

Research Article

Assessment of Drug Therapy Problems Among Type 2 Diabetes Patients with Hypertension Comorbidity in Indonesia

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Abstract

Type 2 diabetes mellitus (T2DM) is a major chronic disease that affects a large number of people worldwide. Hypertension is a common disease comorbidity among T2DM patients, and often those patients received polypharmacy and complex treatment in long term duration. This condition may lead to an increased risk of drug therapy problems (DTPs). This study aimed to assess and determine potential drug therapy problems in type 2 diabetic patients with hypertension comorbidity. Retrospective cross-sectional design was conducted in a hospital setting, especially data sources from the prescription of ambulatory T2DM patients with hypertension. A total of 190 patients were studied. More than half of the participants were female (53.68%). The majority age range of participants was 50-59 years (46.84%). Almost all antidiabetic agents were prescribed as polypharmacy (73.16%). Metformin was the most antidiabetic agent prescribed as monotherapy and combination therapy (63.16%). Almost all antihypertensive agents were prescribed as polypharmacy (63.26%). Amlodipine was the most antihypertensive agent prescribed as monotherapy and combination therapy (34.74%). Among the study participants, 56.84% have at least one of DTPs. Adverse drug reaction was the most frequent (47.22%), followed by ineffective drug therapy (29.63%). Since the potential of DTPs in T2DM patients with hypertension comorbidity is relatively high, early identifying, resolving, and preventing drug therapy problems by the pharmacist is needed to achieve goals of treatment.

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INTRODUCTION

Diabetes Mellitus (DM) has become a popular chronic disease worldwide. The prevalence of DM is 8.8% globally and 8.6% in Southeast Asia. It has been increasing rapidly in low- and middle-income countries (Dunning *et al.*, 2014). Based on a national survey, in the year 2030 number of DM cases Indonesia estimated about 21.3 million (Ministry of Health of the Republic of Indonesia, 2018).

Uncontrolled DM treatment is a serious problem that might be caused by microvascular and macrovascular

complications (Chawla *et al.*, 2016; Cade, 2008) and death (American Diabetes Association, 2015). Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes mellitus (Benjamin *et al.*, 2017). Health problems in many developing countries are in epidemiology transition where chronic Non-Communicable Diseases (NDCs) are major public health concerns due to the enormous financial burden associated with these diseases. Diabetes mellitus and hypertension were top the list of NDCs, these two chronic diseases are the most important risk factor for cardiovascular diseases (Bolarinwa *et al.*, 2018).

Hypertension is the most common disease comorbidity with diabetes. The presence of hypertension with diabetes increases in mortality and drug therapy problems worldwide, with a greater risk in developing countries (Petrie *et al.*, 2018; James *et al.*, 2014). Hypertension and type 2 diabetes mellitus (T2DM) called "lethal duo" which increases the risk of cardiovascular disease 2- to 4-fold over both diseases themselves, such as heart attack, stroke, ischemic heart disease, and microvascular complications (Farský *et al.*, 2018).

Multiple medical conditions have been shown to contribute to drug therapy problems (DTPs) (Gangwar *et al.*, 2014). Similarly, T2DM patients with hypertension often use polypharmacy medication and this may lead to the occurrence of drug therapy problems. Studies show that the number of DTPs per patient linearly increases with the increase in the number of medicines used (Abdulmalik *et al.*, 2019).

Several studies in some countries such as Malaysia, Ethiopia, and Nigeria about DTPs in T2DM with hypertension have shown that each diabetes patients experienced at least one of drug therapy problems (Huri & Wee, 2013; Yimama *et al.*, 2018; Argaw *et al.*, 2019; Hussen & Daba, 2017; Ayele *et al.*, 2018; Ogbonna *et al.*, 2014). Drug therapy problems may lead to elevating morbidity, disability, mortality, health care cost, low adherence, and prolonged hospitalization (Nivya *et al.*, 2015; Claydon-Platt *et al.*, 2012).

In Indonesia, hypertension is a common comorbidity in T2DM patients. However, Indonesia has no adequate and comprehensive studies on DTPs, particularly among T2DM patients with hypertension comorbidity. The aims of this study are to determine pattern prescription of antidiabetic and antihypertensive agents, to assess the prevalence of potential drug therapy problems, and to identify determine of drug therapy problems among T2DM patients with hypertension comorbidity.

MATERIALS AND METHODS

This is a retrospective cross-sectional study design that was conducted in the inpatient ward of secondary care hospital in West Java Indonesia. This study has approval by the hospital education and ethics committee No. 100/DIR/RSAB-BKS/1/2015. A total of 190 patients who admitted to the hospital from January until December 2014 and meet the inclusion criteria. The inclusion criteria were:

1. Adult patient (≥ 40 years old)
2. Diagnosed T2DM with hypertension comorbidity
3. Prescribed at least one antidiabetic agent and antihypertensive agent

The exclusion criteria are patients with the pregnant condition. Data collected from the medical record and the prescriptions of T2DM with hypertension comorbidity. The identified of DTPs was classified based on pharmaceutical care practice the third edition were:

1. Unnecessary drug therapy
2. Need additional drug therapy
3. Ineffective drug therapy
4. Dosage too low
5. Dosage too high
6. Adverse drug reaction
7. Non-adherence/non-compliance (Cipolle *et al.*, 2012).

This study was performed a descriptive analysis of demographic characteristics, pattern prescriptions antidiabetic and antihypertensive agents, as well as type and cause of DTPs.

RESULTS AND DISCUSSION

Demographic characteristics

As many as 190 patients included in this study. More than half of the patients were female (53.68%). The age range of the majority of patients was 50-59 years (46.84%), followed by 60-69 years (30.53%), 40-49 years (12.10%), 70-79 years (8.95%), and more than 80 years (1.58%).

These results were in the line with Zazuli *et al.* (2017) and Ayele *et al.* (2018) who reported majority T2DM patients with hypertension comorbidity were female and age range under 56 years old. Contrasting to Yimama *et al.* (2018) and Argaw *et al.* (2019) who reported that majority T2DM patients and hypertension comorbidity were males. This result pointed risk of hypertension disease in T2DM patients equally between each gender.

Prescription patterns of antidiabetic and antihypertensive agents

Among the participants, only 26.84% received monotherapy antidiabetic. Of the total participants, 73.16% received between two until five antidiabetic agents. Metformin (63.16%) followed by glimepiride (46.84%) were the most frequently antidiabetic agents prescribed as monotherapy and combination with other antidiabetic agents, as presented in **Table I**. This result supported by Yimama *et al.* (2018), Argaw *et al.* (2019), Ayele *et al.* (2018), and Ogbonna *et al.* (2014) who reported metformin as the most antidiabetic agent prescribed for monotherapy or combination. This study contrasts with Zazuli *et al.* (2017) who reported insulin was the most prescribed as monotherapy and combination. Polypharmacy antidiabetic prescriptions are one of the factors identified to influence non-adherence in T2DM patients with hypertension (Atinga *et al.*, 2018).

Table I. Patterns prescription of antidiabetic agents in T2DM with hypertension (n = 190)

Variable category	N (%)
Number of prescription	
Monotherapy	51 (26.84)
2 antidiabetic agents	90 (47.37)
3 antidiabetic agents	35 (18.42)
4 antidiabetic agents	10 (5.26)
5 antidiabetic agents	4 (2.11)
Type of antidiabetic agents	
Metformin*	120 (63.16)
Glibenclamide	10 (5.26)
gliquidone	31 (16.32)
Glimepiride*	89 (46.84)
Pioglitazone	2 (1.05)
Acarbose	7 (3.68)
Linagliptine	36 (18.95)
Sitagliptine	43 (22.63)
Vidagliptine	14 (7.37)
Insulin	15 (7.89)

Combined antidiabetic agents	
Acarbose + Glimepiride	2 (1.05)
Acarbose + Glimepiride + Linagliptin	1 (0.53)
Acarbose + Glimepiride + Metformin	2 (1.05)
Gliquidone + Glimepiride + Metformin + Linagliptin	1 (0.53)
Gliquidone + Linagliptin	2 (1.05)
Gliquidone + Sitagliptin	2 (1.05)
Gliquidone + Metformin + Linagliptin	4 (2.11)
Gliquidone + Metformin + Linagliptin + Sitagliptin + Vidagliptin	4 (2.11)
Glimepiride + Metformin + Linagliptin	6 (3.16)
Glimepiride + Metformin + Sitagliptin	8 (4.21)
Glimepiride + Metformin + Vidagliptin + Sitagliptin	4 (2.11)
Glimepiride + Metformin + Linagliptin + Sitagliptin	4 (2.11)
Glimepiride + Linagliptin	5 (2.63)
Glimepiride + Sitagliptin	2 (1.05)
Glimepiride + Pioglitazon	1 (0.53)
Metformin + Glibenclamid	4 (2.11)
Metformin + Glimepiride	4 (2.11)
Metformin + Gliquidone	6 (3.16)
Metformin + Gliquidone + Glimepiride	6 (3.16)
Metformin + Glimepiride	37 (19.47)
Metformin + Linagliptin	6 (3.16)
Metformin + Sitagliptin	10 (5.26)
Metformin + Vidagliptin	4 (2.11)
Insulin + Acarbose	1 (0.53)
Insulin + Gliquidone	3 (1.68)
Insulin + Gliquidone + Linagliptin	1 (0.53)
Insulin + Glimepiride + Metformin	2 (1.05)
Insulin + Glimepiride + Metformin + Sitagliptin	1 (0.53)
Insulin + Metformin	5 (2.63)
Insulin + Metformin + Sitagliptin	1 (0.53)

* The most prescribed antidiabetic agents

Hypertension is a common comorbidity in diabetic patients, and adequate blood pressure control significantly reduces the risk of macrovascular and microvascular complications. More than half of the participants (63.26%) received more than one antihypertensive agent. This study is in line with Hussen *et al.* (2017) who reported more than half of patients (62.7%) received a combination of two or more antihypertensive drugs. Amlodipine (34.74%) followed by furosemide (17.90%), candesartan (16.84%), captopril (13.68%), and bisoprolol (12.63%) were the five most prescribed antihypertensive agents, as shown in **Table II**. This result is supported by Zazuli *et al.* (2017) who reported amlodipine to be the most prescribed antihypertensive agent in diabetic patients with hypertension. However, these results contradict with study by Yimama *et al.* (2018), Argaw *et al.* (2019), and

Ayele *et al.* (2018) who reported enalapril as the most commonly prescribed antihypertensive drug. This study also contrasts with Hussen *et al.* (2017) who reported the most commonly prescribed antihypertensive medication was hydrochlorothiazide (41.4%). These results confirm that country differences play a very important role in the most prescribed type of antihypertensive agents.

The target blood pressure in T2DM with hypertension is 130/80 mmHg. Initial treatment for T2DM patients depends on the severity of hypertension. Those who have blood pressure between 140/90 to 159/99 mmHg should start with monotherapy. Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor blockers (ARB) are recommended as initial treatment in diabetic patients with hypertension. For patients with blood pressure $\geq 160/100$ mmHg, initial therapy with two antihypertensives is recommended. However, the use of both ACE inhibitors and ARBs in combination is not recommended due to increased side effects such as hyperkalemia, syncope, and acute kidney injury (de Boer *et al.*, 2017). The combination of ACE inhibitors or ARBs with calcium-channel blockers (CCBs) is preferred for nephroprotective, angioprotective, and metabolic effects. This drug is used for normotensive T2DM patients for albuminuria, retinopathy, and stroke prevention (Farský *et al.*, 2018).

Table II. Patterns prescription of antihypertensive agents in T2DM with hypertension (n = 190)

Variable category	N (%)
Number of prescription	
Monotherapy	85 (44.74)
2 anti-hypertension agents	71 (37.37)
3 anti-hypertension agents	22 (11.58)
4 anti-hypertension agents	10 (5.26)
5 anti-hypertension agents	2 (1.05)
Type of antihypertensive agents	
Captopril*	26 (13.68)
Ramipril	3 (1.58)
Candesartan*	32 (16.84)
Irbesartan	8 (4.21)
Telmisartan	8 (4.21)
Valsartan	5 (2.63)
Furosemide*	34 (17.90)
Bisoprolol*	24 (12.63)
Amlodipine*	66 (34.74)
Diltiazem	3 (1.58)

Atenolol	1 (0.53)
Carvedilol	6 (3.16)
Hydrochlorothiazide	1 (0.53)
Losartan	1 (0.53)
Spiroolakton	6 (3.16)
Nifedipin	6 (3.16)
Popranolol	1 (0.53)
Combined antihypertensive agents	
Amlodipine + Atenolol	1 (0.53)
Amlodipine + bisoprolol	9 (4.74)
Amlodipine + Bisoprolol + Furosemida	1 (0.53)
Amlodipin + Bisoprolol + Irbesartan + Captopril	2 (1.05)
Amlodipin + Bisoprolol + Candesartan + Ramipril	1 (0.53)
Amlodipin + Bisoprolol + Captopril	2 (1.05)
Amlodipin + Furosemida Injection	4 (2.11)
Amlodipin + Furosemida	2 (1.05)
Amlodipin + Irbesartan	6 (3.16)
Amlodipin + Candesartan	8 (4.21)
Amlodipin + Irbesartan + Spiroolakton	1 (0.53)
Amlodipin + Candesartan + Bisoprolol	1 (0.53)
Amlodipin + Candesartan + Furosemida	1 (0.53)
Amlodipin + Captopril	11 (5.79)
Amlodipin + Captopril + Furosemid	1 (0.53)
Amlodipin + Captopril + Losartan	1 (0.53)
Amlodipin + Captopril + Nifedipin	1 (0.53)
Amlodipin + Carvedilol + Furosemid	1 (0.53)
Amlodipin + Propranolol	1 (0.53)
Amlodipin + Telmisartan + Furosemid Injection	1 (0.53)
Amlodipin + Valsartan	3 (1.58)
Bisoprolol + Diltiazem	1 (0.53)
Bisoprolol + Furosemid Injection	3 (1.58)
Bisoprolol + Furosemida Injection + Telmisartan	2 (1.05)
Bisoprolol + Irbesartan	1 (0.53)
Bisoprolol + Candesartan	1 (0.53)
Bisoprolol + Candesartan + Furosemida	1 (0.53)
Bisoprolol + Candesartan + Furosemida + Furosemida Injection	1 (0.53)
Bisoprolol + Candesartan + Furosemida + Spiroolakton	1 (0.53)
Bisoprolol + Carvedilol + Candesartan + Furosemida + Furosemida Injection	1 (0.53)
Bisoprolol + Candesartan + Nifedipine	1 (0.53)
Bisoprolol + Captopril	5 (2.63)
Bisoprolol + Captopril + Furosemida Injection	1 (0.53)
Bisoprolol + Captopril + Nifedipine	2 (1.05)
Bisoprolol + Captopril + Nifedipine + Irbesartan + Diltiazem	1 (0.53)
Bisoprolol + Ramipril	1 (0.53)
Bisoprolol + Telmisartan	1 (0.53)
Furosemida injection + Furosemida + Carvedilol + Spiroolakton	1 (0.53)
Furosemida injection + Captopril	1 (0.53)
Furosemida injection + Telmisartan	1 (0.53)
Furosemida + Candesartan	1 (0.53)
Furosemida + Spiroolakton + Carvedilol	1 (0.53)
Irbesartan + Nifedipin	1 (0.53)
Candesartan + Furosemida injection	2 (1.05)
Candesartan + Furosemida + Furosemida injection	1 (0.53)
Candesartan + Captopril	2 (1.05)
Candesartan + Nifedipine	1 (0.53)
Candesartan + Valsartan + Furosemida + Spiroolakton	2 (1.05)
Captopril + Furosemida innjection	1 (0.53)
Captopril + Irbesartan + Furosemida injection	1 (0.53)
Captopril + Telmisartan + Furosemida	1 (0.53)

Captopril + Nifedipine	1 (0.53)
Ramipril + Furosemida injection	1 (0.53)
Furosemida + Spironolakton	1 (0.53)
Telmisartan + Carvedilol + Furosemida + Furosemida injection	1 (0.53)
Valsartan + Hydrochlorothiazide	1 (0.53)
Valsartan + Carvedilol	1 (0.53)

* The most prescribed antihypertensive agents

Treatment of diabetes with comorbid hypertension in COVID-19

At present, in the condition of the pandemic novel coronavirus 2019 (COVID-19), diabetic comorbidities are one of the risk factors for hospitalization and death due to COVID-19. Diabetes was a comorbidity in 22% of non-survivors in a study of 52 intensive care patients (Yang *et al.*, 2020). Other comorbidities such as hypertension in about 20% of cases, cardiovascular disease (16%), and lung disease (6%) are other common comorbidities (Ruan *et al.*, 2020; Wu *et al.*, 2020; Li *et al.*, 2020). In fact, patients with T2DM are at high risk for infection and suffer severe symptoms of COVID-19, including bacterial pneumonia which can be reduced through good blood glucose control (Critchley *et al.*, 2018). Basal-bolus insulin or insulin pump therapy will be preferred in T2DM patients to avoid hyperglycemia and ketoacidosis. It also requires monitoring of blood glucose levels and setting insulin doses to prevent hypoglycemia (Apicella *et al.*, 2020).

The other most common comorbidities in COVID-19 patients besides diabetes are hypertension. Both of these diseases are often treated with ACE inhibitors and ARBs. COVID-19 binds to target cells via angiotensin-converting enzyme 2 (ACE2) expressed in epithelial cells in the lungs, blood vessels, and in the intestine (Wan *et al.*, 2020). Patients treated with ACE inhibitors and ARBs showed an increase in the number of ACE2 (Li *et al.*, 2017). Therefore, there are two hypothetical drugs of choice in comorbid hypertension in COVID-19 infections. Hypothesis by Fang *et al.* (2020) suggests that COVID-19 patients with hypertension, diabetes, and cardiovascular disease treated with ACE inhibitors and

ARBs should monitor ACE2 counts or consider other antihypertensives, CCBs as therapies that are known to not increase the amount of ACE2 expressed and their activities because it can be an appropriate alternative depending on the patient's condition. Another hypothesis by Singh *et al.* (2020) emphasize because of the lack of evidence for the benefits or dangers of using ACE inhibitors and ARBs in patients with diabetes and hypertension with COVID-19, it makes sense for patients to continue using both. This is the following recommendation by the European Society of Cardiology, Hypertension Canada, The Canadian Cardiovascular Society, the UK Renal Association, the International Society of Hypertension, the European Society of Hypertension, and the American Heart Association.

Drug therapy problems

Among the participants, more than half of the participants (56.84%) have at least one of DTPs. The number of DTPs finding is lower than Yimama *et al.* (2018) and Shareef *et al.* (2015), where 82% and 71.1% of participants at least had one of DTPs, respectively. A total of 108 DTPs was identified across the six categories as presented in Table III. Adverse drug reaction was the highest 51 cases (47.22%), followed by ineffective drug therapy 32 cases (29.63%), unnecessary drug therapy 19 cases (17.6%), as well as need additional therapy, dose too low, and dose too high, each of them with two cases (1.85%). These study findings supported by Nazilah *et al.* (2017), Lira *et al.* (2017), and Hartuti *et al.* (2019), which highlighted adverse drug reaction and drug interaction as most common DTPs occurred during polypharmacy treatment prescribed. Potential adverse drug reaction event in the combination of medications treatment higher than single medication treatment. This study contrasting to another study who reported the most common drug therapy problems was the need for additional drug therapy (Yimama *et al.*, 2018; Argaw *et al.*, 2019; Hussen *et*

al., 2017). Percentage of DTP events in this study is visualized in **Figure 1**.

Table III. Causes of DTPs among T2DM with hypertension in hospital setting (n= 108)

Category of DTPs	Causes of DTPs	Frequency (%)
Adverse drug reaction	Drug interaction	32 (29.63)
	Contraindication	19 (17.59)
Ineffective drug therapy	Not the most effective for medical problem	32 (29.63)
Unnecessary drug therapy	Not valid medical indication for the drug therapy at this time	19 (17.60)
Need additional therapy	To attain synergistic/additive effect	2 (1.85)
Dosage too low	Dosage regime not frequent enough	2 (1.85)
Dosage too high	Dosage regime too frequent	2 (1.85)

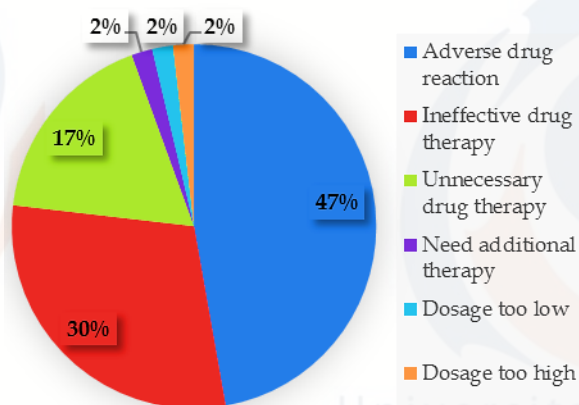


Figure 1. Percentage of DTP events

Among these DTPs, adverse drug reactions were the most common DTP category (47.22%). The possible causes of this DTPs were drug interaction (29.63%) and contraindications (17.59%). Potential drug interactions include antidiabetic and antibiotic, antihypertensive and antifungal, and fellow antihypertensive. Drug interactions may occur in the pharmacokinetic phase caused by inhibitory metabolic mechanisms. Possible side effects are an increased risk of heart blockage and an increased effect of hypoglycemia (Baxter, 2009). The possible drug interactions that occur are presented in **Table IV**.

Table IV. Determinant of drug-drug interaction in T2DM patients with hypertension (n= 32)

Drug-drug interaction	Mechanism	Category	N
Glimepiride-Levofloxacin/Moxifloxacin	Potential to elevate hypoglycemia effect	Pharmacokinetics	12
Amlodipine-Fluconazole	Decrease amlodipine metabolism, might be increase risk of heart block	Pharmacokinetics	3
Atenolol-Amlodipine	Increase risk of heart block	Pharmacokinetics	1
Bisoprolol-Diltiazem	Increase risk of heart block	Pharmacokinetics	1
Bisoprolol-Nifedipine	Increase risk of heart block	Pharmacokinetics	2
Bisoprolol-Insulin	Potential to elevate hypoglycemia effect	Pharmacokinetics	3
Ramipril-Spironolacton	Potential to elevate hypoglycemia effect	Pharmacokinetics	1
Bisoprolol-Amlodipine	Increase risk of heart block	Pharmacokinetics	9

In this study, ineffective drug therapy (29.63%) and unnecessary drug therapy (17.60%) were the second and third most potential DTPs, respectively. Ineffective drug therapy was found in 32 T2DM patients with hypertension who received furosemide because the antihypertensive treatment might be involved in glucose tolerance. Meanwhile, the drug of choice for hypertension with diabetes based on guidelines recommends the use of ACE inhibitors or ARBs or non-dihydropyridine CCBs (James et al., 2014). Unnecessary drug therapy in 10 patients who received antibiotics and nine patients received gastrointestinal drugs without clear indications. Need additional therapy, the dose is too low, and the dose is too high, each only 1.85% of the total DTPs. This insignificant amount might be due to the study being conducted in patients who were hospitalized, where there are better care and collaboration of health professionals with supervised drug administration. Because of the retrospective data

source in this study, non-compliance with treatment was excluded to be assessed in this study.

There are several limitations to this study. First, this study is not from an evaluation of prospective structures or interviews with patients. Second, this study did not assess treatment compliance among T2DM patients with hypertension. However, this study has several advantages, including this research which is a pioneer in the study of DTPs assessment in T2DM patients with hypertension. Besides, this study proposes insights for the drug of choice in T2DM patients and hypertension who are infected with COVID-19.

CONCLUSION

This study highlights the majority of T2DM patients with comorbid hypertension who have at least one drug therapy problem that might have an impact on treatment goals and treatment costs. The role of pharmacists in drug management by detecting, preventing, and solving drug therapy problems can be encouraged to deal with these problems.

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