ORIGINAL RESEARCH

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

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Objective: This study aimed to compare glycemic control and risk of cardiovascular outcomes of metformin-insulin versus metformin-sulfonylurea combination therapies in type 2 diabetes mellitus.

Methods: We conducted a comparative cross-sectional study in five tertiary level hospitals in Addis Ababa, Ethiopia. We enrolled 321 patients with type 2 diabetes mellitus who were on continuous treatment follow-up on either metformin-insulin or metformin-sulfonylurea combination therapy. We interviewed the participants and reviewed their medical records to investigate medication efficacy, safety, and adherence. The primary outcome measure was glycemic control and the secondary outcome measures were composite cardiovascular outcomes.

Results: Of the total participants enrolled, 50.5% (n = 162) were those who received metformin-insulin and 49.5% (n = 159) metformin-sulfonylurea combination therapies for a median of 48 months follow-up. The reduction of Hb1Ac levels was comparable between the metformin-insulin ($-1.04 \pm 0.96\%$) and metformin-sulfonylurea ($-1.02 \pm 1.03\%$), p = 0.912. Patients who received metformin-sulfonylurea had 4.3 times more likely to have achieved target HbA1c level compared to those who received metformin-insulin, $p < 0.001$, adjusted odds ratio (AOR) with 95% CI = 4.31[1.79–10.32]. Risk of composite cardiovascular outcomes was higher in metformin-insulin group (40.5% versus 34.0%), $p = 0.021$. Co-morbidities, body mass index, systolic blood pressure, and HbA1c had a significant association with composite cardiovascular outcomes. Reductions of bodyweight, HDL-C, LDL-C, triglycerides levels, and microvascular complications were different between the two groups, $p < 0.05$.

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)

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Introduction

Diabetes mellitus (DM) is one of the top ten causes of mortality and the fastest growing health emergencies of the 21st century, with 463 million people living with it worldwide in 2019, and this number is projected to reach 578 million by 2030 and 700 million by 2045.[1] The estimated global direct health expenditure on DM 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 complicated form of the disease and accounts for more than 90% of the estimated cases of DM, affecting 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.[4–6] Cardiovascular disease (CVD) is a common complication and a major cause of death in patients with T2DM.[7,8]

Inspite of the introduction of new medicines, treating patients with DM tend to become more challenging due to the progressive nature of the disease.[9,10] The American Diabetes Association recommends lifestyle modification as the first step in treating new-onset T2DM patients.[11] However, to achieve and maintain patient-specific glycemic targets, the majority of patients require glucose-lowering medications. Nowadays, Metformin is the first-line and commonly used pharmacological drug for patients with T2DM because of its potential advantages, including cardioprotective effect, reduction of weight, and prevention of some comorbid diseases.[11–14] If lifestyle modifications and a maximal tolerated dose of metformin therapy fail to achieve the patient's glycemic target within three months follow-up, the regimen would be changed to combination therapy.[11]

Metformin and sulfonylureas are the most commonly used combination therapy in treating T2DM.[15,16] Sulfonylureas are recommended as second-line treatment regimen in the management of T2DM, while they are still widely used also as a first-line treatment instead of metformin.[17] However, treating T2DM patients with a sulfonylureas rather than metformin is associated with a high risk of ischaemic stroke, cardiovascular death, hypoglycemia, and all-cause mortality.[17–20] Besides, the use of sulfonylurea as a 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 sulfonylurea appears to be safer than switching to another drug.[21] Such findings led to new requirements from licensing authorities that all new T2DM therapies should show cardiovascular safety.[9]

Insulin is one of the second-line antidiabetic drug for the treatment of T2DM patients who failed initial metformin monotherapy and lifestyle interventions.[22,23] Though 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.[24] 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 and diabetes-related death among participants assigned to sulphonylurea and insulin therapies.[25] 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.[26] 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 have become high.[27]

American Diabetes Association's current standard of care recommends that newly diagnosed T2DM patients whose HbA1c level ≥8.5% should start a combination treatment either metformin with insulin or metformin with sulfonylureas.[11] However, there is no clear evidence that shows the relative advantages of either metformin-insulin or metformin-sulfonylurea combination on major treatment outcomes.[28] With guidelines moving away from a one-size-fits-all approach and allowing flexibility in choosing a second- or third-line drug, keen individualized medication based on efficacy, risk of hypoglycemia, patient's comorbid conditions, impact on weight, adverse effects, and cost, management in T2DM has become a -challenge.[29,30] 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 been studied yet. Although most of T2DM patients require combination therapy, the choice of an appropriate second-line drug is a critical issue for the prevention of CVD. Therefore, this study aimed to compare glycemic control and risk of cardiovascular outcomes of metformin-insulin versus metformin-sulfonylureas combination therapies in patients with T2DM.

Methods
Study Design
A comparative cross-sectional study was conducted by reviewing T2DM patient's medical records retrospectively

with the support of prospective patients' interviews from December 2019 to March 2020.

Participants

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

Inclusion and Exclusion Criteria

Volunteers who were ≥18 years old with continuous medical records and continuous follow-up either on metformin with insulin or metformin with sulfonylurea combination therapies were eligible. In terms of exclusion criteria, patients with a history of cardiovascular disease (myocardial infarction, stroke, peripheral vascular disease) before the initiation of the combination therapies, those either on monotherapy or triple therapy of antidiabetic drugs, and those with less than three months of follow-up with the combination therapies were, however, excluded from the study.

Sample Size and Study Area

The required sample size was determined using a 50% estimated proportion of T2DM patients who achieved their HbA1c target less than 7%.[27] P = 0.5 and w = 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⇒ 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 as a result, we considered a sample size of 321. We included five tertiary-level governmental hospitals, which were Tikur Anbessa Specialized, St Paul's Specialized, Yekatit 12, Menelik II, and Zewditu Memorial Hospitals. We used a simple random sampling method to select the study sites. The average monthly T2DM patients' load was retrieved from the health information management system office of each hospital. 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.

Outcomes

The primary outcome measure was glycemic control (reduction in HbA1c level). The secondary outcome measures were composite cardiovascular outcomes (myocardial infarction, stroke, heart failure), hypertension, dyslipidemia,

microvascular complications (diabetic neuropathy, retinopathy, and nephropathy), treatment-emergent adverse events (hypoglycemia), and change in bodyweight, blood pressure, fasting blood sugar (FBS) and lipid profiles (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides).

Statistical Analysis

Statistical analyses were carried out using SPSS version 25. Data were expressed as median [interquartile range (IQR)] 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 analyses were done to assess factors associated with glycemic target level and composite cardiovascular outcomes. The results of the analyses were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis with a *p*-value <0.05 was considered statistically significant.

Ethical Considerations

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) and Institutional Review Board of 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. Consent was obtained from participants using approved and locally translated informed consent form. Patients were informed about the details of the study, including the general over view, purpose of the study and risk and benefits, and confidentiality was maintained at all stages of the study. This study was conducted in accordance with the Declaration of Helsinki.

Results
Sociodemographic Characteristics of Study Participants

A total of 321 participants with T2DM were enrolled in the study, of whom 50.5% (n = 162) received

metformin-insulin combination therapy and 49.5% (n = 159) received metformin-sulfonylurea combination therapy. Among the participants, 43.9% (n = 141) 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 < 0.001). The 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 = 0.029). Of the study participants, 60.7% (n = 195) attended regular weekly physical exercise (Table 1).

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 than patients in the metformin-sulfonylurea therapy (36 (12–60) months

Table 1 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%)	<0.001
Age (years)	Mean ± SD	59.45±10.86	58.14±9.89	60.78±11.65	0.029
Residence					0.628
	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					0.055
	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					0.004
	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%)	0.501
Family history of DM	Yes	133 (41.4%)	80 (24.9%)	53 (16.5%)	0.005
Smoking habit	Current smoker	21 (6.5%)	6 (1.9%)	15 (4.7%)	0.043
Alcohol consumption	Yes	68 (21.2%)	22 (6.9%)	46 (14.3%)	0.001
Khat chewing habit	Yes	22 (6.9%)	5 (1.6%)	17 (5.3%)	0.008
Daily vegetable use	Yes	103 (32.1%)	49 (15.3%)	54 (16.8%)	0.550
Daily salt use (tea spoon)	Mean ± SD	0.94±.58	0.92±.58	0.95±.59	0.588
Physical exercise	Yes	195 (60.7%)	85 (26.5%)	110 (34.3%)	0.003
Exercise/week (Minutes)	Median (IQR)	150 (90–160)	105 (90–150)	150 (90–210)	0.053

Notes: 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.
Abbreviations: DM, diabetes mellitus; SD, standard deviation; IQR, inter quartile range.

Vs 60 (36–96) months, P < 0.001). 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 = 0.022) (Table 2).

Glycemic Control and Managements

T2DM patient's HbA1c and FBS level were examined at the beginning of combination therapy and after a median of 48 months follow-up of the combination therapies. Patients who received metformin-insulin combination therapy had a higher HbA1c than those who received metformin-sulfonylurea combination therapy (8.65 ±1.73% vs 7.46±1.50%, respectively; p < 0.001). However, there was no significant difference in HbA1c changes from baseline value between the groups (−1.04 ±.96% vs −1.02±1.03%; p = 0.912). 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 < 0.001) as shown in Table 2. 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 = 0.370). At baseline and after 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 2.

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 < 0.001). There was no significant difference in bodyweight after receiving metformin-insulin and metformin-sulfonylurea combination therapies (75.28±11.10 kg vs 73.04±11.69 kg, respectively; p = 0.081). 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 < 0.001) as shown in Table 2.

The reduction from baseline in SBP was not significantly different with both combination therapies (−3.57 ±16.74mmHg for metformin-insulin vs −5.18±16.88 mmHg for metformin-sulfonylurea; p = 0.415). The reduction from baseline in 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 = 0.389). 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 = 0.307) and target DBP goal (48.8% for metformin-insulin vs 48.5% for metformin-sulfonylurea; p = 0.365) as shown in Table 2.

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 = 0.004). 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 = <0.001). Similarly, the changes from the baseline in the median triglyceride 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 = 0.005) and (−15 mg/dl for metformin-insulin vs −29 mg/dl for metformin-sulfonylurea; respectively; p = 0.021) as shown in Table 2.

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 = 0.021). Among participants, 4.7% developed myocardial infarction, 1.3% stroke, and 11.5% heart failure. 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

Table 2 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%)	0.022
Number of co-morbidities	Median (IQR)	2 (2–3)	2 (2–3)	2 (2–2)	0.001
Duration of treatment (month)	Median (IQR)	48 (24–72)	36 (12–60)	60 (36–96)	<0.001
Baseline weight before Rx (Kg)	Mean ± SD	73.18±11.99	70.00±10.68	76.48±12.41	<0.001
Weight after Rx (Kg)	Mean ± SD	74.17±11.43	75.28±11.10	73.04±11.69	0.081
Change from baseline in weight(Kg)	Mean ± SD	1.22±6.82	5.37±5.92	-3.10±4.68	<0.001
Baseline BMI before Rx (Kg/m^2)	Mean ± SD	26.77±4.35	26.31±4.35	27.25±4.32	0.063
BMI after Rx (Kg/m^2)	Mean ± SD	27.27±4.43	28.37±4.51	26.14±4.06	<0.001
Change from baseline in BMI (Kg/m^2)	Mean ± SD	0.50±2.55	2.02±2.27	-1.11±1.71	<0.001
Baseline HbA1c before Rx (%)	Mean ± SD	8.95±1.70	9.49±1.93	8.49±1.32	<0.001
HbA1c after combination Rx (%)	Mean ± SD	8.01±1.71	8.65±1.73	7.46±1.50	<0.001
Change from baseline in HbA1c (%)	Mean ± SD	-1.03±.20	-1.04±.96	-1.02±1.03	0.912
Proportion of patients achieving target HbA1c before Rx (%)	<7%, N, % ≥7%, N, %	19 (11.9%) 141 (88.1%)	6 (3.8%) 67 (41.9%)	13 (8.1%) 74 (46.3%)	0.226
Proportion of patients achievingtarget HbA1c after Rx (%)	<7%, N, % ≥7%, N, %	56 (32.4%) 117 (67.6%)	14 (8.1%) 65 (37.6%)	42 (24.3%) 52 (30.1%)	<0.001
Baseline FBS before Rx (mg/dl)	Median (IQR)	166 (146–193)	168 (146–195)	165 (146–191)	0.843
FBS after combination Rx (mg/dl)	Median (IQR)	142 (124–172)	144 (122–179)	142 (125–163)	0.610
Change from baseline in FBS (mg/dl)	Median (IQR)	-27 (-47–-4)	-24 (-45–2.1)	-29.5 (-48–-5.4)	0.370
Proportion of patients achieving target FBS before Rx (mg/dl)	<130, N, % ≥130, N, %	40 (13.3%) 261 (86.7%)	18 (6.0%) 131 (43.5%)	22 (7.3%) 130 (43.2%)	0.330
Proportion of patients achieving target FBS after Rx (mg/dl)	<130, N, % ≥130, N, %	102 (32.0%) 217 (68.0%)	52 (16.3%) 108 (33.9%)	50 (15.7%) 109 (34.2%)	0.467
Baseline SBP before Rx (mmHg)	Mean ± SD	135.12±18.21	135.88±18.52	134.39±17.93	0.479
SBP after Rx (mmHg)	Mean ± SD	131.13±16.42	132.61±16.05	129.66±16.71	0.120
Change from baseline in SBP (mmHg)	Mean ± SD	-4.39±16.80	-3.57±16.74	-5.18±16.88	0.415
Baseline DBP before Rx (mmHg)	Mean ± SD	82.00±10.15	81.97±10.33	82.02±10.01	0.968
DBP after combination Rx (mmHg)	Mean ± SD	76.28±8.43	76.87±8.35	75.69±8.49	0.224
Change from baselinein DBP (mmHg)	Mean ± SD	-5.66±11.52	-5.06±11.79	-6.23±11.26	0.389
Baseline HDL-C before Rx (mg/dl)	Median (IQR)	45.0(38.0–53.0)	45.0(39.0–56.8)	45.0 (38.5–53.0)	0.258

(*Continued*)

Table 2 (Continued).

Variables	Category	Total	Treatment		P-value
			Metformin with Insulin (N = 162)	**Metformin with Sulfonylurea (N = 159)**	
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)	0.018
Change from baselinein HDL-C (mg/dl)	Median(IQR)	0.00(-11.5–8.0)	-5.0(-15.0–2.5)	5.0(-5.85–11.0)	0.004
Baseline LDL-C before Rx (mg/dl)	Mean ± SD	118.01±43.57	109.96±44.31	124.59±42.11	0.048
LDL-C after combination Rx (mg/dl)	Mean ± SD	109.57±38.48	113.45±45.37	106.24±31.29	0.245
Change from baseline in LDL-C (mg/dl)	Mean ± SD	-9.21±37.45	6.67±38.33	-21.30±32.12	<0.001
Baseline TC (mg/dl)	Median (IQR)	181 (143–227)	190 (127–219)	201 (147–241)	0.149
TC after combination Rx (mg/dl)	Median (IQR)	175 (133–202)	174 (134–210)	165 (123–198)	0.893
Changefrom baseline in TC (mg/dl)	Median (IQR)	-22 (-53–7)	-15 (-50–23)	-29 (-62–-11)	0.021
Baseline TG (mg/dl)	Median (IQR)	136 (105–187)	126 (89–186)	157 (109–196)	0.063
TG after combination Rx (mg/dl)	Median (IQR)	135 (97–196)	127 (109–190)	132 (93–185)	0.457
Change from baselinein TG (mg/dl)	Median (IQR)	-9 (-30–17)	9 (-18–29)	-15 (-31–-5)	0.005
Cardiovascular outcomes	Yes, N, %	239 (74.5%)	130 (40.5%)	109 (34.0%)	0.021
Myocardial infarction	Yes, N, %	15 (4.7%)	12 (3.7%)	3 (0.9%)	0.031
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%)	0.728
Hypertension	Yes, N, %	184 (57.3%)	101 (31.5%)	83 (25.9%)	0.072
Dyslipidemia	Yes, N, %	215 (67.0%)	121 (37.7%)	94 (29.3%)	0.004
Microvascular complications					
Diabetic neuropathy	Yes, N, %	94 (29.3%)	61 (19.0%)	33 (10.3%)	0.001
Diabetic retinopathy	Yes, N, %	30 (9.3%)	23 (7.2%)	7 (2.2%)	0.003
Diabetic nephropathy	Yes, N, %	15 (4.7%)	7 (2.2%)	8 (2.5%)	0.797
Concomitant medication use	Yes, N, %	238 (74.1%)	128 (39.9%)	110 (34.3%)	0.056
Diuretics	Yes, N, %	66 (20.6%)	41 (12.8%)	25 (7.8%)	0.038
ACEIs	Yes, N, %	138 (43.0%)	76 (23.7%)	62 (19.3%)	0.176
ARBs	Yes, N, %	14 (4.4%)	12 (3.7%)	2 (0.6%)	0.011
BBs	Yes, N, %	43 (13.4%)	29 (9.0%)	14 (4.4%)	0.021
CCBs	Yes, N, %	93 (29.0%)	48 (15.0%)	45 (14.0%)	0.807
Statins	Yes, N, %	224 (69.8%)	125 (38.9%)	99 (30.8%)	0.005
Others*	Yes, N, %	146 (45.6%)	85 (26.6%)	61 (19.1%)	0.010
Antidiabetic Rx emergent AEs	Yes, N, %	81 (25.2%)	43 (13.4%)	38 (11.8%)	0.609
Hypoglycemia	Yes, N, %	102 (31.8%)	55 (17.1%)	47 (14.6%)	0.405

(*Continued*)

Table 2 (Continued).

Variables	Category	Total	Treatment		P-value
			Metformin with Insulin (N = 162)	**Metformin with Sulfonylurea (N = 159)**	
Episode of hypoglycemia/month	Median (IQR)	2.00 (2.00–3.00)	2.00 (2.00–2.75)	2.00 (1.00–3.00)	0.333
Missed dose of antidiabetic drugs	Yes, N, %	98 (30.5%)	44 (13.7%)	54 (16.8%)	0.225
Reason of missed dose					0.758
	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%)	

Notes: 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; Others *Aspirin, nitrates, digoxin, antibiotics, antiretroviral treatment, anti-depressant, anti-asthmatics; Others **Spiritual believes, treatment plan inconvenience, pill burden.
Abbreviations: 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 channel blockers.

0.9%, respectively; p = 0.031). However, there was no significant difference in the proportion of patients who had stroke, and heart failure between the two treatment groups as shown in Table 2.

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 = 0.001) and diabetic retinopathy (7.2% for metformin-insulin vs 2.2% for metformin-sulfonylurea; p = 0.003). However, there was no significant difference in proportion of patients with diabetic nephropathy between the groups (Table 2).

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 = 0.056). Significant higher proportion of patients in the

metformin-insulin treatment group used diuretics (12.8% vs 7.8%, respectively; p = 0.038), angiotensin receptor-blockers (3.7% vs 0.6%, respectively; p = 0.011), Beta-blockers (9.0% vs 4.4%, respectively; p = 0.021), statins (38.9% vs 30.8%, respectively; p = 0.005) and aspirin (26.6% vs 19.1%, respectively; p = 0.010) compared to those in the metformin-sulfonylurea treatment group (Table 2).

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 = 0.609). A higher proportion of patients reported pain at the injection site and weight gain in the metformin-insulin than metformin-sulfonylurea treatment groups though lower in dyspepsia. 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 = 0.405). The median episode of hypoglycemia reported per month was also similar between the two treatment groups (Table 2).

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, khat chewing habit, daily vegetable and fruit consumption, regular exercise, co-morbidities, type of antidiabetic treatment, concomitant medications use, missed doses 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 4.31[1.79–10.32]; p = 0.001) (Table 3).

Factors Associated with Composite Cardiovascular Outcomes

Factors including sex, residence, 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, comorbidities, BMI, HbA1c, and SBP had a significant association with composite cardiovascular outcomes (AOR with 95% CI 0.002[0.000–0.035], p = <0.001; 400.270[2.340–68,469.106], p = 0.022; 0.517[0.304–0.876], p = 0.014 and 0.940[0.892–0.991], p = 0.021), respectively (Table 4).

Discussion

Sustainable glycemic control is the major goal of T2DM management to prevent both micro and macrovascular complications of DM.[31] There was no significant difference in the mean reduction of HbA1c from the baseline between metformin-insulin and metformin-sulfonylurea combination therapies. In contrast to this finding, study elsewhere[32,33] reported that the mean reduction in HbA1c level from the baseline 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 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[34] 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[32] 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. The American diabetes association standard of care guideline recommends that T2DM patient's FBS target should be less than 130 mg/dl.[31] A study elsewhere[32] reported a significantly large proportion of patients in the insulin-based combination therapy achieved FBS <130 mg/dl compared with patients in the oral combination therapies. However, the current study showed a non-significant difference in the proportion of patients having achieved FBS (<130.0 mg/dl) between the two treatment groups. This discrepancy might be attributed to the difference in the duration of follow-up.

Obesity is one of the most common risk factors for T2DM and representing a major global health problem.[35] It aggravates the pancreatic β-cell failure, insulin resistance, and cardiovascular risk.[36] Lowering bodyweight is an indispensable part of T2DM management.[35] 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.[37] Other evidences[25,34] 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.

Lowering blood pressure is notably important to reduce the risk of CVD and diabetes-related deaths.[38] Compared with sulfonylureas, GLP-1 receptor agonists and SGLT-2 inhibitors added to metformin therapy significantly reduced SBP and DBP from the baseline values.[39,40] However, study elsewhere[41] reported there was no

Table 3 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%)	0.693 [0.366–1.314]	0.262	0.885[0.254–3.075]	0.847
	Female	26 (15.0%)	65 (37.6%)	1.00		1.00	
Resident	Addis Ababa	47 (27.2%)	99 (57.2%)	1.053 [0.440–2.519]	0.907	1.067[0.346–3.288]	0.911
	Out of Addis Ababa	9 (5.2%)	18 (10.4%)	1.00		1.00	
Marital status	Single	3 (1.7%)	2 (1.2%)	0.431 [0.062–3.012]	0.396	2.407[0.753–7.695]	0.138
	Married	34 (19.7%)	87 (50.3%)	1.656 [0.704–3.896]	0.248	0.563[0.056–5.690]	0.626
	Divorced	8 (4.6%)	11 (6.4%)	0.890 [0.272–2.910]	0.847	1.242[0.301–5.123]	0.764
	Widowed	11 (6.4%)	17 (9.8%)	1.00		1.00	
Level of education	Unable to read and write	6 (3.5%)	17 (9.8%)	1.417 [0.415–4.834]	0.578	3.358[0.59–19.047]	0.171
	Primary	16 (9.2%)	36 (20.8%)	1.125 [0.417–3.038]	0.816	1.500[0.436–5.159]	0.520
	Secondary	10 (5.8%)	19 (11.0%)	0.950 [0.314–2.875]	0.928	1.824[0.487–6.825]	0.372
	Preparatory	8 (4.6%)	14 (8.1%)	0.875 [0.269–2.850]	0.825	0.908[0.219–3.770]	0.894
	University	16 (9.2%)	31 (17.9%)	1.00		1.00	
Health education	Yes	30 (17.3%)	65 (37.6%)	1.083 [0.572–2.053]	0.806	1.200[0.487–2.956]	0.692
	No	26 (15.0%)	52 (30.1%)	1.00		1.00	
Family history of DM	Yes	27 (15.6%)	56 (32.4%)	0.986 [0.521–1.865]	0.966	0.825[0.377–1.803]	0.629
	No	29 (16.8%)	61 (35.3%)	1.00		1.00	
Smoking habit	Current smoker	6 (3.5%)	8 (4.6%)	0.612 [0.202–1.856]	0.385	0.990[0.235–4.163]	0.989
	Not smoker	50 (28.9%)	109 (63.0%)	1.00		1.00	
Alcohol consumption	Regular drunker	19 (11.0%)	28 (16.2%)	0.613[0.305–1.231]	0.169	0.682[0.234–1.988]	0.483
	Not drunker	37 (21.4%)	89 (51.4%)	1.00		1.00	
Khat chewing habit	Regular chewer	7 (4.0%)	7 (4.0%)	0.445 [0.148–1.339]	0.150	0.795[0.179–3.532]	0.763
	Not chewer	49 (28.3%)	110 (63.6%)	1.00		1.00	
Daily vegetable and fruit consumption	Yes	19 (11.0%)	35 (20.2%)	0.831 [0.421–1.641]	0.594	0.708[0.291–1.722]	0.446
	No	37 (21.4%)	82 (47.4%)	1.00		1.00	
Regular exercise	Yes	32 (18.5%)	76 (43.9%)	1.390 [0.725–2.667]	0.322	2.019[0.882–4.621]	0.096
	No	24 (13.9%)	41 (23.7%)	1.00		1.00	
Co-morbidities	Yes	45 (26.0%)	98 (56.6%)	1.261 [0.554–2.869]	0.581	0.374[0.098–1.425]	0.149
	No	11 (6.4%)	19 (11.0%)	1.00		1.00	
Treatment (Rx)	Met-insulin	14 (8.1%)	65 (37.6%)	3.750 [1.85–7.599]	<0.001	4.308[1.79–10.32]	0.001
	Met-SU	42 (24.3%)	52 (30.1%)	1.00		1.00	
Concomitant Rx	Yes	36 (20.8%)	88 (50.9%)	1.686 [0.846–3.358]	0.137	2.424[0.809–7.261]	0.114
	No	20 (11.6%)	29 (16.8%)	1.00		1.00	
Missed dose	Yes	17 (9.8%)	38 (22.0%)	1.103 [0.554–2.197]	0.779	1.570[0.689–3.580]	0.283
	No	39 (22.5%)	79 (45.7%)	1.00		1.00	
Source of drugs	Free	42 (24.3%)	93 (53.8%)	1.292 [0.608–2.743]	0.505	1.136[0.459–2.814]	0.783
	Paid	14 (8.1%)	24 (13.9%)	1.00		1.00	

Abbreviations: DM, diabetes mellitus; CI, confidence interval; HbA1c, hemoglobin A1c; Rx, treatment; Met, metformin; SU, sulfonylurea.

Table 4 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 Female	93 (29.0%) 146 (45.5%)	48 (15.0%) 34 (10.6%)	2.216[1.330–3.693] 1.00	0.002	0.439[0.051–3.766] 	0.453
Residence	Addis Ababa Out of Addis Ababa	211 (65.7%) 28 (8.7%)	66 (20.6%) 16 (5.0%)	0.547 [0.279–1.074] 1.00	0.080		
Marital status	Single Married Divorced Widowed	8 (2.5%) 159 (49.5%) 24 (7.5%) 48 (15.0%)	4 (1.2%) 60 (18.7%) 13 (4.0%) 5 (1.6%)	3.623[1.376–9.535] 4.800[1.057–21.791] 5.200[1.660–16.290] 1.00	0.009 0.042 0.005	1.780[0.148–21.37] 0.197[0.000–96.244] 3.218[0.194–53.33] 	0.649 0.607 0.415
Level of education	Unable to read and write Primary Secondary Preparatory University	50 (15.6%) 75 (23.4%) 26 (8.1%) 35 (10.9%) 53 (16.5%)	5 (1.6%) 29 (9.0%) 15 (4.7%) 9 (2.8%) 24 (7.4%)	0.267[0.086–0.829] 1.031[0.468–2.272] 1.538[0.614–3.855] 0.686[0.255–1.842] 1.00	0.022 0.939 0.358 0.454		
Alcohol consumption	Yes No	41 (12.8%) 198 (61.7%)	27 (8.4%) 55 (17.1%)	2.371[1.340–4.193] 1.00	0.003	2.936[0.580–14.87] 	0.193
Regular exercise	Yes No	135 (42.1%) 104 (32.4%)	60 (18.7%) 22 (6.9%)	2.101[1.210–3.647] 1.00	0.008	4.935[0.998–24.41] 	0.050
Treatment	Metformin-insulin Metformin-sulfonylurea	130 (40.5%) 109 (34.0%)	32 (10.0%) 50 (15.6%)	0.537[0.322–0.895] 1.00	0.017	1.030[0.250–4.252] 	0.967
Co-morbidities	Yes No	236 (73.5%) 3 (0.9%)	34 (10.6%) 48 (15.0%)	0.009[0.003–0.031] 1.00	<0.001	0.002[0.000–0.035] 	<0.001
BMI	Under weight Normal Over weight Obese	1 (0.3%) 70 (22.7%) 91 (29.4%) 66 (21.4%)	1 (0.3%) 30 (9.7%) 44 (14.2%) 6 (1.9%)	11.000[0.608–198.93] 4.714[1.844–12.054] 5.319[2.141–13.212] 1.00	0.105 0.001 <0.001	400.27[2.34–68,469.11] 6.105[0.403–92.56] 13.076[0.96–177.2] 	0.022 0.192 0.053
Age	Mean ± SD	59.45± 10.86		0.965[0.942–0.989]	0.004	0.958[0.886–1.035]	0.273
HbA1C	Mean ± SD	8.01± 1.71		0.660[0.519–0.838]	0.001	0.517[0.304–0.876]	0.014
FBS	Mean ± SD	150.52± 39.10		0.988[0.980–0.996]	0.002	0.995[0.975–1.015]	0.625
SBP	Mean ± SD	131.13± 16.42		0.935[0.913–0.957]	<0.001	0.940[0.892–0.991]	0.021
DBP	Mean ± SD	76.28± 8.43		0.968[0.937–1.000]	0.049	1.036[0.946–1.134]	0.451
HDL-C	Mean ± SD	45.15± 10.43		1.018[0.982–1.056]	0.332		
LDL-C	Mean ± SD	109.57± 38.48		0.995[0.986–1.005]	0.355		
Total cholesterol	Median(IQR)	175 (133–202)		1.010[0.998–1.022]	0.088		
Triglycerides	Median(IQR)	135 (97–196)		0.996[0.989–1.003]	0.254		

Abbreviations: CV, cardiovascular; CI, confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin A1c; FBS, fasting blood sugar; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; SD, standard deviation; IQR, inter quartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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 the reduction of SBP and DBP from baseline between metformin-insulin and metformin-sulfonylurea combination therapies. Dyslipidemia is a well-known risk factor for CVD in individuals with T2DM.[42] Likewise, a cohort study[43] conducted elsewhere showed that patients with T2DM who had uncontrolled blood pressure, LDL-C, and HbA1c were at high risk of hospitalization due to CVD, whereas those with blood pressure and LDL-C at target had a lower risk of developing adverse cardiovascular events. Moreover, another evidence[44] 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 < 0.001). Another study elsewhere[34] reported that there was no significant difference in lipid profiles between insulin and sulfonylurea added on metformin therapy. In contrast to this finding, 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 = 0.004).

CVD is the most common macrovascular complication and a major cause of death in patients with T2DM.[7,8] An observational cohort study conducted elsewhere[45] 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[46–48] 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. Similar to these findings, the present study showed that a significantly higher proportion of patients had composite cardiovascular outcomes in the metformin-insulin than metformin-sulfonylurea combination therapies. A systematic review of RCTs[24] 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[25] 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 a significantly higher proportion of patients under metformin-insulin combination therapy had myocardial infarction than in those under metformin-sulfonylurea combination therapy. 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 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.[49] A study reported elsewhere[50] indicates that the prevalence of diabetic retinopathy has sharply increased as the HbA1c level increased. A meta-analysis conducted in Sub-Saharan Africa[51] showed that the prevalence of diabetic nephropathy was 41.4% in patients with T2DM. Another study conducted elsewhere[52] 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.

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[53] 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[21,25] have identified patients who were treated with insulin and/or sulfonylurea had experienced hypoglycemia. Another study elsewhere[54] 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.[55] Despite the different glycemic achievements, a similar prevalence of hypoglycemic adverse events was illustrated between the two treatment groups. A higher episode of hypoglycemia was reported in insulin-treated patients.[25] However, this study showed a similar episode of hypoglycemia between groups.

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 five tertiary level 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 did not 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 which calls upon careful interpretation.

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.

Acknowledgments

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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