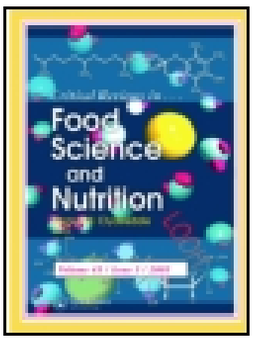

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Atrial fibrillation and its complications in arterial hypertension: The potential preventive role of ω-3 polyunsaturated fatty acids

GianLuca Colussi, Cristiana Catena, Valentina Fagotto, Daniele Darsiè, Gabriele Brosolo, Nicole Bertin, and Leonardo A. Sechi

Division of Internal Medicine, Department of Medicine, University of Udine, Udine, Italy

ABSTRACT

Atrial fibrillation (AF) is the most common type of arrhythmia in the general population with a prevalence that reaches one third of patients with arterial hypertension. Several risk factors frequently associated with hypertension predispose the myocardium to AF by inducing atrial inflammation and fibrosis and altering atrial electrical and mechanical characteristics. AF influences the quality of life of hypertensive patients since it increases incidence of stroke and other thromboembolic events, and mortality. Polyunsaturated fatty acids of the ω-3 family (ω-3 PUFA) have been demonstrated to be beneficial in cardiovascular disease prevention by reducing plasma lipids and blood pressure levels and decreasing the risk of sudden death. These fatty acids can act as potent anti-inflammatory and anti-arrhythmic agents. Many studies have investigated a possible preventive effect of ω-3 PUFA on incident AF reporting contradictory results. This article overviews the evidence currently available on this important topic and provides some conclusive remarks on the possibility that these fatty acids could be beneficial in hypertensive patients.

KEYWORDS

Atrial fibrillation; omega-3 polyunsaturated fatty acids; cardiovascular disease; eicosapentaenoic acid; docosahexaenoic acid; hypertension

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence of 1–2% in the general population. Although the global burden of this condition in the general population is relevant, more attention should be taken in patients with chronic diseases such as arterial hypertension in whom AF prevalence rises up to 30% (Verdecchia et al. 2003; Naccarelli et al. 2009; Wilke et al. 2013). The high prevalence of AF in hypertensive patients has been ascribed to a variety of pathophysiological mechanisms and to specific hypertension-related atrial changes that predispose these patients to AF. Due to the relevant burden of AF in the general population and in patients with hypertension, interventions that can prevent its occurrence would be important. Benefits of polyunsaturated fatty acids of the ω-3 family (ω-3 PUFA) in the prevention of cardiovascular events including sudden death have been reported in previous studies and have been attributed to a hypothetical anti-arrhythmic effect of these fatty acids. This narrative review examines the evidence currently available on the possible benefits of ω-3 PUFA in the prevention of AF in patients with hypertension.

Atrial fibrillation and arterial hypertension

The frequency of the association between hypertension and AF has been clearly established in epidemiological studies. The risk to develop AF is 1.42 times higher in hypertensive than normotensive subjects (Krahn et al. 1995) and the prevalence of hypertension is significantly higher among patients with AF than in matched controls without this arrhythmia (60% vs. 45%, respectively) (Naccarelli et al. 2009). In a study of approximately 2,500 hypertensive patients without AF followed for 16 years, the incidence of a first episode of AF was 4,6 per 1,000 person-year and 33% of patients developed a sustained AF during follow-up (Verdecchia et al. 2003). According to the RE-LY Atrial Fibrillation registry, hypertension is globally the most frequent modifiable risk factor for developing AF with a prevalence in patients that presented with AF to an Emergency Department varying from 42% in India to 81% in Eastern Europe (Oldgren et al. 2014). Overall, hypertension is the most significant population-attributable risk factor for AF beyond age and sex (Hurley et al. 2007) and accounts for more cases of AF than any other risk factor (Benjamin et al. 1994; Kannel et al. 1998).

Although the presence of arterial hypertension is a risk factor widely recognized for AF, levels of blood pressure (BP) above which this risk becomes relevant are still matter of debate. In a case-control study on treated hypertensive patients, the odds ratio (OR) for new onset AF was higher in patients with systolic blood pressure (SBP) above 140 mm Hg (OR 2.3, 95% confidence interval (CI) 1.3-3.9) or below 120 mm Hg (OR 2.0, 95% CI 1.1-3.6) than in those with SBP comprised from 120 and 140 mm Hg. This observation suggested a J-shaped relationship between BP and the occurrence of AF (Thomas et al. 2008). Conversely, prospective cohort studies conducted in healthy American

CONTACT Dr. GianLuca Colussi, MD gianluca.colussi@uniud.it Clinica Medica, Department of Medicine, Academic Hospital of Udine, Piazzale Santa Maria della Misericordia 1, 33100 UD, Udine, Italy.

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women and Norwegian men reported a linear relationship between BP levels and new onset AF. Interestingly, both these studies reported an increased risk of AF even in subjects with high-normal BP (SBP 128–139 mmHg and diastolic BP, DBP, 80–89 mmHg) (Conen et al. 2009; Grundvold et al. 2012). Different from SBP, DBP was shown to be inversely related to the risk of developing AF for a given SBP value (Mitchell et al. 2007; Larstorp et al. 2012), whereas mean BP was not a good predictor of incident AF (Mitchell et al. 2007; Roetker et al. 2014). The evidence collected on SBP and DBP in their relationship with new onset AF puts under the spotlight the possibility of an important causal role of pulse pressure (PP). In the Framingham cohort, an elevated PP predicted incident AF in a 20-year follow-up even after adjustment for major confounders including left atrial dimension, left ventricular mass, and left ventricular fractional shortening (hazard ratio HR 1.23; 95% CI 1.09-1.39 per each 20 mm Hg increase in pulse pressure) (Mitchell et al. 2007). Similar results were reported in the Multi-Ethnic Study of Atherosclerosis (MESA) study (Roetker et al. 2014), in the high cardiovascular risk patients included in the ONTARGET and TRANSCEND trials (Verdecchia et al. 2012), in the hypertensive patients with left ventricular hypertrophy of the LIFE study (Larstorp et al. 2012), and in patients with type 2 diabetes (Valbusa et al. 2012).

Elevated prevalence of AF in hypertensive patients contributes to the increased cardiovascular morbidity and mortality of these patients (Paquette et al. 2000; Vagaonescu et al. 2008). When hypertension coexist with AF the risk of cerebrovascular events is relatively high (2.7% and 4.6% per year in patients with paroxysmal and permanent AF, respectively) (Verdecchia et al. 2003) and elevated BP levels are associated with an increased rate of stroke and systemic embolic events even despite anticoagulation (Lip et al. 2007). This is why hypertension has been included among factors to be considered in the currently used risk scores for thromboembolism in patients with AF (Gage et al. 2001; Lip et al. 2010).

Mechanisms of atrial fibrillation in hypertension

AF ensues from multiple re-entry circuits that are initiated by firing of ectopic atrial foci on a vulnerable myocardial substrate. Refractoriness, slow conduction, and conduction barriers that perpetuate re-entry circuits leading to AF persistence characterize this substrate. Abnormalities of calcium handling are responsible for the ectopic foci, whereas structural and electric remodeling consisting respectively of atrial fibrosis and ion channel dysfunction underlies the vulnerable myocardial substrate (Schotten et al. 2011). Untreated or uncontrolled hypertension induces left ventricular hypertrophy, a condition associated with reduced ventricular compliance, increased ventricular wall stress, and decreased coronary flow reserve. These ventricular changes activate the sympathetic nervous and the renin-angiotensin-aldosterone system that stimulate proliferation and differentiation of fibroblast into myofibroblasts thereby leading to fibrosis of atrial myocardium (Schotten et al. 2011).

Verdecchia et al. prospectively followed a large cohort of more than 2,500 essential hypertensive patients in sinus rhythm without other predisposing clinical condition for AF for 16 years. Patients who developed AF were older, and had higher 24-hour systolic BP, left ventricular mass, and left atrial diameter, although only age and left ventricular mass were independent predictors of AF (Verdecchia et al. 2003). Other predisposing factors for AF have been identified in hypertensive patients including obesity (Dublin et al. 2006), metabolic syndrome (Tanner et al. 2011; Vyssoulis et al. 2013), obstructive sleep apnea syndrome (Gami et al. 2004), left ventricular diastolic dysfunction (Tsang et al. 2002), coronary artery disease (Lau et al. 2009), chronic kidney disease (Horio et al. 2010), and subclinical inflammation (Rizos et al. 2010). These factors predispose to AF because they, either directly or indirectly, interfere with the generation and/or propagation of electric activity in the atrial myocardium (Figure 1).

Blood pressure variability, arterial changes, and atrial fibrillation

Because of the association between BP variability and the risk of stroke (Rothwell et al. 2010), it has been hypothesized that blood pressure variability might predispose to AF. However, in a systematic analysis of 14 randomized trials on pharmacologic treatment of hypertension, Webb and Rothwell did not observe any relationship between BP variability and the occurrence of AF (Webb and Rothwell 2010). Similarly, no relationship between BP variability and incident AF was observed when variability was assessed by ambulatory blood pressure monitoring (ABPM) (Hansen et al. 2010). Thus, greater BP variability does not seem to be associated with higher risk of AF and therefore its association with stroke might depend on other mechanisms such as, for instance, structural and functional changes of arterial vessels.

Previous studies reported that vascular abnormalities that suggest arterial aging are associated with AF (Webb and Rothwell 2014). Adamsson Eryd *et al.* measured the carotid intima-media thickness (IMT), a marker of preclinical atherosclerosis, in 4,846 middle-aged healthy subjects from the general population. In a mean follow-up of 15.3 years, subjects with a carotid IMT in the higher quartile were hospitalized for AF more frequently than subjects with IMT in the lower quartile (HR 1.61, 95% CI 1.14-2.27) (Adamsson Eryd et al. 2014). A prospective analysis of 5,331 patients free from AF and a follow-up of 12 years showed that incident AF was predicted by baseline pulse pressure, a reliable marker of arterial stiffening (Mitchell et al. 2004). The relationship between AF and pulse pressure persisted after adjustment for major cardiovascular risk factors, left atrial dimension, and left ventricular mass (HR 1.26 per 20 mm Hg increment in pulse pressure; 95% CI, 1.12-1.43) (Mitchell et al. 2007). The importance of arterial changes for induction of AF was further supported by the observation that recurrence of AF after catheter ablation in a follow-up of 3 years was independently predicted by indices of arterial stiffening such as pulse pressure and augmentation index (Lau et al. 2013). In the same study, arterial stiffening was associated with lower survival free from AF.

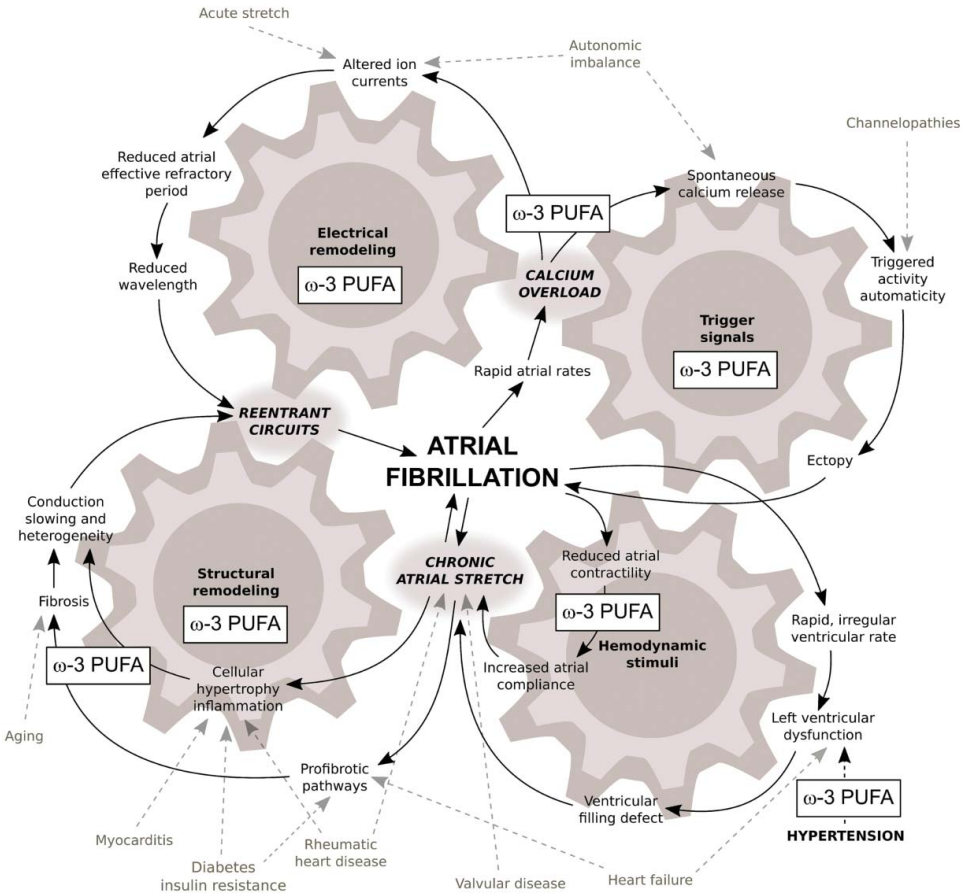

Figure 1. Mechanisms of AF development and maintenance. In this figure is represented the model of "gear wheels" by Schotten et al. (Schotten *et al.* 2011) modified. External risk factors initiate the interconnected wheels movement activating progressively different mechanisms that predispose the myocardium to AF development and its maintenance. In the figure are reported potential mechanisms by which polyunsaturated fatty acids of the ω-3 family (ω-3 PUFA) can interact with the pro-arrhythmogenic process. See text for explanation.

Polyunsaturated fatty acids of the ω-3 family and atrial fibrillation

Polyunsaturated fatty acids of the ω-3 family, ω-3 PUFA, are essential fatty acids that need to be consumed with food because humans lack metabolic pathways able to generate them endogenously. The metabolic precursor of ω-3 PUFA is the 18-carbon long chain with 3-double bonds alpha-linolenic acid (ALA). ALA can be found in vegetable oils, seeds, and nuts. The 20-carbon 5-double bonds eicosapentaenoic (EPA), the 22-carbon 5-double bonds docosapentaenoic (DPA), and the 22-carbon 6-double bonds docosahexaenoic acid (DHA) are synthesized from ALA through the action of desaturase and elongase enzymes. Substantial amounts of EPA, DPA, and DHA can also be obtained by eating fish, fish oil, and other marine foods (Colussi et al. 2007).

The possible benefits of ω-3 PUFA on the cardiovascular system have been extensively evaluated in experimental animal and clinical studies (Colussi et al. 2014). Dietary supplementation with ω-3 PUFA reduces cardiovascular mortality and morbidity by affecting classic and emergent risk factors such as hypertension, hypertriglyceridemia, lipoprotein(a), and markers of inflammation, thrombosis and vascular reactivity (Colussi et al. 2017). Previous observations demonstrated that ω-3 PUFA supplementation decreases cardiovascular mortality by reducing the risk of sudden death (Siscovick et al. 1995; Albert et al. 1998, 2002). In the GISSI-Prevenzione trial (GISSI-Prevenzione Investigators 1999), 11,000 patients with recent myocardial infarction were randomized to be treated with ω-3 PUFA, vitamin E, a combination of the two, or placebo. After a mean follow-up of 3.5 years, ω-3 PUFA reduced by 26% the occurrence of sudden death compared to placebo a benefit that was hypothetically ascribed to anti-arrhythmic effects of these fatty acids resulting in a lower risk of ventricular arrhythmias (Marchioli et al. 2002; Matthan et al. 2005; Billman 2006; Kromhout et al. 2011).

In-vitro and in-vivo experiments showed that ω-3 PUFA affect the cardiac function by a dual mechanism (McLennan 2014). On one hand, mechanisms that occur at low dose exposure ($<$ 1 g/day) might depend upon direct incorporation of ω-3 PUFA in plasma membranes of cardiomyocytes. At this level, ω-3 PUFA affect phospholipid composition, membrane excitability, and myocyte function, thereby improving myocardial contractility, oxygen utilization, and post-ischemic recovery, reducing heart rate and the threshold of inducible arrhythmias. These effects are likely mediated by the influence of plasma membrane PUFA content on transmembrane ion currents and by modulation of calcium handling and intracellular signaling in cardiomyocytes (Honen and Saint 2002a). On the other hand, mechanisms that occur at higher dose ($>$ 3 g/day) might depend upon ω-3 PUFA effect on circulating lipids,

blood pressure, and endothelial and vascular functions (Colussi et al. 2004, 2015b, 2015a). Taken together, these electrophysiological, anti-remodeling, and anti-inflammatory effects of ω-3 PUFA might have beneficial repercussions for AF.

Ingested ω-3 PUFA are incorporated into membranes of atrial and ventricular cardiomyocytes with an efficiency that is higher for DHA (8–10%) than EPA (2–4%) (Garg et al. 2006; Metcalf et al. 2007). Oral supplementation of ω-3 PUFA as fish oil increases concentration of these fatty acids both in plasma and atrial tissue obtained at surgery reaching a maximum effect after 30 days of intervention (Garg et al. 2006; Metcalf et al. 2007). In cultured rat atrial myocytes, asynchronous electrical activity induced by exposure to isoproterenol was reduced by addition of EPA and DHA to the culture medium. This effect of ω-3 PUFA was associated with an increased fluidity of plasma membranes (Jahangiri et al. 2000) and modulation of intracellular calcium traffic (Honen and Saint 2002b). In a rabbit model of atrial stretch-induced vulnerability to AF, feeding with ω-3 PUFA reduced the propensity to develop AF (Ninio et al. 2005). In dogs, ω-3 PUFA infusion prevents atrial electrophysiological remodeling by increasing duration of atrial cells refractoriness during atrial pacing (da Cunha et al. 2007). The ability of ω-3 PUFA to modulate the electrophysiological properties of atrial myocardium has been demonstrated also in humans. Kumar et al. showed that an intra-venous infusion of a high dose of ω-3 PUFA in patients who underwent an electrophysiological study and catheter ablation for sustained ventricular tachycardia or AF slowed atrial conduction and reduced the probability to induce AF (Kumar et al. 2013).

ω-3 PUFA and atrial fibrillation: Observational studies

During past years, cohort studies were conducted in the general population in North America and Europe to assess the effects of dietary ω-3 PUFA content on incident AF providing inconsistent results (Table 1). The Cardiovascular Health Study and the Kuopio Ischemic Heart Disease Risk Factor Study reported a preventive effect of dietary ω-3 PUFA on new onset AF. Although these studies involved less than 5,000 subjects, they included a significant proportion of subjects with hypertension and high cardiovascular risk. In the Cardiovascular Health Study, subjects older than 64 years had a baseline prevalence of AF of 24% and were followed for 10 to 12 years. Initial results indicated that consumption of tuna or other broiled or backed fish 1 to 4 times a week was associated with a 28% risk reduction of new onset AF (Mozaffarian et al. 2004). A more recent analysis of the same cohort included measurements of plasma ω-3 PUFA levels reporting a 29% lower incidence of AF in subjects with elevated levels (Wu et al. 2012). It is important to notice that the association between ω-3 PUFA levels and lower incidence of AF was significant for DHA (23% risk reduction comparing highest versus lowest quartile) but not EPA or DPA (Wu et al. 2012). The Kuopio Study included Finnish men with an age between 42 and 60 years who were followed for 18 years. Baseline prevalence of AF was 11% and elevated serum levels of ω-3 PUFA were associated with a 35% lower incidence of AF. Even in this study, the association between ω-3 PUFA levels and AF was significant only for DHA (Virtanen et al. 2009).

Despite these encouraging results, other observational prospective studies did not report a beneficial effect of ω-3 PUFA on AF incidence. Some of these studies such as the Danish Diet, Cancer, and Health Study (Frost and Vestergaard 2005; Rix et al. 2014), the Rotterdam Study (Brouwer et al. 2006), the Women's Health Initiative (Berry et al. 2010), the Atherosclerosis Risk in Communities (ARIC) (Gronroos et al. 2012), the Women's Health Study (Chiuve et al. 2015), and the combined Swedish Men and Swedish Mammography Cohort (Larsson and Wolk 2017) analyzed large cohorts including more than 10,000 subjects. However, it must be noticed that these studies reported an incidence of AF between 0.8 and 11.3%, much lower than that reported in the Cardiovascular Health Study (20%). The largest of these studies was the combined Swedish Men and Swedish Mammography Cohort in which the dietary habit was assessed in more than 70,000 subjects between 45 and 83 years who were followed for 12 years. Intake of more than five servings per week of all types of fish was not associated with a reduced risk of AF. However, subjects that ate lean fish (cod, saithe/coalfish, or fish fingers/sticks) three or more times per week had a 21% lower incidence of AF than subjects that did not eat fish (Larsson and Wolk 2017). A U-shaped association between ω-3 PUFA intake and AF incidence was observed in Danish subjects aged 50 to 64 years that were followed for 14 years [79]. Also, a trend to a U-shaped relationship was reported in the ARIC study [83] and in patients who developed AF following cardiac surgery (Skuladottir et al. 2011; Metcalf et al. 2014) suggesting possible untoward effects of excess intake of ω-3 PUFA.

A pro-arrhythmic effect of high ω-3 PUFA intake was suggested by the analysis of Frost et al. on the Danish Diet, Cancer, and Health Study cohort where a 34% increase in AF risk was observed in subjects who ate 1.29 g/day of ω-3 PUFA as compared to subjects who ate 0.16 g/day (Frost and Vestergaard 2005). Also, elevated levels of ω-3 PUFA in erythrocyte membranes were associated with a greater probability to develop AF after cardiac surgery (Bjorgvinsdottir et al. 2013). When ω-3 PUFA were directly measured in plasma (Gronroos et al. 2012) or fat (Rix et al. 2013) no association with incidence of AF was found. Other studies examined the role of the type of cooking and fish species as possible causes of the pro-arrhythmic effect of ω-3 PUFA. In the Cardiovascular Heart Study, consumption of fried fish or fish sandwiches more than once a week was associated with a 27% increase of AF incidence (Mozaffarian et al. 2004). In the Framingham Heart Study the consumption of dark fish (salmon, swordfish, bluefish, mackerel, and sardines) was associated with a six-fold increase of AF incidence, although the event rate in this group of subjects was very low (Shen et al. 2011).

In summary, results of observational studies appear inconclusive, even though some remarks can be made. First, the beneficial effect of ω-3 PUFA seems to be more relevant in patients at high cardiovascular risk and in those who eat lean fish. Second, cardiovascular protection appears to be mainly related to the dietary levels of DHA. Third, it is possible that ω-3 PUFA have a pro-arrhythmic effect when fried or dark fish is consumed.

Table 1. Principal observational prospective cohort studies on the effects of fish and $\omega-3$ PUFA on atrial fibrillation.

Study 1st author, publication year, (cohort study name)	Population type	Patients n.	Female %	Type of $\omega-3$ PUFA evaluation	Hypertension notes	Follow-up (years)	AF event number (%)	Effect on AF incidence[a]
Mozaffarian 2004 (Cardiovascular Health Study)	North-American general population-based 65 to 100 years old people	4,815	57	Diet	44% treated hypertensive patients Blood pressure levels were lower according to higher fish intake	12	980 (20.3)	28% risk reduction when consumed tuna or other broiled or backed fish (but not fried fish or fish sandwiches) 1 to 4 times per week compared with <1 time per month (HR = 0.72, 95% CI 0.57-0.90). 31% risk reduction when consumed tuna or other broiled or backed fried fish (but not fried fish or fish sandwiches) >5 times per week compared with <1 time per month (HR = 0.70, 95% CI 0.53-0.93).
Frost 2005 (Danish Diet, Cancer, and Health Study)	Danish general population-based 50 to 64 years old people	47,949	53	Diet	10% treated hypertensive patients Proportion of hypertensive treated patients and blood pressure levels were higher according to higher fish intake	5.7	556 (1.2)	34% risk increase comparing the highest (1.29 g/day) versus the lowest (0.16 g/day of estimated $\omega-3$ PUFA) quintile of $\omega-3$ PUFA from fish intake (HR = 1.34, 95% CI 1.02-1.76).
Brouwer 2006 (Rotterdam Study)	Dutch general population-based >55 years old people	5,184	59	Diet	20% hypertensive patients	6.4	312 (6.0)	No risk reduction comparing the highest (≥144 mg/day) versus the lowest (≤43 mg/day of estimated EPA+DHA) tertile (RR = 1.18, 95% CI 0.88-1.57). No risk reduction comparing fish intake of >20g/day versus no intake (RR = 1.17, 95% CI 0.87-1.57).
Virtanen 2009 (Kuopio Ischemic Heart Disease Risk Factor Study)	Finnish general population-based 42 to 60 years old men	2,174	0	Serum	46% treated hypertensive patients Proportion of hypertensive patients was lower according to higher $\omega-3$ PUFA serum levels	17.7	240 (11.0)	35% risk reduction comparing the highest (>5.3% of total fatty acids) versus the lowest (<3.6%) quartile of serum $\omega-3$ PUFA (HR = 0.65, 95% CI 0.44-0.96).
Berry 2010 (Women's Health Initiative)	North-American general population-based postmenopausal women	44,720	100	Diet	26% treated hypertensive patients	6	378 (0.8)	No risk reduction when consumed >2 servings of non-fried fish per week compared with <1/2 servings per week (OR = 1.17, 95% CI 0.88-1.57)
Shen 2011 (Framingham Heart Study)	North-American general population-based 62± 10 years old people	4,526	56	Diet	30% treated hypertensive patients	4	296 (6.5)	No risk reduction comparing the highest (460 mg/day) versus the lowest (80 mg/day) quartile of estimated EPA+DHA intake (HR = 1.18, 95% CI 0.85-1.64). No risk reduction when consumed >4 servings of fish per week compared with <1 serving per week (HR = 1.25, 95% CI 0.84-1.86). Six times risk increase when consumed >4 servings of dark fish[b] per week compared with <1 serving per week (HR = 6.53, 95% CI 2.65-16.06).

(*Continued on next page*)

Table 1. (*Continued*)

Study 1st author, publication year, (cohort study name)	Population type	Patients n.	Female %	Type of $\omega-3$ PUFA evaluation	Hypertension notes	Follow-up (years)	AF event number (%)	Effect on AF incidence[a]
Wu 2012 (Cardiovascular Health Study)	North-American general population-based 65 to 100 years old people	3,326	60	Plasma	46% treated hypertensive patients	10	789 (23.7)	29% risk reduction comparing the highest (≈6.4% of total fatty acids) versus the lowest (≈2.9%) quartile of plasma $\omega-3$ PUFA (HR = 0.71, 95% CI 0.57-0.89).
Gronroos 2012 (Atherosclerosis Risk in Communities)	North-American general population-based 45 to 64 years old people	14,222	45	Diet	26% hypertensive patients	17.6	1,604 (11.3)	No risk reduction when consuming >2 servings per week of fish compared with no servings per week (HR = 1.00, 95% CI 0.81-1.24). No risk reduction comparing the highest versus the lowest quartile[c] of estimated EPA+DHA intake (HR = 0.92, 95% CI 0.79-1.07).
Gronroos 2012 (Atherosclerosis Risk in Communities, Minnesota field center only)	North-American general population-based 45 to 64 years old people	3,757	52	Plasma	25% hypertensive patients	17.9	401 (10.7)	No risk reduction comparing the highest versus the lowest quartile[c] of plasma EPA+DHA (HR = 0.87, 95% CI 0.66-1.15).
Rix 2013 (Danish Diet, Cancer, and Health Study)	Danish general population-based 50 to 64 years old people	3,221	46	Adipose tissue biopsy	16% self-reported hypertension	13.6	179 (5.6)	No risk reduction comparing the highest (≈1% of total fatty acids) versus the lowest (≈0.4%) tertile of $\omega-3$ PUFA content in adipose tissue (HR = 0.77, 95% CI 0.53-1.10).
Rix 2014 (Danish Diet, Cancer, and Health Study)	Danish general population-based 50 to 64 years old people	55,246	52	Diet	16% self-reported hypertension	13.6	3,284 (5.9)	No risk reduction comparing the highest (>0.99 g/day) versus the lowest (<0.39 g/day) quartile of estimated $\omega-3$ PUFA intake (HR = 1.05, 95% CI 0.93-1.18).
Chiuve 2015 (Women's Health Study)	North-American general population-based ≥45 years old women	33,665	100	Diet	24% hypertensive patients	19.2	1,441 (4.3)	No risk reduction comparing the highest (2.14% of total energy intake) versus the lowest (0.76%) quintile of $\omega-3$ PUFA intake (RR = 1.05, 95% CI 0.80-1.39).
Larsson 2017 (Cohort of Swedish Men and Swedish Mammography Cohort)	Swedish general population-based 45 to 83 years old people	72,984	47	Diet	23% hypertensive patients	12	6,095 (8.3)	No risk reduction comparing the highest (≥0.567 g/day) versus the lowest (<0.243 g/day) quintile of estimated $\omega-3$ PUFA intake (RR = 1.04, 95% CI 0.96-1.13). No risk reduction when consuming ≥5 servings per week of all type of fish compared with ≤3 servings per month (RR = 1.01, 95% CI 0.90-1.13). 21% risk reduction when consuming ≥3 times per week of lean fish[d] compared with no consumption (HR 0.79, 95% CI 0.65-0.95).

[a]Data reported are only those of fully adjusted models including hypertension among confounders.
[b]Dark fish consisted of salmon, swordfish, bluefish, mackerel, and sardines.
[c]Values of $\omega-3$ PUFA in quartiles were not reported.
[d]Lean fish consisted of cod, saithe/coalfish, and fish fingers/sticks.
HR, hazard ratio; RR, relative risk; OR, odds ratio; CI, confidence interval.

Table 2. Principal randomized controlled trials with more than 100 patients on the effect of $\omega-3$ PUFA on recurrent post-cardioversion and post-operative atrial fibrillation (AF).

Study 1st author, publ. year, and location (study name)	Primary outcome	Sample size n.	Mean age, years	Female %	HTN DM IHD[a] %	Follow-up time	$\omega-3$ PUFA treatment fish oil (EPA+DHA) Study type	Control placebo	Effect
Kowey 2010, multicentric, USA	Effect of $\omega-3$ PUFA on the first symptomatic recurrence of AF or flutter in the paroxysmal AF stratum	663 (542 paroxysmal + 121 persistent AF)	60	44	—	6 m	8 g/day per 7 days before cardioversion + 4 g/day after cardioversion until study end Double-blind	Corn oil	52% in $\omega-3$ PUFA and 48% in placebo (p = NS).
Bianconi 2011, multicentric, Italy	Percentage of patients with symptomatic or asymptomatic AF recurrence.	204 (all persistent AF)	69	30	72 18 10	6 m	3 g/day per 7 days before cardioversion + 2 g/day after cardioversion until study end Double-blind	Olive oil	51% in $\omega-3$ PUFA and 59% in placebo (p = NS)
Nodari 2011, monocentric, Italy	Probability of maintenance of sinus rhythm at 1 year after cardioversion	199 (all persistent AF)	70	33	44 35 34	12 m	2 g/day 4 weeks before cardioversion until study end Double-blind	Olive oil	37% events in $\omega-3$ PUFA and 56% in placebo (p = 0.0001)
Kumar 2012, monocentric, Australia	Prevalence of recurrence of persistent AF	178 (all persistent AF)	62	22	52 15 17	12 m	6 g/day at least 4 weeks before cardioversion until study end Open label	—	67% events in $\omega-3$ PUFA and 90% in control (p<0.001)
Macchia 2013, multicentric, Argentina (FORWARD trial)	Prevalence of recurrence of symptomatic or asymptomatic AF	586 (all persistent AF)	66	45	91 13 12	12 m	1 g/day Double-blind	Olive oil	24% in $\omega-3$ PUFA and 19% in placebo (p = NS)
Nigam 2014, multicentric, Canada (AFFORD trial)	Time to symptomatic or asymptomatic AF recurrence lasting 30 sec or more	337 (history of paroxysmal or persistent AF)	61	33	43 8 13	9 m	4 g/day Double-blind	Safflower oil	82±115 days in $\omega-3$ PUFA and 103±18 in placebo (p = NS)
Darghosian 2015, multicentric, USA	Recurrence of symptomatic or asymptomatic AF	190 (history of paroxysmal or persistent AF)	62	43	64 19 12	6 m	4 g/day Double-blind	Corn oil	59% in $\omega-3$ PUFA and 47% in placebo (p = NS)
Calò 2005, monocentric, Italy	AF occurrence lasting more than 5 min after elective CABG surgery	160	66	16	80 32 52	8 d	2 g/day starting 5 days before intervention until hospital discharge Open label	—	15% in $\omega-3$ PUFA and 33% in control groups (p = 0.013)
Heidt 2009, monocentric, Germany	AF occurrence lasting more than 15 min after elective CABG surgery during ICU stay	102	66	31	—	3 d	100 mg/Kg/day i.v. starting on admission until ICU discharge Double-blind	Soya oil	17.3% in $\omega-3$ PUFA and 30.6% in control groups (p<0.05)

(*Continued on next page*)

Table 2. (*Continued*)

Study 1st author, publ. year, and location (study name)	Primary outcome	Sample size n.	Mean age, years	Female %	HTN DM IHD[a] %	Follow-up time	$\omega-3$ PUFA treatment fish oil (EPA+DHA) Study type	Control placebo	Effect
Heidarsdottir 2010, monocentric, Iceland	AF occurrence lasting more than 5 min after CABG ± other cardiac surgery during hospital stay	168	67	21	63	6 d	2 g/day starting 1 week before surgery until hospital discharge or 2 week	Olive oil	54.2% in $\omega-3$ PUFA and 54.1% in control groups (p = NS)
					15		Double-blind		
					—				
Saravanan 2010, monocentric, UK	Any AF occurrence lasting 30 sec or more in continuous ECG monitoring after elective CABG surgery during hospital stay	108	66	20	32	5 d	2 g/day starting from at least 5 days before surgery until hospital discharge or 5 days	Olive oil	56% in $\omega-3$ PUFA and 43% in control groups (p = NS)
					14		Double-blind		
					24				
Sorice 2011, monocentric, Italy	AF occurrence lasting more than 5 min after elective CABG surgery during hospital stay	201	63	18	64	8 d	2 g/day starting 5 days before surgery until hospital discharge	—	11.4% in $\omega-3$ PUFA and 22.8% in control groups (p = 0.033)
					42		Open label		
					—				
Farquharson 2011, monocentric, Australia	AF/ atrial flutter occurrence lasting 10 min or more or requiring intervention in first 6 days after CABG and/or valve procedures	194	64	27	77	21 d	4.6 g/day starting 3 weeks before surgery until discharge or 6 days	Sunflower oil	37% in $\omega-3$ PUFA and 48% in control groups (p = NS)
					31		Double-blind		
					35				
Sandesara 2012, multicenter, USA (FISH trial)	AF occurrence requiring therapy in 2 week after elective CABG surgery	243	63	19	88	14 d	Minimum loading dose 6g presurgery then 2g/day until AF occurrence or 2 weeks	Corn oil	30% in $\omega-3$ PUFA and 33% in control groups (p = NS)
					36		Double-blind		
					42				
Mozaffarian 2012, multicentric, USA, Italy, Argentina (OPERA trial)	AF occurrence of at least 30 sec duration after cardiac surgery during hospital stay	1516	64	28	75	7 d	8–10 g loading dose presurgery in 2–5 days then 2g/day until hospital discharge or 10 days	Olive oil	30.0% in $\omega-3$ PUFA and 30.7% in control groups (p = NS)
					26				
					24				

[a]ischemic heart disease in postoperative AF consists of prior myocardial infarction.

HTN, arterial hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CABG, coronary artery bypass grafting; ICU, intensive care unit; CI, confidence interval; NS, not statistically significant.

ω-3 PUFA and atrial fibrillation: Intervention studies

No intervention studies have been conducted so far to examine the effects of ω-3 PUFA on cardiovascular events in primary prevention. The only evidence in this context comes from a post-hoc analysis of the GISSI-HF trial that included more than 5,800 patients in sinus rhythm who were followed for 4 years. In this analysis, patients who were randomized to 1g/day of EPA+DHA supplementation and patients treated with placebo (olive oil) developed AF with comparable frequency. However, when patients with a previous history of AF were excluded from analysis, ω-3 PUFA supplementation was associated with higher incidence of AF (HR 1.23, 95% CI 1.02-1.48) (Aleksova et al. 2013).

Table 2 summarizes the findings of studies that have tested prospectively the effects of ω-3 PUFA in the secondary prevention or post-operative AF, even in this case there are substantial inconsistencies (Calò et al. 2005; Heidt et al. 2009; Heidarsdottir et al. 2010; Kowey et al. 2010; Saravanan et al. 2010; Bianconi et al. 2011; Farquharson et al. 2011; Nodari et al. 2011; Sorice et al. 2011; Kumar et al. 2012; Mozaffarian et al. 2012; Sandesara et al. 2012; Macchia et al. 2013; Nigam et al. 2014; Darghosian et al. 2015). Only three trials with a reasonable sample size (more than 500 patients) explored the effect of ω-3 PUFA intake on AF recurrence or post-surgical AF. Kowey et al. recruited in multicenter double-blind study 663 American outpatients with a history of paroxysmal or persistent AF in sinus rhythm who were followed for 6 months. Patients were randomized to take either 8 g/day EPA+DHA ethyl esters or placebo (corn oil) for the first 7 days, then 4 g/day or placebo until the study end. Despite a significant blood enrichment of DHA and EPA, ω-3 PUFA supplementation did not change the incidence of recurrent AF (ω-3 PUFA 52%, placebo 46%; HR 1.22, 95% CI 0.98-1.52) (Kowey et al. 2010). The FORWARD study recruited 586 outpatients with paroxysmal AF in a double-blind, multicenter study. More than 90% of patients were hypertensive and were randomly allocated to EPA+DHA supplementation (1 g/day) or placebo with a follow-up of 12 months. Even in this study the incidence of recurrent AF was comparable in the two arms (ω-3 PUFA 24%, placebo 19%; HR 1.28, 95% CI 0.90-1.83) (Macchia et al. 2013). The OPERA study recruited more than 1,500 patients in sinus rhythm who were scheduled for cardiac surgery 75% of whom had hypertension. Patients were randomized to take 8–10 g of EPA+DHA/day or placebo for 3–5 days before surgery followed after surgery by 2 g of EPA+DHA/day until hospital discharge or the 10th day of hospital stay. AF occurred with comparable frequency in the two arms (ω-3 PUFA 30%, placebo 31%; OR 0.96, 95% CI 0.77-1.20) (Mozaffarian et al. 2012).

The effects of ω-3 PUFA supplementation on recurrent or post-surgical AF have been the subjects of a meta-analysis that included more than 4,500 patients recruited in 16 randomized controlled trials conducted from 2007 to 2012 (Mariani et al. 2013). This pooled analysis did not report any effect of ω-3 PUFA administration on both AF recurrence (relative risk RR 0.95, 95% CI 0.79-1.13) and post-operative AF (RR 0.86, 95% CI 0.71-1.04), though heterogeneity was significantly present in both groups. Similar results have been reported in a more recent meta-analysis by Zhang et al. (Zhang et al. 2014). Conversely, another meta-analysis of the same studies included in the previous two reported a slightly significant reduction of post-surgical AF with ω-3 PUFA supplementation (OR 0.75, 95% CI 0.57-1.00, P = 0.050) (Costanzo et al. 2013).

Recently, the AFFORD study rises a warning of a possible pro-arrhythmic effect of ω-3 PUFA. In this study, 337 patients with paroxysmal or persistent AF, 45% of whom had hypertension, were randomized to either 4 g/day of fish oil or placebo (safflower oil). In a 6-month follow-up, 64% of patient eating fish oil and 63% eating placebo developed AF without any statistical difference. However, fish oil intake caused a three-fold increase in recurrence of AF in the subgroup of patients with ischemic heart diseases (HR 2.6, 95% CI 1.1-6.1), although in these patients the change of ω-3 PUFA content in erythrocyte membranes was not related to probability of AF recurrence (Nigam et al. 2014). Similar results were reported by Darghosian et al. in 190 patients with paroxysmal or persistent AF, 65% of whom had hypertension, who were randomized in a 2:1 ratio to take 4 g/day of EPA+DHA or placebo (corn oil) on top of the current anti-arrhythmic therapy. AF recurred in 59% of patients eating ω-3 PUFA and 47% of those on placebo (HR 1.20, 95% CI 0.76-1.90) (Darghosian et al. 2015).

In summary, clinical trials that have explored the effects of ω-3 PUFA supplementation on AF occurrence do not provide any evidence of a preventive effect of these fatty acids for primary and secondary prevention of AF. The only evidence, though very weak, comes from the studies conducted with ω-3 PUFA on post-surgical AF, in particular in patients undergoing coronary artery by-pass graft. On the other hand, a possible pro-arrhythmic effect of high doses of ω-3 PUFA should be taken into account. Based upon current knowledge, it is totally reasonable to fully support the conclusions of the recent science advisory of the American Heart Association that do not recommend use of ω-3 PUFA supplementation for prevention of AF (Siscovick et al. 2017).

Conclusions

AF is the most common sustained arrhythmia in the general population with a prevalence that increases significantly with aging and is frequently associated with arterial hypertension. AF affects cardiovascular morbidity and mortality and remains one of the main causes of stroke. In preclinical and clinical studies, ω-3 PUFA have been shown to effectively prevent AF because of their anti-arrhythmic and anti-inflammatory properties. However, observational studies and intervention trials failed to confirm this protective effect of ω-3 PUFA against AF and its complications. Therefore, based upon current evidence, no recommendation for their use in the context of AF can be done.

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References

Adamsson Eryd, S., G. Östling, M. Rosvall, M. Persson, J. G. Smith, O. Melander, B. Hedblad, and G. Engström. 2014. Carotid intima-media thickness is associated with incidence of hospitalized atrial fibrillation. *Atherosclerosis* 233:673–678.

Albert, C. M., H. Campos, M. J. Stampfer, P. M. Ridker, J. E. Manson, W. C. Willett, and M. Jing. 2002. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *The New England Journal of Medicine* 346:1113–1118.

Albert, C. M., C. H. Hennekens, C. J. O'Donnell, U. A. Ajani, V. J. Carey, W. C. Willett, J. N. Ruskin, and J. E. Manson. 1998. Fish consumption and risk of sudden cardiac death. *Journal of the American Medical Association* 279:23–28.

Aleksova, A., S. Masson, A. P. Maggioni, D. Lucci, G. Fabbri, L. Beretta, L. Mos, A. M. Paino, G. L. Nicolosi, R. Marchioli, et al. 2013. n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *European Journal of Heart Failure* 15:1289–1295.

Benjamin, E. J., D. Levy, S. M. Vaziri, R. B. D'Agostino, A. J. Belanger, and P. A. Wolf. 1994. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 271:840–844.

Berry, J. D., R. J. Prineas, Lan. Horn, R. Passman, J. Larson, J. Goldberger, L. Snetselaar, L. Tinker, K. Liu, and D. M. Lloyd-Jones. 2010. Dietary fish intake and incident atrial fibrillation (from the Women's Health Initiative). *American Journal of Cardiology* 105:844–848.

Bianconi, L., L. Calò, M. Mennuni, L. Santini, P. Morosetti, P. Azzolini, G. Barbato, F. Biscione, P. Romano, and M. Santini. 2011. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. *Europace* 13:174–181.

Billman, G. E. 2006. A comprehensive review and analysis of 25 years of data from an in vivo canine model of sudden cardiac death: implications for future anti-arrhythmic drug development. *Pharmacology & Therapeutics* 111:808–835.

Bjorgvinsdottir, L., D. O. Arnar, O. S. Indridason, R. Heidarsdottir, K. Skogstrand, B. Torfason, D. M. Hougaard, R. Palsson, and G. V. Skuladottir. 2013. Do high levels of n-3 polyunsaturated fatty acids in cell membranes increase the risk of postoperative atrial fibrillation? *Cardiology* 126:107–114.

Brouwer, I. A., J. Heeringa, J. M. Geleijnse, P. L. Zock, and J. C. M. Witteman. 2006. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. *American Heart Journal* 151:857–862.

Calò, L., L. Bianconi, F. Colivicchi, F. Lamberti, M. L. Loricchio, Ede. Ruvo, A. Meo, C. Pandozi, M. Staibano, and M. Santini. 2005. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of the American College of Cardiology* 45:1723–1728.

Chiuve, S. E., R. K. Sandhu, M. V. Moorthy, R. J. Glynn, and C. M. Albert. 2015. Dietary Fat Intake Is Differentially Associated with Risk of Paroxysmal Compared with Sustained Atrial Fibrillation in Women. *The Journal of Nutrition* 145:2092–2101.

Colussi, G., C. Catena, S. Baroselli, E. Nadalini, R. Lapenna, A. Chiuch, and L. A. Sechi. 2007. Omega-3 fatty acids: from biochemistry to their clinical use in the prevention of cardiovascular disease. *Recent Patents Cardiovasc. Drug Discov.* 2:13–21.

Colussi, G., C. Catena, V. Dialti, L. Mos, and L. A. Sechi. 2015a. The vascular response to vasodilators is related to the membrane content of polyunsaturated fatty acids in hypertensive patients. *Journal of Hypertension* 33:993–1000.

Colussi, G., C. Catena, L. Mos, and L. A. Sechi. 2015b. The metabolic syndrome and the membrane content of polyunsaturated fatty acids in hypertensive patients. *Metabolic Syndrome and Related Disorders* 13:343–351.

Colussi, G., C. Catena, M. Novello, N. Bertin, and L. A. Sechi. 2017. Impact of omega-3 polyunsaturated fatty acids on vascular function and blood pressure: Relevance for cardiovascular outcomes. *Nutrition, Metabolism & Cardiovascular Diseases* 27:191–200.

Colussi, G., C. Catena, and L. A. Sechi. 2014. ω-3 Polyunsaturated fatty acids effects on the cardiometabolic syndrome and their role in cardiovascular disease prevention: An update from the recent literature. *Recent Advances in Cardiovascular Drug Discovery* 9:78–96.

Colussi, G. L., S. Baroselli, and L. Sechi. 2004. Omega-3 polyunsaturated fatty acids decrease plasma lipoprotein(a) levels in hypertensive subjects. *Clinical Nutrition* 23:1246–1247.

Conen, D., U. B. Tedrow, B. A. Koplan, R. J. Glynn, J. E. Buring, and C. M. Albert. 2009. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 119:2146–2152.

Costanzo, S., Vdi. Niro, D. Castelnuovo, G. A., D. F., G. M.B., G. de, and L. Iacoviello. 2013. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. *The Journal of Thoracic and Cardiovascular Surgery* 146:906–911.

da Cunha, D. N. Q., R. L. Hamlin, G. E. Billman, and C. A. Carnes. 2007. n-3 (omega-3) polyunsaturated fatty acids prevent acute atrial electrophysiological remodeling. *British Journal of Pharmacology* 150:281–285.

Darghosian, L., M. Free, J. Li, T. Gebretsadik, A. Bian, A. Shintani, B. F. McBride, J. Solus, G. Milne, G. H. Crossley, et al. 2015. Effect of omega-three polyunsaturated fatty acids on inflammation, oxidative stress, and recurrence of atrial fibrillation. *American Journal of Cardiology* 115:196–201.

Dublin, S., B. French, N. L. Glazer, K. L. Wiggins, T. Lumley, B. M. Psaty, N. L. Smith, and S. R. Heckbert. 2006. Risk of new-onset atrial fibrillation in relation to body mass index. *Archives of Internal Medicine* 166:2322–2328.

Farquharson, A. L., R. G. Metcalf, P. Sanders, R. Stuklis, J. R. M. Edwards, R. A. Gibson, L. G. Cleland, T. R. Sullivan, M. J. James, and G. D. Young. 2011. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. *American Journal of Cardiology* 108:851–856.

Frost, L., and P. Vestergaard. 2005. n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *The American Journal of Clinical Nutrition* 81:50–54.

Gage, B. F., A. D. Waterman, W. Shannon, M. Boechler, M. W. Rich, and M. J. Radford. 2001. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 285:2864–2870.

Gami, A. S., G. Pressman, S. M. Caples, R. Kanagala, J. J. Gard, D. E. Davison, J. F. Malouf, N. M. Ammash, P. A. Friedman, and V. K. Somers. 2004. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 110:364–367.

Garg, M. L., J. Leitch, R. J. Blake, and R. Garg. 2006. Long-chain n-3 polyunsaturated fatty acid incorporation into human atrium following fish oil supplementation. *Lipids* 41:1127–1132.

GISSI-Prevenzione Investigators. 1999. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 354:447–455.

Gronroos, N. N., A. M. Chamberlain, A. R. Folsom, E. Z. Soliman, S. K. Agarwal, J. A. Nettleton, and A. Alonso. 2012. Fish, fish-derived n-3 fatty acids, and risk of incident atrial fibrillation in the Atherosclerosis Risk in Communities (ARIC) study. *PloS One* 7:e36686.

Grundvold, I., P. T. Skretteberg, K. Liestøl, G. Erikssen, S. E. Kjeldsen, H. Arnesen, J. Erikssen, and J. Bodegard. 2012. Upper Normal Blood Pressures Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men A 35-Year Follow-Up Study. *Hypertension* 59:198–204.

Hansen, T. W., L. Thijs, Y. Li, J. Boggia, M. Kikuya, K. Björklund-Bodegård, T. Richart, T. Ohkubo, J. Jeppesen, C. Torp-Pedersen, et al. 2010. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 55:1049–1057.

Heidarsdottir, R., D. O. Arnar, G. V. Skuladottir, B. Torfason, V. Edvardsson, G. Gottskalksson, R. Palsson, and O. S. Indridason. 2010. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace* 12:356–363.

Heidt, M. C., M. Vician, S. K. H. Stracke, T. Stadlbauer, M. T. Grebe, A. Boening, P. R. Vogt, and A. Erdogan. 2009. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial

fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thoracic and Cardiovascular Surgery* 57:276–280.

Honen, B. N., and D. A. Saint. 2002a. Polyunsaturated dietary fats change the properties of calcium sparks in adult rat atrial myocytes. *The Journal of Nutritional Biochemistry* 13:322–329.

Honen, B. N., and D. A. Saint. 2002b. Polyunsaturated dietary fats change the properties of calcium sparks in adult rat atrial myocytes. *The Journal of Nutritional Biochemistry* 13:322–329.

Horio, T., Y. Iwashima, K. Kamide, T. Tokudome, F. Yoshihara, S. Nakamura, and Y. Kawano. 2010. Chronic kidney disease as an independent risk factor for new-onset atrial fibrillation in hypertensive patients. *Journal of Hypertension* 28:1738–1744.

Hurley, V., R. Ireson, K. Fletcher, G. Y. H. Lip, F. D. R. Hobbs, J. Mant, and B. A. F. T.A. Investigators. 2007. A cross-sectional study of hypertension in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation in the Aged (BAFTA) randomised controlled trial. *International Journal of Cardiology* 117:152–156.

Jahangiri, A., W. R. Leifert, G. S. Patten, and E. J. McMurchie. 2000. Termination of asynchronous contractile activity in rat atrial myocytes by n-3 polyunsaturated fatty acids. *Molecular and Cellular Biochemistry*. 206:33–41.

Kannel, W. B., P. A. Wolf, E. J. Benjamin, and D. Levy. 1998. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *American Journal of Cardiology* 82:2N–9N.

Kowey, P. R., J. A. Reiffel, K. A. Ellenbogen, G. V. Naccarelli, and C. M. Pratt. 2010. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *JAMA* 304:2363–2372.

Krahn, A. D., J. Manfreda, R. B. Tate, F. A. Mathewson, and T. E. Cuddy. 1995. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *American Journal of Medicine* 98:476–484.

Kromhout, D., J. M. Geleijnse, J. de Goede, L. M. Oude Griep, B. J. M. Mulder, M.-J. de Boer, J. W. Deckers, E. Boersma, P. L. Giltay, and E. J. Zock. 2011. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. *Diabetes Care* 34:2515–2520.

Kumar, S., F. Sutherland, J. M. S. Lee, T. Robinson, P. M. Heck, M. C. G. Wong, N. F. Kelland, M. L. Garg, and P. B. Sparks. 2013. Effects of high dose intravenous fish oil on human atrial electrophysiology: Implications for possible anti- and pro-arrhythmic mechanisms in atrial fibrillation. *International Journal of Cardiology* 168:2754–2760.

Kumar, S., F. Sutherland, J. B. Morton, G. Lee, J. Morgan, J. Wong, D. E. Eccleston, J. Voukelatos, M. L. Garg, and P. B. Sparks. 2012. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm* 9:483–491.

Larsson, S. C., and A. Wolk. 2017. Fish, long-chain omega-3 polyunsaturated fatty acid intake and incidence of atrial fibrillation: A pooled analysis of two prospective studies. *Clinical Nutrition* 36:537–541.

Larstorp, A. C. K., I. Ariansen, K. Gjesdal, M. H. Olsen, H. Ibsen, R. B. Devereux, P. M. Okin, B. Dahlöf, S. E. Kjeldsen, and K. Wachtell. 2012. Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study. *Hypertension* 60:347–353.

Lau, D. H., L. T. Huynh, D. P. Chew, C. M. Astley, A. Soman, and P. Sanders. 2009. Prognostic impact of types of atrial fibrillation in acute coronary syndromes. *American Journal of Cardiology* 104:1317–1323.

Lau, D. H., M. E. Middeldorp, A. G. Brooks, A. N. Ganesan, K. C. Roberts-Thomson, M. K. Stiles, D. P. Leong, H. S. Abed, H. S. Lim, C. X. Wong, et al. 2013. Aortic stiffness in lone atrial fibrillation: a novel risk factor for arrhythmia recurrence. *PloS One* 8:e76776.

Lip, G. Y. H., L. Frison, M. Grind, and S. P. O. R. T. I. F. Invetigators. 2007. Effect of hypertension on anticoagulated patients with atrial fibrillation. *European Heart Journal* 28:752–759.

Lip, G. Y. H., R. Nieuwlaat, R. Pisters, D. A. Lane, and H. J. G. M. Crijns. 2010. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 137:263–272.

Macchia, A., H. Grancelli, S. Varini, D. Nul, N. Laffaye, J. Mariani, D. Ferrante, R. Badra, J. Figal, S. Ramos, et al. 2013. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *Journal of the American College of Cardiology* 61:463–468.

Marchioli, R., F. Barzi, E. Bomba, C. Chieffo, D. Di Gregorio, R. Di Mascio, M. G. Franzosi, E. Geraci, G. Levantesi, A. P. Maggioni, et al. 2002. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 105:1897–1903.

Mariani, J., H. C. Doval, D. Nul, S. Varini, H. Grancelli, D. Ferrante, G. Tognoni, and A. Macchia. 2013. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *Journal of the American Heart Association* 2:e005033.

Matthan, N. R., H. Jordan, M. Chung, A. H. Lichtenstein, D. A. Lathrop, and J. Lau. 2005. A systematic review and meta-analysis of the impact of omega-3 fatty acids on selected arrhythmia outcomes in animal models. *Metabolism* 54:1557–1565.

McLennan, P. L. 2014. Cardiac physiology and clinical efficacy of dietary fish oil clarified through cellular mechanisms of omega-3 polyunsaturated fatty acids. *European Journal of Applied Physiology* 114:1333–1356.

Metcalf, R. G., M. J. James, R. A. Gibson, J. R. Edwards, J. Stubberfield, R. Stuklis, K. Roberts-Thomson, G. D. Young, and L. G. Cleland. 2007. Effects of fish-oil supplementation on myocardial fatty acids in humans. *The American Journal of Clinical Nutrition* 85:1222–1228.

Metcalf, R. G., G. V. Skuladottir, O. S. Indridason, T. R. Sullivan, L. Bjorgvinsdottir, P. Sanders, D. O. Arnar, R. A. Gibson, R. Heidarsdottir, L. G. Cleland, et al. 2014. U-shaped relationship between tissue docosahexaenoic acid and atrial fibrillation following cardiac surgery. *European Journal of Clinical Nutrition* 68:114–118.

Mitchell, G. F., H. Parise, E. J. Benjamin, M. G. Larson, M. J. Keyes, J. A. Vita, R. S. Vasan, and D. Levy. 2004. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 43:1239–1245.

Mitchell, G. F., R. S. Vasan, M. J. Keyes, H. Parise, T. J. Wang, M. G. Larson, R. B. D'Agostino, W. B. Kannel, D. Levy, and E. J. Benjamin. 2007. Pulse pressure and risk of new-onset atrial fibrillation. *JAMA* 297:709–715.

Mozaffarian, D., R. Marchioli, A. Macchia, M. G. Silletta, P. Ferrazzi, T. J. Gardner, R. Latini, P. Libby, F. Lombardi, P. T. O'Gara, et al. 2012. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA* 308:2001–2011.

Mozaffarian, D., B. M. Psaty, E. B. Rimm, R. N. Lemaitre, G. L. Burke, M. F. Lyles, D. Lefkowitz, and D. S. Siscovick. 2004. Fish intake and risk of incident atrial fibrillation. *Circulation* 110:368–373.

Naccarelli, G. V., H. Varker, J. Lin, and K. L. Schulman. 2009. Increasing prevalence of atrial fibrillation and flutter in the United States. *American Journal of Cardiology* 104:1534–1539.

Nigam, A., M. Talajic, D. Roy, S. Nattel, J. Lambert, A. Nozza, P. Jones, V. R. Ramprasath, G. O'Hara, S. Kopecky, et al. 2014. Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress. *Journal of the American College of Cardiology* 64:1441–1448.

Ninio, D. M., K. J. Murphy, P. R. Howe, and D. A. Saint. 2005. Dietary fish oil protects against stretch-induced vulnerability to atrial fibrillation in a rabbit model. *Journal of Cardiovascular Electrophysiology* 16:1189–1194.

Nodari, S., M. Triggiani, U. Campia, A. Manerba, G. Milesi, B. M. Cesana, M. Gheorghiade, and L. Dei Cas. 2011. n-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. *Circulation* 124:1100–1106.

Oldgren, J., J. S. Healey, M. Ezekowitz, P. Commerford, A. Avezum, P. Pais, J. Zhu, P. Jansky, A. Sigamani, C. A. Morillo, et al. 2014. Variations in cause and management of atrial fibrillation in a prospective

registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation* 129:1568–1576.

Paquette, M., D. Roy, M. Talajic, D. Newman, A. Couturier, C. Yang, and P. Dorian. 2000. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *The American Journal of Cardiology* 86:764–768.

Rix, T. A., A. M. Joensen, S. Riahi, S. Lundbye-Christensen, K. Overvad, and E. B. Schmidt. 2013. Marine n-3 fatty acids in adipose tissue and development of atrial fibrillation: A Danish cohort study. *Heart* 99:1519–1524.

Rix, T. A., A. M. Joensen, S. Riahi, S. Lundbye-Christensen, A. Tjønneland, E. B. Schmidt, and K. Overvad. 2014. A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter-a Danish cohort study. *Europace* 16:1554–1561.

Rizos, I., A. G. Rigopoulos, A. S. Kalogeropoulos, S. Tsiodras, S. Dragomanovits, E. A. Sakadakis, E. Faviou, and D. T. Kremastinos. 2010. Hypertension and paroxysmal atrial fibrillation:a novel predictive role of high sensitivity C-reactive protein in cardioversion and long-term recurrence. *Journal of Human Hypertension* 24:447–457.

Roetker, N. S., L. Y. Chen, S. R. Heckbert, S. Nazarian, E. Z. Soliman, D. A. Bluemke, J. A. C. Lima, and A. Alonso. 2014. Relation of systolic, diastolic, and pulse pressures and aortic distensibility with atrial fibrillation (from the Multi-Ethnic Study of Atherosclerosis). *American Journal of Cardiology* 114:587–592.

Rothwell, P. M., S. C. Howard, E. Dolan, E. O'Brien, J. E. Dobson, B. Dahlöf, P. S. Sever, and N. R. Poulter. 2010. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 375:895–905.

Sandesara, C. M., M. K. Chung, D. R. Van Wagoner, T. A. Barringer, K. Allen, H. M. Ismail, B. Zimmerman, and B. Olshansky. 2012. A Randomized, Placebo-Controlled Trial of Omega-3 Fatty Acids for Inhibition of Supraventricular Arrhythmias After Cardiac Surgery: The FISH Trial. *Journal of the American Heart Association* 1:e000547.

Saravanan, P., B. Bridgewater, A. L. West, S. C. O'Neill, P. C. Calder, and N. C. Davidson. 2010. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: A randomized, double-blind, placebo-controlled clinical trial. *Circulation: Arrhythmia and Electrophysiology* 3:46–53.

Schotten, U., S. Verheule, P. Kirchhof, and A. Goette. 2011. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiological Reviews* 91:265–325.

Shen, J., V. M. Johnson, L. M. Sullivan, P. F. Jacques, J. W. Magnani, S. A. Lubitz, S. Pandey, D. Levy, R. S. Vasan, P. A. Quatromoni, et al. 2011. Dietary factors and incident atrial fibrillation: the Framingham Heart Study. *The American Journal of Clinical Nutrition* 93:261–266.

Siscovick, D. S., T. A. Barringer, A. M. Fretts, J. H. Y. Wu, A. H. Lichtenstein, R. B. Costello, P. M. Kris-Etherton, T. A. Jacobson, M. B. Engler, H. M. Alger, et al. 2017. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation* 135:e867–e884.

Siscovick, D. S., T. E. Raghunathan, I. King, S. Weinmann, K. G. Wicklund, J. Albright, V. Bovbjerg, P. Arbogast, H. Smith, and L. H. Kushi. 1995. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 274:1363–1367.

Skuladottir, G. V., R. Heidarsdottir, D. O. Arnar, B. Torfason, V. Edvardsson, G. Gottskalksson, R. Palsson, and O. S. Indridason. 2011. Plasma n-3 and n-6 fatty acids and the incidence of atrial fibrillation following coronary artery bypass graft surgery. *European Journal of Clinical Investigation* 41:995–1003.

Sorice, M., F. P. Tritto, C. Sordelli, R. Gregorio, and L. Piazza. 2011. N-3 polyunsaturated fatty acids reduces post-operative atrial fibrillation incidence in patients undergoing "on-pump" coronary artery bypass graft surgery. *Monaldi Archives for Chest Disease* 76:93–98.

Tanner, R. M., U. Baber, A. P. Carson, J. Voeks, T. M. Brown, E. Z. Soliman, V. J. Howard, and P. Muntner. 2011. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *American Journal of Cardiology* 108:227–232.

Thomas, M. C., S. Dublin, R. C. Kaplan, N. L. Glazer, T. Lumley, W. T. Longstreth, N. L. Smith, B. M. Psaty, D. S. Siscovick, and S. R. Heckbert. 2008. Blood pressure control and risk of incident atrial fibrillation. *American Journal of Hypertension* 21:1111–1116.

Tsang, T. S. M., B. J. Gersh, C. P. Appleton, A. J. Tajik, M. E. Barnes, K. R. Bailey, J. K. Oh, C. Leibson, S. C. Montgomery, and J. B. Seward. 2002. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *Journal of the American College of Cardiology* 40:1636–1644.

Vagaonescu, T. D., A. C. Wilson, and J. B. Kostis. 2008. Atrial fibrillation and isolated systolic hypertension: the systolic hypertension in the elderly program and systolic hypertension in the elderly program-extension study. *Hypertension* 51:1552–1556.

Valbusa, F., S. Bonapace, L. Bertolini, L. Zenari, G. Arcaro, and G. Targher. 2012. Increased pulse pressure independently predicts incident atrial fibrillation in patients with type 2 diabetes. *Diabetes Care* 35:2337–2339.

Verdecchia, P., G. Dagenais, J. Healey, P. Gao, A. L. Dans, I. Chazova, A. S. Binbrek, G. Iacobellis, R. Ferreira, N. Holwerda, et al. 2012. Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease studies. *Journal of Hypertension* 30:1004–1014.

Verdecchia, P., G. Reboldi, R. Gattobigio, M. Bentivoglio, C. Borgioni, F. Angeli, E. Carluccio, M. G. Sardone, and C. Porcellati. 2003. Atrial fibrillation in hypertension: predictors and outcome. *Hypertension* 41:218–223.

Virtanen, J. K., J. Mursu, S. Voutilainen, and T.-P. Tuomainen. 2009. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation* 120:2315–2321.

Vyssoulis, G., E. Karpanou, D. Adamopoulos, S.-M. Kyvelou, V. Tzamou, A. Michaelidis, and C. Stefanadis. 2013. Metabolic syndrome and atrial fibrillation in patients with essential hypertension. *Nutrition, Metabolism & Cardiovascular Diseases* 23:109–114.

Webb, A. J. S., and P. M. Rothwell. 2010. Blood pressure variability and risk of new-onset atrial fibrillation: a systematic review of randomized trials of antihypertensive drugs. *Stroke* 41:2091–2093.

Webb, A. J. S., and P. M. Rothwell. 2014. Physiological correlates of beat-to-beat, ambulatory, and day-to-day home blood pressure variability after transient ischemic attack or minor stroke. *Stroke* 45:533–538.

Wilke, T., A. Groth, S. Mueller, M. Pfannkuche, F. Verheyen, R. Linder, U. Maywald, R. Bauersachs, and G. Breithardt. 2013. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace* 15:486–493.

Wu, J. H. Y., R. N. Lemaitre, I. B. King, X. Song, F. M. Sacks, E. B. Rimm, S. R. Heckbert, D. S. Siscovick, and D. Mozaffarian. 2012. Association of plasma phospholipid long-chain ω-3 fatty acids with incident atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 125:1084–1093.

Zhang, B., Y. Zhen, A. Tao, Z. Bao, and G. Zhang. 2014. Polyunsaturated fatty acids for the prevention of atrial fibrillation after cardiac surgery: an updated meta-analysis of randomized controlled trials. *Journal of Cardiology* 63:53–59.