Research

Effect of Omacor on HRV parameters in patients with recent uncomplicated myocardial infarction – A randomized, parallel group, double-blind, placebo-controlled trial: study design [ISRCTN75358739]

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Abstract

Background: A large body of data derived from animal, epidemiological and clinical studies indicate that n-3 polyunsaturated fatty acids have a favourable effect on the prognosis of patients with cardiovascular disease in general, and on reducing sudden death in particular.

Depressed heart rate variability (HRV), an indicator of impairment of the autonomic nervous system, has been shown to be a powerful predictor of subsequent mortality in patients surviving an acute myocardial infarction. A multitude of studies have demonstrated this strong association, suggesting that the imbalance in the sympathic/parasympathetic system may facilitate emergence of ventricular arrhythmias.

Heart rate variability parameters will be assessed in the present study, with the primary objective of evaluating the possible superiority of Omacor (a highly refined, concentrated omega-3 fatty acid) versus placebo in improving HRV from baseline to endpoint in patients with recent uncomplicated myocardial infarction. Both groups will receive optimal conventional treatment.

The study will also explore and quantify improvement in time domain HRV indices and will assess the safety of administering Omacor to optimally treated post-infarction patients (conventional treatment).

Methods: This multi-centre study will evaluate the effect of Omacor 1 g, o.d. on time-domain HRV parameters in comparison to placebo o.d. in patients with recent uncomplicated transmural myocardial infarction.

Patients will be screened during the first few days after the acute event as appropriate for the patient's condition, and after obtaining informed consent. Based on inclusion/exclusion criteria, a first 24-hour Holter recording will be performed. Two to five days later, screened patients still eligible for the study will undergo a second 24-hour Holter recording. After the second Holter

recording, all patients will be randomly allocated to treatment with Omacor 1 g, o.d. or placebo o.d.

One hundred patients will be followed in double-blind fashion for a six-month period after randomization. Visits, including 24-hour Holter recording and assessment of adverse events, will take place at one-month intervals ± five days after randomization, i.e., six times in all.

Background

More than two decades ago, Bang and Dyerberg [1] insightfully suggested that the low mortality from cardiovascular disease among Greenland Eskimos could be due to the high concentration of n-3 polyunsaturated fatty acids (PUFA) in their diet, which is high in marine vertebrates. These observations triggered extensive studies that focused on the role of marine oils in preventing coronary heart disease [2–8] These studies began primarily in the 1980s, with ongoing efforts geared towards demonstrating that the biochemical and physiological effects of 3-n fatty acids might be beneficial in preventing/reducing atherosclerosis and depressive disorders through effects on the basic functions of neurons and by preventing cardiovascular arrhythmia through effects on the electrophysiology of cardiac myocytes [9,10].

Results derived from laboratory animal studies [11–18], epidemiological and metabolic studies [19–25] as well as from clinical trials [26–32], provide evidence that PUFAs exert some form of basic control over cardiac and neural function, and that this has been largely overlooked, despite current dietary guidelines, which recommend fish consumption twice weekly for prevention of coronary heart disease (CHD) [33].

Results of the GISSI-Prevenzione study [34] (11,323 patients with recent myocardial infarction randomized to Omacor or vitamin E or the combination of the two) showed significantly lower all-cause mortality in the Omacor group, resulting largely from a 45% reduction in sudden cardiac death during 3.5 years of follow-up. Although the mechanism of action of Omacor is still unknown, the benefits appear to relate to reducing lethal arrhythmias rather than to changing cholesterol levels or to any anticoagulant effect.

With the enormous burden of sudden cardiac death that occurs virtually worldwide, and with cardiovascular disease poised to remain the number one killer in the world for at least the next 30 years, there may be substantial public health benefits to understanding PUFA's favourable health effects.

The present study will explore the potential effects of Omacor versus placebo on HRV through repeated assessment of a number of time domain HRV parameters and determination of plasma fatty acid concentrations in patients who have experienced a recent uncomplicated myocardial infarction.

Methods

Patient Population

HRV decreases in the early stages after an acute myocardial infarction [35–42] and spontaneously and slowly normalizes by the end of the first year [43,44]. Its assessment as early as possible after the acute event [45], at pre-discharge from the coronary care unit and on a monthly basis during the ensuing six months therefore is expected to predict further mortality [46].

In the context of the current study, it is expected that improvement in the HRV parameters of actively treated (as compared to placebo treated) patients will significantly diminish risk for arrhythmia-related sudden death.

Subjects will be recruited from the coronary care units of four tertiary hospitals in Poland and from four tertiary hospitals in Lithuania. The study is sponsored by Solvay Pharmaceuticals GmbH, Hannover, Germany and will be carried out in collaboration with Quantum Research, UK [47] and Scope International Life Sciences, Germany [48].

Potentially eligible patients with diagnosed acute myocardial infarction will be selected by the cardiologist in charge. Screening of these patients for the study will be performed during the first 48–72 hours after the acute event.

Subsequent to confirming eligibility and obtaining written consent, a first 24-hour Holter recording will be obtained and the following variables will be checked:

• Medical History

• Physical Examination

• BP and HR

• 12-lead ECG

• LVEF
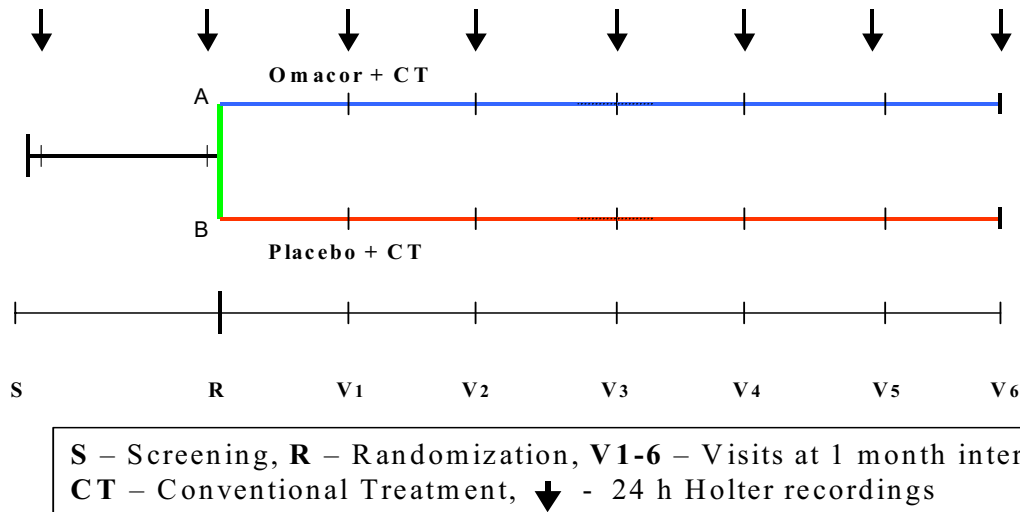
• Troponin T/CK-MB (max values only)

S – Screening, R – Randomization, V1-6 – Visits at 1 month interval ± five days, CT – Conventional Treatment, ↓ - 24 h Holter recordings

Figure 1
Study Design.

• 24-hour Holter recording (HRV)

• Laboratory (blood sampling + urine)

• Current medication

Two to five days later, when the patient's clinical condition is deemed stable and the patient remains eligible for the study, a second 24-hour Holter recording is obtained. The next day, patients are randomly allocated to treatment with Omacor or placebo. The study flow diagram is noted in Fig. 1.

Planned investigations during the monthly visits are displayed in the Investigation Schedule (Table 1).

Apart from study treatment, patients will receive individualized optimal treatment. Post-myocardial infarction follow-up (secondary prevention) will be based on local medical care, to include dietary and physical activity advice.

Randomization and Blinding
The randomization list will be provided by the Department of Clinical Supplies at Solvay Pharmaceuticals BV with the program Almedica (Version 5.3). Patients will be allocated in equal numbers to each sequence. A fixed block size of patients will be used, and only complete blocks of study medication will be provided to the centres.

Within each centre, randomization numbers will be used in ascending order and patients will be allocated to randomization code numbers in chronological order.

The randomization code for study medication will be provided to the investigator in separate sealed envelopes labelled with study number and randomization code numbers. The process of randomization will be concealed.

Inclusion Criteria
Males and females aged 40 years or older, with recent sustained acute myocardial infarction (AMI) will be eligible for the study. Women of childbearing age will be subject to pregnancy testing and will agree to maintain adequate hormonal contraception.

Standard criteria for definition of *acute*, *evolving* or *recent* AMI as well as for *established* AMI will be applied in the patient screening process.

Signed informed consent is required before enrollment in the study can proceed.

Exclusion Criteria
Specific exclusion criteria detailed in the study protocol can be categorized into three groups:

1. Ineligibility based on the physician's decision (the cardiologist in charge) that the patient has a clinical or

Table 1: InvestigationSchedule

	Screen	R	V1	V2	V3	V4	V5	V6
Informed Consent	*							
Incl/Excl Criteria	*	*						
Medical History	*							
Physical Exam	*				*			*
BP and HR	*	*	*	*	*	*	*	*
ECG (12 lead)	*				*			*
HRV	*	*	*	*	*	*	*	*
Lab	*				*			*
Current medication	*	*	*	*	*	*	*	*
ASA								
Diuretic								
Beta-blocker								
Ca antagonist								
ACE-inhibitor								
Ag II								
Lipid lowering								
Nitrates								
Adverse Events		*	*	*	*	*	*	*
Med. dispense	*	*	*	*	*	*	*	
Med. collection		*	*	*	*	*	*	*

hemodynamically unstable condition, or based on the likelihood that the patient needs further invasive investigation, a PTCA or a CABG.

2. The patient is in need of sustained antiarrhythmic therapy (other than a beta-blocking agent administered in the context of secondary prevention of MI).

3. The patient is suffering from a severe concomitant illness (related to any body organ or system) that is likely to affect outcome assessment. Likewise, ineligibility will be declared for patients anticipated to have compliance problems, those participanting in another trial within the past 30 days, those who are pregnant or lactating, or who have a known hypersensitivity to the ingredients in Omacor or intolerability to olive oil. In addition, patients with diabetes mellitus type I and II will be excluded.

Study Outcomes
Prior and Concomitant Therapy
The study protocol calls for every patient to be treated optimally by the physician in charge and to receive comprehensive, individualized advice regarding relevant dietary and physical activity prior to discharge from the hospital. Visits are to be scheduled in the context of the study (monthly visits during the ensuing six months).

Antiarrhythmic therapy is not permitted during study involvement, except for the use of beta-blockers, since these drugs are prescribed in most patients with recent acute myocardial infarction (except for those with clear contraindications). Patients on anticoagulant treatment will undergo regular bleeding time checks according to local routines.

Ethics and Informed Consent
With reference to paragraph 29 in the latest version of The Declaration of Helsinki [49–52] (currently Declaration of Edinburgh, 2000), use of placebo in this particular trial is justified by the need to explore *efficacy* of the product under rigorous experimental conditions, as well as to explore the mechanism of action responsible for the favourable effect of the drug in the targeted population.

Written consent, involving provision of detailed information regarding the study objectives, design, scope of the intervention, risks and benefits, will be obtained for all patients before intiating any study procedures.

Likewise, study documentation is to be subject to the scrutiny of local ethical committees in the two countries participating in the study.

Sample Size and Statistical Analysis
For the primary efficacy variable, the change in (standard deviation of all NN intervals (SDNN) from baseline to six months (or last value in case of dropouts), a normal distribution with a standard deviation of $\sigma = 50$ ms is assumed. If a two-sided two sample t-test with a level of significance of $\alpha = 0.05$ is applied, 45 patients per treat-

Table 2: Time Domain HRV Parameters

Time-domain indices	Description
Mean RR interval	The average NN interval per hour; a single 24 hour average will be reported.
SDNN	Standard deviation of the NN interval every hour; a single 24-hour average will be reported.
SDNNi	Standard deviation of the NN interval in every 5 minutes; a single 24-hour average will be reported.
RMSSD	The root mean square of successive differences of adjacent NN intervals; a single 24-hour average will be reported.
sNN50	Number of pairs of adjacent NN intervals differing by >50 ms; a single 24-hour value for the increases, decreases and total will be reported.
Triangular Index	Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 1/128s; a single 24-hour average will be reported.
sNN6%	Number of pairs of adjacent NN intervals differing by >6%; a single 24-hour value for the increases, decreases and total will be reported.
VPC > 10%/hour	The number of hourly segments with > 10% SVE and VPCs will be reported and the absolute number of SVE and VPCs will also be reported.

ment group will be needed to achieve 80% statistical power and to detect a mean difference of Δ = 30 ms between the treatment groups. One hundred patients will be randomized.

For the primary efficacy parameter, the null hypothesis of equal treatment group means will be tested against the two-sided alternative of different treatment group means at a level of significance of α = 0.05. For this, an analysis of covariance (ANCOVA) model will be applied, to include the treatment group and the medical center as factors and the baseline SDNN as a covariate.

In addition to the analysis of the total patient population, the following subgroups of patients will be evaluated in an exploratory fashion (the definition of these categories may be changed during blind data review):

• Mildly decreased or normal HRV: SDNN > 100 ms

• Moderately decreased HRV: SDNN between 50 ms and 100 ms (inclusive)

• Severely decreased HRV: SDNN < 50 ms

Analysis of secondary efficacy parameters and analysis of safety will be descriptive and exploratory.

Time Domain HRV Indices
The effect of treatment on time domain HRV parameters will be assessed by comparing a number of parameters derived from 24-hour Holter recordings. Time domain indices that are to be assessed and analysed are displayed in Table 2.

The SDNN and the HRV Triangular Index are estimates of the overall HRV. SDNN estimates the long-term components of the HRV, while the RMSSD estimates the short-

term components of the HRV. The sNN50 and 6% family parameters provide useful information about the very short term control of sinus rhythm dynamics in both healthy and diseased individuals, related to parasympathetic regulation.

The 24-hour Holter recordings will be analyzed using the *Lifecard CF* system produced by **Reynolds Medical**, UK [53]. A recording that cannot provide a minimum of 18 hours of data (including the whole night) out of the 24 hour Holter recording will be excluded from the analysis.

The Lifecard CF System [53]
The *Lifecard CF* is a compact Holter Ambulatory ECG Recorder utilizing a digital storage technique to store the ECG recording onto a Compact Flash (CF) card.

The *Lifecard CF* is small and lightweight and provides continuous recording of 2 or 3 channels of ECG. It has a built in display that enables one to monitor the ECG and pacing detection during hook-up. This enables one to verify the ECG quality before starting recording

Recordings are to be analyzed on the Reynolds Medical Pathfinder Digital/700 Series Analysis System, fitted with the appropriate Flashcard reader and will be performed by highly trained analysts from Quantum Research, UK.

A study specific Instruction Manual for use of Holter devices (including patient's hook-up) will be provided to every investigative site.

Discussion
In patients who have experienced an MI, depressed heart rate variability is considered to be a powerful predictor of mortality and of arrhythmic complications (e.g., symptomatic sustained ventricular tachycardia). [8,54]. The predictive value of HRV is independent of other factors

established for post-infarction risk stratification, such as depressed left ventricular ejection fraction, increased ventricular ectopic activity, and presence of late potential. For prediction of all-cause mortality, the value of HRV is similar to that of left ventricular ejection fraction, but HRV is superior to left ventricular ejection fraction in predicting arrhythmic events (sudden cardiac death and ventricular tachycardia) [54]. This suggests that HRV is a stronger predictor of arrhythmic (as opposed to non-arrhythmic) mortality.

The present study is not powered to detect differences in clinical endpoints, in particular sudden death. However, subgroup analysis will be performed in an attempt to reveal eventual differences in HRV between sudden and non-sudden cardiac death. It is not yet established whether depressed HRV is part of the mechanism of increased post-infarction mortality or is merely a marker of poor prognosis. Available data suggest that depressed HRV is not a simple reflection of sympathetic overdrive and/or vagal withdrawal due to poor ventricular performance but that it also reflects depressed vagal activity, which has a strong association with the pathogenesis of ventricular arrhythmias and sudden cardiac death [55]. A stratification of patients on the basis of LVEF is not realistic, given the small sample size; however, recording of LVEF in all patients will allow for an exploratory analysis and hypothesis generation.

Conclusions
Available evidence suggests that Omacor may provide benefit in the immediate post-myocardial infarction period. The present study will evaluate whether EPA and DHA, which constitute 84% of the Omacor tablet, improve time domain HRV parameters and surrogates for arrhythmia-caused sudden death in post-myocardial infarction patients.

Abbreviations
Δ difference

AE adverse event

ALAT alanine aminotranspherase

AMI acute myocardial infarction

ASAT aspartate aminotranspherase

AV atrioventricular

BP blood pressure

Ca^{2+} calcium ions

CCU coronary care unit

CK-MB creatine kinase – isoenzyme MB

CPT-I carnitine palmitoyltransferase I

CHD coronary heart disease

CRF case report form

DHA docosahexaenoic acid

ECG electrocardiogram

EPA eicosapentaenoic acid

FAT fatty acid transporter

GCP good clinical practice

GISSI Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto miocardico

HR heart rate

HRV heart rate variability

ICH International Conference on Harmonization

K_I inhibition constant

K^+ potassium ion

LBBB left bundle branch block

LVEDP left ventricular end diastolic pressure

LVESP left ventricular end systolic pressure

LVEF left ventricular ejection fraction

MI myocardial infarction

mRNA messenger RNA (carriers genetic information for one single protein)

ms milliseconds

n, N number of patients

Na^+ sodium ion

o.d. once daily

Q wave negative deflection on the ECG occuring before the QRS complex

QRS "complex" – depolarisation on ECG

p probability (5% alpha level)

p.o. per oral

PUFA polyunsaturated fatty acids

RBBB right bundle branch block

R wave positive deflection on ECG

RAAS rennin-angiotensin-aldosterone system

RMSSD the square root of the mean of the sum of the segments of differences

between adjacent NN intervals

RR average NN interval, per hour and 24 hour average

SAE serious adverse event

sNN50 number of adjacent NN intervals differing by >50 ms

sNN6% number of pairs of adjacent NN intervals differing by >6%

SDNN standard deviation of all NN intervals

SDANN standard deviation of the averages of NN intervals in all 5 minutes

segments

SDNNi mean of the standard deviations of all NN intervals for all 5 minutes

segments

ST "segment" – repolarisation phase on ECG

T troponine T

Triangular total number of all NN intervals devided by the hight of the histogram of

all NN

Index intervals measured on a discrete scale with bins of 1/128s

VPB ventricular premature beats

WHO World Health Organisation

Competing interests
All authors are employed by Solvay Pharmaceuticals GmbH Hannover, Germany.

Authors' contributions
Study concept and design: Pater, Verboom, Luszick,

Drafting of manuscript: Pater

Statistical expertise: Compagnone

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