Omega-3 Fatty Acids and Mortality Outcome in Patients With and Without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study

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ABSTRACT

Background: There are conflicting data regarding the benefits of omega-3 (*n*-3) fatty acids, most recently in patients with type 2 diabetes.

Objective: Our goal was to evaluate the impact of licensed, highly purified *n*-3 fatty acids on all-cause mortality after myocardial infarction (MI).

Methods: This was a retrospective, matched-cohort study using data from the General Practice Research Database. Patients initiating treatment with 1 g of *n*-3 fatty acids in the 90 days after first MI were identified and each matched to 4 nonexposed patients. Progression to death was compared using time-dependent Cox models to account for potential differences in exposure to other cardiovascular risk–modifying treatments.

Results: A total of 2466 eligible subjects exposed to *n*-3 fatty acids were matched. The majority of patients had concurrent treatment with lipid-lowering therapies, antihypertensives, and antiplatelets after first MI, with subjects exposed to *n*-3 fatty acids having a greater likelihood of concurrent exposure. For those initiating *n*-3 fatty acids within 90 days of first MI, the adjusted hazard ratio (aHR) was 0.782 (95% CI, 0.641–0.995; $P = 0.0159$); for those initiating treatment within 14 days, the aHR was 0.680 (95% CI, 0.481–0.961; $P = 0.0288$). In patients with type 2 diabetes at baseline, the aHRs were 0.714 (95% CI, 0.454–1.124) and 0.597 (95% CI, 0.295–1.211) when initiation was within 90 and 14 days, respectively. Use of *n*-3 fatty acids resulted in a consistent survival benefit under a range of scenarios quantitatively consistent with the overall effect.

Conclusion: After MI, early treatment with licensed *n*-3 fatty acids was associated with improvement in all-cause mortality in patients with and without type 2 diabetes, against a background of contemporary cardiovascular risk–modifying treatments. (*Clin Ther*. 2013;35:40–51)

Key words: all-cause mortality, *n*-3 fatty acids, omega-3 fatty acids, ORIGIN trial, type 2 diabetes.

INTRODUCTION

Essential omega-3 (*n*-3) fatty acid supplementation is associated with improved endothelial and myocardial function and with triglyceride-lowering, anti-inflammatory, antithrombotic, and antiarrhythmogenic effects. High dietary intake of oily fish, and thus marine-derived *n*-3 fatty acids, is also associated with improved cardiovascular disease (CVD) outcomes.[1,2] Several large randomized studies have shown significant improvements in mortality and a reduction in major CVD events after treatment with *n*-3 fatty acids.[3–5] Meta-analyses of such randomized studies have typically demonstrated a beneficial impact on CVD outcomes; however, there are inconsistencies in terms of methods

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and outcomes.[2,6–8] The studies integral to these meta-analyses were heterogeneous: conducted in different populations with postacute or distant myocardial infarction (MI), stable coronary artery disease, heart failure, implantable cardioverter defibrillators, post-stroke, and in those at high CVD risk. Furthermore, included studies evaluated varying doses of *n*-3 supplements (400–4800 mg *n*-3 fatty acids per day) and differing supplements (fish, fish oil, highly purified *n*-3 ethyl esters, and aminolevulinic acid) and had various trial durations.

Most recently, the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial evaluated the impact of *n*-3 fatty acids versus placebo on the risk of progression to all-cause mortality and major cardiovascular events in individuals with dysglycemia.[9] ORIGIN reported no difference in risk between the drug and placebo in >12,000 subjects, with an average 6 years of follow up.

The product evaluated in ORIGIN was a highly purified, stable preparation of 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid ethyl esters; it is the only *n*-3 fatty acid licensed for use as adjuvant treatment in the secondary prevention of MI, which was one of the subpopulations studied in the ORIGIN study. Only 59.1% of patients in the *n*-3 fatty acid arm had an MI, stroke, or revascularization.[10] The product license was based on the findings from the large GISSI-Prevenzione (GISSI-P) study,[4] which demonstrated a reduction of 20% in all fatal events, in large part due to a 45% reduction in sudden cardiac death in patients treated with 1 g/d of *n*-3 fatty acids within 90 days of an acute MI.

The purpose of the current study was to compare survival rates after treatment with licensed *n*-3 fatty acids in routine clinical practice in individuals with and without diabetes who survived their first MI, adjusting for other clinical variables and cardiovascular risk–modifying medications.

METHODS

This retrospective, matched-cohort study used data from the General Practice Research Database (GPRD; replaced by the Clinical Practice Research Datalink from April 2012). GPRD is a longitudinal, anonymized database derived from nearly 700 primary care practices throughout the United Kingdom that are broadly geographically and demographically representative of the country as a whole. At the time of the study, GPRD contained clinical records from >11 million individuals, of whom ~5 million were actively registered. The data captured by GPRD include demographic characteristics, medical history, clinical investigations, and drug prescriptions. The routine data are recorded electronically in general practice and monitored for quality by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Diagnoses in GPRD are recorded by using the Read code classification and have been validated in a number of studies, with results showing a high positive predictive value.[11]

Studies using the GPRD/Clinical Practice Research Datalink are covered by ethics approval granted by the Trent Multicentre Research Ethics Committee (reference 05/MRE04/87). The current study was granted MHRA Independent Scientific Advisory Committee approval (ISAC 12_033).

Selection of Patients With a First MI

The study population comprised patients diagnosed with a first MI whose records had been assessed by the MHRA as meeting research-quality standards. To ensure that the first identified MI was indeed the first occurrence, patients were excluded if the description of the MI implied the existence of a previous infarction event, if patients had been registered at the practice for <180 days before the MI, or if the practice was judged by the MHRA to be recording up-to-standard data for <180 days before that event. Patients were selected if they were prescribed highly purified *n*-3 fatty acids approved in the United Kingdom for secondary prevention after MI at a daily dose of 1 g. Patients were excluded from the study if they were prescribed fish-derived *n*-3 fatty acid preparations not licensed for post-MI secondary prevention at any time after their first MI. People with diabetes other than type 2 were excluded. A flow diagram illustrating patient selection is detailed in **Figure 1**.

Treatment Cohort Selection and Comparative Analysis

From this general study population, a cohort was identified of patients exposed to 1 g of *n*-3 fatty acids for the first time on or after their first MI (the index date). We restricted our analysis to treatment initiation within the recommended time of 90 days[12] and conducted a sensitivity analysis on those initiating treatment with *n*-3 fatty acids within 14 days. Patients were