Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial

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Summary

Background Limited evidence suggests that multifactorial interventions for control of glucose, blood pressure, and lipids reduce macrovascular complications and mortality in patients with type 2 diabetes. However, safe and effective treatment targets for these risk factors have not been determined for such interventions.

Methods In this multicentre, open-label, randomised, parallel-group trial, undertaken at 81 clinical sites in Japan, we randomly assigned (1:1) patients with type 2 diabetes aged 45–69 years with hypertension, dyslipidaemia, or both, and an HbA_{1c} of 6·9% (52·0 mmol/mol) or higher, to receive conventional therapy for glucose, blood pressure, and lipid control (targets: HbA_{1c} <6·9% [52·0 mmol/mol], blood pressure <130/80 mm Hg, LDL cholesterol <120 mg/dL [or 100 mg/dL in patients with a history of coronary artery disease]) or intensive therapy (HbA_{1c} <6·2% [44·3 mmol/mol], blood pressure <120/75 mm Hg, LDL cholesterol <80 mg/dL [or 70 mg/dL in patients with a history of coronary artery disease]). Randomisation was done using a computer-generated, dynamic balancing method, stratified by sex, age, HbA_{1c}, and history of cardiovascular disease. Neither patients nor investigators were masked to group assignment. The primary outcome was occurrence of any of a composite of myocardial infarction, stroke, revascularisation (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting), and all-cause mortality. The primary analysis was done in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00300976.

Findings Between June 16, 2006, and March 31, 2009, 2542 eligible patients were randomly assigned to intensive therapy or conventional therapy (1271 in each group) and followed up for a median of 8·5 years (IQR 7·3–9·0). Two patients in the intensive therapy group were found to be ineligible after randomisation and were excluded from the analyses. During the intervention period, mean HbA_{1c}, systolic blood pressure, diastolic blood pressure, and LDL cholesterol concentrations were significantly lower in the intensive therapy group than in the conventional therapy group (6·8% [51·0 mmol/mol] *vs* 7·2% [55·2 mmol/mol]; 123 mm Hg *vs* 129 mm Hg; 71 mm Hg *vs* 74 mm Hg; and 85 mg/dL *vs* 104 mg/dL, respectively; all p<0·0001). The primary outcome occurred in 109 patients in the intensive therapy group and in 133 patients in the conventional therapy group (hazard ratio [HR] 0·81, 95% CI 0·63–1·04; p=0·094). In a post-hoc breakdown of the composite outcome, frequencies of all-cause mortality (HR 1·01, 95% CI 0·68–1·51; p=0·95) and coronary events (myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty; HR 0·86, 0·58–1·27; p=0·44) did not differ between groups, but cerebrovascular events (stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting) were significantly less frequent in the intensive therapy group (HR 0·42, 0·24–0·74; p=0·002). Apart from non-severe hypoglycaemia (521 [41%] patients in the intensive therapy group *vs* 283 [22%] in the conventional therapy group, p<0·0001) and oedema (193 [15%] *vs* 129 [10%], p=0·0001), the frequencies of major adverse events did not differ between groups.

Interpretation Our results do not fully support the efficacy of further intensified multifactorial intervention compared with current standard care for the prevention of a composite of coronary events, cerebrovascular events, and all-cause mortality. Nevertheless, our findings suggest a potential benefit of an intensified intervention for the prevention of cerebrovascular events in patients with type 2 diabetes.

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Introduction

Type 2 diabetes is associated with vascular complications that decrease life expectancy.[1] Reduction of glucose concentrations decreases the risk of microvascular complications;[2–5] however, glucose control alone does not sufficiently lower the incidence of macrovascular

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for studies assessing the effects of multifactorial interventions in patients with diabetes on cardiovascular disease and mortality using the search terms "multifactorial intervention", "cardiovascular disease", "mortality", and "diabetes", published in English between January, 1986, and April, 2006. The Steno-2 study enrolled 160 patients with type 2 diabetes and microalbuminuria, and tested the effect of an intensive multifactorial intervention on cardiovascular disease compared with conventional therapy. During a mean follow-up of 7·8 years, intensive therapy significantly reduced the risk of cardiovascular disease (hazard ratio [HR] 0·47, 95% CI 0·24–0·73), although glycaemic control in the intensive therapy group was much higher than the target defined by the protocol and HbA_{1c}, blood pressure, and lipid concentrations achieved in the conventional therapy group were very poor compared with targets in current guidelines.

Added value of this study

The results of the J-DOIT3 trial do not fully support the efficacy of intensified multifactorial intervention for the prevention of cardiovascular disease and mortality in Japanese patients with type 2 diabetes. However, findings from a post-hoc analysis suggested that the intervention might provide significant benefit for the prevention of cerebrovascular events, and microvascular complications were also reduced with the intensive intervention.

Implications of all the available evidence

Although the follow-up study of Steno-2 showed that the intensive therapy reduced mortality (HR 0·54, 95% CI 0·32–0·89), the intensive treatment for newly diagnosed patients with type 2 diabetes in the ADDITION-Europe trial, another multifactorial intervention trial, was associated with only non-significant reductions in cardiovascular events (HR 0·83, 0·65–1·05) and all-cause mortality (HR 0·91, 0·69–1·21) compared with the routine care. This result is probably because in the ADDITION-Europe trial risk factors were well controlled even in the routine care group, and the differences in the risk factor values between two groups were smaller than those in our trial. Since the intensive therapy in the J-DOIT3 trial showed potential benefits on cerebrovascular disease and microvascular complications compared with well controlled conventional therapy, our results could affect recommended targets for HbA_{1c}, blood pressure control, and cholesterol reduction for the prevention of these complications in patients with type 2 diabetes in future guidelines.

complications,[3,5–7] in part because achieving normal HbA_{1c} values increases the risk of severe hypoglycaemia, which can trigger acute coronary disease and fatal arrhythmia.[8,9] Thus, most guidelines set an HbA_{1c} target of 7·0% (53·0 mmol/mol), which is far higher than the normal range.

Blood pressure control suppresses macrovascular and microvascular complications,[10,11] and statin treatment to lower LDL cholesterol concentrations prevents macrovascular complications.[12] However, blood pressure targets remain controversial. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recently changed their recommended blood pressure targets from 130/80 mm Hg to 140/90 mm Hg and 140/85 mm Hg, respectively.[13,14] Previous studies,[15,16] however, suggest that systolic blood pressure levels lower than 130 mm Hg are beneficial for stroke prevention. Therefore, the Japan Diabetes Society (JDS) recommends a target of 130/80 mm Hg,[17] given that stroke is more frequently associated with diabetes in Japan than it is in patients with diabetes in Europe and North America.[18]

Findings from the Steno-2 study in Denmark showed that a multifactorial intervention for glucose, blood pressure, and lipid control had beneficial effects on microvascular and macrovascular complications and mortality in patients with type 2 diabetes and microalbuminuria.[19–21] However, the sample size was fairly small, and the mean HbA_{1c} achieved even in the group receiving intensive therapy (7·9%, 62·8 mmol/ml) was much higher than targets specified in current guidelines.[13,17] We did a randomised controlled trial, the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3),[22,23] to compare the effectiveness and safety of an aggressive multifactorial intervention for control of glucose, blood pressure, and LDL cholesterol, with current targets in the Japanese guideline,[17] for prevention of vascular complications and mortality in patients with type 2 diabetes.

Methods

Study design and participants

This multicentre, open-label, randomised, parallel-group study was done in 81 institutions in Japan that had diabetes care clinics with diabetes specialists and educators. The rationale and design of the study and a description of the multifactorial intervention have been reported previously.[22] Briefly, we recruited adults (aged 45–69 years) with type 2 diabetes who had hypertension, dyslipidaemia, or both; HbA_{1c} of 6·9% (52·0 mmol/mol) or higher; and who were treated with diet and exercise alone, diet and exercise plus one oral antidiabetes drug, or diet and exercise therapy plus an α-glucosidase inhibitor and another oral antidiabetes drug. The study protocol was approved by ethics committees at each participating institution. All patients provided written informed consent. A complete list of all inclusion and exclusion criteria can be found in the appendix pp 1–3.

Randomisation and masking

Patients were randomly assigned (1:1) by the dynamic balancing minimisation method[24] with four stratification factors (sex, age [<60 years *vs* ≥60 years], HbA_{1c} [<8·9% (<73·8 mmol/mol) *vs* ≥8·9% (≥73·8 mmol/mol)], and history of cardiovascular disease [yes *vs* no]) to receive either conventional therapy for control of HbA_{1c}, blood pressure, and lipids, as specified in the Japanese guideline (HbA_{1c} <6·9% [52·0 mmol/mol], blood pressure <130/80 mm Hg, LDL cholesterol <120 mg/dL [or 100 mg/dL in patients with a history of coronary artery disease], HDL cholesterol ≥40 mg/dL, and triglycerides <150 mg/dL),[17] or intensive therapy with stricter targets (HbA_{1c} <6·2% [44·3 mmol/mol], blood pressure <120/75 mm Hg, LDL cholesterol <80 mg/dL [or 70mg/dL in patients with a history of coronary artery disease], HDL cholesterol ≥40 mg/dL, and triglycerides <120 mg/dL). Assignments were made by the electronic data capturing system using computer-generated random numbers and minimisation software for group allocation. The computer programs for analyses were developed and run by biostatisticians who were masked to treatment assignment, following the prespecified statistical analysis plan. Neither patients nor investigators were masked to treatment group assignment.

Procedures

Patients in the conventional therapy group were treated in accordance with the Japanese guideline.[17] In brief, this consisted of an oral antidiabetic agent, glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin for glucose control, added according to the pathophysiology of the patient as judged by the physician in charge if the patient did not achieve the target. For blood pressure control, renin-angiotensin blockade or a calcium channel blocker was recommended as the first-line drug, and a statin was recommended for LDL cholesterol control. In the intensive therapy group, all patients maintained their pretrial antidiabetes therapy, along with diet and exercise therapy predetermined by the protocol. In brief, total energy intake was rigorously controlled in patients in the intensive therapy group. Specifically, in patients with a BMI of 25 kg/m² or greater at study entry, the management goal for diet restriction was set at 25 kcal/kg of ideal bodyweight (IBW), and in those with a BMI of less than 25 kg/m², the goal for diet restriction was set at 27 kcal/kg of IBW. The patients in the intensive therapy group were provided with a recordable accelerometer at study entry. They were instructed to walk for at least 15–30 min twice a day. The patients reported on the number of calories consumed and steps taken per day, as measured by the accelerometer. The physicians or nurses in charge were kept informed of their activity status when giving exercise instructions (appendix p 3). If they did not achieve an HbA_{1c} of lower than 6·2% (44·3 mmol/mol) or a reduction in HbA_{1c} of more than 1·0% (11·0 mmol/mol) within 3 months, treatment was intensified in steps, with antidiabetes drugs categorised into four classes (category A: pioglitazone, biguanides, GLP-1 receptor agonists; category B: sulfonylureas and meglitinides; category C: insulin; category D: α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors), as previously described[22] (appendix p 4). All patients in the intensive therapy group received a blood glucose meter for self-monitoring. The physician in charge instructed participants in the intensive therapy group on the frequency and timing of self-monitoring, according to the required level of blood glucose control and antidiabetic treatment; patients taking insulin were encouraged to measure their blood glucose more frequently than those who were not taking insulin, to avoid hypoglycaemia.

All patients in the intensive therapy group maintained their pretrial antihypertension treatment, along with their diet and exercise therapy (predetermined by the protocol). If blood pressure was greater than 120/75 mm Hg after 3 months, patients in the intensive therapy group were prescribed antihypertensive drugs in steps (first-line treatment: angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor) to ensure that the treatment goal was achieved in 3–6 months, as previously described[22] (appendix p 4). All patients in the intensive therapy group received a sphygmomanometer at study entry. They were instructed to measure blood pressure at home at wake-up time and any other convenient time. The results were reported to the physician in charge to detect masked hypertension or hypotension.

All patients in the intensive therapy group maintained their pretrial lipid-lowering treatment, along with diet and exercise therapy predetermined by the protocol. If the lipid control goal in the intensive therapy group was not achieved within 3 months, patients were prescribed lipid-lowering drugs (first-line treatment: high-intensity statin), as previously described[22] (appendix p 4). In both groups, all patients with a history of macrovascular complications received antiplatelet therapy, anticoagulant therapy, or both (eg, low-dose aspirin and warfarin), in accordance with the Japanese guideline. All patients in the intensive therapy group were requested to adhere to lifestyle changes, as previously described (appendix pp 3–4).[22]

Patients in both groups were asked to visit the clinic once per month and blood samples were taken to measure laboratory data including blood glucose concentration and HbA_{1c} at every visit; patients in the conventional therapy group were permitted to visit less frequently (up to every 3 months). At every visit, patients were informed of the results of their HbA_{1c}, blood pressure, and lipid measurements and educated and treated to achieve their allocated targets by the physician in charge and diabetes educators. Urinary albumin was measured every 6 months and an electrocardiogram and chest radiography were done every year. Biochemical data were measured at the laboratories of the study institutions.

Outcomes

The primary outcome was occurrence of any of a composite of macrovascular events and all-cause mortality, as determined by an Endpoint Assessment Committee that was unaware of group assignment. The macrovascular events were defined as myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting.[22] Revascularisations (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting) were judged as outcomes and the operations for the patients who were well controlled by medications or did not show severe stenosis were excluded by the Endpoint Assessment Committee. The main secondary outcome was a composite of myocardial infarction, stroke, and all-cause mortality, which was the original primary outcome and changed when the protocol was modified and approved in 2010, as described in the statistical analysis section. Events were checked at every patient visit by the physician in charge and reported to the central office through the electronic data capturing system, and the central office surveyed and collected the events every 6 months through the system.

Other secondary outcomes were onset or progression of nephropathy, defined as progression from normoalbuminuria (urinary albumin-to-creatinine ratio [UACR] <30 mg/g) to microalbuminuria (UACR ≥30 mg/g to <300 mg/g), or from normoalbuminuria to macroalbuminuria (UACR ≥300 mg/g), progression from microalbuminuria to macroalbuminuria, increase in serum creatinine concentration by twice or more than that at study entry, or end-stage renal failure (permanent dialysis initiated or renal transplant performed); onset or progression of retinopathy, defined as progression from absence of retinopathy to non-proliferative retinopathy or proliferative retinopathy, progression from non-proliferative to proliferative retinopathy, or loss of vision probably caused by retinopathy; and lower limb vascular events (amputation or revascularisation). Nephropathy was assessed by blood sample data at every visit and urinary albumin every 6 months, and reported through the electronic data capturing system. Retinopathy was assessed by ophthalmologist at each institution once per year and reported through the electronic data capturing system. Lower limb vascular events were assessed at every visit by the physician in charge and surveyed at the central office every 6 months through the electronic data capturing system.

All adverse events were collected by the physician in charge at every patient visit and when reported by the patient. Prespecified adverse events included severe and non-severe hypoglycaemia, heart failure and its related symptoms, hyperkalaemia, liver dysfuction and its related laboratory data, rhabdomyolysis and its related laboratory data, malignant neoplasm, and bone fracture. Since the glycaemic control target was strict and pioglitazone was widely used in the intensive therapy group, leading to the potential risk of hypoglycaemia and heart failure, respectively, hypoglycaemia, palpitation, oedema, and shortness of breath were actively surveyed by the physician in charge at every patient visit.

In a post-hoc analysis, the primary composite outcome was broken down into all-cause mortality, a composite of coronary events, and a composite of cerebrovascular events. Coronary events were defined as a composite of myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty; cerebrovascular events were defined as a composite of stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting.

Statistical analysis

The necessary number of primary outcome events and patients were originally estimated as 328 and 2816 in total (30% of patients were expected to have a history of cardiovascular disease), respectively, to verify a 30% risk reduction with 90% power and a two-sided significance level of 5%. At about 1 year after initiation of the study in October, 2007, the event rate was lower than expected and the necessary number of patients was re-estimated as 3338. At the end of the accrual period in March, 2009, however, the final number of participants, 2542 in total, and the proportion of those with history of cardiovascular disease (288 [11%]), fell short of the expectation. The cumulative event rate for the original primary outcome (now the main secondary outcome) during the first 3 years was 1·9% (95% CI 1·4–2·5), which was about one sixth of the original estimate. However, the cumulative event rate for the initial primary outcome plus revascularisations for this period was 3·4% (95% CI 2·8–4·2). Therefore, in January, 2010, the primary outcome was modified, from the occurrence of myocardial infarction, stroke, or all-cause mortality, which was redefined as the main secondary outcome, to the occurrence of myocardial infarction, stroke, all-cause mortality, or revascularisation. Furthermore, we revised the required number of events to 250, by lowering the power to 80%, and participants were to be followed up until the required number of events were expected to have occurred (estimated to be March, 2016, according to the event rate from 2006 to 2014) to ensure adequate power in August, 2015. On this basis, the study was completed in March, 2016, yielding a median intervention period of 8·5 years.[20]

All analyses of the primary and secondary outcomes were done in accordance with the prespecified statistical analysis plan and the intention-to-treat principle using SAS version 9.4. In the analyses presented in this report, imputation was not required for missing values because we used generalised estimating equations for repeated measures (with missing visits), which accommodated for missing values. Time-to-first-event of outcomes was

summarised as a cumulative proportion with the Kaplan-Meier method and compared by use of the log-rank test. Hazard ratios (HRs) representing the treatment effect were estimated by Cox regression analysis with only treatment effect as a covariate.

In a prespecified sensitivity analysis, we did Cox regression analysis with stratification factors and other important prognostic factors (BMI, smoking status, duration of diabetes, fasting plasma glucose concentration, systolic and diastolic blood pressure, and LDL cholesterol, HDL cholesterol, and triglyceride concentrations) as covariates. Additionally, for prespecified subgroup analyses, three risk groups (high, middle, and low risk) were constructed, under blinded review, by the Cox regression of the primary outcome without information on randomisation group (conventional or intensive therapy), from 2^4 subgroups, which corresponded to the combination of two levels for the four stratification factors (sex, age, HbA_{1c}, and history of cardiovascular disease). The calculated HR of each subgroup was ordered and 2^4 subgroups were classified into three groups according to the magnitude of HR.

Time-varying measurements such as HbA_{1c} were analysed with generalised estimating equation models using robust variance adjustment. The time profile including the baseline value was estimated for each of the groups with time–group interaction terms. Group difference and time–group interaction after the intervention were estimated with the baseline value as a covariate. Occurrence of adverse events including malignant neoplasms and deaths were summarised by group and compared using Fisher's exact test. Medications at baseline and final visit were also summarised and medication use at final visit was compared between groups. A two-sided p value of less than 0·05 was deemed significant.

This study is registered with ClinicalTrials.gov, number NCT00300976.

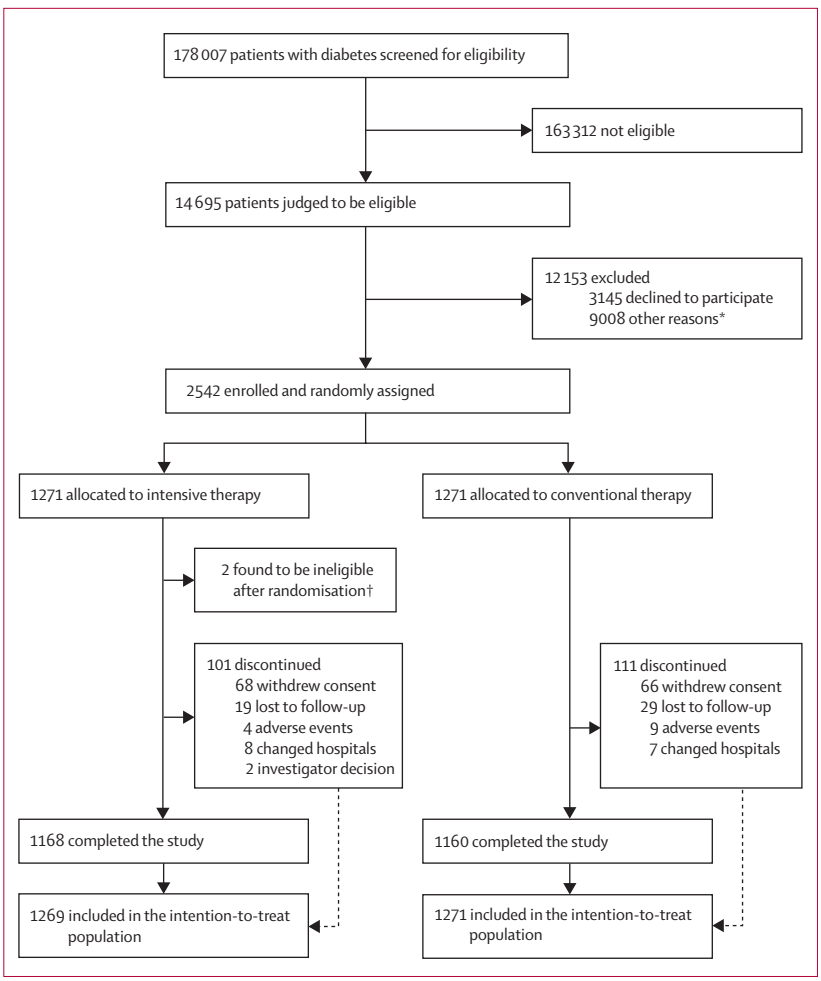


Figure 1: **Trial profile**
*Other reasons were not meeting inclusion criteria, meeting exclusion criteria, investigator decision, or changing hospital before getting consent or registration. †Two patients in the intensive therapy group were found to be ineligible after randomisation and were excluded from the analyses (one had LDL cholesterol ≥200 mg/dL and the other was given insulin at baseline).

Role of the funding source

The J-DOIT3 trial was investigator-initiated. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All study data were collected and retained by the investigators and were not made available to the funding sources. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 16, 2006, and March 31, 2009, we randomly assigned 2542 patients (288 [11%] with a history of cardiovascular disease) to intensive therapy or conventional therapy (1271 in each group; figure 1). Patients remained on the intervention until March 31, 2016. After the blinded review of all patients, two ineligible patients were removed from all analyses; both patients were in the intensive therapy group. Thus, 1269 patients in the intensive therapy group and 1271 in the conventional therapy group were included in the analyses. Baseline characteristics were similar between groups, apart from smoking status, with a higher proportion of patients who were current smokers in the intensive therapy group than in the conventional therapy group (table 1). However, the difference in the proportion between groups had diminished at the final visit as a result of the promotion of smoking cessation (173 [14%] of 1269 in the intensive therapy group were current smokers *vs* 149 [12%] of 1271 in the conventional therapy group at the final visit). Median duration of follow-up was 8·5 years (IQR 7·3–9·0). The frequency of premature discontinuation did not differ between groups (figure 1). Overall, 2328 (92%) patients completed the study.

During the intervention period, mean HbA_{1c} was 6·8% (51·0 mmol/mol) in the intensive therapy group

	Intensive therapy (n=1269)	Conventional therapy (n=1271)
Age (years)*	58·9 (6·4)	59·1 (6·3)
Sex*		
Men	784 (62%)	791 (62%)
Women	485 (38%)	480 (38%)
Duration of diabetes (years)	8·58 (7·00)	8·47 (6·99)
Smoking status		
Current	328 (26%)	267 (21%)
Former	370 (29%)	416 (33%)
Never	571 (45%)	588 (46%)
History of cardiovascular disease*	146 (12%)	142 (11%)
Bodyweight (kg)	65·4 (11·9)	65·9 (12·0)
BMI (kg/m^2)	24·8 (3·6)	24·9 (3·8)
Fasting plasma glucose (mg/dL)†	159·6 (41·5)	158·7 (39·4)
HbA_{1c} (%)*	8·01% (1·05)	7·98% (1·05)
HbA_{1c} (mmol/mol)*	64·0 (11·5)	63·7 (11·5)
Systolic blood pressure (mm Hg)	133·5 (16·9)	134·1 (16·3)
Diastolic blood pressure (mm Hg)	79·3 (10·8)	80·0 (11·1)
LDL cholesterol (mg/dL)‡	125·5 (30·6)	125·6 (31·7)
HDL cholesterol (mg/dL)‡	54·4 (14·9)	54·5 (14·0)
Triglycerides (mg/dL)§	121 (85–180)	123 (88–177)

Data are n (%), mean (SD), or median (IQR). *Dynamic allocation was performed by randomisation adjusted for age, male-to-female ratio, history of cardiovascular disease, and HbA_{1c}. †To convert values for glucose to mmol/L, multiply by 0·05551. ‡To convert values for cholesterol to mmol/L, multiply by 0·02586. §To convert values for triglycerides to mmol/L, multiply by 0·01129.

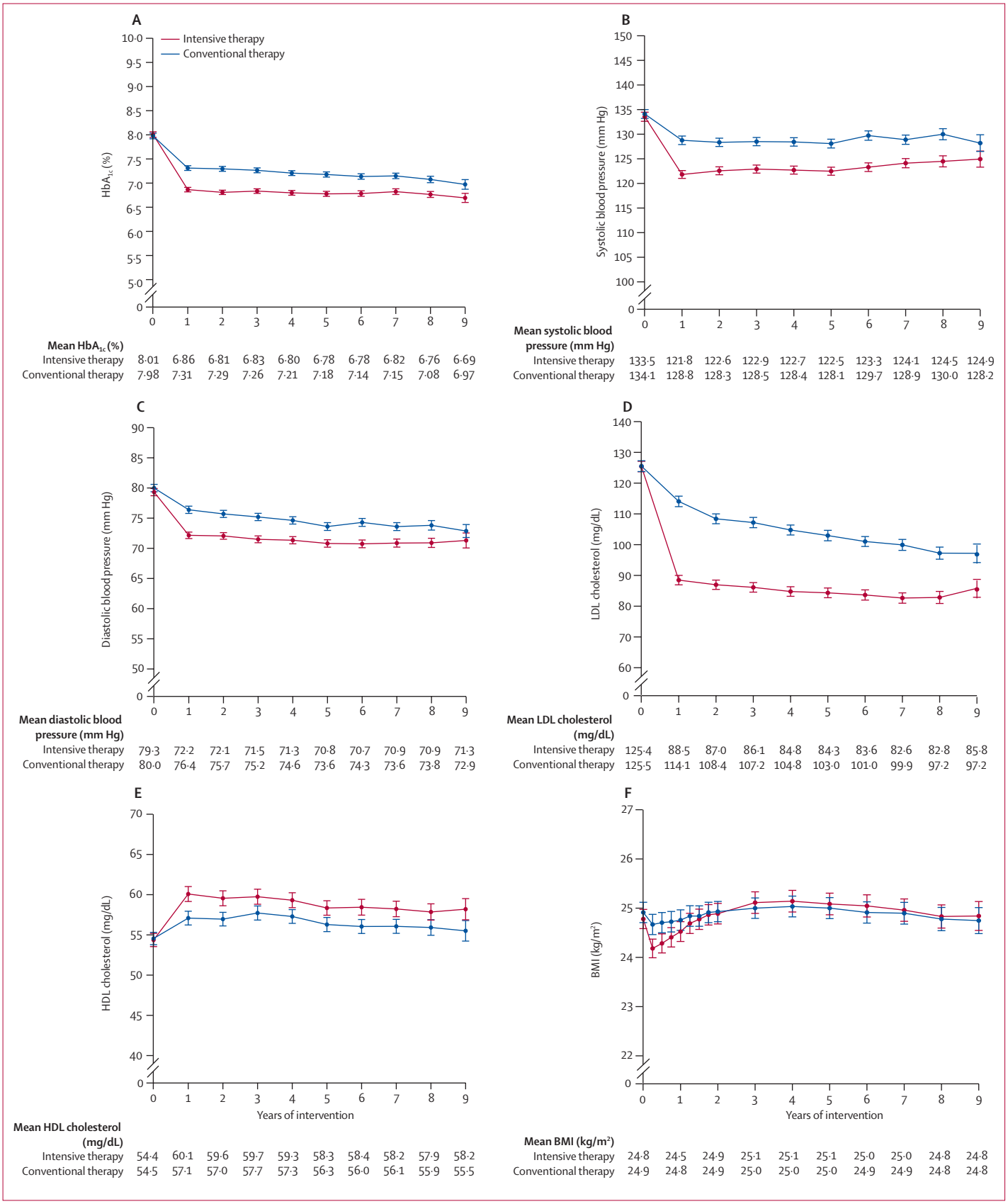
Table 1: **Baseline characteristics**

(223 [18%] patients had achieved HbA_{1c} <6·2% [44·3 mmol/mol] at final visit) and 7·2% (55·2 mmol/mol) in the conventional therapy group (504 [40%] patients had achieved HbA_{1c} <6·9% [52·0 mmol/mol] at final visit; figure 2). Mean blood pressure was 123/71 mm Hg in the intensive therapy group (481 [38%] patients had achieved systolic blood pressure <120 mm Hg and 795 [63%] had achieved diastolic blood pressure <75 mm Hg at final visit) and 129/74 mm Hg in the conventional therapy group (639 [50%] patients had achieved systolic blood pressure <130 mm Hg and 853 [67%] had achieved diastolic blood pressure <80 mm Hg at final visit). Mean LDL cholesterol concentration was 85 mg/dL in the intensive therapy group (550 [43%] patients had achieved LDL cholesterol <80 mg/dL [in those without history of coronary artery disease] or <70 mg/dL [in those with history] at final visit) and 104 mg/dL in the conventional therapy group (935 [74%] patients had achieved LDL cholesterol <120 mg/dL [in those without history of coronary artery disease] or <100 mg/dL [in those with history] at final visit). The differences between the two groups in the mean value during the intervention of HbA_{1c}, systolic blood pressure, diastolic blood pressure, and LDL cholesterol were all significant (all p<0·0001; figure 2). HDL cholesterol concentrations in both groups were raised and sustained during the intervention period, and were consistently higher in the intensive therapy group than in the conventional therapy group (p<0·0001; figure 2). The interaction terms of time and group were significant for HbA_{1c}, systolic and diastolic blood pressure, and LDL cholesterol; however, these were interpreted as quantitative interactions and the group differences were almost stable during the treatment time. BMI transiently decreased in the intensive therapy group immediately after the start of lifestyle modification and later increased with treatment intensification, followed by a gradual decline towards baseline values. BMI remained constant in the conventional therapy group, resulting in no difference between groups (p=0·321; figure 2).

During the trial, patients in the intensive therapy group attended a mean of 70 visits, compared with 63 visits for patients in the conventional therapy group. Regarding antidiabetes drugs, increases in the use of pioglitazone and insulin were greater in the intensive therapy group than in the conventional therapy group (appendix pp 5–6), although insulin use in both groups was much lower than in previous studies.[5–7] Angiotensin II receptor blockers and high-intensity statins were more frequently prescribed for patients in the intensive therapy group than in the conventional therapy group (appendix pp 5–6). Use of antiplatelet treatment did not differ significantly between groups during the intervention period (appendix pp 5–6).

In total, 242 primary outcome events occurred during the intervention period: 109 in the intensive therapy group (45 deaths, five myocardial infarctions, 15 strokes, and 44 revascularisations [five coronary artery bypass surgeries, 37 percutaneous transluminal coronary angioplasties, one carotid endarterectomy, no percutaneous transluminal cerebral angioplasties, and one carotid artery stent procedure]) and 133 in the conventional therapy group (40 deaths, 11 myocardial infarctions, 37 strokes, and 45 revascularisations [eight coronary artery bypass surgeries, 34 percutaneous transluminal coronary angioplasties, no carotid endarterectomies, one percutaneous transluminal cerebral angioplasty, and two carotid artery

Figure 2: **Control of risk factors at baseline and during intervention**
Data are mean (SE) values for (A) HbA_{1c} (mean difference between groups –0·37% [95% CI –0·43 to –0·32; p<0·0001]; time–group interaction p=0·014); (B) systolic blood pressure (mean difference between groups –5·3 mm Hg [–0·61 to –4·5; p<0·0001]; time–group interaction p=0·045); (C) diastolic blood pressure (mean difference between groups –2·9 mm Hg [–3·5 to –2·3; p<0·0001], time–group interaction p=0·022); (D) LDL cholesterol (mean difference between groups –18·2 mg/dL [–19·8 to –16·5; p<0·0001]; time–group interaction p<0·0001); (E) HDL cholesterol (mean difference between groups 2·5 mg/dL [1·8 to 3·2; p<0·0001]; time–group interaction p=0·367); and (F) BMI (mean difference between groups 0·05 kg/m² [–0·05 to 0·15; p=0·321]; time–group interaction p<0·0001). Least square means calculated from the generalised estimating equation method including baseline values and time–group interaction terms are plotted. Group difference is a main effect estimated from the model with baseline values as a covariate. The compound symmetry was used as a temporary correlation structure with robust (sandwich) variance estimation and there was no essential difference due to the change of temporary correlation structure.



Mean HbA_{1c} (%)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	8·01	6·86	6·81	6·83	6·80	6·78	6·78	6·82	6·76	6·69
Conventional therapy	7·98	7·31	7·29	7·26	7·21	7·18	7·14	7·15	7·08	6·97

Mean systolic blood pressure (mm Hg)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	133·5	121·8	122·6	122·9	122·7	122·5	123·3	124·1	124·5	124·9
Conventional therapy	134·1	128·8	128·3	128·5	128·4	128·1	129·7	128·9	130·0	128·2

Mean diastolic blood pressure (mm Hg)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	79·3	72·2	72·1	71·5	71·3	70·8	70·7	70·9	70·9	71·3
Conventional therapy	80·0	76·4	75·7	75·2	74·6	73·6	74·3	73·6	73·8	72·9

Mean LDL cholesterol (mg/dL)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	125·4	88·5	87·0	86·1	84·8	84·3	83·6	82·6	82·8	85·8
Conventional therapy	125·5	114·1	108·4	107·2	104·8	103·0	101·0	99·9	97·2	97·2

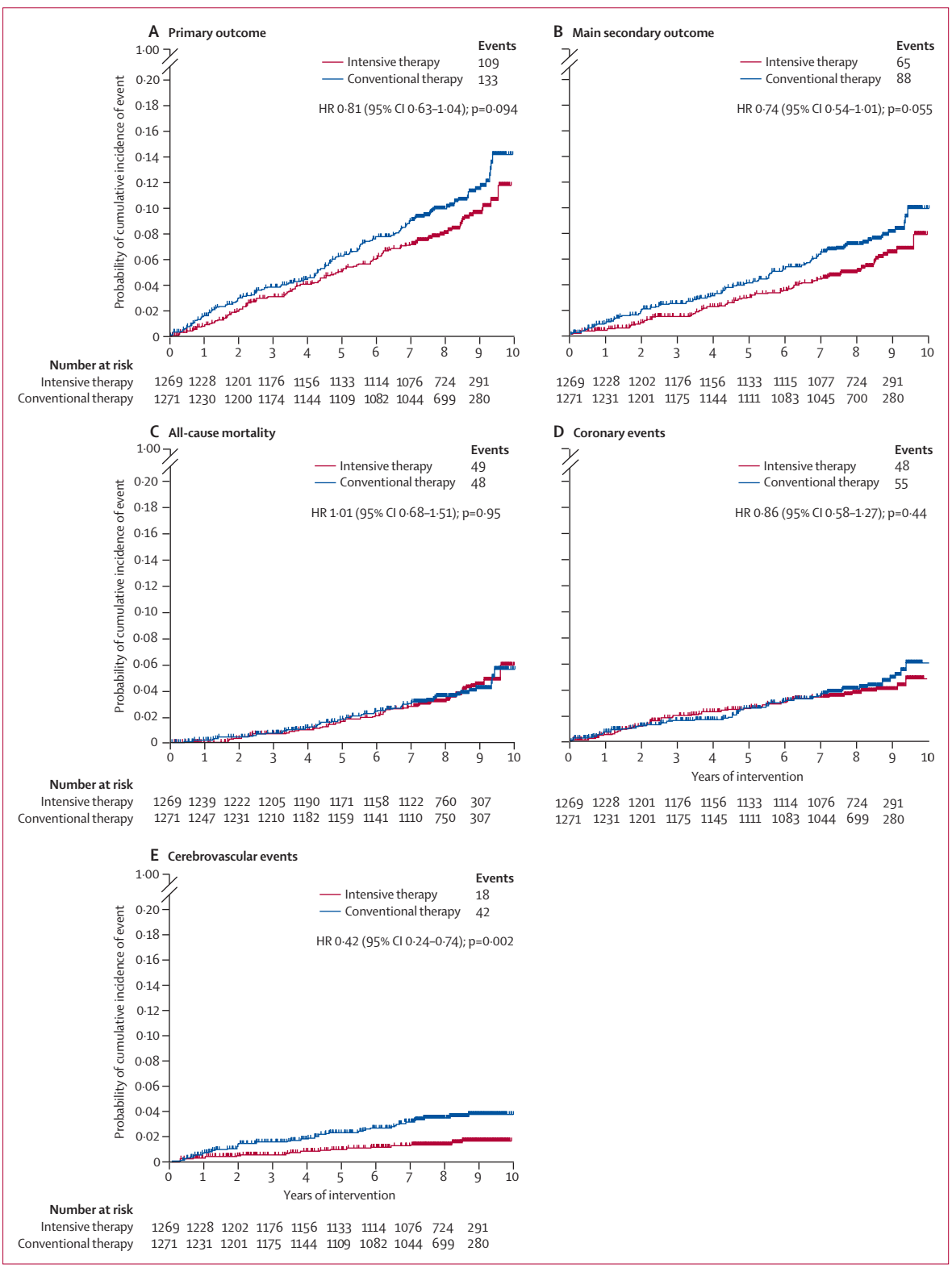
Mean HDL cholesterol (mg/dL)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	54·4	60·1	59·6	59·7	59·3	58·3	58·4	58·2	57·9	58·2
Conventional therapy	54·5	57·1	57·0	57·7	57·3	56·3	56·0	56·1	55·9	55·5

Mean BMI (kg/m^2)

	0	1	2	3	4	5	6	7	8	9
Intensive therapy	24·8	24·5	24·9	25·1	25·1	25·1	25·0	25·0	24·8	24·8
Conventional therapy	24·9	24·8	24·9	25·0	25·0	25·0	24·9	24·9	24·8	24·8

stent procedures]). Three risk strata (low, middle, and high) consisting of the combinations of the four stratification factors (age, sex, history of cardiovascular events, and HbA_{1c} at baseline) were identified from the blinded review of primary events using Cox regression without the treatment effect and these strata were used for confirmatory



stratified analyses of the primary and main secondary outcomes.

Intensive therapy was associated with a non-significant reduction in the incidence of primary outcome events compared with conventional therapy (HR 0·81, 95% CI 0·63–1·04; p=0·094; figure 3). The HR for the main secondary outcome—a composite of all-cause mortality, myocardial infarction, and stroke—was 0·74 (95% CI 0·54–1·01; p=0·055; figure 3).

In the prespecified sensitivity analysis in which the primary outcome result was adjusted for baseline risk factors, the outcome was significantly reduced in the intensive therapy group (HR 0·76, 0·59–0·99; p=0·042). In the adjusted analysis, 105 patients (52 in the intensive therapy group *vs* 53 in the conventional therapy group) and 11 events (six *vs* five) were excluded because of missing values of covariates; however, the results of the (unadjusted) primary analysis for this population (HR 0·79, 95% CI 0·61–1·03; p=0·075) was similar to the result for the intention-to-treat population.

In the post-hoc breakdown of the primary composite outcome, there were no differences between groups in all-cause mortality (HR 1·01, 95% CI 0·68–1·51; p=0·95) or coronary events (HR 0·86, 0·58–1·27; p=0·44; figure 3). However, compared with conventional therapy, intensive therapy was strongly associated with a reduction in cerebrovascular events (mostly stroke; HR 0·42, 95% CI 0·24–0·74; p=0·002; figure 3). This post-hoc finding suggests that the number needed to treat with intensive therapy to prevent one cerebrovascular event is 47·6 at 8 years.

The effect of intensive therapy on the primary outcome and main secondary outcome did not differ significantly in the prespecified subgroups (figure 4). In the post-hoc breakdown of the primary composite outcome, there was no heterogeneity in the effect of intensive therapy on cerebrovascular events or coronary events among the subgroups (appendix pp 10–11).

438 renal events (onset or progression of nephropathy) occurred in the intervention period: 181 in the intensive therapy group and 257 in the conventional therapy group (HR 0·68, 95% CI 0·56–0·82; p<0·0001; figure 5). No patients in either group had end-stage renal failure as a first event; five patients in the conventional therapy group did have to undergo haemodialysis as a result of end-stage renal failure, but they had developed microalbuminuria, macroalbuminuria, or creatinine doubling before receiving haemodialysis; thus, these haemodialysis events were not counted as a secondary endpoint. 679 eye events occurred (onset or progression of retinopathy): 317 in the intensive therapy group and 362 in the conventional therapy group (HR 0·86, 95% CI 0·74–1·00; p=0·046; figure 5). No loss of vision was reported in either group during the study period. Only 19 lower limb vascular events (amptation or revascularisation) occurred: nine revascularisations in the intensive therapy group and ten revascularisations in the conventional therapy group (HR 0·89, 95% CI 0·36–2·20; p=0·80; figure 5). No amputations occurred in either group during the study period.

During the intervention period, 49 (4%) people died in the intensive therapy group and 48 (4%) people died in the conventional therapy group. The most frequent cause of death was cancer in both groups, and the frequency of cancer-related death was similar between groups (32 [3%] in the intensive therapy group *vs* 25 [2%] in the conventional therapy group; appendix p 7). Four patients in the conventional therapy group died from stroke (n=3) or myocardial infarction (n=1) compared with none in the intensive therapy group.

The frequencies of prespecified adverse events are shown in table 2. The incidence of malignant neoplasm was similar between groups (119 [9%] in the intensive therapy group *vs* 137 [11%] in the conventional therapy group; see appendix p 8 for list of primary organs affected). Seven patients in the intensive therapy group and four patients in the conventional therapy group developed severe hypoglycaemia; all recovered after glucose infusion or a brief hospital stay. The proportion of patients who had hypoglycaemia was significantly higher in the intensive therapy group (521 [41%]) than in the conventional therapy group (283 [22%]; table 2). Non-severe oedema not associated with heart failure was more frequent in the intensive therapy group than in the conventional therapy group (table 2). No differences were evident between groups in other adverse events or other severe side-effects (appendix p 9), apart from raised ALT and creatine kinase, which were higher in the intentive therapy group (table 2).

Figure 3: **Cumulative incidence of macrovascular outcome events and all-cause mortality**

The primary outcome (A) was a composite of myocardial infarction, stroke, revascularisation (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting), and all-cause mortality. The main secondary outcome (B) was a composite of myocardial infarction, stroke, and all-cause mortality. All-cause mortality (C) was a post-hoc outcome. Coronary events (D) was a composite of myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty (post-hoc outcome). Cerebrovascular events (E) was a composite of stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting (post-hoc outcome). HR=hazard ratio.

Discussion

In the J-DOIT3 trial, intensive therapy in patients with type 2 diabetes did not significantly reduce the occurrence of either primary outcome (a composite of myocardial infarction, stroke, revascularisation, and all-cause mortality) or main secondary outcome (myocardial infarction, stroke, and all-cause mortality) events compared with conventional therapy. However, there was a significant reduction in the primary outcome after adjustment for prespecified stratification factors and other important prognostic factors, possibly at least partly because smoking status at baseline was imbalanced between the treatment groups. Additionally, in a post-hoc analysis in

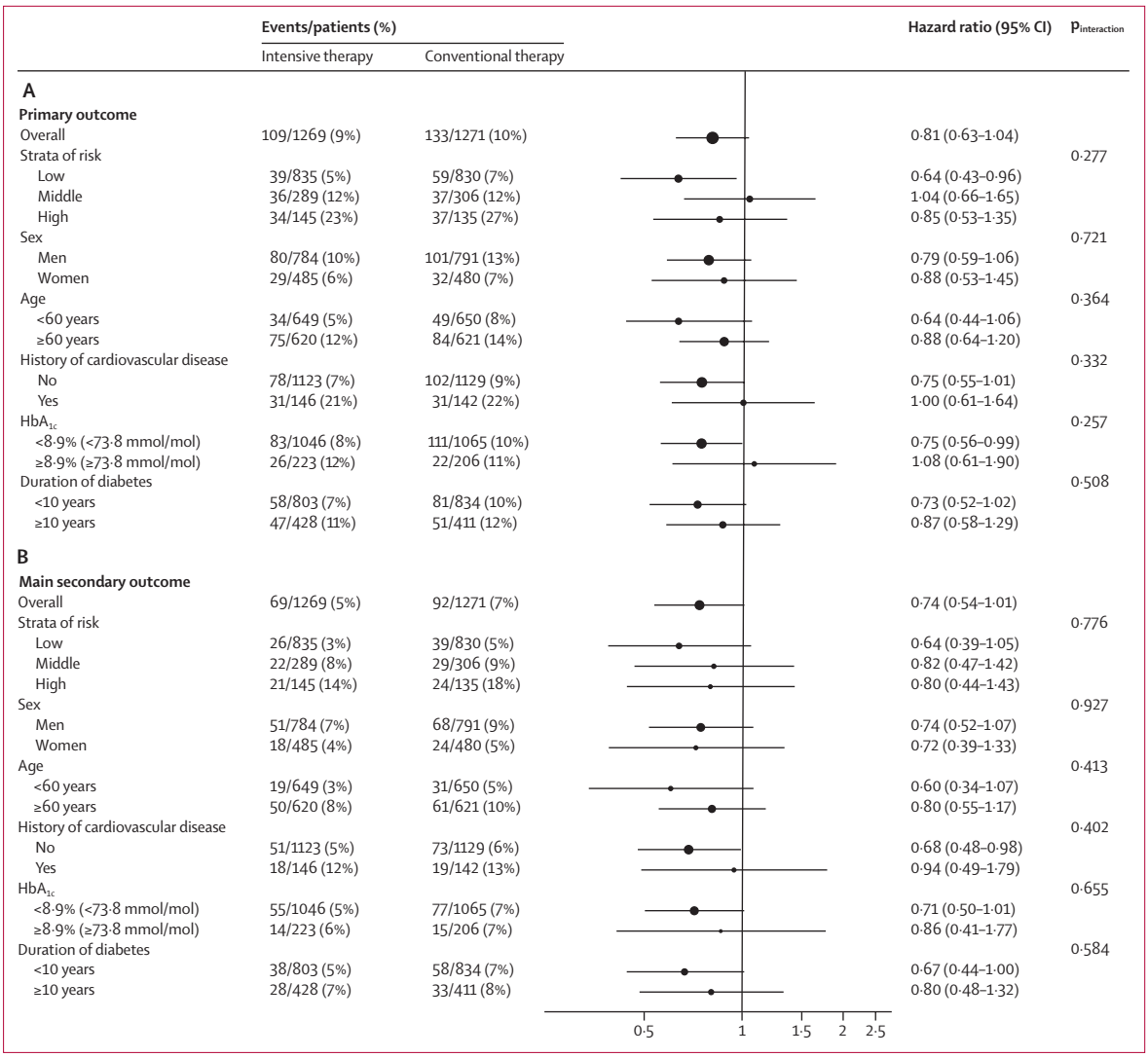


Figure 4: **Subgroup analyses for the effects of intensive versus conventional therapy on the primary and main secondary outcomes**
Hazard ratios and 95% CIs were estimated with the use of Cox regression. p values for interaction were obtained with the Wald test. The analysis according to duration of diabetes was not prespecified (intensive therapy, n=1231; conventional therapy, n=1245); we excluded patients with missing information from the analysis of duration of diabetes. Risk groups were determined by the blind review according to stratification factors (age, sex, history of cardiovascular disease, and HbA_{1c}). Low-risk group, eight strata: (1) <60 years, female, yes, <8·9% (<73·8 mmol/mol), (2) <60 years, female, yes, ≥8·9% (≥73·8 mmol/mol), (3) <60 years, female, no, <8·9%, (4) <60 years, female, no, ≥8·9%, (5) <60 years, male, no, <8·9%, (6) <60 years, male, no, ≥8·9%, (7) ≥60 years, female, no, <8·9%, (8) ≥60 years, female, no, ≥8·9%. Middle-risk group, three strata: (1) ≥60 years, female, yes, <8·9%, (2) ≥60 years, male, no, <8·9%, (3) ≥60 years, male, yes, ≥8·9%. High-risk group, five strata: (1) <60 years, male, yes, <8·9%, (2) <60 years, male, yes, ≥8·9%, (3) ≥60 years, female, yes, ≥8·9%, (4) ≥60 years, male, no, ≥8·9%, (5) ≥60 years, male, yes, <8·9%.

which the primary composite outcome was broken down by event type, compared with conventional therapy, intensive therapy was associated with a significant reduction in cerebrovascular events, mainly stroke, although the other components of the primary outcome (coronary events and all-cause mortality) did not differ between intensive and conventional therapy.

Although intensive therapy was associated with non-significant reductions in primary outcome and main secondary outcome events, our findings showed no clear benefit of this strategy. One possible reason that the trial did not demonstrate a clear benefit was lower power than originally anticipated, partly because glucose, blood pressure, and lipids were well controlled in the conventional therapy group, leading to a smaller number of events than expected. Indeed, whereas the sample size of this trial was nearly 16 times larger than that of the Steno-2 study, which also assessed an intensive multifactorial intervention versus conventional therapy, control of these factors in the conventional therapy group was much better than that in the conventional therapy group of the Steno-2 study (mean HbA_{1c} 9·0% [74·9 mmol/mol],

mean blood pressure 146/78 mm Hg, and mean LDL cholesterol 120 mg/dL). Furthermore, in the intensive therapy group of our study, mean HbA_{1c}, blood pressure, and LDL cholesterol did not reach their respective targets, whereas control of blood pressure and LDL cholesterol in the conventional therapy group were better than the conventional targets. This discrepancy might have resulted in smaller differences in events between the two groups than expected. Additionally, since the event rate of the original primary endpoint (all-cause mortality, myocardial infarction, and stroke) was about a sixth of the expected value, we added revascularisations to the primary composite endpoint in a protocol amendment. This modification might make the difference between groups smaller, because in general the operation of revascularisation tended to be actively performed to protect against myocardial infarction or stroke depending on practice and decisions made at the participating institutions.

The current standard care for diabetes has been shown to decrease the incidence of microvascular and macrovascular complications.[25] Our findings suggest that, compared with current standard care, further intensification of multifactorial care could significantly reduce the incidence of cerebrovascular disease in Japanese patients with type 2 diabetes. Among known risk factors for stroke, blood pressure control has been shown to be particularly important. Nevertheless, the current blood pressure target in the ADA and EASD guidelines, 140/90 mm Hg[13] and 140/85 mm Hg,[14] respectively, is less strict than the previous target of 130/80 mm Hg for patients with diabetes. The new blood pressure targets were determined by examining evidence from a meta-analysis,[26,27] although the guidelines acknowledge that a systolic blood pressure lower than 140 mm Hg might be beneficial for stroke prevention.[13,14]

In our trial, mean systolic and diastolic blood pressure values were lower in the intensive therapy group (123/71 mm Hg) than in the conventional therapy group (129/74 mm Hg), which might account for the robust reduction in cerebrovascular events in the post-hoc analysis. In the ACCORD trial, systolic blood pressure lower than 120 mm Hg was beneficial for stroke prevention,[15] although 34% of the patients in that trial had a history of cardiovascular disease and the rest had much higher risk than did those in our trial, in which most patients had no history of cardiovascular disease. The reason why a relatively small difference in blood pressure in our study resulted in an even larger reduction in stroke compared with the ACCORD trial in which the difference in blood pressure was much larger might be partly caused by the longer intervention period of our trial (mean follow-up 8·5 years *vs* 4·7 years in ACCORD). Thus, our findings support a stricter blood pressure target compared with the current JDS and former ADA and EASD recommendation of 130/80 mm Hg for primary prevention of stroke.

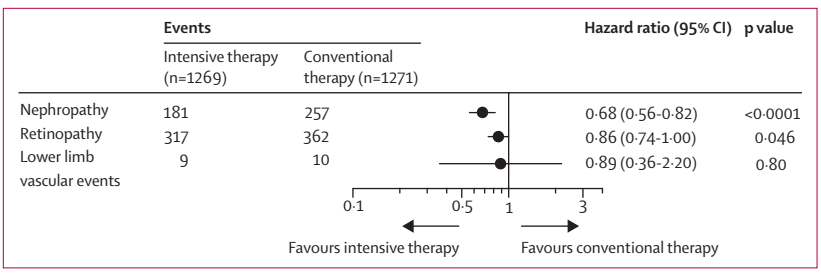


Figure 5: **Onset or progression of nephropathy, onset or progression of retinopathy, and lower limb vascular events**

	Intensive therapy (n=1269)	Conventional therapy (n=1271)	p value*
Patients who had events			
All adverse events	1130 (89%)	1135 (89%)	0·848
All severe adverse events	121 (10%)	127 (10%)	0·738
Prespecified adverse events			
Severe hypoglycaemia†‡	7 (1%)	4 (<1%)	0·386
Hypoglycaemia‡	521 (41%)	283 (22%)	<0·0001
Heart failure	9 (1%)	7 (1%)	0·628
Palpitation‡	67 (5%)	77 (6%)	0·440
Oedema‡	193 (15%)	129 (10%)	0·0001
Shortness of breath‡	37 (3%)	31 (2%)	0·464
Hyperkalaemia	18 (1%)	21 (2%)	0·747
Raised AST	38 (3%)	23 (2%)	0·053
Raised ALT	44 (3%)	18 (1%)	0·001
Liver dysfunction	5 (<1%)	3 (<1%)	0·507
Raised creatine kinase	87 (7%)	52 (4%)	0·002
Rhabdomyolysis	2 (<1%)	1 (<1%)	0·625
Malignant neoplasms	119 (9%)	137 (11%)	0·263
Fracture	143 (11%)	125 (10%)	0·246
Total events			
All adverse events	13 487	10 257	..
All severe adverse events	214	243	..
Prespecified adverse events			
Severe hypoglycaemia†‡	7	4	..
Hypoglycaemia	4274	1229	..

Adverse events are reported irrespective of a causal relation to the investigational treatment. AST=aspartate aminotransferase. ALT=alanine aminotransferase. *Statistical analyses were performed with Fisher's exact test. †Severe hypoglycaemia is defined as hypoglycaemia requiring someone else's assistance or admission to hospital. ‡As part of active surveillance, the physician in charge collected data on hypoglycaemia, palpitation, oedema, and shortness of breath at each visit.

Table 2: **Adverse events**

ADA and EASD guidelines previously recommended an LDL cholesterol target of 100 mg/dL (70 mg/dL for secondary prevention and high-risk patients),[28] although the current ADA guideline does not set a particular target.[13] In the current JDS guideline,[17] the target is 120 mg/dL (100 mg/dL in patients with a history of coronary artery disease). In our study, mean LDL cholesterol concentration was 85 mg/dL in the intensive therapy group, which is close to the concentration

reported for patients treated with atorvastatin in the CARDS study.[12] This LDL cholesterol concentration might have contributed to primary prevention of stroke in our trial. Thus, the target of LDL cholesterol in the future guideline could be changed to a value lower than 100 mg/dL. Furthermore, mean HDL cholesterol concentration was much higher in the intensive therapy group than in the conventional therapy group, presumably because of increased physical activity in the intensive therapy group (data not shown). Such activity increases HDL cholesterol and is an independent protective factor against stroke.[29] Smoking is a strong cardiovascular risk factor, and the proportion of current smokers was higher in the intensive therapy group (26%) than in the conventional therapy group (21%) at baseline; however, the proportion at the final visit was similar in the two groups (12% in the conventional therapy group *vs* 14% in the intensive therapy group).

In the IRIS trial, in which participants had history of stroke or transient ischaemic attack with insulin resistance, but did not have diabetes, pioglitazone significantly suppressed stroke and myocardial infarction compared with placebo.[30] Although in our study pioglitazone use was higher in the intensive therapy group than in the conventional therapy group, its use was not associated with the reduction of cerebrovascular events (data not shown).

In our trial, intensive therapy significantly reduced nephropathy and retinopathy compared with conventional therapy by 32% and 14%, respectively. Microvascular complications were also shown to be prevented by the multifactorial intervention in the Steno-2 study (61% reduction in nephropathy and 58% reduction in retinopathy), although control of glucose and blood pressure was insufficient compared with the current standard of care in the conventional therapy group in Steno-2. By contrast, intensive glucose lowering[5,31] or blood pressure control[32] alone has been shown to provide relatively small reductions in renal events compared with the current standard care, which sets targets for multiple factors to prevent microvascular complications according to the results of a single-factor intervention, such as glucose or blood pressure measurements. Our results suggest that intensified multifactorial intervention is able to reduce renal events associated with type 2 diabetes to a greater extent than the current standard care (which is specifically designed to suppress renal events), although further analysis is needed to assess which factors affect the prevention of renal events and to determine appropriate targets for the variables such as HbA_{1c}, blood pressure, and LDL cholesterol. As for the development or progression of retinopathy, although further glucose lowering from the target in the current guideline has been shown to have a minor benefit,[5,33] our data suggest that intensified multifactorial intervention has a further beneficial effect on prevention of diabetic retinopathy in patients with good glycaemic control compared with the current standard.

Intensive therapy did not significantly reduce coronary events or all-cause mortality in J-DOIT3, partly because the incidences of myocardial infarction and cardiovascular death were very low in both groups, which reflects the success of the current standard of care in preventing macrovascular complications.[25] Indeed, in the ADDITION-Europe trial,[34] which started in 2001, rates of myocardial infarction, stroke, and all-cause death were much lower (4·4, 2·6, and 12·5 per 1000 patients per year, respectively) in patients with newly diagnosed diabetes, even for those receiving conventional therapy, than were rates in the earlier UKPDS 33 trial[3] (17·4, 5·0, and 18·9 per 1000 patients per year, respectively). The Japan Diabetes Complications Study (JDCS) started 10 years before J-DOIT3 and enrolled patients with baseline characteristics similar to those in our trial. The incidences of macrovascular complications and mortality in our trial were almost half those observed in the JDCS trial.[18] Diabetes is associated with premature death from causes such as vascular disease, cancer, and infectious disease.[1] Although vascular disease is the most common cause of death in European and North American countries,[1] 40% of Japanese people with diabetes die from cancer,[35] presumably because cardiovascular mortality is lower. In our study, nearly 60% of deaths were due to cancer, resulting in further reduction in vascular death, and the frequency of cancer-related death did not differ between groups. This finding helps to explain why intensive therapy did not result in a significant decrease in overall mortality.

Severe hypoglycaemia, which was associated with intensive therapy in many clinical trials,[36] might increase the incidence of vascular complications and cause sudden death.[8,9] The very low rate of severe hypoglycaemic episodes in both groups in our study might have contributed to the low incidence of macrovascular complications and mortality. This low rate of severe hypoglycaemia is partly the result of improved lifestyle, including exercise and diet, especially in the intensive therapy group. Such lifestyle changes allow patients to avoid polypharmacy, which is associated with hypoglycaemia, hypotension, and other adverse events. The frequent use of oral antidiabetes drugs with a low risk of hypoglycaemia, including metformin, pioglitazone, and dipeptidyl peptidase-4 inhibitors, and the infrequent use of insulin might account for the low rate of severe hypoglycaemia in our trial, and these drugs (except for pioglitazone) might have also led to the maintenance of a stable bodyweight. The incidence of other adverse events was similar between groups.

Notably, all the institutions included in our trial had a diabetes care clinic with diabetes specialists and educators, whereas in most countries, including Japan, most patients with diabetes are treated by non-specialists. As such, it is not certain whether these results will be applicable to the broader population of patients with type 2 diabetes being treated by non-specialists in primary

care setting. However, the patients in our trial, all of whom were taking two diabetes drugs or fewer at baseline, would often be cared for by non-specialists in clinical practice, and the fairly low cardiovascular risk profile of many of the patients in our trial is fairly representative of patients who would often receive non-specialist care. Therefore, our results could be also relevant to patients treated by primary care providers and other non-specialists, assuming that a treatment regimen or algorithm for non-specialists is developed on the basis of results of this trial.

In conclusion, compared with conventional targets for control of glucose, blood pressure, and lipids, a multifactorial intervention with much stricter targets than those recommended by current guidelines did not significantly reduce coronary events or all-cause mortality in patients with type 2 diabetes, but, in a post-hoc analysis, significantly decreased the risk of cerebrovascular events, as well as leading to reductions in macrovascular complications. A follow-up observational study of J-DOIT3 is underway to assess the legacy effects of the intensive multifactorial intervention on coronary and cerebrovascular events and mortality.[37]

Contributors

KU contributed to the design of the protocol, helped to steer the study, collected and analysed the data, and contributed to the writing of the report. TS helped to steer the study, collected and analysed the data, and contributed to the writing of the report. MK, YOk, SO, HK, MH, AiM, KO, KH, AtM, and KI helped to steer the study and collected and analysed the data. NI, YOh, MN, and TK contributed to the design of the protocol, helped to steer the study, collected and analysed the data, and reviewed and edited the draft report. TK is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

KU reports research funding (to his department) from MSD, Nippon Boehringer Ingelheim, and Novo Nordisk; lecture fees from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Kowa Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho Toyama Pharmaceutical, and Takeda; and grants and endowments from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Kowa Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho Toyama, and Takeda. TS reports lecture fees from AstraZeneca, Daiichi Sankyo, Mitsubishi Tanabe, Novo Nordisk, Sumitomo Dainippon, and Takeda. YOk reports lecture fees from Nippon Boehringer Ingelheim and Takeda. HK reports lecture fees from Astellas Pharma, AstraZeneca, Eli Lilly, Mitsubishi Tanabe, Novartis, Novo Nordisk, Ono Pharmaceutical, and Takeda. MH reports lecture fees from AstraZeneca, Kissei Pharmaceutical, and Mitsubishi Tanabe. AiM reports lecture fees from Nippon Boehringer Ingelheim. KO reports lecture fees from Abbott Japan, ASKA Pharmaceutical, Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Kao Corporation, MSD, Nippon Boehringer Ingelheim, Novo Nordisk, and Takeda. KH reports consulting fees from Kissei Pharmaceutical and Takeda and research support from Novartis. AtM reports lecture fees from Nippon Boehringer Ingelheim. KI reports grants from Ministry of Health, Labour and Welfare of Japan; endowments from Asahi Kasei, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Kissei, Kowa Pharmaceutical, Mitsubishi Tanabe, Mochida, MSD, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Ono, Pfizer, Shionogi, Sumitomo Dainippon, Taisho Toyama, and Takeda; and non-financial support from Sanwa Kagaku. NI reports grants and endowments from Taiho Pharmaceutical and personal fees from Bristol-Myers Squibb and Daiichi Sankyo. YOh reports lecture fees from Eli Lilly and Sanofi; consulting fees from Chugai Pharmaceutical and Kowa Pharmaceutical; personal fees from Shionogi and Daiichi Sankyo; grants and endowments from Eisai; and chairmanship of the board of directors and stock ownership in Statcom. MN reports lecture fees from AbbVie, Astellas Pharma, Daiichi Sankyo, Eli Lilly, Kissei Pharmaceutical, Kowa Pharmaceutical, Kyowa Hakko Kirin, Meiji Seika Pharma, MSD, Novo Nordisk, Sanofi, Ono Pharmaceutical, Taisho Toyama, and Takeda; and grants and endowments from AstraZeneca, Daiichi Sankyo, Kowa Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe, Mochida Pharmaceutical, MSD, Sanwa Kagaku, and Takeda. TK reports research funding (to his department) from Kowa Pharmaceutical, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, and Takeda; lecture fees from Astellas Pharma, AstraZeneca, Eli Lilly, Kissei Pharmaceutical, Kowa Pharmaceutical, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Sumitomo Dainippon, and Takeda; fees for writing booklets from Eli Lilly; grants and endowments from Astellas Pharma, Daiichi Sankyo, Kissei Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe, Novartis, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho Toyama Pharmaceutical, and Takeda; funds for contracted research from Daiichi Sankyo, Sanwa Kagaku, and Takeda; and funds for collaborative research from Daiichi Sankyo and Novartis. All other authors declare no competing interests.

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