

Efficacy and Safety of Prescription Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation

A Randomized Controlled Trial

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ATRIAL FIBRILLATION (AF) IS A highly prevalent disease that is responsible for reduced quality of life, costly hospitalizations, heart failure, stroke, and death.^{1,2} No current therapy, drug, device, or ablation is uniformly effective, and several available therapies have the potential to cause harm.³⁻⁵ Consequently, useful alternatives are being sought.

Fish oils have demonstrable potent electrophysiological, autonomic-modulating, and anti-inflammatory effects in atrial and ventricular tissue and, most importantly, appear to be well tolerated.^{6,7} Thus, these products have been studied in clinical trials involving treatment of AF in a wide range of patients and clinical scenarios, using various doses, and in diverse designs. However, the results of these trials have been mixed,⁸⁻¹³ resulting in confusion among physicians and patients. Many patients use omega-3 polyunsaturated fatty acid supplements or have enhanced their diets heavily with fish products, without a clear idea of why or what they might expect with regard to arrhythmia suppression or safety. Because many omega-3 fatty acid preparations are marketed as food sub-

Context Atrial fibrillation (AF) is common, yet there remains an unmet medical need for additional treatment options. Current pharmacological treatments have limited efficacy and significant adverse events. Limited data from small trials suggest omega-3 polyunsaturated fatty acids may provide a safe, effective treatment option for AF patients.

Objective To evaluate the safety and efficacy of prescription omega-3 fatty acids (prescription omega-3) for the prevention of recurrent symptomatic AF.

Design, Setting, and Participants Prospective, randomized, double-blind, placebo-controlled, parallel-group multicenter trial involving 663 US outpatient participants with confirmed symptomatic paroxysmal (n=542) or persistent (n=121) AF, with no substantial structural heart disease, and in normal sinus rhythm at baseline were recruited from November 2006 to July 2009 (final follow-up was January 2010).

Interventions Prescription omega-3 (8 g/d) or placebo for the first 7 days; prescription omega-3 (4 g/d) or placebo thereafter through week 24.

Main Outcome Measures The primary end point was symptomatic recurrence of AF (first recurrence) in participants with paroxysmal AF. Secondary analyses included first recurrence in the persistent stratum and both strata combined. Participants were followed up for 6 months.

Results At 24 weeks, in the paroxysmal AF stratum, 129 of 269 participants (48%) in the placebo group and 135 of 258 participants (52%) in the prescription group had a recurrent symptomatic AF or flutter event. In the persistent AF stratum, 18 participants (33%) in the placebo group and 32 (50%) in the prescription group had documented symptomatic AF or flutter events. There was no difference between treatment groups for recurrence of symptomatic AF in the paroxysmal stratum (hazard ratio [HR], 1.15; 95% confidence interval [CI], 0.90-1.46; *P* = .26), in the persistent stratum (HR, 1.64; 95% CI, 0.92-2.92; *P* = .09), and both strata combined (HR, 1.22; 95% CI, 0.98-1.52; *P* = .08). Other, secondary end points were supportive of the primary result. A total of 5% of those receiving placebo and 4% of those receiving prescription omega-3 discontinued due to adverse events. Eicosapentaenoic and docosahexaenoic acid blood levels were significantly higher in the prescription group than in the placebo group at weeks 4 and 24.

Conclusion Among participants with paroxysmal AF, 24-week treatment with prescription omega-3 compared with placebo did not reduce recurrent AF over 6 months.

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stances, they have not been subjected to the scientific rigor that is necessary to assess net clinical benefit.¹⁴

We designed this randomized clinical trial to assess the efficacy of a pure prescription formulation of omega-3 fatty acids (prescription omega-3), at a dose considerably higher than what has been tested in previous trials, for preventing recurrent symptomatic AF in a well-characterized patient population with documented, symptomatic paroxysmal or persistent AF, without significant structural heart disease. Given the AF population we analyzed (ie, a relatively healthy population with a high probability of having a recurrence of AF within 6 months), we theorized that if prescription omega-3 exhibited any pharmacodynamic antiarrhythmic effect, it would occur in this specific patient cohort.

METHODS

Study Design

The study design for this clinical trial has been published previously.¹⁵ This 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was designed to assess the efficacy and safety of prescription omega-3 for the prevention of recurrent symptomatic AF. The study was conducted according to the Declaration of Helsinki at 96 US centers. All centers obtained institutional review board approval for the study prior to participant screening. All participants provided written informed consent before enrollment and randomization. Patients were recruited and enrolled in the study from November 2006 to July 2009, with final follow-up on January 21, 2010.

Study Population

A complete description of inclusion and exclusion criteria were previously reported.¹⁵ In brief, participants were at least 18 years old and had a confirmed diagnosis of either symptomatic paroxysmal AF that had never been treated by long-term pharmacological or electrical therapy to terminate an AF episode or had a

diagnosis of symptomatic persistent AF, defined as AF that had been previously successfully treated with pharmacological or electrical cardioversion at least 1 time and were currently in normal sinus rhythm. Inclusion required at least 1 suspected or documented episode of symptomatic AF within 3 months of screening and at least 1 electrocardiographically documented episode of symptomatic AF within 12 months of screening.

Key exclusion criteria were permanent AF, secondary AF (eg, due to hypothyroidism or valvular heart disease), current use of antiarrhythmic therapy (participant must have ceased drug use for at least 5 half-lives before randomization for inclusion), use of amiodarone within the past 6 months, prior ablation therapy for AF, or specific structural cardiac disorders.

Participants either self-reported race/ethnicity or were classified by the investigator. Racial categories included black, African heritage, Asian, Pacific Islander, Hispanic, American Indian, white, or other. Race was obtained as part of the participants' demographic information.

Study Intervention

Participants were randomized to receive 4 g/d of prescription omega-3 (Lovaza, GlaxoSmithKline, Research Triangle Park, North Carolina) or placebo. For the first 7 days of dosing, participants received a loading dose of 8 g/d or 8 placebo capsules, followed by 4 g/d through week 24. Each 1-g capsule of prescription omega-3 contained approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid. Each placebo capsule contained approximately 1 g of corn oil. The clinical research organization, Kendle International, Cincinnati, Ohio, generated the randomization schedule. Site personnel telephoned into an interactive voice response system to obtain a randomization number and were assigned blinded study medication bottles.

Participants were followed up for 6 months. Biweekly transtelephonic monitoring was used to document asymptomatic recurrences of AF and assess symptomatic events. Investigators were blinded to the monitoring results.

Once a participant experienced the primary end point (first documented symptomatic recurrence of AF or atrial flutter), additional therapies to maintain normal sinus rhythm were allowed, but the participant was encouraged to continue taking the blinded study drug and continue attending the planned follow-up to the study's completion.

Study Outcomes

The primary outcome was the effect of prescription omega-3 on the first symptomatic recurrence of AF or flutter, from the first dose of the study drug, in the paroxysmal AF stratum. Symptomatic atrial flutter was treated as an occurrence of symptomatic AF for the primary end point. The principal secondary outcome was first symptomatic recurrence of AF or flutter in the persistent AF stratum and in both AF strata combined.

Statistical Analysis

A total of 295 primary efficacy events in the paroxysmal AF stratum were required to provide at least 90% power to detect a hazard ratio (HR) of 0.682 for prescription omega-3 vs placebo with a 2-sided α of .05. A sample of 663 participants (330 per treatment group) was randomized 1:1 to receive either prescription omega-3 or placebo, stratified by a baseline diagnosis of paroxysmal or persistent AF in a ratio of 5:1. The primary analysis was based on the paroxysmal AF stratum. Due to challenges enrolling participants in the study, enrollment was stopped when the planned 660 number of participants was achieved. By the time we decided to stop enrolling patients, the number of events exceeded the 220 primary events required to achieve 80% power. Two hundred sixty-four primary events accumulated during the study.

During the study, 47 participants' randomization stratum was changed after randomization but before the data lock and analysis following the monitors' review of the source documentation (39 from paroxysmal to persistent and 8 from persistent to paroxysmal AF). All efficacy analyses were based on the revised classification. As previously described and prespecified,¹⁵ efficacy analyses were based on a modified intent-to-treat population as described herein, which comprised all randomized participants with at least 1 postrandomization transtelephonic monitoring electrocardiographic data transfer (or equivalent). The safety analyses were based on the population of all randomized patients who took at least 1 dose of the study medication. The primary analysis was performed using a Cox proportional hazards model adjusting for treatment group, geographical region of enrollment, statin use, and a time-dependent covariate for angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker use to estimate HRs, *P* values, and 95% confidence intervals (CIs) for prescription

omega-3 vs placebo. Participants were censored after initiation of any antiarrhythmic drug, to clearly understand the effect of prescription omega-3. Participants who were event-free at completion of the trial or at early termination were censored at the last available visit date or transmission date, whichever occurred later. Time to event of secondary variables for the paroxysmal and combined strata were analyzed via a Cox proportional hazard model similar to the primary analysis, except using ACE inhibitor or angiotensin II receptor blocker use as a fixed effect because such use had the potential to influence the incidence of AF and flutter events. Given the small number of participants in the persistent stratum, survival analysis was performed using a log-rank test. Analyses of continuous variables were performed using parametric or nonparametric analysis of covariance, *t* test, or Wilcoxon rank-sum test, as appropriate. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

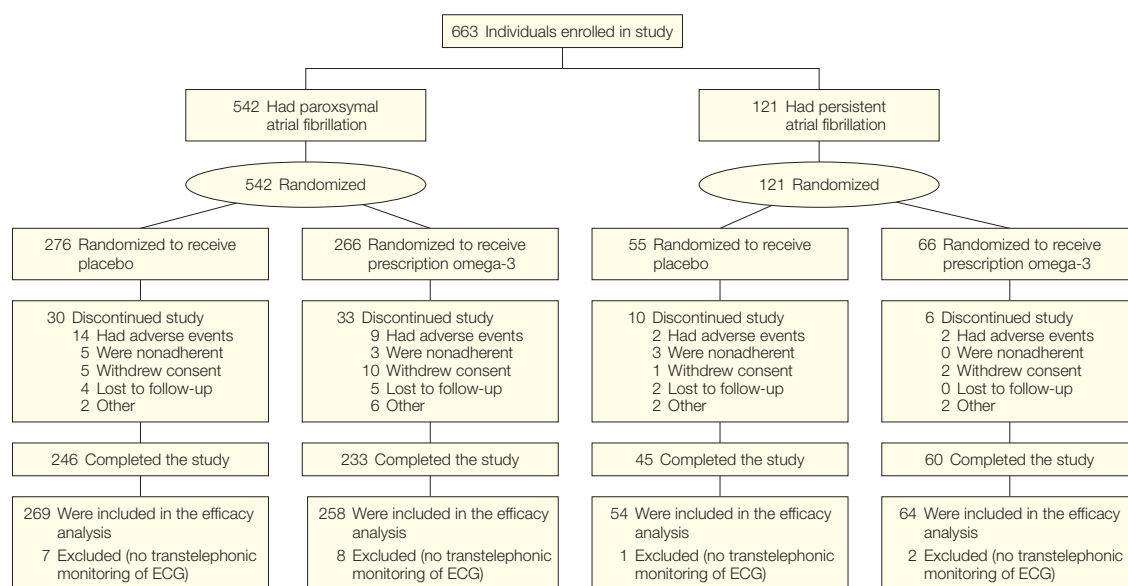
In addition, all raw data and analysis data were provided to an external

academic biostatistician who independently repeated the analyses and confirmed all findings reported herein. In this analysis, participants were not censored at the time of antiarrhythmic drug use (total of 9 participants were not censored at the time of antiarrhythmic drug use. Of those, 8 were in the prescription group and 1 was in the placebo group), and participants also were not censored at the time of study drug termination (1 prescription group participant with a subsequent recurrence). An additional intention-to-treat analysis was performed for the primary end point for each stratum using the original classification at randomization, including all participants as randomized. Because we used the survival analysis method throughout our study, patients with missing data (including those lost to follow-up or who had withdrawn early) were censored at the last available visit if no event occurred at earlier visits.

RESULTS

Of the 663 participants randomized, 584 (88%) completed the study. Of

Figure 1. Study Flowchart



Forty-seven participants' randomization stratum was changed after randomization, based on a review of the participants' past medical history: 39 from paroxysmal to persistent and 8 from persistent to paroxysmal atrial fibrillation. Efficacy analyses were based on the revised classification and are reflected in the modified intention-to-treat efficacy population. ECG indicates electrocardiography.

those, 479 were in the paroxysmal stratum: 246 participants (89%) in the placebo group and 233 (88%) in the prescription group; 105 in the persistent stratum: 45 (82%) in the placebo group and 60 (91%) in the prescription group (FIGURE 1). Premature withdrawals were comparable across treatment groups and strata, with the most frequent reason being adverse events (occurring in $\leq 5\%$ of participants in any treatment group or strata) followed by

consent withdrawal. Demographic and clinical characteristics, electrocardiographic and echocardiographic data, and concomitant medical therapy were comparable across treatment groups and strata (TABLE 1).

Primary and Secondary Outcomes

No statistical difference was observed between treatment groups for the primary efficacy end point in the prespecified modified intention-to-treat analy-

sis, in the approach without censoring participants at time of antiarrhythmic drug use or study drug termination, or in the intention-to-treat analysis including all patients in the groups to which they were randomized. (TABLE 2 and FIGURE 2).

In the paroxysmal stratum, there were 129 documented symptomatic AF or flutter events (48%) in the placebo group and 135 (52%) in the prescription group (HR, 1.15; 95% CI, 0.90-

Table 1. Summary of Mean Randomized Baseline and Demographic Characteristics

Parameters	Atrial Fibrillation Status								
	Combined			Paroxysmal			Persistent		
	Placebo (n = 331)	Prescription Omega-3 (n = 332)	Total (N = 663)	Placebo (n = 276)	Prescription Omega-3 (n = 266)	Total (n = 542)	Placebo (n = 55)	Prescription Omega-3 (n = 66)	Total (n = 121)
Age, mean (SD), y	61.2 (12.26)	59.8 (13.38)	60.5 (12.84)	61.9 (11.57)	60.0 (13.56)	61.0 (12.61)	57.6 (14.85)	58.7 (12.65)	58.2 (13.65)
Sex, No. (%)									
Women	157 (47)	133 (40)	290 (44)	138 (50)	119 (45)	257 (47)	19 (35)	14 (21)	33 (27)
Men	174 (53)	199 (60)	373 (56)	138 (50)	147 (55)	285 (53)	36 (65)	52 (79)	88 (73)
Anthropometry measures, mean (SD)									
Weight, kg	90.4 (22.32)	91.2 (21.61)	90.8 (21.96)	88.8 (21.02)	89.7 (21.70)	89.2 (21.34)	98.4 (26.79)	97.4 (20.26)	97.8 (23.35)
Height, cm	171.6 (11.45)	172.8 (10.40)	172.2 (10.94)	171.0 (11.07)	172.0 (10.22)	171.5 (10.66)	174.7 (12.83)	175.9 (10.61)	175.4 (11.64)
BMI	30.7 (7.31)	30.6 (7.27)	30.6 (7.29)	30.4 (7.02)	30.3 (7.31)	30.3 (7.16)	32.2 (8.53)	31.6 (7.06)	31.9 (7.73)
Race, No. (%)									
White	298 (90)	309 (93)	607 (92)	253 (92)	246 (92)	499 (92)	45 (82)	63 (95)	108 (89)
African American	16 (5)	12 (4)	28 (4)	10 (4)	10 (4)	20 (4)	6 (11)	2 (3)	8 (7)
Other	17 (5)	11 (3)	28 (4)	13 (5)	10 (4)	23 (4)	4 (7)	1 (2)	5 (4)
Cardiac measures, mean (SD)									
Sitting blood pressure, mm Hg									
Systolic	126.4 (15.05)	125.9 (15.66)	126.2 (15.35)	126.1 (14.69)	125.8 (15.66)	125.9 (15.16)	127.9 (16.86)	126.5 (15.74)	127.1 (16.20)
Diastolic	74.9 (9.58)	74.9 (9.36)	74.9 (9.46)	74.7 (9.26)	74.6 (9.53)	74.6 (9.38)	76.2 (11.03)	76.3 (8.58)	76.2 (9.73)
TTM heart rate, beats/min	64.3 (10.95)	63.3 (10.60)	63.8 (10.78)	63.5 (10.50)	63.7 (10.46)	63.6 (10.47)	67.9 (12.47)	61.6 (11.08)	64.4 (12.10)
No. of participants	329	331	660	274	265	539	55	66	121
12-lead ECG heart rate, beats/min	61.4 (10.40)	60.7 (10.41)	61.1 (10.40)	60.9 (10.09)	60.9 (10.48)	60.9 (10.27)	63.9 (11.57)	59.8 (10.14)	61.7 (10.97)
No. of participants	328	331	659	273	266	539	55	65	120
2-dimensional ECG, abnormal, clinically significant, No. (%)	12 (4)	11 (3)	23 (3)	8 (3)	7 (3)	15 (3)	4 (7)	4 (6)	8 (7)
Concomitant medication, No. (%)									
ACEI or ARB									
No	207 (63)	197 (59)	404 (61)	173 (63)	160 (60)	333 (61)	34 (62)	37 (56)	71 (59)
Yes	124 (37)	135 (41)	259 (39)	103 (37)	106 (40)	209 (39)	21 (38)	29 (44)	50 (41)
Antiarrhythmic drug ^a									
No	297 (90)	283 (85)	580 (87)	248 (90)	231 (87)	479 (88)	49 (89)	52 (79)	101 (83)
Yes	34 (10)	49 (15)	83 (13)	28 (10)	35 (13)	63 (12)	6 (11)	14 (21)	20 (17)
Statin									
No	183 (55)	182 (55)	365 (55)	149 (54)	149 (56)	298 (55)	34 (62)	33 (50)	67 (55)
Yes	148 (45)	150 (45)	298 (45)	127 (46)	117 (44)	244 (45)	21 (38)	33 (50)	54 (45)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; ECG, electrocardiograph; TTM, transtelephonic monitoring.

^aAntiarrhythmic drug use was defined as at least 2 weeks of continuous use during the study. Antiarrhythmic drugs could be prescribed once the patient had a recurrence of atrial fibrillation.

1.46; $P = .26$). The primary efficacy results were consistent for the persistent AF stratum and for the 2 strata combined (TABLE 3). In the persistent AF stratum, there were 18 documented symptomatic AF or flutter events (33%) in the placebo group and 32 (50%) in the prescription group (HR, 1.64; 95% CI, 0.92-2.92; $P = .09$), while in the 2 strata combined, there were 147 events (46%) in the placebo group and 167 (52%) in the prescription group (HR, 1.22; 95% CI, 0.98-1.52; $P = .08$).

Results of the primary efficacy end point for the paroxysmal AF stratum were also consistent across all subgroups, including age, sex, race, smoking status, alcohol consumption, ACE inhibitor or angiotensin II receptor blocker use, statin use, and region (FIGURE 3) and all sensitivity analyses (eFigure available at www.jama.com). None of the secondary efficacy end points achieved statistical significance (Table 3).

Tertiary Outcomes

The average heart rate during the first recurrence of symptomatic AF or flutter was lower in the prescription group than in the placebo group (combined strata), with a mean difference between the treatment groups of $-6.88/\text{min}$ (95% CI, -13.12 to -0.64 ; $P = .03$). Analyses of the median percent change from baseline plasma n-3 fatty acids (combined strata) showed no statistically significant difference in total fatty acids between the 2 groups, statistically significant increases in eicosapentaenoic acid and docosahexaenoic acid at weeks 4 and 24, and a statistically significant decrease in arachidonic acid at weeks 4 and 24. The difference in median percent change between the placebo and prescription groups for eicosapentaenoic acid at week 4 was 276.10% (95% CI, 242.70%-309.20%; $P < .001$) and at week 24 was 239.0% (95% CI, 202.60%-276.20%; $P < .001$) in favor of prescription omega-3. The difference in median percent change between the placebo and prescription groups for docosahexaenoic acid at week 4 was 95.6%

Table 2. Summary of Primary and Secondary Efficacy Results for the Paroxysmal Stratum

Outcome Measure	No. (%) of Events		Hazard Ratio (95% CI) ^a	P Value ^a
	Placebo (n = 269)	Prescription Omega-3 (n = 258)		
Primary				
First recurrence of symptomatic AF or flutter	129 (48)	135 (52)	1.15 (0.90 to 1.46)	.26
Independent analysis ^b				
Total No. of participants randomized	276	266		
No. (%) of participants ^b	129 (47)	141 (53)	1.19 (0.93 to 1.35)	.15
First recurrence of symptomatic AF or flutter, sensitivity analysis using the original stratum at randomization	136 (49)	148 (53)	1.15 (0.91 to 1.45)	.25
Secondary				
First recurrence of symptomatic AF, exclusive of flutter	126 (47)	133 (52)	1.17 (0.91 to 1.49)	.21
Independent analysis ^b	126 (46)	140 (53)	1.22 (0.95 to 1.56)	.11
First recurrence of symptomatic or asymptomatic AF or flutter	149 (55)	153 (59)	1.12 (0.89 to 1.40)	.33
Independent analysis ^b	152 (55)	159 (60)	1.13 (0.90 to 1.42)	.29
First recurrence of symptomatic or asymptomatic AF, exclusive of flutter	146 (54)	151 (59)	1.14 (0.90 to 1.43)	.27
Independent analysis ^b	149 (54)	158 (59)	1.15 (0.92 to 1.45)	.21
First recurrence of symptomatic AF or flutter after completion of day 7 ^c	88 (39)	87 (42)	1.09 (0.81 to 1.47)	.57
First recurrence of symptomatic AF, exclusive of flutter after completion of day 7 ^d	86 (38)	86 (42)	1.12 (0.83 to 1.51)	.46
Additional Secondary Efficacy Results for the Paroxysmal Stratum				
	Median		Difference in Medians (95% CI) ^e	P Value ^f
	Placebo (n = 269)	Prescription Omega-3 (n = 258)		
Annualized number of AF or flutter rescue episodes ^g	2.44	4.17	0.070 (–0.09 to 2.08)	.29
Annualized cumulative frequency of symptomatic AF or flutter recurrences ^h	6.81	8.32	0.32 (–0.18 to 2.21)	.22
Annualized cumulative frequency of symptomatic AF recurrences, exclusive of flutter ^{h,i}	6.91	8.30	0.24 (–0.19 to 2.17)	.24

Abbreviations: AF, atrial fibrillation; CI, confidence interval.

^aBased on Cox proportional hazards model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin.

^bValues are based on the independent statistician's analyses (participants with antiarrhythmic drug use were not censored) using Cox proportional hazard model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin.

^cForty-five participants in the placebo group and 53 in the prescription omega-3 group had events that occurred in the first 7 days after randomization were excluded.

^dForty-four participants in the placebo group and 52 in the prescription omega-3 group had events that occurred in the first 7 days after randomization were excluded.

^eThe difference in medians and 95% CIs was produced by the Hodges-Lehmann method.

^fP Values are based on a nonparametric analysis of covariance model: end point (ranked) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus antiarrhythmic drugs.

^gRescue was defined as any pharmacological, electrical, or surgical intervention for the termination or prevention of AF or flutter with a maximum of 1 rescue episode counted per day. All annualized values were calculated by counting the number of rescue episodes, dividing by the number of days receiving treatment, then multiplying that number by 365.25. Thirty-four participants in the placebo group and 37 in the prescription omega-3 group had at least 1 rescue episode.

^hAnnualized cumulative frequency values were annualized by counting the number of episodes of symptomatic AF or flutter recurrences (maximum of 1 per day), dividing by the number of days receiving treatment, then multiplying this number by 365.25. One hundred twenty-nine participants in the placebo group and 140 in the prescription omega-3 group had at least 1 recurrence.

ⁱOne hundred twenty-six participants in the placebo group and 139 in the prescription omega-3 group had at least 1 recurrence.

Abbreviations: AF, atrial fibrillation; CI, confidence interval.

^aBased on Cox proportional hazards model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin.

^bValues are based on the independent statistician's analyses (participants with antiarrhythmic drug use were not censored) using Cox proportional hazard model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin.

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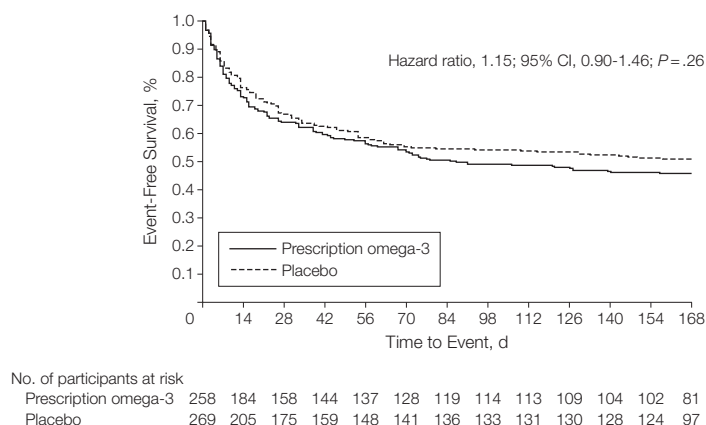
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ⁱOne hundred twenty-six participants in the placebo group and 139 in the prescription omega-3 group had at least 1 recurrence.

Figure 2. First Recurrence of Symptomatic Atrial Fibrillation for the Paroxysmal Stratum

Analysis is based on a Cox proportional hazards model adjusting for treatment, region, and use of angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and statin.

(95% CI, 81.20%-110.0%; $P < .001$) and at week 24 was 100.30% (95% CI, 83.60%-118.0%; $P < .001$) in favor of prescription omega-3. The difference in median percent change between the placebo and prescription groups for arachidonic acid at week 4 was -13.0% (95% CI, -17.60% to -8.20; $P < .001$) and at week 24 was -15.70% (95% CI, -21.0 to -10.60; $P < .001$) in favor of the prescription omega-3.

Study Discontinuation and Adverse Events

Sixteen participants (5%) taking placebo and 12 (4%) taking prescription omega-3 discontinued study medication due to an adverse event. Diarrhea and nausea, the most common adverse events leading to discontinuation or withdrawal, were similar across treatment groups. The overall incidence of treatment-emergent drug-related adverse events was similar across treatment groups (13% placebo; 16% prescription omega-3; TABLE 4); the only drug-related treatment-emergent adverse event that occurred in 3% or more of the participants was nausea noted in 7 participants (2%) in the placebo group and 9 (3%) in the prescription group.

Two deaths occurred, 1 participant in the placebo group and 1 in the prescription group. According to the

investigators, these deaths were considered unrelated to the study drug. A third death occurred approximately 113 days after the participant completed dosing with prescription omega-3 therapy. The investigator considered the death unrelated to the study drug.

Two placebo group participants were discontinued due to abnormal liver function results. High-density lipoprotein and low-density lipoprotein cholesterol levels did not differ between groups. However, the difference between treatment groups in median percent change from baseline was -11.5% (95% CI, -16.70% to -6.50%; $P < .001$) for triglycerides and -11.40% (95% CI, -16.50% to -6.20%; $P < .001$) for very low-density lipoprotein cholesterol. The mean (SD) change from baseline to week 24 in hemoglobin A_{1c} in the placebo group was 0.10% (0.47%), whereas that in the prescription group was 0.01% (0.43%). To convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, by 0.0113.

There was a significant mean decrease from baseline in systolic blood pressure at week 24 in the prescription group compared with the placebo group (mean difference, -2.3 mm Hg; 95% CI, -4.6 to 0.0; $P = .05$). Although the mean heart rate at the time of first recurrence of symptomatic AF or flut-

ter was statistically significantly lower in the prescription group than in the placebo group (combined strata), the decrease from baseline in the heart rate at week 24 in the prescription compared with the placebo group did not reach statistical significance (-1.0/min; 95% CI, -2.8 to 0.7; $P = .24$).

COMMENT

Previous studies have shown that fish-derived omega-3-acid ethyl esters have membrane-modifying, metabolic, autonomic, anti-ischemic, anti-inflammatory, and electrophysiological actions that may be antiarrhythmic^{6,15} with direct electrophysiological actions targeting sodium, potassium, calcium, and magnesium channels and membrane conductance.^{6,16} Observed effects among individuals who have moderate to high consumption of dietary fish, who take prescription omega-3 capsules, or both, have included a reduced frequency of ventricular and atrial arrhythmias in several patient populations, beneficial effects on heart rate variability, and reductions in total mortality by 3 months and risk of sudden death by 4 months in patients after experiencing myocardial infarction in the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto) Prevention Study.^{15,17} In addition, several preclinical and early clinical studies specifically relating to the utility of prescription omega-3 in AF have suggested potential hemodynamic, autonomic, and electrophysiological effects likely to be antifibrillatory or have demonstrated reduced AF induction, persistence, or both.¹⁸⁻²²

Moreover, several prior clinical trials of AF prevention or reduction, all smaller than our study and conducted in more specific patient circumstances, appear to show benefit from omega-3 fatty acids for AF prevention. Calò et al⁹ randomized 160 patients awaiting coronary artery bypass graft (CABG) surgery to usual care or to eicosapentaenoic acid plus docosahexaenoic acid (1.7 g/d) from 5 days before surgery through hospital discharge. The end point, AF lasting longer

than 5 minutes or requiring intervention, was reduced from 33% in the control group to 15% in omega-3 fatty acids group. Mean hours of AF were reduced from 24 to 16 ($P=.12$) and length of stay was reduced from 8.2 to 7.3 days. Biscione et al²² gave 40 pa-

tients with dual chamber pacemakers 1 g/d of omega-3 fatty acids or nothing for treatment periods of 4 months. They observed a 59% reduction in AF episodes and a 67% reduction in AF burden during omega-3 fatty acid administration. In a study by Nodari et

al,²³ AF recurrence was assessed following direct current cardioversion in 70 consecutive persistent AF patients randomized to 1 g/d of prescription omega-3 ($n=30$) or placebo ($n=40$). All received amiodarone, β -blockers, and renin-angiotensin system inhibitors. At

Table 3. Summary of Secondary Efficacy Results for the Persistent and Combined Strata

Outcome Measure	No. (%) of Events							
	Persistent Stratum				Combined Stratum			
	Placebo (n = 54)	Prescription Omega-3 (n = 64)	Hazard Ratio (95% CI)	P Value ^a	Placebo (n = 323)	Prescription Omega-3 (n = 322)	Hazard Ratio (95% CI) ^b	P Value ^b
First recurrence of symptomatic AF/flutter	18 (33)	32 (50)	1.64 (0.92 to 2.92)	.09	147 (46)	167 (52)	1.22 (0.98 to 1.52)	.08
Independent analysis ^c								
No. of patients	55	66			331	332		
Events	19 (35)	34 (52)	1.63 (0.91 to 2.18)	.09	148 (45)	175 (53)	1.25 (1.00 to 1.40)	.05
First recurrence of symptomatic AF, exclusive of flutter	18 (33)	30 (47)	1.50 (0.83 to 2.69)	.17	144 (45)	163 (51)	1.22 (0.98 to 1.53)	.08
First recurrence of symptomatic or asymptomatic AF/flutter	27 (50)	40 (63)	1.29 (0.79 to 2.11)	.30	176 (54)	193 (60)	1.16 (0.94 to 1.42)	.17
First recurrence of symptomatic or asymptomatic AF, exclusive of flutter	27 (50)	38 (59)	1.19 (0.73 to 1.95)	.49	173 (54)	189 (59)	1.16 (0.94 to 1.42)	.17
First recurrence of symptomatic AF/flutter after completion of day 7 ^d	15 (31)	27 (47)	1.68 (0.89 to 3.15)	.10	103 (38)	114 (44)	1.20 (0.92 to 1.56)	.19
First recurrence of symptomatic AF, exclusive of flutter after completion of day 7 ^e	15 (31)	25 (44)	1.51 (0.79 to 2.86)	.21	101 (37)	111 (42)	1.20 (0.92 to 1.57)	.19
Additional Secondary Efficacy Results								
	Persistent Stratum				Combined Stratum			
	Placebo (n = 54)	Prescription Omega-3 (n = 64)	Difference in Medians (95% CI) ^f	P Value ^g	Placebo (n = 323)	Prescription Omega-3 (n = 322)	Difference in Medians (95% CI) ^f	P Value ^h
Annualized No. of AF/flutter rescue episodes ⁱ	2.17	2.24	0.06 (−0.08 to 2.02)	.48	2.19	4.01	0.04 (−0.06 to 1.49)	.22
Annualized cumulative frequency of symptomatic AF/flutter recurrences ^j	4.22	4.35	0.22 (−0.14 to 3.14)	.19	6.48	6.52	0.18 (−0.10 to 2.10)	.10
Annualized cumulative frequency of symptomatic AF recurrences, exclusive of flutter ^k	4.22	4.35	0.25 (−0.09 to 4.31)	.15	6.48	6.52	0.20 (−0.08 to 2.11)	.09

Abbreviations: AF, atrial fibrillation; CI, confidence interval.

^aP value is based on the log-rank test.

^bBased on the Cox proportional hazards model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin plus strata.

^cValues are based on the independent statistician analyses (participants with antiarrhythmic drug use were not censored and the number of participants represent the number randomized) using Cox proportional hazard model: log (hazard ratio) equals treatment plus region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus statin.

^dFive participants in the placebo group and 7 in the prescription omega-3 group in the persistent stratum who had events that had occurred in the first 7 days after randomization were excluded. In the combined stratum, 50 in the placebo group and 60 in the prescription omega-3 group who had events that had occurred 7 days after randomization were excluded.

^eFive participants in the placebo group and 7 in the prescription omega-3 group in the persistent stratum who had events that had occurred in the first 7 days after randomization were excluded. In the combined stratum, 49 in the placebo group and 59 in the prescription omega-3 group who had events that had occurred in the first 7 days after randomization were excluded.

^fDifference in medians and 95% CI produced via Hodges-Lehmann method.

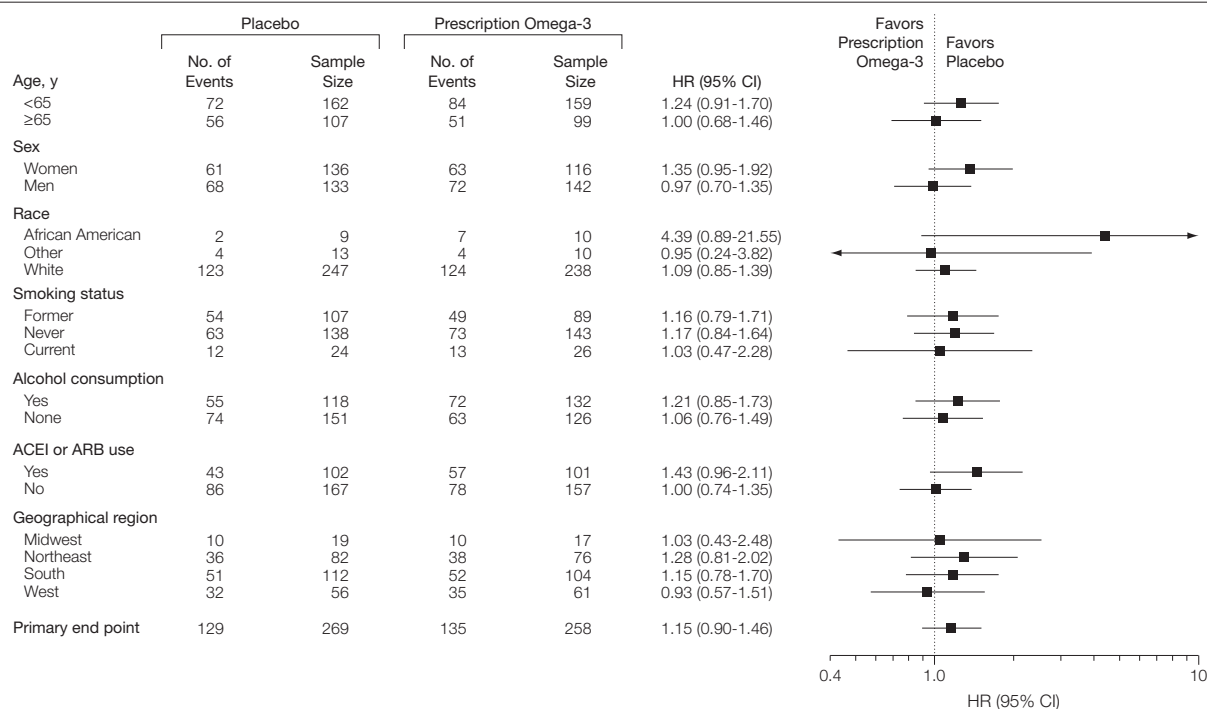
^gP value based on Wilcoxon rank-sum test.

^hP value based on nonparametric analysis of covariance model, the end point (ranked) equals the treatment plus the region plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker plus antiarrhythmic drug plus strata.

ⁱRescue was defined as any pharmacological, electrical, or surgical intervention for the termination or prevention of AF or flutter with a maximum of 1 rescue episode counted per day. All annualized values were calculated by counting the number of rescue episodes, dividing by the number of days receiving treatment, then multiplying that number by 365.25. Eight participants in the placebo group and 21 in the prescription omega-3 group experienced at least 1 rescue episode.

^jAnnualized cumulative frequency values were annualized by counting the number of episodes of symptomatic AF or flutter recurrences (maximum of 1 per day), dividing by the number of days receiving treatment, then multiplying this number by 365.25. Nineteen participants in the placebo group and 34 in the prescription omega-3 group experienced at least 1 recurrence.

^kAnnualized cumulative frequency values were annualized by counting the number of episodes of symptomatic AF/flutter recurrences (maximum of 1 per day), dividing by the number of days receiving treatment, then multiplying this number by 365.25. Nineteen participants in the placebo group and 32 in the prescription omega-3 group experienced at least 1 recurrence.

Figure 3. Analyses of Primary End Point in Paroxysmal Atrial Fibrillation Subgroup

Analyses were performed using a Cox proportional hazards model fitting separate model for each subgroup. ACEI, indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; and HR, hazard ratio.

Table 4. Drug-Related Treatment-Emergent Adverse Events Reported by 2 or More Participants in Either Treatment Group (Safety Population)

Adverse Event	No. (%) of Participants		
	Placebo (n = 331)	Prescription Omega-3 (n = 332)	Total (N = 663)
Any drug-related adverse event	42 (13)	52 (16)	94 (14)
Nausea	7 (2)	9 (3)	16 (2)
Diarrhea	4 (1)	7 (2)	11 (2)
Eructation	2 (<1)	6 (2)	8 (1)
Flatulence	6 (2)	2 (<1)	8 (1)
Constipation	2 (<1)	2 (<1)	4 (<1)
Liver function results abnormal	3 (<1)	1 (<1)	4 (<1)
Dyspepsia	2 (<1)	2 (<1)	4 (<1)
Rash	3 (<1)	1 (<1)	4 (<1)
Blood triglyceride increase	1 (<1)	2 (<1)	3 (<1)
Headache	3 (<1)	0	3 (<1)
Insomnia	2 (<1)	1 (<1)	3 (<1)
Upper abdominal pain	2 (<1)	0	2 (<1)
Gastrointestinal reflux disease	0	2 (<1)	2 (<1)
Vomiting	0	2 (<1)	2 (<1)
Glycated hemoglobin increased	0	2 (<1)	2 (<1)
Dysgeusia	0	2 (<1)	2 (<1)

1, 3, and 6 months after conversion, recurrence rates determined on 24-hour Holter monitoring were 3.3%, 10%, and 13.3% for the prescription omega-3 group and 10%, 25%, and 40% for the placebo group, respectively.

Recently, 3 more post-CABG surgery trials were reported. One trial using prescription omega-3 vs placebo²⁴ failed to show benefit on postoperative atrial fibrillation defined as an episode detected by continuous electrocardiographic monitoring lasting longer than 5 minutes, whereas another trial using intravenous fish oil²⁵ showed efficacy in preventing the occurrence of atrial fibrillation after CABG surgery. In another post-CABG surgery trial in which 260 patients were randomized to receive prescription omega-3 or matching placebo (2 g twice daily for at least 3 doses preoperatively and 2 g/d postoperatively for 14 days or until AF occurred [if sooner]), Sandesara et al¹¹ reported no difference in the incidence of AF or flutter, in length of stay, or in very low adverse event rates. These negative results are consistent with those recently reported by Berry et al²⁶ who found no association between fish or omega-3 fatty intake and incident AF in 44 720 participants in the Women's Health Initiative.

Against this background, our trial—which to our knowledge is the largest cohort to date of mainstream AF patients—was performed. This trial, using a high-dose prescription omega-3 regimen (4 g/d), failed to demonstrate a significant difference from placebo in the primary end point of first recurrence of symptomatic AF or flutter or in any of its secondary end points. In the prescription omega-3 group, we did find a reduction in average ventricular rate during the first AF recurrence, a reduction in triglyceride levels at week 24 that did not occur with placebo, and increased blood levels of the omega-3 fish oils eicosapentaenoic acid and docosahexaenoic acid compared with placebo patients. These observations suggest a biological effect in the patients treated with prescription omega-3, although the reduction in ventricular rate during an AF recurrence may not have been sufficient in degree or consistency to produce a clinically meaningful outcome. There was also no difference between the 2 treatment groups in adverse effects, including bleeding, serious drug-related nonfatal events, or deaths.

Our results were consistent when analyzed using the prespecified modified intention-to-treat analysis, using the independent academic statistician's analysis including participants who were previously censored from the protocol-specified analysis, and using an intention-to-treat analysis that included all randomized patients in the groups to which they were randomized. The results of these latter 2 analyses were not substantially different from the original prespecified analysis and strengthen the conclusion that the omega-3 fatty acids are not useful in the treatment of AF in the study population.

Several factors might contribute to the discordance between our findings and those of other studies. Either the positive results reported in some trials represent a chance effect of small sample sizes or the differences are real. If the latter, there are several possibilities, including differences in the study populations, in population-

specific AF mechanisms, in dosing regimens and product formulations, or in concomitant therapies. In our study, nearly half the events occurred during the first 2 weeks of follow-up, suggesting that fish oil may not have rapid effects, even with high-loading doses.

Our large trial showed no effect in a specific population of AF patients with paroxysmal AF (the majority of participants in our trial) and those with persistent AF who did not have severe heart disease, were not elderly, were without recent cardiac surgery, and were not administered concomitant antiarrhythmic drugs but did receive β -blockers, statins, and ACE inhibitors or angiotensin II receptor blockers. Our study does not provide evidence to support a role for prescription omega-3 therapy in such patients to prevent AF recurrence. However, our results do not exclude potential benefit in combination with membrane-active antiarrhythmic drugs, in different patient populations such as a high-risk primary prevention population (eg, heart failure or those with multiple clinical risk factors) or in the absence of concomitant therapies. These possibilities require evaluation in prospective clinical trials.

Our study has several limitations. First, the primary end point was recurrence of symptomatic, documented AF—a clinically meaningful parameter. Our study was not powered to examine “harder” AF-related end points such as stroke or cardiovascular death. Second, we did not have adequate pilot data to estimate the likely effect size of prescription omega-3 and the most appropriate loading and maintenance dose to study. We also do not know whether omega-3 fatty acids given in capsule form is the same as when ingested through dietary sources, and in this study, dietary information on participants' fish consumption during the trial was not collected. Third, errors in the statistical estimates of our event rates and the magnitude of treatment effect could have contributed to a potential type II error. For instance, our

estimate of AF recurrence in the placebo group was 64.4% but the actual recurrence rate was 48%, and we projected a rather aggressive treatment effect of 0.682 (HR), by assuming an effect as large as the lowest dose of an antiarrhythmic recently approved by the US Food and Drug Administration for AF. We believe that anything less than such a treatment effect would not be clinically meaningful. Although nonsignificant, the directional change of the rate of recurrent AF largely favors placebo. Therefore, it is unlikely that a larger study would have yielded a different primary outcome. In addition, had this study demonstrated a beneficial effect of omega-3 fatty acids, further trials would be needed to confirm the findings and assess clinical outcomes. Fourth, the technique used for assessing recurrences, transtelephonic monitoring, could underestimate asymptomatic AF recurrences. And fifth, it is impossible to weigh the relevance and relative potency of all of the potential mechanisms by which prescription omega-3 might suppress AF. It is possible that 1 or more of the drug's primary effects may only be manifest in certain types of AF patients not well represented in our patient population.

CONCLUSIONS

In this population of patients with symptomatic paroxysmal AF or persistent AF, and no evidence of substantial structural heart disease, prescription omega-3 did not show evidence of reducing the recurrence of symptomatic AF.

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