$\geq$30 kg/m^2 is only 2.3% in men and 3.4% in women aged 20 years and older (Yoshiike et al. 2002), and the mean BMI was approximately 23 kg/m^2 for ages 15–84 years (Yoshiike et al. 1998). Inconsistency in the results of effects of variations in the *FTO* gene on BMI between Japanese and Europians may be due to the relatively small mean and variance of BMI in the former than the latter.

The significant SNPs were located in intron 1 of the *FTO* gene. The rs1558902 and other significant SNPs, for example, rs9939609 and rs1121980, would affect transcriptional activity of the *FTO* gene, although further investigation is necessary. The precise mechanism by which the *FTO* gene leads to obesity development is unclear (Gerken et al. 2007; Sanchez-Pulido et al. 2007). However, the *FTO* gene is expressed in the hypothalamus and regulated by fasting and leptin (Frayling et al. 2007; Gerken et al. 2007). Using large-scale case-control association studies, we determined that the *SCG3* (Tanabe et al. 2007) and *MTMR9* (Yanagiya et al. 2007) genes are involved in susceptibility to the obesity phenotype. These two genes are expressed in the hypothalamus. Genetic studies in mice have suggested that mutations in several genes, such as those encoding leptin, proopiomelanocortin, and melanocortin-4 receptor, are implicated in a monogenic form of inherited obesity (Barsh et al. 2000; Rankinen et al. 2006). Such mutations have also been reported in obese humans. As most such genes are expressed in the hypothalamus and have been indicated to play important roles in the regulation of food intake, genes expressed in the hypothalamus are likely to be good candidates for susceptibility to obesity.

In summary, we have identified the genetic variations in the *FTO* gene that may influence the risk of severe obesity in the Japanese.

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Original Article: Complications

Stratified analyses for selecting appropriate target patients with diabetic peripheral neuropathy for long-term treatment with an aldose reductase inhibitor, epalrestat

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Abstract

Aims The long-term efficacy of epalrestat, an aldose reductase inhibitor, in improving subjective symptoms and nerve function was comprehensively assessed to identify patients with diabetic peripheral neuropathy who responded to epalrestat treatment.

Methods Stratified analyses were conducted on data from patients in the Aldose Reductase Inhibitor—Diabetes Complications Trial (ADCT). The ADCT included patients with diabetic peripheral neuropathy, median motor nerve conduction velocity ≥ 40 m/s and with glycated haemoglobin (HbA_{1c}) ≤ 9.0%. Longitudinal data on HbA_{1c} and subjective symptoms of the patients for 3 years were analysed (epalrestat $n = 231$, control subjects $n = 273$). Stratified analyses based on background variables (glycaemic control, grades of retinopathy or proteinuria) were performed to examine the relationship between subjective symptoms and nerve function. Multiple logistic regression analyses were conducted.

Results Stratified subgroup analyses revealed significantly better efficacy of epalrestat in patients with good glycaemic control and less severe diabetic complications. In the control group, no improvement in nerve function was seen regardless of whether symptomatic benefit was obtained. In the epalrestat group, nerve function deteriorated less or improved in patients whose symptoms improved. The odds ratio of the efficacy of epalrestat vs. control subjects was approximately 2 : 1 (4 : 1 in patients with $HbA_{1c} \leq 7.0\%$).

Conclusion Our results suggest that epalrestat, an aldose reductase inhibitor, will provide a clinically significant means of preventing and treating diabetic neuropathy if used in appropriate patients.

Diabet. Med. 25, 818–825 (2008)

Keywords aldose reductase inhibitor, diabetic peripheral neuropathy, good condition of blood glucose level, polyol pathway

Abbreviations ADCT, Aldose Reductase Inhibitor—Diabetes Complications Trial; AEs, adverse events; ARI, aldose reductase inhibitor; HbA_{1c}, glycated haemoglobin; MFWL, minimum F-wave latency; MNCV, motor nerve conduction velocity; VAS, visual analogue scale; VPT, vibration perception threshold

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Introduction

Various drugs have been developed to treat diabetic neuropathy [1], including aldose reductase inhibitors (ARIs). ARIs suppress the activity of aldose reductase, a rate-limiting enzyme involved in the polyol pathway, which is enhanced in diabetic neuropathy. The effects of ARIs on diabetic neuropathy and diabetes-related complications have been investigated in animal and clinical studies [2,3]. Clinical efficacy of ARIs in diabetic neuropathy has been reported in terms of nerve function, subjective symptoms and histopathological findings of neural tissue [2–4]. Generally, parameters for nerve function, such as nerve conduction velocity and vibration perception threshold (VPT) are used as primary variables of efficacy of ARIs [5–9]. We previously reported the results of the 3-year Aldose Reductase Inhibitor—Diabetes Complications Trial (ADCT), which demonstrated the clinical efficacy of epalrestat, an ARI, in Japanese diabetic neuropathy patients with median motor nerve conduction velocity (MNCV) as the primary endpoint [10]. Stratified analyses of the ADCT data suggested that the effects of epalrestat on median MNCV were most evident in patients with better glycaemic control and without retinopathy or nephropathy [10].

Subjective symptoms may be more important to patients than nerve function. In ADCT, the efficacy of epalrestat was investigated by analysis of subjective symptoms such as numbness of upper and lower extremities, sensory abnormalities of lower extremities and cramp [10].

Here, we report additional analyses of ADCT data [10], in which stratified analyses of subjective symptoms were performed to identify patients likely to experience better responses to epalrestat. We determined the correlation between amelioration of subjective symptoms and nerve function to clarify the significance of ARIs in the treatment of neuropathy. Furthermore, we carried out logistic regression analysis using a comprehensive clinical assessment parameter based on nerve function and subjective symptoms and performed quantitative analysis of the efficacy of epalrestat adjusted for background variables.

Patients and methods

ADCT was conducted at 112 medical facilities in Japan between 1997 and 2003. The protocol was approved by the Institutional Review Board of each medical facility and all patients gave informed consent.

The ADCT methodology has been reported previously [10]. Patients had mild diabetic peripheral neuropathy based on subjective symptoms, no foot ulcers and neurological dysfunction [at least two parameters: MNCV (indispensable) and VPT or Achilles tendon reflex, etc.]. Patients were enrolled if they had a median MNCV ≥ 40 m/s (seemingly reversible) and stable glycaemic control [glycated haemoglobin (HbA_{1c}) ≤ 9.0%, with ± 0.5% variation in the previous 3 months]. Subjects were excluded if the primary cause of the neurological disorder was not diabetes (alcoholic neuropathy, carpal tunnel syndrome, sequelae of cerebrovascular disease, etc.), if they had peripheral arterial disease (ankle brachial pressure index of ≤ 0.8) or severe hepatic or renal disorder, if they were participating in other interventional studies, or if they were receiving other experimental medications for diabetic neuropathy, prostaglandin E_1 preparations or any other medication that affects symptoms of diabetic neuropathy. Patients were randomized to either the epalrestat or control groups; details of the randomization method were described previously [10]. Epalrestat (50 mg) was administered orally three times daily before each meal (150 mg/day). Both groups continued conventional therapy (diet treatment, oral glucose-lowering agents, insulin and anti-hypertensive agents). With the exception of rescue medication, new medication to aid neuropathy control was prohibited.

Study endpoints and measures of outcome

The primary endpoint was change from baseline to study end in median MNCV in the patient's non-dominant arm. This arm was chosen to avoid any bias as a result of possible lower limb impairment caused by the Japanese lifestyle (a tendency to sit straight). Secondary endpoints included changes from baseline to study end in minimum F-wave latency (MFWL) of the median motor nerve and VPT. VPT was measured using a 128-Hz tuning fork by measuring the time in seconds during which the patient felt vibrations. Changes of subjective symptoms of diabetic neuropathy were assessed using a 100-mm visual analogue scale (VAS). For a general measure of symptoms, the mean score was calculated for 10 symptoms (spontaneous pain in upper and lower extremities, numbness of upper and lower extremities, paraesthesia or hyperaesthesia of lower extremities, dizziness, cramp, coldness, abnormal sweating and constipation) and four symptoms in the lower extremities (spontaneous pain, numbness, paraesthesia or hyperaesthesia and cramp). The mean VAS of each symptom ranged from 20 to 30. The symptom score using in this study is the mean VAS of 10 symptoms per patient, although many values were zero. The mean symptom score at the beginning of the study in the control and epalrestat groups was 8.2 and 9.3, respectively.

The response to therapy was determined using a general assessment of subjective symptoms and nerve function. Patients were rated as responders if any of the following changes were observed over the 3-year study period: ≥ 1 m/s increase in median MNCV [11], ≥ 5% decrease in MFWL [12], ≥ 50% increase of time in VPT [13], or ≥ 50% decrease in the mean score for 10 symptoms [14].

Statistical analysis

As for ADCT [10], efficacy analyses were performed in patients who had data for at least 1 year, using the last-observation-carried-forward (LOCF) method [15,16].

Statistical methods included χ^2-tests for nominal scale, Mann–Whitney *U*-tests for ordered categorical scale, two-sample *t*-tests for comparison of mean values between groups and two-way repeated ANOVA for changes in glycaemic control. Multiple logistic regression analysis was conducted using the defined parameters of efficacy. Normalization for the multiplicity of stratified analyses was not performed. All analyses were carried out using SAS Version 8.02 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

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Table 1 Patient characteristics at baseline

Patient characteristics	Control ($n = 273$)	Epalrestat ($n = 231$)	*P*-value
Sex			
Male	161 (59.0)	132 (57.1)	
Female	112 (41.0)	99 (42.9)	0.678*
Age (years)	61.5 ± 9.0	61.0 ± 10.0	0.541†
Duration of diabetes (years)	12.5 ± 8.0	13.2 ± 9.1	0.408†
Duration of neuropathy (years)	3.3 ± 3.6	3.7 ± 4.9	0.363†
HbA_{1c}			
HbA_{1c} before and after treatment			
0 years	7.0 ± 0.1	7.2 ± 0.1	
3 years	7.2 ± 0.1	7.3 ± 0.1	0.122‡
Change over 3 years			
< 7.0%	71 (26.0)	51 (22.1)	
7.0% ≤ HbA_{1c} < 9.0%	156 (57.1)	141 (61.0)	0.470§
≥ 9.0%	46 (16.8)	39 (16.9)	

Data are means ± standard deviation (SD) or *n* (%).
P-values were calculated using *χ^2- tests, †two-sample *t*-test, ‡ANOVA and §Mann–Whitney *U*-test. Duration of neuropathy refers to the mean patient-reported duration of neuropathy symptoms.
HbA_{1c}, glycated haemoglobin.

Results

Patients

Patient clinical characteristics are provided in Table 1. There were no significant differences between the two groups.

In ADCT [10], the control and epalrestat groups included 305 and 289 patients, respectively. Of these, 31 and 55 patients withdrew after < 1 year, respectively; the reasons for withdrawal were a change in hospital (12 patients in each group), co-morbid illnesses (seven in each group), amelioration of symptoms (two epalrestat recipients), adverse events (20 epalrestat recipients), deterioration in symptoms (seven control subjects) or other (five control subjects, 14 epalrestat recipients). Both amelioration of symptoms and adverse events were observed only in the epalrestat group, resulting in a higher withdrawal rate in this group. Additionally, 59 and 53 patients had insufficient data for the primary efficacy analysis, primarily because of the unavailability of an electromyogram or a problem with the measuring technique. Thus, the primary efficacy analysis included 215 and 181 patients in the control and epalrestat groups, respectively.

This analysis included 273 patients in the control group and 231 patients in the epalrestat group, for whom data were available on symptom change and glycaemic control. The correlation between subjective symptoms and median MNCV was analysed in 214 patients in the control group and 179 patients in the epalrestat group.

Changes in glycaemic control

The changes in HbA_{1c} observed in the two treatment groups are shown in Table 1. No significant differences between epalrestat recipients and control subjects in glycaemic control were observed at baseline or over 3 years of treatment.

Stratified subgroup analyses of symptoms

Stratified subgroup analyses were performed to examine the relationship between changes in symptom score for 10 symptoms and glycaemic control, grade of retinopathy and grade of proteinuria (Fig. 1).

In both groups, the mean symptom score improved significantly from baseline at years 1, 2 and 3 (Fig. 1a). The improvement was most evident in the epalrestat group and differences between the two groups were significant at years 1, 2 and 3 ($P = 0.019$, $P = 0.002$ and $P = 0.009$, respectively; Fig. 1a).

HbA_{1c}

In patients with HbA_{1c} < 7.0%, the mean symptom score improved significantly in both groups at year 1, 2 and 3. The improvement was most evident with epalrestat and significant between-group differences were observed at years 1 and 2 ($P = 0.042$ and $P = 0.049$, respectively). In patients with HbA_{1c} ≥ 7.0% and < 9.0%, the control group showed significant improvement in the mean symptom score at year 1, whereas epalrestat recipients showed significant improvement at years 1, 2 and 3. Improvements in the mean symptom score were significantly greater with epalrestat than control at years 2 and 3 ($P = 0.009$ and $P = 0.027$, respectively). In patients with HbA_{1c} ≥ 9.0%, the control group showed no significant improvement in the mean symptom score at any time points, whereas the epalrestat group showed significant improvement at years 2 and 3. There were no significant between-group differences at any time points (Fig. 1a).

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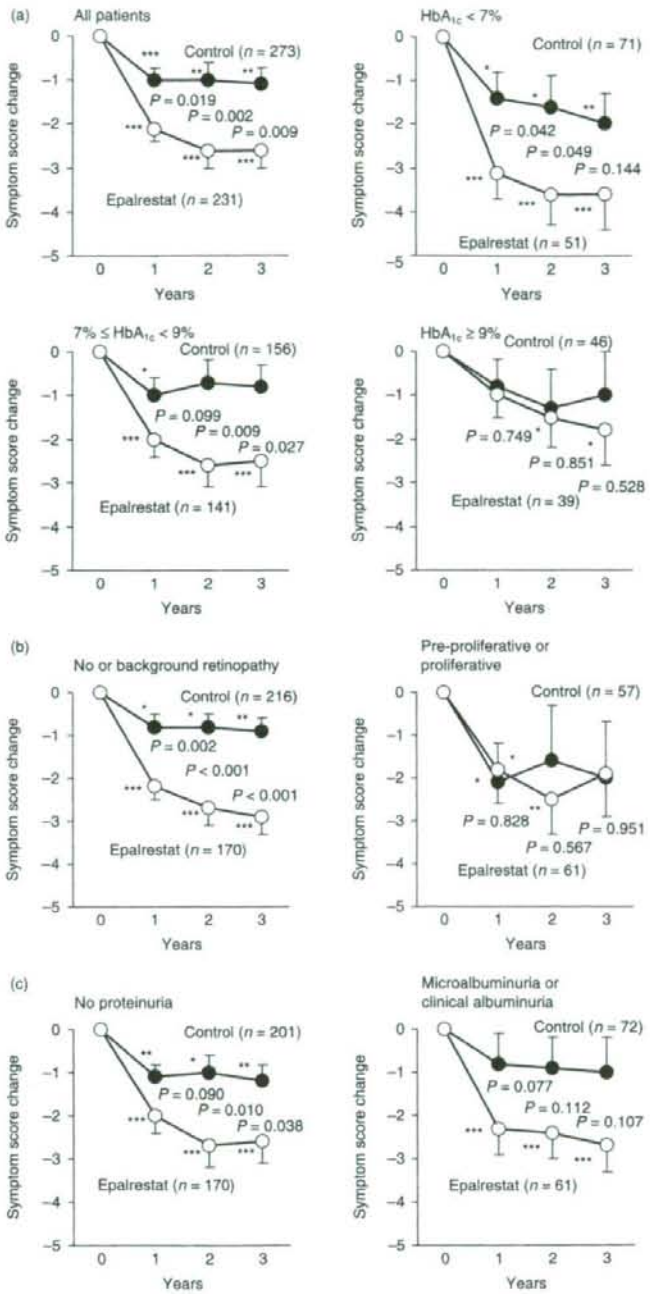

FIGURE 1 Effects of epalrestat on symptom score according to glycated haemoglobin (HbA_{1c}) over 3 years (a), baseline level of retinopathy (b) and baseline level of proteinuria (c). ○, epalrestat group; ●, control group. Data are reported as means ± standard error (SE). *P*-values were calculated using the two-sample *t*-test. $*P < 0.050$, $**P < 0.010$ and $***P < 0.001$ were calculated vs. baseline using the paired *t*-test. *P*-values are stated for between-group differences.

Grade of retinopathy

In patients with no or background retinopathy at baseline, the mean symptom score improved significantly in both groups at years 1, 2 and 3. The improvement was significantly greater in the epalrestat group at years 1, 2 and 3 ($P = 0.002$, $P < 0.001$ and $P < 0.001$, respectively). In patients with pre-proliferative or proliferative retinopathy, the control group showed significant improvement only at year 1, whereas the epalrestat group

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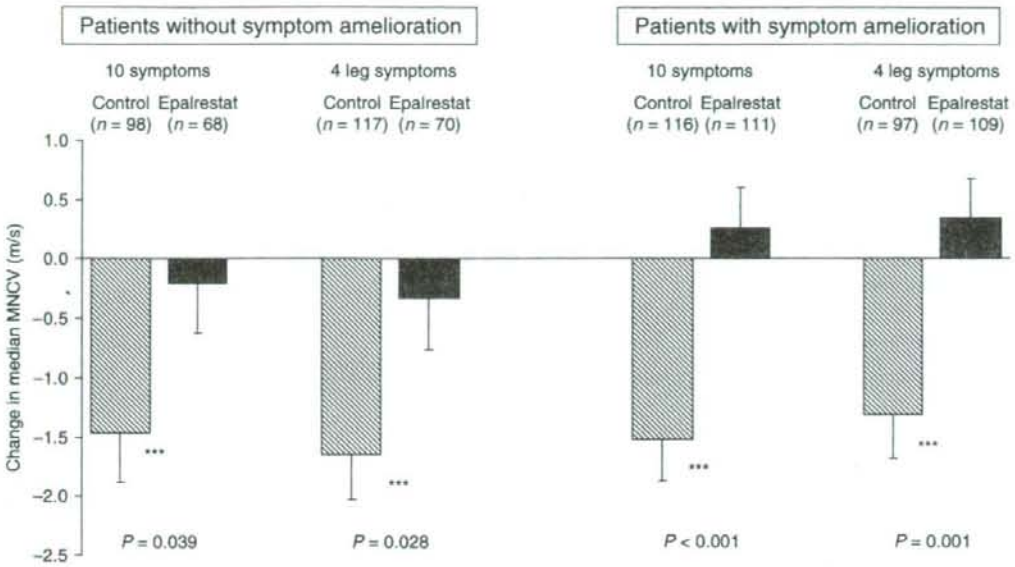

FIGURE 2 Amelioration of symptoms and change in median motor nerve conduction velocity (MNCV) after 3 years. Data are presented as mean ± SE. *P*-values were calculated vs. baseline using a two-sample *t*-test for inter-group comparisons and a paired *t*-test for intra-group comparisons. 10 symptoms: spontaneous pain of upper and lower extremities, numbness of upper and lower extremities, leg paraesthesia or hyperaesthesia, dizziness, cramp, coldness, abnormal sweating, constipation; four leg symptoms: spontaneous pain, numbness, paraesthesia or hyperasthesia, cramp. ***$P < 0.001$ vs. baseline. *P*-values are stated for between-group differences.

showed significant improvement at years 1 and 2; there were no significant between-group differences at any time points (Fig. 1b).

Grade of proteinuria

In patients with no proteinuria at baseline, the mean symptom score improved significantly in both groups at years 1, 2 and 3. The improvement was significantly greater with epalrestat at years 2 and 3 ($P = 0.010$ and $P = 0.038$, respectively). In patients who had microalbuminuria or clinical albuminuria at baseline, the epalrestat group showed significant improvement of the mean symptom score at years 1, 2 and 3, but the between-group differences were not statistically significant at any time points (Fig. 1c). The same trend was observed for four symptoms of the lower extremities (data not shown).

Correlation between subjective symptoms and median MNCV

Figure 2 shows changes from baseline in median MNCV according to symptom amelioration at year 3. In patients without improvement in the mean symptom score of 10 symptoms, deteriorations in median MNCV were -1.47 ± 0.41 m/s in the control group and -0.20 ± 0.42 m/s in the epalrestat group. Significantly less deterioration occurred in the epalrestat group ($P = 0.039$). In patients with improvement in the mean symptom score, median MNCV deteriorated by -1.52 ± 0.35 m/s in the control group and improved by 0.26 ± 0.34 m/s in the epalrestat group. Despite amelioration of symptoms, median MNCV deteriorated to a significantly greater extent in the control group than in the epalrestat group ($P < 0.001$). Furthermore, in the control group, median MNCV significantly deteriorated from baseline regardless of whether patients achieved symptom amelioration. As shown in Fig. 2, the same trend was observed for four symptoms of the lower extremities.

Quantitative analysis of efficacy

The odds ratios (ORs) for achievement of a response to epalrestat therapy, based on analysis of nerve function and symptoms, are depicted in Fig. 3. In the multiple logistic regression model (Model 1), which was adjusted for the duration of diabetes mellitus, baseline HbA_{1c}, HbA_{1c} over 3 years and grades of retinopathy and proteinuria, the OR for achievement of a response to epalrestat therapy was 1.90 [95% confidence interval (CI) 1.32–2.75, $P < 0.001$]. For Model 2, which was stratified by HbA_{1c} over 3 years, the OR of achieving a response to epalrestat therapy was 3.68 (95% CI 1.61–8.43, $P = 0.002$) for patients with $HbA_{1c} < 7.0\%$ and 1.65 (95% CI 1.03–2.64, $P = 0.036$) for those with $HbA_{1c} < 9.0\%$. In patients with $HbA_{1c} \geq 9.0\%$, the OR was 1.42; this value was not significant vs. the control group.

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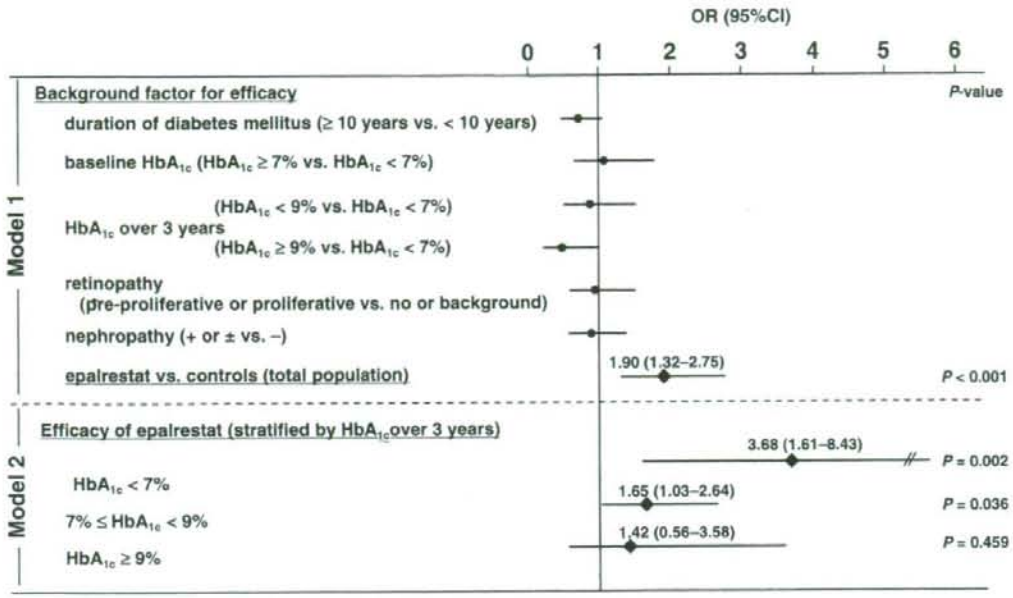

FIGURE 3 Logistic regression analysis analysing the efficacy of epalrestat vs. control. Efficacy analysis was based on a defined index, in which patients satisfying at least one of the following requirements during a 3-year period were classified as responders to treatment and odds ratios (ORs) were calculated: 1, ≥ 1 m/s increase in median motor nerve conduction velocity (MNCV); 2, ≥ 5% decrease in F-wave latency; 3, ≥ 50% increase of time in vibration perception threshold (VPT); 4, ≥ 50% decrease in the mean score of 10 symptoms.

Safety

In ADCT, 26 of 295 subjects (the epalrestat group, including six patients of major protocol deviations) reported adverse events (AEs; 8.8%); these occurred within the first year of treatment in 22 of the 26 subjects. AEs included hepatic function abnormalities (seven cases), gastrointestinal symptoms such as nausea and diarrhoea (eight cases), skin rash/eczema (two cases) and one case each of vertigo, light-headedness, dorsal pruritus, hot flushes, hand stiffness, weakness of a lower extremity, oedema in a lower extremity, thirst and cerebral infarction. There were no severe AEs and no AEs were thought to be directly related to the long-term administration of epalrestat.

Discussion

As it is not expected that cure of diabetes mellitus will be achieved, management of this condition focuses on maintaining long-term glycaemic control and reducing the occurrence and progression of diabetes-related complications, including diabetic neuropathy. If diabetic neuropathy symptoms deteriorate or persist, they can cause immeasurable mental and physical stress to patients [17]; serious complications such as ulcers or necrosis may culminate in amputation of an appendage [18]. Diabetic neuropathy is often associated with considerable mortality [19]. Therefore, it is of paramount importance to diagnose diabetic neuropathy immediately and provide an appropriate response to various risk factors [20,21] for the development and progression of diabetic neuropathy.

The first priority in the treatment of diabetic neuropathy is to maintain long-term glycaemic control. However, even when strict glycaemic control is achieved via traditional treatments, the occurrence and progression of diabetes-related complications remain unavoidable [22]. One important metabolic factor underlying diabetic neuropathy is an enhanced polyol pathway. Suppression of this pathway may be an important treatment strategy for diabetic neuropathy.

Diabetic neuropathy involves diverse symptoms such as spontaneous pain and numbness. Patients often complain of multiple symptoms. To determine distress in individual patients, numerous studies have calculated scores for multiple symptoms [14,23,24]. In this study, we conducted stratified analyses based on background variables, using the mean VAS score for 10 symptoms and the mean VAS score for four symptoms of lower extremities, with the aim of identifying patients expected to respond better to epalrestat therapy. The results indicated that achievement of symptom amelioration differed significantly between the epalrestat group and the control group for patients with HbA_{1c} < 7.0% or < 9.0%, with no or background retinopathy and no proteinuria. These results are consistent with those from stratified analyses on median MNCV

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reported previously [10] and provide evidence from both aspects of nerve function and subjective symptoms that epalrestat is more effective in patients with good glycaemic control and limited complications.

Moreover, in our analyses, patients continuing conventional therapy only (the control group) showed amelioration of symptoms and changes in glycaemic control, but with deterioration in median MNCV. This suggests that suppression of neuropathy progression is difficult to achieve with conventional therapy. In the epalrestat group, however, less deterioration or improvement in median MNCV were observed, regardless of whether patients achieved amelioration of symptoms. This suggests that epalrestat suppresses the enhanced polyol pathway, which is one of the important metabolic factors in the occurrence of diabetic neuropathy, and provides a useful option for treatment of diabetic neuropathy.

In diabetes mellitus, several reports have used multiple logistic regression analysis to determine treatment efficacy outcomes [25–27]. In this analysis, responders and non-responders to treatment were defined based on a general assessment of nerve function and subjective symptoms. Quantitative analysis of the efficacy of epalrestat, after adjustment for background variables, found that the OR was approximately 2 : 1 for the efficacy of epalrestat vs. control and 4 : 1 in patients with $HbA_{1c} < 7.0\%$. The results of our comprehensive assessment of subjective symptoms and nerve function show clinically significant benefit of epalrestat treatment, particularly in patients with good glycaemic control. Although the parameters used in this analysis are of limited applicability, and careful interpretation is required, these data are consistent with previous results from the stratified analyses of median MNCV in ADCT [10], which were quantitatively endorsed.

The existence of bias cannot be ruled out because of the open-label trial design. However, measurement of nerve function by the medical technologist and the assessment of the electromyogram by the specialist physician were carried out under blinded conditions and amelioration and/or deterioration in subjective symptoms were correlated with changes in nerve function in patients treated with epalrestat. Therefore, although the overall design of this study may have some limitations, we consider this bias to have been minimized.

Suppression of an enhanced polyol pathway, which has an important role in the aetiology of diabetic neuropathy, cannot be ignored. Therefore, in addition to improving glycaemic control, treatment with ARIs is expected to play a significant role in the management of diabetic neuropathy. This comprehensive study suggests that epalrestat, an ARI, provides clinically significant benefit in preventing and treating diabetic neuropathy if used in the appropriate patients.

Competing interests

None to declare.

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Reduction in the Recurrence of Stroke by Eicosapentaenoic Acid for Hypercholesterolemic Patients

Subanalysis of the JELIS Trial

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Background and Purpose—The JELIS trial examined the preventive effect of eicosapentaenoic acid (EPA) against coronary artery diseases. Hypercholesterolemic patients received statin only (no EPA group: n=9319) or statin with EPA (EPA group: n=9326) for around 5 years. EPA significantly suppressed the incidence of coronary events in previous analysis. Herein, we investigated the effects of EPA on the primary and secondary prevention of stroke.

Methods—We conducted a subanalysis of JELIS with respect to stroke incidence in the primary and secondary prevention subgroups defined as those without and with a prior history of stroke using Cox proportional hazard ratios, adjusted for baseline risk factor levels.

Results—As for primary prevention of stroke, this occurred in 114 (1.3%) of 8862 no EPA group and in 133 (1.5%) of 8841 EPA group. No statistically significant difference in total stroke incidence (Hazard Ratio, 1.08; 95% confidence interval, 0.95 to 1.22) was observed between the no EPA and the EPA groups. In the secondary prevention subgroup, stroke occurred in 48 (10.5%) of 457 no EPA group and in 33 (6.8%) of 485 EPA group, showing a 20% relative reduction in recurrent stroke in the EPA group (Hazard Ratio, 0.80; 95% confidence interval, 0.64 to 0.997).

Conclusions—Administration of highly purified EPA appeared to reduce the risk of recurrent stroke in a Japanese population of hypercholesterolemic patients receiving low-dose statin therapy. Further research is needed to determine whether similar benefits are found in other populations with lower levels of fish intake. The trial is registered at ClinicalTrials.gov (number NCT00231738). (***Stroke*. 2008;39:2052-2058.)**

Key Words: JELIS ■ EPA ■ stroke ■ clinical trial ■ prevention

Prevention of stroke is a major issue in modern medicine. In the United States, stroke affects more than 700 000 new patients and claims more than 160 000 lives each year, whereas 4.8 million patients suffer from sequelae.[1] In addition, the cost of treatment for stroke reached $53.6 billion in 2004.[1] In Japan, the rate of mortality attributable to stroke is more than twice for men and 1.5-fold for women than those in the United States. Thus, the problem of stroke prevention is also recognized as a national issue in Japan.[2] In comparison to cardiac events, stroke has a higher tendency to leave sequelae and requires long-term rehabilitation and care, and is thus associated with key problems such as increased family burden and medical costs. Although the predominant risk factor for stroke is hypertension,[3] other risk factors exist such as diabetes,[4] hypercholesterolemia,[5–7] smoking,[8] nonvalvular atrial fibrillation,[9] and heavy drinking.[10]

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Medical therapies for preventing stroke, which include antihypertensive, antiplatelet, anticoagulant, and antihyperlipidemic therapies, have been supported by increasing evidence. In particular, in antihyperlipidemic therapy, statins have been found useful to prevent stroke in hyperlipidemic patients with coronary artery disease[11,12]; besides, high dose atorvastatin reduced the risk of stroke in patients with cerebrovascular disease.[13]

In addition, various cohort studies have found that increased fish intake was associated with a lower risk of stroke. In a meta-analysis by He et al, those who ate fish at least once a week had a significantly lower risk of stroke than subjects who ate fish less than once a month.[14] However, the effects of fish or fish oil have not been conclusively determined in randomized controlled trials; whereas Schacky et al[15] showed a lower incidence of stroke, Marchioli et al[16,17] (the GISSI-Prevenzione trial) showed a 22% increase in risk of stroke in the ω3 polyunsaturated fatty acids group, although neither finding was statistically significant.

We have previously reported that in a large prospective clinical controlled trial (JELIS)[18] in which highly purified EPA was given to Japanese hypercholesterolemic patients, EPA significantly reduced coronary events (the primary end point), during the 4.6-year mean observation period in subjects receiving low-dose statin therapy and at the start of the study presumably having higher intake of fish compared to those having a Western style diet judging from their plasma EPA concentration. Herein, we investigated the effects of EPA on the risk of stroke separately for those without a history of stroke (primary prevention) and those with a history of stroke (secondary prevention) at baseline.

Materials and Methods

Study Design and Patients

JELIS was a prospective randomized open-label, blinded end point trial. Stroke was a secondary outcome in the study design of JELIS.[19] The inclusion criteria were hypercholesterolemic patients with serum total cholesterol of 6.5 mmol/L or higher (men aged over 40 to 70 years, women after menopause to 75 years). The exclusion criteria were acute myocardial infarction within the last 6 months, unstable angina pectoris, a history of or complication by serious heart disease (severe arrhythmia, heart failure, primary or secondary cardiac myopathy, valvular heart diseases, congenital heart diseases, etc), cardiovascular reconstruction within the last 6 months, cerebrovascular disorder occurring within the last 6 months, serious hepatic or renal disease, malignant tumor, uncontrollable diabetes mellitus, hyperlipidemia associated with effect of drug such as steroid hormone, hemorrhage (hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage, etc), hemorrhagic diathesis, hypersensitivity to the study drug formulation, planned surgery, or other condition judged inappropriate for inclusion in the study by the physician in charge. The study design as well as the inclusion and exclusion criteria were described in detail elsewhere.[19]

Hypercholesterolemic patients (total cholesterol 6.5 mmol/L or higher) who gave informed consent were randomly assigned to receive EPA with statin (EPA group) or statin alone (no EPA group). A washout period of 4 to 8 weeks of antihyperlipidemic drug was set. All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily. EPA was given at a dose of 1800 mg per day using 300-mg capsules of highly purified (>98%) EPA ethyl ester.

Blood samples were collected to measure serum lipid and plasma total fatty acid concentrations at 6 and 12 months, and then every year during the 5-year follow-up period. Baseline characteristics were collected from self-reports which were written by the study physicians.

Assessment of Stroke Occurrence

Stroke events were reported by the study physicians and assessed using all available computed tomography and MRI data by the regional patient review committee, which was blinded to group allocation. In addition, the final assessment was performed annually by an end point adjudication committee comprised of 3 cardiovascular specialists and one neurologist. The criteria of stroke were similar to the classification of cerebrovascular disease III proposed by National Institute of Neurological Disorders and Stroke.[20]

Fatty Acids Analysis

Serum fatty acid composition was determined by capillary gas chromatography at BML General Laboratory. Briefly, plasma lipids were extracted by the Folch procedure, and then fatty acids (tricosanoic acid, C23:0, as internal standard) were methylated with boron trifluoride and methanol. Methylated fatty acids were then analyzed using a gas chromatograph (GC-17A, Shimazu Corporation) and a BPX70 capillary column (0.25 mm ID×30 m, SGE International Ltd).

Statistical Analysis

We performed a subanalysis concerning stroke on the primary and secondary prevention subgroups. For the recurrence of stroke, this study held a power of 83% under the assumption that the EPA group would show a hazard ratio of 0.82 over the control group. For the initial occurrence of stroke, this study held a power of 92% under the assumption of a hazard ratio of 0.95.

All tests were intention-to-treat analyses with the level of significance set at $P<0.05$ (2-sided). The Wilcoxon 2-sample test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables. For continuous variables to show the change from baseline to follow up, a relative change from baseline was computed. Time-to-event data were analyzed using the Kaplan–Meier method and log-rank tests. Hazard ratios and their 95% confidence intervals were calculated using the Cox proportional hazard model. For the Cox hazard analysis of the primary and secondary prevention subgroups, the following adjustment factors were used: age, sex, smoking, diabetes, and hypertension. We tested for interactions using a model that included an interaction term corresponding to the test for heterogeneity in effects. Statistical analyses were performed using version 5.0.1a of the JMP statistical software program (SAS Institute Inc).

Results

Patient Population

Table 1 shows background data for enrolled patients after randomization, specifically blood pressure, serum lipid level, and plasma fatty acid level. Among all patients randomized to the no EPA (n=9319) and EPA (n=9326) groups, a total of 457 patients in the no EPA group and 485 patients in the EPA group had a history of stroke, whereas 8862 patients in the no EPA group and 8841 patients in the EPA group did not (Table 1). At baseline in the primary prevention subgroup, the rate of smokers, mean of high density lipoprotein cholesterol, EPA concentration, and EPA/AA ratio were significantly higher in the EPA group than in the no EPA group. The rate of coronary heart disease was significantly lower in the EPA group than in the no EPA group at baseline in the secondary prevention subgroup. In the secondary prevention subgroup, ischemic stroke accounted for ≥60% of stroke cases. Table 2 shows serum lipid level, plasma fatty acid level, and blood pressure at the baseline and during the observation period. Low density lipoprotein cholesterol decreased to 3.54 mmol/L

Table 1. Baseline Characteristics of Patients

	Primary Prevention Subgroup			Secondary Prevention Subgroup		
	No EPA Group n=8862	EPA Group n=8841	*P* Value	No EPA Group n=457	EPA Group n=485	*P* Value
Age, y	60±9	61±8	0.105	65±7	66±7	0.537
Male	2728 (31%)	2762 (31%)	0.510	180 (39%)	189 (39%)	0.895
Smoker	1621 (18%)	1739 (20%)	0.019	79 (17%)	91 (19%)	0.556
BMI, kg/m^2	24±3	24±3	0.929	24±3	24±3	0.516
Diabetes	1412 (16%)	1406 (16%)	0.957	112 (25%)	110 (23%)	0.509
Hypertension	3030 (34%)	3085 (35%)	0.333	252 (55%)	244 (50%)	0.138
Coronary artery disease	1705 (19%)	1714 (19%)	0.804	136 (30%)	109 (22%)	0.011
Stroke				457	485	
Cerebral thrombosis				232 (51%)	235 (48%)	0.478
Cerebral embolism				68 (15%)	82 (17%)	0.395
TIA				41 (9%)	45 (9%)	0.871
Cerebral hemorrhage				38 (8%)	42 (9%)	0.850
Subarachnoid hemorrhage				19 (4%)	19 (4%)	0.852
Unknown				59 (13%)	62 (13%)	0.954
Total cholesterol, mmol/L	7.11±0.68	7.11±0.68	0.758	7.06±0.62	7.03±0.57	0.971
LDL cholesterol, mmol/L	4.70±0.75	4.70±0.77	0.302	4.65±0.65	4.65±0.65	0.928
HDL cholesterol, mmol/L	1.51±0.44	1.52±0.46	0.014	1.51±0.55	1.51±0.44	0.928
Triglyceride, mmol/L	1.73 (1.23–2.49)	1.73 (1.23–2.48)	0.123	1.80 (1.37–2.48)	1.80 (1.30–2.44)	0.980
AA, mol%	4.8±1.1	4.7±1.1	0.933	4.7±1.0	4.7±1.2	0.753
EPA, mol%	2.7±1.5	2.9±1.6	<0.0001	2.8±1.7	2.8±1.6	0.763
EPA/AA ratio	0.60±0.34	0.63±0.37	<0.0001	0.63±0.40	0.63±0.40	0.884
SBP, mm Hg	135±21	135±21	0.647	139±22	139±25	0.546
DBP, mm Hg	79±13	79±13	0.134	79±13	80±15	0.295
Antiplatelet agents	1121 (13%)	1053 (12%)	0.134	221 (48%)	205 (42%)	0.061
Antihypertensive agents	3579 (40%)	3499 (40%)	0.272	294 (64%)	298 (61%)	0.396

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; AA, arachidonic acid; EPA, eicosapentaenoic acid.

Values for age, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, SBP, DBP, AA, EPA, and EPA/AA ratio represent the mean±standard deviation. Triglyceride values represent the median (interquartile range).

P values are for the differences between the no EPA and EPA groups.

(−23.6% decrease from baseline) in the no EPA group and to 3.54 mmol/L (−23.3%) in the EPA group of the primary prevention subgroup; it decreased to 3.36 mmol/L (−26.7%) in the no EPA group and to 3.38 mmol/L (−25.8%) in the EPA group of the secondary prevention subgroup. There was no significant difference in the low density lipoprotein cholesterol level between the no EPA and EPA groups of the primary (P=0.493) and secondary prevention (P=0.602) subgroups. The level of triglycerides was significantly reduced by EPA treatment in both subgroups.

Stroke Incidence

In the primary prevention subgroup, stroke occurred in 114 (1.3%) of the 8862 patients in the no EPA group and in 133 (1.5%) of the 8841 patients in the EPA group. EPA had no preventive effect on total stroke, Hazard Ratio (95% confidence interval) of 1.08 (0.95 to 1.22). In addition, no statistically significant intergroup differences were observed for the risks of the following (Table 3, Figure, a): cerebral thrombosis, cerebral embolism, transient ischemic attack, undetermined cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. In the secondary prevention subgroup, stroke recurred in 48 (10.5%) of the 457 patients in the no EPA group and in 33 (6.8%) of the 485 patients in the EPA group. A significant reduction of 20% in the recurrence of stroke in the EPA group was observed (Hazard Ratio, 0.80; 95% confidence interval, 0.64 to 0.997; Table 3, Figure, b). In addition, number needed to treat was 27. Furthermore, no statistically significant intergroup differences were observed for the risks of the following (Table 3): cerebral thrombosis, cerebral embolism, transient ischemic attack, undetermined cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. But there was a borderline significant reduction in cerebral thrombosis. In addition, no interactions between the EPA and the no EPA groups were observed with regard to the recurrence of stroke for age, sex, diabetes, hypertension, smoking, low density lipoprotein cholesterol levels, and systolic blood pressure levels during the observation period.

Discussion

In the present study, in which occurrence and recurrence of stroke among hypercholesterolemic patients in the JELIS

Table 2. Selected Parameters During the Observation Period

	No EPA Group			EPA Group			
	Baseline	Observation Period	% Change From Baseline	Baseline	Observation Period	% Change From Baseline	*P* Value*
Primary prevention subgroup							
Total cholesterol, mmol/L	7.11±0.68	5.89±0.78	−17.0	7.11±0.68	5.84±0.80	−17.6	<0.0001
LDL cholesterol, mmol/L	4.70±0.75	3.54±0.75	−23.6	4.70±0.77	3.54±0.77	−23.3	0.493
HDL cholesterol, mmol/L	1.51±0.44	1.54±0.39	4.5	1.52±0.46	1.54±0.39	3.3	0.836
Triglyceride, mmol/L	1.73 (1.23–2.49)	1.57 (1.17–2.13)	−2.6	1.73 (1.23–2.48)	1.47 (1.09–2.01)	−7.3	<0.0001
AA, mol%	4.8±1.1	5.0±1.0	7.3	4.7±1.1	4.6±0.9	−0.4	<0.0001
EPA, mol%	2.7±1.5	2.9±1.4	20.2	2.9±1.6	5.3±2.3	126.1	0.0000
EPA/AA ratio	0.60±0.34	0.60±0.32	14.4	0.63±0.37	1.21±0.59	136.1	0.0000
SBP, mm Hg	135±21	133±13	−0.7	135±21	133±14	−0.7	0.575
DBP, mm Hg	79±13	78±8	−1.2	79±13	78±8	−1.0	0.986
Secondary prevention subgroup							
Total cholesterol, mmol/L	7.06±0.62	5.69±0.75	−19.3	7.03±0.57	5.64±0.75	−20.0	0.208
LDL cholesterol, mmol/L	4.65±0.65	3.36±0.67	−26.7	4.65±0.65	3.38±0.70	−25.8	0.602
HDL cholesterol, mmol/L	1.51±0.55	1.51±0.39	3.1	1.51±0.44	1.48±0.70	1.8	0.882
Triglyceride, mmol/L	1.80 (1.37–2.48)	1.61 (1.21–2.18)	−4.4	1.80 (1.30–2.44)	1.44 (1.10–1.89)	−12.9	<0.001
AA, mol%	4.7±1.0	5.0±1.0	8.2	4.7±1.2	4.6±0.9	−1.4	<0.0001
EPA, mol%	2.8±1.7	2.8±1.5	15.0	2.8±1.6	5.9±2.3	163.3	<0.0001
EPA/AA ratio	0.63±0.40	0.61±0.36	8.5	0.63±0.40	1.36±0.62	180.9	<0.0001
SBP, mm Hg	139±22	138±14	0.0	139±25	138±15	−0.9	0.607
DBP, mm Hg	79±13	78±8	−0.2	80±15	78±9	−1.0	0.538

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; AA, arachidonic acid; EPA, eicosapentaenoic acid.

Values for total cholesterol, LDL cholesterol, HDL cholesterol, SBP, DBP, AA, EPA, and EPA/AA ratio represent the mean±standard deviation. Triglyceride values represent the median (interquartile range).

P value are for the difference between the no EPA and EPA groups in the observation period.

were analyzed by classifying patients into groups with and without a history of stroke, the preventive effect of EPA on recurrence of stroke was observed. No prospective studies on the preventive effects of fish and fish oil on recurrence of stroke in patients have been reported to date. Incidence of stroke events during the 4.6-year mean observation period was 1.3% in the no EPA group and 1.5% in the EPA group among patients without a history of stroke and 10.5% in the

Table 3. Incidence of Stroke and Cox Hazard Ratio for Stroke

	No EPA Group No. of Events (%)	EPA Group No. of Events (%)	HR, 95% CI	*P* Value
Primary prevention subgroup				
Total stroke	114 (1.3%)	133 (1.5%)	1.08 (0.95–1.22)	0.244
Cerebral thrombosis	41 (0.5%)	36 (0.4%)	0.93 (0.74–1.17)	0.548
Cerebral embolism	13 (0.1%)	11 (0.1%)	0.91 (0.60–1.36)	0.634
TIA	13 (0.1%)	9 (0.1%)	0.82 (0.53–1.25)	0.357
Undetermined cerebral infarction	20 (0.2%)	34 (0.4%)	1.30 (0.99–1.73)	0.057
Cerebral hemorrhage	18 (0.2%)	28 (0.3%)	1.25 (0.93–1.70)	0.129
Subarachnoid hemorrhage	12 (0.1%)	16 (0.2%)	1.15 (0.80–1.70)	0.448
Other cerebrovascular events (details unknown)	4 (0.0%)	2 (0.0%)	0.70 (0.26–1.60)	0.405
Secondary prevention subgroup				
Total stroke	48 (10.5%)	33 (6.8%)	0.80 (0.64–0.997)	0.047
Cerebral thrombosis	23 (5.0%)	13 (2.7%)	0.72 (0.50–1.00)	0.052
Cerebral embolism	2 (0.4%)	6 (1.2%)	1.65 (0.79–4.31)	0.190
TIA	1 (0.2%)	2 (0.4%)	1.45 (0.45–6.73)	0.536
Undetermined cerebral infarction	13 (2.8%)	7 (1.4%)	0.71 (0.44–1.12)	0.140
Cerebral hemorrhage	7 (1.5%)	4 (0.8%)	0.77 (0.39–1.40)	0.390
Subarachnoid hemorrhage	2 (0.4%)	1 (0.2%)	0.69 (0.15–2.23)	0.528
Other cerebrovascular events (details unknown)	1 (0.2%)	0 (0.0%)	...	...

Primary and secondary prevention subgroups; adjusted for age, gender, hypertension, diabetes mellitus, and smoking.

HR indicates hazard ratio; 95% CI, 95% confidence interval; TIA, transient ischemic attack.

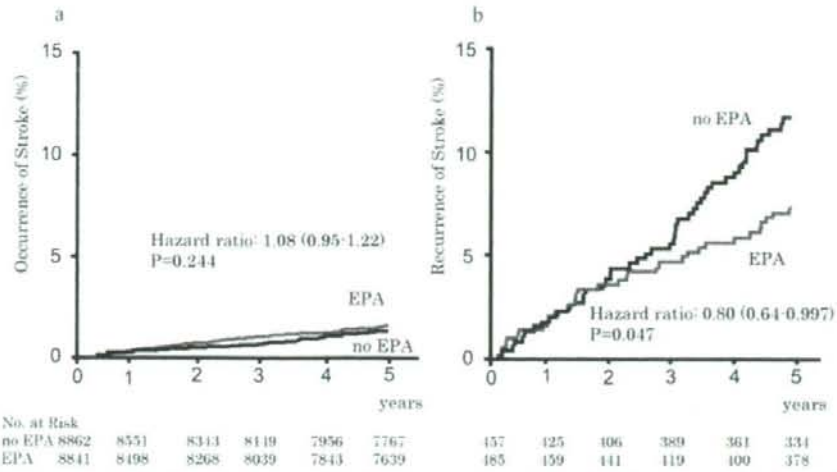

Figure. Kaplan–Meier Curves for stroke in the primary prevention subgroup (a) and the secondary prevention subgroup (b), adjusted for age, gender, hypertension, diabetes mellitus, and smoking.

no EPA group and 6.8% in the EPA group among patients with a history of stroke, indicating a 5- to 8-fold higher incidence among patients with a history of stroke. We have already reported the finding that EPA reduced coronary events in the primary end point analysis of the JELIS.[18] Analysis of stroke as an end point demonstrated the aforementioned effects of EPA on recurrence, particularly of ischemic events, among patients with a history of stroke, who have a high recurrence rate.

The Nurses' Health Study, a cohort study that investigated the relationship between fish intake and stroke, showed that fish intake reduces ischemic events,[21] a finding that is consistent with our results. The Nurses' Health Study also reported that fish intake significantly reduced incidence of lacunar infarction among ischemic events, and that similar results were obtained in terms of ω3 polyunsaturated fatty acids intake.[21] Taken together, these 2 studies suggest that EPA may reduce the risk of thrombotic infarction. However, because the clinical categories of thrombotic infarction (lacunar or atherothrombotic infarction) had not been determined in the JELIS, the type of disease affected by EPA could not be specified based on the present results.

Because we used highly purified EPA rather than fish oil, which contains many fatty acids other than EPA, the present study differs from previous studies that used fish or fish oil in that the preventive effects on stroke can be attributed to EPA. In addition, because EPA possesses a diverse range of pharmacological actions including antihyperlipidemic,[22] antiplatelet,[23,24] antiinflammatory,[25,26] and antiarrhythmic[27] properties, the reduction in risk of ischemic events may be related to multiple properties. Possible mechanisms of action for the reduction of ischemic events by EPA are described below. In a randomized controlled trial, administration of fish oil to patients awaiting carotid endarterectomy resulted in plaque regression as well as increases in EPA and DHA within plaque and reduction in macrophage count.[28] In addition, ω3 polyunsaturated fatty acids reduce the expression of adhesion molecules on endothelial cell[29] and macrophage,[30] and EPA decrease foam cell size and increase collagen fibers in fibrous caps in a plaque model.[31] Macrophage infiltration is an important factor in plaque inflammation and destabilization. These effects of EPA on atherosclerotic tissue were thought to have led to inhibition of the progression of vascular pathogenesis in atherosclerotic cerebral thrombosis. In addition, EPA may have directly acted on platelets and inhibited platelet aggregation and thrombus formation at the affected region. Furthermore, other effects of EPA, including vasodilation,[32] reduction of blood viscosity,[33] and enhancement of red cell deformability,[34] may have contributed to reduction of the risk of lacunar infarction by improving cerebral microcirculation.

In a recent study, recurrence of stroke was reduced by a potent low-density lipoprotein cholesterol lowering therapy using atorvastatin.[13] Lowering of low-density lipoprotein cholesterol was effective to some degree for preventing recurrence of stroke. However, because no differences in low-density lipoprotein cholesterol level were observed between the no EPA and the EPA groups during the study period in the present study, the effects of EPA were unlikely to have been mediated by reductions in low density lipoprotein cholesterol. In addition, no effects were observed on systolic blood pressure and diastolic blood pressure during the study period. Reduction of triglycerides by EPA treatment was significant but limited, 0.17 mmol/L, compared to the no EPA group in the secondary prevention subgroup. Therefore, EPA administration was thought to be a new therapeutic option for preventing recurrence among hypercholesterolemic patients with a history of stroke.

The EPA concentration among Japanese individuals, given as the EPA concentration in the no EPA group of the JELIS in secondary prevention group, was 2.8 mol%, which was approximately 10-fold higher than that of white Americans.[24] In the secondary prevention subgroup, plasma EPA concen-

trations during the observation period were more than 2 times higher in the EPA group (5.9 mol%) compared to the no EPA group. This suggests that even among Japanese individuals, who have relatively high plasma EPA concentrations, further increases in EPA concentration may lead to prevention of recurrence of stroke. Meanwhile, in the primary prevention subgroup, there were more hemorrhagic stroke and undetermined cerebral infarctions in the EPA group, although the difference was not significant. No such signal occurred in secondary prevention subgroup, but sample size was much smaller. Further study is needed regarding cerebral hemorrhage in patients with a history of stroke treated with EPA.

Limitations of this study were its open-label design and the mean low density lipoprotein cholesterol value of 4.65 mmol/L, which was higher than the current treatment target, during the observation period.

Conclusion

EPA could be a therapeutic option for preventing recurrence of stroke in Japanese hypercholesterolemic patients in whom low density lipoprotein cholesterol is suboptimally treated. Further research is needed to replicate these findings and to determine whether EPA is of benefit in populations with lower levels of fish intake and more optimally managed risk factors.

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Disclosures

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Relationship Between Coronary Events and Serum Cholesterol During 10 Years of Low-Dose Simvastatin Therapy

Long-Term Efficacy and Safety in Japanese Patients With Hypercholesterolemia in the Japan Lipid Intervention Trial (J-LIT) Extension 10 Study, a Prospective Large-Scale Observational Cohort Study

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Background Because many Japanese patients with hypercholesterolemia have received statin therapy for nearly a decade, there was a need to investigate the benefit of long-term treatment. The Japan Lipid Intervention Trial (J-LIT) Extension 10 study was planned to continue the original J-LIT study for a total of 10 years.

Methods and Results All 51,321 patients (including 19,905 who agreed to continue the study) were analyzed. Low-dose treatment with simvastatin (mainly 5 mg/day) was continued throughout the study period and serum lipid levels were well controlled over 10 years. Incidence of adverse drug reactions during the 4-year extension period was lower than previously. Serum total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglyceride levels showed a positive correlation with the risk of coronary events, whereas high-density lipoprotein-cholesterol showed an inverse correlation. Patients with an LDL-C level ≥140 mg/dl had a far higher risk of coronary events than those with a level <100 mg/dl.

Conclusions Long-term, low-dose simvastatin therapy was safe and effective in Japanese patients with hypercholesterolemia. Serum LDL-C levels should be <140 mg/dl to decrease coronary risk and a low cholesterol level should be maintained for as long as possible. (*Circ J* 2008; **72:** 1218–1224)

Key Words: Cholesterol-lowering therapy; Coronary heart disease; Efficacy; Safety; Simvastatin

In the early 1990s, the relationship between the serum cholesterol level and the occurrence of coronary heart disease (CHD) in Japanese patients with hypercholesterolemia had not yet been established by large-scale clinical studies. At that time, statins had just become available in Japan for the treatment of hypercholesterolemia. Accordingly, we planned the Japan Lipid Intervention Trial (J-LIT) study[1] a prospective large-scale and long-term nationwide cohort study that was designed to examine the effect on serum lipids and the safety of long-term, low-dose simvastatin therapy, as well as the relationship between lipid levels and CHD in Japanese patients with hypercholesterolemia. The J-LIT study was completed in 1999, demonstrating that low-dose simvastatin therapy was safe and effective, and we have already reported on the relationship between lipid levels and CHD during long-term lipid-lowering therapy[2–4]

The J-LIT study was a 6-year, observational cohort study that enrolled 51,321 patients for open-label treatment with simvastatin (5–10 mg/day). It showed that cholesterol-lowering therapy with simvastatin was effective at controlling lipid levels for 6 years in Japanese patients with hypercholesterolemia and only caused a low incidence of adverse drug reactions (ADRs)[4] The results obtained in the primary prevention cohort also suggested that the target lipid levels during low-dose simvastatin therapy should be <240 mg/dl for total cholesterol (TC), <160 mg/dl for low-density lipoprotein-cholesterol (LDL-C), <300 mg/dl for triglycerides (TG), and ≥40 mg/dl for high-density lipoprotein-cholesterol (HDL-C) to prevent coronary events[2] A similar relationship between serum lipids and coronary events was also found in the secondary prevention cohort[3] In the sub-analysis of the influence on stroke, improvement of lipid levels was shown to be more important for reducing the incidence of cerebral infarction and had less effect on cerebral hemorrhage[5] In patients with diabetes mellitus (DM) and hypercholesterolemia, only strict lipid-lowering therapy was able to prevent coronary events in addition to careful manage-

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ment of their diabetes[6] In hypertensive patients with hypercholesterolemia, blood pressure needs to be tightly controlled to prevent both coronary events and stroke, and serum cholesterol should be also maintained at a low level[7,8]

However, some issues related to the management of hypercholesterolemia require a longer observation period. Once the treatment of hypercholesterolemia is started, lipid-lowering therapy is life-long for most patients. Therefore, it is necessary to evaluate the effect of simvastatin on the lipid profile and its safety over a longer period than 6 years. It also remains unclear what the target serum cholesterol level should be and how long it should be maintained for the prevention of coronary events. In order to confirm the results of the J-LIT study and to find answers to these other questions, we conducted the J-LIT Extension 10 study, in which the patients from the J-LIT study were treated with low-dose simvastatin for an additional 4 years.

We examined the efficacy and safety of low-dose simvastatin therapy, as well as the relationship between serum lipid levels and CHD, over a period of 10 years. This is the first report on the efficacy and safety of statin therapy, as well as the risk of CHD, for Japanese patients with hypercholesterolemia to be based on a large-scale cohort study performed over such a long period.

Methods

Subjects

In the J-LIT study, 51,321 Japanese patients with hypercholesterolemia (men aged 35–70 years and postmenopausal women <70 years old) with a serum TC level ≥220 mg/dl were enrolled during 1992 and 1993. Among those patients, a total of 19,905 patients who agreed to continue the study were followed up for an additional 4-year extension period. We also used all 51,321 patients for analysis.

Study Design

The J-LIT Extension 10 study consisted of the 6-year J-LIT study period[1] and an additional 4-year extension period. The study design was essentially the same for both periods. Patients received open-label simvastatin therapy at a dose of 5–10 mg/day and all patients (including those who discontinued simvastatin for any reason) were monitored for a total of 10 years. Lipid levels, adverse events, and CHD-related events were recorded. Diet and exercise therapy for dyslipidemia were modified by the investigators as needed. No restrictions were placed on the treatment of complications.

The primary endpoint was major adverse coronary events, including acute myocardial infarction and sudden cardiac death. The secondary endpoint was death from any cause (all-cause death). All coronary events during the study period were assessed by the Endpoint Classification Committee. ADRs were evaluated by the Adverse Event Subcommittee. Before enrollment, each patient was informed of the purpose and methods of the study, as well as the effects and possible risks of simvastatin therapy, their right to withdraw from the study at any time, and the measures taken for protection of privacy.

Statistical Analysis

All data were analyzed, including any information obtained after cessation of simvastatin therapy. However, lipid levels measured after the occurrence of diseases other than those of the primary or secondary endpoint were excluded.

Table 1 Baseline Characteristics of Patients in the J-LIT Extension 10 Study

	Initial study (6 years) (n=51,321)	*Extension study (10 years) (n=19,905)*
Age (years)	*57.9±7.9*	*58.2±7.6*
Male (%)	*33.2*	*30.8*
History of CHD (%)	*9.8*	*9.0*
Hypertension (%)	*45.2*	*47.1*
Diabetes mellitus (%)	*15.3*	*13.5*
Obesity (%)	*34.1*	*34.1*
Smoking (%)	*16.8*	*15.5*
Alcohol consumption (%)	*29.4*	*27.9*
Baseline serum lipid levels		
TC (mg/dl)	*269.3±33.9*	*269.1±34.9*
LDL-C (mg/dl)	*182.0±33.4*	*182.3±32.6*
TG (mg/dl)	*196.2±169.4*	*191.0±150.5*
HDL-C (mg/dl)	*52.6±15.1*	*52.9±14.8*

Data are mean±SD.
J-LIT, Japan Lipid Intervention Trial; CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol.
Obesity = body mass index ≥25 kg/m².

Patients were classified into 3–6 subgroups based on their average lipid levels during treatment. TC, LDL-C, TG and HDL-C levels were classified into discrete bands of 20, 20, 150 and 10 mg/dl, respectively. Reference categories were set for the subgroups according to the lowest ranges (<180 mg/dl for TC, <150 mg/dl for TG, <100 mg/dl for LDL-C, and <40 mg/dl for HDL-C). We then calculated the relative risk and 95% confidence interval for each endpoint of each subgroup relative to the reference category, using a Cox proportional-hazards model with adjustment for sex, baseline age (as a continuous variable), hypertension, DM, and smoking. Comparison of the incidence of ADRs in the Initial study and in the Extension study were calculated by chi-square test. Results are expressed as the mean±SD. For all statistical analyses, $p<0.05$ was considered to be significant. All statistical calculations were performed using SAS software (version 6.12, SAS Institute Inc, Cary, NC, USA).

Results

Follow-up

The J-LIT Extension 10 study consisted of the 6-year J-LIT study period (51,321 patients) and another 4-year extension period (19,905 patients who agreed to continue the study). Of the original 51,321 patients, 4,912 were excluded from analysis of lipid-related morbidity and mortality, mainly because of missing lipid data[2,3] The remaining 46,400 patients were divided into a primary prevention cohort (41,801 patients without CHD) and a secondary prevention cohort (4,599 patients with CHD) for analysis of the relationship between lipid levels and coronary events over 10 years. The average follow-up period was 6.8 years.

The baseline characteristics of the patients enrolled in the J-LIT Extension 10 study are shown in Table 1. The age, sex, complications, smoking, alcohol consumption, and baseline serum lipid levels were similar between the patients who were followed up during the extension period and all patients enrolled in the initial J-LIT study.

Of the 51,321 patients, the majority (96.4%) were being treated with simvastatin at 5 mg/day alone at the start of the J-LIT study. Six years later (at the end of the J-LIT study),

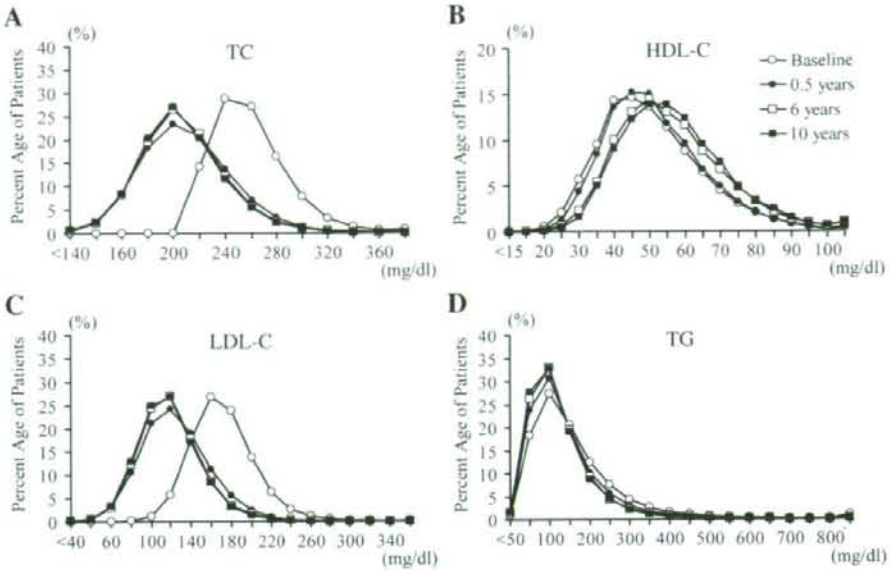

Fig 1. Patient distribution according to serum (A) TC, (B) HDL-C, (C) LDL-C, and (D) TG levels at baseline (○) and after 0.5 years (●), 6 years (□), and 10 years (■) of simvastatin treatment. TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides.

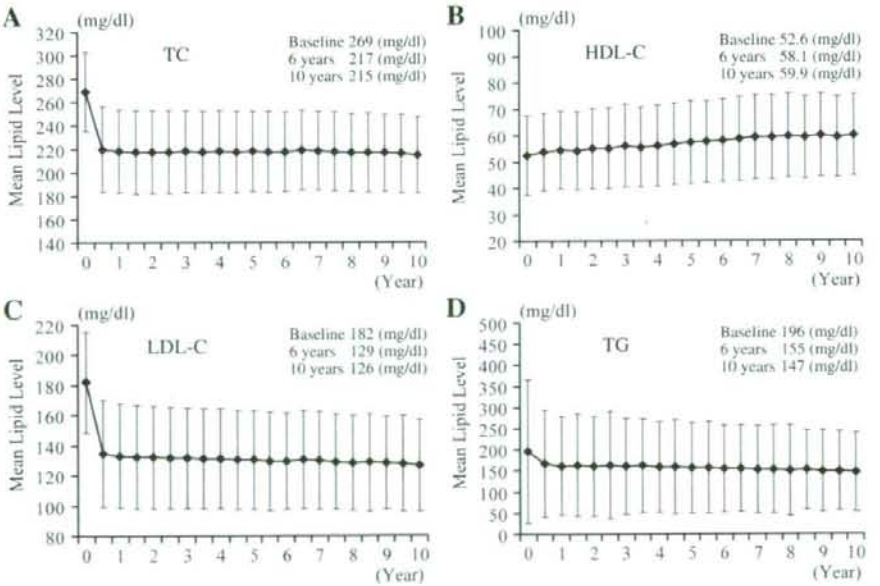

Fig 2. Profile of serum (A) TC, (B) HDL-C, (C) LDL-C, and (D) TG during 10 years of simvastatin treatment. Lipid levels are shown as the mean ± SD. See Fig 1 for abbreviations.

25,074 (68.0%) of 36,895 remaining in the study were receiving lipid-lowering therapy, mainly with simvastatin at 5 mg/day alone (55.6%). At the end of the 10-year period (ie, on completion of the extension study), 17,882 patients remained and 8,603 of them (48.1%) were on lipid-lowering therapy, including simvastatin at 5 mg/day in 36.7%. The main reason why the patients stopped receiving lipid-lowering therapy in the preceding 6 years was moving and/or transfer to another area away from the hospital (64%). The reasons at the end of the 10-year period were no longer visiting hospital (36%) and insufficient effect of therapy (23%).