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GUT MICROBIOTA MODULATION BY POSTBIOTICS IN PATIENTS WITH CORONARY ARTERY DISEASE AND ATRIAL FIBRILLATION

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The aim: *is to improve gut microbiota composition by the long-term postbiotics (glycine and propionic acid) supplementation in patients with coronary artery disease (CAD) and atrial fibrillation (AF).*
Materials and methods: *40 patients were divided into 3 groups: first (CAD) – 14 patients with CAD but without arrhythmias; second (CAD+AF) – 18 patients with CAD and AF paroxysm; and the control group – 8 patients without CAD and arrhythmias. 16 patients from the II group received basic therapy, according to the latest ESC guidelines, and postbiotic supplementation: rebamipide (2-(4-chlorobenzoylamino)-3-[2(1H))-quinolon-4-yl] propionic acid) by 100 mg 3 times a day and glycine by 100 mg 3 times a day during 6 months. 16-S rRNA sequencing checked gut microbiota composition.*
Results: *The II group patients had a significant rise in Pseudomonadota (by taxonomic analysis), Actinobacter Spp. and a decrease in Blautia Spp., Bacteroides Thetaiotaomicron compared with the I group, P<0.05. Long-term postbiotics supplementation for patients with coronary artery disease and atrial fibrillation leads to a significant decrease in Firmicutes/ Bacteroides ratio, P<0.05; a significant rise in Verrucomicrobiota and a decrease in Firmicutes, P<0.05; a significant increase in Lactobacillus spp., Akkermansia muciniphila, Blautia spp., Prevotella spp. and a decrease in Streptococcus spp. and Methanosphaera stadmanae, P<0.05. A significantly lower F/B ratio was found in the patients with long-term postbiotics supplementation in comparison with placebo group patients, P<0.05. A significant increase in Actinomycetota was found in the patients with long-term postbiotics supplementation compared to placebo group patients, P<0.05. A significant increase in probiotic species (Akkermansia muciniphila, Blautia spp., Eubacterium Rectale, and Prevotella spp.) and a decrease in species, associated with cardiometabolic disorders (Streptococcus spp.) was found in the patients with long term postbiotics supplementation in comparison with placebo group patients, P<0.05.*
Conclusion: *Long-term postbiotics supplementation for patients with coronary artery disease and atrial fibrillation leads to positive gut microbiota modulation*
Keywords: *coronary artery disease, atrial fibrillation, gut microbiota composition, postbiotics, propionic acid, amino acids, glycine*

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1. Introduction

Gut microbiota is an integral part of the human body. It acquires at birth, develops with the host and main, and maintains its temporal diversity and stability through adulthood until death. Gut microbiota induces a significant influence on the physical and mental health of the host. The main gut microbiota functions are protective, metabolic, and structural [1]. Its composition violations affect the integrity of the intestinal barrier, neurotransmitters, and the release of gastrointestinal hormones. In turn, gut microbiota disruptions participate in the progression of the mort cardiovascular risk factors. Atrial fibrillation (AF) is the most widespread cardiac arrhythmia in the world. Obesity, diabetes mellitus, atherosclerosis, dyslipidemia, arterial hypertension, obstructive sleep apnea, and inflammatory diseases are known AF risk factors, which are all pathogenetically associated with gut dysbiosis [2, 3]. Coronary artery disease is the most common reason of death all over the world and also the known risk factor of AF. CAD and AF together aggravate the course and prognosis of each other [3, 4]. CAD is characterized by quantitative and qualitative changes in gut microbiota composition and its metabolites, which have pro-atherogenic effects on endothelial cells. According to the literature, CAD is connected with a rise in *Enterobacteriaceae*, *Lactobacillus*, and *Streptococcus* taxa and a decrease in *Bacteroidetes* and *Lachnospiraceae* [5].

Postbiotics are defined as "non-viable bacterial products or metabolic products from microorganisms that have biological activity in the host". They are synthesized by microbial cells, including secreted biosurfactants and proteins, short-chain fatty acids (SCFAs), amino acids, organic acids, bacteriocins, vitamins, and peptides [6]. SCFAs are characterized by strong anti-inflammatory properties through activating SCFA-sensing receptors, named G-protein-coupled receptors (GPCRs), which implement immune regulation and epi-

thelial barrier sustenance. In turn, SCFAs are different in their beneficial and harmful properties. Propionate reduces obesity risk by stimulating glucagon-like peptide-1 and peptide YY release and decreases blood pressure by reducing renin release [3]. In experimental studies, propionate prescription has shown a strong inversive effect on blood pressure regulation through an increase of propionic, butyric, and valeric acids, restoration of NO bioavailability, and a decrease in circulating tryptophan, and trimethylamine levels [7]. Another attractive postbiotics group is amino acids. They are crucial for rebuilding the gut's epithelial cells microvilli, which procure intestinal integrity, what restoring gut homeostasis [8, 9]. Threonine, serine, and glycine are important for gut mucosa production. Lower circulating glycine levels are associated with cardiovascular and metabolic disorders. Glycine administration has described glucose and lipids lowering effects and hepatoprotective, neuroprotective, anti-inflammatory, and antiarrhythmic properties [10, 11].

The aim: is to improve gut microbiota composition by the long-term postbiotics (glycine and propionic acid) supplementation in patients with coronary artery disease and atrial fibrillation.

2. Materials and methods

53 patients were enrolled in the study. They were divided into 3 groups: first (CAD) – 14 patients with CAD but without arrhythmias; second (CAD+AF) – 31 patients with CAD and AF paroxysm; and the control group (CG) – 8 patients without CAD and arrhythmias. CAD and AF diagnoses were based on the latest ESC guidelines [3, 4]. All patients were treated in the Kiev City Clinical Hospital No. 12 in cardiological and therapeutic departments in 2018–2023 years.

Diagnosis CAD was confirmed by a history of coronary artery stenotic changes during invasive coronarography. AF paroxysm was checked by resting 12 leads electrocardiography. Exclusion criteria were reported malignancies, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), valvular AF, heart failure Class III to IV (by New York Heart Association), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, vegetarians and vegans, pregnancy, taking probiotics and antibiotics for a month before the study. No significant difference in risk factors at baseline was seen between investigated groups.

The study was conducted at the base and was approved by the ethical commission of the Kyiv City Clinical Hospital No. 12 (protocol # 8 from 22/08/2018). Informed consent was obtained from all subjects by the Declaration of Helsinki.

Baseline characteristics of study patients include age, gender, history of myocardial infarction (MI), stroke, diabetes mellitus, obesity, body mass index (BMI), uric acid, total bilirubin, GFR, and total cholesterol (TC) levels. Uric acid, total bilirubin, creatinine, and TC were checked by the Kyiv City Clinical Hospital No. 12 laboratory (certificate # PT – 257/21). Advanced age, obesity, hypercholesterolemia, high stages of chronic kidney disease, gout, and hyperbilirubinemia are known risk factors of AF paroxysm development [3]. That is why these baseline characteristics were analyzed and compared; it can help us exclude their influence on the obtained results.

Patients of the II groups received basic therapy (BT), according to the latest ESC guidelines: β-blockers, HMG-CoA-inhibitors (statins), anticoagulants, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers (if necessary), calcium antagonists (if necessary), diuretics (if necessary), and antiarrhythmics (if necessary) [3, 4]. They were divided into the II a and II b groups by stratified randomization. Stratification was done according to the patient's age, gender, body mass index (BMI), and TC. 18 patients formed the II a group, which received additional postbiotic supplementation [6]: rebamipide (2-(4-chlorobenzoylamino)-3-[2(1H))-quinolon-4-yl] propionic acid) by 100 mg 3 times a day and glycine by 100 mg 3 times a day during 6 months. 13 patients formed the II b group, which received only basic therapy. I group and CG patients were examined once on the first day of observation. II group patients were examined twice during the initial investigation and after 6 months of treatment.

Determination of the gut microbiota composition was carried out using quantitative PCR qRT-PCR using primers for the 16S rRNA gene and taxon-specific primers in faeces. Such domains were checked: bacteria – Firmicutes (*Lactobacillus spp., Faecalibacterium prausnitzii, Enterococcus spp., Blautia spp., Streptococcus spp., Eubacterium rectale, Roseburia inulinivorans, Ruminococcus spp.*), Bacteroides (*Bacteroides spp., Bacteroides thetaiotaomicron, Prevotella spp.*), Actinomycetota (*Bifidobacterium spp.)*, Verrucomicrobiota (*Akkermansia muciniphila*), Pseudomonadota (*Escherichia coli, Acinetobacter spp.)* and Archaea (*Methanobrevibacter smithii and Methanosphaera stadmanae*). Also, *Firmicutes/Bacteroides* (F/B) ratio was compared [2].

Results were presented as mean ± standard error or [95 % confidence interval (CI)] for continuous variables or as a number for categorical variables. Variables distribution for normality was checked using the Pearson criterion. Data were compared using the Wilcoxon signed-rank test or Student t-test with two critical regions by the type of distribution [12]. All calculations were done in MATLAB R2014a (License number 271828).

3. Results

The baseline characteristics were investigated in all observed patients. In the I and II groups, uric acid (by 22.66 % and 30.53 % respectively) and TC (by 32.64 % and 43.06 % respectively) levels were significantly higher, and GFR (by 26.16 % and 19.38 % respectively) was significantly lower in comparison with CG, $P<0.05$. In the I and II groups were patients with obesity, diabetes mellitus, stroke, or MI history; such cases were absent in CG. In investigated groups was found no significant difference in age, gender, BMI, total bilirubin, and smoking history, $P<0.05$. The data are shown in Table 1.

Also, the baseline characteristics of treated groups were investigated. The treated groups were completely comparable and had no significant differences. Treated groups have no significant difference. The data are shown in Table 2.

Table 1

Baseline characteristics of the study groups, mean ± standard error

Characteristic /group	I group	II group	CG	P1-2	P2-CG	P1-CG
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18	P>0.05	P>0.05	P>0.05
Men (%)	48.99	47.97	48.15	P>0.05	P>0.05	P>0.05
Smoking (%)	51.01	41.46	40.74	P>0.05	P>0.05	P>0.05
History of myocardial infarction (%)	30.87	26.02	0	P>0.05	P<0.05	P<0.05
History of stroke (%)	8.72	8.13	0	P>0.05	P<0.05	P<0.05
Diabetes mellitus (%)	18.12	14.63	0	P>0.05	P<0.05	P<0.05
Obesity (%)	8.84	12.0	0	P>0.05	P<0.05	P<0.05
BMI (kg/m^2)	27.02±0.33	26.93±0.43	27.12±2.10	P>0.05	P>0.05	P>0.05
Total bilirubin (mmol/l)	11.3±0.09	12.4±0.08	11.7±0.11	P>0.05	P>0.05	P>0.05
Uric acid (mmol/l)	380.5±28.16	404.9±36.11	310.2±29.12	P>0.05	P<0.05	P<0.05
GFR (ml/min)	62.03±2.31	67.73±1.98	84.01±5.48	P>0.05	P<0.05	P<0.05
TC (mmol/l)	5.73±0.37	6.18±0.31	4.32±0.21	P>0.05	P<0.05	P<0.05

Table 2

Baseline characteristics of the treated groups, mean ± standard error

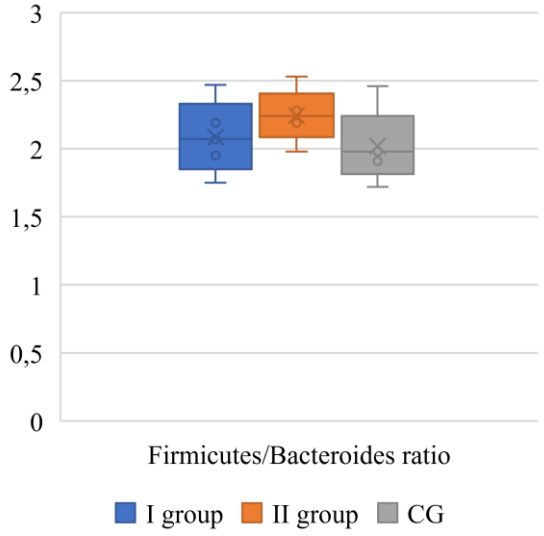
Characteristic /group	II a group	II b group	P
Age (years)	69.61±2.01	67.61±1.07	P>0.05
Men (%)	48.39	47.31	P>0.05
History of myocardial infarction (%)	7.23	9.68	P>0,05
History of stroke (%)	7.23	9.68	P>0,05
Diabetes mellitus (%)	16.13	16.13	P>0,05
Obesity (%)	19.35	9.68	P>0,05
Smoking (%)	25.81	35.48	P>0.05
Uric acid (mmol/l)	369.70±31.99	408.60±37.43	P>0.05
Total bilirubin (mmol/l)	11.51±1.0	12.10±0.72	P>0.05
GFR (ml/min)	64.52±6.83	60.96±2.19	P>0.05
BMI (kg/m^2)	27.97±0.87	26.60±0.48	P>0.05
TC (mmol/l)	5.52±0.26	5.35±0.15	P>0.05

Before treatment, the gut microbiota composition was checked in the investigated groups. The F/B ratio was not significantly different in the investigated groups ($p > 0.05$). By the taxonomic analysis, in the I and II groups, there was a significant increase in *Pseudomonadota* and a decrease in *Actinomycetota* and *Verrucomicrobiota* compared with CG; in the II group compared with the I group, there was a significant rise in *Pseudomonadota* ($p<0.05$). By the species analysis in the I and II groups comparing with CG was a significant rise in *Bacteroides Spp., Faecalibacterium Prausnitzii, Actinobacter Spp., Streptococcus Spp.* and a decrease in *Lactobacillus Spp., Bifidobacterium Spp., Akkermansia Muciniphila, Eubacterium Rectale;* in the I group in comparison with CG was a significant rise in *Ruminococcus Spp.;* in the II group in comparison with CG was a significant decrease in *Roseburia Inulinivorans;* in the II group in comparison with I group was a significant rise in *Actinobacter Spp.* and a decrease in *Blautia Spp., Bacteroides Thetaiotaomicron* ($p <0.05$). Results are present in the Fig. 1.

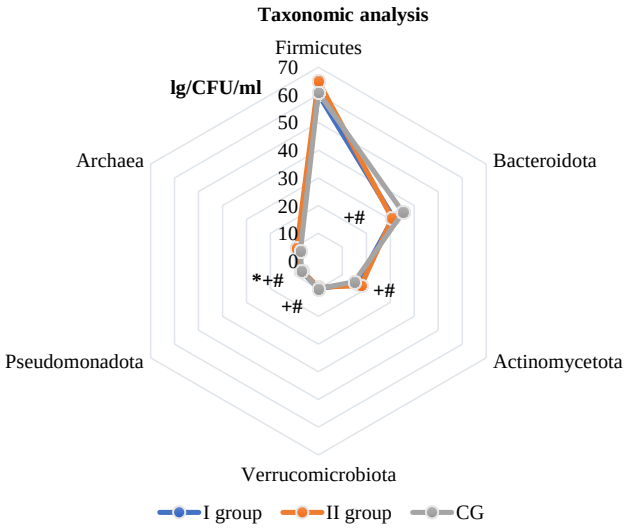
After six months of treatment, the II group of patients (with long-term additional postbiotic supplementation) were secondary investigated. The F/B ratio significantly decreased after treatment in the II a group. According to the taxonomic analysis after treatment in the II group, a significant rise in *Verrucomicrobiota* and a decrease in *Firmicutes* were found.

By the species analysis after treatment, a significant increase in *Lactobacillus spp, Akkermansia muciniphila, Blautia spp., Prevotella spp.*, and a decrease in *Streptococcus spp.* and *Methanosphaera stadmanae* were checked.

Results are present in the Fig. 2.



a



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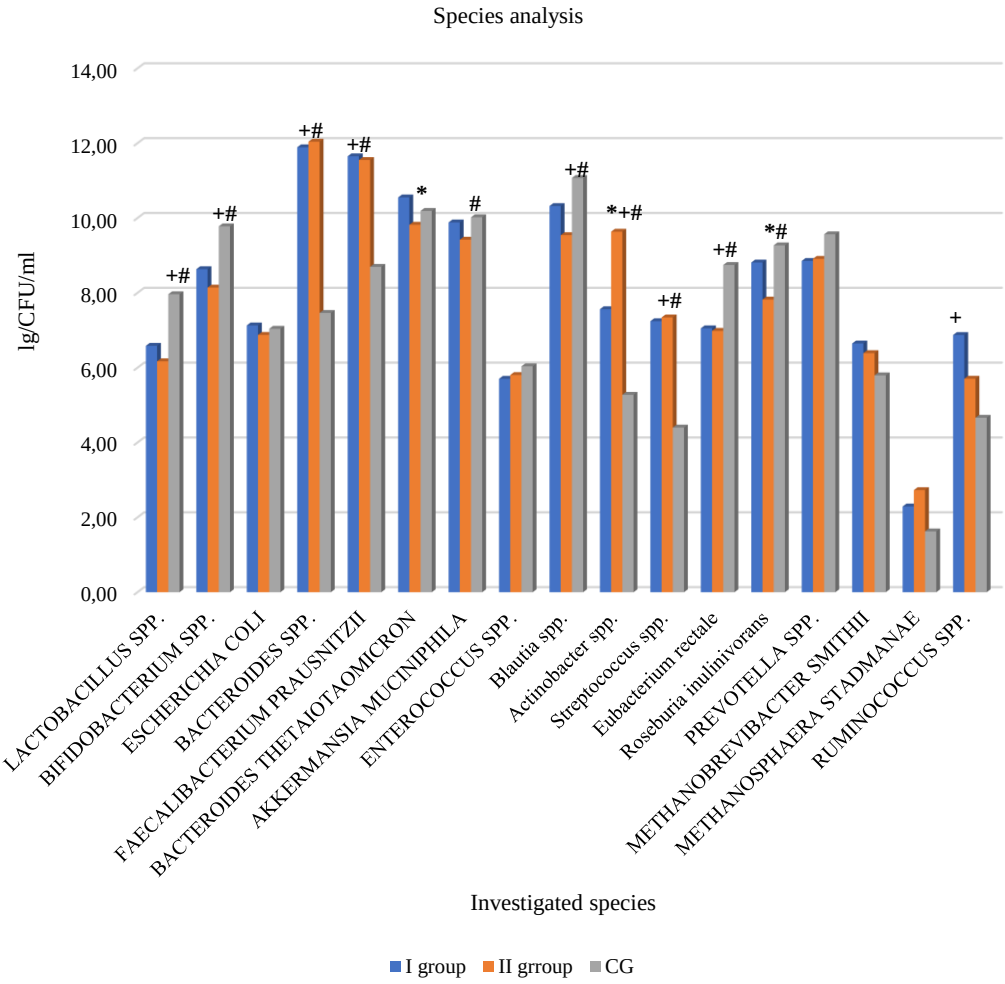
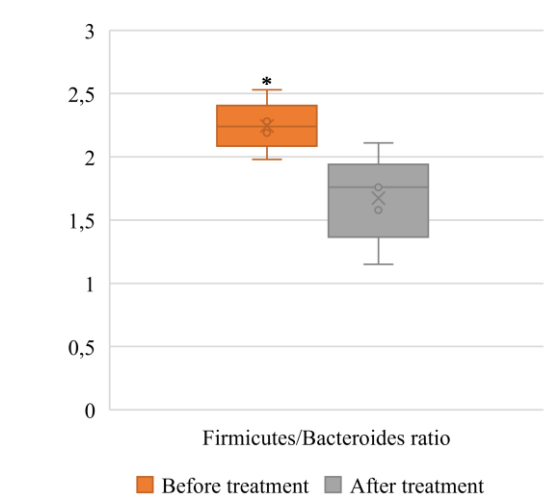


c

Fig. 1. Gut microbiota composition in investigated groups: *a* – F/B ratio; *b* – taxonomic analysis, mean [95 % CI], lg/CFU/ml; *c* – species analysis, mean [95 % CI], lg/CFU/ml; *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG



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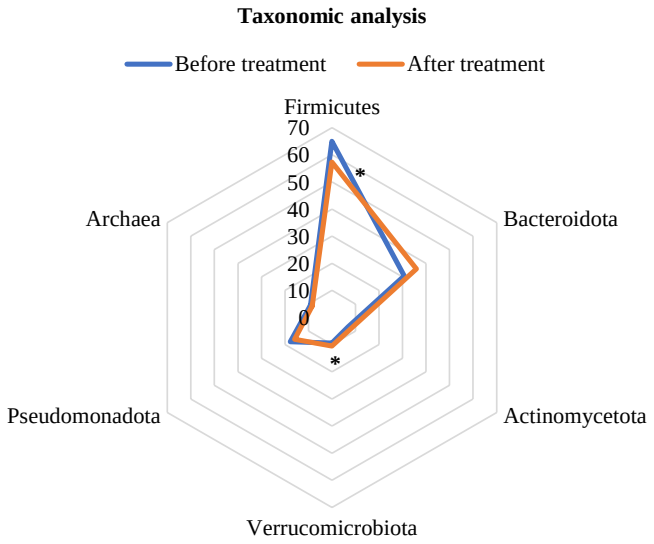

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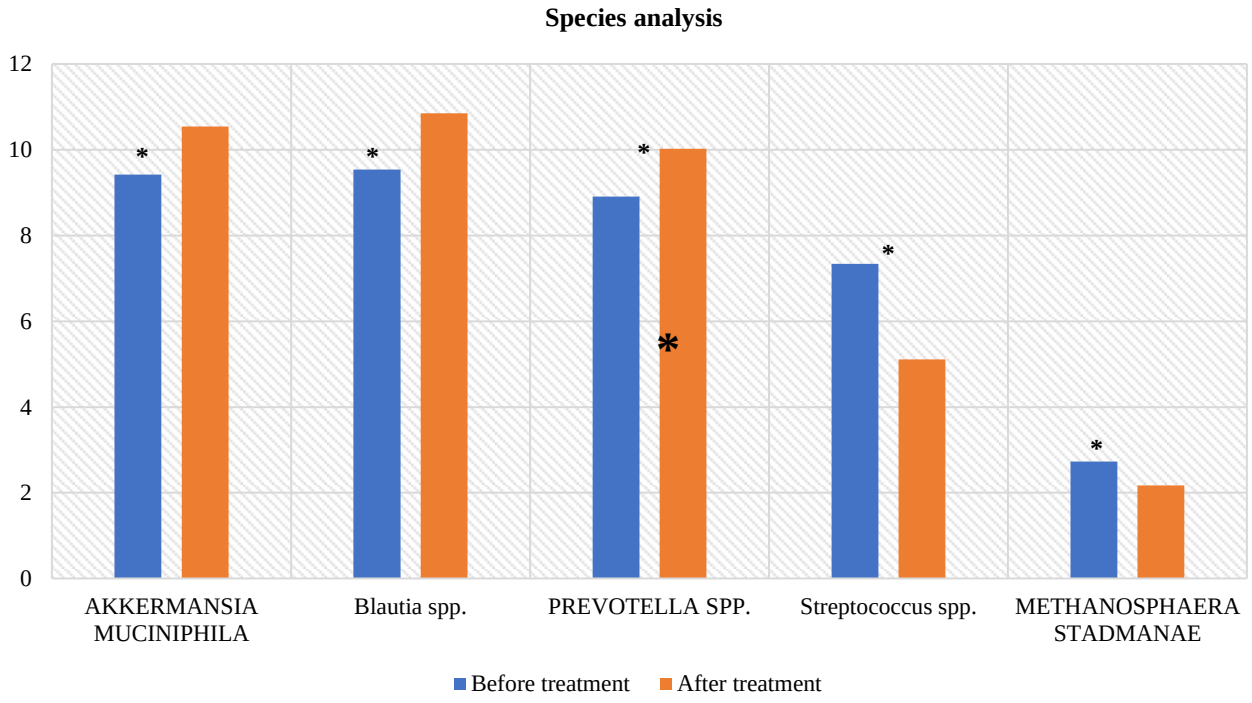

c

Fig. 2. Gut microbiota composition dynamics in long-term postbiotics (propionic acid + glycine) additional supplementation in II a group: *a* – F/B ratio; *b* – taxonomic analysis, mean [95 % CI], lg/CFU/ml;

After six months of treatment, the II b group patients (with only basic treatment) were secondary investigated. The F/B ratio was not significantly changed. According to the taxonomic analysis after treatment in the II group, a significant rise in *Verrucomicrobiota* was found. By the species analysis after treatment, a significant increase in *Akkermansia muciniphila*, *Roseburia inulinivorans*, and a decrease in *Faecalibacterium prausnitzii* was checked. Results are present in the Fig. 3.

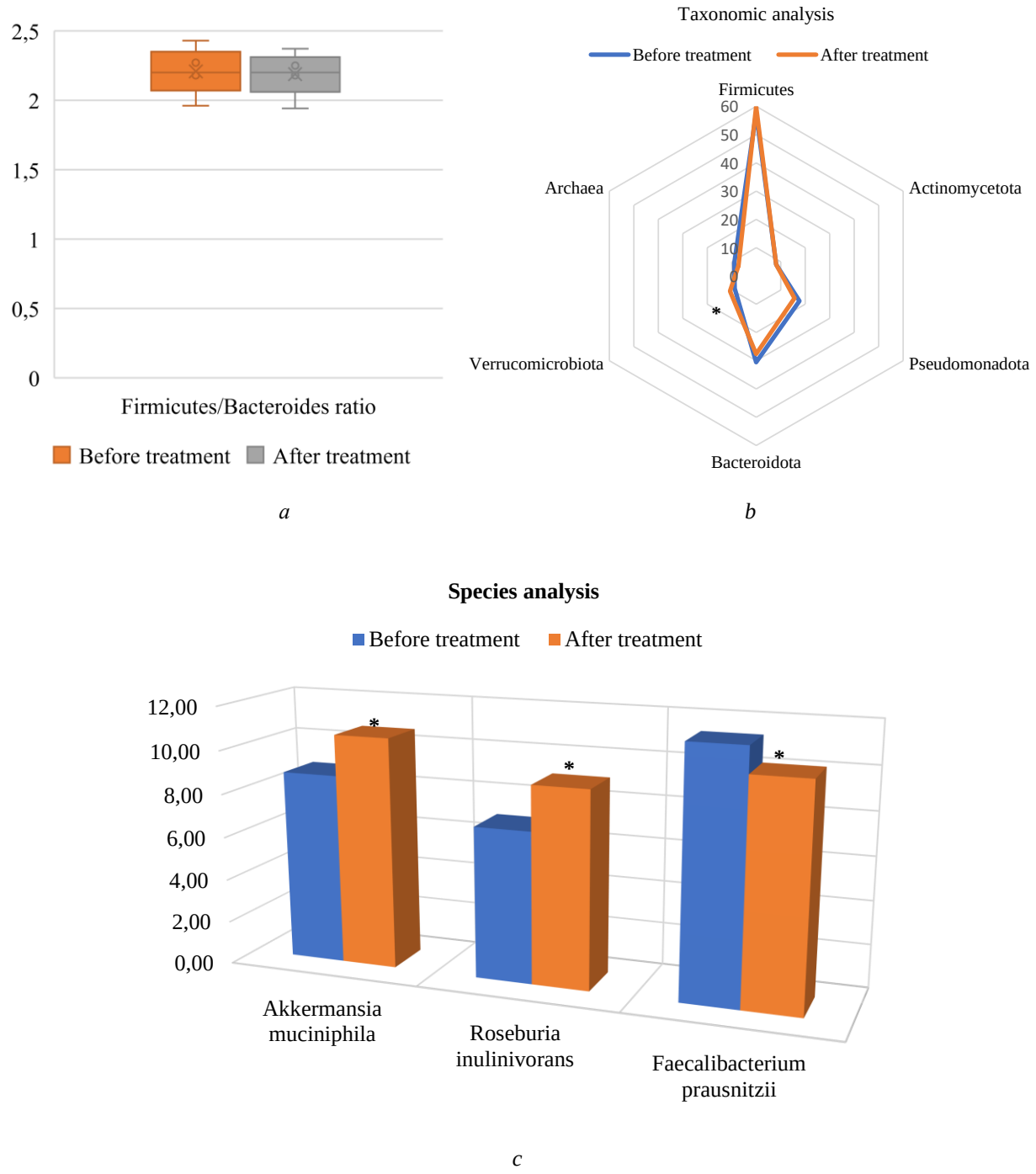

Fig. 3. Gut microbiota composition dynamics in II b group (with only basic treatment): *a* – F/B ratio; *b* – taxonomic analysis, mean [95 % CI], lg/CFU/ml; *c* – species analysis, mean [95 % CI], lg/CFU/ml; *-P<0.05.

Also, we compared the results of both groups after treatment. The F/B ratio was significantly lower in the II a group than in the II b group. According to the taxonomic analysis, *Actinomycetota* was significantly higher in the II a group than in the II b group. By the species analysis *Akkermansia muciniphila, Blautia spp., Eubacterium Rectale,* and *Prevotella spp.* were significantly higher and *Streptococcus spp.* was significantly lower in the II a group in comparison with II b group. Results are present in the Fig. 4.

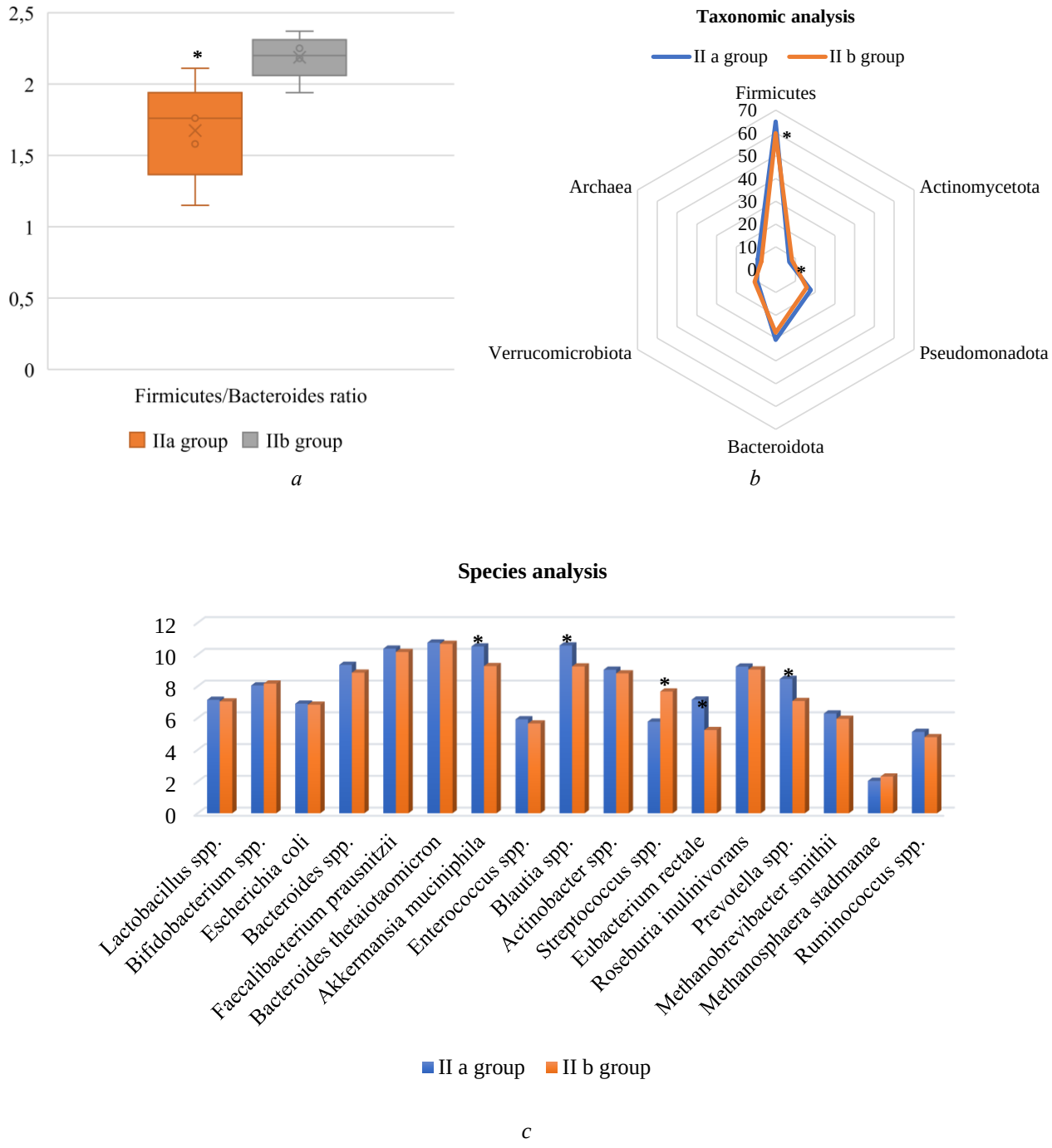

Fig. 4. Gut microbiota dynamical changes composition in the I a and II b group after six months of treatment: *a* – F/B ratio; *b* – taxonomic analysis, mean [95 % CI], lg/CFU/ml; *c* – species analysis, mean [95 % CI], lg/CFU/ml; * – P<0.05.

So, the dynamic changes in gut microbiota composition during six months of treatment were analyzed in patients with CAD and AF paroxysm.

4. Discussion

The F/B ratio is the microbiota index that has been investigated the most. Its increase is commonly associated with obesity, dyslipidemia, cancer, mental disorders, etc. The F/B ratio depends on the patient's lifestyle, which includes physical activity, diet, sleep regime, medicines, bad habits, and environmental patterns. Harmful species, such as *Streptococcus spp.* and *E. coli*, mainly contribute to Firmicutes phylum [2]. Undoubtedly, that decrease in the F/B ratio is a positive gut microbiota modification.

Lactobacillus spp, *Akkermansia muciniphila*, and *Blautia spp.* contributes to probiotic bacteria [13]. According to animal studies, *Lactobacillus* have cardioprotective and anti-ischemic properties and significantly reduce reperfusion tachyarrhythmia by decreasing norepinephrine release and activation of myocardial catalases [14]. Moreover, anticoagulants or protein pump inhibitors prescription,

which is common for patients with AF and CAD, are also associated with *Lactobacillus* decrease [15]. In the animal experiment, *Akkermansia muciniphila* supplementation can prevent AF paroxysm by reducing endotoxemia and circulating trimethylamine-N-oxide levels [16]. *Blautia spp.* has a preventive effect on CAD development [17].

Prevotella spp. is a dominant gut microbiota species for rural populations with traditional lifestyles and diets (non-Westernized populations). High *Prevotella spp.* is closely associated with metabolic health, normal glucose, and lipid homeostasis, and it is commonly connected with a high-fiber diet. On the other hand, it is correlated with inflammatory autoimmune diseases and infections, as well as β-lactam antibiotic resistance. Propionate is the crucial and specific *Prevotella spp*. metabolite occurred from polysaccharides degradation, which is important for host mucosal immunity. So, *Prevotella spp*. is an attractive candidate for the role of new probiotic strains [18].

Streptococcus spp. increase is directly linked with endotoxemia and chronic low-grade inflammation, which is the known basis of most cardiometabolic disorders, including CAD and AF [19]. *Methanosphaera stadmanae* plays an important role in an intestinal immune response. Its rise is used as a marker of gut dysbiosis [20].

So, postbiotics (glycine with propionic acid) supplementation is a new and promising method of gut microbiota modulation.

Limitations of the study. The lack of prior research on the topic is the main limitation of the study.

Perspectives of subsequent scientific research: The influence of investigated postbiotic combination (propionic acid and glycine) on gut microbiota metabolites, inflammatory markers, and lipids exchange will be an interesting further studies topic.

5. Conclusions

Long-term postbiotics (propionic acid in combination with glycine) supplementation for patients with coronary artery disease and atrial fibrillation leads to the following positive gut microbiota composition changes:

1. A significant decrease in Firmicutes/ Bacteroides ratio, $P<0.05$;

2. A significant rise in *Verrucomicrobiota* and a decrease in *Firmicutes*, $P<0.05$;

3. A significant increase in probiotic species (*Lactobacillus spp, Akkermansia muciniphila, Blautia spp., Prevotella spp.)* and a decrease in species associated with cardiometabolic disorders (*Streptococcus spp., Methanosphaera stadmanae),* $P<0.05$;

4. A significantly lower F/B ratio was found in comparison with placebo group patients, $P<0.05$;

5. A significant increase in *Actinomycetota* was found in comparison with placebo group patients, $P<0.05$;

6. A significant increase in probiotic species (*Akkermansia muciniphila, Blautia spp., Eubacterium Rectale,* and *Prevotella spp*.) and a decrease in species associated with cardiometabolic disorders (*Streptococcus spp.)* was found in comparison with placebo group patients, $P<0.05$.

Conflicts of Interest

The authors declare that they have no conflict of interest regarding this research, including financial, personal, authorship, or other nature, which could affect the research and its results presented in this article.

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Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm they did not use artificial intelligence technologies when creating the current work.

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