ORIGINAL ARTICLE

Fish-Oil Supplementation and Cardiovascular Events in Patients Receiving Hemodialysis

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ABSTRACT

BACKGROUND

Cardiovascular disease is the leading cause of death in patients receiving hemodialysis, yet effective preventive therapies remain limited. Supplementation with n–3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may have cardiovascular benefits in the general population, but efficacy among patients receiving hemodialysis is uncertain.

METHODS

In a double-blind, randomized, placebo-controlled trial conducted at 26 sites in Canada and Australia, we assigned adult patients receiving maintenance hemodialysis to daily supplementation with fish oil (4 g of n–3 polyunsaturated fatty acids [1.6 g of EPA and 0.8 g of DHA]) or corn-oil placebo. The primary end point was a composite of all serious cardiovascular events including sudden and nonsudden cardiac death, fatal and nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and fatal and nonfatal stroke. Secondary end points included extension of the primary end point to include noncardiac causes of death, the individual components of the primary end point, and a first cardiovascular event or death from any cause.

RESULTS

Between November 28, 2013, and July 22, 2019, a total of 1228 participants underwent randomization; 610 were assigned to the fish-oil group and 618 to the placebo group. During 3.5 years of follow-up, the rate of serious cardiovascular events was significantly lower in the fish-oil group than in the placebo group (0.31 vs. 0.61 per 1000 patient-days; hazard ratio, 0.57; 95% confidence interval [CI], 0.47 to 0.70; P<0.001). The rate of the extended primary end point that included noncardiac causes of death appeared to be lower in the fish-oil group than in the placebo group, with a hazard ratio of 0.77 (95% CI, 0.65 to 0.90). The hazard ratio for cardiac death was 0.55 (95% CI, 0.40 to 0.75); for fatal and nonfatal myocardial infarction, 0.56 (95% CI, 0.40 to 0.80); for peripheral vascular disease leading to amputation, 0.57 (95% CI, 0.38 to 0.86); for fatal and nonfatal stroke, 0.37 (95% CI, 0.18 to 0.76); and for a first cardiovascular event or death from any cause, 0.73 (95% CI, 0.61 to 0.87). Adherence to the trial regimen and the incidence of adverse events did not differ meaningfully between the groups.

CONCLUSIONS

The rate of serious cardiovascular events among participants receiving maintenance hemodialysis was lower with daily supplementation with n–3 fatty acids than with placebo. (Supported by the Heart and Stroke Foundation of Canada and others; PISCES ClinicalTrials.gov number, ISRCTN00691795.)

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This article was published on November 7, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2513032

Globally, more than 3.8 million people currently receive kidney-replacement therapy for end-stage kidney disease; most are treated with hemodialysis.[1,2] Cardiovascular disease affects more than two thirds of persons receiving hemodialysis and accounts for more than 75% of the associated deaths[3]; cardiovascular mortality is 20 times as high as that in the general population,[4] a finding that highlights the importance of effective cardiovascular management. However, these high-risk patients receiving maintenance hemodialysis are challenged by both traditional and nontraditional cardiovascular risk factors,[5,6] and there are few proven medical interventions for the prevention of cardiovascular events in this population.[6]

The effect of n–3 polyunsaturated fatty acids in reducing the risk of cardiovascular disease was reported more than 50 years ago, yet their effects remain controversial.[7,8] Recent studies have suggested that n–3 fatty acids reduce the risk of cardiovascular events in the general population[9,10] and that there is an inverse relation between n–3 fatty acid blood levels and the risk of cardiovascular events.[11,12] Although n–3 fatty acid blood levels are lower in patients receiving hemodialysis than in the general population,[13,14] it is unclear whether oral fish-oil supplementation can reduce the risk of cardiovascular events and death in this patient population.[15] We hypothesized that among patients treated with maintenance hemodialysis, oral supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the long-chain n–3 polyunsaturated fatty acids found in fish oil, would lead to a lower rate of cardiovascular events than placebo.

Methods

Trial Design and Oversight

The Protection against Incidences of Serious Cardiovascular Events Study (PISCES) was a multicenter, parallel-group, randomized, placebo-controlled, clinical trial that evaluated daily fish-oil supplementation, as compared with corn-oil placebo, in participants receiving hemodialysis. The trial design and protocol (available with the full text of this article at NEJM.org) were developed by the steering committee.[16] The trial and its amendments were approved by the institutional review board at each of the 16 participating sites in Canada and Australia, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. All the participants provided written informed consent before enrollment. An independent data and safety monitoring committee oversaw participant safety and trial progress. The steering committee members were unaware of the trial-group assignments and had access to blinded data, which was analyzed by the trial statistician. All the authors were involved in drafting or review (or both) of the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript.

Participants

Eligible participants were 18 years of age or older, had end-stage kidney disease, were receiving hemodialysis three or four times per week, and were in clinically stable condition before enrollment. Participants who were taking n–3 fatty acid supplements at the time of randomization or had an allergy to fish, soy, corn, or any of their products were excluded. Full eligibility criteria are provided in the protocol.[16]

Randomization, Interventions, and Follow-up

Participants were assigned in a 1:1 ratio to daily oral supplementation with fish oil (4 g of steam-deodorized, citrus-flavored n–3 polyunsaturated fatty acids in four 1-g capsules containing a total of 1.6 g of EPA and 0.8 g of DHA) or citrus-flavored corn-oil placebo (see the Supplementary Appendix, available at NEJM.org). Randomization was performed with an independent, central, Web-based system to ensure concealment of the trial-group assignments and was stratified according to trial site and the presence or absence of any previous cardiovascular event. The randomization sequence was generated by a computerized random-number generator, with permuted blocks of randomly chosen sizes. Adherence to the trial regimen was assessed in a blinded manner at an independent laboratory, where the incorporation of n–3 fatty acids into plasma phospholipids was measured at 3 months in a randomly selected sample of 232 participants who received n–3 fatty acids or placebo.

The first 171 participants who underwent randomization provided written informed consent to be followed for 1 year (in the PISCES-Pilot), after

which they were asked to provide written informed consent again for a further 2.5 years of follow-up (for a total of 3.5 years of follow-up). All the participants who declined to reconsent agreed to include their 1-year data in the analyses. The participants who subsequently underwent randomization were followed for up to 3.5 years.

END POINTS

The primary end point was a composite of all serious cardiovascular events including cardiovascular death (sudden and nonsudden cardiac death, fatal myocardial infarction, and fatal stroke) and nonfatal cardiovascular events (nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and nonfatal stroke). Heart failure was not included, given the common noncardiac etiologic factors of fluid overload in patients receiving hemodialysis. Each serious cardiovascular event was counted (i.e., participants could contribute data on more than one event).

Secondary end points included extension of the primary end point to include noncardiac causes of death, individual components of the primary end point, and a first cardiovascular event or death from any cause. For all outcomes, the primary measure was the number of events per 1000 patient-days, and the secondary measure was the percentage of participants with an event. All serious cardiovascular events were centrally adjudicated by an independent events adjudication committee, the members of which were unaware of the trial-group assignments.

Safety was assessed by monitoring bleeding events. At the time of trial design, bleeding was the principal potential safety concern associated with the ingestion of n–3 fatty acid.

STATISTICAL ANALYSIS

Analyses of the primary and secondary end points included all randomly assigned participants who received at least one dose of fish oil or placebo, according to the intention-to-treat principle and the statistical analysis plan, available with the protocol.[16] In all analyses that included potentially recurrent events, the rates of events were compared between the trial groups with the Prentice–Williams–Peterson gap-time model, an extension of the Cox proportional-hazards model for recurrent events.[17] The rates of cardiovascular death, death from any cause, and the first cardiovascular event or death from any cause were compared between the trial groups with the Cox proportional-hazards model. All time-to-event models were stratified according to cardiovascular history. The only subgroup analysis assessed the primary end point according to history of a cardiovascular event.

We calculated that a sample of 1100 participants, followed for at least 3.5 years, would provide the trial with 82% power, at an alpha level of 0.05, to detect a hazard ratio of 0.825 in the Prentice–Williams–Peterson gap-time model, assuming rates in the placebo group of 0.74 per 1000 patient-days for recurrent cardiovascular events, 0.12 per 1000 patient-days for cardiovascular death, and 0.27 per 1000 patient-days for noncardiovascular death and accounting for a 10% loss to follow-up and a 3% drop-in rate (i.e., participants in the placebo group who took their own nontrial fish-oil supplement). All statistical analyses were performed with R software, version 4.4.2.[18] The 95% confidence intervals for the secondary end points were not adjusted for multiplicity and should not be used for hypothesis testing. Additional details on the statistical analyses are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The trial was conducted at 16 main sites and 10 satellite sites in Canada and Australia. The first participant underwent randomization on November 28, 2013, in the PISCES-Pilot and on August 27, 2015, in the current trial; the last participant underwent randomization on July 22, 2019. The date of the last participant follow-up was March 31, 2023. A total of 1228 participants underwent randomization and received at least one dose of fish oil or placebo (Fig. S1 in the Supplementary Appendix). Baseline characteristics were similar in the trial groups (Table 1 and Table S4). The mean (±SD) age of participants was 64.3±13.7 years, the mean duration of hemodialysis was 3.7±4.1 years, and 35.3% of the participants (434 of 1228) had a history of a cardiovascular event. The trial population appeared to be representative of patients receiving maintenance hemodialysis in the United States and participating countries. Over the course of the trial, there were 1394 patient-years of follow-up among 610 participants in the fish-oil group and 1382 patient-years of follow-up among 618 participants in the placebo group.

Table 1. Summary of Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Fish Oil (N=610)	Placebo (N=618)
Age — yr	64.1±13.5	64.5±13.8
Male sex — no. (%)†	377 (62.2)	387 (63.1)
Body-mass index‡	27.3±6.4	27.5±6.6
Race or ethnic group — no. (%)§		
White	244 (40.0)	244 (39.5)
Asian	99 (16.2)	95 (15.4)
Southeast Asian	76 (12.5)	99 (16.0)
Black	86 (14.1)	71 (11.5)
Other	43 (7.0)	39 (6.3)
Unknown or multiple	62 (10.2)	70 (11.3)
Coexisting conditions — no. (%)		
Diabetes	342 (56.1)	330 (53.4)
Hypertension	522 (85.6)	516 (83.5)
No history of cardiovascular disease — no. (%)	392 (64.3)	402 (65.0)
Median duration of hemodialysis (IQR) — yr	2.3 (1.1–4.9)	2.6 (1.1–4.8)
Median laboratory values (IQR)		
Hemoglobin — g/liter	109 (101–118)	110 (102–118)
Sodium — mmol/liter	137 (135–139)	137 (134–139)
Potassium — mmol/liter	4.7 (4.3–5.1)	4.7 (4.3–5.1)
Bicarbonate — mmol/liter	24 (22–26)	24 (22–26)
Total cholesterol — mmol/liter	3.41 (2.79–4.20)	3.29 (2.84–4.12)
LDL cholesterol — mmol/liter	1.59 (1.15–2.24)	1.50 (1.10–2.22)
HDL cholesterol — mmol/liter	1.04 (0.83–1.29)	1.05 (0.84–1.33)
Triglycerides — mmol/liter	1.29 (0.94–1.95)	1.35 (0.92–1.97)
Medications — no. of participants (%)		
Statin	332 (54.4)	357 (57.8)
Other lipid-lowering agent	37 (6.1)	47 (7.6)
Beta-blocker	301 (49.3)	303 (49.0)
Calcium-channel blocker	277 (45.4)	251 (40.6)
Renin–angiotensin system inhibitor¶	236 (38.7)	244 (39.5)
Diuretic	172 (28.2)	169 (27.3)
Anticoagulant or antiplatelet‖	141 (23.1)	143 (23.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.1129. HDL denotes high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.
† A total of nine participants declined to identify as male or female (four in the fish-oil group and five in the placebo group).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race and ethnic group were reported by the participant.
¶ Renin–angiotensin system inhibitors included angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers.
‖ Aspirin was not included.

PRIMARY END POINT

The rate of all serious cardiovascular events was lower in the fish-oil group than in the placebo group (0.31 per 1000 patient-days vs. 0.61 per 1000 patient-days; hazard ratio, 0.57; 95% confidence interval [CI], 0.47 to 0.70; P<0.001) (Table 2). The percentage of patients with at least one cardiovascular event appeared to be lower in the fish-oil

Table 2. Primary and Secondary End Points.*

End Point	Fish Oil		Placebo		Hazard Ratio (95% CI)†
	No. of Events	Rate	No. of Events	Rate	
		no. per 1000 patient-days		*no. per 1000 patient-days*	
Primary end point					
Primary end-point events among all participants	158	0.31	309	0.61	0.57 (0.47–0.70)
Primary end-point events in subgroups based on history of a cardiovascular event at baseline					
Previous cardiovascular event	81	0.43	164	0.91	0.50 (0.37–0.67)
No previous cardiovascular event	77	0.24	145	0.45	0.55 (0.40–0.76)
Secondary end points					
Primary end-point events plus noncardiac death	266	0.52	381	0.76	0.77 (0.65–0.90)
Death from any cause	175	0.34	195	0.39	0.89 (0.73–1.01)
Components of the primary end point					
Cardiac death	63	0.12	113	0.22	0.55 (0.40–0.75)
Fatal and nonfatal myocardial infarction	49	0.10	96	0.19	0.56 (0.40–0.80)
Peripheral vascular disease leading to amputation	35	0.07	66	0.13	0.57 (0.38–0.86)
Fatal and nonfatal stroke	11	0.02	34	0.07	0.37 (0.18–0.76)
First cardiovascular event or death from any cause	215	0.45	270	0.60	0.73 (0.61–0.87)

* The primary end point was serious cardiovascular events, a composite that included all occurrences of any of the following events: cardiovascular death (sudden and nonsudden cardiac death), nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and peripheral vascular disease leading to amputation. The rates of cardiovascular events were compared between the trial groups with the Prentice–Williams–Peterson gap-time model for the primary end point, the extension of the primary end point to include noncardiac causes of death, and the individual components of the primary end point that were potentially recurrent events. The rates of cardiovascular death, death from any cause, and a first cardiovascular event or death from any cause were compared between the trial groups with the Cox proportional-hazards model.

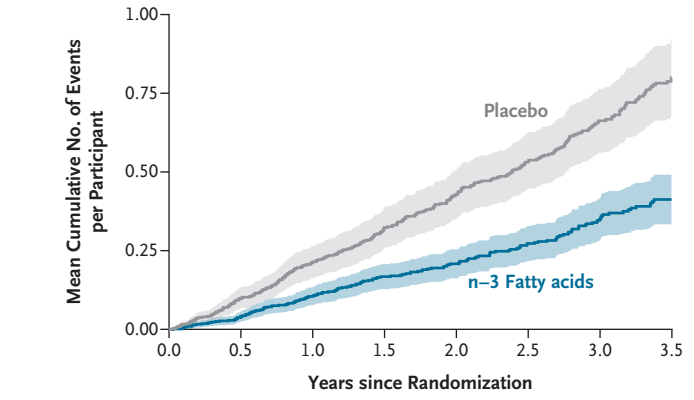
† The 95% confidence intervals for the secondary end points were not adjusted for multiplicity and should not be used for hypothesis testing.

group (20.8% [127 of 610 participants]) than in the placebo group (33.7% [208 of 618 participants]).

The lower rate of cardiovascular events in the fish-oil group appeared to be similar among those with or without a history of cardiovascular events at trial enrollment (Table 2). A total of 16.6% of the participants (101 of 610) in the fish-oil group and 23.1% of the participants (143 of 618) in the placebo group had only one serious cardiovascular event. Recurrent events (two or more) occurred in 4.3% of the participants (26 of 610) in the fish-oil group and in 10.5% of the participants (65 of 618) in the placebo group. The mean cumulative number of serious cardiovascular events per participant was lower in the fish-oil group than in the placebo group throughout the trial (Fig. 1A).

SECONDARY END POINTS

The hazard ratio for the extended primary end point that included noncardiac causes of death was 0.77 (95% CI, 0.65 to 0.90). Among the fish-oil recipients, at least one component of the primary end point or death occurred in 35.2% (215 of 610), as compared with 43.7% (270 of 618) in the placebo group. The rate of each component of the composite primary end point appeared to be lower in the fish-oil group than in the placebo group (Table 2 and Fig. 2). The hazard ratio for a first cardiovascular event or death



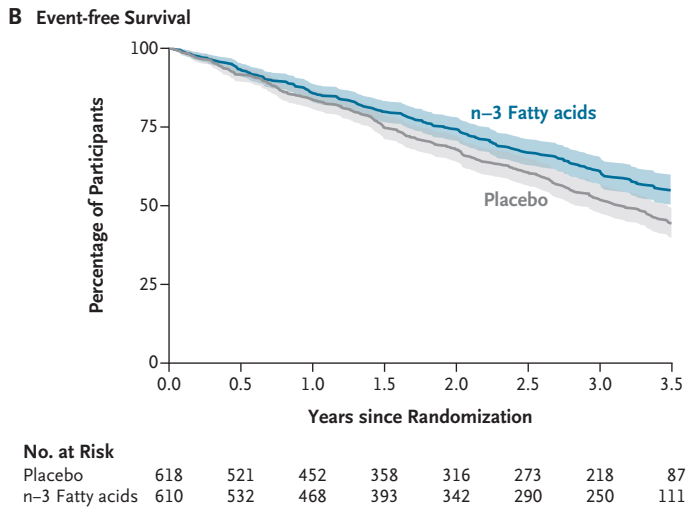


Figure 1. Mean Cumulative Cardiovascular Events and Event-free Survival.

Panel A shows the mean cumulative number of serious cardiovascular events per participant in each trial group. Events included cardiovascular death (sudden and nonsudden cardiac death, fatal myocardial infarction, and fatal stroke) and nonfatal cardiovascular events (nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and nonfatal stroke). The shaded areas are the pointwise 95% confidence intervals. The numbers beneath the figure are the numbers of participants who were still being followed for serious cardiovascular events (i.e., the numbers still alive and who did not have censored data). Panel B shows event-free survival according to trial group. The shaded areas are the pointwise 95% confidence intervals. The numbers beneath the figure are the numbers of those at risk who were still alive, did not have censored data, and had not yet had a serious cardiovascular event.

from any cause was 0.73 (95% CI, 0.61 to 0.87) (Fig. 1B). Estimates from prespecified alternative analyses of recurrent events were consistent with the result of the primary analysis with Prentice–Williams–Peterson gap-time model (Table S5). The percentage of participants with heart failure was 1.6% (10 of 610) in the fish-oil group and 2.3% (14 of 618) in the placebo group, and the percentage of those who received cardiovascular interventions was 8.5% (52 of 610) and 9.9% (61 of 618), respectively. There was no evidence of nonproportional hazards for any outcome analyzed with the Cox model.

INCORPORATION OF FATTY ACIDS INTO PLASMA PHOSPHOLIPIDS

At baseline, n–3 fatty acid levels were similar in the trial groups (Table S6A). A difference in EPA incorporation into plasma phospholipids was found at 3 months, with mean increases of 1.2±1.6 in the fish-oil group and 0.0±0.5 in the placebo group (Fig. S2), with a mean difference of 1.3 (95% CI, 1.0 to 1.6) (Table S6B). These findings confirm both adherence to the regimen by the participants and evidence that the n–3 fatty acids used were sufficient to modify circulating fatty acid composition.

SAFETY

Serious bleeding occurred in 4.8% of the participants (29 of 610) in the fish-oil group and in 7.6% of the participants (47 of 618) in the placebo group. The incidence of other serious adverse events was similar in the trial groups (Table 3 and Table S7A).

DISCUSSION

This multicenter, double-blinded, randomized trial involving 1228 participants treated with maintenance hemodialysis showed that the rate of serious cardiovascular events was approximately 40% lower (hazard ratio, 0.57; 95% CI, 0.47 to 0.70; P<0.001) among those who received 4 g of n–3 polyunsaturated fatty acids daily than among those who received placebo. In the fish-oil group, the effects on the rates of the secondary end points, including the composite of all nonfatal cardiovascular events (nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and nonfatal stroke) and death from any cause, were in the same direction as the effect on the rate of all serious cardiovascular events (the primary end point). The benefits associated with supplementation with n–3 fatty acids appeared to be consistent among participants with or without a history of cardiovascular events. The rate of all serious cardiovascular events among the partici-

pants in the fish-oil group who had a previous cardiovascular event (0.43 per 1000 patient-days) appeared to be similar to that among the placebo recipients who had not had a previous cardiovascular event (0.45 per 1000 patient-days).

The results of this randomized trial are consistent with those of a meta-analysis of previous clinical trials (seven trials involving 1045 participants)[19] and observational studies that suggested that oral supplementation with n–3 fatty acids may reduce the risk of cardiovascular events or cardiovascular death in patients receiving hemodialysis.[19-22] The lower risk of cardiovascular events (hazard ratio, 0.60; 95% CI, 0.42 to 0.90) and of death from any cause (hazard ratio, 0.61; 95% CI, 0.42 to 0.86) reported in a recent multicenter study of patients receiving hemodialysis who had relatively high blood levels of n–3 fatty acids[20] (as compared with those with lower levels) is similar to the lower rate of serious cardiovascular events with daily fish-oil supplementation in our trial. The results of our trial appear to be in alignment with those of other clinical studies of n–3 fatty acids in patients treated with maintenance hemodialysis[23] and confirm the findings of the FISH (Fish Oil Inhibition of Stenosis in Hemodialysis Grafts) trial, a randomized, controlled trial that was designed to evaluate the effect of n–3 fatty acids on vascular-access outcomes.[24] The FISH trial suggested a benefit of treatment with n–3 fatty acids on cardiovascular event–free survival, a secondary outcome (hazard ratio, 0.43; 95% CI, 0.19 to 0.96; P=0.04).[24]

However, the effects of n–3 fatty acids on cardiovascular risk and all-cause mortality are controversial in the general population. Although the results of several large studies suggest that treatment with n–3 fatty acids may reduce the risk of cardiovascular events or death, other studies do not support this conclusion.[25-28] Several key factors may explain the heterogeneous results noted in trials performed in the general population and may also apply to the population of patients who receive maintenance hemodialysis.

Fish oil is rich in n–3 fatty acids, which mainly consist of EPA and DHA. Separately and together, EPA and DHA have a range of potentially beneficial effects, including antithrombotic, anti-inflammatory, antilipid, antiarrhythmic, and remodeling effects on the cardiovascular system.[29,30] Differences in n–3 fatty acid composition (e.g., various ratios of EPA and DHA in studied formulations), n–3 fatty acid dose and delivery (e.g., prescription in capsule form vs. diet servings of fish or other forms of n–3 fatty acid), blood levels in patients at baseline, and cardiovascular risk in patients at baseline are considered to be possible factors that might contribute to between-trial differences in the apparent benefit of supplementation. For example, the positive REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial)[27] used the ethyl ester formulation with a slower and more controlled release of fatty acids, whereas the negative STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia)[28] used the carboxylic acid compound as free fatty acid with enhanced oral bioavailability. It has been speculated that the rapid interaction of this free fatty acid formulation with intestinal mucosa might have been the reason for the greater number of adverse gastrointestinal effects reported in the treatment group (24.7%) than in the placebo group (14.7%), which in turn might have affected adherence and therefore benefit.[29]

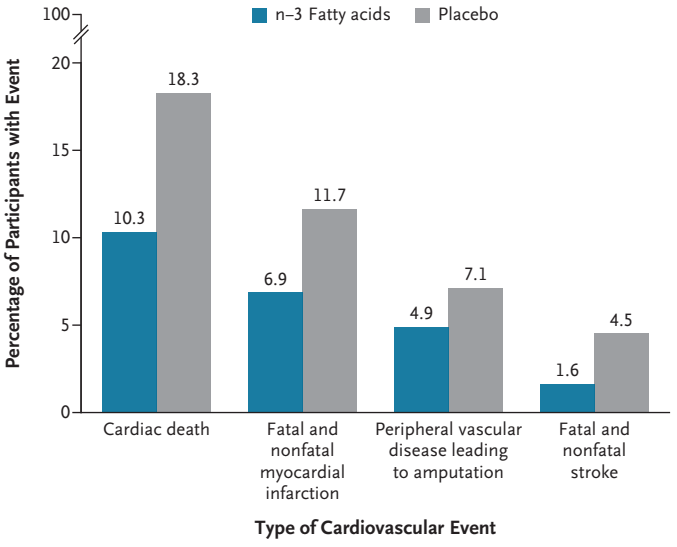


Figure 2. Participants with Cardiovascular Events.

The risk differences (fish oil vs. placebo) and their associated 95% confidence intervals were –8.0 percentage points (95% CI, –12.0 to –3.9]) for cardiac death, –4.8 percentage points (95% CI, –8.2 to –1.4) for fatal and nonfatal myocardial infarction, –2.2 percentage points (95% CI, –5.0 to –0.6) for peripheral vascular disease leading to amputation, and –2.9 percentage points (95% CI, –5.0 to –0.8]) for fatal and nonfatal stroke. Note that differential follow-up was not considered in these analyses of binary events.

Table 3. Safety and Serious Adverse Events.

Serious Adverse Event	Fish Oil (N=610)	Placebo (N=618)
	no. of participants with event (%)	
Infection	124 (20.3)	110 (17.8)
Vascular access–related event	51 (8.4)	63 (10.2)
Dialysis-related event		
Fluid overload	52 (8.5)	48 (7.8)
Other	18 (3.0)	18 (2.9)
Diabetes complication	12 (2.0)	5 (0.8)
Endocrinology-related event	16 (2.6)	21 (3.4)
Hemodynamic problem, multifactorial	39 (6.4)	41 (6.6)
Gastrointestinal tract–related event	56 (9.2)	61 (9.9)
Hematology-related event	11 (1.8)	9 (1.5)
Cancer-related event	6 (1.0)	9 (1.5)
Orthopedics-related event	36 (5.9)	34 (5.5)
Respirology-related event	31 (5.1)	23 (3.7)
General discomfort	12 (2.0)	10 (1.6)
Failure to thrive or cope	15 (2.5)	21 (3.4)
Altered level of consciousness	16 (2.6)	21 (3.4)
Neurology-related event	23 (3.8)	21 (3.4)
Surgery-related event	11 (1.8)	3 (0.5)
Overdose or intoxication	4 (0.7)	4 (0.6)
Trauma	1 (0.2)	1 (0.2)
Allergic reaction	0	1 (0.2)
Bleeding according to type		
Gastrointestinal bleeding	16 (2.6)	26 (4.2)
Cerebral bleeding	10 (1.6)	9 (1.5)
Other type of bleeding	6 (1.0)	13 (2.1)
Total	29 (4.8)	47 (7.6)
Other serious adverse event*	1 (0.2)	2 (0.3)
No serious adverse event	310 (50.8)	316 (51.1)

* Other serious adverse events were "foreign body embedded in soft tissue" (in one participant in the fish-oil group) and "foreign body stuck in oral pharynx" and "left-eye cataract complications" (in one participant each in the placebo group).

The fish-oil capsules used in our trial were 40:20 ethyl ester 1000-mg capsules, with participants ingesting 4 g daily (i.e., 1600 mg of EPA and 800 mg of DHA per day). Doses higher than 1 g per day seem to be more effective,[31] including in persons with chronic kidney disease who are not undergoing dialysis,[32] a finding that was extended to the participants receiving hemodialysis in our trial. Furthermore, patients receiving hemodialysis have markedly lower levels of EPA and DHA in serum phospholipids than the general population.[13,14] The participants who received n–3 fatty acid capsules in our trial had an increase in phospholipid concentration, as compared with the baseline level, which confirmed the findings in a previous study of prescription n–3 fatty acids[10]; there was no change from baseline in the phospholipid concentration in the participants who received corn-oil placebo, which probably had a neutral effect.[33] Corn oil contains approximately 50% linoleic acid (which has antiinflammatory effects)[34] and is a source of the antioxidant vitamin E. Use of corn oil as a placebo has been associated with lower levels of serum lipids and markers of inflammation.[35] It is possible, but unlikely, that corn oil increased the risk of cardiovascular events in the placebo group in our trial.

In addition, persons treated with maintenance hemodialysis have a distinct metabolic, rheologic, inflammatory, and cardiovascular profile that is potentially exacerbated by the treatment itself. Hemodialysis is characterized by a proinflammatory and proarrhythmic milieu, whereby cardiac stunning, ischemia, and vascular dysfunction are exacerbated by the rapid shifts in levels of fluid, sodium, potassium, and calcium. One might speculate that such circumstances might also lead to arrhythmias.

In the presence of n–3 fatty acids, the stimuli for arrhythmias might be lowered by directly inhibiting cardiomyocyte sarcolemma voltage-dependent sodium and L-type calcium currents, thereby prolonging the refractory period, inhibiting depolarization, and increasing cellular electrical stability in partially depolarized myocytes or hyperpolarized potentials.[36] Because patients treated with hemodialysis have low levels of n–3 fatty acid, the cardioprotective properties of n–3 fatty acids may be especially beneficial.

Our trial has several limitations. We enrolled only participants receiving maintenance hemodialysis. Data from participants who transferred to peritoneal dialysis or underwent kidney transplantation were censored from the trial; therefore, the effects of n–3 fatty acid in these participants could not be assessed. Because fish-oil supplements are widely available over the counter, we do not know if participants in either group ingested their own supply of n–3 fatty acid; however, it is reassuring that blood samples from the placebo group showed no change in EPA and DHA

levels. Bleeding events were not adjudicated but followed the definitions outlined in the trial protocol.[16] Although there were historical concerns of increased risk of bleeding, several studies have shown a reduced bleeding risk with n–3 fatty acid,[37-39] which is consistent with our findings. Furthermore, our budget allowed for the analysis of blood specimens for n–3 fatty acid incorporation into plasma phospholipids for only a random sample of participants. However, given that this sample was randomly selected, a complete assessment would probably not change our findings. Many of the trial participants were not receiving therapy that would be considered sufficient to reduce cardiovascular risk in general populations at increased risk, and the results may not be generalizable to patients who are not undergoing dialysis. Less than 60% of the participants were receiving statins, and less than 10% were receiving other lipid-lowering medications. However, many previous clinical trials of promising or proven treatments for heart disease have excluded patients who are treated with dialysis or have shown minimal or a lack of treatment effects in this population,[40] so the use of such medications is often less common. Work is ongoing to assess other secondary and tertiary outcomes, the mechanisms that contributed to the findings from this trial, and the cost-effectiveness of daily oral supplementation with n–3 fatty acids.[16]

In our trial, the rate of serious cardiovascular events among participants receiving hemodialysis was significantly lower among those who received daily supplementation with n–3 polyunsaturated fatty acids (four 1-g fish-oil capsules, containing a total of 1.6 g of EPA and 800 g of DHA) than among those who received placebo.

Supported by grants from the Heart and Stroke Foundation of Canada (G-15-0009388), the Lawson Health Research Institute, the Peter Munk Cardiac Care Innovation Fund (CMT-1516-237), the Kidney CARE Network International, and the National Health and Medical Research Council (APP1123392) and by a donation from Mr. Alexander Epstein. Charmaine Lok was supported by a personnel award from the Heart and Stroke Foundation (7511-A), Ontario Provincial Office.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank DSM (previously Ocean Nutrition Canada) for the in-kind contribution of the n–3 polyunsaturated fatty acid and placebo capsules; the participants receiving hemodialysis; the hemodialysis staff; the students and volunteers who helped throughout the project; Ruth Stastny and the Australasian Kidney Trials Network for their coordination and management of PISCES in Australia; Cathy Forrester for her global oversight and dedication to PISCES and commitment to the patients who participated; and the members of the data monitoring and adjudication committees, the database developer, and randomization manager (Kenneth Stanley, Patrick Lawlor, Lucas Godoy, Jairo Nunes, Ayodele Odutayo, Graham Roche-Nagle, Cheryl Jaigobin, Maryam Yousefi, and Jim Hamer) for their work in the trial.

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