QUALITY OF PRESCRIBING IN TYPE 2 DIABETES AMBULATORY CARE AT WEBUYE DISTRICT HOSPITAL, WESTERN KENYA

By

Imbuki Evans Aketchi (Bpharm)

U51/64062/2013

A thesis submitted in partial fulfilment of the requirements for award of a Master of Pharmacy degree in Pharmacoepidemiology and Pharmacovigilance

Department of Pharmacology and Pharmacognosy

School of Pharmacy

University of Nairobi

NOVEMBER, 2014

DECLARATION

I declare that to the best of my knowledge, this thesis is my original work and has not been presented for a degree in any other university.

Signature.....…… Date.....

Imbuki Evans Aketchi

U51/64062/2013

Declaration by supervisors

This thesis was submitted for examination with our approval as university supervisors:

Dr. Margaret O. Oluka, PhD

Senior Lecturer, Department of Pharmacology and Pharmacognosy

School of Pharmacy

University of Nairobi

Signature.....…… Date.....

Dr. Stanley N. Ndwigah, PhD

Senior Lecturer, Department of Pharmaceutical Chemistry

School of Pharmacy

University of Nairobi

Signature.....…… Date.....

Dr. Eric M. Guantai, PhD

Lecturer, Department of Pharmacology and Pharmacognosy

School of Pharmacy

University of Nairobi

Signature.....…… Date.....

UNIVERSITY OF NAIROBI DECLARATION OF ORIGINALITY FORM

Name of student: Evans Aketchi Imbuki

Registration Number: U51/64062/2013

College of Health Sciences

School of Pharmacy

Department of Pharmacology and Pharmacognosy

Course Name: Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance

Title of the work: Quality of Prescribing in Type 2 Diabetes Ambulatory Care at Webuye District Hospital, Western Kenya.

Declaration

1. I understand what plagiarism is and I am aware of the University's policy in this regard.
2. I declare that this thesis is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my own work has been used, this has properly been acknowledged and referenced in accordance with University of Nairobi's requirements.
3. I have not sought or used the services of any professional agencies to produce this work.
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.
5. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with University Plagiarism Policy.

Signature……. …….

Date……..

ACKNOWLEDGEMENT

I wish to express my sincere gratitude to all those who in various ways provided assistance in the production of this work.

Specifically, I wish to thank the following:

1. My supervisors; Dr. Margaret O. Oluka, Dr. Stanley N. Ndwigah and Dr. Eric M. Guantai, for their patience, invaluable support and encouragement in the course of this work.
2. Dr. Faith Okalebo, for her valuable input in proposal development.
3. My classmates; Ambetsa, Khaemba, Njogo, Wamaitha, Mecca, Mulwa, Jomo, Ndwiga, Gatimbu and Makori, for their continuous support, counsel and encouragement.
4. Dr. Lydia Anyanzwa and her team at Webuye District Hospital Pharmacy department, for making me feel at home during the data collection exercise.
5. Brigid and Simiyu at the records department, Webuye District Hospital, for their support during data collection.

DEDICATION

To my mother Muhonja, my four siblings, my spouse Monicah and my daughter Midecha.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

DEFINITION OF TERMS

Diabetes mellitus (DM)**:** Diabetes mellitus is a metabolic disorder that is associated with elevated blood sugar levels (hyperglycaemia) and disturbances of carbohydrate, fat and protein metabolism. It occurs due to defects in insulin secretion, insulin physiological activity or both.

Hypertension: Hypertension or elevated blood pressure is diagnosed when blood pressure reading is greater than 140/90 millimeters of mercury (mmHg) following 3 separate readings.

Microalbuminuria: Levels of albumin ranging from 30 to 300 milligram (mg) in a 24 hour (h) urine collection.

Overt albuminuria/macroalbuminuria/proteinuria: Defined as a urinary albumin excretion of greater or equal to 300 mg/24 h.

Dyslipidaemia: Lipid abnormalities.

Overweight individual: When an individual's body mass index (BMI) is 25-29.9 kg/m^2.

Obese individual: When an individual's BMI is greater or equal to 30 kg/m^2.

Newly diagnosed type 2 diabetes mellitus patient: One with duration of diabetes less than 1 year.

Elderly patients: Patients aged 65 years and above.

Quality indicator: The quality indicator for the care of type 2 diabetes mellitus as used in this study refers to prescribing acetyl salicylic acid in elderly patients for primary prevention of cardiovascular diseases.

Prescribing quality indicator (PQI): Defined as a measurable element of prescribing for which there is evidence or consensus that it can be used to assess the quality of care provided.

Beers criteria: The updated Beers criteria (2012) deal with potentially inappropriate medicine use in older adults. For T2DM, the criteria recommend that long acting sulfonylureas such as chlorpropamide and glibenclamide should be avoided in older adults

Face validity of prescribing indicator (PI): Implies that the PI is based on literature review or evidence-based clinical guidelines.

Content validity of PI: Implies that the PI is assessed and accepted by a group of experts or professionals in the field.

Operational validity or feasibility: Implies that feasibility of calculation of PI is demonstrated or defended in view of available data.

Quality of prescribing: In this study, an indicator with a minimum outcome of 70 % represented good quality prescribing while that with an outcome below 70 % represented poor quality prescribing. An outcome of not more than 5 % for potential inappropriate medicine use or drug-drug interactions also represented good quality prescribing.

LIST OF ABBREVIATIONS AND ACRONYMS

ACCORD	Action to control cardiovascular risk in diabetes study group
ACEI	Angiotensin converting enzyme inhibitors
ADA	American diabetes association
AGS	American geriatrics society
Alpha (α)-GI	Alpha glucosidase inhibitors
ANPS	Australian National Prescribing Service
ARB	Angiotensin II receptor blocker
ASA	Acetyl salicylic acid
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHF	Congestive heart failure
CI	Confidence interval
COX II	Cyclo-oxygenase II
CP	Comparative prevalence
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
Dl	Deciliter
DM	Diabetes mellitus

DPP-4	Dipeptidyl peptidase-4
EASD	European association for the study of diabetes
ENT	Ear, nose and throat
ERC	Ethics and research committee
FDA	Food and drug administration
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GIP	Glucose independent insulinotropic peptide
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
GOPC	Gynecological outpatient clinic
GP	General Practitioner
H	Hour
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
IDF	International diabetes federation
IHD	Ischemic heart disease
Kg	Kilogram
KNH	Kenyatta National Hospital
LDL	Low density lipoprotein
L	Liter
M^2	Square meters
Mg	Milligram
Mg/dl	Milligram per deciliter

MOH	Ministries of Health
MI	Myocardial infarction
MmHg	Millimeters of mercury
Mmol/L	Millimol per liter
Mmol/ml	Millimol per mol
MOPC	Medical outpatient clinic
NPH	Neutral protamine hagedom
NSAIDs	Non-steroidal anti-inflammatory drugs
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAD	Peripheral artery disease
POPC	Pediatric outpatient clinic
PQI	Prescribing quality indicator
PR	Prevalence ratio
QI	Quality indicator
RCT	Randomized clinical trial
RPG	Random plasma glucose
SBP	Systolic blood pressure
SOPC	Surgical outpatient clinic
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom prospective diabetes study group
UON	University of Nairobi
WHO	World health organization

ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder that is of great public health importance globally. Type 2 diabetes accounts for 90 % of all diabetes. Lifestyle interventions are promoted as the initial management approaches in type 2 diabetes but are known to provide optimal results in only a minority of patients. Pharmacological interventions therefore remain the mainstay approach. Many classes of glucose lowering drugs are available, increasing treatment options from which choices can be made. Quality prescribing of these drugs is recommended as it results in greater improvement in glycaemic control, blood pressure and lipid management. However, in most practices, quality of prescribing is rarely monitored, thereby compromising quality of diabetic care. Prescribing quality indicators, quality indicators and criteria have been developed to monitor quality of prescribing.

Objective: The main objective of this study was to investigate the quality of prescribing in type 2 diabetes mellitus ambulatory care at Webuye District Hospital.

Methodology: This was a retrospective review of patient medical records at Webuye District Hospital, Western Kenya. The target population was type 2 diabetes mellitus patients who visited the diabetic clinic in the year 2013. Fisher's formula for descriptive studies was used to calculate a sample of 369 patients. Sequential sampling of patient attendance lists was applied to retrieve 880 patient records and the first 369 that met the inclusion criteria were picked for this study. A data collection form was designed, pre-tested and validated. Data collected were coded and analysed with Microsoft Office Excel 2007 and STATA® software version 10.1. Bivariate and multivariate logistic regression was used to determine factors influencing prescription of specific drugs.

Results: Of the total 369 type 2 diabetes mellitus patients, 57.2 % were females while 14.9 % were newly diagnosed. The main co-morbidity was hypertension, affecting 70.5 % of the patients. The main drugs prescribed for hyperglycemia were metformin (84.9 %), glibenclamide (47.7 %) and insulin (32.0 %) while those prescribed for cardiovascular risk were hydrochlorothiazide (52.8 %) and enalapril (51.8 %). More than 89.0 % of patients with hypertension were prescribed enalapril or losartan, which represented good quality prescribing. Potential cases of drug-drug interactions were found in 4 % (95 % CI: 2-6) of records reviewed, representing good quality prescribing.

Age, weight and systolic blood pressure were recorded for all 369 patients. Body mass index was recorded for 56 % patients while albuminuria was not recorded for any of the patients. Outcomes for 10 of the 12 selected prescribing quality indicators varied from 99 % for prescribing any antihyperglycaemic or antihypertensive medication to 6 % for prescribing statins in patients with high cardiovascular risk to. Outcomes for the remaining 2 indicators could not be calculated due to absence of eligible patients.

The use of insulin was significantly influenced by glycated haemoglobin [Odds ratio (OR) 1.2, $p < 0.01$] and duration of diabetes (OR 1.1, $p < 0.01$) while the use of losartan or enalapril was significantly influenced by hypertension (OR 19.3, $p < 0.01$). Additionally, use of acetyl salicylic acid was significantly influenced by hypertension (OR 4.1, $p < 0.01$) and age (OR 1.1, $p < 0.01$).

Conclusion: This study established that there was a high rate of adherence to treatment guidelines on choice of drugs for management of hyperglycemia and cardiovascular risk, which represented good quality prescribing. However, there were deficiencies in adequate control of hyperglycemia, hypertension and dyslipidaemia. Outcomes for 6 prescribing quality indicators represented good quality prescribing, while outcomes for 4 others represented poor quality prescribing. There were also deficiencies in quality of prescribing in elderly patients, where nearly half were prescribed glibenclamide; while only one third were prescribed acetyl salicylic acid for primary prevention of cardiovascular disease. Cases of potential drug-drug interactions were below 5 %, which represented good quality prescribing. Glycated hemoglobin level and duration of diabetes significantly influenced use of insulin while hypertension significantly influenced use of enalapril, losartan and acetyl salicylic acid. Age also significantly influenced use of acetyl salicylic acid. Findings from this study provide a framework for policy makers at the Ministry of Health in Kenya to formulate strategies to promote pharmacotherapy outcomes in type 2 diabetes in particular and other chronic diseases in general.

CHAPTER ONE: INTRODUCTION

1.1 Background

The World Health Organization (WHO) defines diabetes mellitus (DM) as a metabolic disorder associated with elevated blood sugar levels (hyperglycaemia) and disturbances of carbohydrate, fat and protein metabolism. It occurs due to defects in insulin secretion, insulin physiological activity or both (WHO, 2011). There are two major types of diabetes mellitus (DM); Type 1 and type 2 DM (T2DM). Type 1 occurs as a result of destruction of insulin secreting beta (β)-cells in the pancreas, usually leading to absolute insulin deficiency [American Diabetes Association (ADA, 2013]. It usually afflicts children and patients require insulin to sustain life. It is characterized by ketoacidosis [Ministries of Health (MOH, 2009].

Type 2 diabetes mellitus (T2DM) occurs due to a progressive insulin secretory defect on the background of insulin resistance (ADA, 2013). It mainly affects adults, majority of whom are obese, with elevated blood pressure (BP). Patients with T2DM may also present with ketoacidosis in stressful conditions or following poor adherence to therapy (ADA, 2013; MOH, 2009). Less common types of DM include gestational diabetes mellitus (GDM) diagnosed during pregnancy that is not overt disease (ADA, 2013). It occurs in approximately 1-5 % of pregnancies (MOH, 2009). Other specific types of diabetes occur due to other causes such as genetic defects in β-cell activity or insulin action or those due to drug or chemical induced causes (ADA, 2013).

The World Health Organization (WHO) estimates that the global prevalence of diabetes in 2008 was 10 % in adults aged 25 years and above (WHO, 2010). More than 371 million people have diabetes worldwide (IDF, 2009) and each year, 3.2 million people globally die from complications of diabetes (Puepet *et al*, 2009).

In Africa, 12.1 million people in the age group 20-79 years had diabetes in 2010. This number is expected to rise to 23.9 million in 2030 (IDF, 2009). In Kenya, where type 2 diabetes is the most prevalent, comparative prevalence of diabetes in the age group 20-79 years was estimated to be 3.5 % in 2010 (IDF, 2009). The Ministry of Health estimates that by 2008, 1.2 million Kenyans were living with diabetes. This number is expected to rise to 1.5 million by the year 2025 (Mc Ferran, 2008).

In management of type 2 diabetes, quality prescribing is recommended since it results in greater improvement in glycaemic control, blood pressure and lipid management. Prescribing

quality indicators, quality indicators and criteria have been developed to monitor quality of prescribing in type 2 diabetes mellitus.

1.2 Problem statement

The burden of diabetes continues to rise globally and it has become one of the major causes of premature death, mainly through increased risk of CVD. Much of the morbidity associated with long term microvascular and neuropathic complications of diabetes can be greatly reduced by interventions that achieve glucose levels close to non-diabetic range (ADA, 2013). Pharmacological management in most practices fails to achieve and maintain glycaemic levels that improve quality of life in T2DM patients (ADA, 2013). Elderly patients are particularly at risk of mortality, experiencing drug-drug interactions, adverse drug reactions and poor treatment outcomes (Steinman *et al,* 2006). T2DM is associated with numerous co-morbidities, which pose challenges in pharmacotherapy

Good quality prescribing for any disease condition entails compliance to treatment guidelines, correct dosing and awareness of potential inappropriate medicines use and drug-drug interactions, among other factors. In most practices however, there has been over-reliance on registration of measurements and clinical outcomes in T2DM management as existing performance indicators to assess quality of care, and not quality of prescribing (Martirosyan *et al,* 2008). In T2DM, considerable evidence exists to support the benefits of appropriate blood pressure control, lipid-lowering therapy, angiotensin converting enzyme inhibitors (ACEI) and antiplatelet drugs. These approaches reduce cardiovascular and microvascular complications in patients with diabetes (Martirosyan *et al,* 2008). Despite the well documented benefits of blood pressure lowering, rates of detection and control of hypertension have been sub-optimal (Patel and Mehta, 2013).

1.3 Justification of the study

Diabetes mellitus is a highly prevalent independent risk factor for CVD. CVD are the major causes of morbidity and mortality in patients with T2DM. They are also the largest contributor to the direct and indirect costs associated with diabetes management (ADA, 2013). Hypertension and dyslipidaemia are the two conditions that commonly co-exist with T2DM. Numerous studies have demonstrated the efficacy of controlling individual risk factors in preventing or slowing development of complications in individuals with T2DM (ADA, 2013).

Lifestyle management is advocated globally as the cornerstone approach in preventing or managing T2DM, hypertension and dyslipidaemia. However, this intervention has been shown to fail in most patients. It has to be eventually supplemented by pharmacological management, which remains the major approach of managing T2DM, its co-morbidities and complications (Nathan *et al,* 2009); IDF, 2012; ADA, 2013). Several studies have shown benefits of quality prescribing in significantly reducing sequelae associated with T2DM and its complications. Despite this, there are still numerous gaps. Failure to use guidelines, wrong drug choice, under prescribing, over prescribing, incorrect dosing, inappropriate use of medicines and failure to recognize major potential drug interactions are some of the setbacks (Steinman *et al*, 2006).

In Kenya, clinical guidelines developed in 2009 by the Ministry of Health do not provide a comprehensive approach in management of T2DM and its co-morbidities. In settings where such guidelines are in use, quality of prescribing may be compromised. It is therefore expected that findings from this study will greatly benefit all health professionals in this setting and Kenya in general. The study also provides a baseline for larger studies. Results from such studies will provide a framework for policy makers at the Ministry of Health to formulate strategies that promote pharmacotherapy outcomes in diabetes in particular and other chronic diseases in general. Such strategies may include review of current guidelines to reflect the comprehensive approach necessary for management of diabetes. Overall, implementation of such strategies will greatly benefit patients through improved quality of life.

1.4 Research question

The research question that this study sought to answer was; what is the quality of prescribing in management of hyperglycemia and cardiovascular risk in T2DM at Webuye District Hospital?

1.5 Study objectives

1.5.1 Main objective

The main objective of the study was to investigate quality of prescribing in type 2 diabetes mellitus (T2DM) ambulatory care at Webuye District Hospital.

1.5.2 Specific objectives

The specific objectives of this study were:

1. To determine quality of prescribing using prescribing quality indicators for management of hyperglycemia in T2DM patients.
2. To determine quality of prescribing using prescribing quality indicators for cardiovascular risk management in T2DM patients.
3. To identify potential inappropriate medicine use and potential drug-drug interactions in T2DM management.
4. To identify factors that influence choice of drugs in management of hyperglycemia and cardiovascular risk in T2DM patients.

CHAPTER TWO: LITERATURE REVIEW

Diabetes mellitus is an important public health challenge in both economically developing and developed countries. It is now the most common non-communicable disease globally, yet half of the people affected are unaware of their status (IDF, 2012). It is often diagnosed when complication are present (Madonna and Peizhong, 2013).

2.1 Criteria for diagnosis of diabetes

The World Health Organization (WHO) has developed criteria for diagnosis of diabetes which has been adopted by other associations, federations and countries, including Kenya. Diabetes is diagnosed if glycated haemoglobin (HbA1c) level is greater or equal to 6.5 % or when fasting plasma glucose (FPG) is greater or equal to 7.0 millimol per litre (mmol/L). It can also be diagnosed if 2 hour-plasma glucose is greater or equal to 11.1 mmol/L during an oral glucose tolerance test (OGTT). In patients with classic symptoms of hyperglycaemia, it is diagnosed if random plasma glucose (RPG) is greater or equal to 11.1mmol/L (WHO, 2006; WHO, 2011; IDF, 2012; ADA, 2013).

2.2 Risk factors for type 2 diabetes mellitus

It is recommended that testing should be considered in adults of any age with a body mass index (BMI) greater or equal to 25 kg/m^2 and one or more of the risk factors for diabetes. Risk factors include physical inactivity/sedentary lifestyle, family history of diabetes, hypertension, high risk race or ethnicity, severe obesity and history of cardiovascular disease (CVD). They also include women with previous history of GDM or with polycystic ovarian syndrome, HbA1c greater or equal to 5.7 %, impaired glucose tolerance or impaired fasting glucose on previous testing (ADA, 2013).

2.3 Management of type 2 diabetes mellitus

There is considerable evidence that support benefits of improved blood glucose, blood pressure and blood lipid control in T2DM. Lifestyle management only provides target glucose levels in a minority of individuals with diabetes and for a limited period of time post-diagnosis. Supplementary pharmacological measures are eventually necessary (IDF, 2012). There is a wide range of pharmacological agents available for management of hyperglycaemia and cardiovascular risk in T2DM patients. However, availability and access of these treatment options is limited in many middle and low income countries. Even when available, they may be prescribed inappropriately (IDF, 2012).

Numerous guidelines provide evidence-based guidance on different approaches in which glucose lowering agents can be used alone or in combination. Adhering to evidence-based national treatment algorithms can improve quality of life and reduce morbidity and mortality associated with T2DM complications. Several studies have however shown that prescribing practices vary considerably (IDF, 2012).

Good glycaemic control remains the cornerstone of managing T2DM and plays a crucial role in preventing or delaying the onset and progression of diabetic complications (Bailey *et al*, 2013). Many guidelines recommend that people with diabetes should maintain HbA1c below 7.0 % as this is an effective way of minimizing the risk of developing microvascular and neuropathic complications (Nathan *et al*, 2009).

Various randomized clinical trials (RCT) have demonstrated the importance of intensive glucose control in minimizing complications in T2DM. The United Kingdom prospective diabetes study [(UKPDS, 1998] reported that a median HbA1c of 7.0 % was achieved in newly diagnosed T2DM in the intensively treated arm. It also demonstrated benefits of intensive glycaemic control in reducing rates of microvascular complications in these patients (Madonna and Peizhong, 2013; Bailey *et al*, 2013). The Kumamoto study reported HbA1c levels of 7.1 % in the intensively treated patients compared to 9.4 % in conventionally treated patients (Ohkubo *et al*, 1995). Additionally, the Action to control cardiovascular risk in diabetes [(ACCORD, 2008)] study group reported 6.4 % and 7.5 % respectively in the intensively treated and conventionally treated patients.

Lifestyle management is recommended as the initial intervention in T2DM management as it is beneficial in controlling hyperglycaemia (Nathan *et al*, 2009). It aims at increasing physical activity, weight reduction (in overweight patients) and smoking cessation. However, it is only effective in a minority of patients and high rates of weight regain limit its role (IDF, 2012; Nathan *et al*, 2009). Accordingly, supplementary pharmaceutical interventions are needed to achieve target blood glucose levels (IDF, 2012).

2.3.1. Medicines used in glucose control therapy

Many classes of glucose lowering drugs are now available, increasing treatment options from which choices can be made. This has left practitioners and diabetic patients with uncertainty regarding the most appropriate treatment option for treatment of T2DM (Nathan *et al*, 2009). Systematic reviews comparing efficacy of medicines for T2DM, excluding alpha (α)-glucosidase inhibitors and insulin have been carried out. They have reported that most of the

medicines are similarly efficacious when used as monotherapy, reducing HbA1c levels by 1 % (IDF, 2012). Classes of medicines used in pharmacological management of hyperglycaemia include:

Biguanides: Metformin is the only biguanide available for clinical use. Its major effect is decreasing hepatic glucose and lowering fasting glycaemia. Typically, metformin monotherapy will lower HbA1c by approximately 1.5 percentage points (Nathan *et al*, 2009). It is generally well tolerated, with most adverse effects being gastrointestinal. It is the drug of choice when initiating glucose lowering therapy in T2DM. It is not associated with weight gain and is recommended as part of the regimen in overweight T2DM patients (Nathan *et al*, 2009; IDF, 2012). Renal dysfunction is considered a contraindication of metformin since it can, in extremely rare circumstances, increase the risk of lactic acidosis (Nathan *et al*, 2009; Bailey *et al*, 2013). Studies comparing metformin monotherapy or in combination with placebo or any other glucose-lowering therapy reported no cases of fatal or nonfatal lactic acidosis in the metformin group (Salpeter *et al*, 2010).

Sulfonylureas: They lower glycaemia by enhancing insulin secretion. They possess efficacy similar to metformin, lowering HbA1c by approximately 1.5 percentage points (Nathan *et al*, 2009). Onset of glucose lowering effect of sulfonylurea monotherapy is relatively rapid when compared with thiazolidinediones. However, maintenance of glycaemic targets over time is not as effective as with thiazolidinedione or metformin therapy (Nathan *et al*, 2009). The major adverse effect is an increased risk of hypoglycaemia, which, although rare, can be prolonged and life threatening (Nathan *et al*, 2009; IDF, 2012). Severe episodes are relatively frequent in the elderly. It is recommended that long acting first generation sulfonylureas such as chlorpropamide and glibenclamide should be avoided in these patients [American Geriatrics Society (AGS, 2012]. Alternatives for this category of patients are second generation sulfonylureas that include glimepiride, glipizide and gliclazide. Weight gain of approximately 2.0 kg is common following initiation of sulfonylurea therapy (Nathan *et al*, 2009). Meta-analysis and systematic review of observational studies comparing sulfonylurea monotherapy or in combination demonstrated a higher all-cause and cardiovascular mortality in patients on sulfonylurea compared to any non-sulfonylurea treatment (Forst *et al*, 2013).

Glinides or meglitinides: They have the same mode of action as the sulfonylureas, although they bind to a different site within the receptor. They are administered more frequently due to a shorter circulating half-life. They lower HbA1c by approximately 0.5 to 1.5 percentage

points. They may cause an increase or decrease in body weight (Bailey *et al,* 2013). Repaglinide is almost as effective as metformin or sulfonylureas, with a similar risk of weight gain as sulfonylureas. Hypoglycaemia is however lower in frequency when compared to sulfonylureas (Nathan *et al,* 2009).

Alpha-glucosidase inhibitors (α-GI): These act by reducing the rate of polysaccharide digestion and absorption in the proximal small intestines, thereby decreasing post-prandial glucose levels without resulting in hypoglycaemia. Examples include acarbose and miglitol which are less effective than metformin, reducing HbA1c levels by 0.5-0.8 percentage points. They are associated with increased flatulence and gastrointestinal symptoms, which may affect adherence to treatment. Studies have estimated that 25-45 % of patients discontinue use of these drugs due to side effects (Nathan *et al,* 2009). A systematic review reported that doses of acarbose of more than 50 mg thrice daily did not offer any additional effect on HbA1c but was associated with more adverse effects. When compared to sulfonylureas, α-GI had an inferior profile regarding glucose control and adverse effects (Van der Laar *et al,* 2005).

Thiazolidinediones or glitazones: These act by increasing the sensitivity of muscle, fat and liver to both endogenous and exogenous insulin. These drugs cause a reduction of 0.5-1.4 percentage points in HbA1c levels when used as monotherapy and appear to have a more durable effect on glycaemic control when compared to sulfonylureas (Nathan *et al,* 2009). Pioglitazone monotherapy can be considered as an alternative to metformin monotherapy where the latter is not tolerated or contraindicated. It has a unique insulin sensitizing action, and can be combined with metformin or as triple therapy to achieve target HbA1c levels. In triple therapy, it is recommended that agents with complementary modes of action are used (Schernthaner, Currie and Schernthaner, 2013).

Adverse effects of pioglitazone include weight gain, congestive heart failure (CHF), bone fractures and macular edema (Schernthaner, Currie and Schernthaner, 2013). Several meta-analyses have suggested a 30-40 % increase in myocardial infarction (MI) with rosiglitazone (Nathan *et al,* 2009). Clinical use of pioglitazone is currently restricted globally because of safety issues and availability of newer and safer agents (Khaled and Heinrich, 2012). However, it is still useful in insulin resistant patients and those with a history of CVD (Schernthaner, Currie and Schernthaner, 2013).

Insulin: Insulin is the oldest of all currently available medicines for management of diabetes and the most effective at lowering glycaemia. When appropriately administered in adequate doses, it can lower any level of elevated glucose to therapeutic goals (Nathan *et al,* 2009). The natural history of T2DM is of progression of beta (β) cell failure hence insulin remains the only glucose lowering therapy capable of maintaining glycaemia despite such progression (IDF, 2012). It also has a beneficial effect on triacylglycerol and high density lipoprotein (HDL) cholesterol levels, especially in patients with poor glycaemic control. However, it is associated with hypoglycaemia and weight gain of approximately 2-4 kg on initiation of therapy (Nathan *et al,* 2009).

The mode of action of injected insulin is similar to endogenous insulin in lowering blood glucose levels. Various types of insulin differ in several ways including source and/or onset and duration of action [Drug information online (DI, 2013]. Based on onset, peak and duration of time, insulin can be classified into rapid acting insulin (insulin lispro and insulin aspart), short acting (insulin regular or soluble insulin), long acting insulin (includes insulin zinc extended) and very long acting insulin (insulin glargine and insulin detemir) (DI, 2013).

Premixed or biphasic insulin: This refers to a mixture of two types of insulin in one vial. In most cases, one insulin type is rapid or short acting while the other type has a longer duration of action. Examples of premixed insulin include insulin isophane/insulin regular (Humulin® 50/50, Humulin® 70/30 and Novolin® 70/30) (DI, 2013). A systematic review demonstrated that bedtime human isophane insulin in combination with oral metformin provides comparable glycaemic control with insulin monotherapy and is associated with less weight gain (Goudswaard *et al,* 2004). Another systematic review has suggested a clinical benefit of treating patients with T2DM with long acting insulin analogues, but with caution (Horvath *et al,* 2009).

Glucagon-like peptide-1 agonists (GLP-1): These act by increasing insulin secretion, potentiating nutrient-stimulated insulin secretion and decreasing glucagon. They decrease HbA1c by approximately 0.5 to 2.0 percentage points (Bailey *et al,* 2013). They are not associated with weight gain and have indirect association with weight loss, especially in early stages of the disease (Freeman, 2011). For example, exenatide is associated with weight loss of 2-3 kg in the first six months of therapy. They are not associated with hypoglycaemia when used as monotherapy but can cause a relatively high frequency of gastrointestinal disturbances (Nathan *et al,* 2009). A meta-analysis has reported that GLP-1 agonists are

effective in reducing HbA1c and post-prandial glucose in patients not responding to metformin and sulfonylureas. Studies also demonstrated similar efficacy to insulin (Monami, Marchionni and Mannucci, 2009).

Dipeptidyl peptidase-4 (DPP-4) inhibitors: These drugs enhance the effect of GLP-1 and glucose dependent insulinotropic peptide (GIP), thereby increasing glucose mediated insulin secretion and suppressing glucagon secretion. Examples in this class include sitagliptin and vidagliptin. They lower HbA1c levels by 0.6-0.9 percentage points and are relatively well tolerated. They do not cause hypoglycaemia when used as monotherapy (Nathan *et al,* 2009). Studies have reported that sitagliptin 100 mg per day was generally well tolerated (Engel *et al,* 2013) and that DPP-4 inhibitors had some theoretical advantages over existing oral therapies when individualized to patients (Richter *et al,* 2008).

2.3.2 Treatment algorithm in 2 diabetes mellitus

The aim of pharmacological therapy is to achieve and sustain HbA1c below 7.0 % and to allow change of interventions at a rapid pace as titration of drugs permits when target glycemic goals are not being achieved (Nathan *et al,* 2009). Oral glucose lowering treatment is recommended when lifestyle interventions alone fail to maintain target glucose levels in new onset T2DM. However, the latter remain anchored as the underlying theme in management of T2DM (IDF, 2012). Monotherapy may be effective in a good number of patients but with time, the progressive nature of T2DM requires combination therapy (Nathan *et al,* 2009).

A patient centred approach is recommended in guiding choice of pharmacological agents. Factors to be considered include efficacy, cost, co-morbidities, potential side effects, risk of hypoglycaemia and patient preferences (ADA, 2013). Figure 2.1summarizes the steps in the treatment algorithm for type 2 diabetes mellitus. These steps include:

Step 1: First line therapy: The consensus statement of the ADA and the European Association for the Study of Diabetes (EASD), recommends that metformin is initiated concurrently with lifestyle interventions at diagnosis since the latter fail in majority of patients (Nathan *et al,* 2009). The IDF also recommends metformin as first line, unless specifically contraindicated, such as in renal impairment. The dose should be titrated to its maximally effective dose within 1-2 months to minimise discontinuation due to gastrointestinal intolerance. Rapid addition of other glucose lowering medicines such as

sulfonylureas should be considered where glucose levels are persistently high (Nathan *et al*, 2009; IDF, 2012).

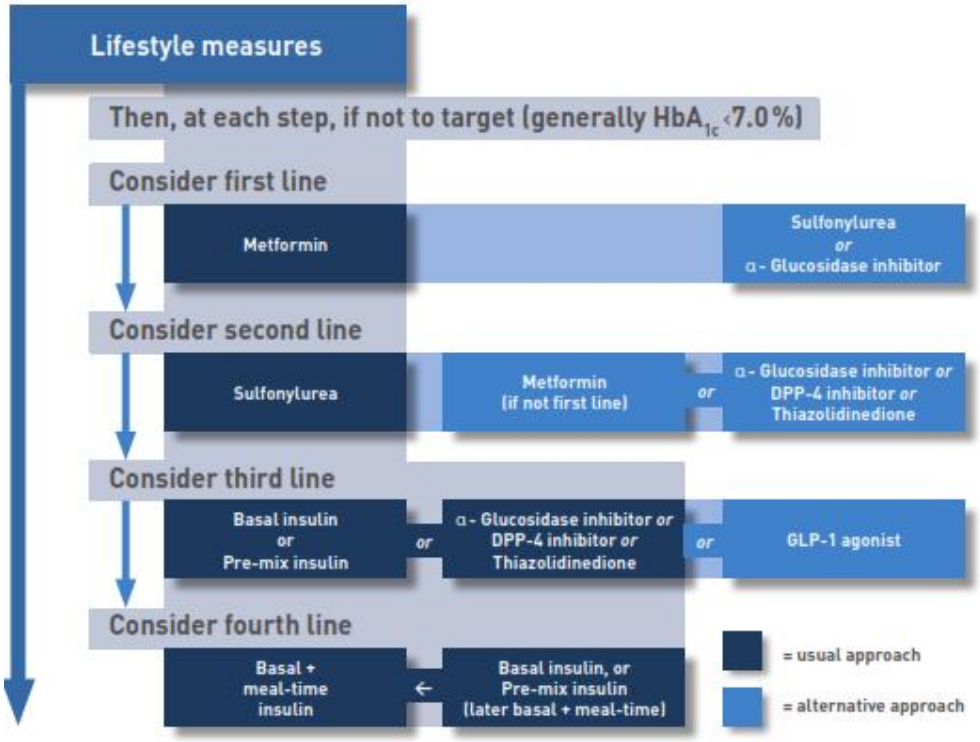


Figure 2.1 Treatment algorithm in type 2 diabetes mellitus (*Source*: IDF, 2012).

A systematic review recommended metformin as the first therapeutic agent of choice in T2DM patients who are overweight or obese, as it may prevent some vascular complications and mortality. Metformin was also shown to produce beneficial changes in glycaemia control, and moderated in weight, lipids, insulinaemia and diastolic blood pressure (Saenz *et al*, 2013).

Step 2: Second line therapy: If lifestyle interventions and maximum tolerated dose of metformin (up to 1 g twice daily) fail to achieve or sustain glycemic goals, it is recommended that a second oral glucose lowering agent is added within 2-3 months, or at any other time when target HbA1c is not achieved (Nathan *et al*, 2009). IDF (2012) recommends addition of a sulfonylurea agent. Alternatively, metformin (if not used as first line), or α-GI, or DPP-4 inhibitor, or rapid acting insulin secretagogue is recommended as an alternative to sulfonylureas (IDF, 2012). On the other hand, ADA and EASD recommend that HbA1c level will determine which agent between sulfonylurea and insulin is added, with basal

(intermediate or long acting) insulin being preferred if the HbA1c level is more than 8.5 %. However, many newly diagnosed T2DM patients will respond well to oral medicines (Nathan *et al,* 2009).

Step 3: Third line therapy: If lifestyle interventions, metformin, basal insulin or sulfonylurea do not achieve target levels, the next step involves starting or intensifying insulin therapy (Nathan *et al,* 2009). The IDF (2012) also recommends using basal insulin as a third agent (if not used already) or a third oral agent from among the following; a DPP-4 Inhibitor, α-GI or a thiazolidinedione. ADA and EASD recommend that a third oral agent can be considered if HbA1c is close to the target level of less than 8.0 %, although this is not as effective and less costly as intensifying insulin therapy (Nathan *et al,* 2009). Insulin intensification involves additional injections that may include short or rapid acting preparations administered after selected meals to prevent post-prandial glycaemia. It has been shown to improve metabolic and clinical outcomes (IDF, 2012).

ADA and EASD recommend that when insulin therapy is initiated, insulin secretagogues (sulfonylureas and glinides) should be discontinued or tapered off then discontinued since their physiological action is not synergistic (Nathan *et al,* 2009). Generally, glucose level lowering agents with different modes of action will have the greatest synergy in combination therapy. Combination therapy decreases HbA1c more than monotherapy by about 1 percentage point. As an example, insulin and metformin is an effective combination in lowering glycaemia while limiting weight gain (Nathan *et al,* 2009).

2.4 Co-morbidities and complications of diabetes

Type 2 diabetes, which accounts for 90 % of all diabetes, has become one of the major causes of premature death, mainly through increased risk of CVD, responsible for up to 80 % of such deaths (Puepet *et al,* 2009; Madonna and Peizhong, 2013; ADA, 2013). Type 2 diabetes has a long asymptomatic preclinical phase which frequently goes undetected. Co-morbidities and complications are often present at the time of diagnosis (MOH, 2009; IDF, 2012). Co-morbidities of T2DM include CVD [such as hypertension, coronary artery disease (CAD), peripheral artery diseases (PAD), microvascular and macrovascular diseases], myocardial infarction (MI) and cerebrovascular accidents (CVA) or stroke (Madonna and Peizhong, 2013). Epidemiological evidence that CVD is the major cause of mortality in people with T2DM is extensively available (IDF, 2012). Hypertension and dyslipidaemia commonly co-

exist with T2DM and are risk factors for CVD, while diabetes itself is an independent risk factor for CVD (ADA, 2013).

Complications of T2DM include microvascular diseases (retinopathy, neuropathy and nephropathy), diabetic foot and lower limb amputations. It is estimated that lower limb amputations are 10 times more common in people with diabetes than in those without, while in certain age groups, those with diabetes have a 2-fold increase in the risk of CVA (WHO, 2010). Diabetic nephropathy occurs in 20-40 % of patients with diabetes and is the single leading cause of end stage renal disease (ADA, 2013). These co-morbidities and complications pose challenges in maintaining quality of care in diabetic patients.

2.4.1 Management of hypertension in type 2 diabetes mellitus

Hypertension affects approximately 20-60 % of patients with diabetes, depending on obesity, ethnicity and age. In T2DM, elevated blood pressure is often part of the metabolic syndrome of insulin resistance, including central obesity and lipid abnormalities (Patel and Mehta, 2013). For patients with blood pressure (BP) above 140/80 mmHg, prompt initiation of pharmacological therapy is recommended, in addition to lifestyle management. Many guidelines recommend that pharmacological therapy for patients with diabetes and hypertension should be a regimen that includes either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). The two may offer some advantages over other agents for the initial or early therapy of hypertension as shown by several studies (IDF, 2012; ADA, 2013).

Angiotensin converting enzyme inhibitors are promoted as first line agents for hypertension in diabetic patients since they appear to have action over and above blood pressure lowering alone (Patel and Mehta, 2013). Results from several randomized clinical trials suggest that ACEI reduce loss of kidney function in individuals with diabetic nephropathy, above and beyond any such effect attributable to BP lowering (Barnett *et al,* 2004). They are also not thought to adversely affect glucose levels (Patel and Mehta, 2013). A systematic review assessing benefits and harms of BP lowering agents concluded that ACEI prevent new onset diabetic kidney disease and death in normoalbuminuric people with diabetes (Lv *et al,* 2012).

Alternatives to ACEI are ARB such as losartan, telmisartan, irbesartan and valsartan. They have been shown to be clinically equivalent in patients with clinical conditions that place them at a high risk of cardiovascular events, such as diabetes and hypertension (Barnett *et al,* 2004). Generally, multiple drug therapy is required to achieve BP targets. When targets are

not reached on maximal doses of ACEI or ARB, it is recommended that other pharmacological agents from other classes are added (IDF, 2012; ADA, 2013). Preferred combinations include ACEI + calcium channel blocker (CCB) or ACEI + low dose thiazide (IDF, 2012). Based on current evidence, it is recommended that hypertension be managed using monotherapy with ACEI or ARB, with addition of CCB or low dose thiazide (or thiazide-like) diuretic if monotherapy fails to control BP adequately (IDF, 2012). The choice of antihypertensive agent to be used should not only aim at controlling hypertension but also on preventing or delaying the development of complications (Patel and Mehta, 2013).

2.4.2 Management of dyslipidaemia

For most diabetic patients, the preferred strategy of dyslipidaemia pharmacological therapy is to lower low density lipoproteins (LDL) level to less than 100 milligram per decilitre (mg/dL) using statins (ADA, 2013). Strong evidence exists that statins reduce the risk of death or CVD events irrespective of age and gender and across a wide range of cholesterol levels (IDF, 2012). IDF (2012) and ADA (2013) recommend that statin therapy should be added to lifestyle modification measures regardless of baseline lipid levels for diabetic patients with overt CVD. Those without CVD who are more than 40 years and have one or more CVD risk factors; family history, hypertension, smoking, dyslipidaemia or albuminuria are also eligible for statin therapy. For low risk patients (without CVD and less than 40 years), statin therapy should be considered if LDL cholesterol remains above 100mg/dl or in those with multiple risk factors (ADA, 2013).

Generally, statin therapy is indicated for T2DM patients with high cardiovascular risk who include women aged above 60 years and men aged above 50 years and/or those with duration of diabetes greater or equal to 10 years and/or those with uncontrolled hypertension and/or those with albuminuria and/or those with HbA1c above 7 % (Martirosyan *et al,* 2008). Statin combination therapy has been shown to offer no additional cardiovascular benefit and should be avoided (ADA, 2013). Fenofibrate may be considered as an additional agent where serum triglyceride levels are above 200 mg/dl and high density lipoprotein (HDL) cholesterol levels are low (IDF, 2012). However, such a combination is associated with an increased risk for abnormal transaminase levels, myositis or rhabdomyolysis (ADA, 2013).

2.4.3 Antiplatelet treatment

The American Diabetes Association (2013) recommends use of aspirin/acetyl salicylic acid (ASA) as a primary prevention strategy in patients with diabetes and at increased CVD risk (10 year risk above 10 %). These include most men above 50 years or women above 60 years

who have at least one additional major risk factor; family history of CVD, hypertension, smoking, dyslipidaemia or albuminuria. In diabetic patients with established CVD, the benefit of long term ASA use in reducing the risk of MI, cardiovascular accident and vascular death is well established (IDF, 2012). Aspirin is not recommended for patients who do not meet the above criteria (10 year CVD risk less than 5%) because of potential bleeding adverse effect (ADA, 2013). As a secondary prevention strategy, ASA (75-162 mg daily) is recommended in all diabetic patients with a history of CVD. It has been shown to be effective in reducing cardiovascular morbidity and mortality in high risk patients with previous MI and stroke. Clopidrogel (75 mg daily) is an alternative in patients with established aspirin allergy (IDF, 2012; ADA, 2013).

2.5 Prescribing quality indicators in type 2 diabetes ambulatory care

Martirosyan *et al* (2010) define a prescribing indicator as "a measurable element of prescribing that can be used to assess quality or efficiency of treatment at patient or health provider level". Alternatively, a prescribing quality indicator (PQI) is defined as a "measurable element of prescribing for which there is evidence or consensus that it can be used to assess the quality of care that is provided" (EuroDURG Quality Indicator Meeting 2004). For reliable measurement of prescribing quality, valid indicators are required (Martirosyan *et al*, 2010).

Martirosyan *et al* (2008) carried out a study to develop and validate a set of PQI for internal use in T2DM management, and assess their operational validity. They considered potential PQI for pharmacological management of hypertension, hyperglycemia, dyslipidaemia and antiplatelet treatment in T2DM based on clinical guidelines. The PQI were assessed on face and content validity. Operational validity of these indicators was assessed using a dataset of 3214 patients registered by 70 general practitioners.

Out of 31 indicators, 14 remained face and content valid. When tested for operational validity, one indicator focusing on percentage of T2DM patients aged 40 years and below with a history of CVD prescribed a statin could not be calculated because of absence of eligible patients. For the final 13 indicators, outcomes varied from 10 % for timely prescribing of insulin to 96 % for prescribing of any glucose lowering medicine for patients with elevated HbA1c levels (Martirosyan *et al*, 2008). These results demonstrated that there were deficiencies in timely intensification of antihyperglycaemic therapy characterized by delays in initiating insulin therapy for deserving T2DM patients. There were also deficiencies regarding prescribing of statins, acetyl-salicylic acid and timely intensification of

antihypertensive treatment. However, nearly all patients with elevated HbA1c levels were receiving glucose lowering therapy (Martirosyan *et al,* 2008). The 13 PQI are all process indicators [Australian National Prescribing Service (ANPS, 2009)] and focus on undertreatment and choice of drugs.

2.6 Quality indicators for the care of type 2 diabetes mellitus in elderly patients

Type 2 diabetes mellitus is an important health condition for the aging population. Prevalence of diabetes rises sharply with age, with prevalence estimates varying from 10-20 % for persons aged 60 years and older, nearly all of whom have T2DM (Shekelle and Vijan, 2007). It is recommended that daily acetyl salicylic acid should be prescribed in elderly T2DM patients not receiving any anticoagulant or antiplatelet drug. This may reduce the risk of MI and mortality from CVD (Shekelle and Vijan, 2007).

According to the American Geriatrics Society (AGS), medication-related problems are common, costly, and often preventable in older adults and lead to poor outcomes. Avoiding the use of inappropriate and high-risk medicines is an important, simple, and effective strategy in reducing medication-related problems and adverse drug effects in older adults (AGS, 2012).The updated Beers criteria (2012) deal with potentially inappropriate medicine use in older adults. For T2DM, the criteria recommend that long acting sulfonylureas such as chlorpropamide and glibenclamide should be avoided in older adults. The rationale behind this is that chlorpropamide has a prolonged half-life and can therefore result in prolonged hypoglycemia. On the other hand, glibenclamide is associated with greater risk of severe prolonged hypoglycemia in older adults (AGS, 2012). Shorter acting agents such as glipizide and gliclazide are more suitable in this category of patients (Abdelhafiz and Sinclair, 2013).

2.7 Potential drug interactions in type 2 diabetes mellitus

Drug interactions occur when the effect of a particular drug is altered when taken concomitantly with another drug, or with food. Drug-disease interactions also occur. Examples of these interactions include the following:

Angiotensin converting enzyme inhibitors (ACEI) + Angiotensin receptor blockers (ARB): Co-administration of an ACEI with an ARB may increase the risk of hyperkalemia, hypotension and renal dysfunction due to additive or synergistic effects on the renin-angiotensin system (DI, 2013).

ACEI /ARB + Potassium-sparing diuretics: Concomitant use of ACEI or ARB together with a potassium-sparing diuretic such as spironolactone may increase the risk of

hyperkalemia. ACE or Angiotensin II inhibition results in decreased aldosterone secretion, which may lead to an increase in serum potassium that may be additive to that induced by potassium-sparing diuretics. This interaction may be mild in most patients with normal renal function. However, life-threatening and fatal hyperkalemia have been reported to occur within days to weeks of receiving the combination in patients with risk factors such as renal impairment, diabetes, old age and in severe or worsening congestive heart failure. It may also occur due to drugs that increase serum potassium such as potassium supplements (DI, 2013). A retrospective study demonstrated that the addition of candesartan to standard medical therapy for heart failure was associated with a 2-3 fold increase in the risk of hyperkalemia, which was further amplified by co-administration with spironolactone or ACEI (DI, 2013).

ACEI/ARB + thiazides + Non-steroidal anti-inflammatory drugs (NSAID): Aspirin, an NSAID, at a dose of less than 150 mg per day, is recommended for antiplatelet treatment for primary or secondary prevention of CVD in eligible T2DM patients. All other NSAIDs, including cyclo-oxygenase II selective inhibitors, should be avoided if possible in T2DM patients. Combination of NSAID + thiazides + ACEI/ARB has been implicated in a significant number of reports of drug-induced renal failure. Extreme caution should be taken with ACEI and NSAID in patients with renal impairment (ANPS, 2009).

Verapamil + β-blockers: When calcium channel blockers, especially verapamil and diltiazem, are used concomitantly with β-blockers, additive reductions in heart rate, cardiac conduction, and cardiac contractility may occur. While this combination may be useful and effective in some scenarios, potentially serious cardiovascular adverse effects such as congestive heart failure (CHF), severe hypotension, and/or exacerbation of angina have been reported to occur. Verapamil and diltiazem may also decrease the clearance of some β-blockers (DI, 2013).

Glitazones + congestive heart failure: Congestive heart failure appears to be a class-specific adverse effect with respect to glitazones. Studies suggest that either rosiglitazone or pioglitazone can exacerbate heart failure. A meta-analysis demonstrated that pioglitazone was associated with increased heart failure without an associated increase in mortality rates (Khaled and Heinrich, 2012).

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a retrospective review of T2DM patient medical records at Webuye District Hospital, western Kenya. Records of patients with T2DM meeting the inclusion criteria who attended the diabetic medical outpatient clinic (MOPC) at Webuye District Hospital during the study period 1st January to 31st December 2013 were used for this study.

3.2 Study setting

Webuye District Hospital is a high volume, 217-bed hospital situated in Webuye town, Bungoma County, western Kenya (*location map in Appendix B*). It began its operations in 1991 and its immediate catchment is about 500000 people. It serves as a referral centre for the county and surrounding counties that include Kakamega, Busia, Uasin Gishu and Tranz Nzoia. On average, it attends to 200-300 outpatients daily, with bed occupancy of about 150 %. It is also a training centre for many colleges and universities, including Webuye Medical Training College and Moi University.

It has specialized outpatient clinics that include MOPC, gynaecology outpatient clinic (GOPC), surgical outpatient clinic (SOPC), paediatric outpatient clinic (POPC), chest/skin clinic, mental health clinic; ear, nose and throat (ENT), ophthalmology and dental units. It also boasts of a specialized diabetic clinic that supports diabetic patients to access medicines and investigations such as HbA1c tests, among other benefits.

3.3 Inclusion and exclusion criteria

All patients with a confirmed diagnosis of T2DM who visited the diabetic clinic in the year 2013 were eligible for inclusion. Patients who were excluded were those with T2DM who did not visit the clinic at least once in the first half of 2013 (with the exception of newly diagnosed patients), those with type 1 DM and/or those who were admitted in the wards.

3.4 Ethical considerations

Approval to carry out this study was granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research committee (KNH/UON ERC) on 4th April 2014, Reference: KNH-ERC/A/86 as outlined in *Appendix C*. Exemption from obtaining informed consent from study participants was also granted by the ethics committee as the study did not involve direct contact with patients or prescribers. Information from patient files was held in strict confidence. Record numbers rather than patient names were used on data collection forms.

Only those details relevant to the study were extracted and the records promptly returned after the desired information had been obtained.

Patients were not exposed to any risk or hazard since the study only involved their records which were not altered in any way. Patients attended to in 2013 were not expected to benefit directly from this study. However, those treated subsequently and future patients may benefit from improved care as a result of recommendations from this study.

3.5 Sample size

Since the design was retrospective descriptive with dichotomous /categorical outcomes, the sample size was estimated using Fisher's formula:

$$n = \frac{Z^2 \text{ X } P(1-P)}{d^2}$$

Where;

n = Estimated sample size

P = Prevalence or proportion

d = Error margin (set at 5 %)

z = Value corresponding to 95 % Confidence Interval (1.96).

Martirosyan *et al* (2008), on testing operational validity of 14 face and content valid PQI of type 2 diabetes ambulatory care, found that outcomes varied from 10 % for timely prescribing of insulin to 96 % for prescribing any antihyperglycaemic medicine in patients with elevated HbA1c levels. Assuming an outcome variability average of 40 % in this region, the estimated sample size was 369**.**

3.5.1 Sampling strategy

Sequential sampling was used. Since majority of the indicators dealt with outcomes in the second half of 2013, the attendance lists for patients attending the diabetic clinic between 01/07/2013 and 31/12/2013 was used to get file numbers for patients who were seen at the hospital during this period. For July 2013, the first and last weeks were chosen, and file numbers for all diabetic patients seen on the two clinic days were recorded. For August, the second and third weeks were chosen, and this process was repeated for the remaining four months. This selection was designed to give a representative sample throughout the year and also within each month in case certain prescribers attended only on certain days or referred

certain patient groups to particular clinics. A total of 880 listed files were retrieved, perused and the first 369 patient files that met the inclusion criteria were picked for use in the study.

3.6 Data collection methods

Data were collected using a data collection form that was designed, pre-tested and validated for this purpose. Clinical information recorded in 369 T2DM patient medical records in 2013 was extracted.

3.7 Definition of variables, indicators and assumptions

3.7.1 Predictor and outcome variables

Both continuous and categorical variables were considered during data collection and analysis. Continuous variables included age, weight, HbA1c, SBP, BMI and duration of diabetes. Categorical variables included sex, marital status, education, occupation, drugs prescribed, co-morbidities, complications and outcomes for indicators. The drugs on the last prescription in the patient medical record in 2013 were used for describing patterns of prescribing. In the case of potential drug-drug interactions, all prescriptions in 2013 were used. Co-morbidities considered included hypertension, obesity, other CVD and previous CVD while complications included retinopathy, peripheral neuropathy, nephropathy and diabetic foot.

In determining factors influencing prescription of specific drugs for hyperglycaemia and cardiovascular risk, predictor variables considered included age, sex, hypertension, previous CVD, other CVD, duration of diabetes, HbA1c, SBP and BMI. Outcome variables considered were use of metformin, glibenclamide, insulin, enalapril, losartan and/or acetyl salicylic acid.

3.7.2 Indicators and Beers criteria

Twelve PQI (Martirosyan *et al,* 2008), one quality indicator [(QI) for the care of T2DM in the elderly] and Beers criteria (AGS, 2012), defined in section 2.5 and 2.6, were adapted for use in this study as summarized in Table 3.1. The inclusion criteria and outcome for each PQI were defined as outlined in *Appendix A.* The QI applied in this study aimed to determine the proportion of elderly T2DM patients prescribed daily acetyl salicylic acid for primary prevention of CVD. The updated Beers criteria (2012) were applied in this study to identify potentially inappropriate medicine use in elderly T2DM patients. Specifically, it was applied to identify the proportion of elderly patients prescribed glibenclamide.

Hypertension was defined as a diagnosis registered in the patient medical record and/or average values of systolic blood pressure greater or equal to 140mmHg and/or based on drugs prescribed. On the other hand, high cardiovascular risk was defined as T2DM women aged above 60 years and men aged above 50 years old and/or with duration of diabetes greater or equal to 10 years and/or with uncontrolled hypertension and/or with HbA1c above 7 %. History of cardiovascular disease was defined as history of myocardial infarction, ischemic heart disease and/or cerebrovascular accident as registered in the patient medical record. Overweight patients were defined as those with BMI 25-29.9 kg/m^2 while patients aged 65 and above years were considered elderly. Additionally, T2DM patients whose duration of diabetes was less than a year were considered newly diagnosed.

3.7.3 Assumptions and cut-off points

For ease of data analysis, two assumptions were made. Firstly, all newly diagnosed T2DM patients were assigned a duration of diabetes of 0.5 years. Secondly, HbA1c levels recorded as greater than 14 % in patient medical records were assigned the level 14.1 %. Due to limited accessible literature on similar studies, cut-off points for outcomes representing good quality prescribing were set. For PQI and QI, a cut-off point for an outcome representing good quality prescribing was set at minimum 70 %. For Beers criteria and potential drug-drug interactions, a cut-off point for an outcome representing good quality prescribing was set at not more than 5 %.

3.8 Data analysis

Data from completed data collection forms were coded numerically (where applicable) and keyed into a computer database using Microsoft Office Excel 2007. Data analysis was then carried out using Microsoft Office Excel 2007 and Stata® software version 10.1. There were two levels of data analysis; descriptive and inferential analysis.

3.8.1 Descriptive analysis

Descriptive statistics applied included median (with inter-quartile range) and proportions. These were applied in analysis of baseline characteristics, drugs, drug-drug interactions and outcomes for the indicators and Beers criteria. For calculation of PQI outcomes, values of SBP and HbA1c registered in the first half of 2013 and prescription data registered in the second half of 2013 were used. This ensured that prescription occurred after observing

elevated values of clinical measurements (Martirosyan *et al,* 2008). For BMI, the last value registered in 2013 was used while data on albuminuria was not available.

Table 3.1 Summary of indicators and Beers criteria

No	PQI description
1	Percentage of T2DM patients with hypertension or SBP greater or equal to 140 mmHg and prescribed any antihypertensive drug.
2	Percentage of T2DM patients prescribed a second antihypertensive drug from a different class if SBP remained greater or equal to 140mmHg with first class antihypertensive drug.
3	Percentage of T2DM non-hypertensive patients with albuminuria prescribed ACE inhibitor or ARB.
4	Percentage of T2DM patients with hypertension and with albuminuria prescribed a multiple drug regimen containing ACEI or ARB
5	Percentage of T2DM patients with hypertension and history of ischemic heart disease or MI prescribed β-blocker.
6	Percentage of prevalent T2DM patients with HbA1c above 7 % and prescribed any oral antihyperglycaemic agent or insulin
7	Percentage of T2DM patients with prescription of one oral antihyperglycaemic drug and not receiving insulin that are prescribed a second oral antihyperglycaemic drug from a different class if HbA1c remained above 7.0 %.
8	Percentage of T2DM patients with 2 oral antihyperglycaemic drugs and not receiving insulin who are prescribed insulin if HbA1c remained above 7.0 %
9	Percentage of incident T2DM patients prescribed metformin as a first choice drug
10	Percentage of overweight prevalent T2DM patients prescribed a multiple drug regime containing metformin
11	Percentage of T2DM patients with high cardiovascular risk who are prescribed a statin
12	Percentage of T2DM patients with history of cardiovascular disease prescribed acetyl salicylic acid
	Quality indicator for care of T2DM in elderly patients
13	Percentage of elderly T2DM patients prescribed acetyl salicylic acid
	Potential inappropriate medicine use in older adults (Beers criteria 2012)
14	Percentage of elderly T2DM patients prescribed a long-acting sulfonylurea

Additionally, the Shapiro-Wilk test for normal distribution was applied to test for normality of continuous variables.

3.8.2 Inferential analysis

Inferential statistics applied included Pearson chi^2 test and multivariate logistic regression. The p-value associated with Pearson chi^2 statistic was used to identify independent variables that significantly influenced choice of specific drugs on bivariate analysis. Multivariate logistic regression analysis reporting crude odds ratio (OR) as the test statistic was then applied to ensure that statistical significance exhibited on bivariate analysis was not due to confounding. Factors showing statistical significance on multivariate logistic regression analysis were further analyzed to obtain adjusted OR (backward stepwise modelling approach). Statistical significance was set at a p-value less than 0.05 in both bivariate and multivariate analyses.

CHAPTER FOUR: RESULTS

4.1 Study cohort

Out of a total of 880 sequentially sampled medical records for T2DM patients that attended the diabetic clinic in the second half of 2013, the first 369 patients meeting the eligibility criteria were included in this study. Of these, 14.9 % were newly diagnosed patients.

4.2 Baseline characteristics of the study cohort

The study cohort consisted of 57.2 % females. The median age was 59 years. Majority of the patients were married (90.8%), while the main occupation was farming (46.1%). The two main levels of education were primary (36.0 %) and secondary (35.8%).

The median weight was 73 kg years while median duration of diabetes, systolic blood pressure (SBP), body mass index (BMI) and glycated hemoglobin (HbA1c) was 4 years, 139 mmHg, 26.1 kg/m^2 and 8.2 % respectively. A total of 26.6 % patients had duration of diabetes 10 years and above while 49.0 % and 75.6 % patients had SBP and HbA1c greater or equal to140 mmHg and 7 % respectively. The Shapiro-Wilk test for normal distribution showed that age ($p = 0.29$) was normally distributed while weight, duration of diabetes, SBP, HbA1c and BMI had skewed distribution. Further analysis showed that 81.1 % patients had 1-3 co-morbidities while 18.7 % patients had none. The main co-morbidity was hypertension, affecting 70.5 % patients. Additionally, 40.7 % patients had 1-2 complications; with the main complication being peripheral neuropathy, affecting 34.4 % patients. Table 4.1 summarizes baseline characteristics of this study cohort.

4.3 Drugs for hyperglycemia and cardiovascular risk management

4.3.1 Drugs for hyperglycemia

Analysis of drugs showed that the three main drugs prescribed for hyperglycemia management were metformin (84.9 %), glibenclamide (47.7 %) and insulin (32.0 %). The main type of insulin prescribed was premixed insulin 70/30 for 29.5 % patients while neutral protamine hagedom (NPH)/human isophane insulin was prescribed for only 2.5 % patients. Prescription of pioglitazone, chlorpropamide and gliclazide were each done for less than 1 % of the patients.

Table 4.1 Baseline characteristics of the study cohort

Variable	Median (IQR) or n (%), N=369
Age (years)	59 (50-67)
Weight (kg)	73 (63-83)
Sex	
Male	211 (42.8)
Female	158 (57.2)
Marital status	
Married	335 (90.8)
Single	19(5.2)
Divorced/separated	2(0.5)
Widowed	13 (3.5)
Education	
No formal education	31(8.4)
Primary	133(36.0)
Secondary	132(35.8)
College	61(16.5)
University	12(3.3)
Occupation	
Unemployed	34(9.2)
Farmer	170(46.1)
Business	61(16.5)
Self-employed	30(8.1)
Formal employment	52(14.1)
Housewife	22 (6.0)
Variables for PQI	
Duration of diabetes (years)	4(2-10)
Glycated hemoglobin (HbA1c)	8.2 (7.0-10.1)
Body mass index (BMI)	26.1 (23.0-30.9)
Systolic blood pressure (SBP)	139 (125-153)
Co-morbidities	
Hypertension	260 (70.5)
Overweight	67(18.2)
Obese	58(15.7)
Other CVD	6(1.6)
Previous CVD	14(3.8)
Other co-morbidity	47(12.7)
Complications	
Retinopathy	14(3.8)
Nephropathy	2(0.5)
Diabetic foot	13(3.5)
Peripheral neuropathy	127(34.4)

***IQR**, Inter-quartile range; **PQI**, prescribing quality indicators; **CVD**, Cardiovascular disease*

Further analysis of the number of drugs prescribed for hyperglycemia showed that 59.1 % patients were on two agents while 37.4 % and 3.3 % patients were on one and three agents respectively. Metformin was the drug mainly prescribed as a single agent (22.0 %) followed by premixed insulin 70/30 (12.7 %) and glibenclamide (2.4 %). The main drug combinations were metformin + glibenclamide (45.3 %) and metformin + insulin (19.2 %).

4.3.2 Drugs for cardiovascular risk

In cardiovascular risk management, the two main drugs prescribed were low dose hydrochlorothiazide (52.0 %) and enalapril (51.8 %), followed by nifedipine (25.5 %) and losartan (20.1 %). In all cases where hydrochlorthiazide was prescribed, the dose was less or equal to 25 mg per day. Low dose acetyl salicylic acid for both primary and secondary prevention of cardiovascular disease (CVD) was prescribed for 20.6 % patients. The rest of the drugs were each prescribed for less than 10 % of the patients and included atenolol (9.5 %) and atorvastatin (6.5 %).

Further analysis of the number of drugs prescribed for cardiovascular risk management showed that 30.1 % patients were on three agents while 26.6 %, 16.0 % and 6.2 % were on two, one and four agents respectively. Enalapril was the drug mainly prescribed as a single agent (13.0 %) followed by hydrochlorthiazide (1.1 %). In instances where two or more drugs were prescribed, the two core drugs in the combination were enalapril + hydrochlorthiazide (40.0 %) followed by hydrochlorthiazide + nifedipine (19.8 %) and hydrochlorthiazide + losartan (13.8 %). Of the patients with hypertension, 89.6 % were prescribed enalapril (61.2 %) or losartan.

4.3.3 Other drugs

Other drugs that included amitriptylline (19.5 %), carbamazepine (3.5 %) and pregabalin (0.8 %) were mainly prescribed for management of peripheral neuropathy. Table 4.2 is a summary of drugs prescribed to T2DM patients.

4.4 Potential drug interactions in type 2 diabetes mellitus

On analysis of prescriptions in patient medical records in 2013, potential cases of pharmacodynamic drug-drug interactions were found in 4 % (95 % CI: 2-6) of the records. The main category of interaction was angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) + thiazide + non-steroidal anti-inflammatory

drug [(NSAID) (3 %)], in which enalapril was prescribed together with hydrochlorthiazide and an NSAID (mainly diclofenac or meloxicam).

Table 4.2 Drugs for hyperglycemia and cardiovascular risk

Category/drug	n (%), N=369
Antihyperglycemics	
Metformin	311 (84.9)
Glibenclamide	176 (47.7)
Insulin	118 (32.0)
Glimepiride	1 (0.3)
Chlorpropamide	1 (0.3)
Pioglitazone	2 (0.5)
Gliclazide	1 (0.3)
Cardiovascular risk management	
Hydrochlorthiazide	192 (52.0)
Enalapril	191 (51.8)
Losartan	74 (20.1)
Nifedipine	94 (25.5)
Atenolol	35 (9.5)
Carvedilol	5 (1.4)
Atorvastatin	24 (6.5)
Acetyl salicylic acid	76 (20.6)
Furosemide	11 (3.0)
Hydrallazine	2 (0.5)
Spirinolactone	1 (0.3)
Digoxin	4 (1.1)
Amlodipine	11 (3.0)
Other drugs	
Carbamazepine	13 (3.5)
Amitriptylline	71 (19.5)
Pregabalin	3 (0.8)

There were however no cases of interactions involving ACEI + ARB, verapamil + beta (β)-blocker or glitazones + congestive heart failure. Table 4.3 summarizes cases of potential drug-drug interactions.

Table 4.3 Potential drug interactions in type 2 diabetes mellitus

Potential drug interaction category	n (%, 95% CI), N=369
ACEI/ARB + thiazide + NSAID	12 (3, 2-6)
ACEI/ARB + potassium-sparing diuretic	2 (0.5, 0.1-2.2)
ACEI + ARB	None
Verapamil + β-blocker	None
Glitazones + congestive heart failure	None
Total	14 (4, 2-6)

ACEI, *angiotensin converting enzyme inhibitor;* ***ARB,*** *angiotensin receptor blocker;* ***NSAID,*** *non-steroidal anti-inflammatory drug*; ***CI****, confidence interval*

4.5 Variables for prescribing quality indicators

Some variables were not available for all patients, possibly because they were not measured every year. Age, gender, weight and SBP were recorded for all patients while BMI was only available for 56 % of the patients. None of the 369 patients had a value recorded for albuminuria in 2013. Table 4.4 summarizes the proportion of patients with a registered value for each variable. The proportion for SBP and HbA1c included newly diagnosed T2DM patients.

Table 4.4 Variables for prescribing quality indicators

Name of variable	n (%), N=369
Age	369 (100)
Gender	369 (100)
Duration of diabetes	369 (100)
SBP	369 (100)
HbA1c	366 (99)
BMI	206 (56)
Albuminuria	None

SBP*, systolic blood pressure;* ***HbA1c****, glycated hemoglobin;* ***BMI****, body mass index*

4.6 Outcomes for selected indicators and Beers criteria

4.6.1 Outcomes for prescribing quality indicators

Twelve (12) PQI were selected to determine quality of prescribing in management of hyperglycemia and cardiovascular risk. The outcome for prescribing any antihyperglycaemic or antihypertensive medication was 99 % in both cases while that for prescribing a statin in patients with high cardiovascular risk was 6 %. Two PQI could not be calculated since none of the 369 patients had a value recorded for albuminuria in 2013. The two indicators were; percentage of T2DM non-hypertensive patients with albuminuria prescribed an ACEI or ARB and percentage of T2DM patients with hypertension and with albuminuria prescribed a multiple drug regimen containing ACEI or ARB.

4.6.2 Outcomes for quality indicator and Beers criteria

The outcome for potentially inappropriate medicine use by prescribing glibenclamide in elderly patients was 47 %. Additionally, the outcome for the quality indicator for the care of diabetes mellitus in elderly T2DM patients by prescribing acetyl salicylic acid for primary prevention of CVD was 33 %. Table 4.5 summarizes outcomes for the selected PQI, QI and Beers criteria.

4.7 Factors influencing choice of drugs

4.7.1 Metformin and glibenclamide

On bivariate analysis, the use of metformin was significantly influenced by other CVD ($p = 0.02$). Age, sex, hypertension, other CVD, duration of diabetes, HbA1c and BMI did not significantly influence use of metformin ($p > 0.05$). On multivariate logistic regression analysis, use of metformin was not significantly influenced by any of the factors analyzed ($p > 0.05$). None of these factors significantly influenced use of glibenclamide following both bivariate and multivariate logistic regression analysis ($p > 0.05$). Table 4.6 summarizes results obtained for metformin

Table 4.5 Outcomes for indicators and Beers criteria

Description of prescribing quality indicator	N	**n**	**% (95% CI)**
Cardiovascular Risk Management			
T2DM patients with hypertension prescribed any antihypertensive drug	256	255	99 (98-100)
T2DM patients prescribed a second antihypertensive drug if SBP remained greater or equal to 140mm/Hg with first class drug	21	17	81 (57-94)
T2DM non-hypertensive patients with albuminuria prescribed ACEI or ARB	—		—
T2DM patients with hypertension and with albuminuria prescribed a multiple drug regimen containing ACEI or ARB	—		—
T2DM patients with hypertension and history of IHD or MI prescribed β-blocker	9	5	56 (23-85)
T2DM patients with high cardiovascular risk prescribed a statin	323	19	6 (4-9)
T2DM patients with history of CVD prescribed acetyl salicylic acid	22	12	54 (33-75)
Hyperglycemia management			
T2DM patients with HbA1c above 7 % prescribed any oral antihyperglycaemic agent or insulin	219	218	99 (97-100)
T2DM patients on 1 oral antihyperglycaemic drug and not on insulin who are prescribed a 2nd oral agent if HbA1c remained above 7.0 %	25	19	76 (54-90)
T2DM patients with 2 oral drugs and not on insulin who are prescribed insulin if HbA1c remained above 7.0 %	46	16	35 (22-50)
T2DM patients prescribed metformin as a first choice drug	55	45	82 (69-91)
Overweight prevalent T2DM patients prescribed a multiple drug regimen containing metformin	123	105	85 (76-90)
Description of quality indicator and Beers criteria			
Elderly T2DM patients prescribed acetyl salicylic acid	114	37	33 (24-42)
ElderlyT2DM patients prescribed a long-acting sulfonylurea (glibenclamide)	108	51	47 (38-57)

***ACEI**, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **T2DM**, type 2 diabetes mellitus; **SBP**, systolic blood pressure; **CI**, confidence interval; **IHD**, ischemic heart disease; **MI**, myocardial infarction*

Table 4.6 Factors influencing use of metformin

Baseline characteristics	N	n	PR (95 % CI)	p-value[a]
Age (years)				
Less than 60	199	165	0.83 (0.77-0.88)	0.44
At least 60	170	146	0.86 (0.80-0.91)	
Sex				
Male	158	132	0.85 (0.79-0.89)	0.74
Female	211	179	0.84 (0.77-0.89)	
Co-morbiditiees				
Hypertension	260	220	0.85 (0.80-0.89)	0.76
Previous CVD	14	12	0.86 (0.56-0.97)	0.88
Other CVD	6	3	0.50 (0.14-0.86)	**0.02**
Duration of diabetes (years)				
Less than 10	271	230	0.85 (0.80-0.89)	0.61
At least 10	98	81	0.83 (0.73-0.89)	
HbA1c (%)				
Less than 7	90	76	0.84 (0.78-0.89)	0.96
At least 7	279	235	0.84 (0.79-0.88)	
BMI (kg/m^2)				
Less than 25	82	66	0.81 (0.70-0.88)	0.28
At least 25	287	245	0.85 (0.81-0.89)	

[a] *Pearson chi; **PR**, preference ratio; **CI**, confidence interval*

4.7.2 Insulin

On bivariate analysis, use of insulin was significantly influenced by duration of diabetes and HbA1c ($p < 0.01$). The prevalence of prescribing insulin was higher in patients with duration of diabetes 10 years and above [prevalence ratio (PR) 0.47] compared to those patients with duration of diabetes less than 10 years (PR 0.27). The same applied to patients with HbA1c greater or equal to 7 % (PR 0.36) compared to those with HbA1c less than 7 % (PR 0.19). Other factors such as age, sex, previous CVD, other CVD, SBP and BMI did not significantly influence use of insulin ($p > 0.05$) as summarized in Table 4.7.

Table 4.7 Factors influencing use of insulin

Baseline characteristics	N	N	PR (95 % CI)	p-value[a]
Age (years)				
Less than 60	199	71	0.36 (0.29-0.43)	0.11
At least 60	170	47	0.28 (0.21-0.35)	
Sex				
Male	158	51	0.32 (0.25-0.40)	0.88
Female	211	67	0.32 (0.26-0.39)	
Co-morbiditiees				
Hypertension	260	85	0.33 (0.27-0.39)	0.67
Previous CVD	14	5	0.36 (0.14-0.64)	0.77
Other CVD	5	1	0.17 (0.01-0.64)	0.42
Duration of diabetes (years)				
Less than 10	271	72	0.27 (0.22-0.32)	< **0.01**
At least 10	98	46	0.47 (0.37-0.57)	
HbA1c (%)				
Less than 7	90	17	0.19 (0.12-0.29)	< **0.01**
At least 7	279	101	0.36 (0.31-0.42)	
BMI (kg/m^2)				
Less than 25	82	33	0.40 (0.30-0.52)	0.07
At least 25	287	85	0.29 (0.25-0.35)	

[a] *Pearson chi;* ***PR****, preference ratio;* ***CI****, confidence interval*

On multivariate logistic regression analysis, duration of diabetes [crude odds ratio (OR) 1.1, p < 0.01)] and HbA1c level (crude OR 1.2, p < 0.01) significantly influenced use of insulin. Other factors such as age, sex, previous CVD, other CVD, SBP and BMI did not significantly influence use of insulin (p > 0.05) and were dropped in subsequent logistic regression analysis. Further logistic regression analysis yielded statistically significant results as shown in Table 4.8. The odds of prescribing insulin were 1.2 times in patients with HbA1c greater or equal to 7 % compared to those with HbA1c less than 7 %. Additionally, the odds of prescribing insulin were 1.1 times in patients with duration of diabetes 10 years and above compared to those with duration of diabetes less than 10 years.

Table 4.8 Logistic regression output for use of insulin (n=365)

Insulin	Adjusted OR	Std error	z	p>[z]	95 % CI
Duration	1.1	0.02	3.8	< **0.01**	1.0-1.1
HbA1c	1.2	0.06	3.5	< **0.01**	1.1-1.3

***OR,** odds ratio**; CI**, confidence interval*

4.7.3 Enalapril or losartan

On bivariate analysis, age, hypertension, duration of diabetes and SBP significantly influenced use of enalapril or losartan (p < 0.01). The prevalence of prescribing enalapril or losartan was high in patients with hypertension (PR 0.90). The prevalence was also higher in patients aged 60 years and above (PR 0.82), with duration of diabetes 10 years and above (PR 0.88) and with SBP greater or equal to 140 mmHg (PR 0.86) compared to those aged less than 60 years (PR 0.63), duration of diabetes less than 10 years (PR 0.66) and with SBP less than 140 mmHg (PR 0.57) respectively. Other factors such as sex, previous CVD and other CVD did not significantly influence use of enalapril or losartan (p > 0.05) as summarized in Table 4.9.

However, on multivariate logistic regression analysis, only hypertension (crude OR 17.3, p < 0.01) and duration of diabetes (crude OR 1.1, p < 0.01) significantly influenced use of enalapril or losartan. Age, sex, previous CVD, other CVD and SBP did not significantly influence use of losartan or enalapril (p > 0.05) and were dropped in subsequent regression analysis. Further logistic regression analysis yielded statistically significant results as shown in Table 4.11. The odds of prescribing enalapril or losartan were 19.3 times in patients with hypertension compared to those without. Additionally, the odds of prescribing enalapril or

losartan were 1.1 times in patients with duration of diabetes 10 years and above compared to those with duration of diabetes below 10 years.

Table 4.9 Factors influencing use of enalapril or losartan

Baseline characteristics	N	n	PR (95 % CI)	p-value[a]
Age (years)				
Less than 60	199	126	0.63 (0.56-0.70)	< **0.01**
At least 60	170	139	0.82 (0.75-0.87)	
Sex				
Male	158	114	0.72 (0.64-0.79)	0.9
Female	211	151	0.72 (0.65-0.77)	
Co-morbiditiees				
Hypertension	260	233	0.90 (0.85-0.93)	< **0.01**
Previous CVD	14	11	0.79 (0.49-0.94)	0.56
Other CVD	6	4	0.67 (0.24-0.94)	0.78
Duration of diabetes (years)				
Less than 10	271	178	0.66 (0.60-0.71)	< **0.01**
At least 10	98	87	0.88 (0.80-0.94)	
SBP (mmHg)				
Less than 140	188	109	0.57 (0.51-0.65)	< **0.01**
At least 140	181	156	0.86 (0.80-0.91)	

[a] *Pearson chi; **PR**, preference ratio; **CI**, confidence interval*

4.7.4 Acetyl salicylic acid (ASA)

On bivariate analysis age, sex, hypertension, previous CVD, and duration of diabetes significantly influenced use of ASA ($p < 0.05$). Other factors such as other CVD, HbA1c,

SBP and BMI did not significantly influence use of ASA ($p > 0.05$) as summarized in Table 4.10. However, on multivariate logistic regression analysis, only age (crude OR 1.1, $p < 0.01$) and hypertension (crude OR 7.6, $p < 0.01$) significantly influenced use of ASA. Sex, previous CVD, other CVD, duration of diabetes, HbA1c, SBP and BMI did not significantly influence use of ASA ($p > 0.05$) and were dropped in subsequent analysis. Further logistic regression analysis yielded statistically significant results as shown in Table 4.11. The odds of prescribing ASA were 4.1 times in patients with hypertension compared to those without. Additionally, the odds of prescribing ASA were 1.1 times in patients aged 60 years and above compared to those aged below 60 years.

Table 4.10 Factors influencing use of acetyl salicylic acid

Baseline characteristics	**N**	**N**	**PR (95 % CI)**	**p-value[a]**
Age (years)				
Less than 60	199	25	0.13 (0.23-0.38	
At least 60	170	51	0.30 (0.13-0.22)	< **0.01**
Sex				
Male	158	41	0.26 (0.19-0.34)	**0.03**
Female	211	35	0.17 (0.12-0.22)	
Co-morbiditiees				
Hypertension	260	69	0.27 (0.21-0.32)	< **0.01**
Previous CVD	14	7	0.50 (0.24-0.78)	< **0.01**
Other CVD	6	3	0.5 (0.14-0.86)	0.73
Duration of diabetes (years)				
Less than 10	271	46	0.17 (0.13-0.22)	
At least 10	98	30	0.31 (0.22-0.41)	< **0.01**
HbA1c (%)				
Less than 7	90	17	0.19 (0.12-0.29)	
At least 7	279	59	0.21 (0.17-0.27)	0.65
SBP (mmHg)				
Less than 140	188	34	0.18 (0.13-0.25)	
At least 140	181	42	0.23 (0.17-0.30)	0.23
BMI (kg/m^2)				
Less than 25	82	16	0.20 (0.12-0.30)	
At least 25	287	60	0.26 (0.16-0.26)	0.78

Table 4.11 Logistic regression output for use of enalapril or losartan and acetyl salicylic acid (n=368)

Enalapril or losartan	**Adjusted OR**	**Std error**	**z**	**p>[z]**	**95 % CI**
Hypertension	19.3	5.84	9.8	< **0.01**	10.7-35.0
Duration	1.1	0.03	3.3	< **0.01**	1.0-1.2
ASA					
Age	1.1	0.01	4.5	< **0.01**	1.0-1.1
Hypetension	4.1	1.73	3.3	< **0.01**	1.8-9.4

OR, *odds ratio****; CI****, confidence interval*

CHAPTER FIVE: DISCUSSION

5.1 Discussion

Outcomes of prescribing quality indicators used in this study demonstrated that quality of prescribing was good for some of the indicators. There was also a high rate of adherence on guideline recommendations on choice of drugs. Cases of potential inappropriate medicine use and drug-drug interactions were low. However, deficiencies were demonstrated in quality prescribing in elderly patients.

5.1.1 Quality of prescribing

More than three quarters of the patients had HbA1c level of at least 7 %, a pointer to deficiencies in adequate control of hyperglycemia. Guidelines recommend that individuals with diabetes maintain HbA1c below 7 % to minimize the risk of complications and co-morbidities (ADA, 2013). Nearly three quarters of the patients with hypertension had systolic blood pressure (SBP) of at least 140 mmHg. This portended inadequate blood pressure control, as the recommended SBP target in T2DM patients with hypertension is below 140 mmHg (ADA, 2013). Additionally, less than 10 % of eligible patients were prescribed a statin, which represented deficiencies in adequate control of dyslipidaemia based on criteria for this indicator.

The number of eligible patients per prescribing quality indicator (PQI) ranged from 9-323, which was consistent with suggested minimum sample size of 5-10 to 30-60 eligible patients per PQI (Martirosyan *et al*, 2010). Some variables were not available for all patients, possibly because they were not measured every year. However, Martirosyan *et al*, (2008) recommend that proportion based PQI are robust to data loss of up to 35 % of an entire sample, since any change in the denominator will cause a change in the numerator. Consequently, outcomes of PQI based on variables available for at least 70 % of the patients were considered sufficiently generalizable.

Data on age, sex, HbA1c, SBP and duration of diabetes were available for 99-100 % of patients; hence outcomes of PQI based on them are sufficiently generalizable in this setting. However, BMI measurement was only available for 56 % of the patients. The outcome of PQI based on BMI with data missing in 44 % of patients may not reflect prescribing quality in this setting. It however provides useful information for health professionals to identify potential problems among patients with available clinical information. None of the 369

patients had a value recorded for albuminuria. As a result, outcomes for two indicators focusing on management of albuminuria in hypertensive and non-hypertensive patients were not calculated.

For the remaining 10 PQI calculated, 5 focused on cardiovascular risk management while the rest focused on hyperglycemia management. The outcomes of PQI measured in this study were consistent with what Martirosyan *et al* (2008) found in their study. Although that study did not aim at assessing quality of prescribing, they found deficiencies regarding prescribing of statins, acetyl salicylic acid and timely intensification of antihypertensive and antihyperglycaemic therapy. They also noted that the performance of some indicators was very good, such as that focusing on prescribing any antihyperglycaemic medication in eligible patients which had an outcome of 96 %. Similar results were obtained in this study cohort, with the 2 indicators focusing on prescribing of any antihyperglycaemic or antihypertensive medication in eligible patients showing a very high outcome of 99 %. Martirosyan *et al* (2008) recommend that if a PQI shows such a high performance over time for the same service provider, it may be dropped, as there is no potential for improvement.

Based on pre-set criteria, six PQI with outcomes above 70 % represented good quality prescribing in T2DM ambulatory care. Four of them focused on hyperglycemia management, implying that there were more deficiencies in cardiovascular risk management. The four PQI focused on prescribing any antihyperglycemic agent, intensifying oral antihyperglycemic therapy, prescribing metformin as the first choice drug or prescribing metformin as part of a multiple drug regimen in overweight T2DM patients. The remaining two PQI focused on prescribing any antihypertensive medication and intensifying antihypertensive therapy in eligible patients.

Conversely, four PQI with outcomes below 70 % represented poor quality prescribing. Three of these focused on prescribing a statin in T2DM patients with a high cardiovascular risk, prescribing β-blockers in those with a history of myocardial infarction or ischemic heart disease and prescribing acetyl salicylic acid in those with a history of CVD. For hyperglycemia management, only one indicator focusing on intensification of insulin therapy had an outcome representing poor quality prescribing. The probable reason for the very low outcome for prescribing statins in T2DM patients with high cardiovascular risk in may have been the high cost attributed to this class of drugs, since they were not part of the essential drugs list in the public supply chain in 2013.

The study cohort consisted of 31.4 % elderly patients, which was consistent with figures available in literature; with the ADA (2013) estimating that more than 20 % of elderly patients have T2DM. The outcome for the quality indicator (QI) focusing on prescribing of acetyl salicylic acid for primary prevention of cardiovascular disease was below 70 %. This represented poor quality prescribing in this category of patients, with only one third of eligible patients being prescribed acetyl salicylic acid.

5.1.2 Choice of drugs

Hypertension was identified as the main co-morbidity, affecting nearly three quarters of patients. This was consistent with the approximation of 20-60 % of patients with diabetes being affected by hypertension (Patel and Mehta, 2013). In managing hypertension in patients with diabetes, angiotensin converting enzyme inhibitors (ACEI) are promoted as first choice agents, with angiotensin receptor blockers (ARB) being recommended as alternatives to ACEI. Evidence suggests that these drugs reduce loss of kidney function in patients with diabetic nephropathy (Barnett *et al,* 2004). In this study, more than 89 % of T2DM patients with hypertension were prescribed either enalapril (more than 60 %) or losartan, which was consistent with guideline recommendations.

In instances where two or more drugs were prescribed for cardiovascular risk management, the two core drugs in the combination were mainly enalapril + hydrochlorthiazide which is consistent with recommendations from guidelines (IDF, 2012). More than 80 % of the patients were prescribed metformin, either singly or in combination. This was consistent with recommendations for prescribing metformin as the first line agent in pharmacological management of hyperglycemia (Nathan *et al,* 2009; IDF 2012; ADA 2013). This was further reinforced by the fact that more than 80 % of the newly diagnosed T2DM patients were also prescribed metformin

5.1.3 Potential inappropriate medicine use

Nearly half of the elderly patients were prescribed glibenclamide which potentially exposed them to the risk of prolonged hypoglycemia. This represented poor quality prescribing as per the pre-set criteria. Cases of potential drug-drug interactions were below 5 %, representing good quality prescribing. Additionally, in all patients prescribed hydrochlorthiazide, a low dose of not more than 25 mg per day was prescribed, indicating adherence to guideline recommendations (IDF, 2012).

5.1.4 Factors influencing choice of drugs

Use of insulin was influenced by glycated hemoglobin level and duration of diabetes. The latter was a particularly important factor, as the natural history of T2DM is of progression of beta (β) cell failure; hence insulin remains the only glucose lowering agent capable of maintaining glycaemia despite such progression (IDF, 2012). Use of enalapril or losartan was influenced by presence or absence of hypertension co-morbidity. This further reinforced the recommendation for prescribing angiotensin converting enzyme inhibitors or angiotensin receptor blockers as first line agents in management of hypertension in T2DM patients (Barnett *et al*, 2004). Additionally, age and hypertension influenced prescribing of acetyl salicylic acid for primary or secondary prevention of cardiovascular disease.

5.2 Study strengths and limitations

The strength of this study was that the targeted sample size of 369 patients was achieved. However, due to the retrospective design, one major limitation was missing data for some variables. Additionally, none of the patients had a value recorded for albuminuria. Other limitations included the fact that it was carried out in one district hospital in a given region only. It also only dealt with ambulatory care T2DM patients seen in 2013.

5.3 Conclusion

This study demonstrated high rates of adherence to treatment guidelines on choice of drugs for management of hyperglycemia and cardiovascular risk, which represented good quality prescribing. However, there were deficiencies in adequate control of hyperglycemia, hypertension and dyslipidaemia.

It also established that while the performance of prescribing quality indicators (PQI) focusing on prescribing any antihyperglycaemic or antihypertensive agent in eligible patients was very good, there were deficiencies with others whose outcomes represented poor quality prescribing. Of particular concern was the below 10 % outcome for the PQI focusing on prescribing statins in type 2 diabetes mellitus (T2DM) patients with a high cardiovascular risk. Only one third of elderly T2DM patients were prescribed acetyl salicylic acid for primary prevention of cardiovascular disease (CVD), which also represented poor quality prescribing. Additionally, nearly half of the elderly patients were prescribed glibenclamide, which exposed them to potential risk of prolonged episodes of hyperglycemia. Cases of potential drug-drug interactions were less than 5 %, which was considered as representing good quality prescribing.

Factors significantly influencing the use of insulin included glycated hemoglobin level and duration of diabetes, while hypertension greatly influenced use of enalapril or losartan in eligible patients. Use of acetyl salicylic acid for primary or secondary prevention of CVD in eligible patients was significantly influenced by age and hypertension.

5.4 Recommendations

Findings of this study will be disseminated in appropriate fora to facilitate implementation. The findings represent an opportunity for the following specific recommendations to be made:

5.4.1 Recommendations for action by Webuye District Hospital

1. The administrator of the hospital should constitute a quality improvement team to deal with indicators with poor outcomes. Specific problems to be addressed include:

I. The four prescribing quality indicators whose outcomes were below 70 %.
II. Low prescribing of acetyl salicylic acid in eligible elderly patients.
III. Inappropriate use of glibenclamide in elderly patients.

2. The administrator should also plan to incorporate investigations for albuminuria and lipid levels for diabetic patients.

5.4.2 Recommendations for future research and policy

1. This study provides a baseline for larger studies.

2. It also provides a framework for policy makers in the Ministry of Health in Kenya to formulate strategies that promote optimal pharmacotherapy outcomes in diabetes in particular and non-communicable diseases in general. Such strategies include:

I. Review of clinical guidelines to reflect the comprehensive approach necessary in management of diabetes.
II. Investment in laboratory monitoring equipment in public hospitals. This will improve access to investigations for albuminuria, glycated hemoglobin and lipid levels.

REFERENCES

Abdelhafiz A. H. and Sinclair A. J. (2013). Management of type 2 diabetes in older people. *Diabetes Therapy,* **4**: 13-26.

Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) (2008). Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine,* **358**: 2545-2559.

American Diabetes Association (ADA) (2013). Standards of medical care in diabetes. *Diabetes care*, **36** (1): S11-S66.

American Geriatrics Society (AGS) (2012). Updated Beers criteria for potentially inappropriate medication use in older adults. *Journal of American Geriatrics Society.*

Australian National Prescribing Service (ANPS) (2009). Indicators of quality prescribing in Australian general practice. Available at http://www.nps.org.au (Accessed 04 Nov. 2013).

Bailey C.J., Aschner P., Del Prato S., LaSalle J., Ji L. and Matthaei S. (2013). Individualized glycaemic targets and pharmacotherapy in type 2 diabetes. *Diabetes and Vascular Diseases Research,* **10** (5): 397-409.

Barnett A.H., Bain S.C., Bouter P., Karlberg B., Madsbad S., Jervell., J. and Mustonen J. (2004). Angiotensin-receptor blockade versus converting enzyme inhibition in type 2 diabetes and nephropathy. *New England Journal of Medicine,* **351**: 1952-61.

Drugs information online (2013). Available at http://www.drugs.com (Accessed 31 Oct. 2013).

Engel S.S., Round E., Golm G.T., Kaufman K.D. and Goldstein B.J. (2013). Safety and tolerability of sitagliptin in type 2 diabetes: a pooled analysis of 25 clinical studies. *Diabetes Therapy*, **4**: 119-145.

Forst T., Hanefield M., Jacobs S., Moeser., G., Shwenk G., Pfutzner A. and Haupt A. (2013). Association of sulfonylurea treatment with all-cause and cardiovascular mortality: a

systematic review and meta-analysis of observational studies. *Diabetes and Vascular Diseases Research*, **10**(4): 302-314.

Freeman J.S. (2011). Optimizing outcomes of glucagon-like peptide-1 agonists. *Journal of American Osteopathic Association*, **111** (2, S1): eS15-eS20.

Goudswaard A.N., Furlong N.J., Valk G.D., Stolk, R.P. and Rutten G.E.H.M. (2004). Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, **4**. Art. No.: CD003418. DOI: 10.1002/14651858.CD003418.pub2 .

Horvath K., Jeitler K., Berghold A., Ebrahim S.H., Gratzer T.W., Plank J., Kaiser T., Pieber T.R. and Siebenhofer A. (2007). Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, **2**. Art. No.: CD005613. DOI:10.1002/14651858.CD005613.pub3.

International Diabetes Federation (IDF) (2009). Diabetes Atlas, 4th Edition. Available at http://www.idf.com (Accessed 17 Sep. 2013).

International Diabetes Federation (2012). Global guideline for type 2 diabetes. Available at http://www.idf.org (Accessed 8 Sep. 2013).

Khaled I.K. and Heinrich T. (2012). After Avandia: the use of antidiabetic drugs in patients with heart failure. *Texas Heart Institute Journal*, **39**(2): 174-178.

Lv J., Perkovic V., Foote C.V., Craig M.E., Craig J.C. and Strippoli G.F.M. (2012). Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database of Systematic Reviews*, **12**. Art. No.: CD004136. DOI: 10.1002/14651858.CD004136.pub3.

Madonna M.R. and Peizhong P.W. (2013). Sex differences in all-cause and cardiovascular mortality, hospitalizations for individuals with or without diabetes, and with diabetes diagnosed early and late. *Diabetes Care*, **36**: 2582-2590.

Martirosyan L., Braspenning J., Denig P., de Grauw W.J.C., Bouma M., Storms. F. and Haaijer-Ruskamp F.M. (2008*)*. Prescribing indicators of type 2 diabetes mellitus ambulatory care. *Quality and Safety in Health Care*, **17**: 318-323.

Martirosyan L., Voorham J., Haaijer-Ruskamp F.M., Braspenning J., Wolffenbuttel B.H.R. and Denig P. (2010). A systematic literature review: prescribing indicators related to type 2 diabetes mellitus and cardiovascular risk management. *Pharmacoepidemiology and Drug Safety*, **19**(4): 319-334.

McFerran L. (2008). Obstacles to diabetes care in Kenya. *Medical journal of therapeutics Africa,* **2**(2): 127-129.

Ministries of Health (Kenya) (2009). *Clinical management and referral guidelines-Vol III: Clinical guidelines for management and referral of common conditions at level 4-6 Hospitals.* MOH, Nairobi. p. 35, p. 89 and pp. 44-48.

Monami M., Marchionni N. and Mannucci E. (2009). Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. *European Journal of Endocrinology,* **160**(6): 909-917.

Nathan, D.M., Buse J.B., Davidson M.B., Ferrannini E., Holman R.R., Sherwin R. and Zinman B. (2009). Medical management of hyperglycemia in type 2 diabetes. A consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association (ADA) and European Association for the study of diabetes (EASD). *Diabetes Care,* **32**(1): 193-203.

Newcombe R.G. (1998). Two sided confidence interval for the single proportion. Comparison of seven methods. *Statistics in* Medicine, **17**: 852-872.

Ohkubo Y., Kishikawa H., Araki E., Miyata T., Isami S., Motoyoshi S., Kojima Y., Furuyoshi N. and Shichiri M. (1995). Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Research and Clinical Practice,* **28:** 103-117.

Patel B.M. and Mehta A.A. (2013). Choice of antihypertensive agents in diabetes subjects. *Diabetes and Vascular Disease Research,* **10**(5): 1385-1396.

Puepet H.F., Uloko A., Akogu I.Y. and Aniekwensi E. (2009). Prevalence of metabolic syndrome among patients with type 2 diabetes mellitus in urban north central Nigeria. *African Journal of Endocrinology and Metabolism,* **8**(1): 10-12.

Richter B., Bandeira-Echtler E., Bergerhoff K. and Lerch C. (2008). Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*. **2**. Art. No.: CD006739. DOI:10.1002/14651858.CD006739.pub2

Saenz A., Fernandez-Esteban I., Mataix A., Ausejo Segura M., Roqué i Figuls M. and Moher D. (2013). Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005, **3**. Art. No.: CD002966. DOI:10.1002/14651858.CD002966.pub3.

Salpeter S.R., Greyber E., Pasternak G.A. and Salpeter E.E. (2010). Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, **4**. Art. No.: CD002967. DOI: 10.1002/14651858.CD002967.pub4.

Schernthaner G., Currie C.J. and Schernthaner G.H. (2013). Do we still need pioglitazone for the treatment of type 2 diabetes? *Diabetes Care*, **36**(2): S155-S161.

Shekelle P. and Vijan S. (2007). Quality indicators for the care of diabetes mellitus in vulnerable elders. *Journal of American Geriatrics Society*, **55**: S312-S317.

Steinman M.A., Landefeld C.S., Rosenthal G.E., Berthenthal D., Sen S. and Kaboli P.J. (2006). Polypharmacy and prescribing quality in older people. *Journal of American Geriatrics Society,* **54**(10): 1516-1523.

UK Prospective Diabetes Study Group [(UKPDS 33) (1998)]. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*, **352**: 837-853.

Van de Laar F.A., Lucasse P.L.B.J., Akkermans R.P., Van de Lisdonk E.H., Rutten G.E.H.M. and Van Weel C. (2005). Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, **2**. Art. No.: CD003639. DOI: 10.1002/14651858.CD003639.pub2

World Health Organization (2006). A report of a WHO/IDF consultation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Available at http://www.who.org (Accessed 29 Aug. 2013).

World Health Organization (2010). Global status report on non-communicable diseases: Burden, morbidity & risk factors. Available at http://www.who.org (Accessed 20 Aug. 2013).

World Health Organization (2011). A report of WHO consultation. Use of glycated hemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Available at http://www.who.org (Accessed 31 Aug. 2013).

Appendix A: Operational definitions for calculation of prescribing quality indicators for type 2 diabetes mellitus (Martirosyan *et al,* 2008).

PQI FOR HYPERTENSION MANAGEMENT

1. **% of T2DM patients with hypertension/systolic blood pressure≥ 140 and prescribed any antihypertensive drug**

Inclusion criteria:
Patients with hypertension/average systolic blood pressure (SBP) ≥ 140 in the period of 01/01/2013 -30/06/2013 (first half of 2013)

Outcome:
-yes (1) if eligible patients (who correspond to inclusion criteria) were prescribed the following antihypertensive (AH) groups: miscellaneous AH drugs, and/or diuretics, and/or β-blockers, and/or calcium antagonists and/or ACEIs/ARBs in the period of 01/07/2013 – 31/12/2013 (second half of 2013)

-no (0) if eligible patients are prescribed none of the mentioned medication groups in the mentioned time period

2. **% of T2DM patients prescribed a 2nd antihypertensive drug from a different class if SBP remained ≥ 140mmHg with 1st class antihypertensive drug**

Inclusion criteria:
Patients with prescription of one antihypertensive drug and with 2 sequential SBP >140 (time period between 2 SBP measurements is up to 4 months) in 2013.

Outcome:
-yes (1) if eligible patients were prescribed a second AH drug (i.e. added to first AH drug) within 5 months (starting from the date of the 1st SBP measurement).

-no, (0) if eligible patients were not prescribed (added) a second AH drug within 5 months (starting from the date of the first SBP measurement)

3. **% of T2DM patients without hypertension with albuminuria prescribed ACE inhibitor or ARB**

Inclusion criteria:
Patients without hypertension and with albuminuria in 2013.

Outcome:
-yes (1) if eligible patients were prescribed any medication from the ACEIs and ARBs group in the second half of 2013.

-no (0) if eligible patients were not prescribed any medication from the ACEIs and ARBs group in the second half of 2013.

4. **% of T2DM prevalent for hypertension patients with albuminuria prescribed a multiple drug regimen containing ACEI or ARB.**

Inclusion criteria:
Patients with hypertension/SBP $\geq$ 140 in the first half of 2013 and with albuminuria in 2013 and prescribed more than 1 antihypertensive medication in the second half of 2013

Outcome:
-yes (1) if eligible patients were prescribed a drug regimen that included any medication from ACEI or ARB group in the second half of 2013
-no (0) if eligible patients were not prescribed any medication from ACEI or ARB group in the second half of 2013

5. **% of T2DM patients with hypertension and history of ischemic heart disease or myocardial infarction prescribed a β-blocker**

Inclusion criteria:

Patients with hypertension/SBP ≥ 140 in the first half of 2013 and history of ischemic heart disease or myocardial infarction.

Outcome:

-yes (1) if eligible patients were prescribed a β-blocker in the second half of 2013.

-no (0) if eligible patients were not prescribed a β-blocker in the second half of 2013.

PQI FOR HYPERGLYCAEMIA MANAGEMENT

6. **% of prevalent T2DM patients with HbA1c > 7 % and prescribed any oral antihyperglycaemic agent or insulin**

Inclusion criteria:

Patients with average HbA1c > 7% in the first half of 2013

Outcome:

-yes (1) if eligible patients were prescribed any oral antihyperglycaemic medication or insulin in the second half of 2013.

-no (0) if eligible patients were not prescribed any oral antihyperglycaemic medication or insulin in the second half of 2013.

7. **% of T2DM patients with prescription of one oral antihyperglycaemic drug and not receiving insulin who are prescribed a 2nd second oral antihyperglycaemic drug from a different class if HbA1c remained > 7.0%**

Inclusion criteria:

Patients with prescription of one oral antihyperglycaemic drug and no insulin and with 2 sequential HbA1c > 7% (period between 2 HbA1c measurements is up to 4 months) in 2013

Outcome:

-yes (1) if eligible patients were prescribed a second (added) oral antihyperglycaemic drug within 5 months (starting from the date of the 1st HbA1c measurement)

-no (0) if eligible patients were not prescribed (added) a second antihyperglycaemic drug within 5 months starting from the date of the first HbA1c measurement

8. **% of T2DM patients with 2 oral antihyperglycaemic drugs and not receiving insulin who are prescribed insulin if HbA1c remained > 7.0 %**

Inclusion criteria:

Patients with prescription of two oral antihyperglycaemic drugs and no insulin and with 2 sequential HbA1c > 7% (period between 2 HbA1c measurements is up to 4 months) in 2013

Outcome:

-yes (1) if eligible patients were prescribed (added) insulin within 5 months (starting from the date of the 1st HbA1c measurement).

-no (0) if eligible patients were not prescribed (added) insulin within 5 months starting from the date of the first HbA1c measurement

9. **% of incident T2DM patients prescribed metformin as a first choice drug**

Inclusion criteria:

Incident diabetic patients (duration of diabetes < 1 year in 2013)

Outcome:

-yes (1) if the first drug prescribed to eligible patients was metformin.

-no (0) if eligible patients were prescribed another antihyperglycaemic medication

10. **% of overweight prevalent T2DM patients prescribed a multiple drug regimen containing metformin**

Inclusion criteria:

All patients with BMI ≥ 25 in 2013 and prescribed more than 1 antihyperglycaemic agent in the second half of 2013.

Outcome:

-yes (1) if eligible patients were prescribed a drug regimen containing metformin in the second half of 2013.

-no (0) if eligible patients were not prescribed metformin in the second half of 2013.

PQI FOR DYSLIPIDAEMIA MANAGEMENT

11. **% T2DM patients with high cardiovascular risk who are prescribed a statin**

Inclusion criteria:

Patients with high cardiovascular risk (women aged > 60 years and men > 50 years old, or duration of diabetes ≥10 years, or average SBP ≥140(i.e. with uncontrolled hypertension), or with albuminuria, or HbA1c ≥ 7%).

Outcome:

-yes (1) if eligible patients were prescribed a statin in the second half of 2013

-no (0) if eligible patients were not prescribed a statin in the second half of 2013

PQI FOR ANTIPLATELET TREATMENT

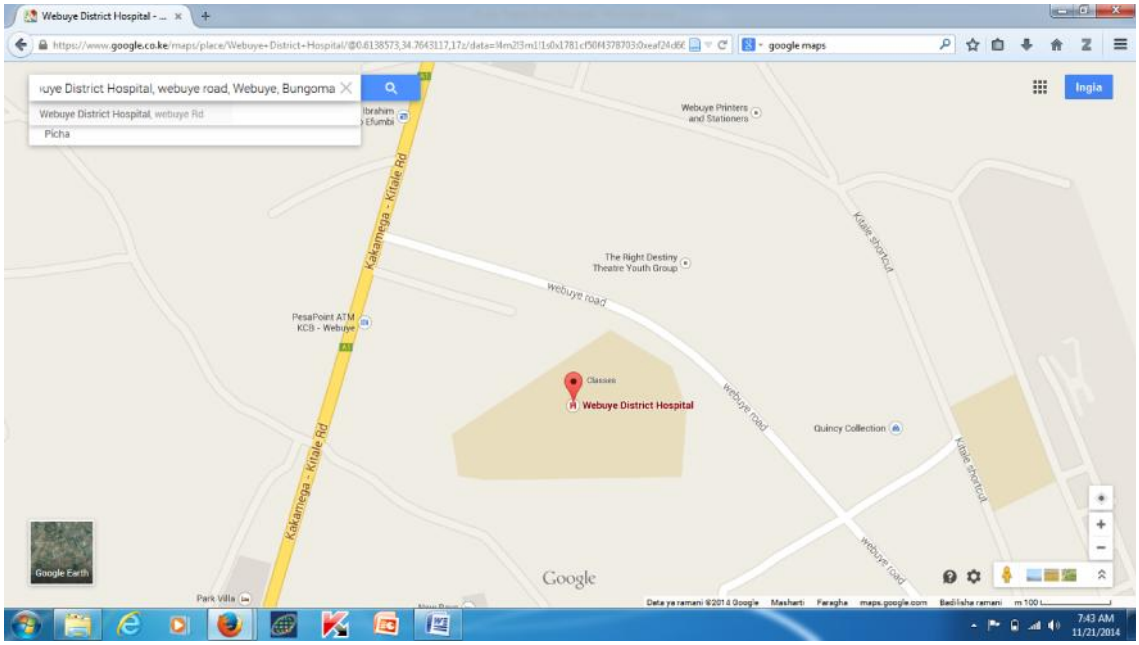
12. **% of T2DM patients with history of cardiovascular disease prescribed acetyl salicylic acid**

Inclusion criteria:
All T2DM patients with history of cardiovascular diseases caused by atherosclerosis (Ischemic heart disease, acute myocardial infarction, stroke/cerebrovascular accident, cerebrovascular disease, atherosclerosis)

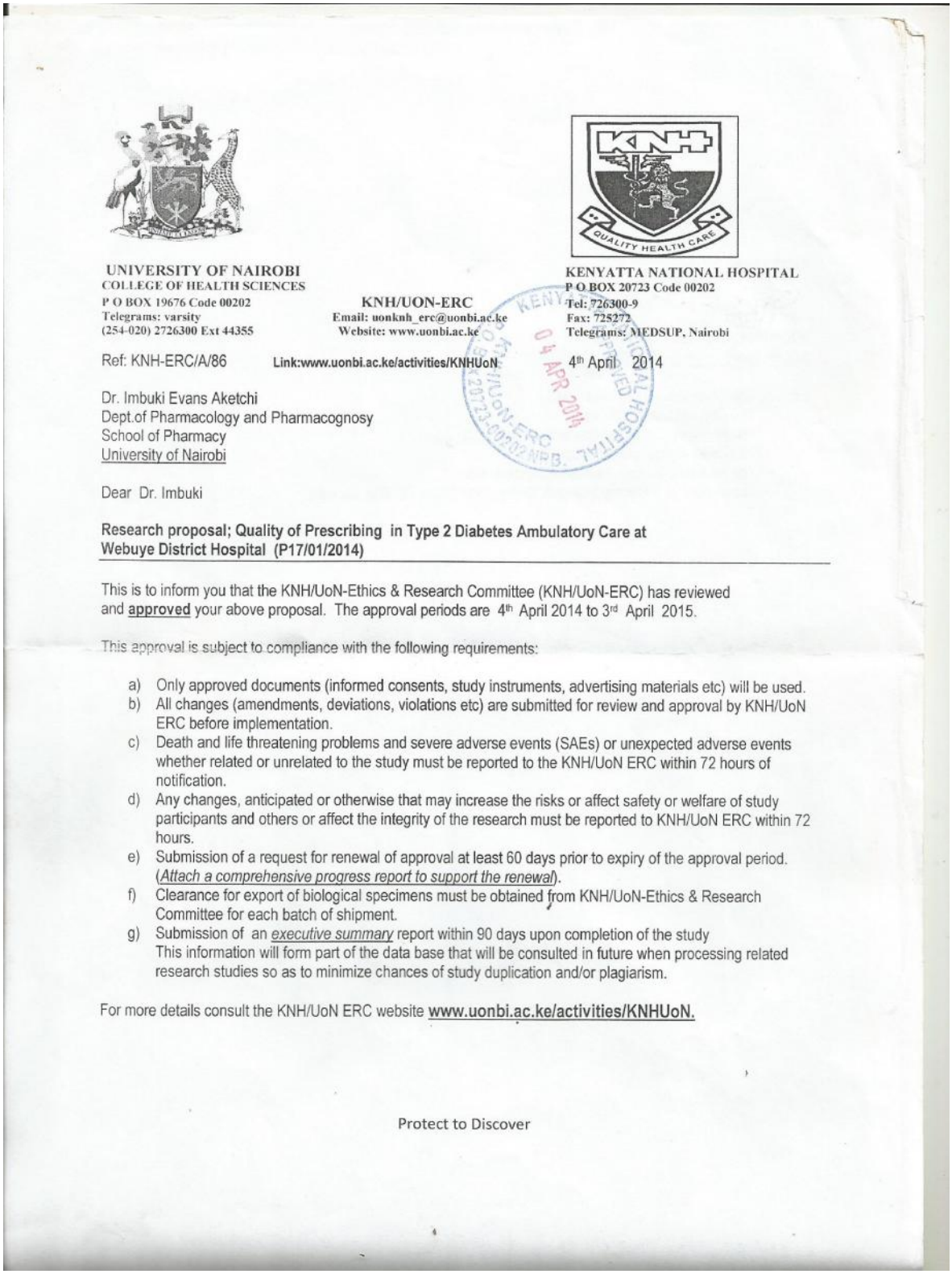
Outcome:
-yes (1) if eligible patients were prescribed acetyl salicylic acid (aspirin) in the second half of 2013.

-no (0) if eligible patients were not prescribed acetyl salicylic acid (aspirin) in the second half of 2013.

Appendix B: Webuye District Hospital location map



Appendix C: Ethics and Research Committee approval



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

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

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

Ref: KNH-ERC/A/86 Link:www.uonbi.ac.ke/activities/KNHUoN 4th April 2014

Dr. Imbuki Evans Aketchi
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr. Imbuki

Research proposal; Quality of Prescribing in Type 2 Diabetes Ambulatory Care at Webuye District Hospital (P17/01/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 4th April 2014 to 3rd April 2015.

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 severe 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) 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*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
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.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Dean, School of Pharmacy, UoN
The Assistant Director, Health Information, KNH
Supervisors: Dr. Stanley Ndwigah, Dr.Margaret Oluka, Dr. E.M. Guantai