Review

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n-3 fatty acids and the risk of atrial fibrillation, review

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Abstract: Atrial fibrillation (AF) is the most frequent type of cardiac arrhythmia that affects over six million individuals in Europe. The incidence and prevalence of AF rises with age, and often occurs after cardiac surgery. Other risk factors correlated with AF comprise high blood pressure, diabetes mellitus, left atrial enlargement, ischemic heart disease, and congestive heart failure. Considering the high prevalence of AF in aging societies, strategies to prevent serious complications, such as stroke or heart failure, are important because they are correlated with high morbidity and mortality. The supplementation of sea-derived n-3 polyunsaturated fatty acids (PUFA) is widely discussed in this context, but the results of experimental and observational studies are in contrast to randomized placebo-controlled intervention trials (RCTs). Specifically, larger placebo-controlled n-3 PUFA supplementation studies with long follow-up showed a dose-dependent rise in incident AF. Daily n-3 PUFA doses of ≥1 g/d are correlated with a 50 % increase in AF risk, whereas a daily intake of <1 g/d causes AF in only 12 %. Individuals with a high cardiovascular risk (CVD) risk and high plasma-triglycerides seem particularly prone to develop AF upon n-3 PUFA supplementation. Therefore, we should exercise caution with n-3 PUFA supplementation especially in patients with higher age, CVD, hypertriglyceridemia or diabetes. In summary, existing data argue against the additive intake of n-3 PUFA for preventative purposes because of an incremental AF risk and lacking CVD benefits. However, more clinical studies are required to disentangle the discrepancy between n-3 PUFA RCTs and observational studies showing a lower CVD risk in individuals who regularly consume n-3 PUFA-rich fish.

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Introduction

The potential protective effects of polyunsaturated fatty acids (PUFA) in cardiovascular diseases (CVD) have been studied extensively. Initial observational studies conducted decades ago reported reduced CVD mortality in subjects with a high n-3 PUFA consumption [1, 2]. Later on, randomized controlled studies showed that the replacement of dietary carbohydrates and saturated fatty acids by PUFA reduces the plasma concentrations of low-density lipoprotein (LDL)-cholesterol and triglycerides, two established factors for CVD risk [3]. Due to such findings, it has been suggested that a healthy diet should incorporate sea fish intake twice a week. Moreover, clinical studies suggested that supplements rich in n-3 PUFA improve cardiovascular health [4].

Atrial fibrillation and chronic diseases

Atrial fibrillation (AF) is a very frequent arrhythmia [5] that affects over six million Europeans [6]. The prevalence of AF rises steadily and represents a great burden to public healthcare systems worldwide. Inflammation and high oxidative stress are believed to be important drivers that promote the development and progression of AF [5]. In this context, the correlation between AF and CRP appears to be unrelated to conventional risk factors. Furthermore, the serum concentration of interleukin six is higher in subjects with chronic AF than in those without. The incidence and prevalence of AF increases with advancing age, and often develops after cardiac surgery. About 25–30 % of patients undergoing bypass operations and 50 % of subjects with coronary and valvular reconstruction are diagnosed with AF in the postoperative phase [7]. Importantly, post-operative AF is correlated with a significant rise in cardiovascular morbidity and mortality, mostly due to stroke and circulatory failure [8]. A pronounced post-operative inflammatory

response seems to contribute to the progression of postoperative AF. A putative mechanism through which n-3 PUFA might mitigate an excessive postoperative inflammatory response is the reduced formation of leukotriene B4 and other proinflammatory eicosanoids [5]. In addition to patients with cardiac surgery, incident AF is also high in the post-acute phase of ischemic cardiac events, where it amplifies the risk of death and stroke. The combination of progressively aging populations worldwide in conjunction with improving health care standards has led to a rapid rise in the incidence and prevalence of AF [9]. Its incidence surges from <0.5 % in subjects in their fifth decade to 10 % in subjects over 80 years old [10, 11]. AF can lead to thromboembolic stroke, congestive heart failure, and other adverse outcomes [12]. In humans with low blood concentrations of n-3 PUFA [eicosapentaenoic fatty acid (EPA) and docosahexaenoic fatty acid (DHA)] the risk of incident AF is significantly increased [13].

Atrial fibrillation, related complications and pathomechanisms

Considering that AF-related complications, such as stroke and heart failure, are correlated with high morbidity and mortality [10], prevention is of pivotal importance. The supplementation of marine n-3 PUFA (EPA and DHA) has been widely discussed in this context, but the results of human intervention studies investigating potential protective effects on CVD are inconsistent [4]. Existing evidence supports the supplementation of n-3 PUFA for lowering the risk of cardiovascular diseases in patients with high plasma triglyceride concentrations [14–16]. Furthermore, a meta-analysis of randomized placebo-controlled intervention trials (RCTs) has shown that n-3-PUFA administration reduces blood pressure and systemic vascular resistance [17]. However, cardiac output has not been altered. There is also data suggesting that n-3 PUFAs increase nitric oxide (NO) production through an induction of endothelial NO synthase (eNOS) expression [4]. In line with this finding, several RCTs have reported an improvement in circulating biomarkers of endothelial dysfunction, such as E-selectin, VCAM-1, or ICAM-1 [18, 19]. Furthermore, the consumption of n-3 PUFA improves flow-mediated vasodilation [20] and arterial stiffness measured by carotid-femoral pulse wave velocity [21]. Merino et al. [22] demonstrated that n-3 PUFA intake enhances the function of small peripheral arteries in subjects with intermediate to high risk of cardiovascular diseases. An improved arterial elasticity measured by pulse contour analysis has also been found in response to n-3 PUFA supplementation in patients on statin therapy [5, 23].

Experimental studies

Experimental studies, in which animals were treated with n-3 PUFA, suggested anti-arrhythmic effects [24]. In rabbits for example, n-3 PUFA lowered the stretch-induced susceptibility to AF [25, 26]. Furthermore, n-3 PUFAs administration significantly improved the effective atrial refractory period (ERP) in a canine model of rapid atrial stimulation [27]. Experimental studies using isolated pulmonary vein preparation suggest that n-3 PUFA administration can influence cardiac electrophysiology and lower the development of AF [28, 29]. EPA reduces pulmonary vein arrhythmogenesis through the mechanoelectrical feedback induced by NO formation [29]. Finally, experimental studies on perfused hearts from rabbits fed with an n-3 PUFA-rich diet indicate an increase in membrane fluidity and a lower stretch-induced fall in the refractory period [25]. The results of experimental *in vivo* and *in vitro* studies are in contrast to human studies, in which dietary or supplemental marine n-3 PUFA consumption showed inconsistent effects on AF [30, 31].

Impact of n-3 PUFA on AF, risk factors and mechanisms

Even RCTs testing the impact of n-3 PUFA supplements on incident AF gave heterogeneous results [32–35]. Larger clinical trials with prolonged n-3 PUFA supplementation showed a dose-dependent increase in AF risk that reaches up to 50 % when daily doses of more than 1 g n-3 PUFA are used [35–37]. In contrast, daily doses of less than 1 g/d are correlated with a 12 % increase in AF risk [36, 37]. Huh et al. concluded that substantial evidence from RCTs indicates that the potential protective effects of n-3 PUFA supplements on vasculature are achieved at the expense of an elevated AF risk [10]. Also, two recent Cochrane's systematic reviews of RCTs found little to no benefit of higher n-3 and n-6 PUFA intake from dietary sources or supplements [38, 39]. The risk of incident AF in response to n-3 PUFA supplements has also been investigated in a meta-analysis by Lombardi et al. [37], which revealed a significantly higher AF risk in subjects with elevated CVD risk and high plasma triglyceride concentrations. The mechanisms mediating AF risk in n-3 PUFA consumers are insufficiently understood [40, 41]. However, established risk factors for AF, such as higher age, increased blood pressure, diabetes mellitus, left atrial enlargement, ischemic heart disease, and congestive heart failure, might interact with n-3 PUFA and cause an incremental risk of AF [5]. Among the discussed mechanisms which lead to increased AF by n-3 PUFA, it has been found that PIEZO proteins may mediate the effect of n-3 PUFA on AF [10]. The

large PIEZO proteins are important for the function of cell ion channels. DHA delays the interaction of PIEZO1 and EPA speeds it up. Thus, the ratio DHA:EPA might be important in this respect. Atrial fibroblasts from patients having AF have higher PIEZO1 expression and activity compared with those from patients with sinus rhythm. It follows that PIEZO1 may support atrial structural remodeling [42].

Randomized clinical trials

While RCTs failed to show consistent beneficial impacts of n-3 PUFA supplementation on CVD endpoints, they have revealed an elevated risk of AF (Table 1). The following section provides a concise overview of existing RCTs and discusses their strengths and weaknesses. The REDUCE-IT trial is a secondary prevention trial, which enrolled a total of 8,179 subjects with established cardiovascular risk factors, such as diabetes mellitus, who were on treatment with statins. Their plasma triglyceride concentrations ranged between 135 and 499 mg/dL [43]. Participants were randomly allocated to receive either 4 g/d of n-3 PUFA or placebo for a median follow-up period of 4.9 years. The primary endpoint was a combination of death from CVD, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. n-3 PUFA supplements significantly lowered the primary endpoint by 25 % [43]. In n-3 PUFA and placebo treated participants, the primary endpoint occurred in 17.2 and 22.0 %, respectively (HR 0.75; 95 % CI 0.68 to 0.83; p<0.001). However, the protective effect of n-3 PUFA supplementation was contrasted by a higher percentage of participants who required hospitalization for AF or flutter compared to placebo-treated subjects (3.1 vs. 2.1 %, p=0.004; HR 1.35; 95 % CI 1.11–1.65 p=0.003). The authors concluded that the beneficial cardiovascular effects of high-dose n-3 PUFA supplementation with 4 g/d were compromised by a higher risk of AF. In the STRENGTH study, administration of the same n-3 PUFA dose for 3.5 years also increased the risk of AF, but did not lower the primary endpoint, when compared to a corn oil-based placebo. This double blind, randomized, multicenter trial included 13,078 participants at increased risk of CVD and elevated plasma triglyceride levels with a median circulating concentration of 240 mg/dL. The participants received usual background therapies, including statins [44]. The primary endpoint was recorded in 785 (12.0 %) n-3 PUFA treated participants and 795 (12.2 %) placebo treated participants, respectively (HR 0.99; 95 % CI 0.90–1.09; p=0.84). At the same time, AF risk significantly increased with an HR of 1.67 (95 % CI 1.28–2.18; p<0.001). The results of REDUCE-IT and STRENGTH, two RCT with similar supplementation regimens and comparable follow-up periods, do not support the administration of high n-3 PUFA doses for the reduction of major CVD events, particularly in high-risk patients. A substantially lower dosage of n-3 PUFA was used in the ASCEND study, another large-scale secondary prevention trial including 15,480 subjects suffering from diabetes mellitus but without signs of coronary atherosclerosis [45]. At baseline, less than 1 % of the ASCEND participants had a previous hospital admission with documented evidence of AF [46]. Participants were allocated randomly to 840 mg/d n-3 PUFA supplementation (EPA plus DHA) or placebo for a mean follow-up of 7.4 years. The primary endpoints were as follows: first serious vascular event, such as nonfatal myocardial infarction, stroke, transient ischemic seizure, or vascular death, excluding confirmed intracranial hemorrhage. During follow-up, 689 (8.9 %) and 712 (9.2 %) participants in the verum and placebo group, respectively, experienced at least one event (HR 0.97; 95 % CI 0.87–1.08; p=0.55). Compared to placebo, low-dose n-3 PUFA administration caused no significant increase of AF risk during follow-up (7.7 vs. 7.6 %; HR 1.02; 95 % CI 0.91 to 1.15). In line with this result, also the VITAL study, a primary AF prevention trial in 25,119 participants (mean age 66.7 years) who were free from AF at study entry, did not show an increased AF risk when using low-dose n-3 PUFA supplementation of 840 mg/d of EPA and DHA [34]. The occurrence of AF over a median follow-up period of 5.3 years was recorded on the basis of self-reported diagnosis and medical records. Amongst the 900 (3.6 %) participants who developed AF, 469 (3.7 %) and 431 (3.4 %) were assigned to n-3 PUFA or placebo (HR 1.09; 95 % CI 0.96–1.24; p=0.19), respectively. Based on the findings from ASCEND and VITAL, low dose n-3 PUFA supplementation with <1 g/d appears to be rather safe in regards to AF risk, but does not reduce serious CVD events. Nevertheless, there is a tendency towards a higher number of AF cases in the n-3 PUFA groups of both studies. Although n-3 PUFA supplementation does not lower first serious CVD events, it might improve outcome after such an event. This question has been addressed in the OMEMI study, where elderly subjects with a recent MI were allocated to receive either 1.8 g/day of n-3 PUFA (930 mg/d EPA and 660 mg/d DHA) or placebo in addition to standard medication [35, 47]. The primary endpoint was a compound of nonfatal myocardial infarction, unplanned revascularization, stroke, all-cause death, and heart failure hospitalization. During two years of follow-up, the primary endpoint was recorded in 108 (21.4 %) participants with n-3 PUFA supplementation and 102 (20.0 %) participants taking placebo (HR 1.08; 95 % CI 0.82–1.41; p=0.60). Newly diagnosed AF and 'micro-AF' were recorded as secondary outcomes on the basis of clinical records and by screening with a Zenicor thumb-ECG. Micro-AF refers to short episodes of rapid

Table 1: Clinical studies (RCTs) of the risk of atrial fibrillation with n-3 PUFA intake

RCT	Number	Follow up years	AF at baseline included	Study drug	Placebo	AF events (% per year)	Types of AF	Risk of AF	AF assessment	Primary endpoint	% Change of primary endpoint
				1 g/d n-3 PUFA							
ASCEND* (Bowman et al. 2018, Parish et al. 2020)	15,480	7.4	No	1 g/d n-3 PUFA (460 mg EPA+380 mg DHA)	Olive oil	301 (0.3)	Main paper: patient-reported AF Research Letter: New onset AF	Main paper: Rate ratio 1.23 (95 % CI 0.98–1.54); Res. Letter:1.02 (95 % CI 0.91–1.15)	Patient-reported AF and comprehensive assessment of AF events	Combination death from CVD, nonfatal MI and stroke, unstable angina, revascularization	Lowered by 25 %
RP (Roncaglioni et al. 2013)	12,505	5	Yes	1 g/day of n-3 PUFA (EPA and DHA<85 % in ratio from 0.9:1 to 1.5:1)	Olive oil	205 (0.3)	Hospitalization for AF	HR 1.23 (95 % CI 0.94–1.62; p=0.15)	AF reported as cause for hospitalization for CVD	Composite of time to death from CVD or hospital admission for cardiovascular causes	Increased by 2 %
VITAL (Albert et al. 2020)	25,119	5.3	No	1 g/d n-3 PUFA (460 mg EPA+380 mg DHA)	Olive oil	900 (0.7)	New onset	HR 1.09 (95 % CI 0.96–1.24; p=0.19)	Incident AF determined by self-reported diagnosis	Incident of AF	AF increased by 9 %
GISSI-HF (Aleksova et al. 2013)	5,835	3.9	No	1 g/d n-3 PUFA (EPA+DHA)	Olive oil	852 (3.7)	New onset	HR 1.10 (95 % CI 0.96–1.26; p=0.19)	AF events during the trial diagnosed with ECGs at each visit	Incident AF	AF increased by 9 %
				>1 g/d n-3 PUFA							
OMEMI (Kalstad et al. 2021, Myhre et al. 2023)	1,014 (only 759 were in AF analysis)	2	NO	1.8 g/d n-3 PUFA (930 mg EPA+660 mg DHA)	Corn oil	43 (2.1)	New onset	HR 1.84 (95 % CI 0.98–3.45; p=0.06)	Incident AF events assessed by clinical reports or ECGs at study visits	Composite of nonfatal AMI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization after 2 years	Increased by 6 %
STRENGTH (Nicholls et al. 2020)	13,078	3.5	Yes	4 g/d n-3 PUFA (EPA+DHA)	Corn oil	230 (0.5)	New onset	HR 1.64 (95 % CI 1.28–2.18; p <0.001)	New AF events reported as tertiary outcome	Combination of CVD death, nonfatal MI and stroke, unstable angina, revascularization	Lowered by 1 %
REDUCE-IT (Bhatt et al. 2019)	8,179	4.9	YES	4 g/d icosapent ethyl (ethyl ester of EPA)	Mineral oil	374 (0.9)	New onset or worsening of AF events	Risk ratio 1.35 (95 % CI 1.11–1.65; p=0.003)	AF reported as prespecified tertiary outcome for hospitalization of AF or flutter	Combination of CVD death, nonfatal MI and stroke, unstable angina, revascularization	Lowered by 22 %

AF, atrial fibrillation; GISSI-HF, Gruppo Italiano perlo Studio della Sopravvivenza nell 'Insuffizienza Cardiaca; RP, The Risk and Prevention Study; VITAL, Vitamin D and n-3 PUFA study; OMEMI, n-3 PUFA in Elderly with Myocardial Infarction; STRENGTH, Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; ASCEND, A Study of Cardiovascular Events in Diabetes; EPA, eicosapentaenoic fatty acid; DHA, docosahexaenoic fatty acid; CI, confidence interval. The bold letters indicate two groups of trials. Trials administering low and high dose PUFA.

irregular atrial activity that are correlated with an elevated risk of newly appearing AF and CVD events [48]. AF and micro-AF were observed in 28 (7.2 %) and 15 (4.0 %) participants on n-3 PUFA supplementation and placebo (HR 1.84; 95 % CI 0.98–3.45, p=0.06), respectively. The biochemical efficacy of n-3 PUFA supplementation has been ascertained by estimation of the EPA and DHA serum concentrations at baseline and study end with median changes of +87 % and +16 %, respectively. In contrast, placebo users showed a lowering of EPA and DHA serum concentrations by −13 % and −8%, respectively. Based on these results, the investigators concluded that high dose n-3 PUFA intake by post MI patients does not improve outcome, but seems to promote the risk of AF and micro-AF. Furthermore, the increase in atrial arrhythmia was associated with higher serum concentrations of EPA. Although the increase in AF risk associated with low-dose n-3 PUFA supplementation of less than 1 g/d was small and not significant in most studies, the reported AF rates were consistently higher in the verum groups than in the respective placebo groups. For example, amongst the 12,513 participants of the Risk and Prevention Study (RP) with several cardiovascular risk factors or pre-existing coronary atherosclerosis, low dose n-3 PUFA administration of 1 g/d (EPA and DHA) was associated with 113 (1.8 %) AF cases compared to 92 (1.5 %) in the placebo group (HR 1.22; 95 % CI 0.93 to 1.61; p=0.15) [49]. The primary endpoints, cardiovascular death and hospitalization for CVD, occurred in 1,478 participants with similar frequencies in the n-3 PUFA group (733/6,239 cases, 11.7 %) and the placebo group (745/6,266, 11.9 %). This resulted in an HR of 0.97 (95 % CI 0.88 to 1.08, p=0.58) and thus negates a protective effect on CVD mortality and morbidity. Also, amongst 5,835 participants of the GISSI-HF study with established heart failure, but without pre-existing AF, 1 g/d of n-3 PUFAs in addition to the prescribed heart failure therapy was associated with 444 (15.2 %) incident AF cases compared to 408 (14.0 %) in the placebo group (unadjusted hazard 1.10, p=0.19) [50]. Interestingly, decreased serum concentrations of n-3 PUFA were independently correlated with an increased incidence of AF at baseline, but not with incident AF during follow-up. In summary, most of the RCTs show a consistent trend or even an increase towards higher AF rates in n-3 PUFA treated individuals.

Meta-analysis and treatment outcomes

This notion is confirmed by a meta-analysis from Lombardi et al. that identified a higher AF incidence in n-3 PUFA supplemented subjects having high cardiovascular risk, established CVD and high plasma triglyceride concentrations [37, 51]. Furthermore, n-3-PUFA supplementation failed to consistently lower CVD morbidity and mortality. Although n-3 PUFA have antiarrhythmogenic properties, their clinical efficacy on the prevention of AF is not consistently supported [52]. Thus, despite a significant association between n-3 PUFA administration and incident AF, the underlying mechanism that mediates this relationship remains elusive. Another meta-analysis investigated RCTs stratified to low dose (≤1 g/d) and high dose (>1 g/d) n-3 PUFA supplementation [36, 45]. This meta-analysis comprised seven clinical trials with 58,939 subjects taking ≤1 g/d and 22,271 subjects taking>1 g/d sea n-3 PUFA for a mean follow-up of 4.9 years). Overall, the intake of n-3 PUFA was linked to a higher risk of newly diagnosed AF (n=2,905; HR 1.25; 95 % CI 1.07–1.46; p=0.013). Moreover, the risk of AF in studies using >1 g/d n-3 PUFA was greater (HR 1.49; 95 % CI 1.04–2.15; p=0.042) than in those using ≤1 g/d n-3 PIUFA (HR 1.12; 95 % CI 1.03–1.22; p=0.024, p for interaction<0.001). The HR for AF per 1 g increase in n-3 PUFA intake has been calculated with 1.11, (95 % CI 1.06–1.15; p=0.001). While Lombardi's [37, 51] meta-analysis with 14 clinical trials and data on 125,763 patients showed an n-3 PUFA-related elevation in AF risk, a large analysis by Qian et al. [53] amongst 54,799 participants from 17 cohorts found no association between incident AF and the concentration of EPA in blood and adipose tissue (HR per interquintile range 1.00 (95 % CI 0.95–1.05). Even more, the study showed that higher circulating levels of DPA, DHA, and EPA+DHA, were linked to a decreased incidence of AF (HRs 0.89 (95 % CI 0.83–0.95), 0.90 (95 % CI 0.85–0.96), and 0.93 (95 % CI 0.87–0.99) [53]. Amongst the participants, 7,720 subjects developed AF over a median follow-up period of 13.3 years.

Table 1 shows an analysis of the RCTs considered in this paper. Four RCTs with n-3 PUFA supplementation of up to 1 g/d did not detect a significant effect on AF risk. Furthermore, the primary endpoint (combination of death from CVD, nonfatal MI and stroke, unstable angina, revascularization) was significantly lowered only in the ASCEND trial but not in RP. Similarly, the three RCTs administering higher n-3 PUFA dosages of >1 g/d unanimously showed a significant increase in AF risk. A significant reduction in cardiovascular risk was only observed in the REDUCE-IT (reduction of cardiovascular events with Icosapent Ethyl-supplementation) trial, where serious vascular events were used as primary endpoint. In this study, participants with high triglycerides were supplemented with a daily dose of 4 g icosapent ethyl (a purified form of eicosapentaenoic acid). This treatment resulted in a statistically significant 25 % reduction of various cardiovascular outcomes. In contrast, in ASCEND, a daily n-3 PUFA dose of 1 g (containing 0.84 g EPA+DHA) was administered to

subjects with diabetes mellitus, but without known CVD. N-3 PUFA supplementation decreased serious vascular outcomes by 25 % in this study. Based on the results from RCTs it can be speculated that factors such as duration of follow up or patient's profile, rather than n-3 PUFA dosage, determine the effect on cardiovascular risk. Furthermore, disease specific medication, matrix-related effects, or the sources of specific supplements could contribute to differences between existing studies. For example, REDUCE-IT used a highly purified icosapent ethyl supplement, which was not the case in the other studies. Furthermore, supplements can be derived from fish or algae, with potentially different biological effects. Fish, for example, is a rich natural source of EPA and DHA, whereas α-linolenic acid (ALA) is the primary plant-derived n-3 PUFA. The latter is of particular interest, as it has been proposed as a sustainable and cheap source of n-3 PUFA that may potentially lower the risk of cardiovascular events and AF [54]. However, a study by Fretts et al. [55] showed no significant relationship between plasma ALA concentrations and incident AF after correction for age, sex, and clinical and demographic factors. Thus, systematic studies should be undertaken to investigate the impact of food items that increase ALA intake and promote its conversion to DHA. The content of EPA and DHA in fish is primarily determined by their intake of phytoplankton, which produces significant amounts of these n-3 PUFA species. Microalgae are a part of phytoplankton [56, 57]. A meta-analysis of 11 RCTs that administered n-3 PUFA through algal oils showed similar effects on CVD risk to fish-derived n-3 PUFA. Also, plasma triglycerides decreased significantly [57]. In summary, the n-3 PUFA dosage seems to be a strong determinant of AF risk, but not CVD risk.

Fish consumption and AF

Additional knowledge regarding the role of n-3 PUFA intake for cardiovascular health can be obtained by looking at sea fish consumption as a source of n-3 PUFA [30]. In a prospective cohort study including 4,815 adults ≥65 years, the intake of tuna and other broiled or baked fish was associated with the concentrations of phospholipid long-chain n-3 PUFA in serum. In contrast, the intake of fried fish or fish sandwiches did not show such a correlation. Over 12 years of follow-up, 980 subjects developed AF. In a multivariate analysis, the intake of tuna or other broiled or baked fish was inversely correlated with the occurrence of AF. Eating fish 1 to 4 times weekly was linked to a 28 % risk reduction of AF when compared to individuals who did not include fish in their regular diet (<1 time monthly; HR0.72; 95 % CI0.58 to 0.91; p=0.005). Participants with ≥5 fish-based meals per week had a 31 % decreased risk of AF (HR0.69; 95 % CI0.52 to 0.91; p=0.008). Thus, in elderly subjects, the regular eating of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, seems to decrease the development of AF. It is concluded that the recommendations regarding fish/n-3 PUFA consumption can be maintained.

Frost et al. [58] investigated the relation between fish-derived n-3 PUFA intake and the risk of AF or flutter in a prospective study including 47,949 participants with a mean age of 56 years (Danish Diet, Cancer, and Health Study). Fish-derived n-3 PUFA intake was estimated with the help of a detailed semiquantitative food questionnaire. Fish-derived n-3 PUFA intake ranged from 0.16 g/d in the first quintile to 1.29 g/d in the fifth quintile. During 5.7 years of follow-up, AF or flutter occurred in 556 subjects (374 men and 182 women). Using the lowest quintile of fish-derived n-3 PUFA intake as a reference, the adjusted HRs for AF or flutter in the following quintiles were 0.86, 1.08, 1.01, and 1.34 (p for trend 0.006). The authors concluded that consumption of fish-derived n-3 PUFA was not linked to a reduction in the risk of AF or flutter. In another interesting study, Brouwer et al. [59] investigated the intake of very long-chain n-3 PUFA from fish and the incidence of AF in the Rotterdam Study. Dietary n-3 PUFA intake was assessed by a semiquantitative food-frequency questionnaire, and AF incidence was continuously monitored during follow-up. Data on dietary n-3 PUFA intake at baseline was available from 5,184 subjects free from AF (2,105 men and 3,079 women, mean age 67.4 years). 29.5 % of the study population did not eat fish at baseline. The mean intake of EPA plus DHA was 146±192 mg/d and the mean daily fish consumption in the total population was 15.7±18.7 g/d, which corresponds to one fish meal per week. During a mean follow up duration of 6.4 years, 312 subjects developed AF. Of note, the risk of AF was comparable in the first and third tertile of EPA and DHA consumption (RR 1.18; 95 % CI 0.88–1.57). Additionally, no difference in AF incidence was detected when comparing individuals with a daily fish consumption of 20 g or more with those who did not eat fish (RR 1.17; 95 % CI 0.87–1.57). It was concluded that a higher intake of EPA and DHA from natural fish sources was unrelated to the incidence of AF. The results are in agreement with the Danish Diet, Cancer, and Health study, where intake of n-3 PUFA from fish was also unrelated to AF risk. In contrast, a prospective cohort study by Mozaffarian et al. [30] revealed an inverse association between the intake of tuna and other broiled or baked fish with the occurrence of AF. Therefore, further studies are needed to clarify the controversial findings.

In summary, the role of n-3 PUFA for cardiovascular health remains insufficiently understood. The beneficial effects observed in *in vitro* and *in vivo* studies could not be confirmed in large RCTs. In fact, the majority of existing supplementation studies did not show an improvement in

CVD outcome, but revealed a dose-dependent elevation in AF risk. Although the increase in AF risk was not statistically significant in all studies, a consistent trend has been observed. The combination of increased AF risk and lacking CVD benefits does not support the intake of n-3 PUFA for preventative purposes. However, more clinical studies are required to disentangle the discrepancy between n-3 PUFA intervention trials and observational studies showing a lower CVD risk in individuals who regularly consume n-3 PUFA-rich sea fish. It can be speculated that the regular consumption of n-3 PUFA-rich fish is more an indicator of a healthy lifestyle rather than a mechanistic factor that actively promotes cardiovascular health. Individuals with a balanced diet are probably more health conscious, which results in an advantageous CVD risk profile with a higher level of physical activity.

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