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No effect of n-3 fatty acids supplementation on NT-proBNP after myocardial infarction: The Alpha Omega Trial

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Abstract

Background: heart failure is a major risk factor for cardiovascular mortality, for which n-3 fatty acids may have beneficial effects. We examined the effect of marine eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and plant-derived alpha-linolenic acid (ALA) on N-Terminal-pro Brain Natriuretic Peptide (NT-proBNP), a biomarker of heart failure.
Methods: we randomly assigned 4837 post-myocardial infarction patients, aged 60–80 years (82% men), to margarines supplemented with a targeted additional intake of 400 mg/day EPA and DHA, 2 g/day ALA, EPA-DHA plus ALA, or placebo for 40 months. In a random selection of 639 patients, NT-proBNP was determined both at baseline and at the end of follow-up. NT-proBNP was $\log_e$-transformed and analysed by type of treatment using analysis of covariance adjusting for baseline NT-proNBP.
Results: patients consumed on average 19.8 g margarine/day, providing an additional amount of 238 mg/day EPA with 158 mg/day DHA, 1.98 g/day ALA, or both, in the active-treatment groups. In the placebo group, the geometric mean level NT-proBNP increased from 245 ng/l (95%-confidence interval [CI]: 207–290) to 294 ng/l (95%-CI: 244–352) after 40 months ($p = 0.001$). NT-proBNP levels were not affected by ALA (+8% versus placebo; 95%-CI: −8% to +25%; $p = 0.34$), EPA-DHA (+2% versus placebo; 95%-CI: −14% to +18%; $p = 0.78$), nor EPA-DHA plus ALA (+9% versus placebo; 95%-CI: −8% to +25%; $p = 0.31$) treatment.
Conclusions: supplementation with modest amounts of EPA-DHA, with or without ALA, did not have a significant effect on NT-proBNP levels in patients with a history of myocardial infarction.

Keywords

n-3 Polyunsaturated fatty acids, alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, NT-proBNP, randomized double-blind placebo-controlled trial

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Introduction

Epidemiological studies have demonstrated an inverse association between consumption of fish and risk of heart failure (HF). A meta-analysis totalling 176,441 subjects and 5480 incident cases of heart failure from seven prospective studies showed that a higher intake of fish was associated with a 15% (95%-CI: 1–27%) lower risk of HF compared with the lower category of fish intake.[1] A study among 2735 adults free of heart disease showed a 48% (95%-CI: 28–62%) lower risk of incident HF in the highest versus the lowest quartile of plasma levels of eicosapentaenoic acid (EPA).[2] A large

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randomized controlled trial (RCT) among patients with HF showed that daily treatment of 1 g EPA and docosahexaenoic acid (DHA) (n = 3494) during a median time of 4 years reduced the risk of all-cause mortality and hospital admissions versus placebo (n = 3481).[3] Experimental studies showed that EPA and DHA have a beneficial effect on the mechanism leading to progression of heart failure as evidenced by improved left ventricular diastolic function, reduction of vascular resistance and attenuated hypertension-related ventricular hypertrophy.[4–7] One small single-blinded RCT among symptomatic chronic HF patients showed that treatment with marine n-3 fatty acids reduced serum N-terminal-pro brain natriuretic peptide (NT-proBNP), a biomarker of heart failure, as compared to placebo.[8]

In the Alpha Omega Trial, totalling 4837 patients, we showed that low-dose n-3 fatty acids did not significantly reduce the rate of major cardiovascular events (n = 671, 13.9%) in post-myocardial infarction (MI) patients.[9] A recent meta-analysis including almost 70,000 randomized patients, also showed that 2 years' supplementation of EPA plus DHA (1.0 g/day), mainly for secondary prevention, did not reduce mortality or cardiovascular morbidity.[10] However, the GISSI-Prevenzione Investigators showed that in post-MI patients the reduction of cardiac death due to supplementation with n-3 fatty acids was most pronounced among patients with systolic left-ventricular dysfunction.[11]

Therefore, in an ancillary study of the Alpha Omega Trial we examined the effect on NT-proBNP of long-term supplementation of marine n-3 fatty acids EPA and DHA, and of plant-derived alpha-linolenic acid (ALA) among post-MI patients, because they are at increased risk of HF.[9] An increased level of the stable biomarker NT-proBNP is an indicator of myocardial ischaemia and left ventricular dysfunction, and therefore a good proxy of HF with independent prognostic value of mortality.[12–14]

Methods

Patients

This study was carried out in a subpopulation of the Alpha Omega Trial, a multi-centre, double-blind, placebo-controlled trial with a 2×2 factorial design, on the effect of low doses of n-3 fatty acids on cardiovascular events. This trial has been described in detail elsewhere.[9,15] Briefly, 4837 independently living Dutch patients who had had an MI, no severe HF, aged 60–80 at baseline, received state-of-the-art antihypertensive, antithrombotic and lipid-modifying drug treatment. These patients were randomized and received one of four trial margarines during 40 months of follow-up. Due to financial constraints two blood samples were scheduled to be drawn, at baseline and after 40 months, in patients randomized before August 2005 (N = 2918). Of all patients randomized prior to August 2005, 233 (8%) patients died during follow-up and 259 (9%) patients had missing blood samples or refused to have their blood taken and/or to participate further in the trial. As previously reported, drop-out was random among the four study groups.[16] Thus two blood samples were available for 2426 patients (yielding 50% of the cohort). Owing to financial constraints NT-proBNP was measured in a random selection of these 2426 patients, equally divided among the four study groups (n = 639/2426; 26%) and matched for age and sex (Figure 1). The Alpha Omega Trial was conducted in accordance with the Helsinki Declaration and approved by a central medical ethics committee in the Netherlands (Office for Human Research Protections #IORG0004004). Written informed consent was obtained from all patients.

Intervention with n-3 fatty acids

Patients were randomly allocated to a daily intake of approximately 20 g of trial margarines that provided a targeted additional daily intake of 400 mg of EPA–DHA (ratio 3:2), a targeted additional daily intake of 2 g of ALA, the combination of EPA-DHA and ALA, or placebo. Dosages were comparable to the recommended dietary allowances (RDAs) for these n-3 fatty acids.[15] Patients were asked to avoid n-3 fatty acids supplements during the trial. For logistical reasons, actual treatment was preceded by 4–6 weeks on placebo margarine. Trial margarines were identical, except for n-3 fatty acids. Compliance was monitored via margarine tub counts, telephone interviews and patient diaries. In samples of randomly selected patients at baseline, after 20 and 40 months of follow-up, n-3 fatty acids in serum cholesteryl esters were determined as an objective measure of compliance.[15]

Serum NT-proBNP measurements

Standardized blood handling procedures for the Alpha Omega Trial are described in detail elsewhere.[17] Briefly, blood samples were obtained at the subjects' homes or at hospital. Tubes were packaged in sealed envelopes and sent via standard postal service to a central laboratory. For the present study blood samples of female patients were thawed for the first time as well as the samples of male patients collected at baseline. Samples of male patients collected at the end of the trial were thawed for the second time.

NT-proBNP levels were measured in stored serum samples (Dimension Vista 1500 analyzer, Siemens). Intra-assay variations for low (mean 73 ng/l),

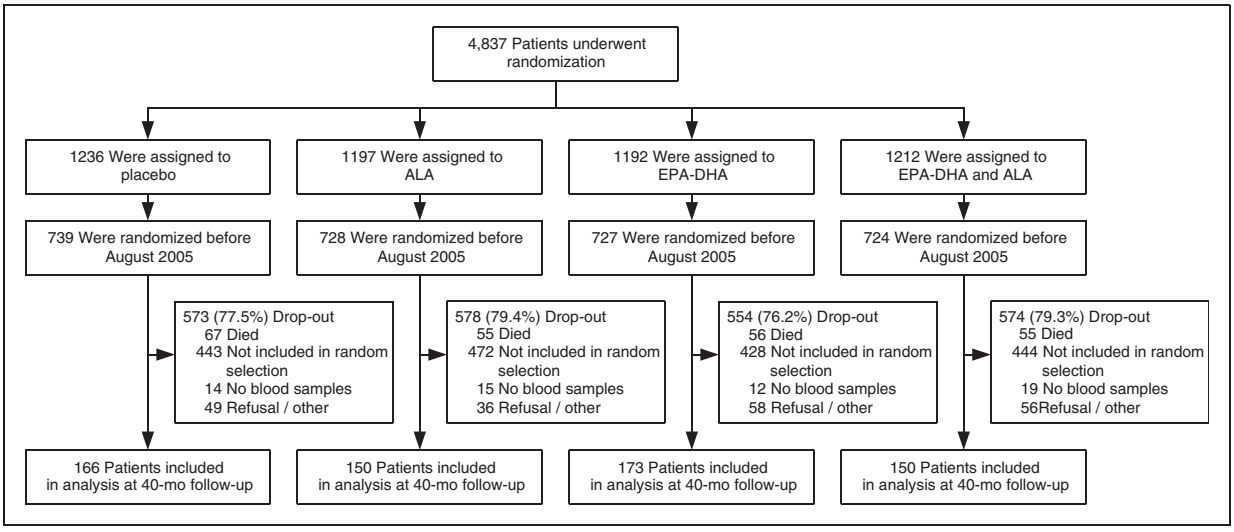

Figure 1. Flow chart of the Alpha Omega Trial: randomization and follow-up.
ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

intermediate (mean 274 ng/l) and high (mean 3661 ng/l) NT-proBNP were 1.55%, 0.88% and 0.90%. Inter-assay variations for low (56 ng/l), intermediate (257 ng/l) and high (3069 ng/l) NT-proBNP were: 3.20%, 2.28% and 2.98%, respectively.

Data collection and follow-up procedures

Patients were interviewed and physically examined by trained research nurses at home or in hospital at baseline. Information on demographic variables, lifestyle habits, current health status and medical history were collected by self-administered questionnaires as previously described in detail.[9] History of symptomatic heart failure was self-reported and collected by a self-administered questionnaire as follows: 'Did a physician ever establish the diagnosis heart failure (decompensatio cordis): yes, no or do not know'. Ethnicity was categorized as: white, black or other. Medication was coded according to the Anatomical Therapeutic Chemical Classification System (ATC). At baseline, anthropometric measures were assessed, and blood pressure was measured. After 40 months, patients were re-invited for an interview and physical examination. Diabetes mellitus was considered present in case of a self-reported physician diagnosis, use of antidiabetic drugs and/or elevated blood glucose. We estimated GFR (eGFR) with the combined creatinine-cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2012.[18–20]

Data analysis

Baseline characteristics in the four groups are presented as mean ± standard deviation (SD), median with interquartile range (IQR) or percentage.[21] Analyses were performed according to the intention-to-treat principle. Differences between groups were tested by *t*-test or chi-squared test, depending on the variable. Since serum concentrations of NT-proBNP were positively skewed, baseline and 40-month levels were $\log_e$-transformed before analyses to obtain normal distributions.[22] The change over time in $\log_e$ NT-proBNP levels in the placebo group was tested using t-test for paired samples. Effects of n-3 fatty acids were tested against placebo using analysis of covariance (ANCOVA), adjusting for baseline $\log_e$ NT-proBNP levels. Back-transformed geometric means are presented with the accompanying 95%-CI. This analysis was repeated after exclusion of non-compliant patients, who consumed <80% of the time trial margarine. Finally, median changes in NT-proBNP from baseline until 40 months of follow-up in the three n-3 fatty acids groups versus the placebo group were compared using the non-parametric Mann-Whitney test, as changes (i.e. delta values) of NT-proBNP after 40 months showed a leptokurtic (i.e. fat-tailed) distribution. Finally, we explored the treatment effect of n-3 fatty acids after stratification for baseline history of HF (yes/no), NT-proBNP level: <300, ≥300 to <900 and ≥900 ng/l, and eGFR <60 or ≥60 ml/min/1.73 m^2.[23–25] All analyses were done using SPSS 21.0 (SPSS, Inc. Chicago, IL).

Results

Descriptives

Baseline characteristics were well-balanced over the four study groups except for current smoking and kidney function (Table 1). Mean age of the 639 patients

Table 1. Baseline characteristics of the 639 patients on the Alpha Omega Trial by treatment group.

Variables	Placebo (N = 166)	ALA (N = 150)	EPA-DHA (N = 173)	EPA-DHA and ALA (N = 150)
Age, years	69.0 ± 5.3	69.4 ± 5.3	68.9 ± 5.6	69.7 ± 5.6
Men, n (%)	140 (84.3)	120 (80.0)	140 (80.9)	124 (82.7)
Time since MI, years	4.8 (3.3)	4.7 (3.8)	4.8 (3.6)	4.4 (3.2)
Self-reported history of heart failure,				
Yes, n (%)	37 (24)	36 (25)	49 (30)	30 (21)
No, n (%)	97 (62)	82 (57)	76 (46)	80 (56)
Do not know, n (%)	23 (15)	27 (17)	40 (24)	34 (24)
Self-reported history of stroke, n (%)	11 (6.7)	11 (7.3)	13 (7.6)	10 (6.7)
Diabetes[a], n (%)	33 (19.9)	31 (20.7)	23 (13.3)	29 (19.3)
Antidiabetic drugs, n (%)	25 (15.1)	21 (14.0)	19 (11.0)	26 (17.3)
Body mass index[b], kg/m^2	27.3 ± 3.5	28.0 ± 3.6	27.9 ± 3.5	27.6 ± 3.6
≥30 kg/m^2, n (%)	31 (18.7)	37 (24.7)	44 (25.4)	28 (18.7)
Systolic blood pressure, mmHg	145 ± 23	145 ± 23	144 ± 21	145 ± 24
Diastolic Blood Pressure, mmHg	82 ± 11	81 ± 11	82 ± 12	81 ± 11
Use of anti-thrombotic drugs[c], n (%)	164 (98.8)	144 (96.0)	171 (98.8)	145 (96.7)
Use of lipid modifying drugs [d], n (%)	134 (80.7)	129 (86.0)	146 (84.4)	128 (85.3)
Use of blood-pressure-lowering drugs[e], n (%)	151 (91.0)	140 (93.3)	162 (93.6)	136 (93.3)
Diuretics	44 (26.5)	30 (20.0)	35 (20.2)	29 (19.3)
Calcium channel blockers	25 (15.1)	37 (24.7)	32 (18.5)	29 (19.3)
Betablockers	114 (68.7)	95 (63.3)	127 (73.4)	93 (62.0)
ACE-inhibitor and/or angiotensin blocker	89 (53.6)	84 (56.0)	91 (52.6)	77 (51.3)
Current smoker, n (%)	28 (16.9)	23 (15.3)	33 (19.1)	11 (7.3)
Alcohol use ≥1 glass/week n/total n (%)	120/166 (72.3)	106/150 (70.7)	130/173 (75.1)	111/150 (74.0)
Fish intake (<5 g/day)[f], n/total n (%)[g]	39/157 (24.8)	24/140 (17.1)	34/161 (21.1)	29/139 (20.9)
Serum cholesterol, mmol/l				
Total	4.95 ± 0.87	4.81 ± 0.98	4.96 ± 0.97	4.86 ± 0.93
LDL	2.86 ± 0.80	2.70 ± 0.82	2.85 ± 0.78	2.78 ± 0.80
HDL	1.20 ± 0.29	1.22 ± 0.29	1.26 ± 0.35	1.27 ± 0.32
Serum triglycerides, mmol/l	1.72 (1.34–2.51)	1.75 (1.27–2.60)	1.59 (1.20–2.19)	1.54 (1.17–2.22)
eGFR creatinine-cystatin C-based[g], ml/min/1.73m^2	79 (18)	81 (16)	78 (18)	77 (17)
Higher education[h], n (%)	26 (15.7)	14 (9.3)	17 (9.8)	16 (10.7)
Physically active (≥3 MET during >5 days/week)[i], n (%)	40 (24.1)	39 (26.0)	37 (21.5)	37 (24.8)

ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI myocardial infarction. Numbers may not add up to the column total because of missing values for some variables. Data are reported as mean ± standard deviation, or median (interquartile range), unless stated otherwise. Because of some missing values for questionnaire data, the total numbers of patients (i.e. 'total n') with complete data are given. [a]Diabetes was considered to be present if a patient reported having received the diagnosis from a physician, was taking glucose-lowering drugs, or had an elevated plasma glucose level (≥7.0 mmol/l in the case of patients who had fasted more than 4 h or ≥11.1 mmol/l in the case of non-fasting patients). [b]Body mass index was calculated as weight in kg divided by height in m^2. [c]Antithrombotic drugs ATC code B01. [d]Blood pressure-lowering drugs ATC codes C02, C03, C07, C08 and C09. [e]Lipid modifying drugs ATC code C10. [f]<5 g/day fish intake equals intake of one fish per month. [g]eGFR: estimated glomerular filtration rate. Combined creatinine-cystatin C-based chronic kidney disease-epidemiology (CKD-EPI) equation 2012.[18] [h]Higher education was defined as higher vocational education or university. [i]Defined as ≥3 metabolic equivalent tasks (MET) on >5 days/week.

was 69 years, 82% were men, 22% were obese, 20% had diabetes and 15% were current smokers (Table 1). Patients' ethnicity was: 98.9% white, 0.3% black and 0.8% other ethnicities. The median (IQR) time after MI at study entry was 4.0 years (2.0–6.4). About 1 in 4 patients had a history of symptomatic HF. The mean systolic blood pressure was 145 mmHg and 88% of the patients received blood pressure-lowering drugs. Statins were used by 83% and 98% of all patients used antithrombotic agents. The median (IQR) serum level of

Table 2. Effect of 40 months of intervention of n-3 fatty acids on change in NT-proBNP in 639 patients of the Alpha Omega Trial, according to study group.

NT-proBNP (ng/l)	Pretreatment values (95%-CI)[a]	Post-treatment values (95%-CI)[a]	Post-treatment values adjusted for pretreatment (95%-CI)[a]	Treatment effect (95%-CI)[b]	*p*-value[c]
Placebo (N = 166)	245 (207; 290)	294 (244; 352)	279 (249; 313)		
Active treatments:					
ALA (N = 150)	208 (175; 248)	278 (231; 334)	303 (269; 342)	+8% (−8% to +25%)	0.34
EPA-DHA (N = 173)	222 (190; 259)	276 (234; 327)	286 (256; 320)	+2% (−14% to +18%)	0.78
EPA-DHA plus ALA (N = 150)	252 (212; 301)	328 (270; 398)	305 (270; 343)	+9% (−8% to +25%)	0.31
n-3 fatty acids groups combined (N = 473)	226 (206; 249)	292 (263; 324)	297 (278; 318)	+6% (−7% to +19%)	0.36

ALA, alpha-linolenic acid; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NT-proBNP, N-terminal-pro brain natriuretic peptide. [a]Values are back-transformed geometric means (95%-CI of the mean), obtained by analysis of covariance (ANCOVA). [b]Back-transformed % effect of active treatment compared to placebo with 95%-CI. [c]*p*-values compared to placebo obtained by ANCOVA.

NT-proBNP in men was 218 ng/l (96 to 447) and in women 306 ng/l (142–583) ($p = 0.01$). Chronic kidney disease (eGFR <60 ml/min/1.73 m^2) was present in 16.4% of all patients, of whom five had an eGFR <30 ml/min/1.73 m^2. Approximately 20% of the patients eat fish less than once a month. The median intake EPA-DHA was 120 mg/d (IQR: 55–200). During the trial fish oil capsules or supplementation had been used by 44 (6.9%) of the 639 participants. The use of fish oil capsules did not differ among the four treatment groups.

Intervention with n-3 fatty acids

The mean intake of trial margarine was 19.8 g/day (SD 3.9) and 96.4% used the margarines >80% of the time. The patients in the EPA-DHA groups received, on average, an additional 238 mg EPA and 158 mg DHA per day, and those in the ALA groups an additional 1.98 g ALA per day. Patients participated in the trial for a median of 41.3 months (IQR: 40.7–42.0). This included a run-in period on placebo margarine of 1–1.5 months; thus the active treatment lasted 40 months.

The daily additional amount of n-3 fatty acids during the trial was reflected in the serum cholesteryl esters. ALA supplementation increased serum ALA by 69% and also serum EPA by 30%, but not serum DHA. EPA-DHA supplementation increased EPA by 44% and DHA by 22%. EPA-DHA plus ALA supplementation increased EPA by 101% and DHA by 35%.

Effect of n-3 fatty acids on NT-proBNP

At baseline, median serum NT-proBNP was 231 ng/l (IQR: 104–470). At baseline, the four treatment groups did not differ in serum NT-proBNP. Of all patients 59% had an NT-proBNP level <300 ng/l and 9% ≥900 ng/l.

After 40 months in the four treatment groups the residuals were normally distributed (Kolmogorov-Smirnov test: $p = 0.2$) and the error variances were equal (White's general homoscedasticity test: $p = 0.13$). In the placebo group, the geometric mean level increased after 40 months by 20%: from 245 ng/l (95%-CI: 207–290) to 294 ng/l (95%-CI: 244–352) ($p = 0.001$). After additional adjustment for current smoking and kidney function the results were similar. After an average 40 months of follow-up, post-treatment adjusted for pretreatment $\log_e$ NT-proBNP values did not differ significantly from the placebo group (Table 2). NT-proBNP levels were not significantly affected by ALA (+8% versus placebo; 95%-CI: −8% to +25%; $p = 0.34$), EPA-DHA (+2% versus placebo; 95%-CI: −14% to +18%; $p = 0.78$), or EPA-DHA plus ALA (+9% versus placebo; 95%-CI: −8% to +25%; $p = 0.31$) treatment. The relative treatment effect of the three n-3 fatty acids intervention groups combined compared to placebo was +6% (95%-CI: −7% to +19%). The compliance in the four treatment groups was 96%. A per-protocol analysis (excluding patients who deviated from the protocol) showed similar results (data not shown).

After stratification for baseline level of NT-proBNP <300, ≥300 to <900, and ≥900 ng/l, the relative treatment effect (95%-CI) of n-3 fatty acids compared to placebo was: +7% (95%-CI: −10% to +24%, $p = 0.42$), +10% (95%-CI: −13% to +34%, $p = 039$) and −5% (95%-CI: −58% to +47%, $p = 0.84$). At baseline the geometric mean NT-proBNP level in patients with (N = 152) and without (N = 335) a history

of HF was 304 ng/l and 199 ng/l, respectively ($p < 0.001$). We found no evidence of interaction between n-3 fatty acids treatment and history of HF (p for interaction = 0.7, see online Supplemental Table).

Non-parametric analysis yielded similar results. After 40 months of follow-up the median change (IQR) of NT-proBNP was in the placebo group +36 ng/l (−36; +196) . After 40 months of intervention the median changes in NT-proBNP were +44 ng/l (−30; +233, P = 0.67) in the ALA group, +30 ng/l

(−41; +199, $p = 0.70$) in the EPA-DHA group, and +31 ng/l (−38; +235, $p = 0.76$) in the EPA-DHA plus ALA group in comparison to placebo. The median change in NT-proBNP was +37 ng/l (−38; +216), in all three n-3 fatty acids groups combined, which did not differ from the change in the placebo-group ($p = 0.91$).

Discussion

An additional daily intake of 396 mg EPA-DHA with or without 2 g ALA over 40 months did not have a beneficial effect in addition to cardiovascular drug treatment on the level of NT-proBNP in patients with a history of MI. In the placebo group there was a 20% increment of NT-proBNP levels after 40 months. The PREVEND-study showed in the general population that doubling of NT-proBNP was associated with a 22% increase in all-cause mortality and a 16% increase in cardiovascular events.[26]

Inflammation is important in the pathogenesis and progression of many forms of HF.[12] Both statins and n-3 fatty acids have anti-inflammatory effects. In the Alpha Omega trial the majority of patients were on statin treatment. Recently, we showed that low-dose n-3 fatty acids in addition to statin therapy do not have a beneficial effect on inflammation as reflected by the level of high-sensitivity C-reactive protein.[16] The present study was too small to merit subgroup analysis in non-statin users to explore the effect on NT-proBNP level. This issue should be studied in a larger population of non-statin users.

Although NT-proBNP is an established marker for HF, non-cardiac factors may also affect level of serum NT-proBNP: levels are higher in women compared to men, increase with ageing, and are lower in people with obesity compared to those with a normal body mass index.[12] However, all these factors were well balanced in the four study groups. Finally, there is an inverse relation between NT-proBNP and kidney function, especially below an eGFR of 30 ml/min/1.73 m^2.[25] We found, however, no evidence of effect-measure modification between EPA-DHA and chronic kidney disease with regard to the effect on the level of NT-proBNP.

We used serum samples for determining NT-proBNP in a central laboratory that had been stored for 2–9 years at −70°C. A previous study demonstrated that NT-proBNP levels have a very good stability for at least 1 year at −80°C and after five freeze–thaw cycles (mean change −1.6%).[27] Another study showed that 2-year frozen storage at −20°C decreases NT-proBNP <10% for more than 90% of the samples.[28]

In contrast with our study, a double-blind RCT in severe symptomatic HF patients (n = 27) showed that supplementation with EPA-DHA improved left ventricular ejection fraction (LVEF) in a dose-dependent fashion.[29] At baseline patients had a mean LVEF of ± 30% and a high level of NT-proBNP of ± 3000 ng/l. After 3 months daily supplementation with 840 mg or 3360 mg of EPA-DHA the increase of LVEF was 2.5% and 5.5%, respectively. Unfortunately, NT-proBNP levels at the end of follow-up were not reported. Zhao et al. showed in a single-blind RCT, including 75 patients aged ≥60 years with symptomatic HF (NYHA class II-III) and a LVEF <40%, that in addition to optimal medical treatment a daily dose of 600 mg EPA-DHA over 3 months (n = 38) resulted in a mean reduction of NT-proBNP from 812 to 674 ng/l (mean change -138 ng/l (−17%); $p = 0.02$) compared to placebo.[8] Finally, the GISSI Prevenzione Investigators showed a stronger beneficial effect on sudden death of 1 g daily marine n-3 fatty acids during 3.5 years in patients with a LVEF ≤50% compared to those with a LVEF >50%.[11] Differences in underlying causes of HF, more severe HF and the higher daily dose of EPA-DHA may explain the stronger effect of EPA-DHA observed in these trials compared to the present study.

This study has several limitations. We could include only a small number of patients due to financial constraints. Furthermore, at baseline there were differences between the four groups with regard to current smoking and kidney function. However, adjustment for differences at baseline did not materially change the results. The dosages of EPA-DHA and ALA, comparable to the RDAs, may have been insufficient to influence NT-proBNP level. Finally, we did not have information on the patients' NYHA classification of HF or LVEF. However, an NT-proBNP level <300 ng/l has a negative predictive value of 99% to exclude a LVEF <40%.[23] An NT-proBNP level >900 ng/l in patients aged 50–75 years identifies those with HF with a sensitivity and specificity of 90% and 82%, respectively, and has a positive predictive value of 82%.[24,30] In the present trial, 59% of all patients had an NT-proBNP level <300 ng/l and only 9% ≥900 ng/l. Taken together, the majority of the patients included in the Alpha Omega Trial probably had a normal LVEF.

Our trial has several strengths. Firstly, it was the largest trial investigating the effect of n-3 fatty acids on NT-proBNP and had a relative long follow-up. Secondly, NT-proBNP was analysed in a central laboratory.

In summary, we showed no beneficial effect of an additional daily amount of 0.4 g EPA-DHA with or without 2 g ALA on NT-proBNP in patients with a history of MI and a low habitual fish intake on top of cardiovascular drug treatment. Future intervention studies should explore the effects of higher doses of n-3 fatty acids supplementation on NT-proBNP.

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http://www.alphaomegatrial.com/website

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Conflicts of interest

None declared.

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