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Design of and rationale for the Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3): a multicenter, open-label, randomized, parallel-group trial

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ABSTRACT

Objective: Multifactorial intervention including the management of levels of blood glucose (BG), blood pressure (BP), and lipids has been suggested to decrease cardiovascular disease (CVD) risk. However, the target ideal and feasible levels for these individual parameters have not been fully evaluated. In this study, we examine the hypothesis that stricter control compared with the current targets in the Japanese guideline for BG, BP, and lipids could efficiently and safely reduce CVD risk.

Research Design and Methods: We screened patients with type 2 diabetes and hypertension and/or dyslipidemia among 81 hospitals in Japan and allocated them into 2 groups: the intensive therapy group (ITG) and the conventional therapy group (CTG). For the 2 respective groups, the target for glycated hemoglobin (HbA1c) is <6.2% (44 mmol/mol) and <6.9% (52 mmol/mol), for BP it is <120/75 mm Hg and <130/80 mm Hg, and for low-density lipoprotein cholesterol it is <80 mg/dL (<70 mg/dL in the presence of CVD history) and <120 mg/dL (<100 mg/dL in the presence of CVD history). The primary end point is the occurrence of CVD events or death by any cause. These patients are scheduled for stepwise intensifications of medication for BG, BP, and lipid control in the ITG, until the number of primary end point events reaches 250.

Results: We recruited 2542 patients and randomly allocated 1271 into the ITG and 1271 into the CTG between June 2006 and March 2009. The mean HbA1c was 8.0% (64 mmol/mol) and the mean duration of diabetes was 8.3 years.

Conclusions: This randomized controlled study will test the hypothesis that strict multifactorial intervention therapy is effective for the prevention of CVDs in patients with type 2 diabetes who are at high CVD risk.

Trial registration number: NCT00300976.

Key messages

- We successfully set up a randomized control study to test the hypothesis that strict multifactorial intervention therapy is effective for the prevention of cardiovascular diseases in patients of type 2 diabetes mellitus at high risk.
- We recruited 2542 patients in 81 facilities in Japan and randomly allocated 1271 patients into the intensive therapy group.
- This study continues until the number of primary end point events, including death, myocardial infarction, and stroke, reaches 250.

INTRODUCTION

The epidemic of type 2 diabetes mellitus is a serious health issue worldwide. In Japan, 9.5 million people are estimated to have this disease (National Health Surveillance 2013) that is characterized by chronic hyperglycemia associated with insufficient insulin action that leads to disorders in glucose, lipid, and protein metabolism. When these metabolic disorders are chronic, they can manifest diabetic microvascular and macrovascular complications. Macrovascular lesions involving large vessels, such as the coronary artery, cerebral artery, or arteries of the lower extremities, account for myocardial infarction, cerebral infarction, and peripheral artery disease, whereas microvascular lesions account for visual impairment, renal failure, and neuropathy. Epidemiological studies, including the Hisayama study, demonstrate that diabetes is associated with a near threefold risk for the onset of macrovascular diseases such as myocardial infarction and stroke, and that this risk becomes greater when it is accompanied by hypertension and/or dyslipidemia.[1] Furthermore, a total of 16 000 patients are estimated to start receiving hemodialysis annually due to diabetic nephropathy, and a large number of patients develop ischemic heart disease or stroke, at an incidence of 17.0/1000 person-years in the Japan Diabetes Complications Study (JDCS).[2] No evidence has been obtained, however, that glycemic control will prevent cardiovascular diseases (CVDs) in patients with diabetes in the Japanese population, although the Kumamoto study showed that intensive insulin therapy reduced the risk of microvascular complications.[3]

Globally, a number of clinical studies evaluating various antidiabetic therapeutic strategies have been conducted to provide evidence that intensive therapy reduces microvascular and macrovascular complications. Of these, the UK Prospective Diabetes Study 33 (UKPDS 33), in which a total of 3867 patients with type 2 diabetes were randomly assigned to intensive therapy with sulfonylurea/insulin or to conventional diet therapy for glycemic control, came to a noteworthy conclusion that intensive therapy led to a decrease in the risk for the onset of microvascular complications among the treated patients, compared with diet therapy alone.[4] Moreover, in the UKPDS 35, in which the results of the UKPDS were further analyzed epidemiologically, it was shown that decreases in glycated hemoglobin (HbA1c) are paralleled with decreases in the risk for mortality, myocardial infarction, and microvascular complications.[5] Furthermore, the 10-year post-trial observational study of UKPDS revealed the existence of a 'legacy effect' that caused intensive blood glucose (BG) control immediately after disease onset to be associated with long-term beneficial effects on the prevention of coronary events and death by any cause.[6] For the patients with advanced type 2 diabetes, the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study demonstrated that pioglitazone added to conventional therapy produced greater reductions in the onset of macrovascular complications than did placebo, indicating that intensive therapy with pioglitazone is efficacious for the secondary prevention of macrovascular complications.[7] However, recent trials challenging whether controlling hyperglycemia to near normal levels of HbA1c could reduce the risk of macrovascular complications, such as the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial,[8] the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified Release Controlled Evaluation) trial,[9] and the VADT (Veterans Affairs Diabetes Trial),[10] failed to show the beneficial effect of intensive BG control for patients with advanced stages of diabetes, presumably due to a marked increase in severe hypoglycemic episodes.

However, the Steno-2 study, in which patients with type 2 diabetes with microalbuminuria were randomly assigned to intensive therapy for rigorous BG, blood pressure (BP), and lipid control or to conventional therapy, reported a reduction in the incidence of microvascular and macrovascular complications in patients treated with multifactorial intensive therapy.[11] Moreover, the 5-year post-trial observational study of Steno-2 showed a significant reduction in macrovascular complications and mortality in the intensive therapy group (ITG),[12] suggesting that the comprehensive and strict control of BG, BP, and lipids brings with it long-term beneficial effects on the prevention of macrovascular complications and death, due to the possible 'legacy effect'. Still, the study had limitations, including the small number of participants, only 160. In addition, glycemic control may not have been sufficient, because the mean HbA1c was nearly 8% (64 mmol/mol) and the achievement rate of the target HbA1c, <6.5% (48 mmol/mol), was around 15%, even in the ITG.

Effectiveness of multifactorial intervention was investigated also in the ADDITION-Europe (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care), in which over 3000 patients with newly diagnosed type 2 diabetes were recruited, whose mean baseline HbA1c was about 7% (53 mmol/mol), resulting in a slight but non-significant reduction in CVD events.[13]

Most recently, the EMPA-REG OUTCOME study showed that a sodium–glucose linked co-transporter 2 (SGLT2) inhibitor, empagliflozin, reduced cardiovascular mortality, with no difference in incidence of myocardial infarction or stroke.[14]

In 2005, the Ministry of Health, Labor and Welfare (MHLW) of Japan developed a new category of research projects, namely 'strategic research', whose target diseases were of the highest social priority and whose results were expected to be immediately applied to the clinical practice and the Japanese healthcare system. In the field of diabetes, three trials were planned; specifically, the Japan Diabetes Outcome Intervention Trial (J-DOIT),[15] including J-DOIT1, aimed at reducing the conversion from impaired glucose tolerance to diabetes through education and lifestyle modification;[16] J-DOIT2 aimed at reducing patient dropout rates from diabetes treatment through improved therapy from primary care physicians;[17] and J-DOIT3 aimed at reducing macrovascular complications through multifactorial interventions. Here, we describe the design of and rationale for J-DOIT3, renamed the Japan Diabetes Optimal Integrated Treatment study for three major risk factors of cardiovascular diseases, which started in 2006 and is, as of this writing, still underway.

RESEARCH DESIGN AND METHODS

Study design

The present trial is a multicenter, open-label, randomized, parallel-group study, conducted to examine the efficacy of intensive multifactorial therapy on the development and exacerbation of diabetic complications, in particular CVDs, and mortality in patients with type 2 diabetes with high risk for CVDs, whose details are available online.[18] In this trial, patients with type 2 diabetes who were at high risk of macrovascular complications were recruited, allocated to either the conventional therapy group (CTG) or the ITG, and followed up (figure 1).

Organization and funding

Research funding is to be accounted for by the MHLW grants in aid, as well as corporate donations, as described later, and to be supplied through the funding agency, which was shifted from the Japan Foundation for the Promotion of International Medical Research Co-operation (the National Center for Global Health and Medicine, Tokyo, Japan), or JF-PIMRC, to the Japan Diabetes Foundation (JDF) in April 2013 (see sFigure 1).

To monitor and assess the research, the foundation organized the Trial Coordinating Committee, the Trial Administrative Committee, the Trial Assessment Committee, the Trial Progress Management Committee, the Safety Assessment Committee, the Central Ethics Committee, and the Endpoint Assessment Committees, whose purposes are referred to online.[18] Among them, the Endpoint Assessment Committees are blinded to the study arm, whereas the Trial Assessment Committee and the Safety Assessment Committee are not. The protocol of this study, as further mentioned later, was approved by the Central Ethics Committee.

Eligibility

Medical institutions were selected in Japan that employed certified diabetologist(s) who were expected to register 50 or more participants (25 or more participants per group) with type 2 diabetes and hypertension and/or dyslipidemia. The inclusion and exclusion criteria, shown in sTable 1 and 2, respectively, were formulated to recruit those patients who were at high risk of CVDs, but still allow for intensification of medication for BG, BP, and lipids.

Informed consent, registration, and random allocation

The physician in charge explained the study particulars in person to each candidate participant to obtain consent to participate in the study, and the written document of informed consent was obtained one or more days after the date of the physician's explanation.

On receiving the patient's registration, the Data Center was to confirm the eligibility of the participant, followed by dynamic allocation to the CTG or to the ITG in a 1:1 ratio through randomization adjusted by the presence or absence of CVD (myocardial infarction, stroke, coronary bypass surgery, percutaneous coronary angioplasty, cerebral revascularization, or cerebrovascular reconstruction), male/female ratio, age (≥60, <60 years old), and HbA1c (≥8.9% (74 mmol/mol), <8.9%), to ensure a balanced allocation of participant characteristics between the groups (figure 1).

After registration, each time the protocol is revised, informed consent is reobtained in all participants receiving investigational treatment. For participants who are

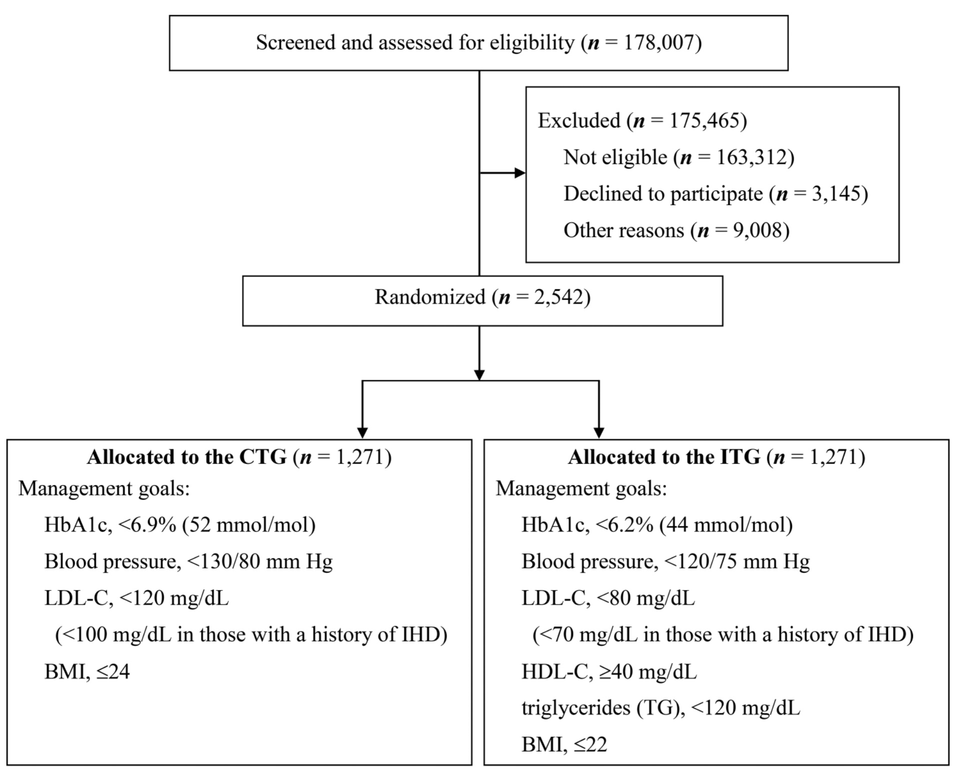

Figure 1 Screening, enrollment, and randomization of study participants (BMI, body mass index; CTG, conventional therapy group; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; ITG, intensive therapy group; LDL-C, low-density lipoprotein cholesterol).

incompetent, consent from a family member or legally authorized representative is received instead.

Management goals and investigational treatment

The treatment goals were to be set in accordance with the 'Treatment guide for diabetes' edited by the Japan Diabetes Society[19] in the CTG, and set stricter in the ITG (figure 1), with rationale as follows. The target HbA1c was the value of 'excellently controlled' in the Treatment Guide (2006), which was defined on the basis of the distribution of the HbA1c of the individuals with normal glucose tolerance. The target BP and low-density lipoprotein cholesterol were set by reference to clinical evidence available when this study was planned, including a meta-analysis on BP lowering by the PSC (Prospective Studies Collaboration),[20] and results of the CARDS (Collaborative Atorvastatin Diabetes Study), an interventional trial of lipid lowering.[21] To achieve these target goals, which have been kept unchanged throughout the course of the study, medications in the ITG are intensified in a stepwise manner in 3–6 months, mainly utilizing drugs proven to prevent CVDs (see sFigure 2).

In the ITG, for glycemic control, all participants maintain treatment after registration with predetermined diet and exercise therapy, and if they fail to achieve an HbA1c<6.2% (44 mmol/mol) in the first 3 months, the treatment is intensified with antidiabetic drugs categorized into 4 groups, mainly those that improve insulin resistance with less risk of hypoglycemia. Among insulin sensitizers, pioglitazone, the only thiazolidinedione derivative available in Japan, was preferred because it had emerging evidence of CVD prevention, such as the PROactive study,[7] when this study was planned. It was also because only low-dose biguanides were allowed to be administered until 2010 in Japan. In the 6 months thereafter, the treatment is to be intensified if they fail to achieve an HbA1c<6.2% or ≥1% decrease in HbA1c (see sFigure 2). If any of the participants receiving treatment on an outpatient basis do not achieve the management goals, hospitalization will be recommended to ensure better glycemic control. All participants in the ITG are provided a BG meter for self-monitoring of BG (SMBG), and the physicians in charge remain informed of the measured results.

All participants maintain treatment for BP on registration with predetermined diet and exercise therapy, and if they fail to achieve BP<120/75 mm Hg in the first 3 months, they are given antihypertensive drugs in steps to ensure that the goal is achieved in 3–6 months, as shown in sFigure 2. All the participants in the ITG are also provided a BP manometer at study entry, and the physician in charge remains informed of these measurements. The physician in charge is to keep informed of self-measured BP for decisions regarding dose escalation or replacement of antihypertensive drugs.

All participants maintain lipid control treatment on registration with predetermined diet and exercise therapy, and if they fail to achieve the lipid control goal in the first 3 months, they are given lipid-lowering drugs, as shown in sFigure 2.

In both groups, all participants with a history of CVDs are given antiplatelet and anticoagulant therapy, such as low-dose aspirin and warfarin, in accordance with the guideline.[19]

It is up to the physician in charge to choose which agent in a class (eg, insulin) to administer. The exceptions are pioglitazone and ezetimibe, both of which are the only drugs in their class (thiazolidinedione derivatives, cholesterol absorption inhibitors, respectively) available in Japan, and so was eicosapentaenoic acid (EPA), which was included in the omega-3 fatty acids thereafter, as is further mentioned later.

Lifestyle modifications

In both groups, the participants are obliged to follow lifestyle modifications as shown in sTable 3. Interventions are intensified, focusing on self-monitoring in daily life, for stricter management goals in the ITG, to improve insulin resistance and reduce body weight. Moreover, the physician in charge remains informed of their measurements and reports on each visit.

The participants in both study groups are instructed on diet by using the "Food exchange lists—dietary guidance for persons with diabetes" edited by the Japan Diabetes Society.[22] Those with diabetic nephropathy in both study groups are encouraged to restrict protein intake in accordance with the guideline.[19]

Observation and evaluation schedule

The frequency of hospital visits had been at least once a month, which was modified in January 2010 as follows: (1) at least once a month in those patients receiving insulin therapy and those patients with unstable glycemic control, and (2) a maximum of 3 months apart in those patients who have almost achieved management goals for glycemic control and other factors and whose conditions are stable (except those receiving insulin therapy). An outline of the observation/evaluation schedule for the study is shown in table 1.

Outcomes

The end points of the study are shown in table 2, and among them the primary end point and the secondary end point (1) are composite end points. The definitions are set forth, as shown in sTable 4, so that the End Point Assessment Committees could verify each event in an objective fashion.

During the course of the study, general investigations are performed on a regular basis to keep track of the incidence of CVD events as well as to see if the study is progressing as planned.

Even when an event defined as a primary or secondary end point occurred in a particular participant, the participant continues to be part of the study and is observed for occurrence of other events.

Table 1 Measures

At regular hospital visits	Body weight, blood pressure (on an outpatient basis) Blood glucose, HbA1c, lipid panel (total cholesterol, LDL cholesterol (non-HDL cholesterol), HDL cholesterol, and triglyceride), hematological examination, hepatic/renal function test, serum electrolytes, and CK
Every 6 months	Urinary albumin–creatinine ratio
Every 12 months	Body height, waist circumference Fasting blood glucose, fasting lipid panel Chest radiograph, echocardiogram, fundus examination Clinical parameters examined centrally ▶ hs-CRP, fasting serum insulin, and GA – Fundus examination is also performed within 6 months prior to the end of the study
At registration, 1 year later, 3 years later, and at the end of the study	Clinical parameters examined centrally ▶ Adiponectin (including high-molecular-weight adiponectin) Questionnaires ▶ SF-36, PAID, BDI, PHRF-SCL (SF), and DHQ – Adiponectin is examined at registration, in March 2013, and at the end of the study
At the end of the study	DTSQ and recognition testing

BDI, beck depression inventory; DHQ, dietary history questionnaire; DTSQ, diabetes treatment satisfaction questionnaire; GA, glycoalbumin; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitive C reactive protein; LDL, low-density lipoprotein; PAID, problem area in diabetes survey; PHRF-SCL (SF), public health research foundation stress check list (short form), SF-36, medical outcomes study-short-form 36-item health survey.

Sample size and study duration

The trial participants were estimated to include those with ischemic heart disease and those without at a ratio of 3:7, with the occurrence of events, including deaths per year, estimated at 4.4% (10% in those with a history of ischemic heart disease and 2% in those without) in the CTG.

To verify a 30% risk reduction in the ITG at the two-sided significance level of 5% with a 90% power, we estimated the required number of events to be 328, and the required number of patients during the original observation period of 3.75 years was calculated to be 1408 participants per arm by using the Shoenfeld-Richter nomograms.

To recruit sufficient participants, we modified the lower limit of HbA1c in the inclusion criteria from 7.4% (57 mmol/mol) to 6.9% (52 mmol/mol) in December 2006.

Table 2 Outcomes

Primary end point	Occurrence of either ▶ Myocardial infarction ▶ Coronary bypass surgery ▶ Percutaneous transluminal coronary angioplasty ▶ Stroke ▶ Carotid endarterectomy ▶ Percutaneous transluminal cerebral angioplasty ▶ Carotid artery stenting ▶ Death (irrespective of its causes)
Secondary end points	1. Occurrence of myocardial infarction, stroke, or death 2. Onset or progression of nephropathy 3. Lower limb vascular events (amputation or revascularization of lower limb) 4. Onset or progression of retinopathy

At the end of the accrual period in March 2009, however, the final number of participating participants, 2542 in total (figure 1), and the ratio of those with previous CVD events, 11.0% (table 3), fell short of the expectation. Thus, we recalculated the required number of events as 250, by lowering the power to 80%, and the participants are to be followed up until the required events occur to test the hypothesis.

However, the annual event rate was about half of the original estimate, probably due to advances in diabetes care in clinical practice. In January 2010, the primary end point was modified, from 'the incidence of myocardial infarction, stroke, or death', which was thereafter included in the secondary end points, to the present one shown in table 2. Now the study duration is expected to be 9.75 years (until March 2016), yielding a mean intervention duration of approximately 8 years.

Safety

The physician in charge is to collect data on adverse events, including any of the following four symptoms by using active surveillance: hypoglycemia, edema, palpitation, and shortness of breath. Among them, occurrence of hypoglycemia is to be judged by the physician in charge by taking results of SMBG also into account. Severe hypoglycemia is defined as hypoglycemia requiring someone else's assistance and/or admission.

Serious adverse events include severe hypoglycemia as well as those defined in the ethical guidelines,[23] which are mentioned later.

The Safety Assessment Committee is to review all reported adverse events, and to make recommendations to the research leader with regard to the handling of the cases (including judgment as to whether the study is

Table 3 Characteristics of the patients at baseline

	CTG (n=1271)	ITG (n=1271)	p Value
Age (year)	59.1±6.3	58.9±6.4	0.462
Men/women	790/481	784/487	0.838
Body weight (kg)	65.9±12.0	65.4±11.9	0.284
Body mass index	24.9±3.8	24.8±3.6	0.342
Cigarette smoking status (%)			0.011
Current	21.0	25.8	
Former	32.7	29.2	
Never	46.3	45.0	
Previous CVD event (%)	10.8	11.2	0.800
Duration of diabetes (year)	8.2±6.9	8.3±6.9	0.751
HbA1c, % (mmol/mol)	8.0±1.1 (64±12)	8.0±1.1 (64±12)	0.442
Fasting serum glucose, mg/dL (mmol/L)	158.8±39.6 (8.81±2.20)	159.6±41.5 (8.86±2.30)	0.614
Systolic BP (mm Hg)	134.1±16.3	133.5±16.9	0.357
Diastolic BP (mm Hg)	80.0±11.1	79.3±10.9	0.106
LDL-C, mg/dL (mmol/L)	125.7±31.8 (3.25±0.82)	125.5±30.6 (3.25±0.79)	0.908
HDL-C, mg/dL (mmol/L)	54.5±14.0 (1.41±0.36)	54.3±14.9 (1.40±0.38)	0.728
Triglyceride, mg/dL (mmol/L)	148.0±98.2 (1.67±1.11)	148.7±104.4 (1.68±1.18)	0.851

Values of the data are expressed as mean ± standard deviation, and p Values were calculated with the use of a two-sample Student t test or the χ^2 test.
BP, blood pressure; CTG, conventional therapy group; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ITG, intensive therapy group; LDL-C, low-density lipoprotein cholesterol.

to be continued with the participants, instructions required to be given to the medical institutions of interest, or whether the trial protocol needs to be revised).

When the ACCORD study was discontinued in February 2008, the research leader temporally suspended new registration and intensification of treatment in the ITG for 2 weeks until the Trial Assessment Committee performed interim analysis and confirmed that (1) CVD events had not been increased in the ITG, (2) occurrence of events had not been correlated with HbA1c, and (3) almost no occurrence of severe hypoglycemia had been seen in the ITG. The Safety Assessment Committee also confirmed that severe adverse events had not been increased in the ITG. Moreover, as was recommended by the committee, the occurrence of death is to be monitored on a real-time basis thereafter.

Discontinuance and dropout

The criteria for treatment discontinuance are the following: occurrence of a serious macrovascular or microvascular disease, occurrence of another serious complicating disease, diagnosis or strong suspicion of type 1 diabetes (including autoantibody positive), difficulties continuing treatment due to adverse events, patient request for discontinuance, patient death, or other cases in which the physician in charge judged continued treatment would be difficult.

Even when the investigational treatment is discontinued, with the participant's consent (for participants who are incompetent, consent from the family member or legally authorized representative), the participant can be followed up on the presence or absence of the primary and secondary end points of the study.

Dropout cases in this study include (1) those who have discontinued investigational treatment without consent of follow-up, and (2) those with whom the study team have lost contact.

Ethical principles

The current trial is to be conducted in accordance with the Helsinki declarations, as well as the 'Ethical Guidelines for the Conduct of Clinical Studies' (The MHLW Bulletin, Vol. 459, 2004) and related notifications (Healthcare Administrative Bureau, the MHLW, order 1 228 001, December 28, 2004), which were integrated into the 'Ethical Guidelines for Medical and Health Research Involving Human Subjects' (the MHLW and the Ministry of Education, Culture, Sports, Science and Technology, December 22, 2014).[23] All of the investigators and subinvestigators responsible for the trial must comply with the ethical standards stated earlier. The study was registered at ClinicalTrials.gov supported by the United States National Institutes of Health as NCT00300976.[24]

Following approval by the Central Ethics Committee, the protocol of this study and its revisions are to be reviewed and approved by the ethics committee of each institution for their feasibility, as well as their ethical and scientific validity.

Data management

In accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, all the data are to be collected from the healthcare institutions by using the electronic data capture system managed by the Data Center and in conformity with the study aims only. Utmost care is to be paid in the handling of personal information, and the participants are to be informed beforehand what personal information is to be composed of and how it is to be used.

Statistical analyses

Descriptive statistics: The event-free survival period as well as the annual percentage of participants remaining event free is to be calculated by the Kaplan-Meier method, and 95% CIs are to be calculated using Greenwood's formula. *Hypothesis testing*: A stratified log-rank test adjusting the stratification factors used for dynamic allocation (except for participating institutions) is to be used to verify the hypothesis that event-free survival is longer in the ITG than in the CTG. Effect size estimates: HR (ITG/CTG) for the event as well as 95% CIs is to be calculated by using the Cox proportional hazards model. The adjustment/stratification factors used for dynamic allocation (except for participating institutions) are to be incorporated into the regression analysis models. Furthermore, any background factors are also to be incorporated, if they are found to potentially affect the estimates.

After analyses of the primary end points, complementary analyses on the secondary end points are to be performed. As part of the safety evaluation, Fisher's exact (probability) method is to be used to compare the percentages of occurrence of adverse events between the CTG and the ITG, and 95% CIs for the differences are to be detected. The analyses are to be based on the intention-to-treat principle. Details of the approach to be taken are to be described in the Statistical Analysis Plan.

History of modifications of the protocol

Modifications in the protocol have been approved by the Central Ethics Committee, including those on inclusion criteria, study duration, frequency of hospital visits, primary end point, funding agency, and the ethical guidelines, as stated earlier.

In addition, new drugs have been added to the available medications in the ITG when at least 1-year safety had been confirmed as a class in clinical practice after appearance on the market. In November 2008, ezetimibe was added to the available medication for dyslipidemia, and in January 2011 DPP-4 inhibitors and GLP-1 receptor agonists were added for hyperglycemia. In December 2012, omega-3 fatty acids were substituted for EPA as a medication for dyslipidemia. Most recently, SGLT2 inhibitors were included in antidiabetic medication in July 2015.

RESULTS

All over Japan, 81 healthcare facilities were selected, and the study was open for patient accrual between June 2006 and March 2009. Among the 178 007 patients with diabetes screened by the facilities, 14 695 were considered eligible, and 5687 received an explanation of the study by the physician in charge. Finally 2542 patients were enrolled, with 1271 allocated to the CTG and the other 1271 to the ITG, until the end of the accrual period, March 2009 (figure 1).

The baseline characteristics, as well as baseline medication, showed no significant change between the CTG and the ITG, except for cigarette smoking status, in which the percentage of current smokers was higher in the ITG (table 3 and sTable 5).

DISCUSSION

The J-DOIT3 Study Group successfully set up a randomized control study to test the hypothesis that multifactorial intervention therapy could be effective for prevention of CVDs in patients with type 2 diabetes in the Japanese population. We put importance on lifestyle modifications, as well as medications, to reduce hypoglycemia and weight gain.

Recently, the results of the EMPA-REG OUTCOME study were reported,[14] but a further study is needed to determine the efficacy of SGLT2 inhibitors in CVD prevention. Moreover, the impact of SGLT2 inhibitors on this study is considered to be limited, because only a small number of patients will be exposed by the agents for a short period until the expected end of this study, since these became available quite recently and were included in the therapeutic regimen.

We recruited >2500 patients with comorbid hypertension and/or dyslipidemia with a mean HbA1c of 8% (64 mmol/mol), and with a mean duration of diabetes of over 8 years. J-DOIT3 is a quite unique study not just because it is the first large-scale trial for East Asian patients with type 2 diabetes who have many different characteristics from Caucasians, but because it also strives to achieve strict and safe control for all the risk factors of vascular complications. Thus, J-DOIT3 will provide novel therapeutic strategies to treat patients with type 2 diabetes for prevention of macrovascular and microvascular complications.

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Contributors KU designed the protocol, steered the study, researched the data, and wrote the manuscript. TS steered the study, researched the data, and wrote the manuscript. MK, YuO, SO, HK, MH, AiM, KO, KH, AtM, and KI steered the study and researched the data. YaO, designed the protocol and steered the study as a biostatistician. MN designed the protocol, steered the study, and researched the data. TK designed the protocol, steered the study, researched the data, and reviewed/edited the manuscript, as the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Collaborators The J-DOIT3 Study Group.

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