17. Nomura S, Kashiwagi S, Fujisawa H, et al: Characterization of local hyperfibrinolysis in chronic subdural hematomas by SDS-PAGE and immunoblot. **J Neurosurg 81**:910–913, 1994
18. Ohta T, Kikuchi H, Hashi K, et al: Nizofenone administration in the acute stage following subarachnoid hemorrhage. Results of a multi-center controlled double-blind clinical study. **J Neurosurg 64**:420–426, 1986
19. Oishi M, Toyama M, Tamatani S, et al: Clinical factors of recurrent chronic subdural hematoma. **Neurol Med Chir 41**:382–386, 2001
20. Park CK, Choi KH, Kim MC, et al: Spontaneous evolution of posttraumatic subdural hygroma into chronic subdural haematoma. **Acta Neurochir 127**:41–47, 1994
21. Sagcan R, Nalbantgil S, Omay SB et al: The effect of type II diabetes mellitus on platelet aggregation in patients who underwent percutaneous transluminal coronary angioplasty. **Coron Artery Dis 13**:45–48, 2002
22. So CC, Wong KF: Valproate-associated dysmyelopoiesis in elderly patients. **Am J Clin Pathol 118**:225–228, 2002
23. Suzuki J, Takaku A: Nonsurgical treatment of chronic subdural hematoma. **J Neurosurg 33**:548–553, 1970
24. Tanikawa M, Mase M, Yamada K, et al: Surgical treatment of chronic subdural hematoma based on intrahematomal membrane structure on MRI. **Acta Neurochir 143**:613–619, 2001
25. Victoratos GC, Bligh AS: A more systemic management of subdural hematoma with the aid of CT scan. **Surg Neurol 15**:158–160, 1981
26. Yoshii K, Seki Y, Aiba T: [Causative factors of recurrence of chronic subdural hematoma.] **No Shinkei Geka 15**:1065–1071, 1987 (Jpn)

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Effect of *Trapidil* on Cardiovascular Events in Patients With Coronary Artery Disease (Results from the Japan Multicenter Investigation for Cardiovascular Diseases-Mochida [JMIC-M])

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A large-scale study was conducted to assess the effect of long-term administration of trapidil on the prognosis of patients with angiographic evidence of coronary artery disease (CAD). A large-scale, multicenter study, the Japan Multicenter Investigation for Cardiovascular Diseases-Mochida was an open-label, randomized trial of 1,743 patients with CAD who were ≤70 years old and had angiographic evidence of >25% stenosis in any coronary artery. We randomly assigned the patients to receive medical treatment either with trapidil 100 mg 3 times daily (trapidil group, n = 873) or without trapidil (control group, n = 870). The mean follow-up period was 924 days. The incidence of cardiovascular events, including cardiac death, nonfatal myocardial infarction, angina pectoris/heart failure requiring hospitalization, and cerebrovascular events was 11.1% in the trapidil group and 14.9% in the control group (relative risk 0.75, 95% confidence interval 0.58 to 0.98, p = 0.036). Thus, long-term intervention with trapidil in CAD reduces the incidence of cardiovascular events and improves the prognosis of patients with CAD. ©2003 by Excerpta Medica, Inc.

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The Japan Multicenter Investigation for Cardiovascular Diseases (JMIC) is a large-scale, multicenter, randomized trial aimed at establishing treatment methods for circulatory diseases. JMIC-Mochida (JMIC-M), 1 of these projects, was conducted to determine whether trapidil could improve the prognosis of patients with coronary artery disease (CAD) in comparison with those who received routine treatment.

METHODS

Study design and patients: JMIC-M was a multicenter, randomized, open-label clinical trial designed to test whether 3-year treatment with trapidil reduces the frequency of major fatal and nonfatal cardiovascular events in patients who had angiographic evidence of CAD. Men and women aged ≤70 years old who were eligible for inclusion were considered for study enrollment.

Inclusion criteria were defined as: (1) angiographic evidence of ≥1 focal coronary lesions with ≥25% stenosis, according to American Heart Association criteria[1]; (2) ≥1 coronary artery without any coronary intervention; and (3) no plan to undergo coronary angioplasty or coronary bypass graft surgery. Patients with acute myocardial infarction within 3 weeks from onset, and patients with unstable angina pectoris, hemostatic disorders or systemic bleeding, or severe hepatic or renal insufficiency were excluded. The study protocol was approved by the local ethics committee or institutional review board at each site, and written informed consent to participate in the study was obtained from each patient before randomization.

Between December 1992 and December 1996, a total of 1,937 patients with CAD were enrolled from 345 institutions in Japan. A parallel design was used as the assignment method. After verifying eligibility, we randomly assigned patients to study groups by using the substitution block method, with each institution considered to be a block. Each block consisted of 8 subjects, including 4 in each group: the trapidil group (trapidil 300 mg/day) and the control group (without trapidil). A total of 1,748 patients were randomly assigned to the study (trapidil group, n = 875; control group, n = 873).

Study medication began within 1 month after cor-

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TABLE 1 Baseline Characteristics

Characteristic	Trapidil (n = 873)	Controls (n = 870)	p Value
Age (yrs) (mean ± SD)	59.4 ± 7.7	59.1 ± 7.9	0.41
Men	696 (80%)	687 (79%)	0.71
Prior myocardial infarction	423 (49%)	396 (46%)	0.53
Angina pectoris	399 (46%)	412 (47%)	
Silent myocardial ischemia	31 (3%)	35 (4%)	
No. of coronary arteries narrowed by ≥50% in diameter			0.10
0	36 (4%)	45 (5%)	
1	295 (34%)	296 (34%)	
2	292 (33%)	326 (37%)	
3	246 (28%)	200 (23%)	
Left main	4 (1%)	3 (1%)	
Systolic hypertension	424 (49%)	417 (48%)	0.84
Hyperlipidemia*	354 (41%)	340 (39%)	0.57
Diabetes mellitus	242 (28%)	222 (26%)	0.31
Obesity†	258 (30%)	245 (28%)	0.56
Smokers	507 (58%)	525 (60%)	0.26
History of revascularization	325 (37%)	310 (36%)	0.49
Ejection fraction (%) (mean ± SD)	64 ± 13	64 ± 14	0.91
Blood pressure (mm Hg) (mean ± SD)			
Systolic	132 ± 18	131 ± 18	0.62
Diastolic	76 ± 11	77 ± 11	0.22
Lipid values (mg/dl) (mean ± SD)			
Total cholesterol	202 ± 36	201 ± 36	0.51
High-density lipoprotein cholesterol	44 ± 12	44 ± 13	0.71
Triglycerides	150 ± 87	151 ± 86	0.88

*Hyperlipidemia was defined as total cholesterol level of ≥220 mg/dl or triglyceride level of ≥150 mg/dl.
†Obesity was defined as a Broca index ≥20.

TABLE 2 Concomitant Medication

Drug Class	Trapidil (n = 873)	Control (n = 870)	p Value
Nitrates	690 (79%)	690 (79%)	0.89
β-blocking agent	177 (20%)	165 (19%)	0.49
Calcium antagonists	659 (75%)	679 (78%)	0.21
Angiotensin-converting enzyme inhibitors	105 (12%)	127 (15%)	0.11
Antihyperlipidemic agents	264 (30%)	275 (32%)	0.54
Antiplatelet agents	415 (48%)	483 (56%)	0.001
Others	323 (37%)	324 (37%)	0.92

onary angiography. In the trapidil group, 300 mg/day of trapidil was added to the patients' current medications. In the control group, no trapidil was added to the current medications. The study duration was 3 years, but patients were withdrawn in cases in which the attending physician judged it impossible to continue. Concomitant drugs, such as nitrates, calcium antagonists, β blockers, angiotensin-converting enzyme inhibitors, and so on, were allowed at the discretion of attending physicians. Although the concomitant use of antiplatelet drugs was prohibited in principle, these drugs were allowed at the discretion of attending physicians in patients with a history of coronary angioplasty or coronary bypass surgery.

Coronary angiograms and left ventriculograms: Coronary angiograms were reviewed in each institute to define subject eligibility. The extent of stenosis in the coronary artery was assessed according to the American Heart Association reporting system.[1] Any stenosis >50% in the coronary artery was considered significant for assessing the number of diseased vessels. Left ventriculograms were obtained at the same time in most cases. Left ventricular volumes were measured according to the area-length method,[2] and ejection fractions were calculated.

End points: The primary end point was a composite of cardiovascular events, including cardiac death, nonfatal myocardial infarction, hospitalization for heart failure, hospitalization due to recurrence of angina pectoris, and cerebrovascular disorders, including stroke or transient ischemic attack. Sudden death, death due to myocardial infarction, death due to heart failure, and death attributable to other coronary causes were classified as cardiac death. Recurrence of angina was defined as typical chest pain with objective evidence of myocardial ischemia or angiographically significant stenosis requiring coronary revascularization (coronary angioplasty or bypass surgery). All events were evaluated blindly by the end point assessment committee.

Statistical analysis: This study was planned to detect a 30% decrease in cardiovascular risk in 3 years, using an 80% power of detection and a statistically significant difference of $p < 0.05$ by a 2-sided test.

All statistical analyses were assessed using SAS version 6.12 (SAS Institute, Cary, North Carolina). Differences between the groups were assessed using Student's *t* test for continuous variables and the chi-square test for absolute categorical variables. For the time-course analysis of an event, the duration up to the first event was investigated using a Kaplan-Meier curve and any statistically significant difference between the curves was determined by using a stratified log-rank test. The relative risk and 95% confidence interval regarding treatment versus trapidil were evaluated by using Cox's proportional hazard model. All the analyses were conducted on an intention-to-treat basis.

RESULTS

A total of 1,748 patients from 345 institutes were randomized between December 1992 and December 1996. Follow-up was completed by December 2000. During the study period, 5 patients (0.43%) withdrew after randomization (2 patients in the trapidil group and 3 patients in the control group). These 5 patients were not included in the analysis. As a result, 873 and 870 patients were assigned to the trapidil and control groups, respectively, and underwent the analysis.

Baseline characteristics were similar between the 2 groups, as listed in Table 1. There were no differences

TABLE 3 Cardiovascular Events According to Study Group

Event	Trapidil (n = 873)	Control (n = 870)	Relative Risk (95% CI)	p Value
Cardiovascular event	97 (11.1%)	130 (14.9%)	0.75 (0.58–0.98)	0.036
Cardiac event	86 (9.9%)	116 (13.3%)	0.75 (0.57–0.99)	0.042
Death from coronary artery disease	3 (0.3%)	10 (1.1%)	0.31 (0.09–1.12)	0.059
Nonfatal myocardial infarction	17 (2.0%)	17 (2.0%)	1.02 (0.52–2.00)	0.946
Hospitalization for angina	64 (7.3%)	86 (9.9%)	0.76 (0.55–1.04)	0.088
Revascularization	51 (5.8%)	72 (8.3%)	0.72 (0.50–1.03)	0.067
New lesion	36 (4.1%)	51 (5.9%)	0.72 (0.47–1.11)	0.133
Restenosis	17 (1.9%)	28 (3.2%)	0.61 (0.34–1.12)	0.108
Hospitalization for heart failure	4 (0.5%)	8 (0.9%)	0.51 (0.15–1.70)	0.264
Stroke	7 (0.8%)	18 (2.1%)	0.40 (0.17–0.95)	0.032
Transient ischemic attack	4 (0.5%)	1 (0.1%)	4.13 (0.46–36.99)	0.168

Relative risk was calculated by Cox proportional-hazards analysis.
p Values were derived with the stratified log-rank test.
CI = confidence interval.

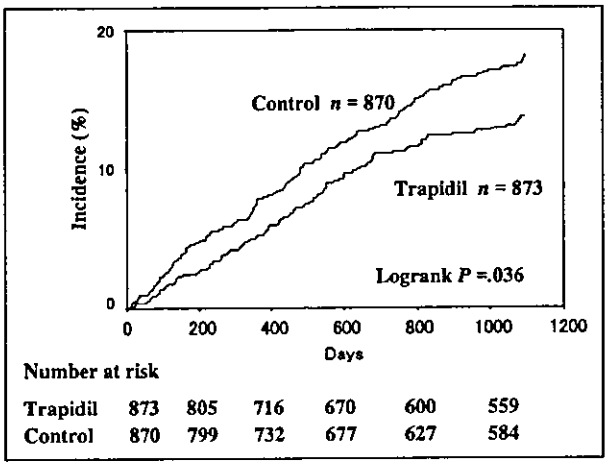

FIGURE 1. Kaplan-Meier curves of the incidence of cardiovascular events in the 2 groups. The number of patients at risk is shown on the *x* axis. Cardiovascular events include cardiac death (including sudden death), nonfatal myocardial infarction, angina pectoris/heart failure requiring hospitalization, revascularization (percutaneous transluminal coronary angioplasty/coronary artery bypass graft surgery), and cerebrovascular accident. The p value was derived with the stratified log-rank test.

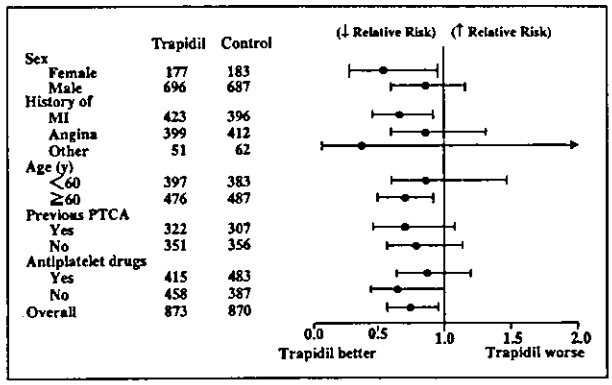

FIGURE 2. Relative risk reduction and 95% confidence interval (CI) of primary end points with trapidil by clinical subgroup. MI = myocardial infarction; PTCA = percutaneous coronary angioplasty.

between the groups with regard to age, gender, history of CAD, CAD severity, cardiovascular risk factors, and previous coronary revascularization via either coronary angioplasty or coronary artery bypass graft surgery. Ejection fraction was measured in 1,207 patients (611 patients in the trapidil group and 596 patient in the control group), and there was no significant difference observed between the groups.

Antiplatelet drugs were administrated significantly more often in the control group (56%) compared with the trapidil group (48%) (Table 2). The frequency of other drugs administered concomitantly during the study period was similar between the groups. The mean observation period was 924 days (2.5 years), showing no difference between the groups.

Cardiovascular events occurred in 97 patients (11.1%) in the trapidil group compared with 130 patients (14.9%) in the control group (Table 3). The relative risk of cardiovascular events in the trapidil group in comparison with the control group was 0.75 (95% confidence interval 0.58 to 0.98, p = 0.036). For the time-course analysis of an event, the duration up to the first event was investigated using a Kaplan-Meier curve (Figure 1). A cardiac event (cardiac death, nonfatal myocardial infarction, hospitalization due to aggravation of angina pectoris or heart failure) occurred in 86 patients (9.9%) in the trapidil group compared with 116 subjects (13.3%) in the control group (Table 3). The relative risk of cardiac events in the trapidil group was 0.75 (95% confidence interval 0.57 to 0.99, p = 0.042). Cardiac death, hospitalization for heart failure, or hospitalization due to the recurrence of angina occurred less often in the trapidil group, but the difference was not significant. Among the 150 patients with recurrence of angina, the incidence of coronary revascularization to either new or restenosis lesions were less in the trapidil group compared with the control group, but the difference did not reach statistical significance. The incidence of stroke was 0.8% in the trapidil group compared with 2.1% in the control group (relative risk 0.40, p = 0.032).

There was no difference in the overall rate of death

TABLE 4 Cardiovascular Events According to Study Group in Those With Previous Myocardial Infarction

Event	Trapidil (n = 423)	Control (n = 396)	Relative Risk (95% CI)	p Value
Cardiovascular event	51 (12.1%)	71 (17.9%)	0.67 (0.47–0.96)	0.028
Cardiac event	45 (10.6%)	65 (16.4%)	0.65 (0.44–0.94)	0.023
Death from coronary artery disease	2 (0.5%)	6 (1.5%)	0.32 (0.06–1.59)	0.142
Nonfatal myocardial infarction	11 (2.6%)	13 (3.3%)	0.81 (0.36–1.80)	0.596
Hospitalization for angina	31 (7.3%)	45 (11.4%)	0.65 (0.41–1.02)	0.059
Revascularization	26 (6.1%)	39 (9.8%)	0.63 (0.38–1.03)	0.061
New lesion	16 (3.8%)	28 (7.1%)	0.54 (0.29–1.00)	0.047
Restenosis	12 (2.8%)	16 (4.0%)	0.71 (0.34–1.50)	0.365
Hospitalization for heart failure	3 (0.7%)	6 (1.5%)	0.47 (0.12–1.89)	0.280
Stroke	4 (0.9%)	5 (1.3%)	0.76 (0.20–2.84)	0.685
Transient ischemic attack	2 (0.5%)	1 (0.3%)	1.91 (0.17–21.06)	0.591

Relative risk was calculated by Cox proportional-hazards analysis.
p Values were derived with the stratified log-rank test.
Abbreviation as in Table 3.

between the groups. However, the number of deaths due to cardiovascular diseases was 4 patients (0.5%) in the trapidil group compared with 13 subjects (1.5%) in the control group; the difference was statistically significant. There was no difference between the 2 groups in the number of deaths due to cancer, accident, or suicide.

Clinical subgroup analysis indicated that trapidil was more beneficial in women, in patients ≥60 years old (Figure 2), and in those with previous myocardial infarction (Figure 2 and Table 4). There were no obvious benefits of trapidil in patients with a history of coronary angioplasty or in those who did not receive antiplatelet agents.

A total of 57 adverse events occurred in 53 patients in the control group and total of 62 adverse events occurred in 57 patients in the trapidil group. The comparison between the trapidil group and control group indicated no significant difference in the deaths due to cancer, accident, suicide, and other serious adverse events. Deaths attributable to cancer occurred in 7 and 6 patients in the trapidil and control groups, respectively. Adverse reactions considered to be related to trapidil treatment, such as gastric discomfort, hepatic dysfunction, skin eruption, vertigo, and headache occurred in 18, 9, 6, 3, and 2 patients, respectively. All symptoms were mild and disappeared after discontinuation of the drug.

DISCUSSION

This study indicates that long-term daily use of 300 mg of trapidil reduces the incidence of cardiovascular events during 3 years in patients with angiographic evidence of CAD. We assumed, based on the differences in the incidence of events between the groups during the study period, that cardiac events and cerebrovascular disorders were prevented in 35 of 1,000 cases and 12 of 1,000 cases, respectively, in the trapidil group.

Trapidil significantly reduced the combined risk of cardiac events, although trapidil did not reduce the incidence of each cardiac event significantly. Trapidil had a tendency to reduce the incidence of cardiac death and hospitalization due to heart failure or recurrent angina; however, the difference did not reach statistical significance. The cardiac event rate in CAD is lower and the prognosis of CAD in Japan is more favorable than those in Western countries.[3] In addition, the long-term prophylactic use of antiplatelet drugs in an at-risk population might cause further reduction of cardiac events.[4–6] Thus, the power of this trial might not be sufficient to detect any significant difference in cardiac events.

There were no significant differences in the use of concomitant medications between the trapidil and control groups besides the use of antiplatelet agents. Despite the significantly more frequent administration of antiplatelet agents in the control group, the low incidence of cardiac events in the trapidil group indicated a prophylactic action of trapidil in addition to its antiplatelet action. Trapidil protects the vascular endothelium by enhancing prostacyclin synthesis and preventing smooth muscle cell proliferation by acting as a platelet-derived growth factor antagonist, which may have significantly reduced the incidence of unscheduled revascularization to a new lesion, as seen in 819 patients with previous myocardial infarction (Table 4). In addition to these antiatherosclerotic actions, trapidil has, according to a recent report, anti-inflammatory activity that may inhibit the development of vulnerable plaques.[7] Although there is no direct clinical evidence, the significant reduction of cardiac events seen in high-risk patients in the Japanese Antiplatelets Myocardial Infarction Study[8] (JAMIS) and in this study further supports the theory that trapidil may inhibit the progression of atherosclerosis and plaque rupture.

Although trapidil was shown to reduce the restenosis rate after coronary balloon angioplasty compared with findings for aspirin,[9] there were no significant differences in the incidence of the urgent intervention to the restenosis lesion between the 2 groups. The exclusion of patients with scheduled intervention led to the low incidence of restenosis in this study and may mask the preventive effect of trapidil on restenosis.

APPENDIX

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Statistician: Hideki Origasa, PhD.

1. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5–40.

2. Dodge H, Sandler H, Baxley W, Hawley R. Usefulness and limitation of radiographic methods for determining left ventricular volume. *Am J Cardiol* 1966;18:10–24.

3. Saito M, Fukami K, Hiramori K, Haze K, Sumiyoshi T, Kasagi H, Horibe H. Long-term prognosis of patients with acute myocardial infarction: is mortality and morbidity as low as the incidence of ischemic heart disease in Japan. *Am Heart J* 1987;113:891–897.

4. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106.

5. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994;330:1287–1294.

6. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;357:89–95.

7. Kato Y, Tsuda T, Hosaka Y, Takahashi T, Shirakawa K, Furusako S, Mizuguchi K, Mochizuki H. Effect of trapidil on effector functions of monocytes related to atherosclerotic plaque. *Eur J Pharmacol* 2000;44:307–316.

8. Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, Ishikawa K, Masuda Y, Yamaguchi T, Motomiya T, Tamura Y, on behalf of the Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. *Am J Cardiol* 1999;83:1308–1313.

9. Maresta A, Balducelli M, Cantini L, Casari A, Chioin R, Fabbri M, Fontanelli A, Preti PAM, Repetto S, De Servi S, Varani E, for the STARC Investigators. Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty. Results of the randomized, double-blind STARC study. Studio Trapidil versus Aspirin nella Restenosi Coronarica. *Circulation* 1994;90:2710–2715.

Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS)

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Hypothesis The principle aim of the current study is to test the hypothesis that the long-term use of highly purified EPA (eicosapentaenoic acid: 1800 mg/day), in addition to HMG-CoA reductase inhibitor, is effective in preventing cardiovascular events in Japanese patients with hypercholesterolemia.

Background Epidemiological and clinical evidence suggest that intake of long-chain polyunsaturated n-3 fatty acids (PUFAs), which are abundant in fish, might have a significant role in the prevention of coronary artery disease, as marine PUFAs have multiple biological functions through lipid-dependent and lipid-independent mechanisms.

Methods The Japan EPA Lipid Intervention Study (JELIS) is a prospective, randomized, open-label, blinded end point trial including both primary and secondary prevention strata, with a maximum follow-up of 5 years. Its main purpose is to examine the clinical effectiveness of EPA oil given as an additional treatment to patients taking HMG-CoA reductase inhibitors for hypercholesterolemia. A primary end point is major coronary events: sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or coronary artery bypass grafting. Secondary end points include all-cause mortality, stroke, peripheral artery disease, and cancer. Baseline study composition comprises 15,000 participants (4204 men and 10,796 women) in the primary prevention stratum and 3645 (1656 men and 1989 women) in the secondary stratum. The minimum age is 40 years for men, women are required to be postmenopausal, and all patients must be ≤75 years of age. The mean age of participants is 61 years, and 69% are female. The schedule for plasma fatty acid composition measurement is as follows: at baseline, at 6 month, and yearly thereafter. The mean baseline total and low-density lipoprotein cholesterol levels were 275 mg/dL (7.1 mmol/L) and 180 mg/dL (4.6 mmol/L).

Results Results are expected in 2005.

Conclusion JELIS is a large clinical trial that will evaluate whether EPA can make an additional improvement in mortality and morbidity of coronary artery disease beyond that of HMG-CoA reductase inhibitor treatment. (Am Heart J 2003;146:613–20.)

Beginning with the study by Dyerberg et al on Greenland Eskimos in the late 1970s,[1] epidemiological studies from many countries including Finland, Italy, Japan, and The Netherlands have suggested that an increased intake of dietary fish or fish oil rich in the long-chain polyunsaturated n-3 fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is inversely related to the risk of atherothrombotic diseases, in particular coronary artery disease (CAD).[2-4]

Results of many prospective observational cohort studies have found that diets rich in marine PUFAs may be protective against major cardiovascular events, including mortality from CAD, total cardiovascular death, all-cause mortality, and nonfatal myocardial infarction.

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Thus, 2 randomized, controlled, secondary prevention trials were performed to examine the effects of dietary fish on the risk of death from CAD in patients after myocardial infarction. The Diet and Reinfarction Trial (DART) reported that patients who were advised to increase their dietary intake of fish to at least 2 fish meals per week had a 29% decrease in all-cause mortality over 2 years.[5] The GISSI-Prevenzione trial showed that there was a 20% decrease in all death, a 30% decrease in cardiovascular deaths, and a 45% decrease in sudden deaths associated with a daily supplement of n-3 PUFAs (1g daily, EPA/DHA = 1:2) in patients with recent myocardial infarction.[6] These trial results are concordant with a body of epidemiological data. It has not yet been proved by clinical trials of primary prevention that marine n-3 PUFAs reduce the mortality and morbidity of CAD in high-risk subjects. Most trials have involved the use of diets supplemented by intake of fish, fish oils, or capsules containing fish oil extracts. These may contain a number of other fatty acids and different components. Thus, an evaluation of the specific effects of each n-3 PUFA was not possible. To date, only a few studies have examined the effects of purified n-3 PUFA preparations in human subjects for short observation periods.

Although the underlying mechanisms of protective action of n-3 PUFAs against CAD remain to be established, their multiple cardiovascular effects have received much attention. The potential mechanisms are lower levels of serum lipids,[7-9] antithrombotic properties and relaxation in coronary arteries,[10-14] anti-inflammatory properties,[15-18] anti-platelet-derived growth factor properties,[19] natural ligands for peroxisome proliferator activated receptors,[20,21] and antiarrhythmic properties.[22]

Rationale for the JELIS

It is well established that cholesterol lowering with hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors conveys potential for primary and secondary prevention of cardiovascular events in hypercholesterolemic patients.[23-26] Preliminary data on pravastatin combined with fish oil have shown several beneficial effects on the lipid profile of patients with a mixed type of hyperlipidemia.[27-29] This combination therapy effectively reduced the concentration of low-density lipoprotein as well as that of total cholesterol. It was also remarkably safe during short-term use and expected to be clinically beneficial.

However, no clinical intervention trial data have been collected to determine whether the addition of EPA to conventional therapy with an HMG-CoA reductase inhibitor is effective in preventing cardiovascular events.

This study is designed to test the fundamental hypothesis that treatment with highly purified EPA ethyl ester together with lipid lowering with an HMG-CoA reductase inhibitor is more effective than treatment without EPA in reducing major coronary events. Such coronary events involve CAD deaths including sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina pectoris. Other objectives are to evaluate the effect of EPA on the frequency of stroke and all-cause death, the long-term safety of EPA, and the relationship between plasma fatty acid levels and the onset of cardiovascular events.

Methods

Study design

The JELIS is a prospective, randomized, open-label, blinded-end point clinical trial designed to examine the clinical efficacy of EPA oil administered as an adjuvant agent to patients under treatment with HMG-CoA reductase inhibitors for hypercholesterolemia. Participants are randomly assigned to either EPA adjuvant treatment or none in an open fashion (ie, an unblinded manner). Because all patients receive reductase inhibitors, we cannot assess whether the inhibitors and EPA work synergistically.

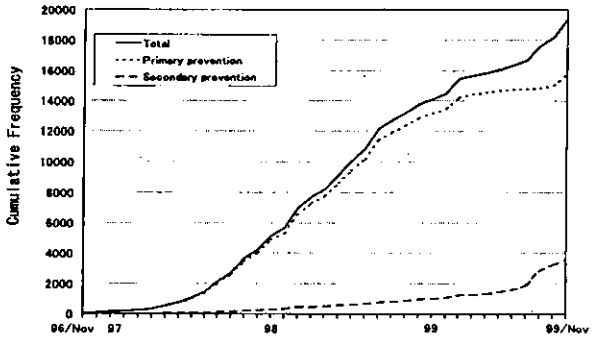
The primary prevention stratum was defined as participants who had (1) no history of myocardial infarction (MI) or angina pectoris and with neither angioplasty/stenting nor coronary artery bypass graft (CABG) until randomization, and (2) no clinical manifestations of angina pectoris or electrocardiograph (ECG) abnormalities at randomization. The secondary prevention stratum was defined as those who had (1) history of well-documented MI or angina pectoris with neither angioplasty/stenting nor CABG until randomization, and/or (2) stable, controlled angina pectoris at randomization.

In the primary and secondary prevention strata, a primary end point is major coronary events, which include sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or CABG. Secondary end points are all-cause mortality, mortality and morbidity of CAD, stroke, peripheral artery disease (arteriosclerosis obliterans [ASO]), and cancer. Clinical end points are ascertained once a year by the Endpoints Adjudication Committee: expert cardiologists and neurologists who are blinded to the assigned groups. However, the assessment of the end points is performed without breaking a key code, by a blinded-end point approach. Each participant is followed-up for a maximum of 5 years.

Random allocation

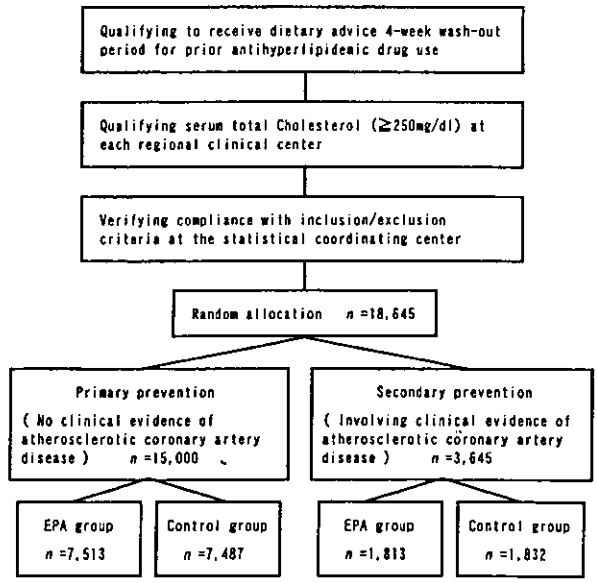
This study used a statistical coordinating center, Toyama Medical and Pharmaceutical University, to manage patient registration, which included the confirmation of eligibility criteria, operation of the randomization scheme, and data management. We used a permuted block randomization with a block size of 4. Multiple blocks were assigned according to the number of participants enrolled at each center. Stratification was based on the prevention stratum (primary or sec-

Figure 1



Monthly chart of the recruitment process.

Figure 2



Trial profile.

ondary). The results of the randomization scheme were concealed to the investigators and participants.

Patient population

Between November 1996 and November 1999, we enrolled a total of 19,466 participants with hypercholesterolemia from all regions of Japan; a total of 821 cases were excluded as ineligible.

The intention-to-treat data set currently involves 18,645 participants, with 15,000 (80%) for primary and 3645 (20%) for secondary prevention who were randomly assigned to EPA plus HMG-CoA reductase inhibitors or HMG-CoA reductase inhibitors only.

The monthly increase of the enrollment is shown in Figure 1, and Figure 2 illustrates the trial profile.

The study patients were recruited by local physicians participating in this study with the help of regional organizing committees. Eligible participants had a total cholesterol level of ≥250 mg/dL (6.5 mmol/L), which corresponds to an LDL cholesterol level of 170 mg/dL (4.4 mmol/L), at baseline. The minimum age was 40 years for men; women were required to be postmenopausal. Maximum patient age was 75 years (due to the 5-years follow-up). Informed written consent was obtained from each patient. All participants are Japanese for the simple reason that highly purified EPA is allowed as treatment for hyperlipidemia in Japan. Inclusion and exclusion criteria are listed in Table I.

Local physicians monitor dietary and medication compliance at every clinical visit.

The schedule of observations is shown in Table II.

Baseline data

Patients were divided into the EPA group (n = 9326) or control group (n = 9319).

The baseline demographic and clinical characteristics of JELIS are shown in Table III.

In the primary prevention stratum (n = 15,000), the mean age was 56 years for men (28%) and 62 years for women (72%). Prevalence of smoking and drinking were 17% and 24%, respectively. Concomitant diseases were prevalent in approximately 47% of the participants in the order of hypertension, diabetes, stroke, hepatic disease, and renal disease. ECG abnormalities were present in 17%. The mean total cholesterol level was 277 mg/dL at baseline with the standard deviation of 28 mg/dL. Mean LDL and high-density lipoprotein (HDL) cholesterol levels were 181 mg/dL and 59 mg/dL, respectively. There was no evidence of high blood pressure on average.

In the secondary prevention stratum (n=3645), the mean age was 62 years for men (45%) and 65 years for women (55%). Prevalence of smoking and drinking were 25% and 30%, respectively. Prior myocardial infarction was present in 28% and stable angina was reported in 79%. Concomitant diseases were found in approximately 58% of the participants, in the order of hypertension, diabetes, stroke, hepatic disease, and renal disease. ECG abnormalities were present in 58%. Mean total cholesterol level was 270 mg/dL at baseline with a standard deviation of 28 mg/dL. Mean LDL and HDL cholesterol were 177 mg/dL and 55 mg/dL, respectively.

Figure 3 shows the plasma fatty acids composition at baseline. C18:2 omega 6 (linoleic acid), C16:0 (palmitic acid) and C18:1 omega 9 (oleic acid) were the dominant fatty acids. C18:0 (stearic acid), C20:4 omega 6 (arachidonic acid), C22:6 omega 3 (docosahexaenoic acid), and C20:5 omega 3 (eicosapentaenoic acid) followed, but no statistically significant differences were observed in the prevention stratum.

Treatment/preparations

EPA is administered at a dose of 600 mg, three times a day after meals (total 1800 mg/day). We use EPADEL Capsule 300TM (Mochida Pharmaceutical Co, Ltd, Tokyo, Japan) con-

Table I. Inclusion and exclusion criteria

Inclusion criteria
- Hyperlipidemic patients with serum total cholesterol of 250 mg/dL or more
  - (Measurement of serum total cholesterol)
    - Serum total cholesterol should be measured twice at interval of 2–4 weeks. A single measurement is acceptable if the cholesterol is measured by blood collection at fasting under strict compliance with dietary advice after withdrawal of the antihyperlipemic drug.
  - (Wash Out)
    - The wash out period of 4 weeks (8 weeks for probucol) is necessary in patients under treatment with antihyperlipemic drug. However, if treatment with the antihyperlipemic drug was started within 6 months of the initiation of the study, the patient can participate in the study without the washout period.
- Men aged 40–75 years or women after menopause to 75 years
- Patients who have already received appropriate dietary advice

Exclusion criteria
- Acute myocardial infarction occurring within last 6 months
- Unstable angina pectoris
- A history or complication of serious heart disease (severe arrhythmia, heart failure, cardiac myopathy, valvular disease, congenital disease, etc.)
- Receiving cardiovascular reconstruction within last 6 months
- Cerebrovascular disorders occurring within last 6 months
- Complication of serious hepatic disease or renal disease
- Malignant tumor
- Uncontrollable diabetes
- Hyperlipidemia arising from the following diseases:
  - Nephrotic syndrome, hypothyroidism, Cushing's syndrome, secondary hyperlipidemia due to other disease
- Hyperlipidemia due to some drugs such as steroid hormone
- Hemorrage (hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage, etc.)
- Hemorrhagic diathesis
- Hypersensitivity to the study drug fomulation
- Patients intending to undergo surgery
- Patients judged to be inappropriate by the physician in charge

Table II. Schedule of the observations during the study period

	Pretreatment period		Treatment period (months)											
	−8	−4	0	2	6	12	18	24	30	36	42	48	54	60
Dietary advice			x			x		x		x		x		x
Compliance check			x			x		x		x		x		x
Smoking and drinking			x			x		x		x		x		x
Vital signs (including ECG)			x			x		x		x		x		x
Adverse and clinical events			←											→
Serum lipids (at each clinical center)	x	x	x		x	x		x		x		x		x
Fatty acids (central laboratory)			x		x	x		x		x		x		x
Clinical visits	x	x	x	x	x	x	x	x	x	x	x	x	x	x

taining 300 mg of highly (>98%) purified EPA ethyl ester (ethyl all-cis-5,8,11,14,17-icosapentaenoate) per capsule. EPA is actually purified from a long-chain polyunsaturated fatty acid present in fish oil (Figure 4). EPADEL Capsule 300 was launched in the Japanese market in 1990 for the treatment of ASO and hyperlipidemia. The usual adult dose is 600 mg of ethyl icosapentaenoate: 2 capsules administered orally 3 times daily immediately after meals.

Concomitant treatment

Either pravastatin or simvastatin was prescribed for all participants as a first-line therapy, these being the 2 HMG-CoA reductase inhibitors available in Japan at the initiation of this study.

Dosage, as recommended by Ministry of Health, Labour and Welfare (MHLW), is as follows: pravastatin 10 mg, once a day or simvastatin 5 mg, once a day. With serious hypercholesterolemia, defined as a serum cholesterol level not controlled by the recommended dosage, these can be increased to 20 mg and 10 mg, respectively.

No treatment with other antihyperlipidemic agents was allowed during the study period. However, other kinds of medications were taken as needed. This regime will be followed for a maximum of 5 years.

Table III. Baseline characteristics of primary and secondary prevention strata

	Primary prevention stratum		Secondary prevention stratum	
	EPA group (n = 7513)	**Control group (n = 7487)**	**EPA group (n = 1813)**	**Control group (n = 1832)**
Age (y)				
≤49 (%)	884 (11.8)	906 (12.1)	114 (6.3)	128 (7.0)
50–59 (%)	2481 (33.0)	2549 (34.0)	413 (22.8)	435 (23.7)
60–69 (%)	2976 (39.6)	2913 (38.9)	806 (44.5)	777 (42.4)
≥70 (%)	1172 (15.6)	1119 (14.9)	480 (26.5)	492 (26.9)
Male	56 ± 10	56 ± 10	62 ± 9	61 ± 9
Female	62 ± 7	62 ± 7	65 ± 7	65 ± 7
Sex (%)				
Male	2113 (28.1)	2091 (27.9)	838 (46.2)	818 (44.7)
Female	5400 (71.9)	5396 (72.1)	975 (53.8)	1014 (55.3)
Smoking (%)	1323 (17.6)	1244 (16.6)	485 (26.8)	435 (23.7)
Drinking (%)	1837 (24.5)	1830 (24.4)	540 (29.8)	542 (29.6)
BMI (kg/m^2)	24.0 ± 3.6	23.9 ± 3.5	24.0 ± 3.9	24.1 ± 4.0
ECG abnormality at resting (%)	1299 (17.3)	1245 (16.6)	1046 (57.7)	1067 (58.2)
CAD (%)				
Angina				
Effort	–	–	1018 (56.2)	1076 (58.7)
Spontaneous	–	–	389 (21.5)	392 (21.4)
Myocardial infarction	–	–	539 (29.7)	495 (27.0)
Angioplasty				
PTCA	–	–	363 (20.0)	328 (17.9)
Coronary bypass	–	–	114 (6.3)	110 (6.0)
Endovascular stent	–	–	130 (7.2)	120 (6.6)
DCA	–	–	9 (0.5)	9 (0.5)
PTCR	–	–	22 (1.2)	18 (1.0)
Others	–	–	11 (0.6)	7 (0.4)
Other complications (%)				
Diabetes	1101 (14.7)	1086 (14.5)	400 (22.1)	414 (22.6)
Hypertension	2521 (33.6)	2451 (32.7)	781 (43.1)	802 (43.8)
Stroke	370 (4.9)	320 (4.3)	108 (6.0)	131 (7.2)
Hepatic diseases	314 (4.2)	304 (4.1)	61 (3.4)	57 (3.1)
Renal diseases	177 (2.4)	181 (2.4)	59 (3.3)	67 (3.7)
Total cholesterol (mg/dL)	276.6 ± 28.0	276.9 ± 27.8	270.0 ± 27.7	270.1 ± 29.0
LDL cholesterol (mg/dL)	180.5 ± 34.5	181.4 ± 33.7	177.1 ± 32.2	176.3 ± 32.9
HDL cholesterol (mg/dL)	59.4 ± 17.7	59.0 ± 18.1	55.4 ± 19.2	55.5 ± 19.6
Triglyceride (mg/dL)	187.9 ± 147.8	189.2 ± 159.5	189.8 ± 127.1	198.6 ± 151.9
Systolic blood pressure (mm Hg)	135.6 ± 18.7	135.5 ± 18.2	137.0 ± 18.0	137.1 ± 18.3
Diastolic blood pressure (mm Hg)	79.7 ± 11.0	79.9 ± 11.1	78.7 ± 10.9	79.3 ± 11.0

Plus-minus values are means ± SD.

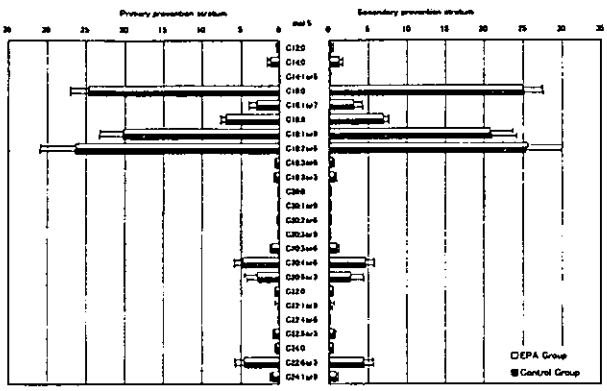
Calculations and analysis

For the primary prevention stratum, CAD morbidity and mortality in the Japanese general population was estimated at 5.3 per 1000 person years.[30] Because the JELIS population is restricted to those with a total cholesterol level of ≥250 mg/dL, we estimated a 10% higher risk for our cohort: 5.8 per 1000 person years. For the secondary prevention stratum, CAD morbidity and mortality was reported at 57.6 per 1000 person years[23] from Scandinavian countries, where people are considered to be at an extremely high risk for CAD compared to Japan. The incidence of CAD in the secondary prevention stratum was estimated as 21.3 per 1000 person years.

In fact, for primary prevention the incidence was 5.8 per 1000 person years in Japan,[30] whereas it was 15.8 per 1000 person years in Scotland.[24] Thus, the ratio of these rates, 2.7 (15.8 divided by 5.8), was used for adjustment. We also assumed that the proportion of participants in the primary prevention stratum would be 65%.

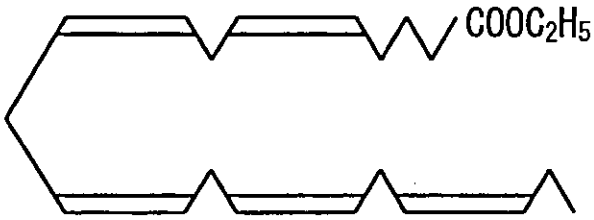
With respect to risk reduction, several megatrials and meta-analyses involving HMG-CoA reductase inhibitors[31] have estimated an approximate 30% reduction of CAD morbidity and mortality compared to none or placebo. Given the DART and GISSI results, we optimistically supposed that EPA would further reduce the risk by 25%, conditional on the use of HMG-CoA reductase inhibitors. Therefore, comedication of EPA with HMG-CoA reductase inhibitors should reduce the risk by 47.5% compared to no treatment.

Figure 3



Fatty acids composition at baseline.

Figure 4



Chemical structure of EPA ethyl ester.

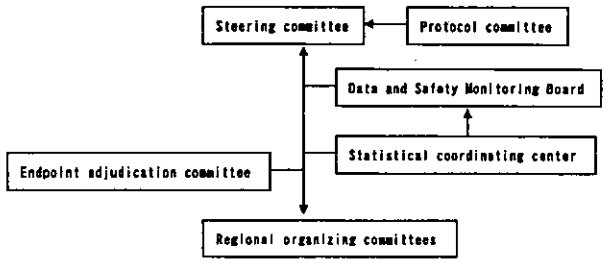
Assuming we perform the log-rank test with 2-sided significance, 12,600 participants are required to achieve a minimum statistical power of 80%. The accrual period is assumed to be 3 years with a follow-up period of 5 years at the most.

As more participants than expected were recruited in the primary prevention stratum (80%), sample size projection correction increased the number of participants required from 12,600 to 18,000.

All analyses follow an intention-to-treat approach. Analyses of time-to-event data are performed using the Kaplan-Meier method and the log-rank test is performed to test treatment group differences. The relative risk and its 95% CI are calculated from the Cox proportional hazard model. Adverse events are compared between groups using the Fisher exact test. The analysis is performed according to the stratum of either primary or secondary prevention. Statistical significance is set at the <5% level with a 2-sided test.

Formal interim analysis is to be performed twice during the trial. The first will be 2 years after the final enrollment of participants (ie, in early 2002). The second will be mid 2004. The final analysis is expected in late 2005. The interim analysis will apply the Lan-DeMets boundary based on the number of cardiovascular events, supported by computing a conditional power to demonstrate the superiority of EPA against the control group, toward the end of the trial.

Figure 5



Organization of JELIS.

Trial organizational structure

The organizational structure of JELIS is illustrated in Figure 5. This study is conducted under the scientific direction of the Steering Committee. The External Data and Safety Monitoring Board is responsible for identifying safety issues and interpreting emerging study data.

Discussion

The preventive effect of n-3 PUFAs for CAD morbidity and mortality has been reported in various epidemiological researches and cohort studies.[32-34] JELIS is the first large-scale, randomized, controlled trial of highly purified EPA in hypercholesterolemia, including both primary and secondary prevention strata and using EPA as an adjuvant treatment with an HMG-CoA reductase inhibitor as the baseline drug. Study patients are expected to demonstrate that cardiovascular events can be further decreased by 25% beyond that expected by the use of HMG-CoA reductase inhibitors alone.

Several large-scale clinical studies have evaluated the effects of HMG-CoA reductase inhibitors in hypercholesterolemia.[23-26] Comparing our study with 4S,[23] WOS,[24] CARE,[25] LIPID,[26] and the currently ongoing MEGA STUDY[34] in Japan, the number of participants enrolled for JELIS surpasses that recorded for all the others. Subgroup analyses by age, sex, and concomitant disease might also produce important information on differences in event rates between Japan and other countries.

Although the inhibitory effect of dietary n-3 PUFAs on cardiovascular events has been assessed in a few case-control studies and in 2 secondary prevention trials, there has been no report on clinical outcomes assessed in randomized controlled trials involving primary prevention cases. JELIS is the first attempt to collect such data.

With respect to secondary prevention cases, randomized controlled trials such as DART[5] and GISSI[6] showed an inhibitory effect of n-3 PUFAs on cardiovas-

cular events. These studies, which advised consumption of meals containing fish or EPA plus DHA preparations, had shorter follow-up periods than JELIS, which has a median duration of 2 years to date, with a range of 1 to 4 years.

Further, because JELIS measured the plasma fatty acid fraction once a year, it is possible to study the relationship between changes in the composition of blood fatty acids, such as EPA, as well as oleic acid and linoleic acid, and the onset of cardiovascular events.

There have been relatively recent discussions on the appropriateness of prescribing cholesterol-lowering drugs to postmenopausal women.[35] Cholesterol-lowering drugs are taken by many Japanese women. The subclass analysis of our study may address the usefulness of these drugs for women.

As noted, we are conducting this trial on an exclusively Japanese population mainly because EPA is an allowed treatment for hyperlipidemia in Japan. Should our fundamental hypothesis be proven, it will then need to be argued whether the results can be extrapolated to non-Japanese populations and whether EPA is differentially effective between populations.

References

1. Dyerberg J, Bang HO, Stoffersen E. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978;2: 117–9.
2. Oomen CM, Feskens EJ, Rasanen L. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. Am J Epidemiol 2000;151:999–1006.
3. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Eng J Med 1985;312:1205–9.
4. Tamura Y, Hirai A, Terano T. Clinical and epidemiological studies of eicosapentaenoic acid (EPA) in Japan. Prog Lipid Res 1986;25: 461–6.
5. Burr ML, Fehily AM, Gibert JK. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757–61.
6. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevention trial. Lancet 1999;354:447–55.
7. Harris WS, Muzio F. Fish oil reduces postprandial triglyceride concentrations without accelerating lipid-emulsion removal rates. Am J Clin Nutr 1993;58:68–74.
8. Wong SH, Fisher EA, March JB. Effects of eicosapentaenoic and docosahexaenoic acids on apoprotein B m RNA and secretion of very low density lipoprotein in HepG2 cells. Arteriosclerosis 1989; 9:836–41.
9. Ando M, Sanaka T, Nihei H. Eicosapentaenoic acid reduces plasma levels of remnant lipoproteins and preventions in vivo peroxidation of LDL in dialysis patients. J Am Soc Nephrol 1999;10: 2177–84.
10. Hirai A, Terano T, Hamazaki T. The effect of the oral administration of fish oil concentration on the release and the metabolism of [14C]arachidonic acid and [14C]eicosapentaenoic acid by human platelets. Thrombosis Res 1982;28:285–98.
11. Hamazaki T, Hirai A, Terano T. Effects of orally administered ethyl estel of eicosapentaenoic acid (EPA; C20: 5, omega 3) on PGI2-like substance production by rat aorta. Prostaglandins 1982;23: 557–67.
12. Okuda Y, Kawashima K, Sawada T. Eicosapentaenoic acid enhances nitric oxide production by cultured human endothelial cells. Biochem Biophys Res Com 1997;232:487–91.
13. Marcmann P, Jespersen J, Leth T. Effect of fish diet versus meat diet on blood lipids, coagulation and fibrinosis in healthy young men. J Intern Med 1991;229:317–23.
14. Radack K, Deck C, Huster G. The comparative effects of n-3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. J Am Coll Nutr 1990;9:352–7.
15. Schmidt EB, Pedersen JO, Ekelund S. Cod liver oil inhibits neutrophils and monocyte chemotaxis in healthy males. Atherosclerosis 1989;77:53–7.
16. Lee TH, Hoover RL, Williams JD. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophils and monocyte leukotriene generation and neutrophils function. N Eng J Med 1985;312:1217–24.
17. Endres S, Ghorbani R, Kelley VE. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Eng J Med 1989;320:265–71.
18. Li Y, Ferrante A, Poulos A. Neutrophil oxygen radical generation: synergistic responses to tumor necrosis factor and mono/polyunsaturated fatty acids. J Clin Invest 1996;97:1605–9.
19. Terano T, Shiina T, Tamura Y. Eicosapentaenoic acid suppressed the proliferation of vascular smooth muscle cells through modulation of various steps of growth signals. Lipid 1996;31:301–4.
20. Murakami K, Ide T, Suzuki M. Evidence for direct binding of fatty acids and eicosanoids to human peroxisome proliferators-activated receptor alpha. Biochem Biophys Res Commun 1999;260: 609–13.
21. Ricote M, Li AC, Wilson TM. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 1998;391:79–82.
22. Leaf A. The electrophysiologic basis for the antiarrhythmic and anticonvulsant effects of n-3 polyunsaturated fatty acids: heart and brain. Lipids 2001;36:107–10.
23. Scandinavian Simvastatin Survival Study group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
24. Shepherd J, Cobbe SM, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New Eng J Med 1995;333:1301–7.
25. Sacks FM, Pfeffer MA, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New Eng J Med 1996;335:1001–9.
26. The Long-term Intervention with Pravastatin Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New Eng J Med 1998; 339:1349–57.

27. Mataki H, Watsuji Y, Iseki O. Effect of eicosapentaenoic acid in combination with HMG-CoA reductase inhibitor on lipid metabolism. J Intern Med 1998;5:35–6.
28. Nordoy A, Bonaa KH, Nilsen H. Effect of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 1998;243: 163–70.
29. Nakamura N, Hamazaki T, Ohta M. Joint effect of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile and plasma fatty acid concentrations in patients with hyperlipidemia. Int J Clin Lab Res 1999;29:22–5.
30. Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up, Hiroshima/Nagasaki Study. Jpn Circ J 1990;54: 414–21.
31. Ross SD, Allen IE, Connelly JE. Clinical outcomes in statin treatment trials: a meta-analysis. Arch Intern Med 1999;159:1793–802.
32. Dolecek TA, Grandits G. Dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial (MRFIT). World Rev Nutr Diet 1991;66:205–16.
33. Shekelle RB, Missell L, Paul O. Fish consumption and mortality from coronary heart disease. New Eng J Med 1985;313:820–1.
34. Nakamura H, for the MEGA STUDY Group. Primary prevention of coronary events with pravastatin in Japanese men and women with mildly or moderately elevated blood cholesterol. J Jpn Atheroscler Soc 1999;26:201–4.
35. Yamamoto A, Horibe H, Mabuchi H. Analysis of serum lipid levels in Japanese men and women: Research Group on Serum Lipid Survey 1990 in Japan. Atherosclerosis 1999;143:55–73.

EBMと生物統計学
Evidence-Based Medicine and Biostatistics

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1. EBM と は

EBM とは Evidence-Based Medicine の略で，日本語では根拠に基づく医療と訳されている（久繁, 1998; 名郷, 1999）．根拠というのは何かというと，それはいわゆる臨床研究のことである．もっと言うと，臨床研究で得られたデータのことである．従って，データに基づいて診療を行うという，きわめて自然なことなのである．データとなると，そこには統計学の入る余地があろう．実際にもそういった理由から，臨床研究において統計学や臨床疫学という学問が重視されるようになった．

EBM という言葉が登場したのは 1992 年のことである（Evidence-Based Medicine Working Group, 1992）．カナダにいる Sackett et al.（2000）によって広められた．EBM というのは概念とか枠組みといった抽象論の話ではなく，診療の実践そのものである．従って，EBM の定義は以下のようになされる．目の前の患者さんに対して，その疑問を明らかにしたうえで，それに関連する現在入手できる最新情報を踏まえ，さらにその患者さんの置かれる状況を勘案して，その患者さんにベストな処方を与えるための行動指針である．言われてみると当たりまえの話だが，「最新情報を踏まえ」という点がポイントである．IT 時代にあって情報へのアクセスが容易になったゆえ，EBM もそれに従って台頭してきたと思われる．この EBM であるが，表 1 に示したような 4 つのステップからなる．

表 1. EBM 実践における 4 ステップ

ステップ	そこで必要とされること
疑問の定式化	分析能力
情報の収集	IT 利用術
情報の吟味	生物統計学・臨床疫学（Chance と Bias）
患者への応用	コミュニケーション技術

EBM では根拠となる臨床研究データを扱うわけであるが，それを信憑性の面から分類している．それは主として研究デザインの面（折笠, 1995）から行っている．分類法には様々な提案があるが，表 2 にように信憑性の高い順でまとめてみた．水準 1 には結果がほぼ一致した RCT（ランダム化比較試験）によるメタアナリシス，大規模な（つまり信頼区間が狭い）RCT，それから臨床研究をするまでもなく明白な事実が含まれている．水準 2 としては，RCT ではなく観察研究によるメタアナリシス，大規模ではない RCT，そしてランダム割付けを伴わない比較試験（CCT: Controlled Clinical Trials）が含まれる．最後の CCT というのは，メタアナリシス又は系統的レビューを国際組織で実施している，コクライングループで考案されたデザイン名である．水準 3 には Cohort 研究が含まれ，水準 4 には Case-control 研究，そして実験研究として前後比較研究が含まれる．水準 5 は Cross-sectional 研究，実験研究として症例集積が含まれる．最後の水準 6 は研究ではなく，単なる経験だけに基づいているものである．

表 2. EBM における根拠水準の順位付け

水準	それに該当する研究デザイン（一部，結果内容も加味）
1a	一致した結果を示す RCT によるメタアナリシス
1b	狭い信頼区間を示す RCT
1c	明白な結果
2a	一致した結果を示す観察研究によるメタアナリシス，RCT
2b	CCT
3	Cohort 研究
4	Case-control 研究，前後比較研究
5	Cross-sectional 研究，症例集積
6	単なる意見や経験のたぐい

このように見てくると，生物統計学の中でも研究デザインという観点が EBM で非常に重視されていることがわかる（折笠, 2000; 折笠, 2001）．また，結果として狭い信頼区間というように，統計学の守備範囲である Chance（偶然）という考え方も必須となっている．EBM ではこうした Chance という考え方に加えて，Bias という概念も大切である．後者はどちらかというと疫学で重視される概念である．総括すると，臨床疫学を駆使して Bias の入っていないデザインかどうかを選別し，得られた結果が偶然ではなく確かなものかどうかは統計学の Chance という観点から判断する．

結果に Bias の入りにくいデザインとして RCT があるが，EBM ではそれが重要なものとして取り上げられている．ただ RCT であれば大丈夫かというと，それは誤りである．そういう理由から，RCT 研究の善し悪しを点検するためのリストが統計家を中心に考案されてきた（Moher et al, 2001）．それを表 3 に示したが，CONSORT 声明と呼ばれている．

表 3. RCT 論文のチェックリスト: CONSORT 声明

表題と要旨

「ランダム割付け」や「ランダム化（無作為化）」という用語を含む.

緒論

どうしてこの臨床試験が必要かの根拠を述べる.

方法

対象の適格条件を述べる.
介入の内容を述べる.
研究仮説を述べる.
主要・副次エンドポイントを定義する.
症例数設定の根拠を述べる.
ランダム化コード票作成法，具体的割り付け手順の隠蔽化を述べる.
盲検化について述べる.
統計解析法について述べる.

結果

患者プロファイルの流れ図を示す.
登録と追跡の期間について述べる.
群ごとにベースラインデータを示す.
解析対象数を明記する.
エンドポイントについて効果サイズと信頼区間を示す.
多重性を意識し，層別解析や調整解析の結果を示す.
重要な副作用について述べる.

コメント

バイアス，症例数不足，多重性について述べる.
一般化可能性について述べる.
総合的に結果を解釈する.

EBM では RCT と同様に，メタアナリシスという研究も重視される．こちらもデザインがメタアナリシスだからといって，一概に信用できるものではない．RCT の場合と同様にして，メタアナリシス論文用のチェックリストも作成された（Moher et al, 1999）．それは QUOROM 声明と呼ばれており，表 4 に日本語訳を示した．これらのチェックリストを利用して，要は Bias と Chance の点からそれぞれの研究の信憑性を評価することである．

表 4. メタアナリシス論文のチェックリスト: QUOROM 声明

表題		
	「メタアナリシス」又は「系統的レビュー」という用語を含む.	
抄録		
	構造化抄録を用いる.	
	目的	臨床疑問を明示する.
	データ	用いた研究のリストなど, 情報源を示す.
	方法	選択基準, 妥当性評価法, データ要約法, 研究特徴, 統合のための統計手法を示す.
	結果	選択した RCT, 除外した RCT を表示し, 知見 (点推定と信頼区間) を示す. また層別解析の結果も示す.
	結論	主たる結果を述べる.
緒論		
	臨床疑問とその介入について調査する理由, 総合評価する根拠を述べる.	
方法		
	検索	情報源と検索条件を示す.
	選択	集団, 介入内容, 評価項目, 研究デザインに関して選択基準と除外基準を示す.
	評価	収集された研究に関して, 妥当性評価の基準と手法を示す.
	要約	データ要約の手順について示す (2 人独立に, など).
	研究	各研究のデザイン特徴を示す項目を示す.
	統合	効果指標, 統合手法, 欠損の取り扱い, 異質性の評価法, 出版バイアスの点検法について示す.
結果		
	流れ図	メタアナリシスの実施に関する流れ図を示す.
	研究	研究ごとにデザイン特徴を示す.
	統合	データ統合の結果を示し, 要約指標を示す.
考察		
	結果の妥当性について, バイアスの可能性について述べる.	

2. 生物統計学との関連性

EBM において生物統計学 (Biostatistics) がどのように関連するか. それは臨床研究の結果について, 正しく評価するさいに必要となる. 得られた結果は P 値で示され, それは $P < 0.05$ であれば通常有意として発表される. この P 値をみると, それはたまたま良い結果になったわけではなく, Chance を超えて良い結果だとわかる. しかし, この P 値だけではどのくらい良かったかということまでは不明である. そこで, P 値と並んで信頼区間が使われるわけである (舟喜と折笠, 2001). 信頼区間を見れば, 悪くてもこのくらい, 良ければこのくらい, といった目安がわか

る．このように，EBM において研究結果が Chance（偶然）で説明できるのか，そうでないかを見分けるには生物統計学の素養が必要となる．

もう一方の素養は，いわゆる臨床疫学（Clinical Epidemiology）と呼ばれるものである．折笠（1995）によると，生物統計学の計画部門と位置付けることもできよう．これは，Chance に対して Bias（偏り）という用語で象徴される．Bias がないかを見分けるためには研究デザインの知識に加えて，その臨床領域の基礎的知識，そして現場でどのようにして実施されたかを知らないと判断が難しい．

統計学的有意というのは $P < 0.05$ になった結果を言うが，たとえ統計学的有意になったとしても，臨床的には意味がないこともある．それを知るためには信頼区間が必要である．例えば，糖尿病治療のための新薬と標準薬があり，新薬では HbA1c を 0.5％下げ，標準薬では 0.3％下げたとしよう．両者の差は 0.2％（95％信頼区間: 0.1～0.3％）であったとする．この結果は統計学的には有意である．帰無仮説の 0％を含んでいないからである．しかし，高く見積もっても新薬は 0.3％より下げるにすぎない．こうなると，臨床的に有意な結果かどうかは疑わしくなる．また，次のことも考える余地があろう．患者背景が HbA1c 9％ など高い集団だとすると，0.3％ではあまり意味がないかもしれない．一方，HbA1c 7％近辺では 0.3％でも臨床的に意味があるかもしれない．

最後に，EBM で用いる特別の統計量（効果指標）について考えたい．その代表例が NNT（Number Needed to Treat）という指標である．Laupacis et al.（1988）がはじめて提唱した統計量であり，2 群のイベント発生率の絶対差の逆数で定義される．例えば，新薬のイベント発生率が 5％，標準薬のそれが 3％としよう．絶対差は 2％（$= 0.02$）である．その逆数をとると，$1 \div 0.02 = 50$ 人となる．この 50 人というのが NNT になる．すなわち 50 人に 1 人の割合で，新薬によりイベントを回避できることを意味する．NNT が小さいほうがその効果は強いことになる．ここで，絶対差の信頼区間は二項分布あるいは正規近似などで容易に求められる．しかし，その逆数の信頼区間となると Delta method など，さらに近似を用いる必要が生じる．さらに面倒なことに，この NNT の信頼区間を図示すると，それは図 1 のように断絶された形となる．0 人をはさんでプラス側では救うほう（有効性）を示し，マイナス側はイベントを増やすほう（危険性）を示す．さらに，その大きさが連続的ではなく，0 人に近づくにつれて有効性・危険性ともに大きくなる．このため変則的な信頼区間になるのである．

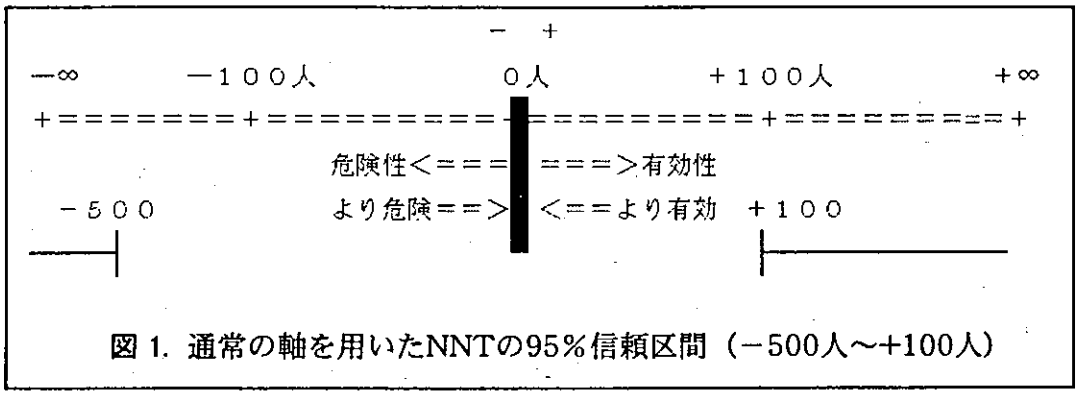

図 1. 通常の軸を用いたNNTの95％信頼区間（－500人～+100人）

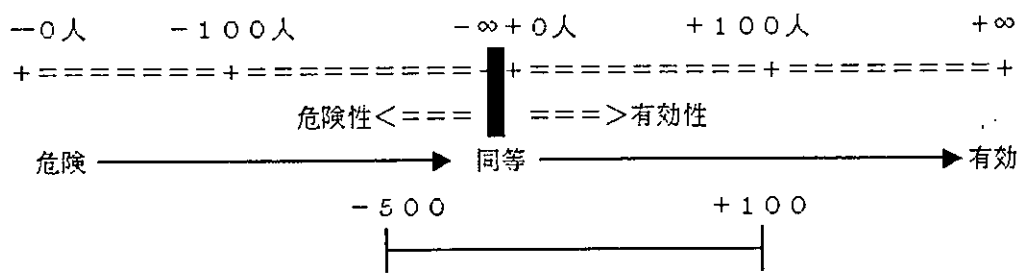

図 2. 軸を変えた時のNNTの95%信頼区間（−500人〜+100人）

信頼区間が途中で断絶されないようにするには，図 2 のように軸を変えないといけない．図 2 では危険から有効へと連続的な軸となっているが，NNT に関してみると変則的となってしまっている．信頼区間（−500 人から +100 人）は，通常なら −500 から −300, −100, 0 を経て +100 まで移行すると考えるだろう．しかし，ここでは −500 から −1000, −∞（+0 人 と同じ）を経て +100 人へ移行するのである．解釈としては，悪く見積もると 500 人に 1 人の割合でイベントを増やす可能性，よく見積もると 100 人に 1 人の割合でイベントを減らすとなる．NNT という EBM 特有の統計量に関する信頼区間の構成法については，Altman（1998）及び Bender（2001）を参照されたい．また，イベント発生までの時間データでの NNT については，Altman and Anderson (1999) が参照になろう．これらの例から，EBM に対する統計学からのチャレンジはさらに必要であることが伺われる．

疫学の分野では Person − year（人年）という単位がよく使われる．これについては統計モデル解析として，Poisson 回帰などの手法が開発されてきた．上の NNT などの解析でも，その Behaviour が変わったものなので，特別な解析法の開発が今後進むことを期待したい．

3. 結果の表示法をめぐって

EBM では特に治療法の臨床成績を示すとき，様々の指標が提案されてきた．時には，その違いに惑わされることもある．1988 年に様々の効果指標が Review されているが（Laupacis et al., 1988），そのとき初めて NNT という指標が提案された．NNT というのは主として有効性のほうを示しているものだが，そうではなく Negative な結果が報告されることもある．いわゆる有害作用を報告した論文である．このときには何人救えるかではなく，何人に危害を及ぼすかということになる．それにあわせて，NNTH（Number Needed To Harm）という指標が提案された．そうであれば，NNT のほうも本来は Benefit だからということで，NNTB（Number Needed To Benefit）と呼ぶこともある．この 2 つの用語は Altman（1998）の中で初めて見られた．有害作用のほうの NNTH については，Bjerre and LeLorier（2000）や折笠（2000a）に見られる事例を参照されたい．これらは臨床家に有用とされる，すべて絶対的な指標である．ただ治療法同士を比較するには，相対的な指標が便利なこともある．その中で NRR（Number Remaining at Risk）という指標も最近提案された（Massel and Cruickshank, 2002）．ここでは EBM でよく登場する