Relation Between Red Blood Cell Omega-3 Fatty Acid Index and Bleeding During Acute Myocardial Infarction

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Omega-3 fatty acids have multiple cardiovascular benefits but may also inhibit platelet aggregation and increase bleeding risk. If this platelet inhibition is clinically meaningful, patients with the highest omega-3 indexes (red blood cell eicosapentaenoic acid plus docosahexaenoic acid), which reflect long-term omega-3 fatty acid intake, should be at the risk for bleeding. In this study, 1,523 patients from 24 United States centers who had their omega-3 indexes assessed at the time of acute myocardial infarction were studied. The rates of serious bleeding (Thrombolysis In Myocardial Infarction [TIMI] major or minor) and mild to moderate bleeding (TIMI minimal) were identified in patients with low (<4%), intermediate (4% to 8%), and high (>8%) omega-3 indices. There were no differences in bleeding across omega-3 index categories. After multivariate adjustment, there remained no association between the omega-3 index and either serious (per 2% increase, relative risk 1.03, 95% confidence interval 0.90 to 1.19) or mild to moderate bleeding (per 2% increase, relative risk 1.02, 95% confidence interval 0.85 to 1.23). In conclusion, no relation was found between the omega-3 index and bleeding in this large, multicenter cohort of patients with acute myocardial infarction, suggesting that concerns about bleeding should not preclude the use of omega-3 supplements or increased fish consumption when clinically indicated. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;109:13–18)

Several previous studies have found no relation between omega-3 supplementation and bleeding in patients with cardiovascular disease, yet most of these studies focused on long-term bleeding risk, and few studied patients with acute myocardial infarction (AMI).1 Patients with AMI are at particularly high risk for in-hospital bleeding because of intensive treatment with multiple potent antithrombotic agents (such as intravenous heparin, glycoprotein IIb/IIIa inhibitors, and dual-antiplatelet therapy) and the use of invasive diagnostic and therapeutic procedures. Accordingly, if guideline-recommended omega-3 fatty acid intake2 is associated with increased bleeding risk in the setting of modern anti-thrombotic regimens, patients hospitalized with AMI who have high red blood cell omega-3 indexes should be most likely to develop bleeding complications. We studied the relation between the omega-3 index and bleeding in 1,523 patients from 24 United States hospitals who had their omega-3 indexes assessed at the time of AMI.

Methods

The design and methods of the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients’ Health Status (TRIUMPH) study have been previously reported.3 Patients were ≥18 years of age, with elevated cardiac biomarkers (troponin or creatine kinase-MB fraction assessed <24 hours after admission) and had supporting evidence of AMI (electrocardiographic ST-segment changes or prolonged ischemic signs or symptoms). Participants were required either to present to the enrolling hospital or to have been transferred within 24 hours of presentation, so the primary clinical decision making occurred at the enrolling center. Patients with elevated cardiac biomarkers caused by elective coronary revascularization were excluded. Trained data collectors performed detailed baseline chart abstractions to document patients’ medical histories, the processes of inpatient care, laboratory results, and treatments. Each patient underwent a standardized interview by a research staff member to document sociodemographic and clinical data. Patients were enrolled in TRIUMPH from April 11, 2005, to December 31, 2008. All 1,523 who were enrolled before September 28, 2007, had red blood cells collected for omega-3 analyses and formed the analytic cohort for the present study. All patients provided written informed consent approved by the partic-
ity risk) if their omega-3 index was moderate omega-3 indices when values were 4% to 8%, and as having a high omega-3 index (favorable, associated with lower mortality risk) when their omega-3 values were >8%.4–6

Trained data collectors prospectively recorded all in-hospital bleeding events, the site of bleeding (cardiac catheterization site, gastrointestinal, intracranial, retroperitoneal, or other), and the severity of bleeding using the Thrombolysis In Myocardial Infarction (TIMI) classification.7 TIMI major bleeding was defined as intracranial hemorrhage or a hemoglobin decrease >5 g/dl. TIMI minor bleeding was assigned if the decrease in hemoglobin was 3 to 5 g/dl in the setting of observed bleeding. Any bleeding episode with a decrease in hemoglobin <3 g/dl was classified as TIMI minimal bleeding. All TIMI categories accounted for blood transfusion, with adjustment of hemoglobin values by 1 g/dl per unit transfused. Because TIMI major and minor bleeding represent clinically meaningful bleeding, the composite of these events was considered together as serious bleeding. TIMI minimal bleeding, which
has not been linked to poor outcomes but could influence recommendations for antiplatelet or anticoagulant therapy, was considered mild to moderate bleeding.

The patient characteristics, treatments and bleeding rates of patients with low, intermediate, and high omega-3 indexes are presented as mean ± SD for continuous variables and were compared using 1-way analysis of variance. Categorical variables are presented as proportions and were compared using chi-square tests. To identify the independent association between the omega-3 index and bleeding, we fit separate hierarchical modified Poisson regression models for each bleeding outcome (serious and mild to moderate). These models accounted for clustering within hospitals by including enrolling hospital as a random variable. We adjusted for potentially important confounders that we identified a priori on the basis of previous research and clinical experience. These covariates included age and gender, history

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Table 2
In-hospital bleeding by omega-3 index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Omega-3 Index</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% to &lt;4% (n = 408)</td>
<td>4% to 8% (n = 1,036)</td>
<td>&gt;8% (n = 79)</td>
</tr>
<tr>
<td>Serious bleeding (TIMI minor or major)</td>
<td>27 (6.6%)</td>
<td>88 (8.5%)</td>
</tr>
<tr>
<td>Mild to moderate bleeding (TIMI minimal)</td>
<td>20 (4.9%)</td>
<td>60 (5.8%)</td>
</tr>
<tr>
<td>TIMI bleeding</td>
<td>361 (88.5%)</td>
<td>888 (85.7%)</td>
</tr>
<tr>
<td>None</td>
<td>23 (48.9%)</td>
<td>86 (58.5%)</td>
</tr>
<tr>
<td>Minimal</td>
<td>7 (14.9%)</td>
<td>12 (8.2%)</td>
</tr>
<tr>
<td>Minor</td>
<td>11 (2.7%)</td>
<td>62 (6.0%)</td>
</tr>
<tr>
<td>Major</td>
<td>16 (3.9%)</td>
<td>26 (2.5%)</td>
</tr>
</tbody>
</table>

Figure 1. Association between the omega-3 index and serious bleeding. Forest plot of multivariate model for TIMI major and TIMI minor bleeding. CI = confidence interval; PCI = percutaneous coronary intervention.

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Coronary Artery Disease/Omega-3 Index and Bleeding During AMI
of chronic heart failure, peripheral arterial disease, initial creatinine, initial hemoglobin, body weight, myocardial infarction type (ST-segment elevation myocardial infarction vs non–ST-segment elevation myocardial infarction), prehospital warfarin use, in-hospital cardiac catheterization or percutaneous coronary intervention, and use of bivalirudin, intravenous heparin, glycoprotein IIb/IIa inhibitors, and thienopyridines. We also tested for clinically and statistically significant interactions (p < 0.05) between omega-3 index and key AMI treatments. These included interactions of omega-3 index with heparin, thienopyridine, bivalirudin, glycoprotein IIb/IIa inhibitor use, and cardiac catheterization or percutaneous coronary intervention. Missing data for model covariates were minimal (2 patients were missing initial creatinine values).

We calculated the power to detect clinically meaningful differences in the rate of bleeding, defined as a 25% relative difference in bleeding rates between groups, for major bleeding and mild to moderate bleeding. We then calculated the power to detect these differences for the comparison of patients with omega-3 indices of <4% versus ≥4% and for omega-3 indexes of ≤8% versus >8%. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

### Results

At the time of AMI, 408 patients (26.8%) had low omega-3 indices (<4%), 1,036 (68.0%) had intermediate values (4% to 8%), and 79 (5.2%) had high omega-3 indices (>8%). The mean omega-3 index was 3.3 ± 0.5%, 5.4 ± 1.0%, and 9.3 ± 1.0% among those in low, intermediate, and high groups, respectively. Patients with higher omega-3 indices were older, more frequently had histories of previous myocardial infarction and coronary revascularization, and had higher discharge to 6-month Global Registry of Acute Coronary Events (GRACE) scores (Table 1). They also had lower admission hemoglobin values, were more likely to be taking omega-3 supplements, and were less frequently treated with fibrinolytic therapy.

There was no crude association between the omega-3 index and either serious bleeding or mild to moderate bleeding (Table 2), and there were no significant differences in the site of bleeding across the omega-3 index categories. There were also no significant differences in bleeding rates after stratifying the population by use of omega-3 supplements at the time of arrival at the hospital (serious bleeding: 14 of 251 [5.5%] using omega-3 supplements vs 103 of 1,258 [8.2%] not using omega-3 supplements, p = 0.18; mild to moderate bleeding: 17 of 251 [6.8%] using omega-3 supplements vs 67 of 1,258 [5.3%] not using omega-3 supplements, p = 0.43).

After multivariate adjustment, there was no significant association between the omega-3 index and the risk for either serious bleeding (per 2% increase in the omega-3 index, relative risk 1.03, 95% confidence interval 0.90 to 1.19, p = 0.66; Figure 1) or mild to moderate bleeding (per 2% increase in the omega-3 index, relative risk 1.02, 95% confidence interval 0.85 to 1.23, p = 0.83; Figure 2). The 2 models demonstrated good discrimination of bleeding.
events (serious bleeding model C statistic = 0.76, mild to moderate bleeding model C statistic = 0.80). There was 99% power to detect a 2% absolute difference in the major bleeding rate and a 1.5% difference in the mild to moderate bleeding rate when comparing patients with omega-3 indexes <4% to those with omega-3 indexes ≥4%. When comparing patients with omega-3 indexes <8% to those with omega-3 indexes ≥8%, there was 97% power to detect a 2% difference in the incidence of major bleeding and 79% power to detect a 1.5% difference in the rate of mild to moderate bleeding between the groups.

When interaction terms were added to the multivariate models, we found no clinically or statistically significant interactions between the omega-3 index and heparin, thienopyridine, bivalirudin, glycoprotein IIb/IIIa inhibitor use, and cardiac catheterization or percutaneous coronary intervention.

Discussion

We found no relation between omega-3 fatty acid levels and bleeding in this large AMI cohort that included detailed assessments of the omega-3 index and bleeding events during hospitalization with AMI. Rather than simply assessing omega-3 supplement use, which could be limited by differences in supplement formulations, adherence to therapy, and other dietary practices, we directly measured patients’ red blood cell fatty acid omega-3 index. Because the proposed link between omega-3 fatty acids and bleeding is impaired platelet aggregation,9,10 this analysis allowed a more direct test of the hypothesis that high red blood cell omega-3 levels omega-3 fatty acids could increase risk for clinically meaningful bleeding. The absence of any relation between the omega-3 index and bleeding at the time of AMI (when patients are at high risk for bleeding because of the use of potent antithrombotic medications and invasive management)11,12 suggests that there is little reason for concern about excessive bleeding in patients who take fish oil supplements concurrent with modern medical therapy for AMI.

Previous studies have reported no significant relation between omega-3 intake and bleeding, even when used in conjunction with antithrombotic regimens, including dual-antiplatelet therapy and warfarin.11,12 Most of these studies were small, and none directly assessed the association between omega-3 fatty acid biomarkers and bleeding. Our study included a much larger cohort of patients, all of whom underwent omega-3 index assessment. Moreover, the detailed collection of patient characteristics and treatments allowed us to account for a broad array of potential confounders. Our findings reinforce previous research, suggesting that there is little evidence of increased bleeding risk related to omega-3 fatty acid intake to counterbalance the established benefits of omega-3 supplementation.16–18

We used the red blood cell omega-3 index to assess the relation between omega-3 fatty acid intake and bleeding. Although non-dietary correlates of the omega-3 index have been reported, the omega-3 index is strongly associated with dietary omega-3 fatty acid intake. In a previous study of patients with AMI, we found that patients who consumed non-fried fish more frequently and those who took omega-3 fatty acid supplements had significantly higher omega-3 indexes.6 Measuring the omega-3 index standardizes the exposure of omega-3 intake, because it reflects the net influence of beneficial dietary practices (omega-3 supplement use and fish intake) and poor dietary practices (such as fast food products, which are commonly low in omega-3 fatty acids). This approach also limits misclassification of the exposure related to poor compliance with omega-3 supplementation and differences in the potency of supplements or fish products consumed by patients.

Our findings should be considered in the context of their potential limitations. We did not assess the omega-3 index in all TRIUMPH participants. However, we did obtain blood samples for omega-3 index testing from all patients enrolled before September 28, 2007, when sample collection ceased for administrative reasons. Accordingly, our study reflects a consecutive series, and there is no reason to suspect selection bias. Second, we modeled the omega-3 index as a linear, continuous variable to maximize statistical power. It is possible that nonlinear relations between the omega-3 index and bleeding could be missed by this approach; however, this is unlikely given the lack of any association between omega-3 indexes and bleeding in either model. Finally, patients received antithrombotic medications and invasive procedures at the discretion of the treating physician, and there were differences in treatment between exposure groups. However, we adjusted extensively for the use of antithrombotic medications and invasive management and found no differences in our results.


