

## JELIS, fish oil, and cardiac events

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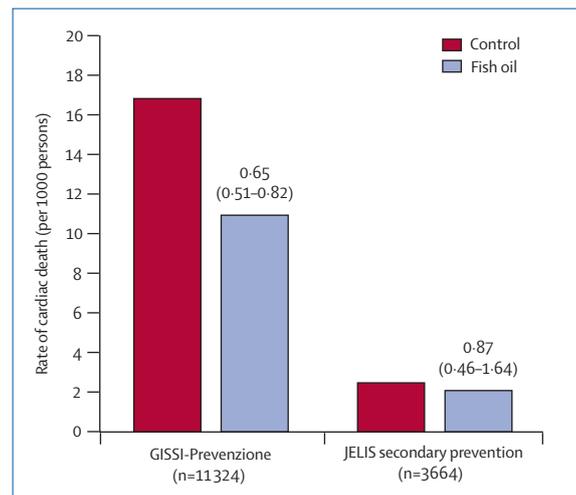
The Japan EPA Lipid Intervention Study (JELIS),<sup>1</sup> in today's *Lancet*, has one expected result and two surprises. The first surprise is that the study was done at all. Compared with drug trials, trials of nutrient factors offer much less financial incentive. Despite evidence suggesting substantial benefits of dietary factors on cardiovascular risk,<sup>2-5</sup> clinical trials to investigate such hypotheses are unusual. Drug trials predominate, often investigating redundant hypotheses or incremental benefits over less expensive (and no longer patented) drugs. JELIS, a large clinical trial of fish oil to prevent coronary events in patients with dyslipidaemia (n=18 645, mean follow-up 4-6 years), bucks this trend. The choice of patients (those with hypercholesterolaemia and treated with a statin) and fish-oil dose (1.8 g per day) suggest a hypothesis focused on serum lipids, particularly triglycerides. Because the best-established cardiovascular benefit of fish oil in US and European populations—reduction in cardiac death—is seen at much lower doses and appears unrelated to serum lipid effects,<sup>6</sup> and because such benefit would be difficult to establish in a Japanese population, the successful planning and execution of JELIS is remarkable.

The expected result of JELIS (although perhaps not to the investigators) was the absence of effect on cardiac death. The benefit of fish or fish-oil consumption for cardiac death is non-linear. In a pooled analysis of prospective observational studies and clinical trials,<sup>6</sup> most risk reduction occurred at modest intake—about 250 mg per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), corresponding to 1-2 servings per week of oily fish. Above this threshold, little additional benefit was seen.<sup>6</sup> In Japan, average fish consumption is one serving of 85 g (3 oz; 900 mg EPA and DHA) per day, and 90% of individuals eat fish at least once a week.<sup>7,8</sup> Thus, most of the population is already above the threshold for preventing cardiac death. In any such population, one would expect low baseline rates of cardiac death, and little further reduction in cardiac death with additional fish-oil consumption.

JELIS confirms this expectation. Overall rates of cardiac death per 1000 person-years were very low: 0.68 in the EPA group and 0.72 in controls (relative risk 0.94, p=0.81). The figure compares results from the JELIS secondary prevention arm and GISSI-Prevenzione,<sup>4</sup> a trial of fish oil (1 g per day) in Italian patients. In controls,

the cardiac death rate per 1000 person-years was 2.5 in JELIS compared with 17 in GISSI-Prevenzione. These two populations were not identical, and other differences apart from fish consumption exist between Japanese and Italian populations. Nevertheless, the difference in cardiac death between these groups was greater than differences in other cardiac events, such as non-fatal myocardial infarction,<sup>1,4</sup> and high background consumption of fish in Japan probably accounts for some of this difference.

The second surprise of JELIS was the significant reduction in non-fatal coronary events. Patients taking EPA had 19% fewer non-fatal events than did controls (p=0.015), due to combined reduction in non-fatal myocardial infarction, unstable angina, and coronary revascularisation. This result is unexpected, because previous studies in US and European populations showed that consumption of fish or fish oil did not strongly affect non-fatal coronary events.<sup>3,4,9-12</sup> Unfortunately, JELIS was an open-label trial, and modest reductions in softer endpoints, such as unstable angina and coronary revascularisation, could have been due to bias resulting from changes in patients' behaviour, physicians' treatment, or event ascertainment. This potential for bias is different from the situation in GISSI-Prevenzione,<sup>4</sup> also an open-label trial, in which benefits occurred for total mortality, the hardest of endpoints, because of specific reduction in sudden death.



**Figure: Cardiac death in patients with prevalent coronary heart disease in GISSI-Prevenzione and JELIS trials of fish-oil consumption**  
Absence of significant effect on cardiac death in JELIS is probably due to much lower baseline risk in controls, attributable at least partly to high background consumption of fish. Figure shows relative risk (95% CI) in each trial, comparing patients taking fish oil with controls.

Thus, based on GISSI-Prevenzione, fish oil is an approved treatment in Europe for patients after myocardial infarction; however, the same is not true in the USA.<sup>13</sup> If any placebo effect could reduce total mortality by 20% and sudden death by 45% (the results of GISSI-Prevenzione), we should all be taking such a placebo.

Nevertheless, the reduction in non-fatal events with fish oil in JELIS should not necessarily be discounted. This result is consistent with observational studies<sup>7</sup> in Japanese populations that indicate a lower risk of non-fatal coronary events with high intake of fish. Trends toward modest reductions in non-fatal coronary events with high intake of fish have also been seen in some US populations.<sup>10,11</sup> In view of the diverse physiological effects of fish oil and their differing dose-response curves,<sup>6</sup> the main benefit at lower levels of consumption might be prevention of primary ventricular arrhythmia, whereas at high levels of consumption (eg, more than 1 g per day of EPA and DHA), modest benefits for non-fatal coronary events could also begin to occur because of, for example, triglyceride-lowering, antihypertensive, or anti-inflammatory effects. Compared with antiarrhythmic effects, these effects could require a prolonged duration of consumption to reduce risk. In this respect, the long follow-up in JELIS is important: most risk reduction occurred after 2.5 years.<sup>1</sup> Notably, the benefits were in addition to statin treatment, and fish oil was safe and generally well tolerated.

Compared with drugs, invasive procedures, and devices, modest dietary changes are low risk, inexpensive, and widely available. We must curb our infatuation with downstream risk factors and treatments, and focus on the fundamental risk factors for cardiovascular disease: dietary habits, smoking, and physical activity. If the millions of heart attacks occurring each year were not

a clarion call, the obesity epidemic certainly should be. The JELIS investigators should be commended, and their efforts should inspire additional clinical trials of the effects of fish oil and other dietary factors and habits on cardiovascular health.

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I declare that I have no conflict of interest.

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## Occipital nerve stimulation for intractable cluster headache



In today's *Lancet*, Brian Burns and colleagues report the effectiveness of an original and innovative treatment, bilateral occipital nerve stimulation, for intractable chronic cluster headache.<sup>1</sup> This primary headache is one of the most disabling forms of head pain, and is characterised by attacks of severe unilateral pain in the periorbital areas that last 15–180 min, recur up to eight times daily, and are accompanied by ipsilateral

autonomic symptoms.<sup>2</sup> Cluster headaches usually occur in bouts (clusters) lasting from a week to a year, separated by pain-free periods of at least a month (episodic cluster headache). But in about 10% of patients these pain-free periods are absent or last less than a month (chronic cluster headache).

Patients with chronic cluster headache usually receive continuous preventive treatments, such as high-dose

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