Omega-3 fatty acids for cardiovascular disease prevention: A practice tool for pharmacists

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Case vignette

Mr. Patel, a 65-year-old man of South Asian descent, is a patient of yours. He has a history of hypertension and type 2 diabetes mellitus. His current medications include acetylsalicylic acid 81 mg daily, ramipril 5 mg daily, amlodipine 5 mg daily, metformin 1000 mg twice daily and atorvastatin 80 mg daily, all of which have been stable for the past 3 months. He provides a copy of his blood work from the previous day, which shows a serum total cholesterol of 4.2 mmol/L, high-density lipoprotein cholesterol (HDL-C) of 1 mmol/L, low-density lipoprotein cholesterol (LDL-C) of 1.8 mmol/L and triglycerides of 2.1 mmol/L. He has an over-the-counter omega-3 fatty acid supplement (1 g per capsule). He read that omega-3 fatty acids are "good for the heart" and inquires whether he should start taking it to reduce his risk of a myocardial infarction (MI).

Introduction

There are 3 primary types of omega-3 (or n-3) polyunsaturated fatty acids: alpha-linolenic acid, which is derived from plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are derived from marine oils (chicken eggs are occasionally fortified with omega-3 fatty acids as well).[1] Omega-6 polyunsaturated fatty acids (e.g., arachidonic acid, linoleic acid) are available through dietary sources, such as vegetable oils, nuts, poultry and eggs.[1] Omega-9 fatty acids, such as oleic acid and erucic acid, are monosaturated fatty acids abundant in vegetable oils and animal fats. Omega-3 and omega-6 fatty acids are essential fatty acids, as they must be obtained from dietary sources, whereas the body can manufacture omega-9 fatty acids. Numerous commercially available fatty acid supplements exist with different combinations of fatty acids (e.g., omega-3, omega-3-6-9), sources (e.g., salmon, krill, squid), formulations, doses and flavours. Most over-the-counter omega-3 fatty acid preparations contain a mixture of both EPA and DHA.

Omega-3 fatty acids have a variety of purported health benefits, including the prevention of cardiovascular disease (CVD).[2,3] The proposed beneficial mechanisms of omega-3 fatty acids include anti-inflammatory and antithrombotic effects, plaque and membrane stabilization and a reduction in serum lipids.[1] High-dose omega-3 fatty acids (2-4 g daily) have also been shown to reduce triglycerides by 25% to 40% and are recommended in the treatment of hypertriglyceridemia.[1,4] Known adverse effects of omega-3 fatty acids are primarily gastrointestinal (e.g., nausea, diarrhea, fishy eructation) and hematologic (e.g., bleeding).[4] As omega-3 fatty acid supplements are often derived from marine sources, caution should be exercised in patients with known fish or shellfish hypersensitivity.

Recently, a number of well-designed randomized controlled trials (RCTs) have been published that investigated various omega-3 fatty acid formulations in the prevention of CVD.[5-9] Pharmacists play a crucial role in educating patients about omega-3 fatty acid supplements due to the variety and availability of over-the-counter products. Thus, it is imperative that pharmacists are familiar with the current data. This practice tool is designed to provide pharmacists with a practical summary of recently published RCT data to support their patients in making evidence-informed decisions about omega-3 fatty acids.

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TABLE 1 Summary of included trials

Study name (year)	Patient population	Intervention	Follow-up, y	Results	Safety
ASCEND[5] (2018)	*N* = 15,480 in the United Kingdom Included: patients aged ≥40 years with DM but without CVD Baseline: age 63 years, 27% female, 4% nonwhite, 94% type 2 DM, 62% HTN, 75% on statin	1 g omega-3 fatty acids (460 mg EPA and 380 mg DHA) PO daily vs placebo (olive oil) 2 × 2 factorial design with acetylsalicylic acid	7.4 (mean)	Composite of nonfatal MI, nonfatal stroke or TIA and vascular death: 8.9% vs 9.2% (RR, 0.97; 95% CI, 0.87-1.08) Vascular death: 2.4% vs 2.9% (RR, 0.81; 95% CI, 0.67-0.99), NNT = 200	No significant between-group differences in the rates of nonfatal serious adverse events
VITAL[6] (2019)	*N* = 25,871 in the United States Included: men aged ≥50 years or women aged ≥55 years without CVD or cancer Baseline: age 67 years, 51% female, 71% white, 20% black, 50% HTN, 14% type 2 DM, 38% on cholesterol-lowering medication	1 g omega-3 fatty acids (460 mg EPA and 380 mg DHA) PO daily vs placebo 2 × 2 factorial design with vitamin D	5.3 (median)	Composite of nonfatal MI, nonfatal stroke and CV death: 3% vs 3.2% (HR, 0.92; 95% CI, 0.80-1.06) MI: 1.1% vs 1.5% (HR, 0.72; 95% CI, 0.59-0.90), NNT = 250	Gastrointestinal bleeding: 2.9% vs 2.9% (HR, 0.99; 95% CI, 0.86-1.14) Stomach upset or pain: 3.8% vs 3.7% (HR, 1.01; 95% CI, 0.97-1.05)
REDUCE-IT[7] (2019)	*N* = 8179 Included: patients aged ≥45 years with CVD or aged ≥50 years with type 2 DM plus ≥1 CV risk factor and fasting TG 1.5-5.6 mmol/L and LDL-C 1.1-2.6 mmol/L on statin therapy Baseline: age 64 years, 29% female, 10% nonwhite, 71% CVD, 58% type 2 DM	2 g icosapent ethyl PO bid vs placebo (mineral oil)	4.9 (median)	Composite of nonfatal MI, nonfatal stroke, coronary revascularization, UA and CV death: 17.2% vs 22% (HR, 0.75; 95% CI 0.68-0.83), NNT = 21 MI: 6.1% vs 8.7% (HR, 0.69; 95% CI, 0.58-0.81), NNT = 39 CV death: 4.3% vs 5.2% (HR, 0.80; 95% CI, 0.66-0.98), NNT = 112	Gastrointestinal disorders: 33% vs 35.1% ($p = 0.04$) Serious bleeding: 2.7% vs 2.1% ($p = 0.06$) AF: 5.3% vs 3.9% ($p = 0.003$), NNH = 72 Peripheral edema: 6.5% vs 5% ($p = 0.002$), NNH = 67

(continued)

TABLE 1 (continued)

Study name (year)	Patient population	Intervention	Follow-up, y	Results	Safety
STRENGTH[8] (2020)	*N* = 13,078 Included: patients aged ≥18 years with CVD or DM and ≥1 CV risk factor or high-risk primary CV prevention and fasting TG 2-5.6 mmol/L and HDL-C <1.1 (men) or <1.2 mmol/L (women) on statin therapy Baseline: age 63 years, 35% female, 18% nonwhite, 70% DM, 56% CVD	4 g omega-3 carboxylic acids (each 1 g capsule contained at least 850 mg of polyunsaturated fatty acids, predominantly EPA and DHA) PO daily vs placebo (corn oil)	3.5 (median)	Composite of nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for UA and CV death: 12% vs 12.2% (HR, 0.99; 95% CI, 0.90-1.09)	AF: 2.2 vs 1.3% (HR, 1.69; 95% CI, 1.29-2.21), NNH = 112 Drug-related adverse events: 22.2% vs 12.9% (*p*-value not reported) Gastrointestinal disorders: 24.7% vs 14.7% (*p*-value not reported)
OMEMI[9] (2021)	*N* = 1027 in Norway Included: patients aged 70-82 years with a recent (2-8 weeks) acute MI Baseline: age 75 years, 29% female, 100% white, 60% HTN, 21% DM, 96% on statin	1.8 g omega-3 fatty acids (930 mg EPA and 660 mg DHA) PO daily vs placebo (corn oil)	2	Composite of nonfatal MI, unscheduled revascularization, stroke, hospitalization for heart failure and all-cause death: 21.4% vs 20% (HR, 1.07; 95% CI, 0.82-1.40)	New-onset AF: 7.2% vs 4% (*p* = 0.06) Major bleeding: 10.7% vs 11% (*p* = 0.87)

AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; PO, by mouth; RR, rate ratio; TG, triglycerides; TIA, transient ischemic attack; UA, unstable angina.

A practical approach for pharmacists

Five double-blind randomized controlled trials investigating omega-3 fatty acids in the prevention of CVD were recently published.[5-9] A summary of the trials is included in Table 1. These data were used to inform the design of an infographic to aid pharmacists in educating their patients about omega-3 fatty acids (Figure 1).

The following is a series of questions to consider when determining whether or not to recommend omega-3 fatty acid supplementation.

1. *Is the patient taking (or wanting to take) omega-3 fatty acids to prevent CVD?*

Omega-3 fatty acids have a variety of purported benefits beyond CVD. Studies have evaluated the effect of omega-3 fatty acids for Alzheimer's disease, dry eye disease, cystic fibrosis, macular degeneration, depression, dementia, inflammatory bowel diseases, autism spectrum disorder and bipolar disorder. An evaluation of the scientific evidence to support or refute the use of omega-3 fatty acids in these conditions is beyond the scope of this practice tool. Nonetheless, if a patient is taking or wanting to take an omega-3 fatty acid supplement, it is important to determine their goals of therapy.

2. *Does the patient have CVD (i.e., secondary cardiovascular prevention)? If so, do they have an elevated triglyceride level?*

The REDUCE-IT trial demonstrated that a novel ethyl ester formulation of pure EPA, known as icosapent ethyl (IPE), reduced cardiovascular events.[7] The majority of patients in this trial had established CVD and were on statin therapy; however, the trial specifically enrolled patients aged ≥45 years with elevated triglycerides (1.5-5.6 mmol/L) and a relatively low LDL-C (1.1-2.6 mmol/L) on statin therapy, which limits the generalizability of the results. The full inclusion criteria for the

FIGURE 1 Infographic summarizing the contemporary trial data

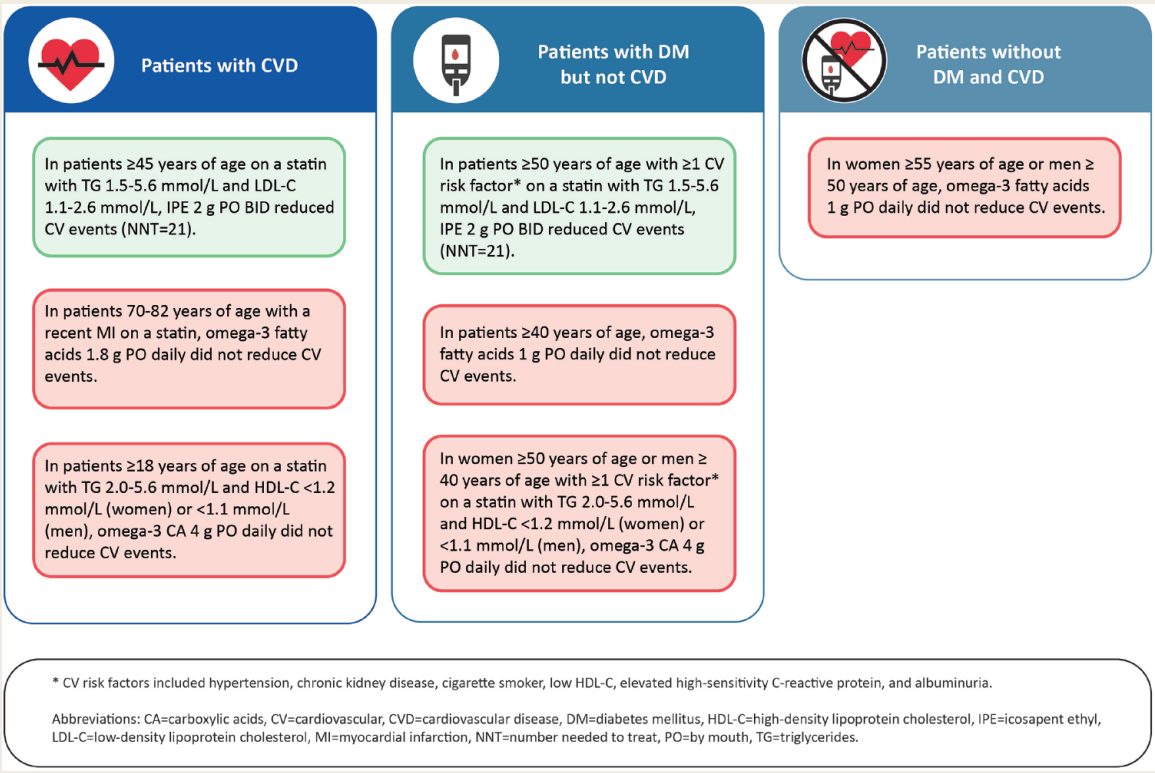

TABLE 2 Inclusion criteria for the REDUCE-IT[7] trial

1. Men and women ≥45 years of age with established CVD (e.g., CAD, cerebrovascular disease or PAD) or ≥50 years of age with DM (type 1 or 2) and ≥1 cardiovascular risk factor (e.g., hypertension, low HDL-C level, cigarette smoker, elevated high-sensitivity C-reactive protein level, renal dysfunction, micro- or macroalbuminuria, retinopathy).
2. Elevated fasting triglyceride level of 1.5 to 5.6 mmol/L.
3. LDL-C level 1.1 to 2.6 mmol/L on stable statin therapy (± ezetimibe) for ≥4 weeks.

CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease.

REDUCE-IT trial are included in Table 2. Conversely, in the STRENGTH trial, an omega-3 carboxylic acid product (comprising both DHA and EPA but with improved bioavailability over traditional omega-3 formulations)—in addition to a statin—was shown to be ineffective at reducing cardiovascular events in patients with CVD (or at high cardiovascular risk) and elevated triglycerides.[8]

The populations of the REDUCE-IT and STRENGTH trials were similar, as both trials included statin-treated patients primarily with established CVD. Furthermore, the relative reduction in triglycerides was similar between both trials (about 20%). Thus, the observed discordance in the results may have been due to the formulation (i.e., not all omega-3 fatty acid formulations are the same). The REDUCE-IT trial used a highly purified EPA-only formulation, while the STRENGTH trial used a carboxylic acid formulation that contained both EPA and DHA. Accordingly, the relative increase in achieved plasma EPA levels was higher in REDUCE-IT vs STRENGTH trial participants.[10] It has also been suggested that the difference in placebo formulation (mineral vs corn oil) may have influenced the results, as patients randomized to mineral oil in the REDUCE-IT trial had increased levels of high-sensitivity C-reactive protein and LDL-C.[10] Notwithstanding, the benefit observed in the REDUCE-IT trial appears to be unique to IPE and thus should not be extrapolated to over-the-counter products. Icosapent ethyl was approved for use by Health Canada in January 2020 and is recommended in the 2021 Canadian Cardiovascular Society dyslipidemia guidelines in patients with CVD or diabetes and ≥1 CVD risk factor who have a fasting triglyceride level of 1.5 to 5.6 mmol/L despite treatment with maximally tolerated statin therapy.[11] Finally, IPE may be cost prohibitive, as the current cost is about $2.45 per capsule (roughly $3600 per year).[12]

The OMEMI trial demonstrated that omega-3 fatty acids 1.8 g daily did not reduce cardiovascular events when added to statin therapy, specifically in patients aged 70 to 82 years with a recent MI but without an elevated triglyceride level (mean 1.3 mmol/L at baseline).[9]

3. *Is this a primary cardiovascular disease prevention patient? If so, do they have diabetes?*

In patients without a history of CVD (i.e., primary prevention) with or without diabetes, 2 well-designed RCTs (ASCEND and VITAL) of >41,000 patients demonstrated that omega-3 fatty acids at 1 g daily (840 mg of marine omega-3 fatty acids, specifically 460 mg of EPA and 380 mg of DHA), similar to 1 capsule daily for many over-the-counter omega-3 fatty acid supplements, did not reduce the risk of cardiovascular events or death.[5,6] In patients specifically ≥50 years of age with diabetes (but not CVD) and an additional cardiovascular risk factor (e.g., hypertension, chronic kidney disease, cigarette smoking), IPE 2 g twice daily could be considered if they meet the other REDUCE-IT trial criteria (Table 1), although this constituted less than one-third of participants.[7]

Case vignette follow-up

Mr. Patel has a history of hypertension and type 2 diabetes but not CVD. He should be advised not to start taking the over-the-counter omega-3 fatty acid supplement he selected, as it was demonstrated not to reduce cardiovascular events in the ASCEND trial.[5] However, he would meet the criteria for the REDUCE-IT trial, as he is ≥50 years of age with diabetes and a cardiovascular risk factor (hypertension).[7] As well, he is on statin therapy and his triglycerides are from 1.5 to 5.6 mmol/L and LDL-C is from 1.1 to 2.6 mmol/L. As such, you could discuss the potential benefits and risks of IPE at 2 g twice daily. Notably, only 10% of the study population was nonwhite. Some additional considerations include his risk of bleeding, as he is currently receiving antiplatelet therapy. You should also discuss his risk of atrial fibrillation, as he has other risk factors, including his age and history of hypertension. Adherence may be a concern, as the dose of IPE requires the addition of 4 capsules to his daily medication regimen, as well as cost. ■

BOX 1 Practice tips

- In general, over-the-counter omega-3 fatty acid products should not be recommended to reduce cardiovascular risk in patients with or without CVD. The combination of EPA and DHA at 840 mg (1 g of omega-3 fatty acids) daily did not reduce cardiovascular events in patients without CVD. Even at a higher dose of 1.8 g daily, EPA and DHA did not demonstrate a benefit in older patients (≥70 years of age) with a recent MI.
- For patients with established CVD (or diabetes and ≥1 cardiovascular risk factor) and hypertriglyceridemia on statin therapy, IPE 2 g twice daily could be recommended to reduce the risk of cardiovascular events. However, this benefit appears to be unique to this formulation of purified ethyl ester EPA.

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