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Potential Drug Interactions in Outpatients with Hypertension and Comorbid Type 2 Diabetes Mellitus at Arifin Achmad Regional General Hospital Riau Province

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Abstract: Hypertension and diabetes mellitus are degenerative diseases that if not managed properly will lead to other disease complications. This condition can cause polypharmacy which has the potential to cause drug interactions. The purpose of this study is to determine the presence or absence of drug interactions used in the treatment of hypertension patients with comorbidities of type 2 diabetes mellitus at Arifin Achmad Hospital, Riau Province. This study was conducted using a descriptive analysis design by collecting retrospective data. The samples are all outpatients diagnosed with hypertension and coexisting type 2 diabetes mellitus from January to December 2024 who met the inclusion criteria. The total sample in this study was 110 samples. In this study use one variable, drug interaction. The instrument used in this study was a patient's medical record. The results obtained were analyzed descriptively with online media screening using Drugs.com and Medscape.com sites and textbook screening such as Stockley's Drug Interactions, 12st edition, 2019 and Drug Information Handbook (DIH), 23rd edition, 2014. The data obtained were analyzed descriptively using percentages. The results showed that there were 70 cases of potential drug interactions. The type of pharmacodynamic interaction was 100% and based on severity there were major interactions of 1.43%, moderate 92.86% and minor 5.71%. These findings indicate the potential for drug interactions in outpatients with hypertension and comorbid type 2 diabetes mellitus, particularly pharmacodynamic interactions.

Keywords: hospital; hypertension and comorbid type 2 diabetes mellitus; pharmacodynamic interactions

1. INTRODUCTION

Hypertension is defined as persistently elevated arterial blood pressure (≥140/90 mmHg) and is often called a "silent killer" due to its asymptomatic progression. It affects over 30% of the global adult population (≈1.13 billion people) [1]. In Indonesia, the overall hypertension prevalence is 30.8% (18–59 years) according to the 2023 National Health Survey, it rises above 50% in those ≥60 years. In Riau Province, the prevalence has climbed to 33.1% by 2022 [2]. Similarly, diabetes mellitus (primarily type 2) is rising worldwide. The International Diabetes Federation reported 537 million adults (20–79 years) with diabetes in 2021, projected to increase to 783 million by 2045 [3]. In Indonesia, diabetes prevalence was 10.9% in 2018 and 11.7% by 2023 [4], in Riau it reportedly doubled from 2021 to 2022 (100% increase) [5]. According to 2021 data from the International Diabetes Federation (IDF), there are approximately 19.5 million to 28.6 million people with type 2 diabetes mellitus (T2DM) in Indonesia, with 40-80% of those with DM at high risk of developing hypertension. This complication is often found in the elderly (>60 years), particularly those with stage 1 hypertension.

Hypertension and type 2 diabetes mellitus often co-occur, sharing risk factors like age and lifestyle. Each condition exacerbates the other via mechanisms like insulin resistance and vascular dysfunction [6]. Managing both conditions usually requires multiple medications. It is well recognized that polypharmacy (e.g. >3 drugs) raises the risk of drug–drug interactions [7]. Drug interactions in hypertensive patients with type 2 diabetes are very high (69.57% - 96%), often involving a combination of antidiabetic drugs (metformin, glimepiride) and antihypertensive drugs

(amlodipine, candesartan). These effects include decreased drug effectiveness, increased risk of hypoglycemia, or side effects such as lactic acidosis due to drug-drug or drug-disease interactions [1][2][8][9]. This drug interaction can have a clinical impact on the success of blood pressure and blood glucose control, thereby potentially leading to treatment failure and increasing the risk of long-term complications in patients. Several studies have reported that interactions between antihypertensive and antidiabetic drugs can cause unstable glycemic and blood pressure control, which ultimately increases the risk of morbidity and the need for treatment adjustments. A drug interaction is a modification of one drug's effect by another substance (drug, food, etc.), which can be pharmacokinetic or pharmacodynamic [7]. Many other studies have investigated the potential for drug interactions. Studies examining the potential for drug interactions in patients with hypertension and Type 2 DM have not detailed these interactions. Multiple studies have reported a high incidence of potential drug interactions among hypertensive patients with type 2 diabetes mellitus, with interaction prevalence reaching as high as 79.6% [10]. Despite these findings, earlier studies often did not provide in-depth analyses regarding the specific drugs involved, interaction severity, or mechanisms of interaction. Consequently, this study offers a more comprehensive approach by systematically identifying medications, evaluating potential interactions, and classifying them according to severity and mechanism.

The management of hypertension and diabetes requires long-term pharmacological therapy. The use of combination drugs for both diseases has the potential to increase the risk of polypharmacy and drug interactions [7], although not every simultaneous use of drugs will cause interactions. This is in line with the study by Awaluudin et al. (2025), which showed that the administration of Nifedipine together with $MgSO_4$ did not result in drug interactions [11]. Drug interactions can affect the effectiveness of therapy and cause unwanted side effects, especially when involving pharmacokinetic or pharmacodynamic mechanisms. Several previous studies, such as those reported by Madania et al. (2022) [12] and Devianti et al. (2022) [10], show that the incidence of drug interactions in hypertensive patients with type 2 diabetes mellitus is quite high.

Preliminary study results at Arifin Achmad General Hospital in Riau Province indicate that the number of outpatient visits for hypertension and type 2 diabetes is quite high. In 2023 and 2024, hypertension ranked fifth and type 2 diabetes ranked ninth among the most common diseases. The large number of prescribed medications increases the risk of drug interactions, making monitoring for potential interactions crucial.

There is still limited research related to drug interactions, especially in outpatients with hypertension with comorbid type 2 diabetes, and similar research has never been conducted at the Arifin Achmad Regional General Hospital in Riau Province, researchers are interested in studying this. Therefore, scientific evidence regarding the clinical relevance, severity, and mechanism of potential drug interactions in hypertensive patients with comorbid type 2 diabetes mellitus, especially in outpatients, is still limited. This study aims to determine the potential for drug interactions in hypertensive patients with comorbid type 2 diabetes at the outpatient department of Arifin Achmad General Hospital in Riau Province. The results of this study are expected to contribute to efforts to improve medication safety, optimize therapy, and enhance the quality of pharmaceutical services at the hospital.

2. MATERIALS AND METHODS

This study is a descriptive analysis design by collecting retrospective data at the Outpatient Department of Arifin Achmad Provincial Hospital in Riau. Research data were obtained from the medical records of outpatients diagnosed with hypertension and comorbid type 2 diabetes mellitus during the period January - December 2024. The study population included all patients who met these criteria, and the sampling technique used was total sampling. Based on the established inclusion and exclusion criteria, 110 samples were analyzed in this study.

The inclusion criteria included outpatients aged ≥18 years with a diagnosis of hypertension and type 2 diabetes mellitus who received at least two types of drugs in one visit and had complete

medical records. The exclusion criteria in this study were incomplete, missing, or unclear patient medical records.

The data collected included patient characteristics, diagnoses, and a list of prescribed antihypertensive and antidiabetic drugs. Potential drug interactions were identified using standard reference sources, namely Stockley's Drug Interactions, 12th edition, 2019 [13] and the Drug Information Handbook, 21th edition, 2012 [14] and supported by the online screening tools Medscape Drug Interaction Checker (https://reference.medscape.com/drug-interactionchecker) [15] and Drugs.com Drug Interactions Checker (https://www.drugs.com/drug_interactions.html) [16] accessed in 2025. The drug interactions found were then classified based on the interaction mechanism into pharmacokinetic and pharmacodynamic, and based on severity into minor, moderate, and major.

The data were analyzed descriptively and presented in terms of numbers and percentages to describe the drug use profile and potential drug interactions in hypertensive patients with comorbid type 2 diabetes mellitus. This study has obtained approval from the Ethics Committee of the Faculty of Medicine, Abdurrab University, Pekanbaru, and research permission from Arifin Achmad Provincial General Hospital, Riau. All patient data is kept confidential and is only used for research purposes.

3. RESULT AND DISCUSSION

This study involved 110 hypertensive patients with comorbid type 2 diabetes mellitus (DM) who were outpatients at Arifin Achmad Regional General Hospital in Riau in 2024. Data analysis revealed that the majority of patients were female. A total of 75 patients (68.18%) were female, and 35 patients (31.82%) were male. Similar demographic data were reported by the 2023 Indonesian Health Survey, which indicated a higher prevalence of hypertension in women compared to men [1, 4]. The higher incidence in women can be explained by hormonal and physiological factors; decreased estrogen levels post menopause lower HDL levels, thereby increasing the risk of hypertension [1]. Additionally, women are at higher risk for type 2 diabetes due to greater increases in body mass index (BMI), a history of gestational diabetes during pregnancy, hormonal factors, and contraceptive use.

The age distribution of patients shows that the 56–65 age group is the most numerous (36 patients, 32.73%), followed by those over 65 years of age (26 patients, 23.64%) and those aged 46–55 years (33 patients, 30.00%). There were no cases in the younger age group (18–25 years), and only 3 patients (2.72%) in the 26–35 age group. This pattern aligns with the fact that the risk of hypertension increases with age [1]. Structural changes in blood vessels with aging lead to increased systolic blood pressure [11]. PERKENI (2019) also reported that age >45 years increases the risk of type 2 diabetes mellitus [17].

Analysis of the drugs used revealed the most commonly prescribed antihypertensive and antidiabetic classes. Out of a total of 179 active ingredients in hypertension medications, the angiotensin receptor blocker (ARB) class was the most common (57 cases, 31.84%) with the active ingredient Candesartan, followed by the calcium channel blocker (CCB) class with Amlodipine (46 cases, 25.70%) (Table 1). Other commonly used medications include beta-blockers, diuretics, ACE inhibitors, and central alpha agonists. The selection of ARBs (such as Candesartan) is based on their effectiveness in lowering blood pressure with a good safety profile and cardiovascular and renoprotective effects [18]. As a CCB, Amlodipine effectively lowers blood pressure and may even improve glycemic control (lowering HbA1c) in patients with type 2 DM [19]. The combination of ARBs and CCBs is also frequently recommended due to their synergistic mechanisms of action in controlling blood pressure and protecting target organs.

Table 1. Number and Percentage (%) of Classes and Active Ingredients of Antihypertensive Drugs Used in Hypertensive Patients with Concomitant Type 2 DM (n=179)

No	Hypertension Medication Group	Active Ingredient	Amount	Percentage (%)
1	Angiotensin Receptor Blocker (ARB)	Candesartan	57	31.84
		Valsartan	7	3.91
		Telmisartan	3	1.68
2	Calcium Channel Blocker (CCB)	Amlodipine	46	25.70
		Nifedipine	19	10.61
		Diltiazem	1	0.56
3	Beta Blocker	Bisoprolol	18	10.05
		Propranolol	3	1.68
4	Diuretic	Hydrochlorothiazide (thiazide)	1	0.56
		Furosemide (loop)	7	3.91
		Spironolactone (potassium-sparing)	9	5.03
5	ACE Inhibitor	Ramipril	6	3.35
6	Central Alpha Agonist	Clonidine HCl	2	1.12
	Total		**179**	**100**

For antidiabetic drugs (total of 166 active ingredients), the biguanide class dominates (Metformin 88 cases, 53.01%), followed by sulfonylureas (Glimepiride 48 cases, 28.91%) (Table 2). Other commonly used medications include gliquidone, acarbose, sitagliptin (DPP-4 inhibitor), and pioglitazone (TZD). The preference for these medications aligns with clinical guidelines, Metformin is the first-line therapy for type 2 DM as it reduces hepatic glucose production and enhances insulin sensitivity without significant risk of hypoglycemia. Metformin also has cardiovascular benefits by improving lipid profiles and lowering blood pressure (Wikannanda et al., 2023) [20]. Second-generation sulfonylureas such as Glimepiride are widely used due to their better safety profile (low risk of hypoglycemia) compared to glibenclamide. The 2019 National PERKENI Guidelines recommend Glimepiride as the primary alternative when Metformin is not tolerated [17].

Table 2. Number and Percentage (%) of Classes and Active Ingredients of Type 2 DM Drugs Used in Hypertensive Patients with Type 2 DM Comorbidities (n=166)

No	Type 2 DM Medication Group	Active Ingredient	Amount	Percentage (%)
1	Biguanide	Metformin	88	53.01
2	Sulfonylurea	Glimepiride	48	28.91
		Gliquidone	8	4.82
3	Alpha-Glucosidase Inhibitor	Acarbose	8	4.82
4	DPP-4 Inhibitor	Sitagliptin	7	4.22
5	Tiazolidinedione (TZD)	Pioglitazone	7	4.22
	Total		**166**	**100.00**

The results of the study show that most potential drug interactions between antihypertensive and antidiabetic drugs are moderate in severity (92.86%), followed by mild/minor interactions (5.71%) and major interactions (1.43%). Moderate interactions generally require therapeutic monitoring because they can affect the effectiveness of treatment without causing fatal effects directly.

The combination of Amlodipine–Metformin is the most frequently found interaction (48.57%). This interaction is pharmacodynamically antagonistic, in which calcium channel blockers

can decrease insulin sensitivity and potentially interfere with patients' glycemic control. These findings are in line with the study by Saputri et al. (2022) [21], which reported that the combination of CCB antihypertensive drugs with metformin most often causes moderate interactions in patients with type 2 diabetes mellitus.

The Nifedipine–Metformin interaction (22.85%) also showed similar effects. A study by Madania et al. (2022) [12] reported that nifedipine can affect glucose metabolism and cause fluctuations in blood sugar levels, requiring periodic monitoring of glucose levels.

The only interaction with a major severity level was found in the Spironolactone–Ramipril combination (1.43%). This interaction is synergistic in potassium retention and has the potential to cause hyperkalemia. These results are consistent with the study by Devianti et al. (2022) [10], which reported that the combination of ACE inhibitors and potassium-sparing diuretics has a high risk of electrolyte disturbances.

Overall, the interaction patterns in this study align with previous research indicating that pharmacodynamic interactions of moderate severity are the most dominant type of interaction in hypertensive patients with comorbid type 2 diabetes, particularly in outpatients undergoing polypharmacy.

Table 3. Number and Percentage (%) of Active Ingredient Combinations Interacting in Hypertensive Patients with Concomitant Type 2 DM (n=70)

No	Combination of Active Ingredients	Amount	Percentage (%)	Severity	Effect
1	Amlodipine + Metformin	34	48.57	Moderate	Amlodipine can decrease insulin sensitivity, potentially reducing the glycemic control of metformin
2	Nifedipine + Metformin	16	22.85	Moderate	Antagonistic effects on blood glucose control due to vasodilation and changes in glucose metabolism
3	Spironolactone + Metformin	6	8.57	Moderate	Risk of kidney dysfunction and lactic acidosis when kidney function declines
4	Ramipril + Metformin	4	5.71	Moderate	ACE inhibitors can increase insulin sensitivity, thereby affecting the therapeutic response to metformin
5	Candesartan + Bisoprolol	2	2.86	Minor	Additive effects of lowering blood pressure and heart rate
6	Ramipril + Amlodipine	2	2.86	Minor	Synergistic effect in lowering blood pressure
7	Spironolactone + Ramipril	1	1.43	Major	Risk of hyperkalemia due to the additive effect of potassium retention.
8	Diltiazem + Metformin	1	1.43	Moderate	Diltiazem can affect glucose metabolism and increase metformin levels
9	Hydrochlorothiazide + Metformin	1	1.43	Moderate	Thiazide diuretics can decrease glucose tolerance.
10	Furosemide + Glimepiride	1	1.43	Moderate	Risk of hypoglycemia due to changes in fluid volume
11	Amlodipine + Hydrochlorothiazide	1	1.43	Minor	Antihypertensive additive effect.
12	Clonidine HCl + Metformin	1	1.43	Moderate	Clonidine may mask the symptoms of hypoglycemia
	Total	**70**	**100.00**		

The potential for drug interactions was also assessed based on medical records. A total of 60 patients (54.55%) were at risk of drug interactions, while 50 patients (45.45%) were not (Figure 1). These results indicate that more than half of patients with varied medication prescriptions have a risk of interactions, likely because these patients frequently take polypharmacy (more than one antihypertensive and antidiabetic medication), thereby increasing the likelihood of interactions.

Similar findings have been reported, indicating that high medication variability increases the likelihood of interactions in patients with comorbidities.

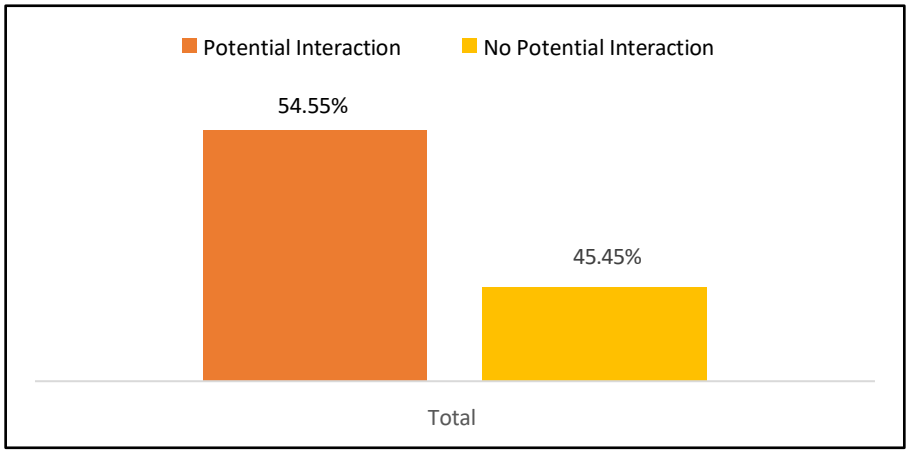

Figure 1. Number and Percentage (%) of Hypertensive Patients with Type 2 DM Comorbidity Potentially Experiencing Drug Interactions (n=110)

Of the 60 patients at potential risk, there were 172 drug interactions identified. A total of 70 interactions (40.70%) were classified as occurring (actual interactions), while 102 interactions (59.30%) did not occur. In other words, approximately 64% of patients with potential interactions (70 out of 110 patients, or 54.55%) actually experienced interactions. The relatively high number of interactions that occurred is due to the complexity of therapy involving hypertension and DM medications. Simultaneous use of medications without proper timing can increase the likelihood of clinical interactions.

The types of interactions that occur are divided into pharmacokinetic (PK) and pharmacodynamic (PD) interactions. Out of the 70 recorded interactions, all were pharmacodynamic interactions (70 cases, 100%), while no pharmacokinetic interactions were found (0 cases) (Table 4). This is consistent with literature findings that pharmacodynamic interactions are more common in combination therapy for hypertension and diabetes mellitus [21]. PD interactions typically occur due to additive or antagonistic effects of drugs on the same target mechanism (e.g., vasodilation or insulin effects). Conversely, PK interactions are relatively rare because hypertension and antidiabetic drugs in these patients generally have different metabolic and excretion pathways [22]. Pharmacokinetic differences (e.g., half-life and bioavailability) minimize metabolic competition, thereby reducing the risk of PK interactions [22]. The focus is more on monitoring clinical response and preventing pharmacodynamic interactions (Saputri et al., 2022; Fitriyah, 2018) [21, 22].

Table 4. Number and Percentage (%) of Pharmacokinetic and Pharmacodynamic Drug Interactions (n=70)

No	Type of Drug Interaction		Amount	Percentage (%)
1	Pharmacokinetics		0	0.00
2	Pharmacodynamics	Synergistic	17	24.29
		Antagonistic	53	75.71
Total			**70**	**100.00**

Finally, based on severity, 70 cases of interactions were categorized as follows: major 1 case (1.43%), moderate 65 cases (92.86%), minor 4 cases (5.71%) (Table 5). The majority of interactions were categorized as moderate, meaning that they required therapeutic monitoring but did not cause immediate serious harm. These findings indicate that most interactions cause clinically significant effects without causing immediate serious complications. The important role of pharmacists is to understand the potential effects of these interactions to prevent complications through coordination of therapy with doctors.

Table 5. Number and Percentage (%) of Drug Interactions Based on Severity Level (n=70)

No.	Severity	Amount	Percentage (%)
1	Major	1	1.43
2	Moderate	65	92.86
3	Minor	4	5.71
	Total	**70**	**100.00**

4. CONCLUSION

This study provides an overview that the use of combination therapy for hypertension and diabetes in outpatients with hypertension and type 2 diabetes mellitus has the potential to cause drug interactions. The interactions that occur are generally related to pharmacodynamic mechanisms and can affect the success of therapy if not properly monitored. Therefore, continuous monitoring of drug use and evaluation of drug interactions are essential as part of efforts to improve the safety and effectiveness of therapy in patients with chronic diseases.

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