Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

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See **Comment** page 1062

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Summary

Background Epidemiological and clinical evidence suggests that an increased intake of long-chain n-3 fatty acids protects against mortality from coronary artery disease. We aimed to test the hypothesis that long-term use of eicosapentaenoic acid (EPA) is effective for prevention of major coronary events in hypercholesterolaemic patients in Japan who consume a large amount of fish.

Methods 18 645 patients with a total cholesterol of 6·5 mmol/L or greater were recruited from local physicians throughout Japan between 1996 and 1999. Patients were randomly assigned to receive either 1800 mg of EPA daily with statin (EPA group; n=9326) or statin only (controls; n=9319) with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Analysis was by intention-to-treat. The study was registered at clinicaltrials.gov, number NCT00231738.

Findings At mean follow-up of 4·6 years, we detected the primary endpoint in 262 (2·8%) patients in the EPA group and 324 (3·5%) in controls—a 19% relative reduction in major coronary events (p=0·011). Post-treatment LDL cholesterol concentrations decreased 25%, from 4·7 mmol/L in both groups. Serum LDL cholesterol was not a significant factor in a reduction of risk for major coronary events. Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8·7%] in the EPA group *vs* 197 [10·7%] in the control group; p=0·048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1·4%] in the EPA group *vs* 127 [1·7%] in the control group; p=0·132).

Interpretation EPA is a promising treatment for prevention of major coronary events, and especially non-fatal coronary events, in Japanese hypercholesterolaemic patients.

Introduction

Epidemiological and clinical evidence suggests a significant inverse association between long-term intake of long-chain n-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and mortality associated with coronary artery disease.[1–7] Thus, the consumption of fish or fish-oil could protect against major events associated with coronary artery disease, especially fatal myocardial infarction and sudden cardiac death. Two large-scale secondary prevention trials, the Diet and Reinfarction Trial and the Gruppo Italiano per lo Studio della Sopravivenza nell' Infarto Miocardico-Prevenzione Trial, reported that increased consumption of fish or fish-oil supplements reduced coronary death in postinfarction patients.[8,9] No randomised trials have examined the effects of n-3 polyunsaturated fatty acids on major coronary events in a high-risk, primary prevention population.

EPA ethyl ester, which is purified from n-3 polyunsaturated fatty acids present in fish oil, is approved by Japan's Ministry of Health, Labour, and Welfare as a treatment for hyperlipidaemia and peripheral artery disease. The biological functions of EPA include reduction of platelet aggregation,[10,11] vasodilation,[12,13] antiproliferation,[14] plaque-stabilisation,[15] and reduction in lipid action.[16,17] Therefore the preventive effects of EPA on major cardiovascular events are of both clinical interest and therapeutic importance.

Primary and secondary prevention trials have proved that cholesterol-lowering treatment with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase—statins—reduces the risk of all-cause mortality and major cardiovascular events in patients with a wide range of cholesterol concentrations, whether or not they have had coronary artery disease.[18–21] Thus, statins are now established as the first-line treatment for hyperlipidaemia.[22] Preliminary data for treatment with a combination of n-3 polyunsaturated fatty acids and statins have shown beneficial effects on the lipid profiles of patients with a mixed type of hyperlipidaemia;[23–25] however, no major long-term inter-

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ventional trial has yet investigated whether the addition of EPA to conventional statin treatment would yield an incremental clinical benefit. The Japan EPA Lipid Intervention Study (JELIS) tests the hypothesis that long-term use of EPA is effective in reduction of major coronary events in Japanese hypercholesterolaemic patients given statins.

Methods

Study design and patients

We did a prospective, randomised open-label, blinded endpoint evaluation (PROBE).[26] Our study design, and inclusion and exclusion criteria are described in detail elsewhere.[27] We recruited 19 466 hypercholesterolaemic patients through local physicians from all regions of Japan between November, 1996, and November, 1999. Figure 1 shows the trial profile. The participants consisted of 5859 men (aged 40–75 years) and 12 786 postmenopausal women (aged up to 75 years), with or without coronary artery disease, which was defined as previous myocardial infarction, coronary interventions, or confirmed angina pectoris. Informed written consent was obtained from all eligible patients before random assignment to either the EPA treatment or control groups.

Eligibility criteria were total cholesterol concentration of 6·5 mmol/L or greater, which corresponded to a LDL cholesterol of 4·4 mmol/L or greater. Exclusion criteria were: acute myocardial infarction within the past 6 months, unstable angina pectoris, a history or complication of serious heart disease (such as severe arrhythmia, heart failure, cardiomyopathy, valvular disease, or congenital disease), cardiovascular reconstruction within the past 6 months, cerebrovascular disorders within the past 6 months, complications of serious hepatic or renal disease, malignant disease, uncontrollable diabetes, hyperlipidaemia due to other disorders, hyperlipidaemia caused by drugs such as steroid hormones, haemorrhage (including haemophilia, capillary fragility, gastrointestinal ulcer, urinary tract haemorrhage, haemoptysis, and vitreous haemorrhage), haemorrhagic diathesis, hypersensitivity to the study drug formulation, patients' intention to undergo surgery, and judgment by the physician in charge that a patient was inappropriate for the study.

The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Secondary endpoints (all-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease, and cancer) are not reported here.

Procedures

We used the statistical coordination centre at the Toyama Medical and Pharmaceutical University to manage patient registration (including confirmation of eligibility criteria), operation of the randomisation scheme, and data management. We used permuted-block randomisation with a block size of four. Blocks were assigned according to the number of participants enrolled at each centre. Patients were divided into two subgroups: one with coronary artery disease (secondary prevention; n=3664) and one without (primary prevention; n=14 981), and stratified accordingly. Patients were randomly assigned to receive EPA with statin (EPA group) or statin alone (controls). All patients first underwent 4–8 weeks of washout from antihyperlipidaemic drugs. Patients also received appropriate dietary advice.

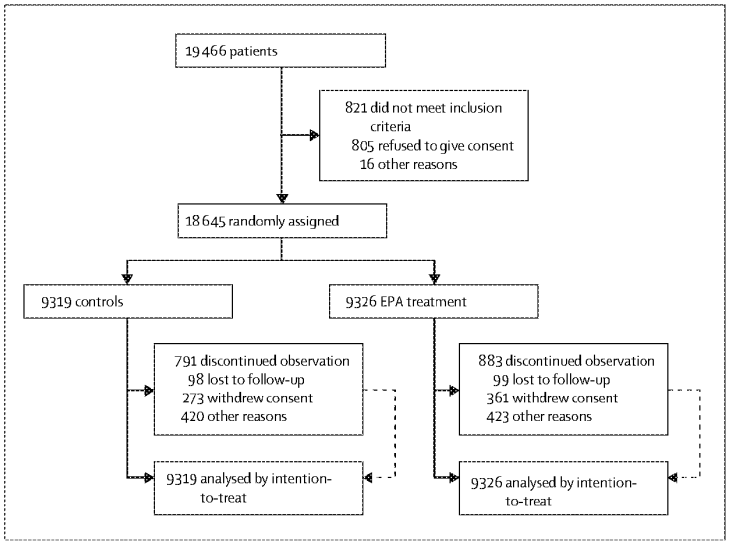

Figure 1: Trial profile

All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment. These statins were available in Japan at the initiation of this study, and these doses were recommended by the Ministry of Health, Labour, and Welfare. For serious hypercholesterolaemia (defined as uncontrolled), this daily dose was increased to 20 mg pravastatin or 10 mg simvastatin. No treatment with other antihyperlipidaemic drugs was allowed during the study. EPA was given at a dose of 600 mg, three times a day after meals (to a total of 1800 mg per day). We used capsules that contained 300 mg of highly purified (>98%) EPA ethyl ester (Mochida Pharmaceuticals, Tokyo, Japan).

Local physicians monitored compliance with dietary advice and medication, and noted adverse events at every clinic visit. Clinical endpoints and severe adverse events reported by local physicians were checked by members of a regional organising committee in a blinded fashion. Then, an endpoints adjudication committee (see webappendix), consisting of three expert cardiologists and one expert neurologist, confirmed them once a year without knowledge of the

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	Controls (n=9319)	EPA treatment (n=9326)
Age (years)	61 (9)	61 (8)
Male	2908 (31%)	2951 (32%)
BMI (kg/m²)	24 (3)	24 (3)
Cardiovascular history		
Myocardial infarction	502 (5%)	548 (6%)
Angina	1484 (16%)	1419 (15%)
CABG or PTCA	433 (5%)	462 (5%)
Risk factors		
Smoking	1700 (18%)	1830 (20%)
Diabetes	1524 (16%)	1516 (16%)
Hypertension	3282 (35%)	3329 (36%)
Serum lipid values		
Total cholesterol (mmol/L)	7·11 (0·68)	7·11 (0·67)
LDL-cholesterol (mmol/L)	4·70 (0·75)	4·69 (0·76)
HDL-cholesterol (mmol/L)	1·51 (0·44)	1·52 (0·46)
Triglyceride (mmol/L)*	1·74 (1·25–2·49)	1·73 (1·23–2·48)
Blood pressure		
Systolic (mm Hg)	135 (21)	135 (21)
Diastolic(mm Hg)	79 (13)	79 (13)
HMG CoA RI		
Pravastatin	5553 (60%)	5523 (60%)
Simvastatin	3417 (37%)	3272 (36%)
Other statin	128 (1%)	110 (1%)
Medication use		
Antiplatelet agent	1342 (14%)	1258 (13%)
Calcium antagonist	2837 (30%)	2796 (30%)
β blocker	791 (8%)	794 (9%)
Other antihypertensive agents	2424 (26%)	2366 (25%)
Nitrate	926 (10%)	863 (9%)
Hypoglycaemic agents	1126 (12%)	1081 (12%)

Data are number of patients (%) or mean (SD), unless otherwise indicated. CABG=coronary-artery bypass grafting. PTCA=percutaneous transluminal coronary angioplasty. LDL=low-density lipoprotein. HDL=high-density lipoprotein. IQR=interquartile range. HMG CoA RI=3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. BMI=body-mass index, which is weight in kg divided by the square of height in metres. *Median (IQR).

Table 1: **Baseline characteristics**

See **Online** for webtable

treatment allocation. The study was approved by an external data and safety monitoring board, by institutional review boards at all hospitals, and by regional organising committees. The data and safety monitoring board also monitored the rate of endpoints twice during the study, in March, 2002, and March, 2004. The study was followed up until November, 2004, because both interim analyses did not reach the stopping boundary.

We sampled blood to measure serum lipid at 6 and 12 months, and then every year until the final follow-up visits. Plasma total fatty acid concentrations for all patients who gave informed consent were measured with capillary gas chromatography every year at a central laboratory.

Statistical analysis

We used a two-sided test at the 5% significance level to estimate that the number of enrolled patients would give the study a statistical power of 80% for detection of a relative reduction of 25% in the primary endpoint rate, when the EPA group was compared with controls. The event rate of the primary endpoint in the control group was assumed to be 0·58% per year for primary prevention and 2·13% per year for secondary prevention; the proportion of primary and secondary prevention strata was assumed to be 4:1. The accrual period was assumed to be 3 years with a follow-up of 5 years for all patients. All analyses were based on the intention-to-treat principle. Time-to-event data were analysed with the Kaplan–Meier method and the log-rank test. The hazard ratio and its 95% confidence interval were computed with the Cox proportional hazard model. We did subgroup analyses with a model that included an interaction term corresponding to the test for heterogeneity in effects. Changes in lipid values were compared by repeated measures of ANOVA. Data were analysed with SAS statistical software (version 8.12).

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The JELIS steering committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were monitored for an average of 4·6 years (SD 1·1). Table 1 shows baseline characteristics of the treatment groups. The mean age of all patients was 61 years and 12 786 patients (69%) were women. Mean concentrations of total cholesterol and triglyceride were 7·1 mmol/L and 1·7 mmol/L; and mean LDL and HDL cholesterol concentrations were 4·7 mmol/L and 1·5 mmol/L, respectively. The webtable shows baseline characteristics for primary and secondary prevention subgroups. Of 3664 patients with documented coronary artery disease, 1050 had a history of myocardial infarction, 2903 of angina pectoris, and 895 angioplasty, stenting, or coronary artery bypass grafting.

Average doses were pravastatin 10·0 mg daily (SD 9·1) and simvastatin 5·6 mg daily (1·8). 16 449 (90%) patients took 10 mg pravastatin or 5 mg simvastatin. The 5-year follow-up rate was 16 971 (91%). Similar proportions of participants remained compliant in each treatment group. Study drug regimens were maintained until trial termination by 6151 (73%) of controls and in the treatment group 5883 (71%) of patients continued to take EPA and 6136 (74%) continued to take statin.

586 patients (262 assigned to EPA and 324 controls) reached the composite primary endpoint. Figure 2 shows Kaplan–Meier curves for the primary endpoint. The 5-year cumulative rate of major coronary events

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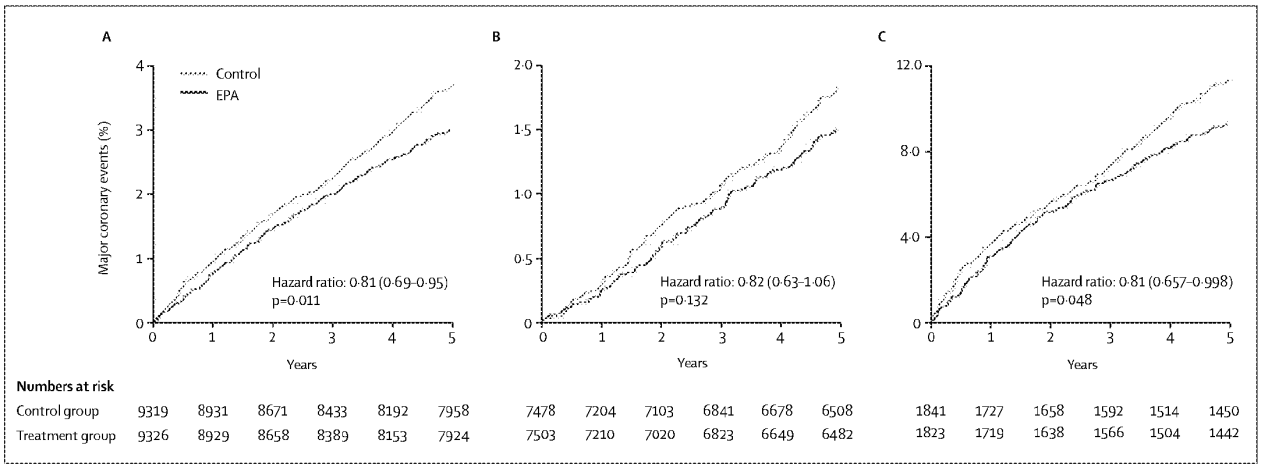

Figure 2: **Kaplan-Meier estimates of incidence of coronary events in the total study population (panel A), the primary prevention arm (panel B) and the secondary prevention arm (panel C)**

was 2·8% in the EPA group and 3·5% in controls, resulting in a significant relative risk reduction of 19% in the EPA group (p=0·011). Figure 3 shows that EPA treatment was associated with a significant reduction of 24% in the frequency of unstable angina. The occurrence of coronary death or myocardial infarction was not significantly lower (22%) in the EPA group than in controls. The frequency of fatal or non-fatal myocardial infarction was not significantly reduced (23%) in the EPA group; however, that of non-fatal coronary events (including non-fatal myocardial infarction, unstable angina, and events of angioplasty, stenting, or coronary artery bypass grafting) was significantly lower (19%) in the EPA group than in controls.

Table 2 sets out major coronary events in the two treatment groups for comparison with specific background characteristics of all populations. For example, we grouped patients according to their LDL cholesterol at baseline. The relative reduction in major coronary events risk in the EPA group was of a similar magnitude in patients with different ranges of LDL cholesterol values, suggesting that LDL cholesterol is not an important factor in reduction of risk for major coronary events.

In the primary prevention subgroup, EPA treatment was associated with a non-significant 18% reduction in major coronary events. Figure 3 shows the non-significant reductions of 18%, 21%, and 20% in coronary death or non-fatal myocardial infarction, fatal or non-fatal myocardial infarction, and non-fatal coronary events, respectively. In the secondary prevention subgroup, allocation to the EPA treatment was associated with a significant 19% reduction in major coronary events. EPA treatment was also associated with a significant 28% reduction in the incidence of unstable angina. This treatment also produced non-significant reductions of 25%, 25%, and 18% in coronary death or myocardial infarction, fatal or non-fatal myocardial infarction, and non-fatal coronary events, respectively.

In the other analyses, stroke occurred in 162 (1·7%) controls and 166 (1·8%) patients given EPA. Figure 3 shows that the frequency of ischaemic and haemorrhagic strokes did not differ between the two treatment groups, and neither did all-cause mortality.

Figure 4 summarises the change in lipid values after treatment. Total and LDL cholesterol at the last clinic visit decreased significantly by 19% and 25% from baseline in both groups, respectively. Triglyceride decreased significantly by 9% from baseline in the EPA group and by 4% in controls (p<0·0001 between groups). Both treatments produced only small changes in HDL cholesterol. The fatty acid concentrations at baseline were the average values for all patients who gave informed consent in the control group (n=8076) and the EPA group (n=8321). Plasma EPA at baseline was 2·9% of total molecules of fatty acids (mol %). To assess the effect of EPA treatment, plasma fatty acid values were compared for all patients who were still compliant after 5 years of observation (controls: n=4854, EPA group: n=4970). Plasma EPA concentration and the ratio of EPA to arachidonic acid at baseline were 93 mg/L and 0·60 in controls, and 97 mg/L and 0·63 in the EPA group, respectively. Plasma EPA concentration and the ratio of EPA to arachidonic acid at year 5 were 93 mg/L and 0·59 in controls. On the other hand, plasma EPA concentration at year 5 was 169 mg/L in the EPA group, which was a 70% increase from baseline. The ratio of EPA to arachidonic acid increased two-fold from 0·63 to 1·23 in the EPA group. Similar results were reported previously.[11,28]

Table 3 shows that a quarter of patients in the EPA group had adverse experiences related to treatment, compared with about a fifth of controls. Rates of

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Event	Number (%) of patients: Control	EPA	p value	Hazard ratio (95 %CI)
All patients				
Major coronary events	324 (3·5)	262 (2·8)	0·011	0·81 (0·69–0·95)
Items of account				
Sudden cardiac death	17 (0·2)	18 (0·2)	0·854	1·06 (0·55–2·07)
Fatal MI	14 (0·2)	11 (0·1)	0·557	0·79 (0·36–1·74)
Non-fatal MI	83 (0·9)	62 (0·7)	0·086	0·75 (0·54–1·04)
Unstable angina	193 (2·1)	147 (1·6)	0·014	0·76 (0·62–0·95)
CABG or PTCA	222 (2·4)	191 (2·1)	0·135	0·86 (0·71–1·05)
Combined endpoint				
Coronary death or MI	113 (1·2)	88 (0·9)	0·083	0·78 (0·59–1·03)
Fatal MI or nonfatal MI	93 (1·0)	71 (0·8)	0·091	0·77 (0·56–1·05)
Coronary death	31 (0·3)	29 (0·3)	0·812	0·94 (0·57–1·56)
Non-fatal coronary events	297 (3·2)	240 (2·6)	0·015	0·81 (0·68–0·96)
Primary prevention of CAD				
Major coronary events	127 (1·7)	104 (1·4)	0·132	0·82 (0·63–1·06)
Items of account				
Sudden cardiac death	4 (0·1)	5 (0·1)	0·736	1·25 (0·34–4·67)
Fatal MI	6 (0·1)	6 (0·1)	0·995	1·00 (0·32–3·11)
Non-fatal MI	45 (0·6)	36 (0·5)	0·321	0·80 (0·52–1·24)
Unstable angina	70 (0·9)	59 (0·8)	0·338	0·85 (0·60–1·19)
CABG or PTCA	74 (1·0)	64 (0·9)	0·400	0·87 (0·62–1·21)
Combined endpoint				
Coronary death or MI	55 (0·7)	45 (0·6)	0·322	0·82 (0·55–1·22)
Fatal MI or nonfatal MI	51 (0·7)	40 (0·5)	0·253	0·79 (0·52–1·19)
Coronary death	10 (0·1)	11 (0·1)	0·822	1·10 (0·47–2·60)
Non-fatal coronary events	119 (1·6)	95 (1·3)	0·102	0·80 (0·61–1·05)
Secondary prevention of CAD				
Major coronary events	197 (10·7)	158 (8·7)	0·048	0·81 (0·66–1·00)
Items of account				
Sudden cardiac death	13 (0·7)	13 (0·7)	0·967	1·02 (0·47–2·19)
Fatal MI	8 (0·4)	5 (0·3)	0·421	0·64 (0·21–1·94)
Non-fatal MI	38 (2·1)	26 (1·4)	0·150	0·70 (0·42–1·14)
Unstable angina	123 (6·7)	88 (4·8)	0·019	0·72 (0·55–0·95)
CABG or PTCA	148 (8·0)	127 (7·0)	0·243	0·87 (0·69–1·10)
Combined endpoint				
Coronary death or MI	58 (3·2)	43 (2·4)	0·156	0·75 (0·51–1·12)
Fatal MI or nonfatal MI	42 (2·3)	31 (1·7)	0·223	0·75 (0·47–1·19)
Coronary death	21 (1·1)	18 (1·0)	0·667	0·87 (0·46–1·64)
Non-fatal coronary events	178 (9·7)	145 (8·0)	0·080	0·82 (0·66–1·02)
Other analyses				
Stroke	162 (1·7)	166 (1·8)	0·785	1·02 (0·91–1·13)
Ischaemic	123 (1·3)	115 (1·2)	0·632	0·97 (0·85–1·10)
Haemorrhagic	39 (0·4)	49 (0·5)	0·272	1·12 (0·91–1·39)
Other type or not determined	5 (0·1)	2 (<0·1)	0·252	0·63 (0·24–1·37)
All-cause death	265 (2·8)	286 (3·1)	0·333	1·09 (0·92–1·28)

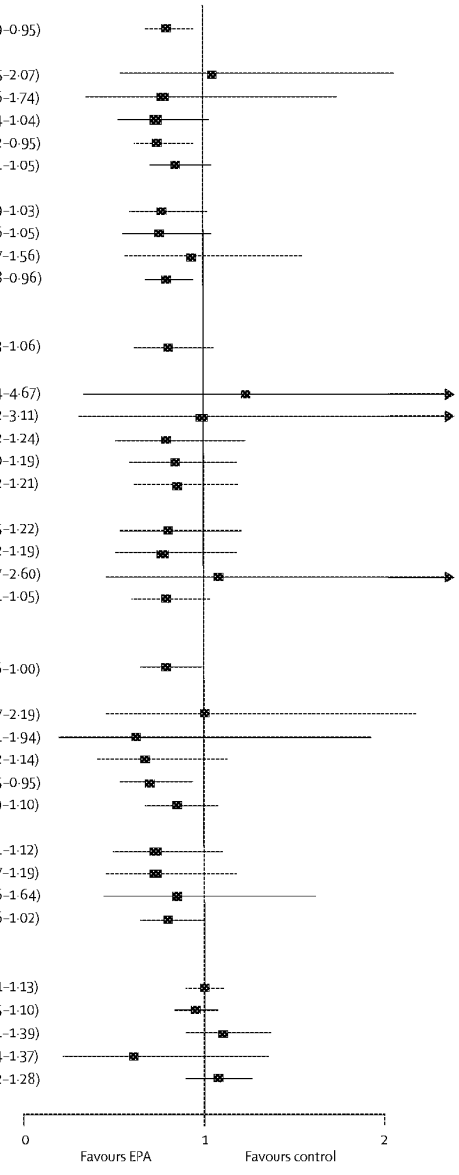

Figure 3: **Estimated hazard ratios of clinical endpoints stratified by prevention stratum**
MI=myocardial infarction. CABG=coronary-artery bypass grafting. PTCA=percutaneous transluminal coronary angioplasty. CAD=coronary-artery disease.

discontinuation because of treatment-related adverse events were 1087 (11·7%) in the EPA group and 673 (7·2%) in the control group. Most adverse effects attributable to EPA allocation were regarded as mild. The following factors were more common in the EPA group than in controls: abnormal laboratory data; gastrointestinal disturbances such as nausea, diarrhoea, or epigastric discomfort; skin abnormalities such as eruption, itching, exanthema, or eczema; and haemorrhages such as cerebral and fundal bleedings, epistaxis, and subcutaneous bleeding. The frequency of new cancers did not differ.

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