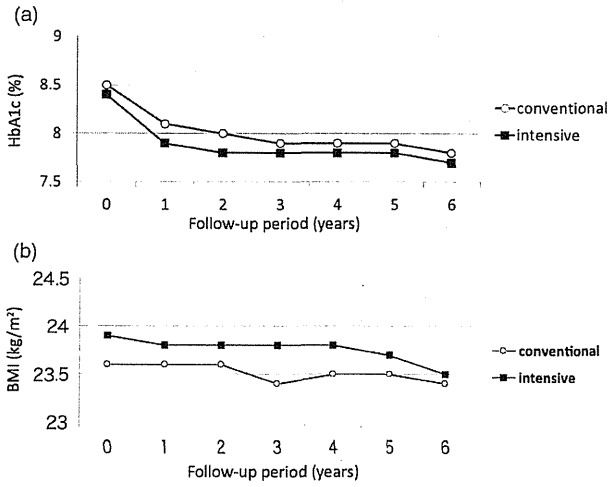

Figure 1 Clinical course of (a) glycated hemoglobin A1c (HbA1c) and (b) body mass index (BMI) in the conventional and intensive treatment groups.

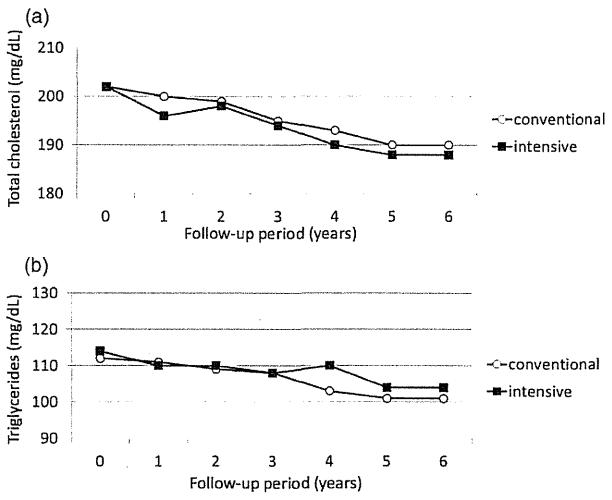

Figure 2 Clinical course of (a) total cholesterol and (b) triglycerides in the conventional and intensive treatment groups.

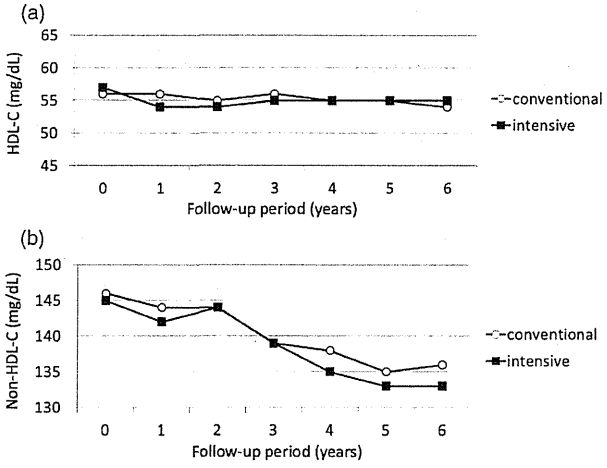

Figure 3 Clinical course of (a) high-density lipoprotein cholesterol (HDL-C) and (b) non-HDL-C in the conventional and intensive treatment groups.

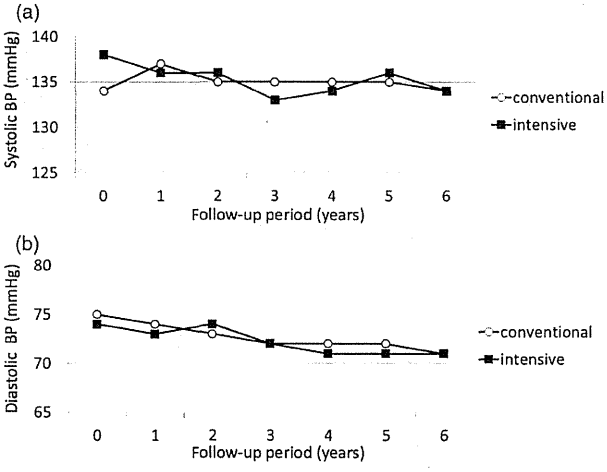

Figure 4 Clinical course of (a) systolic and (b) diastolic blood pressures (BP) in the conventional and intensive treatment groups.

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

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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.

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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.

Geriatr Gerontol Int 2012; **12 (Suppl. 1):** *18–28*

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

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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

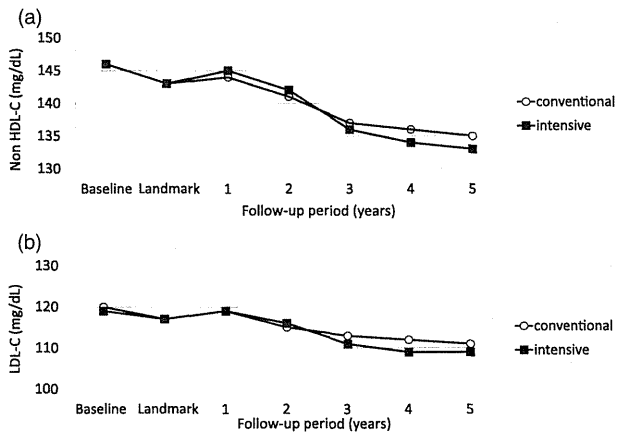

Figure 1 Clinical course of non-high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in conventional and intensive treatment groups. Non-HDL-C and LDL-C showed similar decreases in both groups during the follow-up period after the landmark time.

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.

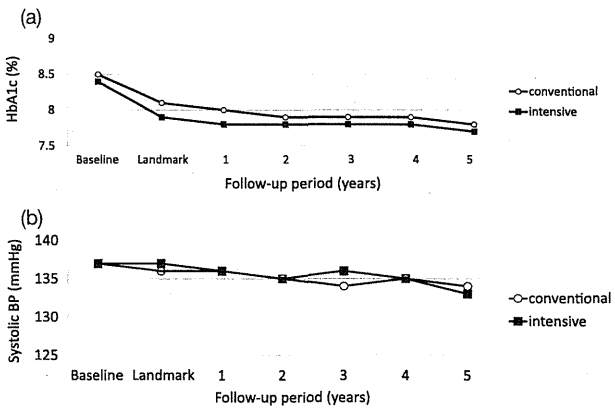

Figure 2 Clinical course of glycated hemoglobin A1c (HbA1c) and systolic blood pressure (BP) in conventional and intensive treatment groups. Decreases in HbA1c and systolic BP were similar in the two groups during the follow-up period after the landmark time.

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

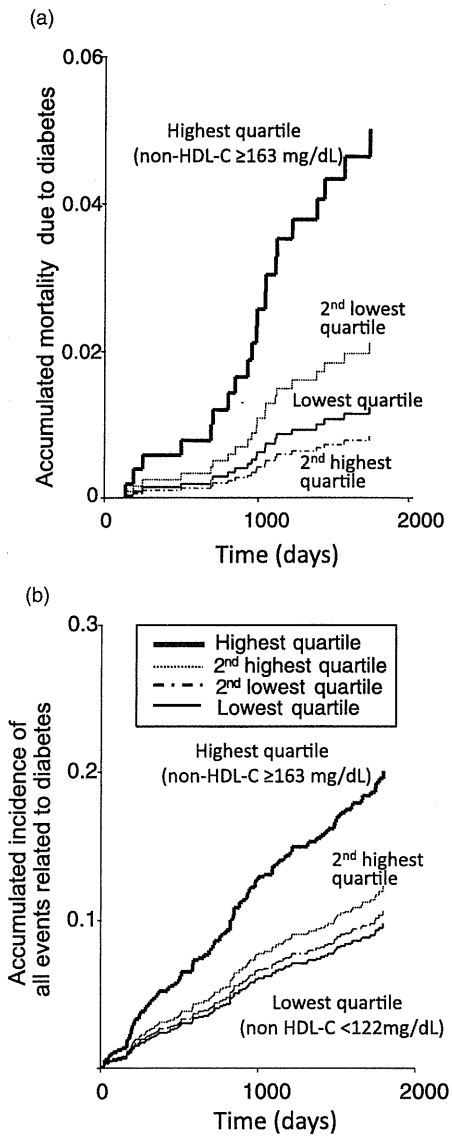

Figure 3 Non-high-density lipoprotein cholesterol (HDL-C) and mortality as a result of diabetes and total diabetes events. The highest non-HDL-C quartile (≥163 mg/dL) had a significantly higher mortality as a result of diabetes than the lowest and second highest quartile ($P = 0.030$ and $P = 0.019$,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

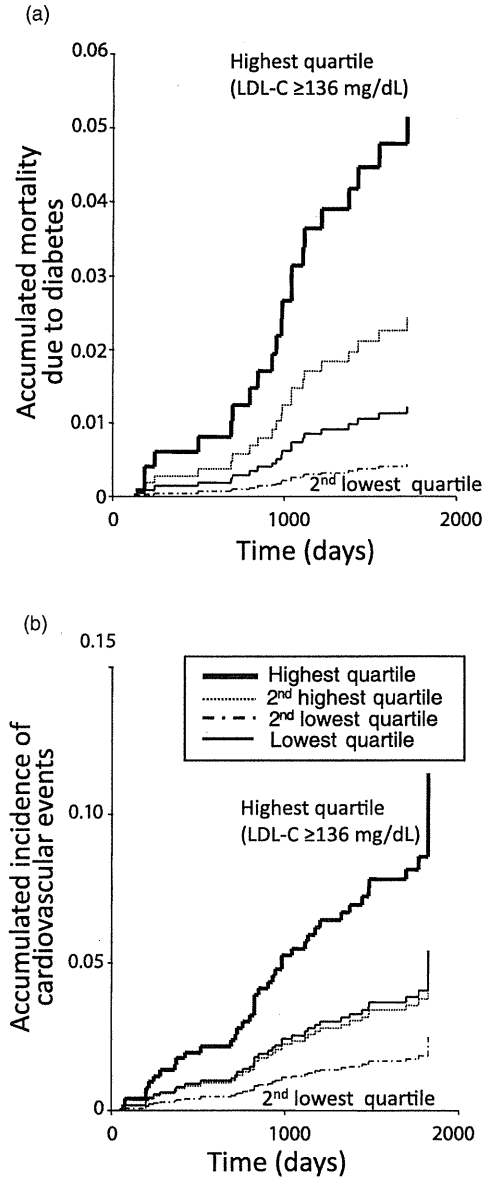

Figure 4 Low-density lipoprotein cholesterol (LDL-C) and mortality as a result of diabetes and incidence of cardiovascular events. The incidence of cardiovascular events or mortality as a result of diabetes was highest in the highest LDL-C quartile (≥136 mg/dL) and lowest in the second lowest LDL-C quartile (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

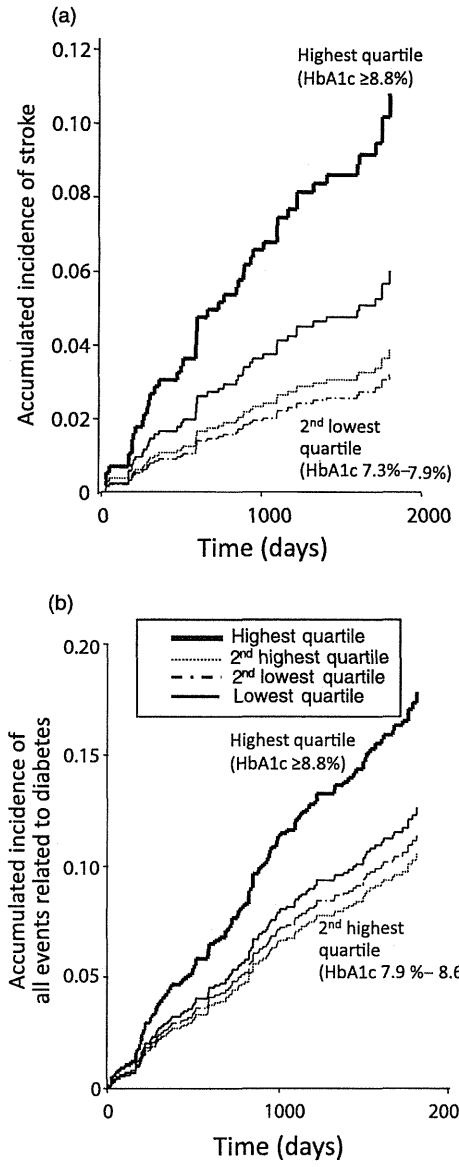

Figure 5 Glycated hemoglobin A1c (HbA1c) and incidence of stroke or all events related to diabetes. The highest HbA1c quartile (≥8.8%) had an increased incidence of stroke compared with the second lowest ($P = 0.003$), second highest ($P = 0.008$) and lowest ($P = 0.092$) quartiles. The incidence of 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.

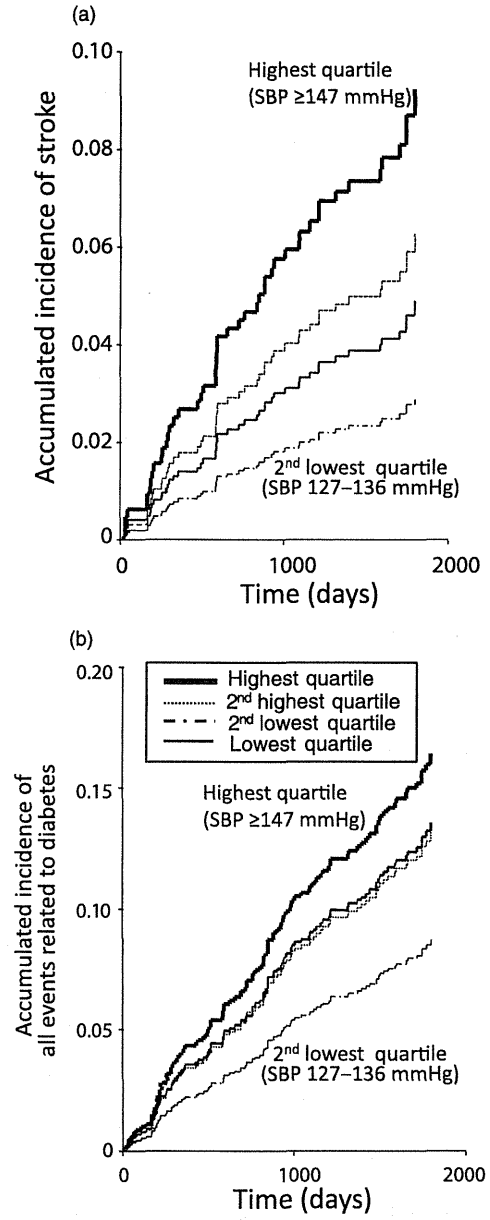

Figure 6 Systolic blood pressure (SBP) and incident of stroke or all events related to diabetes. The highest SBP quartile (≥147 mmHg) had an increased incidence of stroke compared with the second lowest (127–136 mmHg; $P = 0.013$) and lowest (<127 mmHg; $P = 0.083$) quartiles. The incidence of total 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

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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.

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LETTERS TO THE EDITOR

New dorsiflexion measure device: A simple method to assess fall risks in the elderly

Dear Editor,

Hip fracture is the third leading cause yielding bedridden status in Japan, and more than 80% of hip fractures are reported to be caused by falling. There are a variety of causes for falls in the elderly, and one of the significant causes is the inability to lift their toes when they walk. Here, we show a new device to measure dorsiflexion angle, an instrument that we developed to assess fall risks in the elderly.

Participants were requested to stand up straight and step back until the hip leaned on the wall (Fig. 1a). The fulcrum of the instrument was adjusted to the center of the external malleolus (Fig. 1b). The arm of the instrument was set to stay level, adjusting the branching thin arm placed on the ridge of the dorsum of the foot. Then, participants were asked to dorsiflex as much as possible. The mean time to measure bilateral dorsiflexion angles was within 5 min.

We measured dorsiflexion and Fall Risk Index (FRI),[1,2] including the history of falls within the past year, in 131 women (46–89 years, mean age 78.0 ± 7.1 years) and 88 men (46–93 years, mean age 76.2 ± 8.6 years) who visited the fall prevention clinic in Kyorin University Hospital. The occurrence of falls within the past year was 35.6%. Falls occurred 2.0 ± 0.1 times in fallers within 1 year, and women fell more frequently than men (42.7% *vs* 25.0%, $\chi^2 = 7.2$, $P \leq 0.01$). The average FRI score was 6.7 ± 3.4 in non-fallers and 10.6 ± 3.0 in fallers ($P < 0.0001$). Women showed a higher FRI score than men (8.8 ± 3.6 *vs* 7.0 ± 3.8, $P = 0.003$).

This new device appears promising in detecting the high-risk group of fallers, because the dorsiflexion angle was significantly smaller in fallers than non-fallers (right 9.6 ± 8.4 *vs* 13.7 ± 9.6 degrees, $P = 0.012$; left 10.0 ± 8.5 *vs* 14.2 ± 9.8 degrees, $P = 0.014$). Furthermore, the occurrence of falls was more frequent as the dorsiflexion angle decreased in women ($\chi^2 = 6.4$, $P = 0.042$; Fig. 1c), and half of the subjects, whose dorsiflexion angle was less than 10 degrees, experienced falls within a year.

Previously, it was reported that hip fractures occur more frequently in women than men, even though the incidence rate of falls was comparable until the age of 90 years. This is considered to be a result of the higher prevalence of osteoporosis in women.[3] In contrast, the present study found that women less than 90 years-of-age fell more frequently than men in the Japanese population of this age group. We also found that the FRI score was higher in women than men, as has been shown previously.[4] In addition, dorsiflexion angle was

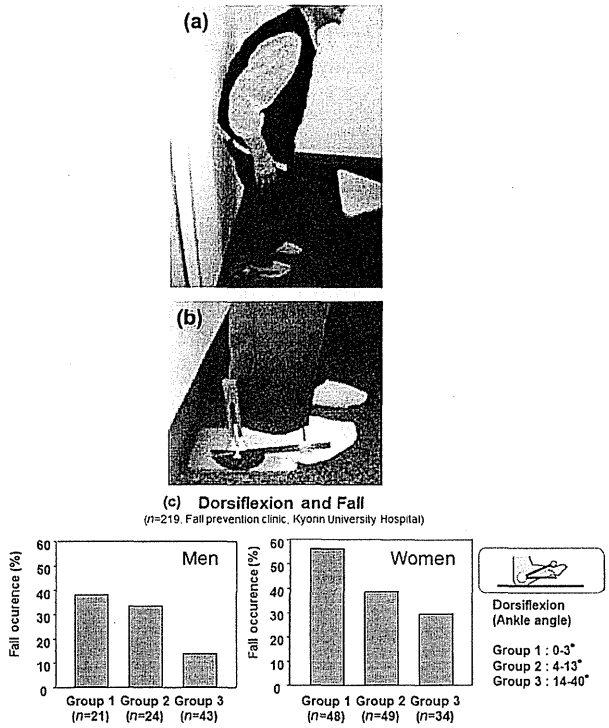

Figure 1 (a,b) How to measure dorsiflexion angle using a dorsiflexion measure device. (c) The relationship between dorsiflexion angle and the occurrence of falls within the past year. In men and women respectively, participants were grouped by tertile according to the dorsiflexion angle.

smaller in women than men (right 10.3 ± 8.4 *vs* 15.2 ± 10.1 degrees, $P = 0.0001$; left 11.0 ± 8.5 *vs* 15.2 ± 10.4 degrees, $P = 0.0013$), and a stepwise increase in the fall occurrence rate according to the level of dorsiflexion angle was evident in women (not significant in men). These results show that less ability to dorsiflex would partly explain the sex difference in the occurrence of falls and ensuing hip fracture.

The new dorsiflexion measure device we report here is easy and less time-consuming to use, and will be sure to help identify a high-risk group of fallers in the elderly.

Disclosure statement

This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients. All authors contributed significantly to this work and are

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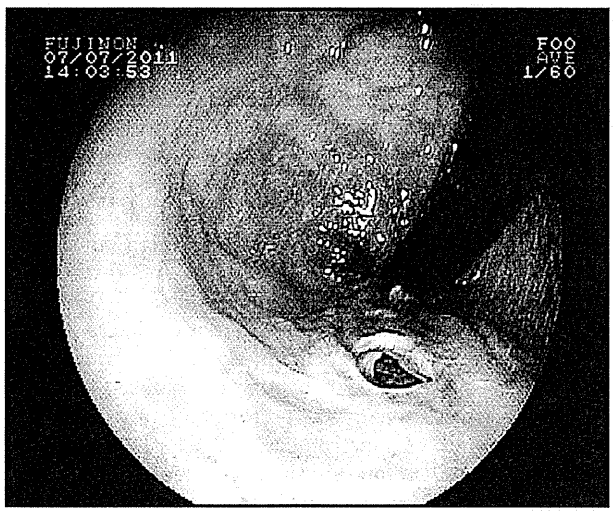
Rectal perforation as a result of self-administration of retrograde enema in an elderly dementia patient

Retrograde cleansing enemas are commonly used in the treatment of chronic constipation, especially in the elderly.[1] We report a case of colorectal perforation as a result of self-administered retrograde water enema in an elderly dementia patient.

A 76-year-old chronically constipated man was admitted to Turkiye Yuksek Ihtisas Hospital Gastroenterology Department in Ankara, Turkey, with a 1-week history of rectal pain. His medical history showed he had the diagnosis of dementia. Clinical examination at that time showed normal vital signs, on examination of the abdomen there was no defense or rebound, digital examination was normal, and respiratory and circulatory system examinations were normal. All laboratory investigations including full blood count, serum amylase, liver function tests, urea and electrolytes were within normal limits. There was no abnormality in abdominal X-ray and abdominal ultrasonography. He was started on a retrograde enema by his family practitioner 7 days earlier for constipation. He described that the pain was precipitated by the first self-administration of the retrograde irrigation enema and the patient denied subsequent use. A preplanned colonoscopy was carried out, and on retroflexion a rectal perforation was detected (Fig. 1). An abdominal computed tomography scan showed perirectal air. Conservative management with intestinal rest and intravenous antibiotics was carried out. The clinical course of the patient was favorable without sepsis or generalized peritonitis. He was discharged home after a 7-day inpatient stay.



Perforation of the rectum and sigmoid colon caused by cleansing enemas, used by chronically constipated patients, has rarely been reported. In the largest series, Paran *et al.* reported that three of 13 patients with rectal perforation as a result of retrograde enema died because of late diagnosis.[2] Gayer *et al.* reported 14 elderly patients (average age 80 years) with rectal perforation as a result of cleansing enema. Surgery was carried out in 10 of 14 patients, and nine of the 14 patients died. Interestingly, in all of these cases the enema was given by paramedic personnel.[3] It is perhaps not so well known that the rectal wall, even in the absence of disease, can be perforated by the tip of a rubber catheter introduced for the purpose of administering a simple cleansing enema.[4] Because of the possible risk of morbidity and mortality, especially in elderly patients in whom the process can be more catastrophic, rectal perforation risk should be kept in mind and administration of rectal cleansing enemas should be carried out gently and carefully by paramedic personnel. Also, the position of the body when inserting the enema tip is important. An enema should be carried out, in principle, with the patient in the left lateral decubitus position.[5]

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RELATIONSHIP BETWEEN TESTOSTERONE AND COGNITIVE FUNCTION IN ELDERLY MEN WITH DEMENTIA

To the Editor: A decrease in sex hormones with aging has been reported to be related to psychosomatic disorders such as late-onset hypogonadism syndrome, frailty, and cognitive impairment in adult men.[1] For example, a community-based cross-sectional study has shown that elderly men with a lower blood concentration of bioavailable testosterone have more-severe impairment of cognitive function.[2] Moreover, a longitudinal study indicated that serum free testosterone (FT) concentration could predict memory performance and cognitive status in elderly men,[3] but it is unknown whether lower testosterone concentration is related to cognitive impairment in individuals with dementia, because the previous studies primarily focused on a healthy community-based population. Also, few studies have addressed the relationship between testosterone and cognitive function in elderly Japanese men.

One recent cross-sectional study showed that total testosterone and FT concentration were associated with activities of daily living (ADLs) in institutionalized elderly men.[4] This study also revealed that a relationship between testosterone and cognitive function could be found even in institutionalized elderly men with physical or neuropsychiatric dysfunction. Thus, whether lower testosterone concentration is related to deterioration of ADL in elderly men with cognitive impairment was longitudinally investigated.

Fifty-two male outpatients attending the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were recruited (mean age 77.0 ± 5.5, range 65–87). Participants' clinical backgrounds were hypertension, 48.9%; diabetes mellitus, 12.2%; and dyslipidemia, 38.1%. None had a history of stroke. Comprehensive geriatric assessment was performed based on basic ADLs (Barthel Index),[5] instrumental ADLs (Lawton and Brody IADLs, 0–5 points in men),[6] cognitive function (Mini-Mental State Examination (MMSE)),[7] mood (Geriatric Depression Scale (GDS), 15 items),[8] and vitality (Vitality Index, 10-point scale).[9] This assessment was repeated 1, 2, and 3 years after baseline assessment at the first visit to the clinic. At the first visit, blood was drawn after an overnight fast and FT concentration was measured using radioimmunoassay. FT values ranged from 1.0 to 53.0 pmol/L (mean ± SD 30.4 ± 11.0 pmol/L). Participants were classified into three groups according to tertile according to the baseline FT value (Figure 1), and the parameters from the comprehensive geriatric assessment were compared between groups and visits. Statistical data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). One-way analysis of variance (ANOVA) was applied for comparisons between groups, and the Fisher post hoc test was applied when significant ($P < .05$). One-way repeated ANOVA was used for comparisons between baseline and the 1-, 2-, and 3-year visits, and the Fisher post hoc test was applied when significant ($P < .05$).

There were no significant differences between groups in age (high, 75.3; middle, 76.6; low, 79.0), basic ADLs (high, 96.9; middle, 99.1; low, 95.3 points), MMSE (high, 23.2; middle, 25.1; low, 23.1 points), GDS-15 (high, 5.1; middle, 4.1; low, 4.6 points), and Vitality Index (high, 9.1; middle, 9.1; low, 8.8 points) at baseline, whereas IADLs tended to be lower (high, 4.1; middle, 4.1; low, 3.4 points, $P = .06$) in the low FT tertile group than in the other groups.

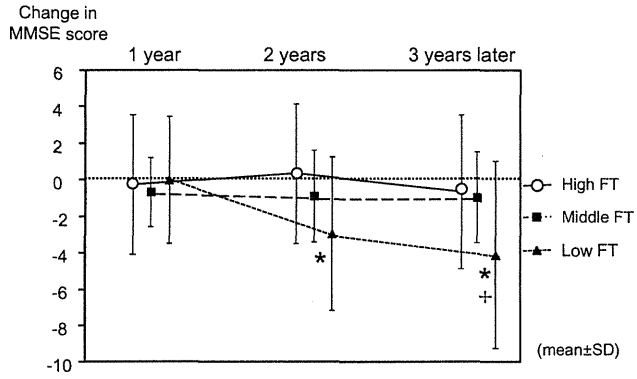

Figure 1. Change in Mini-Mental State Examination (MMSE) score according to tertile of serum free testosterone (FT) level in men. FT tertile: high, >36.1 pmol/L, n = 17; middle, 29.1–35.4 pmol/L, n = 17; low, <28.8 pmol/L, n = 18. *$P < 0.05$ vs highest FT group, +$P < 0.05$ vs middle FT group.

At the 1-year visit, there was no difference in change in MMSE score from baseline between the groups, although the decrease in MMSE score was larger in the low FT tertile group than in the middle and high tertile groups at the 2- and 3-year visits (Figure 1). Also, MMSE scores were lower in the low FT tertile group at the 2- ($P = .009$) and 3-year ($P < 0.001$) visits than at baseline, whereas they were not lower in the middle and high tertile groups. In contrast, there was no such trend in basic ADLs, IADLs, GDS scores, and Vitality Index.

Multiple regression analysis was performed with a decrease in MMSE score as a dependent variable and age; ADLs; body mass index; presence of hypertension, diabetes mellitus, or hyperlipidemia; and FT concentration as independent variables to consider factors affecting cognitive impairment, according to a previous report.[4] Blood FT concentration was found to be an independent predictor of decrease in MMSE score at the 3-year visit ($\beta = 0.492$, $P = .02$).

A number of investigations support the biological plausibility of a protective effect of testosterone against cognitive dysfunction. The present findings from memory clinic outpatients are consistent with previous findings observed in elderly community-based men, showing a relationship between FT concentration and cognitive performance.[3] Furthermore, the present findings indicate that a lower FT concentration could lead to a faster decline in cognitive function in elderly Japanese men who already show cognitive impairment. This study provides fundamental data for the future study of hormone replacement therapy for cognitive decline in elderly adults with low FT.

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Author Contributions: Nagai K designed the research; acquired, analyzed, and interpreted the data; and drafted the manuscript. Shibata S interpreted the data. Kobayashi Y, Yamada Y, Kimura S, Machida A acquired subjects and data and analyzed and interpreted the data. Akishita M and Toba K conceived and designed the research and interpreted the data. Kozaki K supervised the research.

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BASELINE INSTRUMENTAL ACTIVITIES OF DAILY LIVING AND INCIDENT DEMENTIA

To the Editor: Sikkes et al.[1] have written an important paper showing that individuals without dementia with impairment in at least one of nine instrumental activities of daily living (IADLs) at baseline had a significantly higher incidence of dementia at 12 months (24.4%) than individuals without IADL impairment at baseline (16.7%) ($P = .04$). Their 531 participants who were followed for 12 months were relatively young (mean age 69.6), so it was decided to duplicate their study from prospective data from the Wyong Hospital Memory Clinic, 100 km north of Sydney. From 415 individuals attending a memory clinic, community-dwelling individuals aged 60 and older who were free of dementia at baseline and had a Mini-Mental State Examination score (MMSE[2]) of 25 to 30 and a follow-up MMSE and Montreal Cognitive Assessment (MoCA), range 0 (worst) to 30 (best)[3] at 12 months were selected in a consensus conference of a geriatrician (PJ) and a clinical nurse consultant (EH). Each individual's family rated IADLs on the Nottingham scale,[4] which ranged from 0 (worst) to 22 (best). Twenty-two of 82 (27%) converted to dementia at 12 months, compared with Sikkes conversion rate of 20.8% at 24 months—the most likely reason for this difference was that mean age (79.1) was 9.5 years older than theirs (69.6). Stats Direct Version 2.7.8b (StatsDirect Ltd, Altrincham, UK) from November 2011 was used to compare converters and nonconverters. Mean age of the 22 converters at baseline was significantly higher that that of the 60 nonconverters (82.0 ± 5.8 vs 78.0 ± 6.8, $P < .01$), mean IADL score at baseline was significantly lower (13.1 ± 5.3 vs 16.1 ± 4.0, $P = .0236$), MMSE score at baseline was by definition lower (25.6 ± 0.73 vs 27.5 ± 1.50, $P < .001$), and MoCA score at baseline was lower (19.2 ± 3.5 vs 22.8 ± 3.9, $P < .001$). At 12 months, IADL (11.4 ± 5.6 vs 15.4 ± 4.5, $P = .004$), MMSE score (21.6 ± 4.5 vs 27.4 ± 1.6, $P < .001$), MoCA (16.8 ± 3.6 vs 22.8 ± 4.2, $P < .001$) remained significantly lower in converters.

The Nottingham IADL covers seven of the nine IADL items that Sikkes used, excluding medications and finances. Women are more likely than men to perform five of the Nottingham IADL items unless the men live alone with no home care services: cleaning the kitchen, making a hot snack, washing small items of clothing, doing a full clothes wash, and doing housework.

Although the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for dementia include a decline in social and occupational function, there is a surprising lack of research into IADLs as a predictor of incident dementia. This is an important topic for future research and ongoing studies are being conducted in three cohorts: Wyong Memory Clinic; general medical inpatients with delirium or subsyndromal delirium—a prospective randomized controlled trial, Central Coast Australia Delirium Intervention Study; and PhD study, PR DEFEAT DELIRIUM, in outpatients at high risk for incident delirium. One study[5] with 255 community-dwelling individuals attending a memory clinic who were followed an average of 13 months has been published. The 11.4% of participants with antithyroid antibodies had similar outcomes at 12 months with respect to IADLs, decline in IADLs, MMSE and MoCA scores, and transfer to residential care.

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Relationship between interleukin-6 and cerebral deep white matter and periventricular hyperintensity in elderly women

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Aim: We evaluated the relationships between serum levels of high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 with the severity of leukoaraiosis.

Methods: One hundred and thirty-seven elderly women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were enrolled in this study. Leukoaraiosis was assessed by periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score.

Results: Serum log IL-6 level correlated with PVH and DWMH scores, but hsCRP did not. By multinomial logistic analysis, IL-6 was significantly related to DWMH score, independent of age and systolic blood pressure.

Conclusion: IL-6 is presumably an important marker of leukoaraiosis, as is the case with silent cerebral infarction. **Geriatr Gerontol Int 2011; 11: 328–332.**

Keywords: interleukin-6, leukoaraiosis, white matter hyperintensity.

Introduction

Leukoaraiosis, an isointense lesion on T_1-weighted images and hyperintense lesion on T_2-weighted images of magnetic resonance imaging (MRI), is considered to be a type of ischemic change in the brain on the basis of decreased blood flow in the area of leukoaraiosis.[1] In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.[2] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of the geriatric syndromes such as dementia, gait disturbance and functional disability.[3–5] Hence, leukoaraiosis is regarded as a significant brain lesion linking vascular risk factors and the occurrence of geriatric syndromes. Previous research on leukoaraiosis showed that women tended to have more white matter lesions than men,[6] and progression of deep white matter hyperintensity (DWMH) lesion was grater in women than men.[7] Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.[8] Recently, many studies have focused on the relationships between brain ischemia and inflammation. Above all, Hoshi *et al.* demonstrated that serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 levels correlated with silent brain infarction.[9] They suggested an involvement of inflammation in cerebral infarction. However, few studies have examined the relationships between inflammatory markers and other cerebral ischemic changes such as leukoaraiosis.Therefore, we investigated whether serum levels of hsCRP and IL-6 have a relationship with leukoaraiosis in elderly women.

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