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

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Abstract

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 indices (red blood cell eicosapentaenoic [EPA] plus docosahexaenoic acid [DHA]), which reflect long-term omega-3 fatty acid intake, should be at the greatest bleeding risk. We studied 1,523 patients from 24 US centers who had their omega-3 index assessed at the time of AMI. The rates of serious bleeding (TIMI major or minor) and mild-moderate bleeding (TIMI minimal) were identified in patients with low (<4%), intermediate (4–8%) and high (>8%) omega-3 indices. There were no differences in bleeding across omega-3 index categories. After multivariable adjustment, there remained no association between the omega-3 index and either serious (per 2% increase: RR 1.03, 95% CI 0.90–1.19) or mild-moderate (per 2% increase: RR 1.02, 95% CI 0.85–1.23) bleeding. In conclusion, we found no relationship between the omega-3 index and bleeding in this large, multicenter cohort of AMI patients, suggesting that concerns about bleeding should not preclude use of omega-3 supplements or increased fish consumption when clinically indicated.

Keywords

myocardial infarction; bleeding; fatty acids; omega-3; eicosapentaenoic acids; docosahexaenoic acids; outcomes

Several prior studies have found no relation between omega-3 supplementation and bleeding in patients with cardiovascular disease, yet most of these focused upon long-term bleeding

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Data Access and Responsibility:
Drs. Salisbury and Spertus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest and Disclosures:
Adam C. Salisbury, MD, MSc: none
William S. Harris, PhD: Scientific advisor to companies with interests in omega-3 fatty acids such as Monsanto, GSK, Omthera and Acasti Pharma. Dr. Harris also reports ownership interest in OmegaQuant, LLC, a company that offers blood omega-3 testing.
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risk and few have studied patients with AMI.[1] AMI patients are at particularly high risk for in-hospital bleeding due to 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 intake[2] is associated with increased bleeding risk in the setting of modern antithrombotic therapy, patients hospitalized with AMI who have high red blood cell omega-3 indices should be most likely to develop bleeding complications. We studied the relationship between the omega-3 index and bleeding in 1,523 patients from 24 US hospitals who had their omega-3 index assessed at the time of AMI.

METHODS

The design and methods of the TRIUMPH study have been previously reported.[3] Patients were ≥18 years of age, with elevated cardiac biomarkers (troponin or creatine kinase-MB fraction assessed within 24 hours of admission), and had supporting evidence of AMI (electrocardiographic ST-segment changes or prolonged ischemic signs/symptoms). Participants were required either to present to the enrolling hospital or to have been transferred within 24 hours of presentation, so that the primary clinical decision making occurred at the enrolling center. Patients with elevated cardiac biomarkers resulting from an elective coronary revascularization were excluded. Trained data collectors performed detailed baseline chart abstractions to document patients' medical history, the processes of inpatient care, laboratory results and treatments. Each patient underwent a standardized interview by research staff to document sociodemographic and clinical data. Patients were enrolled in TRIUMPH between April 11, 2005, and December 31, 2008. All 1,523 who were enrolled prior to September 28, 2007 had red blood cells collected for omega-3 analyses and formed the analytic cohort for the present study. All patients signed an informed consent approved by the participating institution, and Institutional Review Board approval was obtained at each participating center.

Red blood cells were obtained from EDTA blood samples after the plasma and buffy coat were removed. Briefly, RBC aliquots were heated at 100°C for 10 minutes with methanol containing 14% boron trifluoride. The FA methyl esters generated were extracted with hexane and water and were analyzed with a GC2010 gas chromatograph (Shimadzu Corporation, Columbia, MD) equipped with a 30m capillary column (Omegawax 250, Supelco, Bellefonte, PA). Fatty acids were identified through comparison with a standard FA methyl ester mixture (GLC-727, Nuchek Prep, Elysian, MN). The coefficient of variation for the omega-3 index is <5%. Values are expressed as EPA+DHA as a percentage of total red blood cell fatty acids. Congruent with prior work, patients were classified as having a low omega-3 index (unfavorable, associated with higher mortality risk) if their omega-3 index was <4%, an intermediate value when the omega-3 index was 4%–8% and a high omega-3 index (favorable, associated with lower mortality risk) when the omega-3 value was >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 Hgb decline > 5 g/dl. TIMI minor bleeding was assigned if the drop in Hgb was 3 to 5 g/dl in the setting of observed bleeding. Any bleeding episode with a decline in Hgb < 3 g/dl was classified as TIMI minimal bleeding. All TIMI categories accounted for blood transfusion, with adjustment of Hgb values by 1 g/dl per unit transfused. Since both 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 anti-platelet or anti-coagulant therapy, was considered mild-moderate bleeding.

The patient characteristics and bleeding events of patients with low, intermediate and high omega-3 indices were presented as the mean ± standard deviation for continuous variables, and were compared using one-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-moderate).[8] These models accounted for clustering within hospitals by including enrolling hospital as a random variable. To maximize power, the omega-3 index was modeled as a continuous variable. We adjusted for potentially important confounders that we identified *a priori* based upon the prior literature and clinical experience. These covariates included patients' age and gender, history of chronic heart failure, peripheral arterial disease, initial creatinine, initial hemoglobin, body weight, MI type (ST-segment elevation myocardial infarction vs. non-ST-segment elevation myocardial infarction), pre-hospital 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/IIIa inhibitor use and cardiac catheterization or PCI. Missing data for model covariates were minimal (two patients missing initial creatinine).

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 both major bleeding and mild-moderate bleeding. We then calculated the power to detect these differences for the comparison of patients with an omega-3 index of <4 vs. ≥ 4 and for an omega-3 index of ≤8 vs. > 8. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

At the time of AMI, 408 patients (26.8%) had a low omega-3 index (<4%), 1036 (68.0%) had an intermediate value (4–8%) and 79 (5.2%) had a high omega-3 index (>8%). The mean omega-3 indices were 3.3% ± 0.5%, 5.4 ± 1.0% and 9.3 ± 1.0% in those within the low, intermediate and high groups, respectively. Patients with higher omega-3 indices were older, more frequently had a history of prior MI and coronary revascularization and had higher discharge to 6-month 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 omega-3 indices and either serious bleeding or mild-moderate bleeding (Table 2), and there was no significant difference 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: 14/251 (5.5%) using omega-3 supplements vs. 103/1258 (8.2%) of patients who were not taking omega-3 supplements [p=0.18]; mild-moderate bleeding: 17/251 (6.8%) using omega-3 supplements vs. 67/1258 (5.3%) not taking omega-3 supplements [p=0.43]).

After multivariable adjustment, there was no significant association between the omega-3 index and the risk of either serious bleeding (per 2% increase in the omega-3 index: RR 1.03, 95% CI 0.90–1.19, p=0.66; Figure 1) or mild-moderate bleeding (per 2% increase in

the omega-3 index: RR 1.02, 95% CI 0.85–1.23, p=0.83; Figure 2). Both models demonstrated good discrimination of bleeding events (serious bleeding model c-statistic = 0.76, mild-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-moderate bleeding rate when comparing patients with an omega-3 index of <4% to those with an omega-3 index of ≥ 4%. When comparing patients with an omega-3 index of < 8% to those with an omega-3 index of ≥ 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-moderate bleeding between the groups.

When interaction terms were added to the multivariable 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 PCI.

DISCUSSION

We found no relationship between omega-3 fatty acid levels and bleeding in this large AMI cohort that included detailed assessment of both the omega-3 index and bleeding events during AMI hospitalization. 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. Since 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 supplementation with omega-3 fatty acids could increase bleeding risk. The absence of any relationship between the omega-3 index and bleeding at the time of AMI (when patients are at high risk for bleeding due to 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.

Prior studies have reported no significant relationship between omega-3 intake and bleeding, even when used in conjunction with antithrombotic regimens, including dual antiplatelet therapy and warfarin.[1,13–15] The majority of these studies were small, and none directly assessed the association between omega-3 fatty acid biomarkers and bleeding. Our study includes a much larger cohort of patients, all of whom had the 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 the prior literature, suggesting 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 practices. In a prior study of AMI patients, 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 indices.[6] Measuring the omega-3 index standardizes the exposure of omega-3 intake, since 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 9/28/2007, 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 non-linear relationships 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 indices 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 use of antithrombotic medications and invasive management, and found no differences in our results.

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References

1. Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am J Cardiol. 2007; 99:44C–46C.
2. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106:2747–2757. [PubMed: 12438303]
3. Arnold SV, Chan PS, Jones PG, Decker C, Buchanan DM, Krumholz HM, Ho PM, Spertus JA. Translational research investigating underlying disparities in acute myocardial infarction patients' health status (TRIUMPH): design and rationale of a prospective multicenter registry. Circ Cardiovasc Qual Outcomes. 2011 In press.
4. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004; 39:212–220. [PubMed: 15208005]
5. Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis. 2008; 197:821–828. [PubMed: 17875307]
6. Salisbury AC, Amin AP, Harris WS, Chan PS, Gosch KL, Rich MW, O'Keefe JH, Spertus JA. Predictors of Omega-3 Index in Acute Myocardial Infarction Patients. Mayo Clin Proc. 2011; 86:626–632. [PubMed: 21719619]
7. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987; 76:142–154. [PubMed: 3109764]
8. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159:702–706. [PubMed: 15033648]
9. Bays HE. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol. 2007; 99:35C–43C.
10. Knapp HR, Reilly IA, Alessandrini P, FitzGerald GA. In vivo indexes of platelet and vascular function during fish-oil administration in patients with atherosclerosis. N Engl J Med. 1986; 314:937–942. [PubMed: 3007982]
11. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart

Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation. 2004; 110:e82–292. [PubMed: 15339869]

12. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007; 116:e148–304. [PubMed: 17679616]
13. Watson PD, Joy PS, Nkonde C, Hessen SE, Karalis DG. Comparison of bleeding complications with omega-3 fatty acids + aspirin + clopidogrel--versus--aspirin + clopidogrel in patients with cardiovascular disease. Am J Cardiol. 2009; 104:1052–1054. [PubMed: 19801023]
14. Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, Weiner BH, Slack JD, Kellett MA, Raizner AE, et al. Do fish oils prevent restenosis after coronary angioplasty? Circulation. 1994; 90:2248–2257. [PubMed: 7955181]
15. Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol. 1996; 77:31–36. [PubMed: 8540453]
16. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. Lancet. 2010; 376:540–550. [PubMed: 20638121]
17. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999; 354:447–455. [PubMed: 10465168]
18. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007; 369:1090–1098. [PubMed: 17398308]

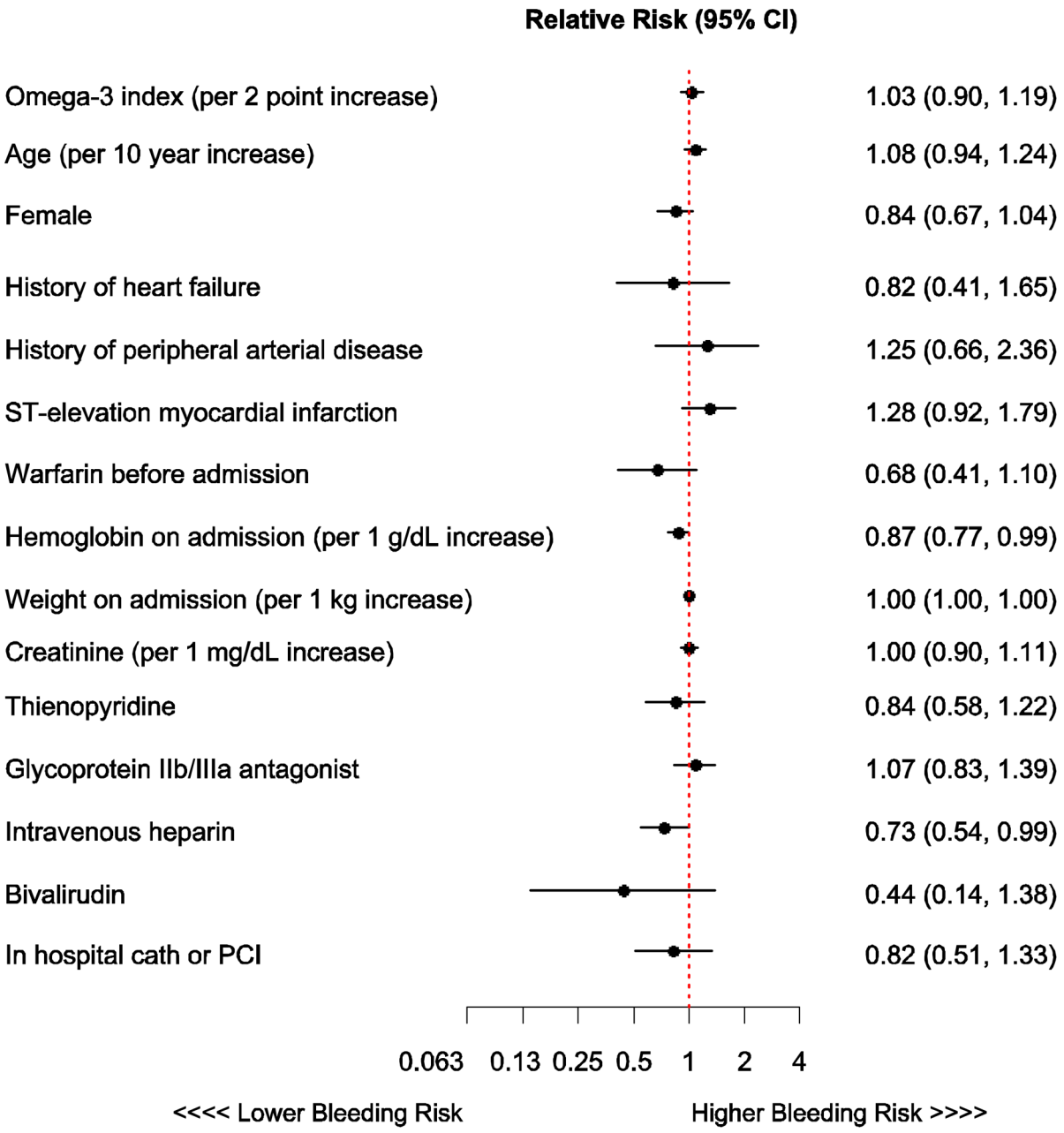

Figure 1. Association between the omega-3 index and serious bleeding

Forest plot of multivariable model for TIMI major and TIMI minor bleeding. TIMI = Thrombolysis in Myocardial Infarction.

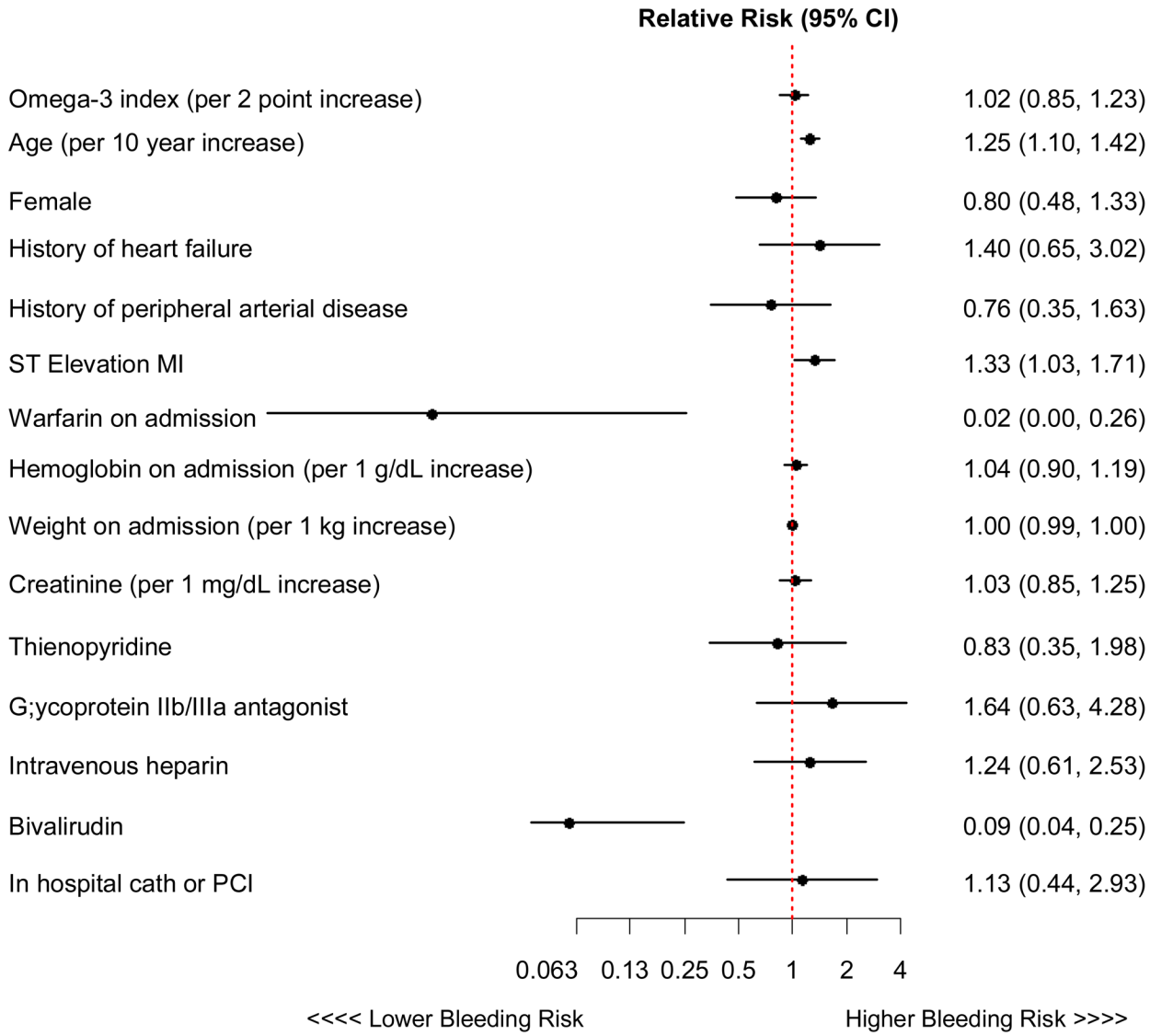

Figure 2. Association between the omega-3 index and mild-moderate bleeding

Forest plot of multivariable model for TIMI minimal bleeding. TIMI = Thrombolysis in Myocardial Infarction.

Table 1

Patient Characteristics by omega-3 index at the time of acute myocardial infarction

Variable	Omega-3 Index			
	0 to <4% (n = 408)	4% to 8% (n = 1036)	> 8% (n = 79)	P-Value
Omega-3 index (%, mean±SD)	3.3 ± 0.5	5.4 ± 1.0	9.3 ± 1.0	< 0.001
Age	54.6 ± 11.0	60.6 ± 12.6	64.0 ± 10.5	< 0.001
Male	287 (70.3%)	682 (65.8%)	60 (75.9%)	0.067
Caucasian	336 (82.4%)	732 (70.8%)	55 (69.6%)	< 0.001
Body mass index (kg/m^2, mean±SD)	29.4 ± 6.5	29.7 ± 6.5	29.1 ± 5.6	0.506
Ejection fraction (%,mean±SD)	48.3 ± 13.7	49.3 ± 13.0	49.4 ± 13.3	0.476
GRACE 6m mortality risk score	90.8 ± 28.0	102.5 ± 30.5	108.8 ± 28.0	< 0.001
Initial hemoglobin (g/dl, mean±SD)	14.5 ± 2.1	14.0 ± 2.1	13.9 ± 2.0	0.001
Creatinine (mg/dl, median (IQR))	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.1 (0.9,1.3)	0.029
Chronic heart failure	21 (5.1%)	96 (9.3%)	8 (10.1%)	0.030
Dyslipidemia	190 (46.6%)	543 (52.4%)	53 (67.1%)	0.002
Hypertension	245 (60.0%)	674 (65.1%)	57 (72.2%)	0.062
Prior peripheral vascular disease	14 (3.4%)	57 (5.5%)	12 (15.2%)	< 0.001
Prior myocardial infarction	72 (17.6%)	191 (18.4%)	25 (31.6%)	0.011
Prior percutaneous coronary intervention	71 (17.4%)	204 (19.7%)	29 (36.7%)	< 0.001
Prior coronary artery bypass grafting	31 (7.6%)	129 (12.5%)	17 (21.5%)	< 0.001
Diabetes mellitus	123 (30.1%)	318 (30.7%)	16 (20.3%)	0.148
Chronic kidney disease	16 (3.9%)	85 (8.2%)	2 (2.5%)	0.004
ST-elevation myocardial infarction	210 (51.5%)	457 (44.1%)	35 (44.3%)	0.039
Admission medications				
Aspirin	129 (31.6%)	438 (42.3%)	47 (59.5%)	< 0.001
Thienopyridine	27 (6.6%)	128 (12.4%)	13 (16.5%)	0.002
Warfarin	17 (4.2%)	39 (3.8%)	5 (6.3%)	0.445
Omega-3 supplements	26 (6.4%)	180 (17.5%)	45 (58.4%)	< 0.001
In-hospital treatments				
Aspirin	391 (95.8%)	983 (94.9%)	79 (100.0%)	0.069
Intravenous heparin	325 (79.7%)	811 (78.3%)	60 (75.9%)	0.720
Low molecular weight heparin	65 (15.9%)	158 (15.3%)	13 (16.5%)	0.922
Fibrinolytic	35 (8.6%)	67 (6.5%)	0 (0.0%)	0.018
Glycoprotein IIb/IIIa antagonist	270 (66.2%)	637 (61.5%)	45 (57.0%)	0.147
Thienopyridine	303 (74.3%)	723 (69.8%)	57 (72.2%)	0.235
Bivalirudin	18 (4.4%)	46 (4.4%)	5 (6.3%)	0.656
In-hospital coronary artery bypass	37 (9.1%)	90 (8.7%)	9 (11.4%)	0.714
In-hospital cardiac catheterization	390 (95.6%)	966 (93.2%)	73 (92.4%)	0.195
In-hospital percutaneous coronary intervention	289 (70.8%)	706 (68.1%)	53 (67.1%)	0.577

Table 2

In-hospital bleeding by omega-3 index

Variable	Omega-3 Index			
	0 to <4% (n = 408)	4% to 8% (n = 1036)	> 8% (n = 79)	P-Value
Serious bleeding (TIMI minor or major)	27 (6.6%)	88 (8.5%)	5 (6.3%)	0.428
Mild-moderate bleeding (TIMI minimal)	20 (4.9%)	60 (5.8%)	5 (6.3%)	0.708
TIMI bleeding				0.072
None	361 (88.5%)	888 (85.7%)	69 (87.3%)	
Minimal	20 (4.9%)	60 (5.8%)	5 (6.3%)	
Minor	11 (2.7%)	62 (6.0%)	5 (6.3%)	
Major	16 (3.9%)	26 (2.5%)	0 (0.0%)	
Bleeding location				0.531
Cardiac catheterization site	23 (48.9%)	86 (58.5%)	7 (70.0%)	
Coronary bypass surgical site	7 (14.9%)	12 (8.2%)	0 (0.0%)	
Gastrointestinal	7 (14.9%)	19 (12.9%)	0 (0.0%)	
Retroperitoneal	3 (6.4%)	8 (5.4%)	0 (0.0%)	
Other	7 (14.9%)	22 (15.0%)	3 (30.0%)	