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Pharmacogenetic analysis of the association between polymorphic variant rs2199936 of the ABCG2 gene and the effectiveness of rosuvastatin therapy in patients with coronary heart disease

Individualization of ventricular extrasystoles pharmacotherapy in patients without cardiac structural changes

European Society of Cardiology Congress (Paris, 2019): results of the most important clinical studies

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Contents

Editor's Welcome

Dear colleagues!

We are happy to present to you the 25th issue of the International Heart and Vascular Disease Journal that contains a leading article as well as original and review articles.

The "Leading article" section presents an original study of the association between polymorphic variant rs2199936 of the ABCG2 gene, total cholesterol, and low-density lipoprotein cholesterol levels in patients with coronary heart disease, and how different rosuvastatin dosages were used in order to achieve target lipid levels. A total of 217 patients were included and followed up for 12 months. The authors established the role of polymorphic variant rs2199936 of the ABCG2 gene in the individual drug response to rosuvastatin treatment. It was concluded that genetic factors contribute to achieving target lipid levels during low-dose rosuvastatin treatment.

Four articles by Russian authors are published in the "Original articles" section. A simultaneous epidemiological study investigated eating attitudes in women aged 25–64 depending on education and marital status. The study identified that single, middle-aged, and poorly educated women were at considerably higher risk of having unhealthy eating attitudes. These tendencies determine the need of developing prevention programs in high risk groups. The second article presents a study that estimates the prognostic value of copeptin levels in comparison with troponin T for assessing the medium-term mortality risk in patients with non-ST-segment elevation acute coronary syndrome when measured within the first 3 hours from the start of symptoms. The study showed that the plasma copeptin level is a valuable short-term and medium-term predictor of fatal and non-fatal cardiovascular events. Copeptin levels were found not to depend on gender, age, or severity and elevated levels may indicate a higher risk of mortality in patients with non-ST-segment elevation acute coronary syndromes within 180 days of the event. The third study assessed the occurrence of cardiovascular disease risk factors and associated multimorbidity in healthcare workers of a general city clinical hospital. Among healthcare workers the most common risk factors were unhealthy diet, lack of physical activity, and excess weight. Multimorbidity was associated with age and family history. The fourth study published in this section investigated the analysis of ventricular extrasystoles (VEs) as a method for individualization of VE pharmacotherapy in patients without cardiac structural changes. The authors concluded that when choosing antiarrhythmic therapy for VE treatment it is important to consider the duration of QRS in all patients without cardiac structural changes.

The "Review article" section presents a report on the 25 most important clinical trials presented at the Hot Line sessions of the 2019 European Society of Cardiology that took place in Paris, France.

We invite authors to submit original papers, review articles, discussions, and opinions on prevailing issues as well as treatment and prevention recommendations.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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LEADING ARTICLE

Pharmacogenetic analysis of the association between polymorphic variant rs2199936 of the ABCG2 gene and the effectiveness of rosuvastatin therapy in patients with coronary heart disease

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Objective. *To determine the association between polymorphic variant rs2199936 of the ABCG2 gene and levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL cholesterol), its dynamics and rosuvastatin dosage in order to achieve target lipid levels in patients with coronary heart disease (CHD).*

Materials and methods. *The study included 217 patients, residents of Central Russia with CHD, II-III functional classes of stable angina aged 40-70 years. Patients received titrated dosages of rosuvastatin from 5 mg / day to 10-20-40 mg in order to achieve target TC and LDL cholesterol levels. The duration of follow-up was 12 months. The association between rs2199936 carriage and lipid levels was established using linear regression analysis; and with rosuvastatin dosage using logistic regression analysis.*

Results. *The decrease of TC and LDL cholesterol levels was significant at the end of 1, 6 and 12 months of follow-up (p <0.0001 for all periods). No genotype associations with initial lipid levels were found. Carriage of variant allele A was associated with more pronounced decrease of TC level according to 1-month follow-up, in both absolute values (mmol / l, p = 0.045) and percentage of initial level (p = 0.014). Lipid metabolism targets achievement was associated with low rosuvastatin doses (5-10 mg / day), G / A genotype (OR = 0.20 95% CI 0.06-0.62, p = 0.0029) and carriage of variant allele A (OR = 0.33 95% CI 0.13-0.82, P = 0.014).*

Conclusion. *This study established the role of polymorphic variant rs2199936 of the ABCG2 gene in the individual drug response to rosuvastatin treatment in patients with coronary heart disease. Thus, genetic factors contribute to the ability to achieve lipids target levels during rosuvastatin treatment.*

Key words: *pharmacogenetics, rosuvastatin, coronary heart disease, cholesterol, ABCG2, polymorphism.*

Conflict of Interest: None declared.

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Introduction

Nowadays it has been established that pharmacological therapy needs personalization due to its unequal effectiveness and the possibility of adverse effects in different patients [1]. Rosuvastatin has been widely used for the management of patients with coronary heart disease (CHD) due to its sufficient hypolipidemic effect in order to reach modern lipid target levels in patients with high cardiovascular risk [2, 3]. However, rosuvastatin has individual effect due to genetically determined characteristics. Pharmacokinetics of this medication is affected by membrane transporter proteins that, along with endogenous substrates transport rosuvastatin. In this regard, ATP-binding membrane transporter of the G2 family that is involved in pharmacological effect of rosuvastatin rather than in other medication from statin group is very remarkable [4, 5]. This protein is encoded by the ABCG2 gene that has significant polymorphism. Carriage of the polymorphic variant rs2199936 of this gene according to pharmacogenetic studies is associated with rosuvastatin lipid-lowering effect increase compared with low-density lipoprotein cholesterol (LDL cholesterol) [4, 6, 7]. We performed pharmacogenetic analysis of polymorphic variant of indicated gene on the effectiveness of rosuvastatin therapy in order to reach target lipid levels among residents of Central Russia, and also established the association between medication dosage needed to achieve target levels and genetic component.

Materials and methods

The study included 217 patients of Slavic origin (self-identification), residents of Central Russia with CHD: with functional classes (FC) II-III of stable angina according to Canadian Cardiovascular Society classification aged from 40 to 70 years. Patients had dyslipidemia, established according to V revision of National recommendations for the diagnosis and management of lipid metabolism disturbances [8], with total cholesterol (TC) level over 4 mmol/l, LDL-cholesterol over 1.8 mmol/l. The sample included men (73%) and women (during menopause). Average age of patients at the time of inclusion in the study was 61.0

± 7.25 years (M ± standard deviation). The study included patients who did not receive statins on regular basis. According to Helsinki Declaration, patients signed informed consent to participate in the study, and Regional Ethics Committee at the Kursk State Medical University of the Russian Ministry of Health approved the study. The exclusion criteria were: individual intolerance to statins, adverse effects during treatment, conditions and risk factors that contribute to their development: increased aspartate aminotransferase and alanine aminotransferase levels over three normal limits, alcoholism, hypothyroidism, myopathy, as well as the history of this condition, including the case of medications adverse effect. Patients with chronic kidney disease with creatinine clearance less than 60 ml/min, as well as patients with concomitant chronic heart failure above IIA class according to Vasilenko-Strazhesko classification, were excluded.

All patients had their genotype and lipid profile determined via blood test. All patients received rosuvastatin starting from 5 mg per day and started a diet with reduction of saturated fats, trans fats and simple carbohydrates. After 1 month of treatment, the lipid profile was determined. In case required targets of TC and LDL-cholesterol were not reached in patients with very high cardiovascular risk [8], higher doses of statins were prescribed (10–20–40 mg sequentially with its increase and control of the lipid profile once a month) until targets were achieved. Patients who achieved target lipid levels continued to receive rosuvastatin in current dosage. Lipids were controlled after 6 and 12 months of the therapy. The level of TC was determined by direct enzymatic assay using "Vitalab Flexor E" automatic analyzer (Netherlands), the concentration of LDL cholesterol was calculated using the Friedewald formula.

5 ml of venous blood was collected for molecular genetic studies (in tubes with 0.5 M EDTA). DNA was isolated using standard two-stage phenol-chloroform extraction with ethanol precipitation method. Multiplex genotyping was performed using MassARRAY 4 genetic analyzer (Agena Bioscience, USA).

Statistical analysis. The normality of the distribution was assessed using Kolmogorov-Smirnov test, the distribution of TC and LDL cholesterol was different from normal, the indicators are presented as median (first to third quartiles). The significance of changes in lipid concentrations during therapy was determined using Wilcoxon signed rank test for paired comparisons. Statistical analysis of obtained data was performed using Statistica 10.0 software. Fisher exact test was used to analyze the frequency distribution of genotypes and its testing for Hardy-Weinberg equilibrium compliance. DNA samples and phenotypic data of 100 patients with CHD from Research Institute of Genetic and Molecular Epidemiology of the Kursk State Medical University who participated in a pharmacogenetic study were used in order to assess the association between genotype and lipid metabolism and to increase study significance [9]. The associations between the polymorphic variant rs2199936 of the ABCG2 gene with lipid metabolism parameters and its dynamics were established using linear regression analysis. The level of statistical significance was established using logarithmic transformation variables. An adjustment for body mass index and medication dosage were made. The association between genotype and medication dosage was evaluated in 115 patients included in the study using logistic regression analysis adjusted for gender, age, body mass index with the calculation of the odds ratio (OR) and 95% confidence interval (95% CI). Regression analysis was performed using the SNPStats tool (https://www.snpstats.net; Spain). A p value less than 0.05 was considered significant.

Results

We compared allele frequencies of the studied polymorphic variant in the population of Central Russia with Europe and East Asia populations due to the presence of pharmacogenetic studies of rosuvastatin in these populations [6, 10, 11, 12]. Allele frequencies were compared with data obtained in the 1000 Genomes Project (1000 Genomes Project, Phase 3) [13]. The frequency of the minor allele A (MAF) in studied population was 0.083 and did not differ significantly (p = 0.6372) from European population (MAF = 0.094), but differed (p<0.00001) from East Asian population (MAF = 0.6372). The frequencies of genotypes of polymorphic variant rs2199936 in studied population for did not deviate from Hardy-Weinberg equilibrium (p = 0.8030).

Carriage of the rs2199936 polymorphic variant was not associated with initial TC and LDL cholesterol levels. The results of the analysis are presented in table 1.

The association between studied polymorphic variant and TC level during rosuvastatin treatment in patients with CHD was established during 1-month follow-up (Table 2). Thus, carriage of the minor allele A was associated with more pronounced hypolipidemic effect of rosuvastatin, expressed both in abso-

Table 1. **The association between polymorphic variant rs2199936 of the ABCG2 gene and initial TC and LDL cholesterol level in patients with CHD**

Gene	Genotype	The frequency of genotypes		TC		LDL-cholesterol	
		n	%	Me (Q1-Q3)	P_{cor}*	Me (Q1-Q3)	p_{cor}*
ABCG2 rs2199936	A/A	2	0,9	5,84 (5,18-6,5)	0,43	3,66 (3,1-4,21)	0,16
	G/A	32	14,7	5,67 (4,75-6,14)		3.51 (2,73-4,16)	
	G/G	183	84,3	5,9 (5,28-6,3)		3.95 (3,22-4,49)	

* The level of statistical significance

Table 2. **The association between polymorphic variant rs2199936 of the ABCG2 gene and TC and LDL cholesterol levels in patients with CHD during rosuvastatin treatment**

Gene (SNP)	Genotype	The frequency of genotypes		Δ TC, 1-month therapy			
		n	%	Mmol/l	%		
				Me (Q1-Q3)	p_{cor}*	Me (Q1-Q3)	p_{cor}*
ABCG2 rs2199936	A/A	2	0,9	-2,12 (-2,40... -1,83)	**0,045**	-36,12 (-36,92... -35,33)	**0,014**
	G/A	32	14,7	-1,56 (-2,34...- 0,94)		-27,13 (-42,40... -16,67)	
	G/G	183	84,3	-1,18 (-1,84 ...-0,68)		-21,89 (-30,82... -11,86)	

* The level of statistical significance with an adjustment for gender, age, body mass index, TC – total cholesterol in blood plasma, LDL-cholesterol – low density lipoprotein cholesterol.

Table 3. **Initial TC and LDL-cholesterol levels in patients with CHD and its dynamics after 1, 6 and 12 months of rosuvastatin treatment (Me (Q1-Q3))**

Parameter	Initial level, mmol/l	1-month therapy		6-months therapy		12-months therapy	
		Δ*, mmol/l	p†	Δ*, mmol/l	p†	Δ*, mmol/l	p†
TC	5,28 (4,61-6,03)	-1,57 (-2,21...-0,94)	**<0,0001**	-1,92 (-2,56...-1,30)	**<0,0001**	-1,93 (-2,49...-1,38)	**<0,0001**
LDL-cholesterol	3,27 (2,70-4,08)	-1,34 (-1,96...-0,85)	**<0,0001**	-1,69 (-2,40...-1,15)	**<0,0001**	-1,62 (-2,29...-1,12)	**<0,0001**

* The dynamics of the parameter to initial level,
† The level of the dynamic's significance of the parameter to initial level according to Wilcoxon signed rank test for paired comparisons, TC – total cholesterol in blood plasma, LDL-cholesterol – low density lipoprotein cholesterol.

Table 4. **The frequencies of alleles and genotypes of polymorphic variant rs2199936 of the ABCG2 gene in patients with low and high doses of rosuvastatin.**

gene (SNP)	genotype, allele	Low dose, n (%)[1]	High dose, n (%)[1]	OR (95 % CI)[2]	p
ABCG2 G>A rs2199936	G/G	39 (69,6)	53 (89,8)	1,00	**0,0029**
	G/A	16 (28,6)	5 (8,5)	**0,20 (0,06-0,62)**	
	A/A	1 (1,8)	1 (1,7)	0,72 (0,03-15,43)	
	A	18 (16,1)	7 (5,9)	**0,33 (0,13-0,82)**	**0,014**

[1] Absolute value and % of patients with indicated genotypes / the frequency of variant allele,
[2] Odds ratio (95 % confidence interval) with an adjustment for gender, age, body mass index.

lute (mmol / l) and in relative (percentage of initial level) values. TC level was not associated with genetic component (p = 0.54 and 0.47 for the dynamics in absolute and relative values during 6 months follow-up, respectively, p = 0.42 and 0.23, respectively, during 12 months follow-up).

The analysis of the association between polymorphic variant rs2199936 and LDL cholesterol level during rosuvastatin treatment showed statistically significant association between genotype and LDL cholesterol level in percentage of the initial level (Δ, %) during 6-months follow-up. The association between the effect during other periods of follow-up were not statistically significant (p=0.28 and 0.14, respectively, for absolute and relative values during 1-month follow-up; p=0.31 and 0.23, respectively, during 12 months follow-up). Initial levels of TC and LDL cholesterol and its dynamics in patients with CHD during rosuvastatin treatment are presented in table 3.

We also estimated the association between the polymorphic variant rs2199936 of the ABCG2 gene and medication dosage needed to achieve target TC and LDL cholesterol levels. Patients were divided into 2 groups: with low rosuvastatin dosages (5 and 10 mg/day, 48%) and with high rosuvastatin dosages (20–40 mg/day, 51.3%). Results of the analysis are presented in table 4.

Patients with heterozygous variant rs2199936 (genotype G / A) more often achieved lipid metabolism target levels with low dosages of studied medication (OR = 0.20 95% CI 0.06-0.62, P = 0.0029) Carriage of the variant A allele was associated with low dosages

of rosuvastatin needed to achieve target lipid levels (OR = 0.33–95% CI 0.13–0.82, P = 0.014).

Discussion

ABCG2 (ATP-binding cassette transporter G2) belongs to the family of translocation ATP-binding proteins and is involved in the transport of both endogenous substances and xenobiotics, including medications. ABCG2 is expressed in enterocytes and provides active transport of rosuvastatin into the intestinal lumen that decreases drug absorption from the gastrointestinal tract. The transporter is also expressed in hepatocytes, where provides excretion of rosuvastatin in bile [4, 5, 7, 14]. Initially, the ABCG2 transporter was known as the breast cancer multidrug resistance protein in chemotherapy. Later it was established that it is also a hepatic excretory transporter, and hepatic is responsible for the excretion of rosuvastatin [6]. The transporter is encoded by the ABCG2 gene that is characterized by polymorphic variants that affect transport protein activity. Carriage of the rs2231142 variant leads to the synthesis of protein with low transport function, and enterocytes excrete rosuvastatin slowly, therefore, the absorption of rosuvastatin, its bioavailability and plasma concentration increases [10]. Carriage of the rs2231142 variant is also associated with enhanced lipid-lowering effect of rosuvastatin [4], that also occurs in patients with rs2199936 polymorphism genotype, that was associated with lipid-lowering effect and had the highest level of significance in the genome-wide association JUPITER study (Justification for Use Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). The last single nucleotide polymorphism (SNP) is in linkage disequilibrium with rs2231142 according to the HapMap project (r2 = 0.81 in North and West European population) [6], and, therefore, the mechanism of the rs2199936 variant influence on protein can probably be similar by functional effect to rs2231142 variant. In the present study, the carriage of rs2199936 was associated with lipid-lowering effect of rosuvastatin in patients with CHD, while the previous JUPITER study confirmed the association of genotype in patients for primary prevention. We established significant associations of rs2199936 with TC level during 1-month therapy with absolute and relative dynamics of this indicator. Moreover, in current study, we used an approach that is similar to clinical practice. Patients underwent a gradual dose titration, that ensured the achievement of TC and LDL-cholesterol target levels, after that we established contribution of genetic factors into treatment results. Polymorphic variant rs2199936 of the ABCG2 gene that was the most significant predictor of enhanced hypolipidemic response in the JUPITER study, proved its significance in patients with CHD in our study.

Conclusion

This pharmacogenetic study established individual drug response to rosuvastatin treatment in patients with CHD, II-III FC of stable angina. The results of the study show the significance of genotyping of polymorphic variant rs2199936 of the ABCG2 gene for prognosing the response to hypolipidemic rosuvastatin treatment in patients with CHD.

We have concluded that:

We established the association between lipid-lowering effect of rosuvastatin on TC level and carriage of the polymorphic variant rs2199936 of the ABCG2 gene. The presence of the minor allele A in the genotype led to hypolipidemic effect increase.

Initial total cholesterol and low-density lipoprotein cholesterol levels were independent of the carriage of the polymorphic variant rs2199936 of the ABCG2 gene.

The presence of the G / A genotype in the polymorphic variant rs2199936, as well as the carriage of the variant A allele, was associated with low doses of rosuvastatin (5-10 mg / day) needed to achieve target levels of total cholesterol and low-density lipoprotein cholesterol in patients with coronary heart disease.

Conflict of interests: None declared.

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Eating attitude in open urban female population in moderately urbanized Siberian city depending on social status

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Objective. *To study eating attitude in women aged 25–64 years in an open urban population depending on education and marital status.*

Materials and methods. *A simultaneous epidemiological study was carried out on a representative sample taken from the electoral lists of Tyumen city and included women aged 25–64 years (the response amounted to 70.3 %). Eating attitude was determined using the WHO questionnaire "Knowledge and Attitude towards Health" and social status — using marital status and education level.*

Results. *The study showed that mostly younger women followed a diet to stay healthy. Depending on social status, the most favorable eating attitude was observed in women who had completed higher education and had a life partner.*

Conclusion. *Our study that was conducted in an open population of moderately urbanized Siberian city shows the importance of introducing the principles of a healthy diet in high-risk groups of the population – single women with low education level, mainly of middle age.*

Key words: *epidemiological study, women population, eating attitude, social status.*

Conflict of Interest: None declared.

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Introduction

Many fundamental studies from experimental researches to multifactorial international trials have shown the connection between diet and atherosclerosis and coronary artery disease (CAD) incidence and mortality rates. It was concluded that changes in nutritional composition of food and its amount played the key role in the development of cardiovascular diseases (CVD) [1]. Numerous epidemiological studies confirmed the connection between fat intake and atherosclerotic disease frequency, blood cholesterol levels, CAD incidence and mortality rates.

Epidemiological studies that were carried out at the end of the 20th century — early 21st century showed that social status plays an important role in CVD development. According to the large cross-sectional studies, family provides different types of support, including emotional and economical. Of note is that family can have opposite effects on males and females. Findings show that women are more affected by the stress from taking care of the family compared with stress at work [3]. Education status and marital status were found to be associated with CAD prevalence and mortality rates. Lower mortality rates were identified in women who equally participated in making decisions and had friendly relationship with their husbands [4]. Family support is considered an important component of social support, as it can help relieve stress and correct behavioral risk factors [3, 5, 6]. At the same time, marriage is considered to have fewer positive effects on women compared with men as they have different family roles. The lowest prevalence of arterial hypertension is identified in women who have never been married. The lowest prevalence of excess weight is also reported in single women [7, 8].

Prospective studies have confirmed the association between somatic, behavioral risk factors, such as irrational diet, and social status. Inverse association between social status and mortality was shown for more economically developed counties [4, 9, 10]. Siberian population studies showed that women had more responsible attitude towards their health. Nevertheless, cardiovascular death relative risk (RR) tended to be higher in married women compared with single ones. RR was significantly higher in less educated women [13, 14].

Therefore, it is important to study behavioral risk factors in women of different social statuses in order to develop prevention programs focused on various social classes in open populations [13, 14].

Objective

The aim of this study was to investigate eating attitude in women aged 25–64 years in an open urban population depending on education and marital status.

Materials and methods

We conducted a cross-sectional epidemiological study that involved women from Tyumen central administrative district. A representative sample was formed using the random number generation method from the electoral lists of Tyumen city and included 1000 women aged 25–64 years (250 people for every decade of life 25–34, 35–44, 45–54, 55–64 years). The response rate was 70.3 %. Eating attitude was determined using the WHO questionnaire "Knowledge and Attitude towards Health" [9]. Marital status was determined by two parameters: presence or absence of a life partner. Education level was determined by three parameters: primary, secondary or higher education.

The study was conducted in accordance with the principles laid down in the Declaration of Helsinki. Study protocol was approved by local ethical committee. Written informed consent was obtained from all participants prior to being enrolled.

Statistical analysis was completed using the IBM SPSS Statistics 21.0 software. Age adjustment was performed by direct standardization based on the age structure of women in the Russian Federation aged 25–64 years. We compared different age groups with age-adjusted values, and values between different social status groups. In order to assess statistical significance of the differences we used Pearson's chi-squared test (χ^2). A p-value less than 0.05 was considered statistically significant.

Results

About 40 % of working age women in an open urban population followed specific diets only occasionally and 25 % of women believed that having a healthy diet was important but kept eating irrationally; 12.3 % of women failed healthier diets, 17.6 % refused to acknowledge that eating healthier was necessary and only 8.6 % of Tyumen women decided to change their diets in order to be healthier and currently stick to rational diet. In different age groups there was no statistically significant difference in negative attitude towards healthy diet, unsuccessful or irregular attempts to follow a specific diet, as well as inability to follow a healthy diet despite acknowledging its importance. We identified statistically significant rising

Table 1. **Eating attitude in women aged 25–64 years of an open Tyumen population**

Question/ Attitude	25–34		35–44		45–54		55–64		Age-adjusted value	
	n=122	%	n=210	%	n=156	%	n=215	%		
Have you tried to change your eating habits?										
1. I do not need to follow a specific diet	18	14,8	34	16,2	26	16,7	44	20,5	17,6	
2. I need to follow a healthier diet but I do not do it	31	25,4	47	22,4	43	27,6	48	22,3	25,0	
3. I failed to follow a healthier diet	10	8,2	27	12,9	21	13,5	25	11,6	12,3	
4. I follow a healthier diet inconsistently	45	36,9	88	41,9	55	35,3	84	39,1	39,8	
5. I have successfully changed my eating habits in order to stay healthy	18	14,8	15	*7,1	11	*7,1	14	*6,5	8,6	

Note: * — statistically significant differences between the younger age group (25–34 years) and other age groups, p <0,05; n — number of people questioned

tendency to change diet in order to stay healthy in the younger age group (25–34 years). More people in their 20s had healthier eating habits compared with the whole population (14.8 % — 6.5 %, p < 0.05), as well as with people aged 35–44 ears (14.8 % — 7.1 %, p < 0.05) and with people aged 45–54 years (14.8 % — 7.1 %, p < 0.05). (Table 1)

In groups with different education level statistically significant difference was identified only between the participants with primary and higher education. More women with primary education tended to refuse to follow a healthy diet compared with those who had completed secondary (50.0 % — 16.1 %, p < 0.05) and higher (50.0 % — 17.6 %, p < 0.05) education. Women who had completed only primary education were not ready to change their eating habits in order to improve their health compared with those who had completed secondary and higher education (5.9 % — 10.4 %, p < 0.05). (Figure 1)

There was no statistically significant difference in negative attitude towards improving eating habits between groups with different marital status as well as between those who were ready to change their diet or followed a new diet inconsistently. We identified statistically significant rising tendency of the questionnaire answers from women who had a life partner to show that they had made unsuccessful attempts to follow a healthier diet (5.9 % — 10.4 %, p < 0.05) or had successfully changed their diet in order to be healthy ((9.3 % — 6.1 %, p < 0.05). (Figure 2)

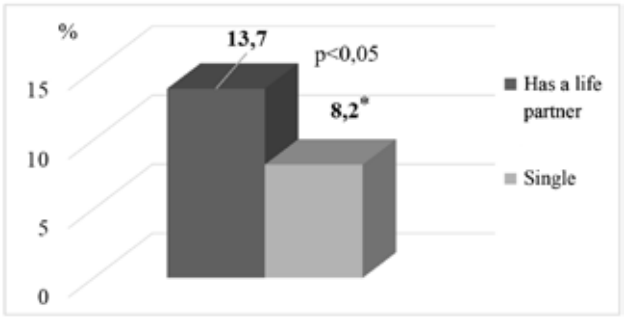

Figure 1. Eating attitude and marital status in women aged 25-64 years in an open Tyumen population

Discussion

Our study shows that in an open Tyumen population aged 25–64 years 60 % of women, mostly in their 20s, made attempts to change their diet.

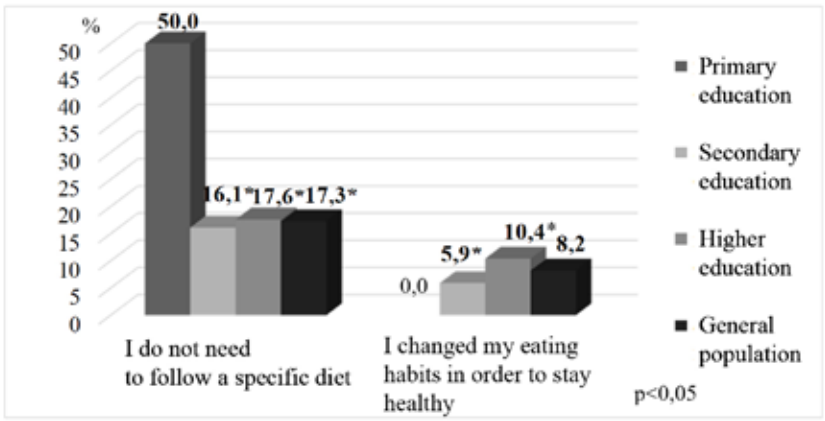

Figure 2. Eating attitude and education level in women aged 25-64 years in an open Tyumen population

Taking into account the results of our previous studies we can conclude that for most Tyumen women fats were the main source of energy and made up 39.3% of daily calorie intake. The participants consumed mostly saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) made up the minority of fats in their diet [16]. According to the WHO recommendations adults should get only up to 30% of total calories from fats. Most authors also suggest that fats should make up no more than 30% of the daily calorie intake and SFAs should make up no more than 10% (13.5% in Tyumen population) [1].

The previous findings show that compared with other age groups younger women consumed the lowest amounts of fats. It could be explained not only by SFAs but also by UFAs consumption that was the lowest in this age group (14.2±1.1 g). Dairy products, vegetable oil and animal fat were the main source of fats in younger women. The minimal amount of fats was consumed from seafood. According to the previous studies there was a lack of vitamins and some minerals in Tyumen population in general and especially in younger women. In this group there was a deficit of all studied parameters of daily ration, except phosphorus and copper. This puts the younger women at a greater risk of CVD and other non-concomitant chronic diseases [16]. These results are consistent with the present study findings that younger women tend to follow a healthy diet and have rational eating habits.

In order to develop an approach to active prevention it is important to study population awareness of the leading CVD risk factors and attitude towards CVD prevention [12]. The highest awareness of CVD risk factors in Tyumen population was identified in those who had completed higher education regardless of its type. These findings are consistent with other studies [8]. Findings from the previous study carried out on Tyumen population showed the highest awareness of risk factors in married individuals and in widows, the lowest — in divorced. Single individuals were moderately aware of CVD risk factors. These findings can be explained by the fact that today people get most information from TV and those who live with their families have more opportunity to spare some time for television. Married people also prioritize health of their families and therefore are more interested in disease prevention [5].

Conclusion

According to the present study young women who had completed higher education and those who had a life partner tended to follow healthier diet.

The tendencies that we identified in an open urban Siberian population determine the need to introduce healthy eating habits to high risk groups such as single poorly educated middle-aged women.

Conflict of interests: None declared.

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Copeptin for risk stratification and medium-term mortality prediction in patients with non-ST-segment elevation acute coronary syndrome

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Summary. *The study estimates prognostic value of copeptin level in assessing medium-term mortality risk in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACSs) measured during first 3 hours from pain syndrome manifestation compared with troponin T.*

The study included 128 patients (52 patients with non-ST-elevation myocardial infarction (NSTEMI), 58 with unstable angina (UA), 18 with unconfirmed coronary event), who were selected using inclusion and exclusion criteria and voluntarily signed written informed consent in order to participate in the study. All patients underwent diagnostic examinations, laboratory tests, including the determination of quantitative troponin T level and quantitative human peptide copeptin level. The use of extended set of predictors including copeptin increases the accuracy of short-term and medium-term prognosis of fatal and non-fatal cardiovascular events up to almost 100%. At the same time, it does not depend on gender, age and condition severity and can indicate mortality in patients with NSTE ACSs up to 180 days of follow-up.

Key words: *copeptin, non-ST-segment elevation acute coronary syndrome, acute myocardial infarction, mortality, troponin T.*

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According to a large number of epidemiological studies, coronary heart disease (CHD) is one of the leading causes of morbidity, mortality and disability in adult population [1,2]. One of the most severe manifestations of CHD include myocardial infarction (MI) and unstable angina (UA) — the most common mortality causes in patients with CHD. Over the last years, the concept of acute coronary syndrome (ACS) has been developed in order to unify medical and diagnostic measures at the stage when an accurate diagnosis cannot be established [3, 4].

According to WHO, ACS can be defined as any group of clinical signs and symptoms that make it possible to suspect acute myocardial infarction (AMI) or unstable angina (UA) and includes MI with ST segment elevation, MI without ST segment elevation, and MI diagnosed by changes in enzymes level, by the presence of biomarkers and late ECG signs [2, 5]. Among patients with acute coronary syndrome without ST segment elevation, it is important to identify groups of patients with myocardial necrosis who have increased risk of complications and death. This group of patients need the most aggressive management strategy including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Biomarkers play an important role in diagnosing and predicting the risks of adverse events in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACSs) and affect diagnostic and therapeutic management strategies. The method of troponin T and I levels determination currently has the highest sensitivity and specificity. An increase of troponin level is defined as the value exceeding the 99th percentile of the normal population-based reference range, however, its use is limited by relatively late increase in blood after MI onset (3–6 hours after the onset of necrosis), as well as possible increase that not associated with myocardial ischemia, for example, in sepsis, pulmonary embolism, subarachnoid hemorrhage, severe cardiac and renal failure [2, 6]. In this regard, it is necessary to search for new biomarkers in order to optimize treatment strategies. For example, Copeptin is 39-amino acid glycopeptide acid that is the C-terminal part of pro-vasopressin. It is secreted by the posterior pituitary gland along with vasopressin and reflects the amount of vasopressin involved in biochemical processes.

Endogenous stress leads to antidiuretic hormone (ADH) activation and release of copeptin, independent of cardiomyocyte necrosis [7, 8]. S. Neuhold and M. Huelsmann (2008) [9] demonstrated in their study that copeptin is more valuable prognostic factor compared with brain natriuretic peptide (BNP) in predicting mortality risk in patients with II–III NYHA functional class of heart failure (HF). Large multicenter randomized study that included 1273 patients with HF showed that the level of copeptin is an independent outcome prognostic factor with 3.9 years median of follow-up [4]. Copeptin level in patients with HF independently or in combination with a wide range of biomarkers [10], including BNP and troponins, can significantly contribute to outcomes prediction [11,12].

Materials and methods

The study included 128 patients who were admitted to the hospital with NSTE ACSs in the first 3 hours after pain onset, with CHD development risk factors and signed written informed consent to participate in the study. They were divided into 3 groups during the study depending on the ACS: group 1 — with the development of acute myocardial infarction, group 2 — with unstable angina, group 3 — with excluded coronary pathology. Groups did not differ significantly by age ($p > 0.05$); the average age of the sample was 64.4±10.8. The distribution by gender between groups was approximately the same: 42.3 % of women in the 1st group, 51.7 % — in the second group and 33.3 % — in the third, the results between women and men did not differ significantly ($p > 0.05$). All the groups were examined according to guidelines with the determination of copeptin and troponin T levels at the time of admission and repeated troponin T determination after 12–72 hours in cases of negative or uncertain results. Diagnostic TnT Test Kit was used to identify cardiac troponin, intended for use with the RADIOMETR AQT90 FLEX analyzer. The study of blood plasma samples for copeptin was performed using a set of reagents manufactured by Phoenix pharmaceuticals according to the manufacturer's instructions and protocol using a competitive enzyme-linked immunosorbent assay.

Statistical analysis

Statistical analysis was done using SPSS STATISTIKA 10 program, version 10/11. Quantitative variables were expressed as mean (standard deviation) or median, depending on the type of distribution, qualitative variables — as frequencies, absolute and relative. The significance of differences between two independent samples was estimated using Mann-Whitney test and Student's t-test. Two independent samples with qualitative characteristics were compared using chi-square test. The analysis of the relationship between characters was done using contingency tables, chi-square test and correlation regression analysis. The correlation between copeptin and nonparametric variables was evaluated using Spearman's rank correlation. The survival function analysis was carried out using the Kaplan-Meyer method. Sensitivity, specificity, positive prognostic and negative values were evaluated by analyzing the area under the curve receiver operating characteristics curve (AUC ROC); the cut-off point of copeptin effectiveness in predicting the risk of HF was determined using AUC ROC. P-value less than 0.05 was considered statistically significant.

Results

The risks of repeated acute cardiovascular complications development and mortality were assessed during the stay (short-term prognosis) and long-term follow-up (medium-term prognosis, observation period 180 days). Examined patients with NSTE ACSs had copeptin level rise > 2.95 ng / ml during the stay that was associated with significant mortality and repeated acute cardiovascular events risk increase RR 96.86 [13.60; 689.68 p <0.00001], with a positive prognostic value of 100.00 % (95 % CI 75.75 % —100.00 %).

Significant level of hospital mortality was observed in group 1 (p <0.0001), groups 2 and 3 had no fatal outcomes (Figure 1). The level of copeptin directly correlated with the development of repeated acute coronary events during short- and medium-term follow-up (rs = + 1, p <0.0001) and with hospital mortality (rs = + 0.7, p <0.0001). 12 patients (23.1 %) from group1 died, 6 of them were diagnosed with repeated myocardial infarction, 5 patients with acute left ventricular failure and 1 patient developed cardiogenic shock. All deceased patients had significant copeptin level increase compared with other patients from group 1. Average copeptin level was 5.1±2.28 ng / ml (median 4.12; 2.91–9.24).

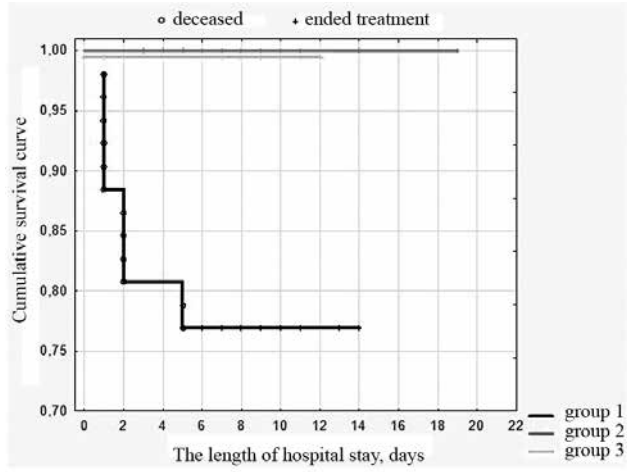

Figure 1. Inpatient Survival Analysis

General survival rate was 90.6 % (116 people) after the hospital stay. During the long-term observation period the number of endpoints (death, the development of repeated acute cardiovascular complications) was 31 % (36 people). By the end of 180 days follow-up, total mortality rate was 6.9 % (8 people). The analysis of mortality showed that 6 participants had repeated AMI with the development of severe heart failure, another 2 patients died from acute left ventricular failure. Mortality rate was equal in the 1st (4 people) and 2nd group (4 people), while there were no deaths 3rd (Figure 2).

Long-term survival analysis showed statistically significant differences between survival curves of the groups (p <0.00022). When comparing the risks of nosocomial and 6-month mortality in patients included in the study, only the difference between the risk of nosocomial mortality was statistically significant. Using the Gehan's criterion we revealed significant differences between groups 1 and 2 (p <0,00063) and groups 1 and 3 (p <0,00858). There were no statisti-

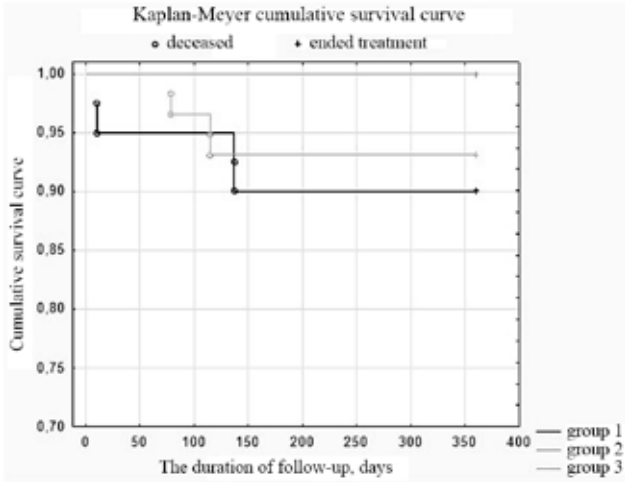

Figure 2. Long-term follow-up survival curves

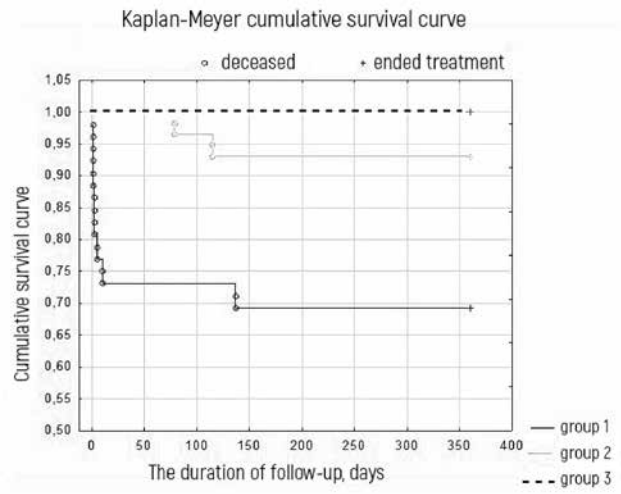

Figure 3. Survival curves during total follow-up (180 days)

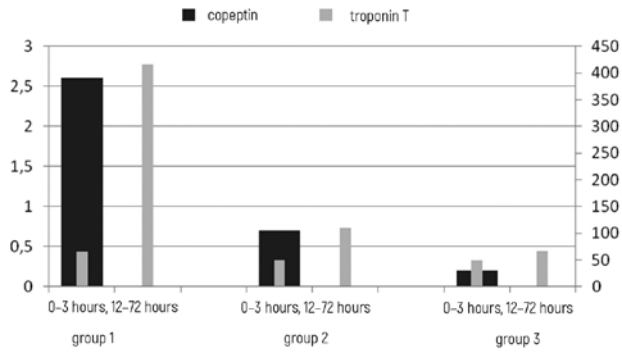

Figure 4. The association between the level of copeptin (ng/ml) and troponin T (ng/l) and mortality, mean values

cally significant differences between groups 2 and 3 (p> 0.05), (Figure 3).

Multivariate analysis (logistic regression) showed that copeptin during the first 3 hours after pain onset — the odds ratio (OR) — 5.27 [1.13–2.46], was stronger independent predictor of primary endpoints achievement during the admission period after MI compared with troponin T, OR 1.02 [0.99; 1.04], (Figure 4).

Positive predictive value of troponin T, as predictor of hospital mortality and recurrent MI, significantly increased after 12–72 hours, OR 4.93, and the cut-off point of troponin T> 147.5 ng / l, determined using ROC analysis, increased the risk of hospital mortality by almost 18 times (RR 17.8 [2.38–131, p <0.0001]) with sensitivity 24 % (95 % CI 14.3–37.4), specificity 100 % (95 % CI 95–100), a positive predictive value of 100 % (95 % CI 75.8–100) and an accuracy of 69.4 % (95 % CI 59–78.1), (Figure 5)

Areas under receiver operating characteristics curves (AUC ROC) after first 3 hours from pain syndrome manifestation were: 0,99 for copeptin (95 % CI 0,99–1,0) and 0,67 (95 % CI 0,5–0,83) for troponin

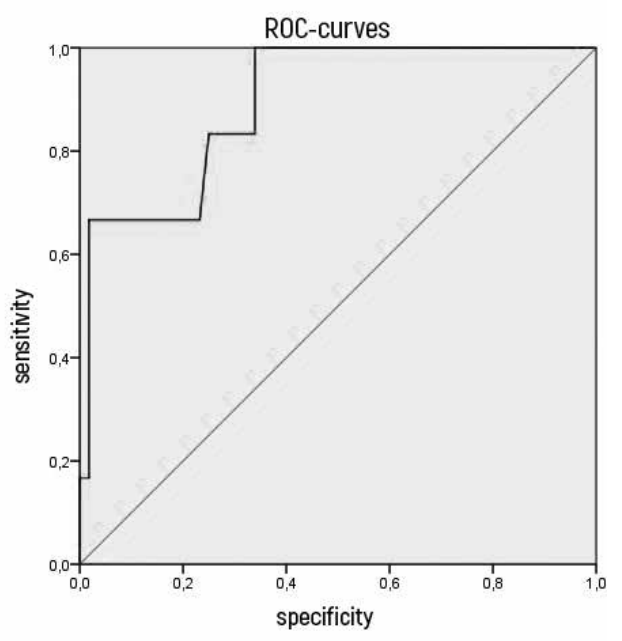

Figure 5. ROC-curve of troponin T level after 12–72 hours ng/l

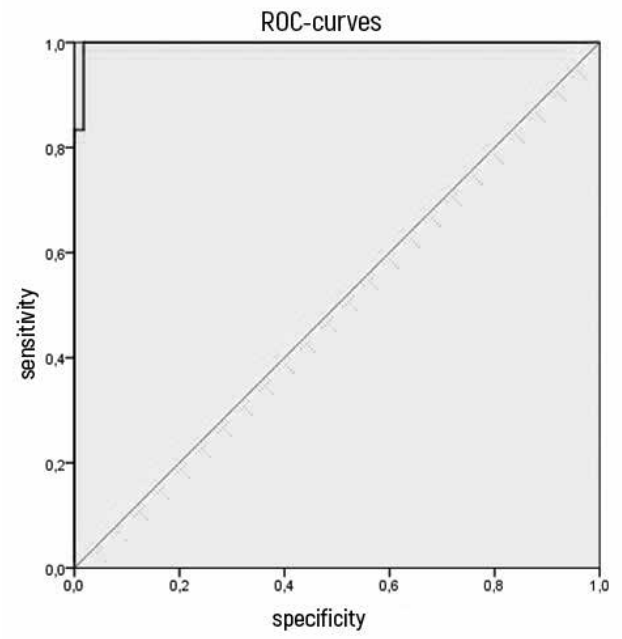

Figure 6. ROC-curve of copeptin level first 3 hours from pain syndrome manifestation

T, respectively (Figure 6, 7). The combination of copeptin and troponin T as recurrent MI and acute cardiovascular complications predictors during first 3 hours after pain syndrome manifestation (the dynamics during 12–72 hours) increased receiver operating characteristics curves to 0,9 (95 % CI 0,81).

The analysis of copeptin possibilities in order to predict the risk of recurrent AMI during 7-day follow-up showed that patients with significantly high copeptin level (median — 4,12 ng/ml, 2,91–9,24) had increased risk of recurrent MI (p < 0,01), when patients

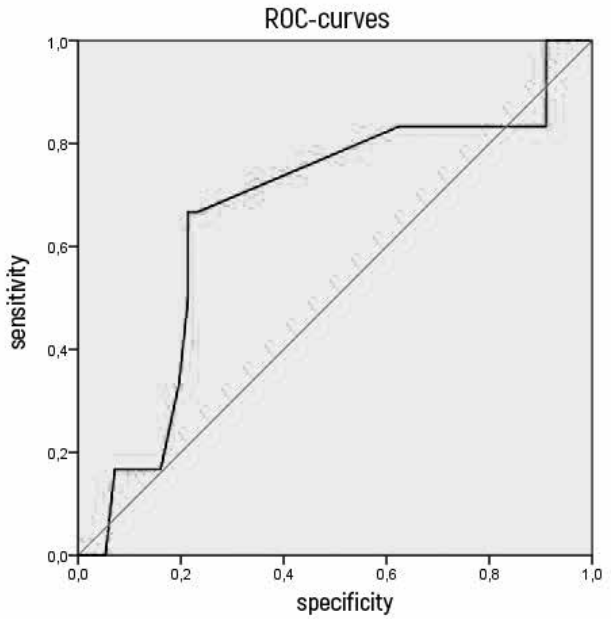

Figure 7. ROC-curve of troponin T (ng/l) level first 3 hours from pain syndrome manifestation

without recurrent MI during 7-day follow-up had significantly lower copeptin level.

According to ROC-curve analysis, copeptin level >2,95 was an independent predictor of AMI, recurrent acute cardiovascular complications and mortality. Therefore, it is possible to use it as predictive marker of acute coronary event during 7-day follow-up after AMI with 85,7% sensitivity (95% CI 60,06–95,9) and 100% specificity (95% CI 96,74–100,00). High sensitivity and specificity of this investigation can be explained by small sample of respondents.

In order to predict mortality, several models of binary logistic regression and algorithms for obtained results processing were developed, coefficients for copeptin were calculated, that are necessary for calculating and interpretation of the parameters.

According to the results of logistic regression analysis, copeptin level determined during the first 3 hours after pain syndrome manifestation, $p \leq 0.00\,001$, was more significant compared with troponin T determined during the same time period for the calculation of mortality risk (table 1).

Event (mortality) possibility was calculated using the formula

$$p = \frac{1}{1 + e^{-z}}$$

Where $z = b_1 * X_1 + b_2 X_2 + \ldots + b_n X_n + a$,

X1 — values of independent variables

b1 — coefficients that are calculated using binary logistic regression

a — constant value

In the classification table calculated using binary logistic regression the parameters of group membership (1=sick, 0=healthy) are opposed to predicted (p) parameters using calculated model. Negative prognosis group membership was $p > 0,5$, positive prognosis group membership — $p < 0,5$.

Developed during the investigation binary logistic regression method can be used in clinical practice for mortality prediction using copeptin and troponin levels estimated at the time of admission.

Conclusion

The results of current study showed that plasma copeptin level is valuable mortality risk and recurrent acute cardiovascular complications predictor in patients with NSTE ACSs. The use of extended set of predictors including copeptin increases the accuracy of short-term and long-term prognosis of fatal and non-fatal cardiovascular events up to almost 100%. At the same time, it is gender, age and condition se-

Table 1. **Multivariable model of factors analysis that affect mortality in patients included into the study**

	Constant B0	Troponin T 0–3 hours ng/l	Copeptin at admission 0–3 hours ng/ml
Coefficient estimation	- 5,723 252	0,11 580 045	1,661931E+00
Coefficient standard error	1,137 556	0,01 380 812	3,854260E-01
t (121) Student's t-test	- 5,031 182	1,844 287	4,311931E+00
p-value	0,000 001 714 155	0,0547 633	3,320181E-05
- 95%CL	- 7,975 345	0,01 153 637	8,988780E-01
+95%CL	- 3,471 159	0,04 313 727	2,424983E+00
χ^2 **Wald test**	25,31 279	1,309 392	1,859275E+01
p-value	0,000 000 490 102	0,06 525 132	1,623186E-05
Odds ratio (units of measure)	0,003 269 062	1,015 926	5,269474E+00
- 95%CL	0,0003 438 363	0,9885 299	2,456845E+00
+95%CL	0,03 108 097	1,044 081	1,130204E+01
Odds ratio (range)		5,254 304	3,760968E+06
- 95%CL		0,9978 044	3,600323E+03
+95%CL		92,7042	3,928781E+09

verity independent mortality indicator. Obtained copeptin values, as well as the calculated coefficients using binary logistic regression method, can be used to stratify patients into groups with low, intermediate and high risk. Methods developed during the study for predicting mortality and recurrent acute cardiovascular complications risks are approximate and require validation using larger group of patients, with the inclusion of obtained logistic regression parameters into the GRACE stratification scale for greater reliability.

Conflict of interests: None declared.

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Multimorbidity and risk factors of chronic diseases in healthcare workers of a general city clinical hospital

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Objective. *To assess the occurrence of risk factors (RF) and associated multimorbidity in healthcare workers of a general city clinical hospital (CCH).*

Methods. *208 healthcare workers (61 men and 147 women) and 127 non-medical professionals (61 men and 147 women, the control group) who underwent medical examination in the outpatient department of the hospital were included. The age of health workers was 45.9± 16.3 years, non-medical professionals — 45.9± 16.3 years. We performed physical examinations, assessed patient histories, risk factors and associated pathologies. Multimorbidity was considered if a patient had at least two of the following: arterial hypertension, diabetes, coronary artery disease, asthma or cancer.*

Results. *Among healthcare workers, the most common risk factors were unhealthy diet (55.8 %), lack of physical activity (47.2 %), and excess weight. Among non-medical professions — excess weight (77.8 %), unhealthy diet (53.6 %), and low physical activity (31.7 %). Multimorbidity was associated with age (OR 1.05, 95 % CI; 1.02–1.08; p=0.002), work in the internal medicine department (OR 11.8, 95 % CI; 3.1–45.0; p <0.001), family history (OR 3.54, 95 % CI; 1.55–82; p=0.003). The cutoff for increased risk of multimorbidity in healthcare workers was age 48.5 (sensitivity 66 %, specificity 66 %).*

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Conclusion. *Prompt detection of co-existent diseases and early detection of behavioral risk factors during the routine examinations of medical workers can reduce the likelihood of multimorbidity, especially in patients under 48.5 years.*

Keywords: *healthcare workers, chronic non-communicable diseases, multimorbidity, risk factor, health.*

Conflict of interests: None declared.

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Introduction

Recently there has been a rise in the number of individuals with co-existent comorbid chronic diseases, that have negative effects on clinical status, quality of life, ability to work and prognosis of these patients. Therefore, it is necessary to detect these diseases early in order to prevent their further development [1,2]. Multimorbidity is considered in individuals who have at least two chronic diseases that negatively affect their functional status and quality of life and increase the disability rate in the population [3].

High relevance of this problem determines the need of new approaches to early detection of co-existent diseases and their risk factors [4]. Elderly population growth leads to the rising need for healthcare and, therefore, increases the load on the national healthcare systems. Hence, the provision of medical services and information about the main risk factors along with prevention of chronic diseases development and progression are important problems in the healthcare of medical workers [5].

The aim of this study is to assess the prevalence of risk factors and multimorbidity in healthcare workers of a general city clinical hospital (CCH).

Materials and methods

The open-label, simultaneous, comparative non-randomized study included 208 healthcare workers of a general CCH (61 men and 147 women) who were enrolled from January 2019 — June 2019. Of these, 82 (39.2 %) had completed higher education (physicians) and 126 (60.8 %) — secondary specialized education (nursing staff).

The control group included 127 non-medical professionals (61 men and 147 women) who underwent annual check-up in the outpatient department of CCH № 13 in 2019. Of these, 65 (51.2 %) had completed higher education and 62 (48.8 %) — secondary specialized education.

We performed physical examinations, assessed patient histories, risk factors and associated pathologies in both groups.

We considered patients as: having hypertension if blood pressure exceeded 140/90 mmHg [6]; being regular smokers if they smoked at least 1 cigarette per day or quit smoking less than a year ago; having unhealthy diet if they consumed less than 300 grams of fruits and vegetables or added extra salt after cooking [7]; having low physical activity if they exercised less than 150 minutes per week or for 75 minutes per week (15 minutes for 5 days per week) [8]. We used the Quetelet formula to calculate the body mass index (BMI (kg/m^2) = weight (kg)/ height (m) 2). Those with BMI<25 kg/m^2 were considered to be in the healthy weight range, with BMI ⩾30 kg/m2 were considered to be obese, and with BMI between 25 kg/m^2 and 30 kg/m^2 were considered to be over- weight [9].

We confirmed the diagnosis of coronary artery disease (CAD) in patients with typical clinical manifestations, history of previous myocardial infarction (MI), or positive functional tests results [10].

We confirmed the diagnosis of diabetes mellitus based on specific clinical findings and history, laboratory tests results, and endocrinologist reports according to the current guidelines [11]. We considered patients as having multimorbidity if they had at least two of the following: arterial hypertension, diabetes, CAD, asthma or cancer.

Written informed consent was obtained from all participants prior to being enrolled. Study protocol was approved by Pirogov Russian National Research Medical University Ethical Committee (protocol № 178, 22nd of October 2018).

Statistical analysis was completed using the StatPlus: mac version 6 (AnalystSoft Inc, USA),), SPSS Statistics version 20.0 (IBM, USA) statistics software. The results are presented as a mean and standard deviation. We used Mann-Whitney U test to compare quantitative variables and for the comparison of qualitative variables we used Pearson's chi-squared test (χ^2) with Yates correction and Fisher's exact test. The associations between variables were evaluated with Pearson's correlation coefficient (r)

when the compared samples were normally distributed; Spearman's correlation coefficient was used for comparison of small or non-normally distributed samples. To rate the effect of a risk factor we used logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI). A two-tailed p-value less than 0.05 was considered statistically significant.

Results

Among the healthcare workers aged 20–85 years (45.9±16.3), 61 were men aged 22–85 years (39.7±17.6) and 147 were women aged 20–85 years (48.4±15.1), p<0.001. Of those, physicians were at the age of 26–70 years (36.7±12.3) and nursing staff at the age of 20–85 years (51.8±15.9), p<0.001.

Among the healthcare workers who had completed higher education 38 (46.3%) were men aged 22–63 years (36.3±7.1) and 44 were women (53.7%) aged 26–70 years (44±10.9), p=0.435. Among healthcare workers who had completed secondary specialized education 23 (18.2%) were men aged 20–85 years (59.1±11.6) and 103 (81.8%) were women aged 22–85 years (50.1± 12.7), p<0.001.

Our study involved 47 (22.6%) healthcare workers from the internal medicine department (26 (55.3%) physicians and 21 (44.7%) nurses); 48 (23%) from the department of surgery (13 (27%) physicians and 35 (73%) nurses); 7 (3.3%) from the department of gynecology (2 (28.5%) physicians and 5 (71.5%) nurses; 15 (7.3%) from the intensive care unit (8 (53.3%) physicians, 7 (46.7%) nurses); 29 (13.9%) form the functional diagnostics department (11 (37.9%) physicians, 18 (62.1%) nurses); 28 (13.5%) for the department of traumatology (10 (35.7%) physicians and 18 (64.3%) nurses); 10 (4.9%) form the department of neurology (3 (30%) physicians and 7 (70%) nurses); 24 (11.5%) from the department of cardiology (9 (37.5%) physicians and 15 (62.5%) nurses).

Among the healthcare workers, 78 (37.5%) worked 24-hour shifts, and 130 (62.5%) worked only day shifts. Healthcare workers had 2–18 (9.4±4.9) years of seniority: men had 8.3±5.2 years and women had 9.8±4.7, p=0.040.

Age, gender, hemodynamic parameters and BMI were similar in healthcare workers and in the control group participants (Table 1).

Risk factors in healthcare professionals and non-medical professionals are shown in Figure 1.

The prevalence of arterial hypertension was higher in the control group compared with the healthcare professionals group, although we have identified no statistically significant difference between the two groups (p=0.055). In the healthcare professionals group 105 (50.4%) had never smoked compared with 70 (55.2%) in the control group, p=0.477. Among healthcare professionals 98 (47.1% Table) consumed more than 200 ml of wine once a week compared with 70 (55.1%) in the control group.

Table 1. **Characteristics of the healthcare workers group and the control group**

Variable	Healthcare workers n=208	Controls n=127	p
Age, years**	45.9**±16.3**	49.2 **±12.9**	0.050
Male sex, n (%)*	61 (29.3)	34 (26.8)	0.706
Family, n (%)*	89 (42.7)	64 (50.4)	0.176
Smoking cessation, n (%)*	29 (13.9)	28 (22)	0.078
Registered with a clinic, n (%)*	39 (18.7%)	59 (46.4)	<0.001
Regular doctor visits, n (%)*	150 (72.1)	45 (35.4)	<0.001
SBP, mm Hg**	122.7±12.1	121.7±11.4	0.457
DBP, mm Hg **	77.9±8.7	77.8±8.6	0.932
HR, beats per minute**	72.9±5.8	73.2±10.0	0.763
BMI, kg/m^2**	26.8±4.9	27.2±2.4	0.462
Excess weight, n (%)*	80 (38.5)	99 (77.8)	<0.001
Obesity, n (%)*	49 (23.6)	10 (7.9)	<0.001
Arterial hypertension, n (%)*	16 (7.7)	19 (14.9)	0.055
Family history of CVD, n (%)*	84 (40.4)	58 (45.7)	0.404

C**omment:** Here and elsewhere: SBP — systolic blood pressure, DBP — diastolic blood pressure; HR — heart rate; CVD — cardiovascular diseases. Data are: *-absolute number of patients, ** — M±*SD*; p — statistically significant difference between the two groups.

Obesity was more prevalent in the healthcare professionals group (23.6%) compared with the control group (7.9%). At the same time, more participants from the control group were excess weight compared with healthcare professionals.

Both groups had unhealthy diet: 92 (44.2%) healthcare workers consumed less than 300 grams of fruits and vegetables compared with 59 (46.4%) in the control group; 68 (32.7%) healthcare workers added extra salt after cooking compared with 47 (37%) in the control group. Healthcare professionals exercised less compared to the control group.

The prevalence of multimorbidity was similar in healthcare professionals and in the control group (Figure 2). Among healthcare professionals 44 (74.6%) physicians and 15 (25.4%) nurses had non-communicable chronic diseases, p<0.001; 20 (33.9%) men and 39 (66.1%) women. In the control group 8 (20.5%) men and 31 (79.5%) women had multimorbidity (Figure 3).

Characteristics of healthcare workers are shown in Table 2.

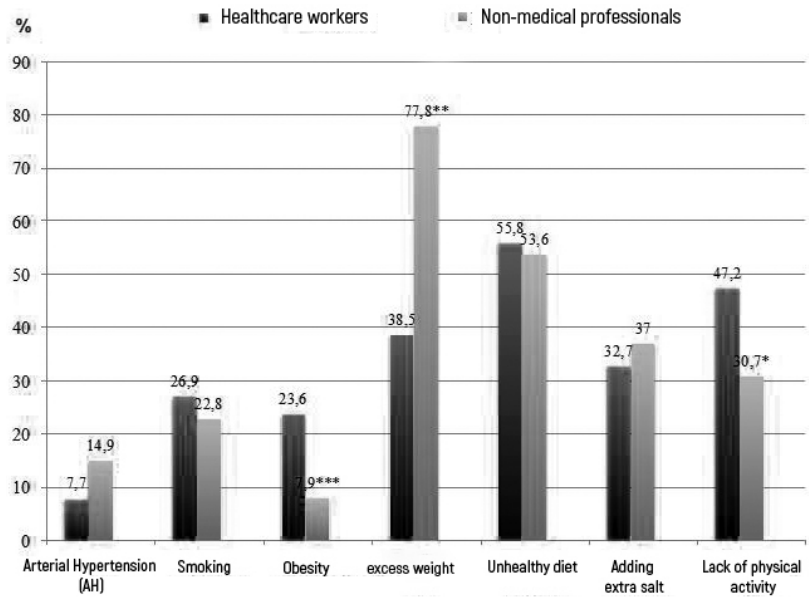

Figure 1. Risk factors in healthcare workers and non-medical professionals; *p* — statistically significant difference between the two groups: * -p=0.005, ** -p=0.001; ***-p=0.002.

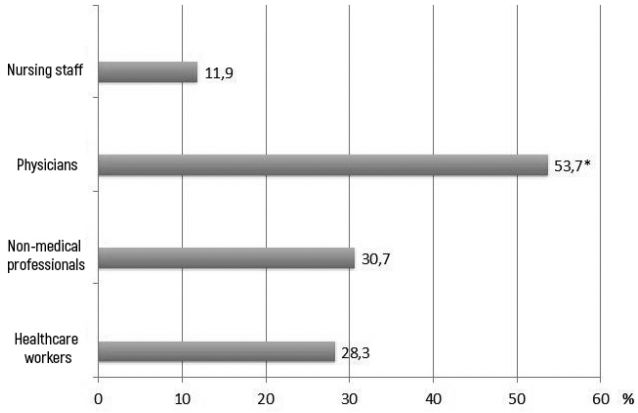

Figure 2. Multimorbidity in healthcare workers (physicians and nursing staff) and non-medical professionals: *-p=0.009 (statistically significant differences between the two groups).

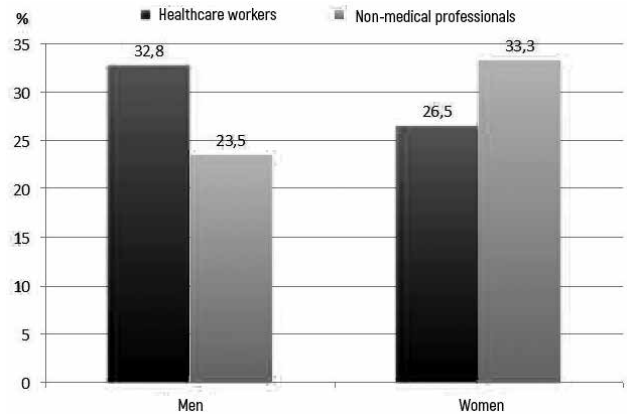

Figure 3. Prevalence of at least two chronic diseases in healthcare workers and non-medical professionals depending on gender.

Older healthcare workers and those who had lower seniority tended to have more comorbid diseases. Hemodynamic parameters and BMI were comparable in both groups of healthcare professionals. We present the characteristics of healthcare workers and non-medical professionals in Table 3.

Age, BMI, blood pressure level and heart rate were similar in healthcare workers and non-medical professionals.

We found positive correlation between the age (p<0.001, r=0.25), work in the internal medicine department (p<0.001, r=0.35), and family history of premature cardiovascular disease (CVD) (p<0.001, r=0.24) of healthcare workers and multimorbidity. We also found negative correlation between active living and multimorbidity (p<0.026, r=-0.15).

Table 2. **Characteristics of healthcare workers with and without multimorbidity**

Value	Multimorbidity		
	Yes (n=59)	No (n=149)	P
Age, years	52.2**±17.5**	43.1**±14.9**	<0.001
Seniority, years	7.1±3.9	10.3**±4**.9	<0.001
BMI, kg/m^2	27.4±3.95	26.6**±5**.3	0.298
SBP, mm Hg	124.9±11.8	121.8±12.1	0.091
DBP, mm Hg.	79.3±8.1	77.36±8.9	0.143
HR, beats per minute	72.3±6.8	73.2**±5**.4	0.334

Comment: Data are M±*SD; p* — statistically significant difference between the two groups.

Multimorbidity was associated with age (OR 1.05; 95 CI 1.02–1.08; p=0.002), work in the internal medicine department (OR 11.8; 95% CI 3.1–45.0, p<0.001), family history of premature CVD (OR 3.54; 95% CI 1.55–8.2; p=0.003).

Table 3. **Characteristics of healthcare workers and non-medical professionals with multimorbidity**

Value	Healthcare workers (n=59)	Non-medical professionals (n=39)	*p*
Age, years	52.9±17.5	50.1±11.31	0.380
MBI, kg/m^2	27.4±3.9	27.1±2.2	0.614
SBP, mm Hg	124.9±11.8	123.3±11.4	0.510
DBP, mm Hg	79.3±8.1	78.8±8.2	0.766
HR, beats per minute	72.3±6.8	73.3±10.22	0.560

Comment: Data are M±*SD; p* — statistically significant difference between the two groups.

The cut-off for point increased risk of multimorbidity in the healthcare workers was age 48.5 (sensitivity 66 %, specificity 66 %). Area under the curve was 0.662±0.045, p=0.001, 95 % CI 0.57–0.75 (Figure 4).

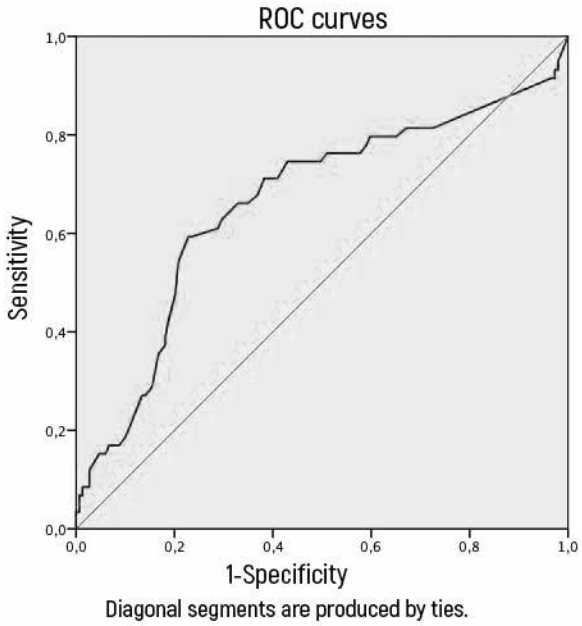

Figure 4. ROC-curve to identify the cut-off for increased risk of multimorbidity in healthcare workers

Discussion

World population ageing and rising life expectancy are accompanied by the increasing number of people who have risk factors such as high blood pressure (19 % of all mortality), excess weight or/and obesity and chronic diseases that undoubtfully affect the development of chronic non-communicable disease complications [12].

The total risk model considers many risk factors that affect the development of one or several diseases and can be effectively used to predict disease progression. Therefore, apart from etiological factors, there are general risk factors that affect the development of multimorbidity.

High workload and responsibility affect emotional and physical health of medical workers, decrease their quality of life, cause diseases and disability. It, therefore, puts healthcare workers in the 'unprotected' segments of the population.

The majority of people involved in healthcare in 2005 were aged 40–44 years and 50–54 years in 2016 [13]. These findings show that the mean age of healthcare workers increases. Therefore, they require special attention in order to stay healthy.

Our study involved 208 healthcare workers (mean age 25.9 years). Of those, 60.8 % were nursing staff. Seniority was 2–18 years (9.4±4.9), 42.7 % had families, 37.5 % worked 24-hour shifts, 62.5 % worked only day shifts. The workers of the internal medicine department and the department of surgery comprised the majority of the sample (22.6 % and 23 % respectively).

High prevalence and low detection of risk factor are still relevant today. Detection of high-risk groups and primary advising of the importance of reducing risk factors are the most important goals of primary health care. It should be applied on the physicians working with healthcare professionals with special attention [14].

Unhealthy diet was the most prevalent risk factor in the healthcare workers (55.8 %). Lack of physical activity was second most prevalent risk factor in this group (47.2 %), followed by excess weight (38.5 %). In general, excess weight was more prevalent in the control group (77.8 %), p<0.001.

We also frequently detected the following risk factors in healthcare workers: adding extra salt after cooking (32.7 %), smoking (26.9 %), obesity (23.6 %), arterial hypertension (7.7 %).

Among non-medical professionals excess weight (77.8 %) was the most prevalent risk factor, followed by unhealthy diet (53.6 %) and low physical activity (31.7 %).

We would like to emphasize the importance of behavioral risk fa**c**tors that people voluntarily let to appear in their lives. Some risk factors are closely related with childhood eating habits that to a large extent determine physical health. Unhealthy eating is associated with over 2 million death cases that are caused by CVD. Lack of fresh fruits in diet (12.5 %) and high sodium concentration in food products (12.0 %) compromise the majority of lethal cases [15]. Excessive salt intake is a significant behavioral risk factor that is widespread in Russia (49.9 %) and is associated with economical loss [16]. Findings of 'Epidemiology of cardiovascular disease in Russian regions' study

show that half of Russia's population aged 25–64 years consume excessive amounts of salt (more men than women) [17].

Both physicians (48.8 %) and nursing staff (60.3 %) had an unhealthy diet (p=0.136). The majority of non-medical professionals (53.6%) had lack of fresh fruits and vegetables in their diets, although no difference between non-medical and healthcare professionals was identified (p = 0.692).

Both non-medical professionals and healthcare professionals added extra salt after cooking (37 % and 32.7 % respectively). Physicians were more likely to add extra salt (39.7 %) compared with nursing staff (32.5 %). This is consistent with the fact that 67.6 % of physicians have an unhealthy diet and consume less than 400 grams of fresh fruits and vegetables [18], and 68.3 % of healthcare workers of CCH add extra salt after cooking [19].

Kobyakova et al. [20] identified lack of physical activity (less than 30 minutes of walking per day) in 45.7 % of physicians (mean age 42.02 years). Tkachenko et al. [19] also identified high prevalence of low physical activity in 74.7 % of healthcare workers of CCH (one out of five was a physician and one out of four was a nurse, mean age 51.6 years).

Our findings are fully consistent with the modern experts' position that complex measures, such as life and work habits modification and formation of positive environment offering support for those trying to live healthy are necessary [21].

Excess weight and obesity are additional problems associated with high risk of cardiovascular disease [7]. 'Epidemiology of cardiovascular disease in Russian regions' study showed that the general prevalence of obesity was 29.7±0.3 %, 30.8±0.4 % in women and 26.6±0.5 % in men (p<0.001).

Kobyakova et al. [20] identified that 34.7 % of Tomsk Oblast physicians aged 42.0±11.3 years were excess weight. Tkachenko et al. [19] also identified high prevalence of obesity (42.5 %) and unhealthy diet (37.1 %) in healthcare workers of CCH aged 51.6 (90.6 % were women).

According to our findings, obesity was less prevalent in physicians (14.6 %) compared with nursing staff (29.3 %), p=0.023. It is consistent with the 'Epidemiology of cardiovascular disease in Russian regions' study findings that education status influences eating habits in adult population. Russian population who had completed higher education tend to have healthier eating habits. Compared with those who had completed secondary specialized education they consume more fresh fruits and vegetables, less salt and animal fat, irrespectively of gender [22]. Most European studies also show that more educated people eat more fruits and vegetables [23].

Smoking is one of the most widespread and significant behavioral risk factors of CVD and their complications. It is crucial to reduce this risk factor in order to reduce mortality rate and improve prognosis of people with and without CVD [24].

According to the 'Epidemiology of cardiovascular disease in Russian regions' study the prevalence of smoking was 25.7±0.3 %. in adults aged 25–64 years. The prevalence of smoking was similar in men (24.6 %) and women (27.9 %). Kobyakova et al. [20] identified that 15.1 % of physicians smoked (mean age 42.02 years). In our study the prevalence of smoking was similar in healthcare workers (26.9 %) and in non-medical professionals (22.8 %), p=0.481. In healthcare workers smoking was less prevalent in physicians (19.5 %) compared with nursing staff (31.7 %), p=0.075. There was no difference in the number of people who had never smoked in healthcare workers compared with non-medical professionals. However, in healthcare workers there were more physicians (68.3 %) who had never smoked compared with nursing staff (38.9 %), p<0.001.

Many studies confirm that behavioral risk factors such as smoking are incredibly widespread [19]. The prevalence of smoking in physicians over 40 years (50.5±11.7) was 14 %, 39 % in men and 6.7 % in women [25]. Zadionchenko et al. showed that 37 % of physicians are regular smokers and 10 % smoke only occasionally [26]. These results indicate that it is important to change the attitude towards smoking in healthcare professionals. Being smokers themselves the majority of physicians are not able to fully support their patients in achieving healthier lifestyle.

It is not possible to fully compare our findings with the findings of other studies on risk factors in healthcare workers. Investigators compare groups with different characteristics, such as inclusion criteria, gender, age or type of medical institution. It is clear, though, that main risk factors are highly prevalent in healthcare workers. Low physical activity, unhealthy diet and obesity are the leading risk factors that contribute to multimorbidity development. We hope that in the future individual characteristics of patients will be considered together with risk factors in order to improve diagnosis and treatment of a multimorbid patient [7].

Multimorbidity risk factors are divided into non-modifiable (age, gender, race) and modifiable. Modifiable risk factors such as arterial hypertension,

obesity, lack of physical activity, smoking) are strongly associated with cardiovascular diseases. These findings show that multimorbidity may be prevalent not only in older patients but also in the younger ones.

Findings of Cardiovascular Disease Registry that involved 3690 out-patients with arterial hypertension, coronary artery disease, and atrial fibrillation show that 77.5 % of patients aged 66.1 ± 12.9 had several CVD [27].

There are sparse data on multimorbidity prevalence in healthcare workers. Navrotsky et al. [28] identified that 66.1 % of healthcare workers have at least two CVD. According to a survey carried out by Zadionchenko et al. [26], 68 % of healthcare workers had arterial hypertension (30.5 %), CAD (17.6 %), and diabetes mellitus (2.6 %). According to Nikolaeva et al. [29], CVD were highly prevalent in physicians (53.5 %) and nursing staff (46.7 %).

According to our findings one out of three healthcare workers and non-medical professionals had chronic non-communicable diseases. The prevalence of multimorbidity was higher in in physicians compared with nursing staff (p=0.009), although the mean age of physicians was lower (p<0.001). Multimorbidity was more prevalent in the older healthcare workers (54<5 years) compared with those of younger age (40.9 years), p<0.001 (9 % men, 91 % women; 56 % physicians, 44 % nursing staff). Therefore, our findings show that the prevalence of multimorbidity increases with age (OR 1.05; p=0.002). Multimorbidity burden requires special attention to physical health of healthcare workers.

Today it is well confirmed that prevalence of diseases increases with age: in people aged 20–29 years the prevalence is 136.2 per 100 full-time workers; in people aged 40–49 years — 176.3 per 100 full-time workers. Hospital managers and physicians tend to have more illnesses (190.2 and 167.7 per 100 full-time workers respectively) [30]. We obtained similar results in our study.

Our study showed that working in healthcare is a health risk by itself as medical workers suffer from significant workload and emotional stress. Among healthcare workers, multimorbidity was associated with age, work in the internal medicine department (OR 11.8; p<0.001) and family history (OR 3.54; p=0.003). The cut-off for increased risk of multimorbidity in the healthcare workers was age 48.5.

Behavioral risk factors are the most prevalent risk factors in healthcare workers. Multimorbidity was more prevalent in physicians (74.6 %) and women (66.1 %). Multimorbidity was associated with age, work in the internal medicine department and family history.

Conclusion

The obtained results show that it is important to detect co-existent diseases and behavioral risk factors (unhealthy diet, lack of physical activity, and excess weight) early during the routine examinations of medical workers as it can reduce the likelihood of multimorbidity. It is also important to ask the patients about their jobs during routine examinations in order to identify high-risk groups.

We have concluded that:

1. The most common risk factors for chronic non-communicable diseases in healthcare workers were unhealthy diet (55.8 %), lack of physical activity (47.2 %), excess weight (38.5 %);

2. Obesity (23.6 %), lack of physical activity (47.2 %), and low medical knowledge (52.4 %) were more prevalent in healthcare workers compared with non-medical professionals; obesity and lack of physical activity were more prevalent in nursing staff compared with physicians.

3. Multimorbidity was prevalent in 28.3 % of healthcare workers aged 45.9 years (74.6 % in physicians and 66.1 % in women). Multimorbidity was associated with older age (over 48.5 years) and family history

4. High-risk groups with priority in chronic non-communicable diseases prophylaxis are: healthcare workers (especially nursing staff) in CCH with obesity and lack of physical activity.

Conflict of interests: None declared.

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Individualization of ventricular extrasystoles pharmacotherapy in patients without cardiac structural changes

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Objective. *To assess the analysis of ventricular extrasystoles (VEs) as the method for individualization of VE pharmacotherapy in patients without cardiac structural changes.*

Materials and methods. *The study included 248 patients aged from 20 to 43 years without cardiac structural changes with IV–V classes of VEs according to B. Rayn classification (1984). VE antiarrhythmic therapy was selected individually, its effectiveness was assessed using daily electrocardiogram. VEs were analyzed according to generally accepted criteria, including the duration of VEs and sinus rhythm QRS complex duration (QRSve and QRSsr). The endpoint was the duration of antiarrhythmic therapy positive effect on the VEs.*

Results. *29.84 % of patients had the greatest positive antiarrhythmic effect of VEs therapy when using class II of antiarrhythmic drugs, 43.95 % — class I, the rest — class III. Positive predictive value of class III antiarrhythmic*

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drugs with QRSve complex duration ≥ 160 ms was 89.23 %, class II –QRSve ≤ 159 ms was 95.63 %. 22.58 % of patients had positive antiarrhythmic effect during 1 year of follow-up (0.86 ± 0.05 years on average), the rest — from 1 to 5 years (3.71 ± 0.11 years on average). The duration of VEs therapy positive effect using class III antiarrhythmic drugs for 1 year correlated with QRSve complex duration ≤ 165 ms (r = 0.91), while classes I and II — QRSve ≤ 145 ms (r = 0, 92).

Conclusion. *All patients without cardiac structural changes, when choosing antiarrhythmic therapy for VE treatment, should consider the duration of QRS. The duration of VEs treatment positive effect during 1 year highly correlated with (at r > 0.90) class III antiarrhythmic drugs, with QRSve duration ≤ 165 ms, classes I and II — with QRSve ≤ 145 ms.*

Key words: *ventricular extrasystoles, individualization of ventricular extrasystoles pharmacotherapy.*

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Introduction

Currently, patients with frequent and stable ventricular extrasystoles (VEs), including patients without cardiac structural changes, in order to select an effective VE pharmacotherapy undergo antiarrhythmic drugs titration that includes an assessment of the frequency and nature of premature complexes according to daily electrocardiogram (ECG) monitoring before and after antiarrhythmic medication intake in medium therapeutic dose for at least 4–5 days [1,2]. However, the definition of VE differentiated antiarrhythmic therapy depending on the nature of premature ventricular complexes in patients without cardiac structural changes has not been given according to the literature available.

Objective of the study — to assess the analysis of ventricular extrasystoles (VEs) as the method for individualization of VE pharmacotherapy in patients without cardiac structural changes.

Materials and methods

The study included 248 patients aged from 20 to 43 years (average age 29.6 ± 0.8 years) — 129 (52.02 %) women and 119 (47.98 %) men (p > 0.05). Inclusion criteria were: the absence of cardiac structural changes, sinus rhythm, the III–V classes of VEs according B. Rayn classification (1984) [1], the sensation of irregular heartbeat, chronic heart failure I–II NYHA class and the presence of signed informed consent to participate in research. The absence of cardiac structural changes was established after the exclusion of cardiac and extracardiac diseases, electrolyte imbalance, the use of medications and /or toxic substances (primarily diuretics, oral contraceptives, alcohol abuse, etc.) that independently or indirectly lead to the development of VEs [3].

In addition to physical examination, all the patients underwent 1–3-day ECG monitoring and an echocardiographic study using the Hitachi EUB-5500 apparatus according to common methods. The calculation of indicators such as the left ventricular ejection fraction (LV EF), left atrium end diastolic volume index, left ventricular mass index, the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole (the A wave) were described previously [3, 4].

VEs analysis was carried out according to generally accepted criteria, including determining the duration of VE and sinus rhythm QRS complexes (QRSve and QRSsr.), the pre-ectopic interval of ventricular ectopy, etc. using a Poly-Spectrum digital electrocardiograph (Neurosoft, Ivanovo) at ECG recording speed of 100–200 mm/sec [1, 3, 4]. In all patients, the risk index of the development of life-threatening ventricular arrhythmias (LTVA) was calculated [3] by the formula: LTVAR = A ÷ B, where LTVAR is LTVA risk in units, A — linear deviation (LD) of corrected pre-ectopic interval PEIcor VE (ms) for at least 20 ventricular extrasystoles, calculated separately for left ventricular extrasystoles (LVE) and right ventricular extrasystoles (RVE), and B — analyzed ventricular extrasystole number (per hour). LTVAR < 0.5 could be a marker of high LTVA risk [1,3].

After daily monitoring of ECG all the patients had cardioprotective therapy, including potassium, sedation therapy, polyunsaturated fatty acids (VITRUM cardio Omega 3, Unifarm, etc.), to eliminate VEs [3]. In case of no effect, differentiation of VE antiarrhythmic therapy was carried out using I–III classes antiarrhythmic agents testing in medium therapeutic doses. When selecting antiarrhythmic medication in order to eliminate VEs in patients with-

Table 1. **The state of hemodynamics, some clinical parameters in groups I, II and III when included in the study (M±m, in brackets — 95% confidence interval of average values)**

Groups of patients / Parameters	Group I n=74	Group II n=109	Group III n=65
Age, years	30,1±1,3 (22–43)	29,9±0,9 (21–42)	28,9±1,2 (20–41)
BMI, kg/m^2	22,3±0,4 (20–24)	22,1±0,1 (19–23)	21,9±0,1 (19–25)
LV EF, %	53,86±0,88 (48–59)	53,12±0,78 (47–61)	54,12±0,78 (47–61)
E/A, units	1,19±0,01 (1,12–1,21)	1,20±0,01 (1,14–1,23)	1,21±0,01 (1,17–1,24)
LA EDVI, ml/m^2	23,56±0,72 (17–31)	23,24±0,69 (18–30)	23,24±0,64 (18–29)
LVMI, g/m^2	86,7±1,6 (74–99)	85,3±1,7 (72–101)	86,3±1,7 (72–101)
The number of VEs during 24hour-follow-up	18 900±2450 (5870–30 730)	18 990±2190 (4980–31 700)	19 890±1970 (5980–32 900)
QRSve, ms	142±2 (125–155)	144±2 (130–159)	179±3 (155–195)*†
QRSsr, ms	92±1 (80–99)	93±1 (89–98)	102±1 (95–108)*†
QRSve/QRSsr	1,54±0,02 (1,42–1,57)	1,55±0,01 (1,46–1,63)	1,74±3 (1,61–1,82)*†
LTVAR, units	0,23±0,02 (0,05–0,41)	0,21±0,02 (0,06–0,42)	0,07±0,01 (0,01–0,24)*†

Comment: BMI — body mass index, LA EDVI — left atrium end diastolic volume index, LVMI — left ventricular mass index
* the differences are significant compared with group I, † — group III compared with group II (p<0,05).

out cardiac structural changes we noted: the character of ectopic beats, its prognostic assessment, the presence of contraindications and possible development of adverse effects [1,3]. Initially, patients were prescribed class II antiarrhythmic drugs, in case of its ineffectiveness — class I or III medications, amiodarone was the last medication to be used. We used metoprolol — 50–100 mg/day, propranolol — 80–160 mg/day, allapinin — 50–75 mg/day, moracizine — 50–100 mg/day, ethacizine — 100–150 mg / day, sotalol — 160–240 mg/day, propafenone — 300–600 mg/day and amiodarone — 600–800 mg/day. The duration of antiarrhythmic therapy was at least 4–5 days, and 8 (10) days for amiodarone. Each subsequent medication was prescribed, after at least 5 half-lives of the previous one [1,3]. All the patients underwent daily ECG monitoring before and after antiarrhythmic therapy, the positive effect criteria included the frequency of extrasystoles decrease over 75% compared with its initial level and the elimination of paired and group extrasystoles [1, 2, 3]. All the patients underwent daily ECG monitoring initially and once in 3–4 days during 7–14 days of antiarrhythmic therapy in order to exclude its arrhythmogenic effect, especially when using Ic class antiarrhythmic agents [1,2,3].

The duration of follow-up ranged from 1 year to 5 years. The observation endpoint was the duration of preserved positive antiarrhythmic effect of the therapy. All the studies, including daily ECG monitoring, were carried out at least once per 3–4 months, monitoring of patients' condition and ECG registration — once a month. Patients performed regular monitoring of their blood pressure and heart rate themselves. Statistical processing of the results was carried out using Student's t-test and χ^2 test and using Statistica 11.0 software.

Results

Metoprolol was the most effective in 43 (17.34%) patients, propranolol in 31 (12.50%), ethacizine in 34 (13.71%), allapinin in 20 (8.06%), propafenone in 55 (22.18%), sotalol in 52 (20.97%) and amiodarone — in the rest. Patients were divided into three groups. 74 (29.84%) patients had the most positive antiarrhythmic effect when using class II agents (group I), 109 (43.95%) patients — class I (group II), and the rest — class III (group III). 17 (22.97%), 25 (22.94%), and 16 (24.62%) patients of groups I, II, and III, respectively, had from 6% to 15%, and the rest over 15% of total ventricular complexes number per day of observation, respectively (p> 0.05). 19 (25.68%), 29 (26.61%) and 18 (27.69%) patients of groups I, II and III, respectively, had episodes of unstable ventricular tachycardia (p> 0.05). 34 (40.48%), 51 (46.79%) and 31 (47.69%) patients of groups I, II and III, respectively, had LVE, in the rest — RVE (p> 0.05), 31 (41.89%), 44 (40.37%) and 27 (41.54%) patients — polymorphic, the rest — monomorphic VEs (p <0.05). After the inclusion in the study, patients from group III showed significantly longer QRSve complex, QRSsr, QRSve / QRSsr ratio, as well as significantly lower LTVAR compared with groups I and II, while there were no significant differences in gender and age, the state of hemodynamics, body mass index, the number of ventricular extrasystoles per day of observation in patients from groups I, II and III (Table 1).

Table 2. **The state of QRSve, QRSve / QRSsr ratio in patients of groups I, II, and III, with the duration of positive VE therapy effect for over (A) and less than a year (B) (M±m, in brackets — 95% confidence interval of average values)**

Groups pf patients	Group I		Group II		Group III	
Parameters	A n=57	B n=17	A n=82	B n=27	A n=53	B n=12
QRSve, ms	137±2 (125–145)	148±2* (140–155)	139±1 (130–145)	152±2* (140–160)	162±1 (155–165)	183±2* (160–195)
QRSve/ QRSsr.	1.45±0.01 (1.42–1.48)	1.51±0.01* (1.46–1.57)	1.46±0.01 (1.44–1.49)	1.57±0.01* (1.48–1.63)	1.63±0.01 (1.61–1.66)	1.72±0.01* (1.64–1.81)
LTVAR, units	0.92±0.08 (0.62–1.21)	2.94±0.14* (1.12–4.57)	0.84±0.07 (0.64–1.43)	2.93±0.07* (1.37–4.63)	0.85±0.12 (0.31–1.36)	2.67±0.18* (1.24–4.41)

* The differences are significant compared with the duration of positive VE therapy effect for over a year (A) ($p < 0.05$).

The number of premature ventricular complexes compared with initial data decreased from 76% to 92% (82 ± 2% on average), from 77% to 96% (average 84 ± 1%) and from 75% to 98% (an average of 83 ± 2%) ($p > 0.05$), in patients from groups I, II and III, respectively, after choosing the most effective VE therapy. LTVAR increased from 0.23 ± 0.02 units to 2.71 ± 0.32 units ($p < 0.05$), from 0.21 ± 0.02 to 2.84 ± 0.36 ($p < 0.05$), from 0.07 ± 0.01 to 2.43 ± 0.24. ($p < 0.05$) in patients of these groups, respectively. Decreased number of VEs after choosing an effective therapy negatively correlated with LTVAR increase ($r = -0.94$). The positive effect of VE therapy with class III antiarrhythmic agents highly correlated with the duration of the QRSve complex ≥ 160 ms and the QRSve / QRSsr ratio ≥ 1.6 units ($r = 0.94$ and $r = 0.92$, respectively), while with classes I and II — with QRSve ≤ 159 ms and the QRSve / QRSsr ratio ≤ 1.59 units ($r = 0.96$ and $r = 0.94$, respectively). Sensitivity, specificity and positive prognostic significance of class III agents positive effect with QRSve duration ≥ 160 ms and QRSve / QRSsr ratio ≥ 1.6 units amounted to 90.28%, 95.81% and 89.23%, respectively, and class II — QRSve ≤ 159 ms and the QRSve / QRSsr ratio ≤ 1.59–94.54%, 85.29% and 95.63%, respectively. Positive antiarrhythmic effect of VE therapy highly correlated with LD PEICor VE ≥ 11 ms ($r = 0.88$) in patients from groups I and II, while in group III — ≤ 10 ms ($r = 0.84$).

17 (22.47%), 27 (24.77%), and 12 (18.46%) patients from groups I, II, and III, respectively, had persisted positive VE therapy effect for 1 year (0.81±0, 05, 0.86±0.05, 0.92±0.05 years on average, respectively), in the rest of patients — from 1 year to 5 years (3.5±0.09, 3.7±0, 11 and 3.9±0.12 years on average, respectively) ($p < 0.05$). Patients with the duration of the antiarrhythmic effect over 1 year from groups I, II, and III had significantly less QRSve complex duration and QRSve/QRSsr ratio, as well as significantly higher LTVAR (Table 2). The duration of VE preserved positive effect during class III antiarrhythmic drugs therapy for over 1 year correlated with QRSve complex duration ≤ 165 ms and the ratio of QRSve / QRSsr. ≥ 1.66 ($r = 0.91$ and $r = 0.89$, respectively), while classes I and II — QRSve ≤ 145 ms and the QRSve / QRSsr ratio ≤ 1.49 ($r = 0.92$ and $r = 0.90$, respectively).

Discussion

Ventricular heart rhythm disturbances including VE management is one of the most complex problem that often prevent the development of life-threatening arrythmias including ventricular tachycardia and ventricular fibrillation [1,2]. Despite the favorable prognosis of VE in patients without cardiac structural changes according to B. Bigger (1984) classification [1], this category of patients needs VE antiarrhythmic therapy in case of subjective sensations of extrasystoles, which affect life quality, and prevention of arrhythmogenic cardiomyopathies and fatal arrythmias [1, 2, 3, 5].

The study included 248 patients aged from 20 to 43 years (average age 29.6±0.8 years). Inclusion criteria were: the absence of cardiac structural changes, sinus rhythm, VE III–V classes according to the classification of B. Rayn (1984) [1], the sensation of irregular heartbeat, chronic heart failure I–II NYHA classes, the presence of signed informed consent to participate in research. The absence of cardiac structural changes was established after exclusion of cardiac and extracardiac diseases, electrolyte imbalance, the use of medications and /or toxic substances that independently or indirectly lead to the development of VEs [3].

In 23,39% of the examined patients, VE comprised 6% to 15% of the total ventricular complexes per day. The rest of patients had over 15% of VE per day. 26.61% of patients had episodes of unstable ventricular tachycardia. 41.12% of patients had polymorphic and the rest — monomorphic VEs.

Nowadays radiofrequency ablation of arrhythmogenic focus is indicated in patients without cardiac

structural changes, with over 15 % of VE of total ventricular complexes number, especially in patients without antiarrhythmic therapy effect or when patient refuses to intake antiarrhythmic therapy [1,2]. This term was the basis for pharmacological antiarrhythmic therapy in patients included in the study.

All the patients underwent fatal ventricular arrythmias risk estimation using LTVAR as LD PEICor VE to the number of VE used for research (VE per hour) ratio [3, 4]. All the patients included in the study had LTVAR index < 0.5 units that indicated high risk of life-threatening ventricular arrythmias [3, 4].

In this study we used antiarrhythmic medications testing in order to select VE antiarrhythmic therapy for all patients [1]. Initially, patients were prescribed class II antiarrhythmic drugs, in case of its ineffectiveness — classes I or III drugs were prescribed, amiodarone was the last medication to be used. All the patients underwent daily ECG monitoring before and after antiarrhythmic therapy, the positive effect criteria included the frequency of extrasystoles decrease over 75 % compared with its initial level and the elimination of paired and group extrasystoles [1, 2, 3]. The duration of antiarrhythmic therapy was at least 4–5 days, and in the case amiodarone — 8 (10) days. After the inclusion in the study, the follow up ranged from 1 to 5 years. The observation endpoint was preserved positive effect of antiarrhythmic therapy.

29.84 % of patients had the greatest positive antiarrhythmic effect of VE therapy during class II antiarrhythmic agents' therapy, 43.95 % — class I, the rest — class III. The positive result of VEs therapy with class III antiarrhythmic agents highly correlated with QRSve complex duration ⩾ 160 ms and the QRSve / QRSsr ratio ⩾ 1.6 units (r = 0.94 and r = 0.92, respectively), while classes I and II — with QRSve ⩽ 159 ms and the QRSve / QRSsr ratio ⩽ 1.59 units (r = 0.96 and r = 0.94, respectively). Positive prognostic significance of class III antiarrhythmic medications positive effect with the duration of QRSve complex ⩾ 160 ms and QRSve / QRSsr ratio ⩾ 1.6 units was 89.23 %, and the significance of classes I and II with QRSve ⩽ 159 ms and the QRSve / QRSsr ratio ⩽ 1.59–95.63 %. The data obtained, apparently, should be taken into account when choosing differential VE therapy in patients without cardiac structural changes.

Nowadays the QRS complex duration over 140 ms is considered one of the arrhythmogenic cardiomyopathy development predictors in patients without cardiac structural changes, and the significance of this indicator directly correlates with QRSsr duration increase. [5,6,7]. The cause of QRS complex expansion in this category of patients has not been studied yet, however, most authors claim that the increase of QRS duration is associated with "oxidative stress" in cardiomyocytes, hyperpolarization of myocardial cell membranes, cardiac excitation slowdown, cardiac fibrosis, etc. [5,6,7,8].

All examined patients had negative correlation between decreased VE frequency after choosing an effective VE therapy and LTVAR increase (r = –0.94). Therefore, this index can be used as additional criterion for VE therapy effectiveness evaluation.

LTVAR was proposed to assess the risk of fatal ventricular arrhythmias development, its increase was associated with decreased risk of fatal arrhythmias and/or effectiveness of antiarrhythmic therapy, and vice versa [3,4]. Similar principle was proposed for the detection of atrial fibrillation using the risk index for the development of this arrhythmia in patients with atrial extrasystoles. The increase of this indicator during antiarrhythmic therapy compared with initial data was associated with positive therapy effect, used for the atrial fibrillation primary prevention [9,10]. LTVAR had similar changes in positive antiarrhythmic VE therapy effect assessment according to data obtained in this study.

Positive antiarrhythmic effect persisted for 1 year in 22.58 % of patients (0.86 ± 0.05 years on average), from 1 year to 5 years in the rest (3.71 ± 0.11 years on average). The duration of preserved VE therapy positive effect using class III antiarrhythmic drugs for over 1 year correlated with the duration of the QRSve complex ⩽ 165 ms and the QRSve / QRSsr. ratio ⩾ 1.66 (r = 0.91 and r = 0.89, respectively), while when using classes I and II — QRSve ⩽ 145 ms and the QRSve / QRSsr ratio ⩽ 1.49 (r = 0.92 and r = 0.90, respectively). It is remarkable that the decrease of premature ventricular complexes number compared with initial data after choosing the most effective VE therapy, regardless of the class of medication — I, II and III, did not differ significantly and averaged 83 %. This shows that the decrease of ventricular extrasystoles number detected during antiarrhythmic drugs testing does not determine the duration of preserved VE positive effect.

Previously obtained data showed that LTVAR increase two or more times compared with the initial data after second and/or third intake of antiarrhythmic medications determines one or more potentially effective antiarrhythmic agents [11]. Subsequently, medication with predicted positive antiarrhythmic

effect duration, including according to data obtained in this study for one year or more, should be used as long-term VE therapy in patients without cardiac structural changes. The above hypothesis will be the subject of further research.

According to the results, positive clinical effect of class II drugs usage highly correlated with LD PEICor VE ≥ 11 ms (r=0.88), while I, III classes and a combination of classes II and I — ≤ 10 ms (r=0.84). These data are notable for patients without cardiac structural changes when choosing differentiated VE antiarrhythmic therapy.

Many previous clinical and experimental studies have shown that identified indicators of LD PEICor VEs, for example, ≤ 10 ms, indirectly confirm the mechanism of "re-entry" and/or the formation of pathological ectopic focus, and the large variability of this indicator — the presence of trigger mechanisms [4]. Therefore, after several antiarrhythmic agents intake, in the presence of trigger mechanisms, cardiomyocytes membrane hyperpolarization decreases that manifests as PEICor increase, then — VE frequency decrease, and after the formation of excitation waves, for example, by "re-entry" mechanism, it fractionizes and divides into two waves that become independent that leads to the appearance of various PEICor premature complexes on ECG and then, when instead of a unilateral block, complete block develops, ectopy stops or its decrease is observed [1,4].
The duration of positive VE antiarrhythmic therapy effect in patients without cardiac structural changes for less than a year can be explained by, firstly, trigger mechanisms transformation (early or delayed afterdepolarization) of ventricular ectopy development, for example, into "re-entry" and vice versa [1], secondly, ion channels damage and / or decreased sensitivity of cardiomyocyte receptors to antiarrhythmic agents, in particular, agents with sympatholytic effect due to "oxidative stress" [1,5,6.7,8], thirdly, premature ventricular complexes might appear before latent myocarditis, cardiomyopathy, arrhythmogenic right ventricular dysplasia development, etc., and pharmacotherapy of these diseases is mainly ineffective or has short-term positive result [1]. Therefore, in patients without cardiac structural changes, radiofrequency ablation of the arrhythmogenic focus is the method of ventricular ectopia treatment in predicting the effectiveness of VE pharmacological antiarrhythmic therapy for less than a year, especially in patients with over 15% extrasystoles of total ventricular complexes, as well as with arrhythmogenic cardiomyopathy and life-threatening ventricular arrhythmias predictors [1,2,6].

Conclusion

All patients without cardiac structural changes, when choosing antiarrhythmic therapy for VE treatment, should consider the duration of QRSve. Positive prognostic significance of class III antiarrhythmic drugs with VEs QRS complex duration ≥ 160 ms was 89.23%, class II –QRSve ≤ 159 ms was 95.63%. 22.58% of patients had positive antiarrhythmic effect during 1 year of follow-up (0.86±0.05 years on average), the rest — from 1 to 5 years (3.71±0.11 years on average). The duration of VE therapy positive effect using class III antiarrhythmic drugs for 1 year correlated with QRS complex duration ≤ 165 ms (r=0.91), while classes I and II — QRSve ≤ 145 ms (r=0, 92). The degree of ventricular extrasystoles frequency decrease detected during antiarrhythmic agents testing does not correlate with the duration of VE therapy positive effect in patients without cardiac structural changes.

We have concluded that:

1. Positive prognostic significance of class III antiarrhythmic drugs with QRSve duration ≥ 160 ms and a QRSve / QRSsr ratio ≥ 1.6 was 89.23%, class II — with QRSve ≤ 159 ms and the QRSve / QRSsr. ratio ≤ 1.59– 95.63%.

2. 22.58% of patients had positive antiarrhythmic effect during 1 year of follow-up (0.86±0.05 years on average), the rest — from 1 to 5 years (3.71±0.11 years on average).

3. The duration of VEs therapy positive effect using class III antiarrhythmic drugs for 1 year correlated with QRS complex duration ≤ 165 ms and the QRSve / QRSsr. ≥ 1.66 ratio (r=0.91 and r=0.89, respectively) (r=0.91), while classes I and II — QRSve ≤ 145 ms and QRSve / QRSsr. ratio ≤ 1.49 (r=0.92 and r=0.90, respectively).

4. The degree of ventricular extrasystoles number decrease detected during antiarrhythmic agents testing does not correlate with the duration of VE therapy positive effect in patients without cardiac structural changes.

Conflict of interests: None declared.

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REVIEW ARTICLE

European Society of Cardiology Congress (Paris, 2019): results of the most important clinical studies

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Summary. *The review article contains a report on the 25 most important clinical trials that were presented at the Hot Line sessions of the European Society of Cardiology (Paris, France, August 31 — September 4, 2019).*

Key words: *cardiology, cardiovascular diseases, clinical trials.*

Conflict of interests: None declared.

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European Society of Cardiology (ESC) Congress together with World Congress of Cardiology, the largest annual scientific and clinical cardiovascular congress, was held in Paris, France from the August 31st to September 4th. It was attended by 32.000 health care workers from 150 countries who took part in over 500 expert sessions.

Five new ESC Clinical Guidelines were presented at ESC Congress 2019:

- Guidelines on diabetes, pre-diabetes, and cardiovascular diseases [1];
- Guidelines for the diagnosis and management of acute pulmonary embolism [2];
- Guidelines for the management of patients with supraventricular tachycardia [3];
- Guidelines for the diagnosis and management of chronic coronary syndromes [4];
- Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk [5].

Full guidelines are available on: https://www.escardio.org/guidelines/clinical-practice-guidelines.

Of particular interest were 25 randomized trials that were recently finished and presented on six Hot Line sessions.

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HOT LINE Session 1

Patients with stable coronary artery disease (CAD) and type 2 diabetes mellitus (DM) are at a high risk of cardiovascular disease (CVD) that can be explained by increased platelet aggregation. The **THEMIS** study [6] suggested that ticagrelor addition during aspirin treatment may lead to atherothrombotic events risk reduction in these patients.

Randomized double blind study involved patients over 50 years of age with stable CAD and type 2 diabetes who were administered ticagrelor (initial dose 90 mg twice daily was later decreased to 60 mg twice daily after the PEGASUS-TIMI 54 study results were received) and aspirin (n=9619) or placebo and aspirin (n=9601). Patients with previous myocardial infarction (MI) or stroke were excluded. Treatment was cancelled more frequently in patients taking ticagrelor compared with those taking placebo (34.5% versus 25.4% respectively). During a median follow-up of 39.9 months the frequency of composite primary efficacy endpoint (cardiovascular death, MI or stroke) was lower in the ticagrelor group compared with placebo group (7.7% versus 8.5% respectively; relative risk (RR) 0.9, 95% confidence interval (CI) 0.81–0.99; p=0.04). Incidence of TIMI major bleeding (primary safety endpoint) was also significantly higher in the ticagrelor group (2.2% versus 1.0% respectively, RR 2.32; 95% CI 1.82–2.94; p<0.001), as well as frequency of intracranial bleeding (0.7% versus 0.5% respectively; RR 1.71; 95% CI 1.18–2.48; p=0.005), but fatal hemorrhages were registered with similar frequency (0.2% versus 0.1% respectively; RR 1.9; 95% CI 0.87-4,15; p=0.11). There was no significant difference in the total number of 'outcomes with irreversible damage' (all-cause mortality, MI, stroke, fatal hemorrhage or intracranial hemorrhage) in the ticagrelor and placebo groups (10.1% versus 10.8% respectively; RR 0.93; 95% CI 0.86–1.02).

In patients with stable CAD and type 2 diabetes with no previous MI or stroke addition of ticagrelor to standard therapy reduces the incidence of ischemic CVD, but at the same time increases incidence of major bleeding compared with placebo. Therefore, for the majority of patients with type 2 diabetes and CAD who meet the criteria for the THEMIS study, addition of ticagrelor to aspirin therapy is not recommended.

One-half of the patients with stable CAD and type 2 diabetes who were involved in the THEMIS study (58%, n=11.154) had undergone percutaneous coronary intervention (PCI), which indicated high ischemic CVD risk. These patients are usually administered aspirin, but THEMIS substudy — THEMIS-PCI study [7] estimated probable improvement of outcomes after ticagrelor addition to standard therapy.

The study involved patients over 50 years of age with type 2 diabetes, stable CAD and who met one of three additional criteria: previous PCI, coronary artery bypass grafting (CABG) or at least one artery 50% stenosis. After randomization the patients were given (received) ticagrelor (n=5558) or placebo (n=5596). During a median follow-up of 3.3 years, the incidence of complications (composite primary efficacy endpoint: cardiovascular death, MI or stroke) was lower in the ticagrelor group compared with the placebo group (7.3% versus 8.6% respectively; RR 0.85; 95% CI 0.74–0.97; p=0.013), but the risks of cardiovascular mortality (3.1% versus 3.3% respectively; p=0.68) and all-cause mortality 5.1% versus 5.8% respectively; p=0.11) were similar. TIMI major bleeding rate was higher in the ticagrelor group compared with the placebo group (2.0% versus 1.1% respectively; RR 2.03; 95% CI 1.48–2.76; p<0.0001), however, comparable rates were identified for intracranial bleeding (0.6% versus 0.6% respectively; p=0.45) and fatal hemorrhage (0.1% versus 0.1%, respectively; p=0.83). In the ticagrelor group reduction in the total number of 'outcomes with irreversible damage' (death from any reason, MI, stroke, fatal hemorrhage or intracranial hemorrhage) was achieved, which determined the 'pure clinical benefit' (9.3% versus 11.0% in placebo group; RR 0.85; 95% CI 0.75–0.95; p=0.005). There was no association with the time of PCI.

In patients with type 2 diabetes and stable CAD with previous PCI the addition of ticagrelor to aspirin reduces the total risk of cardiovascular death, MI and stroke, but increases the risk of bleeding at the same time. Nevertheless, compared with patients without previous PCI addition of ticagrelor provides 'pure clinical benefit' that indicates the feasibility of its administration in patients with high risk of ischemia and low risk of bleeding.

Angiotensin receptor blocker and sacubitril/valsartan were more effective than enalapril in reducing the risk of hospitalizations for chronic heart failure (CHF) or cardiovascular deaths in patients with CHF with reduced ejection fraction (HFrEF). In the randomized **PARAGON-HF** [8] study efficacy and safety of sacubitril/valsartan (purposed dose 97/103 mg twice daily) and valsartan (purposed dose 160 mg twice daily) were compared in 4822 NYHA functional class II–IV patients with ejection fraction 45% or higher.

During a median follow-up of 35 months composite primary endpoint event rate (hospitalization for heart failure or cardiovascular death) was similar in the sacubitril/valsartan and valsartan groups (RR 0.87; 95% CI 0.75–1.01; p=0.059), and, separately, frequencies of cardiovascular deaths (RR 0.95; 95% CI 0.79–1.16) and hospitalizations for heart failure (RR 0.85; 95% CI 0.72–1.00) were comparable. Sacubitril/valsartan was more effective in decreasing functional class of CHF and increasing the quality of life in 8 months (quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire), it also less affected renal function (RR 0.5; 95% CI 0.33–0.77). In the sacubitril/valsartan group hypotension (15.8% versus 10.8% in the valsartan group) and angioneurotic edema (0.6% versus 0.2% respectively) developed more often, and hypokalemia more rarely compared with the valsartan group (13.2% versus 15.3% respectively). Analysis which was planned in advance identified that sacubitril/valsartan was superior to valsartan in patients with lower ejection fraction (57% and less) and in women.

Sacubitril/valsartan does not provide significant reduction in total number of hospitalizations for heart failure and cardiovascular deaths in patients with CHF with ejection fraction 45% or higher. However, some new findings about the benefits of sacubitril/valsartan in patients with CHF with ejection fraction 45–57%, and especially in women, were made.

In patients who had ST-segment elevation MI (STEMI) PCI of the affected artery decreases cardiovascular death and recurrent MI risks. **COMPLETE** [9] study investigated the hypothesis of additional risk reduction in patients who undergo simultaneous PCI of other stenosed coronary arteries.

Patients with MI and multivessel CAD who successfully underwent PCI of the affected artery were randomized for complete PCI revascularization of all angiographically significant lesions (at least 70% vessel diameter stenosis or 50–69% stenosis with low fractional flow reserve) (n=2016) or refusal of complete revascularization (n=2025). During a median follow-up of 3 years significantly less poor outcomes included in primary composite endpoint (cardiovascular death, MI) were observed in patients with complete revascularization compared with patients with PCI of only affected artery (7.8% versus 10.5% respectively; RR 0.74; 95% CI 0.6–0.91; p=0.004), as well as the total number of cardiovascular deaths, MI and revascularizations caused by ischemia (8.9% versus 16.7% respectively; RR 0.51; 95% CI 0.43–0.61; p<0.001). Complete revascularization proved to be beneficial if performed both during the hospitalization and after several weeks (up to 45 days) after the discharge, i.e. complications occurred after considerable time and could be successfully prevented. Considering safety and other outcomes, including stroke, stent thrombosis, major bleeding, acute kidney failure and severe CHF no significant difference between two groups was detected.

This research is the first large randomized study that demonstrated the reduction of severe CVD risk in complete coronary revascularization compared with PCI of only one effected artery in patients with STEMI in multivessel CAD. The reduction in composite primary endpoint event frequency was determined by lower number of non-ST-segment elevation MI (non-STEMI), but not by cardiovascular disease mortality. The study had no statistical power to determine difference in mortality. The COMPLETE project confirmed that complete coronary revascularization is feasible, the statement that was already in STEMI treatment guidelines.

In patients with type 2 diabetes sodium-glucose transport protein 2 (SGLT2) inhibitors reduce the risk of first hospitalization for heart failure, apparently by mechanisms that are independent from their hypoglycemic actions. The hypothesis of the **DAPA-HF** study [10] was that the HFrEF can be effectively treated in patients with diabetes as well as in patients without diabetes.

NYHA II, III and IV patients with LV ejection fraction 40% or less were randomized and administered dapagliflozin 10 mg once daily (n=2373) or placebo (n=2371) in addition to recommended therapy. On average, after over 18.2 months of follow-up, significant reduction in total number of primary endpoint events (hospitalization for heart failure, urgent intravenous CHF therapy, cardiovascular death) in the dapagliflozin group was determined (16.3% versus 21.2% in placebo patients; RR 0.74; 95% CI 0.65–0.85; p<0.001). Both components of primary endpoint — first deterioration of CHF (10.0% versus 13.7% in placebo group; RR 0.70; 95% CI 0.59–0.83; p=0.00 001) and cardiovascular death (9.6% versus 11.5% in placebo group; RR 0.82; 95% CI 0.69–0.98; p=0.03) as well as death from any cause (11.6% versus 13.9% respectively; RR 0.83; 95% CI 0.71–0.97; p=0.022) were identified less frequently in the dapagliflozin group. Decrease in CHF symptoms (Kansas City Cardiomyopathy Questionnaire) was also noted in patients getting dapagliflozin compared with patients

getting placebo. The benefits of dapagliflozin were independent from sacubitril/valsartan therapy as these medications have different mechanisms of action. The frequency of poor outcomes in patients with and without type 2 diabetes appeared to be similar. The frequency of poor outcomes including decreased circulating volume, kidney dysfunction, severe hypoglycemia, amputation and bone fractures were also comparable between two groups.

In patients with HFrEF addition of dapagliflozin to the standard therapy reduces the risk of CHF deterioration or cardiovascular death compared with placebo, irrespective of type 2 diabetes presence. Dapagliflozin that is already successfully used for type 2 diabetes treatment and CHF prevention can also be used in patients with systolic CHF and without diabetes.

HOT LINE Session 2

In the **NZOTACS** (New Zealand Oxygen in Acute Coronary Syndromes) trial [11] ambulance acute coronary syndromes care records were analyzed in order to compare 30-day mortality in 20.304 patients with high-oxygen protocol and 20.568 patients with low-oxygen protocol. The high-oxygen protocol consisted of oxygen delivered by face mask at 6 to 8 L given to all patients with suspected acute coronary syndrome (ACS) (patients presenting with retrosternal ischemic pain or specific ECG findings), irrespective of oxygen saturation levels, with oxygen stopped when clinical evidence indicated the ischemia had resolved. The low-oxygen protocol recommended that oxygen was given only when saturation fell below 90% and stopped when saturation reached 90–94%. ACS was later confirmed in 43% of patients, and in 10% STEMI was diagnosed.

Primary outcome showed that high-oxygen administration did not reduce 30-day mortality compared with low-oxygen (3.02% in the routine-oxygen group and 3.12% in low-oxygen group; RR 0.97; 95% CI 0.86–1.08). At the same time in the group of patients with STEMI who were started on high-oxygen protocol 30-day mortality rates were much lower (8.8% versus 10.6% in low-oxygen protocol group; p=0.016). Reduction in mortality rates was also registered in high-oxygen protocol group in patients with low saturation that was recorded on ambulance arrival (10.1% versus 11.1% in low-oxygen group; RR 0.88; 95% CI 0.70–1.11).

The investigators concluded that patients with suspected ACS and with normal blood oxygen level do not benefit from high-level oxygen administration. European and American clinical guidelines recommend that oxygen be given only when oxygen saturation levels are below 90% in patients with ACS.

It is known that remote ischemic conditioning with transient ischemia and reperfusion applied to the arm has been shown to reduce myocardial infarct size in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). **CONDI-2/ERIC-PPCI** trial [12] investigated whether remote ischemic conditioning could reduce the incidence of cardiac death and hospitalization for heart failure at 12 months.

Patients with suspected STEMI and who were eligible for PPCI were randomly allocated to receive standard treatment (including a sham simulated remote ischemic conditioning intervention — control group, n=2701) or remote ischemic conditioning treatment before PPCI (n=2700). An automated cuff device was used to deliver the remote ischemic conditioning protocol, which comprised four alternating cycles of cuff inflation for 5 min and deflation for 5 min. Study team members collecting the data and assessing outcomes were masked to the treatment allocation. At 12 months post-PPCI frequencies of cardiac death or hospitalization for heart failure (the primary combined endpoint events) were similar in the control group and in the remote ischemic conditioning group (8.6 and 9.4% respectively; RR 1.10; 95% CI 0.91–1.32; p=0.32). No severe adverse side effects of remote ischemic conditioning were observed. It was concluded that remote ischemic conditioning does not improve clinical outcomes (cardiac death or hospitalization for heart failure) at 12 months follow-up in patients with STEMI undergoing PPCI.

ISAR-REACT 5 trial [13] compared efficacy and safety of ticagrelor or prasugrel therapy in patients with acute coronary syndromes for whom invasive evaluation is planned. Patients were randomized to receive standard therapy which included ticagrelor (n=2012) or prasugrel (n=2006). Loading doses were administered differently depending on the type of ACS. Patients with STEMI received the loading dose of ticagrelor (180 mg) or prasugrel (60 mg) soon after randomization. Patients with non-STEMI/unstable angina received ticagrelor after randomization, and prasugrel after randomization and angiography.

At 1 year after randomization, the incidence of the combined primary efficacy endpoint (death, MI, or stroke) was significantly higher in the ticagrelor group (9.3% versus 6.9% in the prasugrel group;

RR 1.36; 95% CI 1.09–1.7; p=0.006). Adverse events included: death from any cause (4.5% vs. 3.7%); MI (4.8% vs. 3.0%); stroke (1.1% vs. 1.0%); definite or probable stent thrombosis (1.3% vs. 1.0%); definite stent thrombosis (1.1% vs. 0.6%) in the ticagrelor and prasugrel respectively. The incidence of safety endpoint (Bleeding Academic Research Consortium type 3, 4, or 5 bleeding) was higher in the ticagrelor group compared with the prasugrel group (5.4% versus 4.8% respectively; RR =1.12; 95% CI 0.83–1.51; p=0.46).

In patients with STEMI/non-STEMI the incidence of death, MI, or stroke is significantly lower in the prasugrel group compared with ticagrelor group, and there was no significant difference in the risk of major bleeding in these patients. Current findings confirm that prasugrel is first line antithrombotic medication in patients with ACS with STEMI and non-STEMI. The open-label nature of the trial and the fact that most of the follow-up was conducted by telephone remain a limitation. The number of patients excluded from the safety analysis was 10 times higher in the prasugrel group compared with the ticagrelor group, which may have influenced the final total number of major bleedings. Previous findings suggest that antithrombotic effects of ticagrelor and prasugrel are similar. Therefore, it seems unlikely that prasugrel was indeed beneficial over ticagrelor and it is necessary to confirm the ISAR-REACT 5 trial findings in a double-blind study.

In the **HISTORIC** trial [14] involved 32.837 patients and estimated different cardiac troponin values measured by high-sensitivity cardiac troponin I (hs-cTnI) assay in order to rule out MI and safely discharge patients directly from ED without increase in poor cardiologic events frequency. After the initial troponin assessment (or after repeated troponin assessment if the symptoms started less than 2 hours before the presentation), low-risk patients (cTnI<5 ng/L) with symptoms that started more than 2 hours prior the presentation were identified. Patients who were considered to be at high risk and had cTnI level higher than the sex-specific 99th centile at presentation were admitted. Intermediate-risk patients with cTnI levels between 5 ng/L and the 99th centile were retested after 3 hours and were sent home if the cTnI was <3 ng/L; they were admitted if it was ≥3 ng/L.

Implementing the early rule-out pathway reduced the time the patients spent in the ED compared with standard rule-out (6.8 versus 10.1 hours respectively; p<0.001). It also increased the proportion of patients sent home without being admitted (74% versus 53% respectively; RR 1.57; 95% CI 1.34–1.83; p<0.001). Frequency of cardiac death and MI (primary safety endpoint) was 1.8% in the early-rule-out pathway group and 2.5% in the standard care group at 1 year (corrected RR 1.02; 95% CI 0.74–1.4). Compared with the patients with cTnI levels between 5 ng/L and the 99th centile patients with cTnI levels below 5 ng/L were at a significantly lower risk of MI or cardiac death at 1 year (5.3% versus 0.7% respectively; corrected RR 0.23; 95% CI 0.19–0.28). Patients with cTnI levels below 3 ng/L were also at a lower risk of MI or cardiac death at 1 year (5.3% versus 0.3% respectively; corrected RR 0.20; 95% CI 0.14–0.29).

The early rule-out pathway implementation may prove useful for both patients and healthcare. A single cTnI test will provide an evaluation that can aid in making a safe decision about the need of hospital admission, which will also lead to cost reduction.

HOT LINE Session 3

UK Biobank study [15] assessed the effect of lower low-density lipoprotein cholesterol (LDL–C) and lower systolic blood pressure (SBP) on the lifetime risk of cardiovascular disease. The study included 438.952 participants who were enrolled in the UK Biobank between 2006 and 2010 and were under observation through 2018. The investigators used LDL–C and SBP scores as instruments to divide participants into groups with lifetime exposure to lower LDL–C, lower SBP, or both. Differences in plasma LDL–C, SBP, and cardiovascular event rates between the groups were compared in order to estimate associations with lifetime risk of cardiovascular disease.

During the observation period 24.980 patients experienced a first major coronary event (coronary death, nonfatal MI, or coronary revascularization). Participants with LDL–C genetic scores 14.7-mg/dL lower than the median levels had lower lifetime risk of major coronary events (OR 0.73; 95% CI 0.70–0.75; p<0.001). Participants with SBP genetic scores 2.9-mm Hg lower than the median also were at a lower risk of major coronary events (OR 0.82 95% CI 0.79–0.85; p<0.001). Participants in the group with both genetic scores lower than the median (13.9-mg/dL lower LDL–C, 3.1-mm Hg lower SBP) were at an even lower risk of major coronary events (OR 0.61; 95% CI 0.59–0.64; p<0.001). In a meta-regression analysis, combined effect of 38.67-mg/dL lower LDL–C and 10-mm Hg lower SBP was associated with a significantly lower lifetime risk of major coro-

nary events (OR 0.22; 95% CI, 0.17–0.26; p<0.001), and cardiovascular death (OR 0.32; 95% CI 0.25–0.40; p <0.001).

Lifelong genetic exposure to lower levels of LDL–C cholesterol and lower SBP is associated with lower cardiovascular risk. However, it cannot be assumed that these findings represent the magnitude of possible benefit from the management of these risk factors.

At 1 year after revascularization patients with stable CAD and atrial fibrillation or those who do not need revascularization are recommended to start oral anticoagulants. However, there are limited data from randomized controlled trials that evaluate this treatment. Moreover, in clinical practice most patients in these situations continue to be treated with combination antiplatelet therapy for more than a year.

An open-label **AFIRE** trial [16] carried out in Japan involved 2236 patients with atrial fibrillation who had undergone PCI (70% of cases) or CABG more than 1 year earlier or who had angiographically confirmed CAD not requiring revascularization. Patients were randomly assigned to receive monotherapy with rivaroxaban (10–15 mg once daily) or combination therapy with rivaroxaban and single antiplatelet agent (70% aspirin, 25% clopidogrel or prasugrel). The trial was stopped early because of high mortality in the combination therapy group. During a median follow-up of 2 years the total number of primary efficacy endpoint events (stroke, systemic embolism, MI, unstable angina requiring revascularization or death from any cause) was not lower in the rivaroxaban monotherapy group compared with the combination therapy group (4.14% versus 5.75% events per patient-year respectively; OR 0.72; 95% CI 0.55–0.95; p<0.001 for non-inferiority). Rivaroxaban monotherapy was superior to combination therapy for the primary safety end point (major bleeding according to the criteria of the International Society on Thrombosis and Hemostasis) with event rates of 1.62% and 2.76% per patient-year, respectively (OR 0.59; 95% CI 0.39–0.89, p=0.01 for superiority).

Rivaroxaban monotherapy was not inferior to combination therapy with rivaroxaban and antiaggregant medication in decreasing the number of ischemic complications and was superior in safety (major bleeding risk). These findings confirm European and American recommendations that anticoagulant monotherapy (e.g. rivaroxaban) should be used in patients with stable CAD and atrial fibrillation.

The **GALACTIC** trial [17] evaluated the hypothesis that early intensive and sustained use of a complex of vasodilators including renin-angiotensin system (RAS) inhibitors improve outcomes compared with the standard therapy due to improve of lung congestion and organ perfusion.

Patients hospitalized for acute heart failure (AHF), NYHA III/IV functional class symptom severity with increased plasma concentrations of natriuretic peptides, and systolic blood pressure of at least 100 mm Hg were randomly assigned to standard care (n=402) or a strategy of early intensive and sustained vasodilation (n=386). In the early intensive and sustained vasodilation group included high doses of common vasodilators, including sublingual and transdermal nitrates from the 1st day, oral hydralazine during first 48 hours to avoid nitrate tolerance, and rapid up-titration of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Other treatment options (aldosterone antagonists, beta-blockers, loop diuretics) were used according to the physician's decision and guidelines in both groups.

Rehospitalization for AHF or all-cause mortality at 180 days was comparable in both groups (30.6% in the intervention group and 27.8% in the standard care group; corrected OR 1.07; 95% CI 0.83–1.39; p=0.592. At 6 days the decrease in shortness of breath was identified in both groups. Frequency of adverse events was higher in the early intensive and sustained vasodilation group compared with the standard care group (82% versus 75% respectively). Headache and systolic arterial hypotension were identified more frequently in the intervention group as well (8% versus 2% in the standard care group).

Among patients with AHF, a strategy of early intensive and sustained vasodilation individualized doses of nitrates, hydralazine, ACEi, ARBs or sacubitril/valsartan did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization compared with usual care. Pulmonary congestion, despite being the sign of AHF, is not an ideal target for therapies. Therefore, it is necessary to focus on the means of prevention, early diagnosis and treatment of heart failure in order to avoid its progression into AHF.

J.J. Miranda presented a trial, conducted in Peru, that investigated **the effect of salt substitution in lowering the blood pressure** [18]. For 3 years households, grocery shops, bakeries, and restaurants in the rural area were provided with free potassium chloride to substitute 25% of sodium chloride in food. The

study involved 91.2% of 2605 adult residents of this area, and people with chronic kidney disease, cardiac disease or those who took digoxin were excluded to avoid hyperkalemia. Blood pressure was evaluated every 5 months for a total of 7 measurements and systolic blood pressure reduced by an average of 1.23 mmHg and diastolic blood pressure by an average of 0.72 mmHg compared with baseline 113.1/72 mmHg (p=0.04 and p=0.022 respectively). Blood pressure reductions were even greater (18%) in individuals with hypertension at baseline and in patients over 60 years (average reductions in systolic and diastolic blood pressures were 1.92 mmHg and 2.17 mmHg, respectively). No adverse effects were observed. Cumulative probability of arterial hypertension development (BP>14/90 mmHg) reduced by 55% compared with baseline (p<0.001) at 3-year follow-up.

The study demonstrates that population-wide substitution of sodium chloride with potassium chloride is effective and feasible. Although there was no significant mean blood pressure reduction, even 2 mmHg reduction is expected to reduce stroke mortality by 10% and CAD by 7%.

Arterial hypertension is the leading cause of cardiovascular disease globally, however, hypertension control in insufficient. The authors of an open randomized controlled trial, **HOPE 4** [19], hypothesized that the efficacy of hypertension control can be improved by an active involvement of primary care physicians and family members, and provision of effective medications to patients with poorly controlled or recently diagnosed hypertension. The study involved 1371 patients from 30 communities in Colombia and Malaysia who were randomly assigned to receive standard care (control group, n=727) or free antihypertensive and statin medications, support from a family member or friend (treatment supporter) in order to improve adherence to medications and healthy lifestyle (the intervention group, n=644).

The primary endpoint was the change in 10-year cardiovascular disease risk estimated by the Framingham Risk Score at 12 months between the participants from the intervention and control groups. All patients completed 12-minth follow-up and the reduction in risk estimate was –6.4% in the control group and –11.17% in the intervention group, with a difference of –4.78% (95% CI -7.11to –2.44; p<0.0001). There was an absolute 11.45 mm Hg reduction in SBP (95% CI –14.94 to –7.97) and a 0.41 mmol/L reduction in LDL (95% CI -0.60 to 0.23) in the intervention group (both p,0.0001). A blood pressure goal of <140 mm Hg was registered in 69% of patients in the intervention group versus 30% in the control group (p<0.0001).

A complex model of care, involving primary care physicians and family members that are familiar with the local context, significantly improved hypertension control. Implementation of this strategy can potentially improve the cardiovascular risk compared with current strategies that are mainly physician focused.

HOT LINE Session 4

Patients with severe renal failure are usually excluded from randomized studies that makes it hard to found optimal CHF therapy for individuals with renal dysfunction.

BB-meta-HF study [20] estimated the influence of beta-blockers on the outcomes in CHF patients with reduced LV ejection fraction and renal function impairment using the data from 10 double-blind placebo-controlled randomized studies (n=16.740). Renal dysfunction was the key marker of CHF patients' mortality, with a 12% increase in the mortality for every 10 ml/min lower eGFR (p<0.001). Positive prognostic effect of beta-blockers (death from all causes absolute risk reduction was 4.7% per year) was most prominent in patients with moderate chronic kidney disease (eGFR 30–44 ml/min/1.73 m^2). No deterioration in renal function in patients taking beta-blockers was observed. Patients with systolic CHF and concomitant atrial fibrillation lacked benefit from beta-blockers regardless of eGFR.

Beta-blockers reduce mortality in patients with CHF with reduced ejection fraction and sinus rhythm, even with moderate kidney dysfunction at baseline. Beta-blockers do not decrease renal function and therefore patients with systolic CHF should receive beta-blocker therapy even with moderate or moderately severe renal dysfunction.

The SYNTAX study compared PCI using first-generation paclitaxel-eluting Taxus stents with CABG in patients with de-novo three-vessel and left main coronary artery disease and reported results up to 5 years. The SYNTAX Extended Survival (**SYNTAXES**) study [21] evaluated 10-year all-cause mortality from these two types of interventions according to the intention-to-treat principle. From 2005 to 2007 1800 patients were randomly assigned to the PCI group (n=903) or to the CABG group (n=897). At 10 years the primary endpoint (death from all causes) was identified in 27% of PCI patients and in 24% of CABG patients

(hazard ration (HR) 1.17; 95% CI 0.97–1.41; p=0.092). Among the patients with three-vessel CAD, 28% had died after PCI versus 21% after CABG (HR 1.41; 95% CI 1.10–1.80); among the patients with left main artery disease — 26% after PCI versus 28% after CABG (HR 0.9; 95% CI 0.68–1.20). These findings were not affected by diabetes.

At 10 years, there was no significant difference in death from all causes between PCI using first-generation paclitaxel-eluting stents and CABG. Of note, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease.

The **MITRA-FR** trial [22] involved patients with mitral regurgitation and symptomatic heart failure treated using guideline-directed medical treatment who were hospitalized at least once in the last 12 months. The patients were randomly assigned to the percutaneous mitral valve repair with the MitraClip device group (the intervention group, n=152) or the medical treatment group (the control group, n=152). At 24 months death from any cause or unplanned hospitalization for heart failure (combined primary endpoint) occurred in 63.8% of patients in the intervention group and in 67.1% of patients in the control group (HR 1.01; 95% CI 0.77–1.34). Death from any cause occurred in 34.9% versus 34.2% respectively (HR 1.02; 95% CI 0.70–1.50) and unplanned hospitalization for heart failure occurred in 55.9% versus 61.8% respectively (HR 0.97; 95% CI 0.72–1.30).

In patients with severe secondary mitral regurgitation, percutaneous repair added to medical treatment does not significantly reduce the risk of death or hospitalization for heart failure at 2 years compared with medical treatment alone. On contrary, a similar COAPT study reported that percutaneous repair with the MitraClip device reduced the frequency of hospitalization for heart failure at 24 months. Mortality differed significantly in MITRA-FR and COAPT (34% and 46% at 2 years respectively), which may be either due to greater severity of cardiac disease in COAPT participants or to higher intensity of medical treatment in MITRA-FR. Assumingly, MitraClip may be beneficial in patients with severe secondary mitral regurgitation in the absence of significant LV dilation, who continue to be symptomatic despite the maximal medical treatment. COAPT and MITRA-FR investigators are planning to continue their observations up to 5 years.

The **DANAMI-2** trial [23] involved 1572 patients with STEMI who were randomized to receive PCI or fibrinolysis therapy. At 16 years death or re-hospitalization for MI (primary composite endpoint) occurred in 58.7% PCI compared with 62.3% with fibrinolysis (RR 0.86; 95% CI 0.76–0.98). No difference in all-cause mortality in two groups was observed, but cardiac death rates were significantly lower in the primary PCI group (18.3% versus 22.7% in fibrinolysis group; RR 0.78; 95% CI 0.63–0.98). The benefit of primary PCI compared with fibrinolysis in patients with STEMI — a reduction in the risk of death or re-hospitalization for MI — was sustained to 16 years.

HOT LINE Session 5

Data from 32 703 patients from 45 countries with chronic coronary syndrome enrolled in the prospective observational CLARIFY [24] registry with a 5-year follow-up, were analyzed. Characteristics and management of patients, as well as the determinants of achieved results were studied.

Frequency of composed primary endpoint (cardiovascular death or non-fatal MI) over a five-year follow-up period was 8.0% (8.1% in men and 7.6% in women). The main independent predictors of primary endpoint complications were previous hospitalizations for heart failure, current smoking, atrial fibrillation, residence in Central/South America, previous MI or stroke, current angina or peripheral artery disease. The association between angina and previous MI was determined (p=0.0016). Frequency of primary endpoint events was higher in patients with previous MI who also had stable angina (11.8% versus 8.2% in patients without angina; p<0.001), and patients without previous MI had no frequency difference of endpoint events independently of angina (6.3% in patients with stable angina and 6.4% in patients without stable angina; p<0.99). Evidence-based secondary prevention measures were successfully implemented in the registry patients.

Described characteristics of patients with chronic coronary syndrome patients show that patients with both angina and prior MI can be identified as a high-risk group despite intensive implementation of secondary prevention measures.

Patient data from **SWEDEHEART** registry [25] were analyzed to evaluate the effect of the long-term use of secondary prevention medications after CABG (statins, beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors and antiplatelet therapy) on mortality.

The study involved all the patients who underwent CABG in Sweden from 200 to 2015 and survived at least 6 months after discharge (n=28.812). Six

months after discharge 93.9 % of patients received statins and 77.3 % eight years later. Figures for beta-blockers were 91.9 % and 76.4 %, for RAAS inhibitors 72.9 % and 65.9 %; for antiplatelets 93.0 % and 79.8 % respectively. These medications were administrated less often to patients aged 75 years and older. After adjustment for age, gender, comorbidities, and use of other secondary preventive drugs, treatment with statins (HR 0.56; 95 % CI 0.52–0.60], RAAS inhibitors (HR 0.78; 95 % CI 0.73–0.84), and platelet inhibitors (HR 0.74; 95 % CI 0.69–0.81) were individually associated with lower mortality risk (all $p < 0.001$). However, beta-blockers did not improve mortality (HR 0.97; 95 % CI 0.90–1.06; $p = 0.54$).

Frequency of secondary prevention medications use after CABG was high in the early post-operative period but decreased significantly. It is essential to use statins, RAAS inhibitors, and platelet inhibitors after CABG, and the use of beta-blockers may be questioned.

The majority of randomized trials on the use of implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death in patients with HFrEF were conducted at the end of the twentieth century. The study investigated the association of ICD and mortality rates in a HFrEF cohort receiving modern treatment. Patients from the **Swedish Heart Failure Registry** [26] who met the European Society of Cardiology criteria for primary prevention of sudden cardiac death with an ICD. The association between ICD use, 1-year and 5-year all-cause and cardiovascular mortality was assessed by Cox regression models in predetermined groups.

Of 16.702 patients who met the criteria only 1599 (10 %) had an ICD implanted. ICD use was associated with a reduction of all-cause mortality risk within 1 year (HR 0.73; 95 % CI 0.60–0.90) and 5 years (HR 0.88; 95 % CI 0.78–0.99). The similar results were observed in all subgroups, including the patients with and without CAD, men and women aged <75 and ⩾75, in those with earlier and later enrollment in Swedish Heart Failure Registry, and in patients with and without cardiac resynchronization therapy.

In a modern HFrEF population, ICD is underused, although it significantly reduces short-term and long-term mortality in all the clinical and demographic subgroups. These finding support better implementation of ICD in systolic CHF.

The **PURE** [27,28] prospective study presents findings from 155.722 participants (21 countries, 5 continents, except Australia) aged 35–70 years, who were enrolled in 2005–2016 with a following follow-up (median = 9.5 years). The investigators compared causes of death in high-income, middle-income, or low-income countries, modifiable risk factors effect on cardiovascular disease events (cardiovascular death, MI, stroke and heart failure) and mortality. According to the findings, mortality was caused by cardiovascular events in 43 %, 42 % and 23 % of cases, and by cancer in 15 %, 30 %, 55 % in high-income, middle-income, or low-income countries, respectively. All-cause mortality rates, adjusted for age and gender, decreased with the increase in income — 13.3, 6.9 and 3.4/1000 patient-years in high-income, middle-income, or low-income countries respectively. When analyzed separately, low income was associated with increased mortality from cardiovascular and respiratory diseases, traumas and infections; and with decreased mortality from cancer. Mortality from cardiovascular causes to mortality from cancer ratio was 3.0, 1.3 and 0.4 in high-income, middle-income, or low-income countries, respectively. The most important cardiovascular disease risk factor was arterial hypertension, followed by high LDL level and air pollution. Smoking, bad diet, poor education and abdominal obesity also increased cardiovascular disease risk. Behavioral and metabolic risk factors were predominant risk factors in high-income countries, and poor education and air pollution were predominant in middle-income and low-income countries.

Most cardiovascular disease cases and deaths can be prevented by adequate control of metabolic and behavioral risk factors in households and individuals. National healthcare policies should focus on risk factors of greatest significance in the specific groups of countries. In low-income and middle-income countries, the greatest benefit can be achieved by smoking limitations, blood pressure control, healthcare investments and better availability of medication for modifiable risk factors correction.

HOT LINE Session 6

The **RAPID-TnT** study [29] investigated the use of earlier high-sensitivity troponin (hs-cTnT) assays to safely exclude MI in patients presented into the emergency department with ACS. Patients were randomly assigned to receive care guided either by the early (0/1-hour) hs-cTnT assessment protocol with exclusion criteria <5 ng/L (n = 1646) or by standard (0/3-hour) assessment protocol with exclusion criteria < 29 ng/L (n = 1642). Participants in the 0/1-hour arm were more likely to be discharged earlier compared with

the standard arm (45.1% versus 32.3% respectively; p<0.001), and the median length of stay was shorter (4.6 hours versus 5.6 hours respectively, p<0.001). Over the 30-day follow-up period primary endpoint events (all-cause death or MI) occurred with the same frequency in both arms (1.0% in the 0/1-hour arm versus 1.0% in the standard arm; RR 1.06; 95% CI 0.53–2.11; non-inferiority p-value=0.06, superiority p-value=0.867). Among the discharged patients, the negative predictive value for the 0/1-hour protocol was 99.6% (95% CI 99.0–99.9%) for 30-day risk of death or MI.

The early (0/1-hour) hs-cTnT assessment protocol which was tested in clinical settings enables earlier discharge of patients with suspected ACS, without worsening the 30-day outcomes. Recent findings suggest the possibility of future changes in suspected ACS patient management.

A randomized, open-label, phase 3b **ENTRUST-AF PCI** study [30] involved patients with atrial fibrillation (AF) requiring oral anticoagulation, who had undergone successful PCI for stable CAD or ACS. Patients were randomized from 4 to 5 days after PCI to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor depending on the investigators' preferences) for 12 months or a vitamin K antagonist (VKA) plus a P2Y12 inhibitor and aspirin (100 mg once daily) for 1–12 months. The edoxaban dose was later reduced to 30 mg once daily if one or more factors (creatinine clearance 15–50 mL/min, weight ⩽60 kg, or concomitant use of potent P-glycoprotein inhibitors) were present. At 12 months the primary safety endpoint events (major or clinically relevant non-major bleeding) occurred in 17% (annualized event rate 20.6%) of patients in the edoxaban group and in 20% (annualized event rate 25.6%) of patients in the VKA group (HR 0.83; 95% CI 0.65–1.05; non-inferiority p-value p=0.0010, superiority p-value p=0.1154). Annualized primary efficacy endpoint event rate (cardiovascular disease, stroke, systemic embolism, MI or stent thrombosis) was 7.3% in the edoxaban group and 6.9% in the VKA group (HR 1.06; 95% CI 0.71–1.69).

In patients with AF who had PCI double antiplatelet edoxaban-based therapy was non-inferior for safety (bleeding risk) compared with the standard triple antithrombotic VKA-based regimen, without significant difference in ischemic events rate.

In an open-label **POPular Genetics** study [31] patients who had undergone primary PCI were randomized to undergo an early genetic testing (n=1242) or to standard treatment with ticagrelor or prasugrel (n=1246). It is known that CYP2C19*2 or CYP2C19*3 alleles are associated with reduced transformation of clopidogrel into its active form. Patients in the genetic testing group who tested positive for CYP2C19*2 or CYP2C19*3 alleles were treated with ticagrelor or prasugrel, and those who tested negative were treated with clopidogrel. At 12 months a total of poor clinical outcomes (primary combined endpoint: death from all causes, MI, stent thrombosis, stroke or major bleeding) occurred in 5.1% in the genetic testing group versus 5.9% in the standard therapy group (p<0.001 for non-inferiority). PLATO major or non-major bleeding rate was 9.8 in the genetic testing group and 12.5% in the standard therapy group (HR 0.78; 95% CI 0.61–0.98; p=0.04).

In patients who had PCI the strategy of genetic testing with CYP2C19 genotype evaluation for oral P2Y12 inhibitor selection was non-inferior compared with standard regimen with ticagrelor or prasugrel in preventing thrombotic events at 12 months.

The DAPA study [32] that began in 2004 was stopped early in 2013 due to slow enrollment of patients who had STEMI. It was originally planned to investigate the reduction in mortality ICD implantation (n=131) compared with medical therapy only (n=135). During a median follow-up of 9 years all-cause mortality rate was 24.4% in the PCI group compared with 35.5 in the medical therapy group (HR 0.58; 95% CI 0.37–0.91; p=0.02); cardiac death occurred in 11.5% versus 18.5% respectively (HR 0.52; 95% CI 0.28–0.99; p=0.04), and including the death from the heart failure — 3.1% versus 5.9 respectively.

The limitations of this study were low statistical power, transition of patients between groups and questionable inclusion criteria.

The next European Society of Cardiology Congress will take place in Amsterdam, Netherlands from the 29th of August to the 2nd of September 2020.

Conclusions

This article presents the materials from the European Society of Cardiology 2019 which were of particular interest according to the authors opinion. More information about the Congress is available on https://www.escardio.org. New scientific findings made in the well-planned and accurately conducted randomized clinical studies will undoubtfully have a great influence on medical practice.

Conflict of interest: None declared.

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Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

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2. Summary with key words
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The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

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Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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XIV. Journal subscription

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On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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