

# Clinical Pharmacoepidemiology Study of Antihypertensive and Antidiabetes Mellitus Drug in DM-Hypertensive Outpatient in a Private Hospital

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**Abstract**—Diabetes mellitus and hypertension are degenerative diseases that require long-term treatment. This study aims to describe the anti DM and antihypertensive drug therapy, clinical output, and the relationship of combination therapy with the clinical output of DM patients with hypertension in private hospitals in Yogyakarta. This study included an observational analytic study with a retrospective cohort design. The sample in this study were 100 DM patients with hypertension with ICD E.11.9 and I.10. The data obtained were analyzed by univariate and bivariate. The bivariate analysis used was chi-square to determine the relationship between combination therapy and clinical outcomes in the form of normal blood sugar levels and blood pressure. The results showed that the most widely used antidiabetic and antihypertensive use was metformin 15.2%, metformin-insulin as part mix 18.4%, amlodipine 14%, and candesartan-amlodipine 12.6%. Most DM patients with hypertension have a blood sugar level and normal blood pressure. The chi-square test results showed that there was a correlation between combination antiDM or antihypertensive therapy with a normal status of blood sugar levels or blood pressure ( $p < 0.05$ ). The conclusion of combination antiDM treatment is not related to the increasing achievement of average blood sugar level status in DM patients with hypertension. Combined antihypertensive treatment increases the chances of DM patients with hypertension achieving normal blood pressure status.

**Keywords**—combination-therapy antihypertension, diabetes mellitus, hypertension, normal-blood pressure

## I. INTRODUCTION

Diabetes mellitus is a progressive chronic disease that has the characteristics of high blood sugar levels. Diabetes caused 1.5 million deaths in 2012. More elevated than optimal blood sugar caused an additional 2.2 million deaths. Forty-three percent of the 3.7 million deaths occur before age 70 (WHO, 2016). The number of people with diabetes mellitus in Indonesia increased from 1.1% (2007) to 2.1% (2013) with the highest prevalence of diabetes mellitus in Yogyakarta (2.6%) (Anonim, 2013). Based on the profile of the Bantul District Health Office in Yogyakarta, diabetes mellitus and hypertension have shown a significant increase in recent years and are always ranked in the top 10 outpatient diseases (District Health Office, 2016).

Diabetes mellitus can cause complications in various body systems (PERKENI, 2015). One of the difficulties of DM is hypertension. Hypertension is most often found in patients with diabetes mellitus and is a risk factor for cardiovascular and microvascular complications in diabetic patients (Fatimah, 2016). Control of the risk of other diseases in diabetes mellitus accompanied by hypertension is done by controlling blood glucose levels and blood pressure with antiDM drugs or antihypertensive drugs. Patients with diabetes mellitus with complications of hypertension often receive several medicines or more than one type of antiDM or antihypertensive drugs with long-term use. The use of combination drugs can cause problems related to drugs or refer to as Drug-Related Problems (DRP), but the accuracy in the selection of drugs is essential to achieve the target blood sugar and blood pressure DM patients with hypertension to avoid further complications (Munger, 2010). The study of the use of antidiabetic drugs and antihypertension carried out at Panembahan Senopati General Hospital Bantul Yogyakarta strengthens that rational treatment can increase the achievement of clinical outcomes in the form of blood glucose levels and blood pressure so that there is a significant relationship between the therapy given to clinical outcomes (Fatimah, 2016). The researcher is interested in conducting research on (i) How is the use of antidiabetic and antihypertensive drugs in patients with diabetes mellitus with complications of hypertension outpatient in PKU Muhammadiyah Hospital Bantul, July 2017 - June 2018 ?, (ii) Is there a relationship between therapy antiDM or antihypertensive combination with blood sugar level or blood pressure control in DM patients with hypertension.

## II. RESEARCH METHODS

### A. Type and Design of Research

This study evaluating the accuracy of antidiabetic and antihypertensive therapy included observational analytic (non-experimental) studies because it did not intervene or treat patients. The design of this study used a retrospective cohort using secondary data obtained through medical records.

Data collection was carried out by recording medical record data of patients with diabetes mellitus complicated by hypertension from July 2017 to June 2018. Analytical data presentation to see the accuracy of therapy included precise

indications, specific drugs, appropriate patients, correct dosages and the relationship between the efficiency of treatment and clinical outcome in patients who were diagnosed with diabetes mellitus with complications of hypertension in PKU Muhammadiyah Hospital Bantul period July 2017 - June 2018.

### B. Research Population and Samples

The target population in this study were patients diagnosed with diabetes mellitus-hypertension. The affordable community in this study were patients with diabetes mellitus with complications of hypertension who underwent treatment at the outpatient installation of PKU Muhammadiyah Hospital, Bantul, Yogyakarta for the period July 2017 - June 2018.

The samples used in this study were patients diagnosed with diabetes mellitus with complications of hypertension who were treated at the outpatient installation of PKU Muhammadiyah Hospital, Bantul, Yogyakarta for the period July 2017 - June 2018 that fulfilled the inclusion and exclusion criteria. Estimated number of samples in this study is based on calculations using the openepi.com application. The proportion used was the results of Fatimah's study (2016), namely the percentage of rational categories that achieved 56% clinical outcome and irrational groups that reached 15% clinical outcome, so that a minimum sample size of 50 was obtained. The sampling technique used purposive sampling was medical record data to fulfil the conditions of inclusion and exclusion criteria. Patients who qualify as samples are patients with inclusion criteria as follows: (i) Patients diagnosed with diabetes mellitus with complications of hypertension outpatient at PKU Muhammadiyah Hospital Bantul period July 2017 - June 2018. (ii) Patients No. 1 with restrictions on comorbidities such as metabolic syndrome, stroke, kidney disease, and neuropathy. (iii) Patients receive antidiabetic and antihypertensive therapy during outpatient care. (iv) Male or female patients aged  $\geq 18$  years.

Patients who routinely control at least five consecutive months. While patients who did not qualify as research subjects were patients with exclusion criteria as follows: (i) Pregnant patients. (ii) Breastfeeding patients. (iii) Medical record data is incomplete, such as no patient age, drug dosage, drug usage rules, TD and GDS results.

### C. Materials and Tools

The material used in this study was medical record data of patients with hypertensive diabetes with complications of hypertension who were treated at the outpatient installation of PKU Muhammadiyah Hospital, Bantul, Yogyakarta period July 2017 - June 2018.

The research tool used was a data retrieval sheet to collect data taken from the patient's medical record including patient identity (age, sex, occupation), diagnosis, drug used and laboratory examination data in the form of blood sugar levels and blood pressure.

### D. Variables Operational

The independent variables in this study were single or combination antiDM or antihypertensive drugs. The dependent variable in this study was the clinical outcome in the form of normal blood sugar levels and blood pressure.

Patients referred to in this study were patients with diabetes mellitus with complications of hypertension as well as using antidiabetic drugs and antihypertensive patients who were treated at the outpatient installation of PKU Muhammadiyah Bantul Hospital for a minimum of 5 months. Patients with diabetes mellitus are patients diagnosed by a doctor and written in the medical record with ICD E.11.9 and ICD I.10. Hypertensive patients are patients diagnosed by a doctor in the medical record with ICD E.11.9 and ICD I.10. Patient demographic data includes patient characteristics, including the following: Gender is information that distinguishes between women and men recorded in medical record data. Age is the age or time unit that measures the time of existence of diabetes mellitus patients with hypertension complications and is expressed in the form of years when undergoing an examination at the outpatient installation of PKU Muhammadiyah Hospital, Bantul. Age is categorized as  $<60$  years and  $\geq 60$  years. Based on the Indonesian Ministry of Health (2016) that non-communicable diseases and degenerative problems occur in the age group  $\geq 60$  years. Job is information on daily activities carried out by patients to get the income recorded in the medical record. Jobs are categorized into 5, namely civil servants, private sector, entrepreneurs, farmers, and not working.

Clinical outcome is the patient's clinical condition for five consecutive months which is marked by changes in blood sugar levels and blood pressure of patients in the fifth (final) month seen from the patient's medical record. Blood sugar level is the result of instantaneous measurement of time. In this study, blood sugar levels when divided into controlled and uncontrolled. Controlled is when there is a decrease in blood sugar levels during the fifth (final) month after antidiabetic treatment by looking at the blood sugar level when (GDS  $<200$  mg / dL). Uncontrolled is when the target blood sugar level when not reached in the fifth month (end) after antidiabetic treatment. Blood pressure is a measure of how healthy the heart is to pump blood throughout the body, usually described by the ratio of systolic pressure to diastolic pressure. In this study, blood pressure was divided into controlled and uncontrolled. Controlled is when there is a decrease in blood pressure in the fifth (final) month after antihypertensive treatment by looking at the patient's blood pressure  $<140/90$  mmHg. Uncontrolled is when the blood pressure target is not reached in the fifth (final) month after antihypertensive treatment.

### E. Research Procedure

The process of this research begins with the preparation stage such as making proposals, arranging research permit documents from the university, making an ethical clearance, making research permit letters to PKU Muhammadiyah Hospital Bantul Yogyakarta and preliminary studies.

We collected data from medical records patients with diabetes mellitus and hypertensive complications that are by the research criteria. Data taken includes patient identity (name, age, gender, occupation), medical record number, date of patient control to hospital, patient diagnosis, laboratory data, drug use, and results of blood sugar levels (BSL) and

blood pressure (BP). The medical record data is recorded on the data retrieval sheet.

#### F. Data Analysis

Univariate analysis was used to determine the description of patient characteristics including age, sex, occupation, other comorbidities, clinical outcomes, antidiabetic and antihypertensive use and to describe the percentage of achievement of therapy targets.

Bivariate analysis using the SPSS statistical program was used to determine the relationship between antidiabetic and antihypertensive combinations with clinical outcomes in the form of normal blood sugar levels and blood pressure status. The bivariate analysis used is chi-square if the analysis results are obtained ( $p < 0.05$ ) then there is a correlation between the accuracy of therapy with clinical outcomes, but if a value is obtained ( $p > 0.05$ ) there is no relationship between the variables tested.

### III. RESULTS AND DISCUSSION

This study was an observational analytic (non-experimental) study using a retrospective cohort method design that aimed to determine the accuracy of antidiabetic and antihypertensive therapy and the relationship of accuracy of treatment with clinical outcomes in the form of current blood sugar levels and blood pressure in outpatient hypertensive diabetic patients in hospitals PKU Muhammadiyah Bantul period July 2017-June 2018. Evaluation of the accuracy of therapy is reviewed based on the exact parameters, the right medication, the right patient, and the correct dose. Data collection was carried out from September 2018 to February 2019. Data were obtained from medical record of patients with diabetes mellitus with ICD E.11.9 and I.10. The sample used as many as 100 outpatients in PKU Muhammadiyah Bantul Hospital who fulfilled the inclusion criteria. We analysed 500 recipes from 100 outpatients care.

#### A. Patient Characteristics

Based on the results of observations of patients with diabetes mellitus data obtained from medical record data at PKU Muhammadiyah Hospital in Bantul for the period July 2017-June 2018, there were 280 patients diagnosed with diabetes mellitus-hypertension. Patients with diabetes mellitus who met the inclusion criteria were subjected to 100 patients from 280 patients. The characteristics of patients in this study are presented. Table I covering age, gender, and occupation.

TABLE I. CHARACTERISTICS OF DIABETIC PATIENTS WITH DIABETES MELLITUS IN PKU MUHAMMADIYAH HOSPITAL BANTUL JULY 2017-JUNE 2018 PERIOD (N= 100)

Characteristic	Patient Number (N)	Percentage (%)
Age		
< 60 year	43	43
≥ 60 year	57	57
Total	100	100
$\bar{X}$ age = 60,4 year		
Sex		
Male	42	42
Female	58	58
Total	100	100
Job		
civil servants	21	21

Privat job	20	20
Entrepreneur	15	15
Farmer	5	5
Labour	39	39
Total	100	100

Characteristics of patients with outpatient diabetes mellitus in PKU Muhammadiyah Hospital Bantul according to age are grouped into periods <60 years and ≥ 60 years. Based on the results of the study in Table VI, the characteristics of age <60 years were 43 patients (43%) while those aged ≥ 60 years were 57 patients (57%) with an average age of 60.4 years. These results indicate that patients with outpatient diabetes mellitus-hypertension in the period July 2017-June 2018 suffer more from the age group ≥ 60 years than the age group <60 years. Age addition is one factor of the many occurrences of diabetes mellitus. By the Indonesian Ministry of Health (2016) wherewith increasing age, physiological functions decline due to the aging process so that many non-communicable diseases appear in the elderly including hypertension, arthritis, stroke, COPD, and diabetes mellitus.

This research is also in line with a study conducted at Panembahan Senopati Hospital Bantul, the prevalence of people with diabetes mellitus at age <60 years is 44.9% while at age ≥ 60 years is 55.1% (Paramitha, 2018). In the elderly, there is a decrease in the ability of insulin secretion by beta cells and insulin resistance. Factors causing insulin resistance in the elderly include a reduction in body mass beyond fat and an increase in fat, especially in the stomach (central obesity) that often accompanies aging (Suastika, 2018).

The results of the study based on the sex characteristics of patients with outpatient hypertensive diabetes mellitus in PKU Muhammadiyah Hospital Bantul in Table I showed that patients with female sex were more (58%) compared to male patients (42%). Paramitha study (2018) in Panembahan Senopati General Hospital Bantul also showed that patients with diabetes mellitus with outpatient hypertension complications were predominantly female, namely 55.1% compared to men 44.9%. Women are more at risk of developing diabetes because physically, women have a higher chance of increasing their body mass index. In addition to the monthly cycle syndrome (premenstrual syndrome), post-menopause, which makes the distribution of body fat quickly accumulated due to hormonal processes (Irawan, 2010).

Based on the characteristics according to the work of patients with outpatient diabetes mellitus in PKU Muhammadiyah Hospital in Bantul grouped into jobs of civil servants, the private sector, entrepreneurs, farmers, and not working. The results of the research listed in Table VI show that there are more outpatients in outpatient diabetes mellitus in PKU Muhammadiyah Hospital, Bantul, as many as 39 patients (39%). The type of work affects the level of physical activity and is closely related to diabetes mellitus. People who don't work tend to lack physical activity while glucose can be converted into energy during physical activity.

Physical activity causes the sensitivity of the insulin receptor to increase so that the blood glucose used for energy metabolism is getting better. Other benefits of physical activity can also keep blood pressure stable within normal limits (RI Ministry of Health, 2010). Consistent with research conducted by Wahyuni (2010), which shows that there is a



significant relationship between work and the incidence of diabetes mellitus. People who do not work tend of 1.39 times to experience the incidence of diabetes mellitus.

### B. Clinical Characteristics and Co-Morbidities

Clinical symptoms and comorbidities of patients with diabetes mellitus with hypertension and concomitant diseases are presented in Table II.

TABLE II. CLINICAL CHARACTERISTICS AND CO-MORBIDITIES OF DIABETIC- HYPERTENSION OUTPATIENT, PKU MUHAMMADIYAH BANTUL HOSPITAL PERIOD JULY 2017-JUNE 2018

Clinical characteristic	Number	Percentage
Blood Glucose level at random		
Normal < 200 mg/dL	79	79
hyperglycemia ≥ 200 mg/dL	21	21
Blood pressure		
Normal < 140/90 mmHg	51	51
hypertension ≥ 140/90 mmHg	49	49
Comorbidity:		
DM HT Neuropathy DM	23	23
DM HT Dyslipidemia	16	16
DM HT OA	6	6
DM HT Stroke	5	5
DM HT PAD	3	3
DM HT CKD	3	3

Note: DM: Diabetes Mellitus; HT: Hipertensi; OA: Osteoarthritis; PAD: Peripheral Artery Disease; CKD: Chronic Kidney Disease

Table II shows that outpatient hypertensive diabetes mellitus patients at PKU Muhammadiyah Bantul Hospital in the period July 2017-June 2018 were more likely to have had blood sugar levels and controlled blood pressure than those who were uncontrolled as many as 79 patients and 51 patients. Table II showed that patients suffering from diabetes mellitus with accompanying DM neuropathy were 23 patients (23%). Patients with diabetes mellitus for a long time can cause complications of diabetic neuropathy. The prevalence of patients with diabetic neuropathy reaches 50%. Diabetic neuropathy is nerve damage that is focal or diffuse due to excessive blood sugar levels (Kuate-Tegueu, 2015). Patients suffering from diabetes mellitus with the accompanying dyslipidemia were 16 patients (16%). Dyslipidemia generally occurs in people with type 2 diabetes mellitus caused by disorders of lipid metabolism. Dyslipidemia in people with diabetes mellitus is characterized by increased insulin levels, low HDL cholesterol, increased LDL, and triglycerides. The low HDL cholesterol is associated with hyperinsulinemia or insulin resistance (Tangvarasittichai, 2015). Patients suffering from diabetes mellitus with an accompanying OA amounted to 6 patients (6%). Osteoarthritis is characterized by cartilage degeneration or degeneration of one or more joints. Several studies report the relationship of osteoarthritis to the duration of diabetes mellitus and poor glycemic control. Also, peripheral neuropathy in patients with diabetes mellitus can increase the risk of osteoarthritis (Nieves-Plaza et al., 2013).

Patients suffering from diabetes mellitus with hypertension with a stroke included five patients (5%). Patients suffering from diabetes mellitus with hypertension of PAD included three patients (3%). Peripheral arterial disease (PAD) is caused due to a blockage or plaque in the arteries. Plates are formed from fat, cholesterol, or other substances. Hypertension and diabetes mellitus are risk factors for peripheral arterial disease. Research by Ilminovia et al. (2015) states that there is a significant relationship between the status of diabetes mellitus and peripheral arterial disease status in

hypertensive patients. Patients with diabetes mellitus have a 2.14 times risk of the incidence of peripheral arterial disease in hypertensive patients. Patients suffering from diabetes mellitus-hypertension with CKD participants were three patients (3%). People with prolonged diabetes mellitus contribute to the emergence of various complications and damage to organs such as the eyes, nerves, heart, and kidneys. Kidney disease in diabetes mellitus is also called diabetic nephropathy, which is included in microvascular complications. High levels of sugar in the blood will make kidney function disrupted (Sari and Hisham, 2014).

### C. Drug Use Based on Drug Class

In this study, the classification of antidiabetic and antihypertensive drugs was carried out for five consecutive months. Patients with diabetes mellitus get the same or different medications on each prescription sheet while undergoing outpatient treatment for five months in a row at PKU Muhammadiyah Hospital Bantul for the period July 2017-June 2018. So that out of 100 patients with diabetes mellitus-hypertension outpatient during five months in a row, there are 500 recipe sheets. The antidiabetic drug group given to patients with diabetes mellitus is presented in Table III.

Based on Table III, a single group of oral antidiabetic drugs used by outpatient hypertensive diabetes mellitus patients at PKU Muhammadiyah Hospital in Bantul for the July 2017-June 2018 period was among them the biguanide group, sulfonylureas, and thiazolidinedione. The most widely used group of oral antidiabetic drugs is the biguanide drug group, metformin, which is 76 prescription sheets (15.2%). Metformin works by reducing glucose production (gluconeogenesis) and improving glucose uptake in peripheral tissues. Patients with dyspepsia must be considered in the use of metformin drugs because of side effects in the digestive tract that can aggravate dyspepsia (PERKENI, 2015). In type 2 diabetes, the formation of sugar by the liver exceeds normal. Metformin inhibits this process so that the need for insulin to transport sugar from the blood into the cell decreases and blood sugar drops. Metformin rarely causes hypoglycemia (Tandra, 2017). According to ADA (2018), metformin is first-line drug therapy for patients with type 2 diabetes mellitus if it is not contraindicated and when lifestyle changes and dietary patterns are not enough to reduce blood sugar levels. The single group of oral antidiabetic drugs that are widely used after metformin is the antidiabetic group of thiazolidinedione, which is pioglitazone HCl as many as 20 prescription sheets (4%). Thiazolidinedione is an agonist of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-gamma). This group has the effect of reducing insulin resistance by increasing the amount of glucose-carrying protein so that it increases glucose uptake in peripheral tissues (PERKENI, 2015).

In certain circumstances, combination therapy of several antidiabetic agents is needed, either a combination of 2 or more oral antidiabetic and antidiabetic combinations with insulin. According to ADA (2018), if the A1C target is not reached after about 3 months, and the patient does not have atherosclerotic cardiovascular disease then it can be considered using a combination of metformin and one of six antidiabetic treatment options, including sulfonylurea,

thiazolidinedione, DPP-4 inhibitor, SGLT 2 inhibitors, GLP-1 receptor agonists, or basal insulin. In this study, the use of two oral antidiabetic combinations in the most widely used patients with diabetes mellitus was the biguanide group with sulfonylureas, namely metformin and gliclazide in 59

prescription sheets (11.8%). It is then followed by a combination of metformin and glimepiride as many as 26 prescription sheets (5.2%).

TABLE III. CLASSIFICATION OF 500 PRESCRIBING ANTIDIABETIC DRUGS IN DIABETIC PATIENTS WITH DIABETES MELLITUS IN PKU MUHAMMADIYAH HOSPITAL, BANTUL, JULY 2017-JUNE 2018 PERIOD

	Group	Drug name	Prescribing Number	%
<b>antiDM monotherapy</b>	Biguanid	Metformin	76	15,2
	Sulfonylurea	Gliclazide	14	2,8
		Glimepiride	5	1
	Thiazolidinedione	Pioglitazone HCl	20	4
<b>Total</b>			115	23
<b>Two antiDM combination</b>	Biguanid-Sulfonylurea	Metformin-Gliclazide	59	11,8
		Metformin-Glimepirid	26	5,2
	Biguanid-Thiazolidinedione	Metformin-Pioglitazone HCl	17	3,4
	Biguanid- <i>Inhibitor</i> Alfa Glukosidase	Metformin-Acarbose	4	0,8
	Sulfonylurea-Thiazolidinedione	Gliclazide-Pioglitazone HCl	11	2,2
		Gliquidone-Pioglitazone HCl	5	1
		Glimepiride-Pioglitazone HCl	5	1
	Sulfonylurea- <i>Inhibitor</i> Alfa Glukosidase	Gliclazide-Acarbose	5	1
	Biguanide-Insulin <i>Rapid Acting</i>	Metformin-Insulin Aspart	24	4,8
		Metformin-Insulin Lispro	5	1
	Biguanide-Insulin <i>Long-Acting</i>	Metformin-Insulin Glargine	20	4
		Metformin-Insulin Detemir	7	1,4
	Biguanid-Insulin Campuran	Metformin-Insulin Aspart Mix	92	18,4
		Metformin-Insulin Lispro Mix	25	5
	Thiazolidinedione-Insulin <i>Rapid Acting</i>	Pioglitazone HCl-Insulin Lispro	10	2
	Thiazolidinedione-Insulin <i>Long-Acting</i>	Pioglitazone HCl-Insulin Glargine	1	0,2
	<i>Inhibitor</i> Alfa Glukosidase-Insulin Campuran	Acarbose-Insulin Aspart Mix	4	0,8
<b>Total</b>			320	64
<b>Three antiDM combination</b>	Biguanid-Sulfonylurea- <i>Inhibitor</i> Alfa Glukosidase	Metformin-Gliclazide-Acarbose	4	0,8
		Metformin-Gliquidone-Acarbose	2	0,4
	Biguanid-Sulfonylurea-Thiazolidinedione	Metformin-Gliclazide- Pioglitazone HCl	13	2,6
		Metformin-Glimepirid- Pioglitazone HCl	5	1
	Biguanid-Thiazolidinedione-Insulin Campuran	Metformin-Pioglitazone HCl – Insulin Lispro Mix	1	0,2
		Metformin-Pioglitazone HCl – Insulin Aspart Mix	26	5,2
	Biguanid-Thiazolidinedione-Insulin <i>Long Acting</i>	Metformin- Pioglitazone HCl - Insulin Glargine	1	0,2
	Biguanid- <i>Inhibitor</i> Alfa Glukosidase-Insulin <i>Long Acting</i>	Metformin-Acarbose-Insulin Detemir	1	0,2
	Biguanid- <i>Inhibitor</i> Alfa Glukosidase-Insulin Campuran	Metformin-Acarbose-Insulin Aspart Mix	5	1
	<i>Inhibitor</i> Alfa Glukosidase-Thiazolidinedion-Insulin <i>Long Acting</i>	Acarbose-Pioglitazone HCl-Insulin Detemir	1	0,2
<b>Total</b>			59	11.8
<b>Four antiDM combination</b>	Biguanid- <i>Inhibitor</i> Alfa Glukosidase-Thiazolidinedione-Insulin Campuran	Metformin-Acarbose-Pioglitazone HCl-Insulin Aspart Mix	6	1,2
<b>Total</b>			6	1,2

The sulfonylurea group can reduce high blood sugar levels by stimulating the release of insulin from pancreatic beta cells. If the pancreas is damaged and can no longer produce insulin, the use of sulfonylurea drugs is no longer active (Mahendra et al., 2008). The sulfonylurea group can be combined with the biguanide group. Sulfonylurea will stimulate pancreatic secretion, which provides an opportunity for biguanide compounds to work effectively so that the combination of the two has mutually supportive effects (Saputri et al., 2016). Also, the combination of metformin and glimepiride can significantly reduce fasting blood glucose, postprandial blood glucose, HbA1c levels, and Hcy levels (Furdiyanti et al., 2017).

In patients with type 2 diabetes mellitus, if lifestyle changes have been made and blood glucose levels are not well controlled using oral antidiabetic, insulin addition should be considered. Also, the use of insulin is given to patients with special conditions such as pregnancy, surgery,

or there are complications such as stroke, kidney failure, infection or there are contraindications to the drug (Tandra, 2017). The most widely used oral antidiabetic combination with insulin in patients with hypertensive diabetes mellitus is a combination of metformin and insulin aspart mix of 92 prescription sheets (18.4%). They are then followed by a combination of metformin with pioglitazone HCl and insulin aspart mix as many as 26 prescription sheets (5.2%). Aspart mix is included in premixed insulin. Mixed insulin contained basal, and prandial insulin. The combination of metformin and insulin can provide better glycemic control; in this case, insulin can control postprandial blood glucose levels, while metformin will control fasting blood glucose. The combination of insulin with metformin also provides a small risk of hypoglycemia and weight gain compared to using insulin alone (Riddle, 2008). The group of antihypertensive drugs given to patients with :

TABLE IV. CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS IN DIABETIC PATIENTS WITH DIABETES MELLITUS IN PKU MUHAMMADIYAH HOSPITAL BANTUL JULY 2017-JUNE 2018 PERIOD (N = 500)DIABETES MELLITUS-HYPERTENSION IS PRESENTED IN TABLE IV

	Groups	Drug names	Prescribing number	%
Antihypertension Monotherapy	ARB	Valsartan	41	8,2
		Telmisartan	11	2,2
		Irbesartan	26	5,2
		Candesartan	20	4
	ACEI	Imidapril	15	3
	CCB	Amlodipin	70	14
		Diltiazem HCl	8	1,6
Total			191	38,2
Two Antihypertension combination	ARB-CCB	Valsartan-Amlodipin	25	5
		Telmisartan-Amlodipine	19	3,8
		Irbesartan-Amlodipine	60	12
		Candesartan-Amlodipin	63	12,6
		Irbesartan-Diltiazem HCl	11	2,2
		Candesartan-Diltiazem HCl	15	3
		Valsartan- Diltiazem HCl	12	2,4
		Telmisartan-Diltiazem HCl	10	2
	ARB-Diuretik	Irbesartan-Furosemid	3	0,6
	ARB-Diuretik Thiazide	Candesartan-Hydrochlorothiazide	5	1
	ACEI-CCB	Imidapril-Amlodipine	25	5
		Perindopril Arginine-Amlodipine	13	2,6
		Imidapril-Diltiazem HCl	5	1
	CCB-Beta Bloker	Amlodipin-Bisoprolol	1	0,2
		Diltiazem HCl-Bisoprolol	5	1
Total			272	54,4
Three antihypertension combination	ARB-CCB-Beta Bloker	Irbesartan-Amlodipin-Bisoprolol	10	2
		Candesartan-Amlodipin-Bisoprolol	3	0,6
		Valsartan-Amlodipine-Propanolol	5	1
		Candesartan- Diltiazem HCl - Bisoprolol	1	0,2
	ARB-CCB-Diuretik	Valsartan-Amlodipin-Spironolakton	5	1
		Irbesartan- Diltiazem HCl - Spironolakton	5	1
	ACEI-CCB-Diuretik Thiazide	Imidapril-Amlodipine-Hydrochlorothiazide	5	1
Total			34	6,8
Four antihypertension	ARB-CCB-Beta Blocker-Diuretik Thiazide	Candesartan-Amlodipine-Bisoprolol-Hydrochlorothiazide	3	0,6
Total			3	0,6

The antihypertensive drug group used in outpatient hypertensive diabetes mellitus patients at PKU Muhammadiyah Bantul Hospital in the period July 2017-June 2018 included ARB, CCB, ACEI, diuretics, and beta blockers. Based on table X, the most widely used single class of antihypertensive drugs is the ARB group (19.6%). Giving ARB is indicated in patients who are intolerant of ACEI. The mechanism of action of ARB is almost similar to ACEI, but the side effects of ARB drugs are less than those of ACEI, especially the effects of dry cough. ARB works by blocking or directly holding the angiotensin I receptor, which is a receptor that mediates the effects of angiotensin II (Dipiro et al., 2015). In this study, a single widely used antihypertensive drug was amlodipine with 70 prescription sheets (14%). Amlodipine belongs to the antihypertensive group CCB with a mechanism of action that slows the rate of calcium through the heart muscle and which enters the blood vessel walls. Amlodipine makes the blood vessels relax and smooth blood flow (Anonim, 2009).

Most CCB groups are combined with ARB antihypertensive groups (43%). The most widely used antihypertensive combination was a combination of candesartan and amlodipine, namely 63 prescription sheets (12.6%). The combination of CCB and ARB has an antiproteinuric effect, so it is useful to prevent the occurrence of diabetic nephropathy in patients with type 2 diabetes mellitus accompanied by hypertension (Kalra et al., 2010). This combination has a synergistic effect with a different mechanism in reducing blood pressure and the side effects of peripheral edema because the use of a single CCB significantly decreases when combined with ARB groups [ (Oktianti et al., 2017)]. Based on the 2014 JNC 8 guideline, treatment of hypertension recommended in patients with diabetes mellitus complicated by hypertension is a class of thiazide diuretics, ACEI, ARB, or single or combination CCB. Hypertensive patients who have difficulty achieving the therapeutic target need a combination of therapy 2 or more drugs to reduce blood pressure.

#### D. Relationship to Antidiabetic or Antihypertensive therapy in Combination with Blood Glucose Level and Blood Pressure Normal

The association of combination or single antiDM or antihypertensive treatment with clinical outcomes aims to determine the effectiveness of antiDM or antihypertensive in achieving the therapeutic target. Analysis of the relative risk of antidiabetic and antihypertensive therapy in clinical outcomes is presented in tables V and VI.

The results of the study in Table V show that 79% of DM patients with hypertension reach the target of therapy which is having normal blood sugar levels (<200 mg/dl) and 21% of DM patients with hypertension not yet achieving the goal of treatment. Opportunities for DM patients with hypertension have a controlled blood sugar level status with single antiDM treatment is 78.26% while combination antiDM therapy is 79.22%. The relative risk of DM patients with hypertension who receive combination antidiabetic therapy with controlled blood sugar level status is 1,012 (CI95%: 0.793 - 1,292, p> 0.05). Based on the results of the study, it is known that the use of a combination or single antiDM drugs is not associated with an increased chance of having a controlled blood sugar level status in DM patients with outpatient hypertension in PKU Muhammadiyah Hospital, Bantul, Yogyakarta.

TABLE V. RELATIVE RISK OF SINGLE AND COMBINED ANTIDIABETIC THERAPY WITH BLOOD GLUCOSE LEVELS WHEN IN OUTPATIENTS WITH DIABETES MELLITUS-HYPERTENSION IN PKU MUHAMMADIYAH HOSPITAL BANTUL JULY 2017-JUNE 2018 PERIOD.

Variable	Normoglycemia	Hyperglycemia	Total	RR
AntiDM Combination	61	16	77	1.012
AntiDM monotherapy	18	5	23	
The results of RR estimation results at 95% confidence intervals with open epi				
Type	Value	Min	max	
Risk in AntiDM combination	79.22%	68.78	86.89	Taylor series
Risk in antiDM monotherapy	78.26%	57.67	90.76	Taylor series
Overall Risk	79%	69.95	85.9	Taylor series
Risk Ratio	1.012	0.7932	1.292	Taylor series
Risk Difference	0.9599%	-18.18	20.1	Taylor series
NNT	105	-	5	

TABLE VI. RELATIVE RISK OF SINGLE ANTIHYPERTENSIVE THERAPY AND COMBINATION WITH BLOOD PRESSURE IN OUTPATIENTS WITH DIABETES MELLITUS IN PKU MUHAMMADIYAH BANTUL HOSPITAL JULY 2017-JUNE 2018 PERIOD

Variable	Normotension	hypertension	Total	
Antihypertension Combination	37	25	62	
Antihypertension monotherapy	14	24	38	
The results of the RR estimation calculation in CI95% with open epi				
Type	Value	Min	Max	type
Risk in antihypertension ombination	59.68%	47.24 %	70.99%	Taylor series
Risk in antihypertension monotherapy	36.84%	23.34 %	52.76%	Taylor series
Overall Risk	51%	41.35 %	60.58%	Taylor series
Risk Ratio	1.62	1.019	2.576	Taylor series
Risk Difference	22.84%	3.232 %	42.44%	Taylor series
NNT	4.38	30.96	2.36	

Table VI shows that as many as 51% of DM patients with hypertension reach the target of therapy, namely having a blood pressure status <140/90 mmHg and as many as 49% of DM patients with hypertension have not reached the standard blood pressure therapy target. The relative risk of patients receiving combined and single antihypertensive therapy with blood pressure obtained a value of 1,620 means that patients who received combination antihypertensive treatment had a chance or opportunity of 1,620 times to achieve controlled blood pressure compared to patients who received single antihypertensive treatment.



### E. Research Limitations

This study has limitations that can affect the results of the investigation. These limitations are.

1. This study is a retrospective study in the form of observations using medical records of patients whose time of occurrence has occurred so that they cannot ask the patient directly if there is other information needed. Some other weaknesses that may arise such as medical record data and patient laboratory data are incomplete, the writing in the medical record is difficult to read, and cannot borrow medical records at any time when used by control patients.
2. The results of the analysis of the accuracy of therapy are limited to the standards set out in the research method. When using other criteria, there will be an analysis of the results of different therapeutic accuracy.

### IV. CONCLUSIONS

Antidiabetic and antihypertensive drugs that are widely used in outpatient hypertensive diabetes mellitus patients in PKU Muhammadiyah Hospital, Bantul, Yogyakarta, July 2017-June 2018 are metformin 15.2%, metformin-insulin as part mix 18.4%, amlodipine 14%, and candesartan-amlodipine 12.6%.

There is a relationship or combination of antidiabetic or single antihypertensive therapy with clinical outcomes of normal blood pressure status, but there is no correlation with the healthy condition of blood sugar levels in outpatient hypertensive diabetes mellitus patients in PKU Muhammadiyah Hospital, Bantul, July 2017-June 2018.

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