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The effect of vitamin D_3 supplementation on atrial fibrillation in generally healthy men and women: The Finnish Vitamin D Trial

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Atrial fibrillation is a common cardiac arrhythmia with high morbidity risk. Observational studies suggest that vitamin D deficiency is associated with higher atrial fibrillation risk but there is limited evidence whether vitamin D supplementation could affect the risk. In these post hoc analyses from the Finnish Vitamin D Trial, we compared the incidence of atrial fibrillation with 5-year supplementation of vitamin D_3 (1600 IU/d or 3200 IU/d) vs placebo.

Clinical Trial Registry number ClinicalTrials.gov: NCT01463813, https://clinicaltrials.gov/ct2/show/NCT01463813 (Am Heart J 2023;000:1–6.)

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adulthood, increasing in prevalence with age and carrying a major burden of morbidity. Therefore, with aging populations, methods to decrease AF risk are needed.

Mechanistic studies suggest a role for vitamin D deficiency in the pathogenesis of AF,[1] and in observational studies vitamin D deficiency has been associated with increased AF risk.[2] However, only a few randomized clinical trials (RCT) have investigated whether vitamin D supplementation could reduce AF risk in general populations. In the Women's Health Initiative (WHI), vitamin D_3 supplementation of 400 IU/d with calcium 1,000 mg/d for a mean 4.3 years did not have an effect on the AF risk.[3] Similarly, in the recent Vitamin D and Omega-3 Trial (VITAL) Rhythm Study, supplementation with 2,000 IU/d of vitamin D_3 did not affect the AF risk over 5.3 years.[4]

The aim of the current analysis was to investigate the effects of 5-year vitamin D_3 supplementation with 1,600 IU/d or 3,200 IU/d on AF risk, compared to placebo, among generally healthy men and women in the Finnish Vitamin D Trial (FIND).

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Methods

Trial design

FIND was a 5-year randomized, double-blind, placebo-controlled supplementation trial of the effects of vitamin D_3 on the incidence of cardiovascular diseases (CVD) and cancer among generally healthy white male and female participants from the general Finnish population. The intervention period ran in September 2012 to October 2018. The design of the study has been described in detail previously.[5] In brief, the inclusion criteria were: male participants aged ≥60 years and postmenopausal female participants aged ≥65 years without history of cancer (except nonmelanoma skin cancer) or CVD (including myocardial infarction, stroke, transient ischemic attack, angina pectoris, coronary artery bypass grafting, or percutaneous coronary intervention). The exclusion criteria were: history of kidney stones, renal failure or dialysis, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis; use of vitamin D >800 IU/d or calcium >1,200 mg/d from all supplemental sources combined (or if taking, willing to decrease or forego such use during the trial).

The recruitment yielded in total 2,495 participants, who were randomized to receive either (1) 1,600 IU/d of vitamin D_3, (2) 3,200 IU/d of vitamin D_3, or (3) placebo (Figure 1). A random sub-cohort of 551 participants participated in the more detailed baseline examinations,

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Table I. Baseline characteristics of the participants.

Characteristic	Overall (n = 2,495)	Placebo arm (n = 830)	Vitamin D_3 1600 IU/d arm (n = 832)	Vitamin D_3 3200 IU/d arm (n = 833)
Female sex, n (%)	1,069 (42.8)	372 (44.8)	349 (41.9)	348 (41.8)
Age, mean (SD), y	68.2 (4.5)	68.2 (4.5)	68.1 (4.5)	68.3 (4.4)
Age group, n (%)				
60-64 y*	620 (24.8)	202 (24.3)	209 (25.1)	209 (25.1)
65-69 y	1089 (43.6)	373 (44.9)	358 (43.0)	358 (43.0)
70-74 y	589 (23.6)	186 (22.4)	203 (24.4)	200 (24.0)
≥75 y	197 (7.9)	69 (8.3)	62 (7.5)	66 (7.9)
Employment status, n (%)	n = 2,469	n = 823	n = 824	n = 822
Full-time work	201 (8.1)	76 (9.2)	61 (7.4)	64 (7.8)
Part-time work	95 (3.8)	27 (3.3)	38 (4.6)	30 (3.6)
Unemployed	61 (2.5)	14 (1.7)	25 (3.0)	22 (2.7)
Retired	2,097 (84.9)	703 (85.4)	692 (84.0)	702 (85.4)
Not working for other reasons	15 (0.6)	3 (0.4)	8 (1.0)	4 (0.5)
Leisure-time physical activity, mean (SD), h/wk†				
Light	13.1 (10.8) (n = 2,172)	13.1 (10.9) (n = 712)	13.3 (11.2) (n = 721)	12.8 (10.5) (n = 739)
Heavy	5.7 (6.5) (n = 1,601)	5.6 (6.3) (n = 525)	5.8 (6.6) (n = 532)	5.9 (6.5) (n = 544)
Smoking regularly‡, n (%)	885 (35.7) (n = 2477)	292 (35.4) (n = 825)	300 (36.5) (n = 823)	293 (35.3) (n = 829)
Education, n (%)	n = 2,483	(n = 827)	(n = 827)	(n = 829)
Vocational education	794 (32.0)	282 (34.1)	271 (32.8)	241 29.1)
At least high school diploma	417 (16.8)	135 (16.3)	149 (18.0)	133 (16.0)
Married, n (%)	1,849 (74.7) (n = 2476)	620 (75.2) (n = 824)	606 (73.5) (n = 825)	623 (75.3 (n = 827)
Body mass index, mean (SD), kg/m†	27.1 (4.3)	27.2 (4.3)	27.1 (4.3) (n = 832)	26.9 (4.3)
	(n = 2491)	(n = 828)		(n = 831)
Alcohol intake, mean (SD), g/d	7 (13)	8 (16)	7 (11)	7 (11)
	(n = 2,464)	(n = 824)	(n = 818)	(n = 822)
Vitamin D intake from diet, mean (SD), IU/d	428 (312)	416 (260)	456 (384)	420 (280)
	(n = 2,464)	(n = 824)	(n = 818)	(n = 822)
Use of own vitamin D supplements, n (%)				
Not at all	1,670 (66.9)	535 (64.5)	566 (68.0)	569 (68.3)
200-400 IU/d	361 (14.5)	133 (16.0)	104 (12.5)	124 (14.9)
>400 - <800 IU/d	74 (3.0)	27 (3.3)	26 (3.1)	21 (2.5)
800 IU/d	390 (15.6)	135 (16.3)	136 (16.3)	119 (14.3)
Daily medication use, n (%)	1,736 (70.1) (n = 2,476)	597 (72.3) (n = 826)	559 (67.9) (n = 823)	580 (70.1) (n = 827)
Antiarrhythmic medication, n (%)	122 (4.9) (n = 2,476)	45 (5.4) (n = 826)	48 (5.8) (n = 823)	29 (3.5) (n = 827)
Hypertension medication, n (%)	1,047 (42.3) (n = 2,476)	353 (42.7) (n = 826)	344 (41.8) (n = 823)	350 (42.3) (n = 827)
Statin medication, n (%)	717 (29.0) (n = 2,476)	255 (30.9) (n = 826)	218 (26.5) (n = 823)	244 (29.5) (n = 827)
Diabetes medication, n (%)	222 (9.0) (n = 2,476)	68 (8.2) (n = 826)	89 (10.8) (n = 823)	65 (7.9) (n = 827)
Self-rated health good or excellent, n (%)	1,460 (59.2) (n = 2,467)	460 (56.0) (n = 822)	493 (60.3) (n = 818)	507 (61.3) (n = 827)

* All are men in this age group.
† Light activity defined as gardening and other light outdoor activities etc., heavy activity defined as physical exercise that causes sweating or heavy breathing.
‡ Smoking regularly defined as smoking almost every day during the last year.

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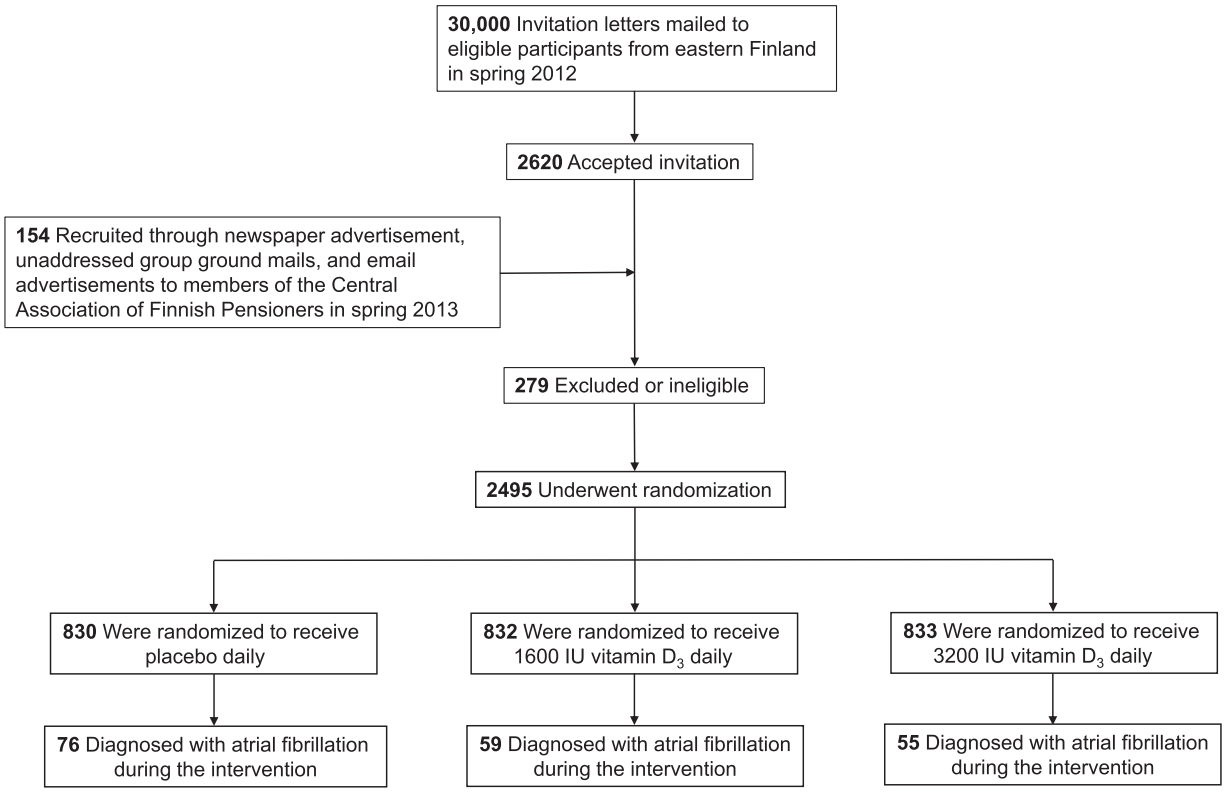
Figure 1



Participant flow chart.

with 512, 533, and 496 participants attending follow-up visits after 6, 12, and 24 months, respectively.[5] Gender-stratified simple randomization in 1:1:1 ratio was carried out by a nonstudy group statistician, based on computerized random number generation.

The study pills were purchased from Galena Pharma Ltd (Kuopio, Finland). The pills contained either 0, 1,600 IU or 3,200 IU of vitamin D_3 per pill. The pills were annually either mailed to the participants or given at study visits. Double-blinding was maintained throughout the study.

The participants completed questionnaires at baseline, after 12, 24, and 36 months and at the trial's end at 60 months.[5] At baseline, 36 and 60 months the questionnaire also included a validated 142-item food-frequency questionnaire. Adherence was assessed with the question "How much of the study pills did you take during the study?" in the final questionnaire. Choices ranged from "<50%" to "100% or almost 100%." Body mass index was calculated based on the weight and height reported in the baseline questionnaire. Serum 25(OH)D_3 concentrations were measured using high-performance liquid chromatography from the samples collected at the baseline ($n = 550$) and after 6 ($n = 511$) and 12 ($n = 532$) months.[5]

All participants were volunteer adults who were entitled to withdraw from the study at any time without explanation. All participants signed a written informed consent. The appropriate study approvals were obtained from the Ethics committee of the Kuopio University Hospital (#30/2010) and from the National Institute for Health and Welfare.

Assessment of AF

AF diagnosis referred to the International Classification of Diseases, 10th Revision code I48. The codes and dates of diagnosis were gathered from 3 national registries: Care Register that records hospital admissions and specialized medical care visits (Data Agreement THL/523/5.05.00/2020), Register of Primary Health Care Visits (THL/523/5.05.00/2020), and Causes of Death Register (TK/1007/07.03.00/2022).

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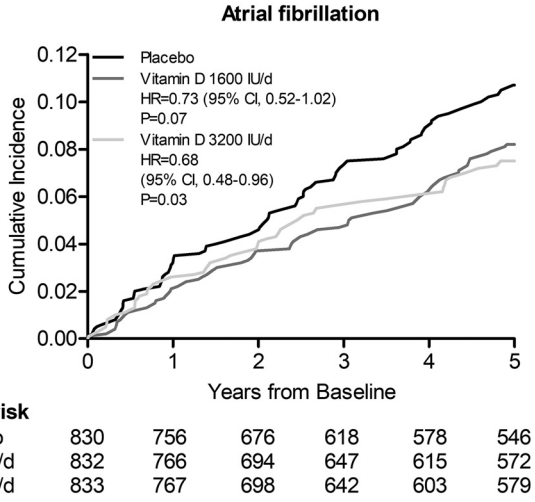
Table II. Hazard of atrial fibrillation in the 3 supplementation arms.

	Placebo ($n = 830$)	1,600 IU/d ($n = 832$)	*P* value	3,200 IU/d ($n = 833$)	*P* value	Combined vitamin D arms vs placebo	*P* value
All participants							
Person-years	3,316.9	3,432.8		3,414.5			
Events, *n*	76	59		55			
Events per 100 person-years	2.29	1.72		1.61			
Hazard ratio (95% confidence interval)	1	0.73 (0.52-1.02)*	.07	0.68 (0.48-0.96)	.03	0.70 (0.53-0.94)	.02
After exclusion of 94 participants with atrial fibrillation diagnosis within the first 2 y of follow-up							
Person-years	3,290.1	3,404.7		3,390.6			
Events, *n*	41	30		25			
Events per 100 person-years	1.25	0.88		0.74			
Hazard ratio (95% confidence interval)	1	0.68 (0.43-1.09)	.11	0.57 (0.35-0.94)	.03	0.63 (0.42-0.94)	.02
After exclusion of 122 participants reporting use of antiarrhythmic medication at baseline							
Person-years	3,175.5	3,288.7		3,328.9			
Events, n	55	37		42			
Events per 100 person-years	1.73	1.13		1.26			
Hazard ratio (95% confidence interval)	1	0.63 (0.42-0.96)	.03	0.70 (0.47-1.05)	.08	0.67 (0.47-0.94)	.02

*Values are from Cox regression analysis, adjusted for age and sex.

Figure 2



Cumulative incidence of atrial fibrillation in the 3 study arms.

Statistical analysis

AF was not a prespecified end point, so the results should be considered as exploratory. Cox proportional hazards regression models were used to predict hazard of AF. Because of the low number of events, we also analyzed the effects after combining the 2 vitamin D arms. Participants contributed follow-up time from randomization until AF diagnosis, death, end of the 5-year follow-up, or withdrawing from the study due to personal reasons ($n = 412$). The models were adjusted for age and sex. IBM SPSS version 27 was used for analyses. Two-sided $P < .05$ was used to determine statistical significance.

Results

The study arms were in balance according to the baseline characteristics (Table I). The mean age of the participants was 68.2 years, and 57% were men. In the sub-cohort with available data, the mean ± SD serum 25(OH)D concentration was 75 ± 18 nmol/L (30 ± 7 ng/mL) (P-difference between the arms = 0.72). After 12 months, the mean ± SD concentrations were 73 ± 18, 100 ± 21 and 120 ± 22 nmol/L in the placebo, 1,600 IU/d and 3,200 IU/d arms, respectively ($P < .001$).

During the mean follow-up of 4.1 years (SD 1.5 years, 10,164.2 person-years), 190 participants were diagnosed with AF. The absolute incidence rate difference was 0.57 (95% CI -−0.10 to 1.25) per 100 person-years between the placebo and 1,600 IU/d arms and 0.68 (95% CI 0.01-1.35) per 100 person-years between the placebo and 3,200 IU/d arms. Compared to the placebo arm, the AF risk was 27% (95% CI −2% to 48%) lower in the partici-

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pants who received 1,600 IU/d vitamin D_3 and 32% (95% CI 4%-52%) lower in the participants who received 3,200 IU/d vitamin D_3 (Table II, Figure 2). In the combined vitamin D arms vs the placebo arm, the risk was decreased by 30% (95% CI 6%-47%) (Table II). The risk reductions were larger after excluding the participants with AF diagnosis during the first 2 years of follow-up (Table II).

We did not have information on participants' AF history, but 122 participants reported using antiarrhythmic medications at baseline (*P*-difference between placebo and 1,600 IU/d arms = 0.75 and between placebo and 3,200 IU/d arms = 0.06). After excluding these participants, those in the 1,600 IU/d vitamin D_3 arm had 27% (95% CI 4%-58%) lower risk of AF diagnosis and those in the 3,200 IU/d arm had statistically nonsignificant 30% (95% CI −5% to 53%) lower risk (Table II).

Discussion

These post hoc analyses suggest that high-dose vitamin D_3 supplementation may reduce incidence of AF in a generally healthy, largely vitamin D sufficient elderly population.

Although observational studies suggest that vitamin D deficiency is associated with higher AF risk,[2] few RCTs have investigated the effect of vitamin D supplementation on AF incidence in healthy people. Among 16,801 postmenopausal women with the mean age of 66.9 years from the WHI, supplementation with 400 IU/d of vitamin D_3 combined with 1,000 mg/d of calcium had no effect on AF incidence, compared to the placebo group, over the average 4.5-year follow-up.[3] The major differences that affect comparability with our study were the lower mean baseline 25(OH)D concentration of 48 nmol/L, much lower vitamin D dose and use of calcium supplementation in addition to vitamin D. In the VITAL Rhythm Study among 25,119 generally healthy men and women with the mean age of 66.7 years and with adjudicated AF cases, 2,000 IU/d of vitamin D_3, with or without 840 mg/d of long-chain omega-3 polyunsaturated fatty acids, did not affect AF incidence over the median follow-up of 5.3 years, either. [4] In VITAL, the mean baseline 25(OH)D of 77 nmol/L was comparable to our study and also the mean concentration after 12 months (104 nmol/L) was comparable to that in our 1,600 IU/d arm.[6] However, the AF incidence rate of ~7 events/1,000 person-years was much lower than in the WHI (~20 events/1,000 person-years) or in our study (~19 events/1,000 person-years). Although several mechanisms have been proposed to explain how vitamin D deficiency can affect pathways relevant to AF development, including catecholamine excess, activation of the renin-angiotensin system, and electrical anomalies,[1] our findings need to be interpreted cautiously as AF was not a prespecified primary outcome and the results differ from those of the other RCTs.

Major strengths of our study include the 2 vitamin D doses, population-based recruitment, and collecting incident AF data from national health records with mostly very good completeness and accuracy.[7,8] Limitations include the lack of information on AF type (paroxysmal/nonparoxysmal) or on participants' AF history at baseline, and lack of adjustment for multiple comparisons. Also, all participants were elderly White men and women from Finland, so the results may not be generalizable to populations with different age-groups and races/ethnicities.

In conclusion, our findings suggest possible benefit in AF prevention with high-dose vitamin D supplementation in an elderly population, despite the relatively high baseline 25(OH)D concentrations. Given the divergent findings from other RCTs, additional RCTs, especially in diverse populations are needed to elucidate the role of vitamin D supplementation in AF prevention.

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Disclosures

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