ADDIS ABABA UNIVERSITY

METFORMIN-INSULIN VERSUS METFORMIN-SULFONYLUREA COMBINATION THERAPIES IN TYPE 2 DIABETES: A COMPARATIVE STUDY OF GLYCEMIC CONTROL AND RISK OF CARDIOVASCULAR DISEASES IN ADDIS ABABA, ETHIOPIA

BY

DESYE GEBRIE (B. PHARM, MSc)

A THESIS PAPER SUBMITTED TO CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND THERAPEUTIC TRIALS FOR AFRICA, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY; IN PARTIAL FULFILLMENT FOR THE REQUIREMENT OF MASTER OF SCIENCE DEGREE IN CLINICAL TRIALS

SEPTEMBER, 2020

ADDIS ABABA, ETHIOPIA

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

CDT-AFRICA

This is to certify that the thesis prepared by Desye Gebrie, titled "**Metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes: a comparative study of glycemic control and risk of cardiovascular diseases in Addis Ababa, Ethiopia**" and submitted to Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University; in partial fulfillment for the requirement of master of science degree in clinical trials, compiles with the regulations of the University and meets the accepted standards originality and quality**.**

Advisors: Prof. Eyasu Makonnen Signature: _____Date: _____

Dr. Tsegahun Manyazewal Signature: _____Date: _____

Dr. Dawit Asmamaw Signature: _____Date: _____

Internal examiner: Prof. Asrat Hailu Signature: _____ Date: _____

External examiner: Dr. Getnet Yimer Signature: _____Date: _____

SEPTEMBER, 2020

ADDIS ABABA, ETHIOPIA

Abstract

Background: The benefits of combination therapies in the management of type 2 diabetes are well-documented, while the comparative glycemic control and cardiovascular outcomes among the different combination options have not been studied well. The study aimed to compare glycemic control and risk of cardiovascular outcomes of metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes mellitus.

Method: A comparative cross-sectional study was conducted in five tertiary level hospitals in Addis Ababa, Ethiopia. About 321 patients with type 2 diabetes mellitus who were on continuous treatment follow up on either metformin-insulin or metformin-sulfonylurea combination therapy were enrolled. Participants were interviewed and their medical records were reviewed to investigate medication efficacy, safety, and adherence. The primary outcome measure was glycemic control (reduction in glycated hemoglobin A1c) and the secondary outcome measures were composite cardiovascular outcomes (myocardial infarction, stroke, heart failure), microvascular complications (diabetic neuropathy, retinopathy, and nephropathy), treatment-emergent adverse events, changes in bodyweight, fasting blood sugar, systolic blood pressure, diastolic blood pressure and lipid profiles (low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides).

Results: Of the total participants enrolled, 162 (50.5%) were those who received metformin-insulin and 159 (49.5%) metformin-sulfonylurea combination therapies for a median of 48 months follow-up. Reduction of HbA1c was not different between the two groups, $p = .912$, with mean ± SD of -1.04 ± .96 % versus -1.02 ± 1.03%, respectively. Patients who received metformin-sulfonylurea are 4.3 times more likely to have achieved target HbA1c level compared to those who received metformin-insulin, $p < .001$ (AOR=4.31 [95% CI 1.79-10.32]). Risk of composite cardiovascular outcomes was higher in metformin-insulin group (40.5% versus 34.0%), $p = .021$. Co-morbidities, body mass index, systolic blood pressure, and HbA1c had a significant association with composite cardiovascular outcomes. Reductions of bodyweight, lipid profiles, and microvascular complications were different between the two groups, $p < .05$.

Conclusion: High proportion of patients who received metformin-sulfonylurea achieved target HbA1c level and had less composite cardiovascular outcomes compared to those who received

metformin-insulin. However, these findings have to be confirmed with randomized control trials to determine risks associated with insulin use, while efficacy is maintained as second-line treatment in patients with type 2 diabetes mellitus.

Keywords: Glycemic control, Cardiovascular diseases, Type 2 diabetes mellitus, Metformin, Insulin, Sulfonylurea, Glycated hemoglobin A1c (HbA1c)

Acknowledgment

First of all, I would like to thank the almighty God and his mother St. Mary who gave me strength and meaning in life.

Secondly my sincere heartfelt thanks go to my advisors Prof. Eyasu Makonnen, Dr. Tsegahun Manyazewal and Dr. Dawit Asmamaw for their valuable comments and support for the completion of this thesis work.

Thirdly my heartfelt thanks go to CDT-Africa, College of Health Sciences, Addis Ababa University for supporting this thesis work.

Lastly, I would like to acknowledge Mekelle University which sponsored me and my beloved families and friends for their care and help in whole of my academic career.

Table of Contents

List of tables

List of appendixes

Abbreviations

AOR	Adjusted Odds Ratio
CI	Confidence Interval
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DPP	Dipeptidyl Peptidase
FBS	Fasting Blood Sugar
GLP	Glucagon Like Peptide
HbA1c	Glycosylated Hemoglobin A1c
HDL-C	High Density Lipoprotein-Cholesterol
HR	Hazard Ratio
IRB	Institutional Review Board
LDL-C	Low Density Lipoprotein-Cholesterol
OR	Odds Ratio
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
SGLT-2i	Sodium Glucose Co-transporter-2 inhibitors
SD	Standard Deviation
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study

1. Introduction

1.1. Background

Diabetes mellitus is one of the top ten causes of death and the fastest growing health emergencies of the twenty-first century, with 463 million people living with it worldwide in 2019, and this number projected to reach 578 million by 2030 and 700 million by 2045 [1]. The estimated global direct health expenditure on diabetes in 2019 was US$ 760 billion and is expected to grow to a projected US$ 825 billion by 2030 and US$ 845 billion by 2045 [2]. Type 2 diabetes mellitus (T2DM) is the most common and complex form of the disease and accounts for more than 90% of the estimated cases of diabetes, impacting the life expectancy, quality of life, and health of an individual [1,3]. Yet, there is no cure for T2DM, while its prevalence is largely increasing, with increased risk of complications including diabetic retinopathy, neuropathy, kidney damage, and cardiovascular complications [4-7]. Cardiovascular disease (CVD) is a common complication and a major cause of death in patients with T2DM [8,9].

Despite the introduction of new medications, treating patients with diabetes tend to become more challenging due to the progressive nature of the disease [10-14]. The American Diabetes Association recommends lifestyle interventions as the first step in treating new-onset T2DM [15]. However, to achieve and maintain specific glycemic targets, the majority require glucose-lowering drugs. Metformin is currently the first-line and widely used pharmacological therapy for patients with T2DM because of its potential benefits, including cardioprotective effect, loss of weight and prevention of some comorbid diseases [15-22]. If lifestyle interventions and a maximal tolerated dose of metformin fail to achieve the glycemic target within 3 months follow-up, the regimen would be changed to combination therapy [15].

Metformin and sulfonylurea are the most widely used combination therapy in T2DM [23, 24]. Sulfonylureas are recommended as second-line treatment in the management of T2DM, while they are still commonly used also as a first-line treatment instead of metformin [25]. However, initiating treatment of type 2 diabetes with a sulfonylurea rather than metformin is associated with higher rates of ischaemic stroke, cardiovascular death, hypoglycemia and all-cause mortality [25-31]. Besides, the use of sulfonylurea as second-line drug is associated with an increased risk of myocardial infarction, all-cause mortality, and severe hypoglycemia, compared

with use of metformin monotherapy; as a result, continuing metformin when introducing sulfonylureas appears to be safer than switching [32]. Such findings led to new requirements from licensing authorities that all new T2DM therapies should show cardiovascular safety [10].

Insulin is one of the second-line antidiabetic drug for the treatment of T2DM patients who failed initial metformin monotherapy and lifestyle interventions [33-34]. One of the rationales for metformin-insulin combination therapy is that by suppressing hepatic glucose production, the patient can retain the convenience of oral medications while minimizing total insulin requirements and reducing weight [35]. Thought insulin has been the preferred drug to be added to metformin when glycated hemoglobin A1c (HbA1c) is markedly elevated, there was no evidence towards improved all-cause mortality or cardiovascular mortality [36].

1.2. Statement of the problem

A randomized controlled trial (RCT) in the United Kingdom Prospective Diabetes Study (UKPDS) in patients with T2DM and risk of complications showed that there was no difference in the rates of myocardial infarction or diabetes-related death among participants assigned to sulphonylurea and insulin therapies. The rates of major hypoglycemic episodes per year are 1·4% with sulfonylurea (glibenclamide), and 1·8% with insulin. Weight gain is significantly higher in insulin (4·0 kg) than glibenclamide (1·7 kg). However, there is a controversial report by University Group Diabetes Program (UGDP) which shows that patients who used sulphonylureas have increased risk of cardiovascular death [37].

There is no significant evidence of long-term efficacy of insulin on any clinical outcome in T2DM. The only benefit could be limited to reducing short term hyperglycemia. However, there is a trend to clinically harmful adverse effects such as hypoglycemia and weight gain [38]. Besides, short-term intensive glycemic control by insulin therapy does not lower the risk of cardiovascular adverse events [39]. Nearly one-third of the population initiated a second-line therapy. However, only 15% achieved a HbA1c target <7% and cardiovascular complication has still been prevalent globally [40]. Despite the availability of many new treatment options for T2DM, the proportion of patients achieving their HbA1c target < 7.0% remained around 50%, and cardiovascular complications has become high [41].

Though several studies have examined the effects of metformin and sulfonylurea medications on cardiovascular risk among diabetic patients, the results were inconsistent [38]. Observational studies and clinical trials with metformin and insulin monotherapy have shown good glycemic control and reduced risk of long-term complications in T2DM. However, use of insulin was associated to atherothrombosis, weight gain, hypoglycemia, unaffordable cost, cold chain requirement and difficulty in administration for the majority of patients [42].

American Diabetes Association's current standard of care recommends that newly diagnosed T2DM patients whose HbA1c level ≥ 8.5% should start combination treatment either metformin with insulin or metformin with sulfonylureas [15]. However, there is no clear evidence which shows that the relative advantage of either metformin-insulin or metformin-sulfonylurea combination on major treatment outcomes including CVD (all-cause mortality, serious adverse events, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke [43]. With guidelines moving away from a one-size-fits-all approach and allowing flexibility in choosing a second/third-line drug, keen personalized based on efficacy, risk of hypoglycemia, the patient's comorbid conditions, impact on weight, adverse effects, and cost, management in T2DM has become a challenge [44, 45]. The benefits of combination therapies for the management of type 2 diabetes are well-documented, while the comparative glycemic control and cardiovascular outcomes among the different combination options have not yet been studied. Although most patients with T2DM require a combination therapy, the choice of a good second-line drug is critical for the prevention of CVD. Therefore, the study aimed to compare glycemic control and risk of cardiovascular outcomes of metformin-insulin versus metformin-sulfonylureas combination therapies in patients with T2DM.

1.3. Literature overview of metformin-based combination therapy and risk of cardiovascular outcomes in Type 2 diabetes mellitus

1.3.1. Metformin and sulfonylurea

Many studies revealed that metformin monotherapy has shown cardio protective effect [42, 46]. Among patients having intensive blood glucose control, metformin showed a greater effect than chlorpropamide or glibenclamide for any diabetes-related endpoint (p=0·0034), all-cause mortality (p=0·021), and stroke (p=0·032). However, early addition of metformin in

sulphonylurea-treated patients was associated with an increased risk of diabetes-related death (96% increased risk [95% CI 2–275], p=0·039) compared with continued sulphonylurea alone [47]. Metformin-sulfonylurea combination therapy was associated with higher risk of subsequent severe hypoglycemia, fatal and nonfatal CVD, and all-cause mortality compared with metformin-DPP-4 inhibitors; adjusted HR (95% CI): 2.07 (1.11–3.86); 1.17 (1.01–1.37); and 1.25 (1.02–1.54), respectively [48].

In the other way, the Sibutramine Cardiovascular Outcomes Trial (SCOUT) has reported that combination therapy of metformin and sulfonylurea was weakly linked with a lower and statistically insignificant primary outcome events (nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, cardiovascular death and all-cause mortality (adjusted HR, 0.81; 95% CI, 0.64–1.015; P = 0.07) [42]. Another study showed low density lipoprotein cholesterol (LDL-C) was decreased 5% by the addition of metformin to sulfonylurea (P <0.001) [49]. Furthermore, patients treated with metformin-glibenclamide fixed dose combination for 6 months had reduced plasma high density lipoprotein cholesterol (HDL-C) (-0.09 mmol/L; p< 0.01) and no change in plasma triglyceride level (0.03 mmol/L; p= 0.733) [50].

1.3.2. Metformin and dipeptidyl peptidase-4 inhibitors

A meta- analysis of 301 RCTs conducted in 2016 showed metformin-dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) was associated with a lower risk of hypoglycemia (odds ratio [OR], 0.12) and weight gain (–0.58 kg) compared to metformin-sulfonylurea. In terms of cardiovascular outcomes, there were no significant differences between metformin-DPP-4 inhibitors and metformin-sulfonylurea for CV mortality, all-cause mortality, serious adverse events, or myocardial infarction. However, combination of DPP-4 inhibitors and metformin exhibited a lower risk of stroke compared with a combination of metformin and sulfonylurea (OR, 0.47; 95% confidence interval [0.23 to 0.95]) [51]. Another systematic review and meta-analysis of 10 RCTs showed that there was no significant difference in efficacy between DPP-4 inhibitors and sulfonylurea when either was added to metformin mono-therapy. In contrast, the safety assessment analysis showed a significant decrease in the risk of hypoglycemic events in patients using DPP-4 inhibitors [24].

A 2-year efficacy and safety study on DPP-4 inhibitors (linagliptin) compared with glimepiride in patients with T2DM inadequately controlled on metformin showed that metformin-linagliptin combination was associated with significantly fewer cardiovascular events (relative risk =0·46, 95% CI (0·23–0·91) and lower hypoglycemia compared to metformin-glimepiride combination [52]. A national wide cohort study elsewhere has reported that there was no significant difference in the risk of ischaemic heart disease (hazard ratio (HR), 1.00; 95% CI 0.81–1.23), ischaemic stroke (HR, 0.95; 95% CI 0.74–1.23), or cardio cerebrovascular death (HR, 0.74; 95% CI 0.46–1.18) between metformin-DPP-4 inhibitor group and metformin-sulfonylurea combination treatment group. However, the risk of hospitalization for heart failure was significantly higher in the DPP-4 inhibitor group than in the sulfonylurea group (HR, 1.47; 95% CI 1.07–2.04) [53]. In addition, a narrative review of cardiovascular safety of DPP-4 inhibitors suggested that DPP-4 inhibitors are additional treatment for patients with T2DM and without established CVD [54]. A systematic review and meta-analysis of sitagliptin compared to sulfonylureas for T2DM inadequately controlled on metformin, sitagliptin users experienced modest weight loss compared to gain with sulfonylureas; however, this difference was around 2 kg, which may not be of major clinical significance for most individuals [23].

1.3.3. Metformin and sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 inhibitors(dapagliflozin) in combination with metformin was shown to be a cost-effective treatment option compared with sulfonylurea from a UK healthcare perspective for people with T2DM who were inadequately controlled on metformin monotherapy [55]. A masked RCT of empagliflozin versus glimepiride add on metformin therapy, empagliflozin 25 mg provided a sustained reduction in HbA1c, weight, blood pressure, and low risk of hypoglycemia compared to glimepiride [56]. A narrative review of metformin and empagliflozin combination therapy showed that addition of empagliflozin to metformin therapy improves glucose control, with a minimal risk of hypoglycemia, while reducing body weight, arterial blood pressure and this combined therapy may be used in patients with established CVD or heart failure [57]. Another RCT of metformin plus canagliflozin versus metformin plus sitagliptin or metformin plus placebo, the canagliflozin group showed reduction in HbA1c, fasting blood sugar (FBS), Systolic blood pressure (SBP). However, episode of hypoglycemia, genital mycotic infection and osmotic diuresis-related adverse event rates were higher with

canagliflozin group [58]. In routine care, sodium glucose co-transporter 2 inhibitors added to metformin therapy had greater effects on cardiometabolic risk factors than sulfonylurea [59].

1.3.4. Metformin and glucagon like peptide 1 receptor agonist

An RCT comparing the glucagon like peptide 1 receptor agonist (liraglutide) to a sulphonylurea as add on to metformin in patients with established type 2 diabetes, more patients in the liraglutide compared with the sulphonylurea group achieved a composite endpoint of HbA1c < 7%, no weight gain and no severe hypoglycemia. Significant reductions were also observed in weight and diastolic blood pressure (DBP) in the liraglutide compared with the sulphonylurea group. There were no episodes of severe hypoglycemia in either group, however, self-recorded episodes of blood glucose ≤3.9mmol/l were significantly lower with liraglutide (incidence rate ratio 0.29, 95% CI 0.19, 0.41, p<0.0001) [60]. A meta-analysis of RCTs, liraglutide in combination with metformin resulted in significant reductions in HbA1c, bodyweight, FBS, and postprandial glucose, and similar reductions in SBP, and DBP compared to control (placebo, sitagliptin, glimepiride, dulaglutide, insulin glargine, and Neutral Protamine Hagedorn). Moreover, liraglutide combined with metformin did not increase the risk of hypoglycemia, but induced a higher incidence of gastrointestinal disorders [61-62].

1.3.5. Metformin and Thiazolidinedione

A randomized, multicenter trial of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin, fewer patients had hypoglycemia in the pioglitazone group than in the sulfonylureas group. Moderate weight gain (less than 2 kg, on average) occurred in both groups. Both treatments groups were effective overall and were not associated with high risk of clinically relevant adverse-effects; however, patients given metformin with pioglitazone had better durability of glycaemia control, and higher HDL-C concentrations than patients given metformin with sulfonylureas. There was no difference in the incidence of any of the pre-specified cardiovascular outcomes, including fatal and non-fatal myocardial infarction or stroke, or all-cause death, during the study between the groups [63]. Addition of pioglitazone to metformin tended to increase plasma HDL-C (0.04mmol/L; p=0.051) at 6 months and significantly reduce plasma triglyceride level (-0.25 mmol/L; P=0.013) compared to metformin alone [50]. A multicenter, randomized, open-label trial reported addition

of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes confirmed to increase the risk of heart failure and of some fractures, mainly in women. Although the data were inconclusive about any possible effect on myocardial infarction, rosiglitazone did not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs [64].

1.3.6. Metformin and a-glucosidase inhibitors

The combination of metformin and a-glucosidase inhibitor is a rational therapy because of their different and complimentary mechanisms of action, which provides effective glycemic control with additional cardiovascular benefits and minimizes occurrence of adverse events [65]. The use of metformin with a-glucosidase inhibitor (acarbose) was associated with significantly lower risks of hospitalizations for major atherosclerotic events (HR =0.69; 95% CI [0.52 to 0.91], ischaemic stroke (HR, 0.68; 95% CI [0.49 to 0.94], and hypoglycemia (HR, 0.23; 95% CI [0.08 to 0.71] compared with use of metformin with sulfonylurea [66]. As add-on to metformin, acarbose reduced HbA1c regardless of baseline HbA1c, age, and renal function [67]. However, a double blind RCT elsewhere shows patients with coronary heart disease and impaired glucose tolerance, acarbose did not reduce the risk of major adverse cardiovascular events, but did reduce the incidence of diabetes [68-69].

1.3.7. Metformin and insulin

Insulin had no significant effects on the risk of CVD, major cardiovascular adverse events, myocardial infarction, stroke, or heart failure [69]. An RCT on metformin with glargine versus metformin with glimepiride on pancreatic ß-cell function in patients with T2DM, symptomatic hypoglycemia was more frequent in glimepiride group (P = 0.01) though severe hypoglycemia did not occur. Metformin with insulin glargine group was as effective as metformin with glimepiride group in controlling hyperglycemia and maintaining ß-cell function in patients with T2DM. Hypoglycemic profile was favorable in the insulin glargine group and less weight gain was observed in the glimepiride group. However, there was no significant difference in lipid profiles between the groups [70]. A retrospective cohort study of patients with T2DM who initiated basal insulin as second or third- line drug showed an increased risk of all-cause

mortality, CVD and severe hypoglycemia compared with newer GLP-1 receptor agonists, SGLT-2 inhibitors and DPP-4 inhibitors [71-76].

1.4. Significance of the study

Although most patients with T2DM require combined drugs to improve glycemic control, the choice of a good second-line drug is critical for the prevention of cardiovascular disease. So, the result of this study will provide evidence on glycemic efficacy and cardiovascular safety of the combination therapies to health policy makers, health professionals and scientific community at large.

2. Objectives

2.1. General objective

- To compare glycemic control and risk of cardiovascular outcomes of metformin-insulin versus metformin-sulfonylurea combination therapies in T2DM patients after ≥ three months follow up.

2.2. Specific objectives

- To compare the change from baseline in HbA1c level between the two treatment groups
- To assess the cardiovascular risk factor control and management between the groups
- To assess composite cardiovascular outcomes between the two treatment groups
- To assess microvascular complications between the two treatment groups
- To identify the long-term adverse events of the two treatment groups
- To determine factors associated with target HbA1c level and composite cardiovascular outcomes

3. Methods

3.1. Study settings

The study was conducted in Addis Ababa, capital city of Ethiopia. According to the 2010 Central statistical agency of Ethiopia population census, the population of Addis Ababa was 2.917 million [77] and it covers 540 square kilometers. Addis Ababa city has 13 governmental hospitals. Four are under the federal ministry of health including Tikur Anbessa Specialized Hospital (TASH), St. Paul's Specialized Hospital, Torhyloch Hospital and Federal Police Hospital. TASH is the teaching hospital for graduate and undergraduate health science students under Addis Ababa University. The hospital has more than 800 beds and provides diagnostic and medical services for approximately 370,000–400,000 patients annually [78]. Nine general hospitals are under the Addis Ababa regional health bureau which includes Yekatit 12 Hospital, Ras Desta Damtew Memorial Hospital, Zewditu Memorial Hospital, Menelik II Hospital, Tirunesh Bejing Hospital, ALRT Hospital, Yeka Kotebe Hospital, St. Petros Hospital and Ghandi Hospital [79]. Except Ghandi Hospital the remaining hospitals are providing diabetes care services. Five governmental hospitals which are providing diabetes care services (TASH, St Paul's Specialized Hospital, Yekatit 12 Hospital, Menelik II Hospital and Zewditu Memorial Hospital) were selected for data collection using simple random sampling method.

3.2. Study design and period

A comparative cross-sectional study was conducted by reviewing T2DM patient's medical record retrospectively with the support of patients' interview from December 2019 to March 2020.

3.3. Study participants

Study participants were T2DM patients who were under metformin with insulin or metformin with sulfonylurea combination therapy.

3.4. Eligibility Criteria

3.4.1. Inclusion criteria

- Patients aged ≥18 years with continuous medical records.
- Willingness to participate in the study.
- Patients with continuous follow-up either on metformin with insulin or metformin with sulfonylurea combination therapy.

3.4.2. Exclusion criteria

- Patients with prior history of cardiovascular disease (myocardial infarction, stroke, peripheral vascular disease) before the initiation of the combination therapy.
- Patients either on monotherapy or triple therapy of antidiabetic drugs.
- Patients with less than three months of follow-up with the combination therapy.

3.5. Sample size determination and sampling procedure

3.5.1. Sample size determination

The required sample size was determined using a 50% estimated proportion of T2DM patients who achieved their HbA1c target less than 7% [41]. P=0.5 and w (tolerable sampling error) = 5% and using 95% confidence level: $n = Z^2\ p\ (1-p)/\ W^2$; Where, n= sample size, z = statistic for 95% level of confidence; w = precision / margin of error/ and p = the estimated proportion of T2DM patients achieving HbA1c level$\Rightarrow$ $n = (1.96)^2 * (0.5) * (1-0.5) / (0.05)^2 = 384$. Adding 10 % for non-response and considering, the emergence of COVID-19 and the state-of-emergency declared, resulting in amendment of the sample size to 321.

3.5.2. Sampling procedure

Five governmental hospitals which are providing diabetes care services were selected by principal investigator using simple random sampling method. The average monthly T2DM patients load was retrieved from the health information management system office of each hospital (Table 1). Based on the average monthly patients load of each hospital, a proportion was

made and a total of 321 T2DM patients were included in the study using a convenience sampling method (Appendix I).

Table 1: List of hospitals and average monthly T2DM patients load

Hospitals	Average monthly T2DM patients load	No. of T2DM patients included in the study
Tikur Anbessa Specialized Hospital	708	102
St. Paul's Specialized Hospital	297	43
Yekatit 12 Hospital	308	45
Menelik II Hospital	292	42
Zewditu Memorial Hospital	617	89
Total	2,222	321

3.6. Outcomes

The primary outcome measure was glycemic control (reduction in HbA1c) and the secondary outcome measures were composite cardiovascular outcomes (myocardial infarction, stroke, heart failure), microvascular complications (diabetic neuropathy, retinopathy, and nephropathy), treatment-emergent adverse events (hypoglycemia), changes in bodyweight, fasting blood sugar, systolic blood pressure, diastolic blood pressure and lipid profiles (low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides).

3.7. Ethical consideration

Ethical approvals were obtained from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University (Ref. No. CDT/18100/19), Institutional Review Board (IRB) of St. Paul's Hospital Millennium Medical College (Ref. No. PH23/232), and Addis Ababa Regional Health Bureau (Ref. No. AAH/7038/227). After securing ethical clearance, an official letter was sent to each hospital to get permission. Full explanation about the purpose of the study was given to authorities of each hospital. Informed consent was obtained from

participants by trained pharmacists using approved and locally translated informed consent form. Patients were informed about the details of the study, including the general over view, purpose, risk and benefits of the study. Participants got adequate time to read, understand and ask questions to decide participation in the study. Data collection was conducted after approval of the study by the director of each hospital and confidentiality was maintained at all stages of the study.

3.8. Data collection and management

3.8.1. Data collection instruments

An interviewer administered questionnaire and a semi structured data abstraction form were developed to collect primary and secondary data respectively. The data collection instrument was translated into local language and had four sections which included socio-demographic characteristics of the participant, medication efficacy, adherence and safety assessment questionnaires.

3.8.2. Recruitment and training of data collectors

Five clinical pharmacists were employed for data collection and a one-day training was given by the principal investigator a day prior to the start of data collection. The training focused on the aim of the study, the content of the data collection instrument and how to deliver it to the participants including how to assure confidentiality.

3.8.3. Screening

One trained clinical pharmacist was assigned in the diabetes center of each hospital. As the patients arrive to the center or clinic, they were screened for eligibility. Patients who fulfilled the eligibility criteria, and volunteer to participate were interviewed and their medical record was assessed. The number of patients screened per day varied with patients load of each hospital. For example, a minimum of 50 and maximum of 100 patients were screened in diabetes center of TASH.

3.8.4. Data collection

Primary and secondary data were collected by trained clinical pharmacists using interviewer administered and semi-structured questionnaire. All relevant information were collected on the data collection form, which included patient's demography (patient card number, age, gender, marital status, residence, family history of diabetes mellitus, smoking habit, daily salt consumption, daily fruit and vegetable consumption, alcohol consumption, level of education, regular exercise trained of the participant, co-morbidity, number of co-morbidities, antidiabetic and concomitant treatments, duration of treatment), primary and secondary outcomes.

3.8.5. Data quality assurance

To assure the quality of the data, interviewer administered questionnaire was properly designed. Then the data collection form was pre tested on 5% patients to check the appropriateness of the questionnaire and make necessary corrections prior to starting the study. Patients included in the pre-test procedure were not included in the actual study to avoid information contamination. Then modification was made as per the results of the pre- test. In addition, data collectors and supervisor involved in the data collection process got appropriate training on the overall study. Furthermore, each filled data collection tool was checked for its completeness every day after data collection by the supervisor and data collectors. Finally, all data were examined for completeness and consistency during data management, storage and analysis.

3.8.6. Statistical analysis

Statistical analyses were carried out using SPSS version 25. Data were expressed as median [interquartile range] for skewed variables, mean ± standard deviation (SD) for normally distributed continuous variables, and the number of cases and percentages for categorical variables. Continuous variables were compared between two groups using an independent sample t-test for normally distributed variables and Mann–Whitney U test for variables with skewed data. Pearson chi-square was used to categorical variables. Bivariate and multivariate logistics regression analysis was done to assess factors associated with glycemic target level and composite cardiovascular outcomes. The results of the analyses were reported as ORs with 95% CIs. Statistical analysis with a p value < 0.05 was considered statistically significant.

4. Results

4.1. Sociodemographic characteristics of study participants

A total of 321 participants with T2DM were enrolled in the study, of whom 162 (50.5%) received metformin-insulin combination therapy and 159 (49.5%) received metformin-sulfonylurea combination therapy. Among the participants, 141 (43.9%) were males. Compared to metformin-insulin combination therapy, metformin-sulfonylurea combination therapy had a greater number of male participants (15.6% vs 28.3%, p<.001). The mean ± SD age of the participants was 59.45±10.86 years, and a significant difference was observed between the groups (58.14±9.89 years in the metformin-insulin group and 60.78±11.65 years in the metformin-sulfonylurea group, p= .029). Most of the participants (86.3%) were resided in Addis Ababa city and there was no significant difference in participant's resident between groups (43.0% vs 43.3%, p=.628). In case of the marital status, the majority of participants (68.2%) were married and there was no significant difference between the groups (p=.055). There was a significant difference in participant's level of education, family history of diabetes mellitus, smoking status, alcohol consumption, and history of chat chewing between groups. Of the study participants, 195 (60.7%) attended regular weekly physical exercise. The overall median of regular weekly physical exercise of participants was 150 minutes and there was no median difference between the groups (105 minutes vs 150 minutes, p=.053). In terms of attending health education, vegetable and salt use, there was no difference between the groups (Table 2).

The median follow-up period from baseline to data collection was 48 (24-72) months. Notably, patients in the metformin-insulin group were more likely to have a shorter history of combination therapy, with a median (IQR) of 36 (12-60) months compared to 60 (36-96) months in patients who received metformin-sulfonylurea combination therapy (P<.001). Patients who received metformin-insulin combination therapy had more co-morbidities than those who received metformin-sulfonylurea combination therapy (44.9% vs 39.3%; p=.022) (Table 3).

Table 2: Demographic characteristics of study participants (N=321)

Variables	Category	Total	Treatment		P-value
			Metformin with Insulin (N=162)	Metformin with sulfonylureas (N=159)	
Sex	Male	141 (43.9%)	50 (15.6%)	91 (28.3%)	<.001
Age (years)	Mean ± SD	59.45±10.86	58.14±9.89	60.78±11.65	.029
Residence					.628
	Addis Ababa	277 (86.3%)	138 (43.0%)	139 (43.3%)	
	Out of Addis Ababa	44 (13.7%)	24 (7.5%)	20 (6.2%)	
Marital status					.055
	Single	12 (3.7%)	2 (0.6%)	10 (3.1%)	
	Married	219 (68.2%)	111 (34.6%)	108 (33.6%	
	Divorced	37 (11.5%)	23 (7.2%)	14 (4.4%)	
	Widowed	53 (16.5%)	26 (8.1%)	27 (8.4%)	
Level of education					.004
	Unable to read and write	55 (17.1%)	26 (8.1%)	29 (9.0%)	
	Primary	104 (32.4%)	64 (19.9%)	40 (12.5%)	
	Secondary	41 (12.8%)	15 (4.7%)	26 (8.1%)	
	Preparatory	44 (13.7%)	22 (6.9%)	22 (6.9%)	
	College/University	77 (24.0%)	35 (10.9%)	42 (13.1%)	
Health education	Yes	180 (56.1%)	94 (29.3%)	86 (26.8%)	.501
Family history of DM	Yes	133 (41.4%)	80 (24.9%)	53 (16.5%)	.005
Smoking habit	Current smoker	21 (6.5%)	6 (1.9%)	15 (4.7%)	.043
Alcohol consumption	Yes	68 (21.2%)	22 (6.9%)	46 (14.3%)	.001
Chat chewing habit	Yes	22 (6.9%)	5 (1.6%)	17 (5.3%)	.008
Daily vegetable use	Yes	103 (32.1%)	49 (15.3%)	54 (16.8%)	.550
Daily salt use (tea spoon)	Mean ± SD	.94±.58	.92±.58	.95±.59	.588
Physical exercise	Yes	195 (60.7%)	85 (26.5%)	110 (34.3%)	.003
Exercise (Minutes)	Median (IQR)	150 (90-160)	105 (90-150)	150 (90-210)	.053

Values are mean ± SD for continuous and normally distributed data, median (IQR) for continuous and skewed data, N (%) for categorical variables; p values for comparison between groups using the independent t-test for parametric or the corresponding Mann–Whitney U test for nonparametric continuous variables, and the chi square test for categorical variable; DM: Diabetes Mellitus; SD: Standard Deviation; IQR: Inter Quartile Range

4.2. Glycemic control and managements

T2DM patient's HbA1c and FBS level were examined at the beginning of combination therapy and after a median 48 months follow-up of the combination therapies. Patients in the metformin-insulin combination group were more likely to have a higher baseline HbA1c than those who received metformin-sulfonylurea combination therapy (with mean ± SD of 9.49±1.93 % vs 8.49±1.32 %, respectively; p<.001). Likewise, patients who received metformin-insulin combination therapy had a higher HbA1c than those who received metformin-sulfonylurea combination therapy (with mean ±SD of 8.65±1.73 % vs 7.46±1.50 %, respectively; p<.001). However, there was no significant difference in HbA1c changes between the groups, with mean ± SD of -1.04±.96 % for metformin-insulin versus -1.02±1.03 % for metformin-sulfonylurea; p=.912). Although there was no statistically significant difference between groups, small number of patients in the metformin-insulin combination group achieved target HbA1c level at baseline (<7%) compared with those in metformin-sulfonylurea combination group (3.8% vs 8.1%, respectively; p=.226). However, after receiving the combination therapies, there was a significant difference in the proportion of patients who achieved the recommended target HbA1c level (< 7%) between patients in the metformin-insulin vs metformin-sulfonylurea combination therapies (8.1% vs 24.3%, respectively; p<.001) as shown in Table 3.

There was no significant difference in FBS at baseline between the two treatment groups, with median (IQR) of 168 (146-195) mg/dl in the metformin-insulin combination group versus 165 (146-191) mg/dl in the metformin-sulfonylurea combination group; p=.843. Patient's median FBS after combination therapy was not also significantly different between groups (144 mg/dl for metformin-insulin vs 142 mg/dl for metformin-sulfonylurea; p=.610). Similarly, the changes from baseline in median FBS between groups were not significantly different (-24 mg/dl for metformin-insulin vs -29.5 mg/dl for metformin-sulfonylurea; p=.370). At baseline and after receiving combination therapy, 13.3% and 32.0% patients, respectively achieved the recommended FBS (<130.00 mg/dl). However, there was no significant difference between patients in the metformin-insulin and metformin-sulfonylurea groups at baseline (6.0% vs 7.3%, respectively; p=0.330) and after a follow-up of combination therapy (16.3% vs 15.7%, respectively; p=0.467) as shown in Table 3.

4.3. Cardiovascular risk factor control and managements

Potential cardiovascular risk factors were assessed at baseline and after a follow-up of combination treatment. Patients treated with the metformin-insulin combination had lower baseline bodyweight than those treated with metformin-sulfonylurea combination (70.00±10.68 kg vs 76.48±12.41 kg, respectively; p<.001). There was no significant difference in the mean bodyweight after receiving metformin-insulin and metformin-sulfonylurea combination therapies (75.28±11.10 kg vs 73.04±11.69 kg, respectively; p=.081). However, the increase in bodyweight with metformin-insulin combination therapy was significantly higher than with metformin-sulfonylurea combination therapy (5.37±5.92 kg vs -3.10±4.68 kg, respectively; p<.001). A significant increase from baseline in BMI was also noted with metformin-insulin combination therapy compared with metformin-sulfonylurea combination therapy (2.02±2.27 kg/m^2 vs -1.11±1.71 kg/m^2, respectively; p<.001) as shown in Table 3.

No significant difference in the mean baseline systolic and diastolic blood pressure was observed in both combination therapies. The reduction from baseline in the mean SBP was not significantly different with both combination therapies (-3.57±16.74 mmHg for metformin-insulin vs -5.18±16.88 mmHg for metformin-sulfonylurea; p=.415). The reduction from baseline in the mean DBP was not also significantly different in both combination therapies (-5.06±11.79 mmHg for metformin-insulin vs -6.23±11.26 mmHg for metformin-sulfonylurea; p=.389). There was no statistically significant difference in the proportion of patients who achieved the recommended target SBP goal (40.0% for metformin-insulin vs 42.0% for metformin-sulfonylurea; p= .307) and target DBP goal (48.8% for metformin-insulin vs 48.5% for metformin-sulfonylurea; p= .365) as shown in Table 3.

There was no significant difference in baseline HDL-C before both combination treatment, with a median HDL-C of 45.00 mg/dl in both groups. However, there was a significant difference in HDL-C after combination treatment, with a lower median HDL-C in patients who received metformin-insulin than those who received metformin-sulfonylurea combination therapies (41.50 mg/dl vs 48.00 mg/dl, respectively; p=.018). There was a significant reduction from baseline in median HDL-C in patients who received metformin-insulin combination therapy compared to those who received metformin-sulfonylurea combination therapy (-5.00 mg/dl vs 5 mg/dl,

respectively; p=.004). Patients who received metformin-insulin combination therapy had a lower mean baseline LDL-C than those who received metformin-sulfonylurea therapy. Metformin-insulin combination treatment significantly increased the mean LDL-C compared with metformin-sulfonylurea treatment from that of the baseline (6.67 mg/dl vs -21.30 mg/dl, respectively; p=<.001). Similarly, the changes from the baseline in the median triglycerides and cholesterol total between the two treatment groups were significantly different (9 mg/dl for metformin-insulin vs -15 mg/dl for metformin-sulfonylurea; p=.005) and (-15 mg/dl for metformin-insulin vs -29 mg/dl for metformin-sulfonylurea; respectively; p=.021) as shown in Table 3.

4.4. Composite cardiovascular outcomes

Of the study participants with known T2DM, 74.5% developed at least one composite cardiovascular outcome over a median of 48 months follow-up. There was a significant difference in the proportion of patients who had CVD between the two treatment groups, with a higher proportion of patients in the metformin-insulin treatment group than metformin-sulfonylurea treatment group (40.5% vs 34.0%, respectively; p=.021). Among participants, 4.7% developed myocardial infarction, 1.3% stroke, 11.5% heart failure, 57.3% hypertension and 67.0% dyslipidemia. A significantly higher proportion of patients who received metformin-insulin combination therapy had myocardial infarction than those who received metformin-sulfonylurea combination therapy (3.7% vs 0.9%, respectively; p=.031). However, there was no significant difference in the proportion of patients who had stroke, heart failure and hypertension between the two treatment groups. Moreover, patients who received metformin-insulin combination therapy had a significant higher proportion of dyslipidemia than those who received metformin-sulfonylurea combination therapy (37.7% vs 29.3%, respectively; p=.004) as shown in Table 3.

4.5. Microvascular complications

Among the patients with overall microvascular complications of diabetes, 29.3% had diabetic neuropathy, 9.3% diabetic retinopathy and 4.7% diabetic nephropathy. There was a significant difference in the proportion of patients with diabetic neuropathy between treatment groups (19.0% for metformin-insulin vs 10.3% for metformin-sulfonylurea; p=.001) and diabetic

retinopathy (7.2% for metformin-insulin vs 2.2% for metformin-sulfonylurea; p=.003). However, there was no significant difference in proportion of patients with diabetic nephropathy between the groups (Table 3).

4.6. Concomitant medication use

Of the study participants, 74.1% used concomitant medications on top of antidiabetic medications. There was no significant difference in the proportion of patients who received concomitant medication between metformin-insulin and metformin-sulfonylurea treatment groups (39.9% vs 34.3%, respectively; p=.056). Significant higher proportion of patients in the metformin-insulin treatment group used diuretics (12.8% vs 7.8%, respectively; p=.038), angiotensin receptor-blockers (3.7% vs 0.6%, respectively; p=.011), Beta-blockers (9.0% vs 4.4%, respectively; p=.021), statins (38.9% vs 30.8%, respectively; p=.005) and aspirin (26.6% vs 19.1%, respectively; p=.010) compared to those in the metformin-sulfonylurea treatment group. However, there was no significant difference in the proportion of patients who received angiotensin converting enzyme inhibitors and calcium channel blockers in both treatment groups (Table3).

4.7. Antidiabetic treatment-emergent adverse events

The proportion of patients self-reported at least one antidiabetic treatment-emergent adverse events during the follow-up period in both metformin-insulin and metformin-sulfonylurea treatment groups were not significantly different (13.4% vs 11.8%, respectively; p=.609) as shown in Table 3. A lower proportion of patients in the metformin-insulin than in the metformin-sulfonylurea treatment groups reported dyspepsia. Impotence was reported in one patient in the metformin-sulfonylurea treatment group. A higher proportion of patients reported pain at the injection site and weight gain in the metformin-insulin than metformin-sulfonylurea treatment groups. Although it was not statistically significant, a slightly large percentage of patients experienced hypoglycemic adverse events in the metformin-insulin than metformin-sulfonylurea treatment groups (17.1% vs 14.6%, respectively; p=.405). The median episode of hypoglycemia reported per month was also similar between the two treatment groups (Table 3).

Table 3: Clinical characteristics of study participants (N=321)

Variables	Category	Total	Treatment		P-value
			Metformin with Insulin (N=162)	Metformin with sulfonylurea (N=159)	
Co-morbidity	Yes, N, %	270 (84.1%)	144 (44.9%)	126 (39.3%)	.022
Number of co-morbidities	Median (IQR)	2 (2-3)	2 (2-3)	2 (2-2)	.001
Duration of treatment (month)	Median (IQR)	48 (24-72)	36 (12-60)	60 (36-96)	<.001
Baseline weight before Rx (Kg)	Mean ± SD	73.18±11.99	70.00±10.68	76.48±12.41	<.001
Weight after Rx (Kg)	Mean ± SD	74.17±11.43	75.28±11.10	73.04±11.69	.081
Change from baseline in weight (Kg)	Mean ± SD	1.22±6.82	5.37±5.92	-3.10±4.68	<.001
Baseline BMI before Rx (Kg/m^2)	Mean ± SD	26.77±4.35	26.31±4.35	27.25±4.32	.063
BMI after Rx (Kg/m^2)	Mean ± SD	27.27±4.43	28.37±4.51	26.14±4.06	<.001
Change from baseline in BMI (Kg/m^2)	Mean ± SD	.50±2.55	2.02±2.27	-1.11±1.71	<.001
Baseline HbA1c before Rx (%)	Mean ± SD	8.95±1.70	9.49±1.93	8.49±1.32	<.001
HbA1c after combination Rx (%)	Mean ± SD	8.01±1.71	8.65±1.73	7.46±1.50	<.001
Change from baseline in HbA1c (%)	Mean ± SD	-1.03±.20	-1.04±.96	-1.02±1.03	.912
Proportion of patients achieving target HbA1c before Rx (%)					.226
	<7%, N, %	19 (11.9%)	6 (3.8%)	13 (8.1%)	
	≥7%, N, %	141 (88.1%)	67 (41.9%)	74 (46.3%)	
Proportion of patients achieving target HbA1c after Rx (%)					<.001
	<7%, N, %	56 (32.4%)	14 (8.1%)	42 (24.3%)	
	≥7%, N, %	117 (67.6%)	65 (37.6%)	52 (30.1%)	
Baseline FBS before Rx (mg/dl)	Median (IQR)	166 (146-193)	168 (146-195)	165 (146-191)	.843
FBS after combination Rx (mg/dl)	Median (IQR)	142 (124-172)	144 (122-179)	142 (125-163)	.610
Change from baseline in FBS (mg/dl)	Median (IQR)	-27 (-47- -4)	-24 (-45-2.1)	-29.5 (-48- -5.4)	.370
Proportion of patients achieving target FBS before Rx (mg/dl)					.330
	<130, N, %	40 (13.3%)	18 (6.0%)	22 (7.3%)	
	≥130, N, %	261 (86.7%)	131 (43.5%)	130 (43.2%)	
Proportion of patients achieving target FBS after Rx (mg/dl)					.467
	<130, N, %	102 (32.0%)	52 (16.3%)	50 (15.7%)	
	≥130, N, %	217 (68.0%)	108 (33.9%)	109 (34.2%)	
Baseline SBP before Rx (mmHg)	Mean ± SD	135.12±18.21	135.88±18.52	134.39±17.93	.479
SBP after Rx (mmHg)	Mean ± SD	131.13±16.42	132.61±16.05	129.66±16.71	.120
Change from baseline in SBP (mmHg)	Mean ± SD	-4.39±16.80	-3.57±16.74	-5.18±16.88	.415
Baseline DBP before Rx (mmHg)	Mean ± SD	82.00±10.15	81.97±10.33	82.02±10.01	.968
DBP after combination Rx (mmHg)	Mean ± SD	76.28±8.43	76.87±8.35	75.69±8.49	.224
Change from baseline in DBP (mmHg)	Mean ± SD	-5.66±11.52	-5.06±11.79	-6.23±11.26	.389
Baseline HDL-C before Rx	Median (IQR)	45.0(38.0-53.0)	45.0 (39.0-	45.0 (38.5-53.0)	.258

(mg/dl)			56.8)		
HDL-C after combination Rx (mg/dl)	Median(IQR)	45.0(36.0-52.0)	41.5(34.3-47.0)	48.0(40.0-55.0)	.018
Change from baseline in HDL-C (mg/dl)	Median(IQR)	.00(-11.5-8.0)	-5.0(-15.0-2.5)	5.0(-5.85-11.0)	.004
Baseline LDL-C before Rx (mg/dl)	Mean ± SD	118.01±43.57	109.96±44.31	124.59±42.11	.048
LDL-C after combination Rx (mg/dl)	Mean ± SD	109.57±38.48	113.45±45.37	106.24±31.29	.245
Change from baseline in LDL-C (mg/dl)	Mean ± SD	-9.21±37.45	6.67±38.33	-21.30±32.12	<.001
Baseline TC (mg/dl)	Median (IQR)	181 (143-227)	190 (127-219)	201 (147-241)	.149
TC after combination Rx (mg/dl)	Median (IQR)	175 (133-202)	174 (134-210)	165 (123-198)	.893
Change from baseline in TC (mg/dl)	Median (IQR)	-22 (-53-7)	-15 (-50-23)	-29 (-62- -11)	.021
Baseline TG (mg/dl)	Median (IQR)	136 (105-187)	126 (89-186)	157 (109-196)	.063
TG after combination Rx (mg/dl)	Median (IQR)	135 (97-196)	127 (109-190)	132 (93-185)	.457
Change from baseline in TG (mg/dl)	Median (IQR)	-9 (-30-17)	9 (-18-29)	-15 (-31- -5)	.005
Cardiovascular outcomes	Yes, N, %	239 (74.5%)	130 (40.5%)	109 (34.0%)	.021
Myocardial infarction	Yes, N, %	15 (4.7%)	12 (3.7%)	3 (0.9%)	.031
Stroke	Yes, N, %	4 (1.3%)	2 (0.6%)	2 (0.6%)	1.00
Heart failure	Yes, N, %	37 (11.5%)	20 (6.2%)	17 (5.3%)	.728
Hypertension	Yes, N, %	184 (57.3%)	101 (31.5%)	83 (25.9%	.072
Dyslipidemia	Yes, N, %	215 (67.0%)	121 (37.7%)	94 (29.3%)	.004
Microvascular complications					
Diabetic neuropathy	Yes, N, %	94 (29.3%)	61 (19.0%)	33 (10.3%)	.001
Diabetic retinopathy	Yes, N, %	30 (9.3%)	23 (7.2%)	7 (2.2%)	.003
Diabetic nephropathy	Yes, N, %	15 (4.7%)	7 (2.2%)	8 (2.5%)	.797
Concomitant medication use	Yes, N, %	238 (74.1%)	128 (39.9%)	110 (34.3%)	.056
Diuretics	Yes, N, %	66 (20.6%)	41 (12.8%)	25 (7.8%)	.038
ACEIs	Yes, N, %	138 (43.0%)	76 (23.7%)	62 (19.3%)	.176
ARBs	Yes, N, %	14 (4.4%)	12 (3.7%)	2 (0.6%)	.011
BBs	Yes, N, %	43 (13.4%)	29 (9.0%)	14 (4.4%)	.021
CCBs	Yes, N, %	93 (29.0%)	48 (15.0%)	45 (14.0%)	.807
Statins	Yes, N, %	224 (69.8%)	125 (38.9%)	99 (30.8%)	.005
Others*	Yes, N, %	146 (45.6%)	85 (26.6%)	61 (19.1%)	.010
Antidiabetic Rx emergent AEs	Yes, N, %	81 (25.2%)	43 (13.4%)	38 (11.8%)	.609
Hypoglycemia	Yes, N, %	102 (31.8%)	55 (17.1%)	47 (14.6%)	.405
Episode of hypoglycemia/month	Median (IQR)	2.00 (2.00-3.00)	2.00 (2.00-2.75)	2.00 (1.00-3.00)	.333
Missed dose of antidiabetic drugs	Yes, N, %	98 (30.5%)	44 (13.7%)	54 (16.8%)	.225
Reason of missed dose					.758
	Forgetting	69 (70.4%)	29 (29.6%)	40 (40.8%)	
	Feeling better	3 (3.1%)	2 (2.0%)	1 (1.0%)	
	Unable to afford	5 (5.1%)	2 (2.0%)	3 (3.1%)	
	Others**	21 (21.4%)	11 (11.2%)	10 (10.2%)	

Source of antidiabetic medication	Free	260 (81.0%)	141 (43.9%)	119 (37.1%)	.007

Values are mean ± SD for continuous and normally distributed data, median (IQR) for continuous and skewed data, *N* (%) for categorical variables; *p* values for comparison between groups using the independent *t*- test for parametric or the corresponding Mann–Whitney *U* test for nonparametric continuous variables, and the chi-square test for categorical variable; Rx: Treatment; BMI: Body Mass Index; HbA1c: Hemoglobin A1c; FBS: Fasting Blood Sugar; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HDL-C: High-Density Lipoprotein -Cholesterol; LDL-C: Low-Density lipoprotein Cholesterol; TC: Total Cholesterol; TG: Triglycerides; ACEIs: Angiotensin-Converting Enzyme Inhibitors: ARBs: Angiotensin-Receptor Blockers; BBs: Beta-Blockers; CCBs: Calcium Chanelle Blockers; Others*: aspirin, nitrates, digoxin, antibiotics, antiretroviral treatment, anti-depressant, anti-asthmatics; Others**: spiritual believes, treatment plan inconvenience, pill burden

4.8. Factors associated with glycemic target level

The following covariates including sex, place of residence, marital status, level of education, family history of diabetes mellitus, smoking habit, alcohol consumption, chat chewing habit, daily vegetable and fruit consumption, regular exercise, co-morbidities, type of antidiabetic treatment, concomitant medications use, missed dose and source of antidiabetic medications were subjected to bivariate and multivariate logistic regression analysis. Of the covariates, type of antidiabetic treatments had a significant association with glycemic target level (AOR with 95% CI 4.308[1.79-10.32]; p=.001) (Table 4).

Table 4: Bivariate and multivariate logistic regression analysis of factors associated with HbA1c target level among patients with T2DM

Covariates	**Categories**	**Outcome variable**		**Crude odds ratio (95% CI)**	**P-value**	**Adjusted odds ratio (95% CI)**	**P-value**
		HbA1C					
		<7%	≥7%				
Sex	Male	30 (17.3%)	52 (47.4%)	.693 [.366-1.314]	.262	.885[.254-3.075]	.847
	Female	26 (15.0%)	65 (37.6%)	1.00			
Residence	Addis Ababa	47 (27.2%)	99 (57.2%)	1.053 [.440-2.519]	.907	1.067[.346-3.288]	.911
	Out of Addis Ababa	9 (5.2%)	18 (10.4%)	1.00			
Marital status	Single	3 (1.7%)	2 (1.2%)	.431 [.062-3.012]	.396	2.407[.753-7.695]	.138
	Married	34 (19.7%)	87 (50.3%)	1.656 [.704-3.896]	.248	.563[.056-5.690]	.626
	Divorced	8 (4.6%)	11 (6.4%)	.890 [.272-2.910]	.847	1.242[.301-5.123]	.764
	Widowed	11 (6.4%)	17 (9.8%)	1.00			
Level of education	Unable to read & write	6 (3.5%)	17 (9.8%)	1.417 [.415-4.834]	.578	3.358[.59-19.047]	.171
	Primary	16 (9.2%)	36 (20.8%)	1.125 [.417-3.038]	.816	1.500[.436-5.159]	.520
	Secondary	10 (5.8%)	19 (11.0%)	.950 [.314-2.875]	.928	1.824[.487-6.825]	.372
	Preparatory	8 (4.6%)	14 (8.1%)	.875 [.269-2.850]	.825	.908[.219-3.770]	.894

	University	16 (9.2%)	31 (17.9%)	1.00			
Health education	Yes	30 (17.3%)	65 (37.6%)	1.083 [.572-2.053]	.806	1.200[.487-2.956]	.692
	No	26 (15.0%)	52 (30.1%)	1.00			
Family history of DM	Yes	27 (15.6%)	56 (32.4%)	.986 [.521-1.865]	.966	.825[.377-1.803]	.629
	No	29 (16.8%)	61 (35.3%)	1.00			
Smoking habit	Current smoker	6 (3.5%)	8 (4.6%)	.612 [.202-1.856]	.385	.990[.235-4.163]	.989
	Not smoker	50 (28.9%)	109 (63.0%)	1.00			
Alcohol consumption	Regular drunker	19 (11.0%)	28 (16.2%)	.613[.305-1.231]	.169	.682[.234-1.988]	.483
	Not drunker	37 (21.4%)	89 (51.4%)	1.00			
Chat chewing habit	Regular chewer	7 (4.0%)	7 (4.0%)	.445 [.148-1.339]	.150	.795[.179-3.532]	.763
	Not chewer	49 (28.3%)	110 (63.6%)	1.00			
Daily vegetable and fruit use	Yes	19 (11.0%)	35 (20.2%)	.831 [.421-1.641]	.594	.708[.291-1.722]	.446
	No	37 (21.4%)	82 (47.4%)	1.00			
Regular exercise	Yes	32 (18.5%)	76 (43.9%)	1.390 [.725-2.667]	.322	2.019[.882-4.621]	.096
	No	24 (13.9%)	41 (23.7%)	1.00			
Co-morbidities	Yes	45 (26.0%)	98 (56.6%)	1.261 [.554-2.869]	.581	.374[.098-1.425]	.149
	No	11 (6.4%)	19 (11.0%)	1.00			
Treatment (Rx)	Met with insulin	14 (8.1%)	65 (37.6%)	3.750 [1.85-7.599]	<.001	4.308[1.79-10.32]	.001
	Met with SUs	42 (24.3%)	52 (30.1%)	1.00			
Concomitant Rx	Yes	36 (20.8%)	88 (50.9%)	1.686 [.846-3.358]	.137	2.424[.809-7.261]	.114
	No	20 (11.6%)	29 (16.8%)	1.00			
Missed dose	Yes	17 (9.8%)	38 (22.0%)	1.103 [.554-2.197]	.779	1.570[.689-3.580]	.283
	No	39 (22.5%)	79 (45.7%)	1.00			
Source of drugs	Free	42 (24.3%)	93 (53.8%)	1.292 [.608-2.743]	.505	1.136[.459-2.814]	.783
	Paid	14 (8.1%)	24 (13.9%)	1.00			

DM: Diabetes Mellites; CI: Confidence Interval; HbA1c: Hemoglobin A1c; Rx: Treatment; Met: Metformin; SU: Sulfonylurea

4.9. Factors associated with composite cardiovascular outcomes

Factors including sex, resident, marital status, level of education, alcohol consumption, regular exercise, type of antidiabetic treatment, co-morbidities, age, HbA1c, FBS, SBP, DBP, HDL-C, LDL-C, cholesterol total and triglycerides were subjected to bivariate logistic regression analysis. Those factors having a p-value <0.20 in the bivariate logistic regression analysis were subjected to multivariate logistic regression analysis. Of the possible factors included in multivariate logistic regression analysis, co-morbidities, BMI, HbA1c, and SBP had a significant association with composite cardiovascular outcomes (AOR with 95% CI .002[.000-.035], p=<0.001; 400.270[2.340-68469.106], p=.022; .517[.304-.876], p=.014 and .940[.892-.991], p=.021, respectively (Table 5).

Table 5: Bivariate and multivariate logistic regression analysis of factors associated with composite cardiovascular outcomes among patients with T2DM

Covariates	Categories	Outcome variable		Crude odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
		Composite CV Outcomes					
		Yes	No				
Sex	Male	93 (29.0%)	48 (15.0%)	2.216[1.330-3.693]	.002	.439[.051-3.766]	.453
	Female	146 (45.5%)	34 (10.6%)	1.00			
Residence	Addis Ababa	211 (65.7%)	66 (20.6%)	.547 [.279-1.074]	.080		
	Out of Addis Ababa	28 (8.7%)	16 (5.0%)	1.00			
Marital status	Single	8 (2.5%)	4 (1.2%)	3.623[1.376-9.535]	.009	1.780[.148-21.376]	.649
	Married	159 (49.5%)	60 (18.7%)	4.800[1.057-21.791]	.042	.197[.000-96.244]	.607
	Divorced	24 (7.5%)	13 (4.0%)	5.200[1.660-16.290]	.005	3.218[.194-53.331]	.415
	Widowed	48 (15.0%)	5 (1.6%)	1.00			
Level of education	Unable to read & write	50 (15.6%)	5 (1.6%)	.267[.086-.829]	.022		
	Primary	75 (23.4%)	29 (9.0%)	1.031[.468-2.272]	.939		
	Secondary	26 (8.1%)	15 (4.7%)	1.538[.614-3.855]	.358		
	Preparatory	35 (10.9%)	9 (2.8%)	.686[.255-1.842]	.454		
	University	53 (16.5%)	24 (7.4%)	1.00			
Alcohol consumption	Yes	41 (12.8%)	27 (8.4%)	2.371[1.340-4.193]	.003	2.936[.580-14.876]	.193
	No	198 (61.7%)	55 (17.1%)	1.00			
Regular exercise	Yes	135 (42.1%)	60 (18.7%)	2.101[1.210-3.647]	.008	4.935[.998-24.405]	.050
	No	104 (32.4%)	22 (6.9%)	1.00			
Treatment	Met with insulin	130 (40.5%)	32 (10.0%)	.537[.322-.895]	.017	1.030[.250-4.252]	.967
	Met with Sus	109 (34.0%)	50 (15.6%)	1.00			
Co-morbidities	Yes	236 (73.5%)	34 (10.6%)	.009[.003-.031]	<.001	.002[.000-.035]	<.001
	No	3 (0.9%)	48 (15.0%)	1.00			
BMI	Under	1 (0.3%)	1 (0.3%)	11.000[.608-	.105	400.270[2.340-	.022

	weight			198.930]		68469.106]	
	Normal	70 (22.7%)	30 (9.7%)	4.714[1.844-12.054]	.001	6.105[.403-92.563]	.192
	Over weight	91 (29.4%)	44 (14.2%)	5.319[2.141-13.212]	<.001	13.076[.965-177.2]	.053
	Obese	66 (21.4%)	6 (1.9%)	1.00			
Age	Mean ± SD	59.45± 10.86		.965[.942-.989]	.004	.958[.886-1.035]	.273
HbA1C	Mean ± SD	8.01± 1.71		.660[.519-.838]	.001	.517[.304-.876]	.014
FBS	Mean ± SD	150.52± 39.10		.988[.980-.996]	.002	.995[.975-1.015]	.625
SBP	Mean ± SD	131.13± 16.42		.935[.913-.957]	<.001	.940[.892-.991]	.021
DBP	Mean ± SD	76.28± 8.43		.968[.937-1.000]	.049	1.036[.946-1.134]	.451
HDL-C	Mean ± SD	45.15± 10.43		1.018[.982-1.056]	.332		
LDL-C	Mean ± SD	109.57± 38.48		.995[.986-1.005]	.355		
Total cholesterol	Median(IQR)	175 (133-202)		1.010[.998-1.022]	.088		
Triglycerides	Median(IQR)	135 (97-196)		.996[.989-1.003]	.254		

CV: Cardiovascular; CI: Confidence Interval; BMI; Body Mass Index; HbA1c: Glycated Hemoglobin A1c; SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; HDL-C: High Density-Lipoprotein-Cholesterol; LDL-C: Low-Density Lipoprotein-Cholesterol; SD: Standard Deviation; IQR: Inter Quartile Range

5. Discussion

This comparative cross-sectional study investigated glycemic control and cardiovascular outcomes of metformin-insulin vs metformin-sulfonylurea combination therapies among patients with T2DM. Long term glycemic control is the major goal of T2DM management to prevent both micro and macrovascular complications of diabetes mellitus [80]. Compared to those who received metformin-sulfonylurea combination therapy, patients who received metformin-insulin combination therapy had a higher HbA1c level at baseline and after a median of 48 months follow-up. However, there was no significant difference in the mean decrease from baseline in HbA1c between the two treatment groups. In contrast to this finding, study elsewhere [81, 82] reported that the mean decrease from baseline in HbA1c level was higher in the metformin-insulin treated groups. This discrepancy might have happened due to differences in study participants and other factors. In the current study, the proportion of patients who achieved the HbA1c target level (<7.0%) was similar in the two treatment groups at baseline, whereas, the proportion of patients in the metformin-sulfonylurea treatment group who achieved the HbA1c target level(<7.0%) was higher compared to those in the metformin-insulin treatment group after a median of 48 months follow-up. In contrast to this finding, an open-label RCT [70] showed metformin with insulin glargine was as effective as metformin with glimepiride in controlling hyperglycemia perhaps due to the different preparations of insulin used in both studies. Moreover, another study [81] showed the proportion of patients who achieved the HbA1c target level (<7.0%) was comparable among different combinations of antidiabetic medications; however, combination with intensified insulin therapy was the most effective treatment in achieving the HbA1c target of 6.5%. The higher proportion of patients in the metformin-sulfonylurea group who achieved the HbA1c target level might be due to the longer duration of follow-up and a greater number of participants attending regular physical exercises.

In the current study, there was no statistically significant difference in the reduction of FBS from the baseline value between the metformin-insulin and metformin-sulfonylurea treatment groups. However, studies conducted elsewhere [81,82] revealed a significant difference between the two treatment groups. This discrepancy might be attributed to the small sample size used in the current study and to the difference in the duration of follow-up. The American diabetes association standard of care guideline recommends that T2DM patient's FBS target should be

less than 130 mg/dl [80]. This study showed a non-significant difference in the proportion of patients having achieved FBS (<130.0 mg/dl) between the two treatment groups. However, another study [81] reported a significantly large proportion of patients in the insulin-based combination therapy achieved FBS <130.0mg/dl compared with patients in the oral combination therapy.

Obesity is one of the main risk factors for T2DM and representing a major worldwide health problem [83]. It aggravates the pancreatic β-cell failure, insulin resistance, and cardiovascular risk [84]. Lowering bodyweight is an indispensable part of T2DM management [83]. Both insulin (more pronounced) and sulfonylurea were associated with weight gain by reducing the amount of glucose excreted in the urine, which leads the tissue to reabsorb glucose and store it as fat [85]. Other evidences [37,38,42,70] also revealed that weight gain was significantly higher with insulin than sulfonylurea. In support of these evidences, the current study showed metformin-insulin combination therapy significantly increased from baseline in bodyweight compared with metformin-sulfonylurea combination therapy. A significant increase from baseline in BMI was also noted with metformin-insulin treatment group compared with metformin-sulfonylurea treatment group.

Lowering blood pressure is significantly important to reduce the risk of CVD and diabetes-related deaths. A 10mmHg reduction in SBP decreased the risk of major CVD events by 20% [86]. Compared with sulfonylureas, GLP-1 receptor agonists and SGLT-2 inhibitors added to metformin therapy significantly reduced SBP, and DBP from the baseline values [60-62, 87]. However, study elsewhere [88] reported there was no significant difference in pulse pressure, SBP, and DBP among different treatment groups. In support of the second evidence, the current finding showed no significant difference in reduction from baseline in SBP and DBP between the two treatment groups. In addition, this study revealed there was no statistically significant difference in the proportion of patients achieved the recommended target SBP and DBP goals between the two treatment groups.

Dyslipidemia is a well-known risk factor for CVD in individuals with T2DM [89]. Likewise, a cohort study [90] conducted elsewhere showed that patients with T2DM who had uncontrolled blood pressure, LDL-C, and HbA1c or with only their HbA1c at target, were at high risk of hospitalization due to CVD, whereas those with all three risk factors controlled or with blood

pressure and LDL-C at target had a lower risk of developing adverse cardiovascular events. Moreover, another evidence [49] showed that LDL-C decreased by 5% with the addition of metformin to sulfonylurea. In support of these evidence, the current study showed that metformin-sulfonylurea combination therapy significantly reduced LDL-C compared with metformin-insulin therapy (p<001). Another study [50] reported that patients treated with metformin-glibenclamide fixed dose combination for 6 months had reduced plasma HDL-C without changing in plasma triglyceride level. Another study elsewhere [70] reported that there was no significant difference in lipid profiles between insulin and sulfonylurea added on metformin therapy. In contrast to these findings, the present finding elucidated metformin-insulin combination therapy reduced HDL-C by 5mg/dl, while metformin-sulfonylurea combination therapy increased HDL-C by 5mg/dl from the baseline value (p=.004).

CVD is the most common macrovascular complication and a major cause of death in patients with T2DM [8,9]. An observational cohort study conducted elsewhere [91] showed patients with T2DM who were under metformin-insulin combination therapy were associated with an increased hazard of a composite of nonfatal cardiovascular outcomes and all-cause mortality compared with those who were under metformin-sulfonylurea combination therapy. Another retrospective cohort study [71-76] reported that T2DM patients who initiated basal insulin as a second or third-line therapy had an increased risk of all-cause mortality, cardiovascular disease and severe hypoglycemia compared with those who received the newer GLP-1 receptor agonists, SGLT-2 inhibitors and DPP-4 inhibitors. Action to control cardiovascular risk in diabetes trial [39] also showed that short-term intensive glycemic control with insulin therapy did not lower the risk of cardiovascular events. Similar to these findings, the present study showed that a significantly higher proportion of patients had composite cardiovascular outcomes in the metformin-insulin combination treatment group than metformin-sulfonylurea combination treatment group. A systematic review of RCTs [36] reported that there was no evidence towards improved all-cause mortality or cardiovascular mortality despite insulin being the preferred drug to add to metformin when HbA1c is markedly elevated. Moreover, RCTs of UKPDS [37] revealed that there was no difference in the rates of myocardial infarction or diabetes-related death between participants in sulphonylurea and insulin therapies. Inconsistent to these findings, the current study showed significantly higher proportion of patients under metformin-insulin combination therapy had myocardial infarction than in those under metformin-sulfonylurea

combination therapy. However, there was no significant difference in the proportion of patients who had stroke and heart failure between the two treatment groups. On the contrary, another study [29, 32] reported that switching to sulfonylureas as second-line drugs have been associated with an increased risk of myocardial infarction, all-cause mortality, and severe hypoglycemia compared with remaining on metformin monotherapy. More clinical trials should be conducted as there are conflicting results, and the choice of second-line antidiabetic medication should be individualized.

Diabetic retinopathy is the most common microvascular complication of diabetes [92]. It is the leading cause of visual impairment and blindness in the populations aged 20–74 years as well as in diabetic patients worldwide, and it may affect up to 60% of T2DM patients [93]. A study reported elsewhere [94] indicates that the prevalence of diabetic retinopathy has sharply increased as the HbA1c level increased. A meta-analysis conducted in Sub-Saharan Africa [95] showed that the prevalence of diabetic nephropathy was 41.4% in patients with T2DM. Another study conducted elsewhere [96] showed that treatment with sulfonylurea was associated with an increased incidence of microvascular complications, especially neuropathy and retinopathy, compared to treatment with vildagliptin. The low prevalence of microvascular complications observed in the current study might be attributed to poor diagnosis and underreporting of cases. Compared with metformin-sulfonylurea combination therapy, metformin-insulin combination therapy was more likely associated with diabetic neuropathy and diabetic retinopathy. However, the proportion of patients with diabetic nephropathy were similar in the two treatment groups.

In the current study, many patients in the metformin-insulin treatment group were more likely to take diuretics, angiotensin receptor blockers, beta-blockers, and lipid-lowering agents compared with those in the metformin-sulfonylurea treatment group. This might be associated to the high prevalence of hypertension, dyslipidemia, and composite cardiovascular outcomes in the metformin-insulin treatment group. In contrast to this study, a retrospective cohort study [97] reported that women with T2DM and CVD were more likely to be obese, hypertensive, and have hypercholesterolemia, but were less likely to take statins and angiotensin-converting enzyme inhibitors.

Many studies [32, 37, 38, 42, 48] have identified patients who were treated with insulin and/ or sulfonylurea had experienced hypoglycemia. Another study elsewhere [98] reported that

prolonged use of both insulin and sulfonylurea may significantly contribute to a greater incidence of hypoglycemia in patients with coronary artery disease. Hypoglycemia affects the cascade of pathophysiology by inducing adrenergic activation and oxidative stress which may lead to worsening of the cardiovascular risk, arrhythmias, and ischemia [99]. In the current study, patients treated with metformin-insulin combination were more likely to take beta blockers which may affect the incidence of hypoglycemia. Despite the different glycemic achievements, similar prevalence of hypoglycemic adverse events was illustrated between the two treatment groups. A higher episode of hypoglycemia was reported in insulin-treated patients [37]. However, this study showed a similar episode of hypoglycemia between groups.

6. Limitations of the study

This study reported important information about glycemic control, cardiovascular risk factors and composite cardiovascular outcomes of metformin-insulin versus metformin-sulfonylurea combination therapies. The study had also many strengths, most importantly it had predefined eligibility criteria for study participants, it was conducted in randomly selected two specialized and three general hospitals which could avoid selection bias. Moreover, the data were collected in a mixed approach from the patient through interviewing and reviewing their medical records which could help the study have detailed information about the participants. However, this study didn't address the different sulfonylurea drugs and doses. In fact, the most prescribed sulfonylurea as add on to metformin was glibenclamide in the study settings. Another limitation of the study was that some data were incomplete in the patient's medical record which might have affected the result of the analysis and which might lead to underreporting of adverse events like hypoglycemia. One more limitation was the small sample size of the study which may lack representative of the general population.

7. Conclusion

From the present study, it can be concluded that metformin-sulfonylurea combination therapy could benefit many patients by helping them achieve target HbA1c level (< 7%) compared to metformin-insulin. Moreover, metformin-sulfonylurea combination therapy could also reduce many of cardiovascular risk factors and composite cardiovascular outcomes compared to metformin-insulin. More clinical trials, however, have to be conducted to confirm the present finding.

8. Recommendation

Based on the finding of this study, it is possible to recommend that flexibility in choosing a second-line drug should be personalized based on efficacy, risk of hypoglycemia, the patient's comorbid conditions, impact on weight, adverse effects, and cost. The present findings should be interpreted cautiously and call for clinical trials comparing the glycemic control, cardiovascular risk factor control, composite cardiovascular outcomes, and overall cost effectiveness and benefits of metformin-insulin versus metformin-sulfonylurea combination therapies in T2DM.

References

1. International Diabetes Federation. IDF diabetes atlas: 9th ed. Brussels, Belgium: International Diabetes Federation, 2019. Available at https://diabetesatlas.org/en/resources/.
2. Williams R, Karuranga S, Malanda B, *et al*. Global and regional estimates and projections of diabetes-related health expenditure: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2020:108072 [Epub ahead of print].
3. Merino J, Guasch-Ferré M, Ellervik C, *et al*. Quality of dietary fat and genetic risk of type 2 diabetes: individual participant data meta-analysis. *BMJ*. 2019;366:l4292. doi: 10.1136/bmj.l4292.
4. Vujosevic S, Aldington SJ, Silva P, *et al*. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol*. 2020, Epub ahead of print. https://doi.org/10.1016/S2213-8587(19)30411-5
5. Maddaloni E, Coleman RL, Agbaje O, *et al*. Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86). *Lancet Diabetes Endocrinol*. 2020;8(3):206-215.
6. Zweck E, Westenfeld R, Szendroedi J. Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;381(21):2075-2076.
7. Asrih M, Gariani K. Impact of SGLT inhibitors on multiple organ defects in diabetes. *Curr Diabetes Rev*. 2019 [Epub ahead of print].
8. Cosentino F, Ceriello A, BaeresFMM, *et al*. Addressing cardiovascular risk in type 2 diabetes mellitus: a report from the European Society of Cardiology Cardiovascular Roundtable. *Eur Heart J*. 2019;40(34):2907-19.
9. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med*. 2019;381(14):1309-1320.
10. Bellary S, Tahrani AA, Barnett AH. Evidence-based prescribing of diabetes medications: are we getting closer? *Lancet Diabetes Endocrinol*. 2020;8(3):176-177.
11. Whyte MB, Hinton W, McGovern A, *et al*. Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: A retrospective cohort analysis. *PLoS Med*. 2019;16(10):e1002942.

12. Manne-Goehler J, Geldsetzer P, Agoudavi K, *et al*. Health system performance for people with diabetes in 28 low- and middle-income countries: A cross-sectional study of nationally representative surveys. *PLoS Med*. 2019;16(3):e1002751.
13. Huang Z, Lum E, Jimenez G, *et al*. Medication management support in diabetes: a systematic assessment of diabetes self-management apps. *BMC Med*. 2019;17(1):127.
14. Sattar N. Advances in the clinical management of type 2 diabetes: a brief history of the past 15 years and challenges for the future. *BMC Med*. 2019;17(1):46.
15. American Diabetes Association. Standards of Medical Care in Diabetes-2019: Abridged for primary care providers. *Clin Diabetes*. 2019;37(1):11-34.
16. Petrie JR, Rossing PR, Campbell IW. Metformin and cardiorenal outcomes in diabetes: A reappraisal. *Diabetes Obes Metab*. 2020 [Epub ahead of print].
17. Blümel JE, Arteaga E, Aedo S, *et al*. Metformin use is associated with a lower risk of osteoporosis in adult women independent of type 2 diabetes mellitus and obesity. REDLINC IX study. *Gynecol Endocrinol*. 2020 :1-5 [Epub ahead of print].
18. Shuai Y, Li C, Zhou X. The effect of metformin on gastric cancer in patients with type 2 diabetes: a systematic review and meta-analysis. *Clin Transl Oncol*. 2020 [Epub ahead of print]
19. Zhou J, Ke Y, Lei X, *et al*. Meta-analysis: The efficacy of metformin and other anti-hyperglycemic agents in prolonging the survival of hepatocellular carcinoma patients with type 2 diabetes. *Ann Hepatol*. 2019 [Epub ahead of print].
20. Zhang K, Yang W, Dai H, *et al*. Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: Results from meta-analysis. *Diabetes Res Clin Pract*. 2020;160:108001.
21. Tseng CH. Metformin use is associated with a lower risk of uterine leiomyoma in female type 2 diabetes patients. *Ther Adv Endocrinol Metab*. 2019;10:2042018819895159.
22. Powell MK, Cempirkova D, Dundr P, *et al*. Metformin Treatment for Diabetes Mellitus Correlates with Progression and Survival in Colorectal Carcinoma. *Transl Oncol*. 2020;13(2):383-392.
23. Sharma M, Beckley N, Nazareth I, *et al*. Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis. *BMJ Open*. 2017;7(10):e017260.

24. Foroutan N, Muratov S, Levine M. Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: Systematic review and meta-analysis. *Clin Invest Med*. 2016;39(2): E48-62.
25. Filion KB, Douros A, Azoulay L, *et al*. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: A population-based cohort study. *Br J Clin Pharmacol*. 2019;85(10):2378-2389.
26. Cheng PC, Hsu SR, Kuo JF, *et al*. Comparing the Effect of Dipeptidyl-Peptidase 4 Inhibitors and Sulfonylureas on Albuminuria in Patients with Newly Diagnosed Type 2 Diabetes Mellitus: A Prospective Open-Label Study. *J Clin Med*. 2019;8(10).
27. Laires P, Kurtyka K, Witt EA, *et al*. Factors associated with physicians' decision to discontinue or down-titrate sulfonylureas for type 2 diabetes patients. *Expert Rev Pharmacoecon Outcomes Res*. 2019;19(1):71-79.
28. McGowan LD, Roumie CL. Sulfonylureas as second line treatment for type 2 diabetes. *BMJ*. 2018;362:k3041.
29. Douros A, Dell'Aniello S, Yu OHY, *et al*. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population-based cohort study. *BMJ*. 2018;362:k2693.
30. Whitlock RH, Hougen I, Komenda P, *et al*. A Safety Comparison of Metformin vs Sulfonylurea Initiation in Patients with Type 2 Diabetes and Chronic Kidney Disease: A Retrospective Cohort Study. *Mayo Clin Proc*. 2020;95(1):90-100.
31. Mekuria AN, Ayele Y, Tola A, *et al*. Monotherapy with Metformin versus Sulfonylureas and Risk of Cancer in Type 2 Diabetic Patients: A Systematic Review and Meta-Analysis. *J Diabetes Res*. 2019;2019:7676909.
32. Ke C, Morgan S, Smolina K, *et al.* Mortality and Cardiovascular Risk of Sulfonylureas in South Asian, Chinese and Other Canadians with Diabetes. *Can J Diabetes*. 2017;41(2):150-155.
33. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S90.
34. Davies MJ, D'Alessio DA, Fradkin J, *et al.* Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the

European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669. Epub 2018 Oct 4.

35. Henry RR, Gumbiner B, Ditzler T, *et al.* Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care*. 1993;16(1):21.
36. Hemmingsen B, Christensen LL, Wetterslev J, *et al*. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. *BMJ*. 2012;344:e1771. Epub 2012 Apr 19.
37. UK Prospective Diabetes Study 9UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352: 837–53.
38. Erpeldinger S, Rehman MB, Berkhout C, *et al*. Efficacy and safety of insulin in type 2 diabetes: meta-analysis of randomised controlled trials. *BMC Endocrine Disorders*. 2016; 16:39.
39. Beigi FI. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial - Clinical implications. *Clinical Chemistry*. 2011; 57:261–263.
40. Carracher AM, Marathe PH, and Close KL. International Diabetes Federation 2017. *Journal of diabetes*. 2018; 10:353–356. doi: 10.1111/1753-0407.12644.
41. Giugliano D, Maiorino MI, Bellastella G, Esposito K. Glycemic control in type 2 diabetes: from medication nonadherence to residual vascular risk. *Endocrine*. 2018; 61:23-27.
42. Ghotbi AA, Køber L, Finer N, *et al*. Association of Hypoglycemic Treatment Regimens with Cardiovascular Outcomes in Overweight and Obese Subjects with Type 2 Diabetes *Diabetes Care*. 2013; 36:3746–3753.
43. Madsen KS, Kähler P,Kähler LK, *et al*. Metformin and second or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2019;4:CD012368.
44. van Baar MJ, van Ruiten CC, Muskiet MH, *et al*. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. *Diabetes Care*. 2018;41(8):1543-56.
45. Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. Waltham MA Up To Date. 2018.

46. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *European heart journal*. 2015;36(34):2288-96.
47. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet*. 1998;352(9131):854-65.
48. Eriksson JW, BodegardJ, Nathanson D, *et al*. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes research and clinical practice*. 2016; 117:39-47.
49. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care*. 2004;27(1):141-7.
50. Comaschi M, Corsi A, Di Pietro C, Bellatreccia A, Mariz S. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. *Nutrition, Metabolism and Cardiovascular Diseases*. 2008;18(5):373-9.
51. Palmer SC, Mavridis D, Nicolucci A, *et al*. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *Jama*. 2016;316(3):313-24.
52. Gallwitz B, Rosenstock J, Rauch T, *et al*. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *The Lancet*. 2012;380(9840):475-83.
53. Kim KJ, Choi J, Lee J, *et al*. Dipeptidyl peptidase-4 inhibitor compared with sulfonylurea in combination with metformin: cardiovascular and renal outcomes in a propensity-matched cohort study. *Cardiovascular diabetology*. 2019;18(1):28.
54. Santamarina M, Carlson CJ. Review of the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and the clinical relevance of the CAROLINA trial. *BMC cardiovascular disorders*. 2019;19(1):60.
55. Charokopou M, McEwan P, Lister S, *et al*. The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. *Diabetic Medicine*. 2015;32(7):890-8.

56. Ridderstråle M, Rosenstock J, Andersen KR, *et al*. Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial. *Diabetes, Obesity and Metabolism*. 2018;20(12):2768-77.
57. Scheen AJ. The safety of empagliflozin plus metformin for the treatment of type 2 diabetes. *Expert opinion on drug safety*. 2018;17(8):837-48.
58. Lavalle-González FJ, Januszewicz A, Davidson J, *et al*. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013;56(12):2582-92.
59. Wilkinson S, Williamson E, Pokrajac A, *et al.* Comparative effects of sulphonylureas, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UK primary care. *Diabetes, Obesity and Metabolism*. 2020.
60. Brady EM, Davies MJ, Gray LJ, *et al*. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: The Treat 4 Ramadan Trial. *Diabetes, Obesity and Metabolism*. 2014;16(6):527-36.
61. Gu J, Meng X, Guo Y, *et al*. The efficacy and safety of liraglutide added to metformin in patients with diabetes: a meta-analysis of randomized controlled trials. *Scientific reports*. 2016;6:32714.
62. Deacon CF, Mannucci E, Ahrén B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes—a review and meta-analysis. *Diabetes, obesity and metabolism*. 2012;14(8):762-7.
63. Vaccaro O, Masulli M, Nicolucci A, *et al*. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA. IT): a randomized, multicenter trial. *The lancet Diabetes & endocrinology*. 2017;5(11):887-97.
64. Home PD, Pocock SJ, Beck-Nielsen H, *et al*. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. *The Lancet*. 2009;373(9681):2125-35.

65. Joshi SR, Ramachandran A, Chadha M, *et al*. Acarbose plus metformin fixed-dose combination in the management of type 2 diabetes. *Expert Opin Pharmacother*. 2014; 15:1611-20.
66. Hsu PF, Sung SH, Cheng HM, *et al*. Cardiovascular Benefits of Acarbose vs Sulfonylureas in Patients with Type 2 Diabetes Treated with Metformin. *J Clin Endocrinol Metab*. 2018;103(10):3611–3619.
67. Fang H, Xu F, Du J, *et al*. Impact of baseline characteristics on glycemic effects of add-on saxagliptin or acarbose to metformin therapy: subgroup analysis of the SMART study in Chinese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2020;doi:10.1111/jdi.13224.
68. Holman RR, Coleman RL, Chan JCN, *et al*. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(11):877–886.
69. Zhu J, Xiaoxia Yu X, Yayuan Zheng Y, *et al*. Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map. *Lancet Diabetes Endocrinol*. 2020; 8:192–205.
70. Moon JS, Ha KS, Yoon JS, *et al*. The effect of glargine versus glimepiride on pancreatic ß-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. *Acta Diabetol*. 2014; 51:277-85. DOI 10.1007/s00592-013-0553-z.
71. O'Brien MJ, Karam SL, Wallia A, *et al*. Association of Second-line Antidiabetic Medications with Cardiovascular Events Among Insured Adults with Type 2 Diabetes. *JAMA Network Open*. 2018;1(8):e186125. doi:10.1001/jamanetworkopen.2018.6125.
72. Aroda VR, Bain SC, Cariou B, *et al*. Efficacy and Safety of Once-Weekly Semaglutide Versus Once-Daily Insulin Glargine as Add-On to Metformin (with or without sulfonylureas) in Insulin-Naive Patients with Type 2 Diabetes (SUSTAIN 4): A Randomised, Open-Label, Parallel-Group, Multicenter, Multinational, Phase 3a Trial. *Lancet Diabetes Endocrinol*. 2017;5:355-366.DOI: 10.1016/S2213-8587(17)30085-2

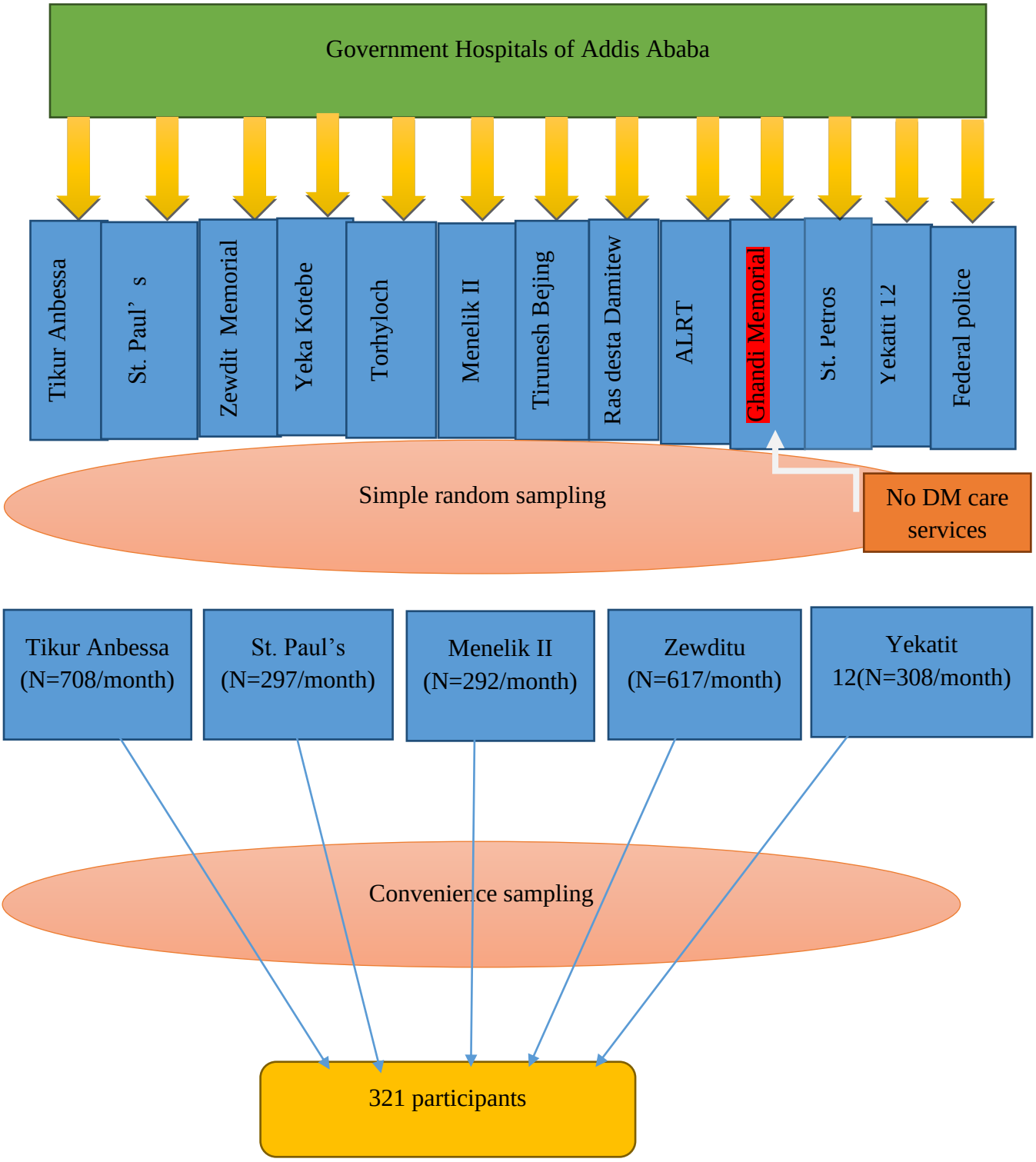
73. Anyanwagu U, Mamza J, Mehta R, *et al*. Cardiovascular Events and All-Cause Mortality with Insulin Versus Glucagon-Like peptide-1 Analogue in Type 2 Diabetes. *Heart*. 2016; 102: 1581-7.DOI: 10.1136/heartjnl-2015-309164.
74. Jil M, Rajnikant M, Richard D, *et al*. The Effects of Dual-Therapy Intensification with insulin or dipeptidylpeptidase-4 Inhibitor on Cardiovascular Events and All-Cause Mortality in Patients With Type 2 Diabetes: A Retrospective Cohort Study. *Diab Vasc Dis Res*. 2017;14:295-303. DOI: 10.1177/1479164116687102.
75. Mogensen UM, Andersson C, Fosbøl EL, *et al*. Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study. *Diabetologia*. 2015; 58:50-58. DOI 10.1007/s00125-014-3372-z.
76. Nystrom T, Bodegard J, Nathanson D, *et al*. Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycemia. *Diabetes Research and Clinical Practice*. 2017; 123:199-20.
77. Central Statistical Agency [Ethiopia] and ICF International. Ethiopia Demographic and Health Survey 2011. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ICF International. 2012.
78. Sibhat SG, Fenta TG, Sander B, Gebretekle GB. Health-related quality of life and its predictors among patients with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Health and quality of life outcomes. 2019;17(1):165.
79. Federal ministry of health. Health and Health Related Indicators. Addis Ababa, Ethiopia. Policy Plan Monitoring and Evaluation Directorate, Ministry of health, 2011.
80. American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2020;41(Suppl 1):S55-S64. doi:10.2337/dc18-S006.
81. Choi SH, Oh TJ, Jang HC. Comparison of Antidiabetic Regimens in Patients with Type 2 Diabetes Uncontrolled by Combination Therapy of Sulfonylurea and Metformin: Results of the MOHAS Disease Registry in Korea. *Diabetes Metab J*. 2017;41(3):170-178. doi:10.4093/dmj.2017.41.3.170.

82. Gitt AK, Bramlage P, Schneider S, Tschöpe D. A real world comparison of sulfonylurea and insulin vs. incretin-based treatments in patients not controlled on prior metformin monotherapy. *Cardiovasc Diabetol*. 2015; 14:13. doi:10.1186/s12933-015-0172-9.
83. Apovian CM, Okemah J, O'Neil PM. Body Weight Considerations in the Management of Type 2 Diabetes. *Adv Ther*. 2019;36(1):44-58. doi:10.1007/s12325-018-0824-8.
84. Cheng V, Kashyap SR. Weight considerations in pharmacotherapy for type 2 diabetes. *J Obes*. 2011; 2011:984245. doi:10.1155/2011/984245.
85. Sola D, Rossi L, Schianca GP, *et al.* Sulfonylureas and their use in clinical practice. *Arch Med Sci*. 2015;11(4):840-848. doi:10.5114/aoms.2015.53304.
86. Ettehad D, Emdin CA, Kiran A, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8.
87. Chen Z, Li G. Sodium-Glucose Co-Transporter 2 Inhibitors Compared with Sulfonylureas in Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Meta-Analysis of Randomized Controlled Trials. *Clin Drug Investig*. 2019;39(6):521-531. doi:10.1007/s40261-019-00781-w.
88. Alemi H, Khaloo P, Mansournia MA, *et al*. Pulse pressure and diabetes treatments: Blood pressure and pulse pressure difference among glucose lowering modality groups in type 2 diabetes. *Medicine (Baltimore)*. 2018;97(6): e9791. doi:10.1097/MD.0000000000009791.
89. American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019;42(Suppl1):S103-S123. doi:10.2337/dc19-S010.
90. Nichols GA, Joshua-Gotlib S, Parasuraman S. Independent contribution of A1C, systolic blood pressure, and LDL cholesterol control to risk of cardiovascular disease hospitalizations in type 2 diabetes: an observational cohort study. *J Gen Intern Med*. 2013;28(5):691-697. doi:10.1007/s11606-012-2320-1.
91. Roumie CL, Greevy RA, Grijalva CG, *et al*. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. *JAMA*. 2014;311(22):2288-2296. doi:10.1001/jama.2014.4312

92. Fowler M. Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*. 2011; 29(3):116–122. doi: 10.2337/diaclin.29.3.116.
93. Zhao C, Wang W, Xu D, *et al*. Insulin and risk of diabetic retinopathy in patients with type 2 diabetes mellitus: data from a meta-analysis of seven cohort studies. *Diagn Pathol*. 2014; 9:130. Published 2014 Jun 27. doi:10.1186/1746-1596-9-130.
94. Zhang R, Li Y, Zhang S, *et al*. The Association of Retinopathy and Plasma Glucose and HbA1c: A Validation of Diabetes Diagnostic Criteria in a Chinese Population. *J Diabetes Res*. 2016; 2016:4034129. doi:10.1155/2016/4034129.
95. Wagnew F, Eshetie S, Kibret GD, *et al*. Diabetic nephropathy and hypertension in diabetes patients of sub-Saharan countries: a systematic review and meta-analysis. *BMC Res Notes*. 2018;11(1):565. doi:10.1186/s13104-018-3670-5.
96. Kolaczynski WM, Hankins M, Ong SH, *et al*. Microvascular Outcomes in Patients with Type 2 Diabetes Treated with Vildagliptin vs. Sulfonylurea: A Retrospective Study Using German Electronic Medical Records. *Diabetes Ther*. 2016;7(3):483-496. doi:10.1007/s13300-016-0177-8.
97. Wright AK, Kontopantelis E, Emsley R, *et al*. Cardiovascular Risk and Risk Factor Management in Type 2 Diabetes Mellitus. *Circulation*. 2019;139(24):2742-2753. doi:10.1161/CIRCULATIONAHA.118.039100.
98. Grenier J, Leiter LA, Langer A, *et al*. Glycaemic control and cardiovascular risk factor management in patients with diabetes with and without coronary artery disease: insights from the diabetes mellitus status in Canada survey. *Eur Heart J Qual Care Clin Outcomes*. 2016;2(4):277-284. doi:10.1093/ehjqcco/qcw013.
99. Connelly KA, Yan AT, Leiter LA, *et al*. Cardiovascular Implications of Hypoglycemia in Diabetes Mellitus. *Circulation*. 2015;132(24):2345-2350. doi:10.1161/CIRCULATIONAHA.115.015946.

Appendixes

Appendix 1:Schematic representation of sampling procedure of T2DM patients in governmental hospitals of Addis Ababa (N=321)



Appendix 2: Participant's information sheet

Title of the study: Metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes: a comparative study of glycemic control and risk of cardiovascular diseases in Addis Ababa, Ethiopia

Principal investigator: Desye Gebrie (Bpharm, MSc)

Principal investigator's institution:

1. Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, Ethiopia
2. School of pharmacy, College of Health Sciences, Mekelle University, Ethiopia

Sponsors: Ministry of Education

Introduction: Greeting! I'm_____. Mr. Desye Gebrie, a post graduate student at Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa, is conducting a research as required for his Master's Degree in clinical trials. You are invited to participate in this research study because you are taking combination therapy for treatment of type 2 diabetes mellitus.

The aim of the research is to compare glycemic control and risk of cardiovascular outcomes of metformin with insulin versus metformin with sulfonylurea therapy in type 2 diabetes mellitus patients in governmental hospitals of Addis Ababa. Your participation would be very valuable, and I will be very grateful if you can assist me by providing the information asked by the data collector and if you allow the data collector to review your medical follow-up chart. Any information collected from you and your medical follow-up chart will remain confidential. Your participation is voluntary and you are not obliged to give information which you don't want to share with us. Whether you participate or not participate in this study, there will not be any consequence on your treatment. It is important that you understand why the research is being done. Please take your time to read or listen through and consider this information carefully before you decide if you are willing to participate. Ask the study data collector if anything is unclear or if you would like more information.

This study has been approved by Scientific and Ethics Review Committee of Addis Ababa University Collage of Health Sciences CDT-Africa, St. Paul's Hospital Millennium Medical College, Yekatit 12 Hospital Medical College and Addis Ababa Regional Health Bureau. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign the informed consent form.

Thank you very much for your time!

Appendix 3: Participant's informed consent form

Title of Study: "Metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes: a comparative study of glycemic control and risk of cardiovascular diseases in Addis Ababa, Ethiopia"

By signing below, I confirm the following:

- I have been given oral and written information for the above study and have read/listen and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I'm not oblige to give information which I don't want to share and this will in no way affect my future treatment.
- I understand that study data collector has interviewed me and direct access to my medical records.
- I understand that my personal details will be treated as confidential.
- I understand that this study has been approved by Scientific and Ethics Review Committee of Addis Ababa University Collage of Health Sciences CDT-Africa, St. Paul's Hospital Millennium Medical College, Yekatit 12 Hospital Medical College, and Addis Ababa Regional Health Bureau.
- I understand the risks and benefits, and I freely give my informed consent to participate under the conditions stated.
- I have received a copy of this informed consent form signed and dated to bring home.

Participant

Name:_____ Signature: _____Date:_____

Impartial witness (if the participants unable to read and write)

Name: _____Signature: _____Date: _____

Data collector

Name: _____ Signature: _____Date: _____

Appendix 4: Data collection tools

I. Socio-demographic characteristics of the study participant	Response
A. Participant's card number	
B. Age of participant (years)	
C. Height (meter)	
D. Gender	☐ Male ☐ Female
E. Residence	☐ Addis Ababa ☐ Out of Addis Ababa
F. Marital status	☐ Single ☐ Married ☐ Divorced ☐ Widower/widowed
G. Level of education	☐ Unable to read & write ☐ Primary ☐ Secondary ☐ Preparatory ☐ College/University
H. Have you ever attained health education	☐ Yes ☐ No
I. Family history of diabetes mellitus	☐ Yes ☐ No
J. Smoking habit	☐ Current smoke ☐ Not smoker
K. Alcohol consumption	☐ Yes ☐ No
L. Chat chewing habit	☐ Yes ☐ No
M. Daily vegetable & fruit consumption	☐ Yes ☐ No
N. Daily salt use (tea spoon)	
O. Regular physical exercise	☐ Yes ☐ No
P. Weekly physical exercise (minutes)	
Q. Co-morbidities	☐ Yes ☐ No
R. Number of comorbidities	
II. Efficacy assessment and clinical characteristics of study participants	**Response**
A. Type of antidiabetic treatment	☐ Metformin with insulin ☐ Metformin with SUs
B. Duration of treatments (month)	
C. Baseline bodyweight before treatment (kg)	
D. Bodyweight after treatment (kg)	
E. Baseline HbA1c before treatment (%)	
F. HbA1c after treatment (%)	
G. Baseline fasting blood sugar level before treatment (mg/dl)	
H. Fasting blood sugar after treatment (mg/dl)	
I. Baseline systolic blood pressure before treatment (mmHg)	
J. Systolic blood pressure after treatment (mmHg)	

K. Baseline diastolic blood pressure before treatment (mmHg)	
L. Diastolic blood pressure after treatment (mmHg)	
M. Baseline high density lipoprotein cholesterol before treatment (mg/dl)	
N. High density lipoprotein cholesterol after treatment (mg/dl)	
O. Baseline low density lipoprotein cholesterol before treatment (mg/dl)	
P. Low density lipoprotein cholesterol after treatment (mg/dl)	
Q. Baseline cholesterol total before treatment (mg/dl)	
R. Cholesterol total after treatment (mg/dl)	
S. Baseline total triglycerides before treatment (mg/dl)	
T. Total triglycerides after treatment (mg/dl)	
U. Composite cardiovascular outcomes after treatment	☐Yes ☐No
V. If yes, type of composite cardiovascular outcomes	☐Myocardial infarction ☐Stroke ☐Heart failure ☐Hypertension ☐Dyslipidemia
W. Microvascular complications	☐Diabetic neuropathy ☐Diabetic retinopathy ☐Diabetic nephropathy
X. Concomitant medication use	☐Yes ☐No
Y. If yes, type of concomitant medication	☐Diuretics ☐ACEIs ☐ARBs ☐BBs ☐CCBs ☐Statins ☐Others----------
III. Safety assessment	**Response**
A. Have you ever experienced antidiabetic treatment emergent adverse events?	☐Yes ☐No
B. If yes, what type of adverse events have you experienced?	1._____ 2._____ 3._____ 4. _____
C. Have you ever experienced hypoglycemic adverse events?	☐Yes ☐No
D. If yes, average episode of hypoglycemic adverse events per month	
IV. Adherence and cost related questionnaires	**Response**
A. Have you ever missed your antidiabetic drugs?	☐Yes ☐No
B. If yes, what was the reason for missing the dose?	☐ Forgetting ☐Feeling better ☐Feeling worse ☐Unable to afford drug price ☐Others----------
C. Source of your antidiabetic drugs	☐Free ☐Paid
D. If you paid, how much birr do you spend for your antidiabetic medications per month	