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Risk of arterial hypertension and work-related stress in the population aged 25–64 in Russia/Siberia (WHO — MONICA psychosocial program)

Ventricular extrasystoles in patients without cardiac structural changes: mechanisms of development, arrhythmogenic cardiomyopathy predictors, pharmacological and non-pharmacological treatment strategies

Updated European guidelines on pre-diabetes, diabetes and cardiovascular disease: Opinion of Russian experts

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Contents

Editor's Welcome

Dear colleagues!

We are happy to present the 26th issue of the International Heart and Vascular Disease Journal, that include are the leading article, original and review articles.

The leading article section presents the results of the study on how stress affects the risk of arterial hypertension within a 16-year observation period in people aged 25–64 years in Novosibirsk, Siberia. It is remarkable that the study was the part of the WHO-MONICA psychosocial program. The period of prospective observation was 16 years and included men (n=657) and women (n= 689). The level of work-related stress was similar in men and women. At the same time, at 16 years of observation relative risk of arterial hypertension was higher in men compared with women.

Two articles are published in the "Original articles" section. The cross-sectional study included 582 men and women aged 30–59 years from 3 major Uzbekistan cites (Samarkand, Fergana and Urgench) with stage 1–3 arterial hypertension and without verified cardiovascular diseases. The objective of the study was to assess additional cardiovascular risk factors. Every second man and woman with arterial hypertension in Uzbekistan are at a high and very high risk of cardiovascular complications. This fact can be explained by arterial hypertension severity, end-organ damage and other risk factors. The article from the Siberian researchers is dedicated to the assessment of the metabolic syndrome prevalence association with family status changes in men of an open population in a moderately-urbanized Siberian city. It was established that patients with metabolic syndrome have stable family status, but high levels of family stress.

The section "Review articles" presents two manuscripts. The first is performed by researches from Saint-Petersburg who analyzed a broad spectrum of issues on premature ventricular contractions in patients without cardiac structural changes. Article presents the main mechanisms of the development of premature ventricular contractions, predictors of arrhythmogenic cardiomyopathy and pharmacological and interventional antiarrhythmic therapy principles. The development of frequent premature ventricular contractions can induce left ventricular dysfunction and lead to the formation of arrhythmogenic cardiomyopathy. The second article presents and substantiates the possibilities of one of angiotensin II receptor antagonists — telmisartan, in various clinical cases from the perspective of evidence-based medicine.

Current issue also presents Russian experts' comments on updated ESC Guidelines on pre-diabetes, diabetes and cardiovascular disease that include information on prioritizing different types of hypoglycemic therapy based on its cardiovascular effects, target lipid levels in patients with diabetes depending on cardiovascular risk, and information on antiplatelet therapy administration. These data may be useful for primary and secondary cardiovascular complications prevention for patients with diabetes mellitus.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

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

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LEADING ARTICLE

Risk of arterial hypertension and work-related stress in the population aged 25–64 years in Russia/Siberia (WHO — MONICA psychosocial program)

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Objective

To study how work-related stress affects the risk of arterial hypertension (AH) within a 16-year observation period in people aged 25–64 years in Novosibirsk, Siberia.

Materials and methods

We examined a random representative sample that consisted of people aged 25–64 years from a district in Novosibirsk in 1994 as a part of the III screening of the WHO-MONICA psychosocial program (men: n=657, mean age 44.3±0.4 years, response rate — 82.1 %; women: n=689, mean age 45.4±0.4 years, response rate — 72.5 %). The screening program included collecting socio-demographic data. The level of work-related stress was assessed with the Karasek scale. The period of prospective observation was 16 years. We used a chi-squared test (χ^2) to assess statistical significance in differences between groups. We used monofactorial and polyfactorial Cox regression model to assess relative risk (RR). We considered p≤0.05 to be statistically significant.

Results

High work-related stress levels were identified in 29.5 % of men and 31.6 % of women (χ^2= 2.574; υ=2 P=0.276). The level of work-related stress was higher in men who worked in a job that involved moderate manual labour compared with women (34.7 % in men vs 17.7 % in women; χ^2=7.755 df=2; p=0.021). At 16 years of observation RR of AH was higher in men (RR=1.4) than in women (RR=1.27). RR was higher in widowed men (RR=2.5), in women aged 25–44, 45–54, 55–64 years (RR=1.699, RR=2.427 and RR=2.694 respectively).

Conclusions

The level of work-related stress is similar in men and women. At the same time, at 16 years of observation RR of AH was higher in men compared with women.

Key words*: work-related stress, arterial hypertension, gender differences, relative risk.*

Conflict of interests: none declared.

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Introduction

The WHO defines "work-related stress" as being the response people may have when presented with work demands and pressures that are not matched to their knowledge and abilities and which challenge their ability to cope [1]. 28 % of working people in Europe (41 million people) are struggling with works-related stress [2]. Work-related stress is associated with cardiovascular disease (CVD) [3], musculoskeletal disorders (especially back pain) [4], anxiety depression [5], fatigue [6, 7], insomnia [8] and alcohol abuse [9]. It was suggested that more than 10 % of work-related disorders are associated with stress at workplace [10]. Finally, work-related stress leads to significant financial losses. For example, estimated total annual cost of stress in the EU is twenty billion dollars (EU-15). This figure is based on the costs to employers resulting from absenteeism, loss of productivity, health care costs and social welfare costs [11, 12].

Work-related stress was identified as an important independent risk factor for arterial hypertension (AH) [13, 14].

This study investigates the effect of work-related stress on the risk of arterial hypertension in men and women aged 25–64 years coming from different social groups in an open population in Novosibirsk, Russia, within a 16-year observation period.

Materials and methods

We examined a random representative sample that consisted of people aged 25–64 years from a district in Novosibirsk in 1994 as a part of the III screening of the WHO-MONICA psychosocial program (men: n=657, mean age 44.3±0.4 years, response rate — 82.1 %; women: n=689, mean age 45.4±0.4 years, response rate — 72.5 %).

The representative sample was formed according to the WHO-MONICA psychosocial program protocol requirements [15].

The screening program included the following parts:

1) Collecting socio-demographic data according to the standardized WHO-MONICA psychosocial program epidemiologic protocol that included ID, ad-

Table 1. **Distribution of the population aged 25–64 years by age groups (III screening program, 1994)**

Gender	Age groups								Total
	25–34 years		35–44 years		45–54 years		55–64 years		
	n	%	n	%	n	%	n	%	
Men	169	50.8	136	45.9	177	47.7	175	50.6	657
Women	164	49.2	160	54.1	194	52.3	171	49.4	689
Total	333	100	296	100	371	100	346	100	1346
χ^2=2.087 df=3; p=0.555									

Table 2. **Distribution of the population aged 25–64 years by marital status (III screening program, 1994)**

Gender	Marital status								Total
	Single (Never married)		Married		Divorced and not remarried		Widowed and not remarried		
	n	%	n	%	n	%	n	%	
Men	45	51.1	559	51.7	40	35.7	13	20	657
Women	43	48.9	522	48.3	72	64.3	52	80	689
Total	88	100	1081	100	112	100	65	100	1346
χ^2=33.113 df=3; p=0.0001									

Table 3. **Distribution of the population aged 25–64 years by level of educational attainment (III screening program, 1994)**

Gender	Level of educational attainment								Total
	Tertiary education		Incomplete tertiary education, secondary specialized education		Secondary education		Incomplete secondary education, primary education		
	n	%	n	%	n	%	n	%	
Men	186	49.2	178	44.3	150	49.2	143	55.6	657
Women	192	50.8	224	55.7	155	50.8	114	44.4	685
Total	378	100	402	100	305	100	257	100	1342
χ^2=8.133 df=3; p=0.043									

Table 4. **Distribution of the population aged 25–64 years by professional status (III screening program, 1994)**

Gender	Professional status*																		Total
	SE		MLE		MAN		ITW		HMW		MMW		LMW		Students		Retired		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Men	28	84.8	55	55.6	65	50.8	84	42	144	88.9	167	63.3	21	17.1	9	81.8	84	34.7	657
Women	5	15.2	44	44.4	63	49.2	116	58	18	11.1	97	36.7	102	82.9	2	18.2	158	65.3	605
Total	33	100	99	100	128	100	200	100	162	100	264	100	123	100	11	100	242	100	1262
χ^2=238.16 df=8; p=0.001																			

Comment
* Professional status:
SE — senior executives
MLE — mid-level executives
MAN — managers
ITW — IT workers
HMW — Heavy manual workers
MMW — Moderate manual workers
LMW — Light manual workers

dress, full name, date of birth, registration date; gender — 1 — male, 2 — female. Distribution of the population by age groups is presented in *Table 1*.

Marital status (Table 2), level of educational attainment (Table 3) and professional status (Table 4) were also taken into consideration.

2) Testing using the psychosocial methods. In order to assess the level of work-related stress we used the Karasek scale [15]. The analyzed risk factor was assessed at baseline without registering its change over time. All methods were strictly standardized and met all WHO-MONICA psychosocial program requirements [15].

The collected data were analyzed in MONICA Data Center in Helsinki, Finland. Quality control was performed in MONICA Quality Control Centers: Dundee (Scotland), Prague (Czech Republic), Budapest (Hungary). All the collected data were approved [15].

All men and women with CVD (coronary artery disease, cerebrovascular disease, AH, myocardial infarction, diabetes) identified before or during the screening process were excluded from the study. The study eventually included 384 women and 190 men aged 25–64 years. The period of prospective observation was 16 years.

The primary endpoint of this study was new arterial hypertension identified during the observation period. We used the information from the results of annual physical exams, patient histories, hospital discharge papers, papers from the district health

Table 5. **Work-related stress in the population aged 25–64 years (III screening program, 1994)**

Age	25–34				35–44				45–54				55–64				25–64			
Gender	M		W		M		W		M		W		M		W		M		W	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Family stress																				
Low	28	17.8	22	17.5	25	16.4	22	18.2	32	26.4	30	20.4	38	27.1	20	14.8	123	21.6	94	17.8
Moderate	84	53.5	66	52.4	82	53.9	57	47.1	55	45.5	76	51.7	58	41.4	69	51.1	279	48.9	268	50.7
Severe	45	28.7	38	30.2	45	29.6	42	34.7	34	28.1	41	27.9	44	31.4	46	34.1	168	29.5	167	31.6
Total	157	100	126	100	152	100	121	100	121	100	147	100	140	100	135	100	570	100	529	100
	χ^2=0.076 υ= 2; p=0.963				χ^2=1.288 υ=2; p=0.525				χ^2=1.577 υ= 2; p=0.455				χ^2=6.495 υ=2; p=0.039				χ^2= 2.574 υ=2; p=0.276			

Table 6. **Work-related stress and marital status in the population aged 25–64 years (III screening program)**

Work-related stress	Marital status															
	Single (Never married)				Married				Divorced and not remarried				Widowed and not remarried;			
	M		W		M		W		M		W		M		ЖW	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Low	7	21.2	7	22.6	83	20.4	70	17.4	6	21.4	11	20.4	4	50	6	15
Moderate	14	42.4	16	51.6	197	48.4	206	51.1	14	50	27	50	2	25	19	47.5
Severe	12	36.4	8	25.8	127	31.2	127	31.5	8	28.6	16	29.6	2	25	15	37.5
Total	33	100	31	100	407	100	403	100	28	100	54	100	8	100	40	100
	χ^2=0.872 df=2; p=0.647				χ^2=1.286 df=2; p=0.526				χ^2=0.017 df=2; p=0.992				χ^2=4.986 df= 2; p=0.083			

Table 7. **Work-related stress and level of educational attainment in the population aged 25–64 years (III screening program)**

Work-related stress	Education level															
	Tertiary education				Incomplete tertiary education, secondary specialized education				Secondary education				Incomplete secondary education, primary education			
	M		W		M		W		M		W		M		W	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Low	27	19.4	24	16.6	25	19.4	28	17.1	22	22	31	24.8	26	24.1	10	11.1
Moderate	69	49.6	75	51.7	66	51.2	83	50.6	39	39	56	44.8	53	49.1	50	55.6
Severe	43	30.9	46	31.7	38	29.5	53	32.3	39	39	38	30.4	29	26.9	30	33.3
Total	139	100	145	100	129	100	164	100	100	100	125	100	108	100	90	100
	χ^2= 0.401 df=2; p=0.818				χ^2=0.407 df= 2; p=0.816				χ^2=1.828 df=2; p=0.401				χ^2=5.626 df= 2; p=0.06			

clinics, death reports, conversations with relative, and autopsy reports.

During the annual physical exams we performed standardized blood pressure measurements on the right hand using mercury sphygmomanometers (we registered the first phase of Korotkoff sounds as systolic arterial pressure and the fifth phase as the diastolic blood pressure and then analyzed the mean). We considered patients to have arterial hypertension if systolic blood pressure was 140 mmHg or higher and/or diastolic blood pressure was 90 mmHg and higher in those individuals who did not receive hypotensive therapy. Hypertension group also included men with normal blood pressure readings if they were taking hypotensive therapy during the exam or stopped taking it less then two weeks prior.

We identified 229 new cases of AH in women and 46 cases in men over the observation period.

The statistical analysis was performed using the SPSS Version 11.5 [16]. We used a chi-squared test (χ^2) to assess statistical significance in differences between groups [17]. We used monofactorial and polyfactorial Cox regression model to assess relative risk (RR) and confidence intervals (CI) [18]. We considered $p \leqslant 0.05$ to be statistically significant.

Results

We identified high work-related stress levels in 29.5% of men and 31.6% of women (χ^2= 2.574; υ=2, p=0.276). We identified higher levels of stress in men (31.4%) and women (34.1%) of older age group of 55–64 years (χ^2=6.495 υ=2; p=0.039) (Table 5).

We identified no differences in work-related stress in men and women depending on marital status (Table 6).

Similarly, we identified no differences in work-related stress in men and women depending on the level of educational attainment (Table 7).

Table 8 presents compared level of work-related stress depending on professional level. We identified higher stress levels in men who worked in a job that involved manual labour compared with women of this

Table 8. **Work-related stress and professional status in the population aged 25–64 years (III screening program)**

WRS	Professional status*																									
	SE				MLE				MAN				ITW				HMW				MMW				LMW			
	M		W		M		W		M		W		M		W		M		W		M		W		M		W	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
L	3	12.5	2	50	10	22.7	8	22.9	10	23.8	19	43.2	13	19.7	27	31	21	19.6	2	22.2	26	22	27	34.2	4	28.6	23	28.8
M	10	41.7	1	25	26	59.1	18	51.4	20	47.6	19	43.2	30	45.5	46	52.9	53	49.5	4	44.4	51	43.2	38	48.1	7	50	39	48.8
S	11	45.8	1	25	8	18.2	9	25.7	12	28.6	6	13.6	23	34.8	14	16.1	33	30.8	3	33.3	41	34.7	14	17.7	3	21.4	18	22.5
Total	24	100	4	100	44	100	35	100	42	100	44	100	66	100	87	100	107	100	9	100	118	100	79	100	14	100	80	100
	χ^2=3.129 df= 2; p= 0.19				χ^2= 0.72 df= 2; p= 0.698				χ^2= 4.775 df=2; p= 0.092				χ^2=7.721 df=2; p=0.021				χ^2=0.089 df= 2; p= 0.957				χ^2=7.755 df=2; p= 0.021				χ^2= 0.01 df= 2; p= 0.995			

Comment: * WRS — work-related stress
L — low
M — moderate
S — severe
SE — senior executives
MLE — mid-level executives
MAN — managers
ITW — IT workers
HMW — heavy manual workers
MMW — moderate manual workers
LMW — light manual workers

Table 9. **Work-related stress and relative risk of arterial hypertension in the open population aged 25–64 years (monofactorial Cox regression model)**

Observation period	Gender	Men				Women			
16 years	Age group	p	RR	95% CI		p	RR	95% CI	
				Lower bound	Upper bound			Lower bound	Upper bound
	25–64	0.05	1.4	1.021	5.491	0.034	1.276	1.018	1.6

Table 10. **Work-related stress and relative risk of arterial hypertension in the open population aged 25–64 years over 16-years observation period (multifactorial Cox regression model)**

Gender / Reference group	Risk group	Men				Women			
		p	RR	95% CI		p	RR	95% CI	
				Lower bound	Upper bound			Lower bound	Upper bound
No stress	Work-related stress	0.3	1.5	0.5	3.9	0.021	1.166	0.917	1.482
Married	Single (Never married)	0.09	2.4	0.5	11	0.568	1.163	0.692	1.955
	Divorced and not remarried	0.1	1.7	0.06	9	0.134	1.581	0.868	2.880
	Widowed and not remarried	0.01	2.5	1.4	14	0.647	1.176	0.587	2.357
Higher education	Tertiary/Secondary specialized education	0.8	1.1	0.3	4.2	0.106	1.319	0.943	1.844
	Secondary education	0.7	0.7	0.1	3.9	0.780	1.056	0.718	1.554
	Incomplete secondary/Primary education	0.5	0.6	0.1	2.5	0.062	1.543	0.979	2.433
MAN. and ITW	Job type	0.8	1.4	0.04	15	0.998	1.002	0.239	4.202
24–34 years	35–44 years	0.08	1.4	0.9	13	0.003	1.699	1.204	2.399
	45–54 years	0.2	1.7	0.02	3.4	0.0001	2.472	1.737	3.518
	55–64 years	0.1	1.9	0.01	4	0.0001	2.694	1.556	4.666

Comment: MAN — managers, ITW — IT workers.

group (34.7% in men vs 17.7% in women; χ^2=7.755 df=2; p=0.021).

Monofactorial regression analysis showed increased AH risk over the 16-year observation period in individuals who had work-related stress (men: RR=1.4; CI 1.021–5.491; p<0.05; women: RR=1.27; CI 1.018–1.6; p<0.034) (Table 9).

Multifactorial modeling that included social parameters and age showed that RR of AH in women who had work-related stress was 1.166 (CI 0.917–1.482; p<0.021) and RR in men was 1.5 (CI 0.5–3.9; p>0.05). In the groups that differed in marital status RR was the highest in the widowed men — 2.5 (CI 1.4–14; p<0.01). No statistically significant differences in AH RR were identified in men and women who had different levels of educational attainment and professional statuses. The comparison of 25–34 age group with the other three age groups showed that the AH RR in women who had work-related stress was 1.699 in the 35–44 age group (CI 1.204–2.399; p<0.003); 2.472 in the 45–54 age group (CI 1.737–3.518; p<0.0001) and 2.694 in the 55–64 age group (CI 1.556–4.666; p<0.0001). We didn't identify any statistically significant differences in the RR of AH in men of different age groups who had work-related stress (Table 10).

Discussion

Multiple factors are associated with the development of CVD and especially AH, including genetic, biological and psychosocial factors. It is well known that working conditions, age and gender can cause the development of AH. Furthermore, some data suggest that the effect of work-related stress on AH development differed between men and women, indicating that it contributed to a different extent depending on gender [19].

In the investigated population of working-age individuals (25–64 years) work-related stress was quite prevalent — almost ⅓ of men and women struggled with high levels of stress at the workplace. Men and women in the older age group (55–64 years) experienced more work-related stress. The level of work-related stress was higher in men who worked in a job that involved moderate manual labour compared with women, which means that "blue collars" are subjected to higher levels of stress compared with "white collars" [13].

Over the 16-year observation period the RR of AH in individuals with work-related stress was noted to be slightly higher in men (1.4) then in women (1.27). After marital status, level of educational attainment, professional status and age were included in the Cox-regression model along with work-related stress, AH risk increased in women (RR=1.6), widowed men (RR=2.5), and in women of all age groups (35–44 years: RR=1.69; 45–54 years: RR=2.47; 55–64 years: RR= 2.64).

Our study was similar to Wiernik et al. 2013 [20] cohort study that included 122 816 individuals (84 994 men). This study identified that work-related stress was a potential risk factor for AH development in women with low professional status. Besides, stress associated with marital life and low socioeconomic status was also investigated as a potential risk factor for AH. Moreover, work-related stress was identified as an independent risk factor for arterial hypertension [13, 20].

Conclusions

1. High work-related stress levels were identified in 29.5 % of men and 31.6 % of women (χ^2= 2.574; υ=2 P;=0.276). We identified higher levels of stress in men (31.4 %) and women (34.1 %) of older age group of 55–64 years (χ^2=6.495 υ=2; p=0.039).

2. The level of work-related stress was higher in men who worked in a job that involved moderate manual labour compared with women (34.7 % in men vs 17.7 % in women; χ^2=7.755 df=2; p=0.021). We identified no differences in work-related stress in men and women depending on the level of educational attainment.

3. Monofactorial regression analysis showed that AH RR in individuals with work-related stress was slightly higher in men (1.4) then in women (1.27) over the 16-year observation period.

4. Multifactorial modeling showed a rise in the RR of AH in several groups: in women who had work-related stress (RR=1.166); in the widowed men (RR=2.5) and in women of the 35–44 age group (RR=1.699), of the 45–54 age group (RR=2.472) and of the 55–64 age group (RR=2.694).

Conflict of interests: None declared.

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Cardiovascular risk assessment in a cohort of patients with arterial hypertension in Uzbekistan

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Objective

To assess cardiovascular risk in a cohort of men and women with arterial hypertension (AH) in a multicenter study in Uzbekistan.

Materials and methods

We conducted a cross-sectional study that included 582 men and women aged 30–59 years from 3 major Uzbekistan cites (Samarkand, Fergana and Urgench) with stage 1–3 AH and without verified cardiovascular diseases. Patients were asked to complete a questionnaire in order to assess demographic, social, behavioral characteristics and risk factors, as well as clinical status and therapy. Cardiovascular risk was assessed with the European SCORE scale.

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Results

The prevalence of smoking was significantly higher in men (70 %) compared with women (2 %). 15 % of men consumed moderate amounts of alcohol. Men tended to have higher arterial pressure readings compared with women. More than 60 % of patients with AH had ECG features consistent with left ventricular hypertrophy. Waist circumference exceeded the threshold by 25 % in women and by 5–11 % in men depending on the region. Mean total cholesterol levels exceeded normal limits by 10 % on average and hyperglycemia was identified in at least 15 % of the participants. High risk was identified in 30 % of participants. A very high risk of cardiovascular disease was identified in 11–13 % of women and in an even higher percentage in men.

Conclusion

Every second man and woman with AH in Uzbekistan are at a high and very high risk of cardiovascular complications. This fact can be explained by AH severity, end-organ damage and other risk factors.

Keywords*: Arterial hypertension, cohort, risk factor, cardiovascular risk.*

Conflict of interest: none declared.

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Introduction

21st century cardiovascular diseases (CVD) are the number one cause of work disability and mortality among adults in Eastern Europe and the Post-Soviet States. Simultaneously, in Western Europe the prevalence of CVD has significantly decreased as a result of the implementation of high-technology and prevention programs [1]. However, it is important to note that high-technology medical care affects prognosis more than it does morbidity. As such, the role of primary prevention in decreasing morbidity is difficult to overestimate. First and foremost, primary prevention involves the timely identification and correction of risk factors (RF). There is a great number of potential risk factors, but the World Health Organization (WHO) identified 7 most significant risk factors for the development of CVD and other chronic non-communicable diseases (CNCD). In clinical practice patients are often seen to have many RF simultaneously, which increases their overall risk of cardio-vascular diseases [2].

Arterial Hypertension (AH) is a common disease in the adult population and is a primary cause of stroke and myocardial infarction (MI). Over several decades many studies have been done to uncover effective treatment of arterial hypertension and reduce the risk of severe cardiovascular events [3]. Hypertension is a target for uncovering other diseases as well, since the overall prognosis is not evaluated solely on the basis of one disease, but on a combination of risk factors. This demonstrates the importance of cumulative scoring scales for the prognosis of disease complications.

In Uzbekistan in 2014 a nationwide study was carried out with the support of international organizations aimed identifying RF of chronic non communicable diseases (CNCD) among working-age individuals. The following information was revealed [4]:

- 37 % — excess intake of salt;
- 16.4 % — low physical activity;
- 20.2 % — excess body weight;
- 33.9 % — elevated arterial pressure.

Undoubtedly, the examination of clinical characteristics of hypertension, risk factors, end-organ damage, and associated diseases will allow for the correction of the resulting attributable risk for cardiovascular events. According to the latest European guidelines both a decrease in blood pressure to target values (which were reviewed to factor in the patient's clinical status and age) and the correction of RF have been shown to be effective in decreasing the risk of cardiovascular events [5]. From this point of view, we considered the clinical study of cardiovascular RF with respect to gender to be important and relevant.

Research objective

To assess cardiovascular risk in a group of men and women with arterial hypertension (AH) in a multicenter study in Uzbekistan.

Materials and methods

We conducted a cross-sectional study that included 582 men and women aged 30–59 years from 3 major Uzbekistan cites (Samarkand, Fergana and Urgench) with stage 1–3 AH and without verified cardiovas-

cular diseases. The study was conducted according to the 2017 agreement between the National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation and the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation of Uzbekistan.

Inclusion criteria. The study included men and women aged 30–59 with stage 1–3 arterial hypertension as classified by the European Society of Hypertension [11], who did or did not have RF or somatic diseases.

Exclusion criteria consisted of: patients aged over 59 years, presence of congestive heart failure (CHF), stable angina, structural heart or vascular defect, stroke of any origin, history of MI, peripheral artery atherosclerosis, renal or liver failure, respiratory distress, stage 3–4 oncological disease, collagenosis, endogenous psychiatric disorder, bilateral renal artery stenosis, alcohol or other substance abuse disorder.

Clinical and instrumental diagnostic methods included **standard questionnaires** using an adapted (Azerbaijanian) version of the ARIC questionnaire: age, marital status, education, social status, family history, smoking, alcohol use, AH characteristics, treatment, and comorbidities [6].

Subjects were considered to be smokers if they smoked at least one tobacco product per day. Smoking status was categorized in the following way: 1) never smoker, 2) former smoker, 3) current smoker. *Alcohol use status* was assessed using the following two categories: 1) has not consumed alcohol in the past year, 2) consumes a small or moderate amount of alcohol (168 ml of ethanol per week for men or 84 g of ethanol per week for women).

Blood pressure was measured using a mechanical pressure cuff with an accuracy of up to 2 mmHg. Measurements were done twice with 5-minute intervals with the patient at rest in a sitting position. Systolic arterial pressure (SAP) was identified by the appearance of Korotkoff sound 1 (phase 1) and diastolic arterial pressure (DAP) by the disappearance of Korotkoff sounds (phase 5). For the analysis the mean of both measurements was used. Heart rate (HR) per minute was also recorded. *Anthropomorphic measurements*: height was measured with an accuracy of up to 0.5 cm; body mass was measured with an accuracy of up to 0.1 kg; body-mass index (BMI, Quetelet index) was calculated as the body weight in kilograms divided by the square of the height in meters; waist circumference was measured with an accuracy of up to 0.5 cm.

Electrocardiography (ECG) was carried out using 12 standard leads with the patient lying down (standardized stationary apparatus was used). For the diagnosis of left ventricular hypertrophy (LVH) the Sokolow-Lyon index and the Cornell voltage ECG criteria were used.

Laboratory studies — blood samples were taken from the cubital vein after 12 hours of fasting with minimal venous occlusion (tourniquet pressure less than 90 mmHg). Blood was centrifuged for 10 minutes at 3000–3500 rotations per minute. Serum total cholesterol (TC) (mmol/l) was measured using enzyme kits using standardized automated analyzers and photocolorimetry. Glucose level (mmoles/litre) in venous plasma was identified after fasting with standardized analyzers using the hexokinase methods.

Cardiovascular risk evaluation. For every patient the risk of fatal CVD within 10 years was identified using the European SCORE scale. Risk was categorized in the following way: 1) low risk — < 1 %; 2) moderate risk — 1–5 %; 3) high risk — 6–9 %; very high risk — 10–14 % [7].

Statistical analysis. Patient data were registered in local study centers using ACCESS MS OFFICE. Editing and statistical analysis was done using SAS (Statistical Analysis System) by members of the National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia. Descriptive numerical characteristics of studied variables included mean prevalence, standard deviation, standard error of the mean; these were calculated using PROC SUMMARY, PROC UNIVARIATE, PROC FREQ. Standard significance criteria were used: x^2 and Student's two-tailed T-test.

Study results and discussion

The primary aim of the study was to identify cardiovascular risk and the prevalence and character of other RF among men and women of working age with AH. This type of multi-center study is the first of its kind in Uzbekistan. The analysis included three different regions of the country, which also allowed for the local evaluation of a wide range of RF. We previously completed a similar study in Azerbaijan, which allowed us to prioritize methods of primary prevention of CVD in patients with AH.

An analysis of socio-demographic indicies (parameters) in the studied group showed that a large ma-

Table 1. **Sociodemographic characteristics of patients with AH from three cities in Uzbekistan**

Variable	Samarkand		Total n=200	Fergana		Total n=179	Urgench		Total n=203
	Women, n=84	Men n=116		Women, n=97	Men, n=82		Women, n=91	Men, n=112	
Age, years	51.1±6.6	52.4±7.2		50.8±7.4	52.1±9.4		49.6±7.4	53.1±6.8	
Marital status, n (%)									
• Married	76 (90.5)	115 (99)	191	89 (92)	80 (97.5)	169	76 (83.5)*	108 (96.4)	184
• Divorced	5 (6)	—	5	2 (2)	—	2	8 (8.8)	3 (2.7)	11
• Widowed	3 (3.5)	1 (1)	4	6 (6)	2 (2.5)	8	7 (7.7)	1 (0.9)	8
Higher education, n (%)	28 (33)	44 (38)	72	26 (27)	33 (40) *	59	19 (20.8)	26 (23)	45
Employment, n (%)	46 (53)	90 (77.5) ***	136	41 (42)	54 (66) **	95	28 (30.7)	70 (62.5) ***	98
Smoking, n (%)	2 (2.3)	92 (79) ***	94	0	56 (68) ***	56	1 (1)	80 (71) ***	81
Alcohol use (Ui. P. Lisitzin groups)		***			***			***	
— Group 1	61 (70)	55 (47)	116	81 (83.5)	32 (39)	113	64 (70.3)	32 (28.5)	96
— Group 2	21 (24)	51 (44)	72	16 (16.5)	46 (56)	62	27 (22)	66 (59)	93
— Group 3	2 (2.3)	10 (9)	12	0	4 (5)	4	0	14 (12.5)	14

Comment.
1. Do not consume alcohol products
2. Consume alcohol products rarely (on festive occasions and family celebrations), no more than once per month on average and in moderate doses (a few units of wine or liquor).
3 Consume alcohol products moderately (1–3 times per month, no more than once per week) in modest amounts during social events (festive occasions, family celebrations, meeting with friends) and without antisocial behavior.

* $p<0.05$, **$p<0.01$, *** $p<0.001$ – statistical differences between compared groups.

Table 2. **ECG and central hemodynamic parameters in men and women with AH from three cities in Uzbekistan**

Variable	Samarkand		Fergana		Urgench, Khiva	
	Women, n=84	Men, n=116	Women, n=97	Men, n=82	Women, n=91	Men, n=112
SAP, mmHg	153.5±21.6	157.5±19.8	154.8±19.4	156.4±17.6	154.9±20.8	159±18.6
DAP, mmHg	95.8±9.5	97.3±10.2	91.2±10.4	90.8±9.5	92.6±10.2	94.7±8.2
HR, beats per minute	77.9±11.3	74.9±10.4	74.6±12.1	72.8±3.2	78.6±12.4	76.8±1.21
ECG signs of LVH, n (%)	64 (73.5)	84 (72.4)	59 (61)	76 (92.6)*	59 (65)	79 (87)

Comment. * $p<0.001$ – statistical differences between the compared groups.

jority of patients with AH were married (on average more than 90 % of cases) (Table 1). The number of patients with AH who also had a higher education was less than 40 %. Employment was greater in men than in women by 50–70 % in all regions. Women most frequently worked as homemakers. Smoking was notably very common among men (on average 70 %), and in women it was far less common (no more than 2 %). Similarly, the majority of women did not consume alcohol. In Samarkand and Fergana there was a similar number of men who did not consume alcohol or who consumed alcohol rarely, whereas in Urgench the distribution was different: approximately 60 % consumed alcohol rarely and 13 % consumed alcohol in moderate amounts.

In all of the studied groups with AH the average values for SAP and DAP were higher than target values despite antihypertensive therapy (however, 30 % of patients were not receiving any therapy) (Table 2). Overall, a tendency towards higher blood pressure values among men was noted as compared with women with AH. More than 60 % of patients with AH had ECG signs of LVH at the time of the study, which undoubtedly is a poor prognostic factor [8]. LVH was more common in men with AH from Fergana and Urgench.

In Uzbekistan a high rate of obesity and excess body weight was noted among working age people [4]. Patients with AH were also noted to have higher levels of anthropometric measurements (Figure 1). In particular, waist circumference (WC) among women was 25 % higher than the cut-off value, while for men this value was higher than the normal by 5–11 % depending on the region. A similar tendency was seen with BMI, which is known to increase the severity of the disease. These parameters are similar to those seen in AH study groups in Azerbaijan and are obviously related to lifestyle and dietary habits in these populations [6].

In the study two markers for CVD were analyzed: TC and fasting glucose levels. Average levels of TC in all groups were above the upper bound of the normal range by 10 % while the highest values were seen in men from the city of Urgench (Table 3). Average fasting glucose values in venous blood demonstrated hyperglycemia (prediabetes and diabetes mellitus type

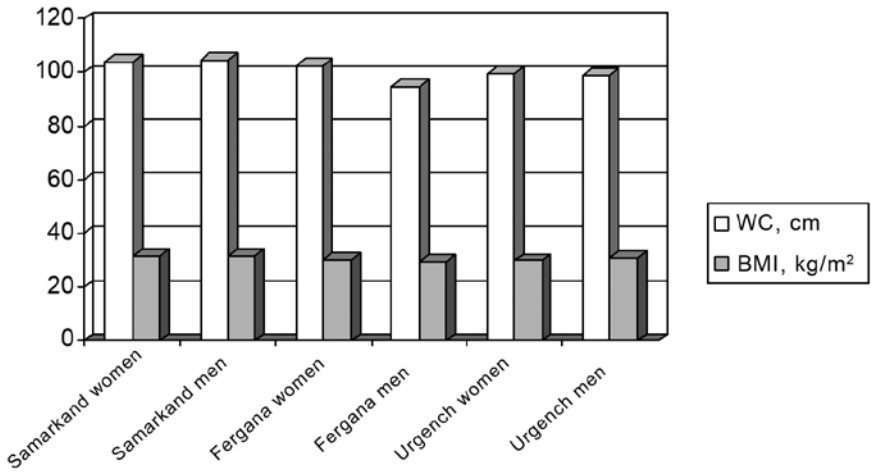

Figure 1. Anthropomorphic measurements in patients with AH. WC = waist circumference (cm), BMI = body mass index (kg/m^2)

Table 3. **Laboratory markers of CVD in three cities of Uzbekistan**

Variable	Samarkand		Fergana		Urgench	
	Women, n=84	Men, n=116	Women, n=97	Men, n=82	Women, n=91	Men, n=112
Total cholesterol, mmol/l	5.4±1.2	5.5±1.1	5.3±1.5	5.4±1.1	5.26±1.2	5.84±1.2*
Glucose, mmol/l	5.3±1.17	5.6±1.3	5.7±1.2	5.5±1.24	5.3±1.21	5.6±1.4

Comment. * $p<0.05$ — statistical significance between the compared groups.

2) in at least 15 % of the studied group. This is determined by the high prevalence of obesity, particularly abdominal obesity. Overall, according to data from the International Diabetes Federation, Uzbekistan and other Post-Soviet States belong to regions of high risk for the development of diabetes mellitus [9,10].

The primary aim of the study was to identify the general risk of cardiovascular events in accordance with the European SCORE scale between men and women with AH as well as RF. Every second patient in the studied group was at moderate cardiovascular risk (Table 4). High risk was seen on average in 30 % of cases. Among women high risk of cardiovascular risk was seen in 11–13 % of cases, while being somewhat higher in male subjects. This is likely due to men more often being smokers and also having higher blood pressure and TC levels on average [11].

It is necessary to note that a similar tendency was seen in our study with patients from Azerbaijan, specifically that high cardiovascular risk was seen two times more often than very high cardiovascular risk. In these two populations there were variations based on gender. Very high risk in patients form Uzbekistan was seen more often among men, while Azerbaijan patients had an opposite tendency [6].

As such, this study group of both men and women with AH were at high or very high cardiovascular risk in up to 50 % of cases, which may be explained by both the severity and multiplicity of risk factors present as well lack of preventative treatment.

Conclusion

In the study group from Uzbekistan one third of men and women with AH were seen to have high cardiovascular risk and one fifth to have very high cardiovascular risk. The number of male subjects at very high risk was by 30–50 % higher than in female subjects. Average values of arterial pressure and WC were notably elevated, as well as TC and glucose. Analysis by gender demonstrates a higher prevalence of smoking and a greater severity of AH and other risk factors in men.

Considering the large prevalence of cardiovascular events in working-age people in Uzbekistan it is

Table 4. **Overall cardiovascular risk according to the SCORE risk chart in patients with AH**

Variable	Samarkand		Fergana		Urgench, Khiva	
	Women, n=84	Men, n=116	Women, n=97	Men, n=82	Women, n=91	Men, n=112
Moderate risk, n (%)	36 (43)	49 (42)	39 (40)	38 (46)	37 (40.6)	43 (38.3)
High risk, n (%)	24 (28)	35 (30)	25 (26)	24 (29)	31 (34)	34 (30)
Very high risk, n (%)	10 (12)	20 (17)	11 (11.3)	15 (18.3)	12 (13)	26 (23.2) *

Comment. * $p<0.05$ — statistical significance between the compared groups.

necessary to implement primary prevention methods among individuals with RF such as AH. Improvement of patient education along with a combination of effective self-control and multifaceted prevention could decrease the risk of cardiovascular events.

Conflict of interests: None declared.

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Association of prevalence of metabolic syndrome and its components and family status changes in men of an open urban population

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Objective

To assess the association of prevalence of metabolic syndrome and its components with family status changes in men of an open population in a moderately-urbanized Siberian city.

Materials and methods

We conducted a cross-sectional epidemiological study of a representative sample formed from the electoral lists of Tyumen. The sample consisted of men aged 25–64 years, the response rate was 85.2%. We used IDF criteria (2005) to assess metabolic syndrome. We evaluated family stress including the stress from family status changes during the last 12 months using the WHO questionnaire "Knowledge and Attitude towards Health".

Results

Metabolic syndrome prevalence in Tyumen men aged 25–64 years was 15.0% (3 or more criteria per IDF). In an open Tyumen population 20% of men lacked stable family status, the same number of men were not able to rest at home, and in one third of men family conflicts were noted. In an open urban population of working age men with both a high prevalence of metabolic syndrome and high levels of family stress we identified certain groups with

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both metabolic syndrome and arterial hypertension (per IDF criteria) who on average had a more stable family status.

Conclusion

As such, when formulating regional preventive programs in the open population of the city of Tyumen and other moderately urbanized Siberian cities it is important to use standardized methodologies and accumulated data. This is necessary to achieve objective monitoring of the epidemiological situation in regards to cardiovascular disease and chronic stress factors such as availability of social care and family status.

Keywords: *Epidemiological study, male population, metabolic syndrome, family stress.*

Conflict of interest: none declared.

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Introduction

According to the Russian Society of Cardiology metabolic syndrome (MS) is characterized by visceral adipose tissue accumulation, peripheral insulin resistance, and hyperinsulinemia that lead to carbohydrate, lipid and purine metabolism disoreders as well as arterial hypertension (AH) [1]. A meta-analysis of major epidemiological studies found the frequency of MS in adult population to be 10 % in China and up to 24 % in the USA. The World Health Organization (WHO) consider MS to be the XXI century pandemic and predict that the rate of MS incidence will rise by 50 % in the following 25 years [2]. The European Botnia Study carried out in Finland in Sweden, showed the independent prognostic role of MS. Mortality in the MS group was 1 % compared with 2.2 % in the control group. The Botnia Study results showed that MS was a more significant risk factor than any of its components [3].

MS is characterized by polygenic predisposition that rarely causes any disease in the absence of specific risk factors associated with modern way of life. The specific risk factors that play the leading role in the development of MS are not clear at this time. The research is currently focused on psychosocial and dietary factors [4–6]. Stress affects the development of cardiovascular disease both in direct way and via irregular adaptation mechanisms (smoking, overeating, alcohol consumption) [7–9]. Many researchers consider the divorced, retired and unemployed individuals to be at the highest risk of stress [10, 11]. Long-standing excess stress and neuroendocrine trophic effects in MS also lead to structural adaptation of the cardiovascular system [2]. The effects of these risk factors are further aggravated by various maladaptive behaviors such as alcohol and drug abuse, smoking, overeating and lack of physical exercise [12, 13].

As such, the latest decade of the XXI century can be characterized by a strong interest in MS, as all its components are conventional risk factors of cardiovascular disease (CVD). The several-fold increase in total cardiovascular risk determines the medical and social significance of MS problem. At the same time, with an incredible material progress of the modern society comes the greater demand for the psychobiological knowledge. The lack of these knowledge may lead to loss of health and wellbeing.

Materials and methods

We conducted a simultaneous epidemiological study of a representative sample of the Central district of Tyumen population. The sample, formed using the random number generation method, included 1000 men aged 25–64 years (response rate 85.0 %), 250 people in each age group: 25–34; 35–44; 45–54; 55–64 (Figure 1).

We used IDF criteria (2005) to assess metabolic syndrome: waist circumference (WC)≥ 94 cm in Caucasian men plus 2 of the following criteria: triglycerides≥ 1.7 mmol/l, HDL–C< 1.0 mmol/l+ hypolipidemic therapy, blood pressure≥ 130/85 mmHg or previous antihypertensive therapy, blood glucose≥ 5.6 mmol/l or type 2 diabetes mellitus (T2DM).

We evaluated family stress including the stress form family status changes during the last 12 months using the WHO questionnaire "Knowledge and Attitude towards Health".

The study was carried out with the accordance with the principles laid down in the Declaration of Helsinki. Study protocol was approved by the Ethical Committees of all the involved clinical centers.

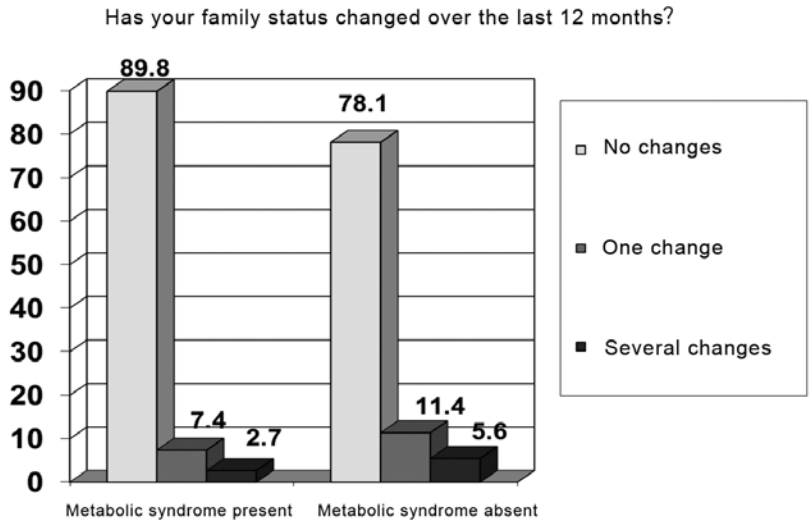

Figure 1. The association between metabolic syndrome prevalence and family status changes in the population of men aged 25–64 years, %.

Written informed consent was obtained from all participants prior to being enrolled.

Statistical analysis was completed using the IBM SPSS Statistics 21.0 software. The results are presented as proportions (in percent) for categorical variables in the four age groups that were analyzed. To correctly compare our data with the data form other epidemiological studies we performed age adjustment by direct standardization based on the age structure of Russian Federation urban population aged 25–64 years. In order to assess statistical significance of the differences we used Pearson's chi- squared test (χ^2) with Bonferroni correction. A p-value less than 0.05 was considered statistically significant.

The aim of this study was to assess the association of prevalence of metabolic syndrome and its components and family status changes in men of an open population in a moderately-urbanized Siberian city.

Results

Metabolic syndrome prevalence in Tyumen men aged 25–64 years was 15.0% (3 or more criteria per IDF) — age adjusted value. Prevalence of MS was significantly higher in the 45–54 age group (10.0–19.8%, p<0.001) and in the 55–64 age group (19.8–31.2%, p<0.01). Statistically significant differences in MS prevalence were found in the following age groups: 25–34 years — 6.8–17.3%, p<0.001; 35–44 years — 10.0–17.3%, p<0.001; 55–64 years — 31.2–17.3%, p<0.001 (Table 1).

At the same time, around 20% of men in the open Tyumen population lacked stable family status, the same amount of men were not able to rest at home, and 1/3 of men family had frequent family conflicts.

Individuals with MS were found to have more stable family status compared with those without MS. Of all participants, 89.8% individuals with MS and 78.1% individuals without MS didn't have any family status changes during the last 12 months (p<0.05) (Figure 1).

Table 2 shows the association of MS components and family-related stress in the male population aged 25–64 years. Both individuals with and without MS answered questions from the "family-related stress" category (severe disease in close relatives, death of a relative, family conflicts during the last 12 months and the ability to rest at home) in a similar way.

At the same time, we identified a more stable family status in individuals with AH compared with the individuals without AH. Of all participants, 88.0% of

Table 1. **The prevalence of metabolic syndrome (according to IDF criteria) in Tyumen men aged 25–64 years**

Age, years	n	MS	
		Absolute number	%
25–34	177	12	6.8***
35–44	228	23	10.0***
45–54	231	46	***19.8
55–64	214	67	**31.2***
25–64	850	148	17.3
Age adjusted value			15.0

Comment: (*) on the left marks statistically significant differences in two age groups, (*) on the right marks statistically significant differences in the age group compared with the general population: * — * — p<0.05; **– p<0.01; *** — p<0.001; n –number of people examined, MS — metabolic syndrome.

Table 2. **Family-related stress and metabolic syndrome components in the population of men aged 25–64 years**

Question/attitude	Metabolic syndrome components									
	Abdominal obesity n=390		Arterial hypertension n=581		Hyperglycemia n=162		Hypertriglyceridemia n=97		Low HDL–C n=42	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
1. Severe disease or death of a close relative during the last 12 months?										
1.1. Yes	96/108	24.7/23.5	136/68	23.4/25.5	37/167	22.8/24.3	22/182	22.7/24.2	11/193	26.2/23.9
1.2. No	293/351	75.3/76.5	445/199	77.1/74.5	125/519	77.1/75.7	75/569	77.4/75.8	31/613	73.8/76.1
2. Has your family status changed over the last 12 months (married, divorced, left family, widowed, child born, other)?										
2.1. No changes	337/378	86.682.2	512/203	88.1/75.7***	137/578	84.6/84.1	86/629	88.7/83.6	35/680	83.3/84.3
2.2. One change	34/57	8.7/12.4	44/47	7.6/17.5***	14/77	8.6/11.2	7/84	7.2/11.2	6/85	14.3/10.5
2.3. Several changes	18/25	4.6/5.4	25/18	4.3/6.7	11/32	6.8/4.7	4/39	4.1/5.2	1/42	2.4/5.2
3. Were there any serious conflicts in your family during the last 12 months?										
3.1. No conflicts	271/312	69.7/67.8	401/182	69.0/67.9	112/471	69.3/68.2	74/509	76.3/67.4	27/556	64.3/68.9
3.2. One conflict	34/36	8.7/7.8	51/19	8.8/7.1	15/55	10.4/8.0	7/63	7.2/8.6	4/66	9.5/8.2
3.3. Several conflicts	70/94	18.0/20.4	107/57	18.4/21.3	31/133	17.8/19.8	14/150	14.4/20.1	10/154	23.8/19.1
3.4. Frequent conflicts	14/18	3.6/3.9	22/10	3.8/3.7	4/28	2.5/3.9	2/30	2.1/3.9	1/31	2.4/3.8
4. Is there anything that prevents you from getting good rest at home?										
4.1. Yes	68/110	17.4/24.0*	120/58	20.7/21.7	32/146	19.8/21.3	17/162	17.5/21.6	10/168	23.8/20.8
4.2. Нет	322/348	82.6/76.0*	461/209	79.3/78.3	130/540	80.2/78.7	80/589	82.5/78.4	32/638	76.2/79.2

Comment. (*) marks statistically significant differences in the presence and absence of metabolic syndrome components:
* — p<0.05; ** — p<0.01; *** — p<0.001; Abs. — absolute number

men with AH and 75.9% of men without AH didn't have any family status changes during the last 12 months (p<0.001); 7.5% of men with AH had one change compared with 17.3% of men without AH (p<0.001). Concerning other components of MS, we identified no significant differences related to family status changes in the last 12 months.

Discussion

Over the last two decades the psychosocial component of population health and its effects on CVD development have been a very important topic in contemporary research. It's gradually becoming one of the most important and complicated problems in modern medical science. Modern Russian society is currently undergoing major transformations that is inevitably leading to the formation of a new social structure and to the development of even stronger stratification [7, 10]. Chronic social stress results in the development of multiple adaptational diseases, and, undoubtfully, MS is one of them [1,4].

Chronic psychosocial stress increases the risk of MS development in a great number of ways. The formation of a specific behavioral pattern leads to activation of the sympathetic nervous system (SNS), secretion of catecholamines and, eventually, blood pressure elevation. Many studies have assessed the connection between stress and blood pressure changes [6, 8, 12]. Some traditional behavioral risk factors such as smoking, lack of physical activity and alcohol abuse as well as socioeconomic status in general are also associated with increased CVD risk in the presence of chronic psychosocial stress [9, 13].

In an open Tyumen population 20% men lacked stable family status, the same number of men were not able to rest at home, and in one third of men family conflicts were noted. At the same time, men aged 25–64 years with MS and AH (a component of MS according to the IDF criteria) were found to have a more stable family status compared with individuals without MS and AH. At the first sight, the identified pattern contradicts the majority of epidemiologic studies that found the CVD risk to be higher in single men [10]. However, according to the results of our previous studies in the Tyumen population, married men were better informed about CVD risk factors and showed more responsibility for their health and readiness to participate in preventive activities [11]. Therefore, more stable family status in men with MS seems reasonable enough. Marriage is considered to be one of the strongest types of social support. Widowhood and divorce, on the contrary, are difficult and stressful life situations. CVD mortality in divorced, widowed and single men who never married was significantly higher compared with married men [3]. As such, married men are considered to be the most protected social group and individuals with MS are in great need of social protection [9].

Conclusions

In conclusion, in working-age men with high prevalence of MS and its components and high levels of

family-related stress we identified a more stable family status. As such, when formulating regional preventive programs in the open population of the city of Tyumen and other moderately urbanized Siberian cities it is important to use standardized methodologies and accumulated data. This is necessary to achieve objective monitoring of the epidemiological situation in regards to cardiovascular disease and chronic stress factors such as availability of social care and family status.

Conflict of interests: None declared.

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Ventricular extrasystoles in patients without cardiac structural changes: mechanisms of development, arrhythmogenic cardiomyopathy predictors, pharmacological and non-pharmacological treatment strategies

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The review article presents critical analysis of clinical studies over the last years, dedicated to ventricular extrasystoles (VEs) detection in practically health individuals, i. e. patients without cardiac structural changes. The development of frequent premature ventricular contractions can induce left ventricular (LV) dysfunction and lead to the formation of arrhythmogenic cardiomyopathy. Therefore, the objective of this article is to determine, based on the analysis of literature and research data, the main mechanisms of VEs development in patients without cardiac structural changes, predictors of LV dysfunction and arrhythmogenic cardiomyopathy induced by premature

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ventricular complexes, and to evaluate the effectiveness of pharmacological and interventional antiarrhythmic therapy. The analysis will show the direction of future clinical studies to improve VEs treatment in patients without cardiac structural changes.

Key words: *ventricular extrasystoles in patients without cardiac structural changes, arrhythmogenic cardiomyopathy prevention principles.*

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Introduction

Ventricular premature contractions or ventricular extrasystoles (VEs) are the most common ventricular arrythmias [1]. Its prognosis depends on the presence of cardiac or extracardiac organic disease, and it is usually considered benign in patients without cardiac structural changes, according to the classification of B. Bigger (1984) [1].

In the 1970s and 1980s, frequent VEs were considered triggers for the development of ventricular tachycardia, ventricular fibrillation, and sudden cardiac death in patients after myocardial infarction (MI) [1]. Therefore, the suppression of VEs was considered essential in these patients. The CAST study showed that antiarrhythmic VEs treatment, especially using class I agents, increased mortality in patients after MI, due to its arrhythmogenic effect, despite effective suppression of premature ventricular complexes [1].

More recent studies have shown that, despite the benign prognosis of VEs in patients without cardiac structural changes, frequent premature ventricular contractions contribute to the development of LV dysfunction and heart failure, and its suppression improves cardiac function [1–3]. On the other hand, VEs in patients without cardiac structural changes can indicate the so-called "arrhythmic" form of arterial hypertension, coronary artery disease, myocarditis, cardiomyopathies, stroke and other cerebrovascular pathology onset, as well as be an independent life-threatening ventricular arrhythmias, atrial fibrillation, and sudden cardiac death predictor [4–10].

Thus, mechanisms of premature ventricular contractions development in patients without cardiac structural changes, risk factors of arrhythmogenic cardiomyopathy development, as well as the effectiveness of VEs pharmacological and interventional treatment are one of the main issues in modern cardiology.

The prevalence of premature ventricular complexes in patients without cardiac structural changes

In early 60s with the introduction of Holter monitor or daily electrocardiogram (ECG) into clinical practice, from 1 to 5 VEs / hour were revealed in 75% of healthy individuals without cardiac structural changes, and over 60 / hour — in 4% during 48-hour ECG monitoring [11–14]. The frequency of VEs detection increased with age, with the presence of any extracardiac pathology and with ECG monitoring duration, and reached about 80% [14]. Similar premature ventricular complexes frequency in patients without cardiac structural changes was found in later studies, the frequency did not differ significantly between men and women [15–19].

Mechanisms of premature ventricular complexes development in patients without cardiac structural changes

Nowadays, it is known that VEs can be caused by various mechanisms, including early or delayed after-depolarization, re-entry, and ectopic pacemaker development [20]. The studies of these mechanisms are mainly based on experimental models and its extrapolation in the development of premature ventricular complexes in patients without cardiac structural changes is limited [21]. The development of delayed after-depolarization is based on Ca++ ions overload in cardiomyocytes [20]. Delayed after-depolarizations are generated by a "transient inward currents" (iti), carried by Na+ and partially K+ ions, controlled by the intracellular concentration of Ca++ ions that are also affected by the entry of Ca++ ions into the cell [20]. Triggered activity induced by delayed after-depolarization is stimulated by heart rate increase, catecholamines, "oxidative stress" in cardiomyocytes, various substances or drugs toxic effects that inhibit intracellular Na-K pumps, for example, digoxin, ß1-adrenoreceptor agonists, etc. [20,22].

Early after-depolarization of cardiomyocytes occur during repolarization or before its completion and cause the development of VEs at the low level of membrane potential — 30 mV. In case such after-depolarization is sufficient, it leads to the appearance of low amplitude action potential. Normally, total ionic current during repolarization is directed outward the cell. When inhibiting the outward and / or increasing background inward current, total current becomes inward that leads to the beginning of membrane depolarization [20,22]. Depolarization can cause cardiomyocyte re-excitation [20,22]. Outward (repolarizing) current decrease can occur in case of decreased membrane permeability to potassium during pronounced extracellular potassium concentration decrease due to hypoxia, heart rate reduction, for example, due to increased vagal tone or action of some toxic substances [20]. VEs caused by early and delayed after-depolarizations are associated with lower cell membranes hyperpolarization compared with arrhythmias caused by re-entry mechanism, thus, cardiomyocyte dysfunctions are potentially reversible: in over 90 % cases, VEs, caused by trigger mechanisms were eliminated after lifestyle modifications (elimination of acute or chronic stress, excessive vagal effects, electrolyte imbalance, autonomic, dysmetabolic disorders, hypoxia, alcohol abuse, coffee, energy drinks, etc.) or after cardioprotective therapy (antihypoxants, antioxidants, potassium preparations, etc.), as well as after classes II or IV antiarrhythmic agents treatment [20–22]. Further membrane hyperpolarization, caused by deeper metabolic disturbances, increases action potential duration and decreases outward and inward currents, for example, the lesion of calcium channels in L-type cardiomyocytes increases repolarization heterogeneity that is usually seen in VEs caused by re-entry mechanism [20–23]. The formation of this mechanism is associated with increased risk of sudden cardiac death due to malignant ventricular arrhythmias development [21,24]. To eliminate premature ventricular contractions, caused by the re-entry mechanism, mainly I and / or III classes of antiarrhythmic agents are used, while II (IV) classes of antiarrhythmic agents have no positive effect [20,21,23,24]. In the absence of positive antiarrhythmic pharmacotherapy effect, the development of VEs in patients without cardiac structural changes is usually caused by ectopic pacemaker development, that is mainly eliminated by radiofrequency ablation [1,21,24].

Clinical evaluation of premature ventricular complexes in patients without cardiac structural changes

VEs in patients without cardiac structural changes are considered "idiopathic" after eliminating potential causes of this arrhythmia and may manifest as heart rate interruptions, subjective sensation of " a beat followed by heart sinking", inspiratory dyspnea during physical activity, lightheadedness, chest pain behind the sternum or in the left side of the chest [1.16.17.21]. Some of these patients have asymptomatic premature ventricular contractions that are usually diagnosed during regular examination [1.17.21]. The absence of clinical symptoms in patients without cardiac structural changes and with VEs may be one of the risk factors for LV dysfunction development that leads to the formation of arrhythmogenic cardiomyopathy. It is also remarkable that many patients without cardiac structural changes with asymptomatic VEs have normal LV function. Time before accidental detection of VEs in these patients and the development of LV dysfunction can be quite long. Some patients have asymptomatic VEs for years or decades before the development of heart dysfunction [1.17.21].

Clinical examination of patients without cardiac structural changes and without clinical manifestations of heart failure often does not reveal any abnormalities, except for irregular heartbeat caused by premature contractions. Standard ECG and 1–3 day 12-lead ECG monitoring can identify VEs and assess its morphology and localization in such patients [1,21]. It should be noted that patients without cardiac structural changes often have variability of VEs during the day, thus, it is better to assess the number of premature ventricular complexes by continuous 48–72-hour ECG monitoring. It is also essential to determine whether LV dysfunction developed before VEs or was caused by premature complexes.

The initial absence of cardiac structural changes is established by transthoracic echocardiography [25] and exclusion of cardiac and extracardiac diseases (rheumatic heart disease, cardiomyopathies, heart defects, mitral valve prolapse, myocarditis, thyrotoxicosis, postmyocarditis cardiosclerosis, obesity, hyperlipidemia, arterial hypertension, various clinical forms of coronary artery disease, short and long QT syndromes, early repolarization, complete blockade of the bundle of His, anemia, chronic lung diseases, nasopharynx, diabetes mellitus, diseases of the gastrointestinal tract, etc.), electrolyte disorders, the use of drugs and / or toxic substances abuse (primarily diuretics, oral contracep-

tives, inhaled beta-adrenoreceptor agonists, alcohol, coffee, energy drinks, etc.) that directly or indirectly cause VEs [1,16,17,21]. When heart dysfunction is detected, it is necessary to assess if it preceded VEs development or was its result [1,17,21]. In case patient's echocardiographic examination does not reveal any structural and functions cardiac impairments [1,25] in patients without any cardiac and extracardiac pathologies, it is necessary to perform stress echocardiography [1,21]. Patients with positive or doubtful results of the stress test, as well as with one large or two small criteria for right ventricular (RV) arrhythmogenic dysplasia, ventricular late potentials, unstable ventricular tachycardia, or who's profession is associated with other people's live risks (pilots, public transport drivers, etc.), underwent invasive and / or non-invasive coronagraph, contrast magnetic resonance heart imaging or stress myocardial scintigraphy with technetium 99 or thallium-201 to determine latent myocarditis, cardiomyopathy or latent myocardial ischemia. [1,21]. If ventricular late potentials are detected in patients with negative results of stress echocardiography, as well as in the case of VEs frequency increase, the development of unstable ventricular tachycardia after the stress test, it is necessary to conduct non-invasive coronary angiography and contrast magnetic resonance imaging, since the results of these research methods identify potential candidates for the surgical removal of premature ventricular contractions in patients without cardiac structural changes [1,21].

Predictors of left ventricular dysfunction development in patients with premature ventricular contractions without cardiac structural changes

LV dysfunction and arrhythmogenic cardiomyopathy do not develop in all patients without cardiac structural changes with premature ventricular contractions [1,21,34]. Asymptomatic VEs may be seen before the development of heart failure [1,17,21]. Predictors of LV dysfunction in patients without cardiac structural changes include the nature of the ventricular contraction (duration of the QRS complex, adhesion intervals), its localization, frequency per hour and / or amount per day of observation, and variability during the day.

The duration of QRS complex of premature ventricular contraction, adhesion intervals, the presence of interpolated VEs

The duration of QRS complex≥ 140 m/s and interpolated VEs are independent predictors of LV systolic and, less often, diastolic dysfunction [26–30]. The causes of QRS complex expansion haven't been well understood yet, however, according to some authors, they may include with cardiac impulse slowdown from the cardiomyocyte to ventricular myocardiocyte during premature contraction [31]. The adhesion interval≤ 600 m / s with low variability (less than 60 m/s) is associated with LV ejection fraction decrease, possibly due to incomplete LV filling and stroke volume decrease [32,33]. However, larger studies are needed to identify the causes of QRS complex changes [1,21].

Ventricular extrasystoles frequency

Previously, the detection of≥ 24 % VEs of all ventricular complexes was considered as independent predictor of arrhythmogenic cardiomyopathy development [18]. However, recent studies have shown that the detection of≥ 10–15 % of premature ventricular complexes of all ventricular contractions can already induce the development of LV dysfunction [21,34]. It is also remarkable that the amount of VEs is a modifiable risk factor for LV dysfunction: pharmacological therapy and / or surgeries reduce total number of premature ventricular complexes, as well as the risk for arrhythmogenic cardiomyopathy [1,17,21].

Premature ventricular contractions localization

About 70–75 % of VEs originate from the right ventricular outflow tract, and the rest — from interventricular septum, papillary muscles, left ventricle free wall or His bundle [1,17,21]. Arrhythmias originating from the right ventricular outflow tract have typical 12-lead ECG pattern — positive QRS complexes in II, III and aVF leads. This VEs morphology is similar to blockade of the left leg of the bundle of His and often indicates origin from the right ventricular outflow tract, although arrhythmias from the aortic valve can also have similar pattern, but with earlier QRS transition [26]. On the other hand, premature ventricular complex morphology, similar to blockade of the right leg of the bundle of His, usually indicates origin from the LV [1,16,17,21]. Nowadays, we can determine the origin of VEs by its various morphologies on ECG: if the QRS complex transition zone (when the R wave of the ventricular extrasystole is approximately equal to the S wave) is seen in the chest leads later than in sinus rhythm, this indicates right ventricular outflow tract origin, and early transition zone in the chest leads — LV origin [35,36]. If the QRS complex transition zone in sinus rhythm and in VEs is detected in

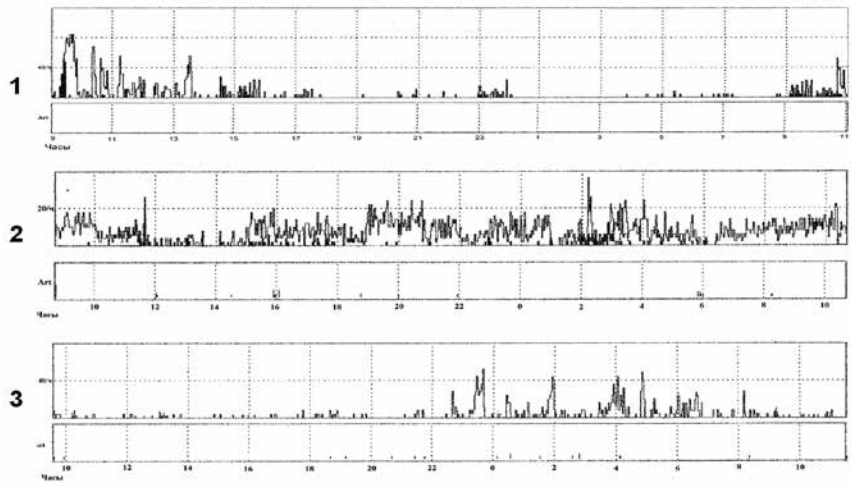

Figure 1. Distribution of VEs during the day: 1 — sympathetic type — extrasystoles are mainly detected in the daytime; 2 — permanent or mixed — extrasystoles are detected continuously throughout 24-hours; 3 — vagal or night type — extrasystoles are detected mainly in the evening and in the nighttime, its frequency decreases after waking up.

lead V3, when the amplitude of the R wave of premature ventricular contraction compared with the amplitude of the R wave of the QRS complex of the sinus rhythm in V2 lead is≥0.6, premature ventricular depolarization from the left ventricle is determined with 95 % sensitivity of and 100 % specificity [37]. In addition, it was proposed to calculate premature ventricular contraction maximum deflection index — the ratio of time from the beginning to the maximum of R or S wave to the duration of QRS complex of premature ventricular contraction. When premature ventricular contraction maximum deflection index≥ 0.55, epicardial origin of VE can be determined [38].

Discussed above ECG features are essential in the initial assessment of VEs in patients without cardiac structural changes to determine treatment strategies to eliminate premature ventricular contractions. Ventricular dyssynchrony can contribute to the development of LV dysfunction, and the right ventricular and epicardial origins of VEs are associated with the highest risk of LV dysfunction and arrhythmogenic cardiomyopathy [39,40].

Variability of premature ventricular contractions during the day

Frequent VEs during the day (Fig. 1, type 2) is an independent predictor of arrhythmogenic cardiomyopathy development [1,21,26].

Gender effect on arrhythmogenic cardiomyopathy development in patients with VEs

Women are more sensitive, therefore, VEs in women are diagnosed earlier than in men. For this reason, women are less likely to develop arrhythmogenic cardiomyopathy, since VEs treatment is usually started earlier. Therefore, male gender is an independent risk factor for the development of arrhythmogenic cardiomyopathy in patients without cardiac structural changes and VEs [1,21,39,40].

Treatment strategies in patients with premature ventricular contractions without cardiac structural changes

VEs treatment in patients without cardiac structural changes with subjective arrhythmia feelings include lifestyle modification, antiarrhythmic pharmacotherapy and radiofrequency ablation to reduce or completely eliminate premature ventricular complexes [1,21,41,42]. Therapy effectiveness was evaluated using 1–3 daily Holter ECG monitoring: before and after pharmacotherapy (for 5–7 days) or catheter ablation, the criterion for positive effect is the reduction of extrasystoles frequency by over 75 % compared with its initial level, as well as the elimination of paired, group extrasystoles and unstable ventricular tachycardia [1,16,17,21]. Lifestyle modification, including reduced caffeine / alcohol consumption, psycho-emotional state monitoring, etc. has low effectiveness in VEs frequency reduction in patients without cardiac structural changes [1,21,39–41]. On the other hand, interventional treatment is generally not considered in patients without subjective arrythmia feeling with frequent premature ventricular complexes and preserved heart function [1,21,41,42]. Most patients without cardiac structural changes with frequent but asymptomatic VEs have normal LV ejection fraction and usually do not develop arrhythmogenic cardio-

myopathy [1,21,40,41,42]. Beta-blockers or calcium channel blockers can be used to reduce VEs frequency. All patients using these antiarrhythmic agents should be informed to contact physician on any heart failure symptoms and conduct ECG at least once every 3–6 months to assess LV ejection fraction [1,21].

Pharmacological treatment

According to the latest guidelines [1,21], radiofrequency ablation of the arrhythmogenic focus is recommended in patients without cardiac structural changes who have over 10–15 % VEs of the total ventricular complexes, as well as in patients who refuse to take antiarrhythmic pharmacotherapy or in case of its ineffectiveness [1,21,34]. This recommendation is the basis of initial antiarrhythmic pharmacotherapy of VEs in this category of patients.

Beta-blockers or calcium antagonists are usually first-line pharmacological treatment for patients without cardiac structural changes with subjective arrhythmia feeling. [1,21]. Numerous randomized studies have shown metoprolol, propranolol, carvedilol and atenolol positive effect on VEs frequency in this category of patients. It is also remarkable that these drugs were most effective in sympathetic or daytime distribution of VEs (Fig. 1, type 1) [1,21,24, 34,40]. It should be noted that anticholinergics, beta-blockers with intrinsic sympathomimetic activity or non-dihydropyridine calcium channel blocker are more effective in patients with vagal or nighttime type of VEs distribution (Figure 1, type 3) [1,21,24,34,40]. The effectiveness of beta-blockers or calcium channel blockers ranges from 15 to 20 %, and its positive clinical effect is observed for 1–2 or, rarely, 3 years [1,21,24,34,40]. Meanwhile, beta-blockers and calcium channel blockers are first-line treatment due to its relative safety and the minimal amount of side effects [1,21].

Classes I and / or III antiarrhythmic agents, such as flecainide, propafenone, mexiletine, ethacyzin, moricizine, allapinin, and sotalol, are referred to second line treatment of VEs in patients without cardiac structural changes [1,16,17,21]. It is known that class I antiarrhythmic agents are contraindicated in patients with LV dysfunction and cardiac structural changes [1,16,17,21]. Therefore, amiodarone is recommended in patients with LV dysfunction, predominantly systolic, without cardiac structural changes to reduce VEs frequency [1,21,24,40,41]. However, its long-term use in patients without cardiac structural changes, especially of a young age, is undesirable due to numerous side effects [1,16,17,21]. Many studies have shown that the efficacy of classes I and III antiarrhythmic agents reaches about 90 %, and positive antiarrhythmic effect, in most cases, does not exceed 4–5 years [1,16,17,21,24,40,41]. A few studies showed that class I antiarrhythmic agents can be effective after at least one unsuccessful radiofrequency ablation [40,41,42]. Now it is known that combinations of antiarrhythmic agents (class II with class I or class III with I) can be effective in VEs frequency reduction in patients without cardiac structural changes, however, unfortunately, there are no large-scale clinical studies on effectiveness and safety of these treatment strategies.

Catheter ablation

Catheter ablation is recommended in patients without cardiac structural changes with frequent monomorphic VEs, only in case of ineffective antiarrhythmic pharmacotherapy or in patients refusing to take antiarrhythmic agents [21,34]. Potential benefits of radiofrequency ablation need to be weighed against the risks of serious complications, that occur in 3 % of patients on average [43–45]. Vascular complications include: ileal artery false aneurism, arteriovenous fistula or inguinal hematoma, cardiac perforation with tamponade, intraprocedural stroke, or sudden death [45,46,47]. In addition, efficacy and risks of complications of catheter ablation depend on VEs anatomical location, and surgeon experience [45,46,47]. These factors are most important when choosing radiofrequency ablation center [45,46,47]. Nevertheless, continuous improvements in ablation technology, energy sources, and advanced software for three-dimensional mapping have allowed radiofrequency ablation to become relatively safe and effective method to reduce frequency or completely eliminate VEs in patients without cardiac structural changes [43,45]. Nowadays, successful ablation can be performed in patients without cardiac structural changes with almost all known localizations of VEs [43,45]. The key to successful interventional elimination of VEs is fluoroscopy control, as well as cardiostimulation, electroanatomical intracardiac mapping and intracardiac echocardiography [43,45]. Cryoablation can be a promising alternative to radiofrequency ablation in cases of complex localization of VEs, for example, left aortic root, the orifice of the left main coronary artery or papillary muscles due to catheter stabilization difficulties and high mobility of the papillary muscles [43,45]. According to many authors, ra-

diofrequency ablation of VEs, originating from right ventricular outflow tract, in patients without cardiac structural changes is superior to drug therapy [43–45.48]. Some researchers showed that the duration of ablation positive effect was longer compared with antiarrhythmic pharmacotherapy [43,44], others — that it was approximately the same [44, 45, 48].

Conclusion

VEs are often observed in patients without cardiac structural changes and can cause LV dysfunction and arrhythmogenic cardiomyopathy. Radiofrequency ablation is recommended in patients with ineffective antiarrhythmic pharmacotherapy, subjective arrythmia feelings as well as with 10–15% monomorphic VEs from of total ventricular complexes. Interventional treatment methods are becoming first-line treatment in patients without cardiac structural changes with monomorphic VEs, especially originating from right ventricular outflow tract. Currently, there is no sufficient evidence to recommend radiofrequency ablation in patients with asymptomatic VEs without cardiac structural changes and preserved LV function. Catheter ablation in these patients, guided only by the frequency and / or amount of VEs, can be a potentially dangerous method with unpredictable result. Further studies are needed to discover molecular, cellular and hemodynamic mechanisms of VEs development in patients without cardiac structural changes as well as LV dysfunction predictors.

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Modern possibilities of angiotensin II receptor antagonists therapy in clinical practice

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Renin-angiotensin aldosterone system hyperactivation is one of the main mechanisms of cardiovascular diseases progression. Nowadays angiotensin II receptor antagonists have a sufficient evidence base as antihypertensive drugs with organoprotective properties. This article presents and substantiates the possibilities of one of angiotensin II receptor antagonist — telmisartan, in various clinical cases from the perspective of evidence-based medicine.

Key words: *angiotensin II receptor antagonists, telmisartan, organoprotective properties, cardiovascular risk.*

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Cardiovascular disease (CVD) is the leading global cause of death. CVD mortality is annually about 31.5% among all-cause mortality and about 45% among noncommunicable diseases mortality [1]. According to 2014 data, half of all-cause mortality in the Russian Federation (44.9% men, 55.4% women) have CVD cause, and over 80% is associated with coronary artery disease (CAD) and brain strokes [2].

Large international studies INTERSTROKE and INTERHEART have shown that arterial hypertension (AH) is one of the main risk factor (RF) for mortality and disability in population. The prevalence of AH among people of working age has recently increased in Russia to 43%, that can be associated with high prevalence of obesity, especially among men [3].

At the same time, it has been shown that high-risk strategies that include identifying patients with high CVD risk with the following RF reduction are effective for primary prevention of cardiovascular disease and its complications [4].

According to the results of many clinical studies, isolated RFs are found only in 10–15% of cases. Therefore, 15% of patients with AH also had lipid metabolism disturbances or obesity, and 64% of patients had a combination of more than three RFs [5]. The results of prospective studies showed that the development or course of CVD is more severe in patients with the combination of, even moderately expressed, RFs compared with one RF. In particular, the RROCAM study showed that a combination of more than two CVD RFs leads to significant increase of sudden death and myocardial infarction (MI) risks (200 among 1000 patients at 8-year follow-up) [6,7].

Today experts agree that RFs should be eliminated as much as possible [8]. Such measures are especially important for people at high and very high CVD risk. According to the Cardiovascular Epidemiology in Russian Federation (ESSE-RF) study, such patients make up about 1/3 of the Russian population [9]. They often require hyperlipidemia, AH, and carbohydrate metabolism disorders management.

The main requirements for modern antihypertensive drugs are:

- solid evidence base;
- achievement of target blood pressure (BP) levels with minimal adverse effects;
- positive or neutral metabolic effect [10].

From this point of view, angiotensin II receptor's antagonists (ARAs II) are of special interest. Nowadays, the drugs affecting renin-angiotensin-aldosterone system (RAAS) are used in AH and chronic heart failure (CHF) treatment, CVD prevention [1, 10, 11]. RAAS hyperactivation is a key mechanism for CVD development and progression according to cardiovascular continuum. The concept of the cardiovascular continuum includes the development of the pathological process from RFs to target organ damage, including heart and blood vessels remodeling and heart failure development [12].

The main RAAS mediator is angiotensin II (AT II). AT II acts on two main subtypes of membrane-bound receptors — AT1 and AT2. AT1 receptors are expressed predominantly in the smooth muscles of blood vessels, heart, liver, adrenal cortex, kidneys, lungs, nerve fibers and some brain areas.

Main AT1 receptors activation effects include:

- blood pressure increase (due to direct vasoconstrictor effect and renal glomerular arterioles spasm, followed by release of renin by juxtaglomerular apparatus cells);
- increased proximal renal tubular sodium reabsorption;
- increased aldosterone, vasopressin and endothelin-1 secretion;
- increased norepinephrine release from sympathetic nerve endings followed by sympathoadrenal system activation;
- stimulation of proliferation of endothelial and vascular smooth muscle cells and cardiomyocytes;
- pro-inflammatory and pro-oxidative effects [13].

Prolonged (or even moderate) increase in AT II concentrations in patients with long-term catecholamine load (sympathetic nervous system activation, stress) and the accumulation of reactive oxygen species in tissues are leading mechanisms for the development of CVD, blood vessels and myocardium remodeling. Experimental studies have shown that AT II causes myocardial hypertrophy even in patients with normal BP [13].

The activation of type 2 receptors, that are mostly expressed in the brain and adrenal glands, causes vasodilation, inhibits smooth muscle and endothelial cells proliferation, reduces cardiomyocyte hypertrophy, suppresses cell apoptosis, and decreases calcium ions concentration inside the cell.

The discovery of specific AT II receptors stimulated the creation of its receptor's selective antagonists. Losartan, first ARA, was synthesized in 1986. Later, other representatives from this group were synthesized. They had class-specific properties and individual characteristics that allowed to use them in

the management of patients with different comorbidities [13]. ARAs became effective agents for the treatment and prevention of CVD with unique properties, including favorable metabolic profile [14]. The so-called "pleiotropic activity" can be explained by AT2 receptors stimulation during selective blockade of AT1 receptors that leads to vasodilation, inhibition of smooth muscle cells proliferation and natriuretic effect, and increases antioxidant defense [15,16].

In addition, some ARAs, for example, telmisartan, stimulate PPAR-γ receptors that activate peroxisome proliferation and reduces inflammation, oxidative stress and smooth muscle cells proliferation, regulates intracellular glucose and lipid metabolism [17].

Pharmacokinetic and pharmacodynamic features of telmisartan

Telmisartan is a potent, long-lasting ARA that selectively and irreversibly blocks AT1 receptors without affecting other receptor's systems involved in the regulation of blood circulation. It is known that the degree of affinity to type 1 angiotensin II receptors is different and has the following decreasing sequence: telmisartan → olmesartan → candesartan → eprosartan → EXP 3174 (active metabolite of losartan) → valsartan → losartan [1, 18–20].

High lipophilicity in combination with a large volume of distribution gives telmisartan the ability to penetrate into tissues and cells, and long half-life provides stable blood pressure in patients with once daily dosage from 40 to 80 mg. Peak plasma concentration of telmisartan (Cmax) is attained within approximately 0.5–1 hour after oral administration. A state plasma concentration is achieved in 5–7 days after administration, and cumulation of the medication after prolonged treatment is unlikely. The bioavailability of telmisartan is 50 %. Plasma protein binding is 99.5 %, mainly with albumin and α1-acid glycoprotein. Telmisartan is metabolized via conjugation with glucuronic acid. Metabolites are pharmacologically inactive. The elimination half-life is over 20 hours. It is excreted through the intestine unchanged, kidneys excretion is less than 2 %. Therefore, it is safe to use telmisartan in patients with renal pathology. The high antihypertensive effectiveness of the drug is combined with its high tolerance [21–23]. One of the new and promising telmisartan mechanisms of action is the ability to stimulate g-receptors, activated by peroxisome proliferator-activated receptor gamma (PPAR-γ). The effects of PPAR-γ receptors stimulation are numerous and diverse. The most well-known is the effect on insulin sensitivity, that is used in patients with type 2 diabetes mellitus (T2DM) with predominant insulin resistance. It is also suggested that, together with other subtypes of PPAR-γ receptors, they regulate the expression of endothelial cell adhesion molecules affecting thrombus formation and the formation of cellular immune response to vasculitis. The production of pro-inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6 and interleukin-1β, is also downregulated by PPAR-γ receptors. Moreover, PPAR-γ receptors can modulate oxidative stress processes by increasing the expression of opposing factors, such as CuZn superoxide dismutase. Another well-known property of PPAR-γ receptors is the ability to reduce macrophage matrix metalloproteinases concentration, that are responsible for atherosclerotic plaque destabilization, as well as the formation and accumulation of glycation end-products. It should be emphasized that the affinity of telmisartan for this receptor is approximately 10–30 times higher compared with other ARAs. Therefore, telmisartan can be called a selective modulator of PPAR-γ receptors [24–26].

The described above effects and strong evidence base allowed to include ARA into the first-line antihypertensive treatment. According to guidelines, ARAs are indicated for primary and secondary CVD prevention in patients with ACE inhibitors intolerance, microalbuminuria, impaired renal function and chronic kidney disease, metabolic syndrome (MS) and diabetes mellitus (DM), myocardial infarction, left ventricular hypertrophy (LVH), atrial fibrillation and CHF. Telmisartan is prescribed to decrease cardiovascular mortality in patients with atherothrombotic CVD (CAD, peripheral artery disease, stroke history) and patients with T2DM with target organ damage [1, 18, 27].

ARAs role in the treatment of patients with CVD is defined, but its use in other clinical situations haven't been clearly established yet. Therefore, we have to rely on the results of multicenter clinical trials.

Antihypertensive effectiveness of telmisartan was evaluated in the MICARDIS Community Access Trial (MICCAT-2) that included 1615 patients with AH. 79 % of patients achieved target BP levels. BP daily monitoring in patients during telmisartan treatment revealed significant BP decrease in the early morning hours, when patients with CVD are the most vulnerable [29]. Multicenter randomized PRISMA I and II trials compared hypotensive effects of once-daily telmisartan of 40–80 mg and ramipril of 2.5–10 mg in

patients with grades I—II AH using daily BP monitoring. After 14 weeks of treatment, the average daily BP reached target levels in telmisartan group that was superior to ramipril group [30, 31]. Patients treated with telmisartan had higher decrease in BP in the last 6 hours of the drug action (early morning hours) compared with ramipril group ($p<0.05$).

Prospective ATHOS study included 1000 elderly patients (aged over 60 years) with predominant systolic blood pressure (SBP) increase and analyzed daily BP profile after 6 weeks of once-daily telmisartan of 40–80 mg with hydrochlorothiazide of 12.5 mg treatment compared with once-daily amlodipine of 5–10 mg with hydrochlorothiazide of 12.5 mg treatment [32]. SBP decrease for the last 6 hours of the dosing interval was comparable between groups of elderly patients. However, the SBP control during 24-hour monitoring in the telmisartan group was significantly higher compared with amlodipine group. Early discontinuation of treatment was observed more often in amlodipine group (11.3%), compared with telmisartan group (5%), mainly due to peripheral edema ($p<0.05$).

Other comparative studies have demonstrated the benefits of telmisartan by the duration and strength of antihypertensive action, especially in the early morning hours, even if the medication was missed, compared with losartan, candesartan and valsartan [29,33].

Many multicenter trials studied the effect of medications on cardiovascular morbidity and mortality, the most significant of them are: ONTARGET, TRANSCEND, PRoFESS.

The ONTARGET study showed the ***effectiveness of telmisartan in reducing cardiovascular mortality***, MI, stroke, or hospitalization for heart failure, similar to ramipril [34].

The TRANSCEND study showed significant decrease in hospitalizations for CVD and MI in patients with AH and high cardiovascular risk and arterial damage of atherosclerotic/diabetic origin during telmisartan treatment. The decrease of LVH severity has also been proven [35]. A combined analysis of the data obtained in PRoFESS study confirmed the effectiveness of telmisartan in cardiovascular mortality, MI and stroke reduction [36]. Comparative retrospective analysis of Lin J.W. et al. (2014) included about 700 thousand patients with high cardiovascular risk and demonstrated potential differences between the most common AT1 receptor blockers in terms of all-cause and cardiovascular mortality reduction [37]. The telmisartan or olmesartan group had 7% lower relative risk of all-cause mortality compared with losartan. A study of the causes of deaths showed that olmesartan reduced relative risk of cardiovascular mortality by 16%, and telmisartan reduced relative risk of cerebrovascular disease mortality by 11% compared with losartan.

ARAs have proven its ***effectiveness in acute cerebrovascular accident frequency reduction, and cerebrovascular complications and cognitive impairment prevention.*** The PRoFESS study showed that telmisartan after 6 months of therapy significantly reduced the risk of recurring stroke compared with placebo [38,39]. A prospective cohort analysis of data obtained from over 800 thousand patients aged over 65 years showed significant decrease in the relative risk of dementia and an improvement in cerebral blood flow in several brain areas according to single-photon emission computed tomography [40,41].

The ability of ARAs to activate PPAR-γ receptors underlies many ***metabolic effects*** of this class of medications. Numerous studies have demonstrated that PPAR-γ receptors contribute to atherogenesis, insulin resistance, oxidative stress, inflammation and fibrosis. Drugs that increase the activity of these receptors can significantly increase insulin sensitivity, reduce the risk atherosclerosis.

Most clinical studies confirmed no effect of telmisartan on plasma lipid levels. However, there are few studies that have shown a significant decrease in total cholesterol (TC), low-density lipoproteins (LDL) and triglycerides (TG) plasma levels compared with baseline in patients with MS during telmisartan treatment [42–44]. One of the studies have shown significant decrease in the amount of visceral fat and increase of high-density lipoproteins (HDL) [43]. This phenomenon is pathogenetically substantiated, but requires further clinical confirmation.

The effect of telmisartan on ***glucose metabolism*** has been studied in randomized controlled trials that included over 1300 patients with AH and T2DM or insulin resistance. During telmisartan treatment, fasting plasma glucose test, fasting plasma insulin level, adiponectin level, and HOMA-IR index — quantitative method for assessing insulin resistance, were identified [45, 46]. Once-daily telmisartan of 80 mg reduced fasting plasma insulin level and peripheral insulin resistance (measured by HOMA-IR index) [47]. The results of meta-analysis showed that 80 mg of telmisartan was superior to other ARAs (including eprosartan, irbesartan, candesartan, valsartan and olmesartan) in fasting plasma glucose level reduc-

tion. Six clinical studies showed adiponectin increase in patients using telmisartan of 80 mg once-daily. PPAR-γ receptors activation increases adiponectin synthesis by adipocytes that is the main protein in the processes of free fatty acids oxidation that enhances insulin sensitivity in skeletal muscles and liver. Thus, adiponectin increase in blood plasma can reduce insulin resistance and inhibit the development of MS and T2DM [45].

It has been shown that ARAs can also reduce the incidence of newly diagnosed diabetes mellitus cases compared with placebo in patients with high cardiovascular risk and / or AH [48,49]. The TRANSCEND and PRoFESS studies revealed that telmisartan reduced the incidence of DM by 16 % reduction compared with placebo [39]. ARAs also showed cardioprotective properties in patients with T2DM. Thus, a population cohort study involved elderly patients with T2DM and showed that telmisartan and valsartan were associated with reduced risk of hospitalization for myocardial infarction, stroke, or heart failure compared with irbesartan [50].

ARAs also have ***nephroprotective effect.*** Many studies have shown that ARAs are the most effective antihypertensive drugs that prevent chronic renal failure [51]. A meta-analysis of twenty randomized controlled trials of telmisartan (including ONTARGET, TRANSCEND, DETAIL, INNOVATION, AMADEO and VIVALDI) that involved a large number of patients with DM showed its effectiveness in proteinuria reduction and prevention. Telmisartan significantly decreased albuminuria and urinary albumin to creatinine ratio compared with other ARAs, angiotensin converting enzyme inhibitors, and other antihypertensive drugs [39]. The ESPRIT study showed antihypertensive effectiveness and high tolerance for telmisartan in patients with difficult-to-control hypertension with chronic kidney disease [52]. Considering the results of above-mentioned studies, as well as the fact that only 2 % of medication is excreted through the kidneys, telmisartan can be used in patients with severe renal impairment on hemodialysis, without dose adjustment according to the glomerular filtration rate.

Thus, nowadays pronounced evidence-based antihypertensive effect and organoprotective properties of ARAs allow us to use them in various clinical situations at all stages of the cardiovascular continuum. Telmisartan has many advantageous pharmacological properties among other representatives of ARAs: the longest half-life (over 20 hours) and the highest lipophilicity and affinity for AT1 receptors. Many clinical studies have shown that telmisartan activates PPAR-γ receptor and, therefore, reduces proteinuria and the progression of kidney and retinal damage in patients with DM, as well as reduces the risk of T2DM in patients with high cardiovascular risk. This medication is indicated to reduce cardiovascular mortality in patients with atherothrombotic diseases (CAD, peripheral arterial damage, stroke history) and in patients with T2DM with target organ damage.

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EXPERT OPINION

Updated European guidelines on pre-diabetes, diabetes and cardiovascular disease: Opinion of Russian experts

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The updated ESC Guidelines on pre-diabetes, diabetes and cardiovascular disease developed by the experts of two European societies were introduced at the 2019 ESC Congress of Cardiology (August 31 — September 4 in Paris, France). The updated guidelines present information on prioritizing different types of hypoglycemic therapy based on its cardiovascular effects, target lipid levels in patients with diabetes depending on cardiovascular risk, and information on antiplatelet therapy administration.

We present Russian experts' comments on the broad spectrum of questions that were introduced in the updated guidelines.

Key words: *diabetes, pre-diabetes, cardiovascular disease, guidelines.*

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The updated ESC Guidelines on pre-diabetes, diabetes and cardiovascular disease were introduced at the 2019 ESC Congress of Cardiology (August 31 — September 4 in Paris, France). This document was developed by the European Society of Cardiology (ESC chairperson of the task force — Francesco Cosentino, Sweden) in collaboration with the European Association for the Study of Diabetes (EASD chairperson of the task force — Peter Grant, England). The updated guidelines present information on prioritizing different types of hypoglycemic therapy based on its cardiovascular effects, target lipid levels in diabetic patients depending on cardiovascular risk, information on antiplatelet therapy administration [1].

Below we present Russian experts' comments on the spectrum of questions that were introduced in the updated guidelines.

Epidemiology and definition of diabetes

M.N. Mamedov

Diabetes is a serious medical and social problem worldwide. Its prevalence is steadily increasing to 10% in developing countries, primarily in India and China. As of 2017 over 60 million adult Europeans have diabetes and the majority of them have not been diagnosed yet. In general, the number of diabetic patients is expected to rise to 600 million by 2045. At the same time there are rising concerns that the age of onset has decreased, and diabetes is now occurring at a younger age [2].

Diabetes and pre-diabetes classification is based on the World Health Organization (WHO) (2006/2011) and the ADA (2019) recommendations [2, 3]. Further investigations are needed in order to determine the effect of gender, ethnicity and age on the diagnostic criteria.

Prediabetes is characterized by impaired fasting plasma glucose (FPG) or glucose tolerance (GT) and is an intermediate stage of diabetes development [4].

Diabetes can be diagnosed with the FPG or hemoglobin A1c (HbA1c) tests. Oral glucose tolerance test (OGTT) is used to diagnose impaired glucose tolerance. Experts recommend to use HbA1c and/or FPG as screening tests in patients with documented cardiovascular disease (CVD). OGTT can be further used in these patients if the results of HbA1c or FPG are inconclusive [3, 4].

Stratification of cardiovascular risk in patients with diabetes and pre-diabetes

The 2016 European guidelines on CVD prevention presented cardiovascular risk stratification in patients with diabetes. In the updated guidelines the central principle remained unchanged [1]:

- Very high-risk group includes individuals with:
- Diabetes and CVD or other end-organ damage;> 3 risk factors;
- Long-standing type 1 diabetes (>20 years).

The high-risk group includes patients with long-standing diabetes (≥10 years) without end-organ damage and other additional risk factors, while the moderate risk group includes young patients (type 1 diabetes<35 years old, type 2 diabetes<50 years old) with diabetes lasting less than 10 years without other risk factors.

Patients with pre-diabetes can also be at high risk for CVD depending on their clinical status and the presence of other risk factors/end-organ damage. In general, risk scoring in patients with pre-diabetes is the same as in the general population, as standard charts are applied.

Prevention of cardiovascular disease in patients with pre-diabetes and diabetes.

Comprehensive measures are used to prevent CVD in patients with impaired glucose metabolism. They include lifestyle modification (diet, physical activity, smoking cessation), pharmacologic therapy to reach glycemic targets, blood-pressure target levels and target lipid levels, as well as antiplatelet therapy for primary and secondary prophylaxis [6–12].

Lifestyle modification principles remain unchanged: lower calorie intake, Mediterranean diet, and moderate physical activity of≥150 min/week. Together these changes can prevent and control DM.

Arterial hypertension

Arterial hypertension (AH) is highly prevalent in patients with DM (>60 % of cases) as well as in patients with pre-DM, which may be explained by obesity and hyperinsulinemia [13]. Multiple clinical studies show that optimal blood pressure control lowers the risk of micro- and macrovascular complications. Blood pressure targets have changed over the last years after a number of major clinical studies have been conducted. In DM patients blood pressure should be targeted to a systolic blood pressure (SBP)<130 mmHg but not<120 mmHg; and older patients with DM — to a SBP 130–139 mmHg. SBP in patients with DM should be targeted to<80 mmHg, but not<70 mmHg.

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are still the central components of combination therapy. Calcium channel blockers (CCBs) or diuretics can be used together with renin–angiotensin–aldosterone (RAAS) blockers. In the majority of cases two-drug regimen is indicated as the initial treatment of hypertension in DM. Of note is that pre-DM patients who take ACEIs or ARBs have lower risks of DM development compared with those who take beta-blockers or diuretics [1, 14].

Lipid-lowering therapy

New target lipid levels depending on the CVD risk have been resented in the updated guidelines:

- In patients with T2DM at moderate CVD risk the target LDL cholesterol (LDL–C) level is<2.5 mmol/l;
- In patients with T2DM at high CVD risk the target LDL–C level is<1.8 mmol/l or reduction of at least 50 %;
- In patients with T2DM at very high CVD risk the target LDL–C level is<1.4 mmol/l or reduction of at least 50 %;

Statins are still considered first-line agents. Ezetimibe can be added if maximal tolerated dose of statins is not sufficient to reach LDL–C target levels [15, 16]. In that case that a high dose of statins combined with ezetimibe is still not sufficient, addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended. Patients with low HDL–C levels and high triglyceride levels are administered fibrates and advised on weight loss (primarily due to reduction in fast-acting carbohydrates and alcohol consumption). Lately, risk factor correction in patients with T1DM, especially in individuals at high CVD risk, has been widely discussed. In this case statins are indicated regardless of the baseline LDL–C levels. Moreover, statins can also be considered for hypercholesterolemia in asymptomatic patients with T1DM> 30 years of age. Statins are not recommended in women of childbearing age [1].

Antiplatelet therapy

The expediency of using antiplatelets for primary prevention has been repeatedly discussed [17]. The ASCEND trial (randomized placebo-controlled study that included 15480 patients) showed that primary prevention with aspirin 100 mg daily significantly decreases the rate of cardiovascular complications (MI, stroke, transient ischemic attack, and death from any cause; p=0.02). It is suggested that in the absence of contraindications aspirin (75–100 mg daily) can be used for primary prevention in patients with DM and at very high/high risk of CVD. At the same time aspirin is not recommended for primary prevention in patients at moderate risk [18]. The use of antiplatelet therapy also rises safety issues, such as gastrointestinal bleeding. Proton pump inhibitors can be used in patients taking low-dose aspirin to protect gastric mucosa [19].

Multifactorial management

In patients with DM associated with≥2 risk factors and at high or very high risk for CVD combination therapy should be considered. Clinical studies have

shown that combination therapy for hypertension, hyperglycemia and dyslipidemia reduces the rate of cardiovascular disease by 75%. However, optimal multifactorial management strategy has not been identified. It is also not clear if there should be any differences in multifactorial management depending on gender [20, 21].

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Coronary artery disease management in patients with pre-diabetes and diabetes

O.A. Shatskaya, I. Z. Bondarenko

The disorders in carbohydrate metabolism worsen the prognosis of CVD [1–3]. DM is prevalent in 20–30 % of patients with coronary artery disease (CAD), and 70 % of patients have been newly diagnosed with DM or impaired glucose tolerance (IGT). Therefore, systemic evaluation of glycemic status is recommended in all patients with CAD [4, 5].

Multiple studies have shown that good glycemic control reduces the risk of microvascular complications in DM patients [6]. The emphasis is made on safety of glycemic control in CVD patients, which means that the targets for glycemic control should be individualized. Moderate glucose control has proven to be effective when compared with more intensive control. Intensive glucose control increases the risk of hypoglycemia which has a negative effect on CVD events development [7–10]. Moreover, intensive glucose control together with an unsatisfactory glycemic profile have a negative effect on CVD events frequency [11–13].

For the first time in the history of DM research the evidence of hypoglycemic agents benefits in patients at high/very high risk of CVD are presented.

Cardiovascular safety is one of the central goals of all clinical studies. Lately more attention has been drawn to new hypoglycemic agents such as glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter-2 (SGLT2) inhibitors. Based on multiple studies of GLP-1: LEADER, SUSTAIN-6, Harmony Outcomes, REWIND и PIONEER) [14–18] and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 и CREDENCE) [19–22] effects these agents have been recommended for patients with DM at high/very-high cardiovascular risk regardless of whether they take metformin or not.

The benefits of GLP-1 agonists are most likely determined by reduction in atherosclerotic CVD events; SGLT2 inhibitors reduce the frequency of heart failure end-points.

Despite the lack of large randomized clinical studies of metformin effects on CVD events, it is clear that long-term use of metformin provides cardioprotective effect, decreases MI risk in DM obese patients and improves CVD prognosis [23–24].

The leading goal of CAD treatment in DM is the prevention of complications and reduction of mortality. The recommended regimen includes beta-blockers, ACEIs and CCBs.

Long-term use of oral beta-blockers leads to mortality reduction in DM patients with a history of MI, especially in those with HF (EF<40 %). Carvedilol and nebivolol are the preferred agents as they improve insulin sensitivity and don't affect glycemic profile [25, 26].

ACEIs are indicated for prevention of CVD events and HF in all patients with DM and stable CAD or acute coronary syndrome (ACS) and left ventricular (LV) systolic dysfunction [27]. ARBs can be used in patients intolerant of ACEIs. Mineralocorticoid receptor antagonists (MRA) are recommended in patients with LV systolic dysfunction or HF after MI [25, 28].

Nitrates and CCBs are indicated for relief of angina symptoms in patients taking beta-blockers who don't have contraindications for this group of agents [29].

Treatment of hypercholesterolemia is one of the most important goals in CVD prevention and CVD mortality reduction in both T1DM and T2DM. Statins are currently considered first-line agents in patients with high LDL–C levels [30]. Ezetimibe can be added if LDL–C target levels have not been achieved [15, 16]. PCSK9 inhibitors are indicated in patients at very high risk of CVD with constantly elevated LDL–C despite the use of high dose statins combined with ezetimibe or in patients intolerant of statins [33–36].

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Chronic heart failure

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Pre-DM and DM are associated with higher risk of chronic heart failure (CHF) with preserved (HFpEF) or reduced (HfrEF) ejection fraction, and 30–40 % of patients involved in clinical studies of CHF treatments had DM [1, 2]. Patients with heart failure and without DM are, at the same time, at high risk of DM development, but the underlying pathophysiological mechanisms require further investigations [3]. Patients in whom DM and CHF (especially HFrEF) coexist are at significantly higher risk of hospitalization for CHF and death from CVD or from all causes [4]. Pre-DM and undiagnosed DM in patients with CHF are associated with higher risk of death and other poor clinical outcomes [5]. Therefore, active screening for carbohydrate metabolism disorders is extremely important in this group of patients.

CHF in patients with DM is most commonly caused by CAD and AH, and prevention and treatment of these disorders result in reduced risk of CHF manifestation. The authors of the updated 2019 European guidelines of pre-DM, DM and CVD agree on the fact that hyperglycemia and insulin resistance directly affect the myocardium. At the same time, there is no conclusive evidence of the existence of specific diabetic cardiomyopathy [6].

The investigation of various CHF treatment options in patients with and without diabetes showed similar efficacy of all standard pharmacologic and non-pharmacologic regimens. The only exception was aliskiren, which is not indicated in patients with DM due to increased risk of negative side effects [7]. It is recommended to use lower dosages of ACEIs, ARBs, sacubitril/valsartan and then to gradually increase them. The follow-up of these patients should include control of potassium and creatinine. Other treatment options in patients with CHF and DM include beta-blockers, ivabradine, digoxin, diuretics, implantable cardiac defibrillator (ICD), mineralocorticoid receptor antagonists (MRA), cardiac resynchronization therapy (CRT), coronary artery bypass graft (CABG) surgery in CAD if two or three coronary vessels are involved [8].

The investigations of CVD outcomes in DM have provided the foundation for updating European guidelines of pre-DM, DM and CVD treatment in DM patients at high risk of CHF or who already have heart failure. First-line agents for DM treatment are SGLT2 inhibitors as they slow down CHF development as well as reduce mortality and the risk of hospitalizations for CHF exacerbations [9, 10]. Furthermore, according to the results of the DAPA-HF study that were pre-

sented at the 2019 ESC Congress, dapagliflozin was found to significantly reduce the total risk of cardiovascular death and hospitalizations for CHF exacerbations as well as the risk of death from any cause in patients with HFrEF with and without DM compared with placebo [11]. Although the mechanisms of such prognostic effects of SGLT2 inhibitors are not completely understood, such treatment results undoubtfully open new perspectives for CHF treatment.

Arrythmias

DM may lead to the development of atrial fibrillation (AF) due to autonomic dysfunction, electromechanical and structural remodeling, glycemic fluctuations, and atrial extrasystoles. Patients with DM and AF are at a significantly higher risk of stroke, CHF, and death from cardiovascular disease and other causes [12]. Therefore, an aggressive approach is required to prevent cardiovascular complications in such situation. As patients with AF sometimes present with only mild symptoms active detection of this type of arrythmia with an ECG is required when feasible. Oral anticoagulants are indicated to reduce the risks in AF. Kidney function should be closely monitored in DM patients in order to avoid drug accumulation and toxicity [13].

Patients with DM, both men and women, have four times increased risk of sudden cardiac death (SCD). The mechanisms behind such a high risk are probably associated with episodes of hypoglycemia that occur during an intensive hypoglycemic therapy [14] and cardiac autonomic neuropathy [15], which may cause QT prolongation. The frequency of SCD is significantly higher in patients with DM and EF<35 % [16]. For such patients and implantation of ICD is indicated. CRT is recommended in those who also have a prolongation of QRS complex [17]. Patients with DM and ventricular arrythmias should undergo the same diagnostic evaluation as those without DM (echocardiography, PCI or MRI) in order to identify cardiac structural pathology that is a more important prognostic factor compared with the presence of arrythmia. Similarly, pharmacological and non-pharmacological antiarrhythmic therapy is the same in patients with and without DM (beta-blockers, antiarrhythmic agents, catheter ablation).

Peripheral artery disease

All arteries except for the aorta, coronary and intracranial arteries are considered peripheral [18]. Peripheral artery disease (PAD) is more prevalent in patients with long-standing DM and in those with suboptimal glycemic control and with presence of known CVD risk factors [19]. Peripheral neuropathy with a reduced sensitivity to pain leads to atypical symptoms of arterial insufficiency in the lower extremities and, therefore, to late diagnosis and treatment of lower extremity artery disease (LEAD). Screening for LEAD is extremely important in patients with CAD. It is recommended to use the ankle-brachial index (ABI) to assess the presence of LEAD. The ABI< 0.9 (or> 1.4 resulting from calcinosis) usually indicated PAD and is associated with an increased risk of cardiovascular complications and death [19, 20]. Exercising for 30–45 minutes 3 times per week is indicated for patients with claudication, although the efficacy of such exercises is lower in DM [21]. Treatment of hyperglycemia can improve outcomes in limb threatening LEAD [22]. In case of severe LEAD revascularization can be considered when feasible, and only if this treatment is unavailable amputation can be performed [18]. In the COMPASS study patients with PAD (44 % with DM) were treated with a combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily. At 23 months the risk of adverse limb events including amputation was reduced by 23 % (p=0.0037) compared with aspirin monotherapy [23]. The results of this study raise the possibility of a novel combination antithrombotic therapeutic regimen in high-risk vascular patients to prevent cardiovascular complications of LEAD (IIa).

Carotid artery disease should be rapidly ruled out in all patients presenting with transient ischemic attack or stroke, although systemic screening is not recommended. Carotid artery revascularization should still be considered in asymptomatic patients with one or more stroke risk factors (previous transient ischemic attack/stroke, ipsilateral silent brain infarction, stenosis progression, high-risk plaques) and if the estimated peri-operative stroke or death rate is<3 % and the patient's life expectancy is>5 years [18]. Carotid artery revascularization is indicated in symptomatic patients if the stenosis is>70 % and should be considered if the stenosis is>50 % if the estimated perioperative stroke or death rate is<6 % [18]. Carotid endarterectomy remains the standard of care and stenting can be considered as an alternative treatment in patients at high risk of post-endarterectomy complications [18]. Post-operatively, both interventions provide the same level of protection from recurrent stroke and have similar rates of repeat revascularization procedures [18]. Carotid revascularization in DM is associated with higher risk of perioperative

stroke and death [25] and restenosis with both techniques [26].

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Cardiovascular safety profile of diabetes drugs

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The latest studies showed that different types of diabetic medications affect cardiovascular diseases and their complications. This problem proved to be relevant when in 2008 the FDA decided to tighten safety requirements for hypoglycemic agents. They should not only improve the glycemia but also have safe cardiovascular profile [1]. At the same time, the principles of hypoglycemic agents use that would take into consideration the effects on cardiovascular system have not been clearly stated until now.

Concerning this issue, the 2019 ESC guidelines are a big step forward, as it divides all the hypoglycemic medications into several groups depending on their cardiovascular safety profiles.

The group of hypoglycemic drugs that clearly increase the CVD risk, primarily, the risk of CHF, include the thiazolidinediones (rosiglitazone and pio-

glitazone) [2] and the DPP-4 inhibitor saxagliptin [3], as they increase the frequency of hospitalizations of DM patients for CHF. The patients with low glomerular filtration rate (GFR≤ 60 ml/min/1.73m^2) and those with high baseline NT-proBNP have the highest risk. As such, rosiglitazone, pioglitazone and saxagliptin are contraindicated in patients with concomitant DM and CVD as well as in those patients who are at high risk of CHF.

The group of hypoglycemic agents that can increase the risk of poor cardiovascular outcomes include insulin, which retains sodium, water, and sulfonylureas, which are associated with high risk of hypoglycemia. The use of these agents in patients with CVD can be considered only after metformin and other medications that have positive effect on prognosis are administered [4].

Agents that have neutral effects on the cardiovascular system include alpha-glucosidase inhibitors (AGIs) and DPP-4 inhibitors (except for saxagliptin). A prospective study of acarbose in patients with IGT and CVD (the ACE study) showed that the use of acarbose doesn't affect the frequency of major adverse cardiac events (MACE) [5]. Cardiovascular safety of DPP-4 (gliptins) inhibitors was comprehensively assessed in several studies. Five major prospective studies have been conducted in patients with DM in order to assess cardiovascular effects of DPP-4 inhibitors such as saxagliptin (SAVOR-TIMI 53) [6], alogliptin (EXAMINE) [7], sitagliptin (TECOS) [8] and linagliptin (CARMELINA, CAROLINA) [9].

In four of these studies it was statistically confirmed that the investigated agents were non-inferior to placebo in regard of primary cardiovascular outcomes (alogliptin, sitagliptin, linagliptin). At the same time, none of the gliptins were beneficial for CVD in the studied patient population (with long-standing DM and CVD).

Metformin, GLP-1 agonists and SGLT2 inhibitors are also considered to have positive effects on cardiovascular system. As for now, there have been no major randomized studies that would assess the effects of metformin on the CVD risk. At the same time. observational and retrospective studies have shown the improvement of cardiovascular prognosis in patients who took metformin for a long time [10]. According to the 2019 ESC Guidelines, metformin should be considered in overweight patients with DM but without CVD or in patients at moderate cardiovascular risk (IIa).

Seven randomized studies have been conducted to investigate the effects of GLP-1 agonists on the cardiovascular outcomes in patients with DM and high cardiovascular risk. It is well known that these agents have some positive effects on some cardiovascular parameters, including the moderate reduction of SAP and weight loss, as well as direct positive effects on heart and blood vessels [11]. Several trials have shown that lixisenatide (ELIXA) [12], exenatide (EXSCEL) [13] and dulaglutide (REWIND) [14] were non-inferior to placebo in regard of primary cardiovascular outcomes which is an indication of positive cardiovascular safety profile. Gradual improvement of outcomes during the treatment can possibly indicate the association of the positive effects with the slowing of atherogenesis.

The best results in regards of cardiovascular safety were shown in SGLT2 trials. This conclusion in based on the results of four randomized trials in patients with DM and high cardiovascular risk. In the EMPA-REG OUTCOME empagliflozin significantly reduced the risk of the composite primary outcome (CV death, non-fatal MI, or non-fatal stroke) compared with placebo, and the reduction was driven mainly by a highly significant reduction in CV death [18]. Positive effects of canagliflozin were shown in the CANVAS and CREDENCE trials. A significant reduction in the composite MACE (CV death, non-fatal MI, or non-fatal stroke) and HF hospitalizations were noted even in patients with very high cardiovascular risk (patients with DM and chronic kidney disease with albuminuria) [19]. DECLARE-TIMI 58 examined the effect of dapagliflozin and revealed no significant reduction of the major MACE. However, dapagliflozin use resulted in the reduced risk of the composite primary out-come (CV death and HF hospitalization). The positive cardiovascular effects of these agents are mostly unrelated to the extent of glucose lowering and occur prior to weight reduction. Rapid and significant reduction in the number of HF hospitalizations in all four studies indicate that the beneficial cardiovascular effects of these agents are more likely the result of their hemodynamic effects (reduced plasma volume, direct effects on cardiac metabolism and function). These effects result in a reduction in HF-associated events [20].

Of note, for the first time the induction monotherapy with SGLT2 or GLP-1 agonists instead of metformin was recommended in patients with T2DM and high/very high cardiovascular risk (the majority of patients). Metformin can be added if the monotherapy is insufficient. SGLT2, GLP-1 agonists, DPP-4 inhibitors, basal insulin and sulfonylureas can be further added in case of persistent hyperglycemia.

The add-on therapy with SGLT-2 inhibitors or GLP-1 agonists with proven beneficial cardiovascular effects is also indicated in the same group of patients (patients with DM and high/very high risk of CVD) who were earlier receiving hypoglycemic agents. In case of insufficient glycemic control one additional agent that has not been used earlier can be added: SGLT2 inhibitor or GLP-1 agonist, DPP-4 inhibitor, basal insulin, sulfonylureas. In patients with DM and high/very high risk of CVD the priority should be given to empagliflozin or liraglutide (IB) as these agents are associated with decreased mortality. As such, GLP-1 agonists and SGLT2 inhibitors are indicated in patients with DM and high/very high cardiovascular risk independently of previous treatment.

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9. For all clinical trials: information about the registration and placement of data on the study in any public register of clinical trials. The term "clinical study" refers to any research project that affects people (or groups of subjects) with/or without a comparative control group, studies the interaction between interventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

10. The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section "Relevance" in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

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).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

Text is printed on A4 sheet, font size — 12 pt, line spacing — 1.5, margins 2 cm on all sides. The system of SI units is used for processing the material, the% sign is put through a space from the number, the value of p is written with a semicolon: $p < 0.0001$; the value of n is written with a small letter (n=20); signs >, <, ±, =, +, — when numerical values are written without a space; the value of "year" or "year" is issued — 2014 or 2002–2014.

The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet "Uniform requirements for manuscripts submitted to biomedical journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

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However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

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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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