2．糖尿病・内分泌内科

入院患者内訳　　２０２３年度

糖尿病	87	
１型DM		11
２型DM		76
内分泌疾患	38	
PA		10
甲状腺疾患		1
電解質異常		14
その他の部位		13
感染症	110	
肺炎		76
尿路感染		26
その他の部位		8
脳梗塞	33	
脳梗塞		32
脳出血		1
睡眠時無呼吸症候群	82	
眩暈症	17	
うっ血性心不全	20	
その他	76	
合計	463	

外来患者数	22,152 人
新外来患者数	1,756 人
時間外救急患者数	1,439 人
入院患者延数	7,627 人

Original article

Effect of comprehensive treatment on the development of atherosclerosis in patients with type 2 diabetes: a 5-year absolute risk follow-up study

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Abstract

Study Aim We investigated the effects of comprehensive treatment on arteriosclerotic diseases in patients with type 2 diabetes using absolute risk assessments for 5 years.

Method The subjects were 91 patients (66 with diabetes and 25 without diabetes) who had undergone comprehensive treatment for more than 5 years in our hospital. The prospective incidence rates for macrovascular disorders, coronary artery disease (CAD), stroke, and cardio-cerebrovascular disease, were calculated using risk factor scores.

Results 1) The management target achievement rates 5 years after enrollment were as follows: diabetes group: blood pressure: 73.1%; low-density lipoprotein cholesterol: 92.3%; and hemoglobin A1c: 59.6%. The comparative rates in the non-diabetic group were: blood pressure: 85.7% and low-density lipoprotein cholesterol: 85.7%. 2) Over the 5 years, the prospective risk of developing CAD increased from 3.8% to 5.0%; stroke, from 11.6% to 14.4%; and cardio-cerebrovascular disease, from 16.6% to 20.4% in the diabetic group. The increased rates compared with enrollment for CAD, stroke, and cardio-cerebrovascular disease showed no differences between the groups, with 31.5%, 24.0%, and 23.0% in the diabetic group vs. 26.6%, 25.9%, and 22.9%, respectively, in the non-diabetic group. The numbers of therapeutic drugs for hypertension, hyperlipidemia, and diabetes showed a difference of 4.0 drugs per patient per day in the diabetes group and 1.6 drugs per patient per day in the non-diabetes group.

Conclusion Comprehensive treatment of macrovascular disease in diabetic patients receiving appropriate medication improved the disease incidence to the same level as that of non-diabetic patients.

Key words: type 2 diabetes, comprehensive treatment, arteriosclerotic vascular disease (ASVD), prospective incidence, absolute risk assessments

Introduction

As patients with diabetes often have multiple risk factors, the AS2022 guideline recommends comprehensive and tight management of blood glucose, lipids, and blood pressure from the early stages of diabetes to prevent arteriosclerotic vascular disease (ASVD) in patients with diabetes [1].

A series of reports from the Steno-2 study have shown that early comprehensive management of multiple risk factors, such as hyperglycemia, hypertension, dyslipidemia, and smoking, prevents ASVD and improves life expectancy in patients with diabetes [2-5]. In the J-DOIT3 study, which was a large-scale clinical study, Japanese patients with type 2 diabetes were randomized to conventional therapy or intensive therapy to achieve better control of hemoglobin (Hb)A1c, blood pressure, low-density lipoprotein cholesterol (LDL-C), and obesity. A significant reduction in the incidence of ASVD was observed in the intervention group with predetermined adjustment for factors such as smoking, demonstrating the importance of comprehensive risk management in Japanese patients [6]. On the basis of these intensive multifactorial interventional studies, it is now common practice for patients with diabetes to receive comprehensive treatment at an early stage in their medical care.

For an overall assessment of the prospective incidence of ASVD, the overlap of major risk factors in individual patients is essential, and it is necessary to assess the absolute risk rather than the relative risk. Accordingly, the Japanese Society of Arteriosclerosis changed its risk assessment from the relative risk of coronary artery disease (CAD) to the absolute risk of all-cause mortality from CAD over a 10-year period in the 2012 edition [7] of the guidelines. However, it is difficult to assess whether such treatment is appropriate in every patient, clinically. This study clinically evaluated and compared the effect of comprehensive treatment on the absolute risk of developing ASVD in outpatients with and without diabetes.

Study Aim

The aim of this study was to use absolute assessments annually for 5 years to determine the prospective incidence (%) of coronary artery disease (CAD), stroke, and cardio-cerebrovascular disease (C-CVD). Comparisons were made between diabetic and non-diabetic patients with respect to incidence rates and treatment details, such as residual risk factors and medication use.

Methods

Subjects

The subjects were patients in our department who underwent annual health check-ups. This study was a primary prevention study, so patients with a history of cardiac or cerebrovascular disease were

excluded. These comprised one patient with angina pectoris and two patients with cerebral infarction in the diabetic group and one patient with cerebral infarction in the non-diabetic group. One patient enrolled in the diabetes group was excluded from the study because he developed angina pectoris and underwent bypass surgery in the third year of enrollment. Finally, we compared 91 patients with diabetes (66 patients, male/female: 45/21, age: 60.4 ± 9.8 years) and those without diabetes (25 patients, male/female: 17/8, age: 61.4 ± 9.9 years) (Figure 1).

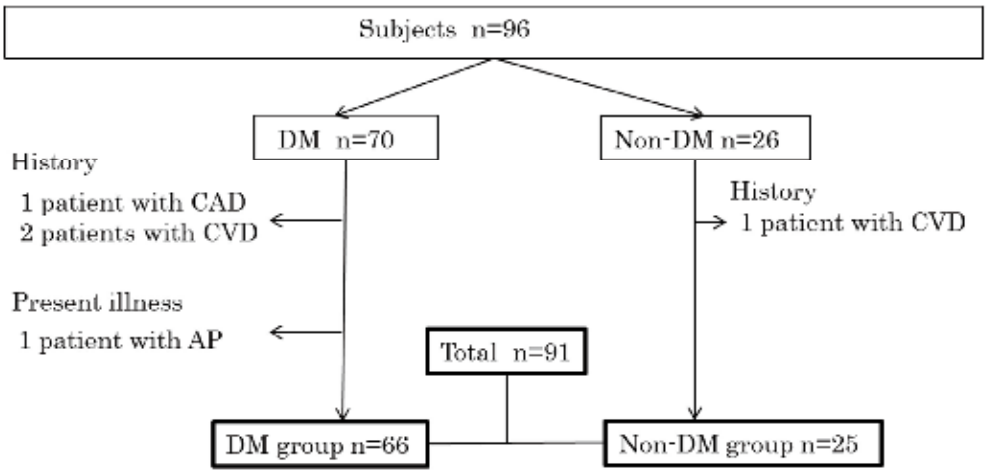

Fig. 1 Study design
This was a primary prevention study, so patients with a history of cardiac or cerebrovascular disease were excluded. These included four patients in the diabetic group and one patient in the non-diabetic group. After excluding these patients, we compared 91 patients: 66 with diabetes and 25 without diabetes
DM, diabetes mellitus; CAD, coronary artery disease; CVD, cerebrovascular disease; AP, angina pectoris

The scores comprised commonly used factors, such as age, sex, blood pressure, serum lipids, presence of diabetes, and smoking.
The management targets (other than age and sex) were determined as follows:

Body mass index (BMI) < 25 kg/m2
High blood pressure < 140/90 mmHg
Hypercholesterolemia
People without diabetes:
LDL-C < 140 mg/dL
People with diabetes:
LDL-C < 120 mg/dL
HbA1c < 7.0%
Smoking cessation

We used the following clinical score system annually for 5 years to assess the prospective incidence of ASVD. Each prospective incidence rate was evaluated on the basis of the score, as follows:

(1) CAD incidence included the incidences of myocardial infarction and angina pectoris, and the Risk Assessment Chart Application for Atherosclerotic Disease Prevention Guidelines 2017 [8] and 2022 [9], in accordance with the Suita study [10, 11].

(2) Stroke incidence combined the incidences of cerebral infarction and

cerebral hemorrhage. The risk score from the Japan Public Health Center-based Prospective study [12, 13] was used.

(3) C-CVD was assessed using scores from the Hisayama study (2006 Risk Score Hisayama Town Study) [14, 15], which included both coronary artery diseases and cerebrovascular diseases.

Comprehensive treatment details were examined on the basis of changes in incidence rates, which were calculated annually.

Ethics approval and consent

The study was approved by our hospital's ethics committee (approval number: 64). Research field: Clinical research, epidemiological research (including observational research); Research subjects: Patients attending the Lifestyle-Related Disease Centre of our hospital; 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 mean ± standard deviation. Comparisons between the diabetic and non-diabetic groups were performed using the unpaired t-test. Statistical analyses were performed using BellCurve in statistics Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and $P < 0.05$ was considered statistically significant.

Results

(1) Management targets and their achievement rates (%) (Figure 2)

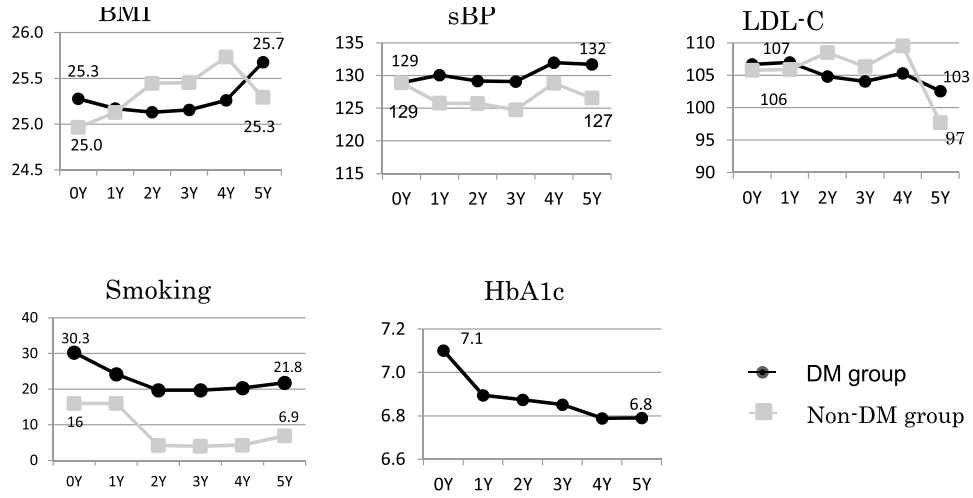

Fig. 2 Management targets and their achievement rates (%)

Each year's progress toward the management targets over the 5-year period are shown. Only the average BMI did not reach the management target value over the 5-year period, in both the diabetic (46.2%) and non-diabetic (57.1%) groups. However, this achievement rate was particularly low in the diabetic group

BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HbA1C, hemoglobin A1C

The annual progression of the achievement of the management targets over the 5-year period is shown in Figure 2. Overall, the target achievement rates at 5 years were 57.5% for BMI, 80% for SBP, 92.5% for LDL-C, and 81.4% for smoking cessation. Of these, the achievement rates in the diabetes group were 46.2% for BMI, 73.1% for SBP, 92.3% for LDL-C, 59.6% for HbA1c, and 78.2% for smoking cessation, while the rates in the non-diabetic group were 57.1% for BMI, 85.7% for SBP, 85.7% for LDL-C, and 93.1% for smoking cessation at 5 years. Only the average BMI did not reach the management target value over the 5-year period, in both the diabetic (46.2%) and non-diabetic (57.1%) groups; the achievement rate was particularly low in the diabetic group.

(2) Prospective incidence (%) of ASVD

The 5-year time course of the prospective incidence of ASVD, i.e., CAD, stroke, and C-CVD, for all patients, and in the diabetic and non-diabetic groups, are shown in Figure 3.

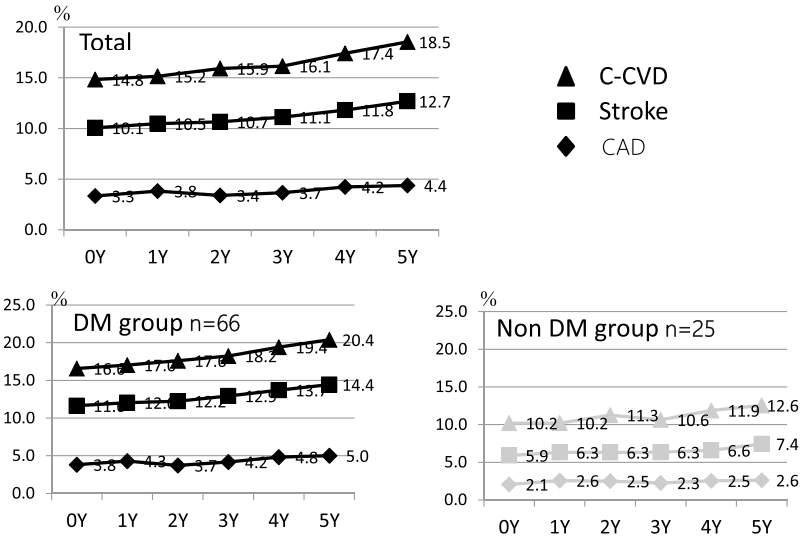

Fig. 3 The 5-year time courses of the prospective incidences of CAD, stroke, and C-CVD in the overall population and in the diabetic and non-diabetic groups

Despite treatment, the annual incidence of each of the three atherosclerotic diseases remained approximately twice as high in patients with diabetes compared with those without diabetes

DM, diabetes mellitus; CAD, coronary artery disease; C-CVD, cardio-cerebrovascular disease

Each score included the patient's age as a risk factor; therefore, the prospective incidence rates increased annually. Despite treatment, the annual incidence of each of the three atherosclerotic diseases remained approximately twice as high in diabetics as in non-diabetics. Previous epidemiological studies reported that the incidences of CAD and stroke and the associated mortality rates are significantly higher in diabetic patients compared with non-diabetic patients. [1,10,12,13,14]. Our results showed that the incidence of each disease was higher in patients with vs. without diabetes in any given year, in the order of C-CVD, stroke, and CAD.

In the scoring system we used, each incidence risk was calculated by adding +5 for patients with diabetes for CAD (in accordance with the Suita study) [10], +7 for stroke (in accordance with the Japan Public Health Center-based Prospective study) [12, 13], and +2 for C-CVD (in accordance with the Hisayama study) [14]. When the incidence rates were recalculated by subtracting the additional score for diabetes, above, from the score for diabetics (or by setting the additional score for diabetics to 0), the incidence rates for both groups were almost identical.

Next, we calculated the rate increase (%) in the incidence of each disease for every year relative to the time of enrollment. We found no difference between the diabetic and non-diabetic groups for the rate increase (%) over the 5-year period (Figure 4).

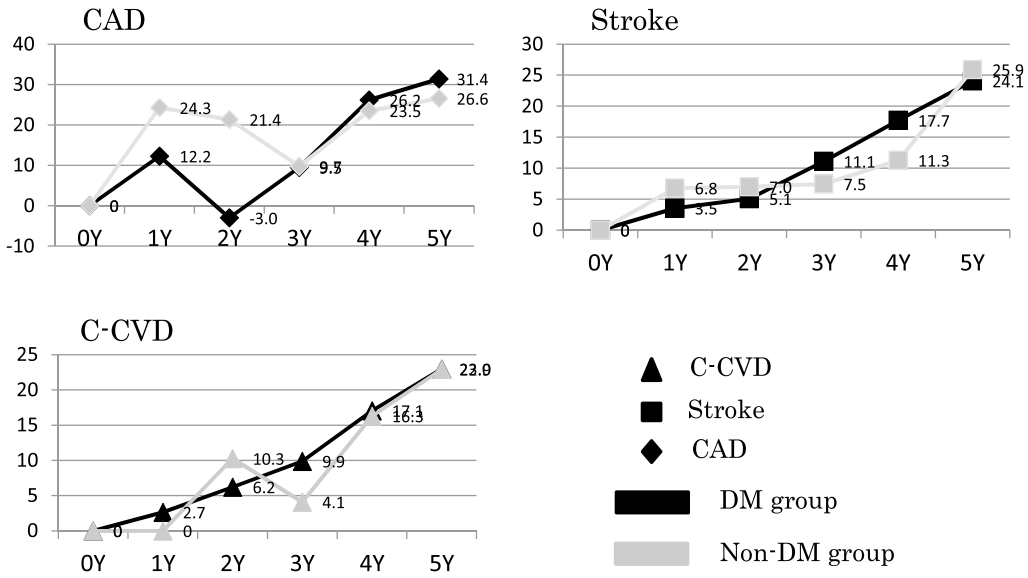

Fig. 4 The image shows the increase in the prospective incidence rates (%) for each year relative to the time of enrollment

We calculated the increase in the prospective incidence rates (%) for each year relative to the time of enrollment. We found no difference between the diabetic and non-diabetic groups for the rate increases (%) over the 5-year period of the study

CAD, coronary artery disease; C-CVD, cardio-cerebrovascular disease

These results suggest that there may be no difference in the prospective incidence of ASVD between the diabetic and non-diabetic groups if both groups are treated comprehensively.

(3) Numbers of drugs used for comprehensive treatment of patients in the diabetic and non-diabetic groups.

Table 1 shows the numbers of medications used during the follow-up period in both groups. During the 5 years from enrollment, the total number of drugs for hypertension, hyperlipidemia, and diabetes averaged 4.0 drugs per patient per day in the diabetes group and 1.6 drugs per patient per day in the non-diabetes group (Table 1). The use of more than twice as many therapeutic drugs (4.0 vs. 1.6, respectively) in the diabetic vs. the non-diabetic group was expected to reduce the incidence of ASVD to the same frequency as that in the non-diabetic group. In other words, the rate of the prospective increase in the number of drugs in the diabetic group was expected to be comparable to that in the non-diabetic group if twice as many agents were used in the diabetic vs. non-diabetic group.

Table 1 Numbers of drugs used for comprehensive treatment (per patient per day) in the diabetic and non-diabetic groups

	DM group		Non-DM group	
	0 years	5 years	0 years	5 years
Antihypertensive drugs	0.7	0.9	0.7	0.8
Antihyperlipidemic drugs	0.5	0.6	0.8	0.8
Diabetic drugs	1.9	2.5	0.0	0.0
Total	3.1	4.0	1.4	1.6

In the DM group (4.0 drugs per person per day), the incidence of atherosclerotic disease was comparable to that in the non-DM group (1.6 drugs per person per day) when multiple therapeutic agents were used. DM, diabetes mellitus; 0 years, at enrollment

(4) Relationship between residual risk factors and numbers of drugs used in both groups at the 5-year assessment (Table 2).

At the 5-year assessment, 41% of the diabetic patients achieved the original target of zero residual risk, with comprehensive treatment, markedly less than the percentage in the non-diabetic group at 64%. Furthermore, the risk factors for 59% of the diabetic patients and 36% of the non-diabetic patients did not reach the targets despite treatment with therapeutic drugs. Therefore, there were cases in both groups in which the risk could not be reduced, even with the use of higher doses of medication. Indeed, when multiple risk factors remained, the number of drugs used was 4.6 in the

diabetic group versus 1.0 in the non-diabetic group (Table 2).

Table 2 Relationship between residual risk factors and the numbers of drugs used in both groups at the 5-year assessment

	DM group			Non-DM group		
No. of residual risk factors at 5 years	0	1	>2	0	1	>2
No. of patients (%)	27 (41%)	26	13	16 (64%)	8	1
Nos. and types of drugs used at 5 years						
Antihypertensive drugs	0.9	1.1	0.9	0.5	1.4	0.0
Antihyperlipidemic drugs	0.6	0.6	0.7	0.9	0.6	1.0
Diabetic drugs	1.9	2.8	3.0	0.0	0.0	0.0
Total	3.3	4.5	4.6	1.4	2.0	1.0

There were cases in both groups in which the risk of atherosclerosis could not be reduced even with the use of higher drug doses. When multiple risk factors remained, the number of drugs was 4.6 per

Discussion

We evaluated the absolute risk of developing ASVD in diabetic patients compared with non-diabetic patients using risk factor scoring systems that were calculated annually for 5 years. The incidence of vascular complications of diabetes and their contribution to mortality have decreased significantly with recent advances in treatment [16]. We assessed the prospective incidence rather than disease-associated mortality because the disease mortality rate is much lower than the prospective incidence [17]. The Japan Diabetes Society has performed five surveys to date on the causes of death among diabetics. The studies were performed every 10 years from 1971 to 2020 [18-22]. The latest report (2010–2020) [22] compared diabetic and non-diabetic patients for the first time in terms of age at death in patients with the same health status. The results showed a difference of 0.6 years for the age at death between Japanese diabetics (75.4 ± 11.1 years) and non-diabetics (74.8 ± 15.9 years). Additional reports on the life expectancy of people with vs. without diabetes with the same health status are shown in Table 3 [22-25]. The table summarizes the reported “age at death” and “life expectancy from the age of 40” for diabetic and non-diabetic patients. The results showed that the difference in age between the two groups was only 0.2–2.6 years.

According to the aforementioned JDS reports [18-22], the proportion of deaths from vascular disease fell by approximately one-quarter, from 39.3% to 10.9%, over the 40-year period from 1981 to 2020. In the latest report by the JDS [22], the proportion of deaths from vascular disease was almost equal between diabetics (10.8%) and non-diabetics (11.3%).

Table 3 Age at death and life expectancy from age 40 years in Japanese patients: comparison between diabetic and non-diabetic patients

	No.		Male		Female		Total		Reference No.
	DM	Non-DM	DM	Non-DM	DM	Non-DM	DM	Non-DM	
Age at death (years)	68,555	164,621	74.4	73.5	77.4	76.6	75.4	74.8	22
	11,154,833	131,123,153	77.4	79.3	82	84.4	79.3	81	23

	No.		Male		Female		Total		Reference No.
	DM	Non-DM	DM	Non-DM	DM	Non-DM	DM	Non-DM	
Life expectancy	N/A	N/A	N/A	39	N/A	45.5	N/A	N/A	24
from age 40 years	6140	24,079	39.2	N/A	43.6	N/A	N/A	N/A	25

The results showed that the difference in age at death between the diabetic and non-diabetic groups was only 0.2–2.6 years.DM, diabetes mellitus; N/A, not applicable

Our study followed the prospective incidence of atherosclerotic diseases in diabetic and non-diabetic patients from a general clinical perspective. Our results showed that the prospective incidence of ASVD in diabetic patients was similar to that in non-diabetic patients when both groups received comprehensive treatment. The results are consistent with those in the recent JDS report [22], indicating that mortality rates associated with vascular disease in diabetic patients are similar to those in the general Japanese population. On the basis of these reports and our study, it is important to actively dispel the diabetes stigma [26] that diabetics have a short life expectancy. It should be noted that the results of this study were based on the use of twice as many drugs in the diabetic group compared with the non-diabetic group; i.e., an average of 4.0 drugs/patient/day vs 1.6 drugs/patient/day, respectively.

In 2008, the US Food and Drug Administration issued guidance to industry requiring studies of cardiovascular outcomes with therapy with glucose-lowering drugs [27]. Since then, a meta-analysis has assessed the cardiovascular safety of newer anti-hyperglycemic agents [28, 29]. The effects of dipeptidyl peptidase 4 inhibitors did not differ significantly from placebo in terms of cardiovascular outcomes [30]. Recently, drugs such as glucagon-like peptide 1 receptor agonists [31, 32, 33] and sodium-glucose cotransporter-2 inhibitors [34, 35] have been introduced, and these are thought to have organ-protective effects in addition to their hypoglycemic effects. Additionally, evidence that supports secondary prevention of cerebrovascular disease [36] and prevention of severe nephropathy [37] with these drugs is accumulating in many large-scale clinical trials. Other drugs with known effects on renal dysfunction and vascular damage, such as renin-angiotensin system inhibitors and AT1 receptor blockers [38-41] for hypertension and 3-hydroxy-

3-methylglutaryl coenzyme A inhibitors (statins) [42, 43] for dyslipidemia, are now standard medications. Notably, in our study, there were a significant number of patients in both groups for whom the risk management goals remained unmet despite increasing drug doses. Furthermore, the prospective incidence of atherosclerotic disease remained high and did not improve in some patients, especially in those with diabetes. Such cases are a problem that leads to so-called clinical inertia [44, 45]. Although our study was limited by its small size, the results are consistent with those in various recent epidemiological studies on the life expectancy of diabetic patients. This study demonstrated once again the importance of comprehensive treatment. However, there is a limit to the effectiveness of treatment (residual risk), and the introduction of new drugs is still expected to help address this, in the future.

In conclusions, we evaluated the effect of comprehensive treatment of atherosclerosis using absolute risk assessment in clinical practice over 5 years. The results showed that the rate of increase in the prospective incidence of atherosclerosis in diabetic patients did not differ from that in non-diabetic patients, when both groups received appropriate medication. It is clear that there are still cases in which comprehensive treatment with standard basic therapies cannot eliminate the residual risk of ASVD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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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.

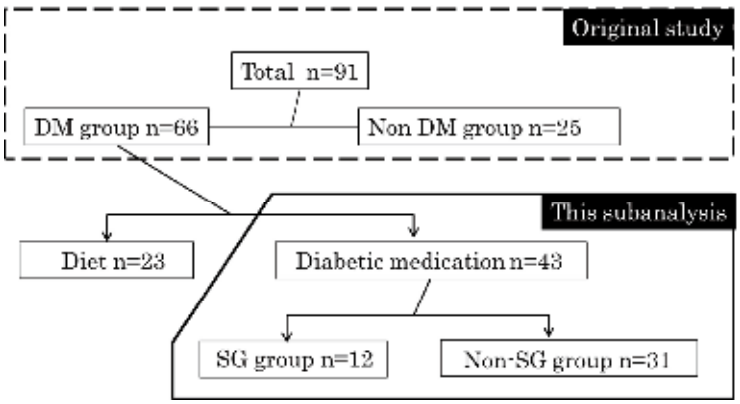

Figure 1 Design of this subanalysis study.
Forty-three patients with DM treated using antihyperglycemic agents over a 5-year period since 2015 were enrolled and divided into those who received an SGLT2 inhibitor (SG group, n=12) and those who did not (non-SG group, n=31). DM, diabetes mellitus; non-SG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

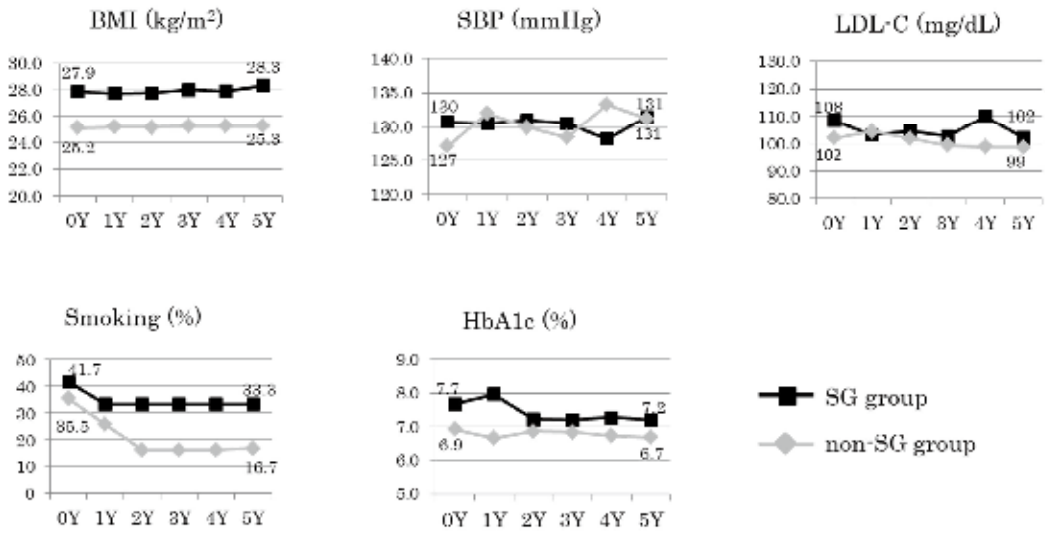

Figure 2 Percentages of management goals achieved between enrollment and year 5.
Systolic blood pressure and LDL-C were maintained at goal. BMI decreased and the smoking cessation rate increased in both study groups and HbA1c decreased in the SG group. However, target values were not reached.
BMI, body 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).

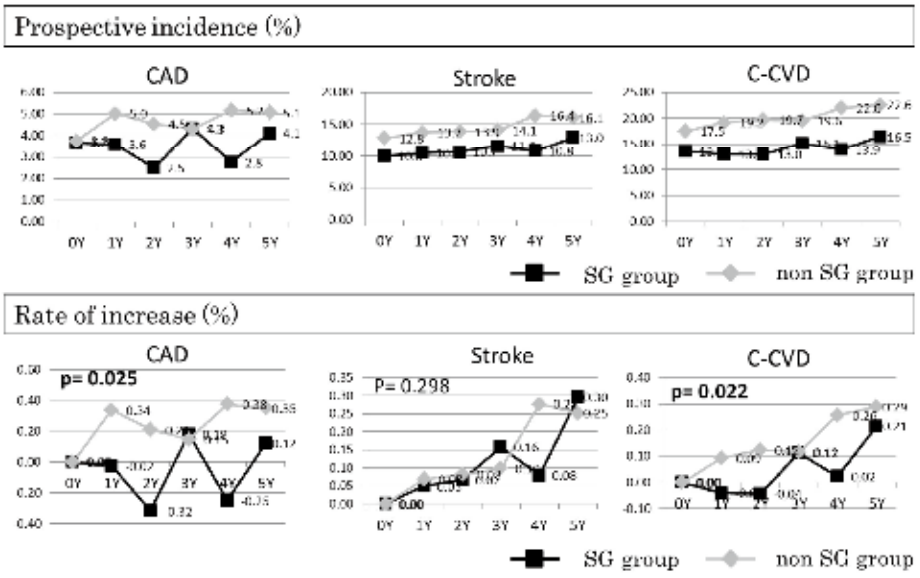

Figure 3 Prospective incidence of ASVD (top column) and annual rate of increase in ASVD (bottom column) over 5 years in the SG group and the non-SG group.
The 5-year prospective incidences of CAD, stroke, and C-CVD were all lower in the SG group than in the non-SG group. The areas under the curve for 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

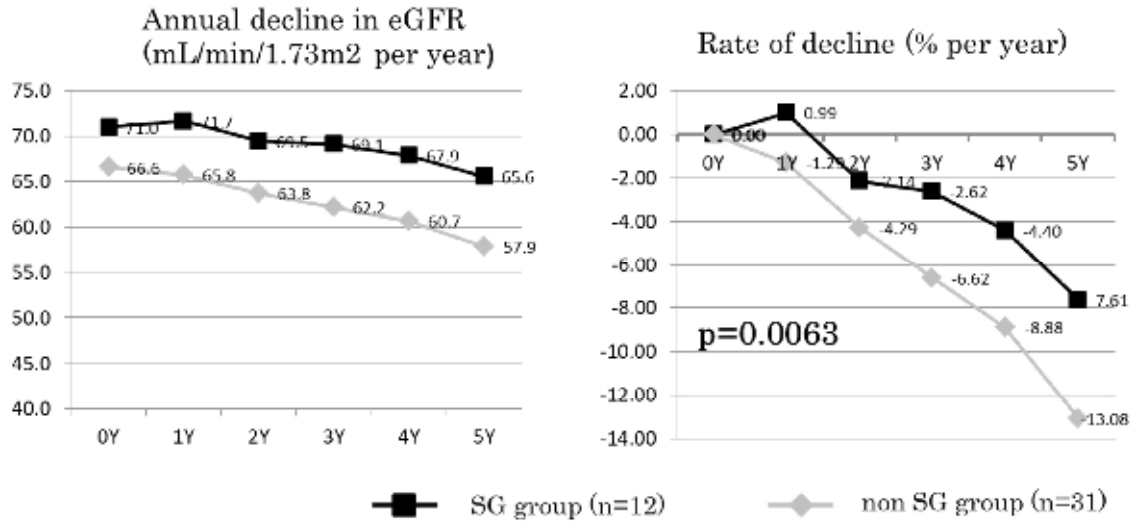

Figure 4 Annual decline and percentage rate of decline in eGFR per year.
The rate of decline was significantly slower in the SG group than in the non-SG group. The rate of decline was suppressed to the level of healthy subjects in the SG group.
eGFR, estimated glomerular filtration rate; non-SG group,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

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Conflicts of interest

The authors declare that they have no conflict of interest.

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