

The Vital Rhythm Trial: Omega-3 Fatty Acid and Vitamin D Supplementation in the Primary Prevention of Atrial Fibrillation

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Disclosures

- The VITAL Rhythm Trial was supported by a grant from National Heart, Lung and Blood Institute (R01HL116690), and the VITAL Trial was supported by grants U01 CA138962 and R01 CA138962, which included support from the National Cancer Institute, National Heart, Lung and Blood Institute, Office of Dietary Supplements, National Institute of Neurological Disorders and Stroke, and the National Center for Complementary and Integrative Health.
- Pharmavite LLC (vitamin D3) and Pronova BioPharma/BASF (Omacor fish oil) donated the study agents, matching placebos, and packaging in the form of calendar packs.
- Dr. Albert reports receiving grant support from St. Jude Medical, Abbott, and Roche Diagnostics.
- Dr. Mora has served as a consultant to Quest Diagnostics and Pfizer. Dr Buring reported that her spouse is on the scientific advisory board of Pharmavite LLC; and receiving personal fees from Pharmavite. Dr Manson reported receiving grants from Mars Symbioscience.



Rationale

- Atrial Fibrillation (AF) is the most common, and growing, heart rhythm disturbance, estimated to affect 33 million people worldwide.
- AF results in significant symptoms that can markedly reduce quality of life, and patients with AF are at elevated risk for stroke, heart failure, myocardial infarction, dementia, and even death.
- Current treatment options, which are employed relatively late in the disease process after AF is established, are associated with significant risks and limited long-term success.
- Despite the pressing need for primary preventive strategies, AF primary prevention randomized controlled trials (RCTs) have not been performed, largely due to concerns regarding feasibility.
- Dietary supplements have appeal in primary prevention given the relative ease of administration to broad populations.
- Both marine omega-3 fatty acids and vitamin D have been implicated in upstream biologic processes involved in electrical and structural remodeling of the atria-- and ---patients with low levels of these nutrients tend to have greater AF risk in observational studies.



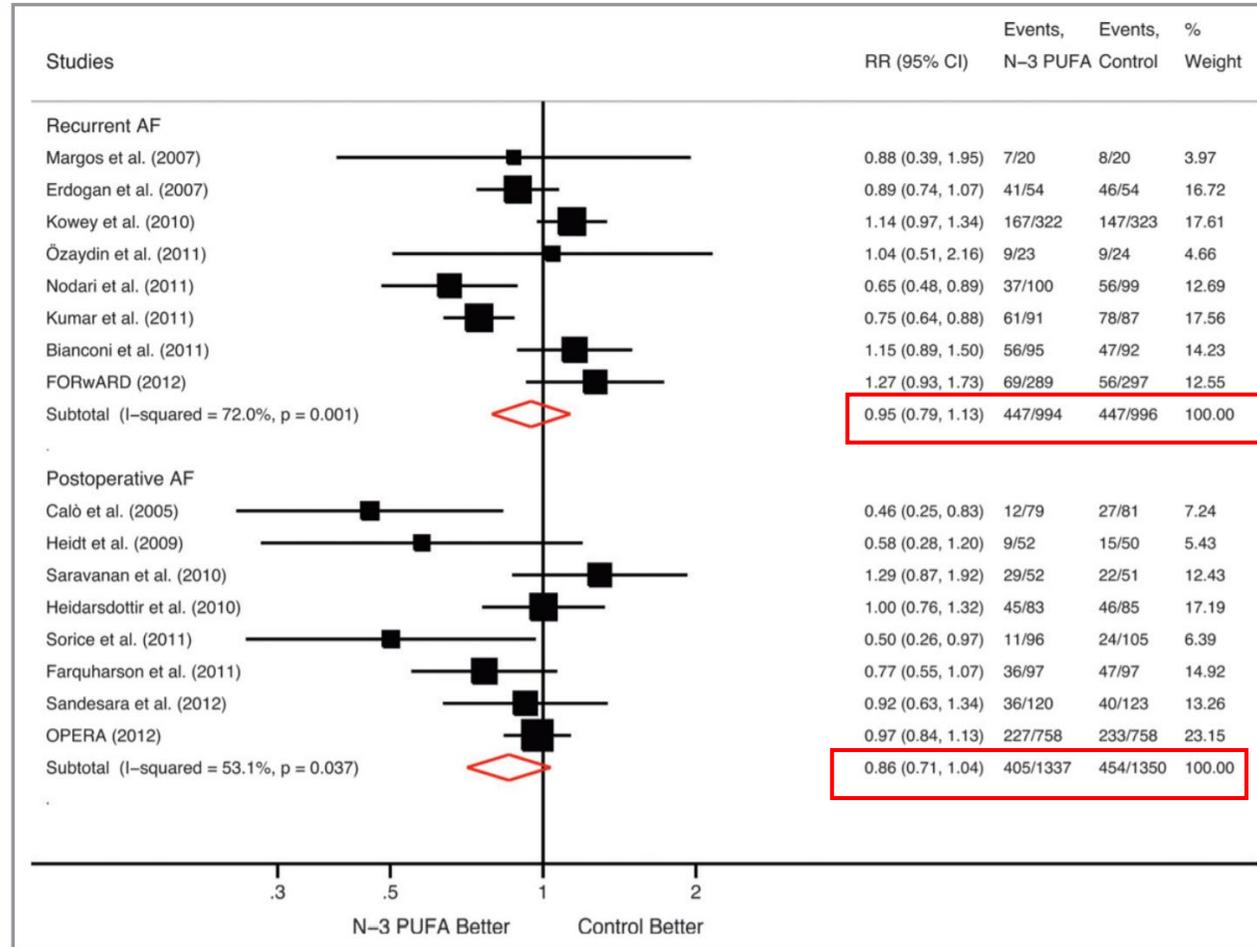
Omega-3 Fatty Acid and AF Randomized Clinical Trials

Recurrent AF

~2000 patients

Post-operative AF

~2700 patients



VITAL RHYTHM TRIAL DESIGN

- The VITAL Rhythm Study (NCT02178410) is ancillary trial of the VITAL trial (NCT01169259), a primary prevention trial of CVD and cancer performed among 25,871 men and women in the United States.
- Double-blind, placebo-controlled randomized trial that tested in a 2x2 factorial design daily supplementation with 2000 IU of vitamin D3 and/or 840 mg of omega-3 fatty acids (Omacor 1g/d; 460 mg EPA + 380 mg of DHA).
- 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 --and --- all were required to have no prior history of CVD, cancer, or AF.
- Pragmatic, mail-based design: Baseline and annual follow-up questionnaires collected information on health status and pill packs containing study agents were distributed by mail.
- AF endpoint: Participants were asked to report new diagnoses of AF on annual follow-up questionnaires and provided permission to review CMS claims data for AF, and then these AF events were then confirmed by medical record review.





VITAL Heart Rhythm Study Population

	Total (N = 25119)	
Age, mean (SD), y	67.0 (7.1)	
	Number	Percent
Sex		
Male	12362	49.2
Female	12757	50.8
Race/Ethnicity^b		
Non-Hispanic/Latinx white	17425	69.4
African American	5052	20.1
Other or unknown	2642	10.5
Hypertension	12911	51.7
Diabetes	3442	13.7
Current Smoker	1798	7.3



Incident AF Events

Primary Endpoint:

*Over 5.3 years of treatment,
900 AF (3.6% of the population)
had a confirmed AF event*

*The study had 92% power to
detect a 20% reduction or increase
in the observed hazard ratio for
incident AF*

AF confirmation	No. (%)
ECG	656 (72.9)
Medical record report	244 (27.1)

Type of AF	No. (%)
Paroxysmal	526 (58.4)
Persistent	346 (38.4)
Unable to be classified	28 (3.1)

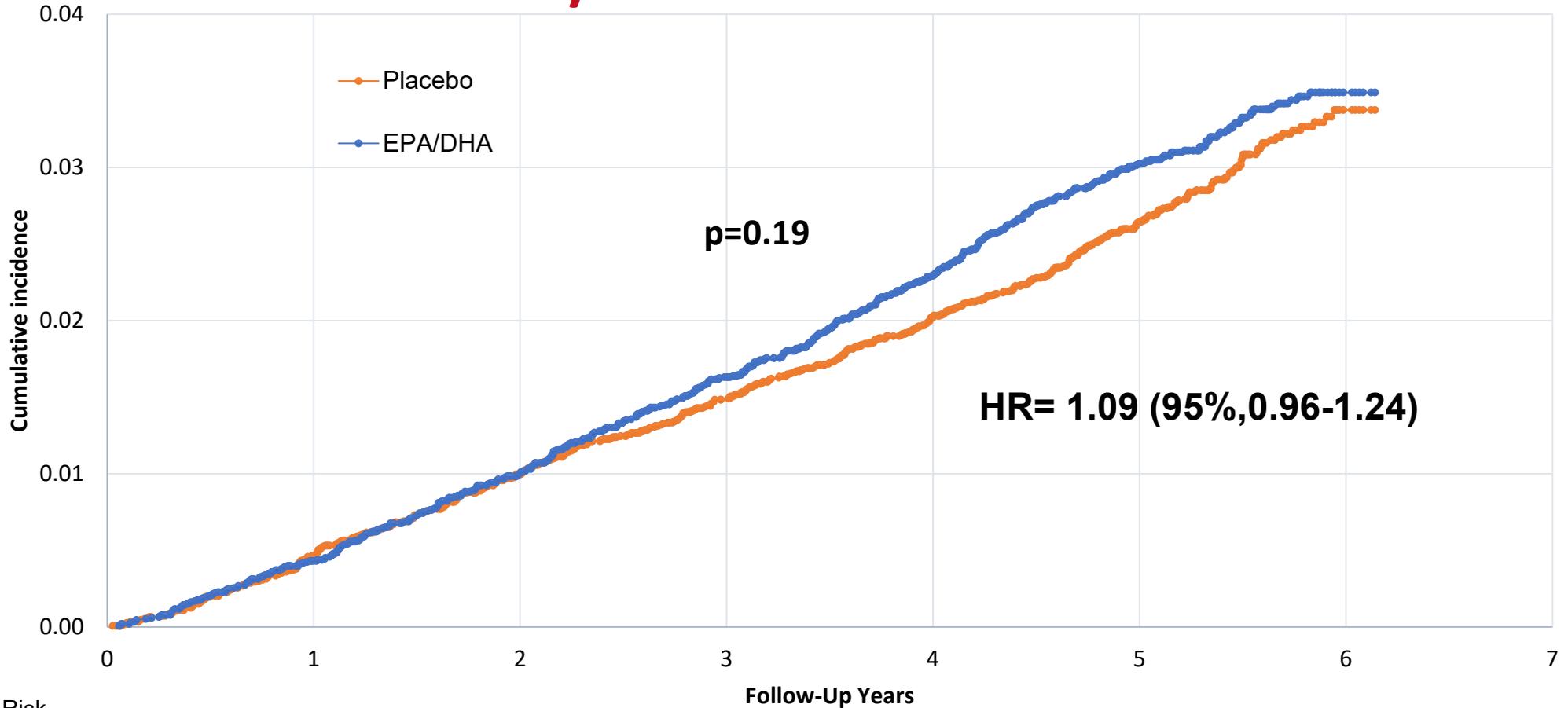
Symptoms present at diagnosis	No. (%)
Yes	557 (61.9)
No	247 (27.4)
Unclear	96 (10.7)
Symptoms may have preceded randomization	58 (6.4)

AF post-cardiac surgery	66 (7.3)
Atrial flutter only	52 (5.8)





Intention to Treat EPA/DHA and Incident Atrial Fibrillation



No. at Risk

	0	1	2	3	4	5	6
Placebo	12577	12476	12328	12165	11858	9456	887
EPA/DHA	12542	12434	12276	12102	11800	9411	869





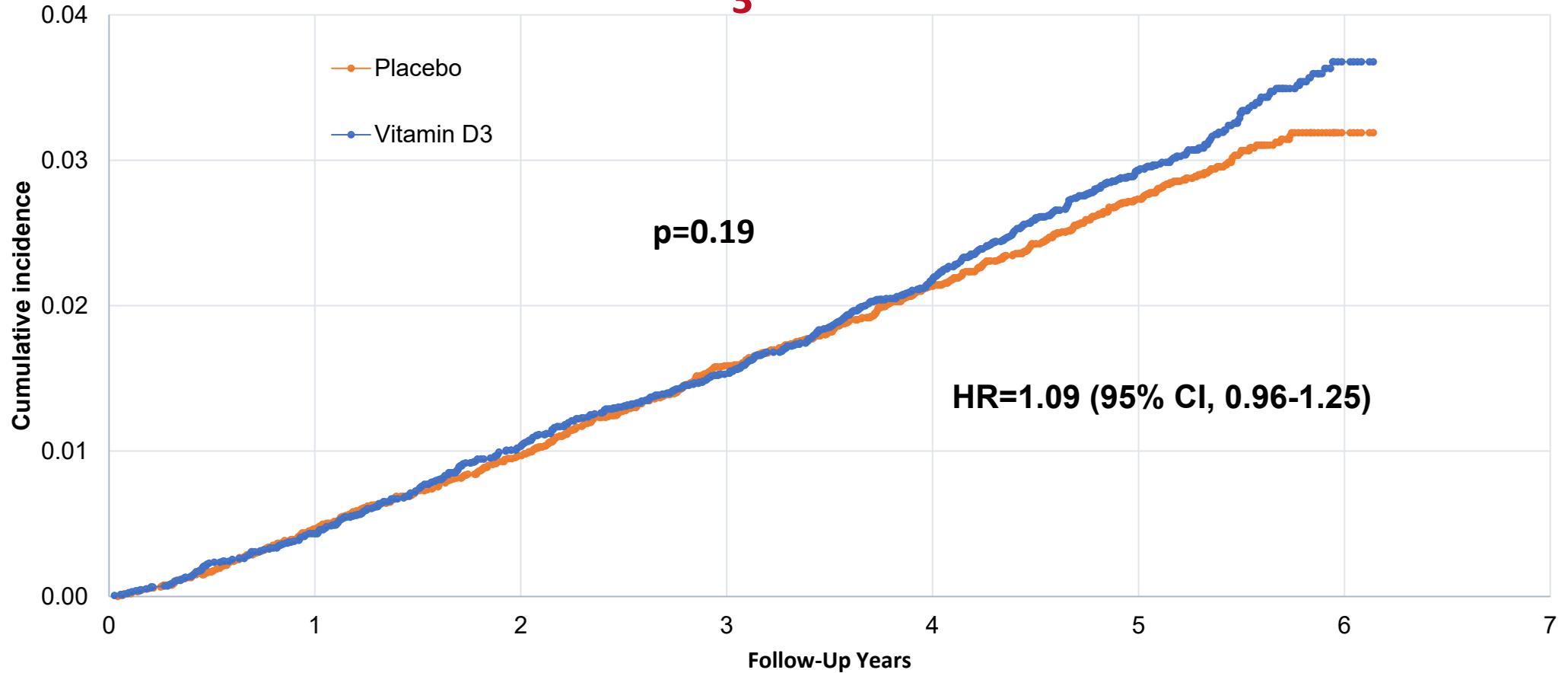
Omega-3 Fatty Acids and Incident AF

End Points	EPA/DHA (n=12542)	Placebo (n=12577)	Hazard Ratio (95% CI)	P value
Primary Endpoint				
All Incident AF	469	431	1.09 (0.96-1.24)	0.19
Sensitivity Analyses				
Excluding AF events with symptoms prior to randomization	440	402	1.10 (0.96-1.26)	0.17
Excluding AF events detected by CMS linkage	389	345	1.13 (0.98-1.31)	0.10
Excluding atrial flutter alone and post-operative AF	410	374	1.10 (0.96-1.27)	0.18
On Treatment Analysis	403	358	1.13 (0.98-1.30)	0.09
Secondary Endpoints				
Paroxysmal AF	271	255	1.07 (0.90-1.27)	0.46
Non-Paroxysmal AF	182	164	1.11 (0.90-1.37)	0.32





Intention to Treat Vitamin D₃ and Incident Atrial Fibrillation



No. at Risk

Placebo	12566	12461	12312	12134	11831	9433	870
Vitamin D ₃	12553	12449	12290	12131	11828	9435	886





Vitamin D₃ and Incident AF

End Points	EPA/DHA (n=12553)	Placebo (n=12566)	Hazard Ratio (95% CI)	P value
Primary Endpoint				
All Incident AF	469	431	1.09 (0.96-1.24)	0.19
Sensitivity Analyses				
Excluding AF events with symptoms prior to randomization	438	404	1.09 (0.95-1.25)	0.22
Excluding AF events detected by CMS linkage	373	361	1.04 (0.90-1.20)	0.60
Excluding atrial flutter alone and post-operative AF	404	380	1.07 (0.93-1.23)	0.36
On Treatment Analysis	383	336	1.09 (0.94-1.27)	0.24
Secondary Endpoints				
Paroxysmal AF	267	259	1.03 (0.87-1.23)	0.76
Non-Paroxysmal AF	188	158	1.20 (0.97-1.48)	0.10



Limitations

Lack of monitoring (screening) for AF:

- AF events in VITAL Heart Rhythm had to be **clinically detected**, and we know from recent studies that there is a proportion of AF that is only detected by monitoring, **screen-detected AF**.
 - Clinical significance of these screen-detected AF events is unknown
 - Any under-detection should be balanced due to randomization

Fixed, Single Dose of Supplements

May not be generalizable to patients with established CVD or younger populations.

Power to detect small elevations and/or reductions in AF risk was limited



Conclusions

VITAL Heart Rhythm:

- Supplementation with 840 mg/day of marine omega-3 fatty acids (EPA/DHA; 1.2:1 ratio) and/or 2000 IU/day of vitamin D₃ did not reduce (or increase) incident AF over a median treatment duration of 5.3 years.
- Our findings do not support the use of either EPA/DHA or vitamin D₃ for prevention of incident AF.
- Future primary prevention AF trials are needed to test other promising strategies.

