Mareev V. Yu.[1,2], Mareev Yu. V.[3,4]

[1] Medical Research and Educational Center of the M. V. Lomonosov Moscow State University, Moscow, Russia

[2] Faculty of Fundamental Medicine, Lomonosov Moscow State University, Moscow, Russia

[3] National Medical Research Centre for Therapy and Preventive Medicine Moscow, Russia

[4] Robertson Centre for Biostatistics. University of Glasgow, Great Britain

Influence of Omega-3 PUFA on Non-invasive factors determining the risk of arrhYthmias eXcess and sudden cardiac death in patients with HFpEF with ischemic etiology (ONYX)

Aim	Patients with heart failure with reduced left ventricular (LV) ejection fraction (HFrEF) who have had acute myocardial infarction have an unfavorable prognosis, largely due to ventricular arrhythmias (VA) and risk of sudden cardiac death (SCD). The optimal treatment (triple neurohormonal blockade plus implantable cardioverter defibrillator and cardiac resynchronization therapy) reduced the risk of SCD primarily due to reverse cardiac remodeling, but has not solved this problem completely. Efficacy of purified ω-3 polyunsaturated fatty acid esters (PUFA) in low doses (1 g/day) in reducing VA and risk of SCD in HFrEF patients was demonstrated in two large randomized clinical trials. The PUFA effects was suggested to be related also with increased heart rhythm variability (HRV) and chronotropic action, which might depend on the drug dose. The present open, prospective, randomized, comparative study in parallel groups evaluated the effect of Omacor in different doses on noninvasive markers of SCD risk in patients with ischemic HFrEF receiving the optimal drug therapy.
Methods	Patients (n=40) were randomized at a 1:1:2 ratio to the control group (n=10), the Omacor 1 g/day treatment group (n=10), and the Omacor 2 g/day treatment group (n=20) and were followed up for 12 months. Clinical evaluation included changes in the CHF functional class (FC) and Clinical Condition Scale (CCS) score; concentration of N-terminal pro-hormone brain natriuretic peptide (NT-proBNP); and peak oxygen consumption during exercise (peak VO_2). The LV function was evaluated by LVEF. Holter ECG monitoring was used for evaluation of HRV (SDNN), average 24-h heart rate (HR), number of ventricular extrasystoles (VE) per hour and severity of VA, and presence of paired VE and VT runs.
Results	Improvement of CHF FC became significant only with the high-dose Omacor treatment (2 g/day). The CCS score showed a tendency towards decrease also with a lower dose (1 g/day) whereas the level of NT-proBNP significantly decreased with both Omacor doses. The increase in LV EF was significant only with the use of Omacor 2 g/day (+3%, p=0.002). A negative chronotropic effect of ω-3 PUFA was observed. Average 24-h HR decreased by 8 bpm (p=0.05) and 11 bpm (p<0.001) with Omacor 1 g/day and 2 g/day, respectively. Either dose of ω-3 PUFA significantly improved VO_2, which directly correlated with LV EF and inversely correlated with HR. The decrease in number of VE was associated not only with improved HRV (SDNN) but also with the decrease in 24-h HR, and thus Omacor 2 g/day significantly decreased the number of VE (by 16 per hour) and dangerous VA (paired VE and VT runs ceased to be detected in 40% of patients).
Conclusion	Since HR, HRV, and VA are closely interrelated, the effect of ω-3 PUFA specifically on these noninvasive markers apparently determines its ability to decrease the risk of SCD in patients with ischemic HFrEF. The antiarrhythmic effect of Omacor was greater with higher doses of this drug.

Keywords	Chronic heart failure; ω-3 polyunsaturated fatty acids; acute myocardial infarction; sudden cardiac death
For citation	Mareev V. Yu., Mareev Yu. V. Influence of Omega-3 PUFA on Non-invasive factors determining the risk of arrhYthmias eXcess and sudden cardiac death in patients with HFpEF with ischemic etiology (ONYX). Kardiologiia. 2020;60(10):86–98. [Russian: Мареев В. Ю., Мареев Ю. В. Влияние Омакора на НеИнвазивные марКеры внезапной сердечной смерти у больных с Сердечной недостаточностью ишемической этиологии (Результаты исследования ОНИКС). Кардиология. 2020;60(10):86–98]

Corresponding author	Mareev Yu. V. E-mail: mareev84@gmail.com

Introduction

XChronic heart failure with reduced left ventricular ejection fraction (HFrEF) remains one of the most adverse cardiovascular diseases (CVDs). It is continuously increasing in prevalence, mostly due to better treatment of diseases leading to decompensation and increased life expectancy [1]. The mortality rate and the risk of repeated hospitalization remain high, although they decrease as new drugs and devices are introduced to treat CHF [2]. HFrEF is most common in patients

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

with coronary artery disease (CAD) and a history of acute myocardial infarction (AMI) [3]. Cardiac remodeling in patients with a history of AMI results in an increased risk of death associated, not only with cardiac decompensation but also with life-threatening ventricular heart rhythm disorders (HRDs) [4, 5]. Thus, the problem of arrhythmic or sudden cardiac death (SCD) in patients with HFrEF who have a history of AMI requires particular attention and special research [6]. Eventually, the use of triple neurohormonal blockade in the treatment of CHF, specifically the strategy including valsartan+sakubitril, and the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in patients with left bundle branch block has reduced the risk of SCD [7, 8]. These effects are associated with reverse LV remodeling [9, 10]. Unfortunately, the possibilities of anti-arrhythmic therapy are not convincing, and they are also associated with many serious adverse events [11, 12]. The results of epidemiological and cohort observational trials suggest that the levels of ω-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic (EPA) and docosapentaenoic (DPA) in the cell membrane and their concentration in the blood plasma are correlated with the risk of SCD in different categories of patients [13, 14].

In this respect, the efficacy of purified PUFA esters in reducing HRDs and the risk of SCD in highest risk patients with HFrEF with a history of AMI [14–16] has been studied in the past 25 years. Experimental and small clinical trials have shown that the combination of EPA and DPA esters (Omacor) have antiarrhythmogenic potential [17]. The central hypothesis is that, due to the stabilization of membrane ion channels, PUFAs acts on the so-called final common pathway of arrhythmogenesis. Notwithstanding the initial stimulus, PUFAs exhibit a protective effect which influences the final trigger mechanism of fatal tachyarrhythmias [18]. Moreover, the effect of PUFAs on heart rhythm variability (HRV) is associated with the activity of the sympathoadrenal system (SAS) [19, 20], as well as their anti-cytokine effects and the effect on platelet aggregation [21, 22] cannot be ruled out.

Two large randomized clinical trials (RCTs) and one observational protocol, including more than 20,000 patients with CHF, most with a history of AMI, have shown a reduction in the risk of death [16, 15, 23]. However, the trial designs, accuracy and intensity of the concomitant therapy, and the correctness of the drug dose are questioned [24]. An increase in the PUFA concentration is known to be individual [25] when the PUFA esters (e.g., Omacor) are used and depends on the administered dose. Doses up to 4 g/day are used to treat hypertriglyceridemia [26], and anti-arrhythmic effects were evaluated in RCTs in patients who received Omacor only 1 g [16, 15].

Objective

The objective of this open-label, prospective, randomized, parallel comparative trial is to evaluate the efficacy of different doses of Omacor for non-invasive risk markers of SCD in ischemic origin CHF and OSSN functional class (FC) II–IV, with LVEF <40% who receive the best possible drug therapy [27].

Inclusion and exclusion criteria

Inclusion criteria: symptomatic CHF of ischemic origin with LVEF <40% (2-D echocardiography, Simpson's method); sinus rhythm; clinically and hemodynamically stable CHF within at least past two weeks; best possible drug therapy of CHF in the screening period.

Exclusion criteria: ω 3 PUFA intolerance; CHF of nonischemic origin; acute forms of IBS (AMI, unstable angina) within the past six months; high-degree sinoatrial and atrioventricular blocks (in the absence of continuous pacing); a history of persistent ventricular tachycardia (VT); malignant neoplasms; consequences of acute cerebrovascular accident limiting a patient's ability to perform physical activity (walking, spirometry); pregnancy; possible pregnancy in the absence of adequate contraception.

Material and methods

Patients were randomized to the control group and the Omacor 1 g/day and 2 g/day groups (1:1:2).

During the maintenance treatment, patients received the best possible concomitant drug therapy of CHF. During the study, HMG-CoA reductase inhibitors (statins) were not recommended to the patients in the follow-up period (after randomization).

After randomization, patients were followed up for 12 months with regular visits to the study site (if necessary or in the case of clinical deterioration). The main procedures at the time of inclusion and after completion of the study:

- Clinical assessment, changes of CHF FC (OSSN), and the Symptomatic Hospital and Outpatient Clinical Score (Mareev's modification).
- Holter ECG monitoring was performed in two leads, V1 and V5, in a Rozinn Holter monitor (USA). The 1996 Astrocard software (JSC Meditek, Russia) was used. 24-hour heart rate (HR), and the main non-invasive marker of HRV,

standard deviation of the R-R mean duration (SDNN), were determined. The mean number of ventricular premature beats (VPBs) per hour and the percentage of patients with Lown-Wolf HRD grades of IV and higher were also calculated.

- Standard 2D echocardiography in a HDI 5000 SonoCT scanner (Netherlands) with a 3.0 MHz sensor and semi-automatic LVEF detection based on Simpson's rule.
- Spiroergometry was conducted on an Ergometrics 900 ergometer (Elema, Germany). Non-invasive gas exchange analysis was performed at rest and throughout exercise using an Oxycon Pro gas analyzer (Jaeger, Germany). The ergometer exercise was performed following the Naughton protocol modified for patients with CHF. Peak oxygen consumption (VO_2) was the value obtained in the last 30 seconds of the exercise.
- NT-proBNP levels were determined by chemiluminescent immunoenzymatic method (IMMULITE 1000, Euro/DPA, USA).

Statistical analysis

The data distribution was assessed by means of the Shapiro-Wilk test.

The quantitative data are described as the median and the interquartile range (Me [25%; 75%]) in the case of the non-parametric distribution and as the mean (M) and the standard deviation (SD) if the distribution is normal. Qualitative data is presented as absolute and relative values. The significance of intergroup differences in terms of qualitative characteristics was assessed using the χ^2 test and two-way Fischer's exact test. The quantitative characteristics were compared between the three groups using the Kraskela–Willis test for parameters with non-parametric distribution and analysis of variance (ANOVA) for parameters with the normal distribution. If differences between the three groups were statistically significant, a pairwise comparison was made using the Mann–Whitney test for non-parametric distribution and Student's t-test for independent samples with the normal distribution. The Benjamini-Hochberg correction for multiple comparisons was used for the pairwise comparisons.

Changes to the qualitative parameters within each group were compared with the Wilcoxon signed-rank test in the non-parametric distribution and Student's t-test for dependent samples in normal distribution.

The correlation was estimated using Spearman's correlation coefficient. The critical significance level was p=0.05. Statistical analysis was performed using the R programming language in the R Studio software.

Results

The study included 40 patients with HFrEF-SR of ischemic origin: 10 patients in the control group; 10 patients in the Omacor 1 g/day groupand 20 patients in the Omacor 2 g/day group. General characteristics of patients are given in Table 1.

As shown in this table, the patients were severely ill and relatively young, with slightly more male patients. Two-thirds had a history of AMI, mean LVEF<30%, high NT-proBNP (>1000 pg/mL), CHF FC III and corresponding VO_2 under stress and SHOCS score. High-grade HRDs (paired VPBs and short runs of ventricular tachycardia (VT)) were identified in the patients: 9 (90%) in the control group, 10 (100%) in the Omacor 1 g/day group, and 18 (90%) in the Omacor 2 g/day group. Holter monitoring showed monotonous tachycardia with a 24-hour heart rate of more than 80 bpm and HRV borderline values (SDNN about 100 ms). Standard therapy was used: all patients received renin-angiotensin-aldosterone system (RAAS) blockers, diuretics and the overwhelming majority of patients received beta-blockers (BBs) and mineralocorticoid receptor antagonists (MCRAs). The three groups were well balanced and did not differ in any of the parameters studied. Changes in the main study indicators are provided in Table 2. As shown in the table, there were no significant changes in any of the parameters studied in the control group. This indicates, to a certain extent, the adequate treatment of ischemic HFrEF. The number of patients with paired VPBs and/or VT did not change and was 9 (90%) in the control group. During the follow-up period, 1 patient died (Month 7 of follow-up), and 6 patients were hospitalized, i.e., 7/10 (70%) patients had a deterioration.

The clinical state only tended to improve during the use Omacor 1 g/day in patients after AMI and with HFrEF. At the same time, NT-proBNP, which reflects myocardial stress to a certain extent, decreased statistically significantly. As the mean 24-hour heart rate declined, the peak oxygen consumption at the maximum load significantly improved. The anti-arrhythmic effect in the Omacor 1 g/day group was moderate, and 8 (80%) patients did not experience life-threatening HRDs after the treatment. However, despite the improved peak oxygen consumption, 4/10 (40%) patients in this group were hospitalized within the 12-month follow-up due to acute decompensation.

In the Omacor 2 g/day group, all the parameters studied, both clinical (FC, SHOCS, and peak VO_2) and biochemical (NT-proBNP), and HRV (SDNN, mean 24-hour heart rate), improved to a statistically significant degree. Anti-arrhythmic effects (VPBs) appeared. In the

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

Table 1. Baseline characteristics per subgroups

Parameter	Control, n=10	Omacor 1 g/day, n=10	Omacor 2 g/day, n=20	p
Age, years	62.6 (2.7)	61.7 (4.3)	62.4 (3.9)	0.801
Male, n (%)	7 (70)	6 (60)	11 (55)	0.731
History of AMI, n (%)	7 (70)	7 (70)	13 (65)	0.945
LVEF, %	23.5 [21.5; 35.0]	28.0 [22.8; 32.5]	27.5 [24.0; 31.0]	0.899
Peak VO_2, mL/min/m^2	11.9 (0.98)	12.4 (1.29)	12.1 (1.27)	0.651
SDNN, ms	102 (16.7)	96.0 (14.1)	101 (13.7)	0.599
VPBs per hour	75.0 [55.2; 94.0]	78.5 [54.8; 106]	84.5 [62.2; 95.0]	0.937
NT-pro-BNP, pg/mL	1117 (323)	1095 (268)	1173 (281)	0.758
CHF FC, median [25%; 75%]	3.00 [2.00; 3.00]	3.00 [2.00; 3.75]	3.00 [2.00; 3.00]	0.960
CHF FC, mean (SD)	2.8 (0.79)	2.9 (0.88)	2.8 (0.62)	0.730
HR 24-hour, bpm	83.5 [79.0; 91.0]	84.5 [76.2; 91.2]	86.0 [78.0; 91.0]	0.979
SHOCS, median [25%; 75%]	4.50 [3.25; 6.00]	4.00 [4.00; 6.50]	5.00 [4.00; 6.00]	0.808
SHOCS, mean (SD)	5.0 (1.94)	5.1 (2.13)	5.1 (1.45)	0.988
ACE inhibitors/ARB, n (%)	10 (100)	10 (100)	20 (100 %)	0.999
Beta-blockers, %	10 (100)	9 (90)	19 (95 %)	0.743
MCRA, n (%)	8 (80)	8 (80)	17 (85 %)	0.999
Diuretics, n (%)	10 (100)	10 (100)	19 (95 %)	0.999

The data is expressed as the mean and the standard deviation (M [SD]) in parametric distribution and as the median and the 25th and 75th percentile (Me [25th; 75th percentiles]) in non-parametric distribution. For the CHF FC SHOCS score, both the medians and the means are specified for more convenience. AMI, acute myocardial infarction; SDNN, standard deviation of the R-R mean duration; LVEF, left ventricular ejection fraction; VPB, ventricular premature beat, NT-pro BNP, N-terminal pro-brain natriuretic peptide; FC, NYHA functional class; SHOCS, Symptomatic Hospital and Outpatient Clinical Score for patients with CHF (Mareev's modification); ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker; MCRA, mineralocorticoid receptor antagonist.

Table 2. Changes of the parameters studied in the three treatment groups

Parameters	Control, baseline	Control, 12 months	p	Omacor 1 g, baseline	Omacor 1 g, 12 months	p	Omacor 2 g, baseline	Omacor 2 g, 12 months	p
LVEF, %, median [25%; 75%]	23.5 [21.5; 35.0]	25.0 [23.5; 31.8]	0.999	28.0 [22.8; 32.5]	29.0 [26.2; 32.0]	0.306	27.5 [24.0; 31.0]	30.5 [28.8; 33.2]	**0.002**
VO_2, mL/min/m^2, mean (SD)	11.9 [11.2; 12.8]	11.1 [10.5; 12.2]	0.103	12.6 [11.9; 13.3]	13.4 [13.2; 13.9]	**0.019**	12.0 [11.4; 12.6]	13.9 [13.5; 14.1]	**>0.001**
SDNN, ms, mean (SD)	102 (16.7)	98.0 (11.1)	0.510	96.0 (14.1)	109 (9.6)	**0.005**	101 (13.7)	125 (9.71)	**>0.001**
VPBs per hour, median [25%; 75%]	75.0 [55.2; 94.0]	74.5 [50.5; 101]	0.541	78.5 [54.8; 106]	70.0 [48.8; 85.5]	0.202	84.5 [62.2; 95.0]	60.5 [41.8; 74.5]	**0.002**
NT-pro BNP, pg/mL, median (SD)	1084 [898; 1293]	862 [716; 1185]	0.160	1075 [929; 1293]	673 [534; 699]	**0.002**	1176 [976; 1300]	611 [486; 704]	**>0.001**
CHF FC, median [25%; 75%]	3.00 [2.00; 3.00]	3.00 [2.00; 3.00]	0.890	3.00 [2.00; 3.75]	2.00 [2.00; 3.00]	0.168	3.00 [2.00; 3.00]	2.00 [2.00; 2.00]	**0.002**
CHF FC, mean (SD)	2.8 (0.79)	2.7 (0.67)	0.730	2.9 (0.88)	2.4 (0.52)	0.140	2.8 (0.62)	2.0 (0.46)	**0.0001**
HR 24-hour, median [25%; 75%]	83.5 [79.0; 91.0]	80.5 [79.2; 92.5]	0.877	84.5 [76.2; 91.2]	76.5 [75.2; 78.0]	**0.050**	86.0 [78.0; 91.0]	75.0 [73.5; 77.5]	**>0.001**
SHOCS, median [25%; 75%]	4.50 [3.25; 6.00]	4.50 [4.00; 5.00]	0.354	4.00 [4.00; 6.50]	3.50 [3.00; 4.00]	**0.037**	5.00 [4.00; 6.00]	3.00 [3.00; 4.00]	**>0.001**
SHOCS, mean (SD)	5.0 (1.94)	4.5 (1.08)	0.470	5.1 (2.13)	3.7 (0.82)	**0.039**	5.1 (1.45)	3.3 (0.80)	**0.0001**

For the CHF FC SHOCS score, both the medians and the means are specified for more convenience. AMI, acute myocardial infarction; SDNN, standard deviation of the R-R mean duration; LVEF, left ventricular ejection fraction; VPB, ventricular premature beat, NT-pro BNP, N-terminal pro-brain natriuretic peptide; FC, NYHA functional class; SHOCS, Symptomatic Hospital and Outpatient Clinical Score for patients with CHF (Mareev's modification); ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker; MCRA, mineralocorticoid receptor antagonist.

third group, 11/20 (55%) patients still experienced life-threatening HRDs after treatment, i.e., 8/20 (40%) patients experienced severe anti-arrhythmic effect during the use of ω-3 PUFAs at the dose of 2 g/day. Within 12 months of follow-up, 1 patient died (Month 4), and 3 patients were hospitalized, i.e., 4/20 (20%) had a total score of the disease deterioration.

Table 3 demonstrates paired comparisons of changes (deltas) of the parameters studied during the treatment. As shown in Table 3, ω-3 PUFAs 1 g/day significantly increased VO_2 at maximum loads and statistically significantly increased HRV (SDNN) in comparison with the control. Differences in the changes in the number of VPBs and 24-hour heart rate were not statistically significant.

In the Omacor 2 g/day group, most of the parameters changed to a statistically significant degree in comparison to the control group. The clinical parameters of CHF severity (FC and NT-proBNP) only tended to change, except for SHOCS scores measured by mean values. The individual changes of NT-proBNP in all patients are shown in Figure 1 by groups. They indicate a clear trend towards a significant decrease in this parameter associated with the increasing dose of Omacor.

The left part of Figure 2 shows individual changes of the most common hemodynamic indicator, LVEF. This to a large extent reflects cardiac remodeling in patients with CHF during the treatment. The effect of both doses of Omacor on LVEF versus standard treatment was negligible and statistically insignificant when groups were compared pairwise, and all the three groups were compared together. The right side of the figure shows individual changes of the most adequate parameter of exercise tolerance, VO_2 at the submaximal physical load. Unlike LVEF, there was highly significant positive change during the use of Omacor in both doses, reaching the maximum with ω-3 PUFAs 2 g/day. This suggests that other factors (other than LV function) are contributing to better oxygen supply at physical load in patients with severe CHF.

The main objective of the study was to evaluate non-invasive markers of SCD in patients with ischemic HFrEF during the use of different doses of ω-3 PUFAs compared to the standard treatment of CHF. SDNN, the number of VPBs per hour and the mean 24-hour HR improved to a statistically significant degree, especially when Omacor 2 g/day was administered, compared to the control (Figure 3). SDNN significantly increased with Omacor 1 g/day compared to the control group,

Table 3. Pairwise and general comparison of changes in the main parameters during the treatment in the subgroups

Parameters	Control, n=10	Omacor 1 g/day, n=10	p, control vs 1 g	Omacor 2 g/day, n=20	p, 2 g vs 1 g	p, 2 g vs control	p, general
LVEF, %, median [25%; 75%]	–0.40 (4.25)	1.10 (3.51)	–	3.00 (3.32)	–	–	0.056
VO_2, mL/min/m², mean (SD)	–0.70 (1.23)	1.20 (1.38)	**0.007**	1.70 (1.33)	0.355	**>0.001**	**<0.001**
SDNN, ms, mean (SD)	–4.00 (12.3)	13.0 (11.0)	**0.007**	24.0 (12.8)	**0.024**	**>0.001**	**<0.001**
ΔVPBs per hour, median [25%; 75%]	15.5 [–4.50; 20.8]	–7.50 [21.75; 6.5]	0.180	–25.00 [–43.5; 6.50]	0.544	**0.009**	**0.010**
NT-proBNP, pg/mL, mean (SD)	–213.70 (365)	–421.50 (282)	0.242	–556.16 (292)	0.242	***0.064***	**0.026**
CHF FC, median [25%; 75%]	0.00 [–0.75; 0.00]	0.00 [1.00; 0.00]	–	–1.00 [–1.00; 0.00]	–	–	0.188
FC, mean (SD)	–0.1 (1.04)	–0.5 (0.92)	0.12	–0.85 (0.72)	0.33	***0.06***	
HR 24-hour, median [25%; 75%]	–2.00 [–2.75; 2.00]	–4.00 [11.75; 0.25]	0.192	–8.00 [–14.0; 4.00]	0.290	**0.006**	**0.009**
SHOCS, median [25%; 75%]	–0.50 [–1.75; 0.75]	–1.00 [–1.75; – 0.25]	–	–2.00 [–2.25; 1.00]	–	–	0.145
SHOCS, mean (SD)	–0.5 (1.5)	–1.4 (1.7)	0.26	–1.8 (1.4)	0.55	**0.04**	–

p general, when the three groups are compared. The pairwise comparison was made only if p was statistically significant for the three groups.
AMI, acute myocardial infarction; SDNN, standard deviation of the R-R mean duration; LVEF, left ventricular ejection fraction;
VPB, ventricular premature beat, NT-pro BNP, N-terminal pro-brain natriuretic peptide; FC, NYHA functional class;
SHOCS, Symptomatic Hospital and Outpatient Clinical Score for patients with CHF (Mareev's modification);
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker;
MCRA, mineralocorticoid receptor antagonist.

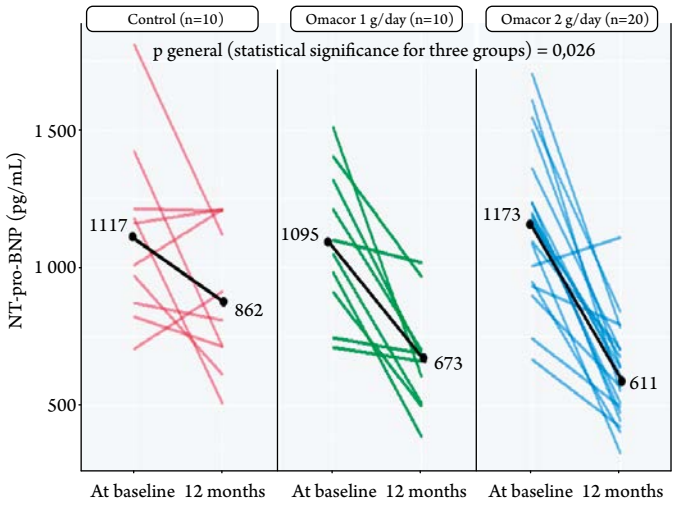
ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

and even more with the dose of 2 g/day. In other words, HRV commonly improves with the use of any doses of ω-3 PUFAs, at least in the treatment of CHF with low baseline SDNN.

Changes in SDNN (the left part of Figure 3) are more evident than changes in the number of VPBs per hour (the right part of Figure 3). However, both parameters improved to a statistically significant degree in the Omacor 2 g/day group.

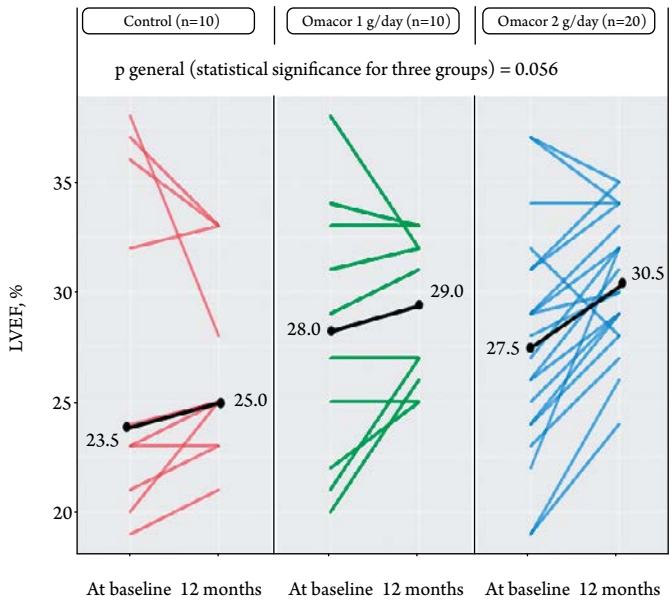
Table 4 shows the correlations between all the indicators studied. Highly significant correlations ($p<0.001$) exceeding 0.5 (Spearman's coefficient) are indicated in red. The closest correlation was observed between CHF FC and SHOCS scores ($r=0.87$ at baseline and $r=0.83$ overtime, $p<0.001$). This confirms the highly informative value of SHOCS in determining the clinical status of patients with CHF. Being a critical parameter of the heart performance, LVEF was closely correlated both at baseline and over time with most of the indicators, which were lowest for HRDs and NT-pro BNP and closest for VO_2, as seen in Figure 2 and Table 4. On the other hand, NT-pro-BNP concentration was least correlated with other parameters, again characterizing it as dependent on many additional factors, not only the severity of CHF, but also the degree of decompensation and congestion, as well as body weight and age. In carefully treated patients (100% regular use of diuretics), changes of this indicator in the ω-3 PUFAs subgroups were evident, as seen in Figure 1, but with less correlated with clinical and hemodynamic indicators and parameters characterizing the risk of HRDs.

Figures 1. Individual changes of NT-pro-BNP during treatment of CHF, including different doses of ω-3 PUFAs compared to the control



Peak oxygen consumption at maximum load increased to a statistically significant degree for both doses of ω-3 PUFAs, and these changes were reversely highly correlated with both increased LVEF, i.e., hemodynamic parameters ($r= 0.51$; $p<0.001$ at baseline and $r= –0.79$; $p<0.001$ during the treatment) and mean 24-hour HR ($r= –0.56$; $p<0.001$ at baseline and $r= –0.58$, $p<0.001$ over time, see Table 4, Figure 4). The simultaneous contribution of both hemodynamic and chronotropic factors to the improvement of oxygen supply at load in patients with ischemic HFrEF treated with Omacor in both doses is of great interest. In the control group, only a significant correlation between peak VO_2 and hemodynamic parameters remains evi-

Figures 2. Changes of LVEF and peak VO_2 in the control group and the ω–3 PUFA (1 g/day or 2 g/day) groups of patients with HFrEF of ischemic origin



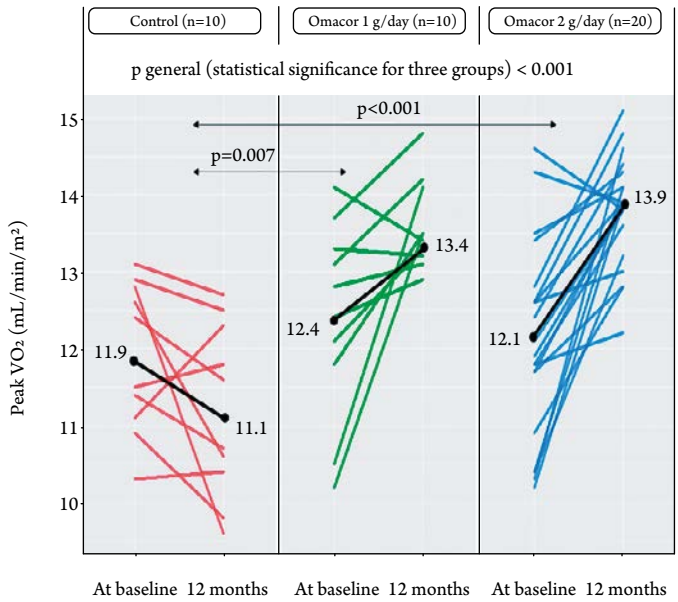


Table 4. Correlations between the parameters studied, using Spearman's coefficient. Total data (n=40)

	LVEF	VO_2, max	SDNN, ms	VPBs per hour	NT-pro-BNP	CHF FC	HR	SHOCS
LVEF		0.79***	0.58***	–0.43**	0.44**	–0.68***	–0.56***	–0.60***
VO_2, max	0.51***		0.61	–0.47**	–0.38*	–0.5**	–0.58***	–0.43**
SDNN, ms	0.70***	0.31		–0.70***	–0.37*	–0.46**	–0.73***	–0.40**
VPBs per hour	–0.44**	–0.21	–0.63***		0.36	0.35*	0.29	0.33*
NT-pro-BNP	0.04	0.04	–0.08	0.13		0.35*	0.29	0.33*
CHF FC	–0.65***	–0.18	–0.46**	0.16	0.08		0.38*	0.83***
HR	–0.55***	–0.56***	–0.69***	0.38*	0.11	0.38*		0.43**
SHOCS	–0.57***	–0.26	–0.30	0.06	0.08	0.87***	0.20	

p-value: *** ≥ 0.001; ** ≥ 0.01; * ≥ 0.05. A gray area between the baseline measurements and a yellow area between changes during the treatment. AMI, acute myocardial infarction; SDNN, standard deviation of the R-R mean duration , LVEF, left ventricular ejection fraction; VPB, ventricular premature beat, NT-pro BNP, N-terminal pro-brain natriuretic peptide; FC, NYHA functional class; SHOCS, Symptomatic Hospital and Outpatient Clinical Score for patients with CHF (Mareev's modification); ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker; MCRA, mineralocorticoid receptor antagonist.

dent, and the correlation with mean 24-hour HR was lost.

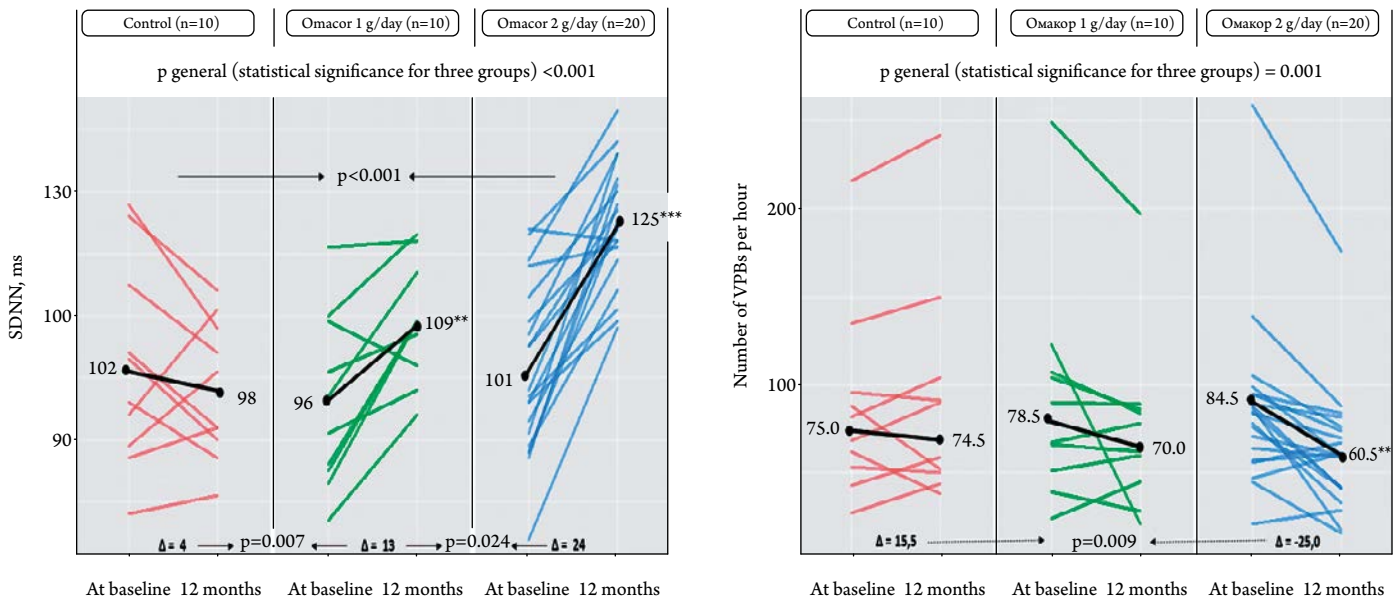
The main objective of our study was to evaluate changes in non-invasive markers of SCD in patients with HFrEF of ischemic origin. These parameters were used to measure HRV (SDNN and, to some extent, mean 24-hour HR) and their association with the rate of VPBs per hour.

As can be seen in Table 4, there is a statistically significant close reverse correlation between SDNN and mean 24-hour HR (r= –0.69; p<0.001 at baseline and r= –0.73; p<0.001 during the treatment). Thus, the higher HR is, the lower is SDNN (i.e., HRV), and the higher are the levels of HRD, as a non-invasive marker of SCD, and vice versa.

Figure 5 and Table 4 demonstrate the correlations between the HRV (SDNN and mean 24-hour HR) and the number of HRDs (VPBs per hour).

On the left, a significant inverse correlation between SDNN and the number of HRDs is shown (r= –0.66; p<0.001 at baseline and r= –0.70; p<0.001 during the follow-up and treatment). This means that the lower HRV and SDNN are, the higher is the risk of HRDs and SCD. A significant correlation between mean 24-hour HR and the number of VPBs per hour is shown on the right. In this case, the correlation is inverse and less close at baseline (r= –0.38; p<0.05) than during the treatment (r= –0.66; p<0.001). Interestingly, the correlation in this case between the chronotropic mechanism and the risk of VPB was not found in the control group and appeared

Figures 3. Changes of HRV (SDNN) and HRDs (VPBs per hour) in the control group and the ω–3 PUFA (1 g/day or 2 g/day) groups of patients with HFrEF of ischemic origin



ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

Abbott

- Способствует восстановлению клеток сердца*, 1, 2
- Снижает риск внезапной сердечной смерти на 45%*, 3
- Хорошо переносится при длительной терапии*, 4, 5

* У пациентов после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ).

ОМАКОР ДЕЛО ЖИЗНИ

ДЛЯ ВТОРИЧНОЙ ПРОФИЛАКТИКИ ПОСЛЕ ИНФАРКТА МИОКАРДА*, 6

Омакор. Регистрационный номер: ЛС-000559. **Международное непатентованное или группировочное наименование:** Омега-3 кислот этиловые эфиры 90. **Лекарственная форма:** капсулы, 1000 мг. **Фармакологические свойства*.** Полиненасыщенные жирные кислоты класса омега-3 – эйкозапентаеновая кислота (ЭПК) и докозагексаеновая кислота (ДГК) – относятся к незаменимым (эссенциальным) жирным кислотам (НЭЖК). Результаты клинического исследования GISSI-Prevenzione, полученные за 3,5 года наблюдений, показали существенное снижение относительного риска смертности от всех причин, нефатального инфаркта миокарда и нефатального инсульта на 15 % ([2-26] p=0,0226) у пациентов после недавно перенесенного инфаркта миокарда, принимавших препарат Омакор по 1 г в сутки. Дополнительно, относительный риск смерти по причине сердечно-сосудистой патологии, нефатального инфаркта миокарда и нефатального инсульта снижался на 20 % ([5-32] p=0,0082). Результаты клинического исследования GISSI-Heart Failure, в котором пациенты с хронической сердечной недостаточностью получали препарат Омакор по 1 г в сутки в среднем в течение 3,9 лет, показали снижение относительного риска смертности от всех причин на 9 % (p=0,041), снижение относительного риска смертности от всех причин и госпитализации по причине сердечно-сосудистых патологий на 8 % (p=0,009), снижение относительного риска первичной госпитализации по причине желудочковых аритмий на 28 % (p=0,013). **Показания к применению.** Гипертриглицеридемия: эндогенная гипертриглицеридемия IV типа по классификации Фредериксона (в монотерапии) в качестве дополнения к гиполипидемической диете при ее недостаточной эффективности; эндогенная гипертриглицеридемия IIb или III типа по классификации Фредериксона в комбинации с ингибиторами ГМГ-КоА редуктазы (статинами), когда концентрация триглицеридов недостаточно контролируется приемом статинов. Вторичная профилактика после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ). **Противопоказания.** Повышенная чувствительность к действующему веществу, сое, арахису или любому из вспомогательных веществ, входящих в состав препарата. Возраст до 18 лет (эффективность и безопасность не установлены). Беременность и период грудного вскармливания. Омакор не следует применять у пациентов с экзогенной гипертриглицеридемией (гиперхиломикронемией I типа). **С осторожностью.** Установленная гиперчувствительность или аллергия на рыбу; возраст старше 70 лет; нарушения функции печени; одновременный прием с пероральными антикоагулянтами; геморрагический диатез; пациенты с высоким риском кровотечений (вследствие тяжелой травмы, хирургической операции); вторичная эндогенная гипертриглицеридемия (особенно при неконтролируемом сахарном диабете). **Применение при беременности и в период грудного вскармливания*.** Назначать Омакор беременным следует с осторожностью, только после тщательной оценки соотношения риска и пользы, когда польза для матери превышает потенциальный риск для плода. Препарат не должен применяться в период грудного вскармливания. **Способ применения и дозы*.** Внутрь, независимо от приема пищи. Во избежание развития возможных нежелательных явлений со стороны желудочно-кишечного тракта (ЖКТ) препарат Омакор может приниматься во время приема пищи. Гипертриглицеридемия. Начальная доза составляет 2 капсулы в сутки. В случае отсутствия терапевтического эффекта возможно увеличение дозы до максимальной суточной дозы – 4 капсулы. Вторичная профилактика инфаркта миокарда. Рекомендуется принимать по 1 капсуле в сутки. **Побочное действие*.** Желудочно-кишечные расстройства (в том числе вздутие живота, боль в животе, запор, диарея, диспепсия, метеоризм, отрыжка, гастроэзофагеальная рефлюксная болезнь, тошнота или рвота). *Перечень всех побочных действий представлен в инструкции по медицинскому применению.* **Передозировка.** Особые указания отсутствуют. Должна быть проведена симптоматическая терапия. **Взаимодействие с другими лекарственными средствами*.** При одновременном применении препарата Омакор с пероральными антикоагулянтами или другими препаратами, влияющими на систему гемостаза (например, ацетилсалициловая кислота или НПВП), наблюдалось увеличение времени свертывания крови. При этом геморрагических осложнений не наблюдалось. Ацетилсалициловая кислота: пациенты должны быть проинформированы о возможном увеличении времени свертывания крови. Совместное применение препарата Омакор с варфарином не приводило к каким-либо геморрагическим осложнениям. Однако необходим контроль соотношения протромбинового времени/международного нормализованного отношения (ПТВ/МНО) при совместном применении препарата Омакор с другими препаратами, влияющими на соотношение ПТВ/МНО, или после прекращения терапии препаратом Омакор. **Особые указания*.** Омакор должен применяться с осторожностью у пациентов с установленной гиперчувствительностью или аллергией на рыбу. В связи с умеренным увеличением времени свертывания крови (при приеме в высокой дозе, т.е. 4 капсулы в сутки) требуется наблюдение за пациентами, имеющими нарушения со стороны свертывающей системы крови или получающими антикоагулянтную терапию или другие препараты, влияющие на систему гемостаза (например, ацетилсалициловую кислоту или НПВП); при необходимости, доза антикоагулянта должна быть скорректирована. Необходимо учитывать увеличение времени свертывания крови у пациентов с высоким риском развития кровотечения. При терапии препаратом Омакор снижается уровень образования тромбоксана А2. Существенного влияния на уровень других факторов свертывания крови не наблюдалось. У некоторых пациентов наблюдалось небольшое, но достоверное повышение активности АСТ и АЛТ (в пределах нормы), при этом отсутствуют данные, указывающие на повышенный риск приема препарата Омакор пациентами с нарушением функции печени. Необходим контроль активности АСТ и АЛТ у пациентов с любыми признаками нарушения функции печени (в частности, при приеме в высокой дозе, т.е. 4 капсулы в сутки). Опыт применения препарата для лечения экзогенной гипертриглицеридемии (гиперхиломикронемии типа 1) отсутствует. Опыт применения препарата при вторичной эндогенной гипертриглицеридемии ограничен (особенно при неконтролируемом сахарном диабете). **Влияние на способность управлять транспортными средствами, механизмами*.** Ожидается, что препарат не оказывает или оказывает несущественное влияние на способность управлять транспортными средствами и работать с механизмами. **Условия хранения.** Хранить при температуре не выше 25 °С. Не замораживать. Хранить в недоступном для детей месте! Условия отпуска. Отпускают по рецепту.

***Полная информация представлена в инструкции по медицинскому применению.**

СИП от 27.09.2019 на основании ИМП от 29.08.2019.

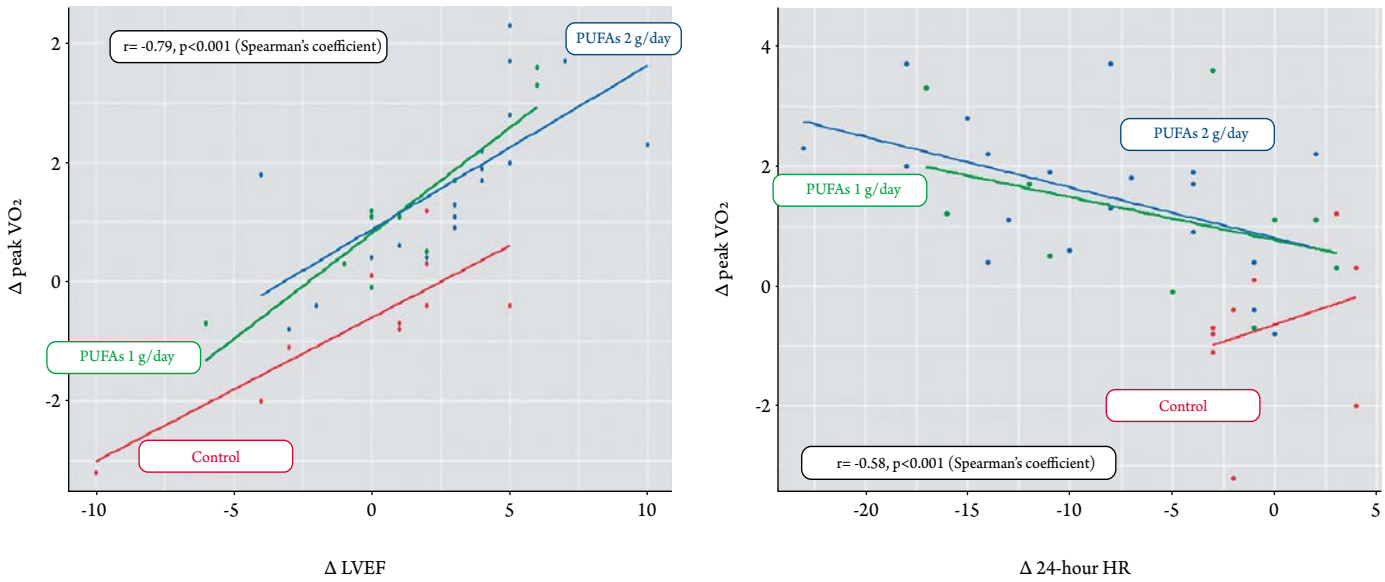
1. Willson Trang W. H., Samara M. A. Polyunsaturated Fatty Acids in heart failure. Should we give more and give earlier? J. Am. Coll. Card. 2011; 57: 880-883. 2. Rupp Heinz. Omacor (Prescription Omega-3-Acid Ethyl Esters 90): From Severe Rythm Disorders to Hypertriglyceridemia. Adv Ther. 2009 Jul; 26(7): 675-90. 3. Marchioli R et al. Early Protection Against Sudden Death by n-3 Polyunsaturated Fatty Acids After Myocardial Infraction. Circulation 2002;105:1897-1903. 4. GISSI-HF investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 372 (9645): 1223-1230. 5. GISSI-Prevenzione investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 1999; 354(9177):447-455. 6. Инструкция по медицинскому применению препарата Омакор от 29.08.2019.

RUS21203I0-2 (v2.0)

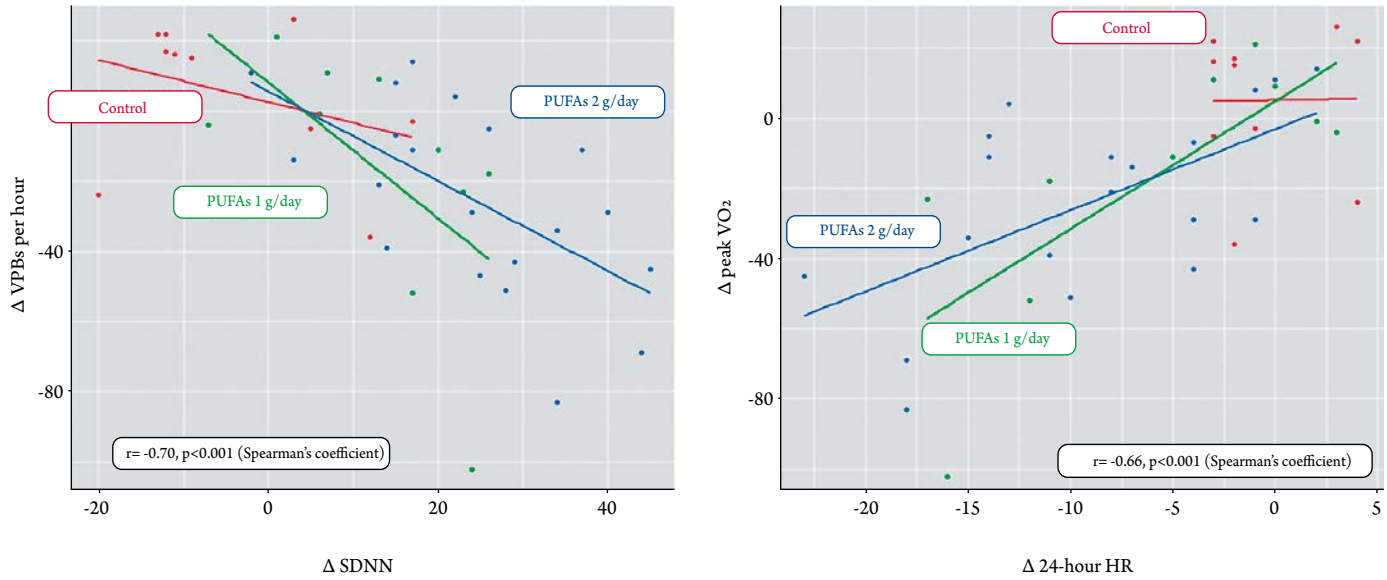
Информация предназначена для медицинских и фармацевтических работников.

ООО «Эбботт Лабораториз», 125171, г. Москва, Ленинградское ш., 16а, стр. 1, бизнес-центр «Метрополис», тел.: (495) 258-42-80, www.abbott-russia.ru

Figures 4. Correlation between changes of LVEF and mean 24-hour HR on the one hand and changes of peak VO_2 at the maximum of physical load on the other hand, in the standard treatment of CHF and in combination with Omacor



Figures 5. Correlation between changes of HRV (SDNN) and mean 24-hour HR on the one hand and changes of the number of VPBs per hour on the other hand in the standard treatment of CHF and in combination with Omacor



when both doses of ω-3 PUFAs are used to treat HFrEF of ischemic origin. Combination of the two charts shown in Figure 5 show that patients with CHF and monotonic tachycardia (low HRV) are at the greatest risk of SCD.

Discussion

The feasibility and efficacy of ω-3 PUFAs in treating CVDs have remained a relevant issue in the past 30 years and are very controversial. Systematic meta-analysis, performed by the most authoritative and independent Cochrane Laboratory in 2018, showed that PUFAs moderately reduce the risk of CAD and cardiovascular morbidity and mortality without an evident reduction in the risk of all-cause death. These effects may be largely attributable to a decrease in the triglyceride levels [28]. However, the main drawback of such analyzes is that they include trials with a wide variety of interventions. They include a fish diet and margarine enriched with PUFAs, fish fat, and formulations with different composition and doses of PUFAs [29]. Thus, to make the correct conclusions, reference needs to be made to the current guidelines on the treatment of CVDs, which recommend using ready-made formulations of ω-3 PUFA esters [30, 31]. All further discussion will concern drugs that contain either a combination of EPA

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

and DHA (Omacor) or only EPA. After completion of the large REDUCE-IT RCT with icosapent ethyl (EPA 4 g/day), which demonstrated a significant decrease in main cardiovascular complications (cardiovascular death+AMI+stroke) by 26% in addition to the best possible therapy, there has been a resurgence in this area of research [26]. One particular challenge, however, is determining what plays a major role in the efficacy of PUFAs, whether it is the composition or dose of the drugs used. In the most recent analysis, after the successful completion of the EPA trial, it was concluded that a 1g increase in the doses of any ω-3 PUFA ethers is accompanied by a further 17% decrease in major cardiovascular complications [32].

This is directly related to the main thesis of our trial, in which we studied the potential effect of the combination of EPA and DHA (Omacor) on the risk of SCD in patients with CAD, with 2/3 cases of AMI and LVEF<40% receiving the best possible treatment [27]. HRDs are known to cause SCD in a significant percentage of patients with LV systolic dysfunction [33]. Moreover, the risk of HRDs is directly associated with the degree of cardiac remodeling and the reduction of EF, especially less than 30% [4]. Thus, the anti-arrhythmic effect of neurohormonal modulators and CRT is associated with the reverse development of cardiac remodeling [9, 10]. This association was especially evident for valsartan+sacubitril, which reduced the risk of SCD by 40%, and this reduction was directly correlated to a decrease of NT-pro-BNP as a marker of cardiac remodeling [8]. On the other hand, the use of anti-arrhythmic drugs (potent inhibitors of the cell membrane ion channels) was ineffective and even unfavorable. It was even more dangerous with more severe structural changes of the heart and higher CHF FC [34–36]. Unfortunately, the use of ICD without considering the cost of the treatment and the risk of serious adverse events also is not the ultimate solution to the problem of CHF, especially in severe CHF and critical cardiac remodeling [7, 37].

Thus, a third option, – the use of ω-3 PUFAs to reduce the risk of SCD after AMI and in CHF, has been studied for more than 20 years. After the completion in 1999 of the GISSI-prevenzione RCT (more than 11,000 patients with a history of AMI), which demonstrated a 45% reduction in the risk of SCD during the administration of Omacor 1 g/day, the future of ω-3 PUFAs remains an issue of some contention [17, 24]. A decrease in the SCD rate contributed to the improved prognosis after AMI [38]. Still full of enthusiasm, many experimental trials have proven the membrane-stabilizing effect of ω-3 PUFAs [39] and the ability to reduce HRV and HRDs [18]. Although experimental data sometimes seems to justify any, even opposite, treatment effects of the same drugs. However, the first clinical trial showed that the combination of EPA and DHA (Omacor) 4 g/day in 5/7 patients with ICD prevented the initial induction of VT [40]. In this connection, three small RCTs of ω-3 PUFAs administered from 0.9 to 2.6 g/day were conducted in the United States and Europe. The Meta-analysis of the work did not show a decrease in the composite endpoint, including death or confirmed VT/VF, with a downward trend in patients with CAD (OR 0.79; 95% CI 0.60–1.06). Interestingly, in the work in which ω-3 PUFAs 2.6 g/day was used, a per-protocol analysis showed a statistically significant decrease in the composite endpoint by 38%, p=0.034. The latter should be verified in new studies of Omacor 2 g/day in high-risk patients to prevent the risk of SCD [41, 42]. Unfortunately, the treatment was not long-term. The groups were heterogeneous. Patients had different LVEF levels and did not undergo the same basic therapy. Finally, the GISSI-HF trial with long-term administration of Omacor 1 g/day in nearly 7,000 patients with HFrEF, cardiac remodeling, and relatively satisfactory treatment of CHF demonstrated a moderate but significant decrease in the risk of total mortality by 9% (intention-to-treat) and 14% (per-protocol) [15]. Subgroup analysis in patients with implanted ICDs showed a decrease in shock rates from 34% to 27% and a significant reduction in the risk of SCD by 32% in patients with ICD without SRT [43]. The increase in LVEF was small (from +1.6% to 2.9%) during the different periods of the study, yet within the same range as in our study [44]. Thus, it was suggested that the mechanism of action of Omacor might be independent of reverse cardiac remodeling. However, in a relatively small number of RCTs, patients with HFrEF who received excellent recommended background therapy with Omacor 2 g/day, experienced a 5% increase in LVEF compared to placebo and a decrease in LV and left atrial (LA) dimensions [45]. In the specially designed OMEGA – REMODELEL RCT, magnetic resonance imaging was used to evaluate LV remodeling in patients with the history of AMI during the treatment with Omacor 4 g/day [46]. LV volume index and the volume of peri-infarction fibrosis were shown to reduce statistically significantly during this treatment. Thus, high doses of ω-3 PUFAs contribute to moderate reverse cardiac remodeling. In summary, there are different interpretations of the ways ω-3 PUFAs influences the mechanisms that determine the risk of SCD at CHF. This effect can vary depending on the used doses and concentration of EPA and DHA in cell membranes [46].

The objective of our study was to search for non-invasive markers SCD (if any) and study how different doses of Omacor (1 g/day and 2 g/day) influence compa-

red to the control in a homogeneous group of patients with CAD and LVEF less than 40% who receive the best possible therapy. The baseline mean LVEF was less than 30% in all patient groups. More than 80% of patients received three-component neurohormonal therapy, and all patients took diuretics continuously, confirming the real severity of CHF manifestations.

The risk of SCD was determined by the quantitative (VPBs per hour at 24 hour ECG monitoring) and qualitative characteristics (percentage of patients with paired VPBs and VT) of HRDs. HRV was determined by the SDNN changes and mean 24-hour HR. Clinical severity was assessed by the changes of CHF FC and SHOCS scores. Changes in the LVEF were considered as a marker of LV remodeling severity. Moreover, the changes of VO_2 were estimated, which is the total indicator of the ability to physical exercises.

The baseline data and changes of the parameters during the treatment confirmed two important facts: close correlation between SHOCS and CHF FC (r=0.87, p<0.001) and between HRV (SDNN) and mean 24-hour HR (r= –0.73, p<0.001). Thus, the SHOCS score characterizes the clinical severity of CHF in an optimal way [47]. The chronotropic component (monotonic tachycardia) is directly correlated to HRV, which largely reflects the excess activity of SAS in CHF [48, 49]. Comparisons of oxygen supply at physical load (peak VO_2 in spiroergometry) initially revealed a significant correlation with the LV function and again with mean 24-hour HR. During treatment, the correlations between peak VO_2 and LVEF became stronger and reached a ratio (r= 0.79, p<0.001), and there was an inverse correlation between VO_2 and 24-hour HR (r= –0.58, p<0.001). The main objective of our study was to search for SCD markers associated with HRDs in patients with HFrEF of ischemic origin. Given that 90% of patients had life-threatening high-grade arrhythmias (paired HPVs and VT), which are independent predictors of SCD in patients with the history of AMI [50], the number of VPBs per hour, based on the results of 24 hour ECG monitoring, was used as an additional criterion susceptible to influence. At baseline, the number of VPBs per hour was reversely correlated only with HRV (SDNN). However, when changes of the parameters during the treatment were evaluated, the number of premature beats was found to be significantly correlated with both SDNN (r= – 0.70; p<0.001) and 24-hour HR (r=0.66, p<0.001). Thus, the chronotropic component in HFrEF turns out to be a very informative indicator. At baseline and during the treatment, tachycardia is associated not only with the severity of CHF (FC, SHOCS), LV function (EF), and oxygen supply at load (peak VO_2), but also with HRV (SDNN) and the rate of HRDs, being factors reflecting the excess activity of SAS and the risk of SCD. The smallest correlation of the parameters studied was found with the biochemical marker of cardiac overload, NT-pro-BNP.

Treatment with ω-3 PUFAs proved to be effective and more pronounced with the dose of 2 g/day [45, 51]. Interestingly, the improvement of CHF FC became significant only with a higher dose of Omacor. SHOCS tended to decrease with Omacor 1 g/day and became significant when the dose was doubled; and the decrease of NT-pro-BNP the most sensitive and significant with both doses of Omacor (Figure 1). The increase of LVEF was small and significant with only Omacor 2 g/day (+3%, p=0.002). The negative chronotropic effect ω-3 PUFAs is of interest. Mean 24-hour HR decreased by 8 bpm, r=0.05 and 11 bpm, r=0.001, with Omacor at 1 g/day and 2 g/day, respectively. At the same time, oxygen supply at load (peak VO_2) and HRV (SDNN) statically significantly improved with both doses of ω-3 PUFAs. The anti-arrhythmic effect of low-dose Omacor (1 g/day) was insignificant both in the number of VPBs and the percentage of patients who had no more VPBs and VT (2 out of 10 patients, 20%). HOWEVER, with the use of a combination of EPA+DHA in a dose of 2 g/day, the number of VPBs (by 16 per hour) was significantly reduced, and the risk of HRDs (in 8/20 patients, 40% stopped detecting paired VPBs and run VT short runs). As seen in Figure 4, a moderate improvement in LVEF and a negative chronotropic component make a two-fold contribution to the increase in oxygen supply at physical load during the treatment of Omacor. Both improved HRV (increased SDNN) and reduced mean 24-hour HR made a two-fold contribution in assessing the severity of anti-arrhythmic action and the potential reduction of the SCD risk (Figure 5). Careful analysis shows that, unlike in the control group, only with Omacor at both doses, there was a significant decrease in mean 24-hour HR and a simultaneous improvement in HRV. Given that HR and HRV are closely correlated, the effects of ω-3 PUFAs on these non-invasive markers determine their ability to reduce the risk of SCD in patients with HFrEF of ischemic origin. The anti-arrhythmic effect of Omacor is greater if higher doses of the drug are administered.

Limitations of the study

The study was open-ended, and no information was collected on the prescription of statins to patients.

No conflict of interest is reported.

The article was received on 14/08/2020

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327

REFERENCES

1. Belenkov Yu.N., Mareev V.Yu. The treatment of congestive heart failure in XXI century: questions and lessons of evidence based medicine. Kardiologiia. 2008;48(2):6–16. [Russian: Беленков Ю.Н., Мареев В.Ю. Лечение сердечной недостаточности в XXI веке: достижения, вопросы и уроки доказательной медицины. Кардиология. 2008;48(2):6—16]
2. Vaduganathan M, Claggett BL, Jhund PS et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet. 2020;396(10244). DOI:10.1016/S0140-6736(20)30748-0
3. Ситникова М. Ю., Лясникова Е. А., Юрченко А. В., Трукшина М. А., Либис Р. А., Кондратенко В. Ю., Дупляков Д. В., Хохлунов С. М., Шляхто Е. Результаты Российского госпитального регистра хронической сердечной недостаточности в 3 субъектах Российской Федерации. Кардиология. 2015;55(10):5-13. https://www.elibrary.ru/item.asp?id=24872760. Accessed August 11, 2020
4. Lester R, Moss AJ, Bigger JT et al. Risk Stratification and Survival after Myocardial Infarction. N Engl J Med. 1983;309(6):331-336. DOI:10.1056/NEJM198308113090602
5. Kearney MT, Fox KAA, Lee AJ et al. Predicting sudden death in patients with mild to moderate chronic heart failure. Heart. 2004;90(10):1137-1143. DOI:10.1136/hrt.2003.021733
6. Huikuri H V., Castellanos A, Myerburg RJ. Medical progress: Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345(20):1473-1482. DOI:10.1056/NEJMra000650
7. Shen L, Jhund PS, Petrie MC et al. Declining Risk of Sudden Death in Heart Failure. N Engl J Med. 2017;377(1):41-51. DOI:10.1056/NEJMoa1609758
8. De Diego C, González-Torres L, Núñez JM et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Hear Rhythm. 2018;15(3):395-402. DOI:10.1016/j.hrthm.2017.11.012
9. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos G V, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: A meta-analytic approach. J Am Coll Cardiol. 2010;56(5):392-406. DOI:10.1016/j.jacc.2010.05.011
10. Ruwald MH, Solomon SD, Foster E et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: Results from the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT) trial. Circulation. 2014;130(25):2278-2286. DOI:10.1161/CIRCULATIONAHA.114.011283
11. Køber L, Torp-Pedersen C, McMurray JJ V et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med. 2008;358(25):2678-87. DOI:10.1056/NEJMoa0800456
12. Bardy GH, Lee KL, Mark DB. et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225-37. DOI:10.1056/NEJMoa043399
13. Albert CM, Campos H, Stampfer MJ et al. Blood Levels of Long-Chain n–3 Fatty Acids and the Risk of Sudden Death. N Engl J Med. 2002;346(15):1113-1118. DOI:10.1056/NEJMoa012918
14. Pottala J V., Garg S, Cohen BE, Whooley MA, Harris WS. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: The heart and soul study. Circ Cardiovasc Qual Outcomes. 2010;3(4):406-412. DOI:10.1161/CIRCOUTCOMES.109.896159
15. GISSI-HF investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9645):1223-1230. DOI:10.1016/S0140-6736(08)61239-8
16. Marchioli R. Dietary supplementation with N-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Lancet. 1999;354(9177):447-455. DOI:10.1016/S0140-6736(99)07072-5
17. Macchia A, Levantesi G, Franzosi MG et al. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. Eur J Heart Fail. 2005;7(5):904-909. DOI:10.1016/j.ejheart.2005.04.008
18. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. In: American Journal of Clinical Nutrition. Vol 71. American Society for Nutrition; 2000. DOI:10.1093/ajcn/71.1.202s
19. Christensen JH, Gustenhoff P, Ejlersen E et al. n-3 fatty acids and ventricular extrasystoles in patients with ventricular tachyarrhythmias. Nutr Res. 1995;15(1):1-8. DOI:10.1016/0271-5317(95)91647-U
20. Christensen JH, Gustenhoff P, Korup E et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: A double blind randomised controlled trial. Br Med J. 1996;312(7032):677-678. DOI:10.1136/bmj.312.7032.677
21. Von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine ω-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest. 1985;76(4):1626-1631. DOI:10.1172/JCI112147
22. Mehta J, Lawson D, Saldeen T. Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acid (PUFA) intake. Am Heart J. 1988;116(5 PART 1):1201-1206. DOI:10.1016/0002-8703(88)90440-1
23. Poole CD, Halcox JP, Jenkins-Jones S et al. Omega-3 Fatty Acids and Mortality Outcome in Patients with and without Type 2 Diabetes After Myocardial Infarction: A Retrospective, Matched-Cohort Study. Clin Ther. 2013;35(1):40-51. DOI:10.1016/j.clinthera.2012.11.008
24. Kimmig LM, Karalis DG. Do Omega-3 Polyunsaturated Fatty Acids Prevent Cardiovascular Disease? A Review of the Randomized Clinical Trials. Lipid Insights. 2013;6:LPI.S10846. DOI:10.4137/LPI.S10846
25. Khler A, Bittner D, Löw A, Von Schacky C. Effects of a convenience drink fortified with n-3 fatty acids on the n-3 index. Br J Nutr. 2010;104(5):729-736. DOI:10.1017/S0007114510001054
26. Bhatt DL, Steg PG, Miller M et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22. DOI:10.1056/NEJMoa1812792
27. Арболишвили Г.Н., Мареев В.Ю. Возможности применения омега-3 полиненасыщенных жирных кислот для вторичной профилактики у больных сердечной недостаточностью ишемической этиологии. Дизайн исследования "ОНИКС" (Влияние Омакора на НеИнвазивные маркеры внезапной сердечной смерти у больных. Журнал Сердечная недостаточность. 2008;9(2 (46)):73-78. https://www.elibrary.ru/item.asp?id=10439180. Accessed August 11, 2020
28. Abdelhamid AS, Martin N, Bridges C et al. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;(11). DOI:10.1002/14651858.cd012345.pub3
29. Torshin IY, Gromova OA, Kobalava ZD. About Errors in Meta-Analyses of Cardiovascular Effects of Omega-3 PUFA Part 1. Pharmacological and Clinical Aspects of Validity in the Era of Post-Genomic Research, Artificial Intelligence and Big Data Analysis. Eff Pharmacother. 2019;15(9):26-34. DOI:10.33978/2307-3586-2019-15-9-26-34
30. Mareev VY, Fomin I V., Ageev FT et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. Kardiologiia. 2018;17(S6):1-164. DOI:10.18087/cardio.2475
31. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37(27):2129-2200. DOI:10.1093/eurheartj/ehw128
32. Hu Y, Hu FB, Manson JAE. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. J Am Heart Assoc. 2019;8(19). DOI:10.1161/JAHA.119.013543
33. Poole-Wilson PA, Uretsky BF, Thygesen K, Cleland JGF, Massie BM, Rydén L. Mode of death in heart failure: Findings from the ATLAS trial. Heart. 2003;89(1):42-48. DOI:10.1136/heart.89.1.42

34. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A Randomized Study of the Prevention of Sudden Death in Patients with Coronary Artery Disease. N Engl J Med. 1999;341(25):1882-1890. DOI:10.1056/NEJM199912163412503
35. Bardy GH, Lee KL, Mark DB et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. N Engl J Med. 2005;352(3):225-237. DOI:10.1056/NEJMoa043399
36. Køber L, Torp-Pedersen C, McMurray JJV et al. Increased Mortality after Dronedarone Therapy for Severe Heart Failure. N Engl J Med. 2008;358(25):2678-2687. DOI:10.1056/NEJMoa0800456
37. Moss AJ, Hall WJ, Cannom DS et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329-38. DOI:10.1056/NEJMoa0906431
38. Marchioli R, Barzi F, Bomba E et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105(16):1897-903. http://www.ncbi.nlm.nih.gov/pubmed/11997274. Accessed June 14, 2018
39. Lavie CJ, Milani R V., Mehra MR, Ventura HO. Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Diseases. J Am Coll Cardiol. 2009;54(7):585-594. DOI:10.1016/j.jacc.2009.02.084
40. Schrepf R, Limmert T, Weber PC, Theisen K, Sellmayer A. Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia. Lancet. 2004;363(9419):1441-1442. DOI:10.1016/S0140-6736(04)16105-9.
41. Leaf A, Albert CM, Josephson M et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005;112(18):2762-2768. DOI:10.1161/CIRCULATIONAHA.105.549527
42. Brouwer IA, Raitt MH, Dullemeijer C et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. Eur Heart J. 2009;30(7):820-6. DOI:10.1093/eurheartj/ehp003
43. Finzi AA, Latini R, Barlera S et al. Effects of n-3 polyunsaturated fatty acids on malignant ventricular arrhythmias in patients with chronic heart failure and implantable cardioverter-defibrillators: A substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial. Am Heart J. 2011;161(2). DOI:10.1016/j.ahj.2010.10.032
44. Ghio S, Scelsi L, Latini R et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: A substudy of GISSI-HF trial. Eur J Heart Fail. 2010;12(12):1345-1353. DOI:10.1093/eurjhf/hfq172
45. Nodari S, Triggiani M, Campia U et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2011;57(7):870-879. DOI:10.1016/j.jacc.2010.11.017
46. Heydari B, Abdullah S, Pottala J V. et al. Effect of omega-3 acid ethyl esters on left ventricular remodeling after acute myocardial infarction. Circulation. 2016;134(5):378-391. DOI:10.1161/CIRCULATIONAHA.115.019949
47. Mareev Y, Gerasimova V, Goryunova G et al. Factors which determine prognosis in chronic heart failure: role of QRS duration and morphology. Russ Hear Fail J. 2012;5:255-266. DOI:DOI: 10.18087/rhfj.2012.5.1722
48. Чухнин Е. В., Амиров Н. Б., Морозова Н. И. Риск внезапной смерти и частота сердечных сокращений – Фундаментальные исследования (научный журнал). Фундаментальные исследования. 2011;(9(3)):558-560. https://www.fundamental-research.ru/ru/article/view?id=28556. Accessed August 12, 2020
49. Мареев В. Ю., Арболишвили, Г. Н. Орлова Я. А., Беленков Ю. Н. Вариабельность ритма сердца при ХСН и ее роль в прогнозе заболевания. Кардиология. 2006;46(12)
50. Scirica BM, Braunwald E, Belardinelli L et al. Relationship Between Nonsustained Ventricular Tachycardia After Non–ST-Elevation Acute Coronary Syndrome and Sudden Cardiac Death. Circulation. 2010;122(5):455-462. DOI:10.1161/CIRCULATIONAHA.110.937136
51. Moertl D, Hammer A, Steiner S, Hutuleac R, Vonbank K, Berger R. Dose-dependent effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of nonischemic origin: A double-blind, placebo-controlled, 3-arm study. Am Heart J. 2011;161(5):915.e1-915.e9. DOI:10.1016/j.ahj.2011.02.011

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1327