SYSTEMATIC REVIEW

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Omega-3 Fatty Acids as Antiarrhythmic Drugs: Upstream Target Modulators Affecting Acute and Long-Term Pathological Alterations in Cardiac Structure and Function

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OBJECTIVES: Postoperative atrial fibrillation (POAF) is a common complication in the acute care period following coronary artery bypass grafting (CABG) surgery that is associated with significant morbidity and mortality in both short-term and long-term settings. Recently, the Vaughn Williams Classification of antiarrhythmic agents, first proposed in 1975 and widely viewed as the authoritative description of their electrophysiologic actions, was updated and notably omega-3 fatty acids (Ω-3 fatty acids) have been included in class VII, described as "upstream target modulators," to mitigate pathological structural and electrophysiological remodeling changes in the aged and/or injured myocardium.

DATA SOURCES: A PubMed literature search was performed.

STUDY SELECTION: Studies examining the significance of complications in patients undergoing isolated CABG surgery were selected for inclusion.

DATA EXTRACTION: Relevant data were qualitatively assessed and narratively summarized.

DATA SYNTHESIS: POAF occurs in approximately 30% of patients, and inflammation from chronic coronary artery disease preoperatively, as well as acute atrial inflammation from surgery postoperatively are the leading causes. Inflammation underlies its pathophysiology; therefore Ω-3 fatty acids not only exhibit antiarrhythmic properties but are an effective anti-inflammatory treatment that may reduce the clinical risks of POAF.

CONCLUSIONS: At present no effective prophylaxis is available to address POAF following CABG surgery. Clinical approaches that focus on the inflammatory response in this setting may optimize the response to treatment. The current literature supports the hypothesis that Ω-3 fatty acids may acutely reduce the inflammatory response via favorable alterations in the metabolism of prostaglandins and leukotrienes (eicosanoids) and specialized pro-resolving mediators.

KEY WORDS: atrial fibrillation; coronary artery bypass grafting surgery; inflammatory response; omega-3 fatty acids; specialized pro-resolving mediators

One of the most significant and recent developments in cardiac medicine was the publication of "Modernized classification of cardiac antiarrhythmic drugs" (1). This update was based on the original work from the renowned pharmacologist and electrophysiologist, E.M.Vaughn Williams, who first described a new antiarrhythmic drug classification system in 1975 (2). There were four basic drug classifications (classes I–IV), and he set out to categorize known "antidysrhythmic" agents according to their individual electrophysiological and pharmacological actions. He was motivated because of a general lack of agreement about the antiarrhythmic drugs available at the

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KEY POINTS

Question: What are the prevalence, outcomes, and therapy for new-onset postoperative atrial fibrillation (POAF) following isolated coronary artery bypass grafting (CABG) surgery?

Findings: In the acute care setting based on an aggregate of five studies involving 336,823 patients, 30% develop POAF, and significant differences in the risk of mortality following CABG surgery were noted in both the short-term and long-term setting confirmed by a large systematic review and meta-analysis (*n* = 129,628 patients). Currently, there is no effective prophylaxis to prevent POAF immediately following CABG surgery.

Meaning: IV administration of precise doses of omega-3 fatty acids during the perioperative period may reduce adverse events arising from POAF after CABG surgery.

time. So, in hopes of providing a "screen," or platform, for the development of new compounds, as well as a closer inspection of the modes of action, he felt that the new classification system would advance the field. About 10 years later (3), he provided an update, where he elegantly described the detailed electrophysiological mechanisms of action for drugs within each class according to the type of cardiac rhythm abnormality. The Vaughn William classification system has been widely adopted by major pharmacology (4) and medical (5) textbooks.

Forty-three years later, the "modernized" version was published, which sought to preserve "the simplicity of the Vaughn Williams framework, while aiding in the understanding and clinical management of cardiac arrhythmic events and facilitating future development in this area" (1). Three new classifications were added (V, VI, and VII) to the original framework. Of note, a new class VII section entitled, "Drugs acting on upstream modulatory targets" was introduced to focus on modifying the impact of long-term pathological changes (i.e., "remodeling") in cardiac tissues. Structural alterations in the heart can occur as a result of "primary electrical remodeling," which occurs in response to a functional insult, such as an altered sequence of electrical activation. In contrast, "secondary electrical modeling" is the result of a structural insult (6), such as myocardial infarction (MI), or from what occurs after cardiac surgery. For example, the authors note (1): "Fibrotic change is an important accompaniment to post-infarct healing, potentially leading to chronic scar-related arrhythmogenesis, pressure overload, and the development of atrial fibrillation ['AFib']." With age, disruptions at multiple biochemical levels can occur, producing pathological changes in remodeling processes (7, 8). Structural remodeling is characterized by atrial enlargement and tissue fibrosis and can lead to conduction disturbances within the myocardium, ultimately producing atrial fibrillation (AF), arising from increased fibrotic changes in the heart.

Abnormalities in intracellular Ca^{+2} metabolism can trigger ectopic activity and/or activation of "pro-fibrillatory remodeling," having direct effects on normal sinus rhythm (9). According to the Centers for Disease Control and Prevention estimates, "between 2.7 and 6.1 million people in the United States have 'AFib' and will increase as the population ages" (10). Furthermore, it is estimated that 12.1 million people in the United States will have AF in 2030 (11).

RISKS OF AF IN THE ACUTE SURGICAL CARE SETTING

Importantly, there are also potential clinical risks from new-onset AF in the short-term or acute care setting. Any "trauma" directly related to the heart muscle, such as acute MI or cardiac surgery, may also acutely exacerbate arrhythmogenic consequences. For example, a canine model to study the effects of cardiac surgery on conduction disturbances showed that atrial inflammation was associated with a proportional increase in the duration of AF (12). Moreover, preoperative differences in the histopathology of atrial tissues (i.e., interstitial fibrosis, vacuolization, and nuclear derangement of myocytes) and the development of postoperative AF in patients undergoing coronary artery bypass grafting (CABG) surgery have been demonstrated (13). During CABG surgery the initial damage to cardiac tissues caused by ischemia during cardiopulmonary bypass (CPB) will induce cell damage by reducing the availability of oxygen and its impact on energy (adenosine triphosphate) generation. Consequently, to maintain the energy necessary to sustain the heart, it must revert from aerobic (via oxidation of glucose and lipids) to anaerobic (via glycolysis) metabolism which is considerably less efficient. The main degradation product

of anaerobic glycolysis is lactic acid and as it accumulates over time, it will eventually inhibit glycolysis, ultimately creating a more severe energy deficit and cell damage. During reperfusion, there is increased production of oxygen-free radicals or reactive oxygen species (ROS) coming directly from (reduced) molecular oxygen, as well as being generated from the oxidation of polyunsaturated fatty acids from vegetable sources such as soybean oil, a major fat source typical in Western diets (14). Oxidation of unsaturated fatty acids leads to the formation of both primary oxidation products (i.e., hydroperoxides and free fatty acids) and secondary oxidation products (i.e., aldehydes and ketones). They can promote oxidative stress as intracellular messengers (15–17), as well as causing cell damage and activating neutrophils and other immune cells, ultimately initiating the release of pro-inflammatory cytokines and the acute phase response (18). Of patients who undergo CABG surgery each year, postoperative atrial fibrillation (POAF) develops within 48 hours, and in the majority of cases, it occurs within 96 hours (24).

The combination of an aging heart, the need for CABG surgery with its implications for pathologic change, and the stress of the associated CPB procedure, as well as a pro-inflammatory diet, can often manifest in the acute care setting as atrial arrhythmia. In fact, the prevalence of new-onset, POAF in patients undergoing isolated CABG surgery consistently reports an prevalence of approximately 30%, as shown in **Table 1**.

RISKS OF AF IN THE LONG-TERM POSTSURGICAL CARE SETTING

As Table 1 also shows, the development of POAF is associated with increased mortality long after CABG surgery. In a systematic review and meta-analysis that focused exclusively on isolated CABG surgery (n = 129,628 patients) and the development of new-onset POAF, there were significant differences in the risk of mortality following CABG surgery in both the short-term and long-term analyses after CABG (25). These observations have been confirmed by others (20, 21, 26). The most recent systematic review and meta-analysis (n = 246,340 patients) showed increased risk in the short-term (e.g., postoperative mortality, stroke, MI), and long-term (e.g., long-term mortality, stroke, and persistent AF) (27). Taken together, recent data indicate that new-onset POAF in patients undergoing isolated CABG surgery is not a benign event and that therapeutic prevention for the short-term with permanent avoidance is a desirable goal (28, 29). At present, there is no effective prophylaxis at this time.

ANIMAL STUDIES SUPPORTING ROLE OF FISH OIL IN REDUCING PACING-INDUCED AF

Dietary omega-3 fatty acids (Ω-3 fatty acids) have been shown to significantly reduce rapid atrial pacing-induced AF vulnerability, possibly via decreasing inflammation and attenuating myocardial endoplasmic

TABLE 1.

Prevalence of Acute Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting Surgery

Reference	Patients	Study Data	New-Onset POAF (%)	Follow-up (yr)	Mortality: POAF Vs NSR
Ahlsson et al (19)	1,419	Single center	29.5	8 (Median)	POAF > NSR
Thorén et al (20)	7,145	Single center	30.6	9.8 (Median)	18% vs 12%[a]
Filardo et al (21)	9,203	Four centers	31.5[b]	3.3 (Mean)	↑ if ≥ 2 atrial fibrillation events
Taha et al (22)	24,523	Four registries	30.0[c]	4.5 (Median)	All causes–not significant
Jawitz et al (23)	294,533	Medicare[d]	30.0	3.7 (Median)	Significant
N	336,823	Weighted AVG	30.05		

AVG = Average, NSR = normal sinus rhythm, POAF = postoperative atrial fibrillation.

[a]$p < 0.001$.

[b]Male/female weighted average.

[c]23.7% prescribed oral anticoagulation without benefit on mortality.

[d]1,117 centers.

"*N*" is the total number of patients from references 19–23.

reticulum (ER) stress and apoptosis in a canine model of AF (30). A fish oil dose of 0.6 g/kg/day in male beagle dogs prevented rapid atrial pacing-induced AF due to decreases in the inflammatory cytokines, interleukin (IL)-1 β, IL-6, and tumor necrosis factor (TNF-α) and downregulation of ER stress-related protein expression levels of glucose-regulated protein78, C/EBP homologous protein, cleaved-caspase12, and phosphorylation of protein kinase R-like ER kinase. Other animal studies have shown that omega-3 or Ω-fatty acids can reduce AF.

POSTULATED MECHANISMS FOR POST-CABG AF: SYMPATHETIC TONE, INFLAMMATION, AND OXIDATIVE STRESS

In the acute situation postoperatively, activation of the complement system releases C-reactive protein (CRP) and pro-inflammatory cytokines such as IL-2, IL-6, and TNF-α close to the onset of POAF (31). These inflammatory markers result in leukocyte activation and release oxidases and nitric oxide. Eventually, this leads to the generation of ROS that contribute to systemic inflammation (32). Postoperative inflammation results in differing refractory periods and conduction velocities in the myocardium which increase susceptibility to aberrant electrical activity, conduction, and re-entry, termed the "anisotropic" atrium (12, 33).

POTENTIAL MECHANISM FOR BENEFICIAL EFFECT OF Ω-3 FATTY ACIDS POST-CABG

Ω-3 fatty acids can potentially reduce post-CABG AF due to two mechanisms. The first is a net reduction in inflammation, which limits fibrosis. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the preferred substrates that compete with arachidonic acid to produce less pro-inflammatory eicosanoids (three-series prostanoids and five-series leukotrienes vs two-series and four-series via ARA, respectively) (34). As mentioned earlier, Ω-6 fatty acids are predominant in western diets (14) and therefore the preoperative CABG patient is often "primed" for a pronounced systemic pro-inflammatory response in the postoperative setting. Acute provision of Ω-3 fatty acids by IV administration rapidly enriches plasma cell membranes (leukocyte and platelet phospholipids) within 60 minutes (35) will modulate the intensity of inflammatory response. Moreover, Ω-3 fatty acids are required for the biosynthesis of specialized pro-resolving lipid mediators (SPMs), the downstream products of EPA and DHA which are known to reduce inflammation and include resolvins, protectins, and maresins (36–38). The second mechanism is an antiarrhythmic effect due to the epoxy and hydroxy metabolites derived from EPA and DHA which have potent antiarrhythmic properties (39).

SUPPORT FOR THE ROLE OF SPMS IN REDUCING INFLAMMATION INVOLVED IN CORONARY ATHEROSCLEROSIS

Atherosclerosis is a disease of chronic inflammation in the arterial wall involving the innate immune system and characterized by monocyte and neutrophil infiltration and differentiation of monocytes to macrophages in the subendothelial space, leading to foam cell and fatty streak formation and advanced plaques (40–42).

On June 20, 2023, the Food and Drug Administration (FDA)-approved colchicine as the first anti-inflammatory therapy preventing the risk of adverse cardiac events (MI, stroke, coronary revascularization, and death) (43) for patients with chronic coronary disease (44). The study by Welty et al (45) reported that the ratio of pro-resolving metabolites of EPA and DHA to pro-inflammatory markers was a better predictor of progression and regression of coronary plaque than the plasma Ω-3 fatty acid index. To explore mechanisms associated with coronary plaque progression, levels of SPMs and pro-inflammatory mediators were measured using liquid chromatography-tandem mass spectrometry in 31 statin-treated patients with stable coronary artery disease randomized to EPA and DHA, 3.36 g daily, or no EPA/DHA (control) for 30 months. Higher plasma levels of EPA + DHA were associated with significantly increased levels of two SPMs-resolvin E1 and maresin 1-hydroxy and 18-hydroxy-eicosapentaenoic acid (HEPE), the precursor of resolvin E1. Those with a median (interquartile range) Ω-3 fatty acid index of 8.4% (8.1–9.6) fell into two groups: the majority had plaque regression whereas a few had plaque progression. Those with plaque progression had a low ratio of (18-HEPE + resolvin E1) to LTB4, a pro-inflammatory mediator. Those with plaque regression had a high ratio of (18-HEPE + resolvin E1) to LTB4. These findings suggest

that the balance between pro-resolving and pro-inflammatory lipid mediators determines the change in coronary plaque and is a better measure of inflammation than CRP in this context.

CLINICAL EVIDENCE OF POTENTIAL ACUTE CARE EFFICACY OF Ω-3 FATTY ACIDS FOR AF

The Ω-3 fatty acids (EPA and DHA) decrease the magnitude of the electrical currents elicited by the activation of calcium (and sodium) channels. Class VII antiarrhythmic drugs stabilize both electrophysiological and structural remodeling that occurs, and therefore the extent of fibrotic changes in cardiac tissues in response to acute MI or following cardiac surgery, as the heart heals from an acute cardiac event. It is likely that the principal mechanism(s) of short-term prevention of AF is perhaps electrophysiologic or reduction in inflammation may be different than the one(s) responsive for chronic prevention.

Of the for drugs listed in class VII, Ω-3 fatty acids and statins uniquely reduce myocardial damage, risks of stroke and cardiac death, as well as abnormal cardiac rhythms. It is important to remember that class VII agents as described (1) are clinically applied to address long-term pathological changes from unrestrained or pathological cardiac remodeling. In this setting, Ω-3 fatty acids could be prescribed via daily oral supplementation. In the acute care setting; however, drug therapy requires prompt delivery of Ω-3 fatty acids (pharmacokinetics) and effect (pharmacodynamics), with the administration of the active pharmaceutical ingredient (API) (e.g., statins or Ω-3 fatty acids), and this is most often accomplished IV. Is there any clinical evidence of efficacy against POAF in patients undergoing CABG surgery with either agent by parenteral administration? As for statin therapy, there is no commercially available IV dosage form; hence we refer to the alternative, that is, the use of IV fish oil-in-water emulsions containing Ω-3 fatty acids in this setting.

There are six main studies (46–51) where IV fish oil emulsion (FOE) has been administered in patients undergoing CABG surgery and a summary of these investigations is provided in **Table 2**.

The summary only includes studies where Ω-3 fatty acids were given IV, and a number of inconsistencies are apparent. A total of 167 patients undergoing CABG surgery received IV Ω-3 fatty acids as intervention therapy. Of the three studies that provided several days

TABLE 2.
Clinical Studies of Fish Oil Emulsion in Coronary Artery Bypass Grafting Patients

Reference	FOE/Total Patients	Comments
Heidt et al (46)	52/102	$n = 52$ for FOE group (0.03 g/kg/d of EPA + DHA), and $n = 50$ for SO emulsion group; regimen started on admission and ended upon discharge; primary endpoint: POAF; 17.3% in FOE vs 30.6% in SO, $p < 0.05$
Veljovic et al (47)	20/40	$n = 20$ for FOE group (3 g of EPA + DHA) and $n = 20$ for saline (NS) group; a single preoperative dose; FOE promoted "metabolic recovery"
Berger et al (48)	14/28	$n = 14$ for FOE group (0.066 g/kg/d of EPA + DHA, one preoperative dose, and two postoperative doses) and $n = 14$ for NS group; significant ↑ uptake in platelet and atrial tissue membranes
Lomivorotov et al (49)	18/39	$n = 18$ for FOE group (0.066 g/kg of EPA + DHA preoperative dose, and 0.033 g/kg/d × 7 d) and $n = 21$ for placebo; POAF; 27.8% in FO vs 19% in placebo, $p = 0.88$
Kolesnikov et al (50)	33/73	$n = 33$ for FOE group (3 g/d of EPA + DHA 5–7 d postoperative) and $n = 40$ for control; POAF; 9.1% in FOE vs 32.5% in placebo, $p < 0.01$
Feguri et al (51)	30/60	$n = 30$ for 2 FOE groups dosed at 0.2 g/kg/hr intraoperatively for 4 hr; no serum triglyceride data; FOE appears to support faster postoperative recovery in coronary artery bypass grafting surgery
N	167/342	

EPA = eicosapentaenoic acid, FOE = fish oil emulsion, DHA = docosahexaenoic acid, POAF = postoperative atrial fibrillation, SO = soybean oil.

of infusion (46, 49, 50), two studies showed a significant reduction in POAF in CABG patients (46, 50), whereas the other (49) showed no such difference. Of the remaining three studies, FOEs were given either as a single preoperative dose (47) or one preoperative dose followed by two postoperative doses (48), but the outcome parameters were mainly metabolic-related. In the final study (51), IV infusion of FOE was uniquely given intraoperatively, and the suggested benefit was "faster recovery." All of the studies were very small and employed different dosages and treatment regimens for the FOE infusions and outcomes, so there were likely significant confounding variables.

POTENTIAL EFFICACY OF A REFINED AND ENRICHED FISH OIL PRODUCT

The FOE product given IV in all of the aforementioned studies was based on a single-source, FDA-approved commercially available injectable dosage form consisting of fish oil triglycerides, which is indicated as a nutritional supplement, that is, "as a source of calories and fatty acids" (52), not as a drug. It is a natural, refined fish oil that complies with the European Monograph or EP 1912 (53), but the Ω-3 fatty acid profile can be highly variable. The product information from the FOE package insert states the following ranges per 10 g of fish oil: EPA mean: 2.0 g, range: 1.2 g (± 40%)–3.0 g (± 50%), DHA mean: 1.9 g, range: 1.3 (± 32%)–3.3 g (± 74%). Indications for API or drugs require very specific therapeutic limits, and a typical United States Pharmacopeia (USP) monograph requires the drug concentration to be ± 10% of the labeled amount. For example, if the EPA + DHA content is labeled at 100 mg/mL, the acceptable API concentration range over its shelf life would be 90–110 mg/mL. In contrast, and according to the manufacturer (54), the FOE nutritional product contains approximately 30 mg/mL of EPA + DHA. If used as a drug, the USP specification range should be 27–33 mg/mL. Consequently, the aforementioned studies in Table 2 were conducted with a nutritional supplement whose concentrations of EPA + DHA are highly variable and therefore may explain the equivocal results observed. Using the same nutritional product in patients with severe COVID-19 infection, a small study (22 patients) using inflammatory markers as endpoints was reported in a Letter to the Editor (55), showing a significant, but transitory reduction in CRP at 48 hours, but not at the end of the study (5 d). This may also be a reflection of the variable concentrations of Ω-3 fatty acids in the nutritional product (56).

Of note, the study by Berger et al (48) gave 0.2 g/kg over 2 hours for each of the three doses (two preoperatively, one postoperatively) that produced transient, but significant, hypertriglyceridemia. The study by Feguri et al (51) gave the same dose, only once intraoperatively, over 4 hours, but serum triglycerides were not measured. The mixed results from these studies were also likely affected by the variability in the delivery of consistent amounts of the proposed API (EPA + DHA) per batch using the same nutritional product as described above.

SAFE DOSING AND EFFICACIOUS DELIVERY OF PARENTERAL Ω-3 FATTY ACIDS

In most fish oil triglyceride products (e.g., capsules, injection), the usual ratio of EPA to DHA is ~1.5:1, whether it is a natural refined fish oil that complies with EP 1912 (53), or one that is both refined and synthetically enriched (57), complying with EP 1352 (58). What differs between these two monographs is the concentration of EPA and DHA, and that depends upon the pharmaceutical quality based on the commercial production processes, that is, one oil that is refined without changing the EPA:DHA concentrations versus the other that is both refined and enriched, that essentially doubles the concentrations of each in a fixed ratio (59). Moreover, as mentioned, the effective antiarrhythmic dose of Ω-3 fatty acids can only be determined if the amount of the API varies no more than ± 10% of the labeled amount.

For the most part, EPA and DHA are the most abundant of the available Ω-3 fatty acids in fish oil triglycerides which have pharmacological effects. Also, the specific dose will need to be optimized to achieve the desired antiarrhythmic response, as routinely performed for several other critical care drugs. Importantly, the maximum infusion rate for safety purposes of the typical long-chain fatty acids derived from soybean oil-based triglycerides (mainly consisting of 18 carbons such as linoleic acid, oleic acid, α-linolenic acid, and stearic acid), is set at 0.11 g/kg/hour (60). For fish oil triglycerides enriched in Ω-3

fatty acids, the infusion should be cautiously started at a lower rate, since these very long-chain fatty acids (≥ 20 carbons such as EPA and DHA) are even more slowly cleared from plasma with implications for hypertriglyceridemia causing severe fat overload syndrome (61).

The main concern is that the rate of the lipid emulsion infusion does not exceed its metabolic utilization rate (48), which can lead to complications related to fat overload, such as severe hypertriglyceridemia, deposition of fat in vital organs causing reticuloendothelial system dysfunction and pulmonary gas diffusion abnormalities in ventilated patients (62). The suggested pharmacological dose range for IV infusion of EPA + DHA in the critical care setting is between 4 and 6 g/day (63). Applying a weight-based regimen, consistent with a typical BMI range of 25–29 ("overweight") for patients undergoing CABG surgery via continuous infusion is presented in **Table 3**. Theoretically, since the therapeutically effective dose is not known and since fat toxicity is a known outcome if the infusion rate exceeds the metabolic rate, the FOE should be administered over 24 hours. However, this infusion regimen is wholly predicated upon the clinical response. Therefore, the ideal dose and infusion time should be carefully titrated, monitored, and correlated with a favorable therapeutic response. It should begin as a "starter" dose preoperatively (e.g., one-fourth of the daily dose over 6 hr), followed by a continuous IV dose over 24 hours that may be optimal. Finally, administering the enriched fish oil triglycerides by continuous IV infusion may afford maximal cardioprotection during the acute postoperative period. These issues should be determined in a formal clinical study.

TABLE 3.

Example of Maximum Daily Dose and Safe Infusion Rate

Weight[a] (kg)	Weight-Based Daily Dose	Infusion Rate Over 24 hr
60	3.6	
70	4.2	
80	4.8	0.06 g/kg/hr
90	5.4	
100	6.0	

[a]Classified as "overweight" based on BMI of 25–29.

CONCLUSIONS

Ω-3 fatty acids exert both electrophysiological and structural effects on the heart that ultimately reduce the negative impact resulting from "accelerated" remodeling changes, which may otherwise lead to clinically significant conduction disturbances. Although their efficacy as a class VII antiarrhythmic agent is related to pathological remodeling in the long-term setting, they may also be beneficial in protecting the heart from developing AF in the acute care, postoperative setting following CABG surgery by inducing favorable electrophysiologic effects, and/or downregulating the inflammatory response by modifying eicosanoid production and enhancing healing mediated by SPMs as metabolites of eicosapentaenoic and docosahexaenoic acids. The Ω-3 fatty acids (and their downstream mediators) produce several "pharmacologic-like" actions upon the cardiovascular system, making them potentially multitargeted API.

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Dr. Driscoll is inventor of U.S. Patent No. US 8,241,672 entitled "Omega-3 enriched fish oil-in-water parenteral nutrition emulsions," filed on March 11, 2009. Dr. Bistrian is co-inventor of U.S. Patent No. 10,328,045 B2 entitled "Dietary emulsion formulations and methods for using the same, filed on September 10, 2015." Dr. Welty has disclosed that she does not have any potential conflicts of interest.

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