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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]

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 75 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.
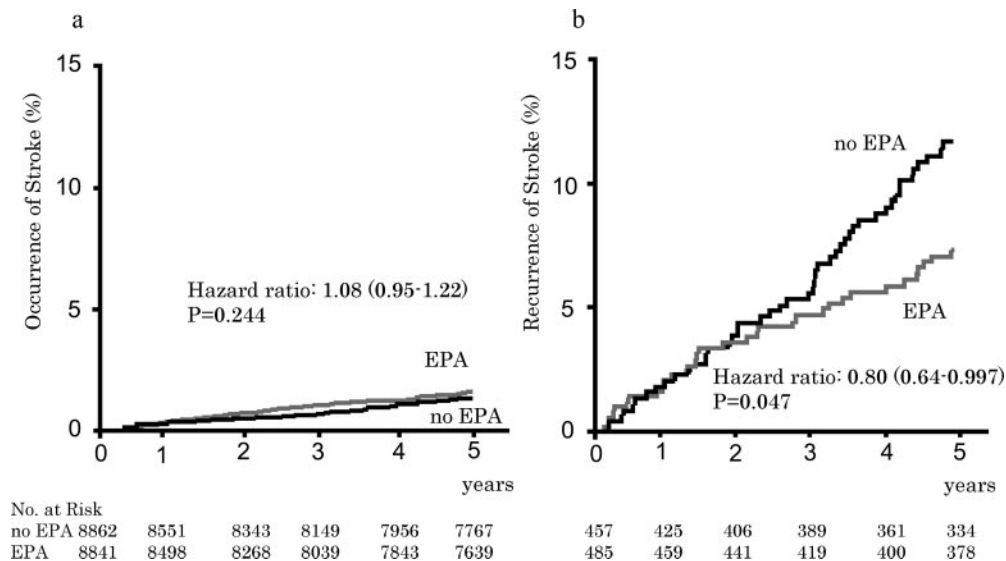
Figure. Kaplan–Meier Curves for stroke in the primary prevention subgroup (a) and the secondary prevention subgroup (b), adjusted for age, gender, hypertension, diabetes mellitus, and smoking.

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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Correction

In the article entitled "Reduction in the Recurrence of Stroke by Eicosapentaenoic Acid for Hypercholesterolemic Patients: Subanalysis of the JELIS Trial" by Tanaka et al,[1] in the "Study Design and Patients" section (page 2053), line 4, "men aged over 40 to 70 years" should read "men aged over 40 to *75* years." The authors regret this error.

The corrected version can be viewed online at http://stroke.ahajournals.org.