The Relationship Between Vitamin D and Postoperative Atrial Fibrillation: A Prospective Cohort Study

Amelie H. Ohlrogge[1,2], Jan Brederecke[1], Francisco M. Ojeda[1], Simon Pecha[2,3], Christin S. Börschel[1,2], Lenard Conradi[3], Vanessa Rimkus[1], Stefan Blankenberg[1,2], Tanja Zeller[1,2,4] and Renate B. Schnabel[1,2]*

[1] Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany, [2] German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany, [3] Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, Hamburg, Germany, [4] University Centre of Cardiovascular Science, University Heart and Vascular Center Hamburg, Hamburg, Germany

Background and Aims: The relationship between postoperative atrial fibrillation (POAF) and 25-hydroxyvitamin D [25(OH)D] concentration as well as vitamin D supplementation has been discussed controversially. The relation of pre-operative vitamin D status and POAF remains unclear.

Methods and Results: We analysed the risk of POAF in a prospective, observational cohort study of n = 201 patients undergoing coronary artery bypass graft surgery (CABG) with 25(OH)D concentration. The median age was 66.6 years, 15.4% were women. The median (25th/75th percentile) vitamin D concentration at baseline was 17.7 (12.6/23.7) ng/ml. During follow-up we observed 48 cases of POAF. In age, sex, and creatinine-adjusted analyses, 25(OH)D was associated with an increased risk of POAF, though with borderline statistical significance [odds ratio (OR) 1.85, 95% confidence interval (CI) 0.87–3.92, p-value 0.107], in further risk factor-adjusted analyses the results remained stable (OR 1.99, 95% CI 0.90–4.39, p-value 0.087). The subgroup with vitamin D supplementation at baseline showed an increased risk of POAF (OR 5.03, 95% CI 1.13–22.33, p-value 0.034).

Conclusion: In our contemporary mid-European cohort, higher 25(OH)D concentration did not show a benefit for POAF in CABG patients and may even be harmful, though with borderline statistical significance. Our data are in line with a recent randomised study in community-based adults and call for further research to determine both, the clinical impact of elevated 25(OH)D concentration and vitamin D supplementation as well as the possible underlying pathophysiological mechanisms.

Keywords: atrial fibrillation, postoperative atrial fibrillation, vitamin D, vitamin D supplementation, 25-hydroxyvitamin D

GRAPHICAL ABSTRACT
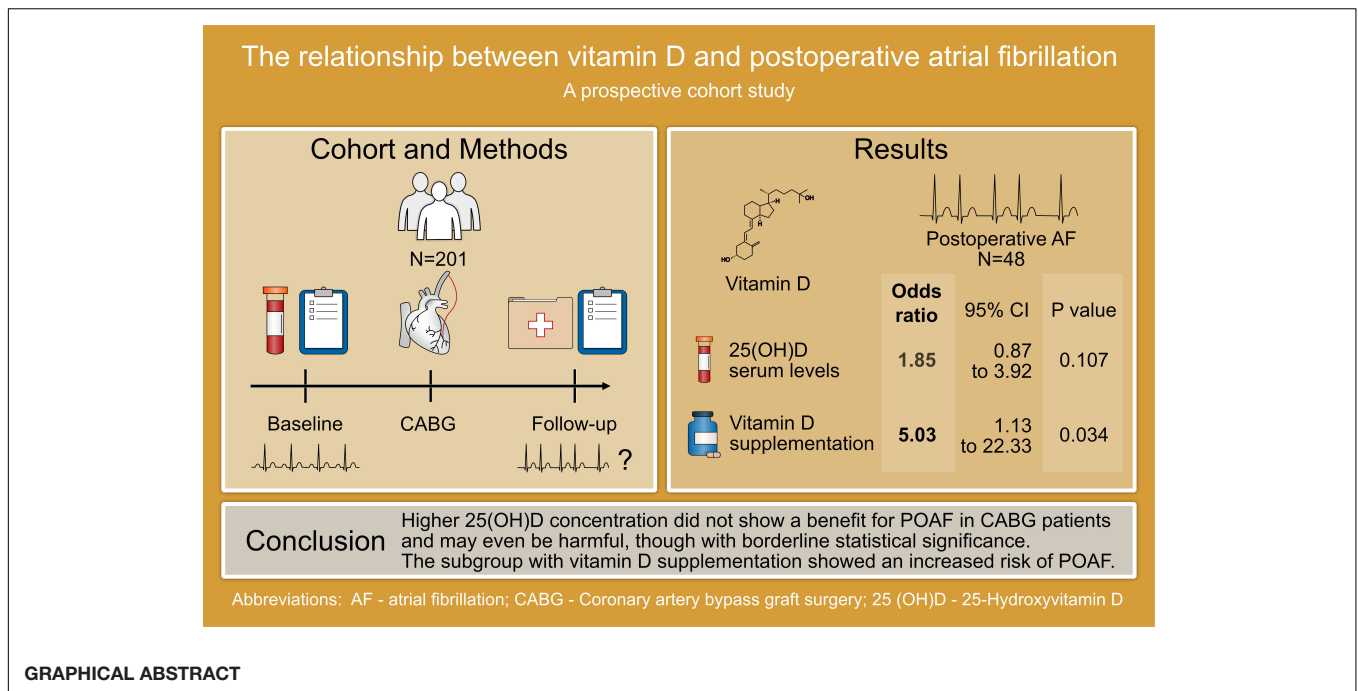
INTRODUCTION

Atrial fibrillation (AF) is a common and serious cardiac arrythmia, with a lifetime risk of 1 in 3 individuals of European ancestry (1, 2). A relevant increase in prevalence is expected due to a longer lifespan and increasing risk factors over the next decades (3, 4). AF is associated with an elevated risk of stroke, heart failure, dementia, and death (5–12). AF often occurs after surgery as postoperative atrial fibrillation (POAF), especially after thoracic and cardiac surgery with incidence rates reported between 20 and 40% for most cardiac surgeries and up to 60% for valve surgery (13–15). The mechanisms of surgery acting as a trigger of AF are not entirely understood. Electrolyte imbalances, inflammation and ischaemia are discussed as triggering factors. POAF increases the length of hospital stay, as well as short- and long-term risk of stroke, mortality and medical costs (16–18). Further, POAF increases the risk of long-term AF about 4–5-fold (17, 19). Understanding the pathophysiology behind the development of AF is key to risk prediction and for potential preventive efforts.

Vitamin D deficiency is a common condition in many societies and influenced, e.g., by geographical latitude and season. Vitamin D status is usually assessed by measuring circulating 25-hydroxyvitamin D [25(OH)D]. Its deficiency is known to be a major risk factor for musculoskeletal diseases; but has also been debated as a risk factor for many other conditions, such as immunologic, endocrine, or cardiovascular. The role of vitamin D and possible benefits of supplementation in AF development has been discussed controversially over the last decade. Whereas smaller, observational studies have shown an association between vitamin D deficiency and the occurrence of AF (20–23), larger cohort studies as well as randomized controlled trials (RCTs) assessing vitamin D supplementation could not confirm these results (24–29). In contrast, the latest RCT in adults in the community, VITAL (Vitamin D and Omega-3) Rhythm Trial, showed a marginally elevated AF risk, though these results did not reach statistical significance in the overall cohort (25).

Therefore, we aimed understand the relationship between circulating 25-hydroxyvitamin D [25(OH)D] and POAF in a cohort study of patients undergoing coronary artery bypass graft surgery (CABG). Further, we analysed the association of vitamin D supplementation and POAF risk.

MATERIALS AND METHODS

Study Cohort

The Atrial Fibrillation in High-Risk Individuals - Biopsy (AFHRI-B) study is an ongoing, prospective, monocentre cohort study designed to improve POAF risk prediction. AFHRI-B is a sub-study of the clinical cohort study (CCS) conducted at the University Heart and Vascular Centre Hamburg (Germany). We included patients 18 years or older undergoing CABG with the support of a heart-lung machine. Individuals who did not have sufficient knowledge of the German language skills to understand the informed consent forms and to participate in the interview were excluded.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft surgery; CI, confidence interval; EDTA, ethylenediaminetetraacetic acid; OR, odds ratio; POAF, postoperative atrial fibrillation; RCT, randomised controlled trial; 25(OH)D, 25-hydroxyvitamin D.

TABLE 1 | Baseline characteristics by sex and POAF.

	Total Cohort N = 201	Women N = 31	Men N = 170	No POAF N = 153	POAF N = 48
Postoperative atrial fibrillation					
POAF No. (%)	48 (23.9)	8 (25.8)	40 (23.5)	–	–
Persistent POAF No. (%)	31 (64.6)	6 (75.0)	25 (62.5)	–	31 (64.6)
Paroxysmal POAF No. (%)	17 (35.4)	2 (25.0)	15 (37.5)	–	17 (35.4)
Cardiovascular risk factors					
Age (years)	66.6 (58.0, 73.1)	68.1 (64.7, 75.5)	65.4 (57.6, 72.7)	64.1 (57.3, 72.9)	69.6 (65.3, 74.9)
BMI (kg/m^2)	27.7 (24.7, 30.4)	26.0 (23.8, 28.6)	27.8 (24.8, 30.5)	27.7 (24.5, 30.3)	27.7 (25.4, 31.2)
Systolic blood pressure (mm Hg)	133.0 (120.0, 145.0)	135.0 (123.5, 143.0)	133.0 (120.0, 145.0)	133.0 (120.0, 145.0)	130.5 (120.0, 145.2)
Diastolic blood pressure (mm Hg)	77.0 (70.0, 82.0)	75.0 (68.5, 83.0)	77.0 (70.0, 82.0)	78.0 (70.0, 82.0)	73.0 (67.0, 81.5)
Hypertension medication No. (%)	164 (81.6)	28 (90.3)	136 (80.0)	125 (81.7)	39 (81.2)
Ever-smoker No. (%)	147 (73.1)	21 (67.7)	126 (74.1)	111 (72.5)	36 (75.0)
Pre-existing conditions					
Heart failure No. (%)	37 (18.4)	6 (19.4)	31 (18.2)	27 (17.6)	10 (20.8)
Myocardial infarction No. (%)	78 (38.8)	10 (32.3)	68 (40.0)	61 (39.9)	17 (35.4)
Diabetes No. (%)	71 (35.3)	10 (32.3)	61 (35.9)	53 (34.6)	18 (37.5)
Vitamin D status					
Vitamin D (ng/ml)	17.7 (12.6, 23.7)	12.6 (10.8, 20.5)	17.9 (13.2, 23.8)	16.9 (12.6, 22.7)	20.7 (13.1, 27.2)
Vitamin D deficiency (%)	121 (60.2)	22 (71.0)	99 (58.2)	98 (64.0)	23 (47.9)
Vitamin D supplementation No. (%)	8 (4.0)	2 (6.5)	6 (3.6)	3 (2.0)	5 (10.4)
Creatinine (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.7, 0.8)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)
Vitamin D measurement in summer No. (%)	140 (69.7)	106 (69.3)	34 (70.8)	106 (69.3)	34 (70.8)

For continuous variables the median, the 25th, and the 75th percentile are displayed.
[1]*BMI, body mass index; POAF, postoperative atrial fibrillation.*

We focused on AF not related to severe heart valve disease and thus excluded individuals with planned valve surgery or high-grade valvular disease. Participation in the study was voluntary. Written informed consent was obtained from all participants. The conduct of this study was approved by the Local Ethics Committee.

Data Collection

Baseline data was collected in form of an interview using a detailed questionnaire, including information on pre-existing conditions, medication, family history, lifestyle, and cardiovascular risk factors. Baseline information was supplemented by a review of the electronical medical record. Blood was taken from the patients before surgery and stored at -80°C. In order to collect postoperative data, questionnaires were mailed to the participants and a standardised telephone follow-up interview took place approximately 30 days after study inclusion. In this interview, changes in wellbeing and habits as well as newly diagnosed cardiovascular diseases, including AF, were recorded. For each study participant, all electrocardiograms available in the electronical medical record were analysed by two experienced investigators. In the case of discrepancies in the diagnosis of AF a third cardiologist or electrophysiologist was consulted. Further information on the course of the postoperative treatment were obtained from the discharge report, rehabilitation discharge letters and from the electronical medical record. The primary outcome was newly diagnosed, postoperative AF. 25(OH)D was measured from ethylenediaminetetraacetic acid plasma using the Abbott ARCHITECT i2000 system by a chemiluminescent

microparticle immunoassay. After exclusion of 33 patients with AF diagnosed before surgery, n = 201 patients remained for our analysis.

Statistical Analyses

The statistical analyses were performed using R version 4.0.5 and there was no missing data in the sample. A p-value of < 0.05 was considered statistically significant. Levels of 25(OH)D as well as creatinine were log-transformed because visual inspection determined the transformed versions to be closer to a normal distribution. Logistic regression models with POAF as the outcome were fitted and corrected for small numbers in categorical predictors using Firth's correction.

For the current analyses, clinical covariables besides age and sex comprised body mass index (BMI), ever smoker, diabetes, systolic and diastolic blood pressure, hypertension medication, heart failure, and myocardial infarction.

A secondary set of analyses also included the season (summer/winter) in which the blood sample was taken. Summer was defined as lasting from June 1st to November 30th. Vitamin D deficiency was defined as serum levels below 20 ng/ml. Lastly, vitamin D supplementation was included in another set of analyses.

RESULTS

Baseline Characteristics

The baseline characteristics are given in **Table 1**. A total of N = 201 patients was included in the analysis. 31 (15.4%) of the
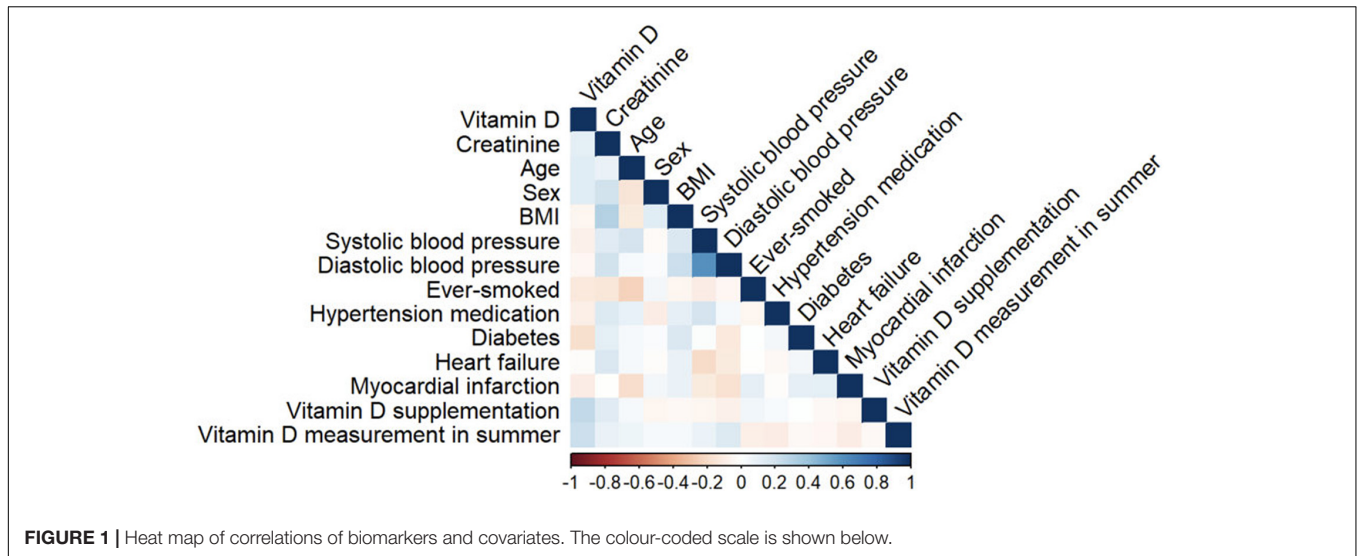
FIGURE 1 | Heat map of correlations of biomarkers and covariates. The colour-coded scale is shown below.

included patients were female. The median age was 66.6 years. $N = 48$ patients (23.9%) of patients developed POAF during follow-up. POAF was persisting in 31 (64,6%) of the patients, whereas 17 (35,4%) of the patients had paroxysmal AF. The median (25th/75th percentile) vitamin D concentration was 17.7 (12.6/23.7) ng/ml, $N = 140$ (69.7%) of patients were enrolled in summer. Vitamin D deficiency occurred in 121 (60.2%) patients. A total of $N = 8$ patients (4.0%) took vitamin D supplementation at baseline.

Patients, who developed POAF were older, had higher vitamin D concentrations and took vitamin D supplementation more often. They also had higher rates of diabetes or heart failure and were more frequently current or former smokers.

Correlations Between Biomarkers and Covariates

We calculated the correlations between the biomarkers and covariates as shown in **Figure 1**. Continuous variables are shown as medians [interquartile range; binary variables are shown as counts (frequencies)].

The strongest correlations were observed between 25(OH)D concentration and vitamin D supplementation ($r = 0.27$). 25(OH)D concentration and measurement in summer showed a correlation of 0.22. Weak correlations between vitamin D and the following covariates were observed: creatinine, age, sex, ever smoking, diabetes.

Logistic Regressions

A first logistic regression model showed higher 25(OH)D concentration to be related to incident AF with borderline statistical significance [odds ratio (OR) 1.85, 95% confidence interval (CI) 0.87–3.92, p-value 0.107] when adjusted for age, sex, and creatinine. In analyses further adjusted for clinical variables the results remained stable (OR 1.99, 95% CI 0.90–4.39, p-value 0.087).
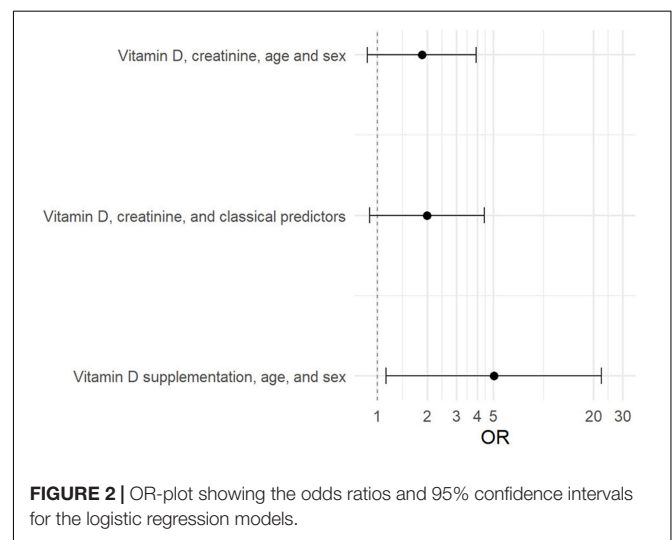
FIGURE 2 | OR-plot showing the odds ratios and 95% confidence intervals for the logistic regression models.

In a secondary analysis, vitamin D supplementation in a model adjusted for age and sex was associated with an increased risk (OR 5.03, 95% CI 1.13 to 22.33, p-value 0.034). The ORs and CIs of all models are compared in **Figure 2**.

DISCUSSION

In our contemporary cohort we did not observe a benefit for higher 25(OH)D concentration or vitamin D supplementation in relation to POAF. In contrast, elevated 25(OH)D concentration showed an increased risk for the occurrence of POAF, though these results reached only borderline statistical significance. Vitamin D supplementation at baseline was significantly associated with an increased risk of POAF in this subgroup, however, the small size of this subgroup needs to be taken into consideration and these findings must thus be treated with caution.

The effects of vitamin D are pleiotropic and involve the modulation of the renin-angiotensin-aldosterone-system, inflammation, and vascular calcification among others [30–32]. Cardiomyocytes express the vitamin D receptor. Alterations of this receptor have genomic effects and change contractility and relaxation of the heart [33, 34]. Vitamin D affects K^+- and Ca^{2+}-currents in mouse ventricular myocytes [35, 36]. Here, a link to the arrhythmia might be established. Another pathophysiological attempt of explanation focuses on the interaction between vitamin D and electrolytes, in particular calcium, but also phosphate and magnesium through parathyroid hormones. Electrolyte imbalance may be causal in the development of AF. It needs to be considered that most of the published literature describes pathophysiological findings for vitamin D deficiency, not for elevated concentration.

The role of 25(OH)D concentration across the whole range of blood concentration for the development of AF remains unclear. Small case-control studies have shown an association between low vitamin D serum levels and incident AF [20–23], whereas larger cohort studies could not confirm these results [26–29]. Two recent, large, prospective, randomised, placebo-controlled studies could not show any benefit of vitamin D supplementation for the occurrence of AF [24, 25]. In contrast, the VITAL Rhythm Study, a double-blind, randomised, placebo-controlled study, also showed a tendency for an increased AF risk associated with long-term 2,000 IU of vitamin D_3 supplementation [25].

Similarly, even though vitamin D deficiency has been shown to be a risk factor for many cardiovascular conditions in multiple observational studies, in many areas large RCTs examining vitamin D supplementation could not demonstrate a convincing benefit of this intervention on hypertension [37], cardiovascular events [38], cardiovascular or all-cause mortality [39]. It is possible, that vitamin D deficiency is not causal, but confounded by its association with lifestyle, cardiovascular risk factors, and comorbidities.

Our subgroup results in patients on vitamin D supplementation who showed an increased risk of POAF should be viewed cautiously and in the light of potential confounding-by-indication. These are observational findings. Patients undergoing major cardiac surgery such as CABG often are a particularly vulnerable and frail group which is not directly comparable to the general population. The median age in our cohort was 66.6 years. Many patients had significant comorbidities such as heart failure, prior myocardial infarction, or diabetes mellitus. The perioperative period is marked by physical and psychological stress as well as severe changes in the daily habits like reduced physical and mental activity [40]. In addition, there can be alterations in nutrition caused by aspects such as decreased appetite or hospital diet with short-term effects on vitamin D concentrations [41–43]. The pre-existing conditions that cause the prescription of vitamin D supplementation in the primary care setting might also increase the risk for AF. Furthermore, patients who take over the counter supplements may significantly differ in lifestyle. On the other hand, including recent evidence from RCTs an actual harmful effect of vitamin D on the development of AF should be considered. Thus, further research on the mechanisms of vitamin in AF is required.

LIMITATIONS

This study is limited by its observational nature which is prone to bias and confounding. The number of outcomes was relatively small, in particular the subgroup of patients with vitamin D supplementation was too small to derive final conclusions. Therefore, the results need to be interpreted with caution. Also, the examined objective was POAF, which in its pathophysiology, patient characteristics as well as clinical presentation is different from incident AF without preceding cardiac surgery. Thus, these results are not entirely transferrable to AF in the general population. However, our findings are in line with recent studies on vitamin D in AF in settings other than POAF. Therefore, further research is necessary to determine both, the clinical impact of 25(OH)D concentration and vitamin D supplementation as well as the potential underlying pathophysiological mechanisms to generate robust evidence on this central vitamin and frequently used supplement. Ideally, clinical trials of vitamin D supplementation could be set up.

CONCLUSION

In contrast to previous observational data, higher 25(OH)D concentration and vitamin D supplementation were not beneficial in relation to the risk of POAF in our study of patients undergoing CABG. Elevated 25(OH)D concentration and vitamin D supplementation rather revealed an increased OR for POAF. Whereas our data need confirmation, they also show the need for further research on the role of vitamin D and the serious and costly disease POAF.

DISCLOSURE

RS has received lecture fees and advisory board fees from BMS/Pfizer outside this work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethikkommission Ärztekammer Hamburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the biomarcare consortium (biomarker for cardiovascular risk assessment in europe). *Circulation.* (2017) 136:1588–97. doi: 10.1161/circulationaha.117.028981

2. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ.* (2018) 2018:k1453. doi: 10.1136/bmj.k1453

3. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. *Am J Cardiol.* (2013) 112:1142–7. doi: 10.1016/j.amjcard.2013.05.063

4. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* (2013) 34:2746–51. doi: 10.1093/eurheartj/eht280

5. Andersson T, Magnuson A, Bryngelsson I-L, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272 186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case–control study. *Eur Heart J.* (2013) 34:1061–7. doi: 10.1093/eurheartj/ehs469

6. De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L, et al. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. data from the alpha study registry. *Eur J Heart Fail.* (2007) 9:502–9. doi: 10.1016/j.ejheart.2006.10.021

7. Kokkinidis DG, Zareifopoulos N, Theochari CA, Arfaras-Melainis A, Papanastasiou CA, Uppal D, et al. Association between atrial fibrillation and cognitive impairment in individuals with prior stroke: a meta-analysis and meta-regression analysis. *Stroke.* (2020) 51:1662–6. doi: 10.1161/STROKEAHA.119.027815

8. Lip GYH, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan G-A, et al. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational research programme pilot survey on atrial fibrillation: heart failure in patients with AF in Europe. *Eur J Heart Fail.* (2015) 17:570–82. doi: 10.1002/ejhf.254

9. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The epidemiology of atrial fibrillation and stroke. *Cardioembolic Stroke.* (2016) 34:255–68. doi: 10.1016/j.ccl.2015.12.002

10. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, et al. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc.* (2021) 2021:2197. doi: 10.1161/JAHA.115.002197

11. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality. *J Am Coll Cardiol.* (2015) 66:1000–7. doi: 10.1016/j.jacc.2015.06.1314

12. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* (1991) 22:983–8. doi: 10.1161/01.str.22.8.983

13. Bessissow A, Khan J, Devereaux PJ, Alvarez-Garcia J, Alonso-Coello P. Postoperative atrial fibrillation in non-cardiac and cardiac surgery: an overview. *J Thromb Haemost.* (2015) 13:S304–12. doi: 10.1111/jth.12974

14. Dobrev D, Aguilar M, Heijman J, Guichard J-B, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol.* (2019) 16:417–36. doi: 10.1038/s41569-019-0166-5

15. Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. *Atr Fibrillation.* (2016) 12:299–308.

16. Bhave PD, Goldman LE, Vittinghoff E, Maselli J, Auerbach A. Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. *Am Heart J.* (2012) 164:918–24. doi: 10.1016/j.ahj.2012.09.004

17. Lee S-H, Kang DR, Uhm J-S, Shim J, Sung J-H, Kim J-Y, et al. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. *Am Heart J.* (2014) 167:593.e–600.e. doi: 10.1016/j.ahj.2013.12.010

18. Lin M-H, Kamel H, Singer DE, Wu Y-L, Lee M, Ovbiagele B. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality: a meta-analysis. *Stroke.* (2019) 50:1364–71. doi: 10.1161/strokeaha.118.023921

19. Konstantino Y, Yovel DZ, Friger MD, Sahar G, Knyazer B, Amit G. Postoperative atrial fibrillation following coronary artery bypass graft surgery predicts long-term atrial fibrillation and stroke. (2016) 18:5.

20. Belen E, Aykan A, Kalay E, Sungur M, Sungur A, Cetin M. Low-level vitamin d is associated with atrial fibrillation in patients with chronic heart failure. *Adv Clin Exp Med.* (2016) 25:51–7. doi: 10.17219/acem/34690

21. Chen WR, Liu ZY, Shi Y, Yin DW, Wang H, Sha Y, et al. Relation of low vitamin D to nonvalvular persistent atrial fibrillation in chinese patients: vitamin D and atrial fibrillation. *Ann Noninvasive Electrocardiol.* (2014) 19:166–73. doi: 10.1111/anec.12105

22. Ozcan OU, Gurlek A, Gursoy E, Gerede DM, Erol C. Relation of vitamin D deficiency and new–onset atrial fibrillation among hypertensive patients. *J Am Soc Hypertens.* (2015) 9:307–12. doi: 10.1016/j.jash.2015.01.009

23. Demir M, Uyan U, Melek M. The effects of vitamin D deficiency on atrial fibrillation. *Clin Appl Thromb.* (2014) 20:98–103. doi: 10.1177/1076029612453762

24. Boursiquot BC, Larson JC, Shalash OA, Vitolins MZ, Soliman EZ, Perez MV. Vitamin D with calcium supplementation and risk of atrial fibrillation in postmenopausal women. *Am Heart J.* (2019) 209:68–78. doi: 10.1016/j.ahj.2018.12.006

25. Albert CM, Cook NR, Pester J, Moorthy MV, Ridge C, Danik JS, et al. Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial. *JAMA.* (2021) 325:1061. doi: 10.1001/jama.2021.1489

26. Vitezova A, Cartolano NS, Heeringa J, Zillikens MC, Hofman A, Franco OH, et al. Vitamin D and the Risk of Atrial Fibrillation - The Rotterdam

Study. *PLoS One.* (2015) 10:e0125161. doi: 10.1371/journal.pone.012 5161

27. Alonso A, Misialek JR, Michos, Eckfeldt J, Selvin E, Soliman EZ, et al. Serum 25-hydroxyvitamin D and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Europace.* (2016) 18:1143–9. doi: 10.1093/europace/euv395

28. Rienstra M, Cheng S, Larson MG, McCabe EL, Booth SL, Jacques PF, et al. Vitamin D status is not related to development of atrial fibrillation in the community. *Am Heart J.* (2011) 162:538–41. doi: 10.1016/j.ahj.2011.06.013

29. Trevisan C, Piovesan F, Lucato P, Zanforlini BM, De Rui M, Maggi S, et al. Parathormone, vitamin D and the risk of atrial fibrillation in older adults: A prospective study. *Nutr Metab Cardiovasc Dis.* (2019) 29:939–45. doi: 10.1016/j.numecd.2019.05.064

30. Cantorna MT, Snyder L, Lin Y-D, Yang L. Vitamin D and 1,25(OH)2D Regulation of T cells. *Nutrients.* (2015) 7:3011–21. doi: 10.3390/nu7043011

31. Forman JP, Williams JS, Fisher NDL. Plasma 25-Hydroxyvitamin D and Regulation of the Renin-Angiotensin System in Humans. *Hypertension.* (2010) 55:1283–8. doi: 10.1161/HYPERTENSIONAHA.109.14 8619

32. Turin A, Bax JJ, Doukas D, Joyce C, Lopez JJ, Mathew V, et al. Interactions Among Vitamin D, Atrial Fibrillation, and the Renin-Angiotensin-Aldosterone System. *Am J Cardiol.* (2018) 122:780–4. doi: 10.1016/j.amjcard.2018.05.013

33. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU. Functional Vitamin D Receptor (VDR) in the T-Tubules of Cardiac Myocytes: VDR Knockout Cardiomyocyte Contractility. *Endocrinology.* (2008) 149:558–64. doi: 10.1210/en.2007-0805

34. Menegaz D, Mizwicki MT, Barrientos-Duran A, Chen N, Henry HL, Norman AW. Vitamin D Receptor (VDR) Regulation of Voltage-Gated Chloride Channels by Ligands Preferring a VDR-Alternative Pocket (VDR-AP). *Mol Endocrinol.* (2011) 25:1289–300. doi: 10.1210/me.2010-0 442

35. Tamayo M, Manzanares E, Bas M, Martín-Nunes L, Val-Blasco A, Jesús Larriba M, et al. Calcitriol (1,25-dihydroxyvitamin D3) increases L-type calcium current *via* protein kinase A signaling and modulates calcium cycling and contractility in isolated mouse ventricular myocytes. *Heart Rhythm.* (2017) 14:432–9. doi: 10.1016/j.hrthm.2016.12.013

36. Tamayo M, Martin-Nunes L, Val-Blasco A, Piedras MJ, Larriba MJ, Gómez-Hurtado N, et al. Calcitriol, the Bioactive Metabolite of Vitamin D, Increases Ventricular K+ Currents in Isolated Mouse Cardiomyocytes. *Front Physiol.* (2018) 9:1186. doi: 10.3389/fphys.2018.01186

37. Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, et al. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. *Prev Chronic Dis.* (2020) 17:190307. doi: 10.5888/pcd17.190307

38. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. *JAMA Cardiol.* (2019) 4:765. doi: 10.1001/jamacardio.2019.1870

39. Zhang Y, Fang F, Tang J, Jia L, Feng Y, Xu P, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ.* (2019) 2019:l4673. doi: 10.1136/bmj.l4673

40. Lopez V, Sek Ying C, Poon C-Y, Wai Y. Physical, psychological and social recovery patterns after coronary artery bypass graft surgery: A prospective repeated measures questionnaire survey. *Int J Nurs Stud.* (2007) 44:1304–15. doi: 10.1016/j.ijnurstu.2006.06.005

41. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med.* (2014) 370:1227–36. doi: 10.1056/nejmra1304623

42. Barton A, Beigg C, Macdonald I, Allison S. High food wastage and low nutritional intakes in hospital patients. *Clin Nutr.* (2000) 19:445–9. doi: 10.1054/clnu.2000.0150

43. Pathirana AK, Lokunarangoda N, Ranathunga I, Santharaj WS, Ekanayake R, Jayawardena R. Prevalence of hospital malnutrition among cardiac patients: results from six nutrition screening tools. *SpringerPlus.* (2014) 3:412–412. doi: 10.1186/2193-1801-3-412

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.