

PREVALENCE, RISK FACTOR, MANAGEMENT AND OUTCOME OF RESISTANT HYPERTENSION: SYSTEMATIC REVIEW

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ABSTRACT

Background: Resistant hypertension (RH) increases the morbidity and mortality from stroke and cardiovascular disease in comparison to hypertension without treatment resistance.

Aims : This systematic review is to review the prevalence, risk factor and management of resistant hypertension.

Methods: This study demonstrated compliance with all requirements by means of a comparison with the standards established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

Result: In the PubMed database, the results of our search brought up 1032 articles, whereas the results of our search on SAGEPUB brought up 29093 articles, our search on SCIENCE DIRECT brought up 96059 articles. The results of the search conducted for the last year of 2014 yielded a total 556 articles for PubMed, 12517 articles for SAGEPUB and 43884 articles for SCIENCE DIRECT. In the end, we compiled a total of 9 papers, 4 of which came from PubMed, 1 of which came from SAGEPUB and 4 of which came from SCIENCE DIRECT. We included nine research that met the criteria.

Conclusion: In summary, the therapy of lowered heart rate includes improving lifestyle modifications, utilizing long-acting thiazide-like diuretics, adding a mineralocorticoid receptor antagonist, and gradually adding antihypertensive drugs with complementary modes of action if blood pressure does not decline.

Keyword: Resistant hypertension, prevalence, management

INTRODUCTION

Blood pressure that stays over normal even after taking three or more antihypertensive drugs in the proper dosage and combination, including a diuretic, is referred to as "resistant hypertension" (RH).¹

Increased sympathetic nerve activity and a relative excess of aldosterone, which causes volume expansion and salt retention, are the hallmarks of RH. It has been suggested that the main factor influencing individuals with resistant hypertension is increased sympathetic nerve activity.⁴

Today, hypertension affects one billion people globally and is directly linked to almost 10 million fatalities annually; as a result, the World Health Organization has classified it as a global public health concern. Blood pressure $\geq 140/90$ mm Hg is considered resistant hypertension, even when three separate antihypertensive medications are taken at appropriate dosages, one of which needs to be a diuretic. Resistant hypertension is another term for the situation in which a person's blood pressure is within goal range but four or more antihypertensive medications are needed.

Based on a comprehensive review and meta-analysis of 24 research, the current data suggests that the prevalence of resistant hypertension affects 140–160 million individuals worldwide, or 14%–16% of all hypertension patients. There are two possible causes of this upward bias in the calculations. First off, four randomised trials were included, which probably exaggerated prevalence because the trials examined a subset of individuals with high cardiovascular risk. Second, few of the 20 observational studies that were included evaluated adherence to antihypertensive medications, which should better represent the burden of resistant hypertension in the real world than randomized research. Based on US claims data, an earlier observational research calculated the incidence of resistant hypertension to be 1.9%. But this estimate has to be updated because it was based on information from 2002 to 2006. Furthermore, evaluating the prevalence of resistant hypertension in contexts other than those previously researched has advantages in terms of broader generalizability.¹⁻⁴

METHODS

Protocol

The author of this study ensured that it complied with the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to guarantee the accuracy of the results that are derived from the investigation.

Criteria for Eligibility

In order to complete this literature evaluation, we looked at published research that discusses the prevalence, risk factor and management of resistant hypertension. This is done to enhance the patient's therapy management and to offer an explanation. This paper's primary goal is to demonstrate the applicability of the issues that have been noted overall.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) English must be used to write the paper. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) A few of the examined studies were released after 2013 but prior to the time frame considered relevant by this systematic review. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

Search Strategy

We used "prevalence", 'risk factor' and "resistant hypertension" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SAGEPUB databases by inputting the words: ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) AND (("resist"[All Fields] OR "resistance"[All Fields] OR "resistances"[All Fields] OR "resistant"[All Fields] OR "resistants"[All Fields] OR "resisted"[All Fields] OR "resistance"[All Fields] OR "resistences"[All Fields] OR "resistent"[All Fields] OR "resistibility"[All Fields] OR "resisting"[All Fields] OR "resistive"[All Fields] OR "resistively"[All Fields] OR "resistivities"[All Fields] OR "resistivity"[All Fields] OR "resists"[All Fields]) AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

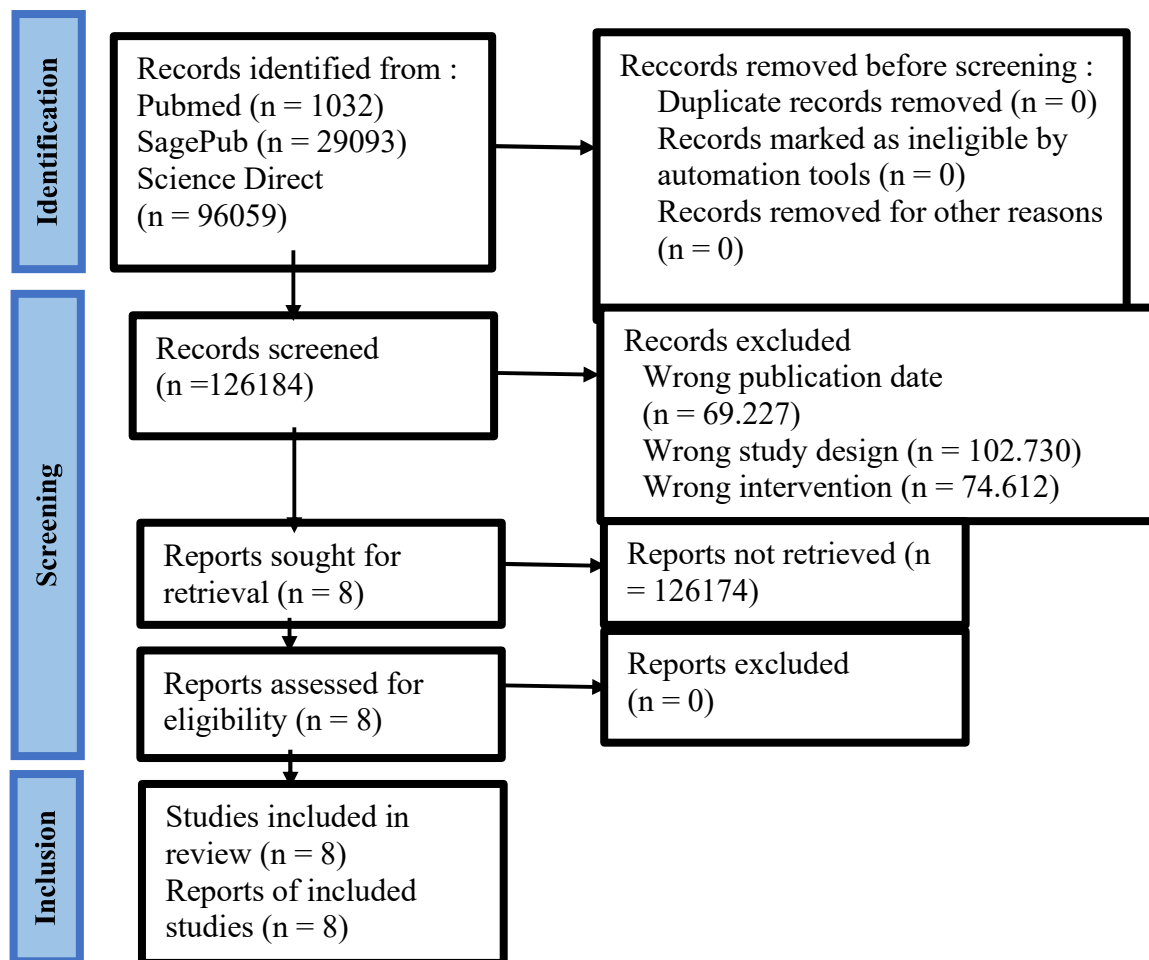


Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 1032 articles, whereas the results of our search on SAGEPUB brought up 29093 articles, our search on SCIENCE DIRECT brought up 96059 articles. The results of the search conducted for the last year of 2014 yielded a total 556 articles for PubMed, 12517 articles for SAGEPUB and 43884 articles for SCIENCE DIRECT. In the end, we compiled a total of 9 papers, 4 of which came from PubMed, 1 of which came from SAGEPUB and 4 of which came from SCIENCE DIRECT. We included nine research that met the criteria.

Hanus, et al⁵ (2017) showed that gender variations were found in the CV risk profiles of RHT patients as well as in characteristics associated with the existence of RHT, despite the fact that the rate of RHT did not differ between men and women. When patients were categorized by age, RHT was less common in women under 40 and in those between 40 and 65. Among patients 65 years of age and beyond, there was a tendency for a greater rate of HT in women.

Jankovic, et al⁶ (2023) showed that both spironolactone by itself or in conjunction with a centrally acting antihypertensive medication is the most efficient and secure supplementary treatment for resistant hypertension. The complete effects of adjuvant treatment, together with notable gains in quality of life, take around six months to materialize.

Moura, et al⁷ (2021) showed that the literature's estimates of the prevalence of RH are not accurate. Numerous treatment classes have been identified for controlling blood pressure; among them, diuretics and ARBs are preferred over CCBs in Rh patients, as well as β -blockers. The reasons for this preference are unknown. This more severe form of hypertension carries a bad prognosis for its patients because of increased cardiovascular risk and renal failure; further study is necessary to fully understand this phenotype.

Jin, et al⁸ (2014) showed that because of its distinctive approach, INSPiRED stands out from all other RDN studies on treatment-resistant hypertension. INPIRED will produce long-term safety and efficacy data, pinpoint hypertension patient groups who respond to RDN but are resistant to therapy, and offer insights into cost-effectiveness. The INSPiRED experiment will yield information that will be useful to health policy makers and guideline committees.

Galceran, et al⁹ (2020) showed that following three months of spironolactone therapy, a drop in eGFR and an increase in sCrea and sK were correlated with a drop in blood pressure. These adjustments were kept in place for a full year. For individuals whose baseline eGFR is ≥ 30 ml/min/1.73 m², spiro lactone is a safe and effective medication for reproductive health.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Hanus et al, 2017 ⁵	Poland	Cross sectional study	7306 patients	Compared to males, women with RHT showed a greater rate of high/very high increased CV risk. Higher PP, the existence of MS, CV illness, and eGFR < 60 mL/min/1.73 m ² were linked in a multivariate model to the presence of RHT in both males and females. RHT was also linked to disorders that cause disability, obesity in the abdomen, and cerebrovascular illnesses in women. RHT was also linked in males to conditions that needed to be treated with non-steroidal anti-inflammatory medications.
Jankovic et al, 2023 ⁶	Serbia	Prospective cohort study	515 patietns	Centrally acting antihypertensives were less effective as an add-on treatment, only reaching the trial goals in less than 70% of patients. Nine individuals (1.7%) have reported adverse medication responses; none of these were considered significant. With spironolactone, the incidence

				rate of hyperkalemia was 0.44%, and one patient (0.22%) had gynecomastia. Spironolactone by alone or in conjunction with a centrally acting antihypertensive medication proved to be the most efficient and secure add-on treatment for resistant hypertension.
Moura et al, 2021⁷	Brazil	Prospective cohort study	104 patients	Statins were chosen as a medication of choice by 51.4% of the hypertension group and 75.8% of the resistant hypertension group. Angiotensin II receptor blockers were taken by 90.9% of patients with resistant hypertension, whereas dihydropyridine calcium channel blockers were utilized by 66.7% of patients. Compared to 25.4% in the hypertension group, 75.8% of those with resistant hypertension utilized beta-blockers.
Jin et al, 2014⁸	Belgium	Randomized controlled study	240 patients	The primary goals for efficacy and safety, evaluated at six months, are the baseline-adjusted between-group differences in 24-hour systolic blood pressure and glomerular filtration rate, as determined by the Chronic Kidney Disease Epidemiology Collaboration equation. The maximum duration of follow-up will be 36 months after randomization. INSPiRED is able to demonstrate a 10-mmHg difference in systolic blood pressure between randomized groups with a two-sided p-value of 0.01 and 90% power.
Galceran et al, 2020⁹	Spain	Retrospective study	216 patients	Three months later, sCrea increased by 0.10 ± 0.04 mg/dL, eGFR decreased by -5.4 ± 1.9 ml/min/1.73 m ² , and sK increased by 0.3 ± 0.1 mmol/l ($p < 0.001$) in every case. A year later, these changes were still in effect. There were no significant differences in BP, sCrea, eGFR, or sK changes between three and twelve months. It is possible to superimpose the individual prospective and retrospective cohorts' results. Nine people (9.9%) in the prospective cohort stopped

				using spironolactone because of adverse effects.
Trimarco et al, 2023¹⁰	USA	Retrospective study	5331 patients	For 91.91 ± 54.7 months, these tTRH patients were followed in accordance with the therapeutic concordance procedure. The findings indicated that 210 patients (75.27%) remained to have uncontrolled blood pressure (uncontrolled tTRH, Group I), whereas 69 patients (24.73%) attained ideal blood pressure management (average BP <140/90 mmHg in at least 50% of follow-up visits, Group II). Remarkably, compared to Group I, Group II had a much less proportion of patients demonstrating a decline in renal function at the end of the second follow-up.
Martial et al, 2023¹¹	USA	Retrospective longitudinal study	209 patients	According to the study (n = 1148 visits), the prevalence of severe hypertension was 38.4% and 79.8%, respectively. Multilevel models showed a 0.66 mmHg (p < 0.001) decrease in diastolic blood pressure and a 0.29 mmHg (p = 0.37) decrease in systolic blood pressure each visit. Individual traits or process adherence did not predict the reduction in blood pressure.
Blumenthal et al, 2021¹²	North Carolina	Randomized clinical study	140 patients	Comparing the groups revealed that C-LIFE decreased clinic SBP more than SEPA did, and that SEPA did not change, while C-LIFE also decreased 24-hour ambulatory SBP. When comparing C-LIFE to SEPA, greater improvements were shown in resting BRS, HF-HRV vs. -0.2 ln ms ² , and FMD vs. -1.4%. PWV and LV mass were similar in all groups.
Ammann et al, 2023¹³	USA	Retrospective study	207705 patients	A goal blood pressure of less than 140/90 mmHg was achieved by roughly 70% of patients who received 3, 4, or ≥5 AHT medication classes, and less than 40% of patients were able to achieve less than 130/80 mmHg. After a year or more of follow-up, the prevalence of uncontrolled hypertension (≥140/90 mmHg) was similar, and the majority of patients' concurrent AHT

				medication classes stayed the same from baseline.
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Trimarco, et al¹⁰ (2023) showed that in populations where achieving normal blood pressure levels is extremely difficult, appropriate selection of antihypertensive drugs and active patient involvement in the treatment of hypertension are especially helpful as they enable satisfactory blood pressure control in less than 25% of the population. Individuals once classified as having uncontrolled tTRH hypertension. Moreover, the onset of hypertension might be considerably delayed by such a hemodynamic response.

Martial, et al¹¹ (2023) showed that medication for hypertension and other chronic illnesses is insufficient, particularly for areas that are difficult to reach and have little access to health services. Extended illnesses necessitate extensive outreach programs. The prevalence of hypertension in rural Timo among those over 40 or pregnant is comparable to that of other rural regions in the region, despite the natural physical activity that comes with living in rural and hilly locations and having easy access to fresh fruit. Haiti and almost doubled. America is the location.

Blumenthal, et al¹² (2021) showed that the best way to implement successful lifestyle modifications is to work with an extensive, interdisciplinary team of medical specialists inside an established cardiac rehabilitation facility. Policymakers should take into account reproductive health as a new rationale for cardiac rehabilitation, with adequate coverage from public and private insurance companies, according to the findings of the TRIUMPH research.

Ammann., et al¹³ (2023) showed that the prior treatment guidelines specified a blood pressure target of <140/90 mmHg, which was not met by up to 33% of these individuals. These results imply that, even with the use of multi-drug regimens, many patients with resistant hypertension and multiple comorbid conditions have suboptimal blood pressure control. They also imply that, in some cases, new drug classes may be required to effectively manage resistant hypertension.

DISCUSSION

Resistant hypertension, or RH, is defined as blood pressure that remains over a target level even after using at least three different classes of adequately dosed antihypertensive drugs, one of which is a diuretic. Assessing possible RH begins with medication adherence.

Husna, et al in their cross sectional study included 7306 hypertensive females and 5069 hypertensive males, showed that the frequencies of RHT (25.1% vs. 24.2%), uncontrolled HT (27.3% vs. 28.8%), and controlled HT (47.6% vs. 47.0%) did not differ between men and women, respectively (p = 0.17). Women were shown to have lower diastolic blood pressure, greater pulse pressure (PP), and an estimated glomerular filtration rate (eGFR) than males among individuals with RHT. Women with RHT were more likely than males to have cerebral-vascular illnesses (16.9% vs. 14.3%; p = 0.062), abdominal obesity, and metabolic syndrome (MS, 70.5% vs. 60.1%; p < 0.001).⁵

A cohort trial including 515 individuals (268 females and 247 males) with an average age of 64.7 ± 10.8 years was used in the study by Jankovic et al. A drop in systolic blood pressure of more than 10 mm Hg and a drop in diastolic blood pressure of more than 5 mm Hg was also observed in 88% of patients receiving add-on spironolactone. Both at home and at work, these individuals were able to get blood pressure readings that were lower than 140/90 mm Hg. Less than 70% of patients received centrally acting antihypertensives as an adjunctive therapy, and they were less successful in meeting trial objectives.⁶

Angiotensin II receptor blockers were used by 90.9% of patients with resistant hypertension, whereas dihydropyridine calcium channel blockers were used by 66.7% of patients, according to a study on the condition conducted in Brazil by Moura et al. In the group with resistant hypertension, beta-blockers were used by 75.8% of patients, as opposed to 25.4% in the hypertension group.⁷ In their trial, Galceran et al. also shown that spironolactone is a safe and effective treatment for RHTN when administered to patients with a baseline eGFR of less than 30 ml/min/1.73 m².⁹

Patients between the ages of 20 and 69 who use at least three antihypertensive medications and have a 24-hour ambulatory blood pressure reading of 130 mmHg systolic or 80 mmHg diastolic or above are eligible with a randomized controlled study by Jin, et al. with 240 treatment resistant hypertensive patients. Because of its unique design, the INSPiRED experiment differs from all prior RDN studies in treatment-resistant hypertension. INSPiRED will yield long-term safety and efficacy data, as well as cost-effectiveness statistics and the identification of the subset of hypertension patients who respond to RDN but are resistant to medication. The information obtained from the INSPiRED experiment will help guide the guidelines committee and policy makers.⁸

The study conducted by Martial et al. had 299 patients. De-identified medical data from 11 biannual outreach clinics between April 2014 and April 2019 were analyzed for the research. This research suggests that just writing prescriptions for chronic conditions like hypertension is probably not going to be sufficient among hard-to-reach populations with limited access to and resources for healthcare. In the case of chronic conditions, extensive outreach is essential.¹¹

In their study, Blumenthal et al. found that an intensive 4-month program of exercise and nutrition modification administered as adjuvant therapy in a cardiac rehabilitation environment improved blood pressure management in a sample of 140 individuals with RH. The patients had a mean age of 63 years old, were 48% female, 59% Black, 31% had diabetes, and 21% had chronic kidney disease. These findings suggest that a comprehensive, multidisciplinary team of medical professionals may be able to accomplish positive lifestyle changes within the context of cardiac rehabilitation in the most efficient way.¹²

In a large population sample research, Ammann et al. found that 207,705 hypertensive patients also took at least three AHT medications concurrently. After a year or longer of follow-up, the concurrent AHT medication classes of most patients did not differ from baseline, and the prevalence of uncontrolled hypertension ($\geq 140/90$ mmHg) was similar.¹³

CONCLUSION

In summary, the therapy of lowered heart rate includes improving lifestyle modifications, utilizing long-acting thiazide-like diuretics, adding a mineralocorticoid receptor antagonist, and gradually adding antihypertensive drugs with complementary modes of action if blood pressure does not decline. It is advised to consult a hypertension specialist if blood pressure is still out of control.

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