Original Article

All-Cause and Cardiovascular Mortality following Treatment with Metformin or Glyburide in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Both metformin and sulfonylurea (SU) drugs are among the most widely-used anti-hyperglycemic medications in patients with type 2 diabetes mellitus (T2DM). Previous studies have shown that treatment with SUs might be associated with decreased survival compared with metformin. This study aimed to evaluate all-cause and cardiovascular mortality rates between glyburide and metformin in patients diagnosed with T2DM.

Methods: This was a cohort study on 717 patients with T2DM (271 undergoing monotherapy with glyburide and 446 with metformin). Data were gathered from 2001 to 2014. All-cause and cardiovascular mortality were end-points.

Results: During the follow-up, 24 deaths were identified, of which 13 were cardiovascular in nature. The group with glyburide monotherapy had greater all-cause mortality (17 (6.3%) in glyburide *vs*. 7 (1.6%) in metformin, *P* = 0.001) and cardiovascular mortality (11 (4.1%) in glyburide *vs.* 2 (0.4%) in metformin; *P* = 0.001). Metformin was more protective than glyburide for both all-cause (HR: 0.27 [0.10 – 0.73] *P*-value = 0.01) and cardiovascular mortality (HR: 0.12 [0.20 – 0.66], *P*-value = 0.01) after multiple adjustments for cardiovascular risk factors. Among adverse cardiovascular events, non-fatal MI was higher in glyburide compared to metformin monotherapy group (3.2% *vs.* 0.8%; *P*-value = 0.03), but not coronary artery bypass grafting (*P*-value = 0.85), stenting (*P*-value = 0.69), need for angiography (*P*-value = 0.24), CCU admission (*P*-value = 0.34) or cerebrovascular accident (*P*-value = 0.10).

Conclusion: Treatment with glyburide is associated with increased all-cause and cardiovascular mortality in patients with T2DM.

Keywords: Cardiovascular diseases, diabetes mellitus, glyburide, metformin, mortality

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Introduction

Type 2 diabetes mellitus is one of the most common chronic diseases with a worldwide prevalence of about 8.3% among adults.[1] During the past decades, its prevalence has been on the rise and is estimated to increase to 9.9% until the year 2030.[1] Diabetes and elevated plasma glucose are directly associated with all-cause and cardiovascular mortality.[2] Hyperglycemic state of diabetes mediates various destructive pathways and is at least partially responsible for chronic diabetes complications.[3] Intensive control of plasma glucose has been shown to slow down the progression of diabetic microvascular complications, including nephropathy, neuropathy, and retinopathy,[4] and the current therapeutic strategies in diabetes mellitus are mainly directed against lowering plasma glucose to slow down its micro- and macro-vascular complications.[3]

About one half of all deaths in diabetic patients are estimated to be due to cardiovascular diseases.[5] The risk of myocardial infarction in patients with diabetes mellitus is equal to non-diabetic subjects with previous history of myocardial infarction.[5] Therefore, prevention of adverse cardiovascular outcomes is at the center of strategies to reduce the burden of this disease. Although intensive control of plasma glucose is associated with decreased microvascular complications, the benefit of intensive control of plasma glucose level (with insulin or sulfonylureas) for reducing cardiovascular and all-cause mortality is open to debate.[6–9]

Although sulfonylureas (SUs) are more potent glycemic controllers, current treatment guidelines mostly recommend the use of metformin as the first-line medication in patients with type 2 diabetes mellitus.[10,11] Observational and experimental studies have shown that treatment with SUs may increase mortality and adverse cardiovascular events in comparison with metformin.[12–16] Some other studies have suggested that combination therapy with SUs and metformin is also associated with higher all-cause and cardiovascular mortality compared to metformin alone.[17] However, not all previous studies have reached the same conclusion.[18–21]

Both SUs and metformin are among the most available (and financially affordable) first-line medications for treatment of diabetes mellitus and are widely used alone or in combination with other hypoglycemic agents.[10,11] This study aimed to compare all-cause mortality, cardiovascular mortality and specific cardiac related events between first-line monotherapy with glyburide and metformin in patients with type 2 diabetes mellitus.

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Methods

Study population

The study design was historical cohort. We used a sample of patients diagnosed with type 2 diabetes mellitus in diabetes clinic of Vali-Asr hospital affiliated with Tehran University of Medical Sciences. Patients' follow up began in April 2001 and continued to December 2014. Recorded data in the patients' files was used for data collection. Type 2 diabetic men and women aged 20 years or higher were enrolled in the study. Treatment regimen for all included patients was lifestyle modification plus monotherapy with metformin or glyburide. Written informed consents were taken from participants as they were included in the study. The ethics committee of Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences approved the study protocol.

Clinical and laboratory measurements

Age, sex, smoking status, drug history, family history of coronary heart disease, and duration of diabetes and other concomitant diseases were obtained through interview and checking medical records. Patients' reporting of cigarette smoking during the preceding year of inclusion was considered as positive cigarette smoking status. Height and weight were measured with light clothing without shoes. Waist circumference was measured at midline between the costal margin and the iliac crest in standing position following expiration. Systolic and diastolic blood pressures were measured twice on each arm after 10 minutes of resting in sitting position. The greatest value of the four measurements was considered as the subject's blood pressure.

After 10 hours of overnight fasting, venous blood samples were obtained for biochemical measurements. Fasting plasma glucose (FPG) and 2-hours post-prandial glucose were measured by glucose oxidase method. HbA1c was measured by high-performance liquid chromatography (DS5 Pink kit; Drew, Marseille, France). To measure triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) direct enzymatic methods were used (Parsazmun kit, Karaj, Iran). Serum creatinine was measured by Jaffe method (Parsazmun kit).

Outcome measures and definitions

The primary endpoint of the study was defined as death of any cause. Mortality was divided into two arms: all-cause and cardiovascular. The exact date of death was considered as the end of follow-up for patients with events. For surviving patients, the date of the last visit, the date of changing their monotherapy regimen to any other anti-hyperglycemic drug, or the time of addition of any other anti-hyperglycemic medication to their monotherapy regimen was considered as the end of follow-up time. Patients were visited regularly every 3 months by an endocrinologist and the type and dosage of treatment (including anti-hyperglycemic, anti-platelet, anti-hypertensive, and lipid-lowering medications) were changed, as indicated. In each visit, the dosage and duration of administration of each medication were updated.

The 2008 American Diabetes Association guideline was used for diagnosis of diabetes mellitus.[22] To diagnose metabolic syndrome, nationally modified version of National Cholesterol Education Program's Adult Treatment Panel III guideline was used. It was defined as positive abdominal obesity (waist circumference ≥ 90 cm for both men and women) plus at least two of the following: 1) Plasma TG ≥ 150 mg/dL or taking TG lowering drugs; 2) HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women or alternatively taking HDL-increasing medications; 3) Blood pressure ≥ 130/85 mmHg or alternatively taking anti-hypertensive medications; 4) FPG ≥ 110 mg/dL.[23] To calculate body mass index (BMI), weight (in kilograms) was divided by height in meters squared (kg/m^2). Glomerular filtration rate (mL/min/1.73 m^2 of body surface area) was estimated as 175 × standardized Cr $^{-1.154}$ (mg/dL) × age$^{-0.203}$ × 0.742 (for female patients).[24]

Statistical Analysis

To express primary characteristics of the study population, continuous variables were presented as mean ± standard deviation (SD) and dichotomous variables were presented as number and percent. *T*-test and Mann-Whitney *U*-test were used for comparing means between the two groups for normally and non-normally distributed variables, respectively. To compare dichotomous variables between the two groups, χ^2-test was used. Cox proportional hazard regression test was used for survival analysis. The glyburide monotherapy group was considered as the referent. Hazard ratios for all-cause and cardiovascular mortality were obtained for metformin monotherapy group compared to the referent. Stepwise adjustment was performed for age, gender, metabolic syndrome, waist circumference, BMI, systolic blood pressure, smoking status, history of CAD, family history of CAD, HbA1c, duration of diabetes, and plasma Cr. Two-sided *P*-values < 0.05 were considered statistically significant. SPSS software for windows (version 20) was used to perform statistical analyses.

Results

A total number of 717 type 2 DM patients (56% females and 44% males) with a mean age of 56.3 ± 11.1 years participated in our study. Glyburide and metformin monotherapy groups consisted of 271 and 446 patients, respectively. The patients were followed for a median of 3 years [interquartile range: 1 – 5 years].

Table 1 presents the principal characteristics of the study population. Both all-cause (6.3% *vs.* 1.6%) and cardiovascular (4.1% *vs.* 0.4%) mortality were higher in patients undergoing monotherapy with glyburide compared to metformin monotherapy group ($P = 0.001$). Age, duration of diabetes, glycemic profile, and systolic blood pressure values were higher in glyburide group (*P*-value < 0.001). Plasma Cr was also slightly elevated in glyburide monotherapy group ($P = 0.023$). We observed no significant difference between the two groups regarding past history or family history of CAD, lipid profile, lipid-lowering medications, diastolic blood pressure, past history of hypertension, anti-hypertensive medications, smoking, and estimated GFR. The presence of metabolic syndrome was more probable and BMI and waist circumference were greater in metformin monotherapy group compared to the glyburide.

Table 2 shows detailed adverse cardiovascular events during the years of follow-up. Patients taking glyburide experienced more non-fatal myocardial infarction (3.2% *vs.* 0.8%, $P = 0.03$). There was no significant difference between the two study groups regarding need for angiography, coronary artery bypass grafting, stenting, CCU admission, or cerebrovascular accidents.

In Cox regression model, metformin was more protective than glyburide for both all-cause (HR: 0.22 [0.09 – 0.52]; *P* =

Table 1. Principal Characteristics Of Study Population.

	Glyburide (n = 271)	Metformin (n = 446)	*P*-value
Age (years)	58.7 ± 10.8	55 ± 11.1	< 0.001
Gender (female/male)[α]	140/131	260/186	0.08
Height (cm)	161.6 ± 8.6	161.9 ± 8.8	0.68
Weight (kg)	71.6 ± 13.2	78.9 ± 14.5	< 0.001
Waist circumference (cm)	95.6 ± 10.9	99.6 ± 11.1	< 0.001
BMI (kg/m^2)	27.4 ± 4.8	30.1 ± 5.2	< 0.001
Smoking n (%)[α]	11 (4%)	8 (1.8%)	0.07
Metabolic Syndrome n (%)[α]	171 (64%)	336 (76%)	< 0.001
CAD n (%)[α]	32 (12%)	47 (11%)	0.11
Family History of CAD n (%)[α]	52 (19%)	89 (20%)	0.69
Duration of diabetes (years)[β]	11.0 ± 7.6	7.4 ± 4.9	< 0.001
FPG (mg/dL)[β]	175.1 ± 63.6	156.1 ± 47.0	< 0.001
PPPG (mg/dL)[β]	259.2 ± 102.2	204.5 ± 78.6	< 0.001
HbA1C (%)	8.1 ± 1.9	7.4 ± 1.4	< 0.001
Total Cholesterol (mg/dL)	196.7 ± 46.9	192.2 ± 45.6	0.23
HDL-C (mg/dL)	44.3 ± 11.5	46 ± 12.2	0.09
LDL-C (mg/dL)	113.1 ± 36.4	109.2 ± 35.4	0.19
Triglycerides (mg/dL)[β]	189.8 ± 94.2	180.4 ± 104.8	0.10
Anti-hyperlipidemic drugs (%)[α]	110 (40%)	201 (45%)	0.22
Statins (%)[α]	103 (37%)	180 (40%)	0.50
Gemfibrozil (%) [α]	19 (7%)	37 (8%)	0.52
SBP (mmHg)	132.3 ± 19.9	126.6 ± 17.6	< 0.001
DBP (mmHg)	80.2 ± 11.2	79.9 ± 9.7	0.73
Hypertension n (%)[α]	117 (43%)	182 (40%)	0.56
Duration of Hypertension (years)[β]	9.19 ± 5.98	10.29 ± 6.81	0.85
Anti-hypertensive drugs (%)[α]	89 (32%)	155 (34%)	0.57
ACEI/ARB (%)[α]	64 (23%)	100 (22.4%)	0.73
Beta blocker (%)[α]	27 (10%)	47 (10%)	0.79
CCB (%)[α]	14 (5%)	34 (8%)	0.19
Creatinine (mg/dL)	1.03 ± 0.28	0.98 ± 0.23	0.023
eGFR (ml/min/1.73 m^2)	73.9 ± 20.9	75.8 ± 19.9	0.25
All-cause mortality[α]	17 (6%)	7 (2%)	0.001
Cardiovascular mortality[α]	11 (4%)	2 (0.4%)	0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; PPPG: post-prandial plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; CAD: coronary artery disease; ACEI: angiotensin converting enzyme inhibitor; ARB: aldosterone receptor blocker; CCB: calcium channel blocker. [α]Variables are compared using χ^2-test; [β]Variables are compared using Mann-Whitney *U*-test.
Note: Data are presented as mean ± standard deviation (SD) or number (percent). Groups were compared using independent samples *t*-test.

Table 2. Adverse Cardiovascular Events In Patients Under Treatment With Glyburide And Metformin.

	Glyburide	Metformin	*P*-value
Non-fatal MI	7 (3.2%)	3 (0.8%)	0.03
Angiography	22 (10%)	27 (7.2%)	0.24
CABG	4 (1.8%)	6 (1.6%)	0.85
Stenting	2 (2.2%)	4 (3.6%)	0.69
CCU admission	9 (9.9%)	7 (6.3%)	0.34
CVA	5 (2.3%)	2 (0.5%)	0.10

MI: myocardial infarction; CABG: coronary artery bypass graft; CCU: cardiac care unit; CVA: cerebrovascular accident.
Note: Data are presented as number (percent). Variables were compared using χ^2-test.

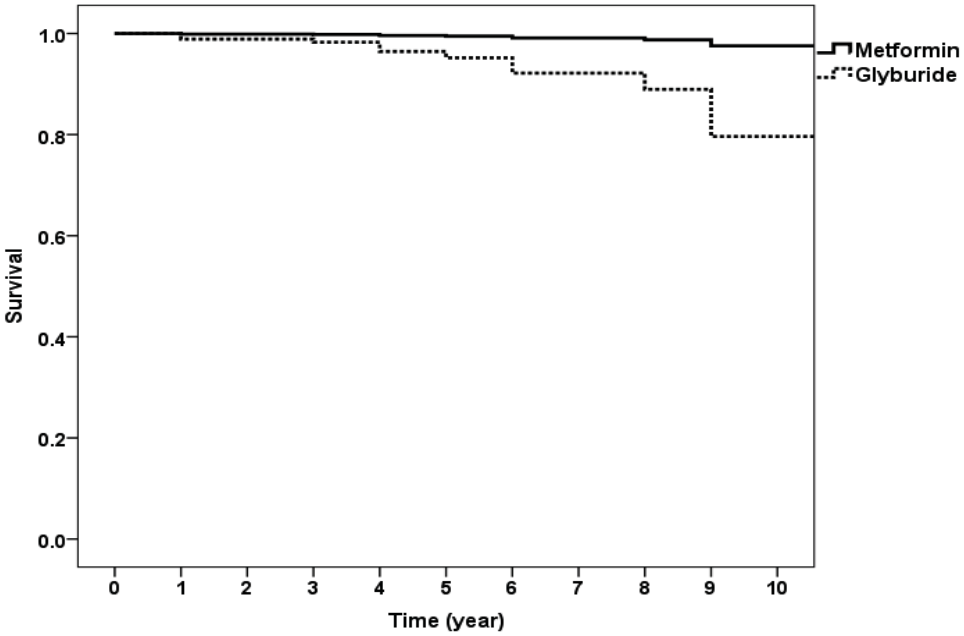

Figure 1. Kaplan-Meier plot of cardiovascular mortality in metformin and glyburide groups.

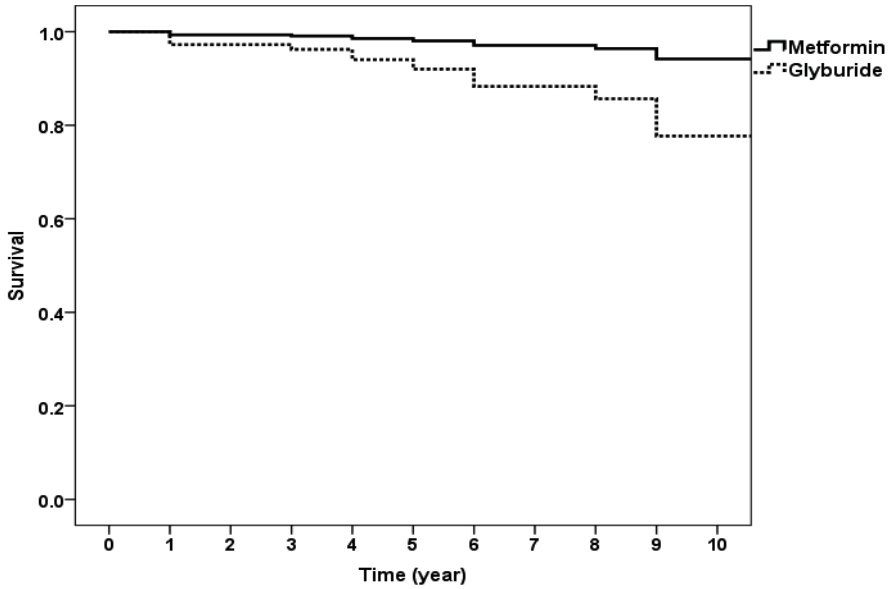

Figure 2. Kaplan-Meier survival plot of all-cause mortality in metformin and glyburide groups.

0.001) and cardiovascular mortality (HR: 0.10 [0.02 – 0.45]; *P* = 0.003). This effect remained significant after multiple adjustments for cardiovascular risk-factors (HR: 0.27 [0.10 – 0.73] *P*-value = 0.01 for all-cause and 0.12 [0.20 – 0.66], *P*-value = 0.01 for cardiovascular mortality). Figures 1 and 2 illustrate Kaplan-Meier survival plots for all-cause and cardiovascular mortality in glyburide and metformin monotherapy groups.

Discussion

In the present study, we showed that monotherapy with metformin in type 2 diabetic patients is associated with lower all-cause and cardiovascular mortality in comparison with glyburide. Potential confounders which could influence the choice of the initial assignment of the medication (metformin or glyburide) were adjusted. The full-adjusted HR (CI) for all-cause and cardiovascular mortality were 0.27 [0.10 – 0.73] and 0.12 [0.20 – 0.66] respectively, for metformin compared with glyburide.

Since the release of United Kingdom Prospective Diabetes Study (UKPDS 34) results in 1998, metformin was recommended as the first-line anti-hyperglycemic medication for overweight patients with type 2 diabetes mellitus.[25] The mentioned study suggested that metformin monotherapy could decrease any diabetes-related endpoint, as well as mortality, in overweight type 2 diabetic

Table 3. Hazard Ratios For Cardiovascular And All-cause Mortality In Patients Under Treatment With Metformin Compared With Glyburide.

Models	All-cause Mortality		Cardiovascular Mortality	
	HR [95%CI]	*P*-value	HR [95%CI]	*P*-value
Model 1	0.22 (0.09 – 0.52)	0.001	0.10 (0.02 – 0.45)	0.003
Model 2	0.27 (0.11 – 0.66)	0.004	0.10 (0.02 – 0.48)	0.004
Model 3	0.31 (0.12 – 0.79)	0.01	0.15 (0.03 – 0.73)	0.01
Model 4	0.28 (0.11 – 0.75)	0.01	0.13 (0.03 – 0.68)	0.01
Model 5	0.27 (0.10 – 0.73)	0.01	0.12 (0.20 – 0.66)	0.01

Model 1 is unadjusted; Model 2 is adjusted for age and gender; Model 3 is additionally adjusted for systolic blood pressure, metabolic syndrome, BMI, smoking, past history of CAD and family history of CAD; Model 4 is additionally adjusted for HbA1c and duration of diabetes; Model 5 is further adjusted for plasma creatinine.

patients compared with diet control alone, insulin, glyburide, or chlorpropamide.[25] Several studies have subsequently suggested that metformin has the advantage of decreased mortality and lower adverse cardiovascular events over SUs.[9,12–16,26–28] Two studies among the mentioned studies also performed propensity score matched analysis to match the patients for the probability of metformin use as the initial treatment.[15,28] However, most of the mentioned studies have analyzed SUs as a composite group and did not compare the effects of different types of SU drugs compared with metformin separately;[9,15,28] as different types of SUs may have different effects on survival when compared with metformin.[12,13,16,26] In a large nationwide study, Schramm, et al. showed that treatment with SUs (including glimepiride, glyburide, glipizide, and tolbutamide) was associated with increased all-cause mortality compared with metformin.[13] The results for cardiovascular mortality and composite endpoint of myocardial infarction, cardiovascular mortality, and stroke were the same in this study. In another retrospective cohort on 23,915 type 2 diabetic patients, Pantalone, et al. showed that treatment with glipizide, glyburide or glimepiride are associated with increased mortality compared with metformin after a median follow-up of 2.2 years.[12] Interestingly, a recent study on 90,463 patients with diabetes mellitus and 90,463 healthy subjects showed that patients with diabetes and under treatment with metformin have better survival than those treated with SUs and even healthy matched controls.[27] Bannister, et al. showed that the survival of metformin-treated patients with type 2 diabetes is at least as long as that of healthy matched controls.[27] Hong, et al. in a randomized double-blind clinical trial enrolled 304 patients with type 2 diabetes mellitus and history of coronary artery disease.[14] The patients were randomly allocated to metformin or glipizide monotherapy for 3 years. After a median follow-up of 5 years, patients treated with metformin had a significantly lower risk of major adverse cardiovascular events than those treated with glipizide.[14]

The superiority of metformin over SUs, regarding all-cause mortality or adverse cardiovascular events, has not been consistent among studies.[18–20] Kahn, et al. performed a large randomized double blind clinical trial on 4,360 patients with type 2 diabetes mellitus.[18] After 4 years of treatment, no difference was observed between glyburide (1,441 patients) and metformin (1,454 patients) for either stroke, fatal or non-fatal myocardial infarction, hospitalization, or all-cause death.[18] In another study, Kahler, et al. analyzed the data of 39,721 type 2 diabetic patients and found no difference in all-cause mortality between patients treated with metformin, glyburide, and the combination of metformin and glyburide.[19]

To date, a vast number of studies have supported the protective effects of metformin in patients with diabetes mellitus. Treatment with metformin is associated with decreased oxidative stress, improved lipid profile, and improved endothelial and platelet function.[30–31] Therapy with metformin could decrease plasma triglyceride, total cholesterol and LDL-C, while serum HDL-C levels is increased or at least unaffected.[31] Metformin could also decrease blood pressure, a well-known cardiovascular risk factor.[31] Several observational studies have also proposed that treatment with metformin can decrease cancer incidence compared with SUs.[32] It was suggested that increased plasma insulin (which may impose mutagenic effects) following treatment with SUs, could contribute to increased risk of cancer.[32] Patients with type 2 diabetes under treatment with metformin have better survival after cancer incidence in comparison with those treated with other glucose-lowering agents or even the general population.[33] However, further randomized clinical trials are still needed to confirm the oncologic benefits of metformin compared with SUs in patients with type 2 diabetes.[34]

The limitations of this study merit consideration. This was an observational cohort study in which the patients were not randomized for treatment allocation. Some of the baseline characteristics of the participants were different between metformin and glyburide groups and lack of randomization is an inherent weakness of such studies. Therefore, to minimize the confounding effects, the results of the multivariable cox-regression analysis were adjusted for confounders which could potentially affect the primary choice of treatment. In addition, subjects with contraindications for metformin or glyburide (e.g. elevated creatinine for metformin) were excluded from the study and did not enter the other treatment group.

In conclusion, we observed that patients with type 2 diabetes receiving glyburide for glycemic control are at increased risk of all-cause and cardiovascular mortality compared with those receiving metformin. According to these results, metformin is recommended as first-line glucose lowering medication in patients with type 2 diabetes mellitus if no contraindication exists. However, as most of previous studies were observational, non-randomized or retrospective,[29] future randomized clinical trials comparing the most widely used types of SUs with metformin could help to resolve the existing controversies.

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