

# Systematic Review: Drug Interactions in the Treatment of Hypertension with Diabetes Mellitus

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**Keywords:** Diabetes Mellitus, Drug, Hypertension, Interactions.

**Abstract:** Hypertension and diabetes are degenerative diseases that can cause a decrease in the body's physiological functions. Regular monitoring of blood pressure and blood sugar levels, along with consistent treatment, can help reduce physical complaints. However, it is important to be aware of potential drug interactions that may affect the effectiveness of treatment and cause unwanted side effects. The objective of this study was to evaluate drug interactions in the treatment of hypertension and diabetes mellitus. A systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Review) guidelines. Relevant published articles were searched for to investigate the use and interactions of drugs in patients with hypertension and diabetes. The literature search was conducted between July and August 2023 using Google Scholar, National Library of Medicine, and Public Health Reviews. The results show that commonly used treatments for hypertensive patients with diabetes mellitus include Amlodipine-Metformin, Furosemide-Metformin, Captopril-Glimepiride, and Captopril-Metformin. It is important to note that the interaction of various drugs can increase the risk of health problems and drug-drug interactions. The literature review's conclusion highlights the significance of evaluating drug interactions in treating hypertension and diabetes mellitus to ensure effective and appropriate treatment.

## 1 INTRODUCTION

Diabetes mellitus and hypertension are degenerative diseases caused by various factors, such as age, oxidative stress, and lifestyle, that lead to a decrease in the body's physiological functions (Madania et al., 2022). The prevalence of hypertension or high blood pressure accompanied by complications of diabetes mellitus, often referred to as the 'Silent Killer,' continues to increase every year (Rosyadi, 2022).

The World Health Organization (WHO) reports that 1.28 billion adults aged 30 to 79 worldwide suffer from hypertension, with two-thirds of them residing in low or middle income countries (WHO, 2023). The number of people affected by hypertension continues to rise annually across the globe. By 2025, it is projected that 1.5 billion people will suffer from hypertension, and 9.4 million people will die from hypertension-related complications each year (Ganga et al., 2022). In 2019, Paraguay, Dominican Republic, Dominica, Argentina, Grenada, Jamaica, Saint Kitts and Nevis, and Brazil had the highest prevalence of hypertension, with rates exceeding 45% (PAHO, 2023). In 2018, Indonesia joined the list of Southeast

Asian countries with the highest incidence of hypertension, affecting 34.1% of the population (Pulungan et al., 2022). Hypertension is the occurrence of increased blood pressure which is characterized by systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg, where symptoms can vary for each individual.

The most common symptoms of hypertension include headache or heaviness in the nape of the neck, vertigo, heart palpitations, fatigue, blurred vision, tinnitus, and nosebleeds (Nurlinda et al., 2022). Hypertension can lead to comorbidities, such as diabetes mellitus, due to shared trigger factors like diet, lack of physical activity, and impaired insulin production in diabetes sufferers, which directly affect blood pressure (Wati et al., 2021). Hypertension in diabetes patients is caused by high blood glucose levels, which lead to intravascular fluid resistance and an increase in body fluid volume. Additionally, damage to the vascular system increases peripheral arterial resistance, resulting in hypertension (Rasdianah & Pakaya, 2023).

Regular control of blood pressure and blood sugar is necessary to reduce physical complaints, and

patients should undergo regular treatment (Simanjuntak & Amazihono, 2023). The treatment options for oral diabetes and hypertension include Amlodipine-Metformin, Furosemide-Metformin, Captopril-Glimepiride, and Captopril-Metformin (Retnowati & Renha Lestari, 2022). It is important to note that drug interactions can lead to unsuccessful treatment of diabetes mellitus and increased blood pressure. When patients take multiple medications, treatment failure is a common problem that can lead to increased toxicity or decreased efficacy of concurrent medications (Abdulkadir et al., 2023). Additionally, the use of multiple drugs increases the risk of health problems and drug-drug interactions (DDIs) (Madania et al., 2022). Drug interactions can be a significant issue that affects patient clinical outcomes. With the complexity of drugs used in current treatments and the tendency for polypharmacy to occur, the possibility of drug interactions is increasing (Susanti, 2021).

## 2 METHODS

A systematic review was conducted to search for published articles on drug use and drug interactions in the treatment of hypertension and diabetes mellitus. The search strategy involved using online database facilities such as Google Scholar, National Library of Medicine, and Public Health Reviews. The search was limited to the years 2019 to 2023 and included Public Health Reviews and the National

Library of Medicine. Researchers searched international and national journals using the keywords 'Drug Interactions in the Treatment of Hypertension with Diabetes Mellitus' and 'Drug Use and Drug Interactions in the Treatment of Hypertension with Diabetes Mellitus' respectively. to 2023. English or Indonesian articles were selected based on their relevance to the inclusion and exclusion criteria. The inclusion criteria were limited to articles published between 2019 and 2023 that discuss treatment and treatment interactions, as well as patient socio-demographics. The exclusion criteria for this study are as follows: articles that are incomplete or not written in English or Indonesian, articles published before 2019, and articles that do not have clear publications or research results that have non-health impacts. The author employed a systematic review method following the PRISMA (Preferred Reporting Items for Systematic Review) stages, which include identification, screening, inclusion, and analysis of relevant article findings. To record treatment and drug interactions, we reviewed articles that met the inclusion criteria. The study recorded and presented all identified risk factors, along with a narrative explanation. Conclusions were drawn based on the collected data on treatment and drug interactions related to hypertension and diabetes mellitus. A literature search was conducted using Public Health Reviews, National Library of Medicine, and Google Scholar, resulting in 7260 articles. However, only 26 articles met the inclusion criteria and were included in the study.

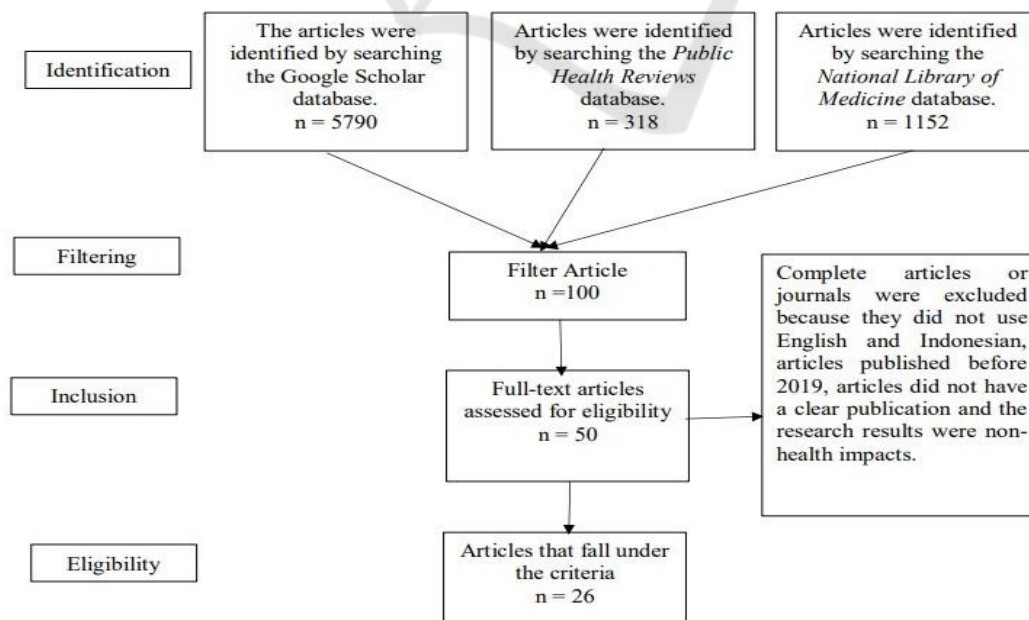


Figure 1: Article collection using the PRISMA method.

### 3 RESULTS AND DISCUSSION

The systematic review analysed several articles and found evidence of drug use and interactions between hypertension and diabetes mellitus treatments. Respondent characteristics, such as age, gender, antidiabetic treatment, and antihypertensive treatment, were also studied. According to Susanti (2021), the majority of patients diagnosed with hypertension complicated by diabetes mellitus were female (76%). Hormonal changes resulting from a

higher body mass index, premenstrual syndrome, and menopause can cause fat to accumulate more easily in the body. In women, the hormone estrogen is unable to produce High Density Lipoprotein (HDL), which can lead to increased blood pressure due to atherosclerosis. According to research by Apristina et al. (2023), the majority of respondents in the elderly category (93.7%) exhibited these characteristics. As age increases, changes occur that can make a person more susceptible to various diseases, including hypertension and diabetes mellitus.

Table 1: Interactions of hypertension and diabetes mellitus drugs.

Hypertension Medicine	Diabetes Mellitus Medicine	Effect	Severity Level	Reference Author
Amlodipine	Metformin	Amlodipine reduces the effects of metformin by pharmacodynamic antagonism and can cause hypoglycemia	Moderate	1. Abdulkadir et al., (2023) 2. Rahmawaty & Pratiwi, (2022) 3. Murwati & Murtisiwi, (2021)
Ramipril	Metformin	Ramipril may increase the toxicity of metformin by an undetermined interaction mechanism that may lead to hypoglycemia	Moderate	1. Agus & Permana, (2023) 2. Rahman & Octavia, (2019)
Captopril	Metformin	Captopril can increase the effects of metformin, thereby increasing the risk of hypoglycemia	Moderate	1. Rasdianah et al., (2021) 2. Ganga et al., (2022)
Furosemide	Metformin	Furosemide used with metformin can cause an increase in metformin levels in the blood, causing hypoglycemia	Moderate	1. Muhammad Fajar et al., (2023) 2. Refdanita & Sukmaningsih, (2021) 3. Fitri et al., (2022) 4. (Susanti, 2021)
Captopril	Glimepiride	Captopril can increase the effects of glimepiride, causing hypoglycemia	Moderate	1. Sa'adah et al., (2018) 2. Retnowati & Renha Lestari, (2022) 3. Risal et al., (2021)
Bisopropol	Glimepiride	Bisoprolol used with glimepiride can inhibit the $\beta$ -2 receptors in the pancreas so that it can reduce the effects of glimepiride and will cause hyperglycemia.	Moderate	1. Iskandar et al., (2021) 2. Oktaverawati & Susanti, (2020) 3. Amellia & Sumiwi, (2023) 4. (2023)
Ramipril	Candesartan	This interaction has a pharmacodynamic mechanism and has a synergistic effect, so it will potentiate each other's effects. Dual inhibition of the renin-angiotensin system may increase the risk of hypotension, hyperkalemia and renal impairment	Moderate	1. Oktianti et al., (2023) 2. Suri et al., (2022) 3. Effendi & Harimu, (2022) 4. Momuat & Annisaa', (2023)
Ciprofloxacin	Glimepiride	Ciprofloxacin increases the effect of glimepiride synergistically so it is necessary to monitor blood sugar levels regularly	Major	1. Tanty et al., (2023)

Table 1: Interactions of hypertension and diabetes mellitus drugs (cont.).

Hypertension Medicine	Diabetes Mellitus Medicine	Effect	Severity Level	Reference Author
Bisopropol	Insulin Lispro	The use of bisoprolol (cardioselective beta blocker) with insulin lispro can increase the risk of hypoglycemia	Moderate	1. Timur et al., (2022) 2. Dungan et al., (2019)
Bisopropol	Metformin	Concomitant use of metformin and bisoprolol can cause hypoglycemia	Moderate	1. Sormin & Salmaa Qoonitah, (2021) 2. (Reskiani et al., 2023)

#### 1. DDI Between Amlodipine and Metformin

Combination therapy using Angiotensin II receptor blocker (ARB) and Calcium-channel blocker (CCB) is more effective in achieving blood pressure targets. This therapy can be administered as monotherapy or in combination. CCBs can cause arterial widening and are commonly used as antihypertensive drugs. Additionally, it has been found that it can reduce resistance in blood vessels, leading to a decrease in blood pressure (Rahmawaty & Pratiwi, 2022). According to Abdulkadir et al., the interaction between metformin and calcium channel blocker drugs, such as amlodipine, can reduce the effectiveness of metformin. This is due to a pharmacodynamic interaction mechanism, which can cause hypoglycemic effects. To avoid hypoglycemia and potential drug interactions, it is necessary to check blood sugar levels before administering this drug and adjust the insulin dose accordingly (Abdulkadir et al., 2023).

#### 2. DDI Between Ramipril and Metformin

Metformin is an oral drug used to lower blood sugar levels. Due to its cationic nature, it has a high potential for drug interactions, which can occur via organic cationic ion transporters in the kidney. When used in combination with ramipril, metformin can cause hypoglycemia due to an increase in its blood sugar-lowering effect. The interaction mechanism between ramipril and metformin is undetermined (Agus & Permana, 2023). When administering both drugs, it is necessary to monitor them closely to avoid any potential adverse effects and maintain a safe distance between them (Rahman & Octavia, 2019).

#### 3. DDI Between Captopril and Metformin

Ganga et al. (2022) suggest that in hypertensive patients with diabetes, ACEI monotherapy (Captopril) is the preferred primary therapy due to its long-term safety and lack of metabolic side effects. Additionally, ACEI therapy is commonly used because it provides kidney protection by causing

vasodilation in the renal efferent arterioles and reducing proteinuria. The combination of metformin and captopril can increase the risk or severity of lactic acidosis and hypokalemia. Patients should monitor their blood glucose levels and recognize early symptoms of hypoglycemia. Rasdianah et al. (2021) suggest this solution.

#### 4. DDI Between Furosemide and Metformin

Furosemide is an antihypertensive drug that can be combined with metformin. However, this combination can cause hypoglycemia as furosemide can increase the plasma concentration of metformin by 22%. Conversely, metformin can decrease the concentration of furosemide and its elimination half-life by 31% and 32%, respectively (Refdanita & Sukmaningsih, 2021). Metformin belongs to the biguanide class of drugs and is the first-line treatment for diabetes. Furosemide, on the other hand, is a loop diuretic. The two drugs have a minor interaction that can increase metformin levels, although the mechanism is not yet understood. It is important to monitor patients to prevent loss of blood glucose control. When discontinuing the drug in patients taking metformin, it is important to monitor their blood glucose levels to prevent hypoglycemia (Fitri et al., 2022). To manage the interaction between these two drugs, the dose should be adjusted and the patient should be closely monitored for potential irregular heartbeat issues (Fajar et al., 2023).

#### 5. DDI Between Captopril and Glimperide

The concurrent use of glimepiride and captopril may have a moderate interaction effect, potentially leading to changes in the patient's clinical status, additional treatment, hospitalization, and/or prolonged length of hospital stay. This is due to the potential for drug interactions when using antidiabetic and antihypertensive medications simultaneously, which can be exacerbated by the patient's overall health condition. Drug absorption requires monitoring during use to anticipate unwanted reactions. When

administering the drug captopril with glimepiride, an ACE inhibitor interaction mechanism can increase glucose uptake by increasing capillary blood flow in skeletal muscle. Therefore, the use of captopril can enhance the effect of glimepiride (Sa'adah et al., 2018). The combination of these two drugs does not have a synergistic effect and instead produces a combination effect that is lower than the effect of each drug individually (Risal et al., 2021).

#### 6. DDI Between Bisoprolol and Glimepiride

Administration of beta blockers that selectively inhibit  $\beta$ -1 is a better choice when given to hypertensive patients with diabetes or peripheral circulatory disorders. The use of carvedilol and bisoprolol is beneficial and recommended for the treatment of heart failure in combination with ACE inhibitors, as stated in JNC VI and VII (Iskandar et al., 2021). Glimepiride is a sulfonylurea drug, and bisoprolol is a beta-blocker drug. These two drugs interact through pharmacodynamic mechanisms. The interaction between these two drugs can cause hypoglycemia in patients. Beta blockers inhibit insulin-induced glycogenesis in patients with diabetes mellitus and delay the recovery of normal blood glucose levels, leading to a decrease in insulin secretion. To manage this interaction, it is recommended to monitor the patient's glucose levels or replace the antihypertensive with a different class of drug (Oktaverawati & Susanti, 2020).

#### 7. DDI Between Candesartan and Ramipril

Suri et al. state that ACE inhibitor drugs and angiotensin receptor blockers (ARB), including candesartan and ramipril, have been shown to be effective in treating hypertension in patients with complications such as atherosclerosis and diabetes. Monotherapy may be more effective than combination therapy in improving blood pressure, renal function, insulin resistance, and plasma adipocytokine profile (Suri et al., 2022). Additionally, the combination of ACEI/ARB with potassium-sparing diuretics may increase blood potassium levels and lead to hyperkalemia (Effendi & Harimu, 2022).

#### 8. DDI Between Ciprofloxacin and Glimepiride

The combination of ciprofloxacin and glimepiride can cause severe hypoglycemia, which may lead to coma or death, particularly in elderly patients and those with kidney problems. It is important to avoid using Glimepiride with quinolone class antibiotics. If therapy cannot be avoided, closely monitoring blood sugar levels when starting therapy with quinolone

class drugs is necessary (Tanty et al., 2023).

#### 9. DDI Between Bisoprolol and Insulin Linspro

The moderate severity category suggests that the effects may be moderate and could lead to organ damage that requires additional therapy (Timur et al., 2022). When using selective beta blockers with insulin, the risk of hypoglycemia is higher than when using non-selective beta blockers with insulin. Therefore, monitoring of sugar levels is necessary. Spacing between bisoprolol and insulin lispro can be used to minimize the occurrence of hypoglycemia (Dungan et al., 2019).

#### 10. DDI Between Metformin and Bisoprolol

Concomitant use of metformin and bisoprolol may lead to hypoglycemia. Therefore, it is necessary to monitor glucose levels or adjust the antidiabetic dose if required (Sormin & Salmaa Qoonitah, 2021). Bisoprolol has a positive effect on the pathogenic mechanisms of arterial hypertension and metabolic syndrome. Similarly, metformin improves carbohydrate and lipid metabolism. However, it may also lower blood pressure and slow the heart rate, which can cause dizziness (Reskiani et al., 2023).

Pharmacodynamic interactions can often be extrapolated to other drugs in the same class because drugs are classified based on their pharmacodynamic effects. This means that the drug acts on the same receptor, site of action, or physiological system without changing plasma levels or other pharmacokinetic profiles (Murwati & Murtisiwi, 2021). Osoro, Amir, Vohra, and Sharma (2023) state that patient compliance is the most significant factor influencing drug-drug interactions. Monitoring is necessary as moderate interaction effects can cause changes in clinical conditions. Moderate interaction events can occur at any age, but they are more likely to occur in older patients due to age-related changes in physiology, increased risk of chronic diseases, and the use of multiple medications (Abdulkadir et al., 2023). Regular and routine medication adherence is crucial for maintaining stable blood pressure and reducing or preventing physical symptoms, ultimately improving the patient's quality of life. Regular and routine medication adherence is crucial for maintaining stable blood pressure and reducing or preventing physical symptoms, ultimately improving the patient's quality of life. It is important to note that subjective evaluations have been excluded from this text. Regular and routine medication adherence is crucial for maintaining stable blood pressure and reducing or preventing physical symptoms,

ultimately improving the patient's quality of life. Tarigan et al. (2022) identified several factors that influence treatment adherence, including knowledge, attitudes, information from mass/electronic media, and family support.

## 4 CONCLUSIONS

According to the results of a systematic review, the treatments most commonly used for hypertensive patients with diabetes mellitus are amlodipine metformin, metformin ramipril, metformin bisoprolol, metformin captopril, glimepiride captopril, furosemide-metformin, bisoprolol-insulin lispro, and ciprofloxacin glimepiride. Of these, ciprofloxacin-glimepiride has the greatest potential effect on hypoglycemia. Meanwhile, the combination of glimepiride and bisoprolol may lead to hyperglycemic effects.

To prevent this interaction, a time lag can be provided when taking the medication. Drug interactions can occur at any age, but are more likely in old age due to changes in physiology, increased risk of chronic diseases, and the need for multiple medications. Follow the instructions closely to ensure uniformity in the volume (Moore and Lopes, 1999).

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