CLINICALLY SIGNIFICANT POTENTIAL DRUG-DRUG INTERACTIONS AMONG ADULT DIABETIC HYPERTENSIVE OUTPATIENTS AT KENYATTA NATIONAL HOSPITAL

MAKITE SIMON LATI

U56/7404/2017

DEPARTMENT OF PHARMACEUTICS AND PHARMACY PRACTICE

UNIVERSITY OF NAIROBI

A research dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of the University of Nairobi.

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DECLARATION OF ORIGINALITY

Name of student:	Makite Simon Lati
Registration number:	U56/7404/2017
College:	College of Health Sciences
School:	School of Pharmacy
Department:	Pharmaceutics and Pharmacy Practice
Course name:	Master of Pharmacy in Clinical Pharmacy
Title:	Clinically Significant Potential Drug-drug Interactions among adult Diabetic Hypertensive Outpatients at Kenyatta National Hospital

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SUPERVISORS APPROVAL

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1. Dr. David Nyamu, PhD
   Senior Lecturer, Department of Pharmaceutics and Pharmacy Practice

   Signature..... Date..... 02/12/2019

2. Dr. Rosaline Kinuthia (B. Pharm, M. Pharm)
   Clinical Pharmacist, Kenyatta National Hospital

   Signature..... Date..... 4/12/2019

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DEDICATION

I dedicate this work to my dear wife Rispah for her unwavering love, encouragement and support.

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ABBREVIATIONS AND ACRONYMS

ACEI- Angiotensin Converting Enzyme Inhibitor

ADA- American Diabetes Association

ARB- Angiotensin Receptor Blocker

ALLHT- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack

AV - Atrioventricular

BMI - Basal Metabolic Index

BP- Blood Pressure

CCB- Calcium Channel Blocker

CNS - Central Nervous System

CKD- Chronic Kidney Disease

CPG- Clinical Practice Guideline

DDI- Drug-drug interaction

DEOPC - Diabetes and Endocrinology Outpatient Clinic

DM - Diabetes Mellitus

ESRD- End stage Renal Disease

HbA1c- Glycated adult hemoglobin

HTN- Hypertension

KNH- Kenyatta National Hospital

NSAID- Nonsteroidal Anti-inflammatory Drug

OADS- Oral Antidiabetic Drugs

PI- Principal Investigator

RAS- Renin Angiotensin System

SMBG- Self-monitoring of blood Glucose

UEC Urea, Electrolytes, Creatinine

UKPDS- United Kingdom Prospective Diabetes Study

OPERATIONAL DEFINITION OF TERMS

Adverse drug event: It is an injury resulting from the use of a drug and includes adverse drug reactions and overdoses**.**

Adverse drug reaction: A response to a drug that is noxious and unintended which occurs during normal use of the drug and at therapeutic doses.

Diabetes mellitus: An endocrine syndrome related to carbohydrate metabolism in which the body is unable to regulate blood glucose**.**

Drug-drug interaction: A change in a drug's effect when the drug is taken together with a second drug.

Hypertension: Consistently elevated blood pressure of >140 mmHg systolic and >90 mmHg diastolic.

Major drug interaction: This is a drug-drug interaction which is usually life-threatening and may in addition raise the need for an intervention such as additional drug therapy to prevent or alleviate the severe adverse drug effects

Minor drug-drug interaction: This is a mild drug-drug interaction which limits the clinical effects of the drugs involved. The effects may manifest as an increase in the severity or frequency of the adverse effects. However, it does not usually require a change in the treatment regimen.

Moderate drug interaction: A drug-drug interaction that may cause worsening of the disease. Also, this type of drug-drug interaction usually requires a change in the drugs used to manage the disease or condition.

Prevalence: The number of cases of a disease existing in a given population at a specific period (period prevalence) or at a particular moment in time (point prevalence).

ABSTRACT

Background: Type 2 diabetes mellitus (DM) and hypertension are common comorbidities in the developing and developed world. Management of these patients requires combination pharmacotherapies which may lead to polypharmacy and subsequently drug-drug interactions. Such interactions may produce undesirable clinical outcomes.

Broad objective: To characterize the clinically potential drug-drug interactions and their significance among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

Methods: This was a tertiary hospital based cross-sectional study done among 104 adult patients from 1st May 2019 to 31st August 2019 at Kenyatta National Hospital. Ethical approval was obtained from the institutional review board under reference number KNH-ERC/A/192. Data on patient demographics, clinical characteristics current prescriptions and strategies for prevention of potential drug-drug interactions were extracted from patient records into predesigned data collection forms. Potential drug interactions were identified using the Micromedex drug interaction checker®. Data was exported to STATA software version 13 for analysis. The level of significance was set at 0.05

Results: There were more females (70.2%) in the study. The mean age of the participants was 61.6 years (SD±10.8). The prevalence of potential drug interactions was high at 57.7%. The average number of interactions was one interacting pair per patient with majority (81.0%) of the prescriptions having moderate drug-drug interactions which were significantly associated with the advanced stage of hypertension (COR=2.63; 95% CI 1.5-4.68; p=0.002), number of drugs prescribed (COR=2.12; 95% CI 1.15-3.92; p=0.020), use of nifedipine(COR=6.42; 95% CI 1.31-31.57; p=0.008) and losartan(COR=4.60; 95% CI 0.99-21.36; p=0.005). The most common potential clinical outcome was hyperkalemic lactic acidosis (14.4%) associated with co-prescribing of enalapril and metformin (14.4%).

Potential drug interactions were minimized through regular blood sugar check (100%) and blood pressure monitoring (98.1%). However, there was minimal monitoring of HbA1c (30.8%) as well as serum urea and electrolytes (17.3%).

Conclusion: The prevalence of potential drug-drug interactions was high. Multi-drug therapy, advanced stage of hypertension and use of nifedipine increased the risk of potential drug-drug interactions which were mitigated through patients monitoring of their disease.

Recommendations: Patients with comorbid diabetes and hypertension would benefit from cautious prescription and use of drugs which are less likely to cause drug-drug interactions as well as close monitoring of blood sugars, blood pressures, HbA1Cs, urea and electrolytes**.** Future large cohort studies may be required to assess the impact of patients monitoring and the actual drug-drug interactions.

CHAPTER ONE: INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (DM) and hypertension are common comorbidities in both the developing and developed world. In 2015, the prevalence of diabetes mellitus was estimated at 9% globally, accounting for about half a million people with the disease. This is predicted to rise to 10.5% (650 million with the disease) by 2040(1). The prevalence of DM in Africa about 4 % in 2015 and this is expected to reach 4.2% by 2040(2). The reasons for the global explosion in the prevalence of these two diseases, especially in Africa have been attributed to the aging populations, rapid urbanization, and increase of unhealthy lifestyles that have been witnessed in Africa during the last few decades(3). Information from population-based studies in a systematic review has estimated the prevalence of diabetes mellitus to range from 1% of Uganda's rural population to 12% in urban Kenya. Notably in Kenya, the epidemiology of both hypertension and diabetes has not been studied to any great extent. However, health care facilities have provided anecdotal evidence suggesting that the incidence of DM and hypertension is rising(4).

The prevalence of hypertension among DM patients is double that of the normal population(5). Diabetic patients have a two to fourfold likelihood of having cardiovascular disease compared to the general population (1). Hypertensive patients usually exhibit insulin resistance and have a greater risk of developing DM than are normotensive individuals(6). Hypertension may also account for up to three quarters of all cardiovascular disease events in people with diabetes. Hypertension also accelerates the progression of diabetic complications which include nephropathy, retinopathy and neuropathy(7).

Morbidity and mortality from DM majorly arise from cardiovascular diseases, which are precipitated by hypertension, a major macrovascular complication of diabetes mellitus. As such, DM and hypertension are closely interlinked because of similar risk factors which include vascular inflammation, endothelial dysfunction, atherosclerosis, dyslipidemia, arterial remodeling and obesity(1).

Management of these comorbid diseases involves several approaches. The American Diabetes Association (ADA) indicates lifestyle modification as the first management approach for these patients (8).

Diabetic hypertensives require combination pharmacotherapies to achieve targeted blood glucose as well as blood pressure goals(9). The use of antihypertensives as well as metformin, other oral anti-diabetic drugs (OADs) and or with insulin are recommended if the glycemic or hypertensive control goals are not achieved with lifestyle changes alone (10). Renin-angiotensin system (RAS) blockers such as Angiotensin Converting Enzyme inhibitors(ACEis) or Angiotensin Receptor Blockers (ARBs) are components of any drug regimen in the treatment of hypertension in diabetes patients (2). Other drug classes include diuretics, β-blockers and calcium-channel blockers(CCBs)(11).

Multiple agents have the potential to interact and produce undesirable effects(12). In addition to keeping both blood pressure and glucose levels controlled, multiple drugs subjects the patient to polypharmacy which may sometimes be irrational(13). Recently, there has been an increase of new formulations of antidiabetic and antihypertensive drugs and even new classes of drugs have been brought to market(5). Subsequently, uninformed use of new drug therapies for any medical condition can be of concern to the patient due to an enhanced likelihood of experiencing drug-drug interactions and unperceived adverse drug events(14). Studies have also indicated that about 60% of patients fear that the prescribed medications may have drug interactions that will cause adverse drug reactions(15). However, in Sub-Saharan Africa which consists Eastern African countries, there is inadequate literature on treatment outcomes and especially drug-drug interactions for diabetic hypertensive patients especially in primary health care settings(4).

Drug-drug interactions occur when several drugs are administered at the same time and the pharmacological effects of one drug affect the other(16). The result of the interaction leads to increase or reduction of the effect of the object drug. Besides, a new and unanticipated effect of either drug may also occur(17). Drug-drug interactions are considered to be therapeutic or harmful depending on the type of drug, or the indication.

Problems arise when they cause a rise in morbidity and mortality, which are otherwise preventable.

The harmful effects of drug-drug interactions include minor, moderate morbidities as well as fatal consequences(18).The avoidance or prevention of drug-drug interactions and their potentially harmful effects is therefore of significant clinical concern(19). This would lower the risk of undesirable drug events in the patients. The overall effect is reduced healthcare expenses and shortened length of hospitalization(12).

The present study intended to characterize potential drug-drug Interactions and their clinical significance among diabetic hypertensive adult outpatients at Kenyatta National Hospital (KNH). The findings were expected to raise awareness among physicians and pharmacists on the burden of potential drug-drug interactions among their diabetic hypertensives. This was expected to enable them to make informed decisions when prescribing and dispensing drug combinations to this group of patients and hence prevent any potential drug-drug interactions.

1.2 Problem statement

The high coexistence of comorbid type 2 diabetes and hypertension poses a great challenge in pharmacological management. This is due to the prescription of multiple medications for both diseases in order to achieve both glycemic and blood pressure control(20k). The resulting multi-drug therapy increases the likelihood of drug-drug interactions(9). Drug-drug interactions are a significant clinical and public health burden(21). In general, the larger the number of drugs prescribed, the more frequent a drug-drug interaction is likely to occur(19). These drug-drug interactions may subsequently lead to adverse drug effects which may include cognitive impairment, dizziness, weight change and cardiac complications which are frequently present in patients with multiple drug therapy(12).

Drug-drug interactions remain among drug-related problems associated with management of diabetic hypertensive patients(22). In a study carried out by the UK Prospective Diabetes Study (UKPDS) to establish management issues in diabetic hypertensives by

Ker (3), it was evident that management of both hypertension and diabetes requires the use of multiple antihypertensive medications.

The study also noted that the use of several medications poses a great risk of challenges such as drug-drug interactions which may worsen the treatment outcomes of both diabetes and hypertension. In a local study, Guantai *et al*(23) found that over 90% of patient's prescriptions had at least one potential dug-drug interaction. However, studies among participants with both DM and HTN remain to be done.

Additionally, a study by Mongi *et al* (20) found out that about 40% of diabetic hypertensive patients were being treated on more than one antihypertensive drug. This in addition to antidiabetic medications was a clear indication of the polypharmacy involved. While the study described the prescription patterns in diabetic hypertensive patients at KNH, it did not dwell on potential drug-drug interactions.

Furthermore, the local studies did not take into account the clinical relevance of the potential drug-drug interactions as proposed by the present study. The present study, therefore, filled the knowledge gaps left by previous studies by assessing potential drug-drug interactions, their clinical significance and strategies for minimizing them among hypertensive diabetic patients. The findings of this study will enable clinicians and pharmacists in making informed choices prescribing and dispensing these medications to potential drug-drug interactions and their possible effects.

1.3 Justification

To date, there have been insufficient studies conducted locally to investigate and document drug-related problems in diabetic patients with hypertension. Related studies have been done in a population in the UK (5). This, therefore, creates a need to carry out such a study locally because of the limited data on drug-drug interactions in diabetic hypertensive patients. For instance, Mwengi *et al*(24), evaluated the management of hypertension among adult diabetic hypertensive outpatients with chronic kidney disease(CKD) at KNH. However, despite having a study population with hypertensive diabetic patients, the study did not assess potential drug-drug interactions in this study

population. This is therefore, an indicator of the need for more studies on potential drug-drug interactions in this group of patients.

In another study carried out to characterize potential drug-drug interactions in hypertensive patients at Kenyatta National Hospital, the prevalence of potential drug-drug interactions was approximately 93% with an average of 3.5 drug-drug interactions per prescription(20). The study suggested that the drug-drug interactions could be compounded by comorbidities and polypharmacy.

These findings indicate the need for clinicians and pharmacists to have adequate knowledge of possible drug-drug interactions as well as their clinical significance to make informed choices when prescribing several drugs to manage patients with diabetes and hypertension(14)

This study, therefore, aimed to raise awareness on the potential drug-drug interactions, their clinical significance and strategies for minimizing them. This was to help in ensuring that patients receive drugs combinations that are safe and effective.

1.4 Objectives

1.4.1 Main objective

To characterize the potential drug-drug interactions and their clinical significance among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

1.4.2 Specific objectives

The study aimed to;

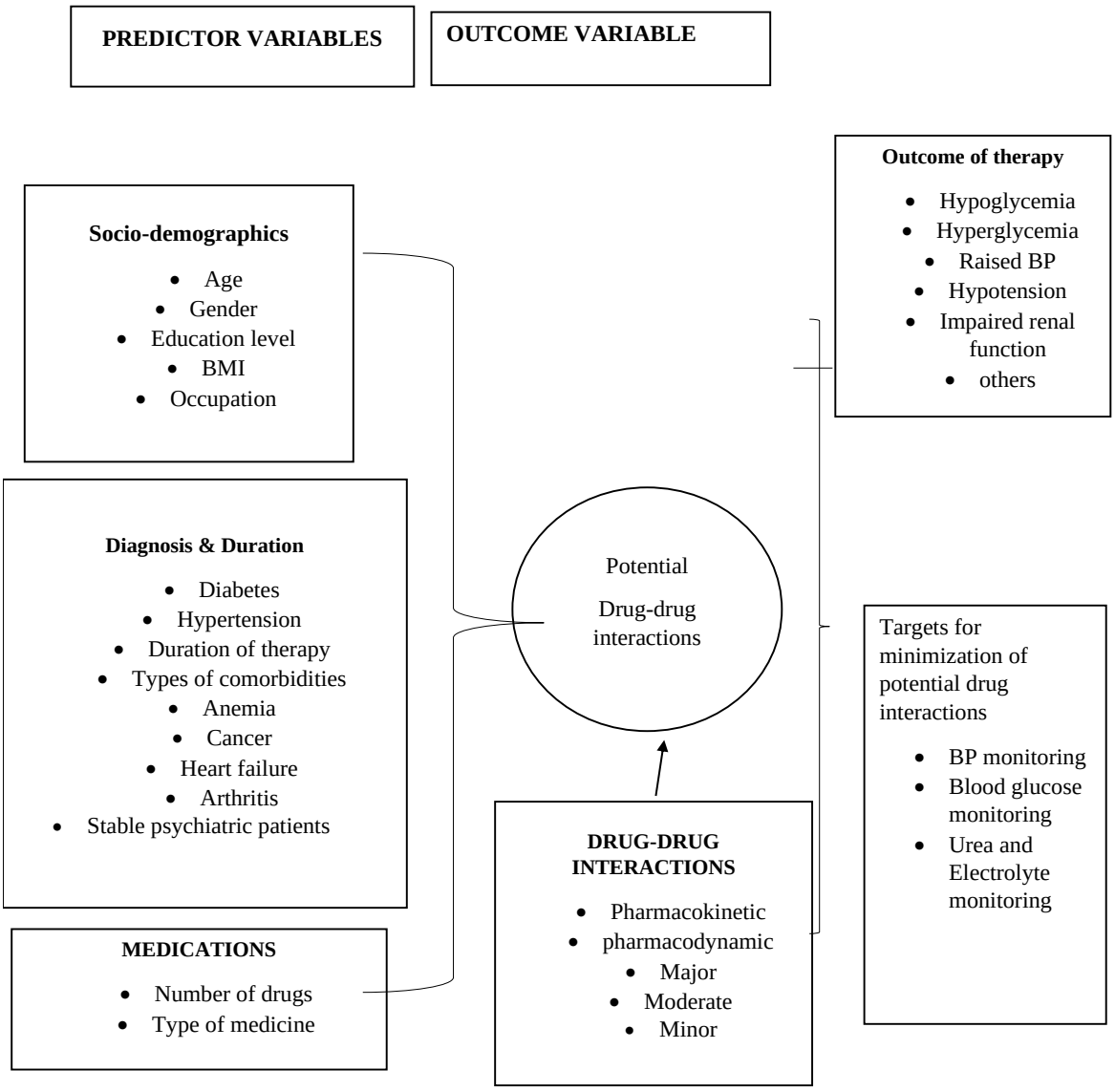
1. Determine the prevalence of potential drug-drug interactions among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

2. Describe the pattern of potential drug-drug interactions among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

3. Find out the clinical relevance of the potential drug-drug interactions among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

4. Identify strategies for minimization of potential drug-drug interactions among adult diabetic hypertensive outpatients at Kenyatta National Hospital.

1.5 Conceptual framework



Source: Author, 2019

Figure 1: Conceptual framework

The main outcome variable for this study was the prevalence of potential DDIs among adult diabetic hypertensive patients at KNH. The main predictive variables were the number of comorbidities, duration of treatment, class, and number of drugs per patient's prescription which were the independent variables. The number of drugs was an indicator of the role of polypharmacy in drug-drug interactions. Other predictive variables were the

number of comorbidities and the duration of diabetes and hypertension. The possible confounding variables were age, gender, inter-individual difference, education level, BMI and occupation of the patient.

Diabetes is associated with several comorbidities with hypertension being the major one. This necessitates the management of these diseases with several drugs. This, in turn, increases the risk of irrational polypharmacy which predisposes the patient to potential drug-drug interactions. Many drug classes exist for the management of elevated BP. The main classes include the ACEIs, ARBs, diuretics, calcium channel blockers (CCBs); β-blockers; vasodilators and centrally-acting antiadrenergics. On the other hand, biguanides, sulfonylureas, Meglitinides, alpha-glucosidase inhibitors and insulin are used in the management of diabetes. The drugs can be used as monotherapy or in combination. The class of a drug is associated with the type of drug-drug interaction. The DDIs also vary in severity which can be grouped into either minor, major or moderate. Any drug chosen for the management of diabetes and hypertension should be correctly indicated, safe and effective. The patient must also adhere to instructions on their medication use.

The clinician's choice of antidiabetic and antihypertensive drugs depends on their knowledge of the patient's condition as well as on the recommendations of the current Clinical Practice Guidelines (CPG). In preventing potential drug-drug interactions, monitoring of lab parameters is crucial. This among other advantages helps in identification and mitigation against possible drug-drug interactions.

The frequency of monitoring of blood pressure, blood glucose, and urea and electrolytes will be an indicator of some preventive measures towards potential DDIs. This is because the most common effects of these DDIs include hypoglycemia hyperglycemia, Raised BP, hypotension or impaired renal function.

CHAPTER TWO: LITERATURE REVIEW

2.1 Burden of Diabetes Mellitus and hypertension

The prevalence of diabetes and hypertension is increasing globally(25). Despite diabetes and hypertension being preventable diseases, they are among the leading causes of death worldwide(26). A study by Zhou *et al*, also noted that patients with hypertension alone often present with insulin resistance(27). Hypertension and diabetes are intertwined diseases that also have several overlapping underlying risk factors. These factors are ethnicity, dyslipidemia, and sedentary lifestyles(28). These comorbidities also share complications which are mainly cardiovascular. Other complications associated with diabetes are retinopathy, nephropathy, and neuropathy(29) According to a prospective study by Hebert *et al*, hypertension remains a major risk factor, especially for diabetic nephropathy(30).

2.2 Management of DM and Hypertension

The initial approach towards management of diabetes and hypertension usually emphasizes on maintaining an ideal body mass index, dietary modification, and physical activity. Notably, lifestyle modification is very effective in the prevention of diabetes and hypertension. Lifestyle modification also prevents the progress of macrovascular complications of the two comorbidities(5). Besides lifestyle modification, most patients require pharmacotherapy to meet treatment goals for blood sugar and blood pressure control. Management of hypertension, hyperglycemia, underlying hypercoagulable states and dyslipidemia requires the use of multiple medications(31). Consequently, the need to use several classes of drugs leads to polypharmacy in the management of hypertensive diabetic patients(32).

Polypharmacy is the prescription, administration or use of more drugs than what has been indicated. This also includes treatment regimens which contain at least one unnecessary drug (33).

Multiple drug use has some benefits which include synergistic effects. However, the likelihood of adverse drug reactions and drug-drug interactions is usually increased in patients on multiple drug therapy.

For instance, a study from Kuopio, Finland by Jyrkka *et al* (34) indicated a high level of polypharmacy which was associated with increased mortality in elderly patients. This was as a result of the adverse drug events as well as the ineffectiveness of some drugs due to drug-drug interactions(34)

2.3 Drug-drug interactions

Drug interactions occur when the response to a particular drug once taken by a patient, is modified by other drugs, environmental factors, nutritional supplements, food, formulation excipients or disease(35). Drug-drug interactions may lower the effectiveness of a drug, cause unexpected side effects or consequently enhance the action of a particular drug. In a study in Brazil by Joice and João, harmful drug–drug interactions were noted to be important as they caused up to 3% of adverse drug reactions requiring hospitalization (36).

Drug-drug interactions can be grouped into two major classes which include pharmacokinetic and pharmacodynamic interactions. As such, pharmacokinetic drug-drug interactions occur when one drug affects the circulating concentrations of a second drug by changing its absorption, distribution, metabolism as well as their elimination profiles. Pharmacodynamic on the other hand, usually involves one drug affecting others by being additive, synergistic or antagonistic(37).

Also, drug-drug interactions can be classified into minor, moderate and major(38). This classification is based on the severity as well as the undesirable effects caused. Minor drug-drug interactions are known to limit the clinical effects of the drugs involved. The effects may manifest as an increase in the severity or frequency of the adverse effects. However, these DDIs do not usually require a change in the treatment regimen. On the other hand, moderate drug-drug interactions may cause a worsening of the disease. Also, this type of DDIs usually requires a change in the drugs used to manage the disease or condition.

Lastly, major drug-drug interactions are usually life-threatening and may in addition raise the need for an intervention such as additional drug therapy to prevent or alleviate the severe adverse drug effects(39).

In a study by Neto *et al*(40) to assess potential DDIs in hypertensive and or diabetic elderly patients, 93.2% had moderate or mild drug-drug interactions while about 7% had severe or highly severe DDIs.

The elderly patients are vulnerable due to multiple drug therapy as a result of several comorbidities(41). For instance, Aljadani and Aseeri (42) found a 90% prevalence of drug-drug interactions among geriatrics and therefore indicated the need for vigilance in prescribing drugs among the elderly.

2.3.1 Drug-drug interactions associated with the management of type 2 diabetes

Type 2 diabetes is managed by use of several drugs from different pharmacological classes. Among antidiabetics, sulfonylureas and biguanides are the most commonly used. Examples of sulfonylureas in use are glibenclamide, glimepiride, gliclazide and glipizide(43). However, there are also other classes of drugs that are available. These include alpha-glucosidase inhibitors such as acarbose, meglitinides such as repaglinide and the thiazolinediones such as pioglitazone. As noted by Cahn *et al*, drugs from different classes are frequently used and have a synergistic effect concerning lowering of blood glucose (44).

Most of the oral antidiabetic agents have the potential to interact with each other. If the result is hypoglycemia or hyperglycemia the effects can be dangerous. The interactions may be pharmacodynamic where another drug independently lowers or raises blood glucose or pharmacokinetic where another drug changes the absorption, metabolism or excretion of the hypoglycemic drug. Both mechanisms can lead to alteration of the apparent efficacy of the hypoglycemic medications. Pharmacokinetic interactions may worsen other adverse drug effects of oral hypoglycaemic drugs

According to a retrospective study by Samardzic on the incidence of DDIs with antidiabetic drug, about 80% of the patients had at least one DDI(45). The main interaction was between antidiabetic drugs and diuretics. The study also noted the need for monitoring antidiabetic therapy to prevent DDIs. A study by Tornio *et al* (46) also showed evidence that oral hypoglycemic agents may interact with other drugs meant to manage co-existing diseases and conditions.

2.3.1.1 Drug-drug interactions associated with use of sulfonylureas

Sulfonylureas are among the most widely used antidiabetic agents in Kenya. According to the National Clinical Guidelines for Management of Diabetes Mellitus(43), glibenclamide, gliclazide, glimepiride, and glipizide are the drugs recommended for use from this class.

Sulfonylureas usually undergo hepatic metabolism. Consequently, their plasma concentrations and activity can be decreased by hepatic enzyme-inducing drugs and increased by hepatic enzyme inhibitors(47).

The American Diabetes Association(ADA)(48) and the British National formulary(49) recommends caution in the use of insulin secretagogues in hepatic disease due to the increased risk of hypoglycemia, especially when used with hepatic enzyme inhibitors.

Another drug-drug interaction among sulfonylureas is observed when used with alcohol. A study by Khan *et.al* recommended a reduction of the dosage of sulfonylureas in severely alcoholic patients. This is due to the potential of precipitating hepatotoxicity when used together(50).

Antacids have been found to enhance the absorption of sulfonylureas and therefore lead to higher peak concentrations of the drugs and increase the risk of temporary hypoglycemia (35). The study by Tornio *et al* (46) established that concomitant administration of magnesium hydroxide with tolbutamide or glibenclamide significantly increased the rate of absorption of the respective sulfonylurea. As a result, sulfonylureas should be given at least one hour before the administration of antacids. On the other hand, there is a decreased absorption rate of sulfonylureas when given concomitantly with cholestyramine(51).

Another drug-drug interaction is that of sulfonylureas and non-steroidal anti-inflammatory drugs. Sulfonylureas may be displaced from protein binding sites by NSAIDs due to their ability to be highly bound to proteins. As a result, this can lead to an increase in unbound sulfonylurea and subsequently cause a temporary decrease in blood glucose(52). A study carried out by Confederat *et al* (53) to assess side effects induced by

sulfonylureas on diabetic patients, it was established that 14% of patients on sulfonylureas and NSAIDs presented with hypoglycemia. Cautious used of the combination of NSAIDs and sulfonylureas was therefore recommended.

2.3.1.2 Drug-drug interactions associated with use of metformin

Another commonly used oral hypoglycemic is Metformin. It is a biguanide that does not undergo metabolism at all but is eliminated in the kidney. It may, therefore, accumulate and result in lactic acidosis if administered with nephrotoxic drugs which induce renal failure(54). Such drugs include contrast media, aminoglycosides, and cyclosporine.

According to a study by Huang *et al*(55) to establish the relationship between lactic acidosis and metformin usage, it was found out that 50% of patients dying from lactic acidosis had previously used metformin. In another study by Angioi *et al*(56), it was found that the use of contrast media and other nephrotoxic drugs was associated with lactic acidosis.

This was also found to raise the mortality rate in patients with acute kidney failure undergoing sustained low-efficiency dialysis. In another study by Hsu *et al*, metformin was also found to worsen renal function significantly in patients with renal disease(54). As such, metformin should be avoided before and for two days after administration of contrast radiography especially in patients with renal disease(57).

The excretion of metformin by the renal tubules was found to be inhibited by cimetidine. In a study by Stockley *et al* (58), cimetidine was found to decrease the renal clearance of metformin over 24 hours by about 25%. However, this process was not affected by other H2-receptor antagonists. This interaction on metformin by cimetidine, therefore, may cause increased plasma levels of metformin which may cause hypoglycemia. The study therefore recommended that clinicians should be aware of this interaction when prescribing these drugs in order to avoid potential DDIs(58).

2.3.1.3 Drug-drug interactions associated with use of thiazolinediones

Thiazolinediones are also another class of hypoglycemic agents currently in use. Initially, troglitazone, rosiglitazone, and pioglitazone were the drugs available in the market from this class. However, troglitazone was withdrawn worldwide due to severe hepatotoxicity(59).

Major DDIs among thiazolidinediones have not yet been reported(60). In Kenya, pioglitazone is the commonly used thiazolinedione(43). The drug has not been implicated in significant drug-drug interactions in studies and clinical use(35).

2.3.1.4 Drug-drug interactions associated with use of alpha-glucosidase inhibitors

Another class of antidiabetic medication is the alpha-glucosidase inhibitors. Acarbose is the only drug from this class that is currently recommended for use in Kenya. Acarbose acts by inhibiting the enzyme alpha glucosidase in the gastrointestinal wall which induces the release of glucose from carbohydrates. The inhibition of this enzyme subsequently causes an increase in the amount of glucose available for absorption across the gut wall (43).

Concomitant administration of acarbose with a sulfonylurea may cause mild hypoglycemia. A study by Vannasaeng *et al*(61), established a small but statistically significant($p>0.05$) reduction of postprandial glucose upon administration of acarbose with a sulfonylurea(62). Despite the mild interaction, there was no contraindication in the use of acarbose with sulfonylureas. However, when used together caution should be observed. Acarbose has also been found to decrease digoxin bioavailability when given at the same time. A study by Miura *et al*(63) to assess the effect of acarbose on absorption of digoxin established a significant decrease in plasma concentrations of digoxin when given with acarbose. The interaction is usually pharmacodynamic. In another study by Hussain *et al*(64), as a result of this potential DDI, the dose of digoxin is usually adjusted when given at the same time with acarbose.

2.3.2 Drug- drug interactions associated with the Management of Hypertension

Many antihypertensive drugs have been shown to have several important interactions. This occurs when they are used with other drugs for the management of comorbid diseases or conditions. When used concomitantly, drug-drug interactions, as well as ineffective blood pressure control, can occur. For instance, Egger *et al* (65) established that among discharged patients, 63% of the potential DDIs was as a result of a combination of ACEIs and potassium-sparing diuretics. The potential adverse effect of this interaction was the precipitation of hyperkalemia**.** However, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), are the most significant prescription drugs that alter blood pressure (66).

The study by Egger *et al*(65) also found out that 23% of potential DDIs in discharged patients was attributed to a combination of ACEIs and aspirin. Aspirin reduces the antihypertensive effect of ACEIs(67). However, most of these patients were on low dose aspirin, and thus the interaction was found to be moderate.

NSAIDs have been found to decrease the blood pressure-lowering ability of diuretics (68). Lapi *et al*(69), established that concurrent use of diuretics, ACEIs or ARBs with NSAIDs increased the risk of acute kidney injury by 31% compared to management with diuretics and ACEIs or ARBs (21%). The study, therefore, recommended vigilance when using a combination of NSAIDs, diuretics, ACEIs or ARBs.

On the other hand, corticosteroids have been found to precipitate hypertension through fluid retention. Of all steroids, mineralocorticoids such as fludrocortisone and hydrocortisone carry the greatest risk of hypertension(70). According to a study by Hussain *et a*l (64), about 6 % of patients on 75mg of fludrocortisone for five months, had to withdraw from the study due to severe hypertension. Prescription of the smallest effective dose of steroids was therefore recommended when to be used in combination with antihypertensives as they may counteract the effect of antihypertensives(70). Erythropoietin is another drug that has also been known to raise blood pressure. In a clinical study by Burgess(71), on the effect of recombinant human erythropoietin on BP in patients on hemodialysis, there was a significant elevation of BP among study

participants. This can be managed by increasing the dose of the antihypertensive agent. This is because use of such drugs is inevitable in most of the patients to whom they are indicated(35)

Drug-drug interactions resulting from use of antihypertensive drugs usually vary depending on the class of drug involved. For instance, diuretics are generally known to potentiate the blood-pressure-lowering effects of all other antihypertensive drug classes (72).

It is therefore important to use diuretics cautiously when administered at the same time with other antihypertensives to prevent hypotension. Diuretics are mainly excreted through the kidney.

They are known to increase both diuresis and natriuresis and therefore can interfere or be interfered with by other drugs that are majorly eliminated through the renal route. Diuretics have also been shown to precipitate lithium toxicity. According to a cohort study by Ott *et al*(73) 3% of the cases of lithium intoxication were attributed to diuretic use.

Thiazide diuretics were shown to have the greatest potential to raise lithium concentrations, with a significant increase in concentrations after initiation of therapy. On the other hand, osmotic diuretics appear to increase lithium clearance and have been recommend as antidotes for lithium toxicity(74).

Loop diuretic are known to potentiate ototoxicity when used at the same time with drugs such as aminoglycosides(75). Estimates of the prevalence of ototoxicity have been found to differ across the literature. The prevalence ranges between 2%–25% for hearing deficits and 1%–10% for vestibular damage(76).

According to Haybach (77), about 10% of patients receiving aminoglycoside treatment may develop ototoxicity with 3% of these patients developing permanent damages This problem is compounded by the use of loop diuretics such as high dose furosemide which was associated with an incidence of 6% in causing ototoxicity. The severity of this damage depends on the age of patient, dose as well as duration of treatment with a diuretic or aminoglycoside or both. The use of aminoglycosides with diuretics is

therefore not recommended(78).However, when their use is inevitable vigilant monitoring of therapy should be observed. Furthermore, hearing tests should be carried out regularly to avoid hearing damage in these patients(79).

Beta blockers are generally well tolerated and DDIs are usually few(80). Combination of beta blockers with other classes of antihypertensives is important in achieving BP control(81). Although long-acting CCBs and beta blockers is an ideal combination for achieving BP, the combination is not recommended because of precipitation of bradycardia and AV block.

The concomitant use of verapamil or high dose diltiazem and beta blockers is not recommended. Mcgourty *et al*(82) found an increased incidence (26%) of bradycardia in patients on verapamil and beta blockers compared to those on beta blockers alone (12%).

Calcium channel blockers (CCBs) are known to potentiate orthostatic hypotension when concomitantly administered with central nervous system depressants. According to Kamaruzzaman *et a*l (83), about 11% of orthostatic hypotension cases were associated with CCBs. Also, 28% of orthostatic hypotension cases were due to CNS depressants. This indicates that the two classes of drugs have significant potential in causing hypotension and should, therefore, be used with caution when prescribed together.

2.3.3 Drug interactions between antihypertensives and hypoglycemic drugs

Several drug-drug interactions between antidiabetic drugs and some classes of antihypertensives have been identified. Many of these DDIs are of moderate clinical significance. Close monitoring of blood glucose levels is recommended when these combinations are administered(84).

A study by Samardzic (46) found out that the most common DDI was attributed to thiazide diuretics (46). The potential DDI between metformin and hydrochlorothiazide, was the most common. Thiazide diuretics were found to decrease the hypoglycemic effect of antidiabetic drugs.

This negative metabolic effects may be attributed to impaired insulin sensitivity, increased basal insulin concentrations, and increased insulin resistance(85). To minimize

potential adverse metabolic effects, it is recommended to start thiazide diuretics at the lowest possible dose.

It has also been shown that the combination of thiazides and beta blockers increases the likelihood of developing type 2 diabetes. For instance, Stump *et al*(86), noted a higher risk of developing type 2 DM with use of beta blockers and thiazide diuretics compared with treatment with either ACEIs, ARBs or calcium channel blockers.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attacks Trial (ALLHAT), chlorthalidone was found to be 43% more likely to cause diabetes than lisinopril and 18% more likely than amlodipine, (87). However, it is unclear whether treatment with thiazide diuretics or beta blockers in diabetic patients leads to any clinically significant adverse events(88). The need to control hypertension in patients with diabetes is, therefore, more important than the possible adverse events. This is because the treatment of hypertension in diabetic patients reduces the incidence of macrovascular complications(89). Meta-analysis studies also recommend that control of blood pressure should be given more priority over drug selection(90).

The most commonly prescribed antidiabetic drug is metformin. The use of metformin is associated with lactic acidosis. As a result, an antihypertensive medication which worsens renal function can lead to the accumulation of metformin and consequently raise the risk of lactic acidosis. Such medications include loop diuretics.

In a cohort study by De Silva *et al* (91), it was shown that using loop diuretics led to an increased risk of deterioration of renal function by 50% over 6 months in patients with chronic heart failure.

Beta-blockers have also been implicated in increased incidences of hypoglycemic reactions when used at the same time with sulfonylureas. Beta-blockers usually mask tachycardia as an initial symptom of hypoglycemia with a higher incidence occurring with non-selective beta blockers(92). Beta-blockers such as bisoprolol or metoprolol are therefore safer for diabetic patients than nonselective beta-blockers(93).

Table 1 shows some drug-drug interactions between antidiabetics and antihypertensives and their respective clinical outcomes.

Table 1: Common drug-drug interactions among antidiabetic and antihypertensive drugs

Drug class	Example of interaction	Clinical significance
Thiazide and thiazide-like diuretics	metformin–hydrochlorothiazide	Thiazide diuretics may lower the therapeutic effect of metformin
ACE inhibitors	glimepiride - ramipril	ACEis may potentiate the blood-glucose-lowering effect of sulfonylureas
Beta blockers	glimepiride - bisoprolol	Beta-blockers may potentiate the hypoglycemic effect of sulfonylureas
Loop diuretics	glimepiride - furosemide	Loop diuretics may decrease the hypoglycemic effect of antidiabetic drugs.
ARBs	glimepiride - losartan	Losartan may decrease the metabolism of sulfonylureas

2.3.4 How to avoid unwanted drug-drug interactions in clinical practice

It is important to prevent drug-drug interactions before initiation of drug therapy for diabetic and hypertensive patients. For instance, the clinician should ensure that they have a full and clear medication history. This includes over-the-counter medication as well as herbal remedies.

Based on knowledge of the clinical effects of the drugs involved, potential pharmacodynamic drug-drug interactions can be anticipated. This raises the need to have adequate pharmacological knowledge (94).

The clinician should also prescribe few drugs in addition to knowing them well. Pharmacokinetic drug–drug interactions are however more difficult to anticipate. This is because they cannot be predicted from the clinical effects of the drugs being prescribed.

Also, recognition of drugs with narrow therapeutic indices and the major risk factors of pharmacokinetic interactions can be crucial in identification of potential drug-drug interactions. Monitoring for adverse drug events or lack of efficacy should also be part of management of patients suffering from diabetes and hypertension. Observing for changes in biomarkers of effect, symptoms or plasma drug levels after prescription can also be useful in identifying drug-drug interactions .Identification of potential DDIs can be useful in reducing harmful effects(95).

2.3.5. Clinical resources for identification of drug–drug interactions

There exist several resources that are available to clinicians for prevention of drug–drug interactions. Such resources include drug-drug interaction checkers which include Lexi-Interact, Medscape, Micromedex Drug Interactions, iFacts, and Epocrates(96).

According to Kheshti *et a*l (96), Lexi-Interact and Epocrates provided the most accurate information on DDIs. Micromedex, Medscape, and iFacts ranked followed in that order. On the other hand, iFacts was the most comprehensive followed by Lexi-Interact. Generally, Lexi-Interact and Micromedex were found to provide competent, complete, easy to use drug interaction checking programs. The study also recommended Lexi-Interact and Micromedex as the most effective and preferably used drug-drug interaction checker.

The clinicians may also refer to current treatment guidelines and drug formularies, such as the British National Formulary. Also, the Australian Medicines Handbook usually has tables listing the major risk factors of pharmacokinetic drug-drug interactions(97)

2.3.6 Strategies for minimization of potential drug interactions among diabetic hypertensive patients

As discussed earlier, several DDIs usually occur between antidiabetic medications and antihypertensive drugs. These interactions may interfere with glycemic or BP control and

consequently lead to adverse drug reactions(60). It is, therefore, crucial to monitor the patient's glucose and BP levels closely.

This has led to the reduction of mortality and morbidity in patients with both DM coexisting HTN(98). For instance, a decrease of HbA1c levels leads to a corresponding decrease in the risk of developing diabetic neuropathy, heart failure and diabetic neuropathy (99).

For instance, McDonnel *et al*(100) found out that 80% of adverse drug reactions were associated with documentation of abnormal physiologic laboratory values associated with the disease or toxic plasma concentrations of a particular drug. Also, the study established that 67% of ADRs were as a result of inadequate drug therapy monitoring. This, therefore, raises the need for regular monitoring of laboratory values associated with the treatment of a particular disease or condition. Krishnan *et al*(101) found that about 47% of patients being treated for DM and other comorbidities had UGC. Of these patients, 23% of the cases of uncontrolled glycemia were due to a drug-drug interaction. Amongst drugs implicated in UGC, diuretics accounted for about 80% of the cases. Salbutamol (9%), cortisones (6%) and other drugs (6%) were also responsible for uncontrolled glycemia. The study also established that about 40% of the study participants did not have HbA1c monitoring in the last 3 months. Among these, 48% had UCG.

The use of thiazide diuretics and spironolactone with metformin may potentiate diuretic-induced renal impairment and precipitate metformin-associated lactic acidosis(17).These patients should, therefore, be checked for signs of lactic acidosis such as hyperventilation, abdominal pain, respiratory distress, malaise, and irregular heartbeat. Tests of renal function such as serum creatinine as well as glomerular filtration rate should also be done regularly for these patients(55).

Dosage correction of metformin might also be required. Diabetic patients on beta blockers should also have their blood glucose closely monitored. This is because beta blockers usually cause hypoglycemia, especially when used with sulfonylureas(92).

Establishing a monitoring plan, in addition, to use of drug-drug interaction checkers and clinical practice guidelines is important in reducing the risk for developing DDI in hypertensive diabetic patients(102). For instance, table 2 shows the recommended targets for BP and blood glucose monitoring by the Kenya guideline on management of type 2 diabetes mellitus.

Table 2: Optimal targets for glycemic and blood pressure control in people with diabetes

Biochemical index	**Optimal targets**
Capillary blood glucose(finger-prick)	4-6.7 mmol/l
2hrs-post prandial	4-8mmol/l
Glycated hemoglobin (HbA1C)	<7%
Blood pressure	<130/80 mmHg
BP with persistent proteinuria	<125/75mmHg

The guidelines recommend that HbA1C tests are supposed to be done at least twice yearly in patients with type 2 diabetes on treatment with hypoglycemics. However, due to the unavailability of this test in most primary and secondary health facilities, a combination of capillary blood glucose and postprandial glucose is done as an alternative (43). Where possible, self-monitoring of blood sugar is recommended. However, in addition to self-monitoring regular supportive cointervention by a clinician or pharmacist is equally important pressure and blood glucose should be measured and recorded at each patient's clinic visit(103).

Supportive measures include assessment of blood glucose, BP which should be done at least once in every 3 months. Potential DDIs and dose adjustment are also interventions that can occur during a patient visit to the diabetic clinic(104). In a study by Hu *et al*(105), there was inconsistency in monitoring of blood glucose.

The study found that only 57% of patients complied with monitoring of blood sugar on their own. This study showed that there is need for supportive cointervention in the monitoring of treatment hypertensive diabetic patients.

2.3.7: Research gap

The major gaps in these literature reviews were inadequate local studies on potential drug-drug interactions in diabetic hypertensive patients. Related studies have been done in the UK(5) and other European countries such as Croatia. This, therefore, creates a need to carry out such a study locally because of the limited data on drug-drug interactions in hypertensive diabetic patients. Locally, Mwengi *et al* (24), studied the management of hypertension among adult diabetic hypertensive outpatients with chronic kidney disease(CKD) at KNH. However, despite having a study population with hypertensive diabetic patients, the study did not assess potential drug-drug interactions in this study population.

In another local study, Guantai *et al*(23) carried out a study on potential drug interactions in hypertensive patients at Kenyatta National. However, studies among participants with both DM and HTN remain to be done. Additionally, Mongi *et al*(20) evaluated the management of hypertension in diabetic and non-diabetic adult patients at KNH(20). While the study described the prescription patterns in hypertensive diabetic patients at KNH, it did not dwell on potential drug-drug interactions. Furthermore, the local studies did not take into account the clinical relevance of the potential drug interactions as proposed in the current study.

Another gap is that some studies did not indicate the classes of potential DDIs in terms of severity. For instance, a study by Samardzic (45) indicated the prevalence of various drug-drug interactions but did not indicate the severity of the drug interaction. The severity of drug interaction is important since it guides the clinician on possible mitigation measures(106). Also, some studies done outside the country had gaps such as the exclusion of all age groups. For instance, a study by Neto *et al*(40) on potential DDIs in diabetic or hypertensive patients only elderly patients were included.

The present study, assesses potential drug-drug interactions, their severity and clinical significance among hypertensive diabetic patients in order to fill the literature gaps. The current study findings would help clinicians and pharmacists in making informed choices prescribing and dispensing these medications to avoid potential drug interactions and their possible effects.

CHAPTER THREE: METHODOLOGY

3.1 Study design

A descriptive cross-sectional study design was used. This design was used because it captures useful descriptive information from the population phenomena at a specific point in time(107). The study aimed to find out the prevalence and clinical significance of potential drug-drug interactions. Cross-sectional studies are suitable in research that involves determining prevailing characteristic in a given population and thus its relevance in the present study.

3.2 Study area and site

The present study was done at Kenyatta National Hospital, a public referral hospital between April and August 2019. It is the largest hospital in Kenya and also the teaching hospital for the University of Nairobi College of Health Sciences and Kenya Medical Training College, Nairobi(106). The hospital has a bed capacity of about 1800 with 50 wards and 22 outpatient clinics. Kenyatta National Hospital was selected as the study area because it takes care of a large number of diabetic and hypertensive patients from all over the country. Furthermore, there are few studies carried out at KNH on potential drug-drug interactions among diabetic hypertensive patients.

The study site was the Diabetic and Endocrinology outpatient clinic (DEOPC). It is located about 500m from the main hospital block, adjacent to the Government Chemist. The clinic is the main entry point for patients diagnosed with DM. Over 60% of these patients have pre-existing hypertension or later develop hypertension. These patients are usually enrolled for appropriate therapy and follow up in the clinic. In other cases, some patients from other facilities across the country are referred to KNH where they are treated in KNH wards and later discharged through the DEOPC for enrollment in outpatient care services and follow-up.

DM clinics also run on Monday, Tuesday and Thursday but the main DM clinic was on Friday. Both endocrinology and DM clinic ran on Wednesdays. About 150 patients with diabetes were seen at the DEOPC every week where 60% have both diabetes and hypertension.

3.3 Target and study population

The target study population was adults (aged ≥18 years) diabetic hypertensive patients out of which the study population was drawn from patients receiving antidiabetic and antihypertensive drug treatment at the DEOPC in Kenyatta National Hospital.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

1. Those who gave voluntary informed consent

2. Adults (aged≥18 years) diagnosed with comorbid HTN and DM.

3. Those undergoing treatment for both HTN and DM

4.Patients on at least one antihypertensive drug and one hypoglycemic agent.

3.4.2 Exclusion criteria

1. Those who declined to give consent.

2. Pregnant women because of the physiological changes that may affect the pharmacokinetics and effect of drugs used for both hypertension and diabetes. Furthermore, the choice of drugs for the management of HTN in these patients is limited and dependent on the trimester of the pregnancy due to potential harm to the fetus.

3. Patients with End-stage renal disease (ESRD) or liver disease because these conditions were likely to alter the pharmacokinetics of antihypertensive and antidiabetic agents. This will, in turn, affect drug-drug interactions as well as glycemic and BP control in this population.

4. Psychiatric patients, patients with dementia and Parkinson's disease. These patients were likely to be mentally unstable and therefore challenging in consenting and subsequent enrollment into the study.

3.5 Sample size

The primary outcome of interest in the present study was the prevalence of potential drug-drug interactions among diabetic hypertensive adult outpatients. Currently available studies on drug-drug interactions among different populations indicate a prevalence varying between 92-96%(14,20).The Cochran (1977) formula was used because it is applicable for surveys.

Therefore, the sample size was calculated as follows:

$n=Z^2pq/d2$

Where;

n=Sample Size;

Z=1.96 (the value of Z corresponding to 95% confidence level).

P=prevalence=94%=0.94(the average estimated prevalence of potential drug-drug interactions from previous studies)

q=l-p=l-0.94=0.06;

d=0.05(the desired precision for this study will be 0.05 which is generally the expected margin of error for most scientific research as well as categorical variables in descriptive studies

By substituting z, p, q, and d;

$n= (1.96^2x0.94x0.94x0.06)/0.05^2$

n= (0.2167/0.0025)

n=86

To cater for non-response, an additional 20% (18participants) were added to make a total of 104 participants.

3.6 Sampling technique, participant recruitment, and consenting process

Random sampling was carried out. This was done to ensure that the sample obtained was truly representative of the target population and to avoid bias. It was expected that all participants meeting the inclusion criteria had an equal chance of being included in the present study. The medical files for patients booked for a particular day are usually obtained from the Health Information Department of Kenyatta National Hospital in the morning of a particular DM clinic day. The files are then taken to the Diabetes and Endocrinology Outpatient Clinic by the records officer and placed in the various clinician rooms. In the present study, the Principal Investigator (PI) went through the files beforehand to come up with a list of adult patients meeting the inclusion criteria. The list of the outpatients' unique file numbers that fitted the inclusion criteria formed a sampling frame. These files were then be tagged for ease of identification from the other patient files. Colored tags were attached firmly on the files to ensure that they remained on the selected files until the end of the study when they were being removed.

On average, about 90 patients attending the DEOPC clinic every week have comorbid HTN and DM. The patients are usually received by the nurse on duty for checking blood sugar and vital signs. The patients are then called to proceed to the clinician's rooms in order of arrival. The principal investigator coordinated with the clinician on duty to ensure that patients with tagged files were allowed to proceed to the PI. This was done to ensure that the normal flow of work was not interrupted.

Once before the PI, a coin was tossed. The 'head' side of the coin was used to decide on which patient to consider for consenting and possible inclusion in the study. Patients who got the 'tail' side of the coin were not considered for consenting and possible inclusion in the study. This indicated a 50% chance of a patient's consideration for inclusion in the study.

This procedure was repeated until an average weekly target of 25 patients is attained.

The patients who got 'heads' after the coin was tossed were first taken through the informed consent process and only those who voluntarily agreed to undertake the present study were included in the study.

It was explained to the patient that participation in the study was to be voluntary whereas refusal to participate in the study would not affect their right to receive care at the clinic. In about five weeks, the desired sample size of 104 participants was attained.

The patients visiting the DEOPC on the minor clinic days are mostly on a monthly or quarterly clinic. These clinics usually take place on Monday, Tuesday, and Thursday and usually involve minor reviews on patient's medication as well as glycemic and BP control. Those attending the major review clinics which take place on Fridays are usually on semi-annual or annual clinics appointments. To avoid duplicate sampling of the patients attending minor clinics over the five weeks of the study, different tags were placed on the files after the first four weeks to distinguish the files.

3.7 Data collection and Study variables.

Upon consenting to participate in the study and signing the declaration forms, copies of these forms were availed to the participant for their reference. Data on patient social demographics were obtained from a brief history taking from patients who gave consent and had been selected for the study. This information was entered into the data collection form (Appendix 4). Data on comorbidities, antidiabetic and antihypertensive drug therapy was abstracted from the patient's file using the data abstraction form. Any potential drug-drug interaction was noted in the data collection form upon entry of one drug followed by subsequent drugs into the Micromedex drug reaction checker (109). The results from the Micromedex interaction checker gave data on the severity and effects of potential DDIs.

To identify strategies for minimization of potential drug interactions among adult diabetic hypertensive outpatients at KNH, data on patient monitoring parameters was collected from the patient's medical file.

This included the presence or absence of evidence for various monitoring parameters for both blood glucose and BP in the last three months. Lab monitoring parameters included blood pressure, blood glucose and other relevant tests depending on the clinical outcome of possible DDI. Adequacy of blood glucose and BP was also be checked by comparing the current BP and blood glucose with targets from clinical practice guidelines.

3.8 Research instruments

The abstracted data from the patient medical files on current medication was checked for potential DDIs using the Micromedex drug interaction checker(112). Upon feeding one drug followed by subsequent drugs, into the program, the Micromedex electronic database was used to identify the type as well as the clinical significance of the potential drug interaction among adult diabetic hypertensive outpatients at KNH.

Micromedex has a separate section known as the Drug-REAX System which describes the DDIs. When the drugs are entered one by one, the program provides the possible DDIs. It also describes existing DDI combinations, their severity, onset and documentation status, in the prescribed regimens. This was then abstracted into a drug-drug interaction data collection form (Appendix 4). This data was then entered and saved into Microsoft Excel 2016.

The information in the data collection form as extracted from Micromedex enabled the classification of DDIs as major, moderate, or minor. The information also helped in finding the prevalence of potential drug-drug interactions which was established by determining the number of potential drug-drug interactions per patients' prescription.

The potential DDIs were then characterized in terms of the individual drugs and their pharmacological classes as well as the frequency with which they were involved in such interactions when prescribed with other drugs for the treatment of both diabetes and hypertension.

The data collection tool also included information on the monitoring of BP and blood glucose for common drug interactions between oral hypoglycemic agents and antihypertensive drugs. The monitoring parameters for BP and blood glucose were used as strategies for minimization of potential DDIs.

3.9 Pilot study

A pilot study was executed to test the completeness, relevance, and efficiency of data collection. This was carried out with 10 subjects (about 10% of the study sample).

3.10 Validity

The validity of the study was achieved and maintained by ensuring that the data collection form was well laid out and relevant concerning the objectives of the study. Also, the study site chosen was expected to give good representation of the general population since KNH, and by extension, DEOPC attends to patients from all parts of Kenya. Also, the sample size used in the study was adequate as per scientific requirements.

3.11 Reliability

Data collection tools were pre-tested as described under the pilot study section for reproducibility before the actual study was done to ensure there are clear and precise responses throughout the study. No amendments were carried out on the instruments as they were expected to be effective and efficient.

3.12 Data management

3.12.1 Data processing

Upon collection, the raw data was be coded. This was followed by entry into a pre-formed Microsoft Excel database version 2016. Daily and routine entries of data were carried out. This was accompanied by routinely checking for completeness and accuracy. Any inconsistencies identified in this process were rectified immediately.

This was followed by daily backing of the database in two hard drives. Once data entry was completed, it was exported to the STATA version 13 software for analysis.

All data entry was done by the principal investigator (PI) and was password-protected. Backed up data was only accessible to the PI only. Also, data cleaning was carried out to correct any errors that may have occurred during the entry process.

3.12.2 Statistical analysis

Data analysis was executed using the STATA version 13 software. Exploratory data analysis (EDA) was done to summarize main characteristics such as age, gender, number of drugs per patient by use of visual methods such as bar charts, histograms and box plots. Information on number of medications was summarized as median and interquartile ranges (IQR). Categorical variables, such as gender, number of potential DDIs per patient and severity of potential DDIs were presented in the form of frequency and percentage tables.

Prevalence was used to illustrate the proportion of hypertensive DM patients visiting the DEOPC who had at least one interacting pair of drugs It was also used to estimate the proportion of patients for each one of the most common interacting pairs. Association between the dependent variable (prevalence of DDIs) and predictive variables (sociodemographic factors, clinical characteristics, polypharmacy and use of a particular class of drug) was determined using bivariate and multivariate logistic regression analysis.

To analyze for strategies for minimization of potential DDIs simple descriptive statistics, such as mean, median mode, range and confidence intervals was used. Such measures included monitoring of BP, blood pressure and other parameters relevant to the potential DDI. The presence or absence of these monitoring parameters as well as adequacy of BP and blood glucose control was presented in frequency tables, bar graphs, and pie charts.

The odds ratios and confidence intervals (CI) were calculated for each variable. The level of significance was set at 0.05.

3.13 Ethical considerations

3.13.1 Ethical approval

Seeking of ethical approval to conduct the study and subsequent registration was carried out through the Kenyatta National Hospital/University of Nairobi- Ethics and Research Committee (KNH/UoN–ERC) under reference number KNH-ERC/A/192. Authority to carry out the study was also granted by the Department of Research and Programs at KNH under reference number MED/42B/VOL.11/. The participants then, signed a

consent declaration form after agreeing to participate in the research (Appendix 3). Participants' data were confidentially stored and concealed by serialized unique numerical identifiers used throughout the study.

Study participants were made aware that the study was voluntary. As such, they were free to withdraw from the research at any point. They were also made aware that they were free to ask any questions and seek clarification about the study during the interview. Furthermore, they were informed that if they have any further concerns about their rights as participants, they were free to contact the KNH/UoN-ERC or the supervisors via contact details provided.

3.13.2 Confidentiality

Participants' unique numbers were generated and used instead of names during the data analysis process to safeguard the participant's identity. Data collection materials were safeguarded by keeping them under lock and key during the entire study.

3.13.3 Risks involved

The present study did not involve any invasive procedures and therefore there were minimal risks to the participants.

3.13.4 Benefits from the study

Findings from the present study were shared with the various concerned departments as well as the participant's regular clinician with the hope of improving patient care. If a potential drug interaction of clinical significance was identified during data collection and before the patients left the hospital, it was documented and also reported to the prescriber for mitigation. Mitigation measures included the removal of the drug from the entire treatment regimen or substitution with another drug where appropriate.

It was expected that prescribers will be enlightened on making informed choices when managing diabetic hypertensive patients. This will promote rational prescribing which will reduce and prevent drug-drug reactions.

3.14 Dissemination plan

The research findings would be shared with medical scholars at the University of Nairobi through the Ministry of Health Department of Curative and Rehabilitative Services aiming at influencing policies and treatment guidelines development. The findings will also be disseminated to the Pharmacy and Poisons Board Department of Pharmacovigilance unit and Kenyatta National Hospital aiming at improving prescribing patterns among clinicians hence influencing patient treatment outcomes. The research findings will also be published in an open access peer-reviewed journal. Also, the dissertation upon completion is expected to be freely accessible in the School of Pharmacy's library.

CHAPTER FOUR: RESULTS

4.1 Sociodemographic characteristics of the study population

Data on sociodemographic characteristics of the study participants was collected and recorded from 104 participants. Their sociodemographic characteristics are presented in **Table 3**.

Table 3: Socio-demographic characteristics (N=104)

Variable	Characteristic	Participants (n)	Percentage (%)
Gender			
	Male	31	29.8
	Female	73	**70.2**
Age (years)			
	18-45 years	7	6.7
	46-59 years	35	33.7
	>59 years	62	**59.6**
Body Mass Index			
	Ideal (18.5 - 24.9)	30	28.8
	Overweight (25.0 - 29.9)	47	**45.2**
	Obese (≥30.0)	27	26.0
Marital status			
	Single	13	12.5
	Married	68	**65.4**
	Separated	1	1.0
	Widowed	22	21.2
Religion			
	Christians	96	**92.3**
	Muslim	8	7.7
Occupation			
	Farmer	15	14.4
	Business/ Self-Employment	26	25.0
	Formal Employment	16	15.4
	Unemployed/retired	47	45.2
Level of education	Informal	5	4.8
	Primary	35	33.7
	Secondary	54	51.9
	College/University	10	9.6

There was gender disparity as majority of the study population (73, 70.2%), were females while (31, 29.8%) were males. The mean age of the patients was 61.6 years (SD±10.8). The youngest and oldest participants were 29 and 87 years old, respectively. The elderly (62,59.6%) represented the largest group. Almost half (47, 45.2%) of the participants were overweight while approximately a quarter (28.8%) maintaining ideal body weight. Most participants (96, 92.3%) were Christians and about half (47,45.2%) were either unemployed or retired. It was also noted that over 95% had at least a primary level of education (Table 3).

4.2 Clinical characteristics of the study population

The diagnosis of diabetes mellitus and hypertension, as well as the presence or absence of additional comorbidities, is represented in **Table 4.**

Table 4: Clinical characteristics of the study patients (N=104)

Variable	Characteristic	Participants(n)	Percentage (%)
Diabetes	Type 1	3	2.9
	Type 2	100	**96.2**
	Other	1	0.9
Duration of Diabetes	<1 year	10	9.6
	1 year	4	3.8
	2 years	2	1.9
	3 years	3	2.9
	More than 3 years	85	**81.8**
Hypertension	Stage 1,2,3	98	**94.3**
	stage 2	35	33.7
	stage 3	18	17.3
	Other	6	5.7
Duration of hypertension	< 1 year	7	6.7
	1 year	3	2.9
	2 years	2	1.9
	3 years	4	3.8
	> 3 years	88	**84.7**

The majority (96.2%) of the study population had type 2 diabetes. It was also noted that over three quarters (81.6%) of the study population had lived with diabetes mellitus for more than three years. In addition to diabetes mellitus, the study population had hypertension as a comorbidity.

The majority, (43.3%) had stage 2 hypertension with 84.7% of the study participants having lived with hypertension for more than 3 years (Table 4).

4.3 Prescription pattern of antidiabetics and antihypertensives

The frequency of use of various antihypertensive and antidiabetic classes of drugs in the study population is presented in **Figures 2 ,3 and 4.** The percentages depict the proportion of the study population using the specific class of drugs.

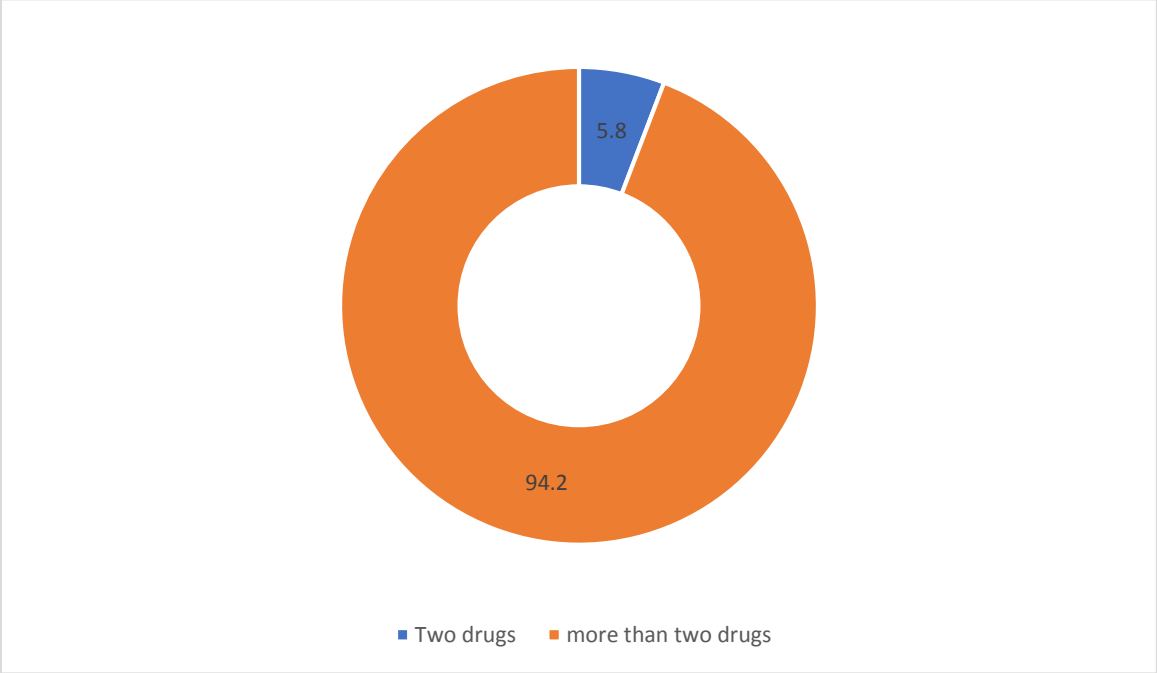


Figure 2: Number of antidiabetic and antihypertensive drugs

Most participants (94.2%) were on more than two drugs for both hypertension and diabetes with (5.8%) on two drugs as shown in **Figure 2**.

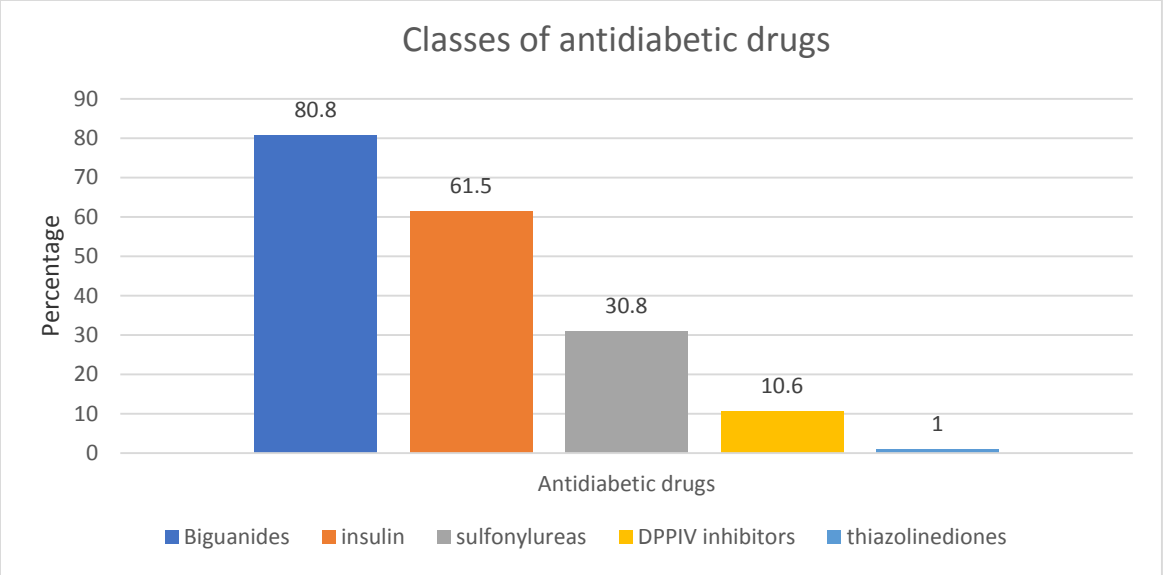


Figure 3: Prescribing pattern of antidiabetic drugs

Key: DPPIV= dipeptidyl peptidase 4

Among antidiabetics, biguanides were the most prescribed (84,80.8%), followed by insulin (61.5%), sulfonylureas (30.8%) dipeptidyl peptidase-4 inhibitors (10.6%) and thiazolinediones (1%) (Figure 3).

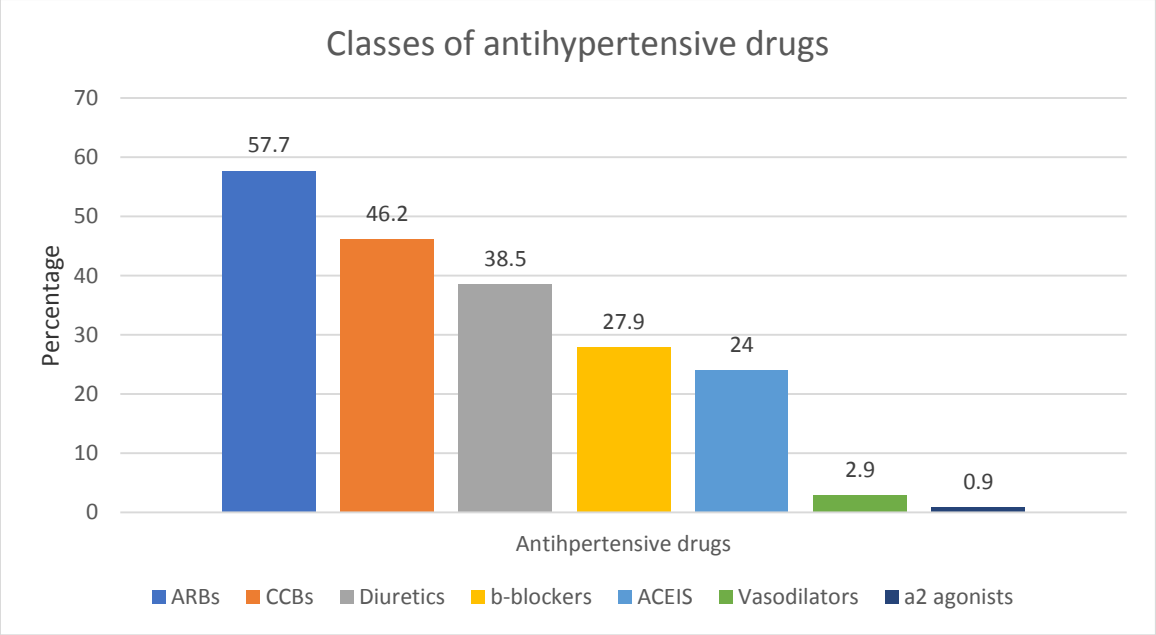


Figure 4: Prescribing pattern of antihypertensives

Key: ACEI= angiotensin-converting enzyme inhibitor ARB=angiotensin receptor blocker CCB=calcium channel blocker

Among antihypertensives, angiotensin receptor blockers (ARBs) were the most frequently prescribed (57.7%) followed by calcium channel blockers (CCBs) (46.2%), diuretics (38.5%), β-blockers (27.9%) and angiotensin-converting enzyme (ACE) inhibitors (24%). The rest were vasodilators or centrally acting antiadrenergics. Most participants were being managed on more than one class of drugs and therefore the percentages do not necessarily add up to 100% (Figure 4).

4.3.1 Frequency of use of specific drugs per class

The frequency of use of specific drug classes is illustrated in **Table 5** below.

Table 5: Prescription pattern of antidiabetics and antihypertensives(N=104)

Variable	Characteristic	Participants (n)	Percentage(%)
ACEI	Enalapril	23	**22.1**
	Other ACEIs	3	2.9
ARB	Losartan	47	**45.2**
Other ARBs	8	7.7	
Diuretics	Hydrochlorothiazide	27	**26**
	Furosemide	8	7.7
	Other diuretics	8	7.7
CCB	Nifedipine	19	**18.3**
	Amlodipine	30	**28.8**
β-blockers	Carvedilol	17	16.3
	Other β-blockers	11	10.6
α_2 agonists	Methyldopa	1	0.9
Sulfonylureas	Glibenclamide	23	**22.1**
	Other sulfonylureas	7	6.7
DPPIV inhibitors	Sitagliptin	11	**10.6**
Biguanides	Metformin	84	**80.8**

Key: ACEI=angiotensin converting enzyme inhibitor ARB=angiotensin receptor blocker CCB=calcium channel blocker DPPIV=dipeptidyl peptidase IV.

Metformin (84, 80.8%) was the most widely prescribed biguanide whereas the most preferred sulfonylurea was glibenclamide (23, 22.1%). Further, sitagliptin (11, 10.6%) was the most preferred DPPIV inhibitor.

Losartan (47, 45.2%) was the most widely prescribed ARB whereas the most preferred CCB was amlodipine (30, 28.8%) followed by nifedipine (19,18.3%). Also, enalapril (23, 22.1%) was the most preferred ACE inhibitor.

Among the diuretics, hydrochlorothiazide (27,26%) was the most prescribed followed by furosemide (LD) (8, 7.7%). Other classes of diuretics accounted for 7.7% of the diuretics prescribed. Among β –blockers, carvedilol (17,16.3%) was the most prescribed (Table 5).

4.4 Potential drug-drug interactions

4.4.1 Prevalence and Pattern of potential drug-drug interactions

The number, severity, and onset of potential DDIs are shown in **Table 6**.

Table 6: Prevalence and pattern of potential drug-drug interactions(N=104)

Variable	Characteristic	Participants (n)	Percentage(%)
DDI	Present	60	**57.7**
	Absent	44	42.3
Number of DDIs	One	60	**57.7**
	Two	21	20.2
	Three	3	2.9
Severity of DDIs	Minor	16	19
	Moderate	68	**81**
Onset of DDIs	Rapid	17	20.2
	Delayed	48	**57.1**
	Unspecified	19	22.7

Key: DDI=drug-drug interaction

A total of 84 drug-drug interactions were identified from the 104 patient prescriptions. Notably,57.7% of the study population had at least one drug-drug interaction. The average number of interactions was one (1). About a fifth (20.2%), of the prescriptions had two drug-drug interactions while 2.9% had three drug-drug interactions.

About three quarters (81%) of the prescriptions had moderate drug-drug interactions while the rest (19%) were minor. The onset of potential drug-drug interactions also varied, with 57.1% of the prescriptions having drug-drug interactions of delayed onset, while 22.7% and 20.2% had unspecified and rapid onset respectively (Table 6). The onset was specified in the results obtained from the Micromedex drug interaction checker. There were a total of 9 possibly interacting pairs of drugs as shown in **Figure 5.**

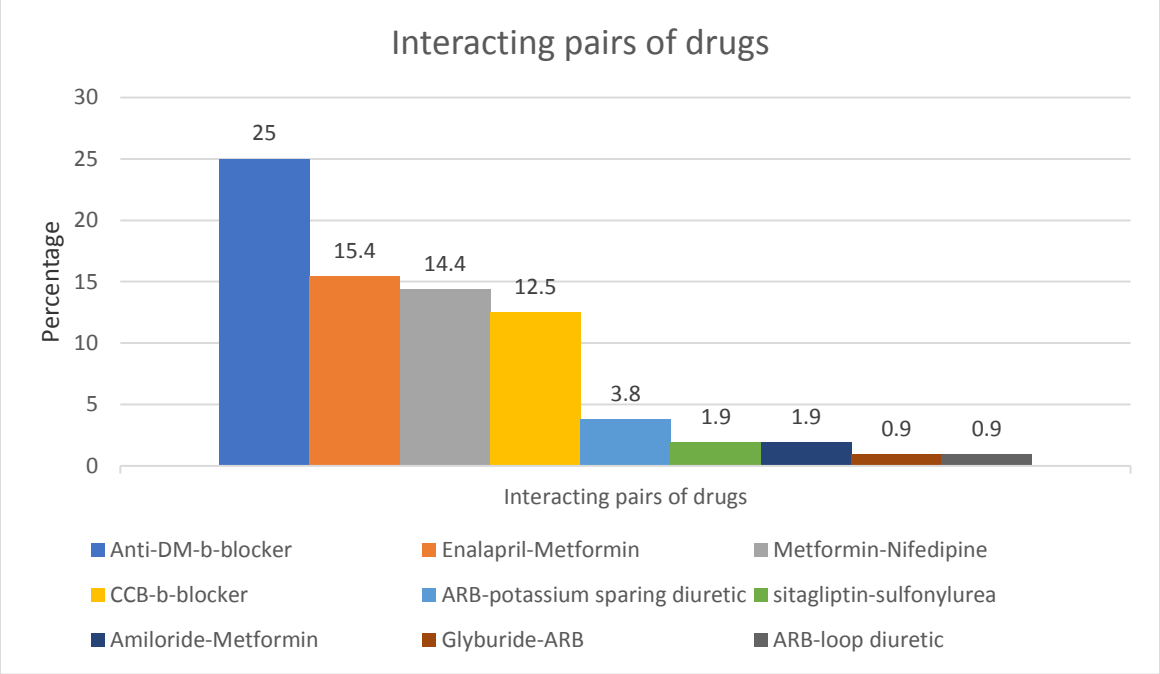


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Figure 5: Interacting pairs of antihypertensives and antidiabetics or both

Key: ARB=angiotensin receptor blocker CCB=calcium channel blocker DM=diabetes mellitus

The most common drug combination that could result into DDI was that of all antidiabetic drugs and a β-blocker (26, 25%) followed by enalapril and Metformin (16,15.4%), Metformin and Nifedipine (15,14.4%) and calcium channel blockers and β -blockers (12, 12.5%). Other potential DDIs included those between ARBs and potassium-sparing diuretics, sitagliptin and sulfonylureas, amiloride and metformin, ARB and thiazide diuretics, ARB and loop diuretics and glyburide and ARBs (Figure 5).

4.5 Clinical significance of potential Drug-drug interactions

The clinical outcomes of potential drug-drug interactions are illustrated in **Figure 6.**

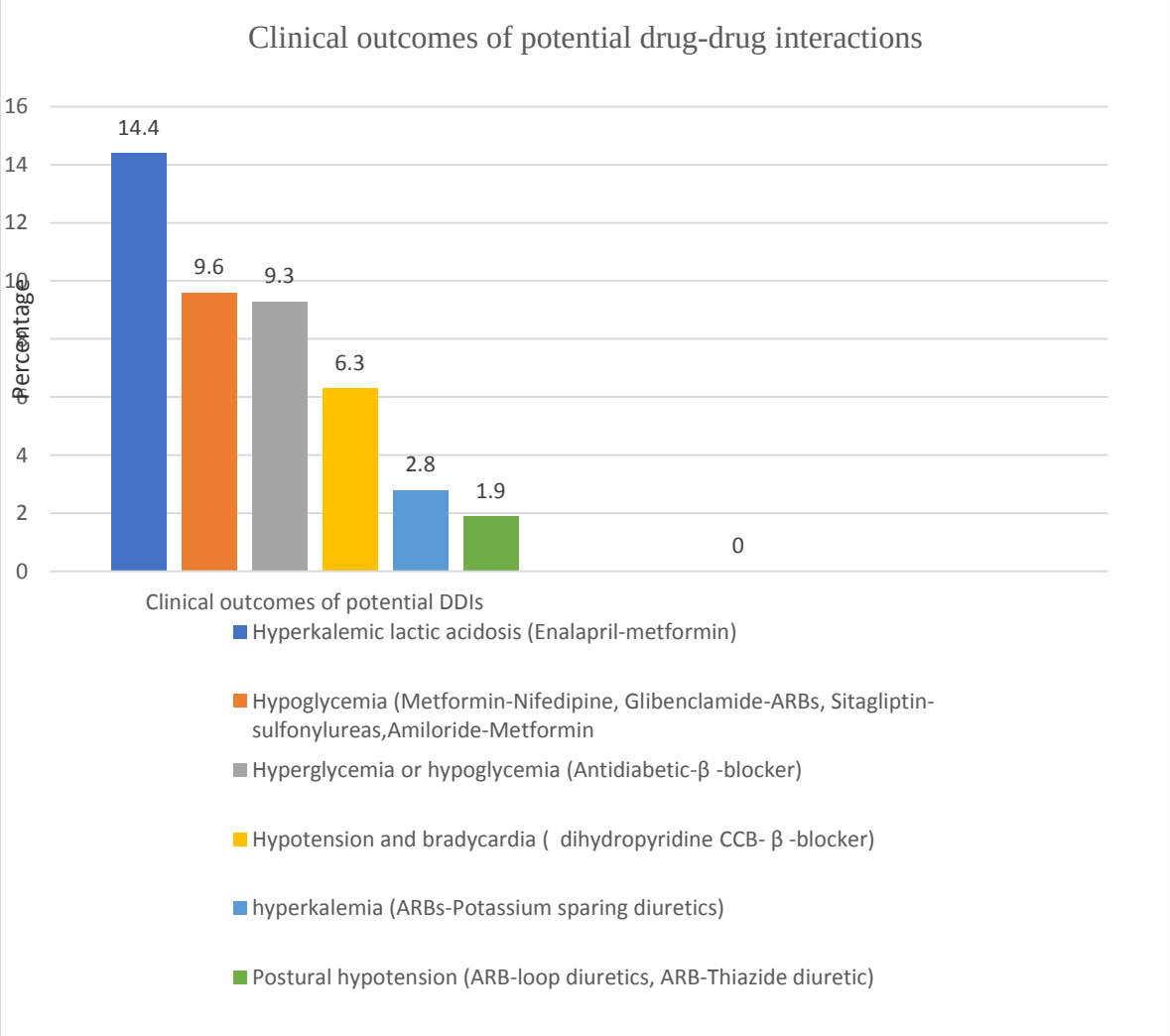


Figure 6: Clinical outcomes of potential drug-drug interactions

Key: ARB=angiotensin receptor blocker, CCB=calcium channel blocker, DDI= drug-drug interaction, DM=diabetes mellitus

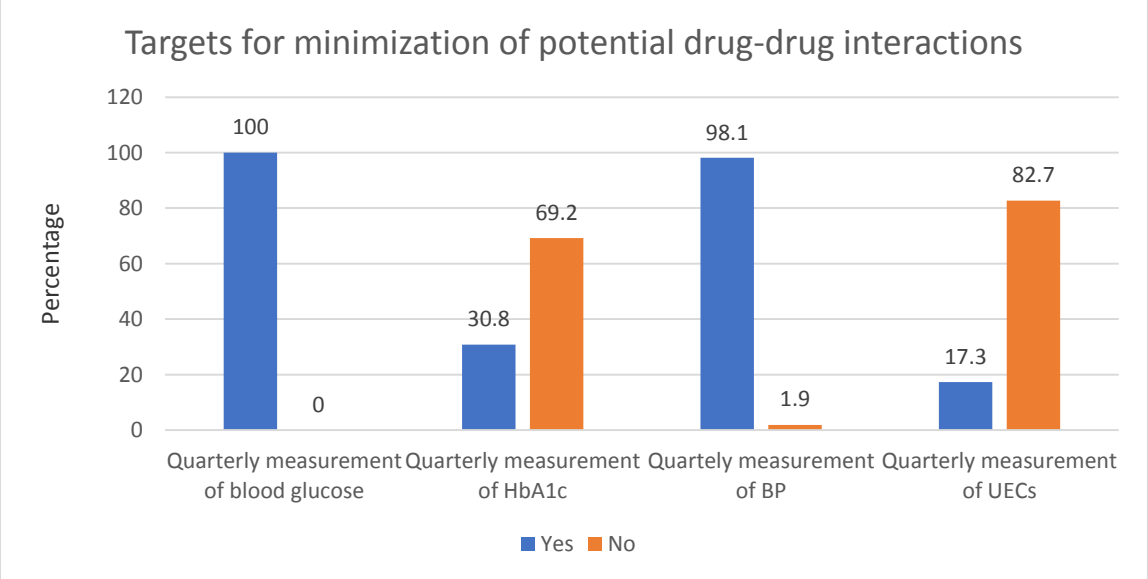
The most common clinical outcome of the potential drug-drug interaction was hyperkalemic lactic acidosis (14.4%) as a result of the use of a combination of metformin and enalapril. This was followed by hypoglycemia (9.6%) resulting from the use of combinations of metformin and nifedipine, glyburide and ARBs, amiloride and metformin as well as the use of sitagliptin and sulfonylureas.

Potential uncontrolled blood sugar levels (hypoglycemia or hyperglycemia) (9.3%) resulting from the use of antidiabetic drugs and b-blockers was also noted. Hypotension and bradycardia (6.3%) were also potentially present induced by the combination of dihydropyridine CCBs and β -blockers while hyperkalemia (2.8%) alone resulted from use of ARBs and potassium sparing diuretics.

A small portion of the study populations had prescriptions resulting into postural hypotension (1.9%) as a result of a combination of ARBs and loop diuretics as well as ARBs and thiazide diuretics (Figure 6).

4.6 Strategies for minimization of potential drug-drug interactions

The frequency of various monitoring parameters aimed at minimizing potential drug-drug interactions is shown in **Figure 7**.



.Figure 7*:* Strategies for minimization of potential drug-drug interactions

Key: DDI= drug-drug interaction, HbA1C=hemoglobin A1C, UEC=urea creatinine and electrolytes

All participants (100%) had blood sugar checked in the last three months while - (98.1%) had blood pressure also checked within the same period. On the other hand, about a third (30.8%) of the study population had their HbA1c levels checked in the last 3 months while 17.3% had urea and electrolyte levels checked in the same period (Figure7).

4.7 Relationship between sociodemographic characteristics of the study participants and drug-drug interactions

The presence or absence of drug-drug interactions was compared with the sociodemographic characteristics of the study population. The results obtained are summarized in **Table 7.**

Table 7: Association between sociodemographic characteristics of the study participants and drug-drug interactions

Variable	Characteristic	Drug interactions		
		Yes	**No**	**p-value**
Gender	Male	**20 (64.5)**	11(35.5)	0.393
	Female	**40 (54.8**)	33(45.2)	
Age	18-59 years	19(45.2)	23(54.8)	0.084
	>59 years	41(66.1)	21(33.9)	
Body mass index	Ideal (18.5-24.9)	28(93.3)	2(6.7)	
	Overweight and obese (>25.0)	32(42.6)	42(57.4)	0.683
Marital status	Single	8(61.5)	5(38.5)	
	Married	32(47.0)	36(52.9)	0.691
	Separated	0(0)	1(100)	
	Widowed	20(90.9)	2(9.1)	
Religion	Christian	55(57.3)	41(42.7)	
	Muslim	5 (62.5)	3(37.5)	0.260
Occupation	Farmer	7(46.7)	8(53.3)	
	Business/self-employed	15 (57.7)	11(42.7)	0.343
	Formal employment	7 (43.8)	9(56.3)	
	Unemployed	31(66)	16(34)	
Level of education	Below secondary	24(60)	16(40)	0.700
	Secondary and above	36(56.2)	28(43.8)	

As seen in Table 7 above, drug-drug interactions were present in 20 (64.5%) males compared to 40 (54.8%) females. However, no statistically significant difference in the existence of drug-drug interactions in the two genders (p=0.393) was found. Similarly, the age, religion, occupation, and level of education was not significantly associated with drug-drug interactions. (Table 7).

4.8 Relationship between clinical characteristics of the study participants and drug-drug interactions

The existence or absence of drug-drug interactions was compared with the clinical characteristics of the study participants and summarized in **Table 8.**

Table 8: Associations between clinical characteristics of the study participants and drug-drug interactions

Variable	Characteristic	Drug-drug interactions		
		Yes	**No**	**p-value**
Diabetes	Type 1	**1(33.3)**	2(66.7)	
	Type 2	**59(59)**	41(41)	0.339
	Other	0 (0)	1(100)	
Duration of diabetes	≤3years	10(52.6)	9(47.4)	
	More than 3 years	50(58.8)	35(41.2)	0.742
Hypertension	Stage 1,2 and 3	55 (56.1)	43(43.9)	
	Other advanced stages	**5 (83.3)**	1(16.7)	**0.031**
Duration of hypertension	≤3 years	6(37.5)	10(62.5)	
	More than 3 years	54(61.4)	34(38.6)	0.435
Presence of other comorbidities	Yes	33(62.3)	20(37.7)	0.223
	No	27(52.9)	24(47.1)	

Drug-drug interactions were present in 1 (33.3%) of participants with type 1 diabetes compared to 59 (59%) study participants with type 2 diabetes. However, there was no statistically significant difference in the existence of drug-drug interactions in the two types of diabetes (p=0.339). Also, the duration of diabetes since diagnosis was not significantly associated with drug-drug interactions (p=0.742).

Moreover, as seen in **Table 8**, the duration of hypertension and presence or absence of other comorbidities was not significantly associated with drug-drug interactions.

Statistically significant associations were found between the stage of hypertension and drug-drug interactions. Fifteen (83.3%) participants with stage 3 hypertension and five (83.3%) with other advanced stages of hypertension had drug-drug interactions which were found to be statistically significant (p=0.031) (Table 8).

4.9 Relationship between antidiabetic and antihypertensive prescribed among the study participants and drug-drug interactions.

Participants on more than two drugs for both diabetes and hypertension had a higher probability of having a drug-drug interaction. For instance, 59 (60.2%) participants using more than two drugs had a drug-drug interaction compared to 1 (16.7%) who were using only two drugs for both diabetes and hypertension. This association was statistically significant (p=0.048). Similarly, a significant association between drug-drug interactions and the use of an ARBs was established. Thirty-one (70.5%) of patients who were not using an ARB had a drug-drug interaction compared to 29(48.3%) using an ARB and had a drug-drug interaction (p=0.024).

Also, participants using a β -blocker were found to have a higher probability of having a drug-drug interaction with the association being statistically significant (p=0.001). For instance, 79 (74.4%) participants using a b-blocker had a drug-drug interaction compared to 31(47.7%) who were not using a β -blocker and had a drug-drug interaction. On the other hand, no statistically significant associations were found between drug-drug interactions and biguanides, insulin, sulfonylureas, DPPIV inhibitors, thiazolinediones, calcium channel blockers, diuretics and the other the drug classes as shown in **Table 9**.

4.9.1 Relationship between individual antidiabetic drug and antihypertensives prescribed among the study participants and the pattern of drug-drug interactions

The existence of drug-drug interactions was compared with the prescribing patterns of individual antidiabetic and antihypertensive drugs and the results obtained are tabulated in **Table 9**.

Table 9: Relationship between drugs prescribed among the study participants and the pattern of drug-drug interactions

Variable	Characteristic	Drug-drug interaction		
		Yes	**No**	**p-value**
Enalapril	Yes	17(73.9)	6(26.1)	
	No	43(53.1)	38(46.9)	0.076
Losartan	Yes	**21(44.7)**	26(55.3)	
	No	**39(68.4**)	18(31.6)	**0.014**
Hydrochlorothiazide	Yes	14(51.9)	13(48.1)	
	No	46(59.7)	31(40.3)	0.796
Furosemide	Yes	8(100)	0(0)	
	No	52(54.2)	4(45.8)	0.011
Nifedipine	Yes	**17(89.5)**	2(10.5)	
		43(50.6)	42(49.4**)**	**0.002**
Amlodipine	Yes	16(53.3)	14(46.7)	
	No	44(59.5)	30(40.5)	0.317
Carvedilol	Yes	**16(94.1)**	1(5.9)	
	No	**44(50.6)**	43(49.4**)**	**0.001**
Methyldopa	Yes	0 (0)	1(100)	
	No	60(58.3)	43(41.7)	0.394
Glibenclamide	Yes	5(21.7)	18(78.3)	
	No	55(67.9)	26 (33.1)	0.451
Sitagliptin	Yes	6(54.5)	5(45.5)	
	No	54(58.1)	39(41.9)	0.825
Metformin	Yes	50(59.5)	34(40.5)	
	No	10(50)	10(50)	0.443

There were associations between drug-drug interactions and prescription of losartan, nifedipine and carvedilol. For instance, 39 (68.4%) participants not using losartan were found to have a drug-drug interaction whereas 21 (44.7%) participants using losartan had drug-drug interactions. This result was found to be statistically significant (p=0.014). Similarly, use of nifedipine was significantly associated with drug-drug interactions (p=0.002). Seventeen (89.5%) participants using nifedipine had a drug-drug interaction whereas 43(50.6%) not using nifedipine did not have drug-drug interactions.

Also, the use of carvedilol was associated with the presence of drug-drug interactions. Sixteen (94.1%) participants using carvedilol had drug-drug interactions compared to 44 (50.6%) who were not using carvedilol and had a drug-drug interaction. This was found to be statistically significant (p=0.001). Use of enalapril, hydrochlorothiazide, amlodipine, furosemide, glibenclamide, metformin, and the rest of the drugs had no significant association with drug-drug interactions indicated in **Table 9.**

4.10 Independent predictors of drug-drug interactions

Forward stepwise logistic regression analysis was carried out to identify and determine the independent predictors of DDIs. The results are illustrated in **Table 10.**

Table 10: Independent predictors of drug-drug interactions(N=104)

Variable	Bivariate analysis COR (95% CI)	P-value	Multivariate analysis AOR (95% CI)	P- value
Number of DM-HTN drugs	2.12 (1.15-3.92)	**0.020***	2.79 (1.11-7.28)	**0.029**
Stage of hypertension	2.63 (1.50-4.68**)**	**0.002***	2.52 (1.34-4.89**)**	**0.007**
Use of Nifedipine	6.42(1.31-31.57)	**0.008***	1.45 (0.65-3.28)	0.451
Use of losartan	4.60(0.99-21.36)	**0.005***	2.50(0.91-7.00**)**	0.142

*Key: COR=Crude Odds Ratio; AOR=Adjusted Odds Ratio; CI=Confidence Interval; N=Sample size; *statistically significant result.*

The number of diabetes and hypertension drugs was found to be an independent predictor of drug-drug interactions (COR=2.12; 95% CI 1.15-3.92; p=0.020). Patients who had more than two drugs for the two comorbidities had 2.1 times the probability of having a drug-drug interaction compared to those who were on two drugs or less (AOR=2.79; 95% CI 1.11-0.7.28); p=0.29), holding all other factors constant.

The stage of hypertension was also an independent predictor of drug-drug interactions. Participants who were on advanced stages of hypertension had 2.6 the times probability of having a drug-drug interaction compared to those with lower stages of hypertension (COR=2.63; 95% CI 1.5-4.68; p=0.002). This prediction was more apparent upon multivariate logistic regression that indicated that those being on advanced stages of hypertension were 2.5 times less likely to have a drug-drug interaction (AOR=2.52; 95% CI 1.31-4.89; p=0.007).

The use of nifedipine was found to be an independent predictor of drug-drug interactions. Patients who were using nifedipine were eight times as likely to have a drug-drug interaction compared to those not using nifedipine (COR=6.42; 95% CI 1.31-31.57; p=0.008). However, this association was lost after multivariate regression analysis. (AOR=1.45; 95% CI 0.65-3.28; p=0.451).

Also, the use of losartan was an independent predictor of drug-drug interactions. Diabetic hypertensive patients who were using losartan were 4.6 times more likely to have a drug-drug interaction compared to those not using losartan (COR=4.60; 95% CI 0.99-21.36; p=0.005). However, this association was lost after multivariate regression analysis. (AOR=2.50; 95% CI 0.91-7.00 p=0.142) (Table 10).

CHAPTER FIVE: DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.1 Discussion

A total of 104 adult diabetic hypertensive patients participated in the study. The mean age of the participants was 61.6 years (SD±10.8). The elderly (59.6%) represented the largest group which suggested that most had advanced age as commonly seen in patients with diabetes and hypertension. These findings concur with other literature which established the prevalence of diabetes and hypertension increases with advancing age (28).

Almost half (45.2%) of the participants were overweight while approximately a quarter (28.8%) had ideal body weight. The number of overweight participants in the present study is slightly higher than observed by Murghabel and Al-Mansouri which indicated that 32.1% of the study population was overweight (110). The higher body mass indices in the current study population may suggest unhealthy lifestyles such as intake of unhealthy diets, physical inactivity, genetic predisposition, among others.

The majority (96.2%) of the study population had type 2 diabetes. This finding tallies with a study carried out by Ayah *et al*, which also indicated that type 2 diabetes is the most prevalent among all other types of diabetes (25). This is because type 2 diabetes is commonly associated with lifestyle factors and advanced age while type 1 diabetes occurs as a result of genetic factors and therefore has a lower prevalence than type 2 diabetes (5).

It was also noted that over three quarters (81.6%) of the study population had lived with diabetes mellitus and hypertension for more than three years suggesting that hypertension and diabetes are common coexisting comorbidities. In comparison, a study by Bhatta, on diabetic drug use and adherence indicates an almost similar prevalence (70.6%) of the coexistence of diabetes and hypertension. The study also showed that among all diabetic complications, cardiovascular complications especially hypertension poses a major threat (111).

Most participants (94.2%) were on more than two drugs for both hypertension and diabetes which concurs with findings by Hazari *et a*l (31). This suggests that the two comorbidities increase the likelihood of multi-drug therapy. Among antidiabetics,

biguanides were the most prescribed hypoglycemic drug class where metformin was the most widely prescribed (80.8%).

This compares with the Kenya National Clinical Guidelines for Management of Diabetes Mellitus which indicates and recommends biguanides as first-choice drugs for management of diabetes (43). The recommendation and wide use of metformin may be because it does not promote weight gaining which a risk factor for both diabetes and hypertension. Also, the study by Bhatta et al (112) found metformin to be the most widely used antidiabetic drug (40.5%). This was however lower than the findings in the present study. The variation in the prevalence of metformin use may be due to difference in study settings as this study unlike the current study was a prospective observational study done in India and evaluated diabetic patients only. Accordingly, metformin is regarded as the first-line drug for most obese patients with type diabetes mellitus. This study supports the above findings as the majority of the study population received metformin.

Among antihypertensives, ARBs and CCBs were the most prescribed while the rest of the population was on diuretics, β-blockers and angiotensin-converting enzyme (ACE) inhibitors. This differs from a study Mwengi *et al* (24), which indicated that CCBs were the most frequently prescribed antihypertensive drug class followed by β-blockers and diuretics. The rest were angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), vasodilators (VDs) or centrally acting antiadrenergics. The differences in prescription patterns may be attributed to differences in the study population. Whereas the current study population included diabetic hypertensives only, the study by Mwengi *et al* (24) included diabetic hypertensives with comorbid chronic kidney disease.

Over two thirds (80.7%) of the prescriptions had a potentially interacting pair of drugs. Notably over half (57.7%) of the study population had at least one drug-drug interaction. This differs from the findings of a study by Ogamba (15) on potential drug-drug interactions among patients with type 2 diabetes and hypertension in Kisii Teaching and Referral Hospital which found that 96% of the study population had at least one drug-drug interaction. The results in this study are therefore comparable with those in the

present study as both indicate a high prevalence of DDI among diabetic hypertensive patients.

In the current study, over three quarters (81%) of the prescriptions had moderate drug-drug interactions while the rest (19%) were minor. This compares with a study by Guantai *et al* which found that majority (79.2%) of the potential drug interactions were moderate while minor interactions accounted for 16.8% of the study population (23). The two studies, therefore, corroborate as there was no huge difference in the findings.

In the current study, the most common drug combination that could result into a drug-drug interaction was that of an antidiabetic drug and a β-blocker. Other common interactions included Enalapril and Metformin, metformin and nifedipine and calcium channel blockers and β-blockers. In comparison, Guantai *et al* found that the most predominant interacting pair was enalapril and furosemide (23). The study also found potential drug-drug interactions between carvedilol and furosemide, insulin and furosemide. The differences in the pattern of drug-drug interactions may be due to differences in the study population. The study by Guantai *et al,* unlike the current study, included hypertensive patients only whereas the current study included patients with both diabetes and hypertension.

The most common potential clinical outcome of the drug-drug interaction was hyperkalemic lactic acidosis (14.4%) as a result of the use of a combination of metformin and enalapril. There were no available prevalence studies on hyperkalemic lactic acidosis induced by metformin and enalapril. However, a case study by Weinberg *et al* indicated that the use of metformin and led to an increased risk of hyperkalemic lactic acidosis ($p=<0.001$) (112). Metformin is known to cause lactic acidosis, especially when given to patients with poor renal function. Diabetic hypertensive patients are treated with ARBs, in this case enalapril, which can result into volume depletion and subsequently cause kidney injury, precipitating lactic acidosis when used concomitantly with metformin. Under such circumstances, metformin can accumulate to toxic levels and cause hyperkalemic lactic acidosis. (54).

Strategies for minimization of potential drug-drug interactions were also identified. All participants had blood sugar checked in the last three months while blood pressure

(98.1%) was also checked in the same period. The Kenya National Clinical Guidelines for Management of Diabetes Mellitus recommends regular monitoring of blood sugar and blood pressure among diabetic hypertensive patients. Although we did not correlate adherence of the practice to clinical guidelines, the findings in this study may be indicative of clinicians' awareness of the recommendations. On the other hand, about a third (30.8%) of the study population had their HbA1c levels checked in the last 3 months while 17.3% had urea and electrolyte levels checked in the same period. Haghighatpanah *et al* (113 indicated that HbA1c is the gold standard for monitoring and evaluation of glycemic control. Another study by Harris (114) on the frequency of blood glucose monitoring concerning glycemic control in patients with type 2 diabetes found out that quarterly monitoring of HbA1C was practiced by 39% of those on hypoglycemic agents. This differs from the findings in the current study which indicate a lower frequency in checking of HbA1c (30.8%). The low frequency of monitoring of HbA1c in the present study may be due to the unavailability of the laboratory test or its prohibitive cost and hence preserved for the few patients with erratic glycemic controls.

The number of diabetes and hypertension drugs and the stage of hypertension were independent predictors of drug-drug interactions as indicated by bivariate analysis (COR=2.12; 95% CI 1.15-3.92; p=0.020) and (COR=2.63; 95% CI 1.5-4.68; p=0.002). respectively. The predictions were affirmed on multivariate regression (AOR=2.79; 95% CI 1.11-0.7.28); p=0.29) and (AOR=2.52; 95% CI 1.34-4.89; p=0.007) respectively. A similar observation was made in a study by Kim *et al* (28*)* that patients on multidrug therapy and advanced stages of hypertension were more likely to have a drug-drug interaction. This suggests that management of hyperglycemia and hypertension requires the use of multiple medications which increase the probability of drug-drug interactions (32).

On the other hand, patients with advanced stages of hypertension may require multiple drug therapy to control blood pressure compared to those with earlier stages of hypertension. the use of severe drugs for hypertension may increase the likelihood of drug-drug interactions.

5.2 Study limitations

This study was retrospective and obtaining all essential data from the medical records was a challenge due to poor record-keeping. This was solved by inflating the sample size by 20%. This study involved participants attending outpatient clinics who had hypertension and comorbid DM without consideration of the type of diabetes or the hypertension stage and therefore the results on potential drug-drug interactions may not be generalized to inpatients or other cohorts. Our study was cross-sectional implying it was a snapshot and therefore could not establish the temporal sequence of the population phenomena under study.

5.3 Conclusion

The study established a high prevalence of potential drug-drug interactions which suggested poor management of diabetes among patients with comorbid hypertension. The drug-drug interactions were significantly increased with the stage of hypertension and the number of prescribed drugs. Patients on ARBs and β-blockers especially losartan and carvedilol, respectively, significantly had potential drug-drug interactions. Angiotensin Receptor blockers (ARBs) were widely prescribed in the study population because patients were diabetic.

The potential drug-drug interactions were associated with undesired clinical outcomes especially hyperkalemic lactic acidosis attributed to the use of metformin and enalapril. With the extensive prescription of antidiabetics especially metformin and potential occurrence of such clinical outcomes, there was a need to closely monitor laboratory parameters such as blood sugar, blood pressure and UECs. Notably, the monitoring frequency of HbA1c and UECs was low. This could be attributed to the unavailability of the laboratory test or its prohibitive cost and hence preserved for the few patients with erratic glycemic controls.

5.4 Recommendations

5.4.1 Recommendations for Change of Practice

Patients with comorbid diabetes and hypertension would benefit from the cautious use of drugs and drug classes likely to cause potential drug-drug interactions. While on these drugs, they should have their blood sugars and blood pressures adequately controlled since worsening of the above physiologic parameters may lead to polypharmacy and consequently poor clinical outcomes.

As such, clinicians should be aware that patients with comorbid hypertension and diabetes are more likely to have potential drug interactions with worsening blood pressure which necessitates multiple prescriptions. Therefore, regular checks and medication therapy management for such patients should be encouraged. Also, regarding the number and type of drugs prescribed for diabetes and hypertension close monitoring of patients' blood sugars, blood pressures, HbA1Cs, urea, and electrolytes should be encouraged. For instance, the use of thiazide diuretics and spironolactone with metformin may potentiate diuretic induced renal impairment and precipitate metformin-associated lactic acidosis(17). Renal function tests such as urea and electrolytes should, therefore, be done regularly for these patients(55). This will, in turn, reduce the likelihood of potential drug-drug interactions and poor clinical outcomes.

5.4.2 Recommendations for Further Research

There still exist gaps in the management of diabetes and hypertension and the risk of potential drug-drug interactions due to polypharmacy and prescription of drugs with a higher likelihood to interact. Future studies to correlate drug-drug interactions with clinical outcomes may help in filling these study gaps.

Besides, considering that this study was cross-sectional and carried out in a relatively short time and including a low number of the study population, prospective cohort studies following up on actual drug-drug interactions involving larger populations and longer durations in different study settings are needed to provide more evidence.

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APPENDICES

5.1 Appendix 1: Eligibility screening form

Study Title: CLINICALLY SIGNIFICANT POTENTIAL DRUG-DRUG INTERACTIONS AMONG ADULT DIABETIC HYPERTENSIVE OUTPATIENTS AT KENYATTA NATIONAL HOSPITAL

Diabetes and Endocrinology Outpatient Clinic

Unique Identifier: _____

DEOPC Number: _____

Criteria	Response	
	YES	NO
1. Adult aged ≥18 years diagnosed with comorbid HTN, DM		
2. Given consent		
3. Been on HTN and DM treatment		
4. Been on at least one antihypertensive drug and one hypoglycemic agent		
5. Not Pregnant		
6. Not psychiatric		
7. without pre-existing End stage renal disease (ESRD) or liver disease		

If all YES, please proceed to the data collection form

5.2 Appendix 2: Researcher information and participant's consent declaration form

STUDY TITLE: CLINICALLY SIGNIFICANT POTENTIAL DRUG-DRUG INTERACTIONS AMONG ADULT DIABETIC HYPERTENSIVE OUTPATIENTS AT KENYATTA NATIONAL HOSPITAL

INSTITUTION	Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi. P.O Box 30197-00400, Nairobi.
PRINCIPAL INVESTIGATOR	Dr. Simon Lati Makite P.O Box 34-90121, Emali, Kenya. Phone number: 0720872197 Email: makitesimonlati@gmail.com
SUPERVISORS	1. Dr. David Nyamu Phone:0722403671 Email: dgitonga@uonbi.ac.ke 2. Dr. Rosaline Kinuthia Phone:0722240599 Email: rkinuthia@knh.or.ke
ETHICAL APPROVAL	Kenyatta National Hospital/University of Nairobi Ethical and Research Committee P.O Box 20723-00100, Nairobi. Tel. 2726300/2716450 Ext 44102 Email: uonknh_erc@uonbi.ac.ke

Introduction

My name is Dr. Simon Lati Makite.I am a postgraduate student at the University of Nairobi, school of pharmacy. I hereby would like to tell you about a study to be conducted by the researchers listed above. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study.

You are requested to feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that might not be clear.

When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research:

i) Your decision to participate is entirely voluntary

ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Protocol No.: _____

WHAT IS THIS STUDY ABOUT?

Diabetes mellitus has been declared a global emergency of the 21st century because of its rapidly increasing global prevalence. Management approaches towards diabetes and hypertension includes non-pharmacological and pharmacological interventions. However, the mainstay of management is pharmacotherapy.

In addition to keeping both blood pressure and glucose levels controlled, multiple drugs subject the patient to polypharmacy which may sometimes be irrational. Subsequently, uninformed use of new drug therapies for any medical condition can be of concern to the

patient due to increased risk of experiencing drug-drug interactions and unperceived adverse drug events.

The present study aims to characterize the potential drug-drug Interactions and their clinical significance among adult diabetic hypertensive outpatients at Kenyatta National Hospital (KNH).

There will be 104 participants in this study randomly selected. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, drug therapy information in your medical file will be used for this study.
The information abstracted will include topics such as your medication history, biodata and comorbidities.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Psychological, emotional, social and physical factors are risks introduced by a medical research. However, a concerted effort must be put in place to mitigate the risk. One of the risks that you may encounter is lack of privacy. Your information will be treated confidential and will use a code number to identify you in a password protected computer database restricted for access using password protected electronically. Signed copies of your consent participation forms will be kept in a locked office file cabinet. Only the principal investigator and assistant researcher will access the documents. Furthermore, this study does not involve any invasive procedures or taking additional medications and therefore no harm to the participants.

ARE THERE ANY BENEFITS?

The findings of this study are expected to raise awareness among physicians and pharmacists on the extent of the burden of drug-drug interactions among their hypertensive diabetic patients. This will in turn enable them to make informed decisions

when prescribing and dispensing drugs combinations to hypertensive diabetic patients and hence prevent any potential drug-drug interactions

WILL BEING IN THIS STUDY COST YOU ANYTHING?

This study will not cost you anything apart from time going through the consent form.

ARE THERE ANY REIMBURSEMENTS?

There will be no payments inform of fiscal, gifts or incentives as a result of participation in the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message or email to the study staff via the contact details provided in this document provided at the bottom of this page. For more information about your rights as a research participant you may contact the Principal Investigator, my Supervisors or the KNH-UoN Ethics and Research Committee using the contacts provided.

If in agreement, please sign the participants consent declaration below;

Participant's consent declaration

I have read this researcher information and consent form or had the information read to me

I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw anytime.

I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:

YES…… NO……

I agree to provide contact information for follow-up:

YES…….NO……

Participants name _____

Participant signature / Thumb stamp _____

Date _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above. The participant has understood and has freely given his/her consent.

Researcher 's Name: _____ **Signature** _____

Date: _____

Role in the study: _____

For more information, contact;

Principal Investigator: Dr. Simon Lati Makite on 0716699863

Supervisors: Dr. David Nyamu on 0722403671

Dr. Rosaline Kinuthia on 0722240599

Ethics Committee KNH-UoN ERC on 2726300, Ext 44102

5.3 Appendix 3: Maelezo kuhusu kushiriki katika utafiti

Kichwa cha Uchunguzi:

KUCHUNGUZA MATATIZO YA UTUMIAJI PAMOJA WA MADAWA TOFAUTI YA TIBA KWA WAGONJWA AMBAO NI WATU WAZIMA WENYE MATATIZO YA MAGONJWA YA KISUKARI NA SHINIKIZO LA JUU LA DAMU.

Mchunguzi mkuu

Dkt Simon Lati Makite-mwanafunzi wa mwaka wa pili akiwa ni mwanafunzi wa chuo kikuu cha Nairobi.

Wasimamizi:, Dkt. Nyamu, Mhadhiri, Chuo Kikuu cha Nairobi

Utangulizi

Mimi ni Simon Lati Makite, mwanafunzi katika chuo kikuu cha Nairobi, kitengo cha shule ya Pharmacy.

Nafanya uchunguzi wa matatizo ya utumiaji pamoja wa madawa tofauti ya tiba kwa wagonjwa ambao ni watu wazima wenye matatizo ya magonjwa ya kisukari na shinikizo la juu la damu kwenye hospitali ya kitaifa ya Kenyatta

UMUHIMU WA MAFUNZO

Ugonjwa wa kisukari umetangazwa kuwa shida ya dharura duniani katika karne ya ishirini na moja.hii ni kwa sababu ya ongezeko katika idadi ya watu walio na ugonjwa wa kisukari. matibabu ya ugonjwa wa kisukari na shinikizo la damu uhusu njia za kutotumia dawa na zile za utumiaji wa madawa.ni Dhahiri kuwa njia kuu ya matitbabu ni utumizi wa madawa.

Ili kupunguza sukari na shinikizo la damu mgonjwa hujipata akitumia madawa mengi ambayo wakati mwingine hayahitajiki. hivyo, uagizaji wa madawa katika matibabu bila kuzingatia maagizo waweza leta madhara kwa mgonjwa. Hii ni kwa sababu ya ongezeko la uwezekano wa madhara yanayoweza tokea wakati madawa yanapotumiwa pamoja.

Lengo letu ni kujua na kuelewa vile madawa huleta athari wagonjwa watu wazima wanapotumia dawa tofauti pamoja katika matibabu ya magojwa ya kisukari na shinikiza la juu la damu.

Kutakuwa na washiriki 104 ambao watachaguliwa bila taratibu katika huu uchunguzi.

Tunakuomba ridhaa yako katika kushiriki katika huu uchunguzi.

USHIRIKI WA KUJITOLEA

Katika mafunzo haya, kuchagua kushiriki ni kujitolea na unaonesha uhuru wako baada ya kukubali kushiriki. Unaweza ukawa nje ya mafunzo kwa muda wote, kwa kufanya hivyo hutakosa faida ambazo utapewa.

HATARI NA MADHARA

Kisaikolojia, kihisia, kijamii na kimwili hizi ni hatari zilizo ndani ya utafiti. Vilevile juhudi halisi ziwepo kupelekea kupunguza hatari, moja wapo unayoweza kukutana nayo ni ukosefu wa usiri. Taarifa inayokusanywa itakuwa ni ya siri na italindwa kwa kutumia nywila inayolindwa na umeme wa mfumo wa taarifa ya madawa. Nakala zako zilizosahiniwa zenye mawazo yako za ushiriki wako zitafungiwa kwenye karatasi la kuhifadhi nyalaka ya kiofisi. Mchunguzi mkuu na mtafiti msaidizi pekee hao ndio watakao fanyia kazi taarifa yako. Zaidi, mafunzo haya hayatahusisha matibabu yoyote.

TAREJESHEWA PESA ZAKO?

Utafiti huu hautakugharimu pesa ila wakati wa kusoma ridhaa.

NA KAMA UTAKUWA NA MASWALI BAADAYE?

Kama una maswali zaidi au lolote ambalo hulielewi kuhusu utafiti huu, tafadhali usisite kuwasiliana nasi kupitia nambari ambazo zimeandikwa hapa chini.

Kwa maelezo zaidi kuhusu haki za mshiriki katika utafiti, wasiliana na;

Mtafiti Mkuu Simon Lati Makite

Simu: 0716699863

Taarifa ya Mshiriki

Nimesoma au nimesomewa nakala hili. Nimepata kuzungumza kuhusu utafiti huu na mtafiti mwenyewe. Maswali yangu yamejibiwa kwa lugha ninayoielewa vizuri. Madhara na manufaa yameelezwa wazi. Ninaelewa kushiriki kwangu ni kwa hiari na kwamba ninao uhuru wa kutoshiriki wakati wowote. Ninakubali bila kushurutishwa kushiriki katika utafiti huu. Ninaelewa kwamba bidii itatiwa kuhakikisha habari zangu zimewekwa siri. Kwa kutia sahihi kwa daftari hili, sijapeana haki zangu za kisheria ambazo ninazo kama mshiriki katika utafiti huu.

Nimekubali kushiriki katika utafiti huu:

NDIO..... LA.....

Jina la Mshiriki: _____

Sahihi / Kidole _____

Tarehe _____

Taarifa ya Mtafiti

Mimi, ninayetia sahihi hapo chini, nimeelezea maswala muhimu ya utafiti huu kwa mshiriki aliyetaja hapo juu na ninaamini ya kwamba ameyaelewa vilivyo na kwamba ameamua bila kushurutishwa kukubali kushiriki.

Jina la Mtafiti: _____ **Sahihi** _____

Tarehe: _____

Kazi yangu kwa utafiti huu: _____

Kwa maelezo zaidi wasiliana na;

Mtafiti Mkuu: Simon Lati Makite Simu:071699863

Wahadhiri: Dkt. David Nyamu Simu:722403671

Dkt. Rosaline Kinuthia Simu:0722240599

Kamati ya Maadili: KNH-UoN ERC on 2726300 Ext 44102.

5.4 Appendix 4: Data collection form

Study Title: CLINICALLY SIGNIFICANT POTENTIAL DRUG-DRUG INTERACTIONS AMONG ADULT DIABETIC HYPERTENSIVE OUTPATIENTS AT KENYATTA NATIONAL HOSPITAL

DATE: _____DEOPC Number_____D.O. E_____

Participants unique number_____

A. DEMOGRAPHICS

1) Age (Years)_____
2) Gender Male (0) Female (1)
3) Weight (Kg)_____Height (Meters)_____BMI(Kg/m^2) _____
4) Marital status: Single (0) Married (1) Separated (2) Divorced (3) Widowed (4) Others (5)
5) Religion: Christians (0) Muslim (1) Others (2)
6) Occupation: Farmer (0) Business/ Self-Employment (1) Formal Employment (2) Unemployed (3)
7) Smoking status: Current smoker (0) Previous smoker (1) Never smoked (2)
8) Alcohol intake status: Currently drinking (0) Previously drinking (1) Never drunk (2)
9) Level of Education: Primary (0) Secondary (1) College/University (2) informal (3)

B. DIAGNOSIS AND CO-MORBIDITIES

10) Diabetes: Type 1(0) Type 2(1) Other (2)
11) Duration of Diabetes :<1 year (0) 1 year (1) 2 years (2) 3 years (3) >3 years (4)
12) Hypertension: Stage 1(0) Stage 2 (1) stage 3(2) other (3)
13) Duration of Hypertension :<1 year (0) 1 year (1) 2 years (2) 3 years (3) >3 years (4)
14) Comorbidities: Arthritis (0) Heart failure (1) Anemia (2) Cancer (3) Others (specify) (4)

C. MEDICATIONS

Indication	Drug Name	Dosage	Frequency	Duration
Diabetes Mellitus	**1.** **2.** **3.** **4.**			
Hypertension	**1.** **2.** **3.** **4.**			
Others (Specify)	**1.** **2.** **3.** **4.**			
Total Number Of Drugs				

D. POTENTIAL DRUG-DRUG INTERACTIONS AND THEIR CLINICAL EFFECTS

Potentially Interacting Pair of Drugs	Type of Potential DDI	Severity of Potential DDI	Clinical Effect of Potential DDI
1.			
2.			
3.			
4.			
5.			
6.			

***KEY:**

Type of potential DDI: Pharmacokinetic (0) pharmacodynamic (1)

Severity of potential DDI: Minor (0) Moderate (1) Major (2)

Clinical effect of potential DDI: Hypoglycemia (0) Hyperglycemia (1)

Hypotension (2) Hypertension (3)

Others(specify) (4)

E. STRATEGIES FOR MINIMIZATION OF POTENTIAL DRUG INTERACTIONS AMONG DIABETIC HYPERTENSIVE PATIENTS.

(Have the following patient monitoring parameters for potential DDIs been checked in the last 3 months?)

i. Blood sugar NO (1) YES (0) Current values_____

ii. HbA1C NO (1) YES (0) Current values_____

iii. Blood pressure NO (1) YES (0) Current values_____

iv. UECS YES (0) NO (1) YES (0) _____

5.5 Appendix 5: Optimal targets for glycemic and blood pressure control in people with diabetes

Biochemical index	**Optimal targets**
Capillary blood glucose(finger-prick)	4-6.7 mmol/l
2hrs-post prandial	4-8mmol/l
Glycated hemoglobin (HbA1C)	<7%
Blood pressure	<130/80 mmHg
BP with persistent proteinuria	<125/75mmHg

5.6 Appendix 6: Ethical approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/192

23rd May, 2019

Simon Lati Makite
Reg. No.U56/7404/2017
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 23 MAY 2019 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Dear Simon

RESEARCH PROPOSAL: POTENTIAL DRUG-DRUG INTERACTIONS AND THEIR CLINICAL SIGNIFICANCE AMONG ADULT DIABETIC HYPERTENSIVE OUTPATIENTS AT KENYATTA NATIONAL HOSPITAL (P215/03/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 23rd May 2019 – 22nd May 2020.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UON
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. David Nyamu, Dr. Rosaline Kinuthia

5.7: Appendix 7: Institutional approval

KENYATTA NATIONAL HOSPITAL
P. O. Box 20723, 00202 Nairobi

Tel: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/HOD-MED/42B/VOL.II/

Date: 10th June 2019

Simon Lati Makite
Department of Pharmaceutics & Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

RE: APPROVAL TO CONDUCT A STUDY AT THE KNH MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration form, permission is hereby granted for you to collect data from the KNH Medicine Department, Diabetic Centre to enable you complete your study on ***"Potential drug-drug interactions and their clinical significance among adult diabetic hypertensive outpatients" at Kenyatta National Hospital.***

Kindly liaise with the Assistant Chief Nurse, Diabetic Centre for facilitation. By a copy of this letter, the ACN, Diabetic Centre is informed and requested to facilitate.

Dr. K. Ndege

Dr. KINOTI NDEGE
Ag. HOD - MEDICINE

Copy to: ACN, Diabetic Centre of Excellence
KNH

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2015 CERTIFIED