Effects of Polyunsaturated Fatty Acid Treatment on Postdischarge Outcomes After Acute Myocardial Infarction

Stephen J. Greene, MD[a], Pier Luigi Temporelli, MD[b], Umberto Campia, MD[c], Muthiah Vaduganathan, MD, MPH[d], Luca Degli Esposti, EconD[e], Stefano Buda, ElEng[e], Chiara Veronesi, MStat[e], Javed Butler, MD, MPH[f], and Savina Nodari, MD[g,*]

Clinical trials studying the efficacy of n-3 polyunsaturated fatty acids (PUFA) in reducing adverse events after acute myocardial infarction (AMI) have yielded conflicting results, and data regarding the influence of n-3 PUFA treatment after AMI in routine clinical practice are scarce. We conducted a retrospective observational cohort study including patients from 5 Italian Local Health Units who were discharged from the hospital with a primary diagnosis of AMI from January 1, 2010, to December 31, 2011. Using unique patient identifiers, patients were linked across governmental hospital discharge, medication prescription, and mortality databases and followed for 12-months post-index discharge. Patient characteristics and risk of all-cause mortality and repeat AMI were compared by n-3 PUFA prescription after discharge (for outcome analyses, defined as ≥2 prescriptions) at a presumed dose of 1 g/day. Overall, 11,269 patients met inclusion criteria, of which 2,425 patients (21.5%) were prescribed n-3 PUFA during follow-up. Patients treated with n-3 PUFA tended to be younger, men, and carry a diagnosis of diabetes and were more likely to be receiving guideline-recommended post-AMI medical therapy, including β blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, and antiplatelet therapy (all p <0.001). After adjusting for patient characteristics and concurrent therapies, n-3 PUFA treatment was associated with reduced all-cause mortality (hazard ratio 0.76, 95% CI 0.59 to 0.97) and recurrent AMI (hazard ratio 0.65, 95% CI 0.49 to 0.87) through 12-month follow-up. In conclusion, in this large, contemporary, observational study of "real-world" Italian patients hospitalized for AMI, the use of n-3 PUFA was independently associated with a robust reduction in all-cause mortality and recurrent AMI. These data support further randomized controlled trials with n-3 PUFA therapy in the post-AMI setting. **(Am J Cardiol 2016;117:340−346)**

Conflicting data exist regarding the protective role of n-3 polyunsaturated fatty acids (PUFA) after acute myocardial infarction (AMI). The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial showed that oral administration of 1 g of n-3 PUFA daily decreased the risk of death, nonfatal AMI, and stroke in patients surviving recent AMI.[1,2] Subsequent randomized trials failed to demonstrate clinical benefit with post-AMI n-3 PUFA use.[3−5] Nevertheless, the neutral results of n-3 PUFA outcome trials published after GISSI-Prevenzione may not be generalizable to "real-world" practice where uptake of guideline-recommended practices is generally lower than in clinical trials. For example, a sizable proportion of patients with AMI, particularly those with non−ST-segment elevation myocardial infarction (NSTEMI) and who are elderly or with co-morbidities such as renal dysfunction may not undergo PCI.[6−8] Additionally, adherence with postdischarge medications after AMI may be low and can negatively impact clinical outcomes.[9,10] Furthermore, existing outcome trial data must now be viewed in the context of the recently presented Effect of Purified Omega-3 Fatty Acids on Reducing Left Ventricular Remodeling after Acute Myocardial Infarction (OMEGA-REMODEL) study, where administration of high-dose n-3 PUFA early after AMI demonstrated significant improvements in left ventricular remodeling and systemic inflammation, compared with placebo.[11] In this context, a reappraisal of n-3 PUFA efficacy is warranted. The goal of the present study was to determine the influence of n-3 PUFA prescription on postdischarge outcomes in a large, "real-world," contemporary cohort of patients with AMI.

[a]Division of Cardiology, Duke University Medical Center, Durham, North Carolina; [b]Division of Cardiology, Fondazione Salvatore Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Veruno, Italy; [c]Medstar Heart and Vascular Institute, Washington, DC; [d]Brigham and Women's Hospital Heart & Vascular Center, Boston, Massachusetts; [e]CliCon S.r.l. Health, Economics, and Outcomes Research, Ravenna, Italy; [f]Division of Cardiology, Stony Brook University, Stony Brook, New York; and [g]Cardiology Section, Department of Clinical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy. Manuscript received September 6, 2015; revised manuscript received and accepted October 30, 2015.

The study was funded by Sigma-Tau Pharmaceuticals. (Pomezia, Italy)

Dr. Nodari had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

See page 345 for disclosure information.

*Corresponding author: Tel: (+39) 030-3996008; fax: +30 030 8377024.

E-mail address: savina.nodari@unibs.it (S. Nodari).

0002-9149/15/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2015.10.050

Table 1
Baseline characteristics by postdischarge n-3 polyunsaturated fatty acid treatment

Variable	n-3 PUFA Treatment		P value
	Yes (n = 2,425)	No (n = 8,844)	
Age (mean ±SD) (years)	63.1 ±12.4	71.0 ±13.3	<0.001
Men	1,884 (77.7%)	5,639 (63.8%)	<0.001
Angioplasty during index hospitalization	557 (23.0%)	2,041 (23.1%)	NS
Anterior/anterolateral AMI during index hospitalization	671 (27.7%)	1,984 (22.4%)	<0.001
Treatment with n-3 PUFA prior to index hospitalization	473 (19.5%)	321 (3.6%)	<0.001
Previous hospitalization for ischemic heart disease	221 (9.1%)	934 (10.6%)	<0.05
Heart failure	45 (1.9%)	453 (5.1%)	<0.001
Peripheral arterial disease	5 (0.2%)	22 (0.2%)	NS
Chronic kidney disease	47 (1.9%)	300 (3.4%)	<0.001
Medications prescribed during follow-up*			
Medication for diabetes	653 (26.9%)	1,984 (22.4%)	<0.001
Medication for hypertension†	1,159 (47.8%)	4,042 (45.7%)	NS
Beta-blocker	2,093 (86.3%)	5,814 (65.7%)	<0.001
ACEI/ARB	2,155 (88.9%)	6,292 (71.1%)	<0.001
Statin	2,372 (97.8%)	6,757 (76.4%)	<0.001
Antiplatelet	2,338 (96.4%)	7,095 (80.2%)	<0.001
Single antiplatelet therapy	620 (25.6%)	2,618 (29.6%)	<0.001
Dual antiplatelet therapy	1,645 (67.8%)	4,342 (49.1%)	<0.001
≥3 antiplatelets	73 (3.0%)	135 (1.5%)	<0.001

Data displayed as n (%), unless otherwise noted.

ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin II receptor blocker; ATC = anatomic-therapeutic-chemical code; PUFA = polyunsaturated fatty acid.

* Patients were defined as treated with n-3 PUFA, β blockers, ACEI/ARB, antiplatelet agents, or statins if they were prescribed ≥1 prescription of the medication during the 12-month follow-up period. Patients were counted as receiving diabetic or hypertension medication if they were prescribed ≥2 prescription of the medication during follow-up.

† Medications for hypertension were defined as antihypertensives (ATC C02), diuretics (ATC C03), or calcium channel blockers (ATC C08).

Methods

This was a retrospective cohort-based integrated analysis of administrative databases maintained by 5 Italian Local Health Units (LHUs) located in the regions of Lombardy, Friuli-Venezia Giulia, Lazio, Campania, and Sicily with a combined population of approximately 4.3 million. Each LHU Ethics Committee approved the present study. Using the hospital discharge database, which includes dates of hospital admission and discharge and discharge diagnoses codes according to the International Classification of Diseases Ninth Revision (ICD-9) classification, patients discharged from the hospital from January 1, 2010, to December 31, 2011, with primary diagnosis of AMI (ICD-9 410) were identified. The date of the index hospital discharge was defined as baseline. The follow-up period extended to 12 months after discharge. Patients who moved to other LHUs during follow-up were excluded. The hospital discharge database was used to assess the history of previous cardiovascular hospitalization, location of the index AMI (i.e., anterior/anterolateral or not), receipt of percutaneous coronary intervention (PCI) during index hospitalization (ICD-9 codes 36.0x, excluding 36.04), and subsequent rehospitalization during follow-up.

Using the numeric code released to each citizen by the LHUs as a unique patient identifier, the hospital discharge database was linked to the following databases: (1) Medications Prescription Database, from which data (according to anatomical-therapeutic-chemical [ATC] codes) regarding postdischarge use of n-3 PUFA, β blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), antiplatelet agents, statins, diabetic medications, and hypertension medications were collected. Data regarding the use of medications for diabetes and hypertension were collected as surrogates for a history of diabetes and hypertension, respectively, (2) mortality database, from which data on mortality, but not cause of death, were collected, and (3) beneficiaries' database, from which data regarding date of birth, gender, and place of residence were collected.

The prespecified coprimary end points were the rates of all-cause mortality (ACM) and repeat AMI at 12-month follow-up. Cosecondary end points included the rates of ACM and repeat AMI at 6-month follow-up. Repeat AMI was defined as the first subsequent hospital admission with discharge diagnosis of AMI.

For descriptive purposes, patients were counted as treated with n-3 PUFA, β blockers, ACEIs/ARBs, antiplatelet agents, or statins if they were given ≥1 prescription of the medication during the 12-month follow-up and as receiving medication for diabetes or hypertension if they were given ≥2 prescriptions of the respective medication during follow-up. For purposes of survival models and outcome analyses, patients were counted as treated with n-3 PUFA and all other medications if they received ≥2 prescriptions of the drug during the 12-month follow-up. With regard to n-3 PUFA dosing, in Italy, only name brand n-3 PUFA is routinely available and reimbursed by the national health system. Thus, the daily dose of n-3 PUFA presumed in this