Effect of Fish Oil Supplementation on Graft Patency and Cardiovascular Events Among Patients With New Synthetic Arteriovenous Hemodialysis Grafts

A Randomized Controlled Trial

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Context Synthetic arteriovenous grafts, an important option for hemodialysis vascular access, are prone to recurrent stenosis and thrombosis. Supplementation with fish oils has theoretical appeal for preventing these outcomes.

Objective To determine the effect of fish oil on synthetic hemodialysis graft patency and cardiovascular events.

Design, Setting, and Participants The Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH) study, a randomized, double-blind, controlled clinical trial conducted at 15 North American dialysis centers from November 2003 through December 2010 and enrolling 201 adults with stage 5 chronic kidney disease (50% women, 63% white, 53% with diabetes), with follow-up for 12 months after graft creation.

Interventions Participants were randomly allocated to receive fish oil capsules (four 1-g capsules/d) or matching placebo on day 7 after graft creation.

Main Outcome Measure Proportion of participants experiencing graft thrombosis or radiological or surgical intervention during 12 months' follow-up.

Results The risk of the primary outcome did not differ between fish oil and placebo recipients (48/99 [48%] vs 60/97 [62%], respectively; relative risk, 0.78 [95% CI, 0.60 to 1.03; $P=.06$]). However, the rate of graft failure was lower in the fish oil group (3.43 vs 5.95 per 1000 access-days; incidence rate ratio [IRR], 0.58 [95% CI, 0.44 to 0.75; $P<.001$]). In the fish oil group, there were half as many thromboses (1.71 vs 3.41 per 1000 access-days; IRR, 0.50 [95% CI, 0.35 to 0.72; $P<.001$]); fewer corrective interventions (2.89 vs 4.92 per 1000 access-days; IRR, 0.59 [95% CI, 0.44 to 0.78; $P<.001$]); improved cardiovascular event–free survival (hazard ratio, 0.43 [95% CI, 0.19 to 0.96; $P=.04$]); and lower mean systolic blood pressure (–3.61 vs 4.49 mm Hg; difference, –8.10 [95% CI, –15.4 to –0.85]; $P=.01$).

Conclusions Among patients with new hemodialysis grafts, daily fish oil ingestion did not decrease the proportion of grafts with loss of native patency within 12 months. Although fish oil improved some relevant secondary outcomes such as graft patency, rates of thrombosis, and interventions, other potential benefits on cardiovascular events require confirmation in future studies.

Trial Registration isrctn.org Identifier: ISRCTN15838383

JAMA. 2012;307(17):1809-1816 www.jama.com

OPTIMAL HEMODIALYSIS requires reliable vascular access. Current options include the arteriovenous fistula, synthetic arteriovenous graft, and central venous catheter, which in the United States are used in 55%, 21%, and 24% of prevalent patients receiving hemodialysis, respectively.[1] The arteriovenous graft was the predominant vascular access type in North America during the early 1990s but fell out of favor owing to its high complication rates and associated costs. For example, thrombosis occurs in more than 50% of all arteriovenous grafts within 1 year after placement, necessitating a salvage procedure in more than 75%.[2,3] Arteriovenous graft thrombosis usually occurs at the venous anastomosis in proximity to a stenotic lesion resulting from aggressive neointimal hyperplasia.[4]

To date, multiple interventions have failed to convincingly or consistently re-

For editorial comment see p 1859.

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duce thrombosis rates.[5-9] A large, multicenter randomized trial of dipyridamole plus low-dose aspirin demonstrated a modest improvement in arteriovenous graft primary patency but poor cumulative arteriovenous graft survival.[10] Because of their antiproliferative, antioxidant, and vasodilatory effects, the omega-3 fatty acids found in fish oils have theoretical appeal for preventing development of arteriovenous graft stenosis and thrombosis.[11-16] Indeed, a small, single-center prospective study of fish oil prophylaxis showed a dramatic (5-fold) improvement in 12-month graft patency[16] and inspired a larger, definitive trial.

We performed a randomized, blinded, controlled trial that compared arteriovenous graft patency and rates of thrombosis and intervention in patients with end-stage renal disease who received oral fish oil supplementation vs placebo following creation of an arteriovenous graft.

METHODS

Sponsor and Study Oversight

The trial was sponsored by 2 peer-reviewed Canadian funding agencies, the Canadian Institutes for Health Research and the Physicians Services Incorporated Foundation. An independent data and safety monitoring committee reviewed the study for safety, data quality, and efficacy using the Lan-DeMets extension of the O'Brien-Fleming stopping rules.[17,18] A planned interim analysis was performed after half of the patients were recruited, to determine whether the study should be stopped early for safety concerns. Discontinuing the study was deemed unnecessary.

Study Design and Patient Population

This study was a multicenter, randomized, placebo-controlled clinical trial enrolling patients with end-stage renal disease who required a new arteriovenous graft access. Details of the study design have been published.[19] Briefly, adult (≥18 years) patients with end-stage renal disease who required a synthetic arteriovenous graft for chronic hemodialysis were eligible. The arteriovenous graft could either be a "first access" ever surgically created or a "subsequent access" after a previously failed access.

Major exclusion criteria were reversible renal failure; active malignancy; pregnancy; malignant hypertension; active major bleed in the prior month; receiving more than 2 antiplatelet agents or anticoagulants (ie, concomitant use of aspirin and warfarin was not an exclusion); life expectancy less than 6 months; surgical revision of a previous access, such as a jump graft (ie, the arteriovenous graft under study needed to be a new graft); arteriovenous graft that failed prior to and including postoperative day 7; ingestion of any form of fish oil at time of randomization; allergy to fish or fish products; and enrollment in another interventional study of arteriovenous grafts.

Patients were enrolled at 12 Canadian and 3 US sites. The institutional review board of each participating study site approved the study protocol. Each patient provided written informed consent before enrollment. The study was conducted with strict adherence to good clinical practice guidelines and the Declaration of Helsinki.

Study Procedures

The study was initiated in November 2003; enrollment closed in December 2009. Patients were randomized (1:1) with concealed allocation to the 2 treatment groups on the seventh postoperative day of their arteriovenous graft creation by a central, independent randomization facility. Patient randomization was stratified by site and first access or subsequent access. Patients were assigned to receive fish oil capsules (four 1-g capsules/d) or matching placebo capsules daily for the 12-month duration of the study. The study capsules (fish oil or placebo) were soft gel capsules that were steam deodorized and flavored with 1% peppermint. The fish oil was MEG-3 (Ocean Nutrition Canada Ltd), which contains 48% (400 mg/capsule) eicosapentaenoic acid (EPA) and 25% (200 mg/capsule) docosahexaenoic acid (DHA). The placebo capsule contained only 1% peppermint-flavored corn oil and was packaged identically to the fish oil. The placebo and fish oil capsules were similar in color, shape, odor, taste, and consistency.

Patients, study coordinators, caregivers, and site pharmacists were blinded to treatment allocation. Only the study independent clinical trials pharmacist who packaged the study treatment had access to the randomization assignment.

Patients initiated study treatment after randomization on day 7 following their graft creation surgery date. Baseline characteristics, including race/ethnicity, were collected using established definitions where available.[20,21] Patients were monitored biweekly with increased frequency as clinically indicated. All sites were required to abide by local graft surveillance protocols, monitoring, or both, that were based on national guidelines and available evidence.[22-26] For example, Canadian sites that performed routine flow surveillance followed Canadian national guidelines for intervention; thus, when arteriovenous graft flows decreased by more than 20% from baseline or to less than 650 mL/min and there was a clinical abnormality, a follow up angiogram was required.[22] If the angiogram disclosed a stenotic lesion of greater than 50%, angioplasty was attempted. Angiography without subsequent intervention to change the vascular access anatomy (ie, angioplasty, stent, revision) was not considered an end point. Of note, participating sites could not change their policy for graft surveillance or monitoring in study patients throughout the duration of the trial. Compliance with ingestion of study capsules was assessed by measurement of EPA incorporation into endogenous cells by gas-liquid chromatography (eAppendix, available at http://www.jama.com).

Outcomes

The predefined primary study end point was the proportion of arteriovenous grafts with loss of native patency within 12 months. Loss of native patency was defined as the graft having a primary event of thrombosis or requiring radiological or surgical intervention to maintain patency following its creation. If a radiological or surgical intervention was

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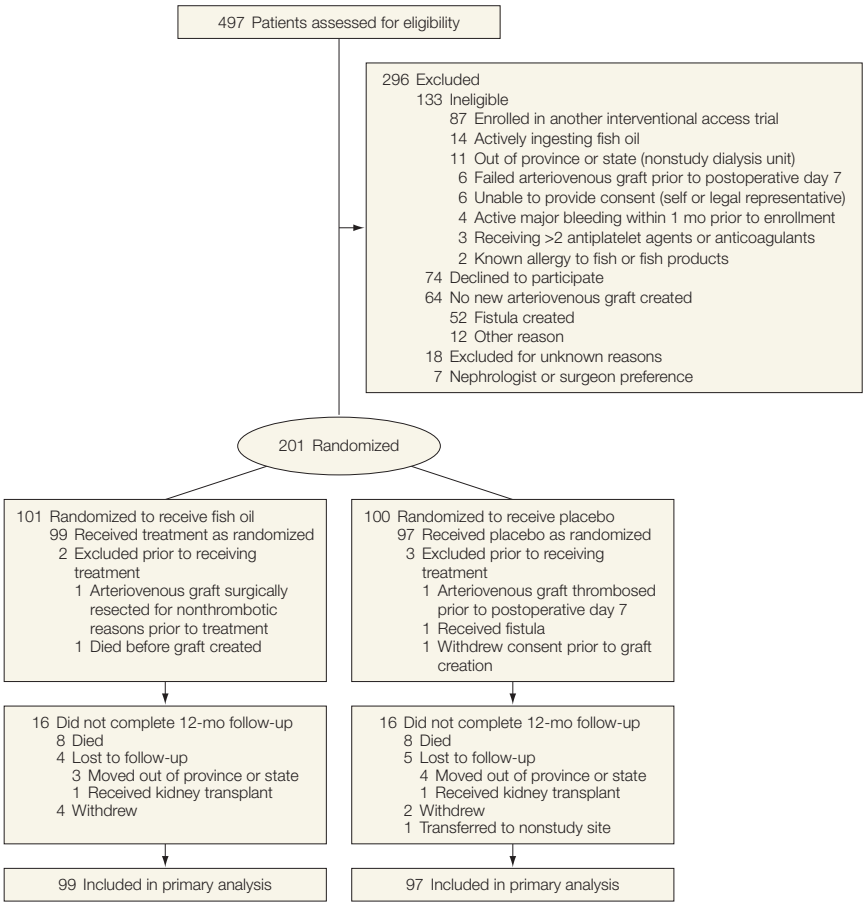
performed, an independent assessor, unaware of treatment allocation, reviewed the radiology or surgical reports to verify the outcomes.

Major secondary end points included the rate (events per 1000 access-days) and proportion of arteriovenous graft thrombosis and radiological or surgical interventions, the time to each event, and cumulative graft patency. Time to loss of native patency is also known as primary unassisted patency.[27] Cumulative arteriovenous graft patency was defined as the time from graft creation to unsalvageable graft loss (when the graft was abandoned). The occurrences of minor and major bleeding episodes, changes in lipid status and blood pressure, hospitalizations for cardiovascular events, and death were determined. All end points reported were prespecified.[19] Follow-up continued for 12 months, regardless of whether the patient reached the primary outcome (to achieve the secondary objectives); patients were censored at kidney transplantation or transfer to a nonstudy facility.

Figure 1. Study Enrollment and Follow-up



Statistical Analysis

Recruitment of 232 patients (116 arteriovenous grafts per group) was initially planned to detect a 30% reduction in the proportion of patients with loss of native patency (from 68% to 47.5%) with 80% power, using a 2-sided statistical test with α of .05 and adjusted for 12% patient loss and nonadherence to study treatment. This sample size was based on results from an earlier study that demonstrated an improvement in 12-month graft patency from 14.9% to 75.6%.[16] Additionally, Canadian pilot data demonstrated loss of graft patency to be 68% at 12 months.[19] Because of a paucity of data at the study design phase, a 30% reduction in loss of graft patency was deemed more conservative than previously observed[16] and feasible from a study standpoint. If the accrual goal of 232 patients was reduced to the observed 201 patients, study power would decrease from 80% to 74%.

Although proportion and rate are both clinically relevant end point measures, we chose a proportion primary end point (proportion with loss of native patency) rather than a Poisson primary end point (primary events per 1000 days), because we could not confirm a priori that the distribution of graft events would follow a Poisson distribution. The time-to-event end point was deemed to have less clinical importance from a patient perspective. Thus, the proportion end point was chosen as the primary end point, and the rate of events and time-to-event end points were classified as clinically important secondary clinical end points. We assessed proportions, their confidence intervals, and their differences using the Fisher exact test[28] and compared groups using relative risk and logistic regression.[29] Outcomes reporting the number of events per 1000 access-days were analyzed using Poisson distribution methods,[30] and comparisons between groups used the incidence rate ratio from a Poisson regression.[31]

Quantitative values were compared between groups using the Wilcoxon rank-sum test or *t* test, depending on distribution. Time-to-event distributions and their confidence intervals were estimated using the Kaplan-Meier method, and groups were compared using the log-rank test and hazard ratio from the Cox proportional hazards model.[32]

Analyses were based on an intention-to-treat approach, except for the exclusion of 5 randomized, blinded participants who did not remain in the study long enough to get to the point at which treatment would be started (FIGURE 1). $P < .05$ was considered statistically significant.

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All *P* values are 2-sided and are unadjusted for multiple comparisons except as noted, where Bonferroni adjustment[33] was used. Analyses were conducted using STATA version 10.0.

RESULTS

Study Population

We assessed 497 patients for eligibility, of whom 201 were randomly assigned to receive fish oil capsules (101 patients) or placebo (100 patients) (Figure 1). The most common reason for ineligibility was patient refusal and creation of a fistula rather than an arteriovenous graft. Five protocol deviations occurred whereby patients were erroneously randomized (eg, received a fistula rather than a graft) before postoperative day 7, but none of these patients received study intervention (Figure 1). Patient demographics and graft characteristics were well balanced between the 2 treatment groups (TABLE 1), except more patients in the fish oil group had a history of congestive heart failure (*P* = .03). Although the difference was not statistically significant, more patients in the fish oil group had forearm arteriovenous grafts (*P* = .13). Both congestive heart failure and a forearm arteriovenous graft location are factors known to increase the risk of thrombosis.[34-36]

Because of slower than expected recruitment[19] and lack of additional funds to continue the study, enrollment was terminated prematurely at 201 patients. The last patient completed study follow-up on December 15, 2010.

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Patients No. (%)	
	Fish Oil (n = 99)	Placebo (n = 97)
Age, mean (range), y	62.5 (28-88)	63.4 (27-87)
Men	47 (47)	51 (53)
Race/ethnicity[a]		
White	64 (65)	59 (61)
Black	16 (16)	15 (15)
South Asian	5 (5)	7 (7)
Southeast Asian	9 (9)	7 (7)
Other	5 (5)	9 (9)
Etiology of end-stage renal disease		
Diabetes	49 (49)	39 (40)
Glomerulonephritis	14 (14)	22 (23)
Hypertension	27 (27)	21 (22)
Tubulointerstitial disorders	1 (1)	2 (2)
Cystic or hereditary disorders	2 (2)	5 (5)
Other/unknown	6 (6)	8 (8)
Hemodialysis duration, mean (range), y	2.76 (0-34)	2.84 (0-25)
Comorbid conditions		
Diabetes	51 (52)	52 (54)
Hypertension	84 (85)	84 (87)
Coronary artery disease	32 (32)	34 (35)
Peripheral vascular disease	17 (17)	12 (12)
Congestive heart failure	26 (26)	13 (13)
Cerebrovascular disease	12 (12)	15 (15)
Current or prior smoking	57 (58)	50 (52)
History of malignancy	14 (14)	12 (12)
Baseline lipids, mean (range), mg/dL		
LDL-C	69.9 (5.4-174.5)	69.1 (7.7-202.3)
Total cholesterol	145.2 (68.7-238.2)	141.3 (35.9-320.1)
Triglycerides	182.3 (41.6-571.7)	159.3 (35.4-690.3)
Medications		
Lipid-lowering agent	67 (68)	55 (57)
Aspirin	57 (58)	51 (53)
Warfarin	26 (26)	20 (21)
Clopidogrel	11 (11)	13 (13)
Dipyridamole and aspirin	0	1 (1)
Prior vascular access	63 (64)	63 (65)
No. of prior accesses, mean (range)	1.1 (0-5)	1.2 (0-7)
No. with ≥2 prior accesses	26 (26)	27 (28)
No. with prior fistulas	73 (74)	72 (74)
Predialysis graft creation	17 (17)	12 (12)
Graft location		
Upper arm	34 (34)	43 (44)
Forearm	61 (62)	49 (51)
Leg	4 (4)	5 (5)
Graft configuration		
Loop	71 (72)	70 (72)
Straight	28 (28)	27 (28)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
SI Conversion factors: To convert LDL-C and total cholesterol values to mmol/L, multiply by 0.0259; to convert triglycerides values to mmol/L, multiply by 0.0113.
[a] South Asian includes patients of East Indian, Pakistani, and Punjabi origins; also known as "Indian sub-continent." Southeast Asian includes patients of Chinese, Japanese, Korean, and Indo-Chinese origins. Other includes patients of Aboriginal, Arabic, Hispanic, Polynesian, mixed, or unknown ethnic origin.

Study Outcomes

There was no significant difference in the proportions of fish oil recipients and placebo recipients with loss of native patency (48% [48/99] vs 62% [60/97], respectively; relative risk, 0.78 [95% CI, 0.60 to 1.03]; *P* = .06) (TABLE 2). However, the rate of these events was significantly lower in the fish oil group (3.43 vs 5.95 per 1000 access-days; incidence rate ratio [IRR], 0.58 [95% CI, 0.44 to 0.75]; *P* < .001) (Table 2). The frequency of thrombosis events was reduced by half in the fish oil group (1.71 vs 3.41 per 1000 access-days; IRR, 0.50 [95% CI, 0.35 to 0.72]; *P* < .001), and the frequency of corrective interventions was lower (2.89 vs 4.92 per 1000 access-days; IRR, 0.59 [95% CI, 0.44 to 0.78]; *P* < .001). All 3 rate comparisons (loss of native patency, thrombosis events, and corrective interventions) per 1000 access-days remained statistically significant after adjusting for multiple end point analyses (*P* < .001) (FIGURE 2).

The 12-month event-free rate (ie, no loss of native patency of arteriovenous graft) was 48% in the fish oil group, com-

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Table 2. Study Outcomes

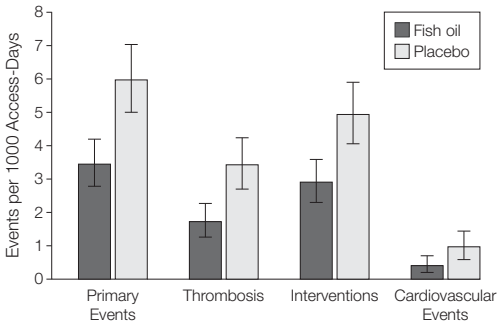
Outcomes	Value (95% CI)			*P* Value
	Fish Oil	Placebo	Group Comparison	
Primary outcome				
Patients with loss of native patency, No./total (%)[a]	48/99 (48) [0.38 to 0.59]	60/97 (62) [0.51 to 0.72]	0.78 (0.60 to 1.03)[b]	.06
Secondary and tertiary arteriovenous graft outcomes				
Primary event rate: primary events per 1000 access-days[c]	3.43 (2.78 to 4.19)	5.95 (5.00 to 7.03)	0.58 (0.44 to 0.75)[d]	<.001
Primary unassisted patency (no loss of native patency) at 12 mo	0.48 (0.38 to 0.58)	0.32 (0.23 to 0.43)	0.68 (0.46 to 0.99)[e]	.045
Cumulative patency at 12 mo	0.72 (0.62 to 0.80)	0.65 (0.54 to 0.74)	0.76 (0.46 to 1.27)[e]	.30
Thrombosis events				
Patients with ≥1 thrombosis event, No./total (%)	33/99 (33) [0.24 to 0.44]	45/97 (46) [0.36 to 0.57]	0.72 (0.49 to 1.04)[b]	.08
Thrombosis rate: thromboses per 1000 access-days	1.71 (1.26 to 2.27)	3.41 (2.70 to 4.24)	0.50 (0.35 to 0.72)[d]	<.001
Thrombosis-free at 12 mo	0.64 (0.53 to 0.73)	0.47 (0.36 to 0.58)	0.62 (0.39 to 0.97)[e]	.03
Radiological or surgical interventions				
Patients with ≥1 intervention, No./total (%)	38/99 (38) [0.29 to 0.49]	48/97 (49) [0.39 to 0.60]	0.78 (0.55 to 1.09)[b]	.15
Intervention rate: interventions per 1000 access-days	2.89 (2.30 to 3.59)	4.92 (4.06 to 5.90)	0.59 (0.44 to 0.78)[d]	<.001
Intervention-free at 12 mo	0.56 (0.44 to 0.66)	0.38 (0.27 to 0.50)	0.68 (0.44 to 1.03)[e]	.07
Cardiovascular outcomes[g]				
Patients with ≥1 cardiovascular event, No./total (%)	9/99 (9) [0.04 to 0.17]	17/97 (18) [0.11 to 0.27]	0.52 (0.22 to 1.17)[b]	.10
Cardiovascular event rate: events per 1000 access-days	0.39 (0.20 to 0.70)	0.95 (0.59 to 1.44)	0.41 (0.20 to 0.85)[d]	.02
Cardiovascular event–free at 12 mo	0.88 (0.77 to 0.93)	0.75 (0.63 to 0.84)	0.43 (0.19 to 0.96)[e]	.04
Blood pressure and antihypertensive medications				
Systolic blood pressure, mean change, mm Hg				
From baseline to 6 mo	–5.11 (–9.90 to –0.33)	2.63 (–1.8 to 7.02)	–7.74 (–14.2 to –1.30)[f]	.02
From baseline to 12 mo	–3.61 (–8.73 to 1.52)	4.49 (–0.72 to 9.71)	–8.10 (–15.4 to –0.85)[f]	.01
Diastolic blood pressure, mean change, mm Hg				
From baseline to 6 mo	–3.85 (–6.56 to –1.13)	0.63 (–2.04 to 3.29)	–4.47 (–8.25 to –0.70)[f]	.04
From baseline to 12 mo	–2.17 (–4.77 to 0.42)	0.13 (–2.43 to 2.68)	–2.30 (–5.91 to 1.31)[f]	.13
Patients who had ≥1 reduction in dose or frequency of antihypertensive medications, No./total (%)	63/99 (64) [0.53 to 0.73]	41/97 (42) [0.32 to 0.53]	1.51 (1.13 to 2.01)[b]	.004
Mean reduction in No. of antihypertensive medications	1.68 (1.25 to 2.10)	0.62 (0.37 to 0.87)	1.06 (0.57 to 1.55)[f]	<.001

[a] Experienced at least 1 of thrombosis or radiological intervention or surgical intervention to maintain patency.
[b] Relative risk group comparison, Fisher exact test *P* value.
[c] Primary event is a thrombosis or radiological intervention or surgical intervention to facilitate patency.
[d] Incidence rate ratio group comparison of fish oil relative to placebo; *P* value from Poisson regression.
[e] Hazard ratio group comparison, *P* value from log-rank test.
[f] Mean change from baseline to 6-month and 12-month values are reported; *P* value from Wilcoxon rank-sum test.
[g] Stroke, peripheral vascular disease, myocardial infarction, congestive heart failure, cardiac-related death.

pared with 32% in the placebo group (hazard ratio [HR], 0.68 [95% CI, 0.46 to 0.99]; *P* = .045) (Table 2 and FIGURE 3). The 12-month thrombosis-free rate was higher in the fish oil group (64% vs 47%; HR, 0.62 [95% CI, 0.39 to 0.97]; *P* = .03). There were no significant interactions between the baseline graft status (first or subsequent access) (*P* = .86) or study site and treatment assignment (*P* = .90). There was no significant difference between the treatment groups with respect to cumulative graft patency; in the fish oil group, 28% had lost their graft by 12 months, compared with 35% of patients who received placebo (HR, 0.76 [95% CI, 0.46 to 1.27]; *P* = .30) (Table 2).

The reasons for arteriovenous graft loss were similar between treatment groups (thrombosis [81.4%], technical cause such as surgical complication or cannulation injury [3.4%], steal syndrome [5.1%], infection [8.4%], and pseudoaneurysm [1.7%]).

Figure 2. Frequency of Arteriovenous Graft Events



Primary events indicates thrombosis and radiological or surgical intervention to maintain graft patency. Interventions indicates radiological or surgical interventions to maintain graft patency. Error bars indicate 95% CIs.

Analysis of cardiovascular outcomes demonstrated superior cardiovascular event–free survival in the fish

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oil group (HR, 0.43 [95% CI, 0.19 to 0.96]; $P=.04$) (Table 2 and Figure 3). Compared with baseline, there were clinically significant reductions in systolic blood pressure at 6 months in the fish oil group (mean decrease of 5.11 mm Hg [95% CI, –9.90 to –0.33]) that were sustained to 12 months (Table 2). Sixty-four percent (63/99) of patients in the fish oil group compared with 42% (41/97) in the placebo group had at least 1 reduction in the dose or frequency of their antihypertensive medications (relative risk, 1.51 [95% CI, 1.13 to 2.01]; $P=.004$). Additionally, patients who received fish oil were able to reduce their numbers of antihypertensive medications (mean reduction, 1.68 [95% CI, 1.25 to 2.10] for fish oil vs 0.62 [95% CI, 0.37 to 0.87] for placebo; mean difference, 1.06 [95% CI, 0.57 to 1.55]; $P<.001$).

No between-treatment differences were seen in serum levels of low-density lipoprotein cholesterol, total cholesterol, or triglycerides. There was no difference in bleeding (9 events in the fish oil group vs 8 in the placebo group; $P>.99$) or other significant clinical adverse events between the 2 treatment groups.

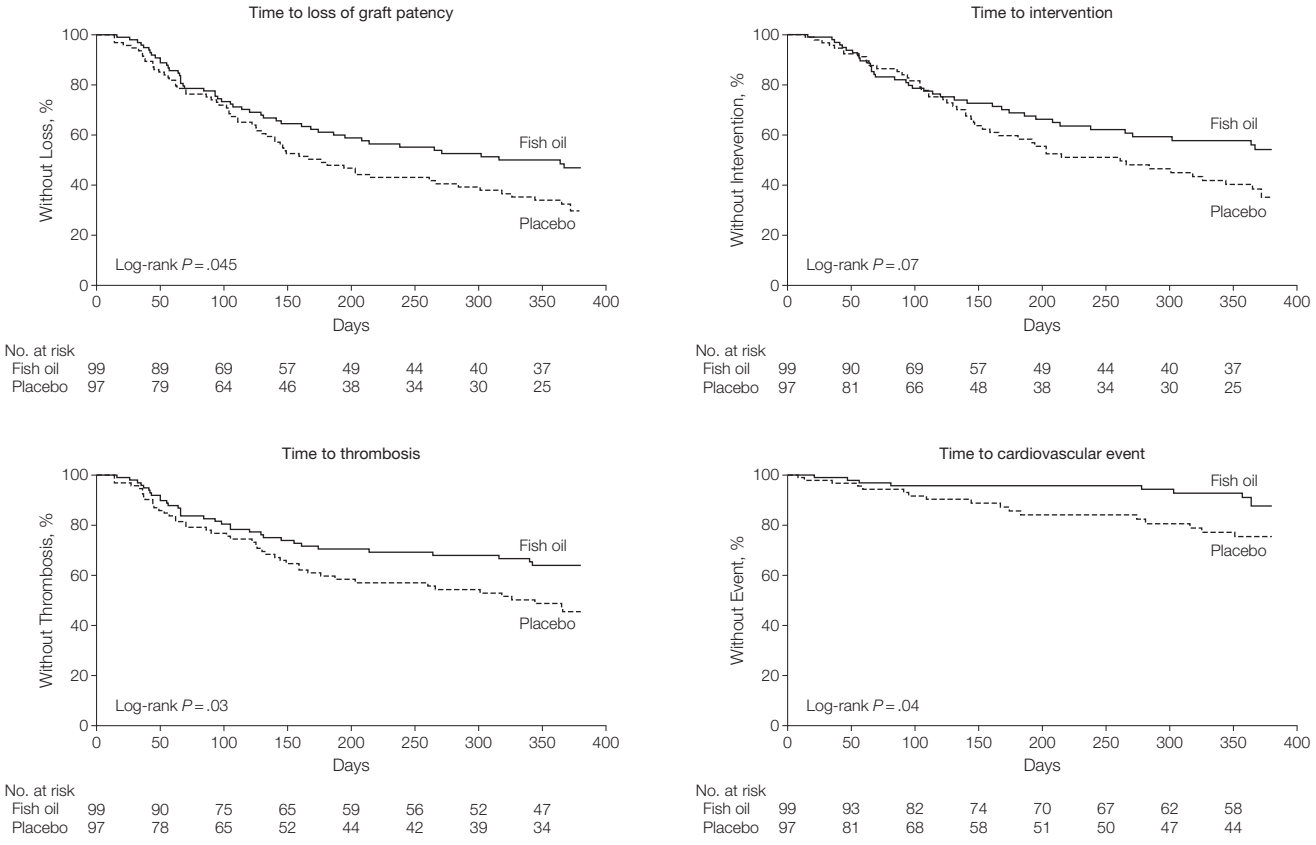
Adherence

At baseline, there was no difference in omega-3 fatty acid composition between the treatment groups (eTable). A significant difference in EPA incorporation into endogenous cells was found between the treatment groups at 3 months (mean increase of 1.76 in the fish oil group vs a mean decrease of 0.45 in the placebo group; mean difference, 2.21 [95% CI, 1.65 to 2.77]; $P<.001$) (eTable), confirming both adherence and evidence that the fish oil formulation was sufficient to modify lipid composition of endogenous cells.

COMMENT

Our study of patients with end-stage renal disease who received a new arteriovenous graft showed that the proportion with graft thrombosis or a radiological or surgical intervention to maintain graft patency did not significantly differ between fish oil and placebo recipients. However, fish oil recipients had a prolonged time without thrombosis, half the thrombosis rate, and a clinically meaningful reduction in frequency of radiological and surgical interventions. Important other findings include improved cardiovascular event–free survival and rate as well as improved blood pressure and a reduction in use of antihypertensive medications in the fish oil group. Although the risk of the pri-

Figure 3. Kaplan-Meier Estimates of Time to First Loss of Native Graft Patency, Thrombosis, Intervention, and Cardiovascular Event



Median time to primary unassisted patency was 354 days in the fish oil group and 176 days in the placebo group. Intervention indicates radiological or surgical intervention to maintain graft patency.

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mary end point was not significantly lower among fish oil recipients, this should be considered in the context of the apparent consistent clinical benefits observed for the secondary outcomes.

Better arteriovenous graft outcomes have been demonstrated in an earlier trial of fish oil prophylaxis in 24 patients, which demonstrated a dramatic reduction in graft thrombosis (24.4% with fish oil vs 85.1% with placebo[16]). Although that trial was small with limited generalizability,[16] it provided an important basis for our study. A second study randomized 29 patients with new forearm loop grafts to receive over-the-counter omega-3 fatty acids (EPA, 0.96 g/d; DHA, 0.6 g/d) vs placebo and did not observe any difference in 8-month graft patency.[37] In addition to the small sample size, the lower doses of EPA and DHA might have contributed to lack of effect.

The fish oil used in our study had strict quality control and a minimum daily delivery of 1.6 g EPA and 0.8 g DHA (EPA, 400 mg/capsule; DHA, 200 mg/capsule).[19] The EPA and DHA components of fish oils have been shown to have antiproliferative, antioxidative, and vasodilatory effects[19] that may affect the pathogenesis of arteriovenous graft stenosis. For example, EPA reduces platelet aggregation in patients receiving hemodialysis,[38] decreases serum viscosity,[39] and may directly inhibit neointimal hyperplasia, which is the usual cause of arteriovenous graft stenosis.[4]

The use of arteriovenous grafts has declined over the last 10 years,[40,41] largely driven by the emphasis on use of fistulas. Arteriovenous grafts may be suitable for patients receiving hemodialysis whose veins are unsuitable for fistula creation or who have experienced prior problems with fistula nonmaturation. However, compared with functioning fistulas, arteriovenous grafts may require a 3- to 4-fold higher frequency of interventions to maintain equivalent long-term patency.[42-44] Identification of safe and inexpensive agents that prolong arteriovenous graft patency and reduce the frequency of interventions to salvage graft complications might encourage increased use of grafts. Previous multicenter randomized studies using warfarin,[9] aspirin plus clopidogrel,[8] or dipyridamole plus aspirin[10] have observed limited improvement in graft longevity but did not assess the rate of complications or interventions to maintain graft longevity.

Large cohort studies have shown an inverse association between cardiovascular morbidity and mortality and fish oil ingestion.[45,46] Fish oil may reduce cardiovascular events by multiple mechanisms, including anti-inflammatory, antiarrhythmic, and plaque-stabilizing effects as well as improved endothelial effects.[47,48] Although some investigators have suggested that fish oil also might improve dyslipidemia,[16,49] we did not find any effect on lipid profile. However, fish oil recipients had better control of blood pressure despite reductions in the dose or frequency and pill burden of antihypertensive medications.

Our study has limitations that should be considered. First, we did not reach our enrollment goal. Perhaps because of lower than expected statistical power, we did not identify a significant difference for the primary end point. However, fish oil exerted a significant beneficial effect on several important and clinically relevant secondary end points. In retrospect, our choice of primary end point may not have been optimal, because it yielded lower statistical power than potential alternatives. However, it was selected based on the available data at the time of study design. Second, the cardiovascular benefits seen in this study should be interpreted with caution, given the small number of participants and events. However, the use of fish oil to prevent cardiovascular events in the dialysis population merits further study.

CONCLUSIONS

Among patients with new synthetic arteriovenous hemodialysis grafts, daily ingestion of fish oil did not decrease the proportion of grafts with loss of native patency within 12 months. However, fish oil showed beneficial effects on some clinically relevant secondary outcomes such as graft patency and rates of thrombosis and corrective interventions, while the potential benefits of fish oil on cardiovascular events deserve confirmation in future studies.

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Author Contributions: Dr Lok had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Lok, Moist, Hemmelgarn, Tonelli, Vazquez, Dorval, Oliver, Donnelly, Allon.
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Statistical analysis: Lok, Stanley.
Obtained funding: Lok.
Administrative, technical, or material support: Lok, Moist, Vazquez, Dorval, Donnelly, Stanley.
Study supervision: Lok, Moist, Hemmelgarn, Tonelli, Vazquez, Dorval, Donnelly, Allon.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Moist reported serving as a consultant for Amgen and Leo and receiving payment for lectures from Roche and Merck. Dr Dorval reported serving as a board member for Gambro; serving as a consultant for Gambro; receiving grants or grants pending from Gambro and Baxter; and receiving payment for lectures from Gambro and Novartis. Dr Oliver reported receiving author royalties from UpToDate and that he is the sole owner of Oliver Medical Management Inc, which manufactures dialysis-related software. Dr Allon reported receiving a grant and travel support from the University of Alabama at Birmingham. Dr Stanley reported serving as the FISH study's independent statistician and that he served as Executive Director of the Center for Biostatistics and AIDS Research at Harvard School of Public Health before retiring. No other authors reported disclosures.
Funding/Support: This study was supported by peer-reviewed grant funding from the Physician's Services Incorporated Foundation and the Canadian Institutes for Health Research (CIHR). During the study, Drs Lok, Hemmelgarn, and Tonelli were supported by CIHR New Investigator Awards. Dr Lok was also supported by the CIHR Randomized Clinical Trials Mentoring Program. Currently, Drs Hemmelgarn and Tonelli are also supported by Alberta Heritage Foundation for Medical Research Population Scholar Awards; Dr Tonelli is supported by a Government of Canada Research Chair. Dr Allon is supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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grant K24 DK59818-01. Dr Vazquez is supported by NIDDK grants 5UO1 DK082240 and R34 DK094115.
Role of the Sponsors: Physician's Services Incorporated and CIHR had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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Online-Only Material: The eAppendix and eTable are available at http://www.jama.com.

Additional Contributions: We are grateful for the scientific and personal dedication given by each of the investigators, without whom this study would not have been possible. We thank Bruce Holub, PhD (Department of Human Health & Nutritional Sciences, University of Guelph, Guelph, Ontario), for his assistance with the gas-liquid chromatography interpretation to determine omega-3 fatty acid cellular incorporation and study compliance. Dr Holub received no compensation for his contributions.

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