Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation
A Randomized Clinical Trial

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IMPORTANCE Atrial fibrillation (AF) is the most common heart rhythm disturbance, continues to increase in incidence, and results in significant morbidity and mortality. The marine omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and vitamin D have been reported to have both benefits and risks with respect to incident AF, but large-scale, long-term randomized trial data are lacking.

OBJECTIVE To test the effects of long-term administration of marine omega-3 fatty acids and vitamin D on incident AF.

DESIGN, SETTING, AND PARTICIPANTS An ancillary study of a 2 × 2 factorial randomized clinical trial involving 25 119 women and men aged 50 years or older without prior cardiovascular disease, cancer, or AF. Participants were recruited directly by mail between November 2011 and March 2014 from all 50 US states and were followed up until December 31, 2017.

INTERVENTIONS Participants were randomized to receive EPA-DHA (460 mg/d of EPA and 380 mg/d of DHA) and vitamin D_3 (2000 IU/d) (n = 6272 analyzed); EPA-DHA and placebo (n = 6270 analyzed); vitamin D_3 and placebo (n = 6281 analyzed); or 2 placebos (n = 6296 analyzed).

MAIN OUTCOMES AND MEASURES The primary outcome was incident AF confirmed by medical record review.

RESULTS Among the 25 119 participants who were randomized and included in the analysis (mean age, 66.7 years; 50.8% women), 24 127 (96.1%) completed the trial. Over a median 5.3 years of treatment and follow-up, the primary end point of incident AF occurred in 900 participants (3.6% of study population). For the EPA-DHA vs placebo comparison, incident AF events occurred in 469 (3.7%) vs 431 (3.4%) participants, respectively (hazard ratio, 1.09; 95% CI, 0.96-1.24; P = .19). For the vitamin D_3 vs placebo comparison, incident AF events occurred in 469 (3.7%) vs 431 (3.4%) participants, respectively (hazard ratio, 1.09; 95% CI, 0.96-1.25; P = .19). There was no evidence for interaction between the 2 study agents (P = .39).

CONCLUSIONS AND RELEVANCE Among adults aged 50 years or older, treatment with EPA-DHA or vitamin D_3, compared with placebo, resulted in no significant difference in the risk of incident AF over a median follow-up of more than 5 years. The findings do not support the use of either agent for the primary prevention of incident AF.

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Visual Abstract

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Supplemental content

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Atrial fibrillation (AF) is the most common heart rhythm disturbance, with an estimated 46.3 million people affected worldwide in 2016.[1] The incidence of AF increases exponentially after age 65 years, with lifetime risk estimates equal to 1 in 3 for White individuals and 1 in 5 for Black individuals.[2] Once established, AF can result in thromboembolic stroke, congestive heart failure, impaired quality of life, and other adverse consequences.[3] Even among populations without established cardiovascular disease (CVD), AF has been associated with elevated mortality.[4] Thus, primary preventive interventions for AF that can be applied to broad populations are needed, and dietary supplements have appeal in this regard.

In observational studies, individuals with low blood levels of marine omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and vitamin D_3 have higher risks of incident AF[5-7]; however, data regarding dietary or supplemental intake of these nutrients on AF risk are mixed.[8-10] As a result, both benefits and risks have been postulated. Randomized clinical trials (RCTs) testing the effect of short-term administration of omega-3 fatty acids on recurrent AF have had disparate results,[11] and recent RCTs testing longer-term treatment with omega-3 fatty acids on CVD events have reported increased risks of AF in participants randomized to active therapy vs placebo.[12-14] Given the common use of these supplements in primary care settings, as well as recent RCT data suggesting potential harm, definitive data on potential risks and benefits on AF incidence in primary care populations are needed. To assess the role of these agents in AF primary prevention, the present study prospectively tested the effects of long-term administration of marine omega-3 fatty acids and vitamin D_3 on incident AF within a large-scale RCT performed among men and women without prior vascular disease.

Methods

Trial Design and Oversight

The VITAL Rhythm Study was an ancillary trial embedded within the Vitamin D and Omega-3 (VITAL) trial. All participants were recruited and enrolled directly by mail and provided written informed consent, and approvals for the parent trial and this study were obtained from the institutional review board of Brigham and Women's Hospital. The design of the parent trial has been previously described.[15,16] In brief, the trial was a double-blind, placebo-controlled randomized trial that tested in a 2 × 2 factorial design daily supplementation with 2000 IU of vitamin D_3 and/or 840 mg of marine omega-3 fatty acids, composed of 460 mg of EPA and 380 mg of DHA, in the primary prevention of CVD and cancer in 25 871 men and women in the United States. The vitamin D_3 dose was designed to test the effect of high-dose supplementation on cancer and CVD in a primary prevention population,[15] and the EPA-DHA dose was recommended by the American Heart Association for cardioprotection among high-risk individuals and was above the dose recommended from dietary intake for the general population.[16] The placebo for vitamin D_3 contained soybean oil, and the placebo for EPA-DHA contained olive oil.

Key Points

Question Does supplementation with marine omega-3 fatty acids and/or vitamin D_3 affect the risk of developing atrial fibrillation (AF)?

Findings In this ancillary primary prevention AF trial that was embedded within a 2 × 2 factorial randomized clinical trial and included 25 119 participants without AF at study entry, there was no significant difference in AF incidence with marine omega-3 fatty acids vs placebo (hazard ratio, 1.09) or with vitamin D_3 supplementation vs placebo (hazard ratio, 1.09) over a median 5.3 years of treatment and follow-up.

Meaning These findings do not support the use of marine omega-3 fatty acids or vitamin D_3 in adults to prevent AF.

For inclusion, men were required to be at least 50 years of age and women were required to be at least 55 years of age. To comply with National Institutes of Health (NIH) reporting requirements, information on self-reported race/ethnicity was collected on the screening questionnaire, which included fixed categories and an unknown category. This information was also used to oversample Black participants, who have higher rates of vitamin D deficiency than other racial groups.[15] Participants were required to have no history of CVD (myocardial infarction, stroke, transient ischemic attack, angina, or revascularization) or cancer and be willing to forgo supplemental vitamin D_3 intake greater than 800 IU/d, supplemental calcium intake greater than 1200 mg/d, and fish oil supplementation during the trial. Safety exclusion criteria are outlined in detail elsewhere and included kidney failure or dialysis, cirrhosis, and history of hypercalcemia.[15] The study agents received Investigational New Drug approval from the US Food and Drug Administration. An independent data and safety monitoring board regularly reviewed data on end points and adverse events. The institutional review board trial protocol and the statistical analysis plan generated from the prespecified analyses in the NIH grant application are available in Supplement 1 and Supplement 2, respectively.

During a 3-month placebo run-in phase and at randomization, all participants completed questionnaires on health status, including information on preceding medical diagnoses inclusive of AF as well as cardiovascular risk factors, medications, lifestyle habits, and diet. Blood samples were requested but not required, and were collected during the run-in period. Plasma phospholipid omega-3 fatty acids (EPA plus DHA as a percentage of total plasma phospholipid fatty acids) and serum 25-hydroxyvitamin D assays were measured in stored samples using liquid chromatography–tandem mass spectrometry–mass spectrometry by Quest Diagnostics.[17]

After successful completion of the run-in period, participants were randomized to receive vitamin D_3, EPA-DHA, both active agents, or both placebos between November 2011 and March 2014. Randomization was computer generated in block sizes of 8 within sex, race, and 5-year age groups, with an equal representation of sex and an oversampling of Black study participants. Participants enrolled in the parent trial who reported a diagnosis of AF at baseline were excluded from follow-up. At 6 months and then annually thereafter, each participant

received a follow-up questionnaire that inquired about new medical diagnoses including AF, medication and supplement use, and lifestyle and clinical risk factors, as well as receiving a resupply of study agents.

Outcome Assessment

The primary outcome of the study was incident AF confirmed by medical record review, and incident paroxysmal and nonparoxysmal AF were prespecified secondary outcomes. Given the common association with AF, atrial flutter events were included in the primary and secondary AF outcomes. The outcomes were identified through 2 methods. First, participants self-reported new diagnoses of AF on annual follow-up questionnaires. Second, the VITAL population was linked to inpatient and outpatient claims data from the Centers for Medicare & Medicaid Services (CMS), and diagnosis codes for AF (*International Classification of Diseases, Ninth Revision* [*ICD-9*] diagnosis code 427.31 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] diagnosis code I48.91) and atrial flutter (*ICD-9* diagnosis code 427.32 and *ICD-10* diagnosis code I48.92) were ascertained. The details regarding the CMS linkage are available in the eAppendix in Supplement 3.

For all participants with an incident AF or atrial flutter diagnosis, either self-reported or identified through CMS linkage, permission was requested to obtain medical records pertaining to the diagnosis and subsequent cardiac evaluation. An end-point committee of cardiologists reviewed medical records and confirmed events according to predefined criteria.[4] Electrocardiographic (ECG) evidence of AF or atrial flutter or a physician's report outlining a diagnosis of either was required for confirmation. The date of onset was defined as the earliest documented occurrence of either arrhythmia within the medical records. If onset was prior to randomization, the participant was excluded from the statistical analysis. For the secondary outcomes, the pattern of AF at the time of diagnosis was classified in accordance with American College of Cardiology/American Heart Association/Heart Rhythm Society and European Society of Cardiology guidelines.[18,19] Exploratory outcomes not reported in this article include repeated ECG characteristics collected in a subset of 911 participants, and cause-specific cardiovascular mortality, including sudden arrhythmic death.

Sample Size and Power Calculations

Based on pretrial assumptions that 23 520 participants without prevalent AF would be enrolled in VITAL and that the 5-year cumulative incidence of AF would be 3.15%, 741 primary outcome events were projected to occur during the trial, providing 90% power to detect a 22% reduction or increase in the observed hazard ratio (HR) for the primary outcome, incident AF, which was well within that observed in observational studies and in a contemporaneous meta-analysis of secondary prevention trials.[5,7,8,20]

Statistical Analyses

Primary Analysis

After excluding AF cases diagnosed prior to randomization (**Figure 1**), participants were analyzed according to randomization group. To ensure balance by randomization remained af-

ter excluding prevalent AF cases, baseline characteristics were compared for each treatment group using *t* tests for continuous variables and χ^2 statistics for categorical variables. There was an a priori assumption of no interaction between agents, and the prespecified analyses examined the pooled main effects of EPA-DHA and vitamin D_3 on incident AF within the 2 × 2 factorial design. The HR for each intervention was estimated in Cox proportional hazard models using indicators for treatment assignment, controlling for the second intervention, age, and sex. Cumulative incidence curves were estimated from the adjusted Cox model. The proportionality assumption was tested using an interaction term for treatment × log time and was met for each of the primary and secondary outcomes. Times to events were calculated as the interval between randomization and the earliest occurrence of confirmed AF event, death, or the end of randomized treatment (December 31, 2017). Participants who did not return an annual questionnaire and/or who had missing data on AF on a questionnaire were assumed to not have AF during that reporting cycle unless subsequently ascertained and confirmed to have AF during that time period.

Three prespecified sensitivity analyses were also performed for the primary outcome. Because determination of the initial onset of AF can be challenging, the first analysis excluded participants who had symptoms that may have been related to AF prior to randomization. Because CMS claims data are available only for select participants, primarily those aged 65 or older, the second analysis limited confirmed AF events to those identified by self-report. Third, an on-treatment, adherence-based analysis that censored follow-up data when a participant discontinued trial capsules or began taking study supplements outside of the trial was performed. In addition, 2 post hoc sensitivity analyses were performed. The first excluded events solely due to atrial flutter or postoperative AF and the second excluded events without a confirmatory ECG.

Secondary Analyses

To assess for treatment interactions in the primary outcome, multiplicative interaction terms in Cox models were used to explore interactions between vitamin D_3 and EPA-DHA. Combination treatment groups (active-active, active-placebo, placebo-active) were compared with the group receiving both placebos using Cox models and cumulative incidence curves. In addition, subgroup analyses were performed that examined effect modification by a priori-selected AF risk factors, dietary fish intake, vitamin D_3 intake, and blood levels of both nutrients at baseline. To test for interactions, cross-product terms were included in the full multivariable model.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc), and a 2-sided *P* < .05 was used to determine statistical significance. Because of the potential for type I error due to multiple comparisons, findings for secondary outcomes and analyses should be interpreted as exploratory.

Results

Among the 25 871 participants enrolled in the parent trial, 752 participants with prevalent AF at baseline were excluded from

Figure 1. Flow of Participants in the VITAL Rhythm Study

401605 Participants completed screening questionnaire and assessed for eligibility

362175 Excluded
  126823 Willing but ineligible[a]
  73707 Willing but enrollment already reached
  61304 Unwilling and ineligible
  56703 Pending receipt of more information
  43122 Eligible but unwilling
  458 Incomplete information provided to determine eligibility

39430 Initially willing and eligible to participate and entered run-in phase

13559 Excluded
  7339 No response to run-in questionnaire
  3989 Ineligible due to poor adherence and/or new diagnosis excluding participation
  1249 Unwilling to continue in trial
  510 Incomplete information provided to determine eligibility
  460 Willing and able but enrollment goal already reached

25871 Randomized

6463 Randomized to EPA-DHA and vitamin D_3 and received intervention as randomized
6272 Followed up for incident atrial fibrillation
191 Excluded (preexisting atrial fibrillation)

6464 Randomized to vitamin D_3 and placebo and received intervention as randomized
6281 Followed up for incident atrial fibrillation
183 Excluded (preexisting atrial fibrillation)

6470 Randomized to EPA-DHA and placebo and received intervention as randomized
6270 Followed up for incident atrial fibrillation
200 Excluded (preexisting atrial fibrillation)

6474 Randomized to 2 placebos and received intervention as randomized
6296 Followed up for incident atrial fibrillation
178 Excluded (preexisting atrial fibrillation)

6026 Alive at end of intervention

6031 Alive at end of intervention

6016 Alive at end of intervention

6054 Alive at end of intervention

238 Developed atrial fibrillation during the trial

231 Developed atrial fibrillation during the trial

231 Developed atrial fibrillation during the trial

200 Developed atrial fibrillation during the trial

12553 Included in primary analysis (vitamin D_3 study active group)

12566 Included in primary analysis (vitamin D_3 study placebo group)

12542 Included in primary analysis (EPA-DHA study active group)

12577 Included in primary analysis (EPA-DHA study placebo group)

Participants were randomized to receive vitamin D_3, marine omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), both active agents, or both placebos between November 2011 and March 2014. Randomization was computer generated in block sizes of 8 within sex, race, and 5-year age groups, with an equal representation of sex and an oversampling of Black/African American participants.

[a] Willing/ineligible category included 76190 individuals with history of cardiovascular disease, cancer, and/or safety exclusion criteria; 32647 individuals unwilling to forgo supplemental vitamin D_3 intake greater than 800 IU/d, supplemental calcium intake greater than 1200 mg/d, or fish oil supplementation during the trial; 13521 men younger than 50 years and women younger than 55 years; and 4465 individuals who reported another exclusion criterion (eg, participation in another trial).

study follow-up (balanced by treatment group; P = .68). The remaining 25119 participants were distributed across 4 randomized treatment groups as shown in Figure 1. The study treatment ended as planned on December 31, 2017, which yielded a median follow-up of 5.3 years (range, 3.8-6.1 years). Table 1 shows the characteristics of the population across the 4 treatment groups. The median age was 66.7 years (interquartile range, 62.4-71.0 years) and 50.8% were women. Partici-

pants who self-identified as Black or African American accounted for 20.1% of the population. Randomization remained balanced for CVD and AF risk factors after exclusion of prevalent AF events (Table 1).

Within the study population, the rate of response to annual questionnaires averaged 93.1%, and 19892 participants (79.2%) were successfully linked to CMS claims data (balanced by treatment group; P = .31). The majority of those linked

Table 1. Baseline Participant Characteristics

Characteristics	EPA-DHA and vitamin D_3 (n = 6272)	EPA-DHA only (n = 6270)	Vitamin D_3 only (n = 6281)	Placebo only (n = 6296)
Age, median (IQR), y	66.6 (62.5-71.0)	66.7 (62.5-71.0)	66.7 (62.4-71.1)	66.6 (62.4-71.0)
Sex, No. (%)				
Female	3192 (50.9)	3176 (50.7)	3192 (50.8)	3197 (50.8)
Male	3080 (49.1)	3094 (49.3)	3089 (49.2)	3099 (49.2)
Race/ethnicity, No. (%)[a]	n = 6147	n = 6130	n = 6142	n = 6160
Non-Hispanic White	4360 (70.9)	4364 (71.2)	4346 (70.8)	4355 (70.7)
Black or African American	1264 (20.6)	1256 (20.5)	1262 (20.5)	1270 (20.6)
Hispanic	243 (4.0)	241 (3.9)	266 (4.3)	249 (4.0)
Asian/Pacific Islander	99 (1.6)	96 (1.6)	86 (1.4)	101 (1.6)
Native American/Alaska Native	60 (1.0)	54 (0.9)	51 (0.8)	50 (0.8)
Unknown	121 (2.0)	119 (1.9)	131 (2.1)	135 (2.2)
Smoking status, No. (%)	n = 6172	n = 6182	n = 6192	n = 6198
Never	3196 (51.8)	3191 (51.6)	3179 (51.3)	3269 (52.7)
Past	2528 (41.0)	2536 (41.0)	2559 (41.3)	2488 (40.1)
Current	448 (7.3)	455 (7.4)	454 (7.3)	441 (7.1)
Hypertension, No./total (%)[a]	3135/6229 (50.3)	3268/6245 (52.3)	3272/6242 (52.4)	3236/6267 (51.6)
Diabetes, No./total (%)[a]	892/6257 (14.3)	845/6261 (13.5)	866/6270 (13.8)	839/6286 (13.3)
Body mass index, median (IQR)[b]	27.2 (24.4-30.9) [n = 6130]	27.2 (24.3-30.8) [n = 6121]	27.1 (24.3-30.7) [n = 6136]	27.0 (24.2-30.7) [n = 6156]
Height, median (IQR), in	67.0 (64.0-70.0) [n = 6160]	67.0 (64.0-70.0) [n = 6149]	67.0 (64.0-70.0) [n = 6158]	67.0 (64.0-70.0) [n = 6188]
Cholesterol-lowering medication use, No./total (%)[c]	2342/6166 (38.0)	2292/6158 (37.2)	2339/6171 (37.9)	2253/6198 (36.4)
CHA_2DS_2-VASc score, No. (%)[d]				
0	768 (12.2)	724 (11.5)	737 (11.7)	751 (11.9)
1	1504 (24.0)	1579 (25.2)	1522 (24.2)	1565 (24.9)
≥2	4000 (63.8)	3967 (63.3)	4022 (64.0)	3980 (63.2)
Aspirin use, No./total (%)	2757/6179 (44.6)	2764/6180 (44.7)	2752/6193 (44.4)	2801/6206 (45.1)
Statin use, No./total (%)	2186/6173 (35.4)	2129/6158 (34.6)	2186/6175 (35.4)	2093/6206 (33.7)
Alcohol consumption, No. (%)[e]	n = 6164	n = 6181	n = 6168	n = 6184
<1 drink/wk	2366 (38.4)	2449 (39.6)	2427 (39.3)	2416 (39.1)
1-6 drinks/wk	2236 (36.3)	2096 (33.9)	2145 (34.8)	2161 (34.9)
1 drink/d	719 (11.7)	767 (12.4)	705 (11.4)	701 (11.3)
≥2 drinks/d	843 (13.7)	869 (14.1)	891 (14.4)	906 (14.7)
Fish consumption, median (IQR), servings/wk[f]	1.5 (0.9-2.5) [n = 6165]	1.5 (0.9-2.5) [n = 6175]	1.5 (0.9-2.5) [n = 6170]	1.5 (0.9-2.5) [n = 6182]
Vitamin D consumption, No. (%)[g]	2638 (42.1)	2674 (42.6)	2672 (42.5)	2678 (42.5)

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IQR, interquartile range.

[a] Race/ethnicity, hypertension, and diabetes were reported by participants.

[b] Body mass index is calculated as weight in kilograms divided by the square of height in meters.

[c] Cholesterol-lowering medications included both statins and nonstatins.

[d] The CHA_2DS_2-VASc score is used to estimate risk of stroke in patients with atrial fibrillation and is calculated as the sum of the following risk factors: congestive heart failure (1 point); hypertension (1 point); age 65-74 years (1 point), age ≥75 years (2 points); diabetes (1 point); prior stroke, transient ischemic attack, or thromboembolism (2 points); vascular disease (myocardial infarction, peripheral arterial disease, or prior aortic plaque; 1 point); and female sex (1 point). All risk factors were ascertained via self-report at baseline.

Possible scores range from 0 to 9, wherein 9 represents the highest risk category. Scores ranged from 0 to 8 in this study sample.

[e] One drink was defined as 1 glass, bottle, or can of beer or light beer; one 5-oz glass of red or white wine; or 1 drink or shot of liquor. Data were reported by participants via food frequency questionnaire.

[f] Data for servings of fish consumption were reported by participants via food frequency questionnaire and included canned tuna (3-4 oz); breaded fish cakes, pieces, or fish sticks (1 serving, store-bought); shrimp, lobster, or scallops as a main dish; dark-meat fish (eg, mackerel, salmon, sardines, bluefish, or swordfish; 3-5 oz); and other fish (3-5 oz). Daily servings were summed across each type of fish and multiplied by 7 to calculate weekly servings.

[g] Restricted to ≤800 IU/d from all sources combined (individual supplements and multivitamins).

to CMS claims data (n = 18 567 [93.3%]) were aged 65 years or older at the time of linkage. The percentage of participants who adhered to study drug and took at least two-thirds of trial capsules was similar across treatment groups (80%-82%).[15,16] The prevalence of outside supplement use remained below 3.5%

for fish oil and ranged from 3.8% to 10.8% for vitamin D (>800 IU/d) at 5 years of follow-up.[15,16]

There were 900 confirmed incident AF events identified by self-report and/or CMS claims during the trial period. The characteristics of these AF cases are shown in the eTable in

Table 2. Incidence and Relative Hazards of AF Among Participants Randomized to EPA-DHA vs Placebo

End points	EPA-DHA (n = 12 542)			Placebo (n = 12 577)			EPA-DHA vs placebo		
	No. of events	Total person-years	Events per 1000 person-years	No. of events	Total person-years	Events per 1000 person-years	Difference in events per 1000 person-years (95% CI)	Hazard ratio (95% CI)[a]	P value
Primary end point									
All incident AF	469	64 942	7.2	431	65 242	6.6	0.6 (−0.3 to 1.5)	1.09 (0.96-1.24)	.19
Sensitivity analyses of primary end point									
AF events excluding those with symptoms preceding randomization	440	64 840	6.8	402	65 154	6.2	0.6 (−0.3 to 1.5)	1.10 (0.96-1.26)	.17
AF events excluding those detected by CMS linkage data alone	389	64 676	6.0	345	64 970	5.3	0.7 (−0.1 to 1.5)	1.13 (0.98-1.31)	.10
AF events excluding atrial flutter alone and postoperative AF[b]	410	64 721	6.3	374	65 055	5.7	0.6 (−0.3 to 1.4)	1.10 (0.96-1.27)	.18
AF events excluding those without ECG confirmation[b]	346	64 587	5.4	310	64 875	4.8	0.6 (−0.2 to 1.4)	1.12 (0.96-1.30)	.15
On-treatment analysis[c]	403	51 005	7.9	358	51 223	7.0	0.9 (−0.1 to 2.0)	1.13 (0.98-1.30)	.09
Secondary end points									
Paroxysmal AF	271	64 942	4.2	255	65 242	3.9	0.3 (−0.4 to 1.0)	1.07 (0.90-1.27)	.46
Nonparoxysmal AF	182	64 942	2.8	164	65 242	2.5	0.3 (−0.3 to 0.8)	1.11 (0.90-1.37)	.32

Abbreviations: AF, atrial fibrillation; CMS, Centers for Medicare & Medicaid Services; DHA, docosahexaenoic acid; ECG, electrocardiographic; EPA, eicosapentaenoic acid.

[a] The hazard ratio for each intervention was estimated in Cox models using indicators for treatment group, controlling for the second intervention, age, and sex.

[b] Post hoc analyses.

[c] Adherence-based analyses that censored follow-up data when a participant discontinued trial capsules or began taking nonstudy fish oil supplements.

Supplement 3. The majority had an ECG documenting AF (n = 656 [72.9%]), and the remainder had AF documented in a physician's note (n = 244 [27.1%]). Five hundred twenty-six (58%) had paroxysmal AF, whereas 346 (38.4%) had persistent AF at the time of diagnosis. The remainder (n = 28 [3.1%]) could not be classified. Five hundred fifty-seven (61.9%) were documented to have symptoms at the time of diagnosis, and 58 (6.4%) had symptoms that may have preceded randomization. The remainder had either no (n = 247 [27.4%]) or unclear (n = 96 [10.7%]) symptoms at the time of diagnosis. Sixty-six (7.3%) had AF after cardiac surgery and 52 (5.8%) had only atrial flutter documented in the medical records. Echocardiograms were available in 775 cases (86.1%), and the median ejection fraction was 60% (interquartile range, 55%-63%).

Omega-3 Fatty Acid Supplementation

The primary outcome of incident AF occurred in 469 (3.7%) participants randomized to EPA-DHA vs 431 (3.4%) randomized to placebo (HR, 1.09; 95% CI, 0.96-1.24; *P* = .19) (**Table 2**). The corresponding AF incidence rates were 7.2 per 1000 person-years for EPA-DHA vs 6.6 per 1000 person-years for placebo (absolute rate difference, 0.6 [95% CI, −0.3 to 1.15] per 1000 person-years). The cumulative incidence of AF over the study follow-up by treatment group is shown in **Figure 2**A. Although the curves appeared to separate after the second year, there was no statistical evidence for time-dependent treatment effects (HR, 1.01; 95% CI, 0.87-1.18; *P* = .88 for time interaction). Randomization to EPA-DHA was also not significantly associated with incident AF in sensitivity analyses

excluding AF events for which symptoms could have occurred prior to randomization (HR, 1.10; 95% CI, 0.96-1.26), analyses limited to AF events identified by self-report (HR, 1.13; 95% CI, 0.98-1.31), analyses excluding cases with a sole diagnosis of atrial flutter or postoperative AF (HR, 1.10; 95% CI, 0.96-1.27), or analyses excluding AF events without a confirmatory ECG (HR, 1.12; 95% CI, 0.96-1.30). Results remained nonsignificant when individuals were censored for nonadherence (HR, 1.13; 95% CI, 0.98-1.30).

For the secondary outcomes of incident paroxysmal AF and nonparoxysmal AF, the HRs were 1.07 (95% CI, 0.90-1.27; *P* = .46) and 1.11 (95% CI, 0.90-1.37; *P* = .32), respectively (Table 2). In subgroup analyses, there was no evidence of effect modification by baseline fish intake, plasma EPA-DHA levels, or AF risk factors on the primary outcome, with the exception of height (**Figure 3**). Participants randomized to the EPA-DHA group who were taller than the median height of 67 in had a higher risk of incident AF (HR, 1.21; 95% CI, 1.02-1.42) compared with those randomized to placebo (HR, 0.86; 95% CI, 1.02-1.42), and there was evidence for a treatment interaction by height (nominal *P* = .02 for interaction).

Vitamin D3 Supplementation

The primary outcome occurred in 469 (3.7%) participants randomized to vitamin D_3 vs 431 (3.4%) randomized to placebo (HR, 1.09; 95% CI, 0.96-1.25; *P* = .19) (**Table 3**). The corresponding AF incidence rates were 7.2 per 1000 person-years for vitamin D_3 vs 6.6 per 1000 person-years for placebo (absolute rate difference, 0.6 [95% CI, −0.3 to 1.15] per 1000 person-

Figure 2. Cumulative Incidence of Atrial Fibrillation According to Randomized Treatment Groups
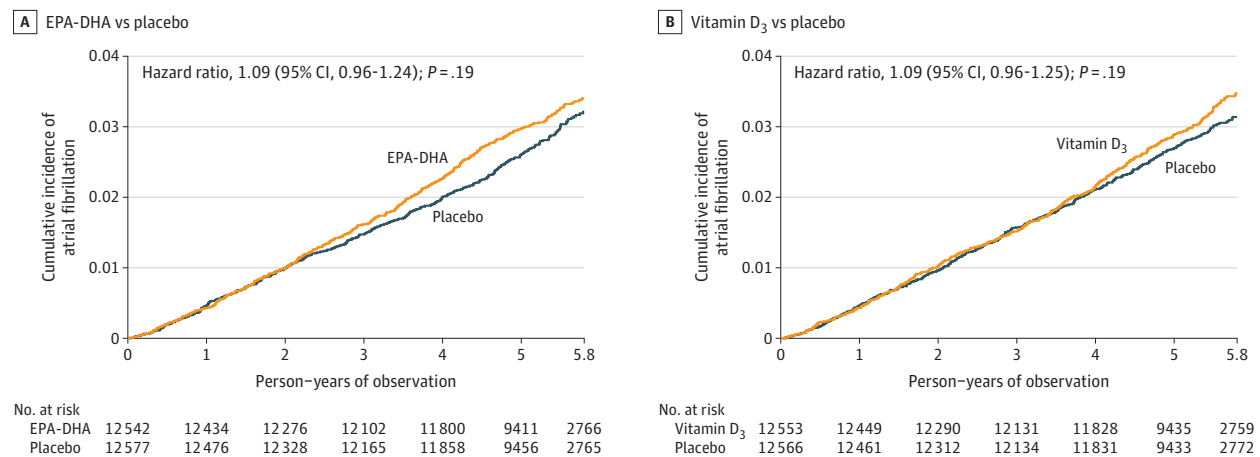
A, Cumulative incidence of the primary end point according to randomized treatment group of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) vs placebo derived from Cox regression models controlling for age, sex, and vitamin D_3 randomization group. Median observation time was 5.3 (interquartile range, 5.0-5.7) person-years. B, Cumulative incidence of the primary end point according to randomized treatment group of vitamin D_3 vs placebo derived from Cox regression models controlling for age, sex, and EPA-DHA randomization group. Median observation time was 5.3 (interquartile range, 5.0-5.7) person-years.

years). Cumulative incidence rates of AF by treatment group are shown in Figure 2B, and there was no evidence for time × treatment interaction (HR, 1.07; 95% CI, 0.92-1.25; P = .39). There remained no significant effect of vitamin D_3 after censoring for nonadherence (HR, 1.09; 95% CI, 0.94-1.27) and in all the prespecified secondary analyses shown in Table 3. For the secondary outcomes of paroxysmal and nonparoxysmal AF, the HRs associated with randomization to vitamin D_3 were 1.03 (95% CI, 0.87-1.23; P = .71) and 1.20 (95% CI, 0.97-1.48; P = .10), respectively (Table 3).

In subgroup analyses (Figure 4), there was no statistical evidence for effect modification by vitamin D_3 supplement use and 25-hydroxyvitamin D serum level on the primary outcome. There was nominal statistical evidence for effect modification by age and alcohol intake (P = .02 and P = .01 for interaction, respectively). The HR associated with vitamin D_3 treatment group was significantly elevated in participants younger than the median age of 66.7 years (HR, 1.44; 95% CI, 1.11-1.86) but not in older participants (HR, 0.99; 95% CI, 0.85-1.15). For alcohol intake, the HR associated with randomization to vitamin D_3 was elevated in those who consumed less than 1 drink per day (HR, 1.23; 95% CI, 1.04-1.44) but not among those who consumed 1 to 2 drinks per day (HR, 1.01; 95% CI, 0.71-1.43) or more than 2 drinks per day (HR, 0.80; 95% CI, 0.59-1.08).
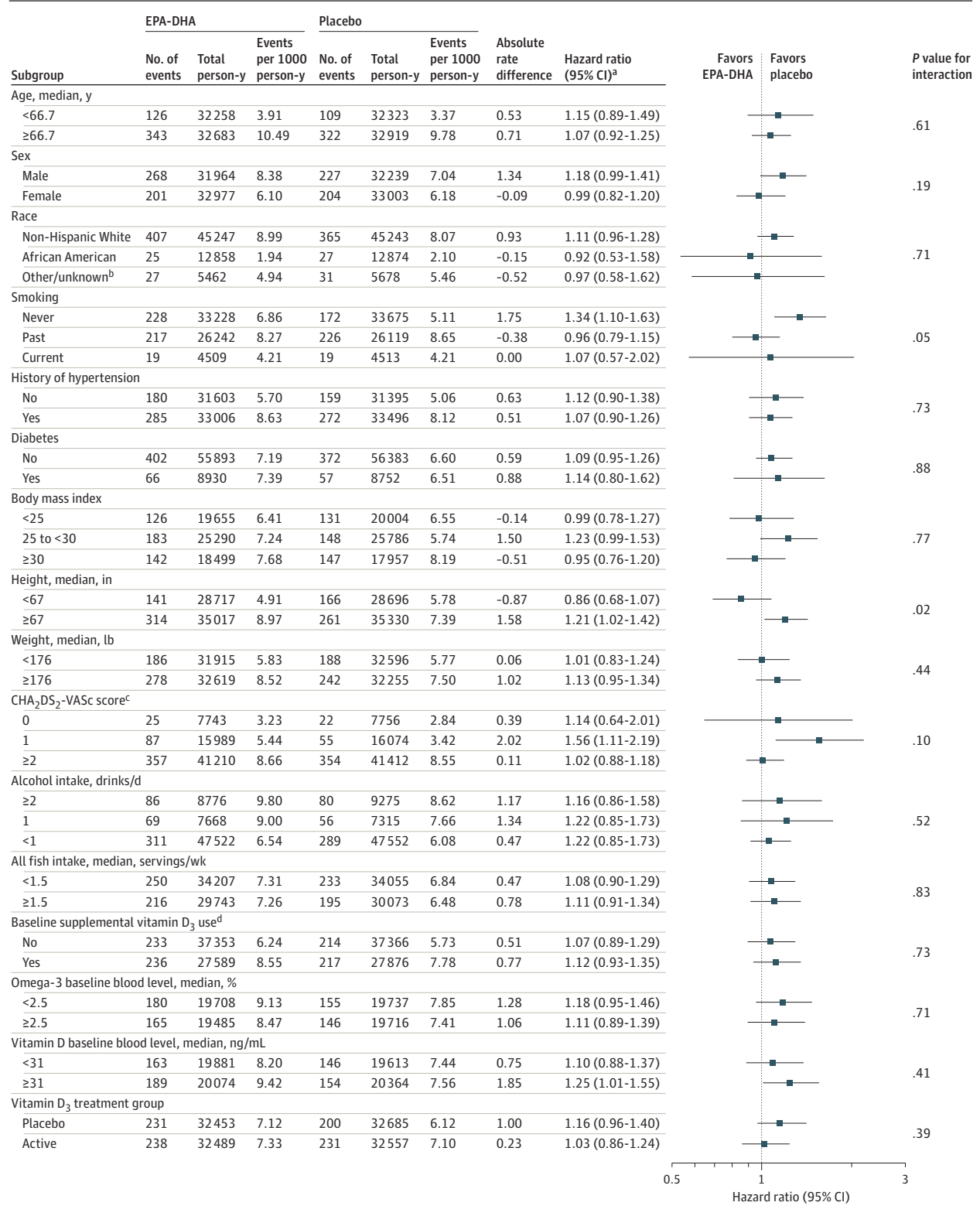
Combined Treatment Effects

There was no evidence for a treatment interaction between vitamin D_3 and EPA-DHA (Figure 3 and Figure 4; P = .39 for interaction). When analyzed according to the 4 treatment groups, compared with participants randomized to both placebos, the HR for incident AF for those randomized to EPA-DHA and placebo was 1.16 (95% CI, 0.96-1.40; P = .13), for those randomized to vitamin D_3 and placebo was 1.16 (95% CI, 0.96-1.40; P = .13), and for those randomized to vitamin D_3 and EPA-DHA was 1.20 (95% CI, 0.99-1.45; P = .06) (eFigure in Supplement 3).

Discussion

In this large-scale, ancillary, AF primary prevention, randomized, double-blind, placebo-controlled trial, supplementation with 840 mg/d of marine omega-3 fatty acids (EPA-DHA; 1.2:1 ratio) and/or 2000 IU/d of vitamin D_3 did not significantly reduce or increase the primary end point of incident AF compared with placebo over a median treatment duration of 5.3 years. There was no evidence for an interaction between the study agents or for effect modification by dietary intake or blood levels of either nutrient. Similarly, there was no statistically significant difference in incidence of secondary outcomes of paroxysmal or nonparoxysmal AF. Overall, these findings do not support the use of supplemental EPA-DHA or vitamin D_3 for the primary prevention of AF and provide reassurance regarding lack of a major risk of AF incidence associated with these commonly used supplements at these doses.

In experimental models, omega-3 fatty acids have been demonstrated to have both direct electrophysiologic actions and favorable effects on biologic processes involved in atrial remodeling.[21-23] Thus far, completed RCTs with AF as the primary outcome have examined the short-term recurrence of AF in patients with established AF or the development of AF after cardiac surgery[11] in relatively small populations. While some studies demonstrated benefit,[24-26] most did not.[27-29] On balance, these secondary prevention trials did not support the use of omega-3 fatty acids as alternatives to antiarrhythmic drugs for the maintenance of sinus rhythm in patients with AF.[11] However, given the upstream actions of omega-3 fatty acids,[23,30] it remained plausible that these agents might be more effective at preventing the development of the atrial substrate leading to AF as opposed to rapidly altering it.[31,32] In this large-scale AF primary prevention trial, no evidence for such a benefit was found. Although it is feasible that benefits might have

Figure 3. Effect of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) on the Primary End Point in Prespecified Subgroups

Subgroup	EPA-DHA			Placebo			Absolute rate difference	Hazard ratio (95% CI)[a]	Favors EPA-DHA Favors placebo	P value for interaction
	No. of events	Total person-y	Events per 1000 person-y	No. of events	Total person-y	Events per 1000 person-y				
Age, median, y										
<66.7	126	32258	3.91	109	32323	3.37	0.53	1.15 (0.89-1.49)		.61
≥66.7	343	32683	10.49	322	32919	9.78	0.71	1.07 (0.92-1.25)		
Sex										
Male	268	31964	8.38	227	32239	7.04	1.34	1.18 (0.99-1.41)		.19
Female	201	32977	6.10	204	33003	6.18	-0.09	0.99 (0.82-1.20)		
Race										
Non-Hispanic White	407	45247	8.99	365	45243	8.07	0.93	1.11 (0.96-1.28)		
African American	25	12858	1.94	27	12874	2.10	-0.15	0.92 (0.53-1.58)		.71
Other/unknown[b]	27	5462	4.94	31	5678	5.46	-0.52	0.97 (0.58-1.62)		
Smoking										
Never	228	33228	6.86	172	33675	5.11	1.75	1.34 (1.10-1.63)		
Past	217	26242	8.27	226	26119	8.65	-0.38	0.96 (0.79-1.15)		.05
Current	19	4509	4.21	19	4513	4.21	0.00	1.07 (0.57-2.02)		
History of hypertension										
No	180	31603	5.70	159	31395	5.06	0.63	1.12 (0.90-1.38)		.73
Yes	285	33006	8.63	272	33496	8.12	0.51	1.07 (0.90-1.26)		
Diabetes										
No	402	55893	7.19	372	56383	6.60	0.59	1.09 (0.95-1.26)		.88
Yes	66	8930	7.39	57	8752	6.51	0.88	1.14 (0.80-1.62)		
Body mass index										
<25	126	19655	6.41	131	20004	6.55	-0.14	0.99 (0.78-1.27)		
25 to <30	183	25290	7.24	148	25786	5.74	1.50	1.23 (0.99-1.53)		.77
≥30	142	18499	7.68	147	17957	8.19	-0.51	0.95 (0.76-1.20)		
Height, median, in										
<67	141	28717	4.91	166	28696	5.78	-0.87	0.86 (0.68-1.07)		.02
≥67	314	35017	8.97	261	35330	7.39	1.58	1.21 (1.02-1.42)		
Weight, median, lb										
<176	186	31915	5.83	188	32596	5.77	0.06	1.01 (0.83-1.24)		.44
≥176	278	32619	8.52	242	32255	7.50	1.02	1.13 (0.95-1.34)		
CHA$_2$DS$_2$-VASc score[c]										
0	25	7743	3.23	22	7756	2.84	0.39	1.14 (0.64-2.01)		
1	87	15989	5.44	55	16074	3.42	2.02	1.56 (1.11-2.19)		.10
≥2	357	41210	8.66	354	41412	8.55	0.11	1.02 (0.88-1.18)		
Alcohol intake, drinks/d										
≥2	86	8776	9.80	80	9275	8.62	1.17	1.16 (0.86-1.58)		
1	69	7668	9.00	56	7315	7.66	1.34	1.22 (0.85-1.73)		.52
<1	311	47522	6.54	289	47552	6.08	0.47	1.22 (0.85-1.73)		
All fish intake, median, servings/wk										
<1.5	250	34207	7.31	233	34055	6.84	0.47	1.08 (0.90-1.29)		.83
≥1.5	216	29743	7.26	195	30073	6.48	0.78	1.11 (0.91-1.34)		
Baseline supplemental vitamin D$_3$ use[d]										
No	233	37353	6.24	214	37366	5.73	0.51	1.07 (0.89-1.29)		.73
Yes	236	27589	8.55	217	27876	7.78	0.77	1.12 (0.93-1.35)		
Omega-3 baseline blood level, median, %										
<2.5	180	19708	9.13	155	19737	7.85	1.28	1.18 (0.95-1.46)		.71
≥2.5	165	19485	8.47	146	19716	7.41	1.06	1.11 (0.89-1.39)		
Vitamin D baseline blood level, median, ng/mL										
<31	163	19881	8.20	146	19613	7.44	0.75	1.10 (0.88-1.37)		.41
≥31	189	20074	9.42	154	20364	7.56	1.85	1.25 (1.01-1.55)		
Vitamin D$_3$ treatment group										
Placebo	231	32453	7.12	200	32685	6.12	1.00	1.16 (0.96-1.40)		.39
Active	238	32489	7.33	231	32557	7.10	0.23	1.03 (0.86-1.24)		

0.5   1   3
Hazard ratio (95% CI)

[a] Cox regression models controlled for age, sex, and randomization group; interactions tested using multiplicative interaction terms.

[b] Includes Hispanic, Asian/Pacific Islander, Native American/Alaska Native, and other, multiple, or unspecified race/ethnicity.

[c] CHA$_2$DS$_2$-VASc score estimates stroke risk in patients with atrial fibrillation (see Table 1 footnote "d" for details). Risk factors were self-reported at baseline. Scores ranged from 0 to 8 in this study.

[d] Restricted to ≤800 IU/d from all sources combined.

Table 3. Incidence and Relative Hazards of AF Among Participants Randomized to Vitamin D$_3$ vs Placebo

	Vitamin D$_3$ (n = 12 553)			Placebo (n = 12 566)			Vitamin D$_3$ vs placebo		
End points	No. of events	Total person-years	Events per 1000 person-years	No. of events	Total person-years	Events per 1000 person-years	Difference in events per 1000 person-years (95% CI)	Hazard ratio (95% CI)[a]	P value
Primary end point									
All incident AF	469	65 046	7.2	431	65 137	6.6	0.6 (−0.3 to 1.5)	1.09 (0.96-1.25)	.19
Sensitivity analyses of primary end point									
AF events excluding those with symptoms preceding randomization	438	64 948	6.7	404	65 046	6.2	0.5 (−0.3 to 1.4)	1.09 (0.95-1.25)	.22
AF events excluding those detected by CMS linkage data alone	373	64 727	5.8	361	64 919	5.6	0.2 (−0.6 to 1.0)	1.04 (0.90-1.20)	.60
AF events excluding atrial flutter alone and postoperative AF[b]	404	64 815	6.2	380	64 962	5.8	0.4 (−0.5 to 1.2)	1.07 (0.93-1.23)	.36
AF events excluding those confirmed by medical record alone[b]	343	64 671	5.3	313	64 790	4.8	0.5 (−0.3 to 1.2)	1.10 (0.95-1.28)	.22
On-treatment analysis[c]	383	50 540	7.6	336	48 640	6.9	0.7 (−0.4 to 1.7)	1.09 (0.94-1.27)	.24
Secondary end points									
Paroxysmal AF	267	65 046	4.1	259	65 137	4.0	0.1 (−0.6 to 0.8)	1.03 (0.87-1.23)	.71
Nonparoxysmal AF	188	65 046	2.9	158	65 137	2.4	0.5 (−0.1 to 1.0)	1.20 (0.97-1.48)	.10

Abbreviations: AF, atrial fibrillation; CMS, Centers for Medicare & Medicaid Services.

[a] The hazard ratio for each intervention was estimated in Cox models using indicators for treatment group, controlling for the second intervention, age, and sex.

[b] Post hoc analyses.

[c] Adherence-based analyses that censored follow-up data when a participant discontinued trial capsules or began taking more than 800 IU/d of nonstudy vitamin D$_3$.

accrued if treatment and follow-up were continued beyond 5 years, the observed cumulative incidence curves and HRs suggest that this would be unlikely.

In addition to hypothesized benefits on AF, there are also data in support of potential adverse effects of omega-3 fatty acids. Recently, 2 separate RCTs testing higher-dose formulations of omega-3 fatty acids performed among patients with established CVD or at high cardiovascular risk reported significantly elevated risks of AF in the treatment groups. In the REDUCE-IT trial, patients randomized to 4 g/d of highly purified EPA ethyl ester (icosapent ethyl) had a 48% higher risk of hospitalization for AF compared with placebo (3.1% vs 2.1%; *P* = .004) over a median 4.9 years of follow-up.[12] In the STRENGTH trial, the incidence of investigator-reported new-onset AF was also greater among participants randomized to 4 g/d of omega-3 carboxylic acid, a mixture of EPA and DHA, vs placebo over a median 3.2 years of follow-up (2.2% vs 1.3%; HR, 1.69; 95% CI, 1.29-2.21; *P* < .001).[13] Another smaller trial performed in an elderly post–myocardial infarction population, the OMEMI trial, reported a nonsignificantly increased risk of incident AF among those without AF at study entry who were treated with 1.8 g/d of omega-3 fatty acids (930 mg of EPA) compared with placebo (HR, 1.84; 95% CI, 0.98-3.45; *P* = .06).[14] These results are in contrast to the more modest, nonsignificant elevation in incident AF (3.7% vs 3.4%; HR, 1.09; 95% CI, 0.96-1.24) observed in this primary prevention trial. The large sample size and greater than anticipated number of AF events in the present study provided adequate power to detect risk elevations of the magnitude reported in these other trials, as evidenced by the upper bound of the 95% confidence inter-

val. However, smaller elevations in AF risk up to 24%, which could be clinically meaningful, cannot be excluded. Potentially, the adverse effect on AF risk may be dose related, and the higher dosages of EPA used in these other studies might account for the significant adverse effect on AF.

To our knowledge, the present study is the only RCT to assess the effect of vitamin D$_3$ supplementation on AF risk. Similar to omega-3 fatty acids, there are multiple upstream long-term mechanisms whereby vitamin D supplementation has been hypothesized to influence atrial structural and electrical remodeling.[33,34] The data in support of supplementation are primarily based on conflicting observational studies that, when combined in meta-analysis, find a positive association between vitamin D deficiency and AF.[6,35] In contrast, a recent post hoc analysis from the Women's Health Initiative did not find a significant association between randomized treatment with 400 IU/d of vitamin D$_3$ and 1000 mg/d of elemental calcium and incident AF based solely on Medicare claims data.[36] The results of the present trial, using a higher dose of vitamin D$_3$ and AF events prospectively ascertained by self-report and CMS linkage and confirmed by medical record review, agree with these latter null findings. In addition, subgroup analyses in patients with vitamin D levels considered deficient (<20 ng/mL) did not suggest a benefit; however, the power to detect a benefit in this much smaller subset of the population was limited.

While there were no significant differences in incident AF for either agent in the overall study population, an increased risk of incident AF associated with randomized treatment was observed in selected subgroups. For omega-3 fatty acids, AF risk

Figure 4. Effect of Vitamin D$_3$ on the Primary End Point in Prespecified Subgroups

Subgroup	Vitamin D$_3$ No. of events	Total person-y	Events per 1000 person-y	Placebo No. of events	Total person-y	Events per 1000 person-y	Absolute rate difference	Hazard ratio (95% CI)[a]	P value for interaction
Age, median, y									
<66.7	138	32173	4.29	97	32408	2.99	1.30	1.44 (1.11-1.86)	.02
≥66.7	331	32873	10.07	334	32730	10.20	-0.14	0.99 (0.85-1.15)	
Sex									
Male	259	32058	8.08	236	32145	7.34	0.74	1.10 (0.93-1.32)	.86
Female	210	32988	6.37	195	32992	5.91	0.46	1.08 (0.89-1.31)	
Race									
Non-Hispanic White	401	45216	8.87	371	45275	8.19	0.67	1.08 (0.94-1.25)	
African American	26	12855	2.02	26	12876	2.02	0.00	0.99 (0.58-1.71)	.68
Other/unknown[b]	33	5599	5.89	25	5540	4.51	1.38	1.35 (0.80-2.26)	
Smoking									
Never	200	33289	6.01	200	33614	5.95	0.06	1.01 (0.83-1.23)	
Past	241	26309	9.16	202	26052	7.75	1.41	1.18 (0.98-1.42)	.50
Current	21	4489	4.68	17	4533	3.75	0.93	1.25 (0.66-2.38)	
History of hypertension									
No	181	31639	5.72	158	31359	5.04	0.68	1.14 (0.92-1.41)	.65
Yes	286	33003	8.67	271	33499	8.09	0.58	1.07 (0.91-1.27)	
Diabetes									
No	398	55892	7.12	376	56384	6.67	0.45	1.07 (0.93-1.23)	.36
Yes	70	9025	7.76	53	8658	6.12	1.63	1.26 (0.89-1.81)	
Body mass index									
<25	128	19740	6.48	129	19919	6.48	0.01	1.03 (0.81-1.32)	
25 to <30	160	25459	6.28	171	25617	6.68	-0.39	0.92 (0.75-1.15)	.09
≥30	168	18352	9.15	121	18104	6.68	2.47	1.36 (1.07-1.71)	
Height, median, in									
<67	159	28745	5.53	148	28668	5.16	0.37	1.07 (0.85-1.33)	.81
≥67	299	35075	8.52	276	35272	7.82	0.70	1.10 (0.94-1.30)	
Weight, median, lb									
<176	189	32089	5.89	185	32422	5.71	0.18	1.03 (0.85-1.27)	.51
≥176	277	32558	8.51	243	32316	7.52	0.99	1.13 (0.95-1.34)	
CHA$_2$DS$_2$-VASc score[c]									
0	27	7825	3.45	20	7673	2.61	0.84	1.33 (0.75-2.38)	
1	73	15747	4.64	69	16316	4.23	0.41	1.11 (0.80-1.54)	.53
≥2	369	41474	8.90	342	41148	8.31	0.59	1.07 (0.93-1.24)	
Alcohol intake, drinks/d									
≥2	73	8963	8.14	93	9089	10.23	-2.09	0.80 (0.59-1.08)	
1	63	7390	8.53	62	7593	8.17	0.36	1.01 (0.71-1.43)	.01
<1	329	47597	6.91	271	47477	5.71	1.20	1.23 (1.04-1.44)	
All fish intake, median, servings/wk									
<1.5	250	34223	7.31	233	34039	6.84	0.46	1.07 (0.90-1.28)	.85
≥1.5	214	29746	7.19	197	30070	6.55	0.64	1.10 (0.91-1.34)	
Baseline supplemental vitamin D$_3$ use[d]									
No	228	37413	6.09	219	37306	5.87	0.22	1.05 (0.88-1.27)	.58
Yes	241	27633	8.72	212	27832	7.62	1.10	1.13 (0.94-1.36)	
Omega-3 baseline blood level, median, %									
<2.5	171	19713	8.67	164	19731	8.31	0.36	1.03 (0.83-1.28)	.65
≥2.5	162	19538	8.29	149	19663	7.58	0.71	1.11 (0.89-1.39)	
Vitamin D baseline blood level, median, ng/mL									
<31	154	19535	7.88	155	19959	7.77	0.12	1.03 (0.82-1.29)	.49
≥31	185	20451	9.05	158	19988	7.90	1.14	1.14 (0.93-1.41)	
Vitamin D deficiency									
Yes (<20 ng/mL)	29	4878	5.94	36	5159	6.98	-1.03	0.88 (0.54-1.44)	.36
No (≥20 ng/mL)	310	35107	8.83	277	34788	7.96	0.87	1.11 (0.94-1.31)	
EPA-DHA treatment group									
Placebo	231	32557	7.10	200	32685	6.12	0.98	1.16 (0.96-1.40)	.39
Active	238	32489	7.33	231	32453	7.12	0.21	1.03 (0.86-1.24)	

Favors vitamin D$_3$ — Favors placebo

Hazard ratio (95% CI) — 0.5, 1, 3

[a] Cox regression models controlled for age, sex, and randomization group; interactions tested using multiplicative interaction terms.

[b] Includes Hispanic, Asian/Pacific Islander, Native American/Alaska Native, and other, multiple, or unspecified race/ethnicity.

[c] CHA$_2$DS$_2$-VASc score estimates stroke risk in patients with atrial fibrillation (see Table 1 footnote "d" for details). Risk factors were self-reported at baseline. Scores ranged from 0 to 8 in this study.

[d] Restricted to ≤800 IU/d from all sources combined.

was modestly increased in taller individuals, and for vitamin D_3, elevations in AF risk were observed in younger individuals and participants who drank less alcohol. Although the HRs and tests for interaction were significant, the *P* values associated with these subgroup analyses have not been adjusted for multiple comparisons. Thus, these findings should be interpreted with caution and considered hypothesis generating.

The present study had several strengths, including the large general population sample with equal representation of women and oversampling of Black study participants, long duration of double-blind randomized treatment, high levels of treatment adherence, and prospective rigorous adjudication of AF end points. To our knowledge, this study is the first randomized, placebo-controlled trial to prospectively test the effect of any intervention on incident AF and is the only trial to test alternative upstream preventive agents for AF in a large enough population over a long enough time period to provide an assessment of the plausible benefits and risks. The study, which was performed by leveraging the infrastructure of the parent trial, illustrates how future trials might be designed to assess the effect of interventions that might jointly affect AF and CVD at marginal additional cost.

Limitations

This study has several limitations. First, despite best efforts to ascertain AF events by 2 methods (self-report and CMS linkage) and obtain records to confirm clinically manifest AF end points with a high degree of specificity within this large pragmatic trial, there is undoubtedly some underdetection of AF,

particularly if asymptomatic or of short duration. However, the proportion of asymptomatic and paroxysmal AF in this study was comparable with that found in a recent trial of patients with newly diagnosed AF identified through traditional methods.[37] It has also become recognized that some AF events may only be detected through screening[38]; however, the clinical significance of these screen-detected AF events is currently unknown.[38,39] Second, the doses of the study agents were chosen based on hypothesized efficacy for prevention of CVD and cancer and not specifically for AF. However, the doses of both agents used in the trial are similar to or greater than that associated with benefit on AF in observational studies,[6,8] and for EPA-DHA, recent literature suggests potential harm at greater doses.[12,13] Third, these results may not be generalizable to younger populations or to patients with established CVD. Fourth, effects on atrial structural and electrical remodeling may take longer than the present study duration to affect AF events. Fifth, even with the large sample size and large number of events, the power to detect small elevations and/or reductions in AF risk was limited.

Conclusions

Among adults aged 50 years or older, treatment with EPA-DHA or vitamin D_3, compared with placebo, resulted in no significant difference in the risk of incident AF over a median follow-up of more than 5 years. The findings do not support the use of either agent for the primary prevention of incident AF.

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Editor's Note

Omega-3 Fatty Acids and Atrial Fibrillation

Gregory Curfman, MD

In 2019, the global market for omega-3 fatty acids reached $4.1 billion, and it is expected to double by 2025.[1] These impressive expenditures reflect the worldwide popularity of these products and the belief by many that omega-3 fatty acids are beneficial to their health. Although the health benefits of these products remain questionable, it is important for consumers who take them to understand their potential risks. In this issue of *JAMA*, the VITAL Rhythm Study[2] examined the risk of atrial fibrillation (AF), the most common cardiac arrhythmia, with intake of omega-3 fatty acids.

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In the past 2 years, 4 randomized clinical trials have provided data on the risk of AF with omega-3 fatty acid intake. In the STRENGTH trial,[3] 13 078 high-risk patients with cardiovascular disease were randomized to receive a high dose, 4 g/d, of a carboxylic acid formulation of omega-3 fatty acids (a combination of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or corn oil. After a median of 42 months, there was no significant difference between the 2 randomized groups in the primary composite cardiovascular end point, but there was an increase in risk of developing AF in the omega-3 fatty acids group compared with the corn oil group (2.2% vs 1.3%; hazard ratio, 1.69; 95% CI, 1.29-2.21; $P < .001$).

In the REDUCE-IT trial,[4] 8179 participants were randomized to a high dose (4 g/d, as in STRENGTH) of an omega-3 fatty acid preparation consisting of purified EPA (icosapent ethyl) or mineral oil. After a median follow-up of 4.9 years, icosapent ethyl resulted in a 25% relative reduction in the primary composite cardiovascular end point compared with mineral oil. As in STRENGTH, there was a significant increase in risk of AF with omega-3 fatty acids compared with mineral oil (5.3% vs 3.9%; $P = .003$).

In a third clinical trial, OMEMI,[5] 1027 older patients who had had a recent myocardial infarction were randomized to receive an intermediate dose, 1.8 g/d, of omega-3 fatty acids (a combination of EPA and DHA) or corn oil. After 2 years, there was no significant difference between the 2 groups in the primary composite cardiovascular end point, but 7.2% of the omega-3 fatty acids group vs 4.0% of the corn oil group developed AF (hazard ratio, 1.84; 95% CI, 0.98-3.45; $P = .06$).

In the VITAL Rhythm Study,[2] published in this issue of *JAMA*, 12 542 participants were randomized to receive a standard dose of omega-3 fatty acids, 840 mg/d (a combination of EPA and DHA) and 12 557 to receive placebo. After a median of 5.3 years, the incidence of AF was 7.2 per 1000 person-years in those taking omega-3 fatty acids vs 6.6 per 1000 person-years in those taking placebo (hazard ratio, 1.09; 95% CI, 0.96-1.24; $P = .19$).

Considered together, the data from the 4 trials suggest, but do not prove, that there may be a dose-related risk of AF with omega-3 fatty acid intake. At a dose of 4.0 g/d, there was a highly statistically significant increase in risk (nearly a doubling). With an intermediate dose of 1.8 g/d, the increase in risk (hazard ratio, 1.84) did not achieve statistical significance, and with a standard daily dose of 840 mg/d, there was no apparent increase in risk (although the data were consistent with as much as a 24% increase in risk). Patients who choose to take omega-3 fatty acids, especially in high doses, should be informed of the risk of AF and followed up for the possible development of this common and potentially hazardous arrhythmia.

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