

# Comparison of Bleeding Complications With Omega-3 Fatty Acids + Aspirin + Clopidogrel—Versus—Aspirin + Clopidogrel in Patients With Cardiovascular Disease

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Fish oil is used to lower triglycerides and for the secondary prevention of cardiovascular events in patients with coronary artery disease. Many of these patients will also be taking aspirin and clopidogrel. Any of these medications alone can increase the risk of bleeding; however, the risk of bleeding in patients taking all 3 of these medications has not been studied. We retrospectively reviewed the medical records for bleeding complications in 182 patients, most with coronary artery disease (mean age  $61 \pm 11$  years, 82% men) and being treated with high-dose fish oil (mean dose  $3 \pm 1.25$  g), aspirin (mean dose  $161 \pm 115$  mg), and clopidogrel (mean dose 75 mg), and in 182 age- and gender-matched controls treated with aspirin and clopidogrel alone. During a mean follow-up period of 33 months, 1 major bleeding episode occurred in the treatment group and no major bleeding episodes occurred in the control group ( $p = 1.0$ ). During follow-up, 4 minor bleeding episodes (2.2%) occurred in the treatment group and 7 (3.9%) in the control group. More patients had minor bleeding complications in the control group than in the treatment group; however, the difference was not statistically significant ( $p = 0.5$ ). In conclusion, high-dose fish oil is safe in combination with aspirin and clopidogrel and does not increase the risk of bleeding compared with that seen with aspirin and clopidogrel alone. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;104:1052–1054)

Clopidogrel, in combination with aspirin, is commonly used in the treatment of patients with unstable angina pectoris and non-ST-segment elevation myocardial infarction, as well as in patients undergoing percutaneous coronary intervention.<sup>1</sup> Often, these patients are treated long term with both antiplatelet agents, especially those receiving a drug-eluting stent. Studies have demonstrated a small, but significant, excess risk of major and minor bleeding with the combination of clopidogrel and aspirin compared to either clopidogrel or aspirin alone.<sup>2–4</sup> Omega-3 fatty acids, used to lower triglycerides and for the secondary prevention of cardiovascular disease,<sup>5–8</sup> also affect platelet aggregation.<sup>9</sup> In clinical practice, patients with coronary artery disease might be taking all 3 of these medications. However, the risk of bleeding from the combination of all 3 drugs has not been studied. The purpose of the present study was to evaluate the risk of bleeding in patients taking high-dose omega-3 fatty acids in combination with aspirin and clopidogrel.

## Methods

Patients were identified from a large private practice cardiology group. The patient database was screened for those who had been prescribed omega-3 fatty acids, as well

as aspirin and clopidogrel. The control group included an equal number of age- and gender-matched patients taking aspirin and clopidogrel but not any omega-3 fatty acid supplements. Patients taking warfarin were excluded from both groups. The university institutional review board approved the study.

We retrospectively reviewed the electronic medical records for patient demographics, a clinical history of coronary artery disease, peripheral vascular or cerebrovascular disease, the patient's fish oil, aspirin, and clopidogrel doses, and the occurrence of bleeding complications. A major bleeding episode was defined as one that had led to a decrease in hemoglobin of  $>2$  g, an intracerebral hemorrhage, or any bleeding episode that required hospitalization. A minor bleeding episode was defined as epistaxis, abnormal bruising, or gastrointestinal bleeding that did not require hospitalization nor led to a decrease in the hemoglobin level of  $>2$  g. The data are presented as percentages and the mean values with standard deviations. Statistical significance was assessed using the 2-tailed Fisher exact test to compare proportions and the Student *t* test to compare the mean values. A *p* value of  $<0.05$  was used to define statistical significance.

## Results

We retrospectively identified 182 patients (mean age  $61 \pm 11$  years, 82% men) who were taking fish oil (mean dose  $3 \pm 1.25$  g), aspirin (mean dose  $161 \pm 115$  mg), and clopidogrel (mean dose 75 mg). No difference was seen in the patient characteristics between the group taking omega-3 fatty acids and the control group (Table 1). Of the 182

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Table 1  
Patient characteristics

Variable	High-Dose Fish Oil Plus Aspirin and Clopidogrel (n = 182)	Aspirin and Clopidogrel Alone (n = 182)	p Value
Age (years)	61 ± 11	61 ± 12	0.70
Men	149 (82%)	140 (77%)	0.29
Women	33 (18%)	42 (23%)	0.29
Coronary artery disease	177 (97%)	180 (99%)	0.40
Peripheral arterial disease	13 (7%)	12 (6.5%)	1.0
Cerebrovascular disease	22 (12%)	13 (7%)	0.15
Diabetes mellitus	50 (27%)	55 (30%)	0.63
Hypertension	106 (58%)	122 (67%)	0.10
Fish oil dose (g)	3 ± 1.25	—	
Docosahexaenoic acid dose (mg)	1,125	—	
Eicosapentaenoic acid dose (mg)	1,395	—	
Clopidogrel dose (mg)	75 ± 0	75 ± 0	1.0
Aspirin dose (mg)	160 ± 115	167 ± 116	0.55

Data are reported as mean ± SD or number of patients (percentages).

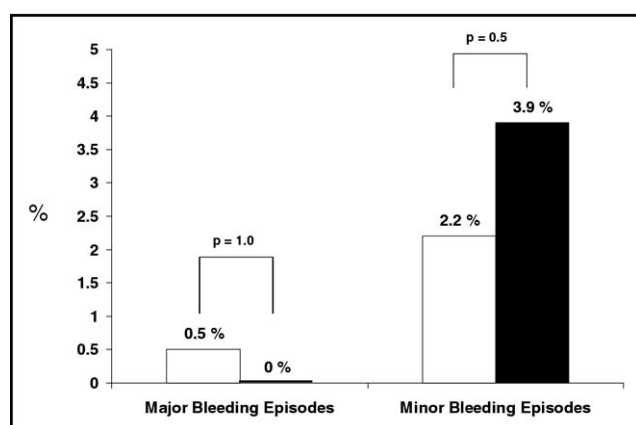


Figure 1. Incidence of major and minor bleeding episodes was low in patients taking high-dose fish oil, aspirin, and clopidogrel (white bars). No difference was found in bleeding episodes in patients taking all 3 drugs (white bars) compared to control group taking aspirin and clopidogrel alone (black bars).

patients taking omega-3 fatty acid supplements, 172 (95%) were using the prescription formulation Lovaza and 10 were using an over-the-counter formulation. Most patients were taking high doses of fish oil, with 140 (77%) of the 182 patients taking >2 g daily.

During a mean follow-up of 33 months, only 1 patient had a major bleeding episode in the group taking omega-3 fatty acid supplements plus aspirin and clopidogrel (rectal bleeding requiring transfusion in 1 patient with rectal carcinoma). No patient in the control group had a major bleeding episode ( $p = 1.0$ ). During follow-up, 4 patients had a minor bleeding episode (2.2%) in the group taking high-dose omega-3 fatty acids plus aspirin and clopidogrel (2 cases of epistaxis, 1 of bruising, and 1 of mild rectal bleeding) compared to 7 patients (3.9%) in the control group with a minor bleeding episode (3 cases of bruising, 1 of hematuria, 1 of mild rectal bleeding, 1 of epistaxis, and 1 of

epistaxis and ear bleeding; Figure 1). More patients had a minor bleeding episode in the control group taking aspirin and clopidogrel alone than in the group taking all 3 medications (high-dose omega-3 fatty acid supplements, aspirin, and clopidogrel), but the difference was not significant ( $p = 0.5$ ).

## Discussion

In our study, the use of high-dose omega-3 fatty acids in patients already taking aspirin and clopidogrel was not associated with an increased risk of excess bleeding. These findings are consistent with those of other studies evaluating the risk of bleeding when omega-3 fatty acids were prescribed in combination with either aspirin or warfarin. Eritsland et al<sup>10</sup> randomized 610 patients already taking either 300 mg of aspirin daily or warfarin after coronary artery bypass surgery to 4 g of prescription formulation omega-3 fatty acids or placebo. They reported no significant difference in the number of bleeding episodes at 1 year in those patients taking high-dose fish oil compared to the placebo group. Leaf et al<sup>11</sup> randomized 551 patients taking 325 mg aspirin daily after percutaneous coronary intervention to an even a higher dose of fish oil, 8 g of omega-3 fatty acids (providing a total of 6.9 g of eicosapentaenoic acid and docosahexaenoic acid daily) or placebo. At 6 months of follow-up, the incidence of bleeding was low at 3%, and no difference in bleeding episodes was detected between the groups. In another small study, no difference was found in the bleeding episodes in patients taking long-term warfarin therapy randomized to ≤6 g of fish oil daily.<sup>12</sup> Our study has provided longer follow-up than the previous studies, and our findings further support the safety of high-dose omega-3 fatty acids when used in combination with antiplatelet or antithrombotic therapy.

Fish oil contains the N-3 polyunsaturated fatty acid eicosapentaenoate. Fish oil supplementation markedly increases the eicosapentaenoate content of phospholipids from red blood cells and platelets and alters their pattern of thromboxane and prostacyclin synthesis. These effects are thought to be responsible for the antiplatelet and antithrombotic properties of omega-3 fatty acids.<sup>9</sup> Although, omega-3 fatty acids at higher doses modestly prolong the bleeding time,<sup>9</sup> little evidence exists to suggest that omega-3 fatty acids, even at high doses, cause clinically significant bleeding. Aspirin inhibits platelet aggregation by inhibition of cyclooxygenase, and clopidogrel reduces platelet activation by way of the adenosine diphosphate receptor-dependent pathways. These findings raised concern that high-dose fish oil could further increase the risk of bleeding in patients already taking aspirin and clopidogrel; however, our results do not support an increased risk of bleeding when high-dose fish oil is prescribed in combination with aspirin and clopidogrel.

Our study had several limitations. First, the study was retrospective. This could have led to either underestimating or overestimating the risk of bleeding in our study patients. However, the incidence of major and minor bleeding episodes seen in our study was within the range of bleeding complications reported by other studies of patients taking combination aspirin and clopidogrel.<sup>2-4</sup> Second, most of

our patients were taking the prescription formulation of omega-3 fatty acids, and high-dose nonprescription formulations might not provide the same safety as the prescription formulation. However, a previous study using a nonprescription formulation of fish oil did not show an increased risk of bleeding when given in combination with aspirin.<sup>11</sup>

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