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It is estimated that over 70% of Canadians take 1 or more natural health products, such as omega-3 polyunsaturated fatty acids (PUFAs) for cardiovascular protection. We sought to systematically identify and assess the best currently available evidence investigating the use of omega-3 PUFAs for the prevention of cardiovascular disease.

On estime que plus de 70 % des Canadiens prennent au moins un produit de santé naturel, comme les acides gras polyinsaturés (AGP) oméga-3 pour la protection cardiovasculaire. Nous avons souhaité recenser systématiquement et évaluer les meilleures données actuelles examinant l'utilisation des AGP oméga-3 pour la prévention des maladies cardiovasculaires.

Omega-3 polyunsaturated fatty acid supplementation in the prevention of cardiovascular disease

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ABSTRACT

Introduction: Omega-3 polyunsaturated fatty acids (PUFAs) have purported protective cardiovascular (CV) effects. We sought to assess the evidence available for the use of omega-3 PUFAs for the prevention of cardiovascular disease (CVD).

Methods: A systematic literature search was conducted using MEDLINE and EMBASE from 1999 to 2015. Placebo-controlled, randomized controlled trials (RCTs) that enrolled over 1000 patients with follow-up greater than 1 year and meta-analyses of RCTs were included.

Results: Eight RCTs and 2 meta-analyses were included. In patients with preexisting CVD, only 1 of 5 included RCTs demonstrated a reduction in CV events with omega-3 PUFAs; however,

the effect size was minimal, and the study was limited by an open-label design and lack of placebo control. Two meta-analyses concluded omega-3 PUFAs do not reduce CV events in addition to standard, evidence-based therapy in patients after myocardial infarction. Of the 3 predominantly primary prevention RCTs, only 1 demonstrated a minor reduction in major coronary events; however, it was also an open-label study. Furthermore, the safety of omega-3 PUFAs should be considered. While data from RCTs have not demonstrated serious safety concerns, omega-3 PUFAs can increase the risk of bleeding and may interact with other medications that affect hemostasis, such as antiplatelet agents and warfarin.

Discussion and Conclusion: There is currently a lack of evidence to support the routine use of omega-3 PUFAs in the primary and secondary prevention of CVD. Pharmacists are ideally situated to engage patients in the discussion of the lack of benefit and possible risk of omega-3 PUFA supplements. *Can Pharm J (Ott)* 2016;149:166-173.

Patient case

A 56-year-old nonsmoking man presents to your pharmacy. He just came from his physician's office, where he was told he has high cholesterol. He was given a prescription for an HMG-CoA reductase inhibitor (statin) for primary prevention but states he would like to try something "natural" first. He currently adheres to a heart-healthy diet and walks his dog daily. His other

comorbidities include hypertension and a positive family history of premature cardiovascular disease (father had a myocardial infarction at age 54). You calculate his Framingham Risk Score, which is in the high-risk level (>20%). He asks about using fish oils (i.e., omega-3 polyunsaturated fatty acids), as he heard they were effective for preventing heart attacks. How would you respond?

Introduction

The beneficial effects of omega-3 polyunsaturated fatty acids (PUFAs) were first noted when researchers identified low rates of cardiovascular disease (CVD) among Greenland Inuit, whose diet consisted of foods high in omega-3 PUFAs, such as whale, fish and seal.¹⁻⁴ This population was also noted to have low levels of serum cholesterol and triglycerides, despite high intake of fat and cholesterol and low intake of fruit and vegetables. Proposed mechanisms for the cardiovascular (CV) protective effects of omega-3 PUFAs include antiarrhythmic effects, improvements in autonomic function, decreased platelet aggregation, decreased blood pressure, improvements in endothelial function, plaque stabilization and reduced atherosclerosis.^{3,4} It has been proposed, however, that a dietary shift to consuming more industrially processed foods, and therefore more saturated fats, may outweigh the proposed benefits of omega-3 PUFAs.³ The most studied omega-3 PUFAs in the prevention of CVD are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Health Canada does not provide an indication for EPA/DHA supplements but supports the claim that they “help maintain/support cardiovascular health.”⁵ This article will summarize recent key evidence for the use of omega-3 PUFAs for the prevention of CVD.

Literature search

A systematic literature search was conducted using MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE from 1999 to August 2015. The search terms *fatty acids* (omega-3 and unsaturated) and *cardiovascular disease* were used. The search was limited to human subjects and English language. In addition, a manual search of the references of included studies was conducted. Only randomized, placebo-controlled trials that enrolled over 1000 patients with follow-up greater than 1 year and reported 1 or more clinically relevant CV outcome (e.g., death from CV cause, myocardial infarction [MI], stroke) were included. Meta-analyses of randomized controlled trials (RCTs) also were included. Two authors (CPW, ARB) independently conducted the search and identified articles for inclusion, and all 3 authors reviewed each included article in full. A total of 361 citations were identified, and 8 RCTs and 2 meta-analyses were included. A summary of the key RCTs is included in Table 1.

KNOWLEDGE INTO PRACTICE

- Omega-3 polyunsaturated fatty acids (PUFAs) have a variety of purported effects that are thought to lower the risk of cardiovascular disease (CVD).
- Based on clinical trial data, omega-3 PUFA supplements lower serum triglyceride levels but do not affect serum low-density lipoprotein cholesterol levels.
- Multiple large, randomized, placebo-controlled trials have shown no benefit with omega-3 PUFA supplements for the primary prevention of CVD.
- There appears to be no benefit with omega-3 PUFA supplements for the secondary prevention of CVD when added to guideline-based pharmacotherapy in both the early and late period after a myocardial infarction.
- Many pharmacies stock omega-3 PUFA supplements. Therefore, pharmacists are ideally situated to engage patients in a discussion specifically about the lack of CVD benefit with omega-3 PUFAs, as well as the potential adverse effects.

Omega-3 PUFAs in primary prevention of CVD

The first large RCT to address the use of omega-3 PUFA supplementation for CVD prevention was published in 2007. This open-label, blinded end-point trial, known as the Japan EPA Lipid Intervention Study (JELIS), investigated EPA supplementation in Japanese patients with high total cholesterol (>6.5 mmol/L).⁷ The trial enrolled 18,645 patients—the largest trial conducted to date. Participants were randomized to EPA 600 mg 3 times daily with a statin (predominantly pravastatin 10 mg or simvastatin 5 mg daily) or statin monotherapy over 5 years. At baseline, the mean age was 61 years, and 69% were female. The trial population was predominantly primary prevention—only approximately 20% had a history of coronary artery disease. The results demonstrated a 0.7% absolute risk reduction (ARR) (19% relative; $p = 0.011$) in the primary end point of major coronary events (sudden cardiac death [SCD], fatal or nonfatal MI, unstable angina [UA], coronary revascularization) with EPA plus a statin (2.8%) compared to statin monotherapy (3.5%), which was primarily driven by a reduction in UA. Other components of the primary outcome were not significantly reduced. Of note, EPA did not reduce major coronary events in the primary prevention subgroup. More patients in the EPA group experienced an adverse event, the most common being pain (e.g., joint pain, lumbar

TABLE 1 Summary of key randomized controlled trials

Author (Year)	Design	Intervention	Patient population	Follow-up, years	Results
GISSI-Prevenzione Investigators (1999) ⁶	R, OL	1 g omega-3 PUFAs (290 mg EPA/580 mg DHA) vs no intervention	<i>N</i> = 11,324 Inclusion: MI within 3 months Baseline: 84% aged ≤70, 15% female	3.5	Composite of all-cause death, nonfatal MI or nonfatal stroke: 12.6% omega-3 PUFAs vs 13.9% control, RR 0.90 (95% CI, 0.82–0.99)
Yokoyama et al. (2007) ⁷	R, OL	1800 mg EPA with statin vs statin monotherapy	<i>N</i> = 18,645 Inclusion: total cholesterol ≥6.5 mmol/L Baseline: mean age 61 years; 69% female, 20% CAD	4.6 (mean)	Composite of SCD, fatal and nonfatal MI, UA, coronary angioplasty or stenting, or CABG: 2.8% EPA vs 3.5% control, HR 0.81 (95% CI, 0.69–0.95)
Rauch et al. (2010) ⁸	R, DB, PC	1 g omega-3 PUFAs (460 mg EPA/380mg DHA) vs PC	<i>N</i> = 3851 Inclusion: MI within 3–14 days Baseline: mean age 64 years, 26% female	1	SCD: 1.5% omega-3 PUFAs vs 1.5% PC, OR 0.95 (95% CI, 0.56–1.60) MACCE: 10.4% omega-3 PUFAs vs 8.8% PC, OR 1.21 (95% CI, 0.96–1.52)
Galan et al. (2010) ⁹	R, DB, PC	600 mg omega-3 PUFAs (EPA:DHA ratio 2:1) vs PC	<i>N</i> = 2501 Inclusion: acute coronary or cerebral ischemic event within 12 months Baseline: mean age 61 years, 20% female	4.7 (median)	Composite of nonfatal MI, stroke or CV death: 6.5% omega-3 PUFAs vs 6.1% placebo, HR 1.08 (95% CI, 0.79–1.47)
Kromhout et al. (2010) ¹⁰	R, DB, PC	18.8 g margarine containing omega-3 fatty acids (226 mg EPA/150 mg DHA) vs PC	<i>N</i> = 4837 Inclusion: MI up to 10 years before randomization Baseline: mean age 69 years, 22% female	3.4 (median)	Composite of fatal or nonfatal CVD, PCI or CABG: 14.0% omega-3 fatty acids vs 13.8% PC, HR 1.01 (95% CI, 0.87–1.17)
ORIGIN Trial Investigators et al. (2012) ¹¹	R, DB, PC	1 g omega-3 PUFAs (465 mg EPA/375 mg DHA) vs PC	<i>N</i> = 12,536 Inclusion: IFG, IGT, or DM and high-risk for CV event Baseline: mean age 64 years, 35% female, 60% CVD	6.2 (median)	Death from CV causes: 9.1% omega-3 PUFAs vs 9.3% PC, HR 0.98 (95% CI, 0.87–1.10)
Risk and Prevention Study Collaborative Group (2013) ¹²	R, DB, PC	1 g omega-3 fatty acids (500–660 mg EPA/330–500 mg DHA) vs PC	<i>N</i> = 12,513 Inclusion: multiple CV risk factors or atherosclerotic vascular disease, but not previous MI Baseline: mean age 64 years, 39% female, 30% atherosclerotic disease	5 (median)	Composite of death, nonfatal MI, nonfatal stroke, CV death or CV hospitalization: 11.7% omega-3 PUFAs vs 11.9% PC, HR 0.97 (95% CI, 0.88–1.08)
Writing Group for the AREDS2 Research Group (2014) ¹³	R, DB, PC	1 g omega-3 PUFAs (650 mg EPA/350 mg DHA) vs PC	<i>N</i> = 4203 Inclusion: macular degeneration Baseline: median age 74 years, 57% female, 19% CVD	4.8 (median)	Composite of CV death, MI, stroke, UA, coronary or carotid revascularization, CHF hospitalization, resuscitated cardiac arrest: 9% omega-3 PUFAs vs 9% PC, HR 0.95 (95% CI, 0.78–1.17)

ACS, acute coronary syndrome; AREDS2, Age-Related Eye Disease Study 2; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DB, double-blind; DHA, docosahexaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MACCE, major adverse cerebrovascular and cardiovascular events; MI, myocardial infarction; OL, open label; OR, odds ratio; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PC, placebo; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acids; R, randomized; RR, relative risk; SCD, sudden cardiac death; UA, unstable angina.

pain, muscle pain), gastrointestinal (GI) disturbances (e.g., nausea, diarrhea, epigastric discomfort), skin abnormalities (e.g., eruption, itching, exanthema, eczema) and hemorrhage (e.g., cerebral, fundal, epistaxis, subcutaneous).

Another largely primary prevention RCT was published in 2013, known as the Risk and Prevention Study.¹² The objective was to determine the effect of omega-3 PUFA supplements in patients with multiple CV risk factors or atherosclerotic vascular disease, but who had not had an MI. A total of 12,513 patients were randomized in a double-blind fashion to 1 g of omega-3 PUFAs daily (ratio of EPA:DHA ranged from 0.9:1 to 1.5:1) or placebo and followed for 5 years. The mean age was 64 years, and 39% were female. Approximately one-third of patients had atherosclerotic disease at baseline. The primary end point, a composite of death, nonfatal MI, nonfatal stroke, CV death or hospitalization, was not significantly lower with omega-3 PUFAs compared to placebo (11.7% vs 11.9%, $p = 0.64$). There was no significant difference in the secondary outcomes of CV death, SCD or all-cause death. The rate of hospital admission for heart failure was lower with omega-3 fatty acids (1.5% vs 2.3%, $p = 0.002$). Omega-3 PUFAs decreased serum triglyceride levels but had no observable effect on total or low-density lipoprotein cholesterol (LDL-C) levels, blood pressure, heart rate or blood glucose. There was no difference in adverse events between groups.

The most recent double-blind RCT, published in 2014, was an ancillary analysis of the Age-Related Eye Disease Study 2 (AREDS2), which enrolled 4203 patients with macular degeneration.¹³ Patients were randomized to omega-3 fatty acids (650 mg of EPA and 350 mg of DHA), lutein, both or placebo and were followed for approximately 5 years. At baseline, the average patient was 74 years, and 57% were female. It was predominantly a primary prevention trial—only 19% had a history of CVD and 44% reported taking a statin. When compared to placebo, omega-3 PUFAs did not reduce the primary composite outcome of CV events (9% vs 9%, $p = 0.64$), nor was there any observed difference in serious adverse events.

Omega-3 PUFAs in secondary prevention of CVD

In 1999, the first large RCT of omega-3 PUFAs in CVD, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial, was published.⁶ The

MISE EN PRATIQUE DES CONNAISSANCES

- Les AGP oméga-3 sont censés avoir divers effets qui réduisent le risque de maladie cardiovasculaire (MCV).
- D'après les résultats des essais cliniques, les suppléments à base d'AGP oméga-3 font baisser les taux de triglycérides dans le sérum, mais n'ont aucun effet sur les taux de cholestérol à lipoprotéines de basse densité dans le sérum.
- Plusieurs études de grande taille, randomisées et contrôlées par placebo ont été effectuées sur les suppléments à base d'AGP oméga-3, et aucune n'a montré de bienfait pour la prévention primaire des MCV.
- De plus, il semblerait que les suppléments à base d'AGP oméga-3 ne sont pas bénéfiques pour la prévention secondaire des MCV lorsqu'ils sont ajoutés à une pharmacothérapie recommandée par les lignes directrices, que ce soit juste après un infarctus du myocarde ou dans la période plus tardive.
- De nombreuses pharmacies ont des suppléments à base d'AGP oméga-3 dans leurs réserves. Les pharmaciens sont donc idéalement placés pour discuter avec les patients de l'absence de bienfaits des suppléments à base d'AGP oméga-3 pour lutter contre les MCV et de leurs effets indésirables potentiels.

objective was to assess the efficacy of omega-3 PUFAs (and vitamin E) on patients with a history of MI in the previous 3 months. The trial included 11,324 patients who were randomized to 1 of 4 open-label groups: omega-3 PUFAs 1 g daily, vitamin E 300 mg daily, both or neither. Follow-up was 3.5 years. At baseline, an average patient was 59 years old and 15% were female. When this trial was conducted, statins were not a part of standard post-MI treatment; thus, only 5% of patients were taking a statin at baseline. Compared to the control group (no treatment), supplementation with PUFAs decreased the combined end point of all-cause death, nonfatal MI and nonfatal stroke by an absolute 1.3% (12.6% vs 13.9%, relative 10% reduction, 95% confidence interval [CI], 1%–18%). In the secondary analyses, there was an observed statistically significant reduction in all fatal events (1.3% ARR), CV deaths (1.1% ARR) and SCD (0.7% ARR) but no difference in nonfatal CV events. While there was a small decrease in triglycerides in the omega-3 PUFAs group, there were no clinically significant changes in any other lipid parameter. Approximately one-third of patients had permanently discontinued treatment in the omega-3 PUFAs group by the end of the study, with the most commonly reported adverse effects being

GI disturbances and nausea. Of note, vitamin E did not reduce the incidence of CV events when compared to no treatment.

The OMEGA trial, published in 2010, explored the effect of omega-3 PUFAs in patients with a recent MI.⁸ This double-blind, placebo-controlled RCT included patients on current guideline-recommended therapy 3 to 14 days post-MI (approximately 82% were on statin therapy). The primary outcome was SCD and secondary outcomes included total mortality and major adverse cerebrovascular and CV events (MACCE). In total, 3851 patients were randomized to 1 g of omega-3 fatty acids (460 mg of EPA and 380 mg of DHA) or placebo and were followed for 12 months. At baseline, the median age was 64 years, and 26% were female. When compared to placebo there was no significant difference in SCD (1.5% vs 1.5%, $p = 0.84$), mortality (4.6% vs 3.7%, $p = 0.18$) or MACCE (10.4% vs 8.8%, $p = 0.10$). There was no difference in serum LDL-C levels or adverse events between groups.

The Alpha Omega trial, also published in 2010, was an RCT that investigated the use of omega-3 PUFAs in patients approximately 4 years after an MI.¹⁰ Participants were randomized in a double-blind fashion to receive 1 of 4 margarines with varying levels of omega-3 PUFAs, compared to placebo margarine, in addition to standard post-MI therapy. The primary end point was a composite of major adverse CV events (MACE). A total of 4837 patients were enrolled. The average age was 69 years, and 22% were female. At baseline, 86% were receiving lipid-lowering therapy (primarily statins). On average, patients consumed about 226 mg of EPA and 150 mg of DHA, 1900 mg of α -linolenic acid, both or neither. After 40 months of follow-up, none of the omega-3 PUFA margarines reduced MACE (14% vs 13.8%, $p = 0.93$), CV death or death from any cause when compared to placebo. There was no difference in adverse events between groups.

The Supplémentation en Folates et Omega-3 (SU.FOL.OM3) study investigated whether omega-3 fatty acids or B vitamins could reduce MACE in patients with a history of ischemic heart disease or ischemic stroke.⁹ Just over 2500 patients were randomized (double-blind) to omega-3 fatty acids (600 mg of EPA and DHA in 2:1 ratio) or matching placebo (or B vitamins or matching placebo) using a 2×2 factorial design. An average patient at baseline was a 61-year-old male around 1 month after an acute coronary syndrome. Approximately 85%

were on lipid-lowering therapy at baseline. After a 4.7-year follow-up, the incidence of MACE (6.5% vs 6.1%, $p = 0.64$), as well as mortality, was not statistically significantly different between groups. Vitamin B supplementation was also not associated with a reduction in CV events. Adverse effects, primarily GI disturbances, cutaneous reactions and nausea, were similar between groups.

Another double-blind, placebo-controlled RCT, known as the Outcome Reduction with an Initial Glargine Intervention (ORIGIN), was published in 2012.¹¹ The goal was to determine if omega-3 PUFAs prevent CV events in patients with dysglycemia (defined as impaired fasting glucose, impaired glucose tolerance or diabetes mellitus) who were at risk or had established CVD. In total, 12,536 patients were randomized to 1 g of omega-3 fatty acids (465 mg of EPA and 375 mg of DHA) or placebo daily and were followed for 6.2 years—the longest trial conducted to date. The average age was 64 years, 35% were female and approximately 60% had a history of CVD. There was no significant decrease in the primary outcome of death from CV causes (9.1% with omega-3 fatty acids vs 9.3% with placebo, $p = 0.72$). There was also no significant reduction in major vascular events, death from any cause or death from arrhythmia. There was a significant decrease in serum triglyceride level observed with active treatment, but no effect on other lipid parameters. Common adverse events included abdominal discomfort and lower GI symptoms, but they were not significantly different between groups.

Given the conflicting data, a meta-analysis by Kwak et al., published in 2012, specifically aimed at investigating omega-3 fatty acids in patients with established CVD.¹⁴ Fourteen studies published from 1995 to 2010 were included, for a total of 20,485 patients. All studies were double-blind, placebo-controlled RCTs, which included SU.FOL.OM3, OMEGA and Alpha Omega. The GISSI-Prevenzione trial was excluded, as it was open label and lacked a placebo control. The primary outcome was a composite of CV events, all-cause mortality, SCD, MI, congestive heart failure, transient ischemia attacks and stroke. The dose of omega-3 PUFAs ranged from 0.4 to 4.8 g per day compared to placebo (e.g., olive oil, corn oil, non-oil). The primary outcome was not statistically significantly different between groups (relative risk [RR], 0.99; 95% CI, 0.89–1.09). Death from CV causes was marginally reduced with omega-3 PUFAs (RR, 0.91; 95% CI, 0.84–0.99) but was not significant when only trials of high

methodological quality were included. No difference in other individual outcomes (e.g., all-cause mortality, SCD, MI) was observed, as well as in adverse events (e.g., GI disturbances or bleeding).

More recently, a meta-analysis by Rizos et al. analyzed 20 RCTs published between 1989 and 2012 that assessed omega-3 PUFAs in patients with CVD, including GISSI-Prevenzione, OMEGA, Alpha Omega, SU.FOL.OM3 and ORIGIN, for a total of 68,680 patients.¹⁵ The mean dose of omega-3 PUFAs was 1.5 g per day, with a median follow-up of 2 years. Outcomes of interest included all-cause mortality, cardiac death, SCD, MI and stroke. Similar to the Kwak et al. meta-analysis, there was no statistically significant difference between omega-3 PUFA supplementation compared to placebo for any of the prespecified outcomes. Of note, CV death was lower with omega-3 fatty acids, but this was not statistically significant when adjusted for multiple comparisons. In addition, there was no observed benefit with higher versus lower doses of omega-3 PUFAs.

Discussion

The previous identification of lower incidences of CVD among populations that consume large amounts of fish, termed the “Eskimo effect” or “Japanese effect,” is based on epidemiologic data rather than RCTs.¹⁻³ More recent data suggest that the incidence of CV death and coronary heart disease among populations with a high fish diet (Greenland Inuit, Alaskan Native) is comparable to Western or Caucasian populations.^{16,17} One explanation is that a gradual shift to a “Westernized” diet high in saturated fats may outweigh the potential benefits of omega-3 PUFAs in these populations.³ Furthermore, inconsistencies in the dose, purity and EPA:DHA ratio of different omega-3 PUFA supplements, as compared to the doses and products studied in the literature, make it difficult to directly apply any benefit noted in the literature to the product available on the market.

Of the 3 predominantly primary prevention trials, only 1 demonstrated a reduction (albeit minor) in major coronary events; however, it was the only study to use an open-label design.⁷ Furthermore, the composite end point in this trial was primarily driven by UA, which was an unblinded, unadjudicated outcome and thus prone to bias. Though more data exist for secondary CV prevention, only 1 of the 5 included RCTs demonstrated a minimal reduction in CV events with omega-3 PUFA supplementation, but it was again limited

by an open-label design and lack of a placebo control.⁶ Two large meta-analyses further support the futility of omega-3 PUFA supplementation in addition to standard, evidence-based therapy in patients post-MI.^{14,15} Until more data are available, the current published literature consisting of several large, placebo-controlled RCTs, supported by meta-analyses, suggests that there is no benefit to omega-3 PUFA supplementation in the prevention of CVD.

Limitations

Omega-3 PUFAs are heterogeneous with respect to EPA and DHA formulation and content. Furthermore, the optimal dose and ratio of EPA:DHA are not known. Thus, it is possible that combining studies with varying doses, ratios and sources is not appropriate. As well, multiple forms of EPA are available, which may further confound results. This review focused specifically on the evidence for omega-3 PUFAs in the prevention of CVD and did not include any data regarding omega-6 PUFAs or the ratio of omega-6 to omega-3 fatty acids. In addition, this review did not investigate the use of omega-3 PUFAs for other conditions or medical problems.

Role of the pharmacist

It is estimated that over 70% of Canadians take natural health products.¹⁸ However, many of these supplements have little or no scientific evidence to support their efficacy and/or safety. On the contrary, omega-3 PUFAs are among the most studied natural health products available on the market, with several contemporary, well-designed clinical trials published since 1999 examining the use of these supplements in the prevention of CVD. Most of these data do not support the use of omega-3 PUFAs in either the primary or secondary prevention of CVD. Pharmacists are in an ideal position to engage patients in the discussion of the potential risks and benefits of omega-3 PUFA supplements. Given this evidence, it is important for pharmacists to educate patients about these data to help them make informed decisions about taking omega-3 PUFAs for the prevention of CVD. This is of particular importance for patients with chronic conditions, due to the high propensity for polypharmacy and high pill burden. One must also consider the cost associated with supplements, as well as the risk of forgoing evidence-based therapies (e.g., statins) in favour of “natural,” non-evidence-based supplements. Safety should also be taken into

consideration with omega-3 PUFA supplements. While data from clinical trials have not demonstrated serious safety concerns at the doses studied, it has been noted in the literature that omega-3 PUFAs can increase the risk of bleeding and may interact with other medications that affect hemostasis, such as antiplatelet agents, flaxseed and warfarin.¹⁸⁻²⁰ It is important to educate patients who make an informed decision to take omega-3 PUFA supplements to monitor for signs of bleeding, such as epistaxis, excessive bruising or melena. Other adverse effects, such as generalized pain,

skin abnormalities or GI disturbances, may affect the patient's quality of life.

Follow-up to patient case

We advocate recommending against the use of omega-3 PUFAs for the primary prevention of CVD in this patient based on a lack of benefit observed in clinical trials. We would advocate discussing the potential benefits and risks of statin therapy in the context of his individualized risk while incorporating his values and preferences into the decision-making process. ■

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