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ORIGINAL RESEARCH

Omega-3 Fatty Acids and Heart Rhythm, Rate, and Variability in Atrial Fibrillation

Philipp Baumgartner, MD; Martin F. Reiner, MD, PhD; Andrea Wiencierz, PhD; Michael Coslovsky, PhD; Nicole R. Bonetti, MD; Mark G. Filipovic, MD; Stefanie Aeschbacher, PhD; Michael Kühne, MD; Christine S. Zuern, MD; Nicolas Rodondi, MD, MAS; Jolanda Oberle, MD; Giorgio Moschovitis, MD; Thomas F. Lüscher, MD; Giovanni G. Camici, PhD; Stefan Osswald, MD; David Conen, MD, MPH; Jürg H. Beer, MD; on behalf of the SWISS-AF Investigators*

BACKGROUND: Previous randomized control trials showed mixed results concerning the effect of omega-3 fatty acids (n-3 FAs) on atrial fibrillation (AF). The associations of n-3 FA blood levels with heart rhythm in patients with established AF are unknown. The goal of this study was to assess the associations of total and individual n-3 FA blood levels with AF type (paroxysmal versus nonparoxysmal), heart rate (HR), and HR variability in patients with AF.

METHODS AND RESULTS: Total n-3 FAs, eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, and alpha-linolenic acid blood levels were determined in 1969 patients with known AF from the SWISS-AF (Swiss Atrial Fibrillation cohort). Individual and total n-3 FAs were correlated with type of AF, HR, and HR variability using standard logistic and linear regression, adjusted for potential confounders. Only a mild association with nonparoxysmal AF was found with total n-3 FA (odds ratio [OR], 0.97 [95% CI, 0.89–1.05]) and docosahexaenoic acid (OR, 0.93 [95% CI, 0.82–1.06]), whereas other individual n-3 FAs showed no association with nonparoxysmal AF. Higher total n-3 FAs (estimate 0.99 [95% CI, 0.98–1.00]) and higher docosahexaenoic acid (0.99 [95% CI, 0.97–1.00]) tended to be associated with slower HR in multivariate analysis. Docosapentaenoic acid was associated with a lower HR variability triangular index (0.94 [95% CI, 0.89–0.99]).

CONCLUSIONS: We found no strong evidence for an association of n-3 FA blood levels with AF type, but higher total n-3 FA levels and docosahexaenoic acid might correlate with lower HR, and docosapentaenoic acid with a lower HR variability triangular index.

Key Words: atrial fibrillation ■ heart rate ■ heart rate variability ■ omega-3 fatty acid ■ rhythm type

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 1% of the global population. Its prevalence is increasing further given the aging population.[1] Thromboembolism and in particular ischemic stroke are the most concerning complications. Despite oral anticoagulation, the residual stroke risk is between 1.11% and 1.80% per year depending on the individual risk and the anticoagulant used.[2,3] Stroke risk stratifications and stroke risk reducing strategies are mainly based on the patient's clinical risk factors, which have been incorporated into the risk stratification scores.[4] Recently, however, it was shown that not only patient inherent risk factors but also heart rhythm related characteristics, such as AF type, affect the risk of thromboembolism, stroke, and death.[5–7] A recent meta-analysis by Ganesan et al showed a 1.38 times increased risk of thromboembolism and a 1.21 times increased risk of death in patients with nonparoxysmal

Correspondence to: Jürg H. Beer, MD, FACP, Cantonal Hospital Baden, Im Ergel 1, CH-5404 Baden, Switzerland and Center for Molecular Cardiology, University of Zurich, Switzerland. Email: hansjuerg.beer@ksb.ch

*A complete list of the SWISS-AF Investigators can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- Higher whole blood levels of total or individual omega-3 fatty acids are not associated with different rates of paroxysmal versus nonparoxysmal type of atrial fibrillation.
- Higher levels of docosahexaenoic acid (DHA) tended associated with a lower heart rate in patients with atrial fibrillation.
- Higher levels of docosapentaenoic acid are associated with a lower heart rate variability index.

What Are the Clinical Implications?

- Although omega-3 fatty acids do not seem to affect atrial fibrillation progression, individual omega-3 fatty acids, particularly DHA, may be useful to control heart rate in patients with atrial fibrillation.

Nonstandard Abbreviations and Acronyms

ALA	alpha-linolenic acid
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
HR	heart rate
HRV	heart rate variability
HRVI	heart rate variability triangular index
n-3 FAs	omega-3 fatty acids
NPAF	nonparoxysmal atrial fibrillation
PAF	paroxysmal AF
SWISS-AF	Swiss Atrial Fibrillation Cohort

AF (NPAF) compared with patients with paroxysmal AF (PAF).[5] Similar results were obtained in other studies providing further evidence that higher AF burden and AF progression increase the risk of stroke and death.[8,9] In addition to the type of AF, heart rate (HR) variability (HRV), a marker of cardiac autonomic function, is a predictor of mortality in patients with AF.[7]

Omega-3 fatty acids (n-3 FAs) include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA). Besides their anti-inflammatory and antithrombotic effects,[10,11] n-3 FAs have been shown to have antiarrhythmic effects, influencing resting HR and HR variability (HRV), cardiac remodeling, and ion channels in clinical and experimental studies.[12,13] Clinical studies with supplementation of n-3 FAs however showed mixed results. Earlier trials found protective effects of fish-rich diet or n-3 FA supplementation against postmyocardial infarction arrhythmias[14] and postcardiac surgery PAF.[15] More recent randomized control trials (RCTs), however, showed neutral or even negative effects with higher rates of newly onset AF or of hospitalizations due to AF during n-3 FA supplementation.[16–19] Much less is known about the effects of n-3 FAs in patients with established AF. Some studies have shown fewer relapses of NPAF with n-3 FA supplementation after electrocardioversion,[20,21] whereas others showed no benefit after electrocardioversion nor in relapse rates of paroxysmal AF.[22,23] To date it is unknown whether n-3 FAs may influence AF progression, that is, progressing from paroxysmal to permanent AF and if n-3 FAs influence HR or HRV in patients with AF.

We therefore determined n-3 FA concentrations in whole blood of 1969 patients with AF in a cross-sectional study and investigated their association with AF type, HR, and HRV. This investigation was part of the SWISS-AF (Swiss Atrial Fibrillation Cohort) study.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data for this study were obtained from the prospective, observational, multicenter SWISS-AF study (ClinicalTrials.gov Identifier: NCT02105844).[24,25] The study enrolled 2415 patients with AF across 14 centers in Switzerland between 2014 and 2017. Inclusion criteria were age≥65 years with documented AF, within the cohort a subgroup of 250 patients <65 years with documented AF were enrolled as well. Exclusion criteria were transient forms of AF (eg, after cardiac surgery or severe sepsis), acute illness within the last 4 weeks, or inability to provide informed consent.[24,25] We considered the baseline data of all 2415 SWISS-AF patients. Of those, 446 patients were excluded (380 due to cardiac pacing, 34 missing baseline omega-3 measurements, 28 missing HRV index (HRVI) data, 2 missing baseline characteristics, 2 missing HR measurements). Finally, 1969 patients were included in the present analysis (Figure 1). The study complies with the Declaration of Helsinki, was approved by the local ethic committees of each participating center, and informed consent has been obtained from all subjects or their legally authorized representative.

Blood Sampling and Whole Blood Fatty Acid Composition

At baseline, venous EDTA-anticoagulated blood was collected according to standard operating procedures, immediately aliquoted into cryotubes, and stored at −80 °C at a centralized biobank at the University Hospital Basel.[11,24] Blood samples were transported

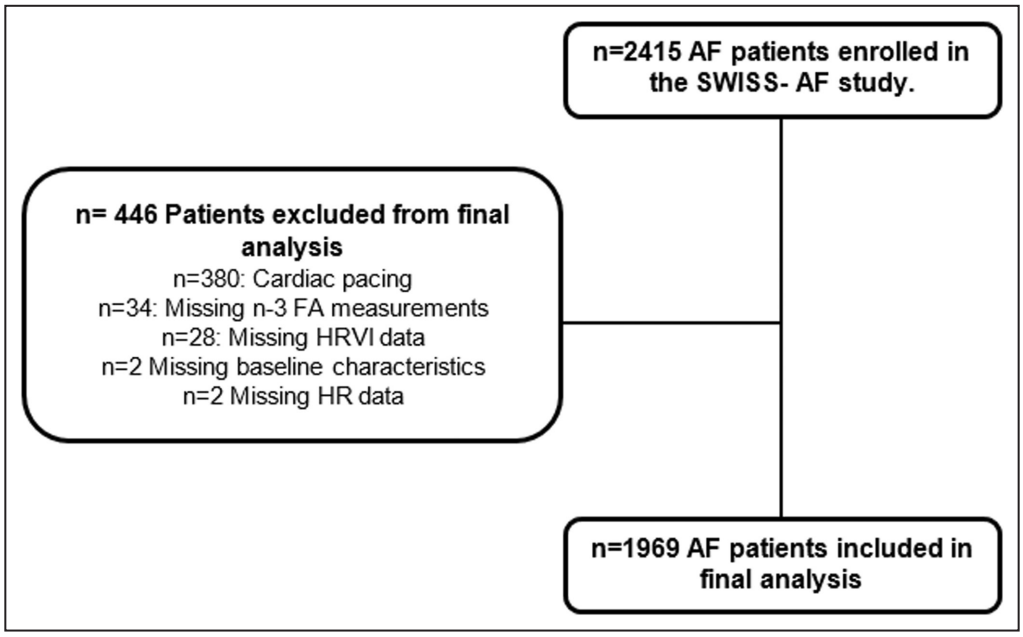

Figure 1. Flow chart of included and excluded patients.
AF indicates atrial fibrillation; HR, heart rate; HRVI, heart rate variability triangular index; n-3 FA, omega-3 fatty acid; and SWISS-AF, Swiss Atrial Fibrillation Cohort.

on dry ice to Omegametrix GmbH, Martinsried, Germany. Whole blood FAs were analyzed by gas chromatography according to the HS-n-3 index methodology as previously described.[26] Results are given as fatty acids (EPA, DHA, DPA, ALA, or total n-3 FAs [EPA+DHA+DPA+ALA]) expressed as a percentage of total identified FAs after response factor correction. The coefficient of variation for FA levels was 5%. Analyses were quality controlled according to DIN ISO 15189.[11]

Assessment of HRV Parameters

At baseline, resting 16-lead ECG recordings of 5 minutes duration were obtained from all participants using the same ECG acquisition technology at all centers (CS-200 Excellence and CS-200 Touch, Schiller AG, Baar, Switzerland) and stored in a central ECG core laboratory at the Cardiocentro in Lugano. The digital ECGs were stored with a sampling frequency of 1 kHz (signal bandwidth 0.04–387 Hz) and a resolution of 1 μV/bit.[24] The HRVI was calculated in sinus rhythm or AF (depending on the current rhythm) as previously described.[7]

Statistical Analysis

The specified primary outcome was type of AF at baseline as a binary variable, divided into paroxysmal (PAF) and persistent or permanent AF (NPAF). Secondary end points were HR and HRVI. We investigated the association of n-3 FAs and type of AF using standard logistic regression to estimate the relationship between n-3 FA levels and the odds for having persistent or permanent AF (ie, NPAF) as opposed to PAF.

The associations between n-3 FAs and HR and HRVI were assessed using linear regression models. As the distributions of HR and HRVI were clearly skewed, the HR and HRVI measurements were transformed to their logarithms before estimating linear regression models. The estimated coefficients were then transformed back to the original scales, where they represent multiplicative effects on the geometric means of the distributions of HR and HRVI, respectively. Each model was estimated once for individual n-3 FAs, that is, EPA, DHA, DPA, or ALA and total n-3 FAs (EPA+DHA+DPA+ALA). We performed 2 different analyses. Model 1 was adjusted for age and sex and model 2 was adjusted for the following variables: age, sex, body mass index, smoking status, alcohol consumption, physical activity, coronary artery disease, family history of AF, hypertension, diabetes, chronic kidney disease, heart failure, history of deep venous thrombosis, hyperthyreosis, hypothyreosis, obstructive sleep apnea syndrome, intake of beta blocker, and antiarrhythmic drugs Ic/III. The variables were chosen based on potential risk on AF progression.

Additionally, we investigated whether associations of n-3 FAs with outcomes are different between sexes and ECG rhythm at baseline (eg, sinus rhythm, AF, or other rhythm). For this, we included interactions between n-3 FAs and sex and baseline ECG rhythm, respectively, in all models and compared the models with and without interaction using

their Akaike's Information Criterion (Akaike 1973) values. All statistical analyses were performed using R version 4.0.2. Finally, we analyzed the end points with the observed quartile class of total n-3 FAs with standardized mean differences. The primary outcome of this substudy was specified before the substudy started and in particular before any statistical analysis concerning the association of heart rhythm and n-3 FAs took place.

RESULTS

Baseline Characteristics

Mean age of the study population was 73 years (SD 8.5) and 27% were female. Most common cardiovascular risk factors were hypertension (69%), active or prior smoking (56%), and diabetes (17%). The majority of patients were taking beta blockers (70%), and 21% were taking class 1c/III antiarrhythmic drugs (Table 1). The FA fractions of EPA, DHA, DPA, ALA, and total n-3 FAs were 0.8%, 3.3%, 1.7%, 0.2%, and 6.0% of total identified FAs, respectively (Table 2).

N-3 FAs Showed No Strong Association With AF Type

We identified 876 (44.5%) patients with PAF and 1093 (55.5%) patients with NPAF. After adjustment for age and sex (model 1), higher levels of total n-3 FAs (odds ratio [OR] 0.92, [95% CI, 0.85–0.99]) and higher levels of DHA (OR, 0.89 [95% CI, 0.78–1.00]) showed an association with a lower prevalence of NPAF (Table 3). DPA (OR, 0.92 [95% CI, 0.65–1.30]), ALA (OR, 1.23 [95% CI, 0.56–2.79]), and EPA (OR, 1.00 [95% CI, 0.70–1.44]) showed no strong association with NPAF. After correction for multiple risk factors (model 2), total n-3 FAs (OR, 0.97 [95% CI, 0.89–1.05]) and DHA (OR, 0.93 [95% CI, 0.82–1.06]) showed only a mild trend for association with NPAF. DPA (OR, 1.07 [95% CI, 0.74–1.54]), ALA (OR, 1.44 [95% CI, 0.63–3.41]), and EPA (OR, 0.99 [95% CI, 0.67–1.45]) showed no association with NPAF (Table 3). Subgroup analysis did not find evidence for differences between men and women in these associations (Table S1) nor did we observe large differences in AF types between quartiles of total n-3 FAs (Table S2).

Higher Levels of DPA Were Associated With a Lower HRVI

After adjustment for age and sex (model 1) higher levels of DPA tended to be associated with a lower HRVI (estimate 0.95 [95% CI, 0.90–1.00]), whereas neither total n-3 FAs (1.00 [95% CI, 0.99–1.01]) nor other individual n-3 FAs EPA (1.02 [95% CI, 0.98–1.08]), DHA (1.00 [95% CI, 0.98–1.02]), or ALA (1.05 [95% CI, 0.93–1.19]) were associated with HRVI. After multivariate adjustment (model 2) higher levels of DPA still correlated inversely with HRVI; 1 percentage increase in DPA concentration was associated with a 6% lower HRVI (estimate 0.94 [95% CI, 0.89–0.99]). As in model 1, neither EPA (1.03 [95% CI, 0.97–1.09]), DHA (1.00 [95% CI, 0.98–1.02]), ALA (1.04 [95% CI, 0.92–1.18]), nor total n-3 FAs (1.00 [95% CI, 0.99–1.01]) were associated with HRVI (Table 3). Subgroup analysis did not find evidence for differences between men and women in the studied associations (Table S1). Analysis of the associations in regard to baseline ECG rhythm found an improvement of the model when taking baseline ECG rhythm into account (Table S3). However, this improvement stems likely from the main effect and not the interaction with n-3 FAs as n-3 FAs did not differ between the different rhythms (Table S4).

Table 1. Baseline Characteristics

Overall population	1969
Mean age at baseline, y (SD)	72.6 (8.5)
Female sex (%)	538 (27.3)
Median body mass index, kg/m^2 (IQR)	27.0 (24.4, 30.4)
Smoking (%)	
Never	862 (43.8)
Past	957 (48.6)
Active	150 (7.6)
Median alcohol units per day (IQR)	0.5 (0.1, 1.3)
Physical activity (%)	935 (47.5)
Coronary artery disease (%)	552 (28.0)
Hypertension (%)	1364 (69.3)
Diabetes (%)	330 (16.8)
Chronic kidney disease (%)	372 (18.9)
Deep venous thrombosis (%)	172 (8.7)
Heart failure (%)	458 (23.3)
Family history AF, mother (%)	
Yes	96 (4.9)
Unknown	816 (41.4)
Family history AF, father (%)	
Yes	65 (3.3)
Unknown	890 (45.2)
Hyperthyreosis (%)	79 (4.0)
Hypothyreosis (%)	204 (10.4)
Obstructive sleep apnea syndrome	276 (14.0)
Beta blockers (%)	1372 (69.7)
Antiarrhythmic drugs Ic/III	418 (21.2)
AF type (%)	
Paroxysmal	761 (45.9)
Persistent	495 (29.9)
Permanent	401 (24.2)

Baseline characteristics of all included patients. AF indicates atrial fibrillation; and IQR, interquartile range.

Table 2. Omega-3 Fatty Acid Fractions

Overall population	Fatty acid fractions, %
N=1969	Mean (SD)
Eicosapentaenoic acid (EPA)	0.8 (0.3)
Docosahexaenoic acid (DHA)	3.3 (0.8)
Docosapentaenoic acid (DPA)	1.7 (0.3)
Alpha-linolenic acid (ALA)	0.2 (0.1)
Total omega-3 fatty acids	6.0 (1.2)

Total omega-3 fatty acids include EPA+DHA+DPA+ALA. ALA indicates alpha-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; and EPA, eicosapentaenoic acid.

Higher Levels of Total n-3 FA and DHA Tended to Be Associated With a Lower HR

Median HR was 67 bpm (interquartile range 58, 78). After adjustment for age and sex (model 1) higher n-3 FA levels (estimate 0.99 [95% CI, 0.98–0.99]) and higher DHA (0.98 [95% CI, 0.97–1.00]) were associated with lower HR. HEPA (0.98 [95% CI, 0.94–1.02]), DPA (1.00 [95% CI, 0.96–1.04]), and ALA (0.99 [95% CI, 0.90–1.07]) were clearly associated with changes in HR. We found that after adjustment for multiple confounders (model 2), higher total n-3 FA levels (estimate 0.99 [95% CI, 0.98–1.00]) and also higher levels of DHA (0.99 [95% CI, 0.97–1.00]) tended to be associated with a lower HR. For 1% higher total n-3 FAs or DHA concentration, HR is reduced by 1%. No association was found with EPA (0.99 [95% CI, 0.95–1.03]), DPA (1.01 [95% CI, 0.97–1.05]), or ALA (1.01 [95% CI, 0.93–1.10]; Table 3). As with HRVI we did not find evidence for differences between sexes (Table S1) and baseline ECG rhythm (Tables S3 and S4).

Table 3. Associations of n-3 FAs With Clinical End Points

Prevalence of NPAF	Model 1	Model 2
EPA	1.00 (0.70–1.44)	0.99 (0.67–1.45)
DHA	0.89 (0.78–1.00)	0.93 (0.82–1.06)
DPA	0.92 (0.65–1.30)	1.07 (0.74–1.54)
ALA	1.23 (0.56–2.79)	1.44 (0.63–3.41)
Total omega-3 fatty acids	0.92 (0.85–0.99)	0.97 (0.89–1.05)
Heart rate variability index		
EPA	1.02 (0.97–1.08)	1.03 (0.97–1.09)
DHA	1.00 (0.98–1.02)	1.00 (0.98–1.02)
DPA	0.95 (0.90–1.00)	0.94 (0.89–0.99)
ALA	1.05 (0.93–1.19)	1.04 (0.92–1.18)
Total omega-3 fatty acids	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Heart rate		
EPA	0.98 (0.94–1.02)	0.99 (0.95–1.03)
DHA	0.98 (0.97–1.00)	0.99 (0.97–1.00)
DPA	1.00 (0.96–1.04)	1.01 (0.97–1.05)
ALA	0.99 (0.90–1.07)	1.01 (0.93–1.10)
Total omega-3 fatty acids	0.99 (0.98–0.99)	0.99 (0.98–1.00)

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, smoking status, alcohol consumption, physical activity, coronary artery disease, family history of atrial fibrillation, hypertension, diabetes, chronic kidney disease, heart failure, history of deep venous thrombosis, hyperthyreosis, hypothyreosis, obstructive sleep apnea syndrome, intake of beta blocker, and antiarrhythmic drugs Ic/III. Total omega-3 fatty acids represent EPA+DHA+DPA+ALA. Data for the rates of NPAF are given as odds ratio (95% CI). For heart rate and heart rate variability index, results are given as multiplicative effects (95% CI). ALA indicates alpha-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; and NPAF, nonparoxysmal atrial fibrillation.

DISCUSSION

In this study, we investigated the association of n-3 FAs with the type of AF, that is, PAF versus NPAF and with HRVI and HR. We found no clear association between individual or total n-3 FAs and AF type. However, we found that total n-3 FA levels and DHA tended to be associated with a lower HR in patients with AF and that higher levels of DPA were associated with a lower HRVI. Figure 2 summarizes the main results of the study.

To our knowledge, this is the first cross-sectional study that investigated the associations of n-3 FAs on heart rhythm in patients with known AF. Previous studies investigated the association of n-3 FAs with new-onset AF or recurring AF after cardioversion or cardiac surgery. In the recently published VITAL (Vitamin D and Omega-3) Rhythm Study, supplementation of 460 mg/d of EPA and 380 mg/d of DHA with or without vitamin D3 did not show a significant reduction of new-onset AF.[16] Rates of NPAF were lower than in our population (38.4% versus 55.5% in our study); however, differences between intervention groups are not reported. In the 2020 OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction) trial, supplementation of 930 mg EPA and 660 mg of DHA after myocardial infarction showed a higher number of new-onset AF without reaching statistical significance.[17] The 2020 published results from the STRENGTH RCT, which studied the effect of supplementation of cumulative 4 g of EPA and DHA in high cardiovascular risk patients showed a small, yet significant increase in newly onset AF.[18] Similarly, in the 2018 published REDUCE-IT (Reduction of Cardiovascular Events With EPA-Intervention Trial) trial, where 4 g of EPA daily was supplemented, more patients in the EPA group were hospitalized for new-onset AF or atrial flutter.[19] In contrast, we did not find a negative effect of EPA on heart rhythm. This could be due to different patient populations, as our study focused on patients with already established AF. Furthermore, a relevant difference may also consist of n-3 FA intake achieved by regular nutrition accompanied by other food components or by taking n-3 supplements. The combined results of these RCTs were recently studied

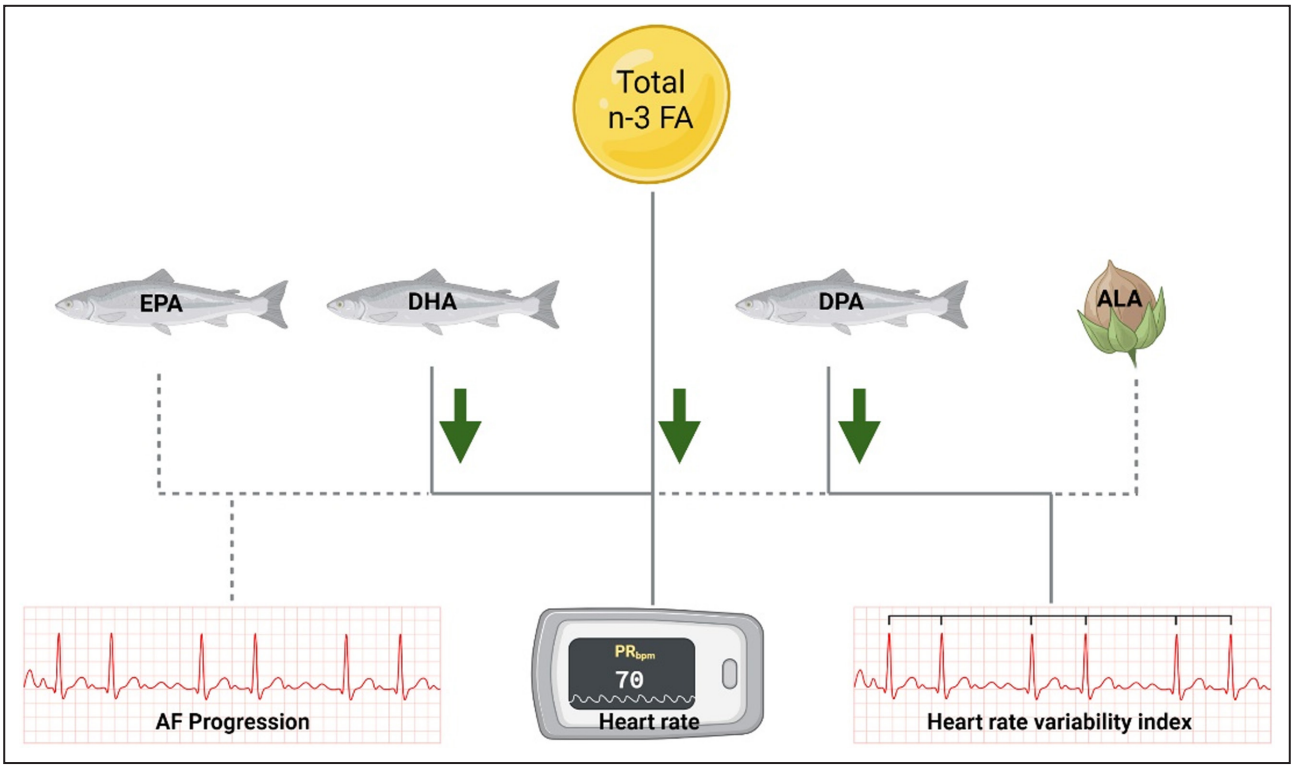

Figure 2. Summary of main results.
Total n-3 FAs and DHA were shown to reduce heart rate, and DPA reduced the heart rate variability index. Dashed lines indicate no significant effect between total or individual n-3 FAs and end points. Symbols of individual n-3 FAs indicate mainly marine or plant-derived origin. AF indicates atrial fibrillation; ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; and n-3 FA, omega-3 fatty acid. Created with BioRender.com.

in a meta-analysis, which showed a 1.37 fold increased risk of AF with n-3 FA supplementation compared with placebo.[27] These results are in contrast to previous results from observational studies where higher levels of n-3 FAs were associated with lower rates of new-onset AF or hospitalization due to AF.[28] In these studies DHA was associated with the largest risk reduction. In our cohort, DHA showed the strongest association with NPAF, which supports the concept that the type of the n-3 FA supplemented or ingested with food is relevant to achieve a clinical benefit. It is possible that DHA has a superior antiarrhythmic effect, as it is the preferred storage form of n-3 FAs in the myocardium[29] and it has been described that accumulation of n-3 FAs in heart cells may increase resistance against arrhythmias. Possible mechanisms on cellular level are prevention of excess calcium influx by inhibition of L-type calcium channels and prolonged inactivation of voltage-dependent sodium channels.[29,30] Whether there is a dose-dependent effect of EPA and/or DHA on AF risk remains open. In the STRENGTH RCT, no differences in the primary outcome were found between tertiles of percent change in FA fractions. In our current study we did not find differences between quartiles of total n-3 FA levels and rates of NPAF, which supports the hypothesis that the type of n-3 FA supplemented (ie, EPA versus DHA) might be important to achieve the desirable effect. Further interventional studies could compare different types of n-3 FA supplementation (ie, EPA versus DHA) to bring additional insight to this matter.

Our study shows an association of DPA with a lower HRVI. This result differs from findings of other studies. An RCT with supplementation of 460 mg/g EPA and 380 mg/g DHA in recipients of renal transplant showed an increase in HRV. However, this was performed in patients without AF, which might explain the different results. Furthermore, DPA, which was associated with a lower HRVI in our study, was not supplemented in this trial.[31] We also focused on the HRVI as a sole marker of HRV as it was the most promising parameter based on previous work. It is possible that other markers of HRV could have yielded different results.

We found an association of a lower HR with higher total n-3 FA and DHA levels. There is evidence from other studies that n-3 FAs may reduce HR, albeit these studies were focused on patients without AF. In 2 RCTs a reduction of HR with supplementation of n-3 FAs was found.[32] This has also been demonstrated in a 2018 published meta-analysis with data from around 3000 participants receiving

n-3 FA supplementation. In this meta-analysis a small yet significant reduced HR (–2.23 bpm) was found with n-3 FA supplementation.[33] The size of this reduction in HR can only be indirectly compared with our findings due to different study design, end points, and heterogeneity of supplementation in this meta-analysis.

We found a 1% decrease in HR per one percentage higher total n-3 FA and DHA concentrations, which would translate to 0.6 to 1 bpm in an individual with normal HR. It has been shown that supplementation of 160 mg EPA and 80 mg of DHA daily leads to a 10% increase in whole blood n-3 FA levels, which would translate to a larger reduction of HR found in our study compared with the aforementioned meta-analysis.[33,34] Another study with higher amounts of EPA and DHA substitution (0.5, 1, and 2 g of EPA and DHA) found even higher increases in EPA+DHA fractions in red blood cells after supplementation for 6 months using the same methodology to determine n-3 FA levels as our study.[35] However, it is likely that the reduction of HR is not linear and that the effect size will diminish below/above a certain level of n-3 FAs. Interestingly, the clinical effect of n-3 FAs on HR reduction was observed only in trials that supplemented with DHA but not in trials with EPA.[33] This supports our findings that specifically DHA lowers resting HR and that this effect is applicable to patients with AF. This finding is important as a lower HR has been associated with lower mortality in patients with AF in the setting of acute myocardial infarction.[36] It is assumed that n-3 FAs lower HR by having a direct effect on cardiac cell membrane electrical excitability. In vitro experiments showed that n-3 FAs lower the resting potential and increase the refractory period duration in cardiac myocyte cells through inhibition of sodium channels and that this mechanism potentially leads to the n-3 FA induced reduction in HR.[37]

Limitations of our study include (1) the cross-sectional design, which does not allow deducing from our results to a causal relationship; (2) the study was performed in patients above 65 years of age in Switzerland and therefore is not applicable to the general population; (3) despite adjustment for multiple risk factors, some results may be skewed to residual confounding, particulary in regards to the secondary end points as variables for adjustment were mainly based on their risk on AF progression; and (4) no information regarding n-3 FA supplementation was available in the data set. Whole blood n-3 FA levels will, however, reflect individual supplementation of n-3 supplementation; we cannot fully exclude that n-3 FA supplementation might influence outcome, but a contribution in clearly <10% can be anticipated in our population.[38] Strengths of our study include the large sample size of 1969 patients with well-classified AF and patient characteristics, the evaluation of n-3 FA content in whole blood by a standardized method, which reliably reflects n-3 FA uptake up to several years independent of interindividual bioavailability.

CONCLUSIONS

We did not find an association between nutritionally achievable n-3 FAs and AF progression. After correction for all confounding factors, however, we found that higher total n-3 FAs and DHA tended to be associated with a lower HR in patients with AF. In addition, higher levels of DPA were associated with a lower HRVI. Although n-3 FAs do not seem to affect AF progression, n-3 FAs, particularly DHA, may be useful to control HR in patients with AF.

ARTICLE INFORMATION

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Affiliations

Department of Internal Medicine, Cantonal Hospital of Baden, Baden, Switzerland (P.B., M.F.R., N.R.B., J.H.B.); Clinical Trial Unit, University Hospital of Basel, Basel, Switzerland (A.W., M.C.); Center for Molecular Cardiology, Laboratory for Platelet Research, University of Zurich, Schlieren, Switzerland (N.R.B., J.H.B.); Department of Cardiology (M.C., S.A., M.K., C.S.Z., S.O.), and Cardiovascular Research Institute Basel (M.C., S.A., M.K., C.S.Z., S.O.), University Hospital of Basel, Basel, Switzerland; Department of Anaesthesiology and Pain Medicine, Inselspital (M.G.F.), and Department of General Internal Medicine (N.R., J.O.), Bern University Hospital, University of Bern, Switzerland; Institute of Primary Health Care (BIHAM), University of Bern, Switzerland (N.R., J.O.); Division of Cardiology, Ende Ospedaliero Cantonale (EOC), Ospedale Regionale di Lugano, Lugano, Switzerland (G.M.); Royal Brompton and Harefield Hospitals, London, UK (T.F.L.); National Heart and Lung Institute, Imperial College, London, UK (T.F.L.); Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland (T.F.L., G.G.C.); Population Health Research Institute, McMaster University, Hamilton, Canada (D.C.); and Department of Neurology, University Hospital of Zurich, Zurich, Switzerland (P.B.).

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Supplemental Material

Appendix S1
Tables S1–S4

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Supplemental Material

Swiss-AF Study Investigators:

University Hospital Basel and Basel University: Stefanie Aeschbacher, , Steffen Blum, Leo Bonati, David Conen, Elisa Hennings, Elena Herber, Vasco Iten, Philipp Krisai, Mirko Lischer, Michael Kühne, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Stefan Osswald, Rebecca Paladini, Anne Springer, Christian Sticherling, Thomas Szucs, Gian Voellmin. Principal Investigator: Stefan Osswald; Local Principal Investigator: Michael Kühne.

University Hospital Bern: Faculty: Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Research fellows: Luise Adam, Carole Elodie Aubert, Martin Feller, Claudio Schneider, Axel Loewe, Elisavet Moutzouri; Study nurses: Tanja Flückiger, Cindy Groen, Damiana Rakovic, Rylana Wenger, Lukas Ehrsam, Alexandra Nuoffer, Nathalie Schwab, Tuhanh Zarrabi Saffari. Local Principal Investigator: Nicolas Rodondi, Tobias Reichlin.

Stadtspital Triemli Zurich: Christopher Beynon, Roger Dillier, Michèle Deubelbeiss, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Samira Murugiah, Jacqueline Nadler, Thayze Obst, Fiona Schlomowitsch, Xiaoye Schneider, Katrin Studerus, Dominik Weishaupt. Local Principal Investigator: Andreas Müller.

Cantonal Hospital Baden: Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Alexandra Grau, Jonas Villinger, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Giulia Montrasio, Stefanie Leuenberger, Franziska Rutz. Local Principal Investigator: Jürg-Hans Beer.

Cardiocentro Lugano: Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli. Local Principal Investigator: Tiziano Moccetti.

Cantonal Hospital St. Gallen: Roman Brenner, David Altmann, Michaela Gemperle. Local Principal Investigator: Peter Ammann.

Cantonal Hospital Fribourg: Mathieu Firmann, Sandrine Foucras. Local Principal Investigator: Daniel Hayoz.

Cantonal Hospital Lucerne: Benjamin Berte, Virgina Justi, Frauke Kellner-Weldon, Brigitta Mehmann, Myriam Roth, Andrea Ruckli-Kaeppeli, Ian Russi, Kai Schmidt, Mabelle Young, Melanie Zbinden. Local Principal Investigator: Richard Kobza.

Ente Ospedaliero Cantonale (EOC) Lugano: Jane Frangi-Kultalahti, Anica Pin, Luisa Vicari Local Principal Investigator: Giorgio Moschovitis.

University Hospital Geneva: Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof Lovblad, Patrick Perret, Philippe Tavel, Cheryl Teres. Local Principal Investigator: Dipen Shah.

University Hospital Lausanne: Nathalie Lauriers, Marie Méan, Sandrine Salzmann. Local Principal Investigator: Jürg Schläpfer.

Bürgerspital Solothurn: Andrea Grêt, Jan Novak, Sandra Vitelli. Local Principal Investigator: Frank-Peter Stephan.

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi-Kultalahti, Augusto Gallino, Luisa Vicari. Local Principal Investigator: Marcello Di Valentino.

University of Zurich/University Hospital Zurich: Helena Aebersold, Fabienne Witassek, Matthias Schwenkglenks.

Medical Image Analysis Center AG Basel: Jens Würfel (Head), Anna Altermatt, Michael Amann, Petra Huber, Esther Ruberte, Tim Sinnecker, Vanessa Zuber.

Clinical Trial Unit Basel: Michael Coslovsky (Head), Pascal Benkert, Gilles Dutilh, Pia Neuschwander, Patrick Simon.

Schiller AG Baar: Ramun Schmid.

Table S1. AIC comparisons for models with sex as interaction term (AIC w) vs. models without interaction term (AIC w/o).

Endpoint	n-3 FAs	Adjustment	AIC w	AIC w/o
AF type binary	Total n-3 FAs	Age / sex adjusted	2662.05	2663.79
AF type binary	EPA, DHA, DPA, ALA	Age / sex adjusted	2671.59	2668.36
AF type binary	Total n-3 FAs	Fully adjusted	2623.60	2623.91
AF type binary	EPA, DHA, DPA, ALA	Fully adjusted	2632.64	2627.91
AF type ordinal	Total n-3 FAs	Age / sex adjusted	4102.85	4107.95
AF type ordinal	EPA, DHA, DPA, ALA	Age / sex adjusted	4111.10	4112.11
AF type ordinal	Total n-3 FAs	Fully adjusted	4026.58	4029.71
AF type ordinal	EPA, DHA, DPA, ALA	Fully adjusted	4033.66	4032.50
Heart rate	Total n-3 FAs	Age / sex adjusted	-351.51	-353.13
Heart rate	EPA, DHA, DPA, ALA	Age / sex adjusted	-340.87	-347.54
Heart rate	Total n-3 FAs	Fully adjusted	-415.40	-416.81
Heart rate	EPA, DHA, DPA, ALA	Fully adjusted	-405.51	-411.94
HRVI	Total n-3 FAs	Age / sex adjusted	1103.59	1102.76
HRVI	EPA, DHA, DPA, ALA	Age / sex adjusted	1110.37	1104.48
HRVI	Total n-3 FAs	Fully adjusted	1106.51	1105.82
HRVI	EPA, DHA, DPA, ALA	Fully adjusted	1112.34	1106.29

AIC = Akaike's Information Criterion, AF = atrial fibrillation, ALA = alpha-linolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HRVI = heart rate variability index, n-3 FA = Omega-3 fatty acids.

Table S2. Primary endpoint by observed quartile class of total n-3 FAs with standardized mean differences.

	Q1	Q2	Q3	Q4	SMD
total n-3 FAs	2.78 - 5.18	5.19 - 5.82	5.83 – 6.60	6.61 – 14.53	
n	506	479	494	490	
AF type (%)					0.152
Paroxysmal	206 (40.7)	227 (47.4)	200 (40.5)	243 (49.6)	
Persistent	178 (35.2)	159 (33.2)	163 (33.0)	133 (27.1)	
Permanent	122 (24.1)	93 (19.4)	131 (265)	114 (23.3)	

AF = atrial fibrillation, Q1-Q4 = quartiles SMD = standardized mean differences.

Table S3. AIC comparisons for models with baseline ecg rhythm (Sinus rhythm, atrial fibrillation, other rhythm) as interaction term (AIC w) vs. models without interaction term (AIC w/o).

Endpoint	n-3 FAs	Adjustment	AIC w	AIC w/o
AF type binary	Total n-3 FAs	Age / sex adjusted	2187.56	2663.79
AF type binary	EPA, DHA, DPA, ALA	Age / sex adjusted	2191.02	2668.36
AF type binary	Total n-3 FAs	Fully adjusted	2191.11	2623.91
AF type binary	EPA, DHA, DPA, ALA	Fully adjusted	2195.53	2627.91
AF type ordinal	Total n-3 FAs	Age / sex adjusted	3283.45	4107.95
AF type ordinal	EPA, DHA, DPA, ALA	Age / sex adjusted	3279.92	4112.11
AF type ordinal	Total n-3 FAs	Fully adjusted	3300.22	4029.71
AF type ordinal	EPA, DHA, DPA, ALA	Fully adjusted	3297.30	4032.50
Heart rate	Total n-3 FAs	Age / sex adjusted	-962.83	-353.13
Heart rate	EPA, DHA, DPA, ALA	Age / sex adjusted	-955.78	-347.54
Heart rate	Total n-3 FAs	Fully adjusted	-963.39	-416.81
Heart rate	EPA, DHA, DPA, ALA	Fully adjusted	-957.25	-411.94
HRVI	Total n-3 FAs	Age / sex adjusted	1052.14	1102.76
HRVI	EPA, DHA, DPA, ALA	Age / sex adjusted	1060.59	1104.48
HRVI	Total n-3 FAs	Fully adjusted	1056.62	1105.82
HRVI	EPA, DHA, DPA, ALA	Fully adjusted	1064.30	1106.29

AIC = Akaike's Information Criterion, AF = atrial fibrillation, ALA = alpha-linolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, HRVI = heart rate variability index, n-3 FA = Omega-3 fatty acids.

Table S4. Omega-3 component measurements by observed ECG rhythm at baseline.

	Sinus rhythm	Atrial fibrillation	Other rhythm	SMD
n	1116	811	42	
Total omega-3 (mean (SD))	6.0 (1.1)	5.9 (1.2)	5.9 (1.2)	0.060
EPA (mean (SD))	0.8 (0.3)	0.8 (0.3)	0.7 (0.2)	0.150
DHA (mean (SD))	3.3 (0.8)	3.2 (0.8)	3.3 (0.8)	0.074
DPA (mean (SD))	1.7 (0.3)	1.7 (0.3)	1.7 (0.2)	0.079
ALA (mean (SD))	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.067

ALA = alpha-linolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, SD = standard deviation, SMD = standardized mean difference