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Cardiovascular effects of omega-3 polyunsaturated fatty acids: position of omega-3 polyunsaturated fatty acids in Russian and international guidelines. Council of Experts

This Expert Council focuses on the meta-analysis of studies on the risk of atrial fibrillation (AF) in patients taking omega-3 polyunsaturated fatty acids (PUFA) and of data on the omega-3 PUFA treatment in patients with cardiovascular and kidney diseases. The major statements of the Expert Council: the meta-analysis of AF risk in patients taking omega-3 PUFA showed an increased risk of this arrhythmia. However, it should be taken into account that the risk of complications was low, and there was no significant increase in the risk of AF when omega-3 PUFA was used at a dose of ≤1 g and a standard dose of the only omega-3 PUFA drug registered in the Russian Federation, considering all AF episodes in the ASCEND study. At the present time, according to Russian and international clinical guidelines, the use of omega-3 PUFA can be considered in the following cases:

- for patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction as a supplement to the basic therapy (2B class of recommendations according to the 2020 Russian Society of Cardiology guidelines (RSC) and the 2022 AHA/ACC/HFSA guidelines);
- for patients with hypertriglyceridemia (>1.5 mmol/l) as a part of combination therapy (IIb class of recommendations and B level of evidence according to the 2021 European guidelines on cardiovascular disease prevention, etc.);
- for adult patients with stage 3-4 chronic kidney disease (CKD), long-chain omega-3 PUFA 2 g/day is recommended for reducing the level of triglycerides (2C class of recommendations). Data on the use of omega-3 PUFA for other indications are heterogenous, which can be partially explained by using different form and doses of the drugs.

Keywords Omega-3 PUFA; meta-analysis; chronic heart failure; triglyceridemia

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Safety as well as efficacy of drugs is always the key focus of experts. Therefore, experts discuss new research findings, literature reviews, and meta-analyses on the possible risks of using even well-known and extensively studied drugs in order to give physicians structured clinical guidelines for prescribing drugs that take into account the individual characteristics and needs of patients and assess potential risks and benefits.

In 2021, a meta-analysis [1] of randomized controlled trials (RCTs) was published, which studied the cardiovascular effects of various forms and strengths of omega-3 polyunsaturated fatty acids (PUFAs) and provided data on the risk of developing atrial fibrillation (AF) (7 RCTs, 81,210 patients). The meta-analysis did not include studies, in which Omega-3 PUFAs were administered for the prevention of post-cardioversion AF recurrences and postoperative AF. The meta-analysis findings showed that the risk of AF increased during the use of Omega-3 PUFAs: hazard ratio (HR) 1.25, 95% confidence interval (CI) 1.07–1.46; p = 0.013.

An additional analysis (3 RCTs, 22,271 patients) assessed the relationship between the onset of AF and doses of omega-3 PUFAs and showed an increased risk both at a dose of ≤1 g/day (4 RCTs, 58,939 patients) and a dose of >1 g/day. The risk was higher with larger doses of Omega-3 PUFAs: HR 1.49 (95% CI 1.04–2.15; p=0.042) and 1.12 (95% CI 1.03–1.22; p=0.024) for >1 g/day and ≤1 g/day, respectively.

The results of the ASCEND study provided in the original article [2] and not in the supplementary publication [3], which contained more information on AF episodes, were used in the meta-analysis. Omega-3 PUFAs at a dose <1 g/day was not associated with a statistically significant increase in the risk of AF, according to sensitivity analysis and additional analysis of the ASCEND data.

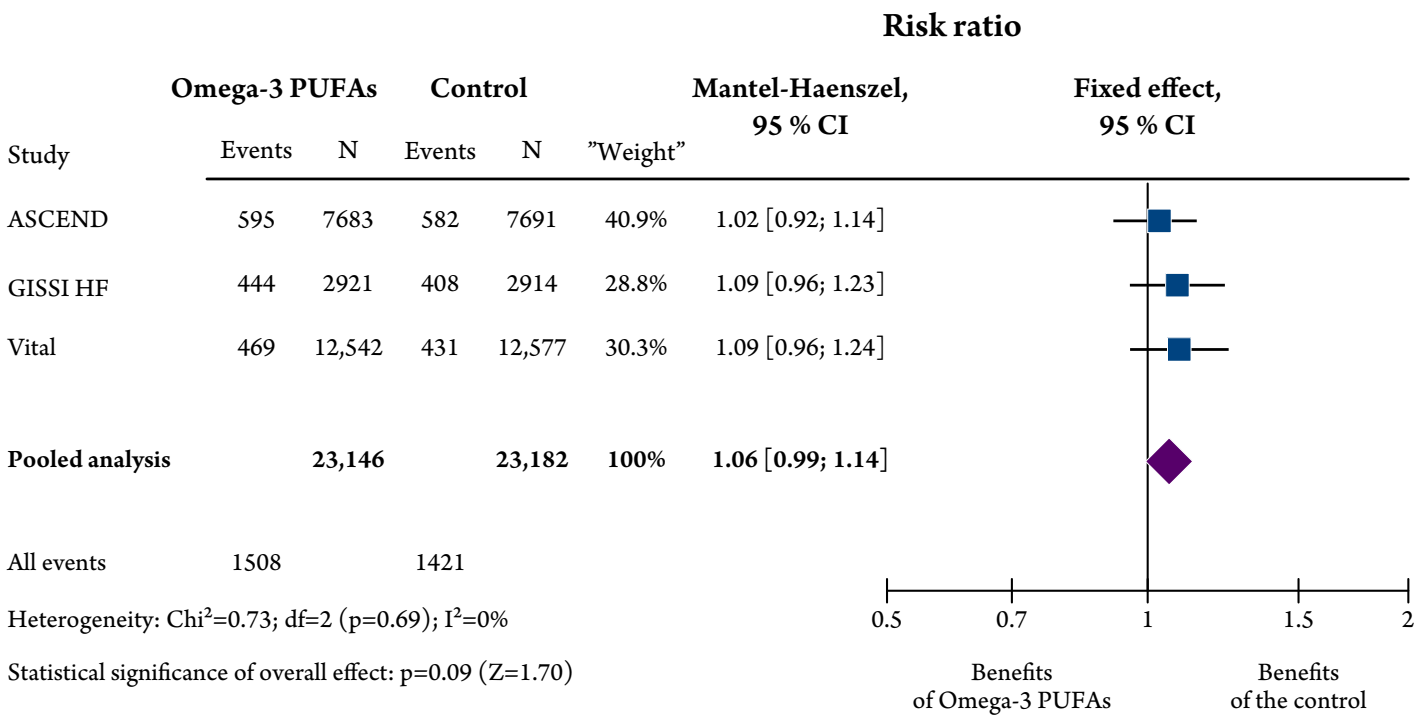
Two additional analyses were carried out specifically for this expert council: the first one included studies of the drug product approved in Russia Omega-3 acids ethyl esters 90, the most pure source of omega-3 PUFAs [4]; the second one included studies using ethyl esters of Omega-3 PUFAs. Data from the supplementary analysis of the ASCEND study are used in both cases [3].

According to the first analysis (3 RCTs, 46,328 patients), there were more cases of AF during the administration of Omega-3 PUFAs than in the placebo group, but the differences were not statistically significant (Figure 1).

The second analysis (5 RCTs, 67,012 patients) with the inclusion of Omega-3 PUFA esters showed an 11% increase in the risk of AF (Figure 2). The number needed to harm was 200 patients, that is the risk of developing AF during the administration of omega-3 PUFA esters was low.

Low risk of AF during the use of omega-3 PUFAs was confirmed by the findings of the FORWARD RCT (n=586) in patients with persistent AF following electrical cardioversion or paroxysmal AF [5] and a meta-analysis of studies of omega-3 PUFAs used to prevent repeated paroxysms and postoperative AF in patients after coronary artery bypass grafting (CABG) [6]. Moreover, Russian RCTs showed a decrease in the risk of postoperative AF during the administration of omega-3 PUFAs following CABG [7, 8], which was also demonstrated by the results of a meta-analysis of studies of omega-3 PUFAs used for the prevention of postoperative AF [9].

Figure 1. Meta-analysis of studies assessing the risk of atrial fibrillation during the administration of Omega-3 acid ethyl esters 90



PUFA, polyunsaturated fatty acids; CI, confidence interval.

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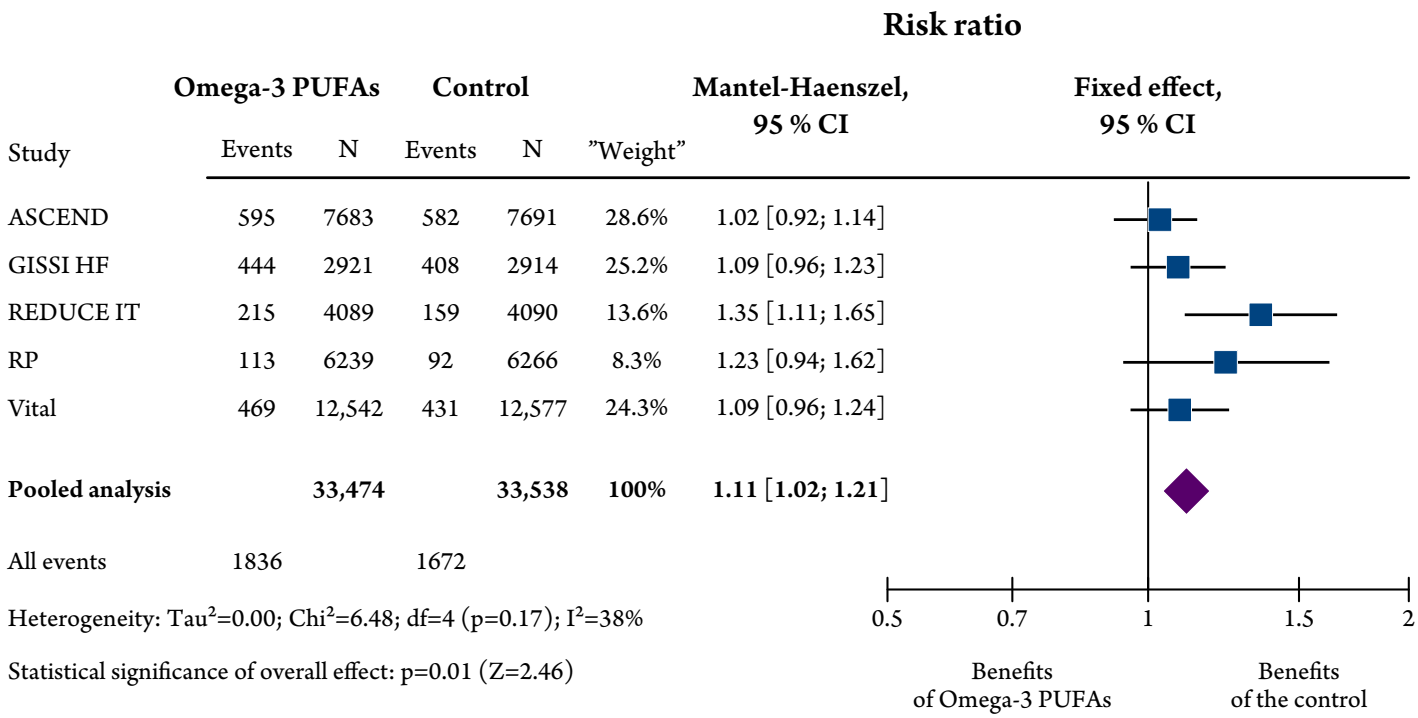
Figure 2. Meta-analysis of studies evaluating the risk of atrial fibrillation during the used of omega-3 PUFA esters



PUFA, polyunsaturated fatty acids; CI, confidence interval.

Indications for the use of omega-3 PUFAs in the Russian and foreign clinical guidelines

The discussion of modern indications is relevant given the findings of the meta-analysis with the described minor increase in the risk of AF in patients who take Omega-3 PUFAs.

Indications for omega-3 PUFAs included in the clinical guidelines are presented in the table. Omega-3 PUFAs are mainly used in patients with chronic heart failure (CHF) or high triglyceride levels.

It should be borne in mind that the indications provided in a package insert may differ from the indications included in the clinical guidelines. The only omega-3 PUFA product approved in the Russian Federation have the following indications in the package insert [17]:

- hypertriglyceridemia: endogenous hypertriglyceridemia of Fredrickson type IV (monotherapy) as an addition to a hypolipidemic diet if it is ineffective; endogenous hypertriglyceridemia of Fredrickson type IIb or III in combination with inhibitors of 3 hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase (statins), when statins fail to sufficiently control triglyceride levels;
- secondary prevention after myocardial infarction (as part of combination therapy): in combination with statins, antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors.

Administration of omega-3 PUFAs in patients with CHF

The efficacy of omega-3 PUFAs in patients with CHF was studied in the GISSI-HF study. The study included 6,975 patients who were divided into 2 groups and received either omega-3 PUFAs (eicosapentaenoic and docosahexaenoic acid esters 1 g) or placebo; the median follow-up period was 3.9 years. Omega-3 PUFAs reduced the risk of all-cause death by 9% (HR 0.91; 95% CI 0.883–0.998; p=0.041) and the composite endpoint (death or hospitalization for cardiovascular causes) by 8% (HR 0.92; 95% CI 0.849–0.999; p=0.009). According to the study, it was necessary to treat 56 people for 3.9 years to avoid one death [18]. Moreover, the risk of hospitalization for ventricular arrhythmias decreased by 28% (p=0.013) in the treatment group, and according to the subgroup analysis (GISSI-HF), the use of omega-3 PUFAs, compared to placebo, reduced the risk of implantable cardioverter-defibrillator (ICD) discharges (HR 0.68; 95% CI 0.48–0.98; p=0.0372), but not the risk of discharges of synchronizer-defibrillators [19]. The GISSI-HF findings suggest the effect of omega-3 PUFAs on ventricular arrhythmias caused by electrical destabilization of the damaged cardiomyocyte membrane in CHF.

The OMEGA-REMODEL (2015) study confirmed that omega-3 PUFAs can positively influence the processes of reverse remodeling in patients receiving modern treatment [20]. The study included 358 patients with a

history of acute myocardial infarction (MI) (day 4–28). Patients were divided in the omega-3 PUFA 4 g/day group and the placebo group. Left ventricular end-systolic volume index decreased in the treatment group according to magnetic resonance imaging performed before and after 6 months of follow-up. Using the omega-3 PUFA dose of 4 g instead of 1 g was not accidental. The European and Russian studies showed that higher doses of omega-3 PUFA are associated with the positive effect on the processes of left ventricular reverse remodeling [21] and heart rhythm variability [22]. These data suggest that doses of omega-3 PUFAs should be taken into account in further studies [23].

According to the 2021 meta-analysis [24] (12 RCTs, 81,364 patients), omega-3 PUFAs reduced the number of repeated hospitalizations for CHF (HR 0.91; 95% CI 0.85–0.98; p = 0.02). It should be noted that the meta-analysis included studies, in which omega-3 PUFAs were studied in patients with CHF (e.g., GISSI-HF) and patients with CVDs, or those facing high risk of developing them, and hospitalizations for CHF were considered as additional endpoints (e.g., VITAL, REDUCE-IT). The doses of omega-3 PUFAs varied from 1 g/day to 6 g/day in different studies.

Administration of omega-3 PUFAs in patients with high triglyceride levels

Hypertriglyceridemia in patients with CVDs or patients at high risk of CVDs is an indication for the administration of omega-3 PUFAs (Table 1). The efficacy of omega-3 PUFAs in such patients was shown in the REDUCE-IT study (n=8,179), which showed that the use of 4 g of eicosapentaenoic acid esters, compared to placebo (mineral oil), reduced the risk of developing cardiovascular complications in patients at high risk of CVDs and patients with documented CVDs [25] and triglyceride levels of 1.52–5.63 mmol/L.

The possibility of using omega-3 PUFAs as carboxylic acids in patients at high risk of CVDs and patients with documented CVDs and elevated triglyceride levels (2.0–5.6 mmol/L) was studied in the STRENGTH study (n=13,078 patients) [26]. There were no differences in the incidence of cardiovascular complications during the use of 4 g of a eicosapentaenoic and docosahexaenoic acid products or placebo (corn oil).

When this paper was published, a serious debate arose about the reasons for the differences between the REDUCE-IT and STRENGTH findings [27]. The following facts were discussed: different composition of omega-3 PUFAs (different ratios of eicosapentaenoic and docosahexaenoic acids and different forms of omega-3 PUFAs: ethyl esters and carboxylic acids).

The administration of mineral oil in the REDUCE-IT study could worsen patients' condition in the control group [28]. However, it should be borne in mind that experimental studies showed mineral oil to be safe, and JELIS RCT showed a decrease in the risk of cardiovascular complications during the use of 1.8 g of eicosapentaenoic acid [29] yet the study was open-label.

In the REDUCE-IT study, there were more patients with coronary artery disease (CAD) (71% vs. 56%) and the higher number of associated complications (22.0% and 12.2% in the placebo groups in REDUCE IT and STRENGTH, respectively).

Other indications for omega-3 PUFAs

The effect of omega-3 PUFAs on the risk of developing CVDs in different patient populations was extensively studied. In 2021, a meta-analysis of all RCTs for the use of omega-3 PUFAs with data on cardiovascular outcomes (40 RCTs, 135,267 patients) was presented [30]. It should be borne in mind that the meta-analysis included RCTs, which included patients with different diseases and used different doses of omega-3 PUFAs. The effects of omega-3 PUFAs may vary depending on the dose and category of patients.

According to this meta-analysis, the rate of acute MI (HR 0.87; 95% CI 0.80–0.96), CAD-related complications (HR 0.90; 95% CI 0.84–0.97), and CAD-related deaths (HR 0.91; 95% CI 0.85–0.98) decreased during the use of omega-3 PUFAs. The study explored different doses of omega-3 PUFAs (from 400 mg to 5500 mg, mean dose 1211 mg/day). A regression analysis showed that increasing the dose of omega-3 PUFA by 1 g/day results in a 5.8% decrease in the risk (p<0.01). There were no differences in effects in the studies using eicosapentaenoic acid monotherapy and the combination of eicosapentaenoic and docosahexaenoic acids. The meta-analysis does not include the results of recent large RCTs STRENGTH and OMEMI.

It should be borne in mind that the effects of omega-3 PUFAs are likely to differ depending on the amount of fish consumed by the subjects as well as the dose of the drug and the category of patients, but also on. According to the VITAL study (n=25,871), which studied the use of a combination of eicosapentaenoic and docosahexaenoic acids (1 g of omega-3 PUFAs) for the primary CVD prevention, there was no decrease in the incidence of cardiovascular complications during the use of omega-3 PUFAs. Subgroup analysis showed a lower risk of complications in patients consuming less than 1.5 servings of fish per week (a 19% reduction; HR 0.81; 95% CI 0.67–0.98). The results of subgroup analysis should always be treated with caution, these findings may have biological implications.

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Table 1. Indications for the use of omega-3 PUFAs according to the Russian and foreign clinical guidelines

Guideline	Indication
Chronic heart failure	
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [10]	Using omega-3 PUFAs may be considered in patients with CHF NYHA class II–IV as an add-on to reduce the risk of death and hospitalization for cardiovascular causes (2B, B-R)
Chronic heart failure 2020 Russian Society of Cardiology Clinical Guideline [11]	For patients with CHF who receive standard therapy with beta-blockers, ACEinhibitors/ARBs/ valsartan + sacubitril, aldosterone antagonists and diuretics, it is advisable to consider the use of omega-3 PUFAs, triglycerides, including other esters and acids, to improve the prognosis. ESC IIb/ (grade of recommendation C and level of evidence 2)
Patients with high triglyceride levels	
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice [12]	For patients at high risk with triglyceride levels > 1.5 mmol/L (135 mg/dL) despite statin therapy and lifestyle changes, omega-3 PUFAs (icosapent ethyl 2 g twice daily) can be considered in combination with statins (IIb B)
2019 ESC/EAS Guidelines on the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk [13]	For patients at high risk with triglyceride levels 1.5–5.6 mmol/L (135–499 mg/dL) despite statin therapy, omega-3 PUFAs (icosapent ethyl 2 g twice daily) should be considered in combination with statins (IIa B)
Diagnosis and correction of lipid metabolism disorders for the prevention and treatment of atherosclerosis (2020) [14]	In patients at high or very high-risk patients with triglyceride levels of 1.5-5.6 mmol/L, despite statin therapy, add fenofibrate and, if the effect is insufficient or in case of fenofibrate intolerance, add omega-3 PUFA 2 g twice daily (IIa B)
	In patients at high risk who reached the target levels of low-density lipoprotein cholesterol and triglyceride levels >2.3 mmol/L; in case of intolerance, add omega-3 PUFA 2 g twice daily (IIb C)
Patients with diabetes mellitus or pre-diabetes	
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [15]	If the target levels of triglycerides are not reached during statin and fibrate therapy, adding high-dose omega-3 PUFAs (4 g/day) or icosapent ethyl can be considered
2022 Standards of Medical Care in Diabetes [16]	1. Patients with diabetes mellitus should be recommended to change lifestyle aiming at reducing body weight (if necessary), DASH (Dietary Approaches to Stop Hypertension), or the Mediterranean diet, reducing intake of saturated fats and trans fats, increasing intake of omega-3 PUFAs, soluble fiber, and plant stanols with food, and increasing physical activity to improve blood lipid profile and reduce the risk of atherosclerotic CVDs (A)
	2. Adding ethyl icosapents to reduce the risk of CVDs can be considered for patients with diabetes mellitus and atherosclerotic CVDs or other CVD risk factors who receive statins and have control amenable low-density lipoprotein cholesterol levels but elevated triglyceride levels (135–499 mg/dL) (A)

HFrEF, heart failure with reduced ejection fraction; ESC, European Society of Cardiology.

Using omega-3 PUFAs in patients after acute MI receives special attention. Classic study GISSI-Prevenzione that included 5,666 patients showed that the administration of 1 g of omega-3 PUFAs reduced the risk of a composite endpoint (death, non-fatal acute MI, and stroke) in patients with a recent history of acute MI (≤3 months) [31]. The GISSI-Prevenzione study was conducted before the widespread use of emergency revascularization and statins for patients with acute MI. In 2010, the OMEGA study was conducted, which included 3,851 patients receiving relevant acute MI therapy, of whom 77.8% underwent emergency stenting, and the majority of patients did not have systolic dysfunction. The use of esters of 1 g of omega-3 PUFAs did not result in better outcomes compared to placebo (olive oil) [32]. In 2018, a meta-analysis was published that did not reveal a decrease in the risk of cardiovascular complications during the use of omega-3 PUFAs in patients with CAD [33].

In 2020, double-blind RCT OMEMI (n=1027) was published, in which the efficacy of a dietary supplement containing 1.8 g of omega-3 PUFAs (a combination of eicosapentaenoic and docosahexaenoic acids) was evaluated in 70–82-year old patients who had suffered acute MI within 2–8 weeks before the enrollment. The use of this form of omega-3 PUFA, compared to placebo (corn oil), did not affect the prognosis [34]. At the same time, the subgroup

analysis of the OMEMI study showed a decrease in the risk of cardiovascular complications depending on the achieved concentration of eicosapentaenoic acid, but the risk of developing AF also increased with its blood levels [35]. Moreover, 4 g of eicosapentaenoic acid reduced the risk of developing cardiovascular complications in patients with a history of MI, according to the subgroup analysis of the REDUCE-IT study [36].

Chronic kidney disease is another indication for the use of omega-3 PUFAs. According to the subgroup analysis of the REDUCE-IT study, the incidence of cardiovascular complications decreased in patients with normal and reduced glomerular filtration rates during the use of 4 g of eicosapentaenoic acid [37]. The 2020 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on nutrition of patients with chronic kidney disease (CKD) recommend adding omega-3 PUFAs to diet therapy in order to normalize blood lipid profile in patients with kidney disease in the following cases [38]:

- The use of 1.3–4 g/day of long-chain omega-3 PUFAs are recommended in adult patients with CKD stage V who receive maintenance hemodialysis, which can be considered as a means to reduce triglycerides and low-density lipoprotein cholesterol (2C) and increase high-density lipoprotein cholesterol (2D).
- The administration of 1.3–4 g/day of long-chain omega-3 PUFAs is reasonable to improve blood lipid profile in adult patients with CKD stage V who receive peritoneal dialysis (expert opinion);
- The use of 2 g/day of long-chain omega-3 PUFAs is recommended in adult patients with CKD stage III–V to reduce triglyceride levels (2C).

Conclusion

The meta-analysis conducted to study the risk of atrial fibrillation in patients during the administration of omega-3 polyunsaturated fatty acids showed an increased risk of developing this type of arrhythmia. However, given the incidence of atrial fibrillation in the ASCEND study, the low risk of complications and the lack of statistically significant increase in the risk of atrial fibrillation during the use of omega-3 polyunsaturated fatty acids at a dose of ≤ 1 g and the standard dose of the only product approved in the Russian Federation, omega-3 polyunsaturated fatty acids, should be taken into account.

According to the Russian and international clinical guidelines, the use of omega-3 polyunsaturated fatty acids can be considered in the following categories:

- Patients with chronic heart failure with reduced left ventricular ejection fraction in addition to the main therapy (Indication Class 2b, the 2020 Russian Society of Cardiology Guideline and the 2022 AHA/ACC/HFSA Guideline) [10, 11];
- Patients with hypertriglyceridemia (>1.5 mmol/L) in a combination therapy (indication class IIb, level of evidence B, the 2021 ESC Guideline on the cardiovascular disease prevention);
- Adult patients with chronic kidney disease stage III–V, long-chain omega-3 polyunsaturated fatty acids 2 g/day, to reduce triglyceride levels (2C).

Findings of the studies of omega-3 polyunsaturated fatty acids for other indications are heterogeneous, which can be partially explained by the use of different forms and doses of drugs.

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Conflict of interest

The authors declare that they gave scientific presentations at symposia and/or spoke at events organized by Abbott Laboratories.

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