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) © 2013 Elsevier HS Journals, Inc.

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

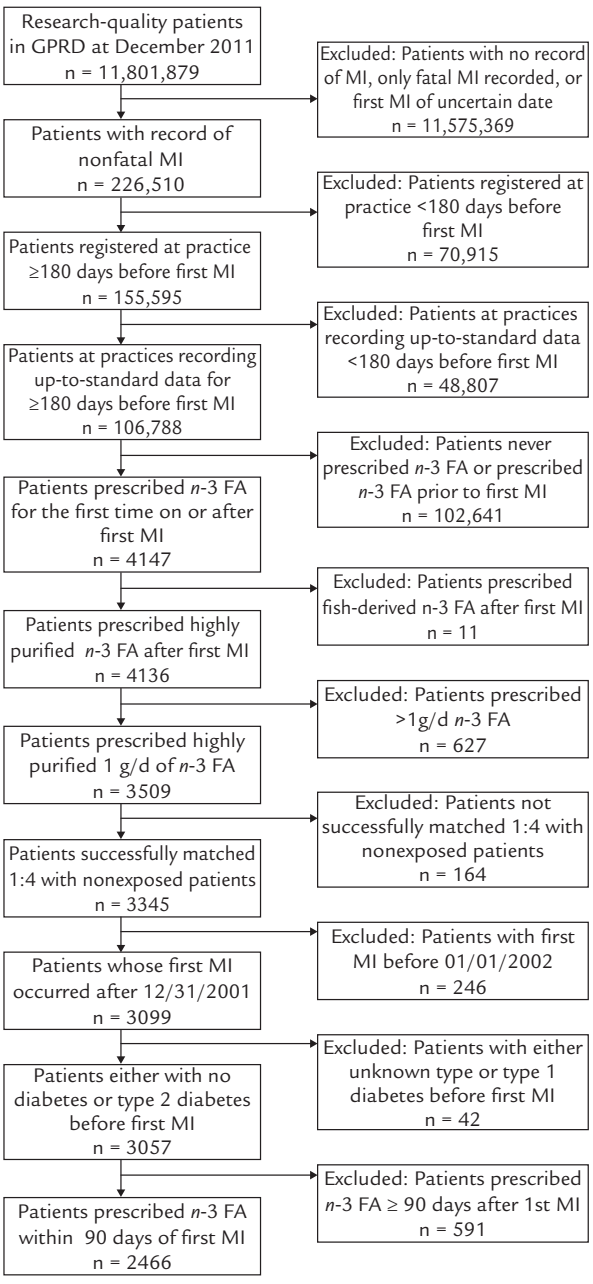

Figure 1. Patient flow diagram for selection of patients exposed to omega-3 fatty acids (*n*-3 FA). MI = myocardial infarction.

excluded from the cohort if any prescription stipulated a daily dose of >1 g, which would imply an indication other than secondary prevention, or if the daily dose could not be determined. Patients were also excluded if they were prescribed *n*-3 fatty acids subsequent to a further cardiovascular event (Figure 1).

Matching Procedure

Each member of the exposed cohort was matched, at random, to 4 patients from the remaining study population who had experienced a previous MI and had not been exposed to *n*-3 fatty acids. They were matched on the following criteria: sex, year of birth (±2 years), year of first MI, smoking status, type 2 diabetes status, registration with a differing general practice (to minimize confounding by indication), and a period of follow-up from their first MI not less than the interval between first MI and first *n*-3 fatty acid prescription in the corresponding exposed patient (to minimize immortal time bias).

The primary end point for this study was all-cause mortality as recorded in GPRD. Mortality was identified from the Read codes recorded in GPRD and from linked Office of National Statistics (ONS) mortality records.

Modeled Comparison of Survival

To determine if there was any identifiable residual confounding and to allow for changes in treatment and other mortality/CVD risk factors after the initial MI event, time-dependent Cox models were used. This modeling was potentially important in accounting for differences after the index date, such as exposure to other cardiovascular risk–modifying medications (eg, statins).

Covariates considered for inclusion in the Cox models were age, sex, diabetes, systolic blood pressure, total cholesterol, body mass index, smoking status, lipid-lowering therapy, antiplatelet therapy, and antihypertensive therapy (incorporating use of β-blockers and drugs affecting the renin–angiotensin system). After a preliminary analysis, a number of covariates were selected and then included in all of the models. Year of *n*-3 fatty acid initiation was also included in the models to account for any temporal effects. Baseline morbidity was characterized using the Charlson comorbidity index. Subjects with missing data were automatically excluded, and the proportional hazards assumption was considered by evaluation of the Kaplan-Meier curves and analysis of the Schoenfeld residuals. Survival patterns were evaluated under a number of alternative scenarios, including: aspirin and clopidogrel monotherapy or combination therapy, individual statin type, baseline LDL-C subgroup, achieved LDL-C subgroup, and those who were ever or never diagnosed with type 2 diabetes. This latter scenario violated a theoretical assumption of the survival model[13] but was nevertheless of interest.

Table I. Baseline characteristics at first myocardial infarction for those with and without type 2 diabetes at baseline, exposed and nonexposed to omega-3 (*n*-3) fatty acids.

	No Previous Type 2 Diabetes			Previous Type 2 Diabetes		
Characteristic	Exposed	Nonexposed	*P*	Exposed	Nonexposed	*P*
No. of patients	2140	8429		326	1283	
Male sex, %	71	71	0.925	73	73	0.925
Age, mean (SD), y	63.34 (12.40)	63.30 (12.33)	0.900	67.88 (10.98)	67.72 (10.87)	0.805
Socioeconomic status, %, IMD quintile						
1	14	22	<0.001	14	18	0.010
2	20	22		17	22	
3	18	19		16	21	
4	20	21		24	21	
5 (most deprived)	27	15		29	19	
Index year of first MI, %						
2002	<1	<1	>0.999	<1	<1	>0.999
2003	1	1		2	2	
2004	6	6		3	3	
2005	6	6		6	6	
2006	7	7		5	5	
2007	11	11		10	11	
2008	15	15		15	15	
2009	21	21		21	21	
2010	21	21		24	24	
2011	12	12		13	13	
Smoking status, %						
Never smoked	30	30	0.997	28	28	0.992
Ex-smoker	31	31		49	49	
Current smoker	39	39		23	23	
BMI, mean (SD), kg/m^2	27.35 (5.81)	27.27 (6.38)	0.716	29.97 (5.64)	29.65 (6.22)	0.455
Blood pressure, mean (SD), mm Hg						
SBP	132.24 (21.03)	133.09 (20.91)	0.121	134.42 (21.28)	134.67 (21.63)	0.858
DBP	77.03 (12.29)	77.17 (12.03)	0.665	75.97 (11.92)	75.52 (12.41)	0.575
Serum cholesterol, mean (SD), mmol/L						
Total cholesterol	5.10 (1.32)	5.08 (1.32)	0.660	4.50 (1.19)	4.45 (1.14)	0.571
HDL-C	1.25 (0.36)	1.28 (0.39)	0.020	1.14 (0.30)	1.15 (0.35)	0.585
LDL-C	3.04 (1.09)	3.06 (1.08)	0.743	2.53 (0.95)	2.52 (0.97)	0.923
Triglycerides, mean (SD), mmol/L	1.72 (0.92)	1.67 (0.92)	0.212	1.93 (0.92)	1.91 (1.02)	0.744
GP contacts in year prior, median (IQR)	6 (2–12)	6 (2–13)	0.619	12 (7–20)	12 (6–22)	0.851
Charlson comorbidity index, median (IQR)	1 (1–2)	1 (1–2)	0.031	3 (2–5)	4 (2–5)	0.216
Diabetes-specific details						
HbA_{1c}, mean (SD), %				7.56 (1.59)	7.65 (1.76)	0.521
Previous diabetes therapy, %						
Lifestyle				40	35	0.110
OHA monotherapy				29	28	
OHA combination therapy				18	19	
Injected therapy				14	19	
Diabetes duration, median (IQR), y				5.44 (1.86–9.91)	6.06 (2.13–11.82)	0.059

IMD = index of multiple deprivation; MI = myocardial infarction; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; GP = general practitioner; IQR = interquartile range; HbA_{1c} = hemoglobin A_{1c}; OHA = oral hypoglycemic agent.

Table II. Exposure to omega-3 (*n*-3) fatty acids and cardiovascular risk–modifying treatments after myocardial infarction.

	No Diabetes			Previous Type 2 Diabetes		
Drug Class	Exposed	Nonexposed	*P*	Exposed	Nonexposed	*P*
Exposure within 90 days						
Lipid-lowering drugs, %	97.6	84.0	<0.0001	96.2	82.8	<0.0001
Antihypertensives, %	98.5	86.6	<0.0001	98.1	87.9	<0.0001
Antiplatelets, %	98.3	84.9	<0.0001	97.8	83.2	<0.0001
Exposure within 12 months						
Lipid-lowering drugs, %	92.4	79.1	<0.0001	91.7	77.9	<0.0001
Antihypertensives, %	95.3	82.9	<0.0001	95.2	84.7	<0.0001
Antiplatelets, %	94.2	79.6	<0.0001	88.9	78.8	<0.0001

RESULTS

Patients and Baseline Characteristics

We identified 2466 eligible first-MI patients subsequently exposed to *n*-3 fatty acids; 326 (13%) had a baseline diagnosis of type 2 diabetes. These patients were matched in a 1:4 ratio to similar patients who had not been prescribed *n*-3 fatty acids post-MI. In the nondiabetes group, the mean (SD) age was 63 (12) years, and 71% were male. The matching was appropriate, resulting in very similar characteristics (Table I), although patients exposed to *n*-3 fatty acids had worse socioeconomic status, generally regarded as an indicator of increased mortality risk.[14] In those with previous type 2 diabetes, the duration of diabetes in the nonexposed cohort was arguably slightly longer, with a mean duration of 6.1 years versus 5.4 years ($P = 0.059$); however, the matching procedure was otherwise consistent.

Treatment With Other Cardiovascular Risk–Modifying Treatments After MI

The majority of post-MI patients had concurrent treatment with lipid-lowering therapies, antihypertensives, and antiplatelets after their first MI. This varied slightly between the various comparator groups used in this study (Table II): patients exposed to *n*-3 fatty acids had a greater likelihood of concurrent exposure to these treatments. Within 90 days in those without diabetes, 98% of exposed patients had received lipid-lowering drugs versus 84% in the nonexposed patients ($P < 0.0001$); for antihypertensive agents, the proportions were 99% versus 87% ($P < 0.0001$), respectively, and for antiplatelet drugs, it was 98% versus 85% ($P < 0.0001$). Thus, it was necessary to account for these factors by using the multivariate, time-dependent models.

Time To Initiation of *n*-3 Fatty Acid Treatment

Of those patients treated with *n*-3 fatty acids, 82% had their treatment initiated in the 90 days after first MI, in line with recommendations and justifying the selection of these subjects for this study.[12] Figure 2 illustrates the cumulative percentage of time to treatment initiation from the first event. Those in the lower tertile of time to initiation were also selected for a sensitivity analysis look-

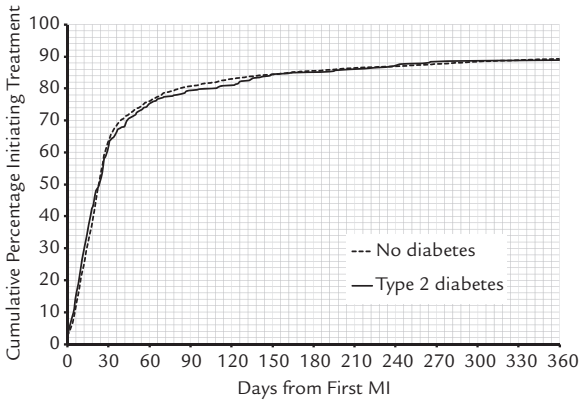

Figure 2. Time to treatment initiation with omega-3 (*n*-3) fatty acids after first myocardial infarction (MI).

Table III. Number of events and crude relative risk values for patients exposed and not exposed to omega-3 (*n*-3) fatty acids.

Parameter	Exposed	Nonexposed
All patients	2466	9712
No. of death events	243	1274
Total follow-up, y	6668	24,943
Deaths per 1000 person-years, no.	36.4	51.1
Crude relative risk (95% CI)	0.708 (0.602–0.833)	$P < 0.0001$
Patients with no previous diabetes	2140	8429
No. of death events	195	1016
Total follow-up, y	5882	22,066
Deaths per 1000 person-years, no.	33.2	46.0
Crude relative risk (95% CI)	0.724 (0.621–0.844)	$P < 0.0001$
Patients with previous type 2 diabetes	326	1283
No. of death events	48	258
Total follow-up, y	786	2878
Deaths per 1000 person-years, no.	61.1	89.7
Crude relative risk (95% CI)	0.686 (0.504–0.934)	$P = 0.0166$

ing at early time to treatment initiation (range, 0–13 days; median, 7 days). Excluded patients, prescribed licensed *n*-3 fatty acids but with initial exposure ≥90 days post-MI, represented 17.9% of patients.

Crude Survival Patterns

Overall, there were 1517 recorded deaths (12.5% of patients). Crude event rates differed according to diabetes status and *n*-3 fatty acid exposure status. In those exposed to *n*-3 fatty acids, the crude event rates were 61/1000 person-years for those with type 2 diabetes at baseline and 33/1000 person-years for those without diabetes at baseline. In those not exposed to *n*-3 fatty acids, the crude event rates were 90/1000 person-years for those with type 2 diabetes at baseline and 46/1000 person-years for those without. These data resulted in crude relative risk values of 0.708 (95% CI, 0.602–0.833; $P < 0.0001$) overall, and 0.686 (95% CI, 0.504–0.934; $P = 0.0166$) for those with diabetes and 0.724 (95% CI, 0.621–0.844; $P < 0.0001$) for those without diabetes, respectively (Table III).

Adjusted Survival Patterns

All of the selected covariates were important in the model in specifying the risk of death, including exposure to all classes of cardiovascular risk–modifying agent (Table IV).

The adjusted hazard ratio (aHR) for all-cause mortality was consistently lower among those exposed to *n*-3 fatty acids, and materially did not differ among those with and without diabetes at baseline survey or in those who developed diabetes during follow-up (Figure 3). When the models were restricted to those who initiated therapy within 14 days, the strength of association for those exposed to *n*-3 fatty acids seemed modestly stronger across the range of subgroups.

The fully specified, time-dependent Cox models evaluating *n*-3 fatty acid exposure within 90 days and within 14 days are detailed in Table IV. The aHRs for these two scenarios were 0.782 (95% CI, 0.641–0.995; $P = 0.0159$) and 0.680 (95% CI, 0.481–0.961; $P = 0.0288$), respectively. In those with type 2 diabetes at baseline, the aHR seemed modestly stronger compared with those without diabetes: 0.714 (95% CI, 0.454–1.124; $P = 0.1453$) when initiating *n*-3 fatty acids within 90 days and 0.597 (95% CI, 0.295–1.211; $P = 0.1532$) when initiating within 14 days (Figure 3).

The association between use of *n*-3 fatty acids and reduced mortality hazard remained constant at approximately –20%, regardless of time-dependent ad-

Table IV. Time-dependent Cox models of the hazard of all-cause mortality for patients exposed to omega-3 (*n*-3) fatty acids initiated within 90 and 14 days of their first myocardial infarction (MI) versus matched, nonexposed patients.

	Initiation <90 Days			Initiation <14 Days		
Model Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Time-dependent covariates (quarterly periods)						
n-3 fatty acid exposure, 1 g/d, yes/no	0.782	0.641–0.955	0.0159	0.680	0.481–0.961	0.0288
Lipid-lowering drug exposure, yes/no	0.433	0.373–0.503	<0.0001	0.445	0.346–0.571	<0.0001
Antihypertensive exposure, yes/no	0.416	0.358–0.483	<0.0001	0.425	0.331–0.546	<0.0001
Antiplatelet exposure, yes/no	0.563	0.485–0.653	<0.0001	0.535	0.415–0.690	<0.0001
Time-fixed covariates (at first MI)						
Age, y	1.069	1.064–1.074	<0.0001	1.060	1.051–1.068	<0.0001
Smoking status vs never			<0.0001			0.0704
Ex-smoker	1.255	1.112–1.417	0.0002	1.222	1.003–1.488	0.0469
Current smoker	1.454	1.255–1.684	<0.0001	1.273	1.002–1.617	0.0482
Socioeconomic status, IMD quintile vs group 1			0.0131			0.7815
2	1.105	0.902–1.353	0.3352	1.166	0.842–1.615	0.3547
3	1.246	1.018–1.525	0.0331	1.079	0.774–1.502	0.6550
4	1.251	1.024–1.527	0.0280	1.031	0.741–1.434	0.8566
5 (most deprived)	1.399	1.145–1.708	0.0010	1.236	0.896–1.706	0.1968
Missing	1.118	0.941–1.327	0.2055	1.073	0.810–1.421	0.6218
Charlson comorbidity index, per unit	1.251	1.224–1.278	<0.0001	1.239	1.197–1.282	<0.0001

HR = hazard ratio; IMD = index of multiple deprivation.

justment for the following: concurrent antiplatelet (yes vs no, aspirin yes vs no and clopidogrel yes vs no, or no therapy vs aspirin/clopidogrel monotherapy vs combination therapy); lipid-lowering strategies (statin yes vs no, or agent specific); and baseline LDL-C subgroup (Joint British Societies' target level of <1.8 mmol/L vs an intermediate level of 1.8–3.0 mmol/L vs high-range level of >3.0 mmol/L) (Figure 4). In analyses stratified according to on-treatment LDL-C subgroup, there was no materially significant difference in observed survival benefit from *n*-3 fatty acids exposure (Figure 5). Similarly, when the association between *n*-3 fatty acid exposure was compared among those receiving single or dual antiplatelet therapy, a consistent benefit was observed with *n*-3 fatty acid exposure. There was no evidence of any significant additional survival benefit in the excluded patients exposed to initial treatment with *n*-3 fatty acids after 90 days (aHR = 1.281 [95% CI, 0.750–2.190]; $P = 0.365$; $n_{\text{exposed}} = 538$). It is worth noting that some of these patients were likely to have initiated *n*-3 fatty acids after a subsequent event.

DISCUSSION

This real-world evaluation of clinical practice complements randomized trial data by demonstrating that treatment with licensed *n*-3 fatty acids was associated with reduced all-cause mortality when initiated early post-MI. Our data are concordant with the 20% re-

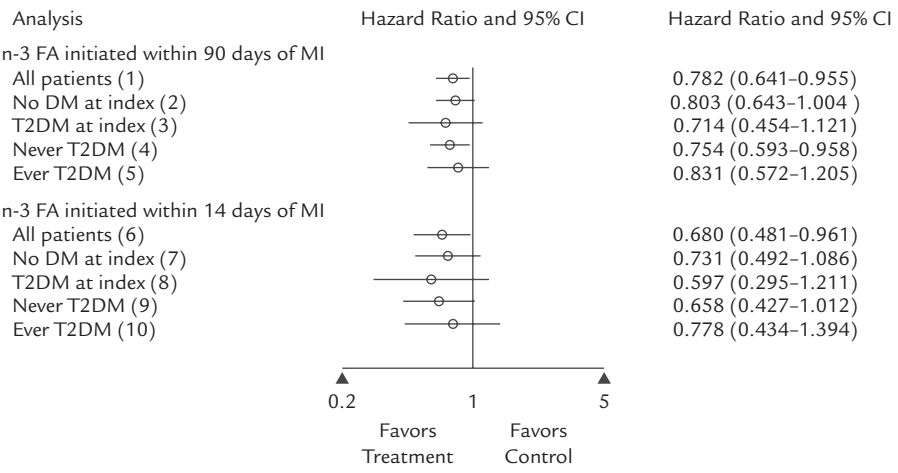

Figure 3. Summary of the time-dependent Cox models showing the adjusted omega-3 fatty acid (*n*-3 FA) exposure hazard ratio for all-cause mortality for differing scenario groups. Analyses (4), (5), (9), and (10) partially violate an assumption of the survival model by specifying emergence of diabetes (or not) as a baseline characteristic but are of interest. *P* = *n*-3 FA parameter estimate.

1. Base analysis for all patients initiating *n*-3 FA within 90 days of first myocardial infarction (MI); see **Table IV** for model specification (n = 12,178; *P* = 0.016).
2. Subgroup analysis of (1) who had no history of diabetes mellitus (DM) before first MI (n = 10,569; *P* = 0.054).
3. Subgroup analysis of (1) who had evidence of type 2 DM (T2DM) before first MI (n = 1609; *P* = 0.145).
4. Subgroup analysis of (1) who had no evidence of T2DM at any time (n = 9581; *P* = 0.021).
5. Subgroup analysis of (1) who had evidence of T2DM at any time (n = 2565; *P* = 0.328).
6. Base analysis for all patients initiating *n*-3 FA within 14 days of first MI; see **Table IV** for model specification (n = 4107; *P* = 0.029).
7. Subgroup analysis of (6) who had no history of DM before first MI (n = 3474; *P* = 0.121).
8. Subgroup analysis of (6) who had evidence of T2DM before first MI (n = 633; *P* = 0.153).
9. Subgroup analysis of (6) who had no evidence of T2DM at any time (n = 3152; *P* = 0.056).
10. Subgroup analysis of (6) who had evidence of T2DM at any time (n = 1010; *P* = 0.398).

duction in all-cause mortality reported in the GISSI-P trial.[4] In our study, treatment initiation with licensed, highly purified *n*-3 fatty acids within 90 days of MI was associated with a reduction in risk of all-cause mortality of 21.8%, independent of other cardiovascular risk–modifying treatments. Our data also demonstrated that earlier treatment initiation, within the 14 days after MI, seemed to increase survival benefit by as much as 40%, the inference being that *n*-3 fatty acid treatment should be initiated as soon as possible. The impact on outcome was similar in those with and without type 2 diabetes and independent of other evidence-based, secondary-prevention medication strategies.

The European Society of Cardiology, the American Heart Association, and other national cardiac societies have evaluated the evidence and converged on a recommendation for post-MI patients to consume 1 g of *n*-3 fatty acids per day.[15–17] The current study confirms that, although not all UK patients receive licensed *n*-3 supplements post-MI, physicians are prescribing in line with the licensed indication and National Institute for Health and Clinical Evidence (NICE) guidelines,[12] with the majority of patients treated with *n*-3 fatty acids receiving them within 90 days and also being treated with other evidence-based cardiovascular risk–modifying therapies. Although the adjusted models accounted for variations in clinical factors and concomitant medication use, it would have been of interest to examine individuals exposed to *n*-3 fatty acids but not to the other treatments. For simplicity, we classified

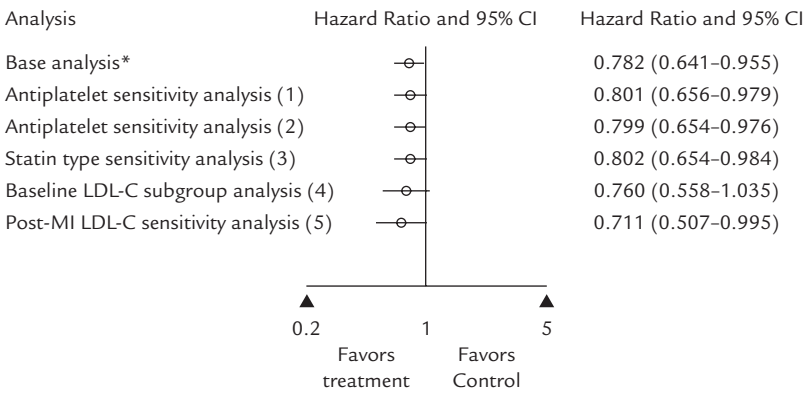

Figure 4. Sensitivity analyses showing the adjusted omega-3 fatty acid (*n*-3 FA) exposure hazard ratio for all-cause mortality for differing parameter modeling. *Model specification shown in **Table IV** for those initiating *n*-3 FA within 90 days of myocardial infarction (MI) (n = 12,178; $P = 0.016$). $P = n$-3 FA parameter estimate.

1. Antiplatelet (yes vs no) substituted by aspirin (yes vs no) and clopidogrel (yes vs no) (n = 12,178; $P = 0.030$).
2. Antiplatelet (yes vs no) substituted by no therapy versus aspirin/clopidogrel monotherapy vs aspirin plus clopidogrel combination therapy) (n = 12,178; $P = 0.028$).
3. Lipid-lowering therapy (yes vs no) substituted by statin therapy (none vs simvastatin vs simvastatin plus ezetimibe vs atorvastatin vs rosuvastatin vs other statin) (n = 12,178; $P = 0.034$).
4. Additional time-fixed parameter, baseline LDL-C subgroup (Joint British Societies' target level of <1.8 mmol/L vs intermediate level of 1.8–3.0 mmol/L vs high-range level of >3.0 mmol/L) (n = 4006; $P = 0.082$).
5. Additional time-variable parameter, post-MI quarterly updated LDL-C subgroup (as in [4] above) (n = 6004; $P = 0.047$).

antihypertensive agents as a single drug class, but this class included drugs such as β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers that are typically used routinely in secondary prevention post-MI regardless of whether the patient is hypertensive.

This epidemiologic study also provides an important evidential adjunct to existing randomized data in that it illuminates some potential limitations in relevant randomized trial designs. The most recent study—the ORIGIN trial—showed no difference in those with dysglycemia exposed to treatment with *n*-3 fatty acids versus placebo.[9] However, as we found no benefit in patients who initiated their *n*-3 fatty acid treatment after the recommended 90-day period, the question remains whether this may have been the case for the patients recruited in ORIGIN, considering that no information related to the time of initiation of *n*-3 fatty acids post-MI was provided in the publication. Although our study had only small numbers in the type 2 diabetes group, we observed that the magnitude of effect was similar in those with diabetes and in those without for all-cause mortality.

Importantly, this study evaluated all-cause mortality as an end point and not CVD events. We believe this to be important because one of the principal mechanisms of action of *n*-3 fatty acids is thought to be their antiarrhythmogenic properties.[1] In almost all study scenarios, this represents a potential reporting bias in that the probability of experiencing a nonfatal MI event could therefore be increased in those exposed to *n*-3 fatty acids. Use of death as the outcome avoids this potential bias and also protects against the issue of competing risks.

This study had inherent limitations. Because study patients were not randomized to treatment, there could be confounding by indication (or allocation bias), and there will in all probability remain residual confounding (accounting for nonrecorded factors). Nonetheless, the matching method seemed to work well. However,

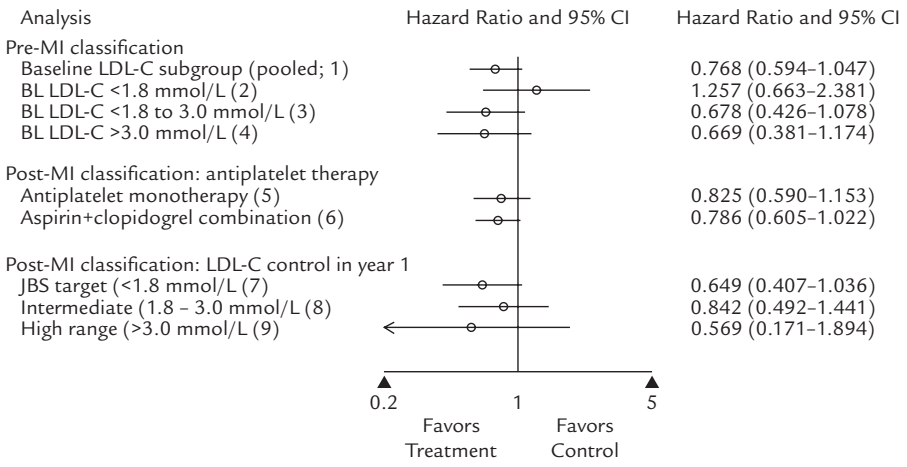

Figure 5. Subgroup analyses using time-dependent Cox models showing the adjusted omega-3 (*n*-3) fatty acid exposure hazard ratio for all-cause mortality. *P* = omega-3 fatty acid parameter estimate.

1. Base analysis (specified in **Table IV**) stratified according to baseline (BL) LDL-C subgroup (last-observation-carried-forward from up to 1 year before index); pooled effect over strata (n = 4006; *P* = 0.095).
2. Joint British Societies' (JBS) target (<1.8 mmol/L) BL LDL-C subgroup (n = 579; *P* = 0.484).
3. Intermediate level (1.8–3.0 mmol/L) BL LDL-C subgroup (n = 1704; *P* = 0.101).
4. High-range level (>3.0 mmol/L) BL LDL-C subgroup (n = 1723; *P* = 0.161).
5. Patients initiating aspirin or clopidogrel monotherapy within 3 months after MI (n = 2702; *P* = 0.260).
6. Patients initiating aspirin and clopidogrel therapy within 3 months after MI (n = 7834; *P* = 0.072).
7. Patients achieving JBS target LDL-C in first year after MI (month 1 excluded; n = 2433; *P* = 0.070).
8. Patients with intermediate LDL-C in first year after MI (month 1 excluded; n = 3057; *P* = 0.531).
9. Patients with high-range LDL-C in first year after MI (month 1 excluded; n = 501; *P* = 0.358).

two covariates (ONS mortality and socioeconomic status) were provided by GPRD only after the specific study patients had been identified and matched; thus, these factors could not be used in the matching process. Interestingly, the patients exposed to licensed *n*-3 fatty acids were of lower socioeconomic status. This may be associated with general practitioners being aware of the potential benefits of *n*-3 fatty acids and therefore prescribing treatment on the understanding that the patient may not otherwise be able or willing to access marine *n*-3 fatty acids through diet or otherwise. Indeed, in the Euroaction Study, only 11% of patients in general practice achieved their recommended level of *n*-3 fatty acids by dietary means.[18] We have not examined the association between *n*-3 fatty acids and major nonfatal cardiovascular events, such as further acute coronary syndrome, need for subsequent percutaneous coronary intervention or coronary artery bypass graft, or recurrence of angina or stroke; this association was outside the remit of this already extensive analysis. However, the results of GISSI-P and other studies would lead us to expect less of an effect on these outcomes with this dose of *n*-3 fatty acids.[4,5,19] In addition, when viewed from a data perspective, case ascertainment for recurrent events can be difficult to distinguish from a recording of medical history. Therefore, we selected an index event (first MI) and primary end point (any death), each of which could be identified with a high degree of confidence.

Recent trials, such as OMEGA and ORIGIN, and a meta-analysis have suggested a lack of benefit of *n*-3 fatty acids in secondary prevention of cardiovascular disease in different patient populations.[9,20,21] In part, it was postulated (methodologic differences aside) that this may reflect a lack of benefit against a background of intensive modern preventative therapy. In the current study, we report on 1517 deaths, almost 10 times more deaths than in the OMEGA trial (although the

annual death rates were similar at 4.8% and 4.2%, respectively), suggesting our study is both representative and adequately powered. In the sensitivity analysis among those receiving dual antiplatelet therapy and those achieving low levels of LDL-C (<1.8 mmol/L), we observed no significant modification of the beneficial effect of *n*-3 fatty acid exposure on mortality (Figures 4 and 5). Taken together, the current data suggest that when *n*-3 fatty acids are prescribed within 90 days (and in particular within 14 days) of an MI, this intervention offers additional protection against all-cause mortality on top of contemporary pharmacotherapy.

In GPRD, linking to ONS mortality records increases the frequency of death events by ~10%. This has a subtle technical impact on this type of study in that it introduces a potential immortal time bias in a very small number of the nonexposed, matched patients because they were subsequently determined to have died before the matching patient was first exposed to the treatment of interest. These corresponding exposed and nonexposed subjects were excluded. A further, subtle limitation of these data relates to the date of the record of MI on the general practitioner's computerized systems. Although we have assumed that the general practitioner has recorded the correct date of the MI from the discharge letter or in discussion with the patient, it is plausible—if not likely—that some of the MI event dates referred to the date at which the general practitioner entered the data onto their system. This would have the impact of slightly shortening the calculated time to treatment initiation that we report here.

These findings have important treatment implications. First, they help explain why some of the clinical trials have resulted in conflicting and sometimes neutral findings. Although we did not examine for dose effects, the timing of administration of *n*-3 fatty acid treatment seems relevant for optimizing survival benefit in secondary-prevention patients post-MI. Very early administration after hospital admission of higher doses of the licensed *n*-3 fatty acids should be evaluated.

CONCLUSION

In routine clinical practice, early treatment with licensed *n*-3 fatty acids after a nonfatal MI was associated with a substantial reduction in risk of death, independent of other cardiovascular risk–modifying treatments, in patients with and without type 2 diabetes.

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All coauthors were involved with the study design. Ms. Jenkins-Jones conducted the data extraction and matching. Dr. Poole conducted the majority of the data analysis. Dr. Currie wrote the first draft, and all coauthors were then involved editorially. Dr. Currie had overall responsibility for the integrity of this study. Drs. Halcox and Ray contributed to the interpretation of the data and editing of the manuscript.

CONFLICTS OF INTEREST

Dr. Poole has consulted for the following manufacturers of diabetic pharmaceuticals: Bristol-Myers Squibb Co (BMS), Eli Lilly & Co Ltd, Novo Nordisk Ltd, and Sanofi-Aventis Ltd. Ms. Jenkins-Jones is employed by a research consultancy receiving funding from pharmaceutical companies. Drs. Carr and Schifflers are employees of Abbott Products Operations AG. Dr. Currie has received research grants from various health-related organizations, including Abbott, Astellas Pharma Inc, Diabetes UK, Eli Lilly, the Engineering and Physical Sciences Research Council, the European Association for the Study of Diabetes, Ferring Pharmaceuticals, GlaxoSmithKline plc (GSK), the Medical Research Council, Medtronic, Merck KGaA, the National Health Service, Pfizer Ltd, Sanofi-Aventis, Shire Pharmaceuticals Ltd, and Wyeth Pharmaceuticals; he also consults for Amylin Pharmaceuticals LLC, Aryx Therapeutics Inc, Astellas, Boehringer Ingelheim GmbH, BMS, Diabetes UK, Eisai Co Ltd, Eli Lilly, Ferring, GSK, Ipsen Ltd, Medtronic Inc, Merck, Pfizer, Sanofi-Aventis, Takeda Pharmaceutical Co, and Wyeth. Drs. Halcox and Ray have received honoraria for lectures and/or consultancies from Abbott, AstraZeneca plc, BMS, Daiichi Sankyo Ltd, Eli Lilly, Kowa Pharmaceutical Europe Ltd, Merck, Novo Nordisk, Pfizer, Roche Products Ltd, and Sanofi-Aventis.

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