Role of Omega-3 Fatty Acids in the Prevention of Atrial Fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 2.6 million people in the United States. It occurs frequently after myocardial infarction and is the most common arrhythmia following cardiac surgery. AF increases the risk of morbidity and mortality from stroke, thromboembolism, and death. AF may be caused by ectopic activity in one or more of the pulmonary veins. Focal ectopic activity can be generated by abnormal atrial automaticity, delayed afterdepolarizations from calcium overload, or early afterdepolarizations secondary to defective repolarization properties. Pathologic mechanisms may include autonomic dysfunction, inflammation, and fibrosis. Omega-3 fatty acids (polyunsaturated fatty acids [PUFAs]) have been shown to induce beneficial effects in the treatment of coronary artery disease. They may also reduce sudden cardiac death and the incidence of arrhythmias. Therefore, studies have been conducted to evaluate the benefits of PUFAs in arrhythmia prevention. This review describes the effects of PUFAs in AF and provides the current literature in the prevention of AF.

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KEY WORDS

Omega-3 fatty acids • Atrial fibrillation • Arrhythmia • Cardiac surgery • Myocardial infarction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 2.6 million people in the United States and 4.5 million people in the European Union.[1,2] It occurs in 0.4% to 1.0% of the general population with increased risk in older individuals (8%-10% risk in those > 80 years).[2]

After a myocardial infarction (MI), cardiac arrhythmias are the most common cause of morbidity and mortality.[3] AF increases the risk of stroke sixfold and all-cause mortality twofold.[1] It also increases the risk of transient ischemic attacks. AF generates ineffective atrial contractions, promoting vascular stasis, thereby leading to thrombus

formation and heart failure.[4] It also induces electrical remodeling, contractile remodeling, and structural remodeling.[5] Most cases are caused by structural heart disease; however, the specific pathogenesis remains undefined.[1]

Possible ectopic activity in one or more of the pulmonary veins may be the initiating factor.[1] Focal ectopic activity can be generated by abnormal atrial automaticity, delayed afterdepolarizations from calcium overload, or early afterdepolarizations secondary to defective repolarization properties.[6] In addition, a small number of functional re-entrant circuits or multiple circuit re-entry may be a causative factor.[6] Pathologic mechanisms may include autonomic dysfunction, inflammation, and fibrosis.[1]

Omega-3 fatty acids (polyunsaturated fatty acids [PUFAs]) have several beneficial effects in the treatment of coronary artery disease.[7-10] PUFAs have also been shown to reduce sudden cardiac death and the incidence of arrhythmias.[11,12] PUFAs have been shown to reduce sudden cardiac death after an MI.[13] Therefore, studies have evaluated whether PUFAs may be helpful in AF. This review describes the role of PUFAs in AF and provides the current literature on their effects in AF prevention.

Mechanisms of Antiarrhythmic Effect

PUFAs have a chemical structure similar to that of antiarrhythmic drugs. It contains docosahexaenoic acid (DHA), which is a 22-carbon chain, and eicosapentaenoic acid (EPA), which is a 20-carbon chain. Both EPA and DHA are composed of polyunsaturated double bonds.[9] PUFAs are safe overall, with minimal side effects; they have caused no known cases of rhabdomyolysis, or liver or renal toxicity.[14] Table 1 lists the various mechanisms of antiarrhythmic action of PUFAs. PUFAs raise the action potential threshold.[15] They also lower sympathetic tone, reduce heart rate, increase the PR interval and parasympathetic tone, and decrease the chance of prolonged QT interval.[15,16]

PUFAs inhibit voltage-gated sodium channels producing membrane hyperpolarization, thereby reducing arrhythmias.[3] PUFAs also inhibit voltage-gated L-type calcium channels, which also attenuates arrhythmias. Calcium released from the sarcoplasmic reticulum may cause calcium overload leading to increased afterdepolarizations, which may contribute to arrhythmias.[3,17] It also inhibits the voltage-gated potassium channel, which prolongs action potential duration.[3]

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Upstream therapies are being evaluated as a method for primary AF prevention.[18] Upstream therapies modify the atrial substrate or use nonantiarrhythmic drugs to activate specific mechanisms to prevent the occurrence (primary prevention) or recurrence of AF (secondary prevention).[18] PUFAs are one such potential agent, along with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins.[18] Upstream therapy mainly focuses on modulating structural changes in the atria, including fibrosis, hypertrophy, inflammation, and oxidative stress. It targets the formation of the substrate that induces AF.[18] It also induces indirect and direct effects on atrial ion channels, gap junctions, and calcium handling.[18] PUFAs have been shown to decrease the expression of genes involved in fibrosis and hypertrophy in the atrial myocardium.[18]

Their antiarrhythmic effects have also been noted in clinical trials.[13,19] The Indian Experiment of Infarct Survival[20] was a randomized, double-blind, placebo-controlled trial assessing the effects of EPA and mustard oil in patients with suspected acute MI. A total of 360 patients received EPA (1.08 g/d),

TABLE 1

Antiarrhythmic Mechanism of Action of Omega-3 Fatty Acids

Outcome	Omega-3 Fatty Acids	Mechanism
Arrhythmias	↓	↑ action potential threshold ↓ action potential duration ↑ relative refractory period Inhibits voltage-dependent sodium channels Inhibits L-type calcium channels Inhibits voltage-gated potassium channels ↓ sympathetic tone ↑ vagal tone

mustard oil, or placebo within 18 hours after onset of MI symptoms. After a 1-year follow-up, cardiac events were significantly lower in the mustard and fish oil group compared with the placebo group (28%, 24.5%, and 34.7; $P \leq .01$). The fish oil group also showed a significant reduction in cardiac arrhythmias compared with the placebo group. The Cardiovascular Health Study[21] showed a reduction in arrhythmia-related ischemic heart disease death from consumption of tuna and broiled or baked fish secondary to PUFAs. This study of patients aged > 65 years, conducted in the United States, showed that higher consumption of tuna or other nonfried fish was associated with a lower risk of arrhythmia-induced ischemic heart disease death.

… increased serum concentrations of PUFAs may be protective for AF, with serum DHA concentrations showing the greatest impact.

New-onset AF

Studies have been conducted to evaluate the role of PUFAs in the prevention of AF in patients with no history of AF (Table 2). In a study by Shen and colleagues,[22] the incidence of AF was evaluated in the Framingham Heart Study with the consumption of alcohol, caffeine, fiber, and PUFAs. A total of 4526 patients without AF were followed for 4 years; 296 developed AF. Lone AF (no history of MI, heart failure, significant heart murmur, hypertension, and electrocardiographic left ventricular hypertrophy) occurred in 28 patients. Only consumption of ≥ 4 servings of dark fish per week was significantly associated with AF risk compared with > 1 serving of dark fish per week (hazard ratio [HR] 6.53; $P < .0001$). Dark fish was classified as salmon, swordfish, bluefish, mackerel, and sardines.[22] However, this group consisted of only 21 patients with 5 reported cases of AF; therefore, the significance may be related to lack of power rather than a specific association. Further investigation will be necessary before any conclusion can be derived.

In a prospective cohort study by Virtanen and associates,[23] 2174 men from the prospective population-based Kuopio Ischemic Heart Disease Risk Factor Study were assessed for the benefits of PUFAs in the risk of AF. Patients were free of AF at baseline and between age 42 and 60 years. Patients were followed for 17.7 years, during which time 240 new AF cases were noted. Heart failure and MI were exclusion criteria. The study revealed that increased serum concentrations of PUFAs may be protective for AF, with serum DHA concentrations showing the greatest impact. Men with the highest serum EPA, docosapentaenoic acid, and DHA concentrations had a 35% reduction in the HR of AF (P for trend = .07). Individual PUFA component analysis revealed that only DHA was associated with reduced AF risk (HR 38% lower; $P = .02$). Therefore, this suggests that PUFAs may prevent AF, with DHA possibly being the specific preventative component.

Mozaffarian and colleagues[24] evaluated the incidence of AF in patients consuming fried, baked, or broiled fish in the Cardiovascular Health Study. The population-based cohort study of 4815 patients aged ≥ 65 years discovered 980 incident cases of AF diagnosed in a 12-year follow-up period. The study revealed that consumption of baked or broiled tuna reduced the incidence of AF, a 28% lower risk with intake of one to four times per week (HR 0.69; $P = .005$). Patients who consumed fish five or more times per week had a 31% lower risk (HR 0.69; $P = .008$). Tuna or other fish intake, not including fried fish or fish sandwiches, was associated with higher plasma EPA and DHA levels. However, consumption of fried fish or fish sandwiches was not associated with reduced incidence of AF. Therefore, baked or broiled tuna provides cardioprotective effects against AF, whereas fried fish may increase the concentration of omega-6 fatty acids, trans-fatty acids, and oxidation products (especially when oils are repeatedly fried), which reduces the effectiveness of AF reduction by PUFAs.

Conversely, PUFAs may also have no effect in AF prevention. The Rotterdam Study[25] evaluated the incidence of AF in 5184 patients consuming fish and intake of DHA and EPA. The population-based, prospective, cohort study followed patients aged ≥ 55 years for a mean duration of 6.4 ± 1.6 years with incident AF occurring in 312 patients. The results revealed no significant effect of fish consumption and intake of DHA and EPA in AF prevention.

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However, these results may have been confounded by a discrepancy

TABLE 2

Summary of Trials of Omega-3 Fatty Acids and Atrial Fibrillation

Study	N	Study Type	AF Incidence (n)	Groups	Endpoints	Results
New-onset AF						
Shen J et al[22]	4526	Prospective	177 men, 119 women; 4-y follow-up	Alcohol, fiber, caffeine, fatty fish intake	AF incidence	No effect on AF risk
Virtanen JK et al[23]	2174	Prospective, population-based	240; 17.7-y follow-up	Men aged 42-60 y; PUFA intake	Benefits of PUFAs in AF prevention	PUFAs reduced AF risk (only DHA specifically)
Mozaffarian D et al[24]	4815	Population-based, cohort	980; 12-y follow-up	> 65 y; fried, baked, broiled fish intake	AF incidence	AF incidence reduced with tuna, baked or broiled fish
Brouwer IA et al[25]	5184	Population-based, prospective	312; mean follow-up 6.4 ± 1.6 years	> 55 y; fatty fish, DHA and EPA intake	AF incidence	No effect on AF incidence
Berry JD et al[26]	44,720	Population-based	378; 6-y follow-up	Fatty fish intake	AF incidence	No effect on AF incidence
Frost and Vestergaard[27]	47,949	Prospective, cohort	556; mean follow-up 5.7 y	Fatty fish intake	AF and atrial flutter incidence	No effect on AF incidence
Post-MI AF						
Macchia A et al[35]	3242	Population-based	4; 3-y follow-up	Post-MI patients receiving PUFAs	AF incidence (1 y post-MI)	PUFAs decreased 1-y post-MI incidence and all-cause mortality
Recurrent/Symptomatic AF						
Kowey PR et al[36]	663	Prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter	167 AF/atrial flutter; 6-mo follow-up	PUFA intake	Symptomatic AF recurrence	No effect on AF recurrence
Persistent AF						
Bianconi L et al[39]	204	Randomized, double-blind, placebo-controlled, multinational	56; 6-mo follow-up	PUFA intake	AF recurrence	No effect on AF recurrence after cardioversion

AF, atrial fibrillation; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; PUFA, polyunsaturated fatty acid (omega-3 fatty acid).

in the exact calculation of dietary fish intake, specific fish type consumed, or inaccurate fish intake amount reported by the study cohort. Intake of high proportions of fried fish (lower in EPA and DHA), or perhaps dark fish, may have counteracted the beneficial effects of PUFAs and reduced their potential clinically significant impact. Patients may have also altered their dietary fish intake during the study, which may have also created additional confounding factors. Also, the different age of patients in this study (≥ 55 years) compared with the Cardiovascular Health Study (≥ 65 years) may have been another confounding factor, because older patients are more likely to develop AF. Therefore, the population in the Rotterdam Study may have a lower risk and be less inclined to achieve clinically significant results.

Berry and associates[26] studied 44,720 postmenopausal participants from the Women's Health Initiative to assess the effects of dietary fish intake on the incidence of AF. In a 6-year follow-up, 378 new cases of AF occurred. However, fish intake (fried or nonfried) did not reduce the incidence of AF. The incidence of AF occurred in a low proportion of the population (1%) compared with 20% of the patients in the Cardiovascular Health Study, which may indicate a lower-risk cohort of patients. Moreover, the consumption of fish in the patients derived from the Women's Health Initiative was much lower compared with the Cardiovascular Health Study. In the Cardiovascular Health Study, approximately 20% of patients reported consumption of five or more servings of fish per week, unlike the Women's Health Initiative participants, of whom < 5% consumed such amounts. Consequently, the decreased fish oil intake may have been inadequate for a positive effect, whereas if higher amounts were consumed, it may be postulated that a beneficial effect may have been observed for AF prevention.

The Danish Diet, Cancer, and Health Study[27] examined 47,949 participants aged 50 to 64 years in a prospective cohort study to assess the effects of fish consumption (based on a food frequency questionnaire) on the incidence of AF or atrial flutter. After a mean follow-up of 5.7 years, 556 patients developed AF or atrial flutter. However, the consumption of fish did not reduce the incidence of AF or atrial flutter. This may be due to lack of adequate fish oil consumption to produce an antiarrhythmic effect. Moreover, the results may have been confounded by an inaccurate assessment of fish intake from the food questionnaire. Also, patients with known heart disease were excluded from the study, which may have reduced the number of patients with AF. Furthermore, the Danish population consumes larger amounts of fish oil compared with the United States so that any additional intake may have produced no clinical benefit. In contrast, the lower baseline fish oil consumption of patients in the United States may explain the beneficial results of PUFAs in the Cardiovascular Health Study because patients may have derived enhanced advantage from the increased fish oil intake. Finally, the study had limited statistical power and only included patients with symptomatic AF or atrial flutter who required hospitalization or outpatient evaluation. Nevertheless, a recent meta-analysis of randomized controlled trials by Liu and associates[28] revealed no significant effects of PUFAs in AF prevention (odds ratio [or] 0.81; 95% confidence interval [CI], 0.57-1.15; $P = .24$). Consequently, conflicting results exist in the use of PUFAs for AF prevention and future studies are necessary before specific recommendations can be provided.

Postoperative AF

Coronary artery bypass graft (CABG) surgery is commonly performed worldwide for coronary artery disease. The most common complication of CABG is postoperative AF (PoAF), which may occur in 25% to 60% of patients.[29,30] PoAF is caused mainly by inflammation and oxidative stress.[31] It is associated with increased hemodynamic compromise, symptoms requiring cardioversion, and use of pressor agents along with infectious, renal, and neurologic complications.[30] PoAF is linked to significant morbidity, long-term mortality, and greater health care costs.[30] Table 3 summarizes the studies evaluating PUFAs for postoperative AF prevention.

Calò and colleagues[29] conducted a prospective, open-labeled, randomized controlled trial of 160 patients to assess the role of PUFAs in preventing AF after isolated CABG. Patients were randomized to receive 2 g/d of PUFAs (850-882 mg of EPA and DHA at a EPA:DHA ratio of 1:2) for at least 5 days before surgery, which was continued until hospital discharge. All patients were followed-up with 4 weeks after hospital discharge with a 12-lead electrocardiogram and physical examination. The primary endpoint was postoperative AF occurrence and the secondary endpoint was the length of hospital stay after surgery. PUFA-treated patients had only 12 cases of AF (15.2%; $P = .013$), whereas the control group had 27 cases (33.3%). An 18.1% absolute risk reduction and a 54.4% relative risk reduction was observed in patients given PUFAs. Also, the PUFA-treated patients were

TABLE 3

Studies of Postoperative Atrial Fibrillation Prevention With Omega-3 Fatty Acids

Study	N	Study Type	AF Incidence (n)	Groups	Endpoints	Results
Calò L et al[29]	160	Randomized, controlled	12	PUFAs prior to CABG	AF incidence; secondary: length of hospital stay	PUFAs reduced postoperative AF ($P = .013$) and hospital stay ($P = .017$)
Mariscalco G et al[32]	530	Prospective, observational	237 early AF, 78 late AF; 4-y follow-up	PUFAs prior to any cardiac surgery	Early and late AF incidence	PUFAs decreased early AF ($P = .006$); PUFAs did not reduce late AF
Heidt MC et al[33]	102	Prospective, randomized, controlled	9	Intravenous fish oil prior to CABG	Postoperative AF incidence	Intravenous PUFAs decreased postoperative AF ($P \leq .05$)
Heidarsdottir R et al[34]	170	Prospective, randomized, double-blind, placebo-controlled	45	PUFAs prior to CABG or valvular surgery	Postoperative AF incidence	PUFAs had no effect on postoperative AF

AF, atrial fibrillation; CABG, coronary artery bypass graft surgery; PUFA, polyunsaturated fatty acid (omega-3 fatty acid).

hospitalized for fewer days than control subjects (7.3 ± 2.1 days vs 8.2 ± 2.6 days; $P = .017$). The study showed that PoAF was reduced by 54.4% with PUFAs. Thus, the antiarrhythmic properties of PUFAs may extend into the atrium to reduce atrial ectopic activity contributing to AF. Furthermore, the anti-inflammatory effects of PUFAs may also reduce the incidence of postoperative AF. Hence, PUFAs may be considered as a preventative medication for AF prior to CABG and it may also reduce patient hospital stay.

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Mariscalco and coworkers[32] evaluated the role of AF prevention in post–cardiac surgery patients with the preoperative administration of 1 g of PUFA daily (median duration of 5 days). In this prospective, observational study, 530 patients were followed for 4 years and analyzed for the incidence of early and late AF. The overall incidence of early AF (occurring in the surgical department) was 44.7% and late AF (occurring in cardiac rehabilitation) was 14.7%.

Early AF occurred in 31.0% of patients in the PUFA group and 47.3% in the control subjects ($P = .006$). Preoperative PUFA administration was independently associated with a 46% risk reduction of early AF (OR 0.54; 95% CI, 0.31-0.92). The development of AF increased hospitalization time compared with absence of AF (10.4 ± 9.8 vs 9.5 ± 9.2 days; $P = .025$). Preoperative PUFA administration also diminished postoperative C-reactive protein compared with control subjects (3.8 ± 2.9 vs 5.1 ± 4.0; $P = .025$). However, preoperative PUFA administration did not favorably reduce the incidence of late AF. Because inflammation occurs most commonly in the immediate postoperative period, the anti-inflammatory effects of PUFAs may only be beneficial in early AF. The study concluded that only early AF was significantly reduced with preoperative PUFA treatment. This is an important finding because postoperative AF is a common arrhythmia that contributes to increased morbidity and mortality.[32] Successful preventative strategies may yield significantly superior postoperative outcomes.

Intravenous infusion of PUFAs may also be beneficial in AF prevention after CABG.

Intravenous infusion of PUFAs may also be beneficial in AF

prevention after CABG.[33] A prospective, randomized, controlled trial of 102 patients who were preoperatively treated with 100 mg fish oil/kg body weight/d, which was continued until discharge from the intensive care unit, was conducted to evaluate the effectiveness of PUFAs in AF prevention.[33] The primary endpoint of postoperative AF occurred in 9 patients (17.3%) compared with 15 (30.6%) in the control group ($P \leq .05$). Also, the PUFA-treated patients were in the intensive care unit and hospital for a shorter time period. Thus, preoperative intravenous PUFA administration may be considered if logistically feasible; otherwise, oral supplementation may be considered prior to cardiac surgery.

However, a prospective, randomized, double-blind, placebo-controlled trial conducted by Heidarsdottir and associates[34] refutes the effectiveness of PUFAs in preventing postoperative AF. A total of 170 patients who underwent cardiac surgery were treated with 1240 mg of EPA and 1000 mg of DHA or olive oil capsules (control group) for 5 to 7 days preoperatively and until hospital discharge. The incidence of postoperative AF was 54.2% in the PUFA group and 54.1% in the control group ($P = .99$). Thus, no difference was noted with the use of PUFAs. This study contradicts the results of Calò and colleagues[29]; however, this study contained a lower-dose ratio of DHA (EPA:DHA ratio of 1.2:1) compared with the study by Calò and colleagues[29] (EPA:DHA ratio of 1:2). Because DHA may induce a greater inhibitory effect on atrial arrhythmia, this may explain the negative results.[23] Furthermore, this study was double-blinded, whereas the study by Calò and colleagues[29] was not, which may have introduced bias in the latter study. Finally, the patients in this study did not have follow-up after discharge, whereas the study from Calò and colleagues[29] followed patients for 4 weeks after discharge. Consequently, the study of Heidarsdottir and associates.[34] may have missed the incidence of AF in that time period. Hence, inconclusive data remain, which suggests that further studies are necessary before definitive treatment recommendations can be advised. The current ongoing Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) trial is a randomized, appropriately powered, double-blind, placebo-controlled, multinational trial that attempts to answer the question of whether PUFAs can reduce the incidence of PoAF. This study was expected to be completed in 2012.[30] (See Note Added in Proof on page e90 of this issue.)

Post–MI AF

Macchia and coworkers[35] studied the occurrence of AF in post-MI patients treated with PUFAs. A population-based study of 3242 patients was conducted in six Italian local health authorities over a 3-year period, during which 215 patients received PUFAs. The study found that PUFAs reduced the relative risk of hospitalization for AF after an MI in patients who were followed for 360 days (HR 0.19; 95% CI, 0.07-0.51). In a matched cohort analysis (only known difference between groups was intake of PUFAs), PUFA supplementation decreased AF incidence (HR 0.13; 95% CI, 0.04-0.44; $P = .001$). PUFAs also attenuated all-cause mortality and 1-year AF incidence after an MI. This is an important finding because AF increases the risk of stroke and death after MI.[35] The PUFA group (n = 215) was minimal compared with the total population (n = 3242), which may have erroneously affected the results; however, the study attempted to correct this factor by propensity scoring. Thus, the results are not definitive, but rather hypothesis generating. Further studies are necessary to elaborate on this potential beneficial outcome.

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Recurrent and Symptomatic AF

AF can be a chronic problem with episodes of conversion to normal sinus rhythm followed by reversion to AF. Kowey and colleagues[36] studied the use of PUFAs for the prevention of recurrent symptomatic AF. In a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial, 663 patients with symptomatic paroxysmal (n = 542) or persistent AF (n = 121; no substantial structural heart disease and normal sinus rhythm at baseline) were enrolled. Patients received either 8 g/d of PUFAs (each gram contained 465 mg of EPA and 375 mg of DHA) for the initial 7 days or placebo (1 g corn oil). Afterward, 4 g/d of PUFAs were given for 24 weeks versus placebo. The primary endpoint was symptomatic recurrence of AF (first recurrence) in the paroxysmal AF group. Secondary endpoints were the first recurrence in the persistent group and both groups combined. In the paroxysmal group receiving PUFAs, 135 (52%) of 258 patients had recurrent symptomatic AF or aflutter. In the persistent AF group receiving PUFAs, 32 (50%)

had recurrent symptomatic AF or aflutter. At 6-month follow-up, PUFAs did not reduce the recurrence of AF in both the paroxysmal or persistent AF patients. Most of the AF or aflutter cases occurred in the first 2 weeks, which may not have been adequate time for PUFAs to exert an antiarrhythmic effect. The study did not include patients with structural heart disease, which may have increased the risk of AF occurrence. Moreover, the transtelephonic approach to assessing AF recurrences may have falsely reduced the quantity of AF recurrences. Finally, the study may imply that PUFAs are not beneficial in preventing AF recurrences, but their lack of utility in preventing new-onset AF may not be a direct correlation. Thus, further studies are required to generate a valid conclusion and define whether PUFAs are valuable in only specific types of AF.

Patients with sustained AF with rapid heart rates may develop symptoms of lightheadedness, chest pain, shortness of breath, fatigue, dizziness, reduced exercise tolerance, and even syncope.[37] In the Fish Oil Research With Omega-3 for Atrial Fibrillation Recurrence Delaying (FORWARD) trial,[38] 1400 patients with a previous history of symptomatic AF (paroxysmal or persistent) were studied to determine if PUFAs could reduce AF recurrence in a randomized, double-blind, placebo-controlled trial. Patients $>$ 21 years who converted to normal sinus rhythm were randomized to 1 g of PUFAs versus placebo to measure the primary endpoint of AF-free survival in a 12-month follow-up period. Secondary outcomes included all-cause mortality, nonfatal acute MI, systemic embolism, heart failure, severe bleeding, all-cause hospitalizations, survival free of thromboembolic events, and hospitalizations for cardiovascular causes. The results have not yet been reported.

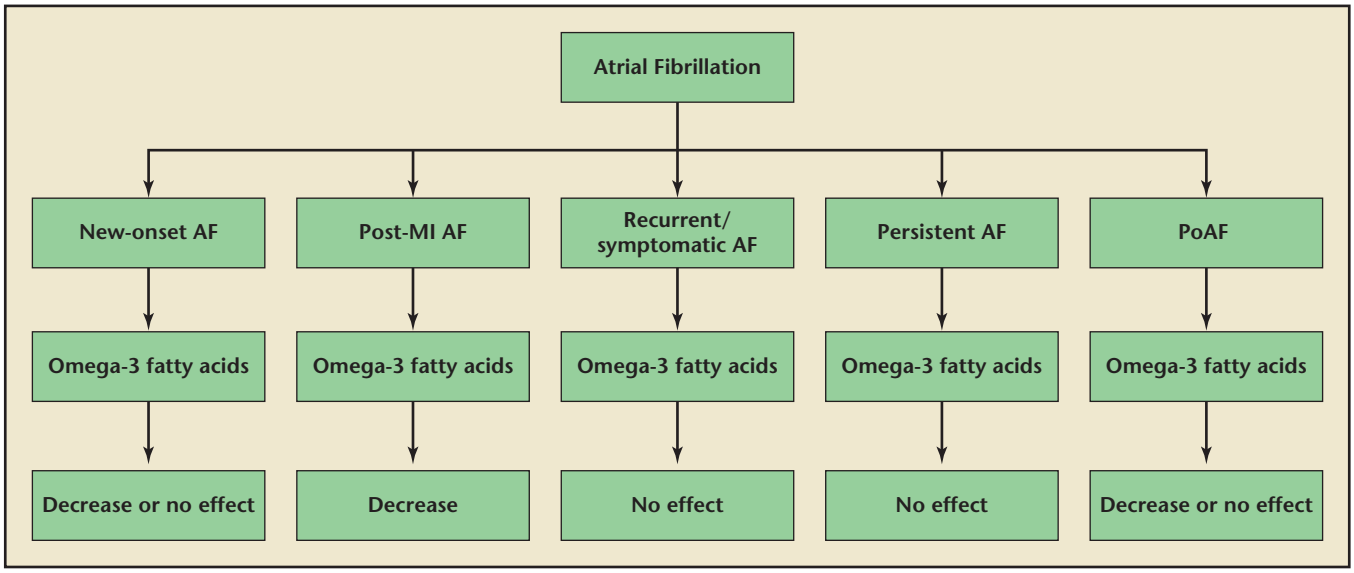
Persistent AF

Bianconi and associates[39] studied the effects on AF prevention in 204 patients with persistent AF who were treated with electrical cardioversion and PUFAs. The study was a randomized, double-blind, placebo-controlled, multicenter study conducted in Italy. The PUFA group comprised 104 patients who received 3 g/d of PUFAs until direct current electrical cardioversion followed by 2 g/d for 6 months. The primary endpoint was AF recurrence. The study found no significant difference in AF recurrence with the use of PUFAs in patients who received electrical cardioversion. This finding may have been caused by a suboptimal dose or an administration that was too short for adequate PUFA incorporation into atrial tissues. Figure 1 summarizes the effects of PUFAs in the prevention of AF based on the various types of AF studied in the several aforementioned clinical trials.

Conclusions

AF is the most common cardiac arrhythmia affecting millions of individuals daily. It may become a chronic disabling problem in normal or structurally abnormal hearts. Therefore, AF prevention will provide a significant improvement of morbidity and mortality from cardiovascular disease.

Figure 1. Benefits of omega-3 fatty acids on various types of atrial fibrillation (AF). MI, myocardial infarction; PoAF, postoperative AF.



Current clinical trials have shown conflicting data regarding the use of PUFAs in AF prevention. Some studies have shown that PUFAs prevent new-incident AF and AF after cardiac surgery, which is also a significant cause of postoperative morbidity and mortality. Consequently, it may be postulated that PUFAs have potential beneficial effects in AF prevention.

Conversely, other studies have shown no benefits in AF prevention. The possible explanations for the conflicting data may be due to inadequate PUFA dosing to achieve a clinical effect, insufficient dietary fish intake, necessity for longer-term follow-up to observe a clinical benefit, or counteracting negative effects possibly induced by consumption of large quantities of fried fish.

However, no definitive evidence exists. Thus, further studies are necessary to investigate the benefits of PUFAs for AF prevention before precise treatment recommendations can be provided. The prospective benefits in preventing new-onset AF or PoAF will have an immeasurable impact in morbidity and mortality reduction along with a tangible decrease in health care costs. Ongoing clinical trials and therapies involving upstream modulation may provide a multifaceted or alternative approach for AF treatment.

Note Added in Proof

New recently released studies after the acceptance of this manuscript show that PUFAs in postoperative AF show no beneficial effect. The randomized, controlled studies include the FISH and OPERA trials. Also, the randomized, controlled FORWARD trial showed no benefits of PUFAs in reducing recurrent AF. Therefore, recently published randomized, controlled trials suggest that PUFAs may have no clinical impact in reducing postoperative or recurrent AF. ■

The author reports no real or apparent conflicts of interest.

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MAIN POINTS

- Atrial fibrillation (AF), common after myocardial infarction and cardiac surgery, increases the risk of morbidity and mortality from stroke, thromboembolism, and death. It also increases the risk of transient ischemic attacks. AF generates ineffective atrial contractions, promoting vascular stasis, thereby leading to thrombus formation and heart failure.
- Polyunsaturated fatty acids [PUFAs] have several beneficial effects in the treatment of coronary artery disease, and studies have evaluated whether PUFAs may be helpful in AF.
- Daily preoperative administration of PUFAs may prevent AF in patients after cardiac surgery. Intravenous infusion of PUFAs may also be beneficial in AF prevention after coronary artery bypass graft. However, two newly published randomized, controlled trials (FISH and OPERA) showed no benefits of PUFAs in reducing postoperative AF.
- Some studies have shown no benefits in AF prevention. The possible explanations for the conflicting data may be due to inadequate PUFA dosing to achieve a clinical effect, insufficient dietary fish intake, necessity for longer-term follow-up to observe a clinical benefit, or counteracting negative effects possibly induced by consumption of large quantities of fried fish.
- The newly published randomized, controlled, FORWARD Trial showed no benefits of PUFAs in reducing recurrent AF. Therefore, more recent trials displayed lack of effect by PUFAs in mitigating AF that refutes the benefits shown in earlier studies. Further research, possibly evaluating upstream modulation, may provide alternative therapies to achieve clinical benefit in AF.

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