Diabetes Ther (2019) 10:1099–1111
https://doi.org/10.1007/s13300-019-0626-2

ORIGINAL RESEARCH

Real-World Data on the Incidence of Macrovascular Complications in Japanese Patients with Type 2 Diabetes: The Sitagliptin Registration Type 2 Diabetes-Juntendo Collaborating Project

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Received: February 22, 2019 / Published online: April 26, 2019

ABSTRACT

Introduction: Type 2 diabetes is associated with vascular complications that deteriorate the quality of life and decrease the life expectancy of individuals. We previously reported the efficacy of sitagliptin for glucose control in patients with type 2 diabetes in the Sitagliptin Registration Type 2 Diabetes-Juntendo Collaborating Project (SPIRITS-J). Through the results of the SPIRITS-J study, we expected that optimal comprehensive management of type 2 diabetes according to current clinical practice guidelines in addition to achieving individualized glycemic goals would reduce macrovascular complications and all-cause mortality in Japan. The aim of this study was to evaluate this hypothesis.

Methods: We investigated the clinical outcomes prospectively in the extended SPIRITS-J study and compared these to previous Japanese cohort studies in the era before widespread use of guidelines. The primary clinical outcome was a composite of myocardial infarction (MI), stroke, and all-cause mortality.

Results: Mean duration of follow-up was 3.5 ± 1.3 years. The crude incidence of the primary outcome per 1000 person-years was 13.9 (non-fatal MI 1.44, non-fatal stroke 4.22, all-cause mortality 8.79 per 1000 person-years, respectively). It is noteworthy that the incidence of MI in the SPIRITS-J study was very much lower than that in a previous Japanese cohort study. In multivariate analysis, both the history of coronary artery disease and low-density lipoprotein cholesterol (LDL-C) were independently associated with incidence of primary clinical outcome.

Conclusion: The extended SPIRITS-J study demonstrated that optimal comprehensive management in patients with type 2 diabetes according to the recent practice guidelines has succeeded in preventing macrovascular

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The members of SPIRITS-J Study Investigators group are listed in the electronic supplementary material.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13300-019-0626-2) contains supplementary material, which is available to authorized users.

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complications in Japan. This study suggests that more intensive LDL-C-lowering therapy is important for further prevention of macrovascular complications even in Japanese patients with type 2 diabetes (UMIN 000004121).

Keywords: All-cause mortality; Cancer; Low-density lipoprotein cholesterol (LDL-C); Macrovascular complications; Myocardial infarction; Stroke; Type 2 diabetes

INTRODUCTION

The prevalence of type 2 diabetes has been increasing dramatically over the past few decades worldwide [1, 2]. Approximately 10 million individuals in Japan are estimated to be suffering from type 2 diabetes [3]. Type 2 diabetes is associated with vascular complications that affect individuals and deteriorate their quality of life (QOL) and decrease their life expectancy [2, 4–7]. Because cardiovascular diseases such as coronary artery disease and stroke are major causes of death in diabetic patients [2, 5, 7, 8], the ultimate goal of management of patients with diabetes is to maintain their QOL and to prolong their life expectancy by preventing vascular complications [9].

Achieving and maintaining favorable glycemic control have been demonstrated to decrease the risk of microvascular complications [10–13]; however, previous clinical trials to assess the effect of targeting intensive glycemic control failed to reduce the incidence of macrovascular complications [11, 13–15]. On the other hand, the Steno-2 study demonstrated that a multifactorial intervention for glucose, blood pressure, and lipid control had beneficial effects on both microvascular complications and macrovascular complications, and even on mortality in patients with type 2 diabetes [16, 17]. Optimal management of type 2 diabetes is necessary to improve metabolic dysfunction and achieve individualized glycemic goals that eventually reduce diabetic complications, morbidity, and mortality. Although optimal levels of blood pressure targets are controversial, randomized clinical trials demonstrated that blood pressure control reduced the incidence of macrovascular and microvascular complications [18–20]. The efficacy of low-density lipoprotein cholesterol (LDL-C)-lowering therapy by statins on macrovascular complications in patients with diabetes mellitus has been established [21, 22]. Management of type 2 diabetes is aimed not merely at glycemic control but also at comprehensive control of traditional cardiovascular risk factors such as smoking cessation, hypertension, and dyslipidemia [9].

We previously reported that sitagliptin was effective for diabetic management and was well tolerated with few hypoglycemic episodes in Japanese patients with type 2 diabetes in the Sitagliptin Registration Type 2 Diabetes-Juntendo Collaborating Project (SPIRITS-J) [23]. We expected that optimal comprehensive management of type 2 diabetes according to current clinical practice guidelines in addition to achieving individualized glycemic goals in the SPIRITS-J study would reduce macrovascular complications and all-cause mortality. Thus, we investigated clinical outcomes prospectively and compared the incidence of macrovascular complications and all-cause mortality between the extended SPIRITS-J study and the previous Japanese cohort studies in the era before widespread use of guidelines.

METHODS

Subjects

The SPIRITS-J study was conducted as an investigator-initiated, multicenter, cohort study at Juntendo University Hospital, its associated hospitals, and primary care clinics. At first, the SPIRITS-J study was planned to evaluate the efficacy and safety of 6-month sitagliptin add-on therapy in Japanese patients with type 2 diabetes treated by diet and exercise, oral hypoglycemic agents (OHAs), and/or insulin therapy. Details of participants in this study were described previously [23]. After the following 6-month intervention period with sitagliptin, the extended cohort study was planned to investigate the long-term clinical outcomes including all-cause mortality and microvascular

and macrovascular complications prospectively until September 30, 2015. The pharmacological approach including continuation of sitagliptin was left to the attending physician's discretion during the follow-up period. We excluded patients with a history of diabetic ketoacidosis or hyperosmolar non-ketonic coma within 6 months, serious infections, renal dysfunction (serum creatinine $\geq$ 13.26 μmol/dL), and pregnant or breast-feeding women.

The ethics committees of the participating hospitals approved the study protocol and informed consent was obtained from each subject. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. This study was registered as the clinical trial UMIN 000004121. The name of the institutional review board that approved this study is the Juntendo Clinical Research and Trial Center at Juntendo University Hospital.

Data Collection and Biochemical Tests

Baseline demographic data were collected for all patients enrolled in this study including age, sex, body mass index (BMI), diabetes duration, diabetes-related complications, medical history, systolic and diastolic blood pressure, lipid profile, random blood glucose, glycated hemoglobin (HbA1c), serum creatinine, ingredient of medication for dyslipidemia, hypertension, diabetes, and other related diseases. Blood test results were obtained from the medical records. Glucose and HbA1c were measured with standard techniques. The value of HbA1c (%) was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = [HbA1c (Japan Diabetes Society) (%) + 0.4%] [24]. The estimated glomerular filtration rate (eGFR) was calculated by the following formula: eGFR (mL/min/1.73 m^2) = 194 $\times$ Age $-$ 0.287 $\times$ Serum creatinine $-$ 0.1094 ($\times$ 0.739 for women) [25]. The clinical characteristics data including body weight, blood sample data, and ingredient of medication were collected during the follow-up period at 1 year (12 $\pm$ 3 months), 2 year (24 $\pm$ 3 months), and 3 year (36 $\pm$ 3 months) visits which were scheduled according to routine clinical practice.

Clinical Outcomes and Assessments

The primary clinical outcome was a composite of myocardial infarction (MI), stroke, and all-cause mortality. Secondary clinical outcomes were new-onset or progression of microvascular complications including retinopathy, nephropathy, and neuropathy, atrial fibrillation, revascularizations (coronary artery bypass surgery, percutaneous coronary interventions, peripheral artery angioplasty, and carotid artery stenting), peripheral artery disease, heart failure requiring admission, and hypoglycemia.

To diagnose acute MI, transient elevation of biochemical markers based on myocardial necrosis was needed in addition to symptoms or electrocardiographic findings which suggested the existence of myocardial ischemia [26]. Stroke was defined as confirmation of abnormal findings by computed tomography, magnetic resonance imaging, or autopsy and consisted of focal or global neurological deficits. Stroke events were classified according to World Health Organization (WHO) criteria [27]. No cases of asymptomatic lesions detected by brain imaging were included. Only first-ever cardiovascular events during the observational period were counted in the analysis. Information about clinical outcomes was collected through an annual report from each physician. The cause of death conformed to the certificate of death. Adjudication of all clinical outcomes was performed by central committees composed of experts in each complication.

New-onset or progression of microvascular complication was defined as follows: retinopathy was progression from absence of retinopathy to non-proliferative retinopathy or proliferative retinopathy, progression from non-proliferative retinopathy to proliferative retinopathy, or loss of vision caused by retinopathy. Nephropathy was progression from normoalbuminuria to macroalbuminuria,

or progression from microalbuminuria to macroalbuminuria, increase in serum creatinine concentration by at least twice the study baseline, or end-stage renal failure. Neuropathy was peripheral nerve disorder independent from spinal canal stenosis or neurological diseases. Severe hypoglycemia is defined as having low blood glucose level that requires assistance from another person to treat. All adverse events were collected by the attending physicians at every patient visit. We assessed the predictive value of clinical risk factors for primary clinical outcomes.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD) or percentage. Differences between baseline data and any observation points were examined for statistical significance using the Student's *t* test. Categorical variables were compared using a Chi-square test, and presented as absolute frequencies with percentages. For the primary event incidence, each participant contributed person-time from the observation start date until date of non-fatal MI, non-fatal stroke, and all-cause death, or end of follow-up, whichever occurred first. For mortality, person-time was accumulated until date of death from any cause or end of follow-up. Hazard ratios (HRs) and 95% confidential intervals (CIs) were estimated by Cox proportional hazards modeling. In multivariable-adjusted analyses, we adjusted for age, sex, history of coronary artery disease, hypertension (yes/no), cigarette smoking (never, current), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, HbA1c, BMI, eGFR, history of retinopathy, or neuropathy, or nephropathy, and hypoglycemia. All analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Clinical Characteristics

We obtained informed consent from 3171 of 3247 patients participating in the SPIRITS-J study. Table 1 shows the baseline clinical characteristics. Of these patients, 492 (15.6%) had a history of coronary artery disease. Approximately 15% of patients suffered from at least

Table 1 Baseline clinical characteristics

	All subjects (n = 3171)
Age (years)	65.0 ± 11.3
Sex (male)	1889 (59.6%)
Body mass index (kg/m^2)	25.1 ± 4.2
Diabetes mellitus duration (years)	10.5 ± 7.6
Hypertension	1978 (65.3%)
Family history of coronary heart disease	266 (14.7%)
Smoking history	
Current	653 (23.3%)
Former	575 (20.5%)
Never	1573 (56.1%)
Comorbidity	
Coronary artery disease	492 (15.6%)
Cerebrovascular disease	303 (9.6%)
Peripheral artery disease	9 (0.3%)
Diabetic microvascular complications	
Retinopathy	456 (14.4%)
Neuropathy	428 (13.6%)
Nephropathy	564 (17.9%)
Medications	
Sulfonylurea	1583 (49.9%)
Thiazolidinedione	695 (21.9%)
Glinide	64 (2.0%)
Alpha-glucosidase inhibitor	428 (13.5%)
Metformin	1255 (39.6%)
Insulin	215 (6.8%)
Aspirin	556 (22.2%)
Statin	1397 (55.7%)

Data are expressed as mean ± SD or percentage

one diabetic microvascular complication. More than half of the patients received treatment by statins. Mean duration of follow-up was 42.8 ± 15.8 months. Follow-up data at 3 years were completely collected from 2259 of 3171 participants. In spite of the pharmacological approach being left to the attending physician's discretion after the 6-month sitaglipition initiation period, not only HbA1c but also BMI, blood pressure, and lipid profiles including LDL-C, non-HDL-C, and HDL-C were well controlled until the end of the follow-up period (Table 2).

Table 2 Baseline and follow-up clinical characteristics

	Baseline	Follow-up
Number of patients	3171	2259
Mean follow-up period (month)		42.8 ± 15.8
Body mass index (kg/m^2)	25.1 ± 4.2	25.2 ± 4.3
Blood pressure (mmHg)		
Systolic	133.2 ± 16.9	131.7 ± 16.1
Diastolic	74.7 ± 12.1	73.1 ± 11.5
Serum creatinine (mg/dL)	0.77 ± 0.51	0.82 ± 0.36
Estimated glomerular filtration rate (ml/min/1.73 m^2)	76.5 ± 22.7	75.7 ± 112.1
Low-density lipoprotein cholesterol (mg/dL)	112.8 ± 30.1	104.2 ± 29.6
Non-high-density lipoprotein cholesterol (mg/dL)	137.9 ± 35.9	128.8 ± 57.7
High-density lipoprotein cholesterol (mg/dL)	55.5 ± 15.1	54.6 ± 16.1
Triglycerides (mg/dl)	155.7 ± 128.3	139.5 ± 85.9
Blood glucose (mg/dl)	174.3 ± 64	152.7 ± 52.6
Hemoglobin A1c (%)	7.8 ± 1.2	7.2 ± 1.09

Clinical Outcomes

During the follow-up period, the total number of primary clinical outcome was 154 (4.9%), which included 12 non-fatal MI (0.38%), 44 non-fatal stroke (1.39%), and 98 all-cause mortality (3.1%) (Table 3). The crude incidence of primary outcome per 1000 person-years was 13.9 (non-fatal MI 1.44, non-fatal stroke 4.22, all cause-mortality 8.79 per 1000 person-years, respectively). A breakdown of all-cause mortality was 21 cases for cardiovascular related sudden death or MI, 3 cases for stroke, 2 cases for hemorrhagic stroke, and 32 cases for cancer (Table 4). New onset of microvascular complications occurred in 6 cases with retinopathy, 1 case with neuropathy, and 9 cases with nephropathy. Hypoglycemic episodes occurred in 82 patients during first 6 months after initiation of sitagliptin [23]. Only 2 patients (2.4%) with sitagliptin monotherapy experienced hypoglycemia, while a higher percentage of patients tended to experience hypoglycemia when combined with sulfonylurea-based therapy or insulin-based therapy (about 75% and 31%, respectively; data not shown). After that, any severe hypoglycemic episode was not reported, although the annual number of hypoglycemic episodes was 2–3% during the follow-up period.

In univariate analysis, the composite incidence of primary clinical outcome was positively associated with age, male sex, history of coronary artery disease, hypertension, use of alpha-glucosidase inhibitor and insulin, and negatively associated with lower and higher BMI (< 19 kg/m^2 and > 25 kg/m^2, respectively), HDL-C, eGFR, and use of statins (Table 5). Diabetic microvascular complications such as neuropathy and nephropathy were associated with diabetic macrovascular complications and all-cause mortality, although diabetic retinopathy did not show a significant association. Patients with type 2 diabetes who were taking statins had a significantly lower incidence of primary clinical outcome by approximately 44% (HR 0.56, 95% CI 0.39–0.80, $p = 0.002$). After stepwise adjustment for various confounders including traditional risk factors, eGFR diabetic microvascular complications, and hypoglycemia, both the history of coronary artery

Table 3 Clinical outcomes

All subjects (n = 3171)	Number of cases (%)	Events per 1000 person-years
MACCE: all-cause mortality, non-fatal MI, non-fatal stroke	154 (4.9)	13.9
All-cause mortality	98 (3.1)	8.79
Cardiovascular disease		
CV death	24 (0.8)	2.15
CVE: SCD, ACS, stroke	105 (3.3)	9.42
Ischemic heart disease		
Sudden death	17 (0.5)	1.52
Acute myocardial infarction	16 (0.5)	1.44
Unstable angina	25 (0.8)	2.24
Coronary revascularization (PCI or CABG)	71 (2.2)	6.37
Heart failure	25 (0.8)	2.24
Cerebrovascular disease		
Ischemic stroke	47 (1.5)	4.22
Cerebral hemorrhage	7 (0.2)	0.63
Transient ischemic attack	10 (0.3)	0.90

Data are expressed as mean ± SD

MACCE major adverse cardiac and cerebrovascular events, *MI* myocardial infarction, *CV* cardiovascular, *CVE* cardiovascular event, *SCD* sudden cardiac death, *ACS* acute coronary syndrome, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

Table 4 Cause of death

Cardiovascular	
Cardiac	
Myocardial infarction	4
Heart failure	5
Cerebrovascular	
Stroke	3
Cerebral hemorrhage	2
Sudden death	17
Cancer	32
Pneumonia	10
Interstitial pneumonia	3
Renal failure	2
Infections	3
Gastrointestinal bleeding	2
Senile	2
Unknown	5
Others	8
Total	98

disease and LDL-C were independently associated with incidence of primary clinical outcome (Table 6).

DISCUSSION

In the extended cohort SPIRITS-J study, the incidence of the primary clinical outcome was 13.9 per 1000 person-years, and the incidences of MI and stroke were 1.44 and 4.22 per 1000 person-years, respectively. From the viewpoint of diabetes management, attending physicians who participated in the SPIRITS-J study carried out the optimal comprehensive risk management throughout the study period. A previous Japanese cohort study, the Japan Diabetes Complications Study (JDCS), in which patients with type 2 diabetes with no history of any vascular disease were registered, revealed incidences of MI and stroke of 3.84 and 6.29 per 1000 person-years, respectively [28]. It is noteworthy that the incidence of MI in the SPIRITS-J study was extremely low, even including patients with prior vascular disease, compared with that in the JDCS. The JDCS was conducted in 1995, in the era before the widespread use of stains and guidelines. However, nowadays, it is well established that optimal risk factor control can prevent the development of diabetic

Table 5 Univariate analysis for primary clinical outcome

Variable	Univariate analysis	
	HR (95% CI)	*p* value
Age (years)	1.07 (1.05–1.09)	< 0.0001
Male	1.54 (1.08–2.20)	0.018
Diabetes mellitus duration (years)	1.00 (1.00–1.00)	0.496
History of coronary artery disease	1.54 (1.03–2.29)	0.034
Hypertension	1.45 (1.00–2.11)	0.050
Current smoker (vs never)	1.13 (0.72–1.79)	0.595
BMI (kg/m^2)		
BMI < 19	0.56 (0.37–0.85)	0.006
BMI > 25	0.44 (0.28–0.68)	0.000
Low-density lipoprotein cholesterol (mg/dl)	1.00 (0.99–1.00)	0.119
Non-high-density lipoprotein cholesterol (mg/dl)	1.00 (1.00–1.01)	0.432
High-density lipoprotein cholesterol (mg/dl)	0.98 (0.97–0.99)	0.002
Triglycerides (mg/dl)	1.00 (1.00–1.00)	0.753
Hemoglobin A1c (%)	1.03 (0.90–1.18)	0.661
Estimated glomerular filtration rate (ml/min/1.73 m^2)	0.97 (0.96–0.98)	< 0.0001
Retinopathy	1.40 (0.92–2.12)	0.120
Neuropathy	1.52 (1.04–2.22)	0.030
Nephropathy	1.55 (1.02–2.34)	0.039
Statin	0.56 (0.39–0.80)	0.002
Sulfonylurea	0.81 (0.50–1.32)	0.393
Thiazolidinedione	0.67 (0.35–1.29)	0.232
Metformin	0.60 (0.35–1.29)	0.059
Alpha-glucosidase inhibitor	2.37 (1.36–4.13)	0.002
Insulin	2.09 (1.22–3.60)	0.008
Aspirin	1.00 (0.66–1.52)	1.000
Hypoglycemia	1.07 (0.43–2.67)	0.883

macrovascular complications [9]. In the SPIRITS-J study, the accomplishment of optimal comprehensive management of type 2 diabetes therefore may result in a lower incidence of diabetic macrovascular complications than those in the JDCS. Because the SPIRITS-J study was not an interventional study, it was hard to reach a conclusion, but our findings supported the advantage of comprehensive risk management according to current guidelines for the

Table 6 Multivariate analysis for primary clinical outcome

Variable	Multivariate analysis							
	Step 1		Step 2		Step 3		Step 4	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.03 (1.01–1.05)	0.002	1.02 (0.99–1.04)	0.272	1.00 (0.97–1.04)	0.881	1.00 (0.97–1.04)	0.917
Male	2.02 (1.27–3.21)	0.003	1.65 (0.82–3.32)	0.162	1.31 (0.60–2.90)	0.500	1.35 (0.60–3.01)	0.469
History of coronary artery disease			2.52 (1.33–4.77)	0.005	2.61 (1.25–5.45)	0.011	2.83 (1.34–5.97)	0.006
Hypertension			1.00 (0.54–1.85)	0.998	0.75 (0.37–1.49)	0.410	0.72 (0.36–1.46)	0.362
Current smoker (vs never)			1.25 (0.64–2.47)	0.515	1.61 (0.72–3.61)	0.250	1.65 (0.73–3.74)	0.230
Low-density lipoprotein cholesterol (mg/dl)			1.01 (1.00–1.02)	0.004	1.02 (1.01–1.03)	0.004	1.02 (1.01–1.03)	0.004
High-density lipoprotein cholesterol (mg/dl)			0.98 (0.85–1.00)	0.059	0.99 (0.97–1.02)	0.416	0.99 (0.96–1.01)	0.393
Triglycerides (mg/dl)			1.00 (1.00–1.00)	0.983	1.00 (1.00–1.00)	0.706	1.00 (1.00–1.00)	0.626
Hemoglobin A1c (%)			1.04 (0.83–1.31)	1.044	1.00 (0.75–1.32)	0.988	0.94 (0.70–1.27)	0.701
Body mass index (kg/m^2)					0.98 (0.90–1.07)	0.651	0.98 (0.90–1.01)	0.639
Estimated glomerular filtration rate (ml/min/1.73 m^2)					0.98 (0.97–1.00)	0.064	0.99 (0.97–1.00)	0.097
Retinopathy							1.56 (0.71–3.40)	0.267
Neuropathy							1.11 (0.53–2.34)	0.775

Table 6 continued

Variable	Multivariate analysis							
	Step 1		Step 2		Step 3		Step 4	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Nephropathy							2.03 (0.90–4.56)	0.087
Hypoglycemia							0.52 (0.07–3.86)	0.523

Step 1: adjusted for age, sex

Step 2: adjusted for age, sex, history of coronary artery disease, hypertension, current smoker, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, hemoglobin A1c

Step 3: adjusted for age, sex, history of coronary artery disease, hypertension, current smoker, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, hemoglobin A1c, body mass index, estimated glomerular filtration rate

Step 3: adjusted for age, sex, history of coronary artery disease, hypertension, current smoker, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, hemoglobin A1c, body mass index, estimated glomerular filtration rate, retinopathy, neuropathy, nephropathy, hypoglycemia

prevention of macrovascular complications in patients with type 2 diabetes. Recently, the Japan Diabetes Optimal Treatment study for three major risk factors of cardiovascular diseases (J-DOIT3), which was a randomized controlled trial, was conducted in Japan to compare the effectiveness and safety of an aggressive multifactorial intervention for control of glucose, blood pressure, and LDL-C to prevent vascular complications and mortality in patients with type 2 diabetes [29]. Although the results of the J-DOIT3 study did not fully support the efficacy of further intensified multifactorial interventions compared with current standard care for the prevention of macrovascular complications and mortality, it suggested a potential benefit for the prevention of cerebrovascular events. Moreover, our study demonstrated an independent association between baseline levels of LDL-C and the primary outcomes along with comprehensive risk management. The results of the SPIRITS-J and the J-DOIT3 studies may be helpful for future guidelines to establish the optimal target levels of LDL-C and blood pressure to prevent macrovascular complications in type 2 diabetes.

On the other hand, the crude incidence in the SPIRITS-J study was comparable to that in the JDCS [30]. The J-DOIT3 study also did not demonstrate the efficacy of multifactorial intensive therapy in all-cause mortality, compared with conventional therapy. Regarding the cause of all-cause mortality, the most frequent cause in the SPIRITS-J study was found to be malignant neoplasms, followed by cardiovascular disease including sudden death, and pneumonia. Epidemiological and clinical studies, which have been conducted mainly in Western countries, demonstrated that the most frequent cause of death in patients with diabetes is cardiovascular disease [4, 31–34]. However, a recent meta-analysis reported a stronger association between diabetes and cancer in Asians than in other populations [35]. The Committee on Causes of Death in Diabetes Mellitus from Japan also demonstrated that the most frequent cause of death was malignant neoplasms followed by infections, and then vascular disease including ischemic heart disease, cerebrovascular disease, and renal failure [5]. Therefore, the lower mortality from cardiovascular disease in Japan, at least, may explain

the reason underlying the similar trend in all-cause mortality, although the multifactorial optimal risk control and intensive therapy achieved a reduction in macrovascular complications in patients with type 2 diabetes.

In the SPIRITS-J study, the duration of diabetes was not associated with primary outcomes. Although type 2 diabetes is recognized as a predictor of mortality from all causes including cardiovascular diseases [30–33], the attributable risk to the evolution of diabetes over time remains unclear, especially in elderly individuals. Because age at the onset of diabetes and the duration of diabetes are interrelated, and duration of diabetes increases linearly with age, these variables cannot be modeled as independent risk factors. Moreover, the follow-up period in our study was too short to investigate an association between the duration of diabetes and clinical outcomes. In addition, hypoglycemia was not associated with an increased risk of primary outcomes. Although severe hypoglycemia might increase the risk of cardiovascular morbidity and mortality [36], no severe hypoglycemic episode was observed in our study. Moreover, the very low incidence of hypoglycemic episodes might have contributed to the low incidence of macrovascular complications and mortality.

Our study has certain limitations. First, the SPIRITS-J study was an observational study without a control arm, which may cause selection bias. Therefore, our results cannot be considered conclusive. Second, there was little information on lifestyle including diet and exercise therapy, drug compliance, and confounding effects by other medications. In connection with this, we will further evaluate a causal relationship between the alpha-glucosidase inhibitor and increased risk of primary outcomes. There were also some missing values in several variables. Third, the measurement methods of laboratory data were not exactly standardized because of the cohort study characteristics. Fourth, the observational period in the SPIRITS-J study was shorter than in the previous cohort study. This may be partially the reason why no significant association was found between diabetic retinopathy and primary outcomes [37, 38].

CONCLUSIONS

We demonstrated a current condition concerning real-world data on type 2 diabetes in the era involving widespread use of clinical practice guidelines in Japan. The extended SPIRITS-J study suggested that the comprehensive medical management according to the recent practice guidelines has succeeded in preventing macrovascular complications in Japanese patients with type 2 diabetes. More intensive LDL-C-lowering therapy is needed to achieve the ultimate goal in patients with type 2 diabetes along with comprehensive medical therapy, which is to maintain their QOL and prolong their lifespan, especially for the secondary prevention of coronary artery disease. Our study may be helpful for future guidelines to establish the optimal target levels of LDL-C to prevent macrovascular complications in type 2 diabetes.

ACKNOWLEDGEMENTS

We thank the participants of the study and Editage (www.editage.jp) for English language editing.

Funding. Financial support for this study is provided by Waksman Foundation, the Clinical Research Center, Juntendo University Graduate School of Medicine and the Center for Lifetime Cancer Education, Juntendo University Graduate School of Medicine. This center received research funds from MSD, Daiichi Sankyo Inc, Novartis Pharmaceuticals, ONO Pharmaceutical Co. and Kyowa Hakko Kirin Co. The authors funded the article processing charges for this publication.

Medical Writing and Editorial Assistance. The authors would like to thank the following primary investigators participated in this trial (Appendix S1) and staffs including Ms. Keiko Wakana, Shoko Abukawa, Rinako Suga, Mayumi Fukuda, Atsuko Shiratori and Yukari Nitta, and Mr Hiroshi Kitagawa and Genichiro Okazaki (Department Center for Lifetime

Cancer Education, Juntendo University Graduate School of Medicine), Megumi Matsumoto (Department of Cardiovascular Medicine) for excellent technical support.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

List of Investigators. For a full list of investigators, please see the Supplementary Material.

Disclosures. Hirotoshi Ohmuara has received lecture fees from Takeda Pharmaceutical Co., MSD K.K., AstraZeneca K.K., Shionogi & Co., Ltd., and research funds from Pfizer Co., MSD K.K., Takeda Pharmaceutical Co., Ltd. Tomoya Mita has received research funding from MSD, Takeda and Lilly. Hirotaka Watada has received lecture fees from Boehringer Ingelheim, Sanofi-Aventis, Ono Pharmaceutical Co., Novo Nordisk Pharma, Novartis Pharmaceuticals, Eli Lilly, Sanwakagaku Kenkyusho, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Dainippon Sumitomo Pharm., Kowa Co. and research funds from Boehringer Ingelheim, Pfizer, Mochida Pharmaceutical Co. Sanofi-Aventis, Novo Nordisk Pharma, Novartis Pharmaceuticals, Sanwakagaku Kenkyusho, Terumo Corp. Eli Lilly, Mitsubishi Tanabe Pharma, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Shionogi, Pharma, Dainippon Sumitomo Pharma, Kissei Pharma, and Astrazeneca. Hiroyuki Daida has received lecture fees from AstraZeneca K.K., MSD K.K., Kowa Pharmaceutical Company Ltd., Sanofi-Aventis K.K., GlaxoSmithKline K.K., Shionogi & Co., Ltd., Daiichi-Sankyo Company, Limited, Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., Pfizer Co., Ltd., Astellas Pharma Inc. and research funds from Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, Nippon Boehringer Ingelheim Co.,Ltd., Astellas Pharma Inc., Novartis Pharma K.K., MSD K.K., Sanofi-Aventis K.K., Otsuka Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Pfizer Co., Ltd., Kowa Pharmaceutical Company Ltd., Shionogi & Co., Ltd., AstraZeneca K.K., Teijin Limited, Morinaga Milk Industry Co., Ltd. Joe Matsuoka, Shuko Nojiri, and Yuji Nishizaki have nothing to declare.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Juntendo Clinical Research and Trial Center at Juntendo University Hospital) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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