Original article

Comprehensive therapeutic and renoprotective effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus: a subanalysis

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Abstract

Background/Aim: Sodium–glucose transport protein 2 (SGLT2) inhibitors are versatile in action and are considered appropriate for treatment of diabetes. In this study, the efficacy of SGLT2 inhibitor therapy for atherosclerosis and protection of renal function in patients with type 2 diabetes was investigated over a 5-year period.
Patients and Methods: Forty-three patients with treated diabetes were divided into an SGLT2 inhibitor group (SG group, n=31) and an SGLT2 inhibitor-naive group (non-SG group). The prospective incidence rates of coronary artery disease, stroke, and cardiocerebrovascular disease (C-CVD) were calculated by scoring risk factors over a period of 5 years. The effect on the estimated glomerular filtration rate was also assessed.
Results: Patients in the SG group were younger and heavier than those in the non-SG group. The prospective incidence rates of coronary artery disease and C-CVD were lower in the SG group than in the non-SG group during 5 years of follow-up. The decline in estimated glomerular filtration rate was maintained at a lower rate in the SG group. The results for coronary artery disease, C-CVD, and renal function were confirmed even when age was corrected for cases under 65 years of age.
Conclusion: Long-term use of SGLT2 inhibitor therapy was effective in the treatment of atherosclerotic disease and had a renoprotective effect.

Key words: type 2 diabetes, sodium-glucose transporter 2 inhibitors, comprehensive treatment, renoprotective effect, glomerular filtration rate

Introduction

Considering that risk factors often overlap in patients with diabetes, strict management of not only blood glucose but also lipid levels and blood pressure (BP) is recommended from an early stage [1, 2]. Sodium–glucose transporter 2 (SGLT2) inhibitors are considered to

be versatile in action and appropriate for the treatment of diabetes from its earliest stages [3, 4]. SGLT2 inhibitors have been used in clinical practice since 2014 in Japan, where the initial recommendation for their use was in relatively younger patients with mild diabetes and kidney dysfunction [5]. Since then, the indications have been expanded to include congestive heart failure and chronic kidney disease [4]. In this study, we evaluated the comprehensive therapeutic effects of SGLT2 inhibitors on atherosclerotic vascular disease and renal function in patients with type 2 diabetes over a 5-year period.

Methods

Since 2015, patients with type 2 diabetes attending our department have been treated with management targets and received regular health check-ups over a 5-year period. The prospective incidence rates of coronary artery disease (CAD), stroke, and cardio-cerebrovascular disease (C-CVD) were calculated based on the following risk factors: age, sex, body mass index (BMI), BP, smoking status, serum lipids, and diabetes status [1, 6].

Subjects

This was a primary prevention study, so patients with a history of cardiac or cerebrovascular disease were excluded. There was one exclusion for cerebral infarction in the SG group and one each for angina pectoris and cerebral infarction in the non-SG group. One patient in the SG group was excluded because he developed angina pectoris and underwent bypass surgery in the third year of enrollment. Finally, 43 patients with diabetes treated using antihyperglycemic agents over a 5-year period since 2015 were enrolled and divided according to whether they did or did not receive an SGLT2 inhibitor (SG group, n=12; non-SG group, n=31; Figure 1). The antidiabetic and other medications used in both study groups are summarized in Table 1. Blood glucose-lowering agents and dipeptidyl peptidase-4 inhibitors were the main anti-diabetes medications used in both groups. Five types of SGLT2 inhibitors were used in the 12 patients in the SG group.

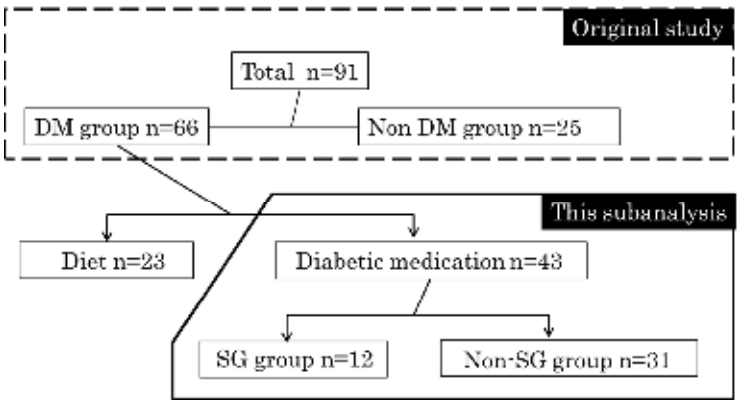

Figure 1 Design of this subanalysis study.
Forty-three patients with DM treated using antihyperglycemic agents over a 5-year period since 2015 were enrolled and divided into those who received an SGLT2 inhibitor (SG group, n=12) and those who did not (non-SG group, n=31). DM, diabetes mellitus; non-SG group, SGLT2 inhibitor-naive group; SG group, SGLT2 inhibitor group

At enrollment in 2015, patients in the SG group were significantly younger and heavier than those in the non-SG group (Table 2). Glycated hemoglobin (HbA1c) was significantly higher in the SG group. There was no statistically significant between-group difference in estimated glomerular filtration rate (eGFR).

Table 1 Details of medications used for multifactorial intervention in the SG group and the non-SG group

medications	SG group n=12			non-SG group n=31	
	no	ratio		no	ratio
Antihypertencive drugs	7	58.3%		20	64.5%
Antihyperlipidemic drugs	7	58.3%		20	64.5%
Diabetic drugs	46	3.8 drugs/pt	Empagliflozin 4	60	19 drugs/pt
SGLT2i	12	100.0%	ipragliflogin 3	0	0.0%
BG	12	100.0%	dapagliflozin 2	16	51.6%
DPP4i	10	83.3%	canagliflozin 2	24	77.4%
AGI	1	8.3%	tofogliflozin 1	8	25.8%
Glinido	0	0.0%		2	6.5%
SU	2	16.7%		2	6.5%
TZD	2	16.7%		4	12.9%
Insulin	5	41.7%		3	9.7%
GLP-1RA	2	16.7%		1	3.2%

Blood glucose-lowering agents and DPP4 inhibitors were the main anti-diabetes agents used in both groups. Five types of SGLT2 inhibitors were used in the 12 patients in the SG group. AGI, alpha glucosidase inhibitor; BG, blood glucose-lowering agent; DPP4i, dipeptidyl peptidase-4 inhibitor; Glinido, rapid-acting insulin secretagogues; GLP-1RA, glucagon-like peptide-1 receptor agonist; non-SG group, SGLT2 inhibitor-naive group; SG group, SGLT2 inhibitor group; SGLT2i, sodium–glucose transport protein 2 inhibitor

Table 2 Comparison of clinical characteristics at enrollment between the SG group and the non-SG group

oY	SG group	non-SG group	p value
n	12	31	
M/F	9 v 3	24 v 7	
age	53.2± 8.2	61.7± 9.0	0.003
BMI	27.9±3.4	25.1±4.2	0.024
LDL-C	108.4±37.4	102.0±28.2	0.273
HDL-C	51.7±7.7	58.7±19.3	0.113
TG	103.3±31.6	99.2±58.3	0.410
sBP	130.7±14.7	127.1±13.8	0.230
dBP	81.9±14.1	78.7±13.8	0.257
HbA1c	7.7±1.2	6.9±1.2	0.034
smoking	5 v 7	11v 20	
eGFR	65.6±13.6	57.9±16.5	**0.084**

There was a significant difference in age and BMI between the SG group and the non-SG group. HbA1c was significantly higher in the SG group and there was no statistically significant between-group difference in eGFR.
BMI, body mass index; dBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-SG group,

Absolute risk assessment

Assessment of the absolute risk of atherosclerotic vascular disease was determined for patients with CAD, those with stroke, and those with C-CVD. Each prospective incidence rate was evaluated annually over 5 years using the following scoring methodology. CAD included myocardial infarction and angina pectoris and was evaluated using the Risk Assessment Chart Application for Atherosclerotic Disease Prevention

Guidelines 2017 [6] and 2022 [7] based on the Suita study [8, 9]. Stroke included the combined incidence of cerebral infarction and cerebral hemorrhage and was assessed using the risk scoring system described in the Japan Public Health Center-based Prospective Study [10, 11]. C-CVD included both CAD and cerebrovascular disease and were assessed using the scoring system from the 2006 Hisayama study [12, 13]. These scores are based on factors such as age, sex, BMI, BP, serum lipids, diabetes status, and smoking status.

Management of target values

The treatment management targets were similar to those in the conventional treatment group in the J-DOIT3 study [14] and also partly in line with the application program for absolute assessment. The targets are as follows: BMI≥25.0; systolic BP≥140 mmHg; low-density lipoprotein cholesterol≥140 mg/dL (in patients without diabetes mellitus) or≥120 mg/dL (in patients without diabetes mellitus); HbA1c ≥7.0%; and smoking cessation.

Ethics statement

The study was approved by our institutional ethics committee (approval number 64). Research field: clinical research, epidemiological research (including observational research). Research subjects: patients attending the Lifestyle-Related Disease Centre at our institution. Evaluation: absolute risk assessment and longitudinal follow-up of macrovascular diseases (coronary heart disease, cerebrovascular disease). All patients provided informed consent.

Statistical analysis

Values are expressed as the mean ± standard deviation and were compared between the SG group and the non-SG group using the unpaired t-test. All statistical analyses were performed using BellCurve in statistics Microsoft Excel (Microsoft Corp., Redmond, WA, USA). A P-value <0.05 was considered statistically significant.

Results

Effect of SGLT2 inhibitor therapy on the prospective incidence of atherosclerotic vascular disease

The percentage of management goals achieved between enrollment and year 5 are shown in Figure 2. BP and low-density lipoprotein cholesterol were maintained at goal. BMI decreased and smoking cessation increased in both groups and HbA1c decreased in the SG group; however, target values were not reached.

The 5-year prospective incidence of atherosclerotic vascular disease (i.e., CAD, stroke, and C-CVD) in the SG group and non-SG group is shown in the upper column in Figure 3. Each score includes patient age as a risk factor. Therefore, the prospective incidence increases year by year. The 5-year prospective incidences of CAD, stroke, and C-CVD were all lower in the SG group than in the non-SG group.

The percentage rates of increase for each year from enrollment is shown in the lower column in Figure 3. Comparing the areas under the curve for the 5-year period, the rates of increase in CAD (p=0.025) and C-CVD (p=0.022) were significantly lower in the SG group than in

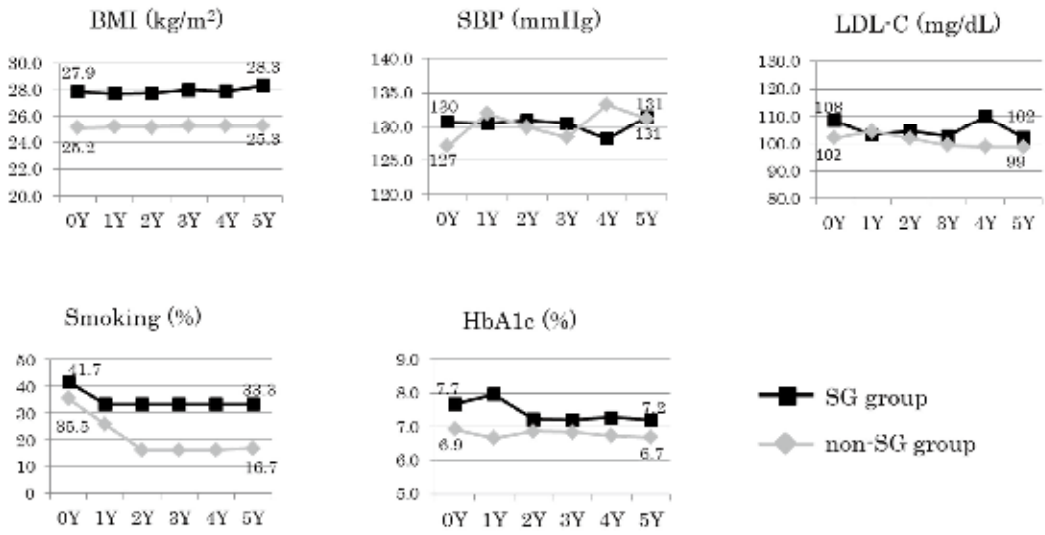

Figure 2 Percentages of management goals achieved between enrollment and year 5.
Systolic blood pressure and LDL-C were maintained at goal. BMI decreased and the smoking cessation rate increased in both study groups and HbA1c decreased in the SG group. However, target values were not reached.
BMI, body mass index; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; non-SG group, SGLT2 inhibitor-naive group; sBP, systolic blood pressure; SG group, SGLT2 inhibitor group

the non-SG group, possibly because of the effect of SGLT2 inhibitor therapy.

Effect of SGLT2 inhibitor therapy on eGFR

The annual change in eGFR over the same 5-year period is shown in Figure 4. The annual decline in eGFR (mL/min/1.73 m2) is shown on the left and the percentage decline from the year of enrollment is shown on the right. The rate of decline was significantly lower in the SG group (1.1 ± 1.4 mL/min/1.73 m2 per year) than in the non-SG group (1.7 ± 2.0 mL/min/1.73 m2 per year). Even in healthy subjects, the decline in eGFR per year is generally reported to be around 1 mL/min/1.73 m2 [15, 16]. Therefore, the rate of decline in eGFR in the SG group was similar to that in healthy subjects.

Considering the close relationship between patient age and eGFR, similar comparisons were made in two groups with no statistical difference in age between them. Next, a comparison of the change in eGFR decline over time was performed in patients aged under 65 years to adjust for the non-significant difference in age between the two groups (SG group, n=11; non-SG group, n=19). The ability of SGLT2 inhibitors to suppress the decline in eGFR was confirmed in patients younger than 65 years of age (p=0.011).

Accordingly, when the prospective incidence and its rate of increase were re-examined in this age group, there was a decrease in CAD (p=0.019) but not in cardiovascular disease (p=0.112).

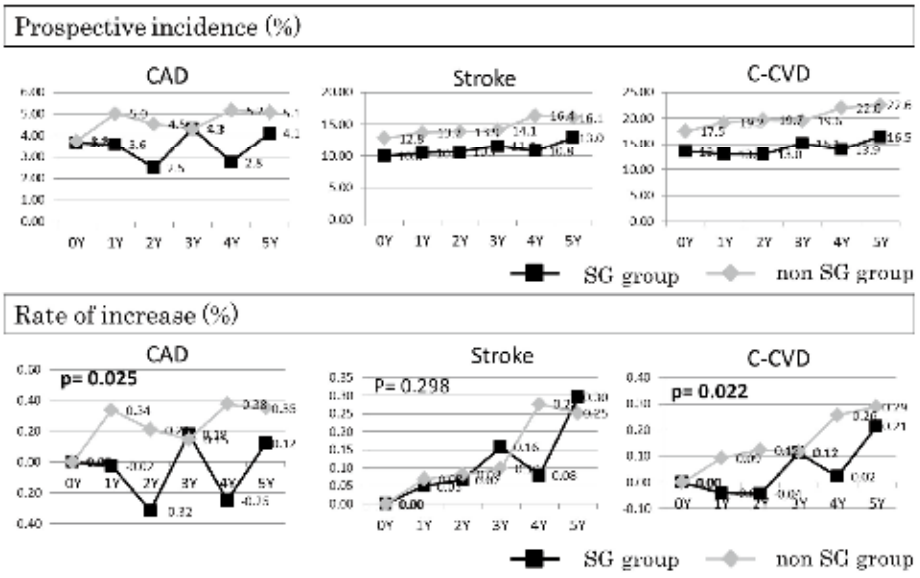

Figure 3 Prospective incidence of ASVD (top column) and annual rate of increase in ASVD (bottom column) over 5 years in the SG group and the non-SG group.
The 5-year prospective incidences of CAD, stroke, and C-CVD were all lower in the SG group than in the non-SG group. The areas under the curve for the 5-year rates of increase in CAD and C-CVD were significantly smaller in the SG group than in the non-SG group, possibly because of the effect of treatment with an SGLT2 inhibitor.
ASVD, atherosclerotic vascular disease; CAD, coronary artery disease; C-CVD, cardiocerebrovascular disease; non-SG group, SGLT2 inhibitor-naive group; SG group, SGLT2 inhibitor group

Discussion

The treatment of diabetes is steadily changing over time. The incidence of vascular complications of diabetes and their contribution to mortality have decreased significantly with recent advances in treatment [17, 18] based on the effects of many novel agents [19] and the results of large clinical trials [14, 20]. The choice of antidiabetic agents should take into account the expectation that they can minimize existing organ damage and future risks, such as atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease [19]. The ultimate goal of diabetes care is to increase life expectancy by improving metabolic abnormalities, preventing complications, and maintaining a good quality of life for the patient [21]. Early intensive treatment of multiple factors, including not only blood glucose but also BP, lipids, and body weight, is important in the management of patients with type 2 diabetes in terms of their future risk of developing macrovascular and microvascular disease [1, 21].

SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists have demonstrated cardiovascular benefit in patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, such

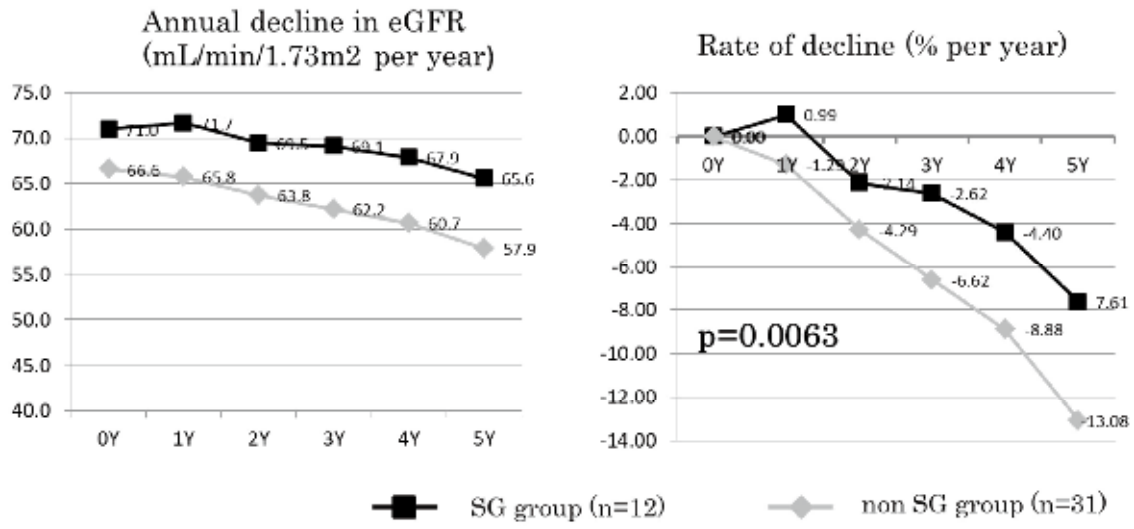

Figure 4 Annual decline and percentage rate of decline in eGFR per year.
The rate of decline was significantly slower in the SG group than in the non-SG group. The rate of decline was suppressed to the level of healthy subjects in the SG group.
eGFR, estimated glomerular filtration rate; non-SG group, SGLT2 inhibitor-naive group; SG group, SGLT2 inhibitor group

as established heart failure or kidney disease, and are included as a grade A recommendation in the 2020 American Diabetes Association guidelines [21].

The SGLT2 enzyme is active from the early stages of type 2 diabetes, and SGLT2 inhibitors inhibit glucose reabsorption in the proximal tubule and increase urinary excretion of glucose [22, 23], so are suitable for use in early therapeutic intervention. In addition to their hypoglycemic effect, SGLT2 inhibitors have multiple metabolic benefits in terms of risk factors for atherosclerotic disease, including reduction in weight (visceral fat) [24], lipid metabolism [25], uric acid levels [26, 27], and BP [28, 29]. They are also expected to have an early beneficial effect on the cardiac response via their diuretic effects [30]. For example, the SGLT2 inhibitor empagliflozin has been reported to reduce all-cause mortality, the risk of cardiovascular death, and hospital admissions for heart failure in patients with type 2 diabetes and cardiovascular disease [31, 32]. Renoprotective effects have also been reported, including slowing of progression of renal damage and a decrease in the incidence of kidney-related adverse events [3, 4, 31, 32].

When SGLT2 inhibitors were introduced into clinical use in Japan in 2014, a recommendation for their use in the treatment of diabetes was initially published by the Committee on the Appropriate Use of SGLT2 Inhibitors. The recommendations for appropriate use of SGLT2 inhibitors [33] mentioned that patients at high risk for dehydration and increased ketoacidosis in response

to SGLT2 inhibitor therapy, such as the elderly, those with extreme weight loss, and those with excessively impaired renal function, would not be candidates for these agents. In accordance with this recommendation, a comparison of data at the time of enrollment in our study in 2015 showed that patients in the SG group were significantly younger and had a higher BMI than those in the non-SG group. HbA1c was higher in the SG group and there was no statistically significant between-group difference in eGFR. Therefore, we reevaluated the data by focusing on patients under 65 years of age and eliminating the age difference and found no between-group difference in the ability of SGLT2 inhibitor therapy to prevent a reduction in eGFR.

The original study upon which this subanalysis is based found no difference in the rate of increase in the prospective incidence of atherosclerotic disease in outpatients receiving treatment regardless of whether or not they had diabetes. In this subanalysis, the SG group exhibited a markedly reduced prospective incidence of CAD and C-CVD, in addition to a notable suppression of the decline in eGFR, when compared with the non-SG group during 5 years of follow-up.

In conclusions, SGLT2 inhibitors prevented the onset of CAD and C-CVD and suppressed the decline in eGFR over time. This small subanalysis shows that SG is beneficial in both the short-term and long-term management of diabetes.

Acknowledgments

The authors thank the staff members in the Department of Diabetes and Endocrinology at Aomori Rosai Hospital and Mutsuko Takebe at our hospital for her help with collection of data. The authors are grateful to Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

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