Disclosure

The authors declare that they have no conflict of interest.

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References

1 Luft BJ, Chua A. Central nervous system toxoplasmosis in HIV pathogenesis, diagnosis, and therapy. *Curr Infect Dis Rep* 2000; **2**: 358–362.
2 Luft BJ, Hafner R, Korzun AH *et al.* Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med* 1993; **329**: 995–1000.
3 Meada T, Saito T, Takeuchi T, Asai T. Evaluation of a nested-pCR to detect 18S rDNA for the diagnosis of toxoplasmic meningoencephalitis. *Kansenshogaku Zasshi* 2005; **79**: 543–548.
4 Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg* 1990; **73**: 720–724.
5 Miguel J, Champalimaud JL, Borges A *et al.* Cerebral toxoplasmosis in AIDS patients, CT and MRI images and differential diagnostic problems. *Acta Med Port* 1996; **9**: 29–36.
6 Masamed R, Meleis A, Lee EW, Hathout GM. Cerebral toxoplasmosis: case review and description of a new imaging sign. *Clin Radiol* 2009; **64**: 560–563.
7 Pawelec G, Effros RB, Caruso C, Remarque E, Barnett Y, Solana R. T cells and aging (update February 1999). *Front Biosci* 1999; **4**: D216–D269.

High risk of adverse drug reactions in elderly patients taking six or more drugs: Analysis of inpatient database

Dear Editor,

Polypharmacy is frequently seen in elderly patients, largely because of the existence of multiple comorbid conditions. All medications have the potential for harm as well as benefit, and thus, physicians must make difficult trade-offs between both sides of guideline-directed care.[1,2] Some drugs are reported to increase adverse drug reactions (ADR), and have been listed as potentially inappropriate medications (PIM), which should not be used generally in elderly patients.[3–5] However, it is still complicated for general practitioners to check PIM for each patient. As polypharmacy is a well-known risk for ADR,[6,7] and the frequency of PIM use rises sharply according to the number of drugs,[7] the optimal number of drugs defining polypharmacy might be of substantial help for physicians. Therefore, we aimed to determine the cut-off number of drugs in relation to ADR using the inpatient database of our geriatric department.

All records of patients aged 65 years or older who were admitted to the Department of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan, from 1995 to 2010 were reviewed. Retrospective use of the patient database was approved by the ethics committee of The University of Tokyo. Records lacking information on ADR or the number of drugs and patients taking no drugs were excluded. Finally, we analyzed the records of 2412 patients (mean ± SD age = 78.7 ± 7.3 years, male 51.3%). ADR was defined as unintended or undesired harmful effects presumably caused by drugs. The occurrence of ADR was assessed before discharge by the physician in charge, and other data were obtained soon after admission. Odds ratios with 95% confidence intervals for ADR were obtained by logistic regression analysis. The receiver operating characteristic (ROC) curve was assessed to define the optimal number of drugs in relation to ADR. Data were analyzed using JMP version 9.0.2 (SAS Institute, Cary, NC, USA).

The number of prescribed drugs per patient was 6.6 ± 3.6 (mean ± SD; range = 1–30), and ADR were observed in 252 patients (10.5%). Patients with ADR were taking more drugs than those without ADR (7.6 ± 3.8 *vs* 6.4 ± 3.5 drugs, $P < 0.0001$ by unpaired *t*-test). ADR was significantly associated with the number of drugs in unadjusted and age- and sex-adjusted logistic regression analysis (data not shown). When ADR were analyzed according to the number of drugs by quintile, the odds ratio of ADR was significantly higher in the groups taking six or more drugs (Fig. 1). Furthermore, ROC analysis showed that the optimal cut-off number of drugs was six, although the sensitivity of 0.560 and specificity of 0.710 were not high, with a small area under the curve of 0.591.

Previously, elderly outpatients taking five to eight drugs were reported to be at greater risk of ADR-related hospitalization than those taking zero to four drugs.[6] Also, we have reported that taking five or more drugs is a risk factor for falls in outpatients.[8] Taking these findings together, it might be reasonable to consider six or more drugs as the cut-off of polypharmacy in terms of ADR in elderly patients. The present study had some limitations; the results were obtained from inpatients managed by geriatricians, and thus might not extend to general outpatients. Next, this database did not have information for types of ADR; so they could not be clarified in detail in the present. According to our previous study, hematological, neurological and

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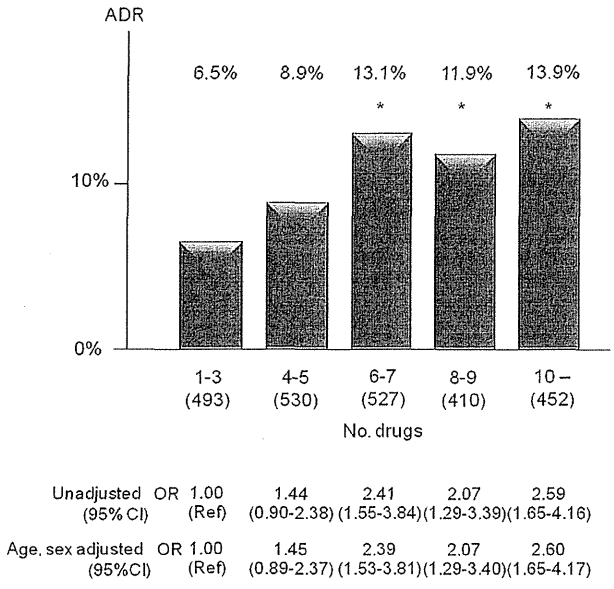

Figure 1 Frequency of adverse drug reactions according to quintile of number of prescribed drugs. Unadjusted and age–sex adjusted odds ratios (95% confidence interval) of adverse drug reactions are shown. *$P < 0.05$ versus one to three drugs. OR, odds ratio.

cardiovascular events were reported to be more frequent than ADR in elderly inpatients,[9] and so, these are possibly the major types in the present study. Also, ROC analysis did not fit well for the present cohort.

In summary, the present study provided the cut-off number of drugs for screening of elderly patients at high risk of ADR. Prospective studies and intervention studies examining the effect of drug reduction on ADR and comorbid conditions are required to confirm this finding.

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References

1 Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med* 2011; **171**: 75–80.
2 Steinman MA, Handler SM, Gurwitz JH *et al.* Beyond the prescription: medication monitoring and adverse drug events in older adults. *J Am Geriatr Soc* 2011; **59**: 1513–1520.
3 Fick DM, Cooper JW, Wade WE *et al.* Updating the beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; **163**: 2716–2724.
4 Gallagher P, Ryan C, Byrne S *et al.* STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; **46**: 72–83.
5 Akishita M, Arai H, Arai H *et al.* Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: commission report of the Japan Geriatrics Society. *Geriatr Gerontol Int* 2011; **11**: 3–7.
6 Marcum ZA, Amuan ME, Hanlon JT *et al.* Prevalence of unplanned hospitalizations caused by adverse drug reactions in older veterans. *J Am Geriatr Soc* 2012; **60**: 34–41.
7 Steinman MA, Landefeld CS, Rosenthal GE *et al.* Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006; **54**: 1516–1523.
8 Kojima T, Akishita M, Nakamura T *et al.* Association of polypharmacy with fall risk among geriatric outpatients. *Geriatr Gerontol Int* 2011; **11**: 438–444.
9 Toba K, Akishita M, Mizuno Y *et al.* Adverse drug reaction in the elderly. *Nihon Ronen Igakkai Zasshi* 1999; **36**: 181–185.

C-kit-positive acute myelogenous leukemia effectively treated with imatinib: A case report and review of the literature

It is highly advisable to choose a strategy to improve the quality of life (QOL), rather than a curative strategy, such as conventional chemotherapy, for very elderly patients with acute myelogenous leukemia (AML). Molecular targeted therapy might also be considered as an important strategy to take into account.[1]

An 88-year-old man was referred to Juntendo University Urayasu Hospital in Chiba, Japan, because of fever and headache in April 2004. The spleen was enlarged to 5 cm below the left costal margin. White blood cell (WBC) count was $61.1 \times 10^4/\mu L$, with 29% blasts and 6.5% basophils. Other data were hemoglobin (Hb) 10.6 g/dL, platelet (plt) $41.0 \times 10^4/\mu L$, lactate dehydrogenase (LDH) 685 IU/L, uric acid (UA) 10.0 mg/dL and C-reactive protein (CRP) 14.6 mg/dL. Bone marrow was myeloid hyperplasia with 27% blasts. Flow cytometer showed that the leukemic cells were positive for myeloperoxidase, CD7, CD13, CD15, CD33, CD34 and c-kit (CD117). Because the leukocytosis with blasts, mild basophilia and splenomegaly resembled blast crisis of chronic myeloid leukemia, and furthermore the patient was very old, imatinib 600 mg daily was tried. Fortunately, imatinib was effective before chromosome analysis later showed trisomy 8. Although the rate of blasts in the peripheral WBC was almost constant, the number of WBC decreased and red blood cells transfusion (RBCT) was not required soon. The patient could leave hospital on day 28 and he had a good QOL. On day 90, the WBC count was 5000/μL with 28% blasts, and Hb and plt were stable; furthermore, the spleen was not palpable. Although generalized edema and pleural effusion occurred as side-effects of imatinib on day 110, they improved with furosemide. However, on day 130, the number of WBC gradually increased,

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Gastrointestinal hemorrhage and antithrombotic drug use in geriatric patients

Dear Editor,

Recent guidelines recommend the aggressive use of antithrombotic medications in patients at high risk of thrombotic events. Although the risk of thrombosis increases with age, critical bleeding related to antithrombotic drug use is frequently seen in older patients.[1] Thus, guideline-directed use of antithrombotic medications might cause more harm than benefits among older patients with multiple comorbid conditions.[2,3] To increase the benefit-to-harm ratio, geriatricians might take care to stratify the risks and totally manage the patients. We hypothesized that such geriatricians' approaches lead to harmless use of antithrombotic medications. For this purpose, we carried out a case–control study to investigate the association between gastrointestinal hemorrhage and antithrombotic drug use.

We analyzed the inpatient registry of the Department of Geriatric Medicine, University of Tokyo Hospital between 1996 and 2007 (2249 patients) to identify patients ≥60 years-of-age who were admitted to the department as a result of gastrointestinal hemorrhage. The database was searched using the keywords of gastrointestinal hemorrhage, melena, hematemesis and anemia. Then, medical records of the extracted patients were reviewed. Finally, a total of 47 patients were defined to fulfil the criteria. Next, using risk-set sampling, we selected four controls per case matched for age, sex and the timing of hospitalization from the same inpatient registry. The data were obtained on prescriptions of antithrombotic drugs (aspirin, warfarin, cilostazol and ticlopidine) and anti-ulcer drugs (proton pump inhibitors and H2 blockers), and comorbid conditions.

Among the cases, causes of gastrointestinal hemorrhage were ulcer (48.9%), cancer (8.5%), ischemic colitis (6.3%), colon diverticulum (4.2%), Mallory–Weiss syndrome (4.2%) and hemorrhoid (2.1%), and 21.2% remained uncertain. As shown in Table 1, 17 cases and 71 controls were taking antithrombotic drugs. Of them, aspirin was most frequently prescribed both in case and control groups. There was no significant difference between case and control groups in the prescription rate of antithrombotic drugs ($\chi^2 = 0.20$, $P = 0.65$) and that of aspirin ($\chi^2 = 0.43$, $P = 0.51$). Furthermore, unadjusted logistic regression analyses showed that antithrombotic drug use and antiulcer drug use was not associated with gastrointestinal hemorrhage. The odds ratio of antithrombotic drug use for gastrointestinal hemorrhage was 0.91 (95% CI 0.46–1.81) after adjustment by age, sex and anti-ulcer drug use. Exclusion of the patients with cancer-related hemorrhage did not fundamentally influence the analytical results (data not shown).

This small case–control study showed no association of admission as a result of gastrointestinal hemorrhage with the use of antithrombotic drugs or aspirin among older patients. As most of the patients were managed by geriatricians in our department, the finding might be limited to the particular facility or cohort, but might not be extended to the general population. It is suggested, however, that geriatricians can make an appropriate decision on the indication and management of antithrombotic drugs for older patients. Although no studies have shown comparable findings in terms of gastrointestinal bleeding, geriatric evaluation and management has been reported to be effective to reduce serious adverse drug events.[4] A recent review on the management of antiplatelet agents[5] also recommended comprehensive strategies to reduce the risk of hemorrhagic complications. Prospective studies with a large sample size are required to confirm this issue. Nevertheless, it is certain that the use of antithrombotic

Table 1 Age, sex and medication use in case and control subjects, and unadjusted odds ratios for gastrointestinal hemorrhage

	Cases ($n = 47$)	Controls ($n = 189$)	Odds ratio (95% CI)
Age (years)	78 ± 10	77 ± 9	1.02 (0.98–1.06)
Men (women = 0, men = 1)	29 (61.7%)	120 (63.5%)	0.93 (0.48–1.79)
Antithrombotic drugs (no = 0, yes = 1)	16 (34.0)	71 (37.5)	0.86 (0.44–1.68)
Aspirin (no = 0, yes = 1)	10 (21.3)	49 (25.9)	0.77 (0.36–1.67)
Anti-ulcer drugs (no = 0, yes = 1)	18 (38.2)	45 (23.8)	0.67 (0.35–1.29)

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medi cations should be carefully determined by considering the risk/benefit balance of each patient.

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References

1 Garcia Roriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343**: 769–772.
2 Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; **294**: 716–724.
3 Man-Son-Hing M, Laupacis A. Anticoagulant-related bleeding in older persons with atrial fibrillation: physicians' fears often unfounded. *Arch Intern Med* 2003; **163**: 1580–1586.
4 Schmader KE, Hanlon JT, Pieper CF *et al.* Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004; **116**: 394–401.
5 Kalyanasundaram A, Lincoff AM. Managing adverse effects and drug-drug interactions of antiplatelet agents. *Nat Rev Cardiol* 2011; **8**: 592–600.

Pituitary insufficiency: A cause of hypoglycemia in an elderly diabetic patient

Dear Editor,

Hypoglycemia most likely occurs in the elderly as a result of poor glucose tolerance. The most common cause of hypoglycemia in elderly patients is antidiabetic drugs. Adrenal insufficiency, insulinoma and pituitary insufficiency are rare causes of hypoglycemia in older age.[1] Particularly in old patients, non-specific findings, such as weakness, fatigue and loss of appetite caused by pituitary insufficiency, might be attributed to aging.[2] Here, we reported an elderly patient with diabetes mellitus and hypopituitarism, presenting with refractory hypoglycemia and acute renal failure under therapy with oral antidiabetic drugs.

A 67-year-old woman was referred to geriatric clinic with symptoms of confusion, irritability, slowness of speech and movements, loss of appetite, nausea, and vomiting. A physical examination of her vital signs showed blood pressure 80/50 mmHg, pulse rate 104/min, body temperature 37.7°C and respiration 24/min. The patient was lethargic with incomplete cooperation (Karnofsky performance score of 30%). She had been taking metformin 2000 mg/day and gliclazide 30 mg/day with the diagnosis of diabetes for 2 years. In the biochemical examination, blood glucose, blood urea-nitrogen, creatinine, sodium and potassium were 32 mg/dL, 60 mg/dL, 3.2 mg/dL, 132 mmol/L and 4.9 mmol/L, respectively. After she was admitted to the geriatric clinic, her glucose infusion was given. Our initial evaluation of the clinical and laboratory parameters suggested that it could be acute renal failure as a result of dehydration and hypoglycaemia, which were the consequence of the prolonged effect of gliclazide. For this reason, oral antidiabetic drugs were discontinued, and glucose infusion was carried out. During her clinical follow up, we realized that her kidney functions had substantially increased. However, hypoglycemia persisted. Afterwards, all of the persistent hypoglycemia, hyponatremia and hypotension were evaluated, and the results were considered to be hypocortisolemia. The patient's other laboratory results, which were obtained during a hypoglycemia period, are presented in the Table 1. The basal serum cortisol (1.38 μg/dL) and adrenocorticototropic hormone levels (less than 0.3 U/L) showed strong evidence of cortisol deficiency. Due to these results, pituitary insufficiency was diagnosed. However, magnetic resonance imaging and magnetic resonance angiography did not show any structural or vascular abnormalities in the hypophysis and brain. Once prednisolone (7.5 mg/day) treatment

Table 1 Endocrinological laboratory results

Parameters		Normal range
Blood cortisol	1.38 ug/dL	6.2–19.4 ug/dL
TSH	0.055 uIU/mL	0.4–4.2 uIU/mL
Free T4	13.24 pmol/L	10.3–23.2 pmol/L
IGF-1	1.00 mg/L	1.73–5.11 mg/L
GH	<3 μg/L	
PRL	0.57 ng/mL	3–20 ng/mL
FSH	2.02 mIU/mL	25.8–134.8 mIU/mL
LH	1.36 mIU/mL	7.7–58.5 mIU/mL
Estradiol	27.96 pg/mL	5–54.7 pg/mL
C peptide	1.02 ng/mL	0.9–7.1 ng/mL
Insuline	2.83 μU/mL	3–28 μU/mL

All the laboratory results were measured between 08.00 hours and 09.00 hours, and confirmed by a second determination.
FSH, follicule stimulating hormone; GH, growth hormone; IGF1, insulin-like growth factor-1; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone; T4, thyroxine.

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Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial – study design, baseline characteristics and effects of intervention

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Aim: To evaluate long-term, multiple risk factor intervention on physical, psychological and mental prognosis, and development of complications and cardiovascular disease in elderly type 2 diabetes patients.

Methods: Our randomized, controlled, multicenter, prospective intervention trial included 1173 elderly type 2 diabetes patients who were enrolled from 39 Japanese institutions and randomized to an intensive or conservative treatment group. Glycemic control, dyslipidemia, hypertension, obesity, diabetic complications and atherosclerotic disease were measured annually. Instrumental activity of daily living, cognitive impairment, depressive symptoms and diabetes burden were assessed at baseline and 3 years.

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Results: There was no significant difference in clinical or cognitive parameters at baseline between the two groups. The prevalence of low activities of daily living, depressive symptoms and cognitive impairment was 13%, 28% and 4%, respectively, and was similar in the two groups. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. With the exception of coronary revascularization, there was no significant difference in fatal or non-fatal events between the two groups. Composite events were also similar in the two groups.

Conclusions: This study showed no significant differences in fatal or non-fatal events between intensive and conventional treatment. The present study might clarify whether treatment of risk factors influences function and quality of life in elderly diabetic patients.
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Keywords: diabetes mellitus, elderly, geriatric assessment, intervention, vascular complications.

Introduction

The prevalence of diabetes increases with age, with approximately 15% of elderly people in Japan having the disorder.[1] These patients often suffer from diabetic microvascular and macrovascular complications.[2] Treatment goals in this elderly diabetic population are to maintain functional abilities and quality of life, and to prevent diabetic complications. Physical functional activities[3,4] and cognitive function[5,6] are more impaired in elderly diabetic patients, with depression and low well-being being major concerns.[7,8] It is therefore important to evaluate the effects of clinical interventions on physical, psychological and mental functions, as well as on disease-related variables, such as diabetic complications, atherosclerotic disease and mortality.

The impact of intensive blood glucose, blood pressure or multiple risk factor intervention on diabetic complications in type 2 diabetes has been evaluated in the United Kingdom Prospective Diabetes Study (UKPDS),[9,10] Kumamoto Study[11] and Steno-2 Study.[12] As only a few elderly people were included in these studies, little is known on the effects of multiple risk factor intervention on diabetic complications and functional prognosis.

We therefore carried out a randomized clinical trial to evaluate the efficacy of multiple risk factor intervention on functional prognosis, and development and/or progression of diabetic complications and cardiovascular disease in elderly people with type 2 diabetes. The present study presents baseline demographic and biomedical characteristics, and describes the major outcome variables measured at baseline.

Methods

Participants

The participants recruited for the Japan Elderly Diabetes Intervention Trial (J-EDIT) were diabetic outpatients at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines of each center's institutional ethical committee.

Initial screening tests included glycated hemoglobin A1c (HbA1c), body mass index (BMI), blood pressure, serum total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). Inclusion criteria included age 65–85 years, HbA1c ≥ 7.9% or HbA1c ≥ 7.4% with at least one of following criteria: BMI ≥ 25 kg/m^2, blood pressure ≥ 130/85 mmHg, serum total cholesterol ≥ 200 mg/dL (or low-density lipoprotein cholesterol [LDL-C] ≥ 120 mg/dL in participants without coronary heart disease [CHD]) or ≥180 mg/dL (or LDL-C ≥100 mg/dL in participants with CHD), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL. Exclusion criteria included a recent (<6 months) myocardial infarction (MI) or stroke, acute or serious illness, aphasia and severe dementia.

Randomization and intervention

A total of 1173 diabetic outpatients were enrolled and randomly allocated to either the intensive or conventional treatment group. The randomized factors were age, sex, diabetes treatment, HbA1c, total cholesterol, triglycerides, HDL-C, blood pressure, diabetic

Table 1 Treatment goals of multiple risk factor intervention studies in patients with type 2 diabetes

	J-EDIT	UKPDS	Steno-2 Study
Mean age (years)	72	52	55
Range	(65–84)	(25–65)	(40–65)
Treatment goals			
Glucose control			
FPG (mmol/L)		<6.0	
HbA1c (%)	<6.9		<6.5
Blood pressure control (mmHg)	<130/85	<150/85	<140/85 (1993–1999) <130/80 (2000–2001)
Cholesterol (mg/dL)	<200 (<180) if one has CHD	none	<190 (1993–1999) <175 (2000–2001)
Triglycerides (mg/dL)	<150	none	<150
HDL-C (mg/dL)	>40	none	>40
Other interventions	BMI <25		Smoking cession Aspirin use

CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol, J-EDIT, Japan Elderly Diabetes Intervention Trial; UKPDS, United Kingdom Prospective Diabetes Study.

microangiopathy, atherosclerotic disease, hypertension, hyperlipidemia and institutions.

The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure (DBP) < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD; Table 1). If HbA1c levels did not reduce to <6.9%, oral hypoglycemic drugs (sulphonylurea, biguanides, α-glucosidase inhibitors and pioglitazone) or insulin therapy was introduced by the physician. If total cholesterol or LDL-C levels did not reach the treatment goal, the physicians were advised to use atorvastatin. Patients with a history of cerebral infarction also had antiplatelet therapy where possible.

The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and then annually. Baseline information included age, sex, medical history, family members with whom they lived, education, employment, height, bodyweight, waist-to-hip ratio, maximum body weight, diabetes duration, family history of diabetes and diabetes treatment. Standardized questionnaires were used to obtain self-reported data on smoking, alcohol, hypoglycemia frequency, nutritional status, dietary habits and adherence, self-efficacy, activities of daily living (ADL), physical activities, comprehensive cognitive function, and psychological status including diabetes burden and depressive symptoms.

Basic ADL was assessed by the Barthel index,[13] whereas functional disabilities were examined by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence.[14] This index includes 13 items and three subscales: instrumental ADL, intellectual activity and social role. The index is well validated and is widely used to measure functional abilities in community-dwelling or institutionalized elderly subjects.[15]

Physical activities were assessed using the Baecke questionnaire.[16] The Folstein Mini-Mental State Examination (MMSE) was carried out to assess comprehensive cognitive function including orientation, memory recall and calculations.[17]

Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale (15 items, GDS-15),[18] whereas diabetes-specific burden and concerns were examined using the elderly diabetes burden scale (EDBS).[19] EDBS is a short revised version of the elderly diabetes impact scale reported previously,[4] and consists of six subscales: symptom burden (4 items), social burden (5 items), diet restrictions (4 items), concern (4 items), treatment satisfaction (3 items) and burden by tablets or insulin (3 items). Each of the 23 EDBS items was rated on a four-point multiple-choice scale. The elderly diabetes burden score was calculated by reversing the scores of the treatment satisfaction subscale and summing the scores of the six subscales. EDBS has good test–retest reliability, construct validity, convergent validity and satisfactory internal consistency.

The frequency of mild or severe hypoglycemia was assessed using questionnaires (number of hypoglycemic episodes and number of comas or emergency hospital visits or admissions as a result of hypoglycemia in a year, month or week). Mild hypoglycemia episodes included the appearance of or recovery from hypoglycemic symptoms. Severe hypoglycemia episodes were defined as

coma, convulsion or incapacity of the patient sufficient to require the assistance of another person.

Nutritional intake was assessed for 1 week using the Yoshimura food frequency questionnaire[20] that estimated food and total energy intake, carbohydrate-, protein- and fat-to-energy ratios, and intake of cholesterol, salt, iron, calcium, vitamins and dietary fiber from portion sizes (relative to the standard amount) and frequency (intake number for 1 week) of 29 food groups.

Measurements

Venous blood was drawn for determination of blood glucose, HbA1c and serum concentrations of total cholesterol, HDL-C and triglycerides at baseline, and then at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. The Japan Diabetes Society (JDS) has standardized several HbA1c assays with the international standard value adjusted by the equation of HbA1c (JDS) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay, and total cholesterol, triglycerides, HDL-C, white blood cells, red blood cells, hematocrit (Ht), blood urea nitrogen (BUN), serum creatinine, uric acid, total protein and albumin by established methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index was calculated as weight in kilograms / (height in meters)^2.

Microangiopathy (retinopathy, nephropathy and neuropathy), macroangiopathy (ischemic heart disease [IHD]), stroke and peripheral vascular disease [PVD]) were assessed at baseline, and then annually. Funduscopic examinations were carried out on dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages: stage 0: no retinopathy; stage 1: dot hemorrhages, hemorrhages or hard exudates; stage 2: soft exudates; stage 3: IRMA or venous deformities; stage 4: neovascularization, preretinal proliferative tissues, vitreous hemorrhages or retinal detachment. Diabetic maculopathy was assessed according to findings of hemorrhages, local edema, hard exudates and diffuse edema at macular areas. Uncorrected and corrected visual acuities, the occurrence of cataract, corneal opacity, glaucoma, age-related macular degeneration, laser photocoagulation, cataract operations and vitrectomy were assessed. Urinary albumin was measured by immunological assay. Mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses was used to classify diabetic nephropathy as no nephropathy (ACR < 30), microalbuminuria (30 ≤ ACR < 300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Follow up

The annual examinations included bodyweight, BMI, waist-to-hip ratio, treatment of diabetes, fasting plasma glucose, serum insulin, total cholesterol, triglycerides, HDL-C, lipoprotein(a), white blood cells, red blood cells, Ht, platelet, BUN, serum creatinine, uric acid, total protein, albumin, blood pressure, visual acuity, microalbuminuria, deep tendon reflexes, neuropathic symptoms, resting electrocardiogram (ECG), chest X-ray, and the occurrence of retinopathy, nephropathy, neuropathy, IHD, stroke and PVD. HbA1c and ACR were measured biannually. Basic ADL, functional abilities, cognitive function, depressive symptoms and nutrition were assessed every other year. Use of medications, including insulin and hypoglycemic, antihypertensive, antihyperlipidemic, antiplatelet and anticoagulant drugs, was checked annually.

Data management and analyses

The main database was stored at the data management and statistical analysis center. A data sheet of each patient was mailed from the study institutions to the data management and statistical analysis center each year. The data was validated by range, combinatorial and historical checks of compatibility with previous data. A visual check of the list of abnormalities and information in the data sheets was carried out by trained staff. The study institutions were notified of unexplained abnormalities in the data that were completed or corrected before entry into the main database.

Data are presented as means ± SD or as proportions, unless otherwise specified. Data for analysis was extracted from the main database, and statistical analysis was carried out using the SAS computer programs. For univariate analysis, we used unpaired *t*-test and χ^2-test to compare baseline clinical characteristics in the two treatment groups. $P < 0.05$ was considered statistically significant.

Data security was maintained by exclusion of patient identities, password access and secure output within the data management and statistical analysis center.

End-points

Fatal and non-fatal events during follow up were certified by at least two members of the expert committee, masked to the participants' diagnosis and risk factor status. Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as

a result of renal failure, hyperglycemia or hypoglycemia. The history of macroangiopathy was obtained from medical records. Ischemic heart disease was classified as present when the patient had (i) a history of MI characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical ECG alterations with occurrence of pathological Q waves and/or localized ST variations) and typical enzymatic changes (creatine phosphokinase); and (ii) a history of angina pectoris, positive treadmill ECG test or positive postload cardiac scintigram, confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset persisting ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. No cases of asymptomatic lesions detected by brain imaging (i.e. silent infarction) were included. PVD was defined as the absence of dorsal pedal artery or posterior tibial artery pulsation and ankle–brachial index <0.8 or the presence of foot gangrene or ulcers.

All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

End-point validation

Possible clinical end-points were noted in the annual data sheets, with the diagnostic criteria for each end-point being predetermined. When an end-point was notified on a data sheet, the administrator requested full information from the data management and statistical analysis center, followed by a review by two clinical assessors of the event assignment committee. Two separate assessments for each end-point were entered on a special data sheet. If there was disagreement on the assessment, a final decision was made after discussions of the committee. The definition of the end-points is shown in the Appendix.

Statistical analysis and criteria for stopping the study

Differences in end-points (deaths or complications) between the two groups were analyzed using the log–rank test. Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. All major analyses were according to assigned allocations (intention to treat), without exclusion of protocol deviants.

The Data and Safety Monitoring Committee examine the end-points annually and will stop the study when the difference in diabetes-related deaths or complications (disease) between the two groups becomes significant ($P < 0.001$, log–rank test).

Results

A total of 1173 outpatients with diabetes, aged over 65 years, were registered between March 2001 and February 2002. After randomization, 585 and 588 patients were allocated to intensive or conventional treatment, respectively. There were no significant differences between the two groups for age, sex, diabetes treatment, BMI, HbA1c, SBP and DBP, total cholesterol, triglycerides, HDL-C levels (Table 2), and number of risk factors (data not shown).

At baseline, the proportion of patients with a low ADL (TMIG Index of Competence ≤ 9), depressive symptoms (GDS-15 ≥ 5), or cognitive impairment (MMSE ≤ 23) were 13%, 28% and 4%, respectively. The prevalence of low ADL, depressive state and cognitive impairment was similar in the two groups (Table 2).

The dropout rate after 6 years was 8.9% (104 cases). HbA1c, total cholesterol, triglycerides, blood pressures and BMI at baseline and during follow up are shown in Table 3 and Figures 1–4. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. Although SBP and DBP, total cholesterol and triglycerides levels tended to decrease by the sixth year compared with the baseline data in both groups, no significant differences in these variables were observed between the two groups during follow up (Figs 1–4). BMI and HDL-C levels did not change over the follow-up period in either group.

Table 4 shows the fatal and non-fatal events during follow up in the two groups. With the exception of coronary revascularization, there were no significant differences in fatal or non-fatal events between the groups ($P < 0.05$, log-rank test). Composite events (death as a result of diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) were also similar in the two groups (Table 5).

Discussion

The J-EDIT study has the potential to determine whether multiple risk factor intervention prevents aggravation of complications and quality of life, and reduces mortality in elderly diabetic patients. The study has three characteristics. First, it is a large-scale study of multiple risk factor intervention in elderly diabetic patients. No or very few elderly patients were included in the UKPDS[9,10] or Steno-2 Study.[12] Second, the multiple interventions involved control of blood pressure, serum lipids, bodyweight and blood glucose. The treatment goals in the intensive treatment group were similar

Table 2 Clinical characteristics of the participants at baseline

	Conventional treatment (n = 588)	Intensive treatment (n = 585)
General characteristics		
Age (years)	71.7 ± 4.7	71.9 ± 4.6
Male (%)	46.3	46.3
Duration of diabetes (years)	18.0 ± 9.9	16.7 ± 8.5
Body mass index (kg/m^2)	24.3 ± 7.3	24.0 ± 3.9
Waist (cm)	83.6 ± 9.9	84.3 ± 10.4
Waist-to-hip ratio	0.89 ± 0.07	0.90 ± 0.07
Smoking (%) (non-/ex-smoker/current smoker)	16:31:53	15:29:56
Smoking (package × years)	848 ± 762	789 ± 601
Family history of diabetes (%)	45.8	39.7
Systolic BP (mmHg)	137 ± 17	137 ± 16
Diastolic BP (mmHg)	75 ± 10	76 ± 10
Clinical status		
Ischemic heart disease (%)	16.3	14.9
Cerebrovascular disease (%)	12.4	13.3
Retinopathy (%)		
Stage 0	53.6	51.7
Stage 1	30.5	31.4
Stage 2	7.8	9.1
Stage 3	3.3	3.4
Stage 4	4.7	4.7
Nephropathy (%) (no/microalbuminuria/persistent proteinuria)	51:30:19	53:30:17
Loss or weakness of ATR (%)	56.8	57.1
Paresthesia (%)	18.5	22.3
Laboratory data		
HbA1c (%)	8.5 ± 0.9	8.4 ± 0.8*
Fasting plasma glucose (mg/dL)	170 ± 53	168 ± 49
Fasting insulin (mIU/mL)	10.9 ± 12.0	10.3 ± 9.6
Total cholesterol (mg/dL)	202 ± 34	203 ± 34
Triglycerides (mg/dL)	131 ± 70	137 ± 110
HDL-C (mg/dL)	56 ± 18	57 ± 19
Uric acid (mg/dL)	5.1 ± 2.0	5.1 ± 1.4
Blood urea nitrogen (mg/dL)	16.9 ± 5.9	17.2 ± 6.1
Creatinine (mg/dL)	0.93 ± 1.2	0.83 ± 0.36
Treatment		
Treatment of diabetes (diet/OHA/insulin)	9.0:60.7:30.3	8.7:61.0:30.3
Sulfonylurea drugs	54.6	56.0
α-Glucosidase inhibitors (%)	30.5	28.0
Biguanides (%)	16.4	15.5
Pioglitazone (%)	4.5	5.2
Glinides (%)	2.3	2.1
Antihypertensive drugs (%)	56.4	57.4
ACE inhibitors (%)	22.9	23.3
ARB (%)	10.1	9.3
Calcium blockers (%)	42.9	41.0
β-Blockers (%)	6.2	5.7
α-Blockers (%)	6.1*	3.4
Diuretics (%)	5.1	7.5
Antihyperlipidemic drugs (%)	40.2	36.8
Statins (%)	30.3	26.5
Fibrates (%)	3.4	3.9
EPA (%)	0.7*	2.7
Nicotinates (%)	1.3	1.4
Probucol	2.2	1.6
Antiplatelet drugs (%)	25.9	27.4
Aspirin (%)	13	15
Geriatric Assessment		
Barthel index (full score: 20)	19.8 ± 0.9	19.8 ± 0.8
Prevalence of any disabilities (%)	11	14
Functional abilities (TMIG index of competence) (full score: 13)	11.6 ± 2.2	11.6 ± 2.2
Geriatric depression scale (full score: 15)	4.3 ± 3.3	4.0 ± 3.2
Depressive symptoms (%) (Geriatric depression scale ≥5)	41	36
MMSE (full score: 30)	28.0 ± 2.4	27.8 ± 3.0
Cognitive impairment (%) (MMSE ≤23)	7	6
Visual impairment (%) (≤0.1)	9	12

ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; ATR, Achilles tendon reflex; BP, blood pressure; EPA, eicosapentenoic acid; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; OHA, oral hypoglycaemic agents; TMIG, Tokyo Metropolitan Institute of Gerontology. *$P < 0.05$.

Table 3 Changes in bodyweights, glycated hemoglobin A1c, serum lipids, and blood pressure at baseline and during the follow-up period

	Conventional treatment							Intensive treatment						
Follow up (years)	0	1	2	3	4	5	6	0	1	2	3	4	5	6
BMI (kg/m^2)	23.6	23.6	23.6	23.4	23.5	23.5	23.4	23.9	23.8	23.8	23.8	23.8	23.7	23.5
HbA1c (%)	8.5	8.1	8.0	7.9	7.9	7.9	7.8	8.4	7.9	7.8	7.8	7.8	7.8	7.7
TC (mg/dL)	202	200	199	195	193	190	190	202	196	198	194	190	188	188
TG (mg/dL)	112	111	109	108	103	101	101	114	110	110	108	110	104	104
HDL-C (mg/dL)	56	56	55	56	55	55	54	57	54	54	55	55	55	55
SBP (mmHg)	137	137	135	135	135	135	134	138	136	136	133	134	136	134
DBP (mg/dL)	75	74	73	72	72	72	71	74	73	74	72	71	71	71

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4 Comparison of fatal events and non-fatal events during the 6-year follow-up period in the conventional and intensive treatment groups

		Number	*P*-value
Fatal event	Myocardial infarction	12	0.083
	Sudden death	13	0.993
	Stroke	6	0.656
	Death due to renal failure	3	0.084
	Death due to hyper/hypoglycemia	1	0.322
	Malignancy	37	0.506
	Pneumonia	10	0.525
	Others	13	0.570
	Subtotal	95	0.291
Nonfatal event	Myocardial infarction	17	0.998
	Angina pectoris	21	0.517
	Coronary revascularization	18	0.0282
	Hospitalization due to heart failure	15	0.190
	Stroke	63	0.281
	Diabetic ulcer or gangrene	12	0.564
	Subtotal	146	
Total		241	

Table 5 Comparisons of composite events (death due to diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) in the conventional and intensive treatment groups

	No. events	*P*-value (log–rank test) Conventional *vs* intensive
Death due to diabetes	35	0.8495
Death not related to diabetes	59	0.2991
Coronary vascular events	55	0.9868
Stroke	67	0.2915
All events related to diabetes	155	0.5573
All events	206	0.2239

Death due to diabetes was defined as sudden death or death from atherosclerotic coronary heart disease (myocardial infarction or heart failure due to ischemia) or stroke, death due to renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

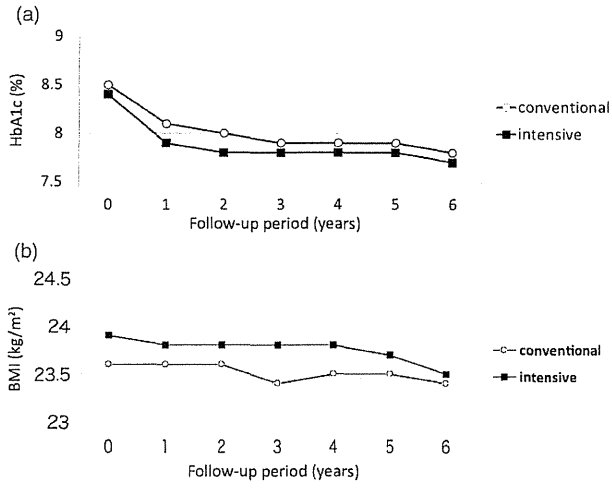

Figure 1 Clinical course of (a) glycated hemoglobin A1c (HbA1c) and (b) body mass index (BMI) in the conventional and intensive treatment groups.

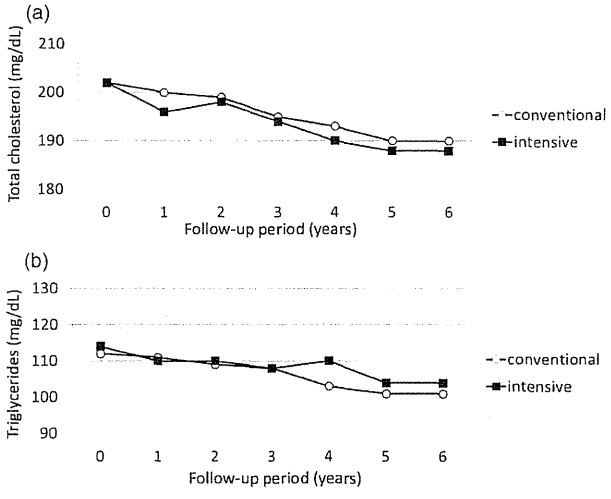

Figure 2 Clinical course of (a) total cholesterol and (b) triglycerides in the conventional and intensive treatment groups.

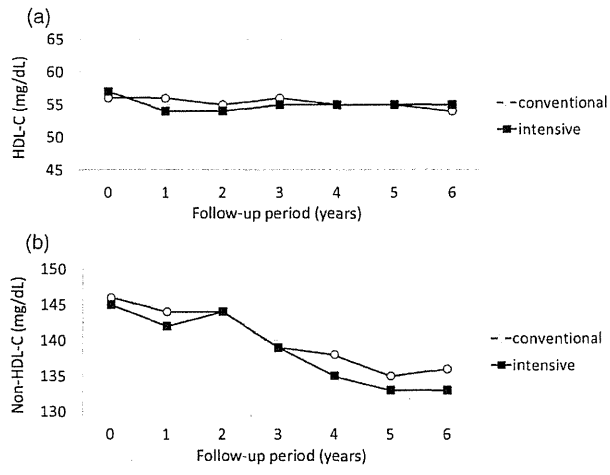

Figure 3 Clinical course of (a) high-density lipoprotein cholesterol (HDL-C) and (b) non-HDL-C in the conventional and intensive treatment groups.

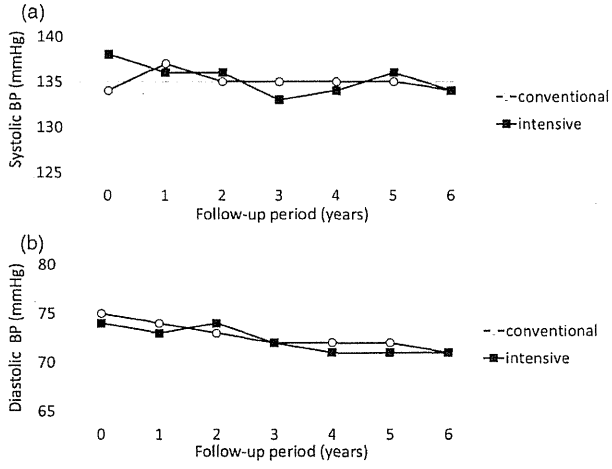

Figure 4 Clinical course of (a) systolic and (b) diastolic blood pressures (BP) in the conventional and intensive treatment groups.

to those in the Steno-2 Study[12] and considerably stricter than those in the UKPDS[9,10] (Table 1). Third, outcome in the study included ADL, cognitive function, depressive mood, well-being and the diabetic-specific psychological state, important components for geriatric assessment of elderly people.

The treatment groups in the study had similar general characteristics, diabetic complications, atherosclerotic disease, blood pressure, metabolic risk factors and prevalence of drug therapy for diabetes, hypertension, and hyperlipidemia, with the prevalence of micro- and macrovascular complications being 50% and 15%, respectively. As patients with poor diabetes control were selected, the prevalence of drug-treated hypertension and hyperlipidemia was high (47% and 65%, respectively). Mean HbA1c level at baseline was 8.5%, lower than that of the UKPDS, but still worthy of improvement. The prevalence of patients with SBP ≥ 130 mmHg (70%), DBP ≥85 mmHg (14%), serum total cholesterol ≥ 200 mg/dL (52%), triglycerides ≥ 150 mg/dL (30%), HDL-C ≤ 40 mg/dL (15%) or BMI ≥ 25 (34%) was also high, showing a need for intervention. The high prevalence and presumably high rate of deterioration of complications and potential risk factors show that the present study had a good chance of determining whether multiple risk factor intervention prevented the development and progression of complications. Therefore, we included both primary and secondary prevention trials.

The oral hypoglycemic drugs differed from those used in previous studies. Oral hypoglycemic drugs might be more beneficial than sulfonylurea drugs for preventing cardiovascular disease in patients with type 2 diabetes. α-Glucosidase inhibitors also prevent cardiovascular disease and progression of carotid atherosclerosis,[21–23] whereas metformin use is associated with lower cardiovascular morbidity and mortality, and attenuated progression of carotid atherosclerosis compared with sulfonylurea therapy.[24,25] Thiazolidinediones attenuate carotid atherosclerosis and restenosis after coronary stent implantation in patients with type 2 diabetes.[26,27]

We did not observe any significant differences in fatal or non-fatal cardiovascular events and composite events, including diabetes-related mortality, between the two treatment groups over the follow-up period. Although we observed significant improvements in HbA1c and LDL-C during the first 2 years in the intensive treatment group, there were no differences in HbA1c, lipid or blood pressure after that time. The similar values in atherosclerotic risk factors in both groups during follow up might account for the same prevalence of events, including cardiovascular and stroke, in the two groups. The results show it is difficult to markedly reduce HbA1c, blood pressure and lipid levels in elderly diabetic patients. The high prevalence of depressive and hypoglycemic symptoms at baseline in our cohort was notable. The intention of physicians to avoid hypoglycemic events and psychological barriers to providing elderly patients with extremely strict glucose control might explain the difficulties associated with aggressive intervention. In fact, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, aggressive glucose control was reported to lead to increased mortality in patients with longstanding diabetes.[28] Cardiovascular autonomic abnormalities, arrhythmia and hypercoagulability as a result of hypoglycemia might be responsible for increasing mortality during aggressive treatment. In addition, elderly patients do not accept the increase in the number of oral drugs or the initiation of insulin therapy.

In conclusion, preliminary analysis in the present study showed no significant differences in fatal or non-fatal events between the intensive and conventional treatment groups. However, as the levels of blood lipids, SBP and HbA1c tended to decrease during the follow-up period, further detailed analysis of the data might clarify to what extent treatment of risk factors influences functions and quality of life in elderly diabetic patients.

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Conflict of interest

There is no conflict of interest. The Japanese Elderly Diabetes Intervention Trial (J-EDIT) Study Group has not cleared any potential conflicts.

References

1 Sekikawa A, Tominaga M, Takahashi K *et al.* Prevalence of diabetes and impaired glucose tolerance in Funagata area, Japan. *Diabetes Care* 1993; **16**: 570–574.
2 Morgan CL, Currie CJ, Stott NC, Smithers M, Butler CC, Peters JR. The prevalence of multiple diabetes-related complications. *Diabet Med* 2000; **17**: 146–151.
3 Gregg EW, Beckles GL, Williamson DF *et al.* Diabetes and physical disability among older US adults. *Diabetes Care* 2000; **23**: 1272–1277.
4 Gregg EW, Mangione CM, Cauley JA *et al.* The Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. *Diabetes Care* 2002; **25**: 61–67.
5 Perlmuter LC, Hakami MK, Hodgson-Harrington C *et al.* Decreased cognitive function in aging non-insulin-dependent diabetic patients. *Am J Med* 1984; **77**: 1043–1048.
6 Araki A, Ito H. Asymptomatic cerebral infarction on brain MR images and cognitive function in elderly diabetic patients. *Geriatr Gerontol Int* 2002; **2**: 206–214.
7 Black SA. Increased health burden associated with comorbid depression in older diabetic Mexican Americans. Results from the Hispanic Established Population for the Epidemiologic Study of the Elderly survey. *Diabetes Care* 1999; **22**: 56–64.
8 Araki A, Nakano T, Oba K *et al.* Low well-being, cognitive impairment and visual impairment were associated with functional disabilities in elderly Japanese patients with diabetes mellitus. *Geriatr Gerontol Int* 2004; **4**: 27–36.
9 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352** (9131): 837–853.
10 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317** (7160): 703–713.
11 Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; **28**: 103–117.
12 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383–393.
13 Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Mid South Med J* 1965; **14**: 61–65.

14 Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG Index of Competence. *Arch Gerontol Geriatr* 1991; **13**: 103–116.
15 Shibata H, Sugisawa H, Watanabe S. Functional capacity in elderly Japanese living in the community. *Geriatr Gerontol Int* 2001; **1**: 8–13.
16 Baecke JAH, Burema J, Frijters JER. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982; **36**: 936–942.
17 Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–193.
18 Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol* 1986; **5**: 165–173.
19 Araki A, Ito H. Development of elderly diabetes burden scale for elderly patients with diabetes mellitus. *Geriatr Gerontol Int* 2003; **3**: 212–224.
20 Takahashi K, Yoshimura Y, Kaigen T, Kunii D, Komatsu R, Yamamoto S. Validation of food frequency questionnaire based on food groups for estimation of individual nutrient intake. *Eiyogaku Zasshi* 2001; **59**: 221–232. (In Japanese.)
21 Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke* 2004; **35**: 1073–1078.
22 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290**: 486–494.
23 Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 2004; **25**: 10–16.
24 Katakami N, Yamasaki Y, Hayaishi-Okano R *et al.* Metformin or gliclazide, rather than glibenclamide, attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes. *Diabetologia* 2004; **47**: 1906–1913.
25 Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. *Diabet Med* 2005; **22**: 497–502.
26 Satoh N, Ogawa Y, Usui T *et al.* Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. *Diabetes Care* 2003; **26**: 2493–2499.
27 Choi D, Kim SK, Choi SH *et al.* Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes. *Diabetes Care* 2004; **27**: 2654–2660.
28 The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.

Appendix

1. Atherosclerotic coronary heart disease (CHD) death – either or both of the following categories:

A. Death with consistent underlying or immediate cause plus either of the following:
   (1) Preterminal hospitalization with definite or suspected myocardial infarction (MI).
   (2) Previous definite angina or definite or suspected MI when no cause other than atherosclerotic CHD could be ascribed as the cause of death.

B. Sudden and unexpected death (requires all three characteristics).
   (1) Deaths occurring within 1 h with or without the onset of severe symptoms.
   (2) No known non-atherosclerotic acute or chronic process or event that could have been lethal.
   (3) An unexpected death of a person who was not confined to their home, hospital or other institution as a result of illness within 24 h before death.

2. Criteria for non-fatal MI – any one or more of the following categories using the stated definition:

A. Diagnostic electrocardiogram (ECG) at the time of the event.
B. Ischemic cardiac pain and diagnostic enzyme profile.
C. Ischemic cardiac pain and equivocal enzymes and equivocal ECG.
D. A routine ECG diagnostic for MI while the previous ECG was not.

3. Angina pectoris

The participants must report pain or discomfort with all of the following characteristics:

(1) The site must include the sternum at any level.
(2) It must occur during a form of exertion or stress and must usually last at least 30 s.
(3) It must on most occasions disappear within 10 min or less from the time of resting or decrease the intensity of exertion.
(4) It must usually be relieved in 2–5 min by nitroglycerine (does not apply if participant has never taken nitroglycerine).

In the case of angina pectoris at baseline, chest pain or discomfort should disappear or be controlled at entry. Reappearance or exacerbation of chest pain or discomfort and fulfilling points (1)–(4) were considered as an event. Subjects with uncontrolled angina pectoris at entry were not enrolled in the study.

4. Cerebrovascular disease

A diagnosis required all of the following:

(1) History of recent onset of unequivocal and objective findings of a localizing neurological deficit documented by a physician.
(2) Findings persist longer than 24 h.
(3) The neurological findings were not referable to an extracranial lesion.
(4) Findings of computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy records classifying the cerebrovascular disease into cerebral hemorrhage, cerebral infarction, or subarachnoidal hemorrhage. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area, and also on the basis of clinical findings of stroke, for which there was evidence of cerebral infarction at autopsy. Cerebral or subarachnoid hemorrhage was classified on the basis of evidence obtained on CT or MRI scans or at autopsy, excluding hemorrhagic conversion of infarction.

In the case of cerebrovascular disease at baseline, the appearance of new unequivocal and objective findings of a localizing neurological deficit documented by a physician that persisted longer than 24 h was considered as an event and classified on the basis of evidence obtained on CT or MRI scanning or at autopsy. Cerebral infarction without obvious neurological symptoms shown by CT or MRI scans taken incidentally was not considered as an event.

5. Composite events

Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as a result of renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

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Non-high-density lipoprotein cholesterol: An important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients

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Aims: To evaluate the association of low-density lipoprotein, high-density lipoprotein and non-high-density lipoprotein cholesterol with the risk of stroke, diabetes-related vascular events and mortality in elderly diabetes patients.

Methods: This study was carried out as a post-hoc landmark analysis of a randomized, controlled, multicenter, prospective intervention trial. We included 1173 elderly type 2 diabetes patients (aged ≥65 years) from 39 Japanese institutions who were enrolled in the Japanese elderly diabetes intervention trial study and who could be followed up for 1 year. A landmark survival analysis was carried out in which follow up was set to start 1 year after the initial time of entry.

Results: During 6 years of follow up, there were 38 cardiovascular events, 50 strokes, 21 diabetes-related deaths and 113 diabetes-related events. High low-density lipoprotein cholesterol was associated with incident cardiovascular events, and high glycated

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hemoglobin was associated with strokes. After adjustment for possible covariables, non-high-density lipoprotein cholesterol showed a significant association with increased risk of stroke, diabetes-related mortality and total events. The adjusted hazard ratios (95% confidence intervals) of non-high-density lipoprotein cholesterol were 1.010 (1.001–1.018, $P = 0.029$) for stroke, 1.019 (1.007–1.031, $P < 0.001$) for diabetes-related death and 1.008 (1.002–1.014; $P < 0.001$) for total diabetes-related events.

Conclusions: Higher non-high-density lipoprotein cholesterol was associated with an increased risk of stroke, diabetes-related mortality and total events in elderly diabetes patients. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 18–28.**

Keywords: diabetes mellitus, diabetic complications, elderly, non-high-density lipoprotein cholesterol, stroke.

Introduction

Although the importance of multiple risk factor intervention on type 2 diabetic complications has been shown in the United Kingdom Prospective Diabetes Study,[1,2] Kumamoto Study[3] and Steno-2 Trial,[4] the merits of modifying blood lipid, blood pressure (BP) and hyperglycemia in elderly (>65 years) diabetic patients are unclear. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that intensive glucose-lowering therapy reduced the risk of non-fatal myocardial infarction in patients with advanced type 2 diabetes and a high risk of cardiovascular disease, but increased the risk of death.[5] Severe hypoglycemia and autonomic neuropathy also predicted cardiovascular mortality in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and ACCORD studies, respectively.[6,7]

Non-high-density lipoprotein cholesterol (non-HDL-C), a major atherogenic lipoprotein, was identified by the National Cholesterol Education Program (NCEP) Expert Panel as a secondary target for preventing coronary heart disease (CHD).[8] Although the associations between non-HDL-C and CHD, ischemic stroke, and mortality are inconsistent,[9–25] the predictive potential of non-HDL-C for CHD or stroke might be similar to or lower than that of low-density-lipoprotein cholesterol (LDL-C) or total cholesterol (TC).[18–23] In elderly diabetes patients, the significance of conventional risk factors including BP, TC, LDL-C and glycated hemoglobin A1c (HbA1c), and non-HDL-C has not been established.

The Japanese Elderly Diabetes Intervention Trial (J-EDIT) is a randomized control trial evaluating the efficacy of multiple risk factor interventions on functional prognosis and development, and/or progression of diabetic complications and cardiovascular disease (CVD) in 1173 elderly type 2 diabetes patients enrolled from 39 Japanese diabetes care institutions. No significant risk reduction in cardiovascular events, stroke or mortality was observed with intensive treatment.[24] Because TC and HbA1c decreased with intensive treatment compared with conventional treatment during the first year,[24] we carried out a landmark analysis 1 year after study entry to evaluate the effects of glucose and lipid control. In particular, we examined whether high non-HDL-C was associated with increased risk of stroke, diabetes-related mortality and total events.

Methods

Participants

J-EDIT was organized between April and December 2000. Participants were recruited from diabetic outpatient departments at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening as per the Helsinki Declaration.

The initial screening tests included body mass index (BMI), BP, serum HbA1c, TC, triglycerides and HDL-C. Eligibility criteria of the participants were: (i) age 65–85 years; and (ii) HbA1c ≥ 7.9% or HbA1c ≥ 7.4%, unless they met the treatment goals of the study. Major exclusion criteria included a recent myocardial infarction or stroke, acute or serious illness, aphasia, or severe dementia.

Randomization and intervention

A total of 1173 >65 years-of-age diabetic outpatients were registered. Within 1 month, the patients were randomly allocated to intensive or conventional treatment groups, as reported elsewhere.[17] The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure < 130 mmHg, diastolic blood pressure < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD). If TC or LDL-C treatment goals were not achieved, the physicians were advised to use atorvastatin. The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia, without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and every subsequent year. Standardized questionnaires were used to obtain self-reported data on smoking and alcohol habits, hypoglycemia frequency, nutritional status, dietary habits, dietary adherence, self-efficacy, activities of daily livings, physical activities, comprehensive cognitive function, and psychological status. Functional disabilities were assessed using the Tokyo Metropolitan Institute of Gerontology Index of Competence.[25] Folstein's Mini-Mental State Examination was used to assess comprehensive cognitive function including orientation, memory recall and calculations.[26] Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale 15.[27] The frequency of mild or severe hypoglycemia was assessed using questionnaires with mild hypoglycemia episodes including both appearance and recovery from hypoglycemic symptoms. Episodes of severe hypoglycemia were defined as coma, convulsion or incapacity of the patient sufficient to require another person's assistance.

Measurements

Venous blood was drawn for measurement of serum glucose, HbA1c, TC, HDL-C and triglycerides at baseline, and at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. HbA1c was expressed as the international standard value adjusted by the equation of HbA1c (Japan Diabetes Society [JDS]) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay method and TC, triglycerides, HDL-C, blood urea nitrogen, serum creatinine, uric acid, total protein and albumin by established standard methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic BP was determined as Korotkoff phase V. Body mass index was calculated as weight (kg) / height $(m)^2$.

Microangiopathy and macroangiopathy were assessed at baseline and then annually. Fundoscopic examinations were carried out through dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages. According to mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses, diabetic nephropathy was classified as no nephropathy (ACR <30), microalbuminuria (ACR 30–300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥ 30 mg/dL). Diabetic neuropathy was defined as a loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Ischemic heart disease was diagnosed when the patients had at least one of the following: (i) a history of myocardial infarction (MI) characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical electrocardiographic alterations with occurrence of pathological Q waves and/or localized ST variations, and typical enzymatic changes (creatine phosphokinase [CPK] CPK-MB); and (ii) a history of angina pectoris and a positive treadmill electrocardiography or positive postload cardiac scintigraphy confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset that persisted ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. Peripheral vascular disease was defined as either the absence of dorsalis pedis or posterior tibial artery pulsation and an ankle – brachial index <0.8, or the presence of foot gangrene or ulcers.

End-points

Fatal and non-fatal events identified during the follow-up period were certified by at least two members of the expert committee, blinded to the participants' diagnosis and risk factor status.

Mortality related to diabetes was defined as death from atherosclerotic coronary heart disease (MI or heart failure as a result of ischemia), sudden death, or death as a result of stroke, renal failure, severe hyperglycemia or hypoglycemia. Cardiovascular events were defined as new onset of MI, angina pectoris or coronary revascularization. Stroke included cerebral infarction and bleeding, but not transient ischemic attacks. Total diabetes-related events consisted of cardiovascular events, stroke, sudden death, death as a result of renal failure, diabetic ulcers or gangrene, or heart failure. Information on macroangiopathies was obtained from medical records.

Statistical analyses

Data are presented as means ± SD or as proportions, unless otherwise specified. Data was extracted from the main database and analyzed using the SAS computer program. Unpaired *t*-test and χ^2-test were used to compare the baseline clinical characteristics of the two treatment groups.

Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. Landmark analyses were carried out to show the effects of time-dependent factors and comprised a survival analysis in which follow up started at the landmark time 1 year after study entry. Only patients who had survived to the landmark time-point were included. Time-dependent risk factors were evaluated at the landmark time-point and analyzed as fixed variables. $P < 0.05$ was considered statistically significant.

Table 1 Clinical characteristics of participants at the landmark time

	Conventional treatment ($n = 496$)	Intensive treatment ($n = 497$)
General characteristics		
Age at baseline (years)	71.6 ± 4.7	71.8 ± 4.5
Male (number, %)	227 (45.8)	225 (45.3)
Body mass index (kg/m^2)	23.8 ± 3.4	23.6 ± 3.5
HbA1c (%)	7.7 ± 1.1	7.5 ± 1.0*
Systolic BP (mmHg)	137 ± 16	136 ± 15
Diastolic BP (mmHg)	73 ± 9	74 ± 9
TC (mg/dL)	200 ± 34	197 ± 33
Triglycerides (mg/dL)	133 ± 89	131 ± 97
HDL-cholesterol (mg/dL)	54 ± 15	56 ± 17
LDL-cholesterol (mg/dL)	116 ± 29	119 ± 30
Non-HDL-cholesterol (mg/dL)	144 ± 33	143 ± 32
Complications		
Ischemic heart disease (%)	16.3	16.9
Stroke (%)	12.9	14.5
Retinopathy (none : simple : proliferative, %)	52.6:44.0:3.5	51.5:45.1:3.3
Nephropathy (none : microalbuminuria : macroproteinuria : chronic renal failure, %)	51.2:32.4:12.4:4.0	48.3:36.6:10.4:4.6
Diabetes treatment (diet alone : OHA : insulin : combination of OHA and insulin, %)	5.1:60.6:20.8:12.4	5.4:62.5:19.2:12.9
Antihyperlipidemic agents (%)	44.9	40.0
Statin (%)	33.2	26.1
Fibrates (%)	3.4	3.6
Antihypertensive agents (%)	60.0	58.9

*$P < 0.05$ vs conventional treatment group. BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycaemic agents; TC, total cholesterol.

Results

A total of 1173 >65 years-of age diabetic outpatients were enrolled in the study. At the landmark time, 32 patients had died, 110 had dropped out or had no successive biochemical data and 37 were excluded because of missing or incomplete data. Data of 993 patients (496 conventional treatment and 497 intensive treatment) were used in the landmark analyses. At the landmark time, there were no significant differences in age, sex, diabetes duration, BMI, BP, TC, triglycerides, HDL-C, LDL-C or non-HDL-C (Table 1). As a consequence of the interventions, HbA1c was significantly lower in the intensive treatment group ($P < 0.05$).

The clinical courses of HbA1c, systolic BP (SBP), non-HDL-C, and LDL-C at the landmark time and during follow up in the two treatment groups are shown in Figures 1 and 2. There was a similar decrease in these parameters in both groups during the follow-up period.

During the 6-year follow-up period, there were 38 cardiovascular events, 50 strokes, 21 diabetes-related deaths and 113 diabetes-related events.

Table 2 shows a comparison of cardiovascular event and mortality incidence during the follow-up period in groups stratified by age, sex, HbA1c, TC, LDL-C, non-HDL-C and SBP. Increased non-HDL-C was associated with an increased incidence of stroke ($P = 0.059$) and total diabetes-related events ($P = 0.020$), but not

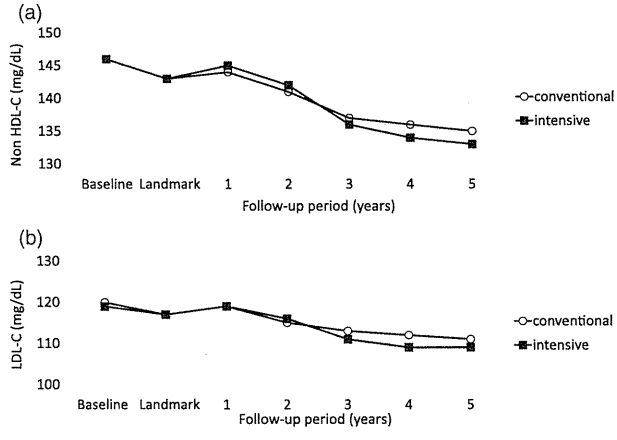

Figure 1 Clinical course of non-high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in conventional and intensive treatment groups. Non-HDL-C and LDL-C showed similar decreases in both groups during the follow-up period after the landmark time.

Table 2 Incidence of cardiovascular events, stroke and mortality after the stratification by age, sex, glycated hemoglobin A1c, lipids and blood pressures

	Cardio vascular events	Stroke	Mortality due to diabetes	All events related to diabetes
Age ≥ 75 years *vs* age < 75 years	5.0% *vs* 4.8% 1.16 (0.58–2.34) *P* = 0.673	8.2% *vs* 4.9% 1.06 (0.999–1.12) *P* = 0.054	2.9% *vs* 1.7% 1.80 (0.75–4.35) *P* = 0.190	16.4% *vs* 11.9% 1.49 (1.01–2.21) *P* = 0.044
Men *vs* women	5.6% *vs* 4.3% 0.71 (0.38–1.32) *P* = 0.276	7.2% *vs* 4.6% 0.65 (0.37–1.13) *P* = 0.124	2.6% *vs* 1.6% 0.62 (0.26–1.47) *P* = 0.278	15.5% *vs* 11.1% 0.67 (0.46–0.97) *P* = 0.035
HbA1c ≥ 8.4% *vs* HbA1c < 8.4%	5.8% *vs* 4.6% 1.46 (0.76–2.77) *P* = 0.254	8.1% *vs* 3.6% 2.35 (1.35–4.09) *P* = 0.003	1.9% *vs* 2.2% 0.94 (0.36–2.42) *P* = 0.897	14.5% *vs* 11.5% 1.38 (0.94–2.02) *P* = 0.101
TC ≥ 200 mg/dL *vs* TC < 200 mg/dL	5.9% *vs* 4.2% 1.48 (0.79–2.79) *P* = 0.222	6.3% *vs* 5.3% 1.29 (0.74–2.26) *P* = 0.374	3.3% *vs* 0.8% 3.62 (1.33–9.88) *P* = 0.012	15.1% *vs* 11.5% 1.39 (0.96–2.02) *P* = 0.082
LDL-C ≥ 115 mg/dL *vs* LDL-C < 115 mg/dL	6.4% *vs* 3.3% 2.04 (1.03–4.06) *P* = 0.040	6.4% *vs* 5.2% 1.48 (0.83–2.63) *P* = 0.181	2.9% *vs* 0.8% 3.98 (1.34–11.8) *P* = 0.013	15.6% *vs* 10.9% 1.63 (1.11–2.39) *P* = 0.013
Non-HDL-C ≥ 140 mg/dL *vs* Non-HDL-C < 140 mg/dL	6.0% *vs* 3.9% 1.53 (0.80–2.95) *P* = 0.203	7.1% *vs* 4.4% 1.78 (0.98–3.23) *P* = 0.059	2.8% *vs* 1.3% 2.11 (0.82–5.45) *P* = 0.121	15.8% *vs* 10.5% 1.58 (1.08–2.33) *P* = 0.020
HDL-C < 50 mg/dL *vs* HDL-C ≥ 50 mg/dL	5.8% *vs* 4.5% 1.27 (0.67–2.37) *P* = 0.465	5.0% *vs* 6.5% 0.70 (0.38–1.26) *P* = 0.233	2.3% *vs* 2.0% 1.11 (0.47–2.64) *P* = 0.812	13.8% *vs* 13.2% 1.01 (0.69–1.47) *P* = 0.959
SBP ≥ 140 mmHg *vs* SBP < 140 mmHg	4.5% *vs* 4.8% 1.06 (0.55–2.05) *P* = 0.869	7.5% *vs* 5.0% 1.85 (1.06–3.25) *P* = 0.032	1.7% *vs* 2.1% 0.81 (0.32–2.03) *P* = 0.650	14.0% *vs* 12.8% 1.24 (0.85–1.81) *P* = 0.266
DBP ≥ 75 mmHg *vs* DBP < 75 mmHg	3.4% *vs* 6.0% 0.59 (0.30–1.17) *P* = 0.130	6.2% *vs* 6.0% 1.27 (0.73–2.20) *P* = 0.406	2.1% *vs* 2.0% 1.04 (0.43–2.51) *P* = 0.930	11.6% *vs* 14.9% 0.86 (0.59–1.26) *P* = 0.434

Incidence, hazard ratios, 95% CI and *P*-values in univariate Cox regression analyses are shown. DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure, TC, total cholesterol.

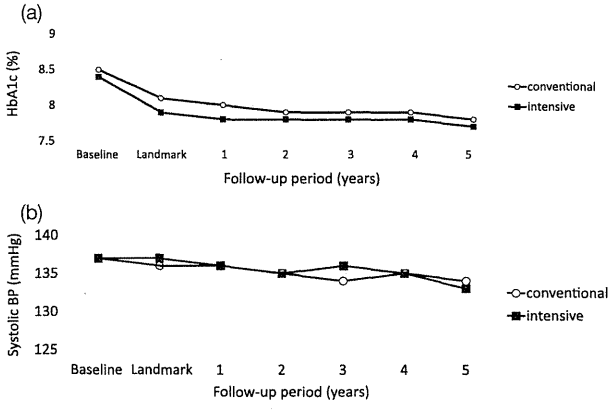

Figure 2 Clinical course of glycated hemoglobin A1c (HbA1c) and systolic blood pressure (BP) in conventional and intensive treatment groups. Decreases in HbA1c and systolic BP were similar in the two groups during the follow-up period after the landmark time.

with cardiovascular events ($P = 0.203$). In contrast, high LDL-C was significantly associated with increased incidence of cardiovascular events ($P = 0.04$), diabetes-related mortality ($P = 0.013$) and total diabetes-related events ($P = 0.013$), but not with stroke ($P = 0.181$). High HbA1c and SBP were also significantly associated with increased incidence of stroke ($P = 0.003$ and $P = 0.032$, respectively).

The patients were divided into quartiles of possible risk factors, and survival curves were compared using age- and sex-adjusted Cox hazard regression models. As shown in Figure 3a, the highest non-HDL-C quartile (≥163 mg/dL) had significantly higher diabetes-related mortality than the lowest (<122 mg/dL; $P = 0.030$) and second highest (143–163 mg/dL; $P = 0.019$) quartiles. Figure 3b shows that the total diabetes-related event was also significantly higher in the highest quartile (≥163 mg/dL) than either the lowest, second