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SYSTEMATIC REVIEW: SIDE EFFFECTS OF RAMIPRIL AND SPIRONOLACTONE DRUG COMBINATION IN CARDIOVASCULAR PATIENTS

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ABSTRACT
Cardiovascular disease is one of the leading causes of death worldwide, especially in developing countries. Combination therapy of ramipril, an ACE inhibitor, and spironolactone, an aldosterone antagonist, is widely used in hypertension and heart failure patients, offering clinical benefits such as blood pressure control and organ protection, but it also poses risks of hyperkalemia and renal dysfunction. This systematic review aimed to evaluate and identify the adverse effects of ramipril–spironolactone combination therapy. A systematic search was conducted in Google Scholar and PubMed NIH Central for articles published between 2020–2024 using the keywords "Ramipril" AND "Spironolactone" AND "Adverse Effect" and "Combination Therapy" AND "Cardiovascular Disease." From an initial 1,026 articles, 38 were screened, 37 remained after duplicate removal, and 3 studies (2 from Google Scholar and 1 from PubMed) met the inclusion criteria. Article selection followed PRISMA 2020 guidelines, and data were extracted on study design, population, interventions, outcomes, and adverse effects. The results indicate that although ramipril–spironolactone combination therapy provides significant cardiovascular benefits, it is consistently associated with hyperkalemia, hypotension, and renal dysfunction; therefore, close monitoring of potassium levels, renal function, and blood pressure is strongly recommended to minimize adverse outcomes.

Keywords: cardiovascular disease; heart failure; hyperkalemia; spironolactone; ramipril

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INTRODUCTION

Cardiovascular disease is one of the leading causes of death globally, with an increasing prevalence, especially in developing countries. Cardiovascular-related disorders such as hypertension, heart failure, and coronary artery disease are conditions that often require complex management and aggressive drug therapy. Risk factors for these cardiovascular disorders such as unhealthy lifestyles, unbalanced diets, and lack of physical activity, as well as the prevalence of smoking and diabetes contribute to high incidence of these diseases. In developing countries, lifestyle changes due to rapid population growth, increased stress levels, and limited access to preventive health services exacerbate the problem. Data shows that in 2018 the prevalence of hypertension in Indonesia reached 34.1% and this condition if not handled properly, will lead to serious complications, including, stroke, and heart failure (Tiara, 2020).

One approach in the treatment of cardiovascular conditions is through the use of drug combinations that act on various physiological mechanisms to provide effective treatment effects, especially in patients with hypertension that are resistant to a single treatment. Ramipril which is an ACE inhibitor and spironolactone which is an aldosterone antagonist are two pharmacological agents that have been widely used for the treatment of patients with heart failure or high blood pressure and can provide more therapeutic effects than the use of single drugs, especially in patients with treatment-resistant hypertension (Rahmawati & Nurwahyuni, 2017). This combination not only helps in blood pressure control, but also in reducing the risk of organ damage due to uncontrolled hypertension (Rahmawati & Nurwahyuni, 2017).

Ramipril is one of the drugs belonging to the group of angiotensin converting enzyme inhibitors (ACE inhibitors) and is one of the most commonly used drugs in the treatment of patients with hypertension and heart failure. Ramipril works by inhibiting the activity of the angiotensin-converting enzyme (ACE) responsible for the conversion of angiotensin I to angiotensin II, a potent vasoconstrictive hormone that increases blood pressure and stimulates the release of aldosterone. Such reduction in angiotensin II production will help ramipril help lower blood pressure, reduce vasoconstriction, and reduce the burden on the heart. This effect is particularly important for patients suffering from heart failure or hypertension because by lowering the pressure in the blood vessels, ramipril can reduce the workload of the heart. This can help prevent the deterioration of heart function and slow down damage to blood vessels (Messerli et al., 2018).

Several clinical studies have shown that regular use of ramipril can significantly reduce morbidity in patients at high risk for cardiovascular complications, including heart attack and stroke. It can also have a protective effect on the kidneys, especially in patients with diabetes, making it a first-line treatment option in high-risk patients (Rosendorff et al., 2015). On the other hand, spironolactone belongs to the class of aldosterone antagonist drugs that have a mechanism of action by blocking aldosterone receptors in the kidneys. Aldosterone is a hormone that plays a role in sodium retention and potassium expression, which in turn contributes to increased blood volume and blood pressure. By inhibiting the action of aldosterone, spironolactone helps increase the excretion of sodium and water through the kidneys, thereby reducing fluid retention and lowering blood pressure. This is particularly beneficial in patients with congestive heart failure, where fluid retention can cause swelling (edema), shortness of breath, and worsening of heart failure symptoms. Several clinical studies have shown that spironolactone not only reduces symptoms in patients with severe heart failure, but can also extend the patient's life expectancy by reducing the risk of hospitalization and death from cardiac complications (Patibandla et al., 2022).

The combination of ramipril and spironolactone is often used in the treatment of patients with heart failure or other cardiovascular diseases, especially in patients who require stronger therapy to control symptoms or prevent complications. However, the combined use of these two drugs is not risk-free. The most common side effect that has occurred with the combined use of ramipril and spironolactone is hyperkalemia, which is an increase in potassium levels in the blood that can lead to serious complications such as cardiac arrhythmias. In addition, renal dysfunction is also a frequent concern due to the effects of both drugs on the renin-angiotensin-aldosterone system (RAAS) which can overload the kidneys (Abbas et al., 2015). The aim of this study using a systematic review approach was to identify and analyze the adverse effects associated with the use of the combination of ramipril and spironolactone in cardiovascular patients. This study was conducted by examining data from various clinical and observational studies, it is hoped that this review can provide a comprehensive picture of the adverse effect profile of this combination, as well as assist clinicians in making decisions to provide recommendations regarding monitoring measures needed to minimize the risk of adverse effects in patients receiving this combination therapy.

METHOD

This study was conducted as a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed using two major databases, Google Scholar and PubMed NIH Central, to identify research articles addressing the adverse effects of combined ACE-inhibitor (ramipril) and spironolactone therapy in patients with cardiovascular disease. The publication timeframe was set between 2020 and 2024, and only articles published in English were included in the analysis. The search strategy employed specific keyword combinations such as “Ramipril” AND “Spironolactone” AND “Adverse Effect” as well as “Combination Therapy” AND “Cardiovascular Disease,” utilizing the Boolean operators AND and OR to refine the search results for more relevant and specific studies.

The inclusion criteria for article selection were original research papers published in peer-reviewed journals, either human or animal studies written in English, that specifically examined the side effects of ramipril and spironolactone combination therapy in cardiovascular patients, with study designs including randomized controlled trials (RCTs), cohort studies, or case-control studies. Articles such as reviews, editorials, letters to the editor, or abstracts without complete data were excluded, as well as studies that did not report adverse effect outcomes.

The selection process began with title screening to identify studies most relevant to the inclusion criteria, followed by full-text review to confirm eligibility. Data extracted from the eligible articles included study design, sample size, patient characteristics, reported adverse events, and key findings related to ramipril and spironolactone combination therapy. All relevant findings were synthesized narratively. Data analysis was carried out by evaluating the included studies using standard methodological qualitative criteria to ensure the validity of the findings. Key information from each study was presented in both tabular and narrative form, thereby providing a comprehensive overview of the types of adverse events that may occur as a result of using this combination therapy in patients with cardiovascular conditions.

RESULT

The literature screening process is carried out using the PRISMA 2020 guidelines to determine the journals that will be used in this review. The following are the data obtained from the screening results:

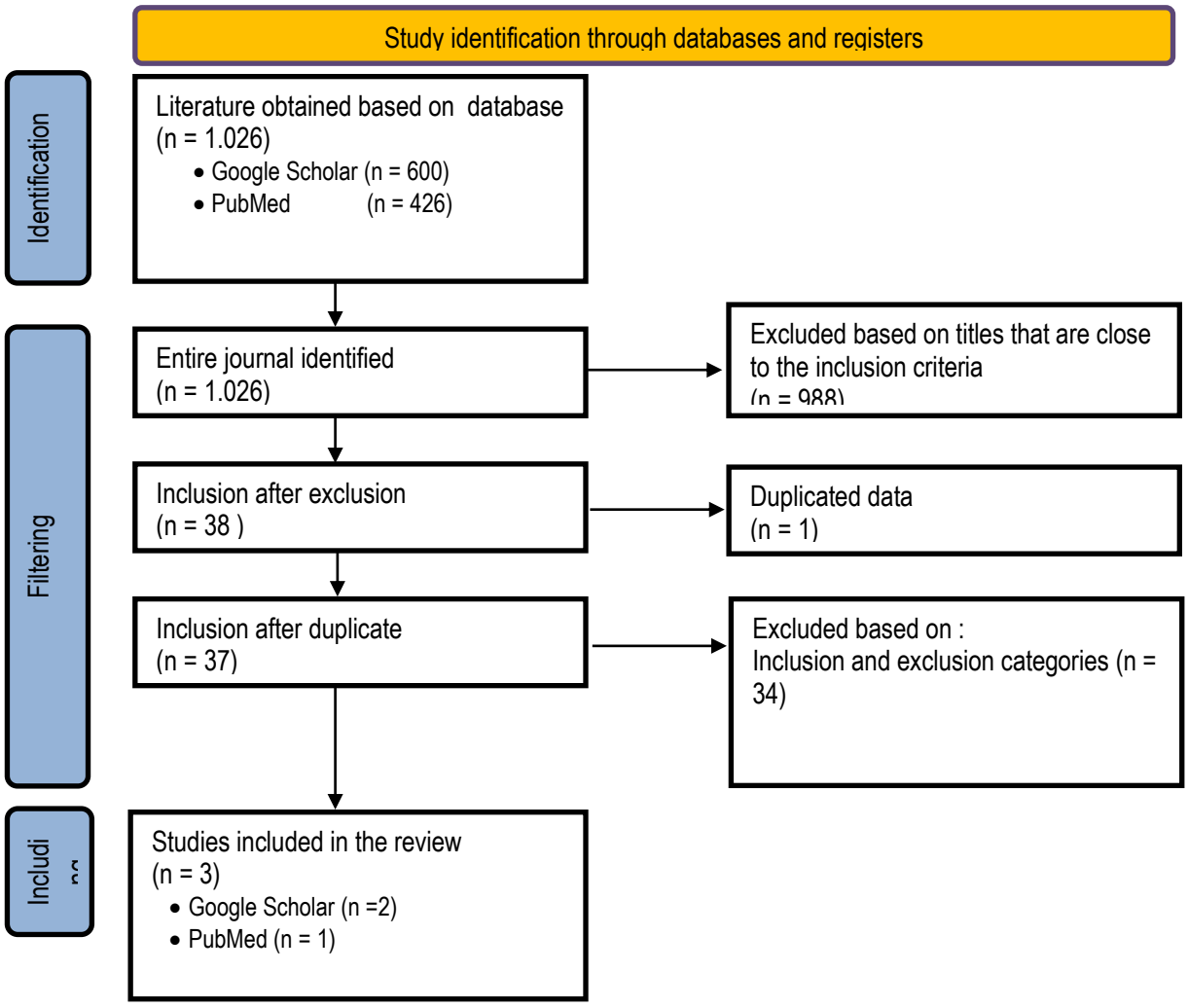

Figure 1. PRISMA diagram of Literature Search and Selection diagram

Based on the PRISMA 2020 diagram, data for 1,026 journal articles were obtained from two databases, namely 600 Google Scholar journal articles and 426 PubMed NIH Central journal articles. After collecting 1,026 articles, the data was filtered by looking at the titles of the journal

articles that were closest to the inclusion criteria. Then, from the screening results, 20 articles from Google Scholar and 18 articles from PubMed NIH Central were obtained, so that the total number of journal articles obtained was 38 that met the initial criteria. Next, a check was made to find duplicates among the journal article data obtained, and of the 38 articles found 1 article that was a duplicate, so the article was excluded from the data for analysis, and the remaining journal articles became 37.

After that, a final screening was conducted based on stricter inclusion and exclusion criteria to assess the relevance of the 37 articles. Based on this process, three selected journals were found to meet all the criteria for inclusion in the systematic review, namely two articles from Google Scholar and one article from PubMed.

Table 1.
Results Characteristics of Studies Included in the Review

Research Title & Year	Study Design	Popuation	Intervention	Duration	Main result	Reported Side Effects
Organoprotective Effects of Spironolactone on Top Ramipril Therapy in a Mouse Model for Alport Syndrome (Rubel et al., 2021)	Anima studies (Mouse Model)	Mice with Alport Syndrome	Ramipril + Spironolactone Combination	100 days	Combination therapy improves kidney function, reduces proteinuria and fibrosis	Hyperkalemia and premature death from compications of therapy
Effect of Spironolactone on Cardiovascular Morbidity and Mortality in Patients with Hypertension and Glucose Metabolism Disorders (ESCAM): a Study Protocol for a Pragmatic Randomised Controlled Trial (Li et al., 2020)	RCT (open-label)	7140 patients with hypertension & metabolic disorders	Spironolactone adjunct to standard therapy	36 months	Significant reduction in cardiovascular events in the Spironolactone group	Hyperkalemia and mineralocorticoid-related side effects
Clinical Efficacy of a Benazepril and Spironolactone Combination in Dogs with Congestive Heart Failure due to Myxomatous Mitral Valve Disease: The BEnazepril Spironolactone STudy (BESST) (Coffman et al., 2021)	RCT (Double-blind)	569 CHF dogs (Myxomatous Mitral Valve Disease)	Benazepril + Spironolactone vs Benazepril Combination	12 months	The combination of Spironolactone and Benazepril is more effective than Benazepril alone in reducing the incidence of CHF	The incidence of adverse events was similar between the groups, with some cases of vomiting more frequent in the combination group

DISCUSSION

This systematic review study focused on evaluating the side effects of the combination of ACEi (Ramipril) with Spironolactone in cardiovascular patients and animal models. The results of the literature screening of journal articles based on the PRISMA 2020 guidelines are three journal articles consisting of one study in humans and two in animal models (rats and dogs). The use of these two animals is considered because they have genetic and physiological similarities with humans, thus making them good models for understanding human diseases, such as mice that have DNA similar to humans and dogs that are often used in cardiovascular and metabolic related research due to similarities in biological systems (Leong et al., 2015). This led the researcher to include both journals discussing these animals in the literature for the systematic review.

The three journal articles analyzed showed that there is a clinical benefit of the combination of ACEi drugs (Ramipril) and Spironolactone in reducing the risk of cardiovascular events. However, the risk of serious side effects such as hyperkalemia and decreased renal function will be a major concern in the clinical use of this therapy (Coffman et al., 2021; Li et al., 2020; Rubel et al., 2021). According to one study, hyperkalemia was the main adverse effect reported in the use of the combination of ACEi and Spironolactone in human patients with hypertension and metabolic disorders (Li et al., 2020). It is said in the study, that therapy with both drugs is very effective in reducing the rate of cardiovascular events. In addition, the drugs also have a risk of increasing serum potassium levels, especially for patients who also have kidney problems or metabolic disorders. Therefore, the use of these drugs requires close monitoring of serum potassium, to prevent electrolyte disturbances such as hyperkalemia that will aggravate patients with cardiovascular disorders (Li et al., 2020).

In another research study with an animal model by Rubel et al. (2021) who examined the effects of the combination of ramipril and spironolactone with a population of rats with alport syndrome, which is one of the progressive kidney diseases. The results showed that this combination provided significant organ protection, reduced fibrosis, and improved kidney function. However, the study also found a risk of hyperkalemia, potentially leading to premature death in some rats. These results suggest that although the combination of ramipril and spironolactone has protective potential, the risk of electrolyte disturbances, especially in patients with renal impairment, remains significant. Therefore, this therapy requires close monitoring of electrolyte levels to prevent serious complications, especially in cardiovascular patients with renal risk (Rubel et al., 2021).

The next study examined dogs with congestive heart failure due to Myxomatous Mitral Valve Disease, where the condition of the mitral valve in the heart becomes thick and deformed, so it cannot close completely and will cause blood to leak back into the left atrium when the heart pumps (Coffman et al., 2021). This study also showed that the combination of benazepril, which is one of the ACEi class drugs, and spironolactone, which is a class of aldosterone antagonist drugs, can provide benefits in reducing the incidence of heart failure, thereby increasing survival in dogs. However, as in previous research studies, the combination of ACEi drugs and aldosterone antagonists has a risk of renal and electrolyte complications such as hyperkalemia. Therefore, dogs undergoing combination therapy with both drugs require close monitoring of serum potassium levels to prevent severe side effects. This study reveals that although the combination of ACE-Inhibitors and spironolactone provides significant cardiovascular benefits, the risk of serious side effects remains, especially in patients at risk of renal complications (Coffman et al., 2021).

Hyperkalemia is not the only risk reported in several studies related to the combination of ACEi and spironolactone, risks such as hypotension are also common, especially in patients receiving this therapy. In one of these studies, it was suggested that the use of spironolactone in addition to standard therapy may increase the likelihood of a significant reduction in blood pressure in hypertensive patients. Decreased blood pressure in the early stages of hypotension can impair organ function, including the kidneys. Therefore, this highlights the importance of careful blood pressure

monitoring during combination therapy, especially in patients at risk of hypotension (Li et al., 2020).

In general, the literature suggests that the combination of ACEi with spironolactone may provide significant clinical benefits in the management of cardiovascular disease, both in humans and animal models. However, there is a risk of adverse effects such as hyperkalemia, decreased renal function, and hypotension that require close monitoring when administering these two drugs in combination (Dipiro et al., 2020). The side effects of these two groups of drugs occur due to their mechanisms, such as the ramipril drug which is an ACEi and has an ACE enzyme inhibitor mechanism that functions to convert angiotensin I into angiotensin II. Angiotensin II is a strong vasoconstrictor and plays a role in increasing blood pressure and stimulating the release of aldosterone, which then causes sodium and water retention and potassium excretion, with the inhibition of the ACE enzyme, angiotensin II production will decrease, resulting in vasodilation, decreased blood pressure, and decreased aldosterone secretion (Shah et al., 2017).

The mechanism of action of ramipril also applies to other ACEi class drugs such as in one of these literature studies using the drug benazepril which belongs to the ACEi drug class. Therefore, the researcher also took the journal article as this literature study. On the other hand, spironolactone drugs work by inhibiting the action of aldosterone receptors, namely mineralocorticoid receptors strictly, with this mechanism sodium reabsorption and water retention does not occur, while potassium retention increases (Patibandla et al., 2022). When these two drugs are combined, they work by inhibiting the secretion of aldosterone, which is a hormone that acts in the kidneys to increase sodium and water retention, and increase potassium excretion. When the release of this hormone is inhibited, it can cause an increase in potassium levels in the body (hyperkalemia), and also the possibility of hyponatremia, where sodium levels in the body are lower than the normal amount (Abbas et al., 2015; Handler & Permanente, 2008).

However, the risk of hyponatremia itself does not occur in patients in general, but in patients who have a high sensitivity to changes in sodium levels, such as the elderly or other severe diseases. In addition, hyponatremia here is not caused directly by low aldosterone release (Handler & Permanente, 2008). In addition to hyperkalemia and hyponatremia, spironolactone and ramipril drugs can increase side effects in the form of hypotension, with the mechanism in ramipril which has a mechanism of action by inhibiting the ACE enzyme which is responsible for changing angiotensin I to angiotensin II, angiotensin II is a strong vasocontractor that will increase blood pressure. So if it is inhibited, it will reduce the formation of angiotensin II so that what was previously vasoconstriction (narrowing of blood vessels) in blood vessels becomes vasodilation (widening of blood vessels), while spironolactone works by inhibiting aldosterone receptors, where aldosterone which has been explained previously can increase sodium and water retention in the kidneys, so that it can cause an increase in blood volume and blood pressure. However, because aldosterone is inhibited, sodium and water retention will be reduced so that it can reduce blood volume and blood pressure (Patibandla et al., 2022; Shah et al., 2017). So based on the mechanism of these two drugs, the most significant side effect is an increased risk of hyperkalemia and hypotension as a result of aldosterone inhibition (Lexicomp, 2023).

Therefore, side effects such as hypotension and electrolyte disturbances (hyperkalemia) will increase the risk of renal impairment and lead to cardiovascular disorders as its final manifestation. Therefore, combination therapy of these two drugs requires close monitoring of blood pressure and serum potassium levels, and correct dosage adjustment to avoid serious complications (Lexicomp, 2023). Although combination therapy may improve clinical outcomes in cardiovascular patients, the high risk of adverse effects, particularly related to the kidneys and blood pressure will remain the first-line treatment in patients with cardiovascular disorders (Dipiro et al., 2020).

CONCLUSION

This systematic review shows that the combination of ramipril and spironolactone is effective in managing patients with hypertension and heart failure. However, the risk of side effects such as hyperkalemia and renal dysfunction cannot be ignored, requiring close monitoring, especially in patients with existing renal risks. Therefore, although this combination provides significant clinical benefits, careful monitoring and dose adjustment strategies are required to ensure therapeutic safety. The combination of ramipril and spironolactone remains a useful therapy in the management of cardiovascular disease, with the proviso that close monitoring of adverse effects should be paramount. With a better understanding of the side effects of this combination therapy, it is hoped that clinical practice can be optimized to improve treatment outcomes in cardiovascular patients.

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