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Coronary and peripheral arteries revascularization in patients with diabetes mellitus: a cardiologist's view

Electrical remodeling and heart rhythm disturbances in patients with primary arterial hypertension

Pathological and clinical aspects of angiotensin receptor-neprilysin inhibitor in patients with congestive heart failure with reduced ejection fraction

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Editor's Welcome

Dear colleagues!

We present the 31st issue of the International Heart and Vascular Disease Journal that includes the leading article, original and review articles.

The leading article section presents the review article on the revascularization strategies in patients with diabetes mellitus and atherosclerotic lesions of various localization. The articles published over the last 5 years in leading peer-reviewed journals according to the PubMed / MEDLINE database were analyzed. The review article provides information on the choice of the myocardial revascularization method in patients with acute coronary syndrome, stable coronary heart disease, peripheral arterial disease, carotid artery stenosis and pharmacological therapy for the prevention of atherosclerotic complications in patients with DM.

The original articles section includes three manuscripts. The article dedicated to the heart rhythm disturbances and cardiac electrophysiological parameters in patients with arterial hypertension included 157 participants. All the patients underwent ECG, BP monitoring, diagnostic transesophageal electrical stimulation of the heart, echocardiography, and the assessment of heart rate variability. The presence of LVH in patients with AH was associated with high incidence of heart rhythm disturbances and cardiac electrical remodeling. The cross-sectional epidemiologic study assessed the changes in the prevalence and intensity of smoking in Tyumen men aged 35-44 and 45-54 years over 5- and 15-year follow up. Follow-up has shown the reduction of smoking prevalence in adult active men over 15 years and the increase of smoking prevalence over 5 years that demonstrated that combined approach to behavioral and psychosocial risk factors is required for efficient smoking prevention programs. The third original article is dedicated to the effectiveness of the early prescription of trimetazidine in patients with acute coronary syndrome and established multivessel coronary artery disease after incomplete revascularization. According to the results of 12-months follow-up, authors concluded that the medication can be used as part of comprehensive rehabilitation measures in patients with acute coronary syndrome and incomplete revascularization.

The review article section presents the work dedicated to the analysis of the existing approaches to prevent atrial fibrillation in patients with metabolic syndrome. Metabolic syndrome is the cause of atrial fibrillation that contributes to the relevance of the study. The second review article analyses the results of randomized clinical trials on the use of angiotensin receptor-neprilysin inhibitor in patients with congestive heart failure. The pathophysiologic basis of medication use and its effects on the prognosis in patients with various heart failure phenotypes are being discussed.

Traditionally, the journal publishes the main highlights of European Society of Cardiology Virtual Congress. This year 4 updates guidelines were presented. The results of 20 international clinical trials that investigated effectiveness and safety of pharmacologic agents and medical devices in patients with various cardiovascular disease have been analyzed.

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.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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LEADING ARTICLE

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Coronary and peripheral arteries revascularization in patients with diabetes mellitus: a cardiologist's view

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Abstract

Diabetes mellitus (DM) is one of the main risk factors for the development of myocardial infarction, stroke and lower-limb amputation that are associated with the acceleration of vascular arteriosclerotic damage. At the certain stage of the atherosclerosis and its complications development, indications for the revascularization appear. In recent years, there has been significant progress in the development and investigation of revascularization methods along with concomitant pharmacotherapy, especially in patients with DM. Using the PubMed / MEDLINE database, we analyzed research articles, meta-analyzes and reviews published over the past 5 years in leading peer-reviewed journals on the problem of coronary and peripheral artery revascularization in patients with DM. This review article provides information on the choice of the myocardial revascularization method in patients with ACS, stable coronary heart disease, peripheral arterial disease of the lower extremities, carotid artery stenosis and pharmacological therapy for the prevention of atherosclerosis complications in patients with DM.

Key words: diabetes mellitus, coronary heart disease, coronary artery bypass grafting, percutaneous coronary intervention, peripheral arterial disease, carotid artery stenosis.

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Diabetes mellitus (DM) is one of the main risk factors for the development of cardiovascular diseases (CVD), including coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), carotid artery disease, which are associated with vascular damage due to atherosclerosis progression [1]. Patients with DM significantly more often undergo coronary and peripheral arteries revascularization, including repeat surgery, compared with general population [2,3]. Therefore, the correct choice of treatment method for patients with atherosclerosis and DM is of primary importance, which include pharmacological therapy, interventional and surgical procedures that have been actively improving over the last years [4,5].

The objective of this study is to collect and review the new data on coronary and peripheral artery revascularization and concomitant pharmacological treatment in patients with DM.

The importance of coronary and peripheral artery studies in patients with diabetes mellitus

CHD in patients with DM is characterized by diffuse rapidly progression with multivessel involvement and arterial calcification, that often requires coronary revascularization in addition to optimal pharmacological treatment. Atherosclerotic plaques in patients with DM exhibit more vulnerable features due to lipid-rich core, macrophage accumulation, and thin fibrous cap, indicating vascular plaque instability [6].

The results of coronary angiography in patients with DM poorly correlate with the hemodynamic (ischemic) significance of atherosclerosis. Fractional flow reserve assessment is more accurate invasive technique that reveals significant hemodynamically stable coronary stenoses that cause myocardial ischemia. The visualization of the myocardium with single-photon emission computed tomography is the non-invasive method that allows to detect coronary stenoses of sufficient hemodynamic severity to induce myocardial ischemia. However, both of these complex and expensive methods do not provide the same degree of accuracy in patients without ischemia with and without DM. Therefore, delayed revascularization in patients without ischemia (ischemia driven revascularization strategy) can be not as safe for patients with DM as for patients without DM.

This fact can be partially explained by high prevalence of microvascular dysfunction, fast diffuse atherosclerosis dysfunction and atherosclerotic plaques features (greater necrotic core and larger calcium content) in patients with DM [7].

The degree of atherosclerotic lesions can be determined invasively using intravascular ultrasound or non-invasively using coronary computed tomographic angiography with the assessment of the coronary artery calcium score. The increase of the coronary artery calcium score by 1 step (from 1–99 to 100–399 and to≥400 Agatston units) is associated with the progressive increase of the relative risk of death [8].

The determination of the intima — media thickness of the carotid arteries using ultrasound scanning in patients with DM does not increase the predictive accuracy for CHD or cardiovascular complications compared with the coronary artery calcium score. On the contrary, large atherosclerotic plaques of the carotid arteries can serve as independent predictors of CVDs and its complications (CHD, ischemic stroke, peripheral arterial disease) [9].

The ankle-brachial index is currently used for the detection of PAD, and the value of<0.90 (or>1.40) is associated with the increased risk of all-cause and cardiovascular mortality in patients with DM [10].

Myocardial revascularization in patients with acute coronary syndrome and diabetes mellitus

The pathogenetic mechanisms of the atherosclerosis development in patients with DM go far beyond the hyperglycemia and lead to frequent stenosis of the left main coronary artery, multivessel coronary artery disease (MVD), diffuse coronary artery disease with frequent involvement of its distal branches [1]. Myocardial revascularization using percutaneous coronary intervention (PCI) is the primary treatment choice for patients with ST-segment elevation acute coronary syndrome (ACS) regardless of the presence of DM [11]. However, PCI is not the best choice for the revascularization of arteries that were not associated with the development of ACS in patients with DM and MVD. In the British Columbia, Canada, all coronary revascularization procedures between 2007 and 2014 in 2.947 patients with ACS, DM and MVD were analyzed.

The frequency of major adverse cardiac or cerebrovascular events — all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke was lower after artery bypass grafting (CABG) surgery compared with percutaneous coronary intervention (PCI) (4.3% versus 8.2%; p<0.01) after the first 30 days and 3.3 years (20.8% versus 33.4%, respectively, p<0.01). Patients after ACS also showed lower frequency of repeat post-discharge revascularization (8.2% versus 22.6% after

PCI, respectively, p<0.01), MI (9.9% versus 17.6%, respectively, p<0.01) and all-cause mortality (12.4% versus 22.3%, respectively, p<0.01), and there were no significant differences in the incidence of stroke (6.2% versus 5.8%, respectively; p= 0.97) [12].

Current European recommendations for coronary revascularization in patients with DM with ACS without ST-segment elevation are mainly based on the studies on the treatment of stable CHD and expert opinion, because the necessary studies with high-level of evidence are clearly insufficient [11]. In the United States, only about ⅓ of patients with DM and MVD undergo CABG during ACS without ST-segment elevation [13]. In the clinical practice, recommendations for myocardial revascularization in patients with stable CHD are also used in patients with ACS. Therefore, the pathophysiology of atherosclerosis in patients with DM is not considered — diffuse long coronary artery lesions. It is thought that CABG is more effective in patients with DM, since PCI targets only the most visible plaques, leaving untreated other lesions that can cause new atherothrombotic events, especially along with pro-inflammatory state after ACS. In addition, patients with DM usually have many other comorbidities (arterial hypertension (AH), chronic kidney disease, heart failure), higher risk of complications after PCI — stent thrombosis and restenosis, which contributes to the prognosis after ACS [14].

Myocardial revascularization in patients with stable coronary heart disease and diabetes mellitus

Stents or Bypass Surgery for the Management of Coronary Heart Disease?

Several studies have compared CABG and PCI in patients with DM and stable CHD. CABG led to an increased risk of cardiovascular adverse events, especially stroke, in the first days and months after the procedure, but in the long-term it was associated with lower incidence of MI and repeated coronary revascularization. The most famous randomized trial FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) showed significant reduction of the amount of major cardiovascular complications (all-cause mortality, MI, and stroke) in patients with DM who underwent CABG compared with PCI during a mean follow-up period of 3.8 years (18.7% versus 26.6%, p=0.005). Longer follow-up for 7.5 years was associated with the decrease of all-cause mortality in patients after CABG compared with PCI (18.3% and 24.3%, respectively, p= 0.01) [15]. The meta-analysis of 11 randomized trials (n= 11518), including FREEDOM data, demonstrated higher 5-year mortality rate in patients with DM and stable CHD after PCI compared with CABG (relative risk (RR) — 1.48 with 95% confidence interval (CI) CI from 1.19 to 1.84, p= 0.0004) [16].

Later, large retrospective study using the database of the province of Canada, Ontario from 2008 to 2017 compared the outcomes of PCI (n= 4519) and CABG (n= 9716) in patients with DM and MVD [17]. In order to eliminate the initial differences between treatment groups, the propensity score matching method was used and allowed to obtain 4301 pairs of patients that were well balanced in 23 parameters. PCI and CABG groups showed similar frequency of early mortality (2.4% versus 2.3%, respectively; p= 0.721), but after 5.5-year follow-up CABG was superior to PCI in all-cause mortality (RR 1.39, 95, CI from 1.28 to 1.51) and the total incidence of major cardiovascular complications (RR — 1.99, 95%, CI from 1.86 to 2.12).

One of the latest meta-analysis of 9 randomized clinical trials of revascularization in patients with CHD and type 2 DM (n=4566) showed that PCI compared with CABG was associated with higher all-cause mortality frequency (RR 1.41, 95% CI 1.22 to 1, 63, p<0.001), cardiac death (RR — 1.56 with 95% CI from 1.25 to 1.95, p<0.001) and repeated revascularization (RR — 2.68 with 95% CI from 1.86 to 3.85, p<0.001) with a comparable frequency of MI (RR 1.20 at 95% CI 0.78 to 1.85, p=0.414) and lower risk of stroke (RR 0.51 at 95% CI from 0.34 to 0.77, p= 0.001). A cumulative meta-analysis of all-cause mortality showed that the differences between CABG and PCI groups reached statistical significance after 3 years of follow-up [18].

Another relatively new meta-analysis of 3 randomized and 5 observational studies (n= 3835) compared 10-year outcomes in patients with type 2 DM and CHD with stenosis of the trunk of the left coronary artery after PCI and CABG. Patients after CABG had lower mortality (RR — 0.85 at 95% CI from 0.73 to 1.00, p= 0.05), the frequency of MI (RR — 0.53 at 95% CI from 0.35 to 0.80, p= 0.002), repeated revascularization (RR 0.34 at 95% CI 0.26 to 0.46, p= 0.00001) and revascularization of the target coronary artery (RR 0.26 at 95% CI from 0.18 to 0.38, p= 0.00001). After 10-year follow-up, the summary of primary adverse cardiac and cerebrovascular events was also significantly lower in patients after CABG compared with

PCI (RR 0.67, 95% CI 0.49 to 0.92, p=0.01). However, CABG was associated with significantly higher risk of stroke (RR 2.16, 95% CI 1.39 to 3.37, p= 0.0007) [19].

Most studies showed that CABG was superior to PCI in patients with DM and CHD. However, the rapid improvement of PCI technology, drug-eluting stents design, and image-guided stent placement in combination with modern antiplatelet and lipid-lowering therapy contribute to the continuous enhancement of PCI results. Currently, there are no prospective studies comparing the latest PCI technologies and CABG in patients with DM.

Which coronary stents are best?

In recent years many studies have compared the results of various stents types implantation. Patients with DM and CHD did not have difference in mortality, MI, and repeated revascularization when using sirolimus-eluting stent or zotarolimus-eluting stent [20]. The ISAR-TEST 5 trial assessed the results of 10-year clinical outcomes in pre-defined subgroups of patients with or without DM randomized to polymer-free sirolimus- and probucol-eluting stent (n=2002) that provides effective drug release without polymer versus zotarolimus-eluting stent (n=1000) implantation [21]. Both new generation drug-eluting stents showed comparable clinical outcomes regardless of the presence of DM and the strategy of polymer covering. It has been shown that the frequency of adverse events after PCI in patients with DM was significantly higher compared with patients without DM and that it increases over time.

Biodegradable-polymer drug-eluting stents provide controlled drug release and complete polymer degradation over time. As a result, the risk of chronic inflammation and atherosclerosis progression decreases that is crucial for patients with DM. The efficacy and safety of the new drug-eluting stents in patients with DM remained unclear for a long time. Bavishi C. et al (2020) presented the combined results of 11 randomized controlled trials of PCI involving 5190 patients with DM and CHD [22]. The average follow-up was 2.7 years, there were no significant differences in the efficacy of revascularization, all-cause mortality, cardiovascular mortality, and MI rates between the groups of patients after the implantation of biodegradable-polymer drug-eluting stents and polymer durable drug-eluting stents. The incidence of stent thrombosis was also similar between the groups (1.66% versus 1.83%, respectively; RR 0.84, 95% CI 0.54 to 1, 31, p=0.45). The meta-regression analysis did not reveal any associations between DM that require insulin treatment and the long-term effectiveness of PCI or thrombosis of the studied stent types.

Recently the comparison of 10-year clinical outcomes following implantation of new generation biodegradable-polymer sirolimus-eluting stents (Yukon Choice PC, n= 1299) and polymer durable everolimus-eluting stents (Xience, n= 652) in patients with and without DM was completed [23]. After 10-year follow up, patients with DM had significantly higher incidence of major adverse cardiac events compared with patients without DM (RR 1.41, 95% CI 1.22 to 1.63, p<0.001) that did not depend on the type of stent. The incidence of definite / probable stent thrombosis was 2.3% in patients with DM and 1.9% in patients without DM (RR 1.27 with 95% CI 0.34 to 2.60, p= 0.52) with no significant differences between the compared stents. Consequently, clinical outcomes in patients with DM after PCI using various new generation drug-eluting stents are significantly poorer compared with patients without DM, and the incidence of adverse events is constantly increasing up to 10 years. So far, the use of new-generation drug-eluting stents in patients with DM does not allow to achieve similar to CABG outcomes, especially when the revascularization of coronary arteries is incomplete.

Is the assessment of multivessel coronary lesions severity necessary?

The assessment of coronary atherosclerosis severity according to the SYNTAX score includes the number of lesions, their complexity and functional significance. The SYNTAX score identifies patients with low (≤22 points), medium (23–32 points), and high (≥33 points) risk, suggesting better outcomes after CABG versus PCI in patients with high risk. However, the results of the FREEDOM study [15] questioned the implementation of the SYNTAX scale for the determination of myocardial revascularization strategy in patients with DM and MVD, and confirmed the superiority of CABG in this category of patients regardless of the SYNTAX score. The FREEDOM project did not reveal significant association between the benefits of CABG versus PCI and SYNTAX scores when enrolling patients into the study [24].

CABG, given that it can be performed with very low risk of complications, represents fundamentally different type of revascularization compared with PCI. By providing the new segments of the coronary arteries after each bypassed stenosis, CABG has 3 impor-

tant effects: 1) perfusion through the graft, similar to PCI, but with the additional distal protection from the development of new lesions of the proximal and middle segments of the arteries; 2) the improvement of endothelial function due to the addition of nitric oxide production by the arterial grafts that can aggravate CHD due to the development of endothelial dysfunction and chronic inflammation [25]; and 3) the development of new collaterals in the recently perfused myocardium [26]. The consequences of the blood flow cessation after successful CABG are significantly less severe compared with PCI that is associated with high morbidity and mortality [27]. On the contrary, low patency of bypass graft is asymptomatic in most cases, despite the fact that previously revascularized segment of the myocardium has no additional perfusion. The CABG surgery also has several aspects that could be improved, including the wider use of arterial shunts, the development of minimally invasive surgical access, the minimization of stroke risk, and the optimization of secondary pharmacological prophylaxis.

Revascularization for patients with peripheral arterial disease and diabetes mellitus

DM is the second most significant risk factor for PAD after smoking, which is present in 20–30 % of patients and increases the presence of this pathology by 2–4 times [28, 29]. Patients with DM and PAD have high rate of disease progression, many functional impairments, low quality of life, frequent development of cardiovascular complications and amputations compared with patients with PAD without DM [30–32]. The therapeutic approach to patients with PAD includes: the relief of specific symptoms of any localization, the prevention of PAD relapse and the prevention of consequences associated with atherosclerosis of coronary and cerebral arteries. Revascularization is recommended for patients with severe intermittent claudication and critical limb threatening ischemia. Endovascular intervention is primary method of revascularization in symptomatic PAD, but the difference in outcomes between this procedure and lower-extremity bypass grafting is still an issue of increased concern. The choice of revascularization strategy in patients with PAD depend on the localization, morphology and prevalence of arterial occlusions, that are detailed in the guidelines on the diagnosis and treatment of PAD [10]. The features of revascularization in patients with PAD and DM are not included in the current guidelines due to the lack of studies in this category of patients.

It is worth noting the results of the analysis of 14 012 860 cases from data base of patients who were admitted with PAD and DM (type 1 DM in 5.6 % of cases, n= 784.720). Patients with type 1 DM were more likely to have severe chronic limb ischemia (45.2 % versus 32.0 %), trophic ulcer (25.9 % versus 17.7 %) or complicated ulcer (16.6 % versus 10.5 %) of lower extremities ($p<0.001$ compared with patients with type 2 DM). Type 1 DM was independently and significantly associated with large number of amputations (adjusted odds ratio, 1.12 with 95 % CI from 1.08 to 1.16, $p<0.001$) [33]. These data require the study of the mechanisms of the observed difference and the development of new approaches to reduce the risk of complications.

In patients with critical limb threatening ischemia and ulcers, surgical or endovascular revascularization is the first-line treatment [34]. To accelerate the process of ulcers healing, negative pressure wound therapy, platelet-rich plasma and other modern wet dressings, systemic anti-inflammatory and antibacterial therapy are used [35].

Revascularization in patients with carotid artery disease and diabetes mellitus

Pharmacological therapy should be recommended for most patients with asymptomatic stenosis (60–99 %) of extracranial segments of the carotid arteries and high surgical risk. Carotid endarterectomy (CE) or carotid artery stenting (CAS) are considered if the risk of perioperative stroke / death is<3 % and the patient's life expectancy is> 5 years.

CE is recommended for patients with symptomatic 70–99 % carotid stenosis; which also should be considered in cases of symptomatic 50–69 % carotid stenosis. Due to the lack of scientific data, CAS of the arteries should be additionally investigated in case of recently revealed symptoms of 50–99 % carotid stenosis and the presence of concomitant pathology, or unfavorable anatomical factors associated with high risk of CE complications. Revascularization of symptomatic 50–99 % carotid stenosis is recommended within 14 days after the onset of symptoms. In each symptomatic case the risk of perioperative stroke / death should be<6 % for carotid revascularization. Revascularization is not recommended in patients with carotid stenosis<50 % [10].

According to the results of 752 carotid revascularizations (58.2 % of CAS and 41.8 % of CE), it was

found that DM was associated with higher periprocedural risk of stroke or death (3.6% with DM versus 0.6% without DM, p<0.05), transient ischemic attack (1.8% with DM versus 0.2% without DM, p> 0.05) and restenosis (2.7% with DM versus 0.6% without DM, p<0.05). During the 36-month follow-up, there were no significant differences in the incidence of death, stroke, and transient ischemic attack between patients with and without DM in CAS and CE subgroups. Patients with DM showed higher rate of restenosis (estimated risk of restenosis: 21.2% in patients with DM versus 12.5% in patients without DM, p<0.05) [36]. DM is also one of the main risk factors for restenosis after revascularization of the carotid arteries according to other authors [37]. In addition, patients with DM have higher risk of ischemic brain damage during CAS, despite the use of embolic protection devices [38].

Pharmacological treatment for the prevention of atherosclerotic complications in patients with diabetes mellitus

Several lifestyle changes should be recommended in addition to pharmacotherapy, such as smoking cessation, healthy diet, obesity correction and regular exercise.

It is known that adequate treatment of DM is essential for successful revascularization, since preoperative glycosylated hemoglobin level of> 8% and, especially, of> 9% is associated with increased mortality and adverse cardiac events after CABG [39]. In the study by Lee HF et al. (2020), the use of sodium-glucose cotransporter type 2 inhibitors (dapagliflozin, empagliflozin) for the treatment of type 2 DM compared with dipeptidylpeptidase-4 inhibitors reduced the risk of heart failure (RR 0.66 with 95% CI from 0.49 to 0.89, p= 0.0062), lower limb ischemia requiring revascularization (RR 0.73 with 95% CI 0.54 to 0.98, p= 0.0367), amputation (RR 0.43 with 95% CI from 0.30 to 0.62, p<0.0001) and cardiovascular mortality (RR 0.67 with 95% CI from 0.49 to 0.90, p= 0, 0089) [40]. Glucagon-like peptide-1 agonists (dulaglutide, liraglutide, semaglutide) are recommended in patients with type 2 DM with established atherosclerotic CVD as more active agents for the prevention of complications [5]. Large randomized trials on the comparison of sodium-glucose cotransporter type 2 inhibitors and glucagon-like peptide-1 agonists with the assessment of cardiovascular outcomes have not been performed. According to the meta-analysis of 8 studies in patients with type 2 DM (n= 77.242), glucagon-like peptide-1 agonists and sodium-glucose cotransporter type 2 inhibitors both similarly reduced the risk of major cardiovascular complications (RR 0.87 with 95% CI from 0.82 to 0.92 and 0.86 with 95% CI from 0.80 to 0.93, respectively) [41].

The treatment of AH in patients with DM should include an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with calcium channel blocker and / or a diuretic to achieve target blood pressure level (systolic<130 mmHg with good tolerance, but> 120 mmHg; in patients aged> 65 years — 130–139 mm Hg; diastolic — <80 mm Hg, but>70 mm Hg) [4, 5].

Statins should be used in patients with DM with atherosclerosis in high doses (the target level of low-density lipoproteins with very high cardiovascular risk — <1.4 mmol/L), which reduces the risk of cardiovascular complications, including number after PCI and CABG [4, 5, 42]. However, patients with DM taking statins may have elevated triglyceride levels associated with higher risk of cardiovascular events [43]. In this case, the additional use of ethyl eicosapentaenoic acid significantly reduces the frequency of PCI (RR 0.68 at 95% CI from 0.59 to 0.79, p<0.0001) and CABG (RR 0.61 at 95% CI from 0.45 to 0.81, p= 0.0005) [44].

Antiplatelet therapy with 75–100 mg / day aspirin is recommended in patients with DM for secondary prevention or in patients with high / very high cardiovascular risk for primary prevention. It is recommended to use the P2Y12 receptor antagonists such as ticagrelor or prasugrel for 1 year in combination with aspirin in patients with DM and ACS as well as in patients after PCI or CABG [4, 5]. In patients with stable atherosclerotic vascular disease, including those with DM, the combination of 2.5 mg 2 times / day rivaroxaban and 100 mg / day aspirin, compared with aspirin alone, reduced the risk of MI, stroke and cardiovascular mortality, as well as large amputations [45], indicating the effect of combined antithrombotic therapy.

Conclusion

Modern treatment of patients with DM especially in combination with atherosclerosis, should be performed by endocrinologist and a cardiologist with the involvement of other specialists, if necessary. A team patient-centered approach for the management of such patients will allow to choose and continue the most effective and safe therapy, where revascularizа-

Table. **The choice of preferred method of arterial revascularization and pharmacological treatment that can improve outcomes in patients with DM**

Cardiovascular disease associated with atherosclerosis	Primary revascularization method	Primary pharmacological treatment	Pharmacological treatment according to indications
ACS	CABG	Dulaglutide / liraglutide / semaglutide; dapagliflozin / empagliflozin; statins; aspirin	P2Y12 receptor blockers
Stable CHD with MVD	CABG		Rivaroxaban
ADLE	Endovascular intervention		
Carotid artery stenosis	catheter endarterectomy		

tion of the coronary and peripheral arteries should have an important place considering indications and contraindications. New pharmacotherapy options for patients with DM and atherosclerotic CVDs can reduce the need for interventional and surgical procedures, as well as improve outcomes after its implementation.

The table summarizes the main ways to improve outcomes of patients with DM and atherosclerotic cardiovascular diseases.

Conflict of interest: None declared.

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Electrical remodeling and heart rhythm disturbances in patients with primary arterial hypertension

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Abstract

Objective. *frequency of heart rhythm disturbances (HRD) and cardiac electrophysiological parameters depending on the presence of left ventricular hypertrophy (LVH) in patients with primary arterial hypertension (AH).*

Materials and methods. *The study included 157 patients (89 men and 68 women) aged from 43 to 65 years (54.2± 6.3 years) with 1–2 grades of AH. All the patients underwent electrocardiography (ECG), blood pressure (BP) monitoring, diagnostic transesophageal electrical stimulation of the heart, echocardiography, and the assessment of heart rate variability (HRV). According to echocardiography, 64 patients (40.8 %) had LVH (group 1), and 93 patients (59.2 %) — had not (group 2).*

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Results. *Various HRD were identified in 68 patients (43.3 %) — in group 1 in 40 patients (62.5 %), and in group 2 in 28 patients (30.1 %). The most common HRD was atrial fibrillation (12.7 %), supraventricular (13.4 %) and ventricular (11.5 %) extrasystoles, the frequency of which was 3–4 times higher in the 1st group compared with the 2nd group. 15 patients (9.6 %) had asymptomatic paroxysmal supraventricular tachycardia and latent sinus node dysfunction. In both groups, patients with HRD, showed greater P-wave dispersion, and the parameters of atrial effective refractory period (aERP) and vagosympathetic balance SDNN were lower compared with patients without HRD.*

Conclusion. *Thus, the presence of LVH in patients with AH was associated with a high incidence of HRD and cardiac electrical remodeling, which should be considered during cardiac risk stratification.*

Keywords: *arterial hypertension, left ventricular hypertrophy, heart rhythm disturbances.*

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Introduction

Primary arterial hypertension (AH) and cardiovascular complications associated with it are still one of the main problems of modern medicine despite significant success that has been achieved in the management of these conditions [1,2]. It has been established that left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular morbidity and mortality that can be at least partially explained by the occurrence of heart rhythm disturbances (HRD) [1,3,4]. It has been shown that the frequency of various HRD in patients with AH reaches 96 % that is 10 times higher compared with normotensive people [5,6]. Moreover, early studies emphasized that HRD in patients with LVH and AH are 10 times more common than in patients without LVH [6,7]. According to epidemiological studies, over 70 % of patients with AH have atrial fibrillation (AF), and 35 % of patients have short and asymptomatic paroxysms of AF [4].

Large number of clinical studies has confirmed the exceptional role of cardiac electrical remodeling in patients with AH without severe morphological changes of the myocardium and coronary vessels [5,8,9]. Is has been established that pathogenetic factors involved in the development and progression of AH, such as autonomic nervous system, neurohumoral, hormonal and electrolyte disturbances, can increase cardiac arrhythmogenic potential [10,11]. The relevance of this issue is also associated with the revision of echocardiographic, diagnostic criteria for LVH in the updated international clinical guidelines for the diagnosis and management of AH [1,8]. Thus, over the past two decades, the threshold values of the left ventricular myocardial mass index (LVMI) for the diagnosis of LVH decreased from 134 g/m^2 to 115 g/m^2 in men and to 95 g/m^2 in women [12]. As the result of the increased sensitivity of the criteria for the diagnosis of LVH, the prevalence of LVH in patients with AH on average increased from 35 % to 50 % [6,12].

It is also important to study the association between the frequency of HRD and markers of arrhythmogenic risk in patients with AH depending on the presence of LVH. It is worth noting that not all the studies confirm the correlation between markers of arrhythmogenic risk and the prevalence and severity of HRD in patients with AH [4,7,9], therefore, further investigations are needed to substantiate the role of cardiac electrical remodeling and arrhythmic syndrome as an unfavorable factor in the cardiac risk stratification.

Objective of the study — to assess the frequency of HRD and cardiac electrophysiological parameters depending on the presence of LVH in patients with primary AH.

Materials and methods

This open clinical trial included 157 patients (89 men and 68 women) aged from 43 to 65 years (mean age 54.2±6.3 years). According to the clinical guidelines "Arterial hypertension in adults" (2020) of the Russian Society of Cardiology [1], 92 patients (58.6 %) had stage I AH and 65 patients (41.4 %) — stage II. According to daily blood pressure level, 74 patients had grade I AH (47.1 %) and 83 patients (52.9 %) — grade II. According to echocardiography, 64 patients (40.8 %) had LVH (group 1), and 93 patients (59.2 %) — had not (group 2). Additionally, 27 patients had type 2 diabetes mellitus (DM) without kidney damage. According to the data of daily blood pressure monitoring in the 1st group the normal dipper pattern was defined in 42 patients

(43.8 %) and in the 2nd group — in 18 patients (29.5 %): χ^2= 3.49 (p= 0.046). It should be noted that all patients received antihypertensive therapy with the achievement of target blood pressure, and the frequency of the prescription of certain classes of antihypertensive medications did not differ significantly between groups.

The study was carried out in accordance with the standards of good clinical practice and the Declaration of Helsinki principles of the World Medical Association. The study protocol was approved by the local Ethical Committee of the Penza Institute for Advanced Medical Studies. Prior to the study written informed consent for participation in the study was waived from all the participants. The study included patients with stable AH of 1–3 grade. The exclusion criteria were: the presence of associated clinical conditions in patients with AH, non-coronary myocardial lesions, valvular heart disease, anemia, and chronic obstructive pulmonary disease.

Structural and functional characteristics of the heart were assessed using Doppler echocardiography on the Acuson X300 apparatus (Siemens-Acuson, Germany) during the sinus rhythm. Left ventricular (LV) end-systolic and end-diastolic volumes, left atrial volume index, LV ejection fraction, cardiac index, LV relative wall thickness and LVMI were calculated. LV diastolic function was assessed by spectral analysis of the diastolic transmitral flow during the sinus rhythm and the maximum speed of rapid and slow LV filling (Ve, Va) and their ratio (Ve / Va), isovolumic relaxation time, and flow deceleration time of rapid LV filling were determined. The criteria for the diagnosis of LVH included: LVMI over 115 g/m^2 in men and over 95 g/m^2 in women [1]. In order to verify the diagnosis some patients underwent various diagnostic imaging methods: chest x-ray, computed tomography and coronary angiography.

Using the method of bifunctional monitoring of ECG and blood pressure for 48 hours (on the Kardiotekhnika-07-AD-3, Russia), we studied daily blood pressure profile, as well as the frequency and possibility of HRD detection, including undocumented ones by conventional ECG at rest that included short episodes and / or asymptomatic paroxysms of tachyarrhythmias and cardiac pauses.

Time and spectral parameters in 5-minute intervals during 24-hour ECG monitoring were analyzed to assess the HRV. The integral indicators of HRV were used: the standard deviation of all normal sinus RR intervals (SDNN) and the ratio of low-frequency and high-frequency power components (LF/HF).

The state of the cardiac conduction system, latent disturbances of heart rhythm and conduction, including "arrhythmogenic readiness" of the atria, were studied by the method of frequent and programmed transesophageal electrical stimulation (TES) of the left atrium using the Astrocard complex (Meditek, Russia). At the same time, the parameters characterizing the state of the cardiac conduction system were determined: sinus node recovery time (SNRT), corrected SNRT (CSNRT), "Wenckebach's point", refractory periods of the atria and atrioventricular junction (RPa, RPav).

The statistical analysis was performed using Statistica 8.0. software. The normality of distribution was assessed using the Shapiro-Wilk test. The significance of differences of the mean values between groups was determined using the Student's t-test. The association between qualitative variables was determined using the Spearman's rank correlation coefficient (R). The Prison χ^2 test was used for the comparison of categorial variables. Data were presented as M± SD. The level of significance was set as p<0.05.

Results

Various HRD were found in 68 patients (43.3 %) — in 40 patients (62.5 %) in group 1, and in 28 patients (30.1 %) — in group 2: χ^2=16.20 (p<0.001) according to standard ECG, daily ECG monitoring and electrophysiological study using TES. At the same time LVH was detected in 24 patients (27.0 %) among patients without HRD, and 40 patients (44.9 %) did not have LVH: χ^2=6.25 (p= 0.013). Evaluation of the diastolic transmitral flow revealed the presence of LV diastolic dysfunction caused by impaired active relaxation of the myocardium in 96 patients (61.2 %), including 55 patients (85.9 %) from the 1st group and 41 patients (44, 1 %) from the 2nd group (p<0.000).

Patients from the 1st group had higher duration of AH and the value of LVMI, and glomerular filtration rate (GFR), calculated using the CKD-EPI formula, was lower compared with the 2nd group (table 1). In addition, patients from the 1st group had higher frequency of metabolic disorders compared with the 2nd group — abdominal obesity (χ^2=3.82, p=0.039) and dyslipidemia (χ^2= 4.19, p=0.031). The frequency of various grades of AH, DM, and the value of GFR did not differ significantly between groups (p>0.05).

The most frequent HRD in patients with AH were: atrial fibrillation, ventricular and supraventricular extrasystoles, as well as various paroxysmal supra-

Table 1. **Clinical characteristics of patients from compared groups (M±SD)**

Parameter	Group 1 (n=64)	Group 2 (n=93)	p
Men, n / %	38/ 59.4	51/ 54.8	is
Age, years	56.3±7.2	54.2±6.9	is
The duration of AH, years	7.6±2.3	6.5±2.1	0.015
1 grade AH, n / %	34 / 53.1	40 / 43.0	is
2 grade AH, n / %	30 / 46.9	53 / 57.0	is
Hereditary burden, n / %	39 / 60.9	47 / 50.5	is
LVMI, г/м^2	119.3±12.4	99.5±9.3	<0.001
Heart rhythm and conduction disturbances, n / %	40 / 62.5	26 / 28.0	<0.001
Type 2 DM, n / %	14 / 21.9	13 / 14.0	is
Chronic kidney disease, n / %	15 / 23.4	17 / 18.3	is
GFR, ml/min/1.73 m^2	65.1±6.3	61.5±7.4	0.026
Abdominal obesity, n/%	22 / 34.4	19 / 20.4	0.039
Body mass index, kg/m^2	28.6±4.5	26.8±4.1	0.003
Dyslipidemia, n / %	28 / 43.8	26 / 28.0	0.031
Smoking, n / %	31 / 48.4	41 / 44.1	is

Is — insignificant

Table 2. **Diagnosis and features of heart rhythm disturbances depending on the presence of LVH in patients with AH**

Types of heart rhythm disturbances	The frequency of heart rhythm disturbances, n / %		
	Group 1 (n=64)	Group 2 (n=93)	Total (n=157)
AF:	13 / 20.3	7 / 7.5	20 / 12.7*
Paroxysmal	8 / 11.0	7 / 7.5	15 / 9.6
Persistent	5 / 7.8	–	5 / 3.2
Paroxysmal atrial flutter	3 / 4.7	2 / 2.2	5 / 3.2
Paroxysmal atrioventricular tachycardia	2 / 3.1	–	2 / 1.3
Paroxysmal atrial tachycardia	2 / 3.1	1 / 1.1	3 / 3.0
Paroxysmal ventricular tachycardia	1 / 1.6	–	1 / 0.6
Ventricular premature beats:	13 / 20.3	5 / 5.4	18 / 11.5*
Single	9 / 14.1	5 / 5.4	14 / 8.9
Paired	4 / 6.2	–	4 / 2.6
Over 500 premature beats per day	7 / 10.9	–	7 / 4.5
Supraventricular premature beats:	10 / 15.6	11 / 11.8	21 / 13.4
Single	5 / 7.8	7 / 6.5	12 / 7.6
Paired	5 / 7.8	4 / 3.2	9 / 5.7
Over 700 premature beats per day	6 / 9.4	3 / 3.2	9 / 5.7
Second-degree atrioventricular block	3 / 4.7	2 / 2.2	5 / 3.2
Second-degree sinoatrial block	2 / 3.1	3 / 3.2	5 / 3.2
Latent sinus node weakness	4 / 6.2	6 / 6.5	10 / 6.4
Complete bundle branch block	9 / 14.1	7 / 7.5	26 / 10.9
Wolff-Parkinson-White syndrome	2 / 3.1	–	2 / 1.3
Combined heart rhythm disturbances	11 / 17.2	5 / 5.4	16 / 10.2*

* –significant differences between groups, p<0.05.

ventricular tachycardias (table 2). At the same time AF and ventricular extrasystoles were 3–4 times more common in patients from group 1 compared with group 2. Sinoatrial (SA) and atrioventricular (AV) conduction disturbances often had latent nature and were mainly detected during electrophysiological investigation and did not depend on the presence of LVH. The combination or alternation of different types of HRD were detected in 16 (24.2 %) out of 66 patients, including 11 patients from group 1 and 5 patients from group 2 (17.2 % versus 5, 4 %, p=0.017). Two patients from group 1 were diagnosed with Wolff-Parkinson-White syndrome.

According to LVMI criteria for the diagnosis of LVH (over 125 g/m^2 in men and over 110 g/m^2 in women), we diagnosed LVH in 49 patients (31.2 %), and among them HRD were detected in 40 patients (81.6 %). These findings can indicate that the use of more "stringent" echocardiographic criteria for LVH is associated with a higher detection rate of HRD: 81.6 % versus 62.5 % (p= 0.021).

The analysis of the associations between HRD and LV diastolic dysfunction in patients with AH showed that HRD are more common in patients with LV diastolic relaxation disturbances, especially paroxysmal AF compared with patients with preserved diastolic function: 17.7 % versus 4.9 % (p=0.019). It has also been shown that the frequency of HRD between patients with hypertrophic LV diastolic dysfunction, when it is combined with LVH, compared with isolated LV diastolic dysfunction does not differ significantly: 74.5 versus 68.3 % (p>0.05). It should be noted that ischemic ST segment depression was not found in the examined patients according to ECG monitoring. At the same time, the maximum ST segment depression in the 1st group was significantly higher compared with 2nd group, regardless of the presence of HRD.

We also analyzed the sensitivity of diagnostic methods in HRD detection. Thus, during the control (planned) ECG at rest, HRD were detected in 39 patients (24.8 %), including 22 patients from group 1 and 14 patients from group 2: 34.4 % versus 15.1 % (χ^2= 8.01; p= 0.004). According to 48-hour ECG monitoring, HRD were detected in 34.4 % of cases, including 20.3 % of patients from group 1 and 5.4 % of patients from group 2: χ^2=4.61 (p=0.032). The TES method revealed unstable and / or asymptomatic paroxysmal supraventricular tachycardias, latent sinus node dysfunction and "ischemic" ventricular extrasystoles in 15 patients (9.6 %). In 12 patients (7.6 %) HRD, espe-

Table 3. **The comparison of cardiac electrophysiological parameters between study groups depending on the presence of HRD in patients with AH (M± SD)**

Parameter	Group 1 (n= 64)		Group 2 (n= 93)	
	Patients with HRD (n=24)	Patients without HRD (n=40)	Patients without HRD (n=65)	Patients with HRD (n=28)
HR, beats/min	70.8±4.2	72.3±4.9	68.3±6.5	73.6±5.0
P-wave dispersion, m/s	42.3±7.4	48.1±5.7*	37.8±5.2†	45.1±6.7*
RPa, m/s	272.3±31.6	256.1±25.0*	292.6±23.5†	263.4±22.5*
SNRT, m/s	1006.4±56.0	1288.0±81.2*	987.2±40.4	1169.6±68.5*§
CSNRT, m/s	254.4±35.8	279.4±65.1*	215.6±27.3†	260.7±31.0*§
Wenckebach's point, imp. / min	141.4±17.5	137.0±21.6	152.3±24.1	148.7±20.3
RPav, m/s	324.7±32.5	318.5±40.6	314.5±42.1	313.5±44.7
SDNN, m/s	66.9±14.1	55.7±15.3*	72.0±13.5	64.1±17.4*§
LF/HF, conventional units	1.2±0.3	1.7±0.4*	1.1±0.2	1.4±0.3*§
Maximum ST segment depression, mm	1.2±0.3	1.2±0.4	0.5±0.2†	0.6±0.2§
Detection of ST segment depression, n /%	8 / 33.3	19 / 47.5	12 / 18.5	6 / 21.4§

* — significant differences between parameters depending on the presence of HRD, p<0.05. † — significant differences between groups of patients without HRD: †<0.05; § — significant differences between groups of patients with HRD; §<0.05.

cially paroxysmal supraventricular tachycardias, debuted or reoccurred during a hypertensive crisis.

The comparative analysis of cardiac electrophysiological parameters showed that SA and AV conduction disturbances are often observed in patients with LVH. In addition, SNRT and CSNRT parameters differed significantly between patients with and without HRD (Table 3). The parameters of anterograde AV-conduction — "Wenckebach's point" and RPa significantly differed between the groups of patients without HRD. It is also remarkable that during the electrophysiological study the values of CSNRT in 10 patients, and the "Wenckebach's point" parameters in 5 patients were "pathological": over 525 m/s and below 110 impulses/min, respectively. The P wave dispersion and RPa that serve as markers of atrial electrical instability, differed significantly between groups of patients with and without HRD. The P wave dispersion in patients without HRD from the 1st group were significantly higher compared with 2nd group (on average by 10.6%; p= 0.013), and the RPa value was significantly lower (on average by 7.5%; p= 0.029).

The spectral parameters of HRV also significantly differed between groups, depending on the presence of HRD. In patients with HRD from group 1 compared with group 2 the SDNN parameter was lower by 13.1% on average (p=0.017), and the LF/HF ratio was higher by 17.7% on average (p<0.001). Difference between groups of patients without HRD was not significant (p>0.05).

Correlation analysis of the HRD development in patients with AH revealed the main correlates that can serve as morphofunctional and electrophysiological markers of arrhythmogenic risk (table 4). It has been shown that the presence of HRD directly correlates with the age of patients, the duration of the disease, LVMI, the maximum LA volume, the P wave dispersion, daily variability of systolic blood pressure (SBP), the LF/HF index and vice versa — with the RPa, Ve/Va and SDNN parameters.

Table 4. **Correlates of heart rhythm disturbances in patients with AH**

Independent variables	Dependent variable — heart rhythm disturbance		
	R	t	p
Men	0.127	1.595	0.113
Age, years	0.321	4.219	< 0.001
The duration of AH, years	0.198	2.509	0.013
P-wave dispersion, m/s	0.190	2.412	0.017
RPa, m/s	– 0.215	– 2.739	0.007
CSNRT, m/s	0.129	1.622	0.107
SDNN, m/s	– 0.192	– 2.433	0.016
LF/HF	0.222	2.839	0.005
LVMI, g/m^2	0.207	0.628	0.01
Left atrial volume index, ml/m^2	0.189	2.399	0.017
LV EF, %	– 0.118	– 1.481	0.141
Ve / Va	– 0.169	– 2.134	0.034
Systolic blood pressure variability, mmHg	0.185	2.348	0.02

Thus, despite the changes in echocardiographic diagnostic criteria for LVH, morphofunctional cardiac remodeling remains a reliable predictor of cardiovascular complications, including the development of prognostically unfavorable cardiac arrhythmias.

Discussion

It is known that morphofunctional cardiac remodeling that leads to transmembrane ion channels impairment is one of the trigger factors of arrhythmogenesis in patients with AH [7, 10, 12]. Therefore, LV diastolic dysfunction, size and function of LV as well as LVH are seem to be the main risk factors of HRD in patients

with AH [11, 13]. AH proved to be strong and independent risk factor for the development of supraventricular and ventricular HRD, the presence and severity of which adversely affects morbidity and mortality, as well as the quality of life of these patients [4, 5, 10]. It has also been proven that the pathogenetic mechanisms of AH development and progression, such as electrolyte disturbances, sympathetic hyperactivity, labile hypertension and episodes of transient myocardial ischemia, contribute to the increase of the cardiac proarrhythmic potential in patients with LVH [4, 11, 14].

The heterogeneity in the results among various studies can be explained by differences in baseline covariates, such as age, gender, coronary insufficiency, DM, systolic dysfunction, etc. Thus, S. Chatterjee et al. (2014) performed the meta-analysis of 10 randomized clinical trials that assessed the relationship between LVH and sustained cardiac arrhythmias in over 27 thousand patients with AH, and found that supraventricular tachycardias in patients with LVH were detected in 11.1% of cases and in patients without LVH — in 1.1% of cases ($p<0.001$), and ventricular arrhythmias — in 5.5 and 1.2% of cases, respectively ($p<0.001$). It has also been shown that the risk of ventricular tachycardia/ventricular fibrillation is 2.8 times higher in patients with hypertensive LVH compared with patients without LVH. However, R. Sultana et al. (2010) showed that various HRD were diagnosed in 90% of cases according to the data of daily ECG monitoring among 500 patients with AH, and they also revealed that the frequency of HRD was higher in women compared with men [6]. It has been shown that the presence of hypertensive LVH also contributes to the progression and the course of existing HRD. Thus, according to data of Ö. Erküner et al. (2018), AF progression, the transformation of paroxysmal AF into persistent and / or permanent form, during 12-months follow-up was observed more often in patients with LVH compared with patients without LVH: 23.3% versus 8.8% ($p= 0.011$) [15].

In patients with AH without complications, various HRD were identified in 43.3% of cases, including 62.5% of patients with LVH and 30.1% of patients without LVH. Paroxysmal supraventricular tachycardias and extrasystoles were prevalent in this category of patients. This can be explained by relatively low LVMI criteria for the diagnosis of LVH compared with previous studies. Therefore, hypertensive LVH is detected relatively more often, when at the same time LVH-associated HRD are rarer. This fact highlights the importance of LVH preventive diagnosis to ensure effective prophylaxis of cardiovascular complications.

Despite the existence of large evidence base according to many clinical studies, paroxysmal tachycardia and heart block associated with systemic AH are still not considered as risk factors in cardiovascular risk stratification [1, 4, 7]. It is known that various biomarkers of myocardial damage, echocardiographic parameters and electrophysiological criteria, such as: P-wave signal averaging, dispersion of the QT interval, HRV, late ventricular potentials, heart rate turbulence, etc., are used to identify electrical instability of the myocardium and the risk of sudden cardiac death in patients with AH. [2, 10].

We have shown that RPa value of less than 240 m/s correlates with the occurrence of paroxysmal AF in patients with AH even without LVH. In addition, an inverse correlation between LV diastolic dysfunction, the Ve/Va index, and the development of paroxysmal supraventricular tachycardias, AF, and atrial extrasystoles was found. This indicates a close relationship between markers of electrical and morphofunctional cardiac remodeling and their role in the occurrence of HRD.

Thus, the results of this study demonstrate that cardiac conduction disturbances and electrical instability of the myocardium are the leading cardiac syndromes in patients with AH, even in those with benign disease course, and/or asymptomatic/ubclinical cardiac lesions. Based on this, the presence of HRD should be considered as a risk factor during cardiac risk stratification in patients with AH, since it has been proven that the occurrence of HRD, including life-threatening tachycardias, can cause cardiovascular complications, including sudden cardiac death.

Conclusion

HRD in patients with benign primary AH are diagnosed in 43.4% of cases, including 62.5% of patients with LVH, and 30.1% of patients without LVH ($p<0.001$). At the same time 18.5% of patients have latent HRD that can be detected only using 24-hour ECG monitoring and/or transesophageal electrical stimulation test.

Revealed correlation between morphofunctional remodeling (presence of LVH and/or LV diastolic dysfunction) with markers of electrical myocardial instability indicates that the new diagnostic criteria for LVMI, which are over 110 g/m^2 in men and over 95 g/m^2 in women, are highly prognostically valuable.

The detection of HRD correlates with the value of LVMI, the presence of LV diastolic dysfunction and

reduced HRV. Electrophysiological parameters of the cardiac conduction system in patients with uncomplicated AH indicate electrical remodeling of the myocardium in patients with and without LVH.

Conflict of interest: None declared.

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ORIGINAL ARTICLES

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Changes in smoking prevalence and intensity in middle-aged men over 5- and 15-year follow up

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Objective. *To assess changes in the prevalence and intensity of smoking in Tyumen men aged 35–44 and 45–54 years over 5- and 15-year follow up.*

Materials and methods. *This is a cross-sectional epidemiologic study of representative cohorts of men aged 35–44 and 45–54 years with follow-up in 1995, 2000, 2010. Prevalence and intensity of tobacco smoking were assessed using WHO questionaries as a part of cardiological screening in regular smokers.*

Results. *Based on the 5-year follow-up of Tyumen population, higher prevalence of irregular smoking and lower percentage of adults who have never smoked were identified in individuals over 40 years of age; 15-year follow-up has shown the reduction of everyday smoking and increase in smoking cessation frequency in adult men aged 35–44 and 45–54 years. Over 5 years, more everyday smokers aged 45–54 years started smoking more heavily; percentage of individuals who smoked less then 10 cigarettes per day has decreased, respectively. Over 15 years, smoking intensity in both age groups hasn't changed.*

Conclusion. *Follow-up has shown the reduction of smoking prevalence in adult active men over 15 years and the increase of smoking prevalence over 5 years. Follow-up was performed in the period of social and economic difficulties in Russia. Combined approach to behavioral and psychosocial risk factors is required for efficient smoking prevention programs.*

Keywords: *epidemiologic study, population monitoring, open population, men, smoking prevalence, smoking intensity.*

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Introduction

Tobacco smoking is one of the leading independent risk factors (RF) of cardiovascular (CV) morbidity and mortality. Although main effects of tobacco are well known, smoking remains the most common RF of coronary artery disease (CAD) in men [1]. Maslennikova et al. investigated how smoking contributed to mortality rates in Russia. Based on their results, 30 % of all male deaths are associated with smoking (25 % in Europe) and the rate of cardiovascular mortality due to smoking is the highest of all countries of European region [2]. Russia has significantly larger smoking population compared with developed countries, although 20-year follow-up has shown the reduction of smoking prevalence but increase in intensity [3]. According to epidemiologic study of cardiovascular disease and its risk factors in the Russian Federation, smoking rate among men aged 25–64 years was 43.5 % [4]. The largest smoking populations were identified in Ural, Siberia and Far East, the smallest — in the Russian southern regions [3, 5, 6]. In 2003 Russia became a Party to the WHO Framework Convention on Tobacco Control and started to implement the framework and tobacco control policy. This included increasing prices and other measures, such as tobacco smoke protection, control of ingredients, packaging, labelling and advertising [7]. At the same time, international experience has shown that integrated educational and legislative measures are necessary to reduce smoking rates in Russia [8].

Smoking prevalence and intensity in Western Siberia still aren't well studied. At the same time, it's crucial to explore real effects of measures that are imposed by the government in order to prevent cardiovascular diseases and other chronic non-communicable diseases in regions with large smoking populations such as Western Siberia [3].

The objective of this study is to assess changes in the prevalence and intensity of smoking in Tyumen men aged 35–44 and 45–54 years over 5- and 15-year follow up.

Materials and methods

This is a cross-sectional epidemiologic study of representative cohorts of men aged 35–44 and 45–54 years with follow-up in 1995, 2000, 2010. Participants were randomly chosen from Tyumen Central District voters lists — 250 people for each age group were selected.

Prevalence and intensity of tobacco smoking was assessed using WHO questionaries as a part of cardiological screening in regular smokers. Regular smokers, or everyday smokers, were adults who admitted to smoking at least one cigarette (or equivalent) per day. There were also participants who have never smoked, quitted smoking and those who smoked just occasionally. Everyday smokers were divided into the subgroups depending on the intensity of smoking: 1–9 cigarettes per day, 10–19 cigarettes per day and 20+ cigarettes (heavy smokers).

The study was carried out in accordance with Declaration of Helsinki. Study protocol had been approved by the local hospital ethical committee. All subjects signed an informed consent statement before participating in this study.

Statistical analysis was performed using IBM SPSS Statistics 21.0. Pearson's chi-squared test was used to compare the groups. $P<0.05$ was considered statistically significant. Bonferroni correction was used to counteract the problem of multiple comparisons.

Results

Changes in the prevalence and intensity of smoking in Tyumen men aged 35–44 and 45–54 years are presented in the following figures.

Prevalence and intensity of tobacco use in everyday smokers aged 35–44 and 45–54 years haven't changed significantly over the study period. Higher prevalence of irregular smoking and lower percentage of adults who have never smoked were identified in individuals aged 45–54 years (7.3–21.5 %, $p<0.001$ and 44.3–21.5 %, $p<0.001$, respectively) (Fig. 1).

15-year follow-up has shown the reduction of everyday smoking and increase in smoking cessation frequency in adult men aged 35–44 and 45–54 years — 65.5–36.0 % and 46.3–35.1 %, respectively. The first screening has shown that more men aged 35–44 years were everyday smokers, but at 15-year follow-up everyday smoking was highly prevalent in both age groups.

As for occasional smoking, over 15 years its prevalence and intensity hasn't changed in both age groups — 9.3–10.5 % in 35–44 age group and 7.3–12.1 % in 45–54 age group ($p>0.05$). Only 2.0 % participants aged 45–54 quit smoking according to the results of the first screening; in the younger age group no one stopped smoking. The second screening showed that 23.7 % participants aged 35–44 years and 20.3 % participants aged 45–54 years, $p<0.001$, quit smoking. Over 15 years, there were no statistically significant differences in the number of individuals who have never smoked (Fig. 2).

The baseline data show that the percentage of people who smoke very few cigarettes per day was

minimal. Percentage of moderate smokers (10–19 cigarettes per day) and heavy smokers (20+ cigarettes per day) in Tyumen population was, on the contrary, very high.

Among young men who smoked every day no changes in smoking intensity were noted; among the older men we have identified significant reduction of percentage of individuals smoking just a few cigarettes (1–9 per day) — from 16.8 % to 5.0 %, $p<0.05$ and increase in the percentage of heavy smokers — from 36.8 % to 62.2 %, $p<0.05$ (Fig. 3).

15-year follow-up has shown that main tendencies have returned to baseline. The third cardiologic screening in men aged 35–44 and 45–54 years has shown that the percentage of light smokers was still minimal, and the percentage of moderate smokers has increased. Heavy smoking was more prevalent in men aged 35–44 years; in men aged 45–54 years, the percentages of moderate and heavy smokers were almost the same (Fig. 4).

Discussion

According to WHO, by 2030 the number of deaths associated with tobacco smoking will rise from 6 to 8 million cases and around 80 % of all deaths occur in developing countries [1]. Treatment of diseases caused by smoking and loss of productivity in smokers will cause significant economic losses. At the same time, data from the 1980–2012 study have shown the reduction of smoking prevalence in men from 41.2 % to 31.1 % [9]. The results from our study were similar to that data. Moreover, the tendencies that we've identified are also supported by the data from the larger studies on Russian population carried out at the same time. These studies have shown that smoking prevalence decreased from 59.8 % to 39.0 % [3]. Authors explain these results by the measures implemented by the Russian government [7].

In the current study we have shown the decrease in everyday smoking prevalence and increase in those who stopped smoking among middle-aged men. Percentage of those who quit smoking according to the first screening during the "perestoyka" period in Russia was extremely low, and close to zero among younger people. Although the number of people who quit smoking hasn't changed over the 5 years of follow-up, during the reform period we could clearly see the effects of the federal preventive measures. Apparently, social factors that we've identified during our study have also

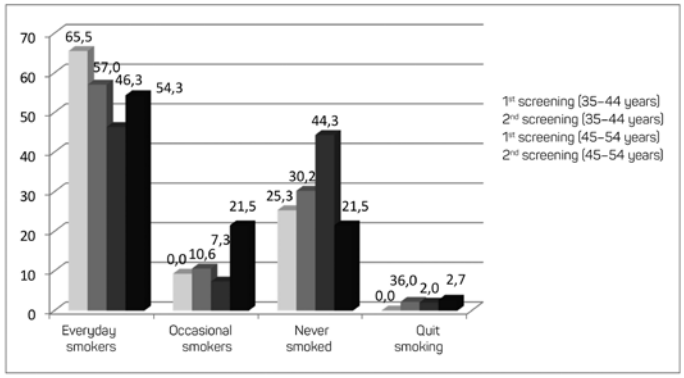

Figure 1. Changes in tobacco smoking prevalence in middle-aged men over 5 years

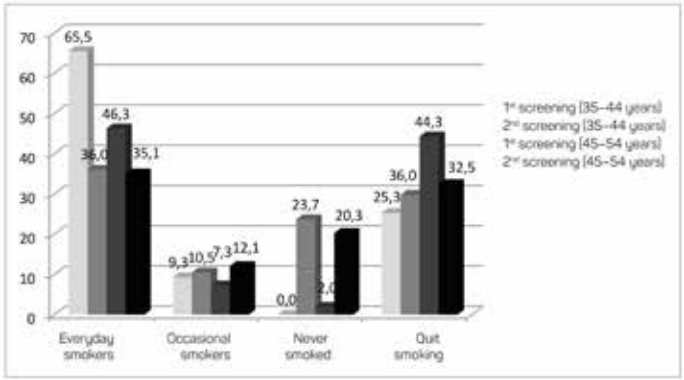

Figure 2. Changes in tobacco smoking prevalence in middle-aged men over 15 years

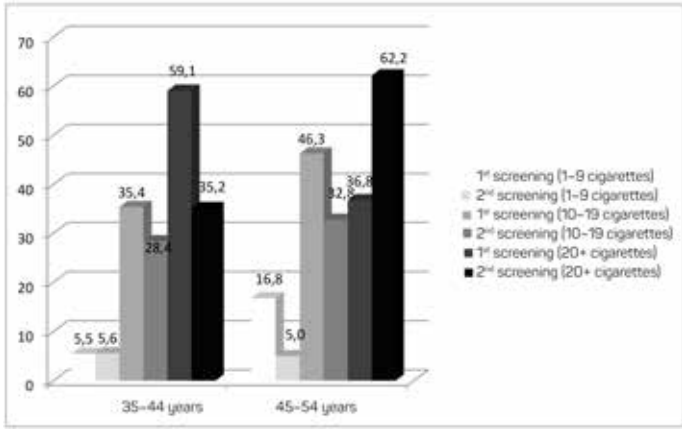

Figure 3. Changes in tobacco smoking intensity in middle-aged men over 5 years

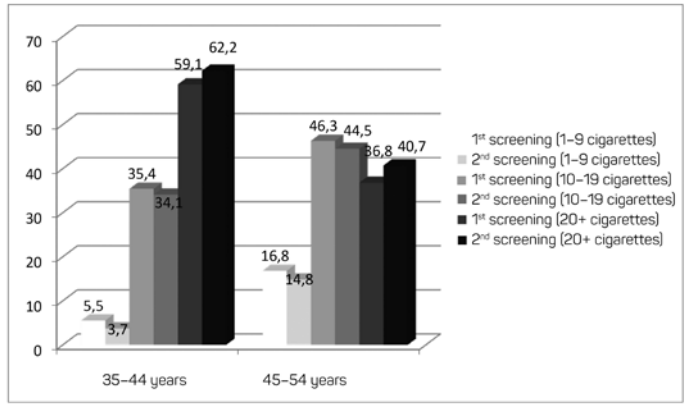

Figure 4. Changes in tobacco smoking intensity in middle-aged men over 15 years

affected Tyumen population apart from general federal measures. Social status, family stress and other chronic stress factors were less prominent and that had a positive effect on smoking prevalence in men of working age [10, 11].

Other epidemiological studies showed the reduction in the percentage of smoking men and increase in smoking intensity in the fifth decade of life. In Tyumen population, intensity of smoking was extremely high in younger people (aged 35–44 years) and decreased to 45–54 years [12]. These results are consistent with the data from our previous studies of male population in Northern Tyumen [5]. We also noted redistribution in the "everyday smokers" — "occasional smokers" — "ex-smokers" — "non-smokers" groups over 5 years of 45–54-year-old males population monitoring. At the same time, in 45–54-year-old men, together with the decrease of occasional smokers percentage we observed the rise in heavy smoking prevalence. These negative changes in smoking intensity over 5 years are undoubtfully the result of massive tobacco advertising in 1996–2001 and the lack of anti-smoking propaganda.

All in all, combined approach to conventional and unconventional risk factors is necessary for creation of the most efficient prevention programs.

Conclusion

Follow-up has shown the reduction of smoking prevalence in adult active men over 15 years and the increase of smoking prevalence over 5 years. Follow-up was performed in the period of social and economic difficulties in Russia. Combined approach to behavioral and psychosocial risk factors is required for efficient smoking prevention programs.

Conflict of interest: None declared.

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Early prescription of trimetazidine in patients with acute coronary syndrome after incomplete myocardial revascularization: the assessment of the prognosis

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Abstract

Objective. *To assess the effectiveness of the early prescription of trimetazidine in patients with acute coronary syndrome (ACS) and established multivessel coronary artery disease syndrome after incomplete myocardial revascularization.*

Materials and methods. *This open-label randomized study included 100 patients with multivessel coronary artery disease syndrome. The randomization was blind into two equal groups: the study group (received 70 mg/day trimetazidine during the entire observation period) and the control group (did not receive trimetazidine). Echocardiography (EchoCG) was performed according to generally accepted technique on the ACUSON 128 XP 10 apparatus (USA) with the study of the following characteristics: left atrium and right ventricle anterior-posterior diameter, end-systolic and end-diastolic diameter of the left ventricle (LV), interventricular septal thickness, left ventricular (LV) posterior*

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wall thickness, end-systolic and end-diastolic volumes, as well as LV ejection fraction (EF) according to the Simpson method.

Results. *According to the results of EchoCG, mean LV EF was 50.72±6.89 % in the modified-release trimetazidine (trimetazidine- MR) group and 52.69± 7.5 % in the comparison group. In addition, significant changes in the Echo CG linear dimensions were diagnosed, and in 100 % of cases there were LV diastolic dysfunction of varying severity. Patients with ACS with early prescription of trimetazidine, required significantly fewer repeat myocardial revascularizations. According to statistical analysis, the Kaplan — Meier curves significantly diverged at the 12th month of study. Thus, the survival coefficient in actively treated patients was 0.72, and 0.54 — in the control group, the differences between groups were 18 % in favor of the trimetazidine-MR use.*

Conclusion. *Early prescription of trimetazidine-MR in patients with ACS and incomplete myocardial revascularization is associated with the decrease of cardiovascular complications during the first year of treatment, which should be considered as an important component of rehabilitation after endovascular intervention.*

Keywords: *trimetazidine-MR, acute coronary syndrome, incomplete myocardial revascularization.*

Conflict of interest: None declared.

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Introduction

Today cardiovascular complications (CVCs) are the main causes of death according to the statistics of the most countries including Russian Federation. Coronary heart disease (CHD) and many other atherosclerotic complications are still the leading causes of death and disability. Surgical treatment of coronary revascularization can improve the survival rate of patients with CHD and today are the primary treatment choice for patients with this pathology [1]. However, despite the improvement of the technology of invasive cardiology, there are still several unresolved issues in clinical practice, including the so-called incomplete revascularization. This approach is commonly observed in patients with acute coronary syndrome (ACS) and multivessel coronary artery disease, at the early stages of its onset, and is associated with the resumption of blood flow in the target artery. This type of revascularization has a number of advantages, but also has significant number of disadvantages, therefore, it has both supporters and opponents. The controversy about the effectiveness or ineffectiveness of incomplete revascularization can continue indefinitely, which will not make it easier for the clinical practitioners who will receive such patients for further treatment. Currently, these patients receive standard therapy, often independent of the degree of restoration of coronary blood flow. However, it should be noted that in this case, even in patients with pronounced positive clinical effect, areas of ischemic myocardial tissue still remain, therefore, additional pathogenetic medications should be considered. Pharmacological therapy prescribed for patients with CHD primary include symptomatic agents. For example, "metabolic" antianginal medication, the modified-release (MR) formulation of trimetazidine, that has been used for a long time in the complex therapy of CHD and showed its effectiveness [2]. Moreover, in recent years, the effect of trimetazidine-MR on cumulative survival rate and quality of life in patients with CHD has become the subject of separate study [3]. Therefore, studies evaluating the prognostic value of this medication in patients with CHD seem to be very relevant.

Objective

To assess the effectiveness of the early prescription of trimetazidine in patients with ACS, established multivessel coronary artery disease and incomplete revascularization.

Materials and methods

The study was conducted in accordance with Good Clinical Practice standards and Declaration of Helsinki principles. The study protocol was approved by the Ethics Committees of all participating clinical centers. Written informed consent was waived from all participants prior to the inclusion into the study.

This open randomized study included 100 patients with multivessel CHD that was defined as at least one hemodynamically significant stenosis (over 50 % in diameter) in at least two main arteries (anterior interventricular artery (AIA), right coronary artery, circumflex artery (CA) in patients with the right type of coronary circulation or AIA and CA — in patients with

the left type) and / or the presence of over 50 % stenosis of the main trunk of the left coronary artery. In all cases, ACS was identified, confirmed by the clinical picture, ECG data and/or significant increase of specific cardiac enzymes. Patients were divided into groups after percutaneous transluminal angioplasty (PTA) and stenting at least in 24 hours after the manifestation of symptoms.

The exclusion criteria were: the presence of concomitant diseases that could affect the final results, including decompensation of diabetes mellitus (DM), uncontrolled arterial hypertension (AH), kidney and liver diseases accompanied by the impaired function of these organs. The exclusion criterion was any planned surgical intervention (primarily cardiac surgery) within 4–6 months after the onset of ACS symptoms. The inclusion criterion was optimal pharmacological treatment.

Randomization was performed in blind manner into two equal groups: the study group (received 70 mg/day trimetazidine during the entire observation period) and the control group (did not receive trimetazidine). The follow-up period was 365 days. The clinical characteristics of the patients are presented in Table 1.

EchoCG was performed according to the generally accepted technique on the ACUSON 128 XP 10 apparatus (USA) and assessed the following parameters: anteroposterior dimension of the left atrium, right ventricle, end-systolic and end-diastolic dimensions of the left ventricle (LV), interventricular septal thickness, LV posterior wall, end-systolic and end-diastolic volumes and left ventricular ejection fraction (LV EF) according to Simpson's method.

Statistical analysis was performed using STATISTICA v.10.0, MS Excel 7.0 software. The normally distributed data were presented as M±m, where M is the mean, m is the standard error, the χ^2 criterion was used to assess the differences between the frequency of certain categorial variables between groups. The probability of adverse event was investigated using the Kaplan-Meier method; the differences between groups were assessed using the Log-Rank test, Breslow, and Taron-Ware tests. The following parameters were assessed in the long-term period: CVC frequency, death, myocardial infarction (MI), repeated interventions. The method of four-field table for case-control studies by Mantel — Haenzel was used to calculate the relative risk coefficient and 95 % confidence interval (CI).

Results

All study participants were divided into equal groups, 50 of them received 35 mg of trimetazidine-MR 2 times a day; 50 patients were included into the control group. The average age of patients from group 1 was 59.54±7.47 years, from group 2–60.36±7.05 years ($p>0.05$). The groups did not differ significantly by the main clinical data, including morphofunctional cardiac parameters (Tables 1, 2). According to the results of EchoCG, average LV EF was 50.72±6.89 % in the trimetazidine-MR group and 52.69±7.5 % in the comparison group. In addition, significant difference in the linear dimensions of the heart chambers were detected, and all the patients had LV diastolic dysfunction of various severity.

The groups included patients with unstable angina and acute myocardial infarction (AMI) with and with-

Table 1. **Initial clinical characteristics of the studied groups**

Parameter	Trimetazidine, n=50		Control, n=50		p
Age	59.32±7.71		59.84±7.3		0.896
The duration of CHD, years	3.2±1.6		2.9±1.9		0.224
Body mass index (kg/m^2)	23.7±2.2		22.9±2.5		0.894
Female gender	17	34 %	15	30 %	0.668
Male gender	43	86 %	45	90 %	0.538
The history of MI	8	16 %	7	14 %	0.701
The history of AH	23	46 %	27	54 %	0.322
Diabetes mellitus	4	8 %	5	10 %	0.175
Smoking	11	22 %	10	10 %	0.788
Statins	18	36 %	23	46 %	0.118
Aspirin	31	62 %	34	68 %	0, 554
ACE inhibitors	22	44 %	24	48 %	0.721
Calcium antagonists	11	22 %	13	26 %	0.483

Table 2. **The main clinical and instrumental parameters of patients with ACS included into the study**

Parameter	Trimetazidine, n=50		Control, n=50		χ^2	p
SBP (mmHg)	138.6± 7.4		141.7± 8.3		0.076	0.775
DBP (mmHg)	78.3± 9.0		77.4± 7.8		69	0.813
Average BP (mmHg)	104.5± 3.4		106.0± 2.7		0.048	0.917
HR (beats/min)	72.2± 4.9		76.1± 3.8		0.376	0.527
LV EF (%)	50.72± 6.89		52.69± 7.5		0.048	0.911
Unstable angina	11	22 %	10	20 %	0.060	0.806
Acute MI with ST-segment elevation	30	60 %	29	58 %	0.041	0.839
Acute MI without ST-segment elevation	9	18 %	11	22 %	0.250	0.617
Anterior MI	18	46.2 %	20	50 %	0.328	0.511
Posterior MI	21	53.9 %	20	50 %	0.367	0.532

Table 3. **The severity of CHD in study participants**

Parameter	Trimetazidine-MR, n=50		Control, n=50		χ^2	p
Killip class I acute heart failure	32	64 %	30	60 %	0.170	0.680
Killip class II acute heart failure	7	14 %	10	20 %	0.638	0.424
Killip class III–IV acute heart failure	0	0 %	0	0 %	—	—
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of two vessels	26	52 %	20	40 %	1.449	0.229
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of three vessels	13	26 %	18	36 %	1.169	0.280
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of more than three vessels	11	22 %	12	24 %	0.056	0.812

out ST-segment elevation. The groups were comparable by the frequency the pathology, and its severity. Acute heart failure (AHF) severity class 1 prevailed in patients with AMI, which was diagnosed in over 60 % of patients in each group; the rest of the patients had AHF severity class II. LV EF in group I: min. — 28 %, max. — 70 %, average — 50.72± 6.89 %. EF in group II: min. — 30 %, max. — 79 %, average — 53.62±7.51 %. According to coronary angiogram (CAG) data, hemodynamically significant stenoses (left coronary artery trunk> 50 %, other arteries>75 %) of two vessels were detected in most patients (Table 3).

Initially, 50 PTA with stenting and incomplete revascularization (mainly target coronary artery) were performed in both groups. During 1-year follow-up CAG was additionally required in 8 patients from in group I (16 %), in 18 (36 %) from group II (χ^2=5.19, p= 0.023). PTA was performed in 6 (12 %) patients from the main group and in 15 (30 %) — from the control group (χ^2= 4.88; p=0.027). As the result, patients with ACS with early prescription of trimetazidine, required significantly fewer repeat myocardial revascularizations. The use of sirolimus-eluting stents was comparable in both groups — in group I they were used in 3 (5.36 %) patients out of 56 (100 %), in group II — in 5 (7.69 %) out of 68 (100 %) (χ^2= 0.203, p= 0.653).

The surgical intervention with complete myocardial revascularization including coronary artery bypass grafting with *cardiopulmonary bypass machine* was required in 8 (16%) patients from the main group and in 7 (14%) patients from the control group (χ^2 = 0.460, p = 0.498). Repeated hospital admissions due

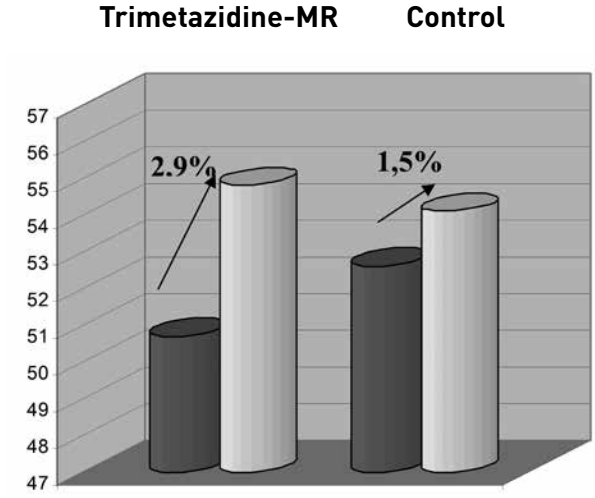

Figure 1. The dynamics of LV EF in study participants

to CHD decompensation were required in 9 (18%) patients from the main group, and in 21 (42%) patients from the control group (χ^2 = 3.673, p = 0.055). During the 12-month follow-up period, the LV EF increased in both groups, mostly in patients receiving trimetazidine (2.9% and 1.5%), but without statistically significant difference (Figure 1). The survival rate during admission was 100% in both groups. The incidence of MI also did not differ between groups – 6 (12%) patients from the main group and 11 (22%) – from the control group (χ^2 = 1.772, p = 0.183).

During the 12-month follow-up, we assessed the survival rate of patients after ACS without adverse events. The analysis was carried out by the Kaplan — Meier method. The observation period was set as the period from the beginning to the end of the follow-up or until the endpoint for each individual patient. The endpoints were: all-cause death, nonfatal MI, acute cerebrovascular accident, decompensation of angina pectoris, the need for cardiac surgery, any admission due to CVD.

According to statistical analysis, the Kaplan — Meier curves significantly diverged at the 12th month of observation. Thus, the coefficient of survival in patients during active treatment was 0.72, and in the control group — 0.54, the difference between the groups was 18 % with the superiority of trimetazidine-MR group (Fig. 2). The probability of error was assessed by the Log-Rank test p= 0.048, with RR — 0.61; 95 % CI 0.36–0.98 (p<0.05). Therefore, in our study, there was significantly lower frequency of CVC in patients with ACS who were administered with "metabolic" antianginal medication after PTA and stenting with incomplete revascularization.

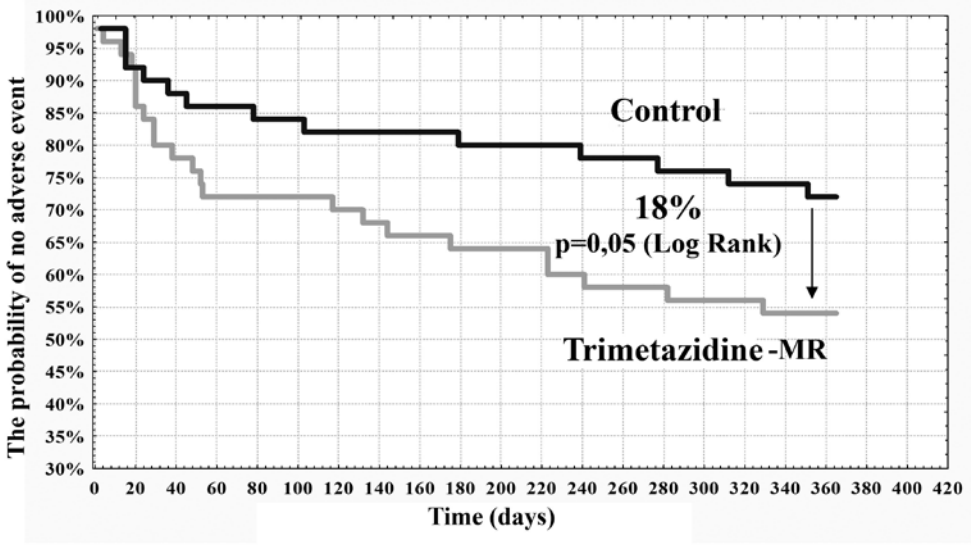

Figure 2. The probability of no adverse cardiovascular events in the study

Discussion

Anti-ischemic agent used in myocardial protection trimetazidine has been successfully used for a long time. Its high efficiency has been proven, but it is usually used as additional tool to enhance basic pharmacotherapy [4]. According to Russian guidelines for the diagnosis and treatment of stable CHD, trimetazidine-MR can be used at any stage of treatment to enhance the antianginal efficacy of hemodynamically active medications, as well as an alternative in case of their intolerance or the presence of contraindications for their use. Thus, the additional prescription of trimetazidine-MR to β-blockers leads to significantly more pronounced antianginal effect compared with the additional prescription of long-acting nitrate. Trimetazidin-MR increases the coronary flow reserve, prevents the consequences of ischemia, reduces the frequency of angina episodes, improves myocardial contractility and increases exercise tolerance in patients with CHD [5, 6]. The mechanism of trimetazidine-MR anti-ischemic effect is associated with the increase of glucose metabolism compared with the metabolism of fatty acids, with the suppression of fatty acid ß-oxidation and the increase of pyruvate oxidation — a glucose metabolite during the ischemia, and, therefore, it maintains of the required level of adenosine triphosphate in cardiomyocytes, decreases intracellular acidosis and excessive accumulation of calcium ions [7].

The use of trimetazidine in patients with ACS is being actively investigated. It is known that this medication can limit cardiac reperfusion injury and, accordingly, reduce myocardial hibernation processes, as well as the frequency of reperfusion arrhythmias [8]. In addition, the preventive use of this cytoprotector reduces the manifestations of transmural ischemia that develops during PTA, and can minimize ECG signs of reperfusion injury[9] and its severity, assessed by the levels of cardiac-specific biomarkers after coronary artery bypass graft surgery, and, therefore, positively affects the prognosis [10].

According to the " Consensus on the role and place of the myocardial cytoprotector Trimetazidine in the treatment of patients with chronic forms of CHD" [11], the use of this antianginal agent before surgical interventions (coronary artery bypass graft surgery, percutaneous coronary intervention) reduces the severity of myocardial injury, that is confirmed by the significant decrease of cardiac-specific biomarkers in the blood and the frequency of perioperative cardiac arrhythmias. Long-term therapy with trimetazidine after surgery has positive effect on the frequency of angina episodes and admissions due to ACS, significantly reduces the severity of myocardial ischemia, including silent myocardial ischemia, the rate of coronary artery restenosis, increases exercise tolerance, quality of life and, consequently, affects the survival rate of patients [12, 13].

Trimetazidine is the most studied "metabolic" antianginal medication. Several clinical studies have revealed the significant range its therapeutic mechanisms of action that are not limited only by its effect on cardiomyocytes. To this date, it is known that trimetazidine inhibits LV remodeling by the reduction of oxidative stress, apoptosis and inflammation, and affects the expression of endothelial nitric oxide synthase. It has been shown that trimetazidine can reduce inflammation in the arterial intima. At least two

clinical studies have shown the significant decrease of the serum C-reactive protein concentration during the therapy with this myocardial cytoprotector [14, 15].

Recently, very successful attempts have been made to study the effect of trimetazidine on the elastic properties of the large arteries. The preclinical trials have demonstrated positive effect of trimetazidine-MR on vascular endothelial cells in patients with arterial hypertension, including refractory hypertension, that reduces the severity of endothelial dysfunction. It has been shown that this effect is associated with intracellular signaling pathways, the intracellular calcium ions in particular, the activity of mitogen-activated protein kinases, the decrease of intracellular concentration of free radicals and the increase of the production of vascular endothelial growth factor [16]. Previously, we found that the use of 70 mg / day trimetazidine-MR for 4 months led to significant improvement of endothelium-dependent reactivity in the radial artery by over 32%, compared with the initial parameters. Improvement of the endothelial function developed along with the increase of the myocardial metabolic equivalent of oxygen uptake and the increase of exercise tolerance [17, 18].

The evaluation of the effect of metabolic antianginal therapy on the survival rate and quality of life in patients with cardiac pathology has been performed in number of studies. It should be noted that only one medication from this group, trimetazidine, has an impressive evidence base on its impact on cumulative survival. The METRO study showed that the early prescription of trimetazidine as antianginal therapy in patients with stable angina pectoris (before the development of myocardial infarction) significantly reduces the 6-month risk of death from ACS by 64% compared with other antianginal agents [19]. The KAMIR study included approximately 10 thousand patients with stable CHD with the history of myocardial infarction, and showed that the additional prescription of trimetazidine-MR to basic therapy during one-year follow-up increased survival rate by 69%, due to the decrease of cardiovascular events and mortality [2]. P. Di Napoliet al., according to 2-year follow-up, noted the increase of cumulative survival in patients with ischemic cardiomyopathy after the additional prescription of this myocardial cytoprotector to traditional therapy [3].

According to the results of the meta-analysis by D. Gao et al., that analyzed results of 4 studies, trimetazidine therapy was associated with lower mortality compared with placebo (7.5% of patients versus 27.5%, respectively). The reduction in the risk of death due to chronic heart failure was 0.29 with 95% CI 0.17–0.49 ($p<0.01$). Cardiovascular events and admissions significantly decreased — RR in the trimetazidine group was 0.42 with 95% CI 0.30–0.58 ($p<0.01$) [20]. Previously, we estimated the 6-year survival rate of patients with CHD and heart failure (LV EF less than 40%). The main endpoint in the active treatment group decreased by 15% ($p= 0.044$) with the 0.51 RR and 95% CI of 0.25–0.92 ($p<0.05$). The combined endpoint, that included all-cause mortality, the occurrence of nonfatal MI and stroke during entire observation period, decreased by 15.5% ($p= 0.025$) with RR 0.61 and 95% CI 0.97–0.35 ($p<0.05$) [4].

In this study we investigated the effect of early administration of the myocardial cytoprotector trimetazidine-MR in patients with ACS and incomplete revascularization after PTA and stenting. Currently, this method of blood flow partial restoration is used due to the number of reasons, including technical difficulties with complete revascularization (distal stenosis, the presence of extended occlusions, multivessel lesions in patients with ACS, etc.). Today, there are no clear recommendations for the management of patients after incomplete revascularization; in most cases, standard therapy is recommended after PTA and stenting that initially implies complete restoration of the blood flow. It should be noted that our study included patients with persistent myocardial ischemia. The additional prescription of trimetazidine to standard therapy led to the significant decrease of absolute risk of CVC by 18%.

Conclusion

Thus, early prescription of trimetazidine-MR in patients with ACS and incomplete revascularization is associated with the decrease of CVC during the first year of treatment, which should be considered as an important component of rehabilitation after endovascular intervention.

Conflict of interest: None declared.

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REVIEW ARTICLES

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Risk assessment for atrial fibrillation in metabolic syndrome depending on the primary prevention strategy

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Today, obesity in the form of metabolic syndrome (MS) and atrial fibrillation (AF) have reached epidemic proportions according to World Health Organization (WHO). AF is present in over 34 million people worldwide and this number is expected to double by 2060. In 25% of patients MS is associated with the development of AF. Although new treatment approaches have emerged over the last years, AF is still associated with an increased risk of complications such as systemic thromboembolism, congestive heart failure (CHF), stroke, myocardial infarction (MI) and other. Thus, AF poses both social and economic problem for healthcare in the most countries due to significant treatment expenses.

In the following review article we analyze the existing approaches to prevent AF in patients with MS depending on the initial risk of its development.

Keywords: *metabolic syndrome, primary prevention of atrial fibrillation*

Conflict of interest: none declared

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Introduction

Over the last years, the prevalence of obesity has reached the pandemic proportions: approximately 2 billion people are overweight, 650 million have abdominal obesity (AO) mostly associated with metabolic syndrome (MS) [1, 2]. In Russia, MS is present in 30 % of population [2]. MS is a leading cause of atrial fibrillation (AF) and includes the number of risk factors such as AO, arterial hypertension (AH), hyperglycemia and hyperlipidemia [2]. AF is the most common arrythmia in the clinical practice and is associated with the increased risk of mortality, stroke, and other complication [3]. Once it has developed, AF relapses in the majority of cases and eventually progresses from paroxysmal to persistent and then to permanent form [4]. There are many well-known AF risk factors such as obesity, AH, diabetes, heart defects, various clinical types of coronary artery disease (CAD), hyperthyroidism, alcohol use, OSA, electrolyte and/or vegetative dysregulation and other [4]. A surge of MS and AF prevalence has been registered in many countries and the number of AF cases is expected to rise from 8.8 million in 2010 to 17.9 million in 2060 [5]. Currently, MS causes around 35 % of AF cases [1, 2].

Therefore, identification of patients with MS at high risk of AF and the development of prevention approaches is one of the most relevant challenges of clinical cardiology today.

Metabolic syndrome, its components and atrial fibrillation

The main cause of MS is primary, genetically determined insulin resistance and hyperinsulinemia. The term "metabolic alteration" was first introduced by K. Jahnke et al (1969) and "metabolic syndrome" — by M. Hanefeld and W. Leoonardt (1981) when they combined various metabolic alterations in overweight patients [2]. In 1988 G. Reaven described insulin resistance as the cause of MS [2].

Currently the diagnosis of MS is based on the following main and additional criteria (metabolic syndrome is present if three or more of the following five criteria are met) [2]:

Main criterion: waist circumference over 94 cm (men) or 80 cm (women);

Additional criteria:

Blood pressure values of systolic 130 mmHg or higher and/or diastolic 85 mmHg or higher or normal blood pressure values achieved with antihypertensive drugs.

Elevated triglycerides>1.7 mmol/l; reduced high-density lipoprotein cholesterol (HDL)<1.0 mmol/l in men and<1.2 mmol/l in women; elevated low-density lipoprotein (LDL)> 3.0 mmol/l;

Elevated fasting glucose> 6.1 mmol/l.

Impaired glucose tolerance — plasma glucose 2 hours after glucose tolerance test>7.8 and< 11.1 mmol/l.

Pathophysiologic processes that lie behind the development of AF in MS patients is complicated and multifactorial. In most cases the increased body mass index (BMI) is associated with higher risk of arrythmia development [2, 3, 6]. A few studies have shown that the rise of BMI by 1 kg/m^2 from the baseline of more than 30 kg/m^2 is associated with 4 % rise of AF risk per year regardless of gender and presence of diabetes or AH [6, 7].

Individuals with MS were observed to have the "obesity paradox" that refers to lower mortality and lower prevalence of AF in patients with higher MBI [8]. Longitudinal prospective studies have shown lower lethality in overweight patients (BMI 25–29 kg/m^2) and in patients with AO (BMI 30–35 kg/m^2) with AF and other cardiovascular disease [7, 8, 9].

AO and high BMI in MS is associated with higher circulating blood volume, cardiac output and ejection fraction that leads to left ventricular (LV) hypertrophy and left atrial (LA) diastolic dysfunction and dilation [2, 3, 4]. Progressive LV hypertrophy and dysfunction can provide a substrate for the development of atrial fibrillation [4, 5, 10].

In patients with MS the risk of AF correlates with the growth of epicardial adipose tissue (EAT) including the LA EAT [11, 12]. The important physiologic functions of epi- and pericardial adipose tissue include thermoregulation, energy accumulation and mechanical protection as well as the parasympathetic regulation of cardiac function. [10–12]. Moreover, EAT produces many pro- and anti-inflammatory adipocytokins, growth factors and metabolic substrates and diffuse directly into the cardiac muscle [10–12]. In patients with MS and AF EAT contained more CD45+ (lymphocyte common antigen), CD3+ T-cells, CD68+ cells (dendritic cells marker), tumor necrosis factor α (TNF-α), IL-1β, IL-6, right atrial nuclear factor kappa B (NF-κB) compared with patients without arrythmias. Moreover, higher TNF-α and L-6 concentrations strongly correlated with fibrosis and atrial lymphomonocytic infiltration [13, 14]. Therefore, local EAT inflammation induced by immune cells and regulated by cytokines is one of the mechanisms of AF development in MS [13, 14].

Apart from inflammation, another important substrate for AF development is myocardial fibrosis in both atria (primarily in the posterior wall of LA) [3, 4, 6, 8] caused by inflammatory cytokines and growth factors such as activin A and matrix metalloproteinase [15, 16]. Activin A belongs to the TGF-β family and induces the expression of TGF-β1 and TGF-β2 [15, 16]. Experiments have shown that TGF-β1 caused atrial fibrosis and increased the risk of AF due to the re-entry waves [15–17].

Apart from AO, other MS components such as AH, diabetes, hyperlipidemia can increase the risk of AF due to fibrosis and structural remodeling of atrial myocardium that lead to the development of various electrophysiologic effects and AF [17].

AH is associated with increased activity of renin-angiotensin-aldosterone system, active aldosterone synthesis by adipocytes and the increase of BMI lead to the progressive LV dysfunction and LA dilation [15–17]. Hyperglycemia and hyperlipidemia in MS are associated with atrial hypertrophy and fibrosis that develop because of the effects of glycation products, TGF-ß, inflammatory cytokines and other metabolic substrates [15–17].

Of note is that the use of alcohol, coffee, smoking, OSA and atrial premature complexes (APCs) can cause LA fibrosis and increase the risk of AF in patients with MS [3, 4, 8].

Currently obstructive sleep apnoea (OSA) is one of the new predictors of AF in MS [18, 19]. Various clinical studies have shown that patients with MS and OSA are at a 4 times higher risk of AF development compared with the patients without respiratory problems during sleep [18, 19]. Similar results were shown in patients with MS who abuse alcohol, coffee, energy drinks, smoking compared with patients without these bad habits [17].

AF in MS due to OSA, overuse of coffee, alcohol, energy drinks and smoking is caused by several mechanisms. Firstly, hypoxia and hypercapnia at the end of apnoea episode leads to activation of the sympathoadrenal system and blood pressure elevation [18, 19]. Secondly, intensive inhaling at the end of apnoea episode increased intrathoracic pressure that led to LA overdistention [18, 19]. Thirdly, hypoxia, hypercapnia, and excessive parasympathetic stimulation due to the vagal activation shortened the effective refractory period and increased the dispersion of impulse conduction in the atria and AF development [18, 19]. Moreover, during the OSA episode pressure in the trachea became negative and that slowed the recovery of cardiac muscle refractoriness and increased AF induction [18, 19]. Lastly, alcohol, caffeine, nicotine, and energy drinks increased the activity of systemic inflammatory "oxidative stress" mediators in patients with MS that, apparently, caused the formation of fibrotic areas and AF [17–19].

However, the effects of OSA alone and in combination with other factors still require further exploration. Therefore, the degree of OSA effects on the development of arrythmia in MS still need to be determined.

Currently the mechanisms of AF development in MS still require further investigation [2, 3]. Lately the theory of AF development due to the diastolic calcium ions overload is being studied [16, 17]. Calcium ions overload initially results into oxidative stress and the appearance of areas with uneven impulse conduction and refractoriness and then — the activation of trigger mechanisms and/or re-entry and development of atrial ectopy [3, 16, 17]. APCs then act as drivers. They form rotors in the posterior LA wall and cause the formation of paroxysmal or persistent or permanent AF [3, 4]. Patients with MS and AF only rarely have the ectopic areas in atria and/or ectopic activity in pulmonary veins [3, 4].

Atrial fibrillation risk assessment in patients with metabolic syndrome

Currently, pulse palpation is recommended for timely diagnosis of AF in all patients, especially in those over 64 years of age. In patients with arrhythmic pulse ECG is performed [3]. However, this approach results in many false positives and increases the load on primary healthcare [20]. The use of automatic or semiautomatic tonometers with ECG registration can significantly reduce the number of false positives and improve AF diagnosis [20]. Lately, a high-risk group of AF development was established among patients over 65 with MS according to the CHA2DS2VASc thromboembolic events risk scale≥1 — in men and≥ 2 in women: these patients are recommended to perform everyday pulse measurements and check the rythm [20–22]. The frequency of AF diagnosis in patients with CHA2DS2VASc score 1–2, 5–6 and 9 was 10 %, 54 % и 71 %, respectively [21, 22].

In the recent years over 21 risk-stratification scales have been proposed for AF risk assessment in MS patients, including Framingham scales (1944–2014) [23]. Meta-analysis has shown that CHARGE-AF scale was most useful for predicting 5-year risk of the first AF episodes [24]. CHARGE-AF includes simple and

common values such as age, gender, anthropometric measures, blood pressure, etc. [23]. For AF risk assessment CHARGE-AF uses the following formula:

$$\text{RiskCHARGE-AF} = 1 - 0.9718412736^{\exp[(\Sigma(B_1,B_2,B_3,B_4,B_5,B_6,B_7,B_8,B_9,B_{10},B_{11}) - 12.5815600]},$$

Where RiskCHARGE-AF — AF risk according to CHARGE-AF (in units), B1-(age in years/5) ×0.5083; B2-ethnicity (Caucasian: 1x0.46491); B3 — (height in cm/10)×0.2478; B4 — (weight in kg/15) ×0.1155; B5 — (systolic blood pressure in mmHg.÷10)×0.1013, B7 — current smoking (1×0.35931), B8 — antihypertensive therapy(1×0.34889), B9 — diabetes(1×0.23666), B10 — history of myocardial infarction (1×0.49659). If the risk of AF was close to 1.0 according to CHARGE-AF, for example, 0.8 and more signified a high 5-year risk of AF. Of note is that in almost all patients with MS, especially in those over 60 years old, the risk of AF development was high according to CHARGE-AF [24]. Accuracy of 5-year prognosis was around 50 % [25].

In other studies, the risk of AF development was assessed using dynamic follow-up models [26, 27]. Based on the 10-year follow-up 1968 MS patients without arrythmias [26] and 1427 — with APCs but without AF prior to the study, were included [27]. According to the results, identification of AF predictors such as LA dilation, LVEF reduction, transmitral flow spectrum reduction, APCs etc after one examination of patients with BMI>30 kg/m^2 determined the presence of this potential risk factor but couldn't provide any time frame of AF development [26]. In turn, a specific time frame when AF can potentially develop, for example, in a patient with MS and APCs can be determined only with follow-up based on the risk index of AF [26, 27]. AF risk index can be calculated using the following formula: [(A÷B) × (C÷D)], where A — filtered P-wave duration in the atrial ECG (m/s), B-Pd (m/s), C — A — linear deviation of corrected preectopic interval (ms) for at least 20 atrial extrasystoles, D-number of atrial extrasystoles per hour [26, 27]. AF risk index is calculated several times with 1–3-month intervals. The development of AF is likely if the index values decrease compared to baseline [26, 27]. Specific time frame of AF development depends both on the baseline AF risk index values and the time during which it decreased to minimal levels when AF developed (0.01–0.02 units) [26, 27]. If the speed of AF risk index reduction is known, a specific time frame in which AF will develop in patients with MS can be easily calculated [26, 27]. The accuracy of certain time-period determination using the follow-up model is around 90 % [26, 27].

Therefore, the assessment of 5- or 10-year AF risk was based mostly on the retrospective analysis of various risk-stratifying models or prospective studies on relatively small samples of patients with MS [23, 26, 27]. Thus, apparently, larger multicenter prospective studies are required to increase the accuracy of predicting the first AF episodes and determine more specific time periods for these episodes (from several months to 1 year).

The choice of atrial fibrillation prevention strategy in patients with metabolic syndrome

All components of metabolic syndrome (AO, AH, hyperlipidemia, impaired glucose tolerance or diabetes) as well as overuse of alcohol, coffee, energy drinks, tobacco smoking, lack of physical activity, OSA and APCs can be classified as potentially modifiable AF risk factors.

Currently three strategies of AF prevention are being discussed [28, 29].

1) Modification of certain MS components are negative risk factors.

2) Complex lifestyle modification with all risk factor correction.

3) The use of antiarrhythmic agents to suppress APCs in patients with MS at a very high risk of AF development in several months to 1 year [28, 29].

Abdominal obesity. Reduction of waist circumference to normal measurements (<80 cm in women and<94 cm in men) and BMI to<25 kg/m^2 decreases the risk of AF by 18–20 % [28, 29]. In most cases, special diets and/or aerobic physical activity are used to reduce BMI. The most effective method of reducing BMI and waist circumference in MS patients was the use of Mediterranean diet [28, 29]. BMI reduction by>10 % in patients with MS was associated with better myocardial contractility, improved LV dysfunction and decreased LA volume and EAT mass [28, 29]. If BMI reduction attempt was unsuccessful in case of baseline BMI>30 kg/m^2 and the presence of all MS components in a patient adherent to regular physical activity, healthy diet etc surgery is the best approach [28, 29].

Controlling plasma glucose levels in patients with metabolic syndrome and diabetes. In patients with MS and diabetes controlling plasma glucose and Hba1c levels and was associated with AF risk reduction by 2.5–3 % [28, 29]. Hypoglycemic therapy of choice in

patients with MS and diabetes includes metformin, glucose-like peptide 1 agonists (liraglutide) or sodium-glucose linked transporter 2 inhibitors (empagliflozin) that normalize plasma glucose levels, help reduce BMI, EAT mass and inflammatory cytokine activity [28, 29]. Previous evidence has shown that the addition of these agents leads to additional AF risk reduction by 5 % or more [28, 29].

Blood pressure control. Reaching target blood pressure values<130/85 mmHg reduces the risk of AF by 20 % [28, 29]. The most effective antihypertensive agents were angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics and beta-blockers [28, 29]. Positive effects of blood pressure control are reversion of heart structural remodeling and improvement of LV dysfunction, LA volume and LV myocardium mass [28, 29].

Blood lipid control. Blood lipid control with statin use was associated with 5 % AF risk reduction in patients with metabolic syndrome; total cholesterol<3.5 mmol/l additionally reduced arrythmia risk by 5 % [28, 29].

Aerobic physical activity. Moderate or high intensity everyday physical activity for 60–90 minutes [28, 29] reduces BMI, waist circumference, LV dysfunction, LA volume and AF risk in patients with metabolic syndrome (additionally to weight loss) by 9–12 % (depending on the baseline BMI and physical activity intensity and duration) [28, 29]. Of note is that in patients with metabolic syndrome at high risk of AF (year after the exam) who used kinesiotherapy (walking speed modulation depending on the heart rate twice a day and more) for at least two hours a day reduced the risk of AF by 70 % compared with the use of first-line therapy (blood pressure, glucose, and lipid control) [28, 29].

Smoking in metabolic syndrome. Smoking cessation reduces the risk of AF by 10 % [28, 29].

Alcohol, coffee, energy drinks use in metabolic syndrome. Avoidance of alcohol, coffee and energy drinks wasn't associated with decreased AF risk in MS patients [28, 29]. The amount of alcohol that doesn't affect the risk of AF in metabolic syndrome is 10 grams of 96 % ethanol per day (equivalent to 60 ml of 40° alcoholic beverages, 240 ml of 9–12° red wine and 660 ml of beer) [28, 29]. Consumption of up to 436 mg of caffeine in coffee or tea per day or up to 660 ml of energy drinks per day didn't increase the risk of AF in metabolic syndrome [28, 29] (one cup of espresso from a coffee machine contains 65–75 mg of caffeine, latte — 30–35 mg, cappuccino — 30–35 mg, americano 80–85 mg, one tea bag — 30 mg for black tea and 25 mg for green teat) [28, 29].

Antioxidants, polyunsaturated fatty acids. Addition of various antioxidants, omega 3-6-9 polyunsaturated fatty acids didn't reduce the risk of AF in patients with metabolic syndrome [28, 29].

Obstructive sleep apnoea management in patients with metabolic syndrome. To alleviate the negative effects of OSA negative pressure continuous positive airway pressure (CPAP) is used. A CPAP machine uses a tube and a face mask to deliver constant and steady air pressure [28, 29]. However, preliminary evidence has shown that AF risk reduction is no more than 5 % [28, 29].

Managing atrial premature contractions in metabolic syndrome. In most cases APCs are considered to have favorable prognosis and don't require pharmacologic therapy except for symptomatic extrasystoles [3]. On the other hand, frequent, stable and/or relapsing APCs can increase the risk of AF because they create uneven electrical impulse conduction in atrial myocardium [26, 27]. Antiarrhythmic agents used in APCs in patients with metabolic syndrome are usually used in individuals at high and very high risk of AF, for example, in the next several months to a year [28, 29]. The studies that investigated the use of antiarrhythmics in APCs in MS for prevention of AF are limited, probably due to high risk of adverse effects of this therapy [29]. Control of APCs in MS reduced the risk of AF by 68 % compared with the use of therapies that control blood pressure, blood glucose and lipid levels [28, 29]. In the absence of pharmacologic therapy effects ablation can be performed [28, 29].

Anticoagulation for thromboembolism prevention in patients with metabolic syndrome at high risk of AF. The International Society on Thrombosis and Haemostasis (ISTH) recommend the use of anticoagulation in patients with metabolic syndrome for deep vein thrombosis, thromboembolic events, and stroke prevention. In patients with BMI⩽40 kg/m^2 or weight⩽120 kg direct oral anticoagulants are recommended (dabigatran, rivaroxaban, apixaban, warfarin); in those with higher values of BMI and weight — only warfarin [30]. AF risk determined by CHARGE-AF highly correlated with potential thromboembolism according to CHA(2)DS(2)-VASc [23]. Therefore, theoretically, 2 and more points according to CHA(2)DS(2)- VASc in patients with metabolic syndrome at high risk of AF can require anticoagulation (bleeding risk according to HAS-BLED [3] should be taken into consideration). Currently there are ongoing studies that investigate the use of anti-

coagulants in patients with MS depending on both the AF risk and thromboembolism risk, stroke. Rhythm abnormalities will be determined with continuous ECG monitoring with loop recorders [3].

Complex lifestyle modification in patients with metabolic syndrome. Complex approach to potentially modifiable AF risk factors and MS components can reduce the risk of AF by 50 % according to the results of retrospective studies [28, 29]. However, to assess the real AF risk reduction in patients with metabolic syndrome large prospective randomized studies are needed.

Conclusion

Over the last years the prevalence of atrial fibrillation has been rising steadily. Considering that AF is associated with a high risk of thromboembolic events and heart failure progression, primary prevention measures need to be developed.

Controlling the modifiable risk factors such as AO, AH, diabetes, impaired glucose tolerance, hyperlipidemia, OSA and others can reduce the risk of atrial fibrillation by 20 % if these risk factors are managed separately and by over 50 % is they are managed together. Therefore, following a healthy lifestyle starting from a young age, including healthy diet, physical activity, low alcohol intake and avoidance of smoking will be the mainstay of AF primary prevention in patients with metabolic syndrome.

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REVIEW ARTICLES

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Pathological and clinical aspects of angiotensin receptor-neprilysin inhibitor in patients with congestive heart failure with reduced ejection fraction

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The current review article discusses the results of randomized clinical trials of angiotensin receptor-neprilysin inhibitor (ARNI) in patients with congestive heart failure. We explore the pathophysiologic basis of ARNI use and its effects on prognosis in patients with various heart failure phenotypes. We present evidence that support earlier initiation of ARNI in patients with decompensated heart failure after hemodynamic stabilization. ARNI tolerance and approaches to dose titration is also discussed.

Keywords: *congestive heart failure, pharmacologic therapy, angiotensin receptor-neprilysin inhibitor*

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Pharmacologic management of congestive heart failure (CHF) is still a relevant issue worldwide. CHF prevalence in the Russian Federation is higher than in western countries and reaches 7% in the general population with lethality in symptomatic patients around 12%. Identification of CHF phenotypes allowed to choose more personalized therapeutic strategies in patients with HF with reduced ejection fraction (HfrEF) and HF with preserved ejection fraction (HFprEF). In 1980-90s the understanding of CHF pathophysiology changed when the role of neurohumoral theory of development and progression of heart failure was shown. Today, the main groups of pharmacologic agents that all patients with CHF should get provide their positive effects by blocking various components of renin–angiotensin–aldosterone system (RAAS). RAAS inhibitor protective effects have been mostly shown in patients with HFrEF [1]. Lately, a new agent, angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan, was developed. Human neutral endopeptidase (neprilysin) inhibition increases concentration of natriuretic peptides, bradykinin and adrenomedullin. There are several types of natriuretic peptides: Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and urodilatin. Natriuretic peptides are polypeptides that have different amino- and carboxyl-terminal ends. Of all the peptides, BNP has the highest clinical value. That is due to the way it is secreted and metabolized. Urodilatin has local or autocrine signaling effects and isn't secreted into the bloodstream. Urodilatin is synthesized in the renal distal tubules and doesn't affect sodium reabsorption. Another NP plasma concentration, CNP, is low and it's metabolized at a high rate. CNP production by the endothelium is increased by various cytokines, growth factors and tumor necrosis factors [2]. Unlike BNP, ANP is less stable in plasma and has slower gene transcription in the setting of chronic atrial distention. ANP accumulates in high concentrations inside the cell and can be rapidly secreted to regulate electrolyte balance in the setting of increased preload. In patients with chronic myocardial distention BNP production is increased. BNP precursor, pro-BNP, is synthesized in cardiomyocytes and in mature myocardial fibroblasts. Intracellular enzyme furin cleaves pro-BNP into active BNP and biologically inactive N-terminal pro b-type natriuretic peptide (NTproBNP). BNP molecule consists of 32 aminoacids, NTproBNP – 76. Half-life of these compounds is 20 minutes for BNP and 120 minutes for NTproBNP [3]. Therefore, for CHF exclusion and assessment of treatment effectiveness in diagnosed CHF it is recommended to measure the levels of BNP precursor NT-pro-BNP. The main effects of ANP/BNP are presented int the following table 1 [4, 5, 6, 7].

NP are degraded by a zinc-dependent protease metalloproteinase – neutral endopeptidase – nepri-

Table 1. **Main effects of type A and B natriuretic peptides**

Organ	Effect
Kidney	Stimulate sodium ions and water excretion, water-electrolyte balance support via: Inhibition of antinatriuretic factors (angiotensin, noradrenalin) and suppression of pathologic water and sodium ions reabsorption in proximal tubule. Vasopressin suppression and reduction of sodium and chloride reabsorption in the loop of Henle; Sodium channels inhibition, sodium pump activity reduction, blockade of vasopressin cAMP-dependent effects, stimulation of sodium secretion in the terminal nephron. Increase of glomerular filtration rate (GFR) by afferent arteriole dilation and efferent arteriole constriction and mesangial cells relaxation and the creation of a larger effective filtration surface area.
Microcirculation	Increased endothelial cell permeability. Water and albumin migration into interstitial place and the reduction of circulating blood volume. Increased postcapillary resistance and microvascular pressure.
Heart	Improvement of LV diastolic function both in healthy individuals and patients with CHF because of cGMP suppression and changes in calcium intracellular metabolism, end-systolic pressure and volume reduction and end-systolic myocardial elasticity improvement. Increase of heart rate and sinoatrial and interatrial impulse conduction via the effects on NRP-A and NRP-C receptors. Sympathetic activity suppression and vagal effects stimulation with positive chronotropic and bathmotropic effects. Fibroblast proliferative and functional activity suppression. Pathologic myocardial remodeling reduction.
Arteries	Sympathetic activity suppression and vasodilation, NO secretion stimulation, angiotensin II effects inhibition (more in aorta, kidney arteries, pulmonary arteries, epicardial coronary arteries). Suppression of smooth muscle cells growth and proliferation.
Veins	Venous relaxation more prominent than arterial. Effects achieved at higher concentrations seen in CHF.
RAAS	Renin, angiotensin II and aldosterone antagonism
The autonomic nervous system (ANS)	Sympathetic nervous system antagonism (studied mostly for ANP)
Lipids and carbohydrate metabolism	Activate lipolysis. Reduce insulin resistance. Stimulate white adipose tissue conversion to brown adipose tissue. Affect insulin secretion via ATP-dependent potassium channels.

lysin, NEP). NEP is also involved in degradation of other vasoactive peptides such as ATI, ATII, endothelin 1, glucagon, enkephalins, oxytocin and bradykinin. Moreover, NEP degrades beta-amyloid and is the marker of various malignancies. Therefore, inhibition of NP degradation combined with ACEi positive effects resulted into the development of pharmacologic agents with double effect – vasopeptidase inhibitors. However, they haven't met all the expectations. Positive effects of omapatrilat in CHF patients were decreased by frequent angioedema cases [8-11]. Then, a new two-component molecule was developed, that consisted of NEP inhibitor neprilysin and ARB valsartan. This component choice was determined by the potential induction of clinical effects and angioedema risk reduction. PARADIGM-HF trial published in September 2014 has shown that 200 mg of sacubitril/valsartan twice per day was more effective in patients with NYHA class II-IV HFrEF compared with enalapril 10 mg twice per day (inclusion criteria: HFrEF, LVEF≤ 35 %). At randomization over 90% of patients were taking beta-blockers and only around 55% - mineralocorticoid receptor antagonists (MRA) (54.2% in treatment group and 57% in control group), 80% were taking diuretics. Patients were included in the trial if screening revealed NT-proBNP≥ 600 pg/mL or ≥ 400 pg/mL in patients who were previously hospitalized for CHF over the past 12 months. The trial included totally 10 513, 9419 were randomized, of those, 34% had concomitant diabetes. Most participants (around 70%) were classified as class II HF. Median follow-up time was 27 months. The trial was ended early because of obvious beneficial effects of sacubitril/valsartan. The main results of this trial are summarized in table 2 [12].

According to table 2, the use of sacubitril/valsartan was associated with statistically significant cardiovascular mortality reduction, hospitalization for CHF exacerbation and all-cause mortality compared with enalapril. Patients in sacubitril/valsartan group also had better quality of life 8 months after discharge. The review of Kansas City Cardiomyopathy Questionnaire (KCCQ) has shown that the standard deviation has decreased by 2.99±0.36 in sacubitril/valsartan group compared with 4.63±0.36 in the control group (p<0.001).

Drug tolerance was similar to enalapril. Although patients in sacubitril/valsartan group developed arterial hypotension more frequently (14%) compared with enalapril (9.2%), it didn't result in them stopping treatment or in any alterations of kidney perfusion. On the contrary, enalapril use was more often associated with kidney dysfunction and higher creatinine levels and was therefore stopped. PARADIGM-HF authors have concluded that neprilysin inhibitors combined with ARBs were more effective in patients with HFrEF compared with ACEi enalapril [12]. Later, in august 2018, the results of TRANSITION study that included 1124 patients (1002 were randomized) with HFrEF (LVEF 29%) were presented at the European Society of Cardiology congress; mean age was 67 years. More than a half of all patients had NYHA class II HF. The study has shown that earlier start of sacubitril/valsartan after CHF exacerbation in a still hospitalized patient was as effective and safe as sacubitril/valsartan initiation in the two weeks after discharge. More than 86% of patients from in-hospital treatment group continued the use of sacubitril/valsartan for up to 10 weeks and 45% of them reached target dose of 200 mg twice a day. Similar results were showed in the group where sacubitril/valsartan was started later during outpatient treatment – 88.8% (p=0.262) continued to use the drug until the end of the study and in 50.4% (p=0.092) target doses were reached. Sacubitril/valsartan was well tolerated. Hyperglycemia and hypotension happened in 0.6% and 0.8% of patients, respectively, in the group of early drug use and in 0.4% (p=0.1) and 0.4% (p=0.6866) of patients who started

Table 2. **PARADIGM-HF results**

Parameter	sacubitril/valsartan n=4187		enalapril n=4212		Relative risk (RR) (95 % confidence interval)	p
	Absolute values	%	Absolute values	%		
Primary composite outcome						
Cardiovascular death or first hospitalization for CHF exacerbation	914	21.8	1117	26.5	0.80 (0.73-0.87)	< 0.001
Cardiovascular death	558	13.3	693	16.5	0.80 (0.71-0.89)	< 0.001
First hospitalization for CHF exacerbation	537	12.8	658	15.6	0.79 (0.71-0.89)	< 0.001
Secondary outcome						
Death from any cause	711	17	835	19.8	0.84 (0.76-0.93)	< 0.001

to take sacubitril/valsartan during outpatient management [13]. Similar results were reported in the PIONEER-HF study that was presented at the 2018 American heart association congress [14]. Patients with LVEF≤40 %, signs and symptoms of CHF decompensation, SBP≥100 mmHg over the past 6 hours in the absence of symptomatic hypotension and the use of intravenous vasodilators in the past 6 hours and intravenous inotropic agents in the 24 hours before randomization. One of the inclusion criteria was an increased level of NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL. Most patients had a history of arterial hypertension: 87.3% in sacubitril/valsartan group and 83.7% in enalapril group; 6.1% of patients in sacubitril/valsartan group and 7.9% of patients in the control group had a history of myocardial infarction. Diabetes was present in 18% of patients in the treatment group and in 20.2% in enalapril group; chronic kidney disease – in 29.5% of patients in the treatment group and in 27.2% of patients in control group). Follow-up period was 8 weeks. Mean NT-proBNP values at different follow-up periods are presented in Table 3 [15].

According to the Table 3, use of sacubitril/valsartan during the 1st week resulted in a significant reduction of NT-proBNP, which means that early administration of this agent is associated with more positive effects in hospitalized patients. By the end on the trial the levels of NT-proBNP have reduced by 46.7%. The ratio of mean NT-proBNP levels taken on the 4th and 8th weeks and baseline values were 0.53 in sacubitril/valsartan group and 0.75 in enalapril group (difference ratio was 0.71; 0.95% CI 0.63-0.81; p<0.001). The use of sacubitril/valsartan was associated with 46% (RR 0.54, 95% CI 0.37-0.79; p=0.001) reduction of composite outcome risk (composite outcome included cardiovascular death or the hospitalization for CHF exacerbation, ventricular assist device implantation, getting on heart transplant waiting list, intravenous diuretics requirement, increase of diuretics dose by more than 50%, the need of additional medications for CHF). Lower risk of composite outcome in sacubitril-valsartan group was primarily due to significantly lower frequency of repeated hospitalizations for CHF – 35 (8%) versus 61 (13.8%). In sacubitril/valsartan group, 51 patient (11.5) left the trial early due to adverse effects of the medication, in enalapril group – 45 (10.1%), mainly because of symptomatic hypotension (11 patients in each group), acute kidney injury (6 patients in control group and 3 patients in the treatment group), hyperkalemia (4 patients in enalapril group and 2 patients in the treatment group), angioedema (6 patients in enalapril group). During 8-week treatment the frequency of adverse events was similar in both groups. More patients in sacubitril/valsartan group developed hyperkalemia (51 – 11.6% versus 41 – 9.3% in enalapril group, RR 1.25; 95% CI 0.84-1.84) and symptomatic hypotension (66 – 15.0% patients versus 56 (12.7%) patients in enalapril group); RR-1.18; 95% CI 0.85-1.64). However, more patients in enalapril group had worsening renal function (65 – 14.7% versus 60-13.6%, RR 0.93, 95% CI 0.67-1.28) and angioedema (6 (1.4%) versus 1 (0.2%), RR 0.17; 95% CI 0.02-1.38) [13, 14]. Results of the PIONEER-HF trial show that earlier initiation of ARNI in patients with decompensated heart failure after hemodynamic stabilization is beneficial. Evidence suggest that sacubitril/valsartan should be used in patients with HFrEF instead of ACEi/ARBs who are symptomatic despite receiving ACEi/ARBs, beta-blockers and MRA to reduce mortality and repeated hospitalizations for CHF. Initial recommended dose of sacubitril/valsartan is 24/26 mg twice a day after hemodynamic stabilization. Therapy should be initiated after at least 36 hours after the last dose of ACEi in starting dose 49/51 mg twice per day if SBP 120 and higher and 24/26 mg twice per day if SBP 100 mmHg and higher but less than 120 mmHg with weekly titration to target dose of 97/103 mg twice per day depending on SBP [14, 15]. Less promising results of sacubitril/valsartan use were received in patients with HFprEF. The PARAGON-HF trial included 4822 patients with class II-IV HFprEF (EF>45%). Mean follow-up period was 57 months. Patients in the control group received valsartan (target dose 160 mg twice per day). Although

Table 3. **Mean NT-proBNP values in the PIONEER-HF trial**

Follow-up periods	Study groups					
	Sacubitril/valsartan			Enalapril		
	n, number of patients	Mean values, pg/mL	CI	n, number of patients	Mean values, pg/mL	CI
Baseline	397	2972	(2700, 3273)	394	2536	(2306, 2788)
1 week	366	1704	(1525, 1903)	368	1944	(1747, 2164)
2 week	373	1733	(1540, 1951)	361	2028	(1819, 2261)
4 week	372	1546	(1368, 1746)	358	1982	(1769, 2221)
8 week	358	1232	(1076, 1411)	356	1595	(1406, 1810)

by the end of the trial sacubitril/valsartan (target dose 97/103 mg twice per day) reduced the risk of primary composite outcome (cardiovascular death, hospitalization for CHF) by 13% (RR 0.87; 95% CI 0.75-1.01; p=0.06), these results were not statistically significant. NYHA class improved in15.0% of patients in sacubitril/valsartan group and in 12.6% of patients in valsartan group (RR 1.45; 95% CI 1.13-1.86). More patients from sacubitril/valsartan group developed hypotension and angioedema. However, frequency of treatment discontinuation due to adverse effects was similar in both groups and rare cases of angioedema didn't result into respiratory obstruction or death. Renal function worsened in 1.4% of patients in sacubitril/valsartan group and in 2.7% of patients in control group (RR 0.5: 95% CI 0.33-0.77). More patients taking valsartan developed hyperkalemia. Result analysis in 12 subgroups of patients has shown that sacubitril/valsartan was more effective in women and in patients with lower LVEF. Risk reduction of primary composite outcome in the subgroup with LVEF≤57% was 22% (RR 0.78; 95% CI 0.64-0.95) and in women 27% (RR 0.73; 95% CI 0.59-0.90). Sacubitril/valsartan beneficial effects were due to decreased frewuency of repeated CHF hospitalizations. Positive changes in NYHA class and kidney function were similar in both men and women taking sacubitril/valsartan. At the same time, life quality improved more in men than in women according to the KCCQ scal. Frequency of adverse effects were similar in both groups [16, 17].

To conclude, sacubitril/valsartan introduction has widened the abilities of pharmacologic HFrEF treatment. Sacubitril/valsartan should be initiated as early as possible after the patient was hemodynamically stabilized. Blood pressure, creatinine, electrolytes should be regularly controlled. In hypotensive parties sacubitril/valsartan should be titrated from 24/26 mg twice per day.

Conflict of interest: none declared.

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European Society of Cardiology Congress 2021 Highlights

In the current review we present the highlights of European Society of Cardiology Virtual Congress 2021. This year 4 updates guidelines were presented. We analyzed the results of 20 international clinical trials that investigated effectiveness and safety of pharmacologic agents and medical devices in patients with various cardiovascular disease.

Keywords: *congress, clinical guidelines, international trials.*

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European Society of Cardiology (ESC) Virtual Congress was held on August 27–30, 2021. Over 39 thousand ESC members from 169 countries took part in the Congress.

4 new clinical practice guidelines were presented:

- CVD Prevention
- Cardiac Pacing
- Valvular Heart Disease
- Heart Failure

Full texts are available at www.escardio.org/Clinical Practice Guidelines.

Hot Line sessions, where the primary endpoints of novel clinical trials are presented, were, as always, the most interesting parts of the Congress. This year, 19 new randomized studies were presented over 4 days.

GUIDE-HF: Haemodynamic-guided management of heart failure did not result in a lower composite endpoint rate of mortality and total heart failure events compared with the control group at 12 months irrespective of ejection fraction. COVID-19 pandemic could've affected the results.

EMPEROR-Preserved Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. These results make empagliflozin the first agent that improves the prognosis in patients with HF with preserved EF.

EMPEROR-Pooled. Pooled analysis of two randomised trials has demonstrated that empagliflozin reduced the risk of heart failure hospitalisation by about 30% in patients with heart failure with a reduced and preserved ejection fraction. The magnitude of the effect on heart failure hospitalisations was similar across a broad range of ejection fractions below 65%.

SMART-MI–ICMs. Implantable cardiac monitors in high-risk, postinfarction patients with cardiac autonomic dysfunction and moderately reduced left ventricular ejection fraction remote monitoring of implantable cardiac monitors (ICM) was effective in early detection atrial fibrillation, higher degree atrioventricular block, fast non-sustained ventricular tachycardia and sustained ventricular tachycardia/ventricular fibrillation.

MASTER-DAPT. Among patients with high bleeding risk who underwent percutaneous coronary intervention (PCI) with a biodegradable-polymer sirolimus-eluting stent abbreviated DAPT was noninferior to standard DAPT regarding net adverse clinical events and major adverse cardiac or cerebral events.

Abbreviated DAPT was superior to standard antiplatelet therapy regarding major or clinically relevant nonmajor bleeding.

ENVISAGE-TAVI AF. Edoxaban is noninferior to vitamin K antagonists (VKAs) for efficacy (the primary efficacy outcome, all-cause mortality, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding) but did not meet criteria for noninferiority for bleeding (bleeding events, primarily gastrointestinal bleeding events, were higher). among patients undergoing transcatheter aortic valve replacement (TAVR) with AF.

FIGARO-DKD. Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes (the primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) in patients with stage 1–4 chronic kidney disease (CKD) with moderate to severe albuminuria. These effects were primarily due to reduced risk of hospitalization for HF.

FIDELITY. FIDELITY was a meta-analysis combining individual patient data from FIDELIO-DKD and FIGARO-DKD. The FIDELITY analysis demonstrates that finerenone reduced the risk of cardiovascular and kidney outcomes compared with placebo across the spectrum of chronic kidney disease in patients with type 2 diabetes.

APAF-CRT. Atrioventricular junction ablation plus cardiac resynchronization therapy was superior to pharmacological therapy in reducing mortality in patients with permanent atrial fibrillation and narrow QRS (≤110 ms) who were hospitalized for HF, irrespective of their baseline EF.

DECAAF II. Image-guided fibrosis ablation in addition to pulmonary vein isolation (PVI) does not improve ablation success rates compared to PVI alone in patients with persistent atrial fibrillation (AF). There was a significant benefit of substrate ablation in patients with stage I or II fibrosis at baseline but no benefit of image-guided fibrosis ablation on atrial arrhythmia recurrence in patients with stage III or IV stage fibrosis at baseline.

TOMAHAWK. Early coronary angiography in out-of-hospital cardiac arrest (OHCA) patients without ST-segment elevation is not superior to a delayed/selective approach for all-cause mortality at 30 days.

RIPCORD 2. Adding systematic fractional flow reserve (FFR) assessment to coronary angiography did not reduce costs, improve quality of life, or reduce major adverse cardiac events or revascularization rates vs. angiography alone in patients undergoing diagnostic coronary angiography for stable angina or non-STEMI. Additional assessment increased the risks due to longer procedures, more contrast and radiation use.

ACST-2. Patients with severe unilateral or bilateral carotid artery stenosis underwent carotid artery stenting (CAS) or carotid endarterectomy (CEA). Patients were followed up for a mean 5 years. The risks of non-procedural stroke, lethal stroke or disabling stroke were similarly uncommon after competent CAS and CEA.

LOOP. In those patients undergoing electrocardiogram (ECG) monitoring using an implantable loop recorder atrial fibrillation was 3-times more frequently detected and treated with anticoagulation. However, it didn't reduce the risk of stroke or systemic arterial embolism in patients at risk.

SSaS. Replacing salt with salt substitute (about 75% sodium chloride and 25% potassium chloride) lowers the risk of stroke in people over 60 years old in 600 villages in rural areas of five provinces in China with high blood pressure or prior stroke.

IAMI. Influenza vaccination reduces the risk of all-cause death, myocardial infarction, or stent thrombosis at 12 months in hospitalised patients with myocardial infarction or high-risk coronary disease.

PRONOUNCE. Among patients with prostate cancer and concomitant atherosclerotic cardiovascular disease taking GnRH antagonist degarelix or the GnRH agonist leuprolidethere there was no difference in the time to first occurrence of a major adverse cardiovascular event (MACE), defined as a composite of death, myocardial infarction, or stroke through 12 months.

STEP. Aggressive blood pressure treatment (SBP target below 130 mmHg but no lower than 110 mmHg) in older hypertensive patients lowers the incidence of cardiovascular events he (acute coronary syndrome, stroke, acute decompensated heart failure, coronary revascularisation, atrial fibrillation, or death from cardiovascular causes) compared to standard therapy (SBP target 130–150 mmHg) without increasing adverse outcomes. Rates of serious adverse events and renal outcomes did not differ between the two groups except hypotension.

AMULET IDE. The Amplatzer Amulet Left Atrial Appendage Occluder has shown superior left atrial appendage (LAA) closure and noninferior safety (procedure-related complications, all-cause death, or major bleeding through 12 months) and effectiveness (reduced risk of ischaemic stroke or systemic embo-

lism through 18 months) in patients with non-valvular atrial fibrillation (NVAF) compared to the Watchman device.

STOPDAPT-2. Among patients with ACS undergoing percutaneous coronary intervention (PCI) the use of one month of dual antiplatelet therapy (DAPT) and subsequent clopidogrel there was a trend toward an increase in cardiovascular events despite a reduction in major bleeding events compared with standard 12 months of DAPT with aspirin and clopidogrel. One-month DAPT and subsequent clopidogrel monotherapy failed to achieve noninferiority for net clinical benefit compared with standard 12-month DAPT after ACS.

The next ESC congress will be held in Barcelona, Spain on August 26–29, 2022.

All references can be found at https://www.escardio.org.

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Journal of the Cardioprogress Foundation

Author Guidelines

MANUSCRIPT PUBLICATION RULES IN THE INTERNATIONAL HEART AND VASCULAR DISEASE JOURNAL

Disclaimer: Edition of rules come into force since November, 2018. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4.500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2.500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file "letter (cover)":

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

"Directional (cover) letter" is scanned. File format. jpeg attached as an additional file of the manuscript.

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

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1. **Any of the authors can submit an article to the journal.** Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

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4. The order of the authors. Authors ' priority should be entered into the system in accordance with the order of the article. The movements are made by small arrows "top" / "bottom", which are located under the data of each of the authors. The data of the author responsible for the correspondence, put a dot in a circle denoting this information. Other authors point do not put.

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7. Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In

the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

1. Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A. V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

2. Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

3. Information on conflict of interest / funding.

The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: "Conflict of interest is not declared." Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

4. Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

5. Information and ethics in the study.

Example of design:

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

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

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Obtaining consent from patients for the study should also be reflected in the Material and methods.

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.

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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
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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.

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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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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.

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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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