

# Polyunsaturated omega-3 fatty acids improve responsiveness to clopidogrel after percutaneous coronary intervention in patients with cytochrome P450 2C19 loss-of-function polymorphism

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## Abstract

**Background:** Antiplatelet properties of omega-3 polyunsaturated fatty acids (PUFA) have been demonstrated in patients with coronary artery disease (CAD). It is unknown whether omega-3 PUFA can enhance platelet inhibition on standard aspirin and clopidogrel treatment in the setting of CYP2C19 loss-of-function polymorphism.

**Aim:** To investigate whether omega-3 PUFA are able to modify platelet responsiveness to clopidogrel therapy in patients with CYP2C19 loss-of-function polymorphism undergoing percutaneous coronary intervention (PCI).

**Methods:** 63 patients with stable CAD undergoing PCI (48 males, mean age  $63.2 \pm 9.6$  years) were enrolled into an investigator-initiated, prospective, single-centre, double-blind, placebo-controlled, randomised study. Patients on standard dual antiplatelet therapy (aspirin 75 mg daily and clopidogrel 600 mg loading dose followed by 75 mg daily) were assigned to receive the addition of 1 g of omega-3 ethyl esters ( $n = 33$ ) or placebo ( $n = 30$ ) for 1 month. Platelet function was measured serially by light transmittance aggregometry in response to 5 and 20  $\mu\text{mol/L}$  ADP at baseline, 12 h, 3–5 days and 30 days after randomisation. CYP2C19\*2 was genotyped at baseline.

**Results:** No significant differences were found in baseline variables, including the frequency of CYP2C19 genetic variants. At least one loss-of-function variant of CYP2C19\*2 was found in 19 (30.2%) patients. In patients with CYP2C19\*1/\*2 and \*2/\*2 variants, maximal platelet aggregation induced by 5 and 20  $\mu\text{mol/L}$  ADP was reduced by 21.4% ( $p = 0.006$ ) and 14.3% ( $p = 0.041$ ), respectively, after 1 month of treatment with omega-3 PUFA as compared to placebo. The beneficial effect of omega-3 PUFA was demonstrated in carriers of CYP2C19 loss-of-function polymorphism, whereas no differences in platelet aggregation between the omega-3 PUFA and placebo groups were found in patients with the 1\*/1\* variant.

**Conclusions:** The addition of omega-3 ethyl esters significantly potentiates platelet response to clopidogrel after PCI mostly in patients with CYP2C19 loss-of-function polymorphism.

**Key words:** angioplasty, clopidogrel, CYP2C19 polymorphism, fish oils

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## INTRODUCTION

Percutaneous coronary intervention (PCI) with stenting is one of the therapeutic approaches in patients with coronary artery disease (CAD), and dual antiplatelet treatment with acetylsalicylic acid (ASA) and clopidogrel is recommended after PCI [1]. However, genetic polymorphisms affecting either clopidogrel metabolism or ADP receptor may be a significant cause of inappropriate response to this drug [2, 3]. Clopidogrel is inactive prodrug that requires double oxidation by the hepatic cytochrome P450 (CYP) to become biologically active [3]. Hepatic enzymes involved in clopidogrel metabolism include CYP1A2, CYP2B6, CYP2C19, CYP3A4/A5, and CYP2C9 [3, 4], and their abnormal activity may be associated with altered plasma levels of active clopidogrel metabolite. Such variability may also result from polymorphisms of genes coding particular CYP enzymes [3]. Clopidogrel metabolism and antiplatelet effect has been shown to be reduced in CYP2C19 681G>A\*2 allele carriers (\*2 refers to the mutated 681A allele, and \*1 to the wild-type 681G allele) [2, 3]. The prevalence of the mutated CYP2C19 681G>A\*2 allele varied depending on the study population [2, 3]. In a study by Malek et al. [2] in a group of 105 Polish patients with acute coronary syndromes, the prevalence of the 681A allele was 20%. Other common mutation, which is in turn associated with ultrarapid enzyme activity, involves the CYP2C19\*17 (C/T) T-allele, which also occurs with varying frequency in different populations, ranging from 4% in China to 20% in Sweden, Ethiopia and New Zealand [3]. Among patients with myocardial infarction treated with clopidogrel, the presence of CYP2C19\*17 (C/T) T-allele was found to be associated with a 22% reduction in major adverse cardiovascular (CV) events at 1 year [5]. Other CYP2C19 polymorphisms associated with reduced activity, \*3 and \*4, are much less frequent. Despite accumulating evidence that even the presence of a single CYP2C19 allele resulting in reduced enzyme activity in patients after PCI is associated with an increased rate of major CV events including in-stent thrombosis [6], clinical significance of these observations and optimal approach to patients with loss-of-function CYP2C19 polymorphisms require further studies.

In the OMEGA-PCI study, we have previously shown that omega-3 polyunsaturated fatty acids (PUFA) given to patients on dual antiplatelet treatment after PCI favourably modify platelet response to clopidogrel [7]. In that study, triple therapy with ASA, clopidogrel and omega-3 PUFA increased platelet inhibition as measured by their response to stimulation with ADP as compared to standard dual antiplatelet therapy [7]. Similar effect of omega-3 PUFA was later confirmed both in healthy volunteers and in patients with CAD [8, 9]. Antiplatelet activity of much larger doses of omega-3 PUFA was previously investigated in patients who were receiving neither ASA nor clopidogrel [10].

The mechanism underlying improved response to clopidogrel elicited by coadministration of omega-3 PUFA has not

been clarified. We aimed to evaluate the prevalence of CYP2C19 polymorphisms associated with loss-of-function or reduced enzyme activity in patients with stable CAD after PCI and their effect on platelet reactivity during treatment with ASA, clopidogrel, and omega-3 PUFA. The present study is an extension of the previously published OMEGA-PCI study [7].

## METHODS

Characteristics of the study group, inclusion and exclusion criteria, and the methodology used were described previously [7]. Below, we briefly summarised the most important facts.

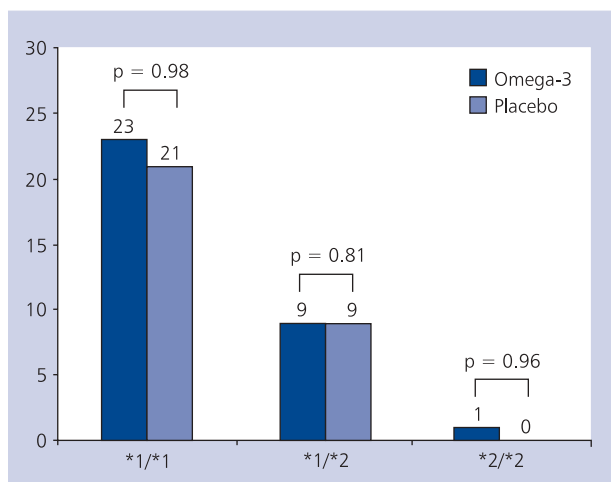
The study group included 63 consecutive patients (48 men, 76.2%; mean age  $63.1 \pm 9.6$  years) with stable CAD who underwent successful PCI with stenting and gave an informed consent for participation in the study.

The study was prospective, randomised, double-blind, and placebo-controlled. Patients were recruited into the study after elective coronary angiography was performed and indications for PCI were established. They were randomly assigned to the receive 1000 mg of omega-3 PUFA (Omacor, PronovaBiocare/Solvay Pharma, Poland, containing 460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA] in a single capsule) or 1000 mg of soybean oil in a single capsule (placebo group). Both in the omega-3 PUFA and the placebo group, the assigned medication was taken once daily for 4 weeks. Initial doses of omega-3 PUFA or placebo were administered together with the loading dose of clopidogrel, 12 to 14 h before PCI. In the next days, all patients received 75 mg of ASA and 75 mg of clopidogrel once daily for 1 month. During that time, other medications were kept unchanged and used in accordance with the current guidelines.

Laboratory testing of platelet reactivity, other laboratory tests and clinical evaluation were performed on four occasions: before administering clopidogrel and omega-3 PUFA or placebo, immediately before PCI, i.e. 12–14 h after administering clopidogrel and omega-3 PUFA or placebo, 3–5 days after PCI, and 1 month after randomisation. Blood for genetic testing was collected before initiation of clopidogrel and omega-3 PUFA or placebo administration. Follow-up laboratory testing at 1 month was not possible in 1 patient in the placebo group and 1 patient in the omega-3 PUFA group.

The study was approved by the ethics committee at the Jagiellonian University and performed in accordance with the guidelines of Good Clinical Practice of the International Conference on Harmonisation (GCP ISH).

Platelet reactivity was determined by light transmittance aggregometry (LTA) upon stimulation with 5 and 20  $\mu\text{mol/L}$  of ADP (Chrono-Log Model 700, Chrono-Log Corp, Haverton, USA) [11]. CYP219 polymorphism was detected using commercially available Drug Metabolism Genotyping Assay kits (TaqMan MGB probes, FAM and VIC dye-labelled). Details were described previously [7].



**Figure 1.** Distribution of CYP2C19\*2 variant in the study groups; data are shown as absolute numbers.

**Statistical analysis**

All continuous variables were expressed as mean values ± SD, and categorical variables were expressed as numbers and percentages. The Kolmogorov-Smirnov test was used to determine normal distribution. The Student t-test was used for normally distributed continuous variables; otherwise, the Mann-Whitney U test was applied. Differences in categorical variables between the study groups were tested using the χ<sup>2</sup> test (with the Yates correction). Intragroup variability in both groups was tested using the Student t-test for paired samples and the nonparametric paired-sample Wilcoxon signed rank test. When more than two variables from the same sample were compared, we used ANOVA for repeated measured or the nonparametric Friedman analysis of variance and Kendall’s coefficient of concordance. All statistical tests were two-sided. Statistical analysis was performed using the STATISTICA 8.0 PL package.

**RESULTS**

Baseline characteristics of the study groups were described previously [7]. Of note, the two groups did not differ in regard to age, gender, body mass index, prevalence of CV risk factors, duration of CAD symptoms, prevalence of previous

myocardial infarction, revascularisation procedures, stroke and symptoms of intermittent claudication, and the results of standard clinical biochemistry testing.

A trend towards a higher prevalence of multivessel CAD was noted in the omega-3 PUFA group (p = 0.056), but other angiographic and procedural variables did not differ significantly between the groups [7].

We also did not find any significant differences between the study groups in regard to concomitant drug therapy, in particular medications that could interfere with the hepatic metabolism of clopidogrel [7].

**CYP2C19 polymorphism and platelet reactivity**

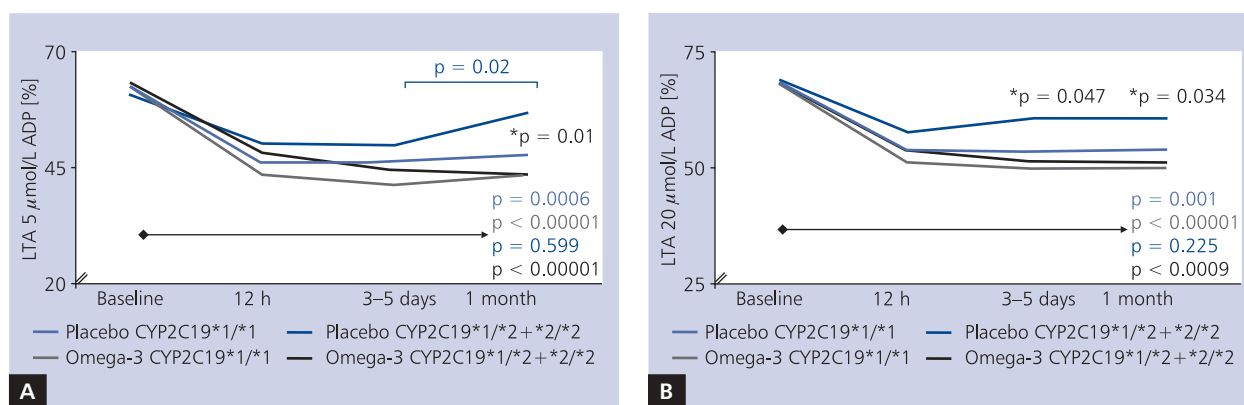
Distribution of CYP2C19 gene polymorphism variants is shown in Figure 1. No loss-of-function \*2 allele was found in 44 (69.8%) patients in the study group. Eighteen (28.6%) patients were carriers of a single CYP2C19 681G>A\*2 allele, and 1 patient was found to have two \*2 alleles. We did not find any differences in the distribution of CYP2C19 alleles between patients assigned to omega-3 PUFA or placebo. The frequency of the G allele was 51/60 (85%) in the placebo group and 55/66 (83.3%) in the omega-3 PUFA group (p = 0.8). Both the placebo group and the omega-3 PUFA group were at genetic equilibrium in regard to this single nucleotide polymorphism (SNP).

We found differences in the response to clopidogrel between the placebo group and the omega-3 PUFA group that were related to the presence of the loss-of-function CYP2C19 gene variant. In patients with CYP2C19\*1/\*1 variant, no differences in the response to clopidogrel were noted at baseline, at 3–5 days and at 1 month between the omega-3 PUFA group and the placebo group (Table 1, Figs. 2A, B).

In patients who were carriers of at least one loss-of-function allele, platelet reactivity upon stimulation with ADP was lower both at 3–5 days and at 1 month of treatment when these patients were additionally receiving omega-3 PUFA (Table 2, Figs. 2A, B). Among patients with CYP2C19\*1/\*2 and \*2/\*2 variants, mean maximum platelet aggregation upon stimulation with 5 μmol/L ADP at 1 month of treatment was 43.4 ± 5.2% in the omega-3 PUFA group compared to 55.2 ± 11.6% in the placebo group (p = 0.006). Thus, 1-month treatment with omega-3 PUFA resulted in an additional inhi-

**Table 1.** Platelet reactivity during treatment with ASA, clopidogrel, and omega-3 PUFA/placebo in patients with the CYP2C19\*1/\*1 variant

	Platelet aggregation in patients with CYP2C19*1/*1 variant [%]			
	ADP 5 μmol/L	ADP 20 μmol/L	ADP 5 μmol/L	ADP 20 μmol/L
Time point	At 3–5 days		At 1 month	
Placebo	46.8 ± 14.1	54.3 ± 17.9	48.1 ± 10.6	54.7 ± 10.6
Omega-3 PUFA	41.3 ± 12.5	50.3 ± 12.3	43.5 ± 10.5	50.5 ± 8.2
P (placebo vs omega-3 PUFA)	0.109	0.212	0.123	0.109



**Figure 2.** Maximum platelet aggregation upon stimulation with 5 mmol/L (A) and with 20 mmol/L (B) ADP in the study groups before percutaneous coronary intervention and at 1 month depending on the presence of the loss-of-function CYP2C19 variants (\*1/\*2 and \*2/\*2). Differences between the study groups are marked with an asterisk. Intragroup differences during follow-up are marked with a solid line of the same colour as the graph for a given group. Below, arrows indicate changes that occurred during the study (measurement I compared with measurement IV), with data on statistical significance coloured the same as the graph for a given group; \*placebo CYP2C19\*1/\*2 + \*2/\*2 vs omega-3 PUFA CYP2C19\*1/\*2 + \*2/\*2

**Table 2.** Platelet reactivity during treatment with ASA, clopidogrel, and omega-3 PUFA/placebo in patients with the CYP2C19\*1/\*2 and \*2/\*2 variants

	Platelet aggregation in patients with CYP2C19*1/*1 variant [%]			
	ADP 5 μmol/L		ADP 20 μmol/L	
Time point	At 3–5 days		At 1 month	
Placebo	49.9 ± 9.7	61.4 ± 10.7	55.2 ± 11.6	60.2 ± 9.7
Omega-3 PUFA	44.4 ± 10.7	51.9 ± 8.0	43.4 ± 5.2	51.6 ± 6.4
P (placebo vs omega-3 PUFA)	0.310	0.048	0.006	0.041

hibition of platelet aggregation upon stimulation with 5 μmol/L ADP by more than 27%. In patients with CYP2C19\*1/\*2 and \*2/\*2 variants treated with omega-3 PUFA, we also noted significantly lower platelet aggregation upon stimulation with 20 μmol/L ADP at both 3–5 days ( $p = 0.048$ ) and 1 month ( $p = 0.041$ ) compared to the control group. Thus, 1-month treatment with omega-3 PUFA resulted in an additional inhibition of platelet aggregation upon stimulation with 20 μmol/L ADP by nearly 17%.

Compared to the baseline values before clopidogrel administration, platelet reactivity at 1 month was significantly lower among patients receiving omega-3 PUFA regardless of the CYP2C19 polymorphism (LTA upon stimulation with 5 μmol/L ADP:  $p < 0.00001$  for all genetic variants) (Figs. 2A, B). Treatment with omega-3 PUFA was therefore associated with low level of platelet reactivity between 12 h after initial administration of omega-3 PUFA and 1 month of this treatment regardless of the CYP2C19 polymorphism.

Response to clopidogrel in patients receiving omega-3 PUFA was similar regardless of the presence of the loss-

-of-function CYP2C19 allele (Figs. 2A, B). As mentioned above, a reduced effect of clopidogrel was noted in patients with CYP2C19\*1/\*2 and \*2/\*2 variants who received placebo. At 1 month in the placebo group, no significant platelet inhibition in response to clopidogrel compared to the baseline values was observed in patients with CYP2C19\*1/\*2 and \*2/\*2 variants ( $p = 0.6$  for LTA upon stimulation with 5 μmol/L ADP,  $p = 0.23$  for LTA upon stimulation with 20 μmol/L ADP).

### Adverse effects

Adverse effects related to the study treatment were described previously [7]. They were mild and their rate did not differ between the placebo and omega-3 PUFA groups. Mild gastrointestinal discomfort (mild diarrhoea, abdominal pain, dyspepsia or nausea lasting less than 72 h) that did not require any additional intervention was noted in 2 patients in the placebo group and 3 patients in the omega-3 PUFA group. One patient stopped taking the study drug without specifying the reason.

## DISCUSSION

Varying response to clopidogrel observed in clinical practice prompted many cardiology centres to study new approaches to improve antiplatelet effect of this drug in patients after PCI. Results of some recent trials, including the GRAVITAS study, cast doubt on the effectiveness of the double maintenance dose of clopidogrel (150 mg) that was hoped to improve outcomes in patients with sustained high platelet reactivity during administration of the standard maintenance dose [12]. However, recent studies by Cuisset et al. [12] indicate that the limited effectiveness of increased maintenance dose of clopidogrel is seen mostly in patients with the loss-of-function CYP2C19\*2 variant [12]. Thus, further studies to define optimal antiplatelet treatment after PCI should particularly target this patient group.

The present study is a subanalysis of our previously published, relatively small randomised study [7] in which we clearly demonstrated that addition of omega-3 PUFA to standard dual antiplatelet therapy with ASA and clopidogrel was associated with a significant reduction of platelet reactivity compared to placebo. That study did not explain, however, the potential mechanism underlying the beneficial effect of omega-3 PUFA. In our present subanalysis, we attempted to clarify the effect of CYP2C19 gene polymorphism on the response of platelet reactivity to omega-3 PUFA administration. We showed that the effect of omega-3 PUFA was particularly beneficial in patients with the loss-of-function CYP2C19 variant. When such patients were on placebo, platelet reactivity was found to be increased despite dual antiplatelet therapy. In contrast, patients with this genetic variant who were administered omega-3 PUFA showed an antiplatelet response similar to that observed in patients with the wild-type allele.

Mechanisms of this beneficial alteration of the antiplatelet effect of clopidogrel in carriers of the loss-of-function CYP2C19 gene variant may be varied [13]. Omega-3 PUFA were shown to affect properties of the platelet membrane, its receptors and ion channels, and thus may potentially modify intracellular signal transduction pathways upon activation of the P2Y<sub>12</sub> receptor [10]. Omega-3 PUFA may also affect metabolic processes related to CYP activity. PUFA and related eicosanoids were shown to be metabolised by the CYP system [14]. Some of these eicosanoids play an active role in platelet activation and blood clotting. Most literature data refer to arachidonic acid which is oxidised, epoxidised, and hydroxylated by the CYP system [13]. These processes result in formation of hydroxyeicosatetraenoic and epoxyeicosatrienoic acids [14]. The latter epoxide products of arachidonic acid metabolism, also known as oxylipids, play complex and often counter-regulatory autocrine and paracrine roles in the CV system [15]. In particular, epoxyeicosatrienoic acids were shown to exert a beneficial vasodilating and anti-inflammatory effect [15]. There are few data in the literature regarding CYP-related metabolism of omega-3 PUFA and interactions

with arachidonic acid metabolism or drugs metabolised by the CYP system. Seminal studies by the group of Vane and Gryglewski [16] showed that EPA inhibits conversion of arachidonic acid into thromboxane A<sub>2</sub> and prostacyclin. Gryglewski et al. [16] also noted that analogues synthesised from EPA show reduced proaggregatory properties (TXA<sub>3</sub> vs TXA<sub>2</sub>) but preserved antiaggregatory properties (PGI<sub>3</sub> vs PGI<sub>2</sub>). Recently, Fer et al. [17] showed that CYP2C9, CYP2C19 and CYP1A2 are physiologically most active in the epoxidation of EPA and DHA [17]. As the same CYP isoforms also metabolise arachidonic acid, Fer et al. [17] were able to demonstrate experimentally that administration of EPA and DHA reduces production of epoxide derivatives of arachidonic acid by 80% and 60%, respectively. As a result, it may shift production of the biologically active eicosanoids from arachidonic acid derivatives to EPA derivatives [17, 18]. The role of CYP-related metabolites of omega-3 PUFA was recently highlighted by Arnold et al. [19] who reviewed experimental and clinical studies in this area and found that these metabolites may be partially responsible for the beneficial effects of omega-3 PUFA in the CV system [19]. The effect of these interactions on platelet activation and blood clotting has not been studied yet. There are also no data in the literature regarding the effect of omega-3 PUFA on clopidogrel metabolism, despite the fact that both are metabolised by similar CYP isoforms (CYP2C9, CYP2C19).

Our findings, indicating the ability to improve platelet response to clopidogrel by coadministering omega-3 PUFA in CAD patients treated with PCI who are carriers of the loss-of-function CYP2C19 genetic variant, may be of significant clinical importance. This is supported by the results of a TRITON-TIMI 38 study subanalysis [20] showing that in patients with the loss-of-function CYP2C19 genetic variant who received invasive treatment of unstable angina pectoris or non-ST segment elevation myocardial infarction, prasugrel reduced the risk of death, recurrent myocardial infarction and stroke by more than 40%. In addition, it has been recently reported that omega-3 PUFA have some other beneficial properties, including decreased thrombin generation, reduction of oxidative stress, and favourable modification of fibrin clot characteristics [21]. These pleiotropic effects of omega-3 PUFA, when combined with standard dual antiplatelet therapy, may in future be of use in patients undergoing PCI [22, 23].

### *Limitations of the study*

We did not evaluate other, more rarely occurring CYP2C19 loss-of-function polymorphisms, e.g. \*3, \*4, and \*5 alleles. The aim of the study was to assess the change in *ex vivo* platelet reactivity after the addition of omega-3 PUFA to standard dual antiplatelet therapy after PCI as compared to placebo. Our study was not designed to evaluate clinical endpoints. Thus, it lacked statistical power to allow any conclusions regarding the rate of CV events in both study groups. We also

did not evaluate the relationship between the dose of omega-3 PUFA and the size of the observed effect of modifying antiplatelet activity of clopidogrel. It cannot be excluded that this effect would be more pronounced with the use of higher doses of omega-3 PUFA.

## CONCLUSIONS

The addition of omega-3 PUFA to dual antiplatelet treatment significantly improves platelet response to clopidogrel only in patients with CYP2C19 loss-of-function polymorphism. Clinical significance of this observation requires verification in further large randomised studies.

**Conflict of interest:** none declared

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# Wielonienasycone kwasy tłuszczowe omega-3 poprawiają odpowiedź na leczenie klopidogrelem po przezskórnej interwencji wieńcowej u chorych będących nosicielami polimorfizmu cytochromu P450 2C19 o typie utraty funkcji

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## Streszczenie

**Wstęp:** Wcześniejsze badania wskazują, że wielonienasycone kwasy tłuszczowe (WKT) omega-3 mają własności przeciwplatek, zarówno stosowane w monoterapii, jak i w skojarzeniu z kwasem acetylosalicylowym (ASA) i/lub klopidogrelem. Nie jest natomiast znany wpływ suplementacji WKT omega-3 na skuteczność leczenia klopidogrelem u chorych poddawanych przezskórnej interwencji wieńcowej (PCI) w zależności od występowania u nich polimorfizmów enzymów cytochromu P450 (CYP) odpowiedzialnego za metabolizm tego leku. Jest to szczególnie istotne u nosicieli odmiany allelu CYP2C19 681G>A\*2 (\*2 oznacza zmutowany allel 681A).

**Cel:** Celem badania była ocena częstości występowania polimorfizmów związanych z utratą lub zmniejszoną aktywnością CYP2C19 (\*2/\*2 lub \*1/\*2) wśród pacjentów ze stabilną chorobą wieńcową poddawanych PCI oraz ich wpływ na reaktywność płytek krwi podczas leczenia ASA, klopidogrelem i WKT omega-3.

**Metody:** Do badania włączono 63 osób ze stabilną chorobą wieńcową poddawanych PCI (48 mężczyzn, śr. wiek chorych 63,2 ± 9,6 roku). Badanie było inicjowane przez badaczy, prowadzone prospektywnie w jednym ośrodku badawczym, metodą podwójnie ślepej próby z randomizacją i kontrolą placebo. Pacjentów poddawanych PCI leczono za pomocą standardowej terapii przeciwplatekowej (ASA 75 mg/d. i klopidogrel w dawce nasycającej 600 mg, a następnie 75 mg/d.), do której dołączono 1000 mg estrów etylowych WKT omega-3 (n = 33) lub placebo (n = 30) na okres miesiąca. Podczas badania towarzysząca farmakoterapia była zgodna z obowiązującymi wytycznymi i nie ulegała zmianie. Ocena laboratoryjną stopnia reaktywności płytek krwi wykonywano 4-krotnie: przed podaniem klopidogrelu i WKT omega-3 lub placebo; 12 h po podaniu klopidogrelu i WKT omega-3 lub placebo, bezpośrednio przed PCI; w ciągu 3–5 dni po PCI oraz miesiąc po randomizacji. Aktywność płytek krwi oznaczano metodą agregometrii optycznej. Agregację płytek krwi indukowano adenylo-dwufosforanem (ADP) o stężeniu 5 i 20 μmol/l. Polimorfizm genetycznego cytochromu P450 2C19 oceniano przed PCI.

**Wyniki:** Porównywane grupy nie różniły się istotnie od siebie pod względem charakterystyki klinicznej, parametrów angiograficznych i zabiegowych oraz towarzyszącej farmakoterapii. Ponadto nie stwierdzono znamiennych różnic w zakresie dystrybucji genetycznej polimorfizmu CYP2C19 między grupami pacjentów, którzy w ramach prowadzonego badania otrzymali WKT omega-3 lub placebo. U 19 (30,2%) chorych występował co najmniej jeden allel o typie utraty funkcji CYP2C19 (\*2). U chorych, którzy byli nosicielami co najmniej jednego allelu o typie utraty funkcji, zarówno w okresie wewnątrzszpitalnym, jak i po miesiącu terapii, reaktywność płytek krwi po stymulacji ADP była niższa niż u tych pacjentów, którzy otrzymywali WKT omega-3. Średnia maksymalna agregacja płytek krwi po stymulacji 5 μmol/l ADP u badanych z polimorfizmem CYP2C19\*1/\*2 i \*2/\*2 otrzymujących WKT omega-3 po miesiącu leczenia wynosiła 43,4 ± 5,2% i była niższa o 12,4% niż u osób otrzymujących placebo, u których była równa 55,2 ± 11,6% (p = 0,006). Wśród chorych będących nosicielami CYP2C19\*1/\*2 i \*2/\*2 leczonych WKT omega-3, w porównaniu z grupą kontrolną, odnotowano także znamienne niższe wartości agregacji płytek krwi po stymulacji 20 μmol/l ADP zarówno po 3–5 dniach (p = 0,048), jak i po miesiącu leczenia (p = 0,041). Z kolei w grupie pacjentów z polimorfizmem CYP2C19\*1/\*1 nie zaobserwowano różnic w odpowiedzi na klopidogrel między grupą chorych leczonych WKT omega-3 a pacjentami otrzymującymi placebo.

**Wnioski:** Suplementacja podwójnej terapii przeciwplatekowej przy zastosowaniu WKT omega-3 jedynie u nosicieli polimorfizmów CYP2C19 o typie utraty funkcji poprawia odpowiedź płytek krwi na leczenie klopidogrelem.

**Słowa kluczowe:** angioplastyka wieńcowa, klopidogrel, polimorfizm CYP2C19, olej rybi

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