

# Drug-related problems in Type 2 diabetic patients with hypertension in Cimahi, West Java, Indonesia: A prospective study

Zulfan Zazuli, Azmi Rohaya, I. Ketut Adnyana

*Department of Pharmacology and Clinical Pharmacy, School of Pharmacy Institut Teknologi Bandung, Bandung, Indonesia*

## Abstract

**Introduction:** Type 2 diabetic patients whom also diagnosed with hypertension often received a complex medication regimen. The situation may lead to the increased risk of drug-related problems (DRPs). The aim of the study was to identify the DRPs in Type 2 diabetic patients whom also diagnosed with hypertension in the following domains: Problems, causes, and interventions. **Subjects and Methods:** The prospective study was conducted from October to December 2015 at a secondary care hospital in Indonesia involving 90 inpatients who meet the predetermined inclusion criteria. Identification and classification of DRPs were based on the Pharmaceutical Care Network Europe version 5.01. Correlation among patient's independent factors and the number of DRPs was also analyzed using bivariate analysis. **Results:** As many as 261 DRPs were identified, averaging 2.88 (standard deviation = 0.23) problems per patient. Drug choice problem was the most frequent problems ( $n = 144$ , 55.17%) while drug/dose selection was the main causes ( $n = 184$ , 62.16%). From a total 155 interventions, the majority was conducted at patient/carer level ( $n = 94$ , 60.65%). The bivariate analysis showed that the number of medications ( $r = 0.49$ ,  $P < 0.01$ ) and the length of stay ( $r = 0.25$ ,  $P < 0.05$ ) significantly correlated with the number of DRPs. Based on linear regression analysis, the number of medications significantly predicted the number of DRPs ( $\beta = 0.50$ ,  $P < 0.001$ ). **Conclusion:** Since the risk of DRPs in Type 2 diabetic and hypertension patients is relatively high, early detection by the pharmacist is needed to ensure the safety and effectiveness of drug therapy.

**Key words:** Clinical pharmacy services, drug-related problems, hypertension, medication error, Type 2 diabetes mellitus

## INTRODUCTION

Diabetes has become a global health problem and economic burden worldwide. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. The World Health Organization estimates that adults who were living with diabetes increase from 108 million in 1980 to 422 million in 2014.<sup>[1]</sup> A study reported that global age-standardized diabetes prevalence increased from 4.3% in 1980 to 9.0 in 2014 in men and from 5.0% to 7.9% in women.<sup>[1,2]</sup> Diabetes responsible for causing 1.5 million deaths in 2012.<sup>[1]</sup> A reviewed studies addressed a large economic burden caused by diabetes, most directly affecting patients in low-middle-income countries.<sup>[3]</sup> Diabetic patients often accompanied by hypertension. This comorbid may lead to serious

cardiovascular complications, for example, heart attack, stroke, and kidney failure.

The diabetic patients are more vulnerable in experiencing drug-related problems (DRPs) than other chronic diseases since its multicomorbidity results in complexity therapeutic options.<sup>[4]</sup> Moreover, diabetes mellitus type often accompanied by various comorbidities. The situation results in increasing the risk of DRPs. Pharmaceutical Care Network Europe (PCNE) described a DRP as an event or circumstance involving drug therapy that actually or potentially interferes

### Address for correspondence:

I. Ketut Adnyana, Pharmacology and Clinical Pharmacy, School of Pharmacy Institut Teknologi Bandung, Bandung, Indonesia. E-mail: ketut@fa.itb.ac.id

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with desired health outcomes.<sup>[5]</sup> Previous study in Malaysia showed that each diabetic patient experienced at least one DRP<sup>[6,7]</sup> while a study in Denmark showed at least four DRPs per patient.<sup>[8]</sup> However, Indonesia has a lack of studies on DRPs in such patients, particularly on secondary healthcare facility setting.

The study aims to identify the DRPs in Type 2 diabetic patients whom also diagnosed with hypertension in the following domains: Problems, causes, and interventions. The study also determines the factors that were significantly associated with DRPs in Type 2 diabetic patients with hypertension. The result of the study will provide pharmacist as well as other healthcare professionals' clear description concerning the pattern of DRPs in such patients and would be helpful for pharmacists to create the strategy to prevent such DRPs developed.

## SUBJECTS AND METHODS

### Study Design and Setting

The prospective study was conducted in the inpatient ward of a secondary care hospital in Cimahi, West Java, Indonesia following research approval by the hospital education and ethics committee No. 070/2162/RSUD-CBBT.

### Subjects

The minimum sample size ( $n = 62$ ) was calculated using equation at 5% Type 1 error, precision of 0.3 DRPs and standard deviation (SD), based on previously done study,<sup>[6]</sup> of 1.2 DRPs. A total 90 inpatients whom admitted to the hospital between October 1 and December 31, 2015 and fulfilled the inclusion criteria were included in the study. The inclusion criteria were: (1) Adult patients (>18 years old), (2) diagnosed with at least Type 2 diabetes mellitus and hypertension, and (3) prescribed with at least one antidiabetic agent and antihypertension, whereas the exclusion criteria were: (1) Diagnosed with Type 2 diabetes mellitus and hypertension but not prescribed any antidiabetic agent and antihypertension agent and (2) pregnant during the hospitalization period.

### DRPs Identification and Classification

The hospital pharmacists assessed the DRPs based on clinical judgment supported by updated evidence-based disease management guideline and literature.<sup>[9-11]</sup> The pharmacists were also urged to be involved in a team discussion to minimize the bias caused by the diversity of their clinical judgment. The identified DRPs were classified based on the PCNE Classification for DRPs V 5.01.<sup>[5]</sup> The causes of DRPs and type of intervention by pharmacists were also recorded.

### Statistical Analysis

Categorical variables were shown as frequencies and percentages while numerical variables were described using means and SD. Bivariate analysis was conducted to determine factors that were significantly associated with DRPs in Type 2 diabetic patients with hypertension. Statistical analyses were performed using a data analysis freeware.

## RESULTS

### Demographic Characteristics

As many as 90 patients meet the inclusion criteria of the study. Most of the patients were female ( $n = 74$ , 82.8%) and the rest were male. The majority of the patients were under 56 years of age ( $n = 52$ , 57.8%) confirming that the onset of Type 2 diabetic patients with hypertension was shifting to the younger age population. The mean of patients' age was 57.73 years (SD = 10.14).

### Clinical Characteristics

Majority of hypertension cases found of the patients ( $n = 48$ ; 53.3%) was classified as Stage II hypertension. Most of the Type 2 diabetic patients had one comorbidity ( $n = 32$ ; 35.6%) beside hypertension. As many as 6-10 medications were prescribed to majority patients ( $n = 56$ ; 62.2%). In addition, as many as 58 patients (64.4%) admitted to hospital for  $\leq 7$  days. Most of the patients were shown improvement ( $n = 84$ ; 93.3%) when they were discharged from the hospital. The patients' clinical characteristics are summarized in Table 1.

Kidney disease was the most common comorbidities found in the Type 2 diabetic with hypertension patients ( $n = 47$ ; 52.2%) followed by heart disease ( $n = 25$ , 27.8%) and stroke ( $n = 24$ ; 26.7%).

### Medication Used in Type 2 Diabetic with Hypertension Patients

Various antidiabetic agents prescribed to the patients. As many as 38 patients (74.5%) received dual antidiabetes therapy, with majority patients prescribed with insulin glargine and insulin aspart combination ( $n = 15$ ; 29.4%). Nine patients (17.6%) received monotherapy while only four patients (7.8%) received triple therapy.

Clinicians preferred dual therapy in the management of hypertension ( $n = 26$ ; 43.3%) with amlodipine-valsartan combination become the most frequent antihypertensive prescribed ( $n = 17$ ; 28.3%). The choice of antihypertensive agent was inconsistent with the evidence-based

**Table 1: Patients' clinical characteristics**

Parameters	n (%)
Age	
≤55 years	52 (57.8)
>55 years	38 (42.2)
Sex	
Female	74 (82.8)
Male	16 (17.2)
Hypertension classification	
Stage II (TD ≥ 160/>100 mmHg)	48 (53.3)
Stage I (TD=140-159/90-99 mmHg)	29 (32.2)
Pre-hypertension (TD=120-139/80-89 mmHg)	13 (14.0)
Number of comorbidities	
1	32 (35.6)
2	30 (33.3)
3	16 (17.8)
0	8 (8.9)
4	3 (3.3)
5	1 (1.1)
Number of medications received	
6-10	56 (62.2)
11-15	20 (22.2)
>15	8 (8.9)
1-5	6 (6.7)
Length of stay	
≤7 days	58 (64.4)
8-14 days	27 (30.0)
≥15 days	5 (5.6)
Discharge outcome	
Improved	84 (93.3)
Death	6 (6.7)
Worsen/unimproved	0 (0)

guideline.<sup>[9,12,13]</sup> Instead of prescribing angiotensin converting enzyme or angiotensin receptor blocker, clinicians preferred to prescribe calcium channel blocker. A total of 23 patients (38.3%) received monotherapy while amlodipine became the most preferred antihypertensive agent ( $n = 15$ ; 25%).

## DRPs

Problems concerning drug choice were the most common (55.2%) DRPs encountered with “no drug prescribed but clear indication” being the most frequent problem (25.3%). Overall, as many as 261 DRPs were identified, averaging 2.88 (SD = 0.23) problems per patient. The details of the type of DRPs found in patients are shown in Table 2.

Most of the DRPs were caused by drug/dose selection (62.2%) with “inappropriate drug selection” being the most common cause (25.3%) followed by “synergistic/preventive drug required and not given” (22.3%) [Table 3]. “Drug use process” was the second most frequent cause (26%).

Table 4 shows that most of the pharmacist's intervention to resolve DRPs was conducted at patient/carer level (60.7%) by providing medication counseling and spoke to the family member/caregiver (38.7% and 21.9%, respectively). Intervention at the prescriber level came in second with 27.7% with the majority on informing the prescriber (18.7%).

## Factors that Associated with DRPs in Type 2 Diabetic Patients with Hypertension

We try to determine the factors that were significantly associated with DRPs in Type 2 diabetic patients with hypertension using bivariate analysis. Based on the analysis, we found that the number of medications ( $r = 0.49$ ,  $P < 0.01$ ) and the length of stay ( $r = 0.25$ ,  $P < 0.05$ ) significantly correlated with the number of DRPs. Based on linear regression analysis, the number of medications significantly predicted the number of DRPs ( $\beta = 0.50$ ,  $P < 0.001$ ).

## DISCUSSION

Diabetes mellitus has become an emerging threat to Indonesia. In 2015, the International Diabetic Federation (IDF) stated that Indonesia was ranked 7<sup>th</sup> in countries with the largest numbers of people with diabetes. The IDF estimated that 10 million of Indonesian adults live with diabetes with national prevalence 6.2% (5.4-6.7%).<sup>[14]</sup> In addition, the IDF also predicted that people with diabetes in Indonesia will rapidly increase to 16.2 million in 2040.<sup>[14]</sup> The risk of financial burden to the country newly established health system Jaminan Kesehatan Nasional or National Health Insurance in the future should be considered. As a consequence, the country should work hard to prevent and combat the disease.

On the other hand, Type 2 diabetic patients may encounter some problems to the patients related to their disease and medications. The majority of Type 2 diabetic patients were accompanied with at least one comorbidities. One of the most common comorbidities was hypertension that may lead to other cardiovascular and cerebrovascular disease in the future. The situation may lead to higher risk of DRPs. Based on our findings, the average number of DRPs in Indonesian hospital is slightly higher than those in a Malaysian study.<sup>[6]</sup> However, a Danish study showed higher case of DRPs than ours<sup>[8]</sup> since the study measures the DRPs in community settings by home interview based on patients personal experience. An Australian study showed that medication-related problems on diabetic patients were associated with 7.2% hospital admissions.<sup>[15]</sup> Not remembering to refill medications was the

**Table 2:** Type of DRPs found on patients

Code	Detailed classification	Frequency (%)
P1	Adverse reactions	30 (11.4)
P1.1	Side effect suffered (non-allergic)	23 (8.8)
P1.2	Side effect suffered (allergic)	4 (1.5)
P1.3	Toxic effects suffered	4 (0.8)
P2	Drug choice problem	144 (55.2)
P2.1	Inappropriate drug (not most appropriate for indication)	30 (11.5)
P2.2	Inappropriate drug form (not most appropriate for indication)	0 (0)
P2.3	Inappropriate duplication of therapeutic group or active ingredient	20 (7.7)
P2.4	Contraindication for drug (including pregnancy/breast feeding)	4 (1.5)
P2.5	No clear indication for drug use	24 (9.2)
P2.6	No drug prescribed but clear indication	66 (25.3)
P3	Dosing problem	28 (10.7)
P3.1	Drug dose too low or dosage regime not frequent enough	19 (7.3)
P3.2	Drug dose too high or dosage regime too frequent	7 (2.7)
P3.3	Duration of treatment too short	1 (0.4)
P3.4	Duration of treatment too long	1 (0.4)
P4	Drug use problem	11 (4.2)
P4.1	Drug not taken/administered at all	9 (3.5)
P4.2	Wrong drug taken/administered	2 (0.8)
P5	Interactions	47 (18.0)
P5.1	Potential interaction	45 (17.2)
P5.2	Manifest interaction	2 (0.8)
P6	Others	1 (0.4)
P6.1	Patient dissatisfied with therapy despite taking drug (s) correctly	0 (0)
P6.2	Insufficient awareness of health and diseases (possibly leading to future problems)	0 (0)
P6.3	Unclear complaints. Further clarification necessary	0 (0)
P6.4	Therapy failure (reason unknown)	1 (0.4)
	Sum total	261 (100)

DRP: Drug-related problems

most commonly reported medication adherence problem in Type 2 diabetic patients.<sup>[16]</sup>

We found that drug choice problem was the most frequent problems while a Malaysian study showed that the most common DRPs encountered were insufficient awareness of health and diseases.<sup>[6]</sup> For example, pharmacists found that no antihypertensive prescribed but clear indication of hypertension. Both our study and the previous study found that most of the DRPs was caused by drug/dose selection.

We also determined that the number of medications and the length of stay significantly correlated with the number of DRPs. This finding was consistent with the previous study.<sup>[6]</sup> However, the previous study also found significant associations with renal impairment, cardiovascular disease, and elderly status. Our findings were similar to a study by Koh *et al.* which is shown that among patients with

polypharmacy, age, and gender may not be as important as the number of drugs prescribed as predictors of experiencing a DRPs.<sup>[17]</sup> A study by Viktil *et al.* also stated that the number of DRPs per patient was linearly related to the number of drugs used on admission.<sup>[18]</sup>

The majority of the pharmacist intervention for DRPs resolutions was conducted at patient/carer level, such as providing counseling and education to the family. Pharmacists' direct involvement on Type 2 diabetic with hypertension patient therapy may provide a solution in early detection of DRPs. Previous research stated that the involvement of the clinical pharmacist in diabetic patients helps in identification and prevention of DRPs.<sup>[19]</sup> A comprehensive and a brief individually targeted intervention for patients with Type 2 diabetes by pharmacist could improve implementation of drug therapy.<sup>[20]</sup> Moreover, pharmacist involvement in multidisciplinary healthcare team may promote quality

**Table 3:** Classification of DRPs causes found on patients

Code	Detailed classification	Frequency (%)
C1	Drug/dose selection	184 (62.2)
C1.1	Inappropriate drug selection	75 (25.3)
C1.2	Inappropriate dosage selection	13 (4.4)
C1.3	More cost-effective drug available	0 (0)
C1.4	Pharmacokinetic problems, including ageing/deterioration in organ function and interactions	0 (0)
C1.5	Synergistic/preventive drug required and not given	66 (22.3)
C1.6	Deterioration/improvement of disease state	0 (0)
C1.7	New symptom or indication revealed/presented	0 (0)
C1.8	Manifest side effect, no other cause	30 (10.1)
C2	Drug use process	77 (26.0)
C2.1	Inappropriate timing of administration and/or dosing intervals	17 (5.7)
C2.2	Drug underused/under-administered	19 (6.4)
C2.3	Drug overused/over-administered	8 (2.7)
C2.4	Therapeutic drug level not monitored	22 (7.4)
C2.5	Drug abused (unregulated overuse)	1 (0.3)
C2.6	Patient unable to use drug/form as directed	10 (3.4)
C3	Information	16 (5.4)
C3.1	Instructions for use/taking not known	13 (4.1)
C3.2	Patient unaware of reason for drug treatment	3 (1.0)
C3.3	Patient has difficulties reading/understanding Patient Information Form/Leaflet	0 (0)
C3.4	Patient unable to understand local language	0 (0)
C3.5	Lack of communication between healthcare professionals	0 (0)
C4	Patient/psychological	17 (5.7)
C4.1	Patient forgets to use/take drug	13 (4.1)
C4.2	Patient has concerns with drugs	0 (0)
C4.3	Patient suspects side effect	3 (1.0)
C4.4	Patient unwilling to carry financial costs	0 (0)
C4.5	Patient unwilling to bother physician	0 (0)
C4.6	Patient unwilling to change drugs	0 (0)
C4.7	Patient unwilling to adapt lifestyle	1 (0.3)
C4.8	Burden of therapy	0 (0)
C4.9	Treatment not in line with health beliefs	0 (0)
C4.10	Patient takes food that interacts with drugs	0 (0)
C5	Logistics	2 (0.7)
C5.1	Prescribed drug not available (anymore)	2 (0.7)
C5.2	Prescribing error (only in case of slip of the pen)	0 (0)
C5.3	Dispensing error (wrong drug or dose dispensed)	0 (0)
C6	Others	0 (0)
C6.1	Other cause	0 (0)
C6.2	No obvious cause	0 (0)
	Sum total	296 (100)

DRP: Drug-related problems

improvement in safe medication management<sup>[21]</sup> and reduce medical cost.<sup>[22]</sup> The pharmacist may also use a checklist tool

to assist them to identify issues in therapy and management of their Type 2 diabetes patients systematically and enable



**Table 4:** Classification of interventions on DRPs found on patients

Code	Detailed classification	Frequency (%)
	No intervention	0 (0)
I1	At prescriber level	43 (27.7)
I1.1	Prescriber informed only	29 (18.7)
I1.2	Prescriber asked for information	0 (0)
I1.3	Intervention proposed, approved by Prescriber	9 (5.8)
I1.4	Intervention proposed, not approved by Prescriber	5 (3.2)
I1.5	Intervention proposed, outcome unknown	0 (0)
I2	At patient/carer level	94 (60.7)
I2.1	Patient (medication) counseling	60 (38.7)
I2.2	Written information provided only	0 (0)
I2.3	Patient referred to prescriber	0 (0)
I2.4	Spoken to family member/caregiver	34 (21.9)
I3	At drug level	18 (11.6)
I3.1	Drug changed	2 (1.3)
I3.2	Dosage changed	11 (7.1)
I3.3	Formulation changed	0 (0)
I3.4	Instructions for use changed	0 (0)
I3.5	Drug stopped	5 (3.2)
I3.6	New drug started	0 (0)
I.4	Other intervention or activity	22 (14.2)
I4.1	Other intervention	22 (14.2)
I4.2	Side effect reported to authorities	0 (0)
	Sum total	155 (100)

DRP: Drug-related problems

earlier intervention to improve metabolic control.<sup>[23]</sup> The intervention may lead to better therapeutic outcomes by rationalizing drug therapy. However, this study did not measure the outcome of the pharmacist intervention.

Our study has two major limitations. First, it was conducted only in one secondary healthcare facility so it is difficult to generalize the findings. Second, we did not investigate the outcome of the pharmacist intervention so that the effectiveness of the intervention was not able to be measured. This narrow scope of study calls for a larger, wider, and longer period of confirmatory study, for example, a multicenter study.

To summarize, we found that the risk of DRPs in Type 2 diabetic and hypertension patients was relatively high. Early detection by the pharmacist is needed to ensure the safety and effectiveness of drug therapy and minimize the risk of medication error.

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