Alpha Omega Trial

Statistical Analysis Plan
Main analysis

Final version

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1.0 Introduction

1.1 Statistical Analysis Plan

This Statistical Analysis Plan (SAP) is developed to guide the statistical analysis of the Alpha Omega trial data and the production of the statistical output. The document was developed after review of the Alpha Omega trial protocol, including its amendments, and the Case Record Forms (CRFs), but before any trial data had been released. The SAP provides detailed information of the populations that will be analyzed, the subject characteristics and the efficacy and safety parameters that will be evaluated, as well as the specific statistical methods that will be applied. This version of the SAP is designed for the main results analysis, i.e. the relation between randomly allocated treatment and the primary and secondary study endpoints. A modified version will be created for analyses that focus on cognitive decline and mental well-being as ancillary endpoints.

1.2 Role of the funding source

The Alpha Omega trial was sponsored by the Netherlands Heart Foundation, US National Institutes of Health (NIH/NHLBI) and Unilever. This SAP was prepared by the Executive Committee and the independent statistician only, and none of the funding source providers had any influence or control on the planned analyses. The analyses will be conducted, and the results interpreted and reported independently of the trial sponsors.

2.0 Protocol summary

2.1 Protocol development

The Alpha Omega trial is registered at ClinicalTrials.gov as study NCT00127452 (see http://clinicaltrials.gov/ct2/show/NCT00127452). The original protocol was released on Augustus 3, 2005, and underwent several changes since then. Most importantly, because of an unexpected low incidence of the original primary endpoint (coronary heart disease [CHD]-related mortality), the Steering Committee had decided to

- redefine the primary endpoint as a composite of fatal cardiovascular disease (CVD), non-fatal myocardial infarction (MI), non-fatal cardiac arrest, non-fatal stroke, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG);
- extend the follow-up to 40 months (original: 36 months);
- increase the sample size to a maximum of 5000 subjects (original: 4000).

This summary is based on the protocol version that is described in the design paper of the Alpha Omega Trial by Geleijnse et al, Am Heart J. 2010 Apr;159(4):539-546.e2.

2.2 Background

In the 1970s, a low incidence of CHD was observed among Inuit populations living in their native environment in Greenland, who consumed diets that were very high in marine mammals and fish (Bang 1975). Moreover, an inverse dose-response relationship was observed between much lower intakes of fish and CHD mortality in 852 middle-aged Dutch men with 20 years of follow-up (Kromhout 1985). Men who consumed at least 30 g of fish per day (1-2 fish meals per week) had only half the risk of fatal CHD compared to men who did not eat fish. Since then, evidence for a cardio protective effect of fish intake has accumulated. A meta-analysis of 11 prospective cohort studies showed a 15% lower risk of fatal CHD for fish intake once a week, up to 38% for intakes >5 times per week, compared to fish once per month or less (He 2004a). Beneficial effects of fish on CHD have mainly been attributed to marine n-3 fatty acids, that is, eicosapentaenoic acid (EPA; C20:5, n-3) and docosahexaenoic acid (DHA; C22:6, n-3).

Mozaffarian and Rimm reviewed the published literature through April 2006 for prospective cohort studies and randomized controlled trials on intake of fish or fish oil and CHD (Mozaffarian 2006). In their analysis, the consumption of 1 to 2 servings of fish per week was related to a 36% lower risk of fatal CHD. Intake of 250 mg/ d of EPA + DHA was considered sufficient to prevent CHD mortality, with no further benefit of higher intakes. Léon et al performed a meta-analysis of 12

randomized controlled trials of fish oil supplementation, mainly in cardiac patients (Léon 2008). Fish oil supplementation was related to a 20% reduction in risk of cardiac mortality, and none of the trials provided evidence in favor of control treatment. More recently, observational and experimental data have also suggested a protective effect of n-3 fatty acid intake against nonfatal cardiac events in Japanese subjects (Iso 2006; Yokoyama 2007).

A low level of fish intake may also protect against stroke. Dutch men who consumed >20 g of fish per day had only half the risk of stroke compared with men who consumed less fish (Keli 1994). He et al summarized 8 prospective cohort studies of fish intake and stroke with >200,000 subjects that were published until 2003 (He 2004b). The relative risk of incident stroke was 0.87 (95% CI 0.77-0.98) in subjects who consumed fish once a week compared to those who did not eat fish or consumed fish less than once per month. This protective association was confined to ischemic stroke (0.69, 95% CI 0.48-0.99).

For alpha-linolenic acid (ALA; C18:3, n-3), the n-3 fatty acid derived from plant foods, there is also evidence for a beneficial effect in the cardiovascular system although less consistent than for EPA + DHA (Brouwer 2004; Wang 2006; Harris 2008). A meta-analysis of 5 prospective cohort studies showed an inverse relationship between ALA intake and fatal CHD, indicating an overall risk reduction around 20% that was borderline statistically significant (Brouwer 2004). In a population-based case-control study in Costa Rica, levels of ALA in adipose tissue were significantly inversely associated with risk of nonfatal myocardial infarction (MI) (Campos 2008).This relation was nonlinear, with no further benefit for intakes above approximately 0.65% energy (1.79 g/d). With regard to stroke, data on the effect of ALA intake are scanty. Blood ALA levels were inversely related to incident stroke in MRFIT (Simon 1995).

2.3 Objective

The aim of the Alpha Omega study is to examine whether cardiovascular mortality and morbidity can be prevented in post-myocardial infarction patients by low-dose supplementation of (very-)long-chain n-3 polyunsaturated fatty acids (PUFA).

2.4 Study participants

Eligible for participation were men and women aged 60-80 years who had a clinically diagnosed MI up to 10 years before randomization. Study participants were identified and recruited from 32 Cardiology centers in The Netherlands.

2.5 Design

The Alpha Omega Trial is a multicenter, randomized, double-blind, placebo-controlled clinical trial. Equal numbers of eligible subjects were randomly allocated according to a 2x2 factorial design to one of the following treatment strategies:

1. EPA + DHA: Experimental

Margarine spread that yields 400 mg of EPA + DHA per day for an average margarine use of 20 grams per day;

2. ALA: Experimental

Margarine spread that yields 2 grams of ALA per day for an average margarine use of 20 grams per day;

3. EPA + DHA plus ALA: Experimental

Margarine spread that yields 400 mg of EPA + DHA per day plus 2 grams of ALA per day for an average margarine use of 20 grams per day;

4. Placebo: Placebo Comparator

Margarine spread that contains no EPA, DHA or ALA (exchanged for oleic acid).

The intervention period was set at 40 months. Research staff, participants and couriers for margarine transport were blinded towards the type of margarine that subjects received. Margarines for the trial were produced at regular intervals by Unilever, Vlaardingen, The Netherlands. A frequently consumed margarine available on the Dutch market served as the basis for trial margarines. Enriched margarines and placebo were of identical taste and appearance to ensure double-blind conduct of the trial. Treatment codes could not be derived from margarine tubs. After 4-6 weeks on placebo margarine, trial margarines (8 tubs of 250 g) were delivered free of charge to subjects' homes every 12 weeks by cooled courier transport.

2.6 Data collection

At baseline, data were collected on demographic factors (including educational level), lifestyle (including smoking status and alcohol use), medical history, self-perceived health, and current health status. Dietary data, including intake of different types of fish, were collected by a 203-item food frequency questionnaire that was an extended version of a previously validated food frequency questionnaire. Physical activity was also assessed by a validated questionnaire. Self-reported medication of the participants was coded according to the Anatomical Therapeutic Chemical Classification System (ATC). Subjects were physically examined by trained research nurses at home

or in the hospital, which included anthropometry, blood pressure, heart rate, and blood sampling. The Mini-Mental State Examination was performed to test cognitive function. Subjects with Mini-Mental State Examination scores ≤21 were excluded to avoid problems with trial procedures and dietary recall. Body weight (kg) and height (cm) were measured with the subject wearing light indoor clothing without shoes, and the body mass index (kg/m^2) was computed. Waist circumference (cm) was measured at the midpoint between the bottom rib and the top of the hipbone. Systolic and diastolic blood pressures (corresponding to the 1^{st} and 5^{th} Korotkoff sounds, respectively) were measured with the subject seated, after a 10-minute rest. Measurements were performed twice on the left upper arm with an automatic device (Omron HEM-711), and values were averaged. Finally, venous blood (30 mL) was drawn for the assessment of serum lipids, plasma glucose, and the fatty acid composition of plasma cholesteryl esters. Buffy coats were stored for DNA analysis. We asked subjects to remain fasted if physical examination was scheduled before 10:30 AM or to consume only a light meal when the examination was scheduled after 10:30 AM and to refrain from smoking and drinking coffee 1 hour before blood sampling.

2.7 Study endpoints

2.7.1 Endpoint reporting

A continuous update of the vital status of trial participants was provided by the National Institute for Public Health and the Environment (RIVM), Bilthoven, via a computerized link with the municipal health registries in the Netherlands. A 100% follow-up for vital status was achieved. All subjects provided contact details of a close relative or friend (not a household member) and gave informed consent to contact their general practitioner (GP) and cardiologist for information. For subjects who died, the GP was asked to fill out a standard form on primary and contributing causes of death. Specific questions were added to enable coding of cardiac arrest and sudden death, including the time of occurrence of first symptoms. Additional information on fatal events was obtained from the hospital, nursing home, or family members (by telephone). In addition, for all subjects who died, the death certificate was obtained from the Dutch National Mortality Registry (Statistics Netherlands).

Subjects were asked to record all hospitalizations and changes in medication in a structured patient diary. In addition, subjects informed research staff about vacations, change of address, and hospitalizations by means of postage-paid reply cards. Spontaneous notifications of health problems by letter, e-mail, or telephone were also recorded in the computer database by research staff. Follow-up for nonfatal cardiovascular events and cardiac interventions (PCI, CABG) was performed by research staff through annual telephone interviews. Self-reported nonfatal cardiovascular events, including MI, cardiac arrest, and stroke, and cardiac interventions were verified against hospital

records at the cardiology clinic by a trained research nurse. Only events for which documentation on the clinical diagnosis (e.g., hospital discharge records or letter) could be retrieved will be considered in the analysis.

2.7.2 Follow-up

According to the original protocol, the first 4000 trial participants were followed for the incidence of endpoint events for a period of 40 months since their randomization. On 27 September 2005, the Steering Committee decided to enlarge the sample to a maximum of 5000. The Steering Committee also decided to terminate the follow-up on November 5, 2009 for all participants. Consequently, the maximal follow-up of these additional subjects may vary from 30-39 months. Anecdotally, participants from the original cohort might have a follow-up that exceeds 40 months. Analyses of the primary and secondary (efficacy) endpoints that are described below are based on data that emerged during the maximum available follow-up for each individual participant.

2.7.3 Endpoint adjudication process

Events were coded according to International Classification of Diseases, 10th revision (ICD-10), by 3 independent members of the Endpoint Adjudication Committee (EAC), who remained blinded for the subjects' identity, treating physicians, and allocated treatment. EAC members coded all events independently, and regular meetings were organized to reach consensus in case of discrepancies.

2.7.4 Efficacy endpoints

2.7.4.1 Primary efficacy endpoint

The primary efficacy endpoint of the trial is the incidence of a Major Cardiovascular Event (MCE), which is defined as the composite of incident CVD, any PCI or CABG. Incident CVD comprises nonfatal MI and mortality from ischemic heart disease (ICD-10 codes I20-I25), nonfatal and fatal cardiac arrest (I46), sudden death undefined (R96), mortality from heart failure (I50), and nonfatal and fatal stroke (I60-I69).

2.7.4.2 Secondary efficacy endpoints

Secondary efficacy endpoints include

- incident CVD, which comprises nonfatal MI and mortality from ischemic heart diseases (ICD-10 codes I20-I25), nonfatal and fatal cardiac arrest (I46), sudden death undefined (R96), mortality from heart failure (I50), and nonfatal and fatal stroke (I60-I69);

- fatal CVD, which comprises mortality from ischemic heart disease (I20-I25), fatal cardiac arrest (I46), sudden death undefined (R96), mortality from heart failure (I50) and fatal stroke (I60-I69);
- fatal CHD, which comprises mortality from ischemic heart disease (I20-I25), fatal cardiac arrest (I46), sudden death undefined (R96);
- all-cause mortality, defined as death from any cause;
- the composite of sudden death undefined (R96) and nonfatal and fatal cardiac arrest (I46);
- the composite of sudden death undefined (R96), nonfatal and fatal cardiac arrest (I46), and self-reported placement of any implantable cardioverter-defibrillator (ICD) during follow-up, verified in medical records.

2.7.5 Safety endpoints

No formal safety endpoints are defined for the Alpha Omega study. Shortly after the study had started, evidence emerged of a potentially adverse effect of alpha-linolenic acid on prostate cancer. Therefore, the Steering Committee decided to collect data on (self-reported) prostate cancer.

2.8 Sample size calculation

Originally, we calculated the sample size needed to detect an effect of EPA + DHA on fatal CHD, with the following assumptions: (1) incidence of CHD mortality of 4% per year in post-MI patients aged 60 to 80 (on placebo), based on trials carried out in the 1990s; (2) relative risk of CHD mortality of 0.75 (i.e., a 25% risk reduction compared to placebo) for low-dose treatment with EPA + DHA; (3) duration of treatment of 3 years; and (4) 2-way analysis. For a 2-sided α of .05 and a power of 80%, at least 3408 subjects would be needed to demonstrate an effect of EPA + DHA, and we targeted at a sample size of 4000 subjects, allowing for a yearly dropout rate of 5%. For ALA, under the assumption of a relative risk of 0.80, the power for demonstrating an effect on CHD mortality with this number of subjects was 67%. During the course of the study, the overall mortality rate was 23 per 1000 person-years. This rate was substantially lower than anticipated, likely due to improved therapy of MI patients in the acute phase and more effective pharmacologic treatment of hyperlipidemia and hypertension in recent years. For this reason, the Steering Committee approved an increase in sample size to a total of 4800 subjects and an extended duration of intervention, that is, from 36 to 40 months.

3.0 Statistical handling policy

3.1 Analysis conventions

This section details general policies to be used for the statistical analysis. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

3.2 Significance testing

All statistical tests will use a significance level of α=0.05. Two-tailed tests will be performed for all analyses that use statistical testing. Confidence intervals will be presented with 95% degree of confidence.

All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value $\leq$0.05 will be considered statistically significant.

3.3 Multiplicity

No adjustments for multiplicity are planned within any of the analyses performed.

3.4 Data summarization

Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables. In addition quartiles will be presented in cases where a non-parametric analysis of continuous data is performed.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value.

All percentages will be rounded to one decimal place. The number and percentage of responses will be presented.

All analysis and summary tables will have the population sample size for each treatment group in the column heading.

3.5 Missing data

The investigators were instructed to obtain complete CRFs. Missing data will not be imputed.

3.6 Data distribution and model checking

For the analysis of dichotomous data Chi-square tests (with continuity correction) will be used, presented with the 95% confidence interval for the difference in proportions (normal approximation, large sample theory). If expected cell frequencies are small (less than 5), then Fisher's exact tests will be used instead.

For the analysis of continuous data that were measured at one point in time one-way analysis of variance (ANOVA) and unpaired Student's *t* tests will be used. For the analysis of continuous data that were repeatedly measured over time, two-way ANOVA and paired Student's *t* tests will be used. If the assumptions underlying ANOVA (normal distributions of residuals, homogeneity of variances) or Student's *t* tests (normal population distribution, particularly relevant for small samples) are not satisfied, then non-parametric tests will be applied instead.

The incidence of endpoint events over time will be studied by the method of Kaplan-Meier. It is assumed that the censoring is not linked to factors which are associated with the (event-free) survival time variable, and that the individuals censored at any time are representative of those individuals at risk of an endpoint event at that time (i.e. the censoring process is assumed to be uninformative). If the number of censored cases seems high then this assumption will be explored. The log rank test will be used to study differences in the incidence of endpoint events over time in relation to allocated treatment.

For the analysis of the relation between allocated treatment and the incidence of study endpoints Cox proportional hazards regression model will be applied. The assumption of proportional hazards will be assessed by visual judgment of the log-minus-log (event-free) survival plots.

3.7 Software

Version 9.1, or later of SAS® will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

4.0 Statistical analyses

4.1 Analysis populations

The patient populations to be studied are defined as follows:

4.1.1. Intention-to-treat

The intention-to-treat (ITT) population includes all subjects who were assigned a randomization number.

4.1.2. Per protocol

The following per protocol (PP) populations have been defined:

- PP-10: This population includes all subjects in the ITT population who had an average margarine intake of at least 10 gram per day (which is equivalent to the target of >200 mg/d extra EPA + DHA and >1 g/d extra ALA).
- PP-20: This population includes all subjects in the ITT population who had an average margarine intake of at least 20 gram per day (which is equivalent to the target of >400 mg/d extra EPA + DHA and >2 g/d extra ALA).
- PP-EXP: This population includes all subjects in the ITT population actually exposed to margarine use. The exposed period is defined as the time period between the date of first delivery of trial margarines to the participant's home until the date at which the last trial margarine was consumed.

4.1.3. Main analysis population

The ITT population is considered the main analysis population.

4.2 Subject demographics and pre-treatment characteristics

Subject demographics and pre-treatment characteristics will be summarized for the ITT and PP populations. The demographics and pre-treatment characteristics will be summarized for each treatment group and for all subjects.

4.2.1 Demographics

The summary of demographics will include gender, age at entry into the study and race.

4.2.2 Medical history and risk factors

The summary of medical history and CVD risk factors will at least include body mass index (kg/m^2), waist circumference (cm), non-fasting serum total cholesterol (mmol/L), non-fasting serum high-density lipoprotein cholesterol (mmol/L), non-fasting serum triglycerides (mmol/L), non-fasting serum glucose (mmol/L), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), time since last MI (y), self-reported history of stroke, presence of diabetes mellitus, history of cardiac interventions (PCI and CABG), smoking, alcohol use, alcohol intake in alcohol users only (g/d), fish consumers, fish intake in consumers only (g/d).

4.2.3 Medication

The summary of prior and concomitant medication will at least include supplements containing n-3 PUFA and the following drugs, ordered by ATC code:

- A10 Drugs used in diabetes
- A10A Insulin
- B01 Antithrombotic medication
- C01 Cardiac therapy
- C02 Antihypertensives
- C03 Diuretics
- C04 Peripheral vasodilators
- C05 Vasoprotectives
- C07 Beta blocking agents
- C08 Calcium channel blockers
- C09 Agents acting on the renin-angiotensin system
- C10 Lipid modifying agents
- C10AA HMG CoA reductase inhibitors (statins)
- G03 Sex hormones and modulators of the genital system

In addition, the following groups of medication will be created and analyzed:

- All blood pressure lowering drugs: C02 + C03 + C07 + C08 + C09
- Aspirin: A01AD05 + B01AC06 + N02BA01

4.3 Monitoring of compliance, CVD risk factors and medication

As a measure of compliance to margarine use, the fatty acid composition of plasma cholesteryl esters (as a biomarker of n-3 fatty acid intake) was assessed in randomly selected subsets of men (n=405) and women (n=405) at baseline, and after 20 and 40 months of follow-up. CVD risk factors (see 4.2.2), the use of n-3 PUFA supplements and changes in CVD medication (see 4.2.3) were also assessed in these subsets of patients during follow-up. Descriptive and inferential (differences in relation to randomly allocated treatment) statistics for the abovementioned variables will be determined in the randomly selected subsets at baseline, after 20 months and after 40 months.

4.4 Efficacy analysis

All efficacy analyses will be performed for the ITT and PP populations. Efficacy parameters will be determined for all 4 randomly allocated treatments.

4.4.1 Efficacy of EPA + DHA

The subjects who are randomized to EPA + DHA alone or to EPA + DHA plus ALA will be merged in one cohort (i.e. EPA + DHA experimental treatment). Their efficacy parameters will be compared with the cohort of subjects who are randomized to ALA alone or to placebo (i.e. EPA + DHA placebo). Thus an estimate of the efficacy of EPA + DHA treatment will be obtained.

4.4.2 Efficacy of ALA

The subjects who are randomized to ALA alone or to EPA + DHA plus ALA will be merged in one cohort (i.e. ALA experimental treatment). Their efficacy parameters will be compared with the cohort of subjects who are randomized to EPA + DHA alone or to placebo (i.e. ALA placebo). Thus an estimate of the efficacy of ALA treatment will be obtained.

4.4.3 Primary efficacy analyses

For the primary efficacy analyses, the following parameters / statistics will be determined for each of the comparator groups:

- total number of primary efficacy endpoint events;total sum of the follow-up (years) since randomization until the incidence of the primary efficacy endpoint;
- the incidence-rate of the primary endpoint, which is defined as the number of primary efficacy endpoint events divided by the total sum of the follow-up;

- the cumulative event-free survival for the primary efficacy endpoint. Although endpoint events that occur after 40 months follow-up will be taken into account, Kaplan-Meier event-curves will be truncated at 40 months follow-up for esthetic reasons.

The relation between randomly allocated treatment and the incidence of the primary efficacy endpoint will be described by

- an incidence rate ratio;
- a crude, unadjusted hazard ratio; Cox proportional hazard regression analysis will be conducted with randomly allocated treatment as independent predictor variable and the incidence of the primary efficacy endpoint as dependent outcome variable;
- adjusted hazard ratios; two multivariable Cox proportional hazard regression analyses will be applied. In the first model, the effect of randomly allocated treatment will be adjusted for age and gender only. In the second model, the effect of randomly allocated treatment will be adjusted for age, gender, blood pressure, blood lipids, diabetes and smoking behavior (current versus past or never), whereas a generalized estimating equation will be used for the estimation of model parameters, to reckon with the fact that observations in subjects who are recruited in the same hospital might not be entirely independent.

If a statistically significant difference will be observed in the incidence of the primary efficacy endpoint between subjects randomized to EPA + DHA compared to those randomized to EPA + DHA control (i.e. ALA alone or double placebo) based on all available follow-up, then

- cumulative event-free survival for the endpoint will be determined at 6 months and 12 months follow-up; a crude hazard ratio will be determined based on a simple Cox regression model; statistical significance will be claimed if the corresponding p-value is ≤ 0.025;
- the possible modification of the EPA + DHA effect by ALA will be studied; the above described multivariable Cox regression models will be extended with an EPA + DHA * ALA interaction term;
- the effect size will also be expressed as 'number needed to treat (NNT)'.

If a statistically significant difference will be observed in the incidence of the primary efficacy endpoint between subjects randomized to ALA compared to those randomized to ALA control (i.e. EPA + DHA alone or double placebo) based on all available follow-up, then

- cumulative event-free survival for the endpoint will be determined at 6 months and 12 months follow-up; a crude hazard ratio will be determined based on a simple Cox regression model; statistical significance will be claimed if the corresponding p-value is ≤ 0.025;
- the possible modification of the ALA effect by EPA + DHA will be studied; the above described multivariable Cox regression models will be extended with an ALA * EPA + DHA interaction term;

- the effect size will also be expressed as 'number needed to treat (NNT)'.

4.4.4 Secondary efficacy analyses

For the secondary efficacy analyses, the following parameters / statistics will be determined for each of the comparator groups and for each of the secondary efficacy endpoints:

- total number of endpoint events;
- total sum of the follow-up (y) since randomization until the incidence of the endpoint;
- the incidence-rate of the secondary endpoint, which is defined as the number of endpoint events divided by the total sum of the follow-up;
- the cumulative event-free survival for the endpoint.

Unadjusted Cox Proportional Hazard regression analysis will be conducted to study the relation between randomly allocated treatment and the incidence of the secondary efficacy endpoint.

4.5 Safety analysis

The number of (self-reported) incident cases of prostate cancer will be reported for all 4 randomly allocated treatments

4.6 Subgroup analyses

All analyses will be repeated in strata according to

- age (<70 vs. ≥70 y);
- gender (men vs. women);
- years since the index MI (<median vs. ≥median);
- background average intake of EPA + DHA (<50 mg/d vs. ≥50 mg/d and <100 mg/d vs. ≥100 mg/d);
- background average intake of fish (<5 g/d vs. ≥5 g/d and <10 g/d vs. ≥10 g/d).

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6.0 List of abbreviations

ACE	angiotensin converting enzyme
ALA	alpha-linolenic acid
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical Classification System
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CRF	case record form
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EAC	Endpoint Adjudication Committee
EPA	eicosapentaenoic acid
GP	general practitioner
ICD	implantable cardioverter-defibrillator
ICD-10	WHO – International Classification of Diseases, 10th revision
ITT	intention to treat
MCE	Major Cardiovascular Event
MI	myocardial infarction
n-3 PUFA	n-3 (omega-3) polyunsaturated fatty acid(s)
NNT	number needed to treat
PCI	percutaneous coronary intervention
PP	per protocol
SAP	statistical analysis plan
SD	standard deviation