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Original Article

Long-term effects of metformin versus sodium glucose transporter 2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes

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Abstract: Objectives: To compare the long-term cardiovascular effects of Metformin and sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM). Methods: A retrospective study was conducted on 692 T2DM patients treated between January 2020 and January 2023. Patients were divided into two groups: SGLT2i group (n = 460) and Metformin group (n = 232) according to their treatment protocol. Data on demographics, blood glucose/lipid profiles, echocardiographic parameters, and cardiovascular outcomes were collected over a 2-year follow-up period. Outcomes included myocardial infarction (MI), stroke, mortality, and hospitalization for heart failure (HHF). Results: Both treatments significantly reduced blood glucose levels, with Metformin showing greater improvements in glycated hemoglobin (HbA1c). SGLT2i demonstrated superior reductions in triglycerides and total cholesterol levels. Echocardiography revealed enhanced diastolic function with SGLT2i. Moreover, SGLT2i significantly reduced MI and HHF risk, though safety profiles were similar except for higher genital infection incidence in the SGLT2i group. Conclusions: While Metformin remains effective for glycemic control, SGLT2i offers distinct cardiovascular benefits, notably in reducing the risks of MI and HHF.

Keywords: Type 2 diabetes mellitus, cardiovascular disease, metformin, sodium glucose transporter 2 inhibitors, myocardial infarction, heart failure

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, leading to hyperglycemia and an increased risk of multiple complications, particularly cardiovascular diseases (CVD) [1]. With the global prevalence of T2DM continuing to rise, it poses a substantial public health burden due to both its immediate effects and long-term complications, which substantially contribute to morbidity and mortality [2]. CVD remains the leading cause of death among individuals with T2DM, underscoring the importance of cardiovascular risk management in diabetes care [3].

Metformin, a traditional first-line therapies for T2DM, exerts its glucose-lowering effect primarily through enhancing insulin sensitivity and decreasing hepatic glucose production [4]. It has been extensively studied and is known to effectively reduce glycated hemoglobin (HbA1c) levels and potentially reduce CVD risk by improving glycemic control and lipid profiles [5]. However, as diabetes progresses, many patients require additional pharmacological interventions to achieve optimal metabolic and cardiovascular outcomes.

Sodium Glucose Transporter 2 Inhibitors (SGLT2i) have emerged as a novel class of antidiabetic medications that promote urinary glucose excretion by inhibiting SGLT2, a transporter responsible for renal glucose reabsorption in the proximal renal tubules [6]. Beyond their glycemic effects, SGLT2i have demonstrated significant cardioprotective benefits in multiple

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cardiovascular outcome trials, including reduced incidence of hospitalization for heart failure (HHF) and favorable renal outcomes, suggesting advantages over traditional antidiabetic agents such as Metformin [7].

While both Metformin and SGLT2i demonstrate efficacy in managing glycemic levels, their long-term comparative effects on cardiovascular outcomes remain an area of active investigation. Given their distinct mechanisms of action, these agents may exert differential or complementary effects on cardiovascular risk profiles. Existing literature highlights the need to understand these broader therapeutic impacts to guide individualized treatment strategies, especially considering the heterogeneity of T2DM and its cardiovascular manifestations [8].

This study aims to address this knowledge gap by retrospectively analyzing the long-term effects of Metformin versus SGLT2i on cardiovascular outcomes in patients with T2DM.

Materials and methods

Materials

A retrospective analysis was conducted on 692 patients diagnosed with Type 2 Diabetes at Qingdao Central Hospital, University of Health and Rehabilitation Sciences between January 2020 and January 2023. Patients were divided into two groups based on their treatment methods: the SGLT2 inhibitor group (n = 460) and the metformin group (n = 232). Clinical data were extracted from the hospital's electronic medical record system, including demographic characteristics, blood glucose levels, blood lipid profiles, echocardiographic findings, cardiovascular outcomes, adverse events, and infection-related complications. The study was approved by the ethics committee of Qingdao Central Hospital, and the requirement for informed consent was waived.

Inclusion and exclusion criteria

Inclusion criteria: 1) Age ≥ 18 years; 2) Diagnosis of diabetes ≥ 6 months according to the American Diabetes Association (ADA) criteria, defined as one or more of the following: HbA1C ≥ 6.5%, fasting blood glucose (FBG) ≥ 7.0 mmol/L, 2-hour postprandial blood glucose ≥ 11.1 mmol/L, or random plasma glucose ≥ 11.1 mmol/L, accompanied by typical hyperglycemia symptoms or hyperglycemic crises [9, 10]; 3) Diagnosis of T2DM confirmed by etiological classification [10, 11]; 4) High adherence to prescribed medications; 5) Availability of complete medical records; 6) Regular follow-up.

Exclusion criteria: 1) Type 1 Diabetes; 2) Recurrent hypoglycemic episodes [12]; 3) eGFR < 45 ml/min; 4) Blood pressure < 90/50 mmHg (1 mmHg = 0.133 kPa); 5) History of malignant tumors; 6) Presence of atrial fibrillation; 7) Cardiac enlargement or heart diseases secondary to infection, autoimmune diseases, congenital heart defects, or heart failure following acute myocardial infarction [13]; 8) Pregnancy or lactation; 9) History of psychiatric or neurological disorders, or cognitive impairment.

Treatment approach

For patients with T2DM who are intolerant to metformin or require cardiorenal protection, SGLT2 inhibitors (SGLT2i) were prioritized as the preferred treatment; for other patients, metformin remained the first-line therapy, with treatment decisions also considering patient preference and financial accessibility. Patients in the SGLT2i group were treated with Dapagliflozin tablets (manufactured by AstraZeneca Pharmaceutical Co., Ltd., China, registration numbers HJ20170119/HJ20170120). The initial dose was 5 mg once daily. If further glycemic control was needed and renal function permitted, the dose was increased to 10 mg once daily, taken before breakfast after 1 to 2 weeks of initial treatment.

Patients in the metformin group received Metformin Hydrochloride tablets (manufactured by Sino-American Shanghai Squibb Pharmaceuticals Ltd., registration number H20023370). The initial dosage was 500 mg once daily, taken with meals to minimize gastrointestinal side effects. If well tolerated and additional glucose control was required, the dose was titrated by 500 mg/day every 1-2 weeks, up to a maximum daily dose of 2,000 mg, administered in two or three divided doses. Both groups received consistent adjunctive therapies as needed and were followed every six months.

Data collection

Patient data were collected from the electronic medical records, including demographic information such as age, body mass index (BMI), smoking history, alcohol consumption history, duration of T2DM, educational level, marital status, blood pressure, eGFR, and urine albumin-to-creatinine ratio (UACR). The eGFR was calculated using the following formula: $eGFR = 141 \times \min(Scr/k, 1)^{a} \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black], where Scr is serum creatinine (mg/dL), K is a gender specific constant (male = 0.9, female = 0.7), A is also a gender specific index (male = -0.411, female = -0.329) [14]. UACR was calculated by dividing urinary albumin concentration (mg/L) by urinary creatinine concentration (mg/L). A 10 ml first-morning urine sample was collected from each patient and analyzed using enzymatic chemiluminescence immunoassay (Roche Diagnostics, cobas pro e 801, Switzerland).

Biochemical testing

Triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), FBG, and HbA1c levels were assessed at baseline and at the 2-year follow-up [15]. A 5 ml sample of fasting venous blood was collected and centrifuged at 3,000 rpm for 10 minutes using a refrigerated high-speed centrifuge (TLD 12A, Hunan Xiangxi Scientific Instrument Factory, China). Blood lipids, glucose levels, and HbA1c were then measured using an automated biochemical analyzer (AU5811, Shanghai Kehua Bio-engineering Co., Ltd., China).

Echocardiography

Echocardiographic assessments were performed before treatment and during the two-year follow-up using an Aplio i800 ultrasound system (Canon, Japan) equipped with a cardiac transducer. The left atrial volume index (LAVI) was measured using two-dimensional echocardiography in accordance with standard protocols [16]. Spectral Doppler was employed to record early (E) and late (A) diastolic mitral inflow velocities, and the E/A ratio was calculated. Tissue Doppler imaging was employed to determine early diastolic mitral annular velocities (e') at the septal and lateral walls of the left ventricle. The average ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') ratio was calculated. These indices, combined with LAVI and maximum tricuspid regurgitation velocity, were used to comprehensively grade left ventricular diastolic function.

Standard M-mode echocardiography was utilized to measure left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), interventricular septal thickness (IVST), and posterior wall thickness (PWT). Left ventricular ejection fraction (LVEF) was calculated using the Simpson's method to evaluate left ventricular systolic function [17].

Result evaluation

Patients were followed for 2 years to assess cardiovascular outcomes. The primary outcomes included the incidence of myocardial infarction (MI), stroke, hospitalization for heart failure (HHF), and all-cause mortality. Secondary outcomes included blood glucose levels, lipid profiles, and left ventricular diastolic/systolic function.

Safety assessments included adverse events that occurred during treatment or within seven days following the final dose of study medication. Events were categorized according to the Medical Dictionary for Regulatory Activities, version 18.0 [18]. Adverse events of special interest included confirmed hypoglycemic events (plasma glucose ≤ 70 mg/dL [3.9 mmol/L] or episodes requiring assistance), as well as events indicating urinary tract infections, genital infections, acute renal failure, diabetic ketoacidosis, and thromboembolic events [19].

Statistical analysis

Statistical analyses were conducted using SPSS 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as frequencies and percentages [n (%)]. For datasets with ≥ 40 observations and expected frequencies (T) ≥ 5, the Pearson chi-square test (χ^2) was applied. When $1 \leq T < 5$, the continuity correction chi-square was applied. In cases where the sample size was < 40 or T < 1, Fisher's exact test was used.

Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally dis-

Table 1. Comparison of demographical characteristics between the two groups of patients

Parameters	SGLT2i group (n = 460)	Metformin group (n = 232)	t/χ^2	P
Age (years)	64.36 ± 4.23	64.45 ± 4.58	0.253	0.801
Body Mass Index (kg/m^2)	30.73 ± 3.59	30.36 ± 4.02	1.167	0.244
Female/Male	210 (45.65%)/250 (54.35%)	104 (44.83%)/128 (55.17%)	0.042	0.837
Smoking history (Yes/No)	115 (25%)/345 (75%)	56 (24.14%)/176 (75.86%)	0.062	0.804
Alcohol consumption history (Yes/No)	125 (27.17%)/335 (72.83%)	65 (28.02%)/167 (71.98%)	0.055	0.814
Blood pressure control			0.125	0.724
SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	178 (38.7%)	93 (40.09%)		
SBP < 140 mm Hg and DB*P* < 90 mm Hg	282 (61.3%)	139 (59.91%)		
Estimated glomerular filtration rate			0.506	0.776
90 ml/min/1.73 m^2	105 (22.83%)	48 (20.69%)		
60 to < 90 ml/min/1.73 m^2	242 (52.61%)	123 (53.02%)		
< 60 ml/min/1.73 m^2	113 (24.57%)	61 (26.29%)		
Urine albumin-to-creatinine ratio			1.381	0.501
< 30 mg/g	277 (60.22%)	138 (59.48%)		
30 to 300 mg/g	142 (30.87%)	67 (28.88%)		
> 300 mg/g	41 (8.91%)	27 (11.64%)		
Course of type 2 diabetes			0.618	0.892
≤ 1 years	12 (2.61%)	5 (2.16%)		
> 1 to 5 years	71 (15.43%)	33 (14.22%)		
> 5 to 10 years	117 (25.43%)	56 (24.14%)		
> 10 years	260 (56.52%)	138 (59.48%)		
Marital Status (Married/Unmarried)	432 (93.91%)/28 (6.09%)	215 (92.67%)/17 (7.33%)	0.39	0.532
Educational Level (High school or below/College or above)	254 (55.22%)/206 (44.78%)	116 (50%)/116 (50%)	1.687	0.194

SGLT2i, Sodium Glucose Transporter 2 inhibitors; SPB: systolic blood pressure; DBP: diastolic blood pressure.

tributed data were presented as means ± standard deviations (X ± s) and compared using the independent samples t-test. Non-normally distributed data were reported as median (interquartile range [IQR], 25th-75th percentile) and analyzed using the Wilcoxon rank-sum test. A two-sided *p*-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline demographic and clinical characteristics were compared between patients in the SGLT2i group and the metformin group (**Table 1**). The mean age was similar between the two groups (64.36 ± 4.23 years vs. 64.45 ± 4.58 years; *P* = 0.801). BMI also showed no significant difference (30.73 ± 3.59 kg/m^2 vs. 30.36 ± 4.02 kg/m^2; *P* = 0.244). Gender distribution was comparable, with females constituting 45.65% of the SGLT2i group and 44.83% of the metformin group (*P* = 0.837).

Histories of smoking and alcohol consumption were evenly distributed across both groups (*P* > 0.05). Approximately 40% of patients in each group had uncontrolled blood pressure (*P* = 0.724). There were no significant differences in eGFR (*P* = 0.776) or UACR (*P* = 0.501). Other baseline characteristics, including disease course (*P* = 0.892), marital status (*P* = 0.532), and educational level (*P* = 0.194), also showed no statistically significant differences. These findings confirm the two groups were well-matched at baseline, providing a balanced foundation for subsequent comparative analysis.

Blood glucose levels

Prior to treatment, FBG levels were comparable between the SGLT2i group (10.16 ± 2.29 mmol/L) and the metformin group (9.86 ± 2.16 mmol/L) (*P* = 0.102) (**Figure 1A**). Two years after treatment, FBG levels decreased significantly in both groups, with the SGLT2i group showing a significantly lower level (8.07 ± 2.21 mmol/L) compared to the metformin group (8.42 ± 2.09 mmol/L) (*P* = 0.045) (**Figure 1B**). Similarly, before treatment, HbA1c level was 8.96 ± 2.04% in the SGLT2i group and 9.03 ± 2.45% in the metformin group (*P* = 0.728) (**Figure 1C**). Two years after treatment, both

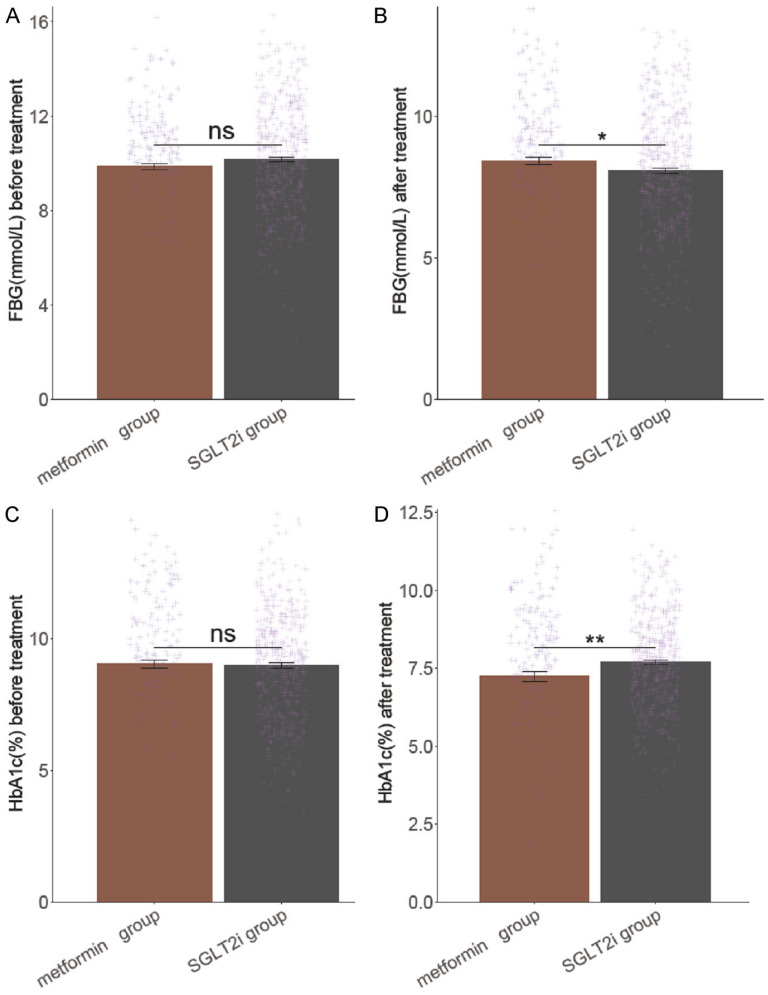

Figure 1. Comparison of blood glucose levels between the two groups before and after treatment. A: FBG before treatment; B: FBG 2 years after treatment; C: HbA1c before treatment; D: HbA1c 2 years after treatment. Notes: GLT2i, Sodium Glucose Transporter 2 inhibitors; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin A1c. ns: no significant difference, $*P < 0.05$, $**P < 0.01$.

groups demonstrated significant reductions in HbA1c levels, with the metformin group exhibiting a more pronounced reduction (7.24 ± 2.31%) compared to the SGLT2i group (7.71 ± 1.52%) ($P = 0.005$) (**Figure 1D**). These findings indicate that both treatments effectively reduced blood glucose levels over the study period, with metformin showing a greater improvement in HbA1c levels.

Blood lipid levels

Baseline TG levels were comparable between the two groups (1.91 ± 0.21 mmol/L vs. 1.93 ± 0.13 mmol/L) ($P = 0.059$) (**Table 2**). After two years, TG levels significantly decreased in both groups, with the SGLT2i group achieving a greater reduction (1.81 ± 0.28 mmol/L vs. 1.85 ± 0.14 mmol/L; $P = 0.007$). TC levels were also initially similar between the two groups (5.80 ± 0.63 mmol/L vs. 5.75 ± 0.47 mmol/L, $P = 0.288$), but were significantly lower in the SGLT2i group (5.57 ± 0.59 mmol/L) than in the metformin group (5.68 ± 0.44 mmol/L) after treatment ($P = 0.005$). LDL levels did not differ significantly either at baseline (SGLT2i: 3.95 ± 0.18 mmol/L, metformin: 3.93 ± 0.26 mmol/L, $P = 0.284$) or after treatment (SGLT2i: 3.81 ± 0.25 mmol/L, metformin: 3.82 ± 0.31 mmol/L, $P = 0.953$). HDL levels were also comparable before treatment (SGLT2i: 1.36 ± 0.27 mmol/L, metformin: 1.38 ± 0.16 mmol/L, $P = 0.378$), with a significant decrease in the SGLT2i group (1.17 ± 0.25 mmol/L) compared to the metformin group (1.24 ± 0.31 mmol/L) after two years ($P = 0.002$). These results demonstrate that both treatments improved lipid profiles, with SGLT2i showing more favorable reductions in TG and TC levels.

Echocardiographic findings

Diastolic function was assessed by echocardiography over a two-year period. Initially, the E/e' ratio, an indicator of left ventricular diastolic function, was similar between the SGLT2i group (9.85 ± 2.21) and the metformin group (10.02 ± 2.23) ($P = 0.334$) (**Figure 2A**). However, after treatment, both groups showed significant improvement, with the SGLT2i group showing a more marked decrease to 8.94 ± 1.58 compared to 9.43 ± 2.04 in the metformin group ($P = 0.002$) (**Figure 2D**). The LAVI was also comparable before treatment (SGLT2i: 34.83 ± 4.63 ml/m^2, metformin: 35.06 ± 4.98 ml/m^2, $P = 0.556$) (**Figure 2B**), but was significantly lower in the SGLT2i group after treatment (33.01 ± 6.52 ml/m^2 vs. 34.05 ± 5.44

Table 2. Comparison of blood lipid profile between the two groups before and after treatment

Parameters		SGLT2i group (n = 460)	Metformin group (n = 232)	t	P
TG (mmol/L)	Before Treatment	1.91 ± 0.21	1.93 ± 0.13	1.893	0.059
	Two Years After Treatment	1.81 ± 0.28	1.85 ± 0.14	2.693	0.007
TC (mmol/L)	Before Treatment	5.80 ± 0.63	5.75 ± 0.47	1.064	0.288
	Two Years After Treatment	5.57 ± 0.59	5.68 ± 0.44	2.846	0.005
LDL (mmol/L)	Before Treatment	3.95 ± 0.18	3.93 ± 0.26	1.074	0.284
	Two Years After Treatment	3.81 ± 0.25	3.82 ± 0.31	0.059	0.953
HDL (mmol/L)	Before Treatment	1.36 ± 0.27	1.38 ± 0.16	0.883	0.378
	Two Years After Treatment	1.17 ± 0.25	1.24 ± 0.31	3.067	0.002

SGLT2i, Sodium Glucose Transporter 2 inhibitors; TG, Triglycerides; TC, Total Cholesterol; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein.

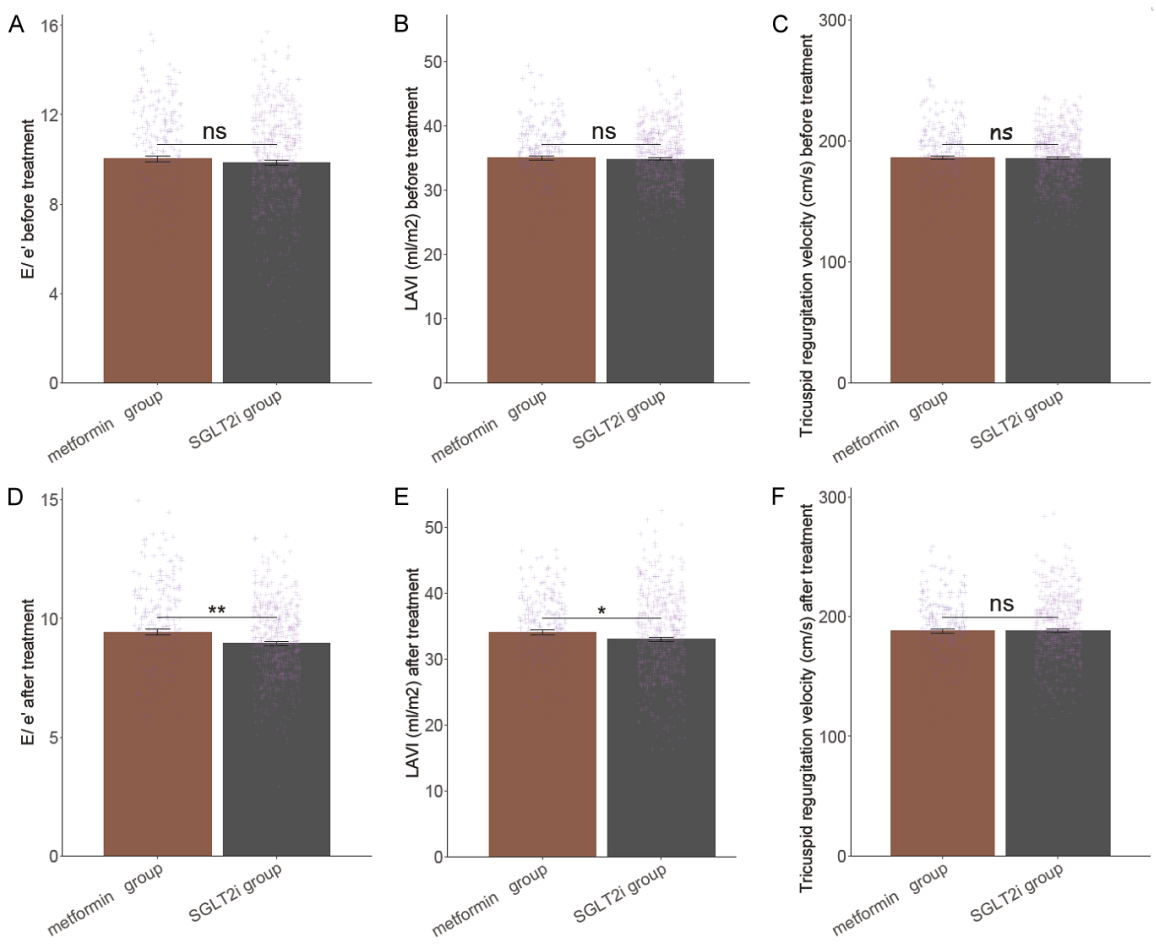

Figure 2. Comparison of left ventricular diastolic function between the two groups before and after treatment. A: E/e' before treatment; B: LAVI before treatment; C: Tricuspid regurgitation velocity before treatment; D: E/e' 2 years after treatment; E: LAVI 2 years after treatment; F: Tricuspid regurgitation velocity 2 years after treatment. Notes: SGLT2i, Sodium Glucose Transporter 2 inhibitors; LAVI, left atrial volume index; E/e', ratio of early diastolic transmitral flow velocity (E) to early diastolic mitral annular velocity (e'). ns: no significant difference, *P < 0.05, **P < 0.01.

ml/m^2; *P* = 0.028) (**Figure 2E**). TRV did not change significantly in either group (baseline: 185.65 ± 21.58 cm/s vs. 186.23 ± 24.56 cm/s, *P* = 0.763) (post-treatment: 188.16 ± 27.95 cm/s vs. 187.98 ± 26.31 cm/s, *P* = 0.937) (**Figure 2C**, **2F**). These findings suggest

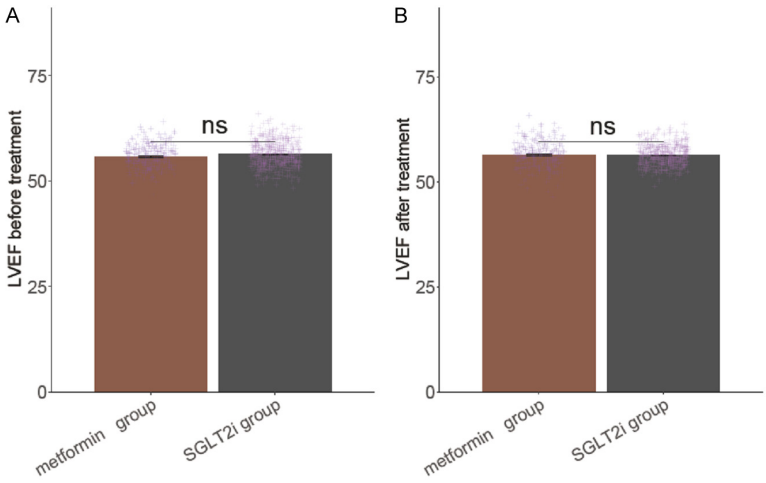

Figure 3. Comparison of left ventricular systolic function between the two groups before and after treatment. A: LVEF before treatment; B: LVEF 2 years after treatment. Notes: SGLT2i, Sodium Glucose Transporter 2 inhibitors; LVEF, left ventricular ejection fraction. ns: no significant difference.

that both treatments contributed to diastolic function improvement, with SGLT2i showing a greater impact on the E/e' ratio and LAVI.

Prior to treatment, the baseline LVEF was comparable between the two groups (56.31 ± 3.02 vs. 55.85 ± 2.89; t = 1.938, P = 0.053) (**Figure 3**). After two years, the SGLT2i group showed a slight increase in mean LVEF to 56.38 ± 2.46, while the metformin group demonstrated a mean LVEF of 56.51 ± 3.17 (t = 0.547, P = 0.585), indicating that neither treatment led to a significant change in left ventricular systolic function over the studied period.

Adverse events

The incidence of hypoglycemia was similar between the two groups, occurring in 28.26% of patients in the SGLT2i group and 28.02% in the metformin group (χ^2 = 0.005, P = 0.946) (**Table 3**). Rates of renal adverse events were also comparable, with acute renal failure observed in 5.22% of the SGLT2i group versus 6.47% in the metformin group (χ^2 = 0.452, P = 0.502), and acute kidney injury occurring in 0.87% and 1.29% of patients, respectively (χ^2 = 0.015, P = 0.902).

A low incidence of diabetic ketoacidosis was observed in the SGLT2i group (0.22%), with no cases reported in the metformin group (P = 1.000). Thrombotic events were rare and similar between groups (0.65% vs. 0.86%; χ^2 = 0, P = 1.000). Urinary tract and genital infections showed comparable frequencies between treatment arms (**Table 4**). These findings demonstrate similar safety profiles for both therapies regarding these monitored adverse events.

Primary cardiovascular outcomes

The composite incidence of MI, stroke, HHF, or mortality was 2.61% in the SGLT2i group and 4.74% in the metformin group (χ^2 = 2.183, P = 0.14; **Table 5**). However, individual analysis revealed significant differences for MI (0.22% in the SGLT2i group vs. 2.16% in the metformin group; χ^2 = 4.671, P = 0.031) and HHF (0.65% in the SGLT2i group vs. 3.02% in the metformin group; χ^2 = 4.510, P = 0.034). No significant differences were observed for stroke (χ^2 = 0.065, P = 0.798) or mortality (χ^2 = 0, P = 1.000) between the groups.

Discussion

In this study, we compared the 2-year cardiovascular and metabolic outcomes of two widely used antidiabetic treatments - metformin and SGLT2i - in patients with T2DM. Both therapies significantly reduced blood glucose levels; however, their mechanisms of action differ substantially. Metformin lowers glucose levels primarily by suppressing hepatic gluconeogenesis and enhancing insulin sensitivity, without stimulating insulin secretion [20]. In contrast, SGLT2i promotes renal glucose excretion by preventing glucose reabsorption in the proximal tubules, thereby reducing plasma glucose independently of insulin [21]. This fundamental difference may explain the differential clinical outcomes observed, where patients in the metformin group exhibited a more significant reduction in HbA1c levels than the SGLT2i group. This finding is consistent with metformin's established role as a first-line therapy in T2DM and suggests that its glycemic efficacy remains robust across diverse patient populations [22].

Table 3. Comparison of adverse events between the two groups

Parameters	SGLT2i group (n = 460)	Metformin group (n = 232)	χ^2	P
Hypoglycemia	130 (28.26%)	65 (28.02%)	0.005	0.946
Acute Renal Failure	24 (5.22%)	15 (6.47%)	0.452	0.502
Acute Kidney Injury	4 (0.87%)	3 (1.29%)	0.015	0.902
Diabetic Ketoacidosis	1 (0.22%)	0 (0%)	0	1
Thrombotic Events	3 (0.65%)	2 (0.86%)	0	1

SGLT2i, Sodium Glucose Transporter 2 inhibitors.

Table 4. Comparison of the incidence of urinary tract infections and genital infections between the two groups

Parameters	SGLT2i group (n = 460)	Metformin group (n = 232)	t/χ^2	P
Urinary Tract Infection				
Male	35 (7.61%)	15 (6.47%)	0.301	0.583
Female	49 (10.65%)	26 (11.21%)	0.049	0.825
Genital Infection				
Male	17 (3.7%)	2 (0.86%)	4.637	0.031
Female	16 (3.48%)	2 (0.86%)	4.166	0.041

SGLT2i, Sodium Glucose Transporter 2 inhibitors.

Table 5. Comparison of primary cardiovascular outcomes between the two groups

Parameters	SGLT2i group (n = 460)	Metformin group (n = 232)	χ^2	P
MI/stroke/HHF/mortality	12 (2.61%)	11 (4.74%)	2.183	0.14
MI	1 (0.22%)	5 (2.16%)	4.671	0.031
Stroke	2 (0.43%)	0 (0%)	0.065	0.798
Mortality	2 (0.43%)	1 (0.43%)	0	1
HHF	3 (0.65%)	7 (3.02%)	4.51	0.034

SGLT2i, Sodium Glucose Transporter 2 inhibitors; MI, myocardial infarction; HHF, hospitalization for heart failure.

In terms of lipid metabolism, patients in the SGLT2i group experienced more notable improvements in TG and TC levels compared to those in the metformin group. These lipid-lowering effects may be attributed to SGLT2i-induced reductions in visceral adiposity and improvements in insulin sensitivity, which favorably modify the metabolic processes affecting lipid levels [23]. Given the high prevalence of dyslipidemia in patients with T2DM, these improvements are clinically relevant, as effective lipid control is essential for reducing cardiovascular risk [24]. While both treatments were effective in reducing LDL levels, only SGLT2i therapy showed an improvement over time, possibly due to indirect metabolic effects associated with renal glucose excretion. The decreased HDL levels in the SGLT2i group, however, warrant further investigation due to the established protective role of HDL in cardiovascular health, raising questions about the overall cardiovascular benefits of SGLT2i, despite improvements in other lipid parameters.

Echocardiography revealed a more pronounced improvement in left ventricular diastolic function in patients treated with SGLT2i compared to those receiving metformin. This observation may be attributed to SGLT2i-induced osmotic diuresis and natriuresis, which reduce both preload and afterload, hence improving cardiac function [25]. In contrast, the cardiovascular benefits of metformin appear to arise primarily through systemic metabolic improvements rather than direct hemodynamic effects. The reduction in LAVI and the E/e' ratio in the SGLT2i group suggests amelioration of structural cardiac changes typically associated with diabetic cardiomyopathy. These findings rein-

force the cardioprotective potential of SGLT2i not only as a glycemic control agent but also as a therapeutic agent with significant cardiorenal protective effects, aligning with findings from previous cardiovascular outcome trials [26].

The neutral impact on LVEF across both groups implies that neither treatment markedly influences systolic function over the span of our study. It is important to note that while diastolic dysfunction was a precursor to more severe cardiac disease, systolic function tends to remain unaffected in early disease stages, which might explain the static LVEF results observed.

Regarding cardiovascular events, the incidence of MI and HHF was significantly lower in the SGLT2i group compared to the metformin group. These results support the emerging evidence highlighting SGLT2i's benefits in reducing major adverse cardiovascular events [27]. The reduction in HHF may be attributed to the combined effects of SGLT2i on blood pressure, body weight, and intravascular volume status, all crucial contributors to heart failure pathophysiology. Although both treatments exert metabolic benefits, the unique natriuretic and hemodynamic effects of SGLT2i may account for its superior performance in heart failure prevention [28].

In terms of safety, both groups demonstrated comparable adverse event profile, with similar incidences of hypoglycemia, acute renal failure, and other complications. However, a higher incidence of genital infections was observed in the SGLT2i group, which aligns with the known adverse effect profile of this drug class [29]. These infections are attributed to increased urinary glucose concentrations that promote microbial growth in the genitourinary tract, necessitating patient education about personal hygiene and early symptom recognition [30]. The absence of significant renal complications support the renal safety of both treatments in patients with preserved renal function, although caution remains warranted in those with pre-existing renal impairment.

The comparative analysis between metformin and SGLT2i in our study suggests that while both medications offer cardiovascular benefits, their mechanisms and clinical implications differ substantially. Metformin remains the foundational therapy with proven metabolic and moderate cardiovascular benefits, particularly in early-stage T2DM [31, 32]. In contrast, SGLT2i appears to offer more targeted cardiovascular protection. This distinction supports the growing paradigm of personalized treatment selection based on individual patient risk profiles.

Despite offering valuable insights, our study has several limitations. First, its retrospective design may introduce selection bias and limit causal inference. Second, reliance on available medical records may result in incomplete data capture, particularly for lifestyle factors, medication adherence, and unmeasured confounders. Third, the sample size, though adequate for detecting differences in major cardiovascular outcomes, may not be sufficient to assess rare adverse events or to fully generalize findings to diverse populations. Furthermore, the follow-up duration, though clinically meaningful, may not fully capture long-term complications or delayed therapeutic effects. These limitations highlight the need for future prospective studies to validate our findings and explore the underlying mechanisms in more detail.

Conclusion

In summary, our study delineates both shared and divergent effects of metformin and SGLT2i in the management of T2DM. While metformin remains a first-line treatment choice due to its glucose-lowering efficacy and established safety profile, SGLT2i offers a compelling alternative or adjunct therapy with additional cardiovascular benefits, particularly in reducing HHF and improving lipid profiles. These observations suggest a pivotal role for SGLT2i in the comprehensive management of T2DM, particularly in patients with elevated cardiovascular risk.

Clinical decision-making should consider individual patient characteristics, preferences, and comorbidities to optimize treatment outcomes. Future prospective, large-scale, multicenter studies are warranted to validate these observations and further define the long-term cardiovascular and metabolic implications of these therapeutic strategies in diverse patient populations.

Disclosure of conflict of interest

None.

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