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	none	<190 (1993–1999)
	(<180) if one has CHD		<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.
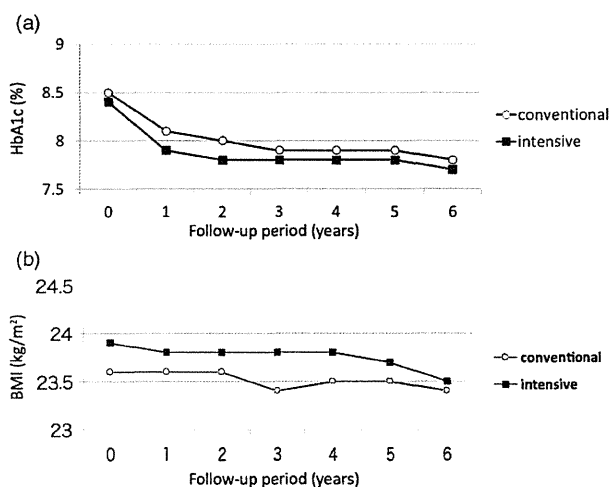
Figure 1   Clinical course of (a) glycated hemoglobin A1c (HbA1c) and (b) body mass index (BMI) in the conventional and intensive treatment groups.
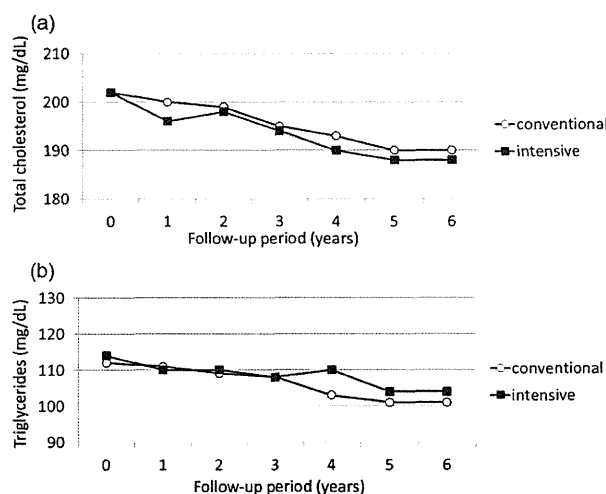

Figure 2   Clinical course of (a) total cholesterol and (b) triglycerides in the conventional and intensive treatment groups.
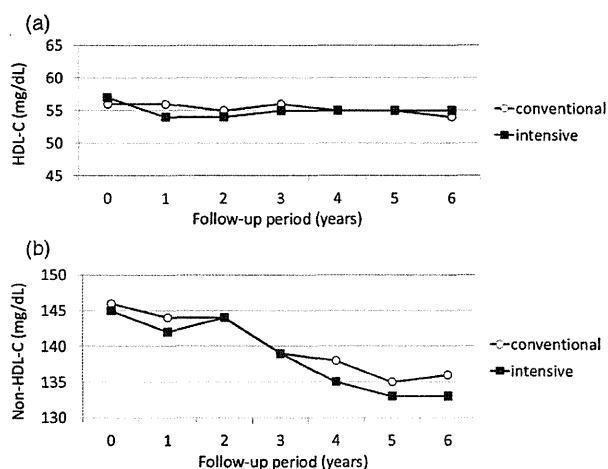

Figure 3   Clinical course of (a) high-density lipoprotein cholesterol (HDL-C) and (b) non-HDL-C in the conventional and intensive treatment groups.
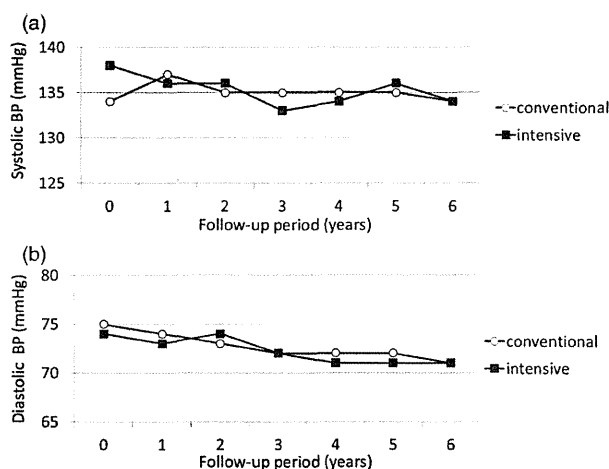

Figure 4   Clinical course of (a) systolic and (b) diastolic blood pressures (BP) in the conventional and intensive treatment groups.

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.

Acknowledgments

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.

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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.

ORIGINAL ARTICLE

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

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 $\geq$ 7.9% or HbA1c $\geq$ 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/m², 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/m²)	23.8 ± 3.4	23.6 ± 3.5
HbA1c (%)	7.7 ± 1.1	$7.5 \pm 1.0*$
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
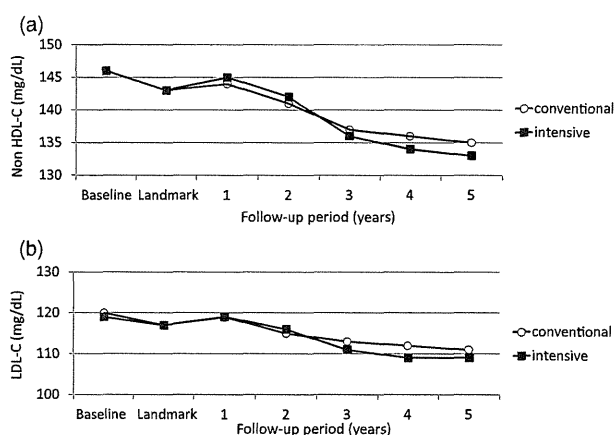

Figure 1 Clinical course of non-high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in conventional and intensive treatment groups. Non-HDL-C and LDL-C showed similar decreases in both groups during the follow-up period after the landmark time.

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

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.
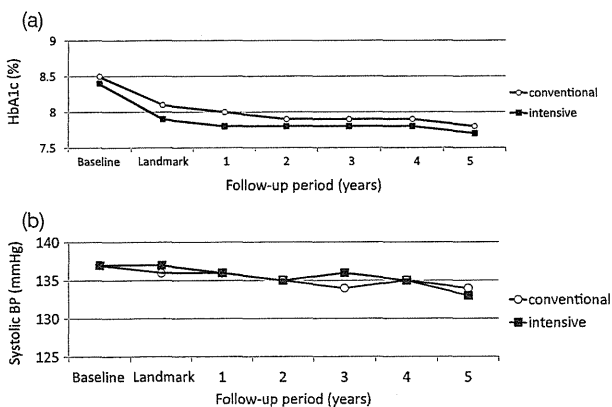

Figure 2 Clinical course of glycated hemoglobin A1c (HbA1c) and systolic blood pressure (BP) in conventional and intensive treatment groups. Decreases in HbA1c and systolic BP were similar in the two groups during the follow-up period after the landmark time.

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
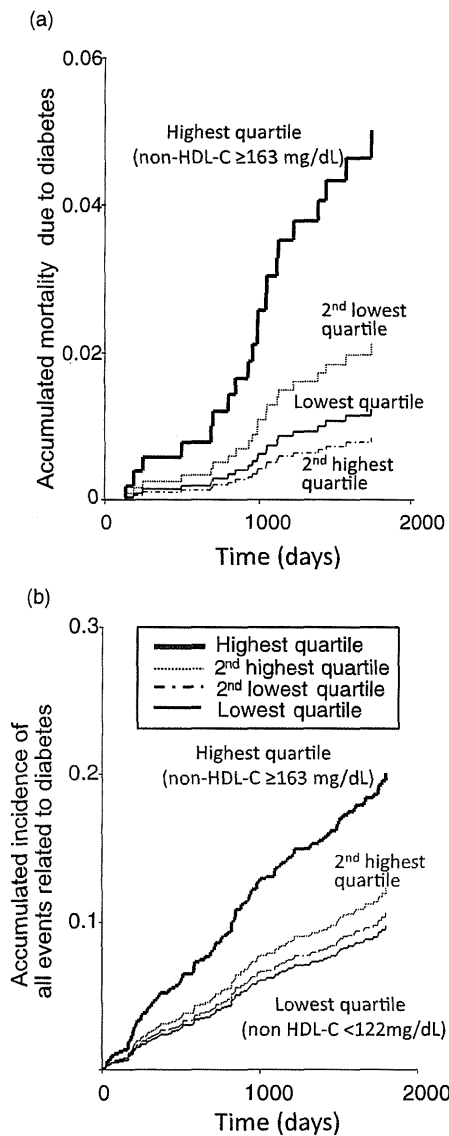
(a)

(b)

(a)

(b)

Figure 3 Non-high-density lipoprotein cholesterol (HDL-C) and mortality as a result of diabetes and total diabetes events. The highest non-HDL-C quartile (≥163 mg/dL) had a significantly higher mortality as a result of diabetes than the lowest and second highest quartile ($P = 0.030$ and $P = 0.019$, respectively). The accumulated incidence of total diabetes events was also significantly higher in the highest non-HDL-C quartile (≥163 mg/dL) than the lowest, second lowest and second highest quartiles ($P = 0.003$, $P = 0.031$, and $P = 0.008$, respectively).

Figure 4 Low-density lipoprotein cholesterol (LDL-C) and mortality as a result of diabetes and incidence of cardiovascular events. The incidence of cardiovascular events or mortality as a result of diabetes was highest in the highest LDL-C quartile (≥136 mg/dL) and lowest in the second lowest LDL-C quartile (99–116 mg/dL). This suggests the existence of a J-curve incidence for stroke according to LDL-C distribution.

lowest or second highest quartiles ($P = 0.003$, $P = 0.031$ and $P = 0.008$, respectively). Stroke incidence tended to be greatest in the highest non-HDL-C quartile ($P = 0.099$; vs the lowest quartile, $P = 0.076$; vs the second lowest quartile, $P = 0.080$; vs the second highest quartile). Similarly, cardiovascular event also tended to be increased in the highest non-HDL quartile compared with the second lowest ($P = 0.065$) and second highest quartiles ($P = 0.088$).
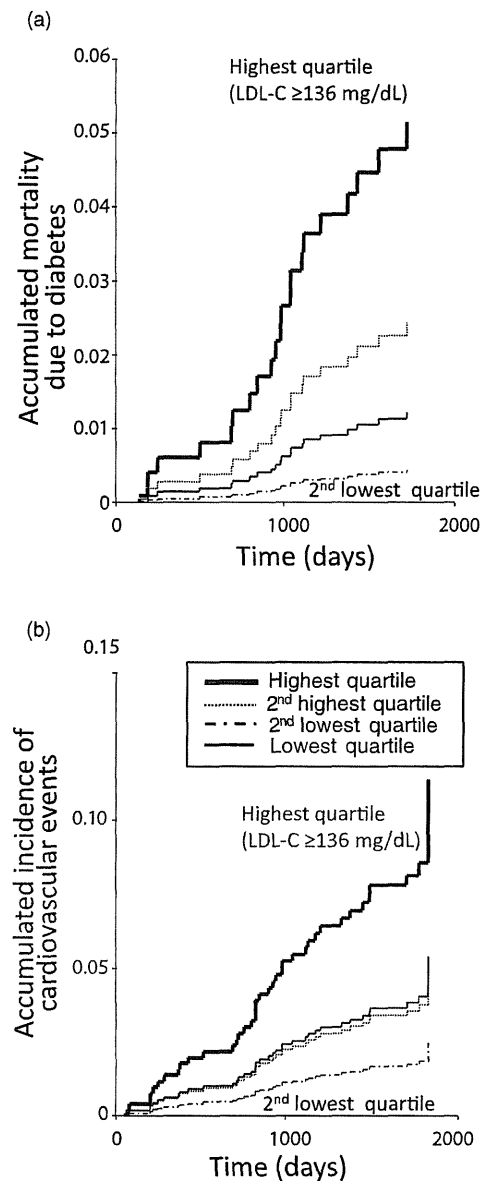
Figure 4a and b show that cardiovascular event or diabetes-related mortality incidence was greatest in the highest LDL-C quartile (≥136 mg/dL) and lowest in the second lowest LDL-C quartile (99–116 mg/dL). This suggested the existence of a J-curve incidence for stroke according to LDL distribution.

Figure 5a and b show that the highest HbA1c quartile (≥8.8%) had a significant increase in the incidence of
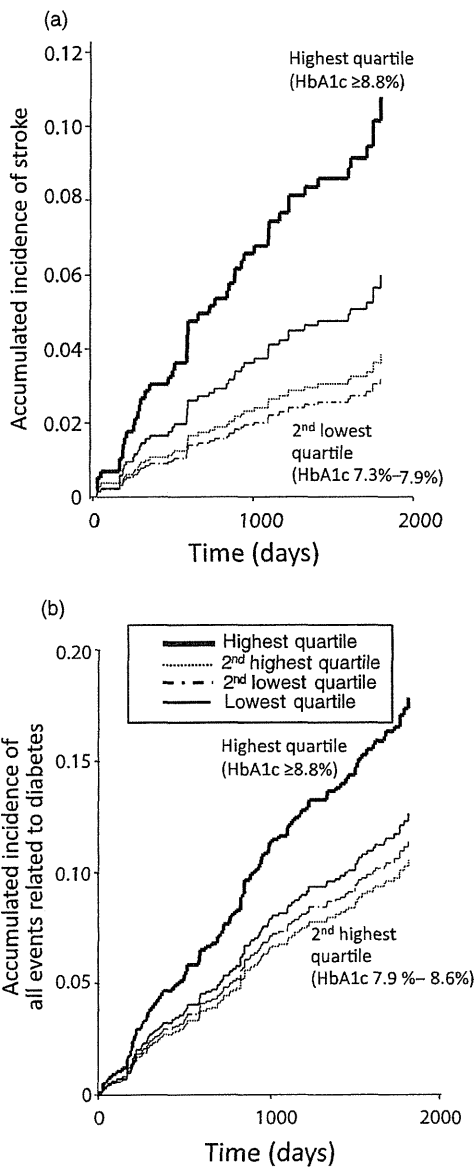
Figure 5 Glycated hemoglobin A1c (HbA1c) and incidence of stroke or all events related to diabetes. The highest HbA1c quartile (≥8.8%) had an increased incidence of stroke compared with the second lowest ($P = 0.003$), second highest ($P = 0.008$) and lowest ($P = 0.092$) quartiles. The incidence of stroke was lowest in the second lowest HbA1c quartile (7.3–7.9%). This suggests the existence of a J-curve incidence of stroke according to HbA1c distribution. The highest HbA1c quartile (≥8.8%) had a significant increase in diabetes-related events compared with the second lowest ($P = 0.031$) and second highest quartiles ($P = 0.058$), but not the lowest quartile group.

Figure 6 Systolic blood pressure (SBP) and incident of stroke or all events related to diabetes. The highest SBP quartile (≥147 mmHg) had an increased incidence of stroke compared with the second lowest (127–136 mmHg; $P = 0.013$) and lowest (<127 mmHg; $P = 0.083$) quartiles. The incidence of total diabetes events in the highest SBP quartile (≥147 mmHg) was significantly greater than only the second lowest quartile ($P = 0.023$). This suggests the existence of a J-curve incidence of stroke according to SBP distribution.

stroke and total diabetes-related events compared with the second lowest HbA1c quartile ($P = 0.003$ for stroke and $P = 0.031$ for total diabetes events). Interestingly, stroke incidence was lowest in the second lowest HbA1c quartile (7.3–7.9%) compared with the other three quartiles, resulting in a J-curve incidence for stroke
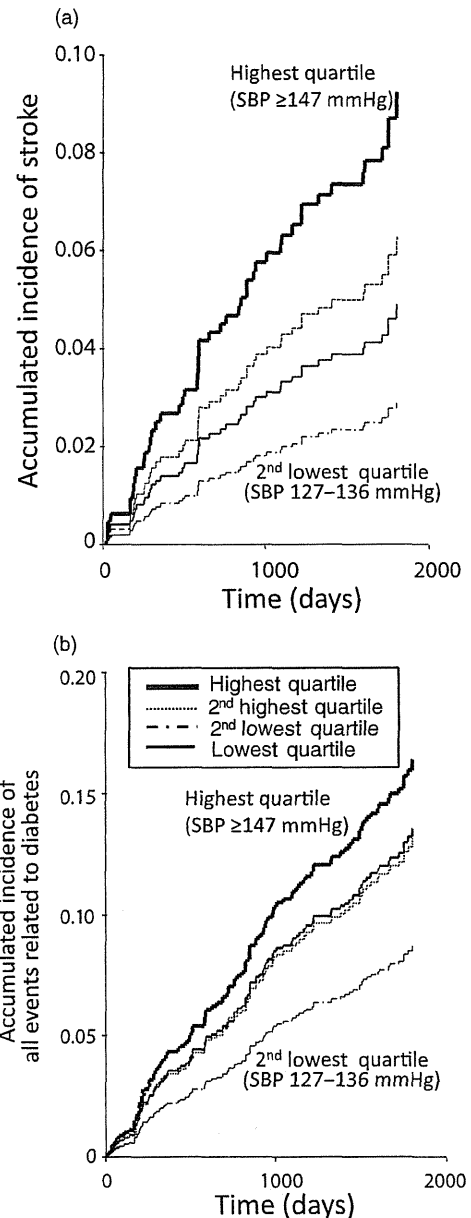
according to HbA1c distribution. Similarly, the highest SBP quartile (≥147 mmHg) had an increased incidence of stroke and total diabetes-related events compared with the second lowest SBP quartile (127–136 mmHg; $P = 0.013$ for stroke and $P = 0.023$ for total diabetes-related events; Fig. 6a,b). The incidence of stroke or total diabetes-related events was also lowest in the

Table 3 Variables associated with incident composite events in multivariate Cox regression analyses after the landmark time

	Number of events	Significant variables	Hazard ratio (95%CI)	Significance
CVE (fatal MI + non-fatal MI + angina pectoris + coronary revascularization)	35	Age	1.028 (0.955–1.107)	0.460
		Sex	0.663 (0.328–1.342)	0.253
		HbA1c	1.182 (0.856–1.631)	0.309
		LDL-C	1.011 (1.000–1.021)	0.045
		HDL-C	0.996 (0.973–1.019)	0.705
		SBP	1.004 (0.983–1.026)	0.706
Stroke	48	Age	1.080 (1.016–1.148)	0.013
		Sex	0.466 (0.255–0.850)	0.013
		HbA1c	1.364 (1.093–1.701)	0.006
		Non-HDL-C	1.010 (1.001–1.018)	0.029
		HDL-C	1.003 (0.985–1.022)	0.734
		SBP	1.017 (0.999–1.035)	0.067
Diabetes-related mortality	21	Age	1.123 (1.023–1.232)	0.015
		Sex	0.471 (0.188–1.180)	0.108
		HbA1c	0.851 (0.516–1.402)	0.526
		Non-HDL-C	1.019 (1.007–1.031)	<0.001
		HDL-C	1.019 (0.991–1.047)	0.183
		SBP	0.994 (0.966–1.023)	0.691
Total diabetes events (CVE + stroke + sudden death + renal death + diabetic foot + heart failure)	108	Age	1.081 (1.038–1.125)	<0.001
		Sex	0.560 (0.376–0.834)	0.004
		HbA1c	1.149 (0.957–1.378)	0.136
		Non-HDL-C	1.008 (1.002–1.014)	0.005
		HDL-C	1.004 (0.991–1.017)	0.532
		SBP	1.008 (0.996–1.019)	0.215

CVE, cardiovascular event; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

second lowest SBP quartile, showing a J-curve incidence for stroke according to SBP distribution.

Table 3 shows the variables that were significantly associated with incident composite events. Using six variables (age, sex, HbA1c, SBP, non-HDL-C and HDL-C), non-HDL-C was significantly and independently associated with increased risk of stroke, diabetes-related mortality and total events. The adjusted hazard ratios (95% CI) for non-HDL-C were 1.010 (1.001–1.018, $P = 0.029$) for stroke, 1.019 (1.007–1.031, $P < 0.001$) for diabetes-related mortality and 1.008 (1.002–1.017; $P = 0.005$) for total diabetes-related events. When LDL-C was added to the model for total diabetes-related events, non-HDL-C remained significant ($P = 0.007$), whereas LDL-C did not. The significant association between non-HDL-C and total diabetes-related events persisted after the addition of statin treatment to the model ($P = 0.005$).

High HbA1c was also independently associated with incident stroke. Using six variables (age, sex, HbA1c, SBP, LDL-C and HDL-C), LDL-C was the only significant predictor for cardiovascular events ($P = 0.045$).

Discussion

The significance of several risk factors, such as serum lipid abnormalities and increased HbA1c, for stroke and mortality has not been shown clearly in elderly type 2 diabetes patients. The present study used a landmark analysis to show that non-HDL-C, SBP and HbA1c were independent predictors for stroke development during a 6-year follow-up period. A weak, significant association between non-HDL-C and stroke was found in agreement with several prospective studies.[9,10] In the Emerging Risk Factors Collaboration study on 302 430 people from 68 long-term prospective studies, the hazard ratios for ischemic stroke were 1.12 (95%CI:1.04–1.20) for non-HDL-C and 1.02 (95%CI:0.94–1.11) for triglycerides. However, the hazard ratio for ischemic stroke was approximately fourfold weaker than that for coronary heart disease.[9] The Women's Health Study also showed that compared with the lowest non-HDL-C quintile, the highest quintile had multivariate-adjusted hazard ratios for ischemic stroke of 2.45 (95%CI:1.54–3.91), higher than the ratios for HDL-C or LDL-C[10]. These

findings show non-HDL-C might be an important risk factor for stroke, even in elderly diabetes patients.

We also showed that non-HDL-C predicted diabetes-related mortality and total diabetes-related events. The predictive power of non-HDL-C for mortality was stronger in high-risk CHD patients associated with vascular intervention, chronic renal failure or diabetes mellitus.[11-15] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) trial on acute coronary syndrome patients receiving either pravastatin 40 mg or atorvastatin 80 mg, non-HDL-C, HDL/TC and Apolipoprotein (Apo) B / Apo A1 predicted death or acute coronary events.[11] In the Bypass Angioplasty Revascularization Investigation (BARI) Study, non-HDL-C was a strong and independent predictor of non-fatal MI and angina pectoris at 5 years compared with LDL-C or triglycerides, even after adjustment for potential covariates in patients undergoing angioplasty revascularization or bypass-surgery.[12] Nishizawa *et al.* showed that non-HDL-C in predialysis serum was a significant and independent predictor of cardiovascular mortality in hemodialysis patients.[13] In the European Community funded Concerted Action Programme into the epidemiology and prevention of diabetes (EURODIAB) Prospective Complication Study, non-HDL-C, age, pulse pressure and waist-to-hip ratio were independent predictors for all-cause mortality in type 1 diabetes patients.[14] Herman *et al.* showed the discriminatory power of non-HDL-C was similar to Apo-B in diabetes patients because of the discriminant ratio and unbiased equation of equivalence.[15] Non-HDL-C was also shown to be a better predictor of CVD mortality or acute myocardial infarction (AMI) than LDL-C or TC.[16-18] In the present study, the predictive potential of non-HDL-C was stronger in diabetic patients who had a residual risk beyond LDL-C.

Our finding in the landmark study that patients with a non-HDL-C > 163 mg/dL had a significantly increased incidence of stroke, diabetes-related death and total events compared with those with a non-HDL-C < 122 mg/dL suggests that lipid lowering with a statin is of considerable importance, even in the elderly diabetes patients. This result is in agreement with a report from the Japanese Circulatory Risk in Communities Study[19] showing an association between non-HDL-C and CHD incidence, with the greatest discriminative power at non-HDL-C > 140 mg/dL. In contrast, in the National cholesterol education program-III (NCEP-III) guidelines, the optimal goal of non-HDL-C in CHD patients was <100 mg/dL.[17] The decrease in non-HDL-C after the landmark time in both our intensive and conventional treatment groups might represent an effect of statin treatment, and might also explain the differences in events described here. In the Collaborative Atorvastatin

Diabetes Study, treatment decreased both LDL-C and non-HDL-C, leading to prevention of stroke and cardiovascular events.[28] The present results suggest that even in elderly high-risk diabetes patients, a reduction of non-HDL-C using a statin might be beneficial for preventing CVD, stroke and mortality.[29]

The reason for the lack of significant associations between non-HDL-C and cardiovascular events remains unclear. In contrast, LDL-C was a significant predictor of cardiovascular events in the present study. The differences in predictive power of non-HDL-C and LDL-C for CVD and stroke might reflect variability in the vulnerability of cerebral and coronary arteries to lipoproteins. Non-HDL-C in combination with a Apo-B100, remnant lipoproteins and small, dense lipoproteins might be involved in stroke events as a consequence of biological actions beyond LDL-C. Alternatively, the predictive power of non-HDL might be affected by age,[20] sex,[21,22] ethnicity[23] and lifestyle habits.

The present data showed high HbA1c predicted stroke in elderly people with type 2 diabetes. In a Finnish elderly cohort, HbA1c and fasting, and 2-h glucose predicted stroke events.[30] In the Diabetes among Indian Americans (DIA) study, HbA1c and smoking were predictors for stroke in men without previous stroke, whereas therapy with insulin plus oral agents predicted stroke in men with a history of stroke.[31]

In contrast, stroke incidence in the present study was lowest in the second lowest HbA1c quartile (7.3–7.9%), resulting in a J-curve incidence for stroke according to HbA1c distribution. The study on the UK General Practice Database showed low and high HbA1c were both associated with increased large-vessel disease and all-cause mortality in 27 965 diabetic patients,[32] possibly because of hypoglycemia, leading to arrhythmia, cardiovascular autonomic abnormalities, QT prolongation, and induction of prothrombotic and proinflammatory markers. Moderately abnormal glucose control with HbA1c around 7.5% (JDS, 7.1%) with no hypoglycemia during follow up might have a beneficial effect on stroke in high-risk, elderly diabetic patients.

Similarly, the lowest incidence of stroke and total diabetes events in the second lowest SBP quartile (127–136 mmHg), and the lowest incidence of cardiovascular events and total diabetes events in the second lowest LDL-C quartile (99–116 mg/dL) suggest the existence of a J-curve. The J-curve effect of BP lowering has been reconsidered recently, with recommendation that aggressive BP control should be undertaken carefully in high-risk, older diabetes patients.[33,34] A review of observational studies shows a trend where all-cause mortality was highest when TC was lowest.[35] Only a few randomized control trials have not provided evidence of an effect of lipid-lowering treatment on mortality in ≥80 years-of-age patients.[35] Although it is not possible

to disregard the possibility that comorbidities, such as inflammation and malnutrition, are associated with an increased incidence of stroke in the lowest SBP and LDL-C groups, cautious and comprehensive management of BP and LDL-C is also required in older people with diabetes.

The present study had several limitations. First, our cohort comprised high-risk, elderly Japanese subjects, and therefore our results cannot be generalized to other populations. Second, the study population was limited by a relatively small sample size compared with other published reports, and it is likely that the lack of significant relationships between variables reflects inadequate statistical power rather than a true negative result. Finally, the landmark analysis after 1 year of intervention did not completely reflect the effects of temporal changes in the parameters over the entire follow-up period, although some tracking effects of lipid parameters were observed.

In conclusion, this relatively large-scale prospective study showed non-HDL-C was an important predictor for stroke, diabetes-related mortality and total diabetes events in high-risk, elderly type 2 diabetes patients. Non-HDL-C reflected several pathological lipoproteins, including LDL-C, ApoB, triglycerides, remnant lipoproteins and small, dense lipoproteins.[36] Measurement of non-HDL-C might therefore be useful for evaluating the effects of lipid intervention using statin, fibrates and eicosapentaenoic acid in elderly people with diabetes. However, further studies including sophisticated randomized trials are necessary to elucidate the role of non-HDL-C on vascular events.

Acknowledgments

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.

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