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Cardiovascular Therapeutics

Krill Oil for Cardiovascular Risk Prevention: Is It for Real?

James M. Backes, PharmD,[*] and Patricia A. Howard, PharmD, FCCP, BCPS (AQ CV)[†]

Omega-3 fatty acids play an important role in cardiovascular health. Although it is suggested that individuals obtain these nutrients through diet, many prefer to rely on supplements. Fish oil supplements are widely used, yet large capsule sizes and tolerability make them less than ideal. Recently, krill oil has emerged as a potential alternative for omega-3 supplementation. This article will discuss what is known about krill oil and its potential use in cardiovascular risk prevention.

Consumption of the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has generally demonstrated numerous health benefits including lower rates of cardiovascular disease (CVD).[1] These findings have been observed in studies using both increased dietary omega-3 fatty acids and supplementation.[1] It should be noted, however, that not all studies support the use of omega-3 fatty acids. Controversy has been generated by recent studies indicating neutral effects on cardiovascular events among individuals receiving optimal drug therapy.[2,3] In an effort to explain these discordant findings, it has been suggested that the ability to demonstrate cardiovascular benefit with omega-3 fatty acids may now be more challenging as the standard of care for CVD prevention has improved. Experts speculate that higher doses of EPA+DHA and longer study durations may be needed to provide benefit in an era of optimal medical therapy.[4]

Despite this ongoing debate, major professional organizations continue to support the use of omega-3 fatty acids from fish or fish oil supplementation to prevent CVD. Common dietary sources of these essential fatty acids include "oily" fish such as salmon, sardines, herring, and albacore tuna.[1] As an alternative, EPA+DHA can also be obtained in various preparations of fish oil and krill oil. Fish oil has been extensively studied and remains one of the most commonly utilized supplements in the United States.[5] However, despite the paucity of well-designed studies examining krill oil, the market share of this omega-3 source continues to increase. Recent data indicate that krill oil presently represents 14% of total omega-3 sales.[6] This finding is likely the result of consumers seeking the potential health benefits of omega-3 fatty acids, while searching for an alternative to fish oil. Krill oil has been promoted to the public through media advertisements and consumer publications suggesting that one small krill oil pill a day provides cardioprotection similar to that of fish oil. In this article, we take a look at the current evidence and provide a perspective for pharmacists having to differentiate and recommend omega-3 products to patients for CVD prevention.

PRODUCT DIFFERENTIATION

Krill are small shrimp-like crustaceans found in all oceans and serve as a major food source for much of the marine life. Particularly abundant supplies that can be fished are the Antarctic krill or *Euphausia superba*. Similar to fish, krill consume a diet rich in omega-3 fatty acids (eg, algae) and are thereby a natural source of EPA and DHA.[7]

Although there are similarities, numerous differences exist between krill oil and fish oil. Krill oil is only available as a supplement, primarily in softgel formulation. Fish oil is available in both prescription and supplement formulations including softgels and liquid. More important, however, are the differences in omega-3 content and delivery.[7] The EPA+DHA content of krill oil is markedly less per softgel (and serving) compared to fish oil. For example, the dose

[*]Professor, Department of Pharmacy Practice, and Assistant Director, Atherosclerosis and LDL Apheresis Center, University of Kansas Medical Center; [†]Professor and Vice Chair, Department of Pharmacy Practice, University of Kansas Medical Center, Mailstop 4047, 3901 Rainbow Boulevard, Kansas City, KS 66160; phone: 913-588-5391; fax: 913-588-2355; e-mail: phoward@kumc.edu

of EPA+DHA of pure krill oil products may range from ~45 to 200 mg/softgel compared to ~300 to 2,250 mg/softgel or teaspoon among the various fish oil formulations.[5,8,9]

The fatty acid form is also a key factor differentiating these agents. The EPA+DHA found in krill oil is primarily incorporated in phospholipids, whereas omega-3 fatty acids in fish oil are generally present as triglycerides or ethyl esters.[10] Some data have suggested that phospholipids are more efficient at delivering EPA+DHA.[11] This difference in chemical form may therefore impact the absorption and bioavailability of the EPA+DHA and the dose required to achieve the various cardiovascular effects.

A measure used to determine differences in absorption and cardiovascular benefit is the omega-3 index. This biomarker measures the EPA+DHA content in red blood cell membranes as a percentage of total fatty acids and is inversely related to coronary heart disease (CHD) risk.[12] Based on epidemiological and randomized controlled trial data, an omega-3 index of less than 4% is considered high risk, 4% to 8% is moderate risk, and more than 8% is low risk for CHD mortality in adults.[12] This cardioprotection from EPA+DHA appears to be the result of multiple vascular effects such as arrhythmia prevention and possible plaque stabilization,[13,14] as well as reductions in numerous parameters including triglyceride concentrations,[15] systemic blood pressure,[16] heart rate,[17] platelet aggregation, and inflammation.[18,19] Although a limited number of studies comparing the effects of krill oil and fish oil on the omega-3 index have suggested greater increases with krill oil,[20,21] newer data do not support these findings.[22]

The impact of krill oil on triglycerides and lipoproteins is not fully elucidated, but available data indicate only modest changes.[23] In contrast, fish oil is well established for triglyceride lowering with doses of up to 4 g of EPA+DHA daily producing reductions of 20% to 50%. Modest increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are also generally observed with fish oil.[1,24]

One component that is present in krill oil, but generally absent in fish oil, is astaxanthin. This colorful carotenoid antioxidant is responsible for the red color observed in salmon meat, cooked shellfish, and certain krill oil supplements. Although this powerful antioxidant has previously demonstrated HDL-C increasing properties, clinical benefits and therapeutic use of astaxanthin remain unclear.[25]

Other properties that may differentiate these agents include pill size and potential for gastrointestinal (GI) adverse events. A common patient complaint with fish oil is the large softgel size and difficulty with swallowing. Liquid fish oil is an alternative, but many have an aversion to the taste and oily consistency plus the inconvenience of required refrigeration. The size of krill oil softgels is markedly smaller and may be more suitable for individuals with swallowing difficulties. GI complaints, such as the "fish burp," are common with omega-3 preparations.[1] Advertising claims have suggested that krill oil produces "less fishy aftertaste," however there are minimal data to support this statement.

Cost may also be an important consideration for patients choosing omega-3 products. Typically, supplemental fish oil is considerably less expensive compared to krill oil. A cost analysis of common products indicated that fish oil supplements range from 1 to 15 cents while krill oil is approximately 30 cents per 100 mg of EPA+DHA.[5] Similarly, although prescription fish oil is generally costly, out-of-pocket price to the patient may be offset by prescription insurance coverage. The difference in price with krill oil is partially due to the need for immediate processing once the krill is harvested to prevent spoilage.[7] This high sensitivity to degradation also raises concerns regarding product quality. For instance, 1 of 2 krill oil products tested by an independent lab indicated spoilage and less EPA+DHA content than what was listed on the labeling.[5] Additionally, clinicians should be watchful for krill oil/fish oil blends marketed as "krill oil," which are commonly found in retail settings.[5] These products often contain higher levels of EPA+DHA than pure krill oil products, but a substantial amount may be derived from fish oil.

CLINICAL STUDIES OF KRILL OIL

A randomized, double-blind, controlled parallel trial evaluated the effects of krill oil on plasma concentrations of EPA and DHA as well as other indicators of safety, tolerability, and selected metabolic markers.[20] This 4-week study was conducted in overweight and obese subjects who were otherwise generally healthy. Subjects were not taking other lipid-altering medications or fish oil supplements and were not regularly consuming fish. A total of 76 participants were randomized to 1 of 3 groups: krill oil, fish (menhaden) oil, or olive oil (control) at a daily dose of 2 g. Subjects were told to take four 500 mg capsules per day. The daily doses of EPA and DHA were 216 mg and 90 mg with the krill oil compared

to 212 mg and 178 mg with the fish oil. Subjects completed a GI tolerability questionnaire and a checklist for assessing general symptoms. Compliance was monitored by subject interviews and capsule counts. At the end of the trial, significant increases were seen in plasma levels of EPA and DHA as compared to control with no significant differences between krill oil and fish oil. Safety and tolerability were also comparable.

Very few randomized studies have examined the effects of krill oil on cardiovascular health or hyperlipidemia. In one of the earliest trials, krill oil (source: Neptune krill oil) was evaluated as a natural treatment for hyperlipidemia in a 12-week double-blind, randomized trial.[26] Patients with mildly high to very high cholesterol (193.9-347.9 mg/dL) and triglyceride levels (203.8-354.4 mg/dL) were given krill oil, fish oil, or placebo for 12 weeks. Krill oil was given as either a low dose of 1 or 1.5 g daily or a high dose of 2 or 3 g daily based on the person's body mass index (BMI; <30 or ≥30). The fish oil group received a daily 3 g dose providing 540 mg of EPA and 360 mg of DHA. Placebo patients were given microcrystalline cellulose. Each of the 4 groups included 30 patients with no crossover. Compared to baseline, both the low- and high-dose krill oil groups demonstrated improvements in all lipid parameters compared to fish oil or placebo. Total cholesterol decreased 13% to 18% for both krill oil groups versus a 6% decrease for fish oil and a 9% increase for placebo (all *P*s < .001 compared to baseline). LDL-C was lowered 32% to 39% with krill oil compared to a 5% decrease with fish oil and a 13% increase with placebo (all *P*s <.001 compared to baseline). HDL-C increased 42% to 60% ($P < .001$) with krill oil compared to 4% increases with either fish oil or placebo ($P = .002$ and $P = .850$, respectively, compared to baseline). Triglyceride levels showed nonsignificant decreases with low-dose krill oil, fish oil, or placebo. However, the high-dose krill oil group showed a 27% reduction ($P = .028$). Following the initial 12-week study, patients in the low-dose krill oil group continued for another 12 weeks. These patients were able to maintain lipid reductions and in some cases achieve further reductions during this follow-up phase with a lower maintenance dose of 500 mg per day. While the findings for krill oil were impressive, the magnitude of the changes in lipid measures was considerably higher than what one might expect. Additionally, comparison is limited by the fact that the EPA and DHA content of the krill oil supplements was not provided. Thus these findings require further validation.

An open-label randomized parallel study examined the comparative effects of krill oil and fish oil in 122 participants documented to have no other routine sources of omega-3s.[21] Participants were randomized to 1 of 3 groups: krill oil 3 g daily, fish oil 1.8 g daily, or no supplementation for 7 weeks. A total of 115 participants finished the study. The krill oil used in this study was extracted from Antarctic krill. The daily dose was 6 capsules, each containing 500 mg of oil providing 90.5 mg EPA + DHA and 103.5 mg of omega-3 polyunsaturated fatty acids (PUFAs). The omega-3 fish oil source was a Norway product given in a daily dose of 3 capsules containing 600 mg each of fish oil with 288 mg EPA + DHA and 330 mg of omega-3 PUFAs. In total, the daily amount of krill oil was approximately 63% of the dosage contained in the fish oil.

Blood samples were taken after an overnight fast of at least 12 hours at baseline and at the final visit. Plasma levels of EPA, DHA, and docosapentaenoic acid (DPA) increased significantly during the intervention in both the krill oil and fish oil groups compared to control. During the intervention phase, small changes were seen in levels of HDL-C, LDL-C, and triglycerides. However, the only significant change was the increase in LDL-C within the fish oil group ($P = .039$). No differences were seen in the HDL-C / triglyceride ratio within the fish oil or control groups. Conversely, the ratio was significantly increased in the krill oil group. Changes in apolipoprotein B (Apo B-100) were minor and nonsignificant for all study groups. Only the within change in Apo B-100 levels for the krill oil group was significant. In addition, no significant increases were seen among the 3 groups in markers for inflammation, hemostasis, or oxidative stress. Withdrawal rates were similar among the 3 groups. The comparable increases in EPA and DHA among the krill oil users despite a lower dose of omega-3 PUFAs compared to the fish oil group are consistent with earlier studies suggesting that krill oil is a more bioavailable source of omega-3 PUFAs.

Another study specifically addressed the impact of krill oil on serum triglycerides and the omega-3 index.[23] In a double-blind, randomized, placebo-controlled trial, 300 patients with triglyceride levels of 150 to 499 mg/dL were given varying doses of krill oil (0.5, 1, 2, or 4 g per day) or olive oil (placebo) for 12 weeks. These amounts of krill oil corresponded to 100, 200, 400, or 800 mg of EPA+DHA per day. Participants reported low consumption of fatty fish defined as less than twice per month. Fasting triglyceride levels were measured at baseline, 6, and

12 weeks. In an effort to increase statistical power, the final analyses pooled all krill oil patients regardless of dose. Compared to placebo, patients on krill oil demonstrated a 10.2% reduction in triglyceride levels. No differences in LDL-C levels were observed. Perhaps the most important finding from this study was the significant increase in the omega-3 index in all krill oil groups seen at both 6 and 12 weeks. The corresponding changes were 8%, 18%, 29%, and 73% for the 0.5, 1, 2, and 4 g krill oil dose compared to -3% with placebo. A major limitation of this study is the high intra-individual variability that occurred in the fasting triglyceride measurements. Because this had not been taken into account in the power calculations, the investigators were forced to pool all of the krill oil users into one group despite varying doses. Overall, the average daily dose of krill oil was 1.875 g providing 385 mg of EPA+DHA. This resulted in approximately a 6% reduction in triglyceride levels compared to baseline. This daily dose is lower than that used in earlier studies evaluating triglycerides. Additional studies with multiple measurements of triglyceride levels for each individual will be needed to confirm these findings.

The minimal number of clinical studies and substantial heterogeneity of designs preclude any definitive conclusions. Taken as a whole, however, these randomized trials provide preliminary evidence that krill oil is at least equivalent to and perhaps better than fish oil at increasing blood levels of EPA and DHA. However, it is not known whether these changes would translate into improved cardiovascular outcomes. Additional studies are needed to further explore the effects of krill oil on the lipid panel and, in particular, the potential impact on triglyceride reduction.

CLINICAL RECOMMENDATIONS

Data supporting the use of EPA+DHA for potential cardiovascular benefit were derived from trials involving increased fish consumption or fish oil supplementation. These findings shaped the recommendations for the American Heart Association's (AHA) Scientific Statement on Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease.[1] Key messages from this document are summarized in **Table 1.** Essentially, patients must consume a lower 1 g dose of EPA+DHA for cardioprotection or a higher 2 to 4 g dose for triglyceride reduction. Although the lower dose can often be achieved with dietary fish, the high dose generally requires supplementation. Additionally, in our experience, most patients prefer the convenience of supplementation to that of dietary intake regardless of the intended purpose.

The AHA position statement, published in 2002, does not recognize krill oil as an omega-3 supplement. This is understandable considering that the emergence of krill oil began after the AHA recommendations. However, no other major position statements regarding cholesterol or cardiovascular risk prevention that have been published more recently address the appropriate use of krill oil, including the 2013 ACC/AHA cholesterol guidelines.[27] As such, krill oil should not be considered first-line therapy for omega-3 intake and cardioprotection. Additionally, krill oil does not appear to be effective for clinically relevant triglyceride lowering, because randomized controlled trials indicate only modest reductions.[23] Therefore, krill oil cannot be recommended for hypertriglyceridemia at this time.

Because of these factors, krill oil currently has a limited role in cardiovascular risk prevention, with the potential to expand as more research is completed. Most studies evaluating the impact of krill oil on the omega-3 index indicate efficient absorption of EPA+DHA.[20,21] The omega-3 index is reflective of the EPA+DHA consumption recommended by the AHA and the potential for cardioprotection.[12] Thus, it is reasonable to consider krill oil as an alternative for achieving cardiovascular benefits in patients who are unable to increase fish consumption or utilize fish oil. Specific patient groups that may be candidates for krill oil include those with an aversion to dietary fish and individuals unable to swallow the large fish oil softgels or who have a dislike for the liquid. If the efficient uptake of EPA+DHA from krill oil that has been observed in smaller studies is replicated in larger randomized controlled trials, patients may be able to obtain cardioprotection at a lower EPA+DHA intake than what is currently recommended by the AHA. Additionally, krill is sensitive to degradation and the process for obtaining the key components is more complex than that of fish oil. In view of these issues, we emphasize the importance of pharmacists recommending krill oil products only from reliable manufacturers.

CONCLUSIONS

The potential cardiovascular benefits of dietary omega-3 fatty acids are well documented. For individuals who cannot achieve adequate dietary intake or require higher doses for triglyceride reduction, fish oil supplements are proven to be an effective alternative. Likewise, the initial studies of krill oil

Table 1. American Heart Association guidelines for omega-3 fatty acid consumption[1]

Goal	Recommendation
Cardioprotection	
Patients without a history of CVD	Consume oily fish 2 or more times weekly.
Patients with a history of CHD	Consume 1 g daily of EPH+DHA, preferably from oily fish. Fish oil supplements may be used with physician consultation.
Triglyceride lowering	Consume 2-4 g daily of EPA+DHA as capsules with physician consultation.

Note: CHD = coronary heart disease; CVD = cardiovascular disease; EPA+DHA = eicosapentaenoic acid+docosahexaenoic acid.

appear promising, offering the efficient delivery of omega-3 fatty acids in a smaller, more convenient capsule. However, the cardiovascular benefits of krill oil remain unproven. Pharmacists should encourage patients and consumers to increase their dietary intake of fish in order to meet the recommended AHA guidelines. For individuals with inadequate consumption, fish oil supplements should be recommended. For those who are unwilling or unable to tolerate fish oil supplements, krill oil appears to be a safe alternative with the potential for comparative benefits. Pharmacists should advise patients on the appropriate dose or serving size of supplements needed to obtain the necessary amount of omega-3s for cardioprotection. Patients seeking triglyceride lowering should be advised to consult with their physician about using the required higher dosage of supplemental or prescription fish oil products.

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