# Recent Clinical Trials Shed New Light on the Cardiovascular Benefits of Omega-3 Fatty Acids

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**ABSTRACT:** Three recent clinical trials have demonstrated the benefits of marine omega-3 fatty acids on cardiovascular disease end points. In the Vitamin D and Omega-3 Trial (VITAL), 840 mg/d of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) resulted in a 28% reduced risk for heart attacks, 50% reduced risk for fatal heart attacks, and 17% reduced risk for total coronary heart disease events. In the ASCEND trial (A Study of Cardiovascular Events in Diabetes), cardiovascular disease death was significantly reduced by 19% with 840 mg/d of EPA and DHA. However, the primary composite end points were not significantly reduced in either study. In REDUCE-IT (the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial), there was a 25% decrease in the primary end point of major cardiovascular events with 4 g/d EPA (icosapent ethyl) in patients with elevated triglycerides (135-499 mg/dL) who also were taking a statin drug. For clinical practice, we now have compelling evidence of the cardiovascular benefits of omega-3 fatty acids. The findings of REDUCE-IT provide a strong rationale for prescribing icosapent ethyl for patients with hypertriglyceridemia who are on a statin. For primary prevention, the goal is to increase the population intake of omega-3 fatty acids to levels currently recommended, which translates to consuming at least one to two servings of fish/seafood per week. For individuals who prefer taking omega-3 fatty acid supplements, recent findings from clinical trials support the benefits for primary prevention.

## INTRODUCTION

Recommendations from 2002 about long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for the primary and secondary prevention of cardiovascular disease (CVD) have been tempered by more recent clinical studies that did not show CVD benefits.[1,2] Herein, we briefly describe why the latter studies may have shown no benefit[3] and review three very recent major clinical trials that did show CVD benefits of omega-3 fatty acids. These studies included healthy individuals, patients with diabetes, and patients with mildly elevated triglycerides taking statin drugs.[4-6] We also describe possible mechanisms that explain the cardiovascular benefits of omega-3 fatty acids, define current long-chain omega-3 fatty acid intakes, and advise clinicians about what can be done in practice to first determine and then optimize the omega-3 fatty acid intake for their patients.

## RECENT STUDIES SHOWING BENEFITS OF OMEGA-3 FATTY ACIDS FOR PRIMARY AND SECONDARY PREVENTION OF CVD

### *Vitamin D and Omega-3 Trial (VITAL)*

The Vitamin D and Omega-3 Trial (VITAL) is the largest, most ethnically diverse omega-3 randomized controlled trial (RCT) focused on primary prevention.[4] VITAL assigned more than 25,000 people to either 1 g/d of omega-3 acid ethyl esters (O3AEE; providing 840 mg EPA and DHA), 2,000 IU of vitamin D3 (generic cholecalciferol), both O3AEE and vitamin D3, or dual placebo for approximately 5 years (Table 1).[4-6] The goal was to investigate whether O3AEE and/or vitamin D could reduce the risk for cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. O3AEE was the first omega-3 "drug" approved by the US Food and Drug Administration (FDA) and has been available by prescription for several years, but only for the treatment of very high triglycerides (TG).

In VITAL, O3AEE demonstrated no benefit for cancer outcomes compared to placebo, nor did it significantly reduce major CV events, which was the trial's primary outcome. Accordingly, the authors concluded that "supplementation with n—3 fatty acids did not result in a lower incidence of major CV events or cancer than placebo," which was widely reported in the press. However, there were several statistically significant effects on prespecified secondary outcomes worth noting, including a 28% reduced risk for heart attacks, 50% reduced risk for fatal heart attacks, and 17% reduced risk for total coronary heart disease events.[4] These effects were most pronounced in people with low fish intake (below the median of 1.5 servings per week) and African Americans. For heart attacks specifically, those with low fish intake who were in the O3AEE group experienced

| RANDOMIZED CONTROLLED TRIAL | COUNTRY | SAMPLE SIZE/SUBJECT TYPE | YEARS OF FOLLOW-UP | EPA+DHA DOSE | FINDINGS |
|---|---|---|---|---|---|
| ASCEND[5] | United Kingdom | 15,480/patients with type 2 diabetes | 7.4 | 840 mg | Composite end point not significantly altered<br>Risk for vascular death ↓ by 19% (95% CI, 1%-33%) |
| VITAL[4] | United States | 25,871/older adults without history of CVD or cancer | 5.3 | 840 mg | Composite end point not significantly altered<br>Risk for heart attack ↓ by 28% (95% CI, 10%-41%)<br>Risk for total CHD ↓ by 17% (95% CI, 3%-29%) |
| REDUCE-IT[6] | International (11 countries) | 8,179/statin-treated patients with median TG levels of 216 mg/dL and other CVD risk factors | 4.9 | 3,600 mg (EPA only) | Primary CVD end point ↓ by 26%<br>Significant reductions in several secondary end points |

*Table 1.*
Comparison of three major trials of omega-3 fatty acids reported in 2018. ASCEND: A Study of Cardiovascular Events in Diabetes; VITAL: Vitamin D and Omega-3 Trial; REDUCE-IT (the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; CVD: cardiovascular disease; TG: triglycerides; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; CHD: coronary heart disease

a significant 19% reduction in the primary end point, whereas there was no reduction or individuals with higher baseline fish intake. For African Americans, there was a significant 77% reduction in heart attacks in the O3AEE group, a 49% reduction in the need for coronary revascularization, and a 53% reduction in total coronary heart disease.

However, VITAL was considered a "null" study because the primary end point of composite major CV events was not significantly reduced (8% reduction, 95% CI, -20% to 6%). The primary end point was unaffected because it was a combination of three CV outcomes, including two that were not reduced by O3AEE treatment (total stroke and death from CVD) and one that was (total myocardial infarction). Thus, pooling them together produced an overall null effect. But should a failure to reduce the risk for stroke and death from CVD nullify the success in reducing rates of myocardial infarction (MI)? In our view, the problem is the convention requiring that the success or failure of a trial depends *completely* on the effect of the intervention on only one prespecified primary end point–to the exclusion of all other findings. In the case of VITAL, had total MI or coronary heart disease (CHD) been the predefined end point (which would have been reasonable given the long history of demonstrated benefits of omega-3 fatty acids in CVD, but which could not have been confidently foreseen when the trial was being designed), the findings of the study would have been positive. It is true that one cannot go on a fishing expedition for effects with significant p-values in such trials, but the finding of an effect on total CHD or MI should not be considered unexpected or exploratory in VITAL. Thus, despite the published conclusions and subsequent reporting in the media, we contend that this is a positive trial for omega-3 fatty acids, especially given the relatively low dose of EPA and DHA used (< 1 g/d), the fairly short follow-up period, and the focus on primary prevention.

### *A Study of Cardiovascular Events in Diabetes (ASCEND)*

ASCEND was a 7-year RCT in the United Kingdom that tested the effects of EPA, DHA, and aspirin on CVD events in 15,480 patients with diabetes and no diagnosis of CVD (Table 1).[5] The omega-3 product and dose were the same as in VITAL[4]–one capsule per day of O3AEE–and the placebo was a 1-gram capsule of olive oil. The effects of aspirin in this population were reported in a separate publication and can be summarized as reduced risk for CVD counterbalanced by an increased risk for major bleeding.[7] ASCEND also was considered a null omega-3 trial because the primary end point–again, a composite of risk for nonfatal MI, nonfatal stroke, transient ischemic attacks,

and "vascular death" (including fatal CHD, fatal stroke, and death from other "vascular" causes, in other words, CVD death)—was only 3% lower in the omega-3 group and did not achieve statistical significance. However, as in VITAL, some components were affected and others were not. There was no effect of EPA and DHA on the first three outcomes, but CVD death was significantly reduced by 19%. This important benefit was largely overlooked in the publication, which concluded that their findings did not support the current recommendations for routine dietary supplementation with omega-3 fatty acids to prevent vascular events in patients with diabetes.[5] As with VITAL, we take exception to this conclusion since the omega-3 fatty acids clearly provided an important benefit. The reduction in total CVD deaths should not be dismissed simply because this relatively low dose of omega-3 fatty acids did not reduce the risk for all possible CVD end points. In fact, a reduced risk of CV death tends to be the common denominator in most large studies of omega-3 supplementation.[8,9]

### *Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)*

As opposed to VITAL and ASCEND, REDUCE-IT used icosapent ethyl (IPE; brand name Vascepa, Amarin Corporation), which is EPA in ethyl ester form. Vascepa was the second FDA-approved omega-3 drug indicated for TG lowering.[6] It differs from O3AEE that contain both EPA and DHA in the ethyl ester form.

REDUCE-IT was designed to investigate whether IPE combined with statin therapy was superior to statin therapy alone when used to prevent long-term CV events in high-risk patients with mixed dyslipidemia. Over 8,000 patients at increased risk of CVD were followed for approximately 5 years (Table 1). Participants were required to have TG levels of 135 to 499 mg/dL as well as known CVD or diabetes and at least one other CV risk factor. Average low-density lipoprotein cholesterol was ~75 mg/dL (on statins) and average TG levels were ~216 mg/dL (normal is < 100 mg/dL). Participants were randomized to either 4 g/d IPE or a placebo.

IPE significantly reduced CV events by 25%. The following outcomes were also significantly reduced with IPE treatment:

- CV death, heart attack, or stroke in the secondary prevention population: 28% ($P < .001$)
- CV death or nonfatal heart attack: 26% ($P < .001$)
- Fatal or nonfatal heart attack: 31% ($P < .001$)
- Urgent or emergent revascularization: 35% ($P < .001$)
- CV death: 20% ($P < .03$)
- Hospitalization or unstable angina: 32% ($P < .002$)
- Fatal or nonfatal stroke: 28% ($P < .01$)
- Total mortality, nonfatal heart attack, or nonfatal stroke: 23% ($P < .001$)

Comparatively, IPE was a more effective add-on agent to statins for reducing adverse CVD outcomes in REDUCE-IT than virtually every hypolipidemic drug tested in the last 12 years, including but not limited to: evolocumab, alirocumab, ezetimibe, niacin, torcetrapib, anacetrapib, and evacetrapib.[10-16] Additionally, it was safer and had fewer side effects than any of these other drugs. This is a strong refutation of the view that "fish oil does not work"—a conclusion that is based on studies providing approximately a quarter of the omega-3 dose used here.[3,17] The fact that the 4 g/d dose of EPA in REDUCE-IT was remarkably effective strongly reinforces that dose is an important consideration. The outcomes from a larger study with a similar design as REDUCE-IT, the Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial, which is using 4 g/day of EPA and DHA (as free fatty acids), are expected in late 2020 and will help to clarify this.[18]

## WHY DID PREVIOUS OMEGA-3 STUDIES FAIL?

Many trials have been conducted to assess the effects of long-chain omega-3 fatty acids on CV end points. Studies published prior to 2018 are described in Table 2.[19-30] In general, early trials—including DART, GISSI-P, JELIS, and GISSI-HF—reported beneficial effects on CV outcomes,[21-23] whereas more recent trials, such as Alpha Omega, OMEGA, SU.FOL.OM3, ORIGIN, AREDS2, and R&P, reported neutral effects.[24-27,30] This discrepancy may be attributed to methodological limitations of later trials that biased results toward the null and confounded the interpretation of results. The limitations include short intervention duration, lengthy event-to-enrollment interval in secondary prevention, low omega-3 dose, and high background fish intake.[3] In addition, three trials had insufficient statistical power due to lower-than-anticipated event rates, likely due to advancements in standard of care.[25,26,28] For example, in GISSI-P, only 5% of participants at baseline and 45% of participants at follow-up used cholesterol-lowering medications, whereas approximately 85% of participants in both Alpha Omega and SU.FOL.OM3 used lipid-lowering agents.[21,24,26] Although it is possible that < 1 g/d of omega-3 fatty acids does not add to the risk reduction provided by modern, state-of-the-art CV pharmacotherapy, the results of ASCEND and VITAL suggest that they may provide additional benefit.

## EFFECTS ON LIPIDS/LIPOPROTEINS AND OTHER POTENTIAL MECHANISMS OF ACTION

One mechanism for improved CVD outcomes are effects on lipids and lipoproteins. Omega-3 fatty acids have well-

| TRIAL, YEAR | OMEGA-3 INTERVENTION | CONTROL | STUDY POPULATION | DURATION (YEARS) | PRIMARY OUTCOME(S) | |
|---|---|---|---|---|---|---|
| Diet and Reinfarction Trial (DART) 1989 [19,20] | Dietary advice to consume ≥2 servings of fatty fish per week<br>Supplement subgroup: 3 g/d of fish oil (~840 mg/d EPA+DHA)* | No dietary advice | Men recovered from MI (N = 2,033) | 2 | Ischemic heart disease events (ischemic heart disease death and nonfatal MI)<br>Total mortality | RR: 0.84 95% CI, 0.66-1.07<br>RR: 0.71 95% CI, 0.54-0.93 |
| Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto micardico Prevenzione (GISSI-P) 1999 [21] | 840 mg/d EPA+DHA as ethyl esters | Standard of care | Adults with previous MI in last 3 months (N = 11,323) | 3.5 | Death, nonfatal MI, nonfatal stroke<br>CV death, nonfatal MI, nonfatal stroke | RR: 0.90 95% CI, 0.82-0.99<br>RR: 0.89 95% CI, 0.80-1.01 |
| Japan EPA Lipid Intervention Study (JELIS) 2007 [22] | 1,800 mg/d EPA as ethyl esters with statin | Statin only (no omega-3 fatty acids) | Adults with hypercholesterolemia, with or without a history of coronary artery disease (MI > 6 months) (N = 18,645) | 4.6 | Major coronary event (sudden cardiac death, fatal and nonfatal MI, and other nonfatal events) | HR: 0.81 95% CI, 0.69-0.95 |
| Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca-Heart Failure (GISSI-HF), 2008 [23] | 840 mg/d EPA+DHA as ethyl esters | Unspecified placebo oil | Adults with chronic heart failure (N = 6,975) | 3.9 | All-cause mortality<br>All-cause mortality or hospitalization for CVD | HR: 0.91 95.5% CI, 0.833-0.998<br>HR: 0.92 99% CI, 0.849-0.999 |
| Alpha Omega 2010 [24] | Margarine containing 226 mg EPA and 150 mg DHA | Placebo or ALA-containing margarine | Adults with MI within 10 years (N = 4,837) | 3.4 | Major CV events (fatal and nonfatal cardiovascular events and cardiac interventions) | HR: 1.01 95% CI, 0.87-1.17 |
| OMEGA 2010 [25] | 840 mg/d EPA+DHA as ethyl esters | Olive oil placebo | Adults with acute MI (3-14 days) (N = 3,851) | 1 | Sudden cardiac death | OR: 0.95 95% CI, 0.56-1.60 |
| Supplmentation en Folates et Omega-3 (SU.FOL.OM3) 2010 [26] | 600 mg/d EPA+DHA at a ratio of 2:1 | Placebo | Adults with acute coronary or cerebral ischemic event within < 1 year (N = 2,501) | 4.7 | Major CV events (composite of nonfatal MI, stroke, or death from CVD) | HR: 1.08 95% CI, 0.79-1.47 |
| Outcome Reduction with an Initial Glargine Intervention (ORIGIN) 2012 [27] | 840 mg/d EPA+DHA as ethyl esters | Olive oil placebo | Adults with CVD plus dysglycemia (N = 12,536) | 6.2 | Death from CVD | HR: 0.98 95% CI, 0.87-1.10 |
| Risk and Prevention (R&P) 2013 [28,29] | 840 mg/d EPA+DHA as ethyl esters | Olive oil placebo | Adults with high CVD risk without previous MI (N = 12,513) | 5 | Death or hospitalization from CVD | HR: 0.98 95% CI, 0.88-1.08 |
| Age-Related Eye Disease Study 2 (AREDS2) 2014 [30] | 350 mg DHA and 650 mg EPA | Corn oil placebo | Adults with intermediate or advanced age-related macular degeneration in one eye (N = 4,203) | 4.8 | CVD mortality (sudden death, death due to MI, heart failure, or stroke) and CVD morbidity (MI, stroke, unstable angina, coronary and carotid revascularization, hospitalized congestive heart failure, resuscitated cardiac arrest) | HR: 0.95 95% CI, 0.78-1.17 |

*Supplements were provided to those who were intolerant to fish.
**The primary end point was originally the cumulative rate of death, nonfatal MI, and nonfatal stroke but was changed following intermediate analyses indicating low event rates.

*Table 2.*
Study design and primary results from clinical trials assessing the effects of long-chain omega-3 fatty acid interventions on cardiovascular disease events. CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; MI: myocardial infarction; CVD: cardiovascular disease; ALA: alpha-linolenic acid

established TG-lowering effects and effects on other lipoproteins based on dose and pretreatment lipid/lipoprotein concentrations.[31,32] For example, they are effective at reducing elevated TG at a prescription dose of 4 g/d, the same dose administered in REDUCE-IT to patients with TG levels of 135/150-500 mg/dL.[6] In patients with this degree of TG elevation, a 20% to 30% reduction in fasting values is typical and often accompanied by small reductions in non–high-density lipoprotein cholesterol and apolipoprotein B. Cotreatment with a statin does not appear to influence the degree of TG reduction achieved by omega-3 fatty acids, although this has not been thoroughly evaluated. In people with very high TG (≥ 500 mg/dL), 4 g/d prescription O3AEE or IPE is indicated to reduce the risk of pancreatitis and also results in TG reductions > 30%. The dearth of studies directly comparing prescription omega-3 fatty acids (ie, O3AEE and IPE) precludes any firm conclusions regarding the comparative effects of these agents on TG as well as other lipids and lipoproteins. Studies evaluating 2 g/d versus 4 g/d of prescription omega-3 fatty acids found that the lower dose provided roughly one-half the TG-lowering efficacy, which in some cases was not significantly different from placebo.[33-36] In people with fasting TG < 150 mg/dL, reductions in TG may not be apparent, even at these higher doses. The ~1 g/d dose used in many RCTs is not effective for reduction of TG but is likely to impact other risk pathways discussed below.[37]

Other potential mechanisms by which omega-3 fatty acids reduce CVD risk may be apparent at lower doses. Omega-3 fatty acids affect interrelated risk pathways including arrhythmia, coagulation, vascular health, blood pressure, plaque stability, and inflammation.[2,38,39] A rich and growing area of research continues to elaborate how omega-3 fatty acids can affect these physiological processes, including relatively recent discoveries of an expanding universe of oxygenated metabolites of EPA and DHA termed oxylipins and specialized pro-resolving lipid mediators.[40] For example, a hydroxylated product of EPA, 18-HEPE, has been shown to reduce fibrotic remodeling of the heart.[41] These risk pathways may be more responsive in people with very low dietary intakes and tissues stores, as evidenced by the VITAL study finding of greater risk reduction for people with below-median fish intake (< 1.5 serving/wk).[4] In summary, omega-3 fatty acids dose-dependently influence multiple CVD risk pathways.

## CURRENT INTAKES OF OMEGA-3 FATTY ACIDS

EPA and DHA intake vary considerably among different countries and populations, as reviewed by Richter et al.[42] For instance, intake is relatively high in Japan (~1.3-2.5 g/d) and in Greenland Inuits (~4.5-10.5% of total fatty acids, at least in the 1970s) because of their reliance on whale, seal, and fish meat. Conversely, in the United States, Australia, Belgium, Germany, the United Kingdom, and Canada, average daily intake falls far short of the recommendation for CVD prevention (~500 mg/d EPA/DHA), with intakes approximating 100 to 290 mg/d or less. In the United States, the National Health and Nutrition Examination Survey (NHANES) has consistently shown a low intake. For example, over the 2003-2014 NHANES survey cycles, the mean intake of EPA, DHA, and EPA plus DHA from foods was 33 mg/d, 64 mg/d, and 97 mg/d, respectively, and previous analyses of NHANES data have reported similarly low dietary intakes.[43] Use of EPA/DHA supplements significantly increase total EPA and DHA intake, but use of these supplements in the United States is low.[43,44] Evidence also suggests that EPA and DHA intake may be particularly low in specific segments of the population, such as children/adolescents, pregnant women and/or women of childbearing age, and certain ethnicities.[43,44] The primary food sources of omega-3 fatty acids are oily fish/shellfish. However, it should be noted that the omega-3 content of fish varies by species and can also be influenced by the fish's diet, whether wild-caught or farm raised. In general, the best sources of omega-3 fatty acids are salmon, herring, anchovies, sardines, and rainbow trout.[42] Compared to oily fish, white fish such as tilapia tend to be much lower in omega-3 content.

## HOW CAN CLINICIANS ASSESS OMEGA-3 STATUS IN THEIR PATIENTS?

Although a preliminary estimate of omega-3 status could be made by assessing the patient's dietary intake of foods high in omega-3 fatty acids, a direct assessment can be obtained by measuring the Omega-3 Index (O3I). This is a blood test that reports the proportion of EPA and DHA in red blood cell membrane fatty acids (as a percent of total fatty acids). The O3I is an evidence-based marker of EPA and DHA intake as well as CVD risk.[45,46] For CVD risk, a target range of 8% to 12% was proposed in 2004 for reduced risk of primary cardiac death, and subsequent research has confirmed this target as clinically relevant.[47,48]

Relative to assessing dietary intake, Jackson et al. recently published associations between the O3I and reported intake of fish and supplements in 3,458 individuals.[45] On average, the O3I increased in a dose-dependent manner with increasing frequency of fish intake (approximately 0.5 percentage points per increase in frequency of fish meals/wk) and was 2.2 percentage points higher in individuals who reported using supplements. However, over 80% of the study population had an O3I less than 8%, and those following the American Heart Association (AHA) recommendation of two fish meals per week without supplement use had an

average O3I of 5.8% ± 1.5%.[49] It should be noted that in those achieving the AHA recommendation, the O3I range was 3.3% to 11.4%, which spans the full high-to-low risk spectrum. Thus, in individual patient care, testing omega-3 status is preferred to estimating intakes based on dietary assessments. Since the O3I is a red blood cell-based marker, it only needs to be tested every 4 to 6 months and can be measured in either red blood cells (from anticoagulated whole blood) or a dried blood spot using antioxidant-treated filter paper. The O3I cannot be ascertained from a plasma essential fatty acid panel.

## SUMMARY

Over the last 25 years, the sands have shifted regarding the effects of marine omega-3 fatty acids on CVD. After the benefits found in earlier studies were not confirmed in subsequent trials, questions were raised about the recommendation to consume omega-3 fatty acids to reduce CVD risk. However, the trial results released in the last 12 months have again upended conventional wisdom. For the general population and those with diabetes, about 1 g/d of omega-3 fatty acids reduced the risk of both death from CVD and having an MI. For those with high TG who take statins, 4 g/d of EPA dramatically reduced the risk for several CVD outcomes, including CV death. As previously noted, the dose of omega-3 fatty acids is likely a main factor in whether significant effects are observed. Collectively, we are at a point where the question can be asked: How should we translate these results into clinical practice? For primary prevention, the prudent and practical advice is to recommend at least one to two fish/seafood servings per week, which is consistent with current dietary guidelines. Following this recommendation would improve omega-3 intake and status in most individuals but would likely not be sufficient to reach an intake of 1 g/d of omega-3 fatty acids, a level that provides significant CV benefit for many patients. A higher dose of omega-3 fatty acids (approximately 4 g/d of EPA and likely 4 g/d of EPA+DHA, as well) is also an effective adjunct for CV treatment in those with high TG who take statins. Finally, measuring the patient's omega-3 status (eg, with the O3I) can monitor whether the patient's plan of care is efficacious in achieving protective omega-3 blood levels.

*Conflict of Interest Disclosure:*
Kristina Harris Jackson is an employee and shareholder and William Harris is the founder and CSO of OmegaQuant Analytics, LLC.

*Keywords:*
eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA, omega-3 fatty acids

## KEY POINTS

- Clinical trial results released in the past 12 months have demonstrated clear benefits of omega-3 fatty acid intake for cardiovascular disease risk, with significant reductions in risk of heart attacks, other major cardiovascular events, and cardiovascular disease death.
- The mixed results regarding the effects of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the primary and secondary prevention of cardiovascular disease from previous studies may be due in part to methodological limitations, such as using composite end points, a short intervention duration, low omega-3 fatty acid supplementation dose, and high background fish intake.
- Based on results from REDUCE-IT, the addition of 4 g/d of EPA should be considered for statin-treated patients who have cardiovascular disease or diabetes and elevated triglycerides.
- For clinical practice, evidence from the most recent clinical trials supports the recommendation to consume at least one to two servings of fish/seafood per week, with additional primary prevention benefits conferred by consuming ~1 g/d of EPA and DHA.

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