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Effects of Moderate-Dose Omega-3 Fish Oil on Cardiovascular Risk Factors and Mood After Ischemic Stroke

A Randomized, Controlled Trial

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Background and Purpose—Fish-derived omega-3 fatty acids have long been associated with cardiovascular protection. In this trial, we assessed whether treatment with a guideline-recommended moderate-dose fish oil supplement could improve cardiovascular biomarkers, mood- and health-related quality of life in patients with ischemic stroke.

Methods—Patients with CT-confirmed stroke were randomized to 3 g/day encapsulated fish oil containing approximately 1.2 g total omega-3 (0.7 g docosahexaenoic acid; 0.3 g eicosapentaenoic acid) or placebo oil (combination palm and soy) taken daily over 12 weeks. Serum triglycerides, total cholesterol and associated lipoproteins, selected inflammatory and hemostatic markers, mood, and health-related quality of life were assessed at baseline and follow-up. The primary outcome was change in triglycerides. Compliance was assessed by capsule count and serum phospholipid omega-3 levels (Australian Clinical Trials Registration: ACTRN12605000207617).

Results—One hundred two patients were randomized to fish oil or placebo. Intention-to-treat and per-protocol (>85% compliance) analyses showed no significant effect of fish oil treatment on any lipid, inflammatory, hemostatic, or composite mood parameters measured. Adherence to treatment based on pill count was good (89%) reflected by increased serum docosahexanoic acid ($P<0.001$) and eicosapentaenoic acid ($P=0.0006$) in the fish oil group. Analysis of oil composition, however, showed some degradation and potentially adverse oxidation products at the end of the study.

Conclusions—There was no effect of 12 weeks of treatment with moderate-dose fish oil supplements on cardiovascular biomarkers or mood in patients with ischemic stroke. It is possible that insufficient dose, short duration of treatment, and/or oxidation of the fish oils may have influenced these outcomes. **(*Stroke*. 2009;40:3485-3492.)**

Key Words: DHA ■ EPA ■ fish oils ■ ischemia ■ omega-3 ■ stroke

Some controversy surrounds cardiovascular protection and encapsulated omega-3 polyunsaturated fatty acids (PUFA) derived from fish.[1,2] Although long chain PUFAs docosahexaenoic acid (DHA, C22:6n−3) and eicosapentaenoic acid (EPA, C20:5n−3) have long been associated with decreased cardiovascular disease,[3,4] not all trials have been supportive of clinical improvement.[1] Trials such as Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)- Prevenzione,[4] the largest prospective omega-3 trial to date, and the first Diet and Reinfarction Trial (DART)[5] showed benefits after myocardial infarction as did the recent GISSI-HF.[6] However, the second DART trial of >3000 men with stable angina showed an unexpected increase in cardiac deaths after advice to supplement with encapsulated oils, albeit lessened with oily fish.[7]

Most studies of fish oils have involved patients with coronary artery disease. Less is known of effects in patients with stroke in which epidemiology shows modest beneficial effects of fish/fish oil capsules, more commonly for prevention of ischemic rather than hemorrhagic stroke,[8–10] but in which the evidence is inconclusive.[11,12] In ischemic stroke atherosclerosis is a common underlying etiology, and adverse lipid profile and arterial inflammation are important risk factors for recurrent events. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are important determinants of atherosclerotic plaque formation, and even

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moderately raised triglycerides may increase cardiovascular risk. Low-density lipoprotein particle size (LDLps) is also a key factor in the genesis of atheroma[13] with small, dense LDL particles having a greater rate of flux into the arterial wall and greater susceptibility to oxidation.[14] Triglycerides play a central role in regulating LDL subfractions and can lead to catabolism of protective high-density lipoprotein cholesterol (HDL-C) and generation of small, dense, highly atherogenic LDL particles. Fish oils may decrease triglycerides and redistribute LDLps toward larger, less dense particles characteristic of the low cardiovascular risk "pattern A" phenotype,[13,15] although they may also adversely increase concentrations of LDL-C.[16] Other putative mechanisms for fish oils include antiarrhythmic, anticoagulant, and anti-inflammatory effects[17,18]; antiatherosclerotic effects on triglycerides and small dense LDL-C[13,19–21]; and blood pressure-lowering.[22] Hence, fish oil supplementation is recommended in high-risk patients and is popularly used across the general community for broader health benefits.

There have been no large intervention trials investigating effects of fish oils in patients with stroke. An early pilot study showed no effect of fish oils on cholesterol fractions or platelet function.[23] The aim of the Fish Oils in Stroke (FOILS) study was to evaluate cardiovascular effects of moderate-dose (1 g DHA+EPA) fish oil supplementation as recommended by American Heart Association guidelines for patients with established coronary artery disease.[3] Indicators of mood and quality of life were also assessed given that stroke-associated depression is common and fish oils have been associated with improvement in mood.[24]

Methods

Study Protocol

The FOILS study was a randomized, double-blind trial to investigate the effect of moderate-dose (3 g/day) encapsulated fish oils on cardiovascular risk and mood in patients with ischemic stroke. The trial was undertaken at a single hospital site in Auckland, New Zealand, from July 2004 to March 2006 with the first and last patients randomized on July 29, 2004, and December 23, 2005, respectively. Treatment was a 12-week intervention with encapsulated fish oils (approximately 1.2 g/day omega-3 PUFA) or matching placebo (palm and soy oils[25–27]). The randomization was a blocked (varying block sizes), unstratified design sequence. It was implemented using treatment packs blinded for treatment with sequential allocation of packs to patients after confirmation of inclusion criteria and was generated using an automated Internet-based system held at the Clinical Trials Research Unit, University of Auckland. Participants were dispensed capsules with instructions to take 3×1-g capsules each morning with food, to abstain from other fish oil supplements, and maintain their habitual diet. Outcomes at baseline and 12-week follow-up included anthropometry, hematology, biochemistry, blood pressure, questionnaires to assess health-related quality of life and mood, compliance, and adverse events (AEs). Blood samples were collected fasted. Compliance was assessed by capsule count and through analysis of serum phospholipid fatty acid methyl esters (FAMEs). Telephone contact was made at 6 and 11 weeks. The trial was approved by the Auckland Human Ethics Committee X, Auckland, New Zealand, and all participants provided written informed consent.

Participants

Participants were aged >45 years, clinically stable, and with a history of CT-confirmed first-ever or recurrent ischemic stroke of probable noncardioembolic etiology >3 months before registration. Exclusion criteria included intolerance/hypersensitivity to fish/fish oils, current use of fish oil supplements, malabsorptive bowel diseases, or participation in a concurrent clinical trial. Stroke was defined using World Health Organization criteria of "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin."[28] Recruitment was predominantly by hospital admissions with one patient recruited from newspaper advertisements.

Table 1. Composition of the Fish Oil and Placebo Treatments

Fatty Acid Composition Area Percent Ethyl Ester	Fish Oil* (Hoki livers)	Placebo Oil† (Palm+soy)‡
Σ SFA	5.74	33.0
C14:0	0.13	0.53
C16:0	2.83	28.18
C18:0	2.06	4.32
C20:0	0.29	BLQ
C22:0	0.35	BLQ
C24:0	0.08	BLQ
Σ MUFA	40.38	31.3
C16:1	0.67	BLQ
C18:1 oleic	16.62	31.3
C18:1 cis 11	2.57	BLQ
C20:1	15.21	BLQ
C22:1	2.59	BLQ
C24:1	2.35	BLQ
Σ n6 PUFA	10.52	29.5
C16:2	0.19	BLQ
C18:2	0.78	29.5
C20:2	0.6	BLQ
C20:3	0.17	BLQ
C20:4	7.92	BLQ
C21:5	0.34	BLQ
C22:4	0.52	BLQ
Σ n3 PUFA	37.5	3.29
C18:3	0.39	3.29
C20:3	0.46	BLQ
C18:4	0.47	BLQ
C20:4	2.09	BLQ
C20:5 (EPA)	8.21	BLQ
C22:5	3.53	BLQ
C22:6 (DHA)	22.3	BLQ
Other	5.91	2.83
Pretrial		
Peroxide value	0.2	N/A
P anisidine	6.3	N/A
Posttrial		
Peroxide value, range	0.8–2.8	4.8–12.3
P anisidine, range	22.2–29.0	2.0–4.1

*Fatty acid composition measured.

†Fatty acid composition calculated from Foodworks (Foodworks-on-line Ltd, Version 5, 1998–2007), Auckland, NZ.

‡Ratio of palm:soy oil, 53:47.

BLQ indicates below level of quantification; N/A, not available.

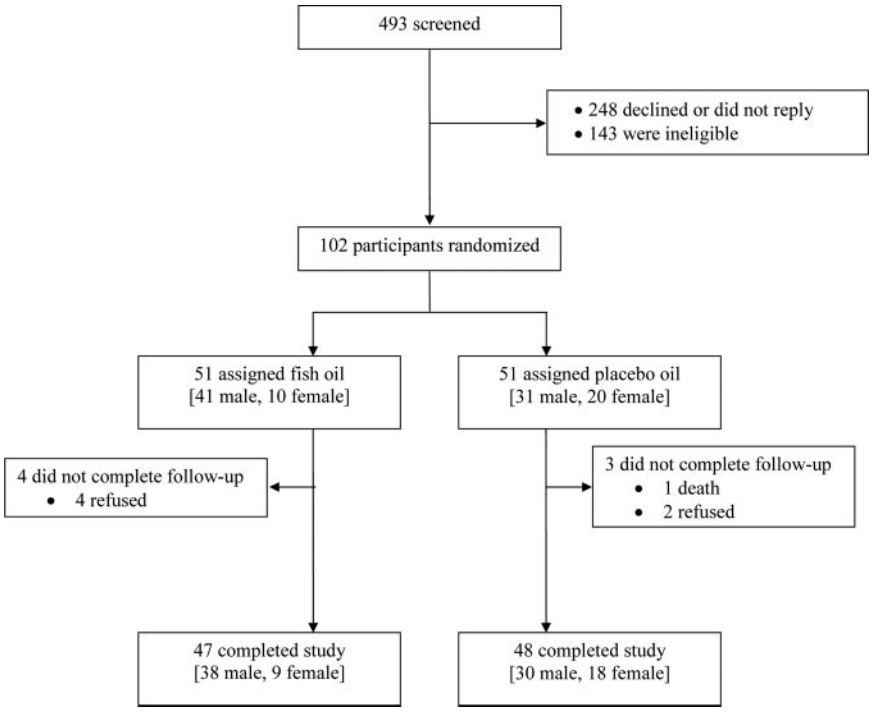

Figure. Participant flowchart.

Fish Oil and Placebo Supplements

The 3-g/day fish oil supplement contained approximately 1.2 g/day total omega-3 PUFA. Table 1 outlines the fatty acid composition of the fish oil and placebo. The fish oil was made from processed Hoki liver oil, a southern ocean fish found in waters surrounding Australia and New Zealand. Random samples of fish oil and placebo capsules were stored at ambient temperature and later analyzed for fatty acid profile to confirm randomization.

Outcome Measures

The primary outcome was change in serum triglycerides between baseline and 12 weeks. Secondary outcomes included parameters of lipid profile TC, LDL-C, LDLps, HDL-C; inflammatory markers, including high-sensitivity C-reactive protein, liver function tests, white cell count, erythrocyte sedimentation rate, and ferritin; fibrinogen; and blood pressure. Mood was assessed using a 28-item General Health Questionnaire,[29] and mental and physical health-related quality of life were assessed using the 36-item Short Form questionnaire (SF-36).[30]

Analytical Methods

The fatty acid composition of the fish oil was verified using gas chromatography methodology after generation of fatty acid esters (MIRINZ Centre Analytic Laboratory, Hamilton, New Zealand). Blood lipids, inflammatory, and hemostatic markers were analyzed by a diagnostic laboratory (Lab Plus, Auckland, New Zealand). LDLps was measured by Skylight Biotech Inc (Akita, Japan) using a high-sensitivity duel-detection lipoprotein-profiling high-performance liquid chromatography separation system.[31] High-performance liquid chromatography with gel permeation columns was used as an alternative method to ultracentrifugation for classification and quantification of lipoproteins on the basis of particle size. The method quantified 20 lipoprotein subclasses from both cholesterol and triglyceride components within the major classes of chylomicrons (>80 nm particle size), very-low-density lipoprotein (VLDL) (30 to 80 nm), LDL (18 to 30 nm), and HDL (8 to 18 nm) fractions. Subclasses of relevance were large LDL, 28.6 nm; medium LDL, 25.5 nm; small LDL, 23.0 nm; very small LDL_1, 20.7 nm; very small LDL_2, 18.6 nm; and very small LDL_3, 16.7 nm.

FAME analyses of serum phospholipids provided a qualitative assessment of treatment compliance and were extracted and analyzed using standard methods.[32]

Statistical Analyses

Initial sample size calculations indicated that 220 participants would be required for 90% power to detect a 15% difference in change in serum triglycerides between treatment and placebo groups. However, on the basis of a blinded interim analysis during data safety review of AEs of the first 50 randomized participants, lower than predicted variance in the primary outcome serum triglycerides led to 102 participants randomized into the trial. Data were analyzed using intention-to-treat in which no dropouts were replaced and all randomized participants were included in analyses. Missing at follow-up data were imputed using last value carried forward. Analysis of covariance (ANCOVA) was used to deal with potentially unbalanced baseline data. A blinded analysis prereview was performed to determine required adjustments for potential confounders and to establish rules for the per-protocol analysis. Probability values as presented in data tables were calculated from ANCOVA for the difference between fish oil and placebo treatment over time adjusted for 3 factors: baseline measurement, gender, and age. The blinded prereview included examination of adjustments for factors such as concurrent medications and years since ischemic stroke performed as exploratory or sensitivity analyses to ensure the robustness of estimates in the primary analysis and for which all were shown to have no effect on the trial outcomes. A per-protocol analysis was also performed based on >85% compliance. Distribution of continuous end points was assessed for normality; however, there was no requirement for transformation. No adjustments for multiplicity were carried out for secondary end points, AEs, or other end points. $P<0.05$ level of statistical significance was used. Analyses were carried out using SAS Version 9.1 (SAS Institute Inc, Cary, NC) and SPLUS (Insightful Corp, Seattle, Wash). Data are mean±SD.

Results

One hundred two participants were randomized into the trial with 51 participants allocated to each treatment group (Fig-

Table 2. Baseline Characteristics of the Participants

	Fish Oil	Placebo Oil
All, n	51	51
Male, n	41	31
Female, n	10	20
Age, years	64, 10	65, 12
Body mass index, kg/m^2	29.2, 5.4	28.5, 5.5
Waist circumference, cm		
Male	102, 12	101, 10
Female	95, 18	93, 15
Triglycerides, mmol/L	1.63, 0.8	1.65, 1.1
TC, mmol/L	4.67, 0.9	4.59, 1.0
HDL-C, mmol/L	1.41, 0.3	1.45, 0.3
LDL-C, mmol/L	2.53, 0.9	2.35, 0.7
TC:HDL-C ratio	3.50, 1.0	3.29, 0.9
Systolic blood pressure/diastolic blood pressure, mm Hg	132/80	136/80
Years since last ischemic stroke*	1.18 (0.5, 2.1)	0.90 (0.5, 2.3)
Lipid-lowering medications, including statins, n (% of patients)	40 (78%)	38 (75%)
Blood pressure-lowering medications, n (% of patients)	30 (59%)	37 (73%)
Insulin or oral glucose-lowering medications, n (% of patients)	8 (16%)	4 (8%)

Values are mean, SD.
*Median (interquartile range).

ure). Seven participants withdrew consent or were lost to follow-up at 12 weeks and hence 95 participants completed the intervention. There were 42 AEs (fish oil: n=22; placebo: n=20) of which 6 were serious AEs (fish oil: n=4; placebo: n=2), including one participant randomized to placebo who died as a result of an acute myocardial infarction. Serious AEs in the fish oil group were chest pain, palpitations, congestive heart failure, and elective hip replacement, none of which were assessed as related to treatment by the principle investigator.

Baseline Characteristics

Participants were predominantly overweight, older men (n=72) and women (n=30) with central adiposity with an ischemic stroke approximately 1 year previously. Across treatment groups, participants had similar serum lipids, including triglycerides of 1.6 mmol/L, and other cardiovascular biomarkers (Table 2). In both groups, approximately 80% (n=40, n=38) of participants were on therapies for serum lipid-lowering, including statins, 60% to 70% (n=30, n=37) on blood pressure-lowering therapies, and 8% to 16% (n=8, n=4) on oral hypoglycemic agents and/or insulin for diabetes mellitus. Body weight was stable over 12 weeks.

Compliance

Compliance to treatment as assessed by return capsule count at 12 weeks was approximately 90%. This was reflected in a significant increase in circulating omega-3 PUFA over 12 weeks with higher DHA ($P<0.001$) and EPA ($P=0.0006$) in the fish oil group compared with placebo (Table 3).

Serum Markers of Cardiovascular Disease

There were no significant effects of treatment on serum lipids, including the primary outcome variable serum triglyceride, or on inflammatory or hemostatic markers (Table 4) or indicators of mood (Table 5). It is notable that there was no decrease in serum triglycerides in this trial; rather, there was

Table 3. Circulating Serum Phospholipid Fatty Acid Profile of Participants at Baseline and 12-Week Follow-Up

FAME (% of total fatty acids)	Fish Oil			Placebo Oil			
	Baseline (n=51)	Week 12 (n=47)	Percent Change	Baseline (n=51)	Week 12 (n=48)	Percent Change	*P* Value†
Σ Trans*	0.82, 0.54	0.71, 0.27	−7.38, 48.7	0.72, 0.25	0.70, 0.24	0.67, 60.6	0.7500
Total 18:1*	10.69, 1.6	10.82, 1.61	1.51, 17.6	11.02, 1.75	10.78, 1.6	−0.75, 12.4	0.6097
Σ MUFA	13.0, 1.75	12.86, 1.82	−1.48, 8.9	13.33, 2.0	12.76, 1.82	−3.31, 8.2	0.5029
18:2n-6	19.61, 3.84	19.13, 3.64	0.94, 15.6	20.66, 3.31	21.07, 3.32	2.79, 9.9	0.3363
20:2n-6	0.31, 0.07	0.31, 0.05	2.57, 15.8	0.32, 0.06	0.33, 0.07	3.58, 10.8	0.6007
20:3n-6	3.05, 0.63	2.89, 0.63	−5.32, 13.7	3.08, 0.64	3.11, 0.67	−0.41, 11.5	0.0139
20:4n-6, AA	10.17, 2.31	9.18, 2.09	−9.91, 14.6	8.96, 2.14	8.88, 2.13	−0.81, 10.5	0.0028
22:4n-6	0.29, 0.06	0.21, 0.06	−26.12, 19.5	0.28, 0.06	0.21, 0.07	−25.10, 19.1	0.9634
22:5n-6	0.24, 0.08	0.17, 0.05	−25.65, 15.6	0.22, 0.08	0.21, 0.07	−2.86, 18.7	<0.0001
Σ n-6 PUFA	33.8, 2.78	31.94, 2.9	−5.00, 6.7	33.59, 2.52	33.87, 2.83	0.86, 5.1	<0.0001
20:5n-3, EPA	1.24, 0.91	1.63, 0.72	42.20, 52.2	1.26, 0.58	1.37, 1.22	6.50, 42.0	0.0006
22:5n-3	1.12, 0.26	1.06, 0.21	−2.73, 17.5	1.08, 0.23	1.05, 0.23	−1.99, 15.8	0.7213
22:6n-3, DHA	3.90, 1.12	5.29, 1.31	38.25, 29.7	4.10, 1.01	4.20, 1.02	3.86, 17.2	<0.0001
Σ n-3 PUFA	6.66, 1.97	8.54, 1.92	30.03, 24.5	6.89, 1.48	7.21, 2.07	4.70, 15.5	<0.0001

Values are mean, SD.
*Two outliers have been removed to calculate percent change and ANCOVA analysis.
†*P* value is calculated from ANCOVA for difference between fish oil and placebo treatment over time adjusted for baseline measurement, gender, and age.
AA indicates arachidonic acid; MUFA, monounsaturated fatty acid; FAME, fatty acid methyl esther.

Table 4. Effects of Fish Oil or Placebo Treatment on Serum Lipid Profile and Inflammatory and Hemostatic Markers

	Fish Oil			Placebo Oil				
	Baseline (n=51)	Week 12 (n=47)*	Mean Change, SEM	Baseline (n=51)§	Week 12 (n=48)‖	Mean Change, SEM	Treatment Difference Mean, CI (lower, upper)	*P* Value†
Primary outcome								
Triglyceride, mmol/L	1.63, 0.8	1.72, 1.3	0.12, 0.13	1.65, 1.1	1.61, 1.0	−0.06, 0.12	−0.059 (−0.39, 0.27)	0.72
Secondary outcomes								
TC, mmol/L	4.67, 0.9	4.68, 1.1	0.01, 0.11	4.59, 1.0	4.54, 0.9	−0.047, 0.10	0.035 (−0.24, 0.31)	0.80
HDL-C, mmol/L	1.41, 0.3	1.41, 0.4	0.01, 0.03	1.45, 0.3	1.43, 0.3	−0.003, 0.02	0.013 (−0.06, 0.08)	0.70
LDL-C, calculated, mmol/L	2.53, 0.9	2.51, 0.9	−0.002, 0.08	2.35, 0.7	2.36, 0.7	0.002, 0.08	0.004 (−0.21, 0.22)	0.97
LDL-C, measured, mmol/L	2.10, 0.7	2.24, 0.7	0.133, 0.07	2.05, 0.5	2.12, 0.6	0.079, 0.07		0.56
LDLps, nm‡	25.01, 0.4	24.83, 0.4	−0.149, 0.07	25.07, 0.4	24.8, 0.5	−0.221, 0.06		0.40
Large LDL-C, mmol/L	0.60, 0.2	0.61, 0.2	0.033, 0.03	0.60, 0.2	0.57, 0.2	−0.016, 0.02	−0.033 (−0.086, 0.020)	0.22
Medium LDL-C, mmol/L	0.74, 0.2	0.77, 0.2	0.035, 0.03	0.72, 0.2	0.72, 0.2	0.004, 0.02	−0.035 (−0.102, 0.032)	0.30
Small LDL-C, mmol/L	0.46, 0.2	0.50, 0.2	0.001, 0.03	0.44, 0.1	0.47, 0.2	0.028, 0.02	−0.001 (−0.057, 0.054)	0.96
Very small LDL-C_1, mmol/L	0.20, 0.1	0.22, 0.1	0.0083, 0.01	0.18, 0.1	0.22, 0.1	0.029, 0.01	0.008 (−0.02, 0.037)	0.57
Very small LDL-C_2, mmol/L	0.08, 0.0	0.10, 0.0	0.0038, 0.01	0.07, 0.0	0.10, 0.0	0.025, 0.005	0.004 (−0.01, 0.018)	0.58
Very small LDL-C_3, mmol/L	0.03, 0.0	0.04, 0.0	0.0007, 0.003	0.03, 0.0	0.04, 0.0	0.012, 0.002	0.001 (−0.005, 0.006)	0.78
TC:HDL-C ratio	3.50, 1.0	3.46, 1.0	−0.008, 0.09	3.29, 0.9	3.32, 0.9	0.012, 0.08	0.003 (−0.23, 0.23)	0.98
Apo B, g/L	0.86, 0.2	0.88, 0.3	0.022, 0.02	0.82, 0.2	0.82, 0.2	0.022, 0.02	0.00 (−0.06, 0.06)	1.00
Other parameters								
High-sensitivity C-reactive protein, mg/L	3.95, 6.3	4.22, 8.9	0.059, 1.32	3.06, 3.2	4.35, 6.1	1.02, 0.81	0.96 (−2.11, 4.03)	0.54
Erythrocyte sedimentation rate, mm/hr	7.35, 9.6	9.87, 13.8	1.745, 0.89	11.39, 16.7	10.4, 11.0	−0.30, 1.03	1.45 (−4.13, 1.23)	0.29
Ferritin, μg/L	277, 268	249, 224	−11.6, 10.1	197, 210	192, 222	−7.8, 7.8	3.7 (−21.6, 29.1)	0.77
Fibrinogen, g/L	3.71, 0.9	3.84, 1.1	0.08, 0.10	3.71, 1.0	3.76, 1.0	0.06, 0.11	0.012 (−0.32, 0.29)	0.94

Values are mean, SEM, and CI.
*LDL-C calculated, n=46 (non-evaluable in 1 patient due to high serum triglyceride); erythrocyte sedimentation rate, n=45.
†*P* value is calculated from ANCOVA for difference between fish oil and placebo treatment over time adjusted for baseline measurement, gender, and age.
‡LDL particle size, defined as particles within the range16 to 30 nm; see "Methods" for details of particle size definitions.
§LDL-C calculated, n=50.
‖LDL-C calculated and high-sensitivity C-reactive protein, n=47.

an unexpected increase on fish oil treatment, albeit nonsignificant, and a decrease on placebo of +7% and −3%, respectively. The absence of triglyceride-lowering was confirmed on per-protocol (>85% compliance to treatment) analysis and with the exclusion of one participant with an outlying extreme triglyceride value (9.0 mmol/L) in the fish oil group at 12 weeks, which normalized after the end of the trial. Also notable alongside the lack of triglyceride-lowering

Table 5. Effects of Fish Oil or Placebo Treatment on Health-Related Quality of Life

	Fish Oil			Placebo Oil				
	Baseline (n=51)	Week 12 (n=51)	Mean Change, SEM	Baseline (n=51)	Week 12 (n=51)	Mean Change, SEM	Treatment Difference Mean, CI	*P* Value*
SF-36 questionnaire								
Physical component scale	44.7, 9.1	44.8, 10.1	0.07, 1.02	42.5, 10.5	44.9, 10.3	2.38, 0.77	2.31 (−0.24, 4.85)	0.08
Mental component scale	49.4, 10.6	48.6, 10.3	−0.68, 1.55	47.8, 10.2	49.6, 10.8	1.48, 1.12	2.16 (−1.63, 5.96)	0.26
General Health Questionnaire—28-item								
Total score	3.1, 4.3	2.3, 4.0	−0.67, 0.43	4.3, 5.0	2.0, 3.1	−2.08, 0.53	−1.41 (−2.76, −0.06)	0.04
Somatic symptom	4.4, 3.3	3.7, 3.1	−0.71, 0.43	4.5, 3.5	3.7, 2.9	−0.71, 0.44	0.00 (−1.21, 1.21)	1.00
Anxiety and insomnia	4.5, 3.9	4.1, 3.7	−0.35, 0.49	4.5, 4.5	3.1, 3.2	−1.20, 0.46	−0.84 (−2.17, 0.48)	0.21
Social dysfunction	7.5, 2.2	6.7, 2.6	−0.69, 0.35	8.2, 3.3	6.2, 3.0	−1.92, 0.42	−1.24 (−2.33, −0.14)	0.03
Depression	1.6, 2.7	1.3, 2.2	−0.10, 0.23	1.9, 3.2	1.3, 2.3	−0.65, 0.35	−0.55 (−1.39, 0.29)	0.20

Mean, SD.
**P* value is calculated from ANCOVA for difference between fish oil and placebo treatment over time adjusted for baseline measurement, gender, and age.

was an absence of AEs on LDL-C. Table 4 also shows mean LDLps to be unchanged from baseline as were circulating concentrations of large, medium, small, or very small LDL-C. Blood pressure was also unaffected by fish oil treatment.

Mood

The fish oil treatment had no effect on health-related quality of life. The 28-item General Health Questionnaire total score was significantly different between treatments, a consequence of a decrease on placebo (fish oil: −0.8 units, placebo: −2.3 units, $P=0.04$; Table 5). Similarly, of the 28-item General Health Questionnaire components, only social dysfunction differed between treatments (fish oil: −0.8 units, placebo: −2.0 units; $P=0.027$) with no effect on somatic symptoms, anxiety, insomnia, or depression. It is unlikely that these small changes in mood scores are of clinical significance.

Discussion

In this trial of patients with ischemic stroke, there was no evidence that treatment with moderate-dose, encapsulated fish oils over 12 weeks improved cardiovascular markers, including triglycerides and LDLps, inflammatory and hemostatic parameters, blood pressure, health-related quality of life, or mood. The absence of triglyceride-lowering was particularly unexpected because this cardiovascular biomarker has the strongest evidence base as summarized in a recent systematic review, which concluded that most studies assessing triglycerides have shown a decrease of at least 15% with fish oils.[19] It is notable, however, that Balk and colleagues[19] concluded that supplementation with fish oils is associated with lower rates of cardiovascular mortality and sudden death but not stroke. Similarly, GISSI-HF has recently shown lower rates of cardiovascular death, sudden cardiac death, myocardial infarction, and hospital admission but not stroke in n-3 PUFA-treated patients.[6] Although evidence of cardiovascular protective effects of fish and/or fish oil capsules in patients at risk of ischemic stroke has been shown in some epidemiological studies,[8–10] not all are confirmatory.[11,12] Skerrett and Hennekens[33] showed consistency of evidence between consumption of fish/fish oils across ecological, cross-sectional, and case control studies but inconclusive in prospective cohort studies. No consistent relationship between fish consumption and stroke was again shown in a recent European cohort study.[12] Although some inconsistencies may be due to differences in study design, it has been suggested that different types of fish consumed and/or methods of preparation (eg, baking, frying) may play a role[12] as may consumption of encapsulated oils rather than dietary fish. A randomized, placebo-controlled intervention is the most reliable way to assess effects of fish oils.

There are several possible explanations for lack of efficacy in our study. First, 1 g/day DHA+EPA may have been too low a dose, although similar doses were used in GISSI-Prevenzione[4] and GISSI-HF[6] in which low–moderate-dose fish oil was cardioprotective and led to guidelines recommending approximately 1 g/day DHA+EPA for patients with documented cardiovascular disease.[3] Certainly trials have shown triglyceride-lowering with modest dose fish oil,[27,34] although higher doses may result in greater effects.[19] The proportion of DHA:EPA may also be important, but although they cannot be regarded as equivalent, there is no consensus over the optimal ratio.[21,35–37] We cannot attribute lack of effect to poor adherence, which was good when estimated from capsule counts and serum phospholipids. Other potential explanations include the relatively short 12-week intervention period and the moderately elevated baseline triglycerides. Higher baseline levels may be associated with greater triglyceride-lowering.[19] Approximately 80% of participants in FOILS were prescribed statins, which lower TC by inhibiting HMG-CoA reductase, stimulating LDL receptors, and increasing clearance of LDL-C from circulation. Statins, however, have less effect than fibrates or niacin in decreasing triglycerides, and it has been shown that 3-month treatment with DHA-rich fish oil can improve lipids in patients taking statins.[38] Another factor is sample size, which may have been too small to detect more modest beneficial effects of fish oils, which, when applied widely across whole populations, may have important public health implications but have arguably questionable benefits in the management of individual patients.

It is possible that lack of efficacy is a true effect. There are clear differences between increasing fish consumption in which fish replaces other animal proteins, and supplementation with fish oil capsules in which omega-3 PUFAs are added without the parallel benefit of decreased saturated fats. Much of the epidemiology showing protective benefits in patients with stroke has identified relationships between fish and morbidity/mortality, only sometimes accounting also for encapsulated oils. Another factor with encapsulated oils is the propensity for oxidation and rancidity over time.[39] Fish oils are easily oxidized during processing and after encapsulation. High numbers of double bonds render DHA and EPA more susceptible to lipid oxidation than other fatty acids with rapid formation of hydroperoxides (HPODE), the initial degradation product in free radical-catalyzed lipid oxidation. Whether oxidized fish oils are less efficacious for cardioprotection is not known, but there is evidence of adverse effects on lipid and chylomicron metabolism from circulating oxidized products such as conjugated dienes (a marker of lipid hydroperoxides) and adverse changes in hemostatic clotting and endothelium-dependent vascular dilatation. It is possible, therefore, that oxidation of fish oil during the study may have influenced the results.

Conclusions

This study is one of few clinical trials to investigate fish oil supplementation after ischemic stroke. Contrary to other studies in different cardiovascular risk populations, there was no evidence that a moderate-dose encapsulated fish oil improved cardiovascular biomarkers in this high-risk group. Insufficient dose and oxidation of encapsulated oils are potential explanations for lack of cardiovascular improvement. Until results of large-scale studies of fish oil supplementation in poststroke populations such as the ongoing SU.FOL.OM3 (SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids) trial[40] are available,

these factors may need to be considered when formulating guidelines and public health policy regarding health benefits of fish oil supplementation in patients with ischemic stroke.

Appendix of Investigators

Sally D. Poppitt, PhD, fundraiser, trial steering committee, trial design and interpretation, senior author; Colin A. Howe, PhD, trial steering committee member, trial manager, trial design and interpretation, coauthor; Fiona E. Lithander, PhD, trial steering committee member, trial design and interpretation, coauthor; Karen M. Silvers, PhD, trial steering committee member, trial design and interpretation, coauthor; Ruey-Bin Lin, MSc, biostatistician; John Croft, trial steering committee member, provision of treatment (n-3 PUFA, placebo) oils; Yogini Ratnasabapathy, MBBS, FRACP, patient recruitment, clinical oversight. Robert A. Gibson, PhD, head, analytic laboratory; Craig S. Anderson, MBBS, FRACP, PhD, fundraiser, trial steering committee chair, trial design and interpretation, coauthor.

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Disclosures

J.C. has a consultancy relationship with Nutrition Labs New Zealand.

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