

Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease

A Science Advisory From the American Heart Association

ABSTRACT: Multiple randomized controlled trials (RCTs) have assessed the effects of supplementation with eicosapentaenoic acid plus docosahexaenoic acid (omega-3 polyunsaturated fatty acids, commonly called fish oils) on the occurrence of clinical cardiovascular diseases. Although the effects of supplementation for the primary prevention of clinical cardiovascular events in the general population have not been examined, RCTs have assessed the role of supplementation in secondary prevention among patients with diabetes mellitus and prediabetes, patients at high risk of cardiovascular disease, and those with prevalent coronary heart disease. In this scientific advisory, we take a clinical approach and focus on common indications for omega-3 polyunsaturated fatty acid supplements related to the prevention of clinical cardiovascular events. We limited the scope of our review to large RCTs of supplementation with major clinical cardiovascular disease end points; meta-analyses were considered secondarily. We discuss the features of available RCTs and provide the rationale for our recommendations. We then use existing American Heart Association criteria to assess the strength of the recommendation and the level of evidence. On the basis of our review of the cumulative evidence from RCTs designed to assess the effect of omega-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events, we update prior recommendations for patients with prevalent coronary heart disease, and we offer recommendations, when data are available, for patients with other clinical indications, including patients with diabetes mellitus and prediabetes and those with high risk of cardiovascular disease, stroke, heart failure, and atrial fibrillation.

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In 2002, the American Heart Association (AHA) published a scientific statement, "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease."¹ At that time, evidence from 2 large randomized controlled trials (RCTs) demonstrated that eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) supplements significantly reduced fatal cardiac events.^{2,3} The 2002 scientific statement recommended that additional studies be done to confirm these findings and to define the health benefits of omega-3 fatty acid supplements for both primary and secondary prevention of cardiovascular disease (CVD). On the basis of the evidence summarized in 2002, the AHA recommended that patients with documented coronary heart disease (CHD) consume \approx 1 g/d EPA+DHA, preferably from oily fish, but EPA+DHA supplements could be considered in consultation with a physician.¹ In the ensuing years, multiple RCTs have been conducted to evaluate the effects of supplementation of EPA+DHA, provided as prescription medications, supplements, or enriched margarine, on the occurrence of clinical CVD.

In this update to the 2002 scientific statement, we limited the scope of our review to large RCTs of supplementation with major clinical CVD end points. Details of the RCTs reviewed for this report are provided in evidence Tables 1 through 7. Secondarily, we considered evidence from meta-analyses of RCTs. Post hoc subgroup findings, such as among nonstatin users, from RCTs that were exploratory and hypothesis generating are not reviewed here because the purpose of this advisory is to evaluate the effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation on primary clinical CVD outcomes in the patient populations enrolled in the RCTs. We also did

not conduct a comprehensive review of the literature on the health effects of supplementation, in part because the goal of our focused review is to determine whether there was a need to update the 2002 AHA recommendations related to the impact of omega-3 PUFA supplementation on clinical CVD. We note that observational studies have focused on fish intake or circulating omega-3 PUFAs and have not specifically assessed the effects of omega-3 PUFA supplementation on clinical CVD.

In this advisory, we provide recommendations for clinicians and patients when supported by available evidence from RCTs of clinical CVD. We do not provide recommendations based on observational studies, physiological or mechanistic studies in human subjects, or a consensus of expert opinion when evidence is insufficient. We indicate in the text and Table 8 when the authors of the advisory failed to reach a consensus on the class of recommendation, and we present both the majority and minority recommendations. We discuss various features of the available RCTs that may have contributed, at least in part, to inconsistent findings in the results of prior RCTs. Heterogeneity in the indications, study populations, interventions, and outcomes has challenged both quantitative and qualitative efforts to synthesize the evidence on omega-3 PUFA supplements and clinical CVD. We focus on the effects of omega-3 PUFA (the term we use to refer to the marine-based omega-3 PUFA, EPA, and DHA) supplementation in this advisory. This report does not examine studies of dietary omega-3 PUFAs from seafood and dietary intake of plant-based omega-3 PUFA such as α -linolenic acid and clinical CVD.

Table 1. Trials of Prevention of CVD Mortality in Diabetes Mellitus/Prediabetes

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|--|---|--|--|--|--|
| ORIGIN Bosch et al ⁴ 2012 | Randomized double-blind, placebo-controlled clinical trial n=12 536 6.2 y | Inclusion criteria: multicountry patients age \geq 50 y with diabetes mellitus treated with \leq 1 oral agent, IGT, or IFG, and history of CVD, albuminuria, LVH, or PVD (59% had prior MI, stroke, or coronary revascularization) Exclusion criteria: HbA _{1c} \geq 9%, history of CABG within past 4 y with no intervening CVD event, severe heart failure, or cancer that might affect survival | Intervention: n=6281 840 mg/d EPA+DHA Comparator: n=6255 Placebo (olive oil) | Primary end point: CVD death; 1055 events; RR, 0.98 (95% CI, 0.87–1.10) | Strengths: large sample size, long duration of follow-up, large number of primary events, large number of arrhythmic deaths (547 events) Limitations: high background dietary EPA+DHA intake (median, 210 mg/d) at baseline |

CABG indicates coronary artery bypass graft surgery; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HbA_{1c}, hemoglobin A_{1c}; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LVH, left ventricular hypertrophy; MI, myocardial infarction; ORIGIN, Outcome Reduction With Initial Glargine Intervention Trial; PVD, peripheral vascular disease; and RR, relative risk.

OMEGA-3 PUFA (FISH OIL) SUPPLEMENTS

Nonprescription Omega-3 PUFA Supplements

In 2012, 7.8% of adults in the United States (18.8 million) reported consuming a fish oil dietary supplement within the prior 30 days.¹⁸ The primary source of nonprescription omega-3 PUFA supplements is fish oil, composed primarily of triglycerides. Some preparations are now available as ethyl esters and phospholipids. These supplements frequently contain other essential nutrients, including vitamin D, vitamin E, and mixed tocopherols.¹⁹ A recent US Department of Agriculture survey of omega-3 PUFA supplements concluded that the most common amounts per dose were 180 mg for EPA and 120 mg for DHA.²⁰ The US Department of Agriculture supported a study that chemically analyzed a representative group of commonly available omega-3 PUFA supplements and concluded that the analytical content of EPA and DHA was for the most part reflective of the labeled amounts.²⁰ The omega-3 PUFA supplements that have been voluntarily tested to confirm content independently can be identified by the presence of the US Pharmacopeia Convention symbol on the label.²¹

Prescription Preparations

Currently, there are 5 prescription omega-3 PUFA products available in the United States that are approved for the indication of treating severe hypertriglyceridemia. These include 4 preparations of omega-3-ethyl esters of EPA with or without DHA and 1 preparation composed of omega-3 PUFAs in the free fatty acid form.²² The amount and ratio of EPA and DHA vary in different preparations. Of note, the bioavailability of EPA and DHA also varies by the chemical form: Products containing ethyl esters may have somewhat lower bioavailability than the free fatty acid forms.²³ Absorption of both ethyl esters and free fatty acids is enhanced by the presence of dietary fat.^{24–26}

OMEGA-3 PUFA SUPPLEMENTATION AND CLINICAL CVD

In the synthesis below, we briefly summarize the primary clinical questions, approach, findings, and implications of the available RCTs of omega-3 PUFA supplementation and clinical CVD. The details of the RCTs reviewed in the advisory, including the study name, clinical indication, study population, sample size, dose and formulation, follow-up, major findings, and limitations, are provided in the evidence Tables 1 through 7 and are not included in the text.

PRIMARY PREVENTION OF CHD

There are no reports from RCTs that have targeted exclusively the primary prevention of CHD, that is, the effects

of omega-3 PUFA supplements in the general population of patients without prior CHD. No recommendation for treatment with omega-3 PUFA supplements can be made for this segment of the population.

PREVENTION OF CVD MORTALITY IN DIABETES MELLITUS/PREDIABETES

One large RCT (details provided in Table 1) was designed to examine the effects of omega-3 PUFA supplementation on cardiovascular death among patients with or at risk for diabetes mellitus (based on impaired fasting glucose, impaired glucose tolerance). In the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention), the 12 536 patients randomized to omega-3 PUFA supplement or placebo were at high risk of CVD, with the majority having had a prior CHD event.⁴ Supplementation with omega-3 PUFA did not affect the risk of death resulting from cardiovascular causes or the other prespecified secondary cardiovascular outcomes. Additionally, post hoc subgroup analyses of patients with and without diabetes mellitus or markers of dysglycemia from 5 large RCTs of omega-3 PUFA supplementation (all included patients with and without prior clinical CHD) yielded mixed findings.^{6,8,12,27,28} There was little evidence of a lower risk of CVD among patients with or at risk for diabetes mellitus in 2 trials and some evidence that these patients may benefit as much as or more than those without dysglycemia in the 3 other trials. Taken together, available data do not support omega-3 PUFA supplementation among patients with diabetes mellitus or prediabetes to prevent cardiovascular events. We note that there is a large ongoing RCT in the United Kingdom, ASCEND (A Study of Cardiovascular Events in Diabetes), that seeks to examine the effects of omega-3 PUFA supplements on cardiovascular events among patients with diabetes mellitus and free of prior clinical CVD.²⁹

Overall, the current evidence from RCTs suggests no benefit of omega-3 PUFA supplementation among patients with or at risk for diabetes mellitus to prevent CVD (Treatment is not indicated: *Class III: No Benefit Recommendation*).

PREVENTION OF CHD AMONG PATIENTS AT HIGH CVD RISK

In addition to the ORIGIN trial, 3 trials (details are provided in Table 2) enrolled patients at high CVD risk with and without prior clinical CHD.^{4–7} In each of these trials, the patients enrolled who were free of prior clinical CHD were considered at high risk for CHD on the basis of the presence of prior atherosclerotic disease in another vascular bed; for example, stroke or peripheral vascular disease, diabetes mellitus, or hypercholesterolemia.

Table 2. Trials of Prevention of CHD Among Patients at High CVD Risk

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|---|--|---|--|---|---|
| JELIS Yokoyama et al ⁵ 2007 | Randomized open-label, blinded end-point analysis n=18 645 4.6 y | Inclusion criteria: Japanese men (age, 40–75 y) and women (postmenopausal to 75 y), total cholesterol ≥ 6.5 mmol/L on statins, and with (20%) or without (80%) prior CVD Exclusion criteria: acute MI, revascularization, or stroke within past 6 mo; unstable angina pectoris, severe arrhythmia, heart failure, cardiomyopathy, or valvular disease | Intervention: n=9326 1.8 g/d EPA Comparator: n=9319 Usual care (open label) | Primary end point: major coronary event (combined SCD, fatal and nonfatal MI, unstable angina, coronary revascularization); 586 events; RR, 0.81 (95% CI, 0.69–0.95) | Strengths: large sample size, long duration of follow-up, reasonable number of primary events Limitations: open-label, EPA only, inclusion of soft CVD end points, few cardiac deaths (60 events), very high background fish intake in Japan |
| Risk and Prevention Risk and Prevention Study Collaborative Group ⁶ 2013 | RCT n=12 513 5 y | Inclusion criteria: Italian patients with prior CVD (but not MI), ≥ 4 CVD risk factors (age ≥ 65 y, male, hypertension, high cholesterol, current smoker, obesity, family history of CVD), diabetes mellitus and ≥ 1 CVD risk factor, or otherwise at increased risk for CHD (30% had prior atherosclerotic CVD) Exclusion criteria: prior MI | Intervention: n=6244 850 mg/d EPA+DHA Comparator: n=6269 Placebo (undefined) | Primary end point: CVD death or CVD hospitalization; 1478 events; RR, 0.98 (95% CI, 0.88–1.08) | Strengths: large sample size, long duration of follow-up, large number of primary events Limitations: because of lower-than-expected event rate, primary end point was altered during the trial to include all CVD hospitalizations; few cardiac deaths (158 events); high background fish intake at baseline (76.7% of patients consumed ≥ 1 serving/wk) |
| AREDS2 Bonds et al ⁷ 2014 | RCT n=4203 4.8 y | Inclusion criteria: US patients age 50–85 y with intermediate or advanced macular degeneration (19.2% had prior CVD) Exclusion criteria: recent CVD event in past 12 mo | Intervention: n=2147 1000 mg/d EPA+DHA (factorial design with 10 mg lutein+2 mg zeaxanthin) Comparator: n=2056 Placebo (undefined) (factorial design with 10 mg lutein+2 mg zeaxanthin) | Primary end point: CVD death, MI, stroke, unstable angina, coronary or carotid revascularization, hospitalized CHF, or resuscitated cardiac arrest; 370 events; RR, 0.95 (95% CI, 0.78–1.17) | Strengths: long duration of follow-up Limitations: ocular (rather than cardiovascular) inclusion criterion, modest sample size and numbers of primary events, inclusion of soft CVD end points, few hard CVD end points (178 events) |

AREDS2 indicates Age-Related Eye Disease Study 2; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; JELIS, Japan EPA Lipid Intervention Study; MI, myocardial infarction; RCT, randomized controlled trial; RR, relative risk; and SCD, sudden cardiac death.

Table 3. Trials of Secondary Prevention of CHD and SCD Among Patients With Prevalent CHD

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|---|--|--|---|---|--|
| DART Burr et al ³ 1989 | Randomized open-label, blinded end-point analysis n=2033 2 y | Inclusion criteria: English men age <70 y with recent MI (average 41 d prior) Exclusion criteria: diabetes mellitus, already eating fish or whole grains, planned cardiac surgery | Intervention: 2 servings/wk fatty fish or fish oil capsules (0.5 g/d) Comparator: usual care (open label) | Primary end points: CHD death or nonfatal MI; 224 events; RR, 0.84 (95% CI, 0.66–1.07) CHD death; 194 events; RR, 0.71 (95% CI, 0.54–0.93) | Strengths: moderate number of events and statistical power Limitations: open-label, intervention arm could choose either advice to consume fatty fish or to receive fish oil capsules, little modern drug or revascularization therapy that may reduce generalizability to the modern era |
| GISSI-Prevenzione GISSI-Prevenzione Investigators ² 1999 | Randomized open-label, blinded end-point analysis n=11 324 3.5 y | Inclusion criteria: Italian men with recent MI (within 3 mo), no age limits Exclusion criteria: other major condition limiting prognosis (eg, cancer, overt heart failure) | Intervention: 882 mg/d EPA+DHA Comparator: usual care (open label) | Primary end points: death, nonfatal MI, and nonfatal stroke; 1513 events; RR, 0.85 (95% CI, 0.74–0.98) CVD death, nonfatal MI, and nonfatal stroke; 1187 events; RR, 0.80 (95% CI, 0.68–0.94) | Strengths: large sample size, moderate duration of follow-up, large number of primary events, large number of cardiac deaths (520 events) and sudden deaths (286 events) Limitations: open-label, modest drug or revascularization therapy that may reduce generalizability to the modern era |
| OMEGA Rauch et al ⁸ 2008 | RCT n=3804 1 y | Inclusion criteria: German patients age ≥18 y with recent MI (within 2 wk); modified because of low event rate to add age ≥70 y, EF <40%, diabetes mellitus, or no revascularization Exclusion criteria: no major exclusions | Intervention: 840 mg/d EPA+DHA Comparator: placebo (olive oil) | Primary end point: sudden deaths or sudden cardiac arrest followed by successful resuscitation but death within 3 wk; 57 events; RR, 0.95 (95% CI, 0.56–1.60) | Strengths: moderate sample size Limitations: short duration of follow-up, very few primary events and low statistical power, high background intake of fish (<5% with no fish consumption) that increased during the trial |
| Alpha Omega Kromhout et al ⁹ 2010 | RCT n=4837 3.4 y | Inclusion criteria: Dutch patients age 60–80 y, history of MI (up to 10 y prior) Exclusion criteria: low intake of margarine (delivery vehicle), cancer, unintended weight loss | Intervention: 376 mg/d EPA+DHA 1.9 g/d ALA Comparator: placebo (margarine) | Primary end point: major cardiovascular events (fatal and nonfatal CVD events plus coronary revascularization); 675 events; RR, 1.01 (95% CI, 0.87–1.17); RR, 0.95 (95% CI, 0.68–1.32) | Strengths: moderate sample size, moderate duration of follow-up, large number of primary events Limitations: low dose of EPA+DHA, modest number of cardiac deaths (138 events), moderate to high background intake of fish (median, 1 serving/wk) |

(Continued)

Table 3. Continued

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|---|---|---|---|---|---|
| SU.FOL.OM3 Galan et al ¹⁰ 2010 | RCT n=2501 4.7 y | Inclusion criteria: French patients age 45–80 y with recent coronary or cerebral ischemic event (median, 101 d); modified to add recent acute coronary syndrome Exclusion criteria: receiving methotrexate, chronic renal disease | Intervention: 600 mg/d EPA+DHA Comparator: placebo (undefined) | Primary end point: major cardiovascular events (nonfatal MI, stroke, or CVD death); 157 events; RR, 1.08 (95% CI, 0.79–1.47) | Strengths: moderate sample size, long duration of follow-up Limitations: modest number of primary events and statistical power, few cardiac deaths (40 events) |

ALA indicates α -linolenic acid; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DART, Diet and Reinfarction Trial; DHA, docosahexaenoic acid; EF, ejection fraction; EPA, eicosapentaenoic acid; GISSI-Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; MI, myocardial infarction; OMEGA, Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; RCT, randomized controlled trial; RR, relative risk; SCD, sudden cardiac death; and SU.FOL.OM3, Supplementation With Folate, Vitamin B₆ and B₁₂ and/or Omega-3 Fatty Acids.

Two of the 3 trials showed no benefit from omega-3 PUFA supplementation on clinical CHD.^{6,7}

The JELIS trial (Japan EPA Lipid Intervention Study) reported results by prior CVD status.⁵ Although 80% of the patients had no prior clinical CVD, all of the patients had a total cholesterol >6.5 mmol/L (>250 mg/dL). Patients were randomly assigned to either statin alone or statin with 1800 mg/d EPA. The primary end point was a composite outcome comprising major coronary events, including sudden cardiac death (SCD), fatal and nonfatal myocardial infarction (MI), and other nonfatal events (unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting). The composite outcome was reduced among patients treated with the omega-3 PUFA supplement: The relative risk (RR) reduction was 19% ($P=0.01$) overall, 19% ($P=0.048$) in those with prior CVD, and 18% ($P=0.132$) in those without prior CVD (P for interaction=0.95). The risk reduction occurred primarily from a reduction in unstable angina, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty. There was little evidence of risk reduction in the hard end points of nonfatal MI and CHD death.

Overall, there was a lack of consensus on whether current evidence from RCTs suggested no benefit of omega-3 PUFA supplements among patients at high CVD risk, in part because of differences in the weight given to the results of the JELIS trial. Although the majority of coauthors concluded that treatment is not indicated (*Class III: No Benefit Recommendation*), a minority of coauthors concluded that treatment of these patients is reasonable (*Class IIb Recommendation*).

SECONDARY PREVENTION OF CHD AND SCD AMONG PATIENTS WITH PREVALENT CHD

Five large RCTs, the details of which are provided in Table 3, have evaluated the effects of omega-3 PUFA supplementation on clinical cardiovascular events in patients with prior clinical CHD.^{2,3,8–10} The average dose of omega-3 PUFA was \approx 1000 mg/d, and the average mean duration of the trials was 2 years (range, 1.0–6.2 years). Primary end points varied across these trials. To increase statistical power, several trials evaluated the effects of supplementation on a primary end point that combined major adverse cardiovascular events such as the sum of nonfatal MI, fatal CHD, stroke, and CVD death, sometimes also including coronary revascularization and angina.

The 2 trials in patients with prior CHD, cited in the 2002 statement, suggested a benefit of omega-3 PUFA supplementation.^{2,3} One trial demonstrated a reduction in hard CVD end points (CVD death, nonfatal MI, and nonfatal stroke: RR, 0.80; 95% confidence interval [CI], 0.68–0.94) among patients with recent MI (within 3 months), attributable mostly to a reduction in SCD.² A second trial found that providing an omega-3 PUFA supplement or fish advice significantly reduced CHD death but not total CHD among patients with recent MI (mean, \approx 1.5 months). Of note, only one third of the patients in the second RCT took an omega-3 PUFA supplement.³ It was included in the 2002 report, in part because this report focused both on dietary intake and omega-3 PUFA supplementation.

Since the 2002 report, 3 additional secondary prevention trials have examined the impact of omega-3

Table 4. Trials of Primary Prevention of Stroke

| Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|-----------------------------------|---|--|---|--|---|
| Rizos et al ¹¹ 2012 | Meta-analysis of randomized trials (random effects) n=68 680 20 trials (18 supplement; 2 diet) Median, 2 y (range, 1–6.2 y) | Inclusion criteria: RCT with supplement or diet vs control group; patients from primary, secondary, or mixed ASCVD prevention trials, including ICD trials Exclusion criteria: studies with treatment duration <1 y; studies without major ASCVD end points | Intervention: n=31 674 Median, 1000 mg/d EPA+DHA (IQR, 530–1800 mg/d; mean, 1510 mg/d) Comparator: n=31 605 Placebo, diet, or usual care | Primary end point: All-cause mortality; 7044 events; RR, 0.96 (95% CI, 0.91–1.02) Cardiac death; 3993 events; RR, 0.91 (95% CI, 0.85–0.98) Sudden death; 1150 events; RR, 0.87 (95% CI, 0.75–1.01) Myocardial infarction; 1837 events; RR, 0.89 (95% CI, 0.76–1.04) Stroke; 1490 events; RR, 1.05 (95% CI, 0.93–1.18) | Strengths: large sample size, large number of events, individual ASCVD events assessed separately Limitations: controversial level of statistical significance ($P=0.0063$) used to adjust for multiple comparisons; not an individual-patient meta-analysis; inclusion of heterogeneous study designs |

ASCVD indicates atherosclerotic cardiovascular disease; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; RCT, randomized controlled trial; and RR, relative risk.

PUFA supplementation on clinical cardiovascular events. Each found little evidence of an effect of fish oil on its primary clinical CVD end point. These trials included a short-term (1 year) trial that focused on the prevention of SCD (n=57 events) among patients with recent MI,⁸ a trial evaluating major adverse cardiovascular events in patients with a distant history of MI (median interval, 3.7 years),⁹ and a trial in patients with a recent history of MI, unstable angina, or ischemic stroke (within 1 year).¹⁰ Another RCT, not included in our evidence table, reported that advice to increase fish intake or omega-3 PUFA supplementation in patients with clinical angina increased the risk of SCD³⁰; however, this was a study of primarily dietary advice, not supplementation.

A meta-analysis published in 2012 examined the effects of omega-3 PUFA supplementation and dietary intake in 20 RCTs that enrolled patients at high CVD risk or prevalent CHD and patients with an implantable cardioverter-defibrillator (total n=68 680). That meta-analysis demonstrated a reduction in CHD death (RR, 0.91; 95% CI, 0.85–0.98), possibly as the result of a lower risk of SCD (RR, 0.87; 95% CI, 0.75–1.01).¹¹ Seven of the trials reported the findings for SCD as a separate outcome. Of note, the magnitude of the reduction in total mortality, shown to be attributable mostly to a reduction CHD death, was greater in the studies published before 2002 than in the more recent studies.

Taken together, the cumulative findings from RCTs suggest that omega-3 PUFA supplements may reduce CHD death, possibly through a reduction in ischemia-induced SCD, among patients with prior CHD, but the treatment does not reduce the incidence of recurrent nonfatal MI. Additionally, given that the benefit likely

outweighs any risk of treatment, the majority of coauthors concluded that treatment with omega-3 PUFA supplements is reasonable for the secondary prevention of CHD death (*Class IIa Recommendation*); a minority of coauthors preferred a slightly lower strength of recommendation for treatment of patients with this indication (*Class IIb Recommendation*).

PRIMARY PREVENTION OF STROKE

No reports from RCTs of omega-3 PUFA supplements have targeted stroke prevention; that is, stroke was not the primary outcome in any RCT. However, stroke was included as part of a composite clinical CVD outcome in 9 of 20 RCTs included in a recent meta-analysis¹¹ (Table 4). In this meta-analysis, there was little evidence of a reduction in stroke events in those treated with omega-3 PUFA supplements (RR, 1.05; 95% CI, 0.93–1.18; $P=0.47$). The findings were similar when examined by whether the study sample had prior clinical CHD, the dose of omega-3 PUFA, and study blinding. The meta-analysis did not examine the effects of omega-3 PUFAs on hemorrhagic and ischemic stroke separately. Of note, other meta-analyses reported similar findings.^{31–33}

In the 2 studies that examined stroke subtype (ischemic and hemorrhagic) separately, there was little difference in the effects of omega-3 PUFA supplements on the risk of each stroke subtype.^{5,12} Since the meta-analysis in 2012, 2 additional RCTs have reported the effect of omega-3 PUFA supplementation on stroke outcomes.^{6,7} In both of these studies, there was little evidence that omega-3 PUFA supplementation reduced the risk of stroke, both fatal and nonfatal, although there

Table 5. Trials of Secondary Prevention of Outcomes in Patients With Heart Failure

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|---|---|---|--------------------------------------|---|--|
| GISSI-HF Tavazzi et al ¹² 2008 | RCT n=6875 3.9 y | Inclusion criteria: patients with HF | Intervention: 840 mg/d EPA+DHA | Primary end points: Total mortality; 1969 events; RR, 0.91 (95% CI, 0.83–0.99) Total mortality or hospitalization for CVD; 4034 events; RR, 0.92 (95% CI, 0.85– 0.99) | Strengths: large sample size, large numbers of events and statistical power, long duration of follow-up, patients on intensive modern medical therapy Limitations: fewer patients (9%) with HF with preserved ejection fraction; lack of information on background omega-3 PUFA intake |
| | | Exclusion criteria: acute coronary syndrome or revascularization within 1 mo; planned cardiac surgery within 3 mo; significant liver disease | Comparator: placebo (olive oil) | | |

CI indicates confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure; HF, heart failure; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; and RR, relative risk.

was a small number of events. Of note, there also is little evidence to suggest that omega-3 PUFA supplementation increases the risk of stroke.

Overall, there is no proven benefit of omega-3 PUFA supplementation as a means to reduce the risk of stroke among patients without a history of stroke (*Class III: No Benefit Recommendation*).

SECONDARY PREVENTION OF STROKE

No RCTs have been designed to examine the effects of omega-3 PUFA supplements on cardiovascular events, either stroke or other CVDs, among patients with a prior stroke. However, in a post hoc analysis of patients with a history of stroke from JELIS, recurrent stroke occurred in 33 of the 485 patients (6.8%) randomized to EPA versus 48 of 457 patients (10.5%) in the control group, for a risk reduction of recurrent stroke of 20% (RR, 0.80; 95% CI, 0.64–0.997; number needed to treat, 27).³⁴ Given the post hoc analysis, small number of events, borderline statistical significance unadjusted for multiple testing, and other limitations of the study mentioned elsewhere in this advisory, the findings from JELIS should be considered hypothesis generating.

Overall, there is no evidence of benefit of omega-3 PUFA supplementation as a means to reduce the risk of recurrent stroke or other CVDs among patients with a prior stroke (*No Recommendation*).

PRIMARY PREVENTION OF HEART FAILURE

To date, no published RCTs have assessed the effect of omega-3 PUFA supplements on the primary prevention of heart failure. On this basis, no recommendation for treatment with omega-3 PUFA supplements can be made for the primary prevention of heart failure.

SECONDARY PREVENTION OF OUTCOMES IN PATIENTS WITH HEART FAILURE

In a large RCT (details provided in Table 5) among patients with chronic heart failure (New York Heart Association class II–IV), the effects of omega-3 PUFA supplements on the risk of morbidity or mortality were examined. Among patients with clinically diagnosed heart failure (of any type, severity, and cause), omega-3 PUFA supplementation reduced the risk of total mortality (death resulting from any cause) by 9% (RR, 0.91; 95% CI, 0.833–0.998; $P=0.041$) and the risk of cardiovascular-related hospitalizations or death by 8% (RR, 0.92; 95% CI, 0.849–0.999; $P=0.009$) after prespecified adjustment for hospitalization for heart failure during the preceding year, previous pacemaker, and aortic stenosis.¹² Of note, 91% of the patients enrolled in the RCT had heart failure with reduced ejection fraction (left ventricular ejection fraction <40%), limiting the generalizability of the findings in this population. These findings suggest that omega-3 PUFA supplementation may reduce heart failure–related hospitalizations and death in patients with heart failure with reduced ejection fraction. However, heart failure is a heterogeneous disorder, particularly among older adults and women, and further trials are needed to determine whether the benefits of omega-3 PUFA supplementation on prognosis vary according to the type, severity, and cause of heart failure.

Although based on a single, large RCT, treatment with omega-3 PUFA supplements is reasonable among patients with heart failure with reduced ejection fraction (*Class IIa Recommendation*). RCTs are needed among patients with heart failure and preserved ejection fraction.

Table 6. Trials of Secondary Prevention of AF in Patients With Prior AF

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|--|--|--|--|--|---|
| Kowey et al ¹³ 2010 | RCT n=663 6 mo | Inclusion criteria: age ≥ 18 y, symptomatic paroxysmal or persistent AF, in normal sinus rhythm at baseline | Intervention: 6.7 g/d EPA+DHA for 7 d, then 3.4 g/d for the duration of the study | Primary end point: symptomatic recurrence of AF (including flutter) | Strengths: double blinding, tested higher dose of omega-3 PUFA relative to prior smaller trials, low dropout rate Limitations: lack of information on dietary (background) omega-3 PUFA intake, lower-than-expected AF recurrence rate, may have underestimated AF recurrence because of ascertainment method (transtelephonic monitoring) |
| | | Exclusion criteria: permanent AF, secondary AF (eg, caused by hypothyroidism), current use of antiarrhythmic therapy, use of amiodarone within past 6 mo, prior ablation therapy for AF, specific structural cardiac disorders | Comparator: placebo (corn oil) | Combined AF recurrence; 314 events; RR, 1.22 (95% CI, 0.98–1.52) | |
| | | | | In participants with paroxysmal AF: 264 events; RR, 1.15 (95% CI, 0.90–1.46) | |
| | | | | In participants with persistent AF: 50 events; RR, 1.64 (95% CI, 0.92–2.92) | |
| FORWARD Macchia et al ¹⁴ 2013 | RCT n=586 12 mo | Inclusion criteria: age ≥ 21 y, previous symptomatic AF that recovered to normal sinus rhythm | Intervention: 0.85 g/d EPA+DHA | Primary end point: time to first recurrence of an AF episode (symptomatic or asymptomatic); 125 events; RR, 1.28 (95% CI, 0.90–1.83) | Strengths: double blinding, low dropout rate Limitations: early stoppage of trial reduced statistical power, did not assess dietary (background) omega-3 PUFA intake |
| | | Exclusion criteria: contraindications for use of omega-3 PUFA; heart failure in NYHA class IV; acute coronary syndromes, coronary artery bypass surgery, or valve replacement within the past 3 mo; clinically significant valvular disease; known diagnosis of Wolff-Parkinson-White; planned or recent implantation of pacemaker or implantable cardioverter-defibrillator; planned or recent ablative treatment for AF; any arrhythmia associated with an acute reversible condition; advanced chronic lung disease; and pregnancy or lactation | Comparator: placebo (olive oil) | | |
| Mariani et al ¹⁵ 2013 | Meta-analysis n=1999 (894 events) 0.5–1 y | Inclusion criteria: RCTs evaluating any dose and formulation of omega-3 PUFAs, administered as pharmacological preparations. Studies could be double-blind, placebo-controlled, or unexposed controlled trials. Patients could be randomized with AF or in sinus rhythm (ie, before or after reversion). | Intervention: 0.6–3.4 g/d EPA+DHA | Primary end point: AF recurrence; RR, 0.95 (95% CI, 0.79–1.13) | Strengths: systematic review and quantitative synthesis of data including large number of participants and events, careful evaluation of potential sources of heterogeneity Limitations: potential bias in the included trials (eg, several of the trials had open-label designs) |
| | | Exclusion criteria: nonrandomized studies, those that did not report data on AF occurrence during follow-up, those with no follow-up (ie, evaluating the electrophysiological effects of 1 or few doses of omega-3 PUFAs), non-English studies | Comparator: placebo | | |

AF indicates atrial fibrillation; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FORWARD, Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation; NYHA, New York Heart Association; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; and RR, relative risk.

PRIMARY PREVENTION OF ATRIAL FIBRILLATION

There are no data from large randomized, placebo-controlled RCTs of the effect of omega-3 PUFA supplementation on the primary prevention of atrial fibrillation (AF). On this basis, no recommendation for treatment with omega-3 PUFA supplements can be made for the primary prevention of AF. This clinical question should be the focus of future RCTs.³⁵

SECONDARY PREVENTION OF AF IN PATIENTS WITH PRIOR AF

Two large RCTs, details provided in Table 6, have examined the effect of omega-3 PUFA supplementation on the risk of recurrent AF.^{13,14} In a large RCT, supplementation with omega-3 PUFAs did not reduce recurrent AF in patients overall (RR, 1.22; 95% CI, 0.98–1.52; $P=0.08$) or among subgroups of patients with paroxysmal or persistent AF examined separately.¹³ Another large RCT also found little evidence of benefit of omega-3 PUFA supplementation on recurrent AF (RR, 1.28; 95% CI, 0.90–1.83; $P=0.17$).¹⁴ In a meta-analysis that included these 2 larger and 6 smaller RCTs, the risk reduction estimate for the effect of omega-3 PUFA supplementation on recurrent AF was 0.95 (95% CI, 0.79–1.13).¹⁵ Two additional RCTs have been published since the meta-analysis, and both reported little evidence of benefit of omega-3 PUFA supplementation on recurrent AF.^{36,37} The consistent null findings in RCTs is notable given the diverse study design features, including patient characteristics, duration of treatment, and dose of omega-3 PUFA.

Overall, high-quality evidence from multiple RCTs does not support omega-3 PUFA supplementation to prevent recurrent AF (*Class III: No Benefit Recommendation*).

AF AFTER CARDIAC SURGERY

In a large, placebo-controlled RCT of short-term omega-3 PUFA supplementation for the prevention of postoperative AF after cardiac surgery, omega-3 PUFA did not reduce the risk of postoperative AF (RR, 0.96; 95% CI, 0.77–1.20; $P=0.74$; Table 7).¹⁶ Five additional placebo-controlled RCTs also have reported null findings, although these other trials were limited by low statistical power (range of postoperative AF events in these RCTs, 24–91).^{38–42} A meta-analysis including all 6 placebo-controlled RCTs found an RR of 0.92 (95% CI, 0.78–1.10).¹⁷

Overall, findings from placebo-controlled RCTs, including 1 large, adequately powered RCT, do not demonstrate a benefit of omega-3 PUFA supplementation as a means to prevent postoperative AF in patients undergoing cardiac surgery (*Class III: No Benefit Recommendation*).

MECHANISMS

Although not the focus on this advisory, various mechanisms could plausibly explain clinical outcome benefits derived from omega-3 PUFA supplementation. We note that a recent review by 2 of the coauthors of this advisory (D.M. and J.W.) examined available evidence, including mechanistic studies, related to the effects of omega-3 PUFAs (including dietary omega-3 PUFAs) on molecular pathways and risk factors.⁴³ The proposed mechanism for the effect on CHD death is related to the physiological effects of omega-3 PUFAs in the setting of ischemia-induced ventricular fibrillation, which includes stabilization of ischemic-induced myocyte membrane resting depolarization, rather than major effects on atherosclerotic progression, plaque stability, plaque rupture, or thrombosis.⁴³ Consistent with this hypothesis, 2 of 3 trials showing benefit were among patients with recent MI, few of whom underwent revascularization procedures,^{3,44} in which ischemia-induced ventricular fibrillation is a major cause of death. The largest trial found that benefits were attributable to reduced SCD rather than other types of cardiac death or nonfatal MI.⁴⁴ Although omega-3 supplementation affects multiple risk factors and pathways that might account for the observed benefit of supplementation in patients with heart failure and impaired left ventricular function, whether there is a predominant mechanism that accounts for this effect requires further investigation. Of note, the doses of omega-3 PUFA supplements (≈ 1000 mg) used in the studies cited in this advisory, except for the dose used in the JELIS study (1800 mg), are generally too low to meaningfully lower triglyceride levels.^{45–48}

CLINICAL IMPLICATIONS

For the major clinical indications of omega-3 PUFA supplementation noted above, we summarize the strength of the recommendation and the level of evidence for omega-3 supplementation on the basis of RCTs of clinical end points in Table 8. The criteria used to assign the strength of the recommendation and the level of evidence are included in the [Data Supplement Table](#). We concluded that available evidence does not support the use of omega-3 PUFA supplements in the general population who are not at high CVD risk, including those with diabetes mellitus and prediabetes. Given the available evidence, there was a lack of consensus about the benefits of treatment among those at high CVD risk, as noted above. On the basis of the cumulative evidence from RCTs with clinical end points, we reassessed the recommendations made in the 2002 scientific statement and continue to suggest that, in consultation with a physician, omega-3 PUFA supplementation is reasonable for secondary prevention of CHD in patients with a

Table 7. Trials of AF After Cardiac Surgery

| Study, Author, Year | Trial Design, No. of Subjects, Duration | Patient Population | Intervention and Control | End Point Results (Primary End Point) | Strengths and Limitations |
|--|--|--|--|--|--|
| OPERA Mozaffarian et al ¹⁶ 2012 | RCT n=1516 10 d | Inclusion criteria: patients scheduled for cardiac surgery in 28 centers in the United States, Italy, and Argentina in sinus rhythm at enrollment | Intervention: 8.4 g/d EPA+DHA for 3–5 d (or 6.7 g over 2 d) preoperatively and 1.7 g/d until postoperative day 10 | Primary end point: occurrence of PoAF of at least 30-s duration and documented by rhythm strip or ECG; 460 events; RR, 0.96 (95% CI, 0.77–1.20) | Strengths: double blind, large number of events, assessed heterogeneity by background fish intake and circulating omega-3 PUFA biomarker level, low dropout rate |
| | | Exclusion criteria: regular use of fish oil, known allergy or intolerance to fish oil or olive oil, being currently pregnant, existing or planned cardiac transplantation or use of ventricular assist device, or being unable or unwilling to provide informed consent | Comparator: placebo (olive oil) | | |
| Mozaffarian et al ¹⁷ 2013 | Meta-analysis n=2687 In hospital to a maximum of 2 wk (859 events) | Inclusion criteria: randomized trials of oral or intravenous fish oil administration that evaluated PoAF after cardiac surgery | Intervention: 1.7–4.5 g/d EPA+DHA | Primary end point: PoAF, based on 6 placebo-controlled RCTs that found an RR of 0.92 (95% CI, 0.78–1.10) | Strengths: systematic review and quantitative synthesis of data including large number of participants and events and careful evaluation of potential sources of heterogeneity |
| | | Exclusion criteria: trials with additional concomitant interventions, observational studies, and duplicate publications | Comparator: placebo | | |

AF indicates atrial fibrillation; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; OPERA, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation; PoAF, postoperative atrial fibrillation; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; and RR, relative risk.

recent CHD event such as a recent MI. We also added a new recommendation for patients with heart failure with reduced left ventricular function, in whom treatment with omega-3 PUFA supplementation might also be considered. In contrast, available evidence either is lacking or does not support the use of omega-3 PUFA supplements as a therapy to prevent incident or recurrent stroke and AF. Finally, it is noteworthy that within the context of the low doses used in the large RCTs of clinical cardiovascular events, there was little evidence of major adverse effects such as stroke or bleeding associated with omega-3 PUFA supplementation (data not shown).⁴⁹

DISCUSSION

In this advisory, we focus on evidence from RCTs related to the use of omega-3 PUFA supplements to reduce the risk of clinical CVD. Recent evidence has raised questions about the recommendations included in the AHA scientific statement of 2002 related to secondary prevention of CHD and SCD.^{8–10} Furthermore, evidence related to outcomes in patients with heart failure and AF was unavailable at that time. Below, we briefly summarize some of the issues in the interpretation and application of this evidence.

CHD represents multiple physiological processes, including chronic progression of stable atherosclerotic

Table 8. Omega-3 PUFA Supplementation for Prevention of Cardiovascular Events: Recommendations for Clinical Use by Indication and Population

| Indication (Population) | Recommendation | Class (Strength) of Recommendation | Level (Quality) of Evidence | Comments |
|--|----------------------------|------------------------------------|-----------------------------|--|
| Primary prevention of CHD (general population [without CHD]) | No recommendation | ... | ... | One RCT in participants from the general population (VITAL) is ongoing. |
| Prevention of CVD mortality in diabetes mellitus/prediabetes | Treatment is not indicated | III* | B-R | Based on 1 large RCT (ORIGIN) in patients with diabetes mellitus or prediabetes. One RCT in diabetic patients (ASCEND) is ongoing. |
| Prevention of CHD among patients at high CVD risk (mixed populations with and without CHD) | Treatment is not indicated | III*† | B-R | Of 4 large RCTs, 3 (ORIGIN, R & P, AREDS2) did not show benefit (although they were individually underpowered to show differences in cardiac death), and 1 open-label RCT (JELIS) showed a benefit in total CVD events resulting from reduction in nonhard cardiovascular end points (angina, revascularizations). |
| Secondary prevention of CHD and SCD among patients with prevalent CHD | Treatment is reasonable | IIa† | A | Of 2 large RCTs, 1 (GISSI-Prevenzione) showed benefit and 1 (Alpha Omega) did not. Of 3 small RCTs, 1 (DART) showed benefit and 2 (OMEGA, SU.FOL.OM3) did not. Meta-analysis (Rizos et al ¹¹) yields a significant risk ratio for cardiac death of 0.9. |
| Primary prevention of stroke (high CVD risk [with or without prevalent CHD]) | Treatment is not indicated | III* | B-R | Based on meta-analysis of RCTs with stroke as a secondary outcome (Rizos et al ¹¹). No RCTs have been performed with stroke as primary outcome. |
| Secondary prevention of stroke | No recommendation | ... | ... | No RCTs performed. |
| Primary prevention of heart failure | No recommendation | ... | ... | No RCTs performed. |
| Secondary prevention of outcomes in patients with heart failure | Treatment is reasonable | IIa | B-R | Based on 1 large RCT (GISSI-HF) in patients receiving current state-of-the-art heart failure care. |
| Primary prevention of AF | No recommendation | ... | ... | No RCTs performed. |
| Secondary prevention of AF in patients with prior AF | Treatment is not indicated | III* | A | Based on several RCTs. |
| AF after cardiac surgery | Treatment is not indicated | III* | A | Based on 1 large RCT (OPERA) and a meta-analysis of all existing RCTs. |

AF indicates atrial fibrillation; AREDS2, Age-Related Eye Disease Study 2; ASCEND, A Study of Cardiovascular Events in Diabetes; CHD, coronary heart disease; CVD, cardiovascular disease; DART, Diet and Reinfarction Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; GISSI-Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; JELIS, Japan EPA Lipid Intervention Study; OMEGA, Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; OPERA, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation; ORIGIN, Outcome Reduction With Initial Glargine Intervention Trial; PUFA, polyunsaturated fatty acid; R & P, Risk and Prevention Study; RCT, randomized controlled trial; SCD, sudden cardiac death; SU.FOL.OM3, Supplementation With Folate, Vitamin B₆ and B₁₂ and/or Omega-3 Fatty Acids; and VITAL, Vitamin D and Omega-3 Trial.

*No proven benefit.

†The panel did not reach consensus on this indication, with some preferring a Class IIb Recommendation.

ic plaque (occurring over years, resulting in angina), plaque instability (occurring over weeks to months), acute plaque rupture (occurring over seconds, resulting in acute coronary syndrome), thrombosis and coagula-

tion (occurring over minutes to hours, resulting in acute MI), and ischemia-induced cardiac arrhythmia (occurring over seconds, resulting in CHD death). Similarly, SCD can result from different underlying processes, includ-

ing ischemic-induced ventricular fibrillation, other arrhythmias caused by acute ischemia, and a range of cardiac arrhythmias arising from underlying structural heart disease rather than acute ischemia. Although some determinants of the different pathways leading to these conditions are shared (eg, high blood pressure increases chronic progression of atherosclerosis, acute plaque rupture, and SCD), each of these risk pathways also has distinct etiologic and physiological determinants. Just as omega-3 PUFAs have varying dose and time responses on pathways of cardiovascular risk, the effects on clinical cardiovascular events also appear to vary, depending on the specific end point and its pathophysiological determinants.

The reduction in CHD mortality, presumably by reducing SCD, is a likely benefit of omega-3 PUFA therapy. However, the magnitude of this effect has become more uncertain over time. The cumulative meta-analysis of 20 studies included in our review calculated an $\approx 10\%$ reduction in CHD death and SCD but also revealed a striking variation in effect size by study date, with earlier studies showing large reductions and later studies showing no benefit.¹¹ Several explanations could account for these discrepant results.

First, observational evidence supports a nonlinear effect of omega-3 PUFA on CHD death.⁵⁰ With increasing public focus on omega-3 consumption,^{51,52} the background dietary consumption of fish in recent trials was generally higher than that observed in earlier studies. (High dietary consumption was particularly evident in JELIS, which was conducted in Japan.) Consequently, many subjects in recent trials may have already been consuming AHA-recommended amounts of omega-3 PUFAs (eg, at least 1–2 weekly servings of fatty fish) so that additional modest omega-3 PUFA supplementation (eg, 1 g/d) would produce little measurable benefit on the risk of CHD death.

Second, it is possible that omega-3 PUFA supplementation has little benefit in the presence of maximal medical treatment of CHD (eg, statin therapy, β -blockers, angiotensin-converting enzyme inhibitors, aspirin, and revascularization). As noted above, fewer patients in the earlier trials received statin therapy or revascularization after MI; these therapies were much more common in recent trials. Potential interaction by background medications was examined in the primary results reports of several trials. One trial⁴ identified effect modification by statin or β -blocker use, although statistical power in these subgroup analyses was limited.^{7,53}

Third, post hoc power calculations indicate that most recent trials in post-MI patients were substantially underpowered to detect a clinically meaningful effect on CHD death, with even less power to detect an effect of omega-3 PUFA supplementation on the risk of SCD.⁴³ Several of these trials had to alter and expand their primary end point during follow-up because

of lower-than-anticipated event rates. Indeed, the risk of recurrent events among contemporary patients with CHD events is much lower than the corresponding risk of post-MI patients from 15 to 20 years ago. Thus, the role of omega-3 PUFA supplements in the patient with CHD who receives optimal guideline-based therapy in 2017 is not entirely settled.

On the other hand, we note that even if the benefit based on the cumulative evidence is quantitatively modest, a potential reduction in CHD death of 10% would justify the use of a relatively safe therapy such as omega-3 PUFA. Although benefits also could be greater in certain subsets of patients with CHD such as those with a low ejection fraction or low circulating levels of omega-3 PUFAs from marine sources, this will need to be demonstrated in future RCTs. Several trials of omega-3 PUFA supplementation that may address some of these issues are underway.

Other efforts to synthesize the available evidence on the effects of omega-3 PUFA supplements on clinical CVD may have come to different conclusions. These differences likely reflect differences in the purpose and approach to synthesizing the available evidence. We have taken a clinical approach, focusing on RCTs with clinical cardiovascular outcomes and the most common indications for omega-3 PUFA supplements related to clinical cardiovascular events. We have not conflated the question of the role of omega-3 PUFA supplementation with the effects of omega-3 PUFA intake from seafood on clinical CVD, in part, because supplementation and dietary intake of omega-3 PUFAs differ in many ways. Furthermore, the patient populations, restriction to RCTs with clinical cardiovascular end points, and clinical recommendations addressed in this advisory on omega-3 PUFA supplements differ from the study populations and observational study designs available to assess the impact of omega-3 PUFA intake from seafood on CVD. In an effort to reduce the confusion among clinicians, patients, and the public, we have restricted this advisory to clinical questions related to omega-3 PUFA supplements.

Although we did not conduct a formal systematic evidence review of the health effects of omega-3 PUFA supplements, we agreed on the parameters of the scientific advisory before beginning the review and sought to be transparent. Whereas clinical scientists frequently differ in how best to handle heterogeneity in study design and findings, especially when findings appear to be inconsistent, we recognize that clinicians and patients need to make decisions in the context of uncertainty. Because RCTs of major disease end points, when available, should trump studies of intermediate end points and mechanistic studies when clinical decisions are being made, we restricted our focus to RCTs. As noted previously, except for JELIS, all of the RCTs used low doses of omega-3 PUFA supplements. Higher doses of omega-3 PUFA supplements are being studied in ongoing RCTs

(REDUCE-IT [Reduction of Cardiovascular Events With EPA–Intervention Trial] and STRENGTH [Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia]). Additionally, most of the RCTs were of relatively short-term duration of omega-3 PUFA intake. We acknowledge that a lack of evidence of a benefit differs from evidence of a lack of effect. We look forward to future reports that address the gaps in evidence that we documented. As findings from ongoing RCTs are reported, we will assess the need to further update this advisory. Importantly, we note that the risk of major adverse effects such as bleeding and stroke associated with omega-3 PUFA supplementation was low in the RCTs of clinical cardiovascular outcomes (data not shown). In this context of uncertain benefit but no apparent major risk, patient preferences should also influence clinical decisions.

CONCLUSIONS

Although recent RCT evidence has raised questions about the benefits of omega-3 supplementation to prevent clinical CVD events, the recommendation for patients with prevalent CHD such as a recent MI remains essentially unchanged: Treatment with omega-3 PUFA supplements is reasonable for these patients. Even a potential modest reduction in CHD mortality (10%) in this clinical population would justify treatment with a relatively safe therapy. We now recommend treatment for patients with prevalent heart failure without preserved left ventricular function to reduce mortality and hospitalizations (9%) on the basis of a single, large RCT. Although we do not recommend treatment for patients with diabetes mellitus and prediabetes to prevent CHD, there was a lack of consensus on the recommendation for patients at high CVD risk. On the other hand, we do not recommend treatment to prevent incident stroke among patients at high CVD risk and recurrent AF. Because there are no reported RCTs related to the primary prevention of CHD, heart failure, and AF, we were not able to make recommendations for these indications. RCTs in progress with clinical CVD end points may inform recommendations related to these potential indications for omega-3 PUFA supplementation.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association

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Supplemental Table 1: The criteria used to assign the Class of Recommendation (COR) and the Level of Evidence (LOE)

| | | SIZE OF TREATMENT EFFECT | | | |
|---|---|--|---|--|---|
| | | CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered | CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment | CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED | CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i> |
| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses | <ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses |
| | LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies | <ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies |
| | LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care | <ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care | <ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care | <ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care | <ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should is recommended is indicated is useful/effective/beneficial | is reasonable can be useful/effective/beneficial is probably recommended or indicated | may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective | COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B | | | |

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.