Fish oil: Physiologic effects and administration

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INTRODUCTION

Ecologic studies in the 1970s reported low rates of coronary heart disease death among the Inuit people of Greenland who consumed high amounts of dietary fat from seafood [1]. This observation led to extensive research examining the health effects of dietary fats in seafood, including the discovery that the long-chain omega-3 polyunsaturated fatty acids in fish oil, eicosapentaenoic acid (20:5n-3), and docosahexaenoic acid (22:6n-3) contribute to these benefits (figure 1) [2-22].

This topic will discuss the physiologic effects of fish oil on cardiovascular and metabolic systems as well as issues related to fish oil administration, including preparations, dosing, and safety.

The effects of fish oil supplementation on pregnancy and infant outcomes and on dementia are reviewed separately:

- (See "Fish consumption and marine omega-3 fatty acid supplementation in pregnancy".)
- (See "Enteral long-chain polyunsaturated fatty acids (LCPUFA) for preterm and term infants".)
- (See "Prevention of dementia", section on 'Omega-3 fatty acids'.)

NOMENCLATURE

The two major categories of polyunsaturated fatty acids (PUFAs) are the omega-3 (also called n-3) and omega-6 (n-6) fatty acids, based on the location of the first double bond in the fatty acid chain at the third or sixth carbon. The three major dietary omega-3s are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). EPA and DHA are long-chain omega-3 PUFAs present in fish, shellfish, and (in much lower amounts) some other animal foods (figure 1). They are the major components of fish oil supplements. ALA is an intermediate-chain omega-3 PUFA present in certain plants and their oils, such as flaxseed and walnuts. When referring to EPA and DHA, common terms include "long-chain omega-3 fatty acids," "seafood-derived omega-3 fatty acids," and "marine omega-3 fatty acids." In this topic, all omega-3 fatty acids are assumed to be long-chain unless otherwise specified [23].

OVERVIEW

Given the widespread discussion of the potential benefits of marine omega-3 fatty acids in the scientific literature and lay press, patients may have questions about fish oil supplementation, most notably in relation to cardiovascular disease (CVD) reduction. In contrast to many other dietary supplements that have few observed physiologic effects, meta-analyses of clinical trials have shown that omega-3 fatty acids (dietary or supplementary) have multiple cardiovascular and metabolic effects (figure 2) [24]. Although many of these effects (described below) are modest in size and dose-dependent, they provide biologic plausibility for the lower risk of CVD seen in many observational studies and some, but not all, clinical trials of omega-3 fatty acid consumption [24].

The US Food and Drug Administration (FDA) considers cardiovascular risk reduction in selected patients with mild hypertriglyceridemia an off-label indication for prescription preparations of omega-3 fatty acids. The FDA has also determined that food labeling stating that consuming marine omega-3 fatty acids in food or dietary supplements may reduce the risk of hypertension and coronary heart disease meets the "credible evidence" standard for a qualified health claim but does not meet the "significant scientific agreement" standard required for an authorized health claim [25,26].

These issues are discussed in the following topics:

- (See "Overview of primary prevention of cardiovascular disease in adults", section on 'Omega-3 fatty acids'.)
- (See "Prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Marine omega-3 fatty acids'.)

- (See "Hypertriglyceridemia in adults: Management", section on 'Treatment goals'.)
- (See "Lipid management with diet or dietary supplements".)

POTENTIAL EFFECTS ON CARDIOVASCULAR AND METABOLIC SYSTEMS

Effects on specific cardiovascular and metabolic systems are described below and vary by dose and time (figure 3) [21].

System effects

- **Cardiovascular outcomes** – The role of fish oil in preventing cardiovascular outcomes (eg, stroke, myocardial infarction) is unclear. Several large clinical trials in patients with hypertriglyceridemia have yielded mixed results on whether omega-3 fatty acid consumption reduces the risk of cardiovascular events or death. This is discussed separately. (See "Hypertriglyceridemia in adults: Management", section on 'Effects on cardiovascular outcomes'.)

- **Lipids** – Consumption of high-dose omega-3 fatty acids lowers serum triglyceride concentrations by 25 to 50 percent, an effect within the range of efficacy of other triglyceride-lowering drugs [27-29]. The dose-response appears linear, with little triglyceride lowering with dietary doses or low-dose eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA; <1 g/day) and more significant lowering with higher doses (3 to 4 g/day) (figure 3) [30]. The clinical use of fish oil on lipid lowering, including among patients with hypertriglyceridemia, is discussed in more detail elsewhere. (See "Hypertriglyceridemia in adults: Management", section on 'Treatment goals' and "Lipid management with diet or dietary supplements", section on 'Omega-3 fatty acids'.)

  Both EPA and DHA reduce fasting and postprandial triglycerides, mainly by reducing hepatic very low-density lipoprotein (VLDL) cholesterol production but also by increased conversion of VLDL to intermediate-density lipoprotein and low-density lipoprotein (LDL) [31,32].

- **Atrial fibrillation** – Although observational studies suggest that dietary EPA+DHA is associated with lower incidence of atrial fibrillation, neither low- nor high-dose fish oil supplementation prevents recurrent or postsurgical atrial fibrillation in interventional studies [33-38]. In contrast, high-dose EPA and/or DHA supplementation (ie, 3 to 4 g/day) is associated with a modest increase in incidence of atrial fibrillation in meta-analyses of

trials [39-42]. This is discussed separately. (See "Hypertriglyceridemia in adults: Management", section on 'Safety'.)

- **Blood pressure and systemic vascular resistance** – Fish oil consumption can lower systolic and diastolic blood pressure, including reductions in individuals with untreated hypertension.

  In a meta-analysis of 70 randomized trials conducted among generally healthy adults (excluding persons with drug-treated hypertension, secondary hypertension, and established cardiovascular disease), EPA and DHA supplementation reduced systolic blood pressure by 1.5 mmHg and diastolic blood pressure by 0.99 mmHg [43]. The largest effects were seen in those with untreated hypertension, among whom systolic and diastolic blood pressure were reduced by 4.5 and 3.1 mmHg, respectively.

  In a meta-analysis of 12 randomized, controlled trials among 1028 children or adolescents with overweight or obesity, fish oil supplementation lowered systolic blood pressure by 2.5 mmHg, with no significant effect on diastolic blood pressure [44].

  Animal studies and observational studies in humans suggest that fish oil reduces blood pressure by reducing systemic vascular resistance (ie, lower arteriolar resistance), with changing cardiac output [45,46]. In vitro studies demonstrate that omega-3 polyunsaturated fatty acids induce nitric oxide production, modulate endothelial activation, and modify the location and function of cell membrane caveolae proteins, including endothelial nitric oxide synthase [47-50].

  In short-term trials in humans, EPA and DHA consumption increases biomarkers of nitric oxide production, mitigates peripheral vasoconstrictive responses to norepinephrine and angiotensin II, improves arterial wall compliance, and enhances vasodilatory responses [51-55]. In a meta-analysis of 14 randomized controlled trials, fish oil supplementation reduced pulse wave velocity, a measure of arterial stiffness [56]. These effects, separately or in sum, could account for lowering of systemic vascular resistance.

- **Heart rate and heart rate variability** – Fish oil appears to reduce heart rate (HR).

  - In meta-analyses of randomized trials, fish oil supplementation (median dose 3.5 g/day, median duration eight weeks) reduced resting HR by 1.6 to 2.2 beats per minute [57,58]. The HR-lowering effect did not appear to be dose dependent at doses ranging from 1 to 15 g/day (ie, supplement-level doses). By contrast, observational studies suggest a more dose-dependent effect at lower (ie, dietary) doses, at least to a threshold of approximately 300 mg/day EPA+DHA (figure 3) [45,57,59].

Experimental studies in animals suggest that HR lowering could result from direct cardiac electrophysiologic effects of fish oil [18,19,60]. EPA and DHA may also lower HR in humans by more indirect effects, such as by improving left ventricular diastolic filling or augmenting vagal tone [61].

- The effect of fish oil on heart rate variability (HRV) is uncertain. HRV is influenced by underlying resting HR, autonomic function, circadian rhythms, and underlying cardiac health. Results from trials evaluating fish oil supplementation and HRV have been inconsistent possibly due to small numbers, variable doses of fish oil used, relatively short durations (weeks to months), or limited periods of HRV assessment [62-65].

- Although animal and in vitro studies demonstrate an effect of omega3 fatty acids on myocyte electrophysiology, confirmation of a direct antiarrhythmic effect on human hearts is limited by the absence of any reliable and easily obtainable biomarker of such effects [17-19,66-68].

- **Cardiac function** – Evidence suggests that fish oil may affect various aspects of cardiac function.

  Left ventricular diastolic filling consists of two phases: an early phase of active (energy-dependent) relaxation and a second phase of more passive (compliance-dependent) filling (with a final brief phase due to atrial contraction). Abnormalities of early relaxation are among the earliest signs of ischemic heart disease, while abnormal passive filling (reduced compliance) often results from longstanding hypertensive heart disease or ischemic heart disease. In a small trial of healthy men, seven weeks of fish oil (4 g/day) improved the early phase of diastolic filling [69]. This relatively acute improvement suggests a functional or metabolic, rather than structural, effect on energy-dependent filling. In a small trial among patients with ischemic heart failure, eight weeks of fish oil (2 g/day) reduced the E/e' ratio, a measure of abnormal diastolic filling, compared with placebo (-9.47 versus -2.1 percent) [70].

  Fish oil may also improve the second (compliance-dependent) phase of diastolic filling by augmenting or preventing decline in ventricular compliance. In a cohort study of older adults, habitual modest fish consumption was associated with a trend toward lower electrocardiographically defined left ventricular mass and with a higher E/A ratio, a measure of more normal diastolic filling [45].

  In healthy adults, fish oil from either diet or supplementation does not appear to impact cardiac systolic function [45,69,71], except for higher-cardiac stroke volume as a result of slower resting HR (increasing filling time) and enhanced diastolic filling [45,72]. However,

fish oil appears to improve left ventricular ejection fraction among individuals with established heart failure [73,74].

Fish oil appears to modulate maximum oxygen needs during exercise. In one randomized trial of 16 athletes, fish oil consumption improved myocardial efficiency, reducing myocardial oxygen demand without a decrement in performance [75]. Similarly, in another randomized trial among 26 trained men, 1.4 g/day EPA+DHA for eight weeks reduced relative oxygen consumption during vigorous exercise without altering peak performance [76].

Each of these findings on fish oil and cardiac diastolic function, systolic function, and oxygen demand require confirmation in larger studies.

- **Endothelial function** – In a meta-analysis of 42 randomized trials among 3555 adults, fish oil supplementation lowered levels of vascular cell adhesion molecule 1, a circulating marker of endothelial dysfunction, with nonsignificant trends in lower intercellular adhesion molecule 1 ($p = 0.07$) and P-selectin ($p = 0.06$) and no effects on E-selectin [77].

  In a meta-analysis of 32 randomized trials including 2385 participants, fish oil increased flow-mediated vasodilation, a noninvasive surrogate for endothelial function, compared with placebo [78]. Doses of fish oil varied, and treatment durations ranged from 4 to 48 weeks.

- **Bleeding/platelet function** – Clinically apparent effects of fish oil on bleeding are not evident at commonly used doses of up to 4 g/day. High doses of EPA (3 to 15 g/day) increase bleeding time, but this has not been associated with higher rates of clinical bleeding [79]. Omega-3 fatty acids suppress platelet activating factor in experimental in vitro studies, but in human trials significant effects of fish oil consumption on platelet aggregation are not reliably seen [29]. Clinical effects on bleeding have not been seen. (See 'Bleeding' below.)

- **Inflammation** – Fish oil may have several anti-inflammatory effects due to the role of EPA and DHA as precursors to specific eicosanoids and other inflammatory mediators as well as resolvins, protectins, and maresins that play crucial roles in active resolution of inflammation [80,81].

  In meta-analyses of randomized trials, fish oil supplementation had a lowering effect on C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) [82-84]. Significant reductions in inflammatory markers have also been seen in meta-analyses of randomized trials of fish oil supplementation among patients with end-stage kidney

disease [85], human immunodeficiency virus infection [86], polycystic ovary syndrome [87], and cancer [88].

Among adults with elevated high-sensitivity CRP (hs-CRP, ≥2 mcg/mL) and metabolic risk factors, both EPA and DHA (supplemented separately, 3 g/day for 10 weeks each) reduced levels of inflammatory markers, with both shared and differential effects related to distinct downstream lipid mediators including specialized pro-resolving lipid mediators (SPMs) [89].

In a network meta-analysis, EPA and DHA evaluated separately had similar effects on reducing CRP, IL-6, and TNF-alpha [90].

A discussion of fish oil for use in arthritis is provided separately. (See "Complementary and alternative therapies for rheumatic disorders", section on 'Fish and botanic oils'.)

- **Glucose and insulin** – Fish oil may improve glycemic control and insulin sensitivity among individuals with prevalent diabetes, although meta-analyses of randomized trials have found inconsistent results.

  - In a meta-analysis of 24 randomized trials in individuals with type 2 diabetes, omega-3 supplementation modestly reduced fasting plasma glucose (FPG), glycated hemoglobin (A1C), and estimated homeostatic model assessment of insulin resistance (HOMA-IR) [91].

  - In a meta-analysis of six randomized trials among 331 women with gestational diabetes, fish oil supplementation reduced FPG, fasting insulin, and HOMA-IR [92].

  - By contrast, a meta-analysis of 13 randomized trials in patients with type 2 diabetes showed no significant improvements in FPG, A1C, or HOMO-IR with fish oil supplementation [93].

  Fish oil supplementation may improve insulin sensitivity in children at increased risk of diabetes. In a meta-analysis of 13 trials of 1132 participants <18 years of age, omega-3 fatty acids significantly improved insulin sensitivity [94]. Trial participants were predominantly children and adolescents with metabolic disease (eg, obesity, hypertriglyceridemia, metabolic dysfunction-associated steatotic liver disease [MASLD]).

- **Adiposity and body composition** – Fish oil may alter body weight and composition and increase levels of adiponectin.

In a meta-analysis of 11 randomized controlled trials including 617 persons with overweight or obesity, supplementation reduced waist circumference by 0.53 cm but did not significantly affect body mass index (BMI) [95]. By contrast, in a meta-analysis of 12 randomized controlled trials including 1028 children and adolescents with overweight or obesity, fish oil supplementation reduced BMI by 0.96 kg/m^2 but did not significantly reduce waist circumference [44]. In 22 randomized, controlled trials with 1366 patients with MASLD, fish oil supplementation reduced liver fat compared with placebo (pooled risk ratio 1.52, 95% CI 1.09-2.13) and also reduced BMI by 0.46 kg/m^2 [96].

In a meta-analysis of 15 controlled trials with 1504 participants, fish oil supplementation did not significantly alter overall appetite [97].

Fish oil supplementation may increase levels of plasma adiponectin, a marker of adipocyte health [90]. As an example, in a meta-analysis of 43 trials in 3434 individuals, omega-3 fatty acid supplementation modestly increased adiponectin levels compared with placebo but did not significantly affect plasma leptin [98]. Other meta-analyses have demonstrated similar results in participants with diabetes and polycystic ovary syndrome [87,99].

The clinical role of omega-3 fatty acid supplementation in individuals with hepatic steatosis is discussed separately. (See "Management of metabolic dysfunction-associated steatotic liver disease (nonalcoholic fatty liver disease) in adults", section on 'Therapies with uncertain benefit'.)

- **Mental health and cognition** – The potential effects of fish oil supplementation on anxiety, depression, and cognitive function are discussed separately. (See "Complementary and alternative treatments for anxiety symptoms and disorders: Herbs and medications", section on 'Omega-3 (n-3) polyunsaturated fatty acids' and "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Omega-3 fatty acids' and "Mild cognitive impairment: Prognosis and treatment", section on 'Herbs and nutritional supplements'.)

Pharmacokinetics and pharmacodynamics — EPA and DHA are absorbed from the gastrointestinal tract and, as with other dietary fatty acids, are transported to the liver largely as triglycerides in chylomicron particles. From the liver, EPA and DHA are released into the circulation as triglycerides in lipoprotein particles (such as LDL cholesterol and high-density lipoprotein [HDL] cholesterol) and as plasma phospholipids. Smaller amounts circulate as free fatty acids, largely bound to albumin.

EPA and DHA are incorporated into cell membrane phospholipids throughout the body, with particular enrichment in the heart and brain, and stored in adipose tissue as triglycerides.

Consumption of fish oil increases the concentration of EPA and DHA in plasma lipids and membrane phospholipids within days, with maximal incorporation at approximately two weeks [100]. Increases are dose-dependent but nonlinear, with a larger increase at lower doses and then smaller increments with increasing doses [100].

Physiologic effects of omega-3 fatty acids appear to result from altered cell membrane fluidity and function following incorporation of these fatty acids into cell membranes, which then modulate protein receptor responses; binding of omega-3 fatty acids to cytoplasmic lipid-binding proteins (eg, peroxisome proliferator-activated receptor [PPAR]-gamma) that regulate gene transcription; direct interaction and influence of omega-3 fatty acids on membrane channels and proteins, such as G-protein-coupled receptors; and production of omega-3 fatty acid metabolites such as eicosanoids and specialized pro-resolving mediators (SPMs) including resolvins or protectins (figure 4).

Following cessation of consumption, washout occurs within one to three days in plasma lipid fractions but takes much longer (one to two months) for cell membranes [100]. Relatively minor pharmacokinetic differences are seen between different oral formulations of fish oil (eg, triglycerides versus ethyl esters) [101].

Compared with EPA and DHA, other omega-3 fatty acids such as docosapentaenoic acid (DPA, 22:5n-3) are present in much smaller amounts in fish oil but may be biologically active and have important metabolites following consumption [102]. DPA concentrations in blood and tissues appear to reflect endogenous synthesis (from dietary EPA) to a greater extent than direct dietary DPA consumption. EPA can also be metabolized to prostaglandin E3, an eicosanoid that mediates inflammation and thrombosis. Very little EPA (<5 percent) is converted to DHA, although this conversion occurs to a greater extent in women, particularly during pregnancy [103].

For most health effects, the relative biologic importance of EPA versus DHA versus their associated metabolites is not well-established, except for early brain development for which DHA appears to be more important [104-107].

Role of dose and duration — Generally speaking, the physiologic effects of fish oil occur within weeks to months of habitual consumption. At typical dietary intakes (<300 to 500 mg/day), compared with little or no intake, observational studies suggest lower risk of fatal coronary heart disease and sudden death, suggesting that antiarrhythmic effects, if present, may predominate. With low-dose supplements (approximately 1 g/day), the additional physiologic effects described above may have small to modest impact on other clinical outcomes. With high-dose supplements (>2 to 3 g/day), additional physiologic effects such as triglyceride

lowering become more meaningful and may lead to modest reductions in total cardiovascular events over months to years [20,21,40,108-112].

ADMINISTRATION

Preparations — Omega-3-acid ethyl esters are available by prescription, or as nutritional supplements (not regulated by the US Food and Drug Administration [FDA]). These doses of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) contained in these supplements are significantly lower than those used to treat hypertriglyceridemia or in studies of fish oil to reduce cardiovascular endpoints [113]. (See "Hypertriglyceridemia in adults: Management", section on 'Marine omega-3 fatty acids'.)

These preparations are generally omega-3 polyunsaturated fatty acids (PUFAs) as ethyl esters derived from small pelagic fish used for fish feed. Omega-3 fatty acid supplements can also be derived from formulations produced by algae. Krill oil, made from the small crustacean that is its namesake, also contains omega-3 PUFA, but as phospholipids and free fatty acids rather than ethyl esters.

Preparations available by prescription include the following [114]:

- Omega-3-acid ethyl esters (Lovaza) – Each 1 g capsule contains omega-3 fatty acids as ethyl esters sourced from fish oils, including approximately 465 mg of EPA and 375 mg of DHA.
- Icosapent ethyl (Vascepa) – Each 1 g capsule contains approximately 878 mg of highly purified EPA as an ethyl ester (also available in a 0.5 g capsule).
- Omega-3 phospholipid (CaPre, investigational) – Each 1 g capsule contains omega-3 fatty acids as phospholipids (approximately 60 percent) and free fatty acids (approximately 40 percent) sourced from krill oils, including approximately 310 mg of EPA and DHA.
- Omega-3-carboxylic acids (Epanova) – Each 1 g capsule contains omega-3 fatty acids as free fatty acids, including approximately 550 mg of EPA and 200 mg of DHA. After the phase III Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial failed to demonstrate Epanova's superiority over placebo in reducing cardiovascular endpoints, its production was discontinued in the United States [115]. (See "Hypertriglyceridemia in adults: Management", section on 'Effects on cardiovascular outcomes'.)

The choice of specific preparations for treating hypertriglyceridemia is discussed separately. (See "Hypertriglyceridemia in adults: Management", section on 'Choice of agent'.)

Supplement products commonly available at major drug or health food stores contain the labeled amount of EPA and DHA [116]. Different specific fish oil supplements contain varying amounts of EPA and DHA, depending on their formulation. Most formulations contain between 20 and 40 percent total EPA+DHA combined with other omega-3 fatty acids, monounsaturated fats, saturated fats, and gelatin or glycerin [117,118]. Consequently, a 1 g supplement capsule typically contains between 200 and 400 mg of EPA and/or DHA.

For more information on preparations, refer to the drug information monograph for omega-3-acid ethyl esters (fish oil) included within UpToDate.

Absorption — Fish oil supplements should be taken with a meal that contains fats, as the gastrointestinal absorption of ethyl ester and triglyceride formulations of omega-3 fatty acids is highest when consumed with a high-fat meal. The absorption of formulations that are predominantly free fatty acids (eg, Epanova) or phospholipids (eg, CaPre) have less dependence on being consumed with a meal or a high-fat meal. While absorption rates of these various formulations can vary, all omega-3 fatty acid formulations raise blood and tissue levels compared with not taking such supplements.

Side effects — In a pooled analysis of randomized clinical trials, the most common side effects of fish oil consumption were gastrointestinal disturbances such as nausea, occurring in approximately 4 percent of individuals at doses below 3 g/day and in approximately 20 percent of individuals at doses of 4 g/day or higher [20].

Perhaps the most common symptom causing discontinuation of fish oil supplements is "fishy taste" following eructation (burping). Freezing the fish oil, switching to a different formulation, consuming with meals, or changing intake to a different time of day may minimize this symptom in some people.

SAFETY

In small trials, fish oil capsules up to 12 g/day (containing 6 g/day omega-3 fatty acids) have been administered for more than two years without serious adverse events [119,120].

Although even these very high doses of fish oil appear to be safe, the US Food and Drug Administration (FDA) recommends that the general population not exceed 3 g/day of eicosapentaenoic acid and docosahexaenoic acid combined, with up to 2 g/day from dietary

supplements, without the guidance of a clinician [121,122]. Higher dosing is approved by the FDA under the guidance of a clinician.

The FDA has approved fish oil at a dose of 4 g/day for prescription therapy of hypertriglyceridemia [117]. In the REDUCE-IT trial, which used this formulation, overall rates of adverse events and serious adverse events were generally similar between treatment and placebo groups, with a few small differences [123]. The few differences should be interpreted cautiously given multiple comparisons and lack of prespecified hypothesis or plausible biology for such effects.

Bleeding — Available evidence suggests that fish oil supplementation does not significantly increase the risk of perioperative or other bleeding. Representative studies include the following:

- In an analysis of the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) trial, high-dose omega-3 fatty acids (8 to 10 g loading dose over two to five days preoperatively, followed by 2 g/day postoperatively) did not increase bleeding risk in 1516 patients undergoing cardiac surgery (odds ratio 0.81; 95% CI 0.53-1.24; absolute risk difference 1.1 percent lower [95% CI -3.0 to 1.8]) [124]. Those randomized to fish oil received significantly fewer total units of red blood cell transfusions (1.61 versus 1.92 units with placebo).

- A systematic review of randomized trials and case-control studies identified no increase in bleeding or transfusions either peri- or postoperatively in those taking fish oil [79].

- In a 2020 systematic review of omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease, increased intake of long-chain omega-3 fatty acids did not increase bleeding risk [125].

Contaminants — Commercially available fish oil capsules contain no appreciable mercury, which is tightly bound to fish proteins rather than present in the lipid fraction [21,126].

Significant exposure to contaminants from fish oil is not a clinical concern [21]. Fish oil capsules contain small amounts of polychlorinated biphenyls (PCBs; 0 to 450 ng/g) [127,128] and dioxins (0.2 to 11 TEQ pg/g) [129,130], with concentrations proportional to those in the fish species from which the fish oil is derived. Notably, given the small absolute quantities of fish oil that would be consumed (1 to 4 g/day), the absolute amounts of PCBs or dioxins that can be consumed from fish oil supplementation is extremely low.

Maternal ingestion of fish during pregnancy and lactation are discussed in detail separately. (See "Fish consumption and marine omega-3 fatty acid supplementation in pregnancy" and "Maternal nutrition during lactation", section on 'Fish intake'.)

Cancer risk — Overall, the available evidence does not support any major effects of fish or fish oil consumption on cancer risk. Systematic reviews and meta-analyses of numerous large prospective observational studies have generally found no significant effects of fish consumption on risk of any type of cancer [131,132], nor have randomized trials of fish oil [9,22,123]. Some studies [133-135], though not all [136], have suggested an association between higher levels of omega-3 fatty acids and increased risk of prostate cancer; however, meta-analyses of all studies found no consistent associations between dietary or blood biomarker levels of omega-3 fatty acids and prostate cancer [137,138].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Healthy diet in adults".)

SUMMARY AND RECOMMENDATIONS

- **Active constituents of fish oil** – Animal and human studies have identified the long-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA, 20:5n-3), and docosahexaenoic acid (DHA, 22:6n-3) as major active constituents in fish/seafood and fish oil. (See 'Potential effects on cardiovascular and metabolic systems' above.)
- **Potential clinical role**
  - **Patients with hypertriglyceridemia** – High daily doses of EPA and/or DHA (3 to 4 g/day) can lower serum triglyceride levels by 25 to 50 percent. The role of fish oil in the treatment of hypertriglyceridemia is discussed separately. (See "Hypertriglyceridemia in adults: Management", section on 'Marine omega-3 fatty acids'.)
  - **Other patients** – The role of omega-3 fatty acid supplementation in lipid management in patients without hypertriglyceridemia is discussed separately. (See "Overview of primary prevention of cardiovascular disease in adults", section on 'Omega-3 fatty acids' and "Lipid management with diet or dietary supplements".)

- **Atrial fibrillation** – Omega-3 fatty acids do not appear to reduce the risk of recurrent atrial fibrillation, and high-dose fish oil supplementation may increase the risk of atrial fibrillation. (See 'System effects' above and "Hypertriglyceridemia in adults: Management", section on 'Safety'.)

- **Other cardiovascular effects** – Based on the mixed findings of trials, the efficacy of fish oil supplementation for reducing clinical cardiovascular outcomes, such as cardiovascular mortality, myocardial infarction, and stroke, remains unclear. While some studies suggest that omega-3 fatty acids (dietary or supplementary) have potential cardiovascular and metabolic benefits (figure 2), these effects are modest in size and dose dependent. (See 'Overview' above and "Hypertriglyceridemia in adults: Management", section on 'Effects on cardiovascular outcomes'.)

- **Preparations** – Fish oil preparations are available by prescription or as nutritional supplements, each of which have a different composition and dose. They are generally derived from small pelagic fish used for fish feed or from formulations produced by algae. (See 'Preparations' above.)

- **Safety** – Existing evidence suggests that fish oil supplements are safe. They have not been associated with an increased risk of bleeding or cancer, and significant exposure to contaminants from fish oil is not a major concern. The US Food and Drug Administration advises the general population not to exceed 3 g/day of EPA and DHA combined, with up to 2 g/day from dietary supplements, without the guidance of a clinician. (See 'Overview' above and 'Safety' above.)

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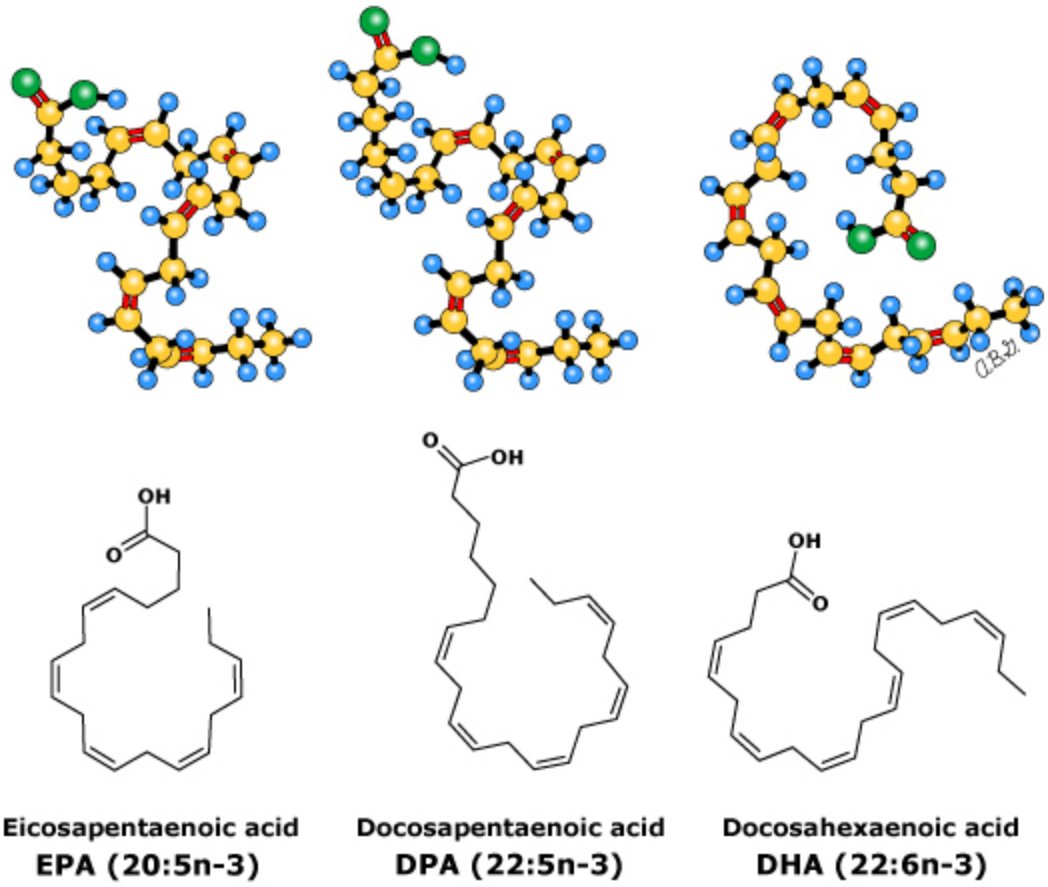
Topic 5365 Version 80.0

GRAPHICS

Structure of long-chain n-3 PUFA found in fish oil



Long-chain n-3 PUFA are almost exclusively derived from seafood sources and include eicosapentaenoic acid (EPA,20:5n-3), docosapentaenoic acid (DPA,22:5n-3), and docosahexaenoic acid (DHA,22:6n-3). Given the long carbon chains and multiple double bonds, these fatty acids have complex 3-dimensional configurations, very different from the relatively straight chains of most other fatty acids.

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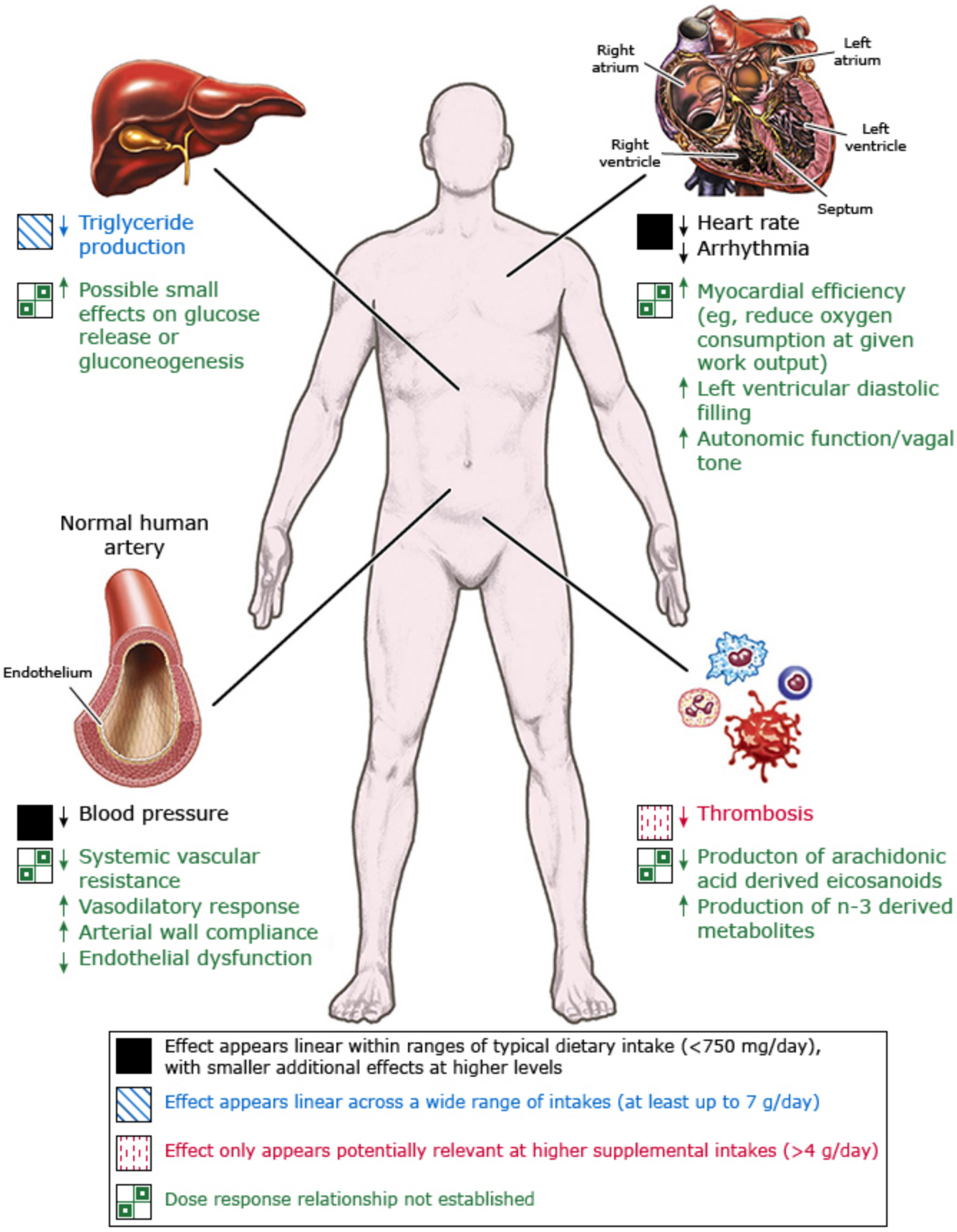
n-3 PUFA: n-3 polyunsaturated fatty acids.

Graphic 58051 Version 3.0

Physiologic effects of n-3 PUFA



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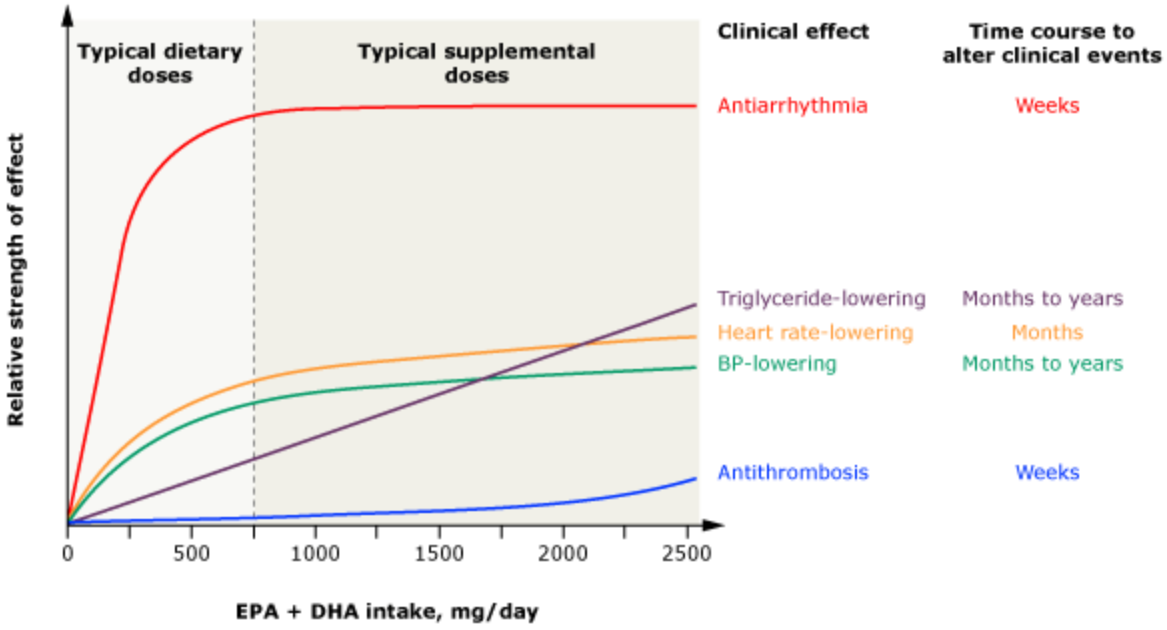
Graphic 107606 Version 1.0

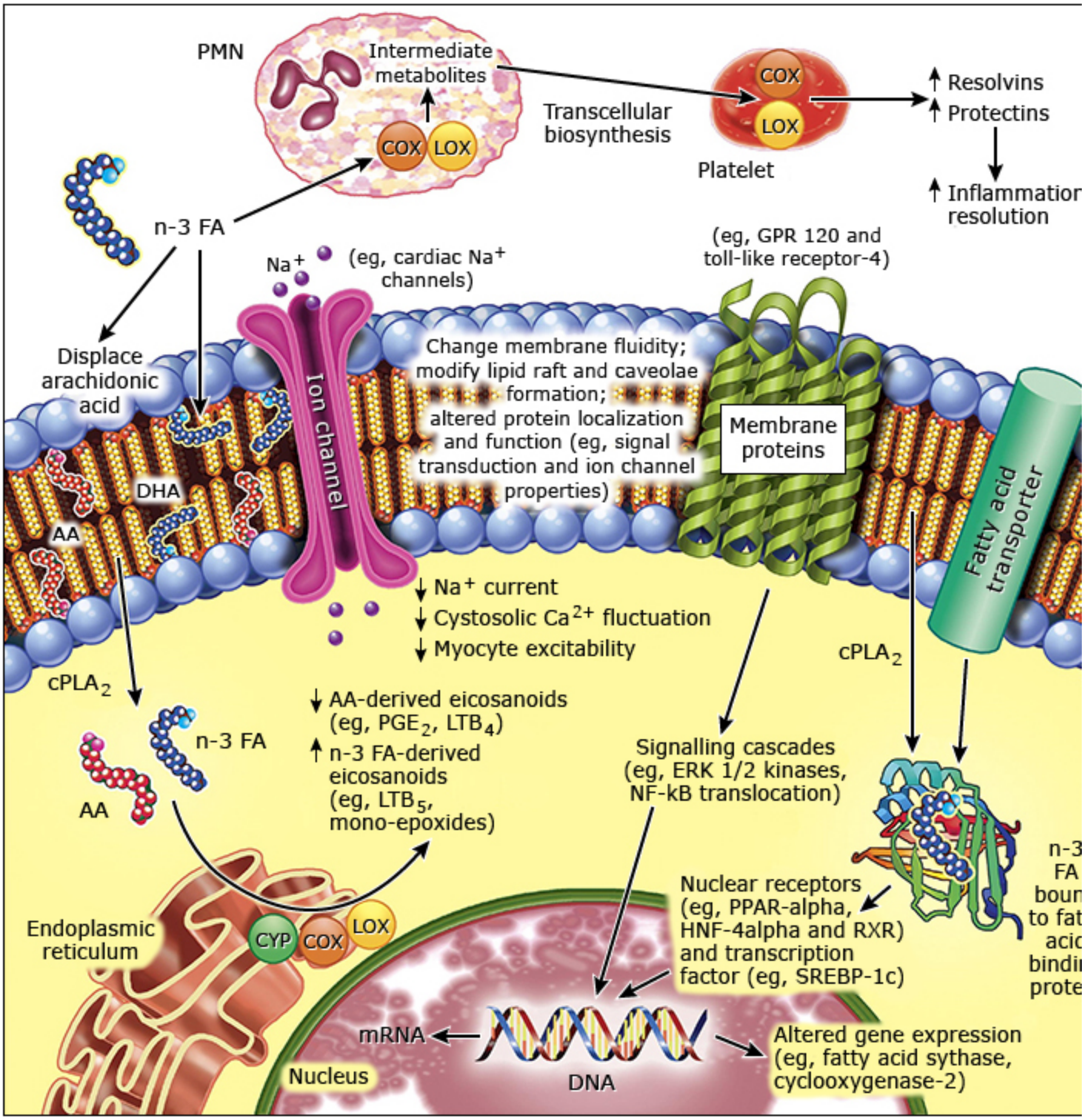
Schema of potential dose responses and time courses for altering clinical events of physiologic effects of fish or fish oil intake



Schema of physiologic effects of n-3 PUFA consumption. The relative strength of effect denotes the relative impact of n-3 PUFA consumption on the physiologic effect (eg, triglyceride-lowering). The time course to alter clinical events denotes the expected duration of consumption for the physiologic effect to alter disease outcomes. For example, the dose-response for antiarrhythmic effects appears to be initially steep with a subsequent plateau, and effects on disease outcomes may occur within weeks, whereas the dose-response for triglyceride-lowering is more gradual and monotonic, and effects on disease outcomes may require months or years of intake. Potentially important effects of n-3 PUFA on endothelial, autonomic, and antiinflammatory responses are not shown because the dose- and time-responses of these effects are not well-established. Physiologic effects are not necessarily exclusive: eg, antiarrhythmic effects may be partly mediated by effects on blood pressure (BP) or heart rate.

Graphic 78417 Version 5.0

Pathways affected by n-3 PUFA



n-3 polyunsaturated fatty acids (n-3 PUFA) modulate multiple molecular pathways that together contribute to their physiological effects. First, the physicochemical properties of cellular and organelle membranes are influenced by their lipid composition **(center)**. Incorporation of n-3 PUFA into these membranes alters membrane fluidity and biophysics of lipid rafts that modulate protein function and signaling events. For example, enrichment of cellular membranes with n-3 PUFA disrupts dimerization and recruitment of toll-like receptor-4, which might contribute to anti-inflammatory effects by down-regulation of nuclear factor-kappaB (NF-kB) activation. Ion channels such as sodium (Na^+), L-type calcium (Ca^{2+}), and Na^+– Ca^{2+} exchangers might be similarly modulated by n-3 PUFA incorporation into lipid

membranes. Second, n-3 PUFA seem to directly interact with membrane channels and proteins **(center)**. For example, direct modulation of ion channels or G-protein-coupled receptor 120 (GPR 120) might contribute to antiarrhythmic or antiinflammatory effects, respectively. Third, n-3 PUFA directly regulate gene expression via nuclear receptors and transcription factors **(lower right)**. n-3 PUFA are natural ligands of many key nuclear receptors in multiple tissues, including peroxisome proliferator-activated receptors (PPAR; -alpha, -beta, -delta, and -gamma), hepatic nuclear factors (HNF-4; -alpha and -gamma), retinoid X receptors (RXR), and liver X receptors (alpha and beta). Interactions between n-3 PUFA and nuclear receptors are modulated by cytoplasmic lipid binding proteins (eg, fatty acid [FA] binding proteins) that transport the FAs into the nucleus. n-3 PUFA also alter function of transcription factors such as sterol regulatory element binding protein-1c (SREBP-1c). Such genetic regulation contributes to observed effects of n-3 PUFA on lipid metabolism and inflammatory pathways. Fourth, after release from phospholipids by cytosolic phospholipase A_2 ($cPLA_2$), PUFA including n-3 PUFA are converted to eicosanoids by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) enzymes **(lower left)**. n-3 PUFA displace arachidonic acid (AA) in membrane phospholipids, reducing the production of AA-derived eicosanoids (eg, prostaglandin E_2 [PGE_2]) while increasing those generated from n-3 PUFA. This altered eicosanoid profile might influence inflammation, thrombosis, and vascular function. Fifth, emerging evidence suggests that n-3 PUFA play an important role in inflammation resolution via specialized pro-resolving mediators (SPMs), including resolvins or protectins that are n-3 PUFA metabolites derived from actions of COX and LOX **(top)**. Biosynthesis of SPMs seems to require involvement of two or more cell types ("transcellular biosynthesis"), with one cell type converting the n-3 fatty acid to metabolic intermediates, and the second cell type converting these intermediates into the SPMs. n-3 PUFA-derived SPMs seem to be key drivers of inflammation resolution programs that reduce chronic inflammation in a wide range of animal models. The roles of each of these molecular pathways in the cardiovascular protection of n-3 PUFA represent promising areas for future investigation.

DHA: docosahexaenoic acid; DNA: deoxyribonucleic acid; ERK: extracellular signal-regulated kinase; LTB: leukotriene B; mRNA: messenger ribonucleic acid; PMN: polymorphonuclear leukocyte.

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