Expert Opinion: Omega-3 Fatty Acids and Bleeding—Cause for Concern?

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Omega-3 fatty acid ethyl esters have well-known triglyceride-lowering properties and were shown >30 years ago to inhibit platelet function. With the recent US Food and Drug Administration (FDA) approval of these agents for treating severe triglyceride elevations, concerns about excess bleeding naturally arise. However, an objective assessment of the evidence for clinically significant bleeding reveals that such concerns are unfounded. As such, the benefits of triglyceride lowering with omega-3 fatty acids more than outweigh any theoretical risks for increased bleeding. **(Am J Cardiol 2007;99[suppl]:44C–46C)**

As the health benefits of omega-3 fatty acids become clearer, interest in defining the potential adverse effects of these nutrients naturally increases. In the review by Bays[1] in this supplement, the possibility of increased risk for bleeding with omega-3 fatty acids is addressed. Bays clearly describes the role of omega-3 fatty acids in eicosanoid metabolism, which forms the biochemical basis for the concern for increased bleeding with omega-3 fatty acids. He concludes that although there is little evidence for increased risk for clinically significant bleeding with omega-3 fatty acid supplementation, clinicians should be mindful of this as a theoretical possibility. This commentary provides a more detailed discussion of the evidence supporting this conclusion.

The relevant clinical question is the following: What is the evidence that taking long-chain omega-3 fatty acids in doses of 1–4 g/day causes clinically significant bleeding? To answer that question, studies were examined in which these doses (and typically even greater doses) were provided to patients who underwent major vascular surgery (coronary artery bypass grafting or endarterectomy) or femoral artery puncture for either diagnostic cardiac catheterization or percutaneous transluminal coronary angioplasty.

There have been 2 studies in which patients who underwent coronary artery bypass grafting were given omega-3 fatty acids, 2 trials including carotid endarterectomy, and 15 trials in which omega-3 fatty acids were tested in patients who underwent femoral artery catheterization. These studies are summarized in Table 1,[2–20] along with the concomitant medications and findings with regard to bleeding complications. In these studies, the risk for clinically significant bleeding was virtually nonexistent.

Several years ago, Knapp[21] reviewed the published research regarding omega-3 fatty acids and human thrombosis and hemostasis. In addition to noting the lack of significant bleeding with omega-3 fatty acid supplementation in cardiovascular studies to date, he also referred to studies in pregnant women in which supplementation with omega-3 fatty acids 2.7 g/day did not lead to increased blood loss at delivery,[22] and he noted that supplemented dialysis patients were not at increased risk for bleeding.[23,24] There had been 1 report that fish oil (5 g) caused increased risk for nosebleeds in children with hypercholesterolemia,[25] but this could not be replicated in a later trial in children on dialysis.[26]

Thus, the experience has been virtually unanimous: omega-3 fatty acid supplements do not increase the risk for clinically significant bleeding, even in patients also being treated with antiplatelet or antithrombotic medications. Anecdotal reports of an increased bruising tendency have not been tested in a controlled setting, nor has the possible adverse interaction between omega-3 fatty acids and newer antiplatelet drugs (eg, clopidogrel) been examined directly.

Given our present knowledge, I would agree with Bays[1] that we are "confident" that omega-3 fatty acids do not increase risk for adverse bleeding episodes. However, I would consider the evidence to be at the "A" (well designed randomized controlled clinical trials)—instead of "C" (reports to regulatory agencies; multiple case studies; strong trends; prospective cohort studies; metabolic or clinical surrogate studies)—level, given the number of randomized, controlled clinical trials in which these agents were found to be safe, bearing in mind that more studies are still needed to determine the combined effects of glycoprotein IIb/IIIa inhibitors and omega-3 fatty acids. Nevertheless, in considering the risks and benefits of omega-3 fatty acids for cardiovascular risk reduction, the latter continue to outweigh the former.

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Table 1
Summary of reports of the effects of omega-3 fatty acids on bleeding complications

Procedure	EPA + DHA Dose (Product)	Pretreatment (days)	Duration (mo)	Patients (n)	Concomitant Medications	Bleeding Complications
CABG[2]	3.4 g (Omacor)*	2	12	610	Aspirin or warfarin	"The bleeding time increased moderately in both groups, and there was no group difference"
CABG[3]	4.3 g (unnamed) fish oil[†]	28	To surgery	30	Heparin during CABG	"The patients . . . did not have significantly increased bleeding at or after surgery compared to matched controls"
PTCA[4]	3.6 g (MaxEPA)[‡]	0	12	108	None	No patient had undesirable bleeding effects, and the combination appears quite safe
PTCA[5]	3.0 g (MaxEPA)[‡]	1–2	6	120	Aspirin, dipyradimole, CCB, nitrates	Only adverse events reported were: nausea (n = 4) and diarrhea (n = 1)
PTCA[6]	6.9 g (NIH Fish Oil)[§]	12–14	6	447	Aspirin	"No difference in clinically significant bleeding was noted. . . . All bleeding times were within the normal range"
PTCA[7]	5.4 g (MaxEPA)[‡]	7	6	82	Aspirin and dipyradimole	"We did not observe a significant prolongation of bleeding time"
PTCA[8]	3.15 g (Ameu)[‖]	0	4.5	204	Aspirin	"None of the patients demonstrated or reported on bleeding complications"
PTCA[9]	4.5 g (Promega)[¶]	0	6	194	Aspirin	No specific mention of bleeding, but stated that "six months of therapy appears safe"
PTCA[10]	5.4 g (MaxEPA)[‡]	6	4.5	814	Aspirin (all); 50% also taking low-molecular-weight heparin	"Bleeding less frequent in fish oil group"
PTCA[11]	3 g (MaxEPA)[‡]	1	4	108	Aspirin	"No patient suffered from bleeding complications"
PTCA[12]	3 g (MaxEPA)	4.3	6	107	Aspirin and CCB	"No patients suffered from bleeding complications during follow up"
PTCA[13]	4.5 g (MaxEPA)[‡]	21	6	205	Aspirin	"None of the patients reported bleeding . . . attributable to the fish oil supplements"
PTCA[14]	6 g (Super EPA 500[H] or Promega[‖])	5.4	4.5	242	Aspirin and dipyradimole	4 events in 124 patients in the omega-3 group: at PTCA, 2 at puncture site; on study, 1 gastrointestinal bleed requiring transfusion and 1 heme-positive stool (nonsignificant vs placebo)
PTCA[15]	5.1 g (Omacor)*	14	6	388	Aspirin, nitrates, heparin, and nifedipine, all during procedure	Bleeding not mentioned: "no obvious adverse effects to the capsules were noted"
PTCA[16]	5.1 g before, 2.6 g after (Esapent)*	30	6	257	Aspirin	"Lack of any significant side effect [on] bleeding"
Endarterectomy[17]	1.4 g/day (MaxEPA)[‡]	42	Through surgery	170	Aspirin (100% of patients)	"No bleeding complications were noted during the intervention period or in the immediate period post-surgery" (P. Calder, personal communication)
Endarterectomy[18]	16–21 g/day (MaxEPA)[‡]	Median 30	Through surgery	29	None listed	"There were no clinically significant bleeding complications" (J. Rapp, personal communication)
Coronary angiography[19]	3.3 g for 3 mo; 1.6 g for 21 mo[‡]	None	24	223	Aspirin (91% of patients)	"Minor hematoma, but no other complication, was associated with the second episode of coronary angiography"
Coronary angiography[20]	4.8 g (Promega)[H]	None	28	59	Aspirin (95% of patients)	"There were no serious adverse events related to bleeding. This was not an issue for the cardiologists doing the caths" (F. Sacks, personal communication)

CABG = coronary artery bypass grafting; CCB = calcium channel blocker; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; EPA and DHA composition of products used (ee = ethyl ester; tg = triglyceride): Esapent: trade name of Omacor in Italy at that time; MaxEPA (or Ameu): 30% EPA + DHA tg; ratio = 1.5:1.0; NIH Fish Oil: 80% EPA + DHA ee; ratio = 1.5:1.0; NIH fish oil (fish oils test materials-now defunct); Omacor: 84% EPA + DHA ee; EPA/DHA ratio = 1.2:1.0; Promega: 50% EPA + DHA ee; ratio = 2.3:1.0; PTCA = percutaneous transluminal coronary angioplasty; Super EPA 500: 56% EPA + DHA ee; ratio 1:1; Unnamed fish oil; 43% EPA + DHA ee; ratio 2.3:1.0. * Pronova Biocare, Oslo, Norway; [†] PGE Technologies, Marblehead, MA; [‡] Seven Seas Health Care, Hull, United Kingdom; [§] National Institutes of Health, Office of Dietary Supplements; [‖] Omega-Pharma, Berlin, Germany; [¶] Parke-Davis, Morris Plains, NJ; [H] Pharmacaps Corporation, Elizabeth, NJ.

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