Several epidemiological and large randomized, clinical trials carried out in the general population and in patients with cardiovascular disease have reported a significantly lower incidence of sudden cardiac death (presumably arrhythmic) with high dietary fish consumption or omega-3 polyunsaturated fatty acid (PUFA) supplements. This has prompted interest in exploring the antiarrhythmic potential of PUFAs in patients at particularly high risk of sudden arrhythmic death (ie, patients with internal cardioverter-defibrillators for secondary prevention), but the results were unexpectedly disappointing: the meta-analysis of the controlled studies failed to show any benefit from treatment with PUFAs. At about the same time, a proof-of-concept open-label study demonstrated a remarkable 65% reduction in the occurrence of atrial fibrillation (AF) after coronary artery bypass grafting surgery, and the search for antiarrhythmic activity of PUFAs in atrial tachyarrhythmias has begun.

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Various animal models of AF, including atrial pacing, simultaneous atrioventricular pacing, vagal stimulation, cardiac surgery and sterile pericarditis, and congestive heart failure induced by ventricular tachypacing or intracoronary infusion of doxorubicin, have been used to demonstrate the effects of PUFAs on electric and structural atrial remodeling. In these experiments, treatment with PUFAs prevented significant shortening of the atrial effective refractory period associated with AF, reduced inducibility of AF and duration of induced AF, and attenuated atrial fibrosis although a difference in response was noted in some models (eg, lack of effect in atrial tachypacing was reported).

Results in the clinical arena have been less consistent. Although an early open-label and a larger observational study reported a reduction in the incidence of postoperative AF, 3 subsequent trials with a more rigorous design (double-blind, placebo-controlled) did not reproduce these results. Similarly, in several epidemiological analyses, high dietary-fish consumption conferred no benefit on the prevention of AF in the general population, and some even reported a strong trend toward more AF among individuals eating >5 fish meals per week.

Several secondary prevention trials of PUFAs in AF have been published fairly recently, and some are available as preliminary reports. Among these, 4 randomized studies (3 double-blind, placebo-controlled) that enrolled patients with either paroxysmal or cardioverted persistent AF and patients scheduled for electric cardioversion of AF showed no effect of therapy with PUFAs on the incidence of recurrent AF either as monotherapy or in addition to conventional antiarrhythmic drugs.

In the current issue of Circulation, Nodari et al report the results of a double-blind, placebo-controlled study of PUFA supplements in patients with recurrent persistent AF who previously had, on average, 2 cardioversions. The study was first presented at the American College of Cardiology Sessions in Atlanta in March 2010. Of 254 screened patients, 199 were randomized to therapy with PUFA 2 g/d with an eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) ratio of 1.2, or placebo (olive oil) starting 4 weeks before electric cardioversion. In contrast to the 2 previous studies, significantly fewer patients who received PUFAs had a recurrence of AF after 1-year follow-up compared with placebo (37% versus 56%). The mean time to first recurrence was 168±116 days in the PUFA arm and 139±113 days in the placebo arm; there was no difference in the proportion of patients with symptomatic AF recurrence (40% versus 44%). In addition, therapy with PUFAs may have facilitated electric cardioversion as judged by the number of patients with cardioversion failure (2% versus 6%) and the number of patients cardioverted with a single shock (78% versus 33%).

A recent meta-analysis of 5 studies in 1179 patients (621 events), including the preliminary data from Nodari et al, showed no effect of PUFAs on secondary prevention of AF (odds ratio 0.83, 95% confidence interval 0.48 to 1.45; P=0.51). However, there was significant heterogeneity between studies because of differences in patient populations, follow-up duration, and dosage, type, and duration of treatment with PUFAs.

There are some differences in the study populations (the Table). Nodari et al included patients with more refractory AF (ie, with recurrent AF after previous cardioversion) and more advanced underlying heart disease, who were slightly older and had a lower left ventricular ejection fraction than those in other trials, which was the likely reason for higher rate of recurrence in the placebo arm in the Nodari study. All patients were treated with amiodarone. The trial is a clear outlier with respect to the reduction of AF in the PUFA arm (the Figure). One interpretation of this result may be that PUFAs have a synergistic effect with antiarrhythmic drug
therapy and specifically with amiodarone. However, this is not supported by the results of an admittedly smaller and less robustly designed trial reported by Özaydin et al.11 that did not show any difference in the recurrence rates between combination therapy with amiodarone and PUFAs and amiodarone alone.

Another contributing factor may be the duration of pre-treatment with PUFAs and antiarrhythmic therapy before cardioversion. An interesting finding in the study by Nodari et al was the absence of a high recurrence rate in the first 30 to 40 days of treatment. Indeed, in both negative studies, the majority of AF recurrences occurred within the first 30 to 40 days of treatment. The ability of PUFAs to increase parasympathetic tone may theoretically be proarrhythmic in younger individuals with normal hearts in whom a vagal component may play a role in promoting AF. The proportion of such patients with lone AF or mild cardiovascular disease was higher in the studies that failed to demonstrate a benefit from PUFA therapy. Further, in the study by Kowey et al8, a smaller and less robustly designed trial reported by Özaydin et al11 that did not support the results of an admittedly smaller and less robustly designed trial reported by Özaydin et al11 that did not show any difference in the recurrence rates between combination therapy with amiodarone and PUFAs and amiodarone alone.

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Several other issues warrant discussion. Unlike other trials, which used regular transtelephonic monitoring,8,9 Nodari et al
relied on scheduled clinic visits, self-reporting, and notification from other health professionals after incidental detection of AF (eg, anticoagulation clinics). In addition, unlike previous trials, there was no monitoring of adherence with therapy and no evidence of correlation with plasma membrane EPA/DHA content because no such measurements were reported. The confounding effect of dietary fish intake must also be considered given that none of the reported studies appears to have adequately controlled for this. These limitations of the study raise the question of whether the positive result in this relatively small and suboptimally controlled (limited monitoring of AF recurrence and of adherence to therapy) may reflect a random effect rather than any conclusive antiarrhythmic consequence.

The mechanism of potential antiarrhythmic action of PUFAs is complex and, similarly to that of statins, is probably the result of their many pleiotropic effects on atrial electrophysiology and structure. These effects range from modulation of membrane fluidity and the consequent activity of multiple membrane proteins, counteraction of the arrhythmogenic effects of atrial stretch, antiinflammatory and antioxidant actions, decrease of endothelial dysfunction, regulation of profibrotic activity of mitogen activated protein kinases and matrix metalloproteinases and reduction of the expression of proinflammatory and profibrotic genes. Unlike other upstream therapies, PUFAs also have direct electrophysiological effects on several ion channels which are relevant in AF, such as \( I_{Na} \), \( I_{Kar} \), \( I_{Kach} \), \( I_{to} \), and \( I_{Ca,L} \) currents and the \( Na^+/Ca^{2+} \) exchanger. Animal studies have reported the protective effect of PUFAs in relatively unremodeled atria, but there has been no study demonstrating reverse remodeling.

The content of individual PUFAs, mainly EPA and DHA, may be more important than the total PUFA concentration because the electrophysiological effects produced by different PUFA components are not the same. DHA exerts a stronger sodium current block whereas EPA (and -linolenic acid found in vegetable oils) have a greater potential to block potassium currents. In the population-based Kuopio Ischaemic Heart Disease Risk Factor Study high serum DHA content was associated with a 38% reduction in relative risk of incident AF, but no such association was found for EPA. In the secondary prevention studies, DHA levels increased to a lesser extent than that of EPA. Kowey et al reported a greater increment in EPA content (about 250–300% from baseline) compared with DHA concentration (a 100% increase). Also in the study by Bianconi et al, EPA levels more than doubled, whereas DHA levels only increased by 25%.

In conclusion, although the theoretical background and experimental evidence suggest an antiarrhythmic effect of PUFAs in AF, this has not been demonstrated in randomized clinical trials. The dose of PUFAs that may produce the antiarrhythmic effect and the duration of treatment have not been established, and the patient populations that may best benefit from this therapy have not been identified. The 2010 European Society of Cardiology Guidelines have made no recommendations on the use of PUFAs for prevention of AF because of the absence of robust evidence. The contribution from Nodari is consistent with basic science data but curiously at odds with similar clinical studies. We must await the results from on-going secondary prevention trials, including the large FORoARD (Fish Oil Research with \( \omega-3 \) for Atrial Fibrillation Recurrence Delay) study, which is expected to enroll 1400 patients with paroxysmal or persistent AF, A Randomized Double-Blind Placebo-Controlled Study to Evaluate the Effect of PUFAs on Arrhythmia Recurrence in Atrial Fibrillation (AFFORD) (NCT02135130, n=332), and NCT00552084, which will also explore the effects on inflammatory markers and cytokines, and 2 smaller trials in patients undergoing left atrial ablation for AF (NCT00791089 and NCT00841451).

Disclosures
Dr Camm is an advisor/speaker/investigator for Servier, Novartis, Sanofi, Astra Zeneca, Xention, Bristol-Myers Squibb, Menarini,
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