of patients reported adverse events (59% in the eGFR 25-35 subgroup and 53% in the eGFR 30-45 subgroup).
Xia et al.[15] (2021)	China	RCT	238 patients	The meta-analysis showed a significant reduction in office blood pressure and 24-hour ambulatory blood pressure 1 month after renal denervation (RDN). The decrease persisted for 24 months, with systolic and diastolic blood pressure showing differences. eGFR measurements obtained after RDN were not significantly different from before. Urinary albumin-to-creatinine ratio levels were significantly reduced at 3 months and 6 months after RDN. Heart rate showed no significant changes and few major complications were encountered.
Liu et al.[11] (2023)	China	RCT	8 patients	The study involved eight patients with CKD stages who underwent renal denervation

				(RDN) using a catheter-based system. Despite treatment with three antihypertensive drugs, office BP ≥150/90 mmHg and ambulatory BP ≥135 mmHg decreased by 6 months after RDN. Heart rate and estimated glomerular filtration rate (GFR) showed no significant change post-RDN.
Gajulapalli et al.[2] (2024)	USA	Review	-	Resistant hypertension and CKD have a high prevalence, with significant renal issues. Treatments like ROX coupler, renal denervation, baroreflex activation therapy, and percutaneous revascularization showed promise in reducing blood pressure. However, further research is needed to validate long-term efficacy and safety. Renal artery stenosis, caused by atherosclerosis, is a significant concern, with revascularization showing significant relief in some cases.
Mohammad et al.[6] (2024)	Ireland	RCT	226 patients	The results showed a significant reduction in CKD progression, with a reduction in office and 24-hour ambulatory blood pressure, kidney function, and serum creatinine levels, suggesting an interruption in natural progression.

The study by Rossignol et al. showed a significant difference in the cumulative dose of spironolactone between the patiromer group and placebo group, with a 16.0% difference. The patiromer group showed higher serum K+ levels and lower automated office blood pressure (AOBP) reductions from baseline to week 12. However, no significant interaction was found between the two groups. The study also showed normal NT-proBNP levels in both groups.[13]

The study from Agarwal et al. compared spironolactone and eGFR treatment in different treatment groups. Significant differences were observed in spironolactone use compared to patiromer, with 55.9% remaining on spironolactone at week 12. Systolic AOBP reductions were statistically significant for both treatment groups, with gastrointestinal disorders being the most common adverse effects (AE).[14]

The study by Xia et al. showed a significant decrease in office BP and 24-hour ambulatory BP monitoring before and after renal denervation (RDN), reducing the incidence of hypertension in patients with end-stage renal disease (ESRD). Antihypertensive medications showed a significant decrease after RDN, with moderate heterogeneity among studies. However, three major complications were reported, including pseudoaneurysm and hematoma, and two cases of progression to ESRD and dialysis-related complications.[15]

According to a study by Liu et al. showed that RDN treatment significantly reduced BP and GFR in patients with renal artery stenosis. The mean creatinine-based eGFR was 46.5 ± 33.0 ml/min/1.73 m2, with no significant changes in kidney function. No significant changes in serum biochemistry were observed postprocedural. Real-time renal artery imaging showed no focal irregularities of the renal arteries postoperatively, and all patients underwent a Doppler scan at 6-month follow-up.[11]

The study from Gajulapalli et al. showed significant renal problems are present in a high frequency of CKD and resistant hypertension. Promising treatments for lowering blood pressure included baroreflex activation therapy, ROX coupler, renal denervation, and percutaneous revascularization. Nevertheless, more investigation is required to confirm long-term safety and efficacy. Atherosclerosis-related renal artery stenosis is a serious issue, yet revascularization can provide a great deal of relief in certain situations.[2]

The study by Mohammad et al. reported a significant difference in systolic and diastolic office blood pressure outcomes after using RDN. The effect was found to be significant, with no significant difference in creatinine levels or eGFR levels. However, complications like renal artery dissection and hematoma were reported.[6]

DISCUSSION

The results of the AMBER study conducted by Rossignol et al. showed that administering patiromer orally daily significantly increased the number of chronic kidney disease patients who continued taking spironolactone after 12 weeks of treatment.[13] This was attributed to a lower incidence of hyperkalemia during spironolactone medication. The trial also demonstrated that patiromer was more tolerable than a placebo.[14] However, as it was only a phase II trial, the results cannot be used to draw long-term conclusions about renal and cardiovascular outcomes. Nonetheless, the results suggest that patiromer can prevent hyperkalemia in the mixed HFrEF/HFpEF population and safely allow the use of spironolactone.[13] Since hyperkalemia is a primary cause of renin-angiotensin-aldosterone system inhibitor (RAASi) non-use or underdosing in HFrEF patients, this finding has significant therapeutic implications.[16] The ongoing DIAMOND study is currently testing the potential of patiromer to improve cardiovascular outcomes.[17] The Agarwal et al. study highlights the use of patiromer, a K1-binding medication, to lower morbidity and mortality in individuals with resistant hypertension and chronic kidney disease.[14,18,19] However, it is less frequently utilized by those with diabetes, rHTN with CKD, and congestive heart failure.[20] The study found comparable effectiveness among CKD subgroups, but in the eGFR 25–30 subgroup, cessation started as early as two weeks in advance. Similarly, in patients with eGFRs of 30 ml/min per 1.73 m2, the study did not find any clear indications of damage. In severe chronic kidney disease, there may be a slight increase in calcium absorption, which should be taken into account. The safety and effectiveness of patiromer in combination with spironolactone are noteworthy for this patient population since they are frequently left out of randomized controlled trials.[14]

Studies have shown that patients with advanced renal disease (ESRD) and chronic kidney disease experience significant changes in blood pressure (BP) following renal denervation (RDN).[15] RDN effectively eliminates sympathetic nerve overactivity, resulting in a systemic decrease in sympathetic tone that is particularly noticeable in those with CKD. As the disease progresses, this decline becomes more pronounced.[21] RDN blocks renal afferent and efferent sympathetic neurons, modifying renal physiology and central sympathetic outflow to help CKD patients achieve long-term BP reduction. Inhibiting the renin-angiotensin system and reducing blood pressure can also decrease enhanced renin secretion and renal tubular salt reabsorption.[22] However, the duration of the BP drop is uncertain until the sympathetic nerves have healed from the damage. Since sympathetic nerve activity plays a significant role in the development and progression of CKD, further extensive clinical trials are needed to determine the potential role of RDN in ESRD.[15] While RDN may have benefits in treating CKD, including kidney protection,[23] it is essential to conduct more research to confirm its safety and repeatability and evaluate its impact on therapeutic outcomes, as 11 patients have reported problems and negative effects.[15]

Liu et al.'s study delve into the efficacy and safety of renal denervation treatment using radiofrequency in high-risk patients with advanced CKD and uncontrolled hypertension in China.[11] The research shows that administering bilateral RDN treatment significantly lowers blood pressure measurements, similar to other hypertensive patients with normal or impaired renal function.[24,25] However, there was no significant change in the night-to-day BP ratio. This study indicates that RDN treatment is safe and effective for high-risk patients with advanced CKD and persistent hypertension, with no significant improvement or further deterioration of renal function. Renal vascular abnormality is a major concern for patients with advanced CKD, with 77% excluded due to thin renal arteries. The study recognizes limitations such as a single-center analysis, a small sample size, and a six-month follow-up. Further research is necessary to address the issue of reinnervation in RDN patients and evaluate its effectiveness.[11] Renal denervation is safe for patients with CKD and has not been linked to any significant side effects. Mohammad et al.'s analysis of 11 trials involving 226 patients with CKD and treatment-resistant hypertension revealed a substantial decrease in both systolic and diastolic OBP and systolic and diastolic 24-hour ABP.[6] RDN aims to reduce sympathetic outflow and blood pressure, which affects not only hypertension but also atrial fibrillation, heart failure, and OSA.[26] Elevated sympathetic nerve activity and hypertension are linked to the progression of CKD and can benefit patients with renal artery disease. Treatment-resistant renal dialysis can stabilize eGFR and creatinine, lower blood pressure, and enhance CKD patients with uncontrolled hypertension for up to 24 months.[6]

The prevalence of resistant hypertension and chronic kidney disease is high, with blood pressure often remaining above the desired goal despite multiple antihypertensive agents. Managing normal blood pressure in these patients is challenging

due to CKD-related factors, such as accelerated atherosclerosis and adverse effects. The ROX coupler, which creates a central arteriovenous anastomosis, has demonstrated a significant reduction in office systolic blood pressure compared to the control group. However, the potential for widespread use remains uncertain.[2] Hyperactivity in the sympathetic nervous system is a significant factor in resistant hypertension, and reducing hyperactivity is a potential treatment strategy. Renal denervation, a catheter-based device, has demonstrated promising results in reducing blood pressure while having no significant adverse effects on renal function.[2] Various devices, such as Baroreflex activation therapy, the first-generation Rheos system, the second-generation Neo system, and the MobiusHD device, have shown the potential to decrease blood pressure. However, their long-term efficacy and safety are yet to be verified in large randomized controlled trials.[27] Atherosclerosis-induced renal artery stenosis affects blood flow to the kidneys, resulting in hypertension. Optimal medical therapy is preferred for atherosclerotic renal artery stenosis, with percutaneous revascularization being the preferred technique.[28] However, randomized controlled trials have shown that renal artery revascularization did not result in a change in systolic blood pressure compared to medical therapy.[2]

CONCLUSION

The safety and effectiveness of patiromer, a K1-binding medication, have been shown to improve cardiovascular outcomes in patients with CKD and hypertension. The results of a phase II study showed that patiromer can prevent hyperkalemia and safely allow the use of spironolactone, which is a primary cause of renin-angiotensin-aldosterone system inhibitor non-use or underdosing in HFrEF patients. However, the results cannot be used to draw long-term conclusions about renal and cardiovascular outcomes. Renal denervation (RDN) treatment has shown promising results in reducing blood pressure without significant adverse effects on renal function. However, further research is needed to confirm its safety and repeatability and evaluate its impact on therapeutic outcomes. The prevalence of resistant hypertension and chronic kidney disease is high, and managing normal blood pressure in these patients remains challenging due to CKD-related factors.

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