Marine omega-3 fatty acids and coronary heart disease

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Purpose of review
To provide an overview of the key earlier intervention studies with marine omega-3 fatty acids and to review and comment on recent studies reporting on mortality outcomes and on selected underlying mechanisms of action.

Recent findings
Studies relating marine omega-3 fatty acid status to current or future outcomes continue to indicate benefits, for example, on incident heart failure, congestive heart failure, acute coronary syndrome, and all-cause mortality. New mechanistic insights into the actions of marine omega-3 fatty acids have been gained. Three fairly large secondary prevention trials have not confirmed the previously reported benefit of marine omega-3 fatty acids towards mortality in survivors of myocardial infarction. Studies of marine omega-3 fatty acids in atrial fibrillation and in cardiac surgery-induced atrial fibrillation have produced inconsistent findings and meta-analyses demonstrate no benefit. A study confirmed that marine omega-3 fatty acids reduce the inflammatory burden with advanced atherosclerotic plaques, so inducing greater stability.

Summary
Recent studies of marine omega-3 fatty acids on morbidity of, and mortality from, coronary and cardiovascular disease have produced mixed findings. These studies raise new issues to be addressed in future research.

Keywords
docosahexaenoic acid, eicosapentaenoic acid, fish oil, mortality, omega-3 fatty acid

INTRODUCTION
The long chain highly unsaturated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in seafood, especially in the flesh of so-called oily or fatty fish. EPA and DHA are also found in fish oil and fish liver oil supplements, in other supplements based on krill oil, and in licensed pharmaceutical grade ethyl ester formulations [1]. In this article, EPA and DHA are referred to as marine omega-3 fatty acids to reflect their origin. Marine omega-3 fatty acids have been long associated with the traditional Inuit and Japanese diets, in which they were considered to be the causal agent in the observed low incidence of cardiovascular mortality [2]. They have been demonstrated to beneficially alter a range of cardiovascular risk factors, suggesting a slowing or reduction in atherosclerotic processes, perhaps explaining the protective effects on cardiovascular morbidity and mortality [2–5,6,7]. The aim of this article is firstly to provide an overview of the key earlier intervention studies with marine omega-3 fatty acids reporting on mortality and then to review and comment on recent studies in this area and on selected underlying mechanisms of action.

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Curr Opin Cardiol 2012, 27:000–000
DOI:10.1097/HCO.0b013e32835f8ebd

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Lipids and heart disease

KEY POINTS

- Ecological, prospective, and case–control studies suggest a beneficial effect of marine omega-3 fatty acids on cardiovascular morbidity and mortality.
- There is increasing understanding of a broad range of molecular and cellular actions of marine omega-3 fatty acids that favourably impact on physiological processes and cardiovascular risk factors.
- Earlier, large secondary prevention trials of marine omega-3 fatty acids reported lower mortality due to reduced cardiovascular events. A reduction in sudden death has implicated an important role for an antiarrhythmic action of marine omega-3 fatty acids.
- Three fairly large secondary prevention trials published recently have not confirmed the benefit of marine omega-3 fatty acids towards mortality. However, each of these three trials has significant limitations.
- Trials of ventricular fibrillation, atrial fibrillation, and cardiac surgery-induced atrial fibrillation have produced inconsistent findings. However, antithrombotic activity and an antiinflammatory action within advanced plaques may be key actions of marine omega-3 fatty acids in reducing cardiovascular events and mortality.

OVERVIEW OF KEY EARLIER INTERVENTION STUDIES

The Diet and Reinfarction Trial (DART) [8] was the first randomized controlled trial (RCT) (n = 2033) to investigate the effects of intervention with marine omega-3 fatty acids on secondary prevention of myocardial infarction (MI). The study showed a 29% reduction in all-cause mortality (mainly due to cardiovascular events) compared with controls, in men advised to eat approximately 300 g of oily fish (this is two or three servings) per week, or to take fish oil capsules providing an equivalent intake of marine omega-3 fatty acids (500–900 mg/day). The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto (GISSI)-Prevenzione study [9] enrolled patients (n = 11,324) within 3 months of having an MI (median time since MI approximately 15 days) and studied the effects of marine omega-3 fatty acids (885 mg EPA + DHA/day) and/or vitamin E with up to 3.5 years of follow-up. Marine omega-3 fatty acids significantly lowered by 15% the risk of the combined primary outcome of death and nonfatal cardiovascular events. This benefit was due almost entirely to decreased mortality (20% reduction in total deaths, 30% in cardiovascular deaths, and 45% in sudden deaths). More recently, the largest RCT with marine omega-3 fatty acids to date (n = 18,645), the Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) [10], found that, after a mean follow-up of 4.6 years, there was a 19% relative reduction in the risk of major coronary events in hypercholesterolaemic patients given 1800 mg/day EPA as a supplement and 10 mg/day pravastatin, or 5 mg/day simvastatin compared with patients given statins alone. Across all patients, a higher plasma EPA content during treatment was inversely associated with risk of major coronary events [11]. However, unlike the previous studies, the reduction in events was related to a reduction in nonfatal coronary events. The population was Japanese, in which dietary intake of fish is commonly high, and the investigators postulated differing mechanisms for protective effects of marine n-3 fatty acids at low and high background intakes. Several subanalyses of JELIS have been published. Incidence of coronary heart disease (CHD) was lower with EPA (+ statins) compared with statins alone, regardless of the number of risk factors present [12]. In patients with high serum triglycerides and low high-density lipoprotein cholesterol, EPA (+ statins) reduced the risk of CHD by 53% compared with statins alone [12]. The authors suggested that EPA may be especially beneficial in patients with abnormal triglycerides and high-density lipoprotein cholesterol. The treatment with EPA and statins resulted in a 22% decrease in the CHD incidence in patients with impaired glucose tolerance and an 18% decrease in normoglycaemic patients compared with statins alone [13]. After adjustment for baseline risk factor levels, the incidence of major coronary events was significantly lower (by 56%; P = 0.041) in patients with peripheral arterial disease receiving EPA and statins than receiving statins alone [14]. In the GISSI Heart Failure study [15], patients (n = 7046) with New York Heart Association heart failure class II–IV were randomized to receive 885 mg/day of EPA and DHA or placebo, and were followed up for a median of 3.9 years. All-cause mortality was lower by 9% in the omega-3 fatty acid group (P = 0.041), whereas cardiovascular admissions to hospital were lower by 8% (P = 0.009). This demonstrated that the addition of omega-3 fatty acids in well treated heart failure patients provides a significant additional clinical benefit to conventional treatment. A recent study [16] examined the effects of 2 g/day marine omega-3 fatty acids for 12 months on left ventricular systolic function in chronic heart failure due to nonischaemic dilated cardiomyopathy. Marine omega-3 fatty acids increased left ventricular ejection fraction, decreased New York Heart Association heart failure class and resulted in lower hospitalization rates for heart failure compared with placebo.
SOME RECENT STUDIES FAIL TO CONFIRM THAT MARINE OMEGA-3 FATTY ACIDS REDUCE MORTALITY

Some recent studies report an absence of effect of marine omega-3 fatty acids on hard cardiovascular outcomes. In the Supplementation en Follates et Omega-3 (SU.FOL.OM3) trial, 2501 patients with a history of MI, unstable angina, or ischaemic stroke received a daily dietary supplement containing B-group vitamins, EPA and DHA (600 mg/day), both, or neither for a median follow-up period of 4.7 years [17]. EPA and DHA had no significant effect on major cardiovascular events, defined as a composite of nonfatal MI, stroke or death from cardiovascular disease. In addition to the lower dose of marine omega-3 fatty acids used compared with GISSI-Prevenzione, JELIS and GISSI Heart Failure, the incidence of major cardiovascular events was lower than anticipated, compromising the power of SU.FOL.OM3 to detect a significant effect. Also the initiation of use of marine omega-3 fatty acids was delayed (MI, acute coronary syndrome or ischaemic stroke within the previous 12 months; median time since the event at study entry 101 days) compared with the relatively early post-MI intervention in GISSI-Prevenzione.

In the ALPHA-OMEGA trial, 4837 MI survivors who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy received one of four trial margarines for 4 months; two of these provided a targeted daily EPA and DHA intake of 400 mg [18]. One of these groups received EPA and DHA and the other EPA and DHA in combination with the plant omega-3 fatty acid, α-linolenic acid, at 2 g/day. A third group received α-linolenic acid (2 g/day) alone, whereas the fourth group was the placebo group and received a standard margarine. Compared with placebo or α-linolenic acid alone, there was no effect of consuming EPA and DHA on the primary endpoint (composite of fatal and nonfatal cardiovascular events and cardiac interventions) or on several secondary endpoints. The dose of EPA and DHA used in ALPHA-OMEGA is lower than that used in DART, GISSI-Prevenzione, JELIS, and GISSI Heart Failure. Furthermore, patients were enrolled up to 10 years after MI (median time 3.7 years), in contrast to GISSI-Prevenzione, in which the delay from the event to study enrolment was less than 3 months. Nevertheless, results from ALPHA-OMEGA showed a trend towards reduced death from CVD in diabetic patients receiving EPA and DHA. Indeed, in a recently published subgroup analysis of the 1014 diabetics enrolled in ALPHA-OMEGA, compared with placebo, those receiving omega-3 fatty acids (combined marine and plant) showed an 84% reduction in risk of ventricular arrhythmia-related events ($P = 0.01$) and a 72% reduction in risk of the combined endpoint of ventricular arrhythmia-related events and fatal MI ($P = 0.007$) compared with placebo [19*]. EPA and DHA alone reduced these outcomes by 42 and 40%, respectively, compared with placebo but these effects did not reach statistical significance.

The OMEGA trial examined the effect of EPA and DHA (885 mg/day) on sudden death over 1 year in 3851 MI survivors (MI 3–14 days prior to study entry) given current guideline-adjusted treatment [20]. There was no effect of EPA and DHA on sudden cardiac death (primary endpoint), total mortality, major adverse cardiovascular events, or revascularization in survivors. Incidence of sudden death and mortality was very low in the population studied and rather less than anticipated, severely compromising study power to detect an effect. It seems likely that a sample size of more than 20 000 would be required to detect a 30% reduction in sudden death in the OMEGA trial, yet it was set up in anticipation of having power to identify a 45% reduction, based upon GISSI-Prevenzione. Follow-up in the OMEGA trial was shorter than in GISSI-Prevenzione, JELIS, and GISSI Heart Failure, although significant effects on major outcomes were seen within 3–9 months in GISSI-Prevenzione [21].

Thus, although three recently published studies have failed to replicate the benefits on hard endpoints reported in earlier studies, each of these recent studies has significant limitations that result in failure to unequivocally demonstrate whether marine omega-3 fatty acids can reduce major coronary and cardiovascular events and mortality in patients on current treatment regimens. These limitations relate to the marine omega-3 fatty acid dose used, the lag between when MI occurred and initiating omega-3 fatty acid treatment, length of follow-up, and sample size. The question of whether marine omega-3 fatty acids lower major cardiovascular endpoints, including sudden death and mortality, in at risk patients on the treatment regimens currently used remains unresolved.

Data from several other recently published studies do support a reduction in mortality and in adverse cardiac outcomes with marine omega-3 fatty acids. Benedetto et al. [22*] examined the effect of 885 mg EPA and DHA/day on all-cause mortality (the primary outcome), need for revascularization, and a composite of death, MI or cerebrovascular events over 12 months among patients ($n = 930$) discharged from hospital following coronary artery bypass grafting (CABG). Although there was a control group ($n = 1170$) who did not receive any intervention, the study was not randomized, it cannot be said to be placebo-controlled, and it may not have
Lipids and heart disease

been blind. The patients who were discharged on marine omega-3 fatty acids had a 49% lower risk for late mortality, a 48% lower need for repeat revascularization, and a 44% lower risk for the composite outcome. Subgroup analyses showed that the mortality benefit associated with omega-3 fatty acids was particularly strong in patients with poor left ventricular function. In a prospective cohort study of 956 patients with stable CHD at study entry, those with fasting blood levels of EPA and DHA at or above the median value had a 27% lower risk of all-cause mortality over a median follow-up period of 5.9 years compared with those with levels below the median [23]. The authors suggest that a low blood omega-3 fatty acid level is an independent risk marker for death from any cause in patients with stable CHD. In another prospective study, plasma phospholipid EPA, DHA and total omega-3 fatty acids at study entry were inversely associated with risk of incident congestive heart failure over the follow-up period [24**]. In a case–control study, red blood cell EPA and DHA were lower in patients with acute coronary syndrome (n = 668 vs. n = 680 controls) [25].

MECHANISMS OF ACTION

Marine omega-3 fatty acids exert a variety of actions on cell physiology and function [1,26**]. Many of these actions require that the fatty acids be incorporated into the cell membrane, from where they can influence the physical properties of the membrane, the assembly of signalling platforms termed lipid rafts, intracellular signalling cascades leading to gene expression, and the formation of various lipid mediators including prostaglandins, leukotrienes, resolvins, and endocannabinoids. Typically, these actions are rather slow to induce, but are long lasting, and they underlie the effects of marine omega-3 fatty acids that lead to lowered blood triglyceride concentrations, reduced inflammation, decreased blood pressure, improved endothelial reactivity, reduced resting heart rate, increased heart rate variability, and decreased platelet aggregation [2–5,6*,7**]. Some of these actions would serve to slow atherosclerosis and so would contribute to a protective effect of marine omega-3 fatty acids towards CHD. An inverse relationship between serum marine omega-3 fatty acid levels and carotid intima–media thickness was reported in one study [27], suggesting a protective effect towards atherosclerosis in humans. Many of the actions of marine omega-3 fatty acids most likely require intakes above 1g/day, which are difficult to achieve through diet alone. In contrast to the slow-onset effects described above, EPA and DHA also have direct effects that do not require their incorporation into membranes. These rapid effects include actions on ion channels which are believed to underlie antiarrhythmic actions (see below) and actions on specific G-protein coupled receptors that influence inflammatory responses of macrophages and insulin action in adipocytes [28].

VENTRICULAR AND ATRIAL FIBRILLATION

As several studies report that marine omega-3 fatty acids reduce risk of sudden death, a favoured mechanism has been an antiarrhythmic action [29]. In vitro studies with isolated cardiomyocytes showed that exposure to free EPA or DHA resulted in inhibition of voltage-dependent sodium, potassium, and L-type calcium channels, with DHA being more potent [30]. In perfused rabbit hearts and in feeding studies with rats and monkeys, marine omega-3 fatty acids had an antiarrhythmic effect [5], whereas in dogs intravenous marine omega-3 fatty acids prevented exercise-induced ventricular fibrillation [5]. Human trials of marine omega-3 fatty acids and recurrent ventricular tachycardia or ventricular fibrillation have been equivocal. Double-blind, placebo-controlled RCTs in patients with implanted cardioverter-defibrillators (ICDs) produced conflicting findings. One study showed a prolonged time to first ICD discharge (i.e., a reduction in probably recurrent ventricular tachycardia or ventricular fibrillation), with most benefit in patients with preexisting CHD [31], another showed no effect [32], and the third showed an increased need for ICD discharge [33]. None of these three studies reported any effect of marine omega-3 fatty acids on mortality, but they were all of much smaller size than the secondary prevention trials described above. Duration of treatment varied within these trials, but averaged 12 months in two of them [31,32] and almost 15 months in the third [33]. Meta-analysis of the three trials using ICDs [34] showed no overall effect on ventricular tachycardia/ventricular fibrillation, but suggested that patients may show a differential response which may relate to the key factor in the initiation of the ventricular tachycardia or ventricular fibrillation.

Until recently, atrial fibrillation had received less attention as a target for marine omega-3 fatty acids than ventricular fibrillation. However, a number of studies in animal models have demonstrated lower susceptibility to atrial fibrillation with marine omega-3 fatty acids [5]. A very recent report examined the relationship between plasma phospholipid omega-3 fatty acids at study entry and atrial fibrillation over a prolonged period of
follow-up among 3326 older men and women [35**]. DHA and total marine omega-3 fatty acid levels showed an inverse relationship with relative risk of atrial fibrillation, suggesting that marine omega-3 fatty acids may have a role in primary prevention of atrial fibrillation.

Over the last 18 months, a series of trials of marine omega-3 fatty acids reporting effects on atrial fibrillation have been reported. Kowey et al. [36] provided marine omega-3 fatty acids (8 g/day for the first 7 days and then 4 g/day for 23 weeks) or placebo to patients with atrial fibrillation (n = 663). There was no difference between treatment groups for the primary outcome (rate of recurrence of atrial fibrillation in participants with paroxysmal atrial fibrillation) or for secondary outcomes related to atrial fibrillation. Bianconi et al. [37*] randomized patients with persistent atrial fibrillation to receive 3 g/day of omega-3 fatty acids until electrical cardioversion (>1 week) and 2 g/day thereafter (n = 104) or to placebo (n = 100); duration of treatment was 6 months. Rate of recurrence of atrial fibrillation (primary outcome) and time to recurrence were not different between groups. Nodari et al. [38**] randomized patients with persistent atrial fibrillation and at least one relapse after cardioversion to placebo or 1.7 g/day marine omega-3 fatty acids until electrical cardioversion 4 weeks later (n = 94 per group) and then for a further year. At the 1-year follow-up, the probability of maintenance of sinus rhythm was higher in the marine omega-3 fatty acid group. Finally, in a controlled, open-label study, Kumar et al. [39*] examined whether marine omega-3 fatty acids (n = 91) or placebo (n = 87) commenced more than 1 month prior to electrical cardioversion and continued thereafter reduces recurrence of persistent atrial fibrillation. Fish oil was continued until return of persistent atrial fibrillation or a maximum of 1 year; mean duration of fish oil treatment was 56 days precardioversion and a total of 242 days in follow-up. At 90 days, atrial fibrillation recurrence was 62% lower in the marine omega-3 fatty acid group (P < 0.001). Thus, of these four recent studies, all with rather similar designs, two favour an effect of marine omega-3 fatty acids and two do not. One of the negative studies had the largest sample size and used by far the highest dose of marine omega-3 fatty acids; the other three studies were of similar size and used about 2 g EPA and DHA/day. One of the favourable studies was not double blind. A meta-analysis that included three of these studies [36,37*,38**] concluded that there was no effect of omega-3 fatty acids on recurrence of atrial fibrillation [40*].

A different approach has been to study the effect of marine omega-3 fatty acids on atrial fibrillation induced by coronary surgery. The first such study, which was randomized and controlled but open label, reported a more than 50% reduction in atrial fibrillation post-CABG in patients given 1.7 g EPA and DHA/day in the immediate postoperative period until discharge [41]. A second study with a similar design but blinded and also providing the omega-3 fatty acids for several days prior to surgery failed to confirm this benefit [42]. Similarly, Heidarsdottir et al. [43] reported that 2.2 g EPA and DHA/day for 5–7 days before CABG and/or valve repair surgery and postoperatively until discharge had no effect on atrial fibrillation. However, in an uncontrolled, open-label, and possibly nonblind study, preoperative marine omega-3 fatty acids lowered ‘early atrial fibrillation’, but not ‘late atrial fibrillation’, compared with patients not taking omega-3 fatty acids [44]. Sorice et al. [45*] identified that a reduction in CABG-induced atrial fibrillation in patients receiving marine omega-3 fatty acids (1.7 g EPA + DHA/day) for more than 5 days per surgery and then until hospital discharge occurred only in those patients who received surgery ‘on pump’. Finally, Farquharson et al. [46*] investigated high-dose omega-3 fatty acids (4.6 g EPA + DHA/day) versus placebo given for 3 weeks prior to CABG or valve procedures until 6 days postsurgery. Incidence of atrial fibrillation in the first 6 days after surgery tended to be lower in the omega-3 group, as did time to onset of atrial fibrillation. Overall, the promise of the early finding of Calò et al. [41] has not been fulfilled by the more recent, often better-conducted trials. Nevertheless, the more recent trials do point towards some benefit from marine omega-3 fatty acids in this setting. However, preoperative administration and a high dose of EPA and DHA are required and it is possible that omega-3 fatty acids will be effective only when specific types of surgical intervention are used. Two recent meta-analyses concluded that overall there is no effect of marine omega-3 fatty acids on cardiac surgery-induced atrial fibrillation [40*,47*].

**PLATELET FUNCTION, BLOOD COAGULATION, AND FIBRINOLYSIS**

One of the earliest described mechanisms of cardiovascular protection by marine omega-3 fatty acids among Inuit and Japanese populations was a reduction in platelet reactivity [48–50]. This is related to modified platelet (and presumably also endothelial) fatty acid composition, resulting in an altered profile of proaggregatory and antiaggregatory eicosanoids being produced [51–54]. The effect of marine omega-3 fatty acids on platelet aggregation is dose dependent [53]. The resulting inhibition
increases bleeding time, although effects of marine omega-3 fatty acids on coagulatory and fibrinolytic factors [55,56] may also be involved in this. Recent studies have addressed the effect of marine omega-3 fatty acids on these outcomes in patients with CVD. In a RCT, Gajos et al. [57**] studied the effect of 885 mg EPA and DHA/day for 1 month on plasma fibrin clot properties and thrombin formation in patients with stable CHD following percutaneous coronary intervention; all patients were encouraged to increase consumption of oily fish. Marine omega-3 fatty acids increased fibrin clot permeability, indicating larger pores in the fibrin network, decreased clot lysis time, indicating increased susceptibility to fibrinolysis, decreased thrombin concentration and generation, and decreased platelet reactivity, even though patients were already on dual antiplatelet therapy with clopidogrel and aspirin. Fibrinogen concentration was unaffected. The study indicates novel antithrombotic effects of marine omega-3 fatty acids, which may decrease the risk of thrombotic events after percutaneous coronary intervention. It is remarkable that a dose of less than 1 g EPA and DHA/day had such profound effects. Moertl et al. [58**] provided 0.885 or 3.54 g EPA and DHA/day to patients with advanced chronic heart failure for 12 weeks in a RCT. They demonstrated a dose-dependent reduction in monocyte–platelet aggregates, the percentage of tissue factor positive monocytes, and soluble tissue factor, and soluble P-selectin concentrations. These findings suggest a role for marine omega-3 fatty acids in controlling thrombosis in patients with chronic heart failure. Most recently Mackay et al. [59] studied the effect of 0.885 g EPA and DHA/day for 6 weeks on platelet activation in patients with peripheral arterial disease. There was no effect on ex-vivo platelet aggregation in response to two agonists, or on platelet P-selectin expression, platelet fibrinogen binding or von Willebrand factor concentration. The low dose of marine omega-3 fatty acids used may explain the lack of effect seen.

PLAQUE STABILIZATION

Plaque rupture is the acute occurrence that exposes the plaque contents to the highly prothrombotic environment of the vessel lumen [60–62], so initiating thrombosis that may lead to MI or other vascular event. Plaque rupture is essentially an inflammatory event and the characteristics of an atherosclerotic plaque that make it vulnerable to rupture are a thin fibrous cap and increased numbers of inflammatory cells such as macrophages. An intervention study conducted in patients awaiting carotid endarterectomy showed that marine omega-3 fatty acids are incorporated from fish oil supplements (providing 1.4 g EPA + DHA/day) into advanced atherosclerotic (carotid) plaques and that this incorporation is associated with structural changes consistent with increased plaque stability [63]. A follow-up study, using 1.8 g EPA and DHA/day, confirmed the higher EPA content of carotid plaque phospholipids in patients receiving marine omega-3 fatty acids and the association between a higher EPA content of the plaque and lower plaque inflammation and instability [64]. Furthermore, mRNA levels for matrix metalloproteinase-7, metalloproteinase-9, and metalloproteinase-12 were lower in plaques from patients who had received marine omega-3 fatty acids. The findings of the two human studies have been confirmed in an animal study with EPA [65].

CONCLUSION

Three fairly large secondary prevention trials published recently have not confirmed the previously reported benefit of marine omega-3 fatty acids towards mortality [17,18,20]. However, each of these three trials has quite substantial limitations, meaning that the question of whether marine omega-3 fatty acids reduce mortality in at-risk patients taking the current range of medications remains unanswered. Earlier trials investigating the effect of marine omega-3 fatty acids on ventricular fibrillation were inconsistent [31–34], whereas a number of recent studies in atrial fibrillation [36,37*,38**,39*] and in cardiac surgery-induced atrial fibrillation [42–44,45*,46*] have also produced an unclear outcome and meta-analyses concluded that there is no benefit [40*,47*]. It is possible that marine omega-3 fatty acids do reduce ventricular fibrillation, atrial fibrillation, and cardiac surgery-induced atrial fibrillation, but only in a subgroup of patients. Recent studies demonstrate novel actions of marine omega-3 fatty acids that would reduce risk of thrombosis [57**,58**], whereas a recent study confirmed that marine omega-3 fatty acids reduce the inflammatory burden within advanced atherosclerotic plaques, so inducing greater stability [64]. It is possible that an antiinflammatory effect within advanced plaques is a key action of marine omega-3 fatty acids in reducing cardiovascular events and mortality.

Acknowledgements

None.

Conflicts of interest

P.C.C. serves on the Danone Scientific Advisory Board on Immunity and on the Scientific Advisory Board of Aker
Biomarine; acts as a consultant to the Danone Research Centre for Specialised Nutrition; in the past 5 years has acted as a consultant to Mead Johnson Nutritionals, Vifor Pharma, and Amarin Corporation; has received speaking honoraria from Solvay Healthcare, Solvay Pharmaceuticals, Pronova Biocare, Fresenius Kabi, B. Braun, Abbott Nutrition, Baxter Healthcare and Nestle; currently has research funding from Vifor Pharma and Abbott Nutrition; is elected President of the International Society for the Study of Fatty Acids and Lipids, an organization that is partly supported by corporate membership fees, mainly from the food and supplements industries; serves on the Council of the British Nutrition Foundation, on the Board of Directors of the European Neutraceutical Association, and on the Board of Directors of ILSI Europe, all organizations that are partly funded by the food and supplements industries. P.Y. has no conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest. ■■ of outstanding interest.

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


Broad ranging state-of-the-art review covering clinical effects and underlying mechanisms.


Broad ranging state-of-the-art review covering clinical effects, risk factors, underlying mechanisms, and current recommendations in some detail.


17. Novel study demonstrating that EPA and DHA (1.7 g/day as pharmaceutical grade ethyl esters) increase left ventricular systolic function and functional capacity and reduces hospitalizations for heart failure.


21. Subgroup analysis of the ALPHAs-OMEGA trial reporting that diabetics receiving omega-3 fatty acids (marine, plant, or combined marine and plant) had an 84% reduction in risk of ventricular arrhythmia-related events and a 72% reduction in risk of the combined endpoint of ventricular arrhythmia-related events and fatal MI.


25. Reported that EPA and DHA (885 mg/day as pharmaceutical grade ethyl esters) given for 13 months after discharge from hospital lowered risk of late mortality, the need for repeat revascularization, and of the composite outcome of death, MI or cerebrovascular events. Subgroup analyses showed that the mortality benefit associated with omega-3 fatty acids was particularly strong in patients with poor left ventricular function.


Recent update on molecular and cellular mechanisms of action of marine omega-3 fatty acids.


Lipids and heart disease


A novel prospective cohort study of 3236 adults without heart failure or atrial fibrillation at study entry, demonstrating an inverse association between plasma phospholipid DHA and total omega-3 fatty acids at study entry and risk of incident atrial fibrillation over the follow-up period, suggesting that marine omega-3 fatty acids may have a role in primary prevention of atrial fibrillation.


Reported no effect of marine omega-3 fatty acids on rate of, or time to, recurrence of atrial fibrillation.


Reported better maintenance of sinus rhythm over a 1-year follow-up period in patients with persistent atrial fibrillation given EPA and DHA (1.7 g/day as pharmaceutical grade ethyl esters).


Reported lower recurrence of atrial fibrillation in patients receiving fish oil.


Meta-analysis of five trials of omega-3 fatty acids in recurrent atrial fibrillation and five trials in new onset atrial fibrillation following cardiac surgery. Found no effect in either group or when the two groups were combined.


Interesting study reporting that EPA and DHA (1.7 g/day as pharmaceutical grade ethyl esters) given for several days precardiac surgery and until hospital discharge reduced atrial fibrillation in patients who received surgery ‘on pump.’


Reported a trend towards an effect of high dose EPA and DHA (4.6 g/day) given for several days precardiac surgery and until hospital discharge on incidence and time to onset of atrial fibrillation.


Highly novel study reporting that EPA and DHA (885 mg/day as pharmaceutical grade ethyl esters) increased fibrin clot permeability and decreased clot lysis time, thrombin concentration and generation, and platelet reactivity in patients who had undergone percutaneous coronary intervention, even though they were already on dual antiplatelet therapy.


60. Cawood AL, Ding R, Napper FL, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis 2012; 221:514–520.


