

## **Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial.**

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**BACKGROUND:** N-3 polyunsaturated fatty acids (PUFAs) from oily fish protect against death from cardiovascular disease. We aimed to assess the hypothesis that incorporation of n-3 and n-6 PUFAs into advanced atherosclerotic plaques increases and decreases plaque stability, respectively.

**METHODS:** We did a randomised controlled trial of patients awaiting carotid endarterectomy. We randomly allocated patients control, sunflower oil (n-6), or fish-oil (n-3) capsules until surgery. Primary outcome was plaque morphology indicative of stability or instability, and outcome measures were concentrations of EPA, DHA, and linoleic acid in carotid plaques; plaque morphology; and presence of macrophages in plaques. Analysis was per protocol.

**FINDINGS:** 188 patients were enrolled and randomised; 18 withdrew and eight were excluded. Duration of oil treatment was 7-189 days (median 42) and did not differ between groups. The proportions of EPA and DHA were higher in carotid plaque fractions in patients receiving fish oil compared with those receiving control (absolute difference 0.5 [95% CI 0.3-0.7], 0.4 [0.1-0.6], and 0.2 [0.1-0.4] g/100 g total fatty acids for EPA; and 0.3 [0.0-0.8], 0.4 [0.1-0.7], and 0.3 [0.1-0.6] g/100 g total fatty acids for DHA; in plaque phospholipids, cholesteryl esters, and triacylglycerols, respectively). Sunflower oil had little effect on the fatty acid composition of lipid fractions. Fewer plaques from patients being treated with fish oil had thin fibrous caps and signs of inflammation and more plaques had thick fibrous caps and no signs of inflammation, compared with plaques in patients in the control and sunflower oil groups (odds ratio 0.52 [95% CI 0.24-0.89] and 1.19 [1.02-1.57] vs control; 0.49 [0.23-0.90] and 1.16 [1.01-1.53] vs sunflower oil). The number of macrophages in plaques from patients receiving fish oil was lower than in the other two groups. Carotid plaque morphology and infiltration by macrophages did not differ between control and sunflower oil groups.

**INTERPRETATION:** Atherosclerotic plaques readily incorporate n-3 PUFAs from fish-oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 PUFAs does not affect carotid plaque fatty-acid composition or stability over the time course studied here. Stability of plaques could explain reductions in non-fatal and fatal cardiovascular events associated with increased n-3 PUFA intake.