# Omega-3 Polyunsaturated Fatty Acids: the Role in Prevention of Atrial Fibrillation in Patients with Coronary Artery Disease after Coronary Artery Bypass Graft Surgery

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**Aim.** To estimate the role of omega-3 polyunsaturated fatty acids (PUFAs) administration in atrial fibrillation (AF) prevention after planned coronary artery bypass graft (CABG) surgery.

**Material and Methods.** Studied were 306 patients divided into two groups: patients of group I didn't receive PUFAs (158 patients, 82.7% males) and patients of group II received PUFAs (148 patients, 89.3% males). PUFAs were prescribed in daily dose 2000 mg 5 days before surgery and in daily dose 1000 mg in postoperative period during 21 days.

**Results.** Postoperative AF (POAF) occurred in 29.7% patients in group I and in 16.9% patients in group II (p=0.009). We found that after CABG in patients of the I group median IL-6 level was 39.3% higher (p=0.001), interleukin-10 – 20.2% higher (p=0.01), superoxide dismutase – 78.9% higher (p<0.001), malondialdehyde – 33.8% higher (p=0.03), docosahexaenoic acid – 31.8% lower (p=0.01) and omega-3 index – 43.4% lower (p=0.04) than in patients of the II group.

According to multivariate regression analysis we found significant association between the factors of inflammation, oxidative stress and the risk POAF development.

**Conclusions.** In patients who took PUFAs, we found less activation of inflammation, oxidative stress, the increasing of docosahexaenoic acid and omega-3 index accompanied by the decreasing of POAF development rates up to 12.8%.

**Key words:** atrial fibrillation, coronary artery bypass graft surgery, polyunsaturated fatty acids, oxidative stress, inflammation.

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### Introduction

The issues of postoperative atrial fibrillation (AF) prevention remain relevant in cardiac surgery. Postoperative AF is a multifactorial complication in patients with coronary artery disease (CAD) undergoing planned coronary artery bypass graft (CABG) surgery. The literature discusses the role of various indicators of inflammation, markers of oxidative stress, troponin and natriuretic peptide in the development of this arrhythmia [1]. According to the literature, the tactics of treating patients in order to prevent the development of postoperative AF included the appointment of antiarrhythmic drugs (in particular, amiodarone), cardiac glycosides, beta-blockers, calcium antagonists, which in some cases could provoke the development of hypotension. bradycardia, and atrioventricular block. [2, 3]. The use of omega-3 polyunsaturated fatty acids (PUFAs) to prevent new cases of postoperative AF has shown conflicting results [4, 5]. When using these drugs in practice, physicians need to take into account the prescribed dose, duration of drug intake, as well as the way of administration of omega-3 PUFAs, which contributes to changes in plasma and tissue levels of this drug and may explain the diversity of clinical studies results [6]. The omega-3 index significance is currently being considered. This index is the percentage of PUFAs composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in erythrocyte membranes [7, 8]. Assessment of this parameter can characterize an individual response to the use of omega-3 PUFAs and contribute to a better understanding of their pharmacokinetics and pharmacodynamics. However, at present, the literature contains conflicting data on the prescription of omega-3 PUFAs before CABG to prevent new cases of postoperative AF, and there is also insufficient information on the effect of omega-3 PUFAs on the content of EPA, DHA and omega-3 index in the erythrocyte membrane in patients with postoperative AF, who underwent CABG.

The study aim was to study the role of omega-3 polyunsaturated fatty acids (PUFAs) in preventing the development of atrial fibrillation (AF) after planned coronary artery bypass graft (CABG) surgery

## Materials and methods

The fundamental principles were adopted in the formation of the study design, reflecting the compliance of the study with uniform standards for presenting test results (CONSORT recommendations) (Fig. 1). The study protocol was approved by the local ethics committee of the federal state budgetary educational institution of higher education at the Samara State Medical University of the Ministry of Health of Russia (No. 166 dated 12/02/2015).

306 patients (85.9% of men, average age was 62.0 [57.0; 66.0] years) with coronary artery disease who were scheduled for CABG were included in the study from 2015 to 2018 after receiving informed consent to participate. The patients were followed up for 12 months. Patients underwent 12-lead ECG registration to detect postoperative AF, and bedside 3-lead ECG monitoring during their stay in the intensive care unit. Registration at

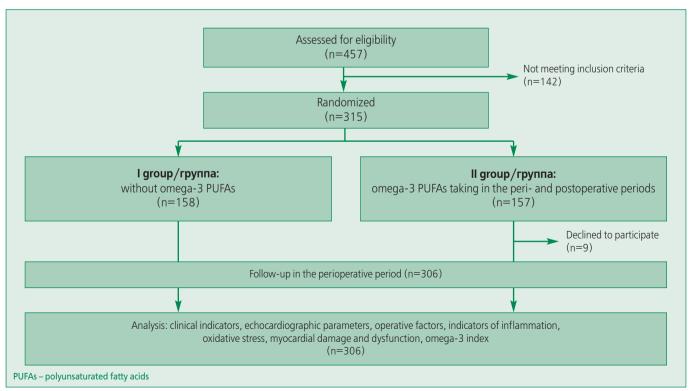


Figure 1. Study design

the stationary stage was carried out daily, as well as when a patient complained of palpitations, rhythm disturbances and a feeling of air lack.

The diagnosis of stable angina was based on the European guidelines for the treatment of patients with stable coronary artery disease (2013) [9].

Indications for CABG were determined in accordance with the recommendations for myocardial revascularization [10].

Patients were randomized into two groups depending on the prescription of omega-3 PUFAs (1000 mg) in the preoperative and postoperative periods: patients of group I didn't take omega-3 PUFAs (n=158; 131 [82.9%] of men); the median age was 63.0 [57.0; 67.0] years), patients of group II took omega-3 PUFAs (n=148; 132 [89.2%] of men); the median age was 60.0 [57.0; 64.0] years). Omega-3 PUFAs were prescribed at a dose of 2000 mg per day 5 days before CABG and at a dose of 1000 mg per day in the postoperative period for 21 days. The drug was given to patients as part of the study.

All patients underwent a study of the content of interleukins: 6 (IL-6), 8 (IL-8) and 10 (IL-10). The concentrations of NT-proBNP, troponin, plasma superoxide dismutase (SOD), malondialdehyde (MDA), reduced glutathione (RG) and the activity of glutathione reductase (GR) enzymes, omega-3 index were also investigated. The concentration determination of interleukins, as well as NTproBNP and plasma SOD was carried out by enzyme immunoassay on a Thermo Scientific Multiscan FC analyzer (China) using test systems from Vector-Best JSC (Novosibirsk, Russia) and Cytokin JSC (St. Petersburg, Russia). The concentration of troponin was measured using a UNI-CEL® DXI 600 ACCESS immunochemical analyzer (Beckman Coulter, USA). The levels of MDA, RG and the activity of glutathione reductase in erythrocytes were calculated spectrophotometrically on a LOMO SF-56 spectrophotometer (St. Petersburg). Determination of the omega-3 index was carried out by chromatographic analysis. The study of the parameters was carried out before the operation and on average 3-4 days after the intervention.

Echocardiography was performed using Logiq-5; 7 (USA) ultrasound scanners in M-, B-, D- modes.

Statistical processing of the results was carried out using the Statistica 7.0 software package (StatSoft Inc., USA). The data obtained were analyzed using nonparametric statistical methods, because the data didn't match the normal distribution. Continuous variables are presented as the median (Me), as well as the 25th and 75th percentiles [Q25; Q75], qualitative variables are presented as the absolute number of patients (n) and percent (%). Mann-Whitney's U test was used to assess the statistical significance of differences in continuous variables for unlinked indicators, and Wilcoxon's test was used for linked indicators. Chi-square test was used to assess the statistical

significance of differences between qualitative variables. Binary logistic regression was used to identify indicators associated with the development of postoperative AF. Cut-off points of continuous indicators were assessed using ROC analysis with determination of sensitivity and specificity. Differences were considered statistically significant at p <0.05.

## **Results**

Patient characteristics are presented in Table 1.

There were no statistically significant differences between the groups in terms of clinical data.

Postoperative AF developed in 29.7% patients of group I, and in 16.9% patients of group II (p=0.009).

We carried out a comparative analysis of echocardiographic parameters between the groups (Table 2). We didn't find statistically significant differences in the studied echocardiographic parameters between the groups of patients.

Next, we assessed the factors of surgical intervention (Table 3). We didn't find statistically significant differences between the groups in the following parameters: time of extracorporeal circulation, time of aortic clamping, time of myocardial ischemia, performing CABG on the beating heart, and the number of shunts applied.

Assessment of laboratory parameters of inflammation, oxidative stress, myocardial damage and dysfunction before CABG showed no statistically significant differences between the groups.

Analysis of changes in the presented parameters after CABG in patients in group I showed an increase in the IL-6 level by 83.4% (p<0.001), IL-8 by 78.2% (p<0.001), IL-10 by 48.3% (p<0.001), NT-proBNP by 74.1% (p<0.001). Plasma SOD activity decreased by 30% (p<0.001), erythrocyte glutathione reductase activity increased by 10.2% (p=0.040), erythrocyte RG level decreased by 21.4% (p=0.002), MDA level increased by 32% (p=0.001).

Assessment of the concentration of these indicators after CABG in group II showed an increase in the IL-6 level by 74% (p<0.001), IL-8 by 68.2% (p<0.001), IL-10 by 42.3% (p<0.001), NT-proBNP by 72% (p<0.001). Plasma SOD activity decreased by 82.8% (p<0.001), erythrocyte glutathione reductase activity increased by 11.3% (p=0.040), erythrocyte RG level decreased by 32% (p=0.003), MDA level increased by 19% (p=0.030).

After CABG, we noted a significant increase in the IL-6 concentration by 39.3% (p=0.001) and IL-10 concentration by 20.2% (p=0.010) concentration among patients of group I compared with group II. We noted a decrease in plasma SOD activity by 78.9% (p<0.001) among patients of group II, and an increase in MDA concentration by 33.8% (p=0.030) among patients of group I.

Table 1. Clinical characteristics of patients

Parameter	Group I (n=158)	Group II (n=148)	р
Men, n (%)	131 (82,9)	132 (89,2)	0,110
Age, years	63,0 [57,0;67,0]	60,0 [57,0;64,0]	0,060
Smoking, n (%)	108 (68,5)	110 (74,5)	0,540
BMI>30 kg/m², n (%)	74 (47,1)	58 (39,4)	0,080
Functional class of angina II, n (%)	43 (27,3)	44 (29,4)	0,620
III, n (%)	101 (63,8)	81 (55,0)	0,070
IV, n (%)	4 (2,6)	0 (0)	-
History of myocardial infarction, n (%)	101 (64,3)	103 (69,4)	0,700
Duration of coronary artery disease, months	23,0 [9,0;84,0]	18,0 [5,0;60,0]	0,060
Arterial hypertension, n (%)	157 (99,2)	145 (98,3)	0,490
Functional class of chronic heart failure according to NYHA			
II, n (%)	135 (85,4)	132 (89,4)	0,330
III, n (%)	23 (14,6)	16 (10,8)	0,330
Diabetes mellitus, n (%)	27 (17,4)	30 (20,3)	0,820
History of cerebrovascular accident, n (%)	13 (8,2)	8 (5,4)	0,450
Atherosclerosis of the arteries of the brachiocephalic vessels, n (%)	156 (98,7)	143 (96,4)	0,060
Atherosclerosis of the arteries of the lower extremities, n (%)	125 (79,0)	126 (85,0)	0,170
Chronic obstructive pulmonary disease, n (%)	19 (12,0)	29 (19,6)	0,100
Medication therapy before surgery, n (%)			
Beta-blockers	127 (80,4)	118 (79,7)	0,890
ACEi/ARBs	112 (70,8)	109 (73,4)	0,590
Calcium antagonists	48 (30,3)	39 (26,3)	0,440
Prolonged nitrates	74 (46,7)	57 (38,8)	0,170
Diuretics	18 (11,5)	13 (8,9)	0,450
Statins	82 (52,0)	83 (56,3)	0,880
Acetylsalicylic acid	126 (79,6)	121 (82,2)	0,120
Clopidogrel	63 (39,8)	58 (39,2)	0,900

We didn't find any differences in other parameters (Table 4).

We assessed the omega-3 index in groups I and II (Table 5). Analysis of the preoperative EPA, DHA and omega-3 index concentration between groups I and II didn't reveal statistically significant differences.

After CABG, we observed a change in the content of PUFAs and omega-3 index in the groups presented. In group I, we found a decrease in the content of EPA by 25% (p=0.140), DHA by 47.9% (p=0.080), omega-3 index by 26.3% (p=0.020). In group II, we found an increase in the content of EPA by 33.3% (p=0.29), DHA by 31.8% (p=0.010), omega-3 index by 44.3% (p=0.010).

In the postoperative period, the DHA concentration in group II was 55% higher (p=0.030), and the omega-3 index was 43.4% higher (p=0.040) compared with group I.

According to univariate regression analysis, the odds ratio (OR) of postoperative AF in patients who underwent CABG was 5.5 (95% confidence interval [CI] was 1.4-21.1, p=0.010) for the RG hemoglobin concentration after surgery  $\leq$ 0.194 µmol/g, 5.3 (95% CI was 1.97-14.4, p=0.001) for IL-6 after surgery >19.53 pg/ml, 0.42 (95% CI was 0, 26-0.68, p=0.0003) for omega-3 index after surgery  $\geq$ 1.83%, 6.6 (95% CI was 2.4-14.5, p=0.0002) for plasma SOD after surgery >1129.6 U/g, 3.4 (95% CI was 1.1-11.2, p=0.040) for MDA hemoglobin after surgery >0.78 µmol/g.

The multivariate regression analysis included indicators significantly associated with the development of postoperative AF according to univariate analysis.

According to multivariate regression analysis, the odds ratio of postoperative AF in patients who underwent CABG was 4.0 (95% CI was 1.1-14.3, p=0.030) for the hemoglobin RG concentration after surgery  $\leq 0.194 \, \mu \text{mol/g}$ ,

Table 2. Echocardiographic parameters

Parameter	Group I	Group II				
	(n=158)	(n=148)	р			
LA, diameter, mm	39,0 [37,0;42,0]	40,0 [38,0;43,0]	0,230			
LVEF, %	58,0 [49,0;65,0]	58,0 [49,0;65,0]	0,700			
LV ESS, mm	35,0 [31,0;40,0]	35,0 [32,0;42,0]	0,770			
LV EDS, mm	52,0 [48,0;57,0]	54,0 [50,0;59,0]	0,340			
LV ESV, ml	51,5 [43,0;65,0]	61,0 [40,5;84,5]	0,070			
LV EDV, ml	125,0 [106,0;140,0]	137,0 [107,5;168,0]	0,080			
LA – left atrium, LVEF – left ventricular ejection fraction, LV ESS – left ventricular end-systolic						
size, LV EDS – left ventricular end-diastolic size, LV ESV – left ventricular end-systolic volume,						
IV FDV = left ventricula	er and-diastolic volume					

Table 3. Surgical parameters of patients

Parameter	Group I (n=158)	Group II (n=148)	р	
Left Main Coronary				
Artery ≥50%, n (%)	30 (19,3)	40 (27,2)	0,090	
Number of shunts, n (%)				
1	11 (7.0)	13 (8,8)	0,550	
2	51 (32,3)	42 (28,4)	0,460	
3	81 (51,5)	77 (52,0)	0,890	
4	15 (9,7)	16 (10,8)	0,700	
Beating heart surgery, n (%)	15 (9,8)	17 (11,5)	0,570	
Artificial circulation time, min	61,0 [49,0;69,0]	59,0 [51,0;70,0]	0,800	
Aortic clamping time, min	36,0 [26,0;41,0]	34,0 [28,0;41,0]	0,980	
Ischemia time, min	13,0 [7,0;18,0]	14,0 [8,0;20,0]	0,500	

4.4 (95% CI was 1.3-15.4, p=0.020) for IL-6 after surgery >19.53 pg/ml, 0.4 (95% CI was 0.3-0.54 , p<0.001) for omega-3 index after surgery  $\geqslant$ 1.83%, 4.5 (95% CI was 1.2-17.8, p=0.040) for plasma SOD after surgery >1129.6 U/g. The association with postoperative AF became statistically insignificant (p>0.05) for postoperative MDA hemoglobin concentration >0.78 µmol/g.

# Discussion

Several aspects of the effect of omega-3 PUFAs on reducing the risk of postoperative AF are considered in the

literature [11, 12]. Experiments have shown that omega-3 PUFAs have pleiotropic effects, such as antiarrhythmic, antithrombotic, hypotriglyceridemic, anti-inflammatory and several others, which are explained by the influence of various mechanisms [13]. We note that omega-3 PUFAs at low concentrations exhibit a rapidly developing antiarrhythmic effect that doesn't require acid biotransformation [14].

According to L. Darghosian et al., the effectiveness of omega-3 PUFAs in the prevention of recurrent AF is controversial, and their effect on inflammation and oxidative

Table 4. Indicators of inflammation, oxidative stress, myocardial damage and dysfunction in groups without omega-3 PUFAs and with omega-3 PUFAs

Parameter	Group I (n=96)		р	Group II (n=96)		р
	Before surgery	After surgery		Before surgery	After surgery	
IL-6, pg/ml	4,1 [2,6;21,5]	24,7 [10,6;50,8]	<0,001*	3,9 [1,7;13,4]	15,0 [8,3;29,5]	<0,001* 0,001†
IL-8, pg/ml	1,7 [1,2;3,0]	7,8 [4,6;12,4]	<0,001*	2,1 [1,4;3,3]	6,6 [4,2;9,0]	<0,001*
IL-10, pg/ml	4,6 [3,4;8,1]	8,9 [5,7;13,2]	<0,001*	4,1 [2,8;7,5]	7,1 [3,9;12,5]	<0,001* 0,010†
Plasma SOD, U/g	2132,6 [1050,4;4589,9]	1495,4 [709,8;2434,1]	<0,001*	1834,6 [912,0;2577,6]	314,8 [217,6;614,0]	<0,001* <0,001†
RG, µmol/g of hemoglobin	0,28 [0,2;0,38]	0,22 [0,15;0,3]	0,002*	0,28 [0,19;0,34]	0,19 [0,15;0,31]	0,003*
Glutathione reductase enzymes, activity, mmol/g of hemoglobin	3,53 [2,96;4,59]	3,93 [3,13;4,68]	0,040*	3,31 [3,06;3,91]	3,73 [3,32;4,27]	0,040*
MDA, μmol/g of hemoglobin	0,32 [0,24;0,41]	0,71 [0,45;1,27]	<0,001*	0,38 [0,34;0,74]	0,47 [0,36;1,46]	0,030* 0,030†
NT-proBNP, pg/ml	112,2 [29,0;244,1]	433,6 [202,5;604,8]	<0,001*	88,1 [50,0;166,2]	314,3 [191,0;519,0]	<0,001*
Troponin I, µg/l	-	1,67 [0,97;2,9]		-	1,3 [0,87;2,4]	

Table 5. Concentration of PUFAs and the level of omega-3 index in the group without the use of omega-3 PUFAs and the group with the use of omega-3 PUFAs

Parameter	Group I (n=96)		р	Group II (n=96)		р
	Before CABG	After CABG		Before CABG	After CABG	
Eicosapentaenoic acid (C 20:5), %	0,64 [0,41;1,05]	0,48 [0,2;0,9]	0,14*	0,74 [0,19;1,82]	1,11 [0,3;1,72]	0,290*
Docosahexaenoic acid (C 22:6), %	5,36 [2,55;6,22]	2,79 [0,78;5,55]	0,08*	4,23 [1,2;5,86]	6,2 [3,83;7,95]	0,010* 0,030 <sup>†</sup>
Omega-3 index, %	5,29 [2,59;6,85]	3,9 [1,02;6,9]	0,02*	3,84 [1,23;6,33]	6,89 [4,82;9,64]	0,010* 0,040†

<sup>\*</sup> compared to the period before surgery in the same group; †compared with the period after surgery in the opposite group

CABG - coronary artery bypass grafting

stress in this population is unknown [15]. Stanger O. et al suggested that the prescription of omega-3 PUFAs as antioxidant protection may reduce the risk of AF in the group of patients who underwent CABG [16].

According to our data, the prescription of omega-3 PUFAs was accompanied by a decrease in the incidence of postoperative AF during planned CABG when compared with the group not taking this drug. Our results are consistent with the meta-analysis data by H. Wang et al. [5]. At the same time, the author emphasizes that the effectiveness of the omega-3 PUFA use is noted against the background of isolated CABG surgery, without the presence of previous AF, as well as when the EPA/DHA ratio is <1. Thus, the assessment of the inflammation factors, oxidative stress and the omega-3 index will make it possible to assess changes in the above parameters that determine the risk of postoperative AF during planned CABG in patients taking omega-3 PUFAs.

The levels of inflammation indicators were lower in patients taking omega-3 PUFAs when compared with patients without the drug. The literature contains conflicting data.

Bo L. et al showed a decrease in the IL-6 concentration and tumor necrosis factor- $\alpha$  under the effect of omega-3 PUFAs in an experiment with endothelial cells of the human umbilical vein [17]. F. Zhang et al demonstrated in an experiment that the use of omega-3 PUFAs statistically significantly reduced the IL-6 level, epidermal growth factor, and reactive oxygen species, thereby exerting a protective effect on the cells of the Lyberkun's crypt of rats and, thereby, protecting them from damage by heavy metals [18]. At the same time, we need to take into account the data obtained by M.S. Ellulu et al, who indicate that the use of omega-3 PUFAs for 8 weeks didn't lead to a statistically significant decrease in the IL-6 concentration in patients with arterial hypertension and diabetes mellitus [19]. The authors explained the lack of

the drug effect on the IL-6 concentration by prescribing a low dose, as well as a short period of patients' observation.

During CABG, several authors note an increase in troponin level due to prolonged myocardial ischemia and the use of artificial circulation [20]. In our study, troponin increased after CABG, but there were no significant differences between the groups of patients without prescription and with the use of omega-3 PUFAs. The data obtained differ from the results of M.L. Narducci et al, who showed an association of troponin with the risk of postoperative AF [21].

We also didn't find statistically significant differences in NT-proBNP concentration among patients who took omega-3 PUFAs before CABG versus patients who did not take this drug. Our results are consistent with the literature data [22].

Oxidative stress is considered to be one of the mechanisms responsible for the occurrence of postoperative AF [23, 24]. The development of this stress is associated with the activation of free radical oxidation and/or a decrease in antioxidant protection, which is accompanied by the accumulation of various reactive oxygen species. These oxygen species provoke the development of oxidative modification of protein and lipid molecules, as well as the membrane structure damage and its further disruption. Also, reactive oxygen species are intracellular signals involved in the regulation of various cellular processes, including apoptosis [25].

We found statistically significantly low plasma SOD levels and low MDA levels among patients taking omega-3 PUFAs compared with patients without omega-3 PUFAs intake. Our results are partially consistent with literature data. The data of a meta-analysis by J. Heshmati et al demonstrated that the use of omega-3 PUFAs significantly increases the activity of serum glutathione peroxidase and total antioxidant capacity, as well as decreases the

MDA level. However, the effect of omega-3 PUFAs on the activity of nitrite oxide, glutathione, SOD, and catalase was insignificant [26].

According to our data, an increase in the content of EPA, DHA and omega-3 index was observed in the erythrocyte membrane during the use of omega-3 PUFAs after CABG, which is consistent with literature data [27].

Benedetto U. et al conducted a comparative analysis of three randomized controlled trials involving 431 patients and devoted to the role of omega-3 PUFAs in the postoperative AF development in patients undergoing cardiac surgery [28]. The authors summarized the findings of these studies and found that omega-3 PUFAs didn't significantly affect the risk of this arrhythmia IOR was 0.89: 95% CI was 0.55-1.44; p=0.63]. At the same time, the performed meta-regression analysis showed a tendency of benefit to prescribing omega-3 PUFAs if the ratio between EPA and DHA is within 1:2 (Q model=7.4; p=0.02), as well as when insufficient adherence to betablockers before CABG is noted (Q model=8.0; p=0.01). Thus, we can conclude from this analysis that the intake of omega-3 PUFAs doesn't generally reduce the prevalence of postoperative AF in patients undergoing cardiac surgery [28]. At the same time, the authors emphasize that several factors could have influenced this result, and this needs to be confirmed or refuted in further studies.

Saravanan P. et al obtained data that the intake of omega-3 PUFAs doesn't reduce the risk of postoperative AF after CABG surgery. But the authors demonstrated a

statistically significant increase in serum EPA and DHA concentrations in those patients who received this drug, compared with the placebo group. At the same time, EPA and DHA in the tissue of the right atrial appendage studied during CABG were statistically significantly higher against the background of taking omega-3 PUFA [29].

Thus, we have shown in this study that the development of postoperative AF is associated with postoperative concentrations of RG, IL-6, plasma SOD, omega-3 index, which is confirmed by our previous work [30].

*Study limitations.* The study was single-center, it included a small number of patients, the observation of patients was limited to the preoperative and postoperative periods.

## Conclusion

Thus, a lower activation of the inflammation and oxidative stress parameters was observed against the background of an increase in the DHA level and the omega-3 index among patients taking omega-3 PUFAs after CABG, which was accompanied by a decrease in the incidence of AF. The beneficial effect of PUFAs revealed by us, most likely, determines the preventive effect of this drug group on the postoperative AF development.

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