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Journal of the Cardioprogress Foundation

The role of cardiovascular diseases in the development of Alzheimer's disease and cognitive impairment, including COVID-19

The role of cardiac adipose tissue depots in assessing the risk of paroxysmal atrial fibrillation in patients with coronary heart disease and arterial hypertension

Ventricular arrhythmias and prevention of sudden cardiac death

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International Heart and Vascular Disease Journal

Journal of the «Cardioprogress» Foundation

Volume 11, № 38, June 2023

Contents

Editor's Welcome

Dear colleagues!

We present to your attention the next, thirty-eighth issue of the International Heart and Vascular Disease Journal that includes the leading, original and review articles.

The "leading article" section opens with a paperwork that presents data on the relationship between Alzheimer's disease and cardiovascular diseases. Early manifestations of Alzheimer's disease are cognitive impairments, which in real clinical practice are first encountered by primary care physicians. Older age and co-morbidities are important risk factors. A large increase of cognitive and psycho-emotional disorders was observed after COVID-19.

The "Original Articles" section presents three publications. The first article analyses the role of cardiac adipose tissue depots in predicting the risk of paroxysmal atrial fibrillation in patients with CHD. Epicardial fat thickness and interatrial septal thickness, in combination with waist circumference measurements, may serve as prognostic criteria for the risk of atrial fibrillation in men with CHD. In the second article, the authors compare the prognostic significance of complications according to the short-term scales in patients with Non-ST-elevation acute coronary syndrome without percutaneous coronary intervention. The study, which included 122 patients, recommended the use of the GRACE scale among 5 scales to assess the prognostic significance of short-term complications, regardless of the adverse outcome type. The third article investigates morphological changes indicating that postinfarction tissue participates in cardiac repair. Heart biopsy specimens from 35 patients who died following acute myocardial infarction or unnatural death (car accident) and showed large foci of postinfarction tissue were analysed. According to the authors, myocardial infarction is a compensatory and adaptive process aimed at correcting the anatomical and physiological discrepancy between the hypertrophied myocardium and the state of the coronary vessels affected by the atherosclerotic process arising during postnatal ontogenesis.

The "Review Articles" section presents two works. The article by Moscow experts highlights the rational of antiplatelet drugs in the novel coronavirus infection using acetylsalicylic acid as an example. The severe course of COVID-19 is associated not only with the development of inflammatory alveolar lesions, but also with endothelial dysfunction leading to micro- and macrothrombosis in the vascular bed. Platelet activation is also involved in the pathogenesis of thrombotic complications, and the use of antiplatelet agents in COVID-19 is justified. The second article is based on the updated European recommendations for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Modern insights into genetics, imaging and the large body of clinical data for risk stratification of ventricular arrhythmias and sudden cardiac death, as well as advances in diagnostic evaluation and therapeutic strategies, have contributed to the revision of previous recommendations.

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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International medical review

Specialists from medical centres in the US, Canada and Europe evaluated the effectiveness of transcatheter aortic valve repair for tricuspid regurgitation.

The study involved 350 patients with severe tricuspid regurgitation. They were divided into two groups: the first group underwent transcatheter edge-to-edge tricuspid valve repair (TEER) and the second group received drug therapy.

Patients who underwent transcatheter repair had a 48% lower risk of adverse outcomes than those who received drug therapy.

According to the MEJM journal

Researchers have determined the optimal level of systolic blood pressure that should be maintained in patients with type 2 diabetes to reduce the risk of cardiovascular disease (CVD).

The researchers registered 7.799 major cardiovascular events and 4.130 CVD-related deaths. The average systolic blood pressure level achieved after taking antihypertensive medication ranged from 117 to 144 mmHg, and the researchers found that a reduction in all-cause mortality was already achieved when systolic blood pressure levels were below 140 mmHg, with no additional benefit from further reduction.

According to the Hypertension journal

Researchers from the Southern Medical University in China studied the effect of phone calls on the incidence of hypertension.

Mobile phone users were 7% more likely to develop high blood pressure than non-users. Participants who talked on their mobile phones for 30 minutes or more per week were 12% more likely to develop high blood pressure than those who spent less time on the phone.

Participants who used a mobile phone to make or receive calls at least once a week were considered mobile phone users. The average age of the participants was 64 years.

According to the European Heart Journal

A study by the US researchers has shown that depression during pregnancy increases the likelihood of cardiovascular disease after childbirth.

The presence of antenatal depression increased the risk of coronary heart disease among all participants by 83%, and arrhythmia or cardiac arrest by 60%. It also increased the likelihood of cardiomyopathy by 61% and arterial hypertension by 32%.

Participants without hypertensive disorders during pregnancy were 84% more likely to develop CHD, 42% more likely to have a stroke, and 85% more likely to have an arrhythmia or cardiac arrest.

According to the JAHA journal

According to the researchers, the risk of ischaemic stroke and major circulatory embolism appeared to be increased in women with atrial fibrillation (AF) who were vaccinated against COVID-19. A similar association was not confirmed in men. Vaccination had no effect on bleeding development.

At the same time, an increased risk of ischaemic stroke or systemic embolism after COVID-19 was observed in this population in both women (17.42-fold) and men (6.63-fold).

Given the increased risk of these complications after COVID-19, prophylactic vaccination is recommended for patients with atrial fibrillation.

According to the European Heart Journal

A group of researchers has found that the continuation of beta-blockers for more than one year after a myocardial infarction (MI) in patients without heart failure or left ventricular systolic dysfunction does not improve cardiovascular outcomes.

The analysis showed that the odds of cardiovascular complications and death were similar between participants who continued to take beta-blockers and those who did not during the 4.5 years of follow-up (adjusted odds ratio was 0.99).

The study included 43.618 patients who had myocardial infarction, with or without ST elevation, between 2005 and 2016.

According to the Heart journal

The researchers assessed the outcomes of intensive drug-assisted blood pressure lowering treatment in older adults admitted to hospital for different conditions, except for cardiovascular disease

Intensive hypotensive therapy raised the likelihood of all negative outcomes by 28%. Meanwhile, intravenous hypotensive drugs augmented this likelihood by 90%.

Data from 66.140 elderly patients hospitalized with non-cardiac conditions who had an increased blood pressure during the first two days of hospitalization were analysed. The participants had an average age of 74 years.

The researchers highlighted that the results do not suggest a requirement for intense reduction in blood pressure for elderly patients after the hospitalization. Additionally, the results indicate a necessity for further research to establish revised target blood pressure levels in these cases.

According to the Circulation journal

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The role of cardiovascular diseases in the development of Alzheimer's disease and cognitive impairment, including COVID-19

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Abstract

Alzheimer's disease (AD) is a complex neurological disease with a long latency period, which belongs to the group of neurodegenerative diseases. It is the most common neurogeriatric pathology that is characterized by the accumulation of beta-amyloid protein in the form of amyloid plaques and Tau protein (pTau) forming neurofibrillary glomeruli (NFG) in the neuronal bodies due to genetic factors.

However, cardiovascular diseases (CVD), including arterial hypertension (AH), has been found to be a significant risk factor. Early manifestations of AD include cognitive impairment (CI), which in real clinical practice is first encountered by primary care physicians: general practitioners, internists, cardiologists, neurologists. In addition, due to the COVID pandemic the number of patients with AD has significantly increased. CI is the most frequent neurological complication in the post-covid period, therefore, its timely diagnosis and correction will allow to slow down the progression of AD.

Key words: Alzheimer's disease, cognitive impairment, arterial hypertension, COVID-19, cholinesterase inhibitors, neuroprotective therapy.

Conflict of interest: none declared.

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Alzheimer's disease (AD) is a neurological, incurable, degenerative (atrophic) disease of the brain that manifests itself as a rapidly progressive decline in a person's cognitive and intellectual abilities. The disease was first described in 1906 by Alois Alzheimer, a professor of neurology and psychiatry from Frankfurt. It was subsequently named after him.

As life expectancy increases, the number of people suffering from CI and dementia is rising. According to World Health Organization (WHO) experts, Alzheimer's disease is the most common cause of dementia in old age and accounting for 50 % of all dementia cases in people over the age of 80. The WHO recognises Alzheimer's disease as one of the 4 major medical and social problems of modern society. It is the 6th leading cause of death worldwide (3rd in economically developed countries), and the number of deaths is increasing. According to the WHO, 46.8 million people had dementia in 2015, and this number is expected to triple by 2050. Caring for people with Alzheimer's disease is economically very costly, with global expenditure on dementia-related interventions totalling $818 billion in 2015, of which 85 % was spent on social and family costs rather than medical care. AD could lead to a global health and social care crisis in the next 20 years [1, 2]. Therefore, the issues of early diagnosis of this pathology and the search for optimal and timely treatment are very relevant.

It has been established that hereditary cases of Alzheimer's account for about 1 %, the remaining cases are sporadic: 13 % — in people over 65 years of age; 50 % — over 80 years of age.

In Russia, 1.4 million (4.5 %) elderly patients suffer from Alzheimer's disease. In Moscow, every 21st person over the age of 60 suffers from this pathology. Professor V. Zakharov in his speech at the Fifth All-Russian Congress on Gerontology and Geriatrics stated that Alzheimer's disease is widespread, but little known and difficult to diagnose, not all patients are detected in the latent stage, so the real picture is even worse [3].

AD aethiology

The aetiology of AD is not fully understood. It is assumed that a number of risk factors (RFs), the presence of AroE-4 and inflammatory markers lead to a cascade of pathological reactions in the brain, and within a decade an Alzheimer's type neurodegenerative disease develops, up to dementia.

The pathogenesis of the disease remains unspecified, and the following hypotheses have been suggested:

- The cholinergic hypothesis. AD is caused by a decrease in the synthesis of the neurotransmitter acetylcholine.
- The amyloid hypothesis — an accumulation of beta-amyloid protein caused by genetic factors, with the formation of plaques between neurons. The gene encoding amyloid-precursor-protein (APP) from which beta-amyloid is formed is located on chromosome 21. Amyloid deposition in the walls of small vessels of the arachnoid mater and cerebral cortex is observed in all patients with AD (Fig.1).
- The glomerular or tau hypothesis, proposes that oxidative stress leads to a disruption of the tau protein structure (Fig. 2), its aggregation and transformation into neurofibrillary glomeruli (NFGs) through the formation of pathological bonds with oxidised proteins [3, 4].

Brain atrophy (temporal and parietal lobe hippocampus) occurs as a result of nerve cell death. Amyloid plaques compress the structures of neurons, disrupting their connections with other cells and leading to their death. These changes reduce the number of nerve cells by up to 30 % or more. When the number of nerve cells and the connections between them are critically reduced, the brain can no longer manage its functions.

Forms of Alzheimer's disease (according to ICD-10)

F00.0. Dementia in Alzheimer disease with early onset

Dementia in Alzheimer disease with onset before the age of 65, presenile dementia, type 2

F00.1. Dementia in Alzheimer disease with late onset

Dementia in Alzheimer disease with onset after the age of 65, senile dementia, type 1

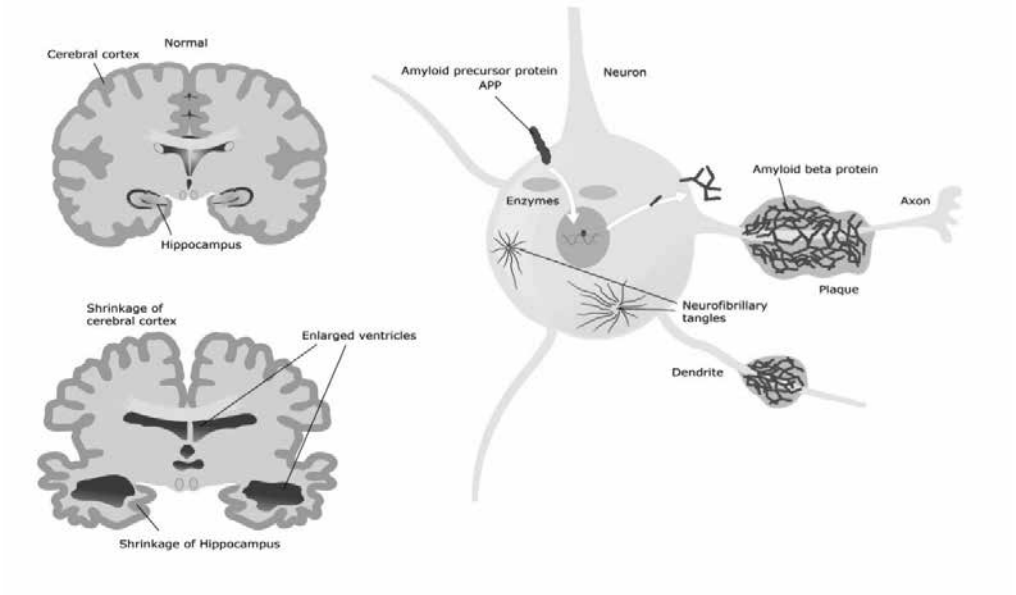

Fig. 1. Pathogenetic patterns of AD development

F00.2. Dementia in Alzheimer disease, atypical or mixed type

— The presenile type is characterised by a rapid progression with the development of aphasia, apraxia, agnosia, alexia. Often has a family history of AD or Down syndrome. Homogeneous structure of the syndrome: aphasic-apraxic-agnostic dementia.

— Senile type develops after the age of 65, slowly progressive. Memory impairment, confabulations predominate, usually sporadic. Different clinical forms of dementia.

Alzheimer's disease risk factors:

• Older age, family history of the disease, especially with early onset of dementia before the age of 60;

• CVD, uncontrolled AH in the middle and old age, atherosclerosis of the main vessels of the head, dyslipoproteinaemia (DLP); AH during pregnancy (associated with an increased risk of developing RFs even decades after delivery);

• Carbohydrate metabolism disorders, obesity (metabolic syndrome), head injury, hypodynamia, smoking, chronic hypoxia, hyperhomocysteinemia, sleep disorders, deficiency of B vitamins, folic acid;

• Female gender;

• Low educational level and low intellectual activity during life, episodes of depression in young and middle age [5–7].

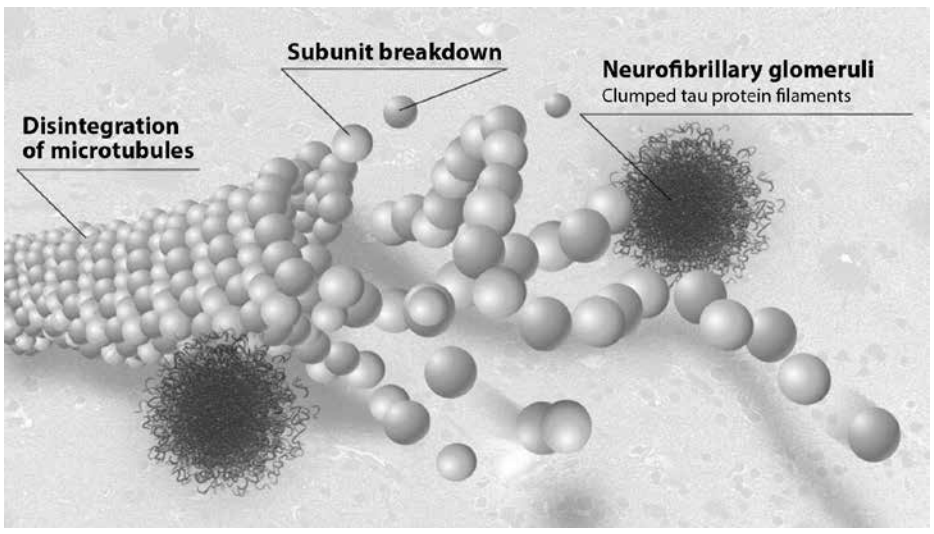

Fig. 2. Scheme of Tau-protein formation

Clinical course of AD, stages of the disease

An American psychiatrist Neil Buchholz explained the difference between ordinary forgetfulness and what happens in Alzheimer's: "If you forget where you put your keys, that's not a disease yet, but if you don't know what to do with the keys, what they're for, that's a problem".

At the 1st stage of the disease (initial stage): gradual development of CI — mild subjective and objective disorders of short-term memory, attention, difficulties in spatial orientation, errors in professional activity. Depression may occur. Normal functioning. The first symptoms are often confused with manifestations of ageing or stress response and can be detected by a detailed neurovegetative testing. Such cognitive impairment tends to appear within 8 years prior to diagnosing.

Stage 2 of mild dementia (MMSE 19-26): mild memory impairment; difficulty in learning new information, performing complex household tasks, spatial orientation; limited interests, decreased initiative, lasting up to 1 year.

Stage 3 moderate dementia (MMSE 10-18): progressive cognitive deficits (apraxia, aphasia, agnosia, alexia, acalculia, agraphia), loss of long-term memory, impaired acquisition of current information and functioning in daily life.

Stage 4 dementia (MMSE 0-9): Total loss of intellect. Agitation, sleep rhythm disturbance, total inability to perform daily activities, hygiene skills, cachexia, epilepsy [5]. The final loss of function leads to death, mainly from CVDs.

When diagnosing Alzheimer's, it is important to bear in mind Rebo's Law, which states that "Recently acquired knowledge and skills are lost, and long-standing ones are lost in the opposite order to that acquired during life (i.e. a patient at the onset of the disease remembers the distant past, but not what happened yesterday or in the recent past).

Modern methods of diagnostics

Modern diagnostic methods include:

1) Neuroimaging techniques: CT, MRI. PET-CT most clearly visualises the pathological signs of Alzheimer's disease in the form of amyloid plaques and tau proteins in neurons.

2) Cerebrospinal fluid biomarkers: decreased beta-amyloid and increased tau protein. The study is carried out at a mild and moderate stage of the disease, when dementia has not yet developed.

3) Neuropsychological tests to determine the severity of the disease and assess the effectiveness of the therapy.

MMSE test — a short scale for assessing mental status, which allows you to determine the severity of the disease (mild, moderate, severe) by scores. Clock "drawing" test, clock copying, delayed reproduction test, etc. [1, 5, 6].

AD treatment

It should be noted that there is no drug for the treatment and prevention of Alzheimer's disease. The aim of treatment is to prevent the progression of CI and dementia.

The "gold standard" for overcoming cholinergic deficiency and improving cognitive function is the administration of anticholinesterase inhibitors (donepezil, velaxin) and acetylcholine donors (choline alphoscerate, gliatilin, cereton). Velaxin is an antidepressant, but indirectly affects cholinergic receptors as a pharmacological side effect. The therapeutic efficacy and safety of this group of drugs has been demonstrated in numerous national and international clinical trials in mild and moderate stages of the disease, and they may be able to prevent or delay dementia [8]. The 2-year, double-blind, multicentre ASCOMALVA study was conducted to evaluate the efficacy of combined therapy with donepezil and gliatilin in patients with chronic cerebral ischaemia and Alzheimer's disease. In the group of patients with AD, significant positive results were obtained according to the CI scales (MMSE and ADAS-cog).

Neuroprotective therapy to preserve neuronal viability: glutamate receptor blockers: acatinol memantine, nootropics, divase, antioxidants, neurotransmitters — cerebrolysine. The use of these drugs has been well documented. A relatively new drug is Divase — an innovative drug consisting of antibodies targeting the brain protein S-100 and antibodies against endothelial NO synthase.

To improve the neurotransmission, it is necessary to improve blood flow in the narrowest segment of blood flow — the microcirculatory vessels. To deliver cholinergic drugs, nootropics, oxygen, glucose and other metabolic agents, it is necessary to improve the microcirculation in the cerebral arteries, to increase the elasticity and deformability of erythrocytes, their ability to pass in the narrowest segments of capillaries. An example of such a drug is naphthidrofu-

ryl, which affects the microcirculation with a proven positive effect on cognitive functions (vasodilatory effect, improves blood rheology and platelet haemostasis, increases ATP concentration, reduces oxidative stress, increases resistance of brain cells to hypoxia). From the cardiologist's point of view, prescribing a choline supplier and other drugs in combination with microcirculation-improving drugs is important in the management of patients with Alzheimer's disease. An analysis of 9 randomised, blinded, placebo-controlled trials involving 847 patients with Alzheimer's disease, vascular dementia and mixed dementia showed improvement in behavioural and cognitive functions; improvement in patients' functional activity; good tolerability of naftidrofuryl [8].

It is recommended to correct the risk factors for the development of AD, especially CVD, metabolic risk factors for the development of CVD (obesity, AH, impaired carbohydrate and lipid metabolism). Medications that worsen cognitive function (benzodiazepines, anticonvulsants, antipsychotics, central cholinolytics, digitalis drugs) should be avoided unless necessary [9].

Discussing the CVD-Alzheimer's relationship

Genetic-based CVDs play an important role in developing AD. Many genetic polymorphisms have now been shown to be associated with developing CVD. At this stage, it has already been established that chronic non-communicable diseases (CNCDs), which have reached epidemic scales, cause 71 % of deaths, mainly due to CVD, oncology, COPD and diabetes. The development of these diseases is caused by modifiable risk factors, among which AH, diabetes, obesity, smoking and hypodynamia play the most important role. It has been shown that the development of CVD is possible with a certain combination of behavioural and genetic RFs Thus, there is a certain correlation between AD and CVD at the level of the individual genome with gene expression in different cells of the organism. There is no doubt that the role of macro- and microcirculation plays an important role in brain homeostasis. It is through the bloodstream that not only the metabolites necessary for normal neuronal function are delivered, but also various free oxygen radicasl, pro-inflammatory cytokines, vasoconstrictors in the case of endothelial dysfunction (ED). This leads to the development of the cardio-cerebral continuum (CCC) and ultimately to neurodegenerative changes in the brain ending with neuronal death.

Therefore, there is a certain link between CVDs and beta-amyloid accumulation, which leads to inflammatory responses and neuronal death. The question remains as to why the beta-protein is not cleared from the brain, and what causes it to accumulate. Why does the tau-protein accumulate in the neuron? Perhaps there is a deficiency of cerebral autoregulation due to the developed AH, which is the trigger for the development of hypertensive encephalopathy through to dementia. The simplified scheme presented here begins to claim that Alzheimer's disease is a new cardiovascular pathology.

Research is being carried out around the world to understand the pathogenetic mechanisms and to develop effective drugs for Alzheimer's disease. Our task is to draw the attention of primary health care to the existing very serious problem of cardio-cerebral relationships and to consider any cardiac pathology as a marker of brain pathology, including Alzheimer's disease. It is necessary to carry out large-scale studies to determine the extent of the relationship and to further clarify the mechanisms for preventing the development of AD.

Age is a non-modifiable risk factor for the development of CVD and AD, particularly in older age groups. The main mechanism of cellular ageing is oxidative stress, which leads to progressive ageing and shortening of DNA telomere ends. The measurement of telomeres in patients with CVD, and possibly AD, has prognostic value and may help to identify individuals in need of preventive measures. A number of epigenetic studies have also demonstrated the importance of microRNAs in the pathogenesis of myocardial infarction, stroke and chronic heart failure (CHF). The role of the metagenome, the genetic material of the microbiota, which is involved in the homeostasis of the whole organism and is an important factor in biochemical interactions, should also be considered. The metagenome has already been linked (it was sequenced in 2010) to the development of AH, lipid disorders, obesity and other diseases. The mechanisms by which the metagenome interacts with the human body are still under investigation and have not been fully elucidated. Perhaps more precise targets indicating the possible development of CVD and AD will be revealed by further epigenetic studies taking into account the metagenomic status. Therefore, a per-

sonalised approach to the diagnosis and treatment of CNCDs is highly relevant [10]. The idea of personalised medicine is already being researched, and steps are being taken in Russia to introduce genetic panels into clinical practice to assess the effectiveness of drugs. In order to develop programmes to prevent the development of CNCDs, including CVD and AD, the development of an individual genetic passport is underway.

The development of CI as a complication of COVID 19

Negative effects of SARS-CoV-2 on the development of CI, independent of the severity of the disease course, were revealed during the pandemic. Advanced age, co-morbidities (AH, DM, obesity, COPD) are factors for the development of CI. There is a significant amount of cognitive and psychoemotional disorders developing after COVID-19. Dementia was the third most common neurological complication, accounting for 0.7%, which is 1.7 times the average population risk [11, 12]. The adverse effects are mediated by the direct neurotoxic effect of the virus on brain cells. SARS-COV-2, after proteolytic cleavage of its protein by S-serine protease, binds to the transmembrane ACE-2 and enters type 2 pneumocytes, macrophages, cardiomyocytes, pericytes (perivascular cells located on capillaries), causing endothelitis with thrombosis of small and large vessels. Pericytes are particularly abundant in the brain and the blood-brain barrier system, its permeability increases. Fibrinogen, viral particles, immunocompetent cells enter the brain parenchyma, which induces the inflammatory process, vasogenic oedema develops, oxidative stress, activation of microglia (macrophages) of the CNS.

Another factor is social isolation. It has been found that 50% of patients with mild CI and AD have a marked decline in cognitive function, and one in six patients have delirium. Walking difficulties and depressive disorders have also been reported. Following coronavirus infection, Alzheimer's disease manifests rapidly (1-6 months) [3]. Thus, a new coronavirus infection may lead to the development of clinical symptoms of AD. Therefore, physicians need to be vigilant in recognising these symptoms in order to promptly prescribe basic therapy with drugs that improve cerebral microcirculation. Additional therapy of post-covid syndrome includes prescription of: vitamins (including vitamin D), trace elements (selenium, magnesium, zinc, iron), antiplatelet drugs for cardiovascular and cerebrovascular risks, antihypoxants and antioxidants, nootrops, statins (for cardiovascular and cerebrovascular risks), anxiolytics.

Cardiologist's perspective on CI in cardiac patients

It has been established that the development of CVD increases the risk of CI and psychoemotional disorders by 2–3 times compared to healthy individuals and increases up to 40%, leading to a worse prognosis due to cardiovascular events (including suicide). These patients die on average 20 years earlier than the general population (Lancet, 2018). The most important and best studied major RF of CVD development is AH. AH is a RF of AD development as well and also worsens the prognosis of coronavirus infection, especially in the postcovid period. CIs are found at all stages of AH and are well reported.

Cognitive functions (CF) — complex brain functions through which the process of rational perception of the world and purposeful interaction with it is carried out. Gnosis, praxis, intellect, memory and speech are the five basic functions.

- Gnosis — the perception of information, the ability to combine elementary sensations and holistic images. An agnostic patient sees an object, can describe it, but does not recognise it.
- Praxis is an arbitrary, purposeful motor action; patients with apraxia are unable to perform a particular action due to a loss of ability, despite the absence of a paresis.
- Intelligence — the ability to analyse information, to identify similarities and differences, general and specific, major and minor, the ability to abstract, solve a problem, make conclusions.
- Memory — the ability to capture, store and repeatedly reproduce the received information. Moreover, subjective complaints of patients about memory do not correspond to its true disorders, which are detected by special methods of research.
- Speech — the ability to understand spoken language and to express one's thoughts by using verbal means (words) [1, 11].

Neuropsychological testing is recommended for the assessment of CI, which makes it possible to identify and assess the cognitive disorder (CD). In outpatient practice it is convenient to use the most optimal test "Mini-Cog" (S. Borson, 2000). It is a

combination of the three-word memory test and the drawing of a clock: 1) repeat after the doctor and memorise 3 words (for example: apple, circle, chair); 2) draw a clock face with hands and write the time (for example, 10 minutes to noon); 3) name 3 words that were memorised at the beginning of the test. The interpretation of the test is as follows: if the patient has remembered 1 or 2 words, the drawing of the clock is analysed. If it is correct, there is no cognitive disorder (CD); if it is incorrect, there is a CD. The test has a sensitivity of 99 % and a specificity of 93 %. The test can be administered to patients with speech and language disorders.

CVDs, including myocardial infarction (MI) and stroke, are leading causes of all-cause mortality and account for a high proportion of disability in the able-bodied population. It is known that acute and chronic brain damage is caused by a number of CVDs, but the leading ones remain: CHD, AH, CHF, arrhythmia (more commonly atrial fibrillation), DLP, acquired heart defects and prosthetic heart valves.

Role of CVDs in the development of cerebrovascular disorders

In the last decade, an interdisciplinary field of medicine such as cardioneurology has emerged as a result of the recognition of the relationship between cardiac and cerebral pathology. One of the important directions of cardioneurology is the study of neurological disorders in patients with cardiac pathology [11]. In modern literature, the terms "cardiogenic encephalopathy", "cardiogenic dementia", CCC and others have emerged. Therefore, prevention and treatment of patients with these co-morbidities will be optimised by the early detection of chronic cardiac diseases leading to progression of cerebrovascular pathology and clarification of the pathogenetic mechanisms. It should be emphasised that this is not only a medical problem. It is also a very important social problem.

The development of cardio-cerebral diseases is based on common RFs: AH, DLP, DM, smoking, obesity, alcohol abuse, unbalanced diet, hypodynamia, prolonged psycho-emotional stress, etc., which cause general remodelling of CVDs, parallelism of pathological processes in heart and brain. Common in the pathogenesis of cardioneurological pathology is the development of active free radical oxidation (FRO). FRO is a process of direct transfer of oxygen to the substrate with formation of peroxides, ketones, aldehydes, inducing reactions of peroxidation with participation of reactive oxygen species — superoxidants, hydrogen peroxide, hydroxyl radical.

It is sometimes difficult to determine the true role of cardiac pathology in the development of chronic cerebrovascular disease [CVD]. However, the main cause of CVD is cardiovascular pathology, namely:

- CHD (myocardial infarction, arrhythmias, CHF with reduced LV ejection fraction);
- AH and hypertensive crises;
- cardiogenic cerebral emboli;
- cardiogenic syncope with development of post-ischaemic encephalopathy;
- DLP and hypercholesterolaemia;
- atherosclerosis of both extra- and intracranial vessels;
- neurological complications of infective endocarditis.

CVDs can lead to the development of dyscirculatory encephalopathy (DEP), which is based on the following pathogenetic aspects: impaired autoregulation of cerebral blood flow; impaired rheological properties of blood; DLP; intravascular activation of haemostatis.

In DEP, the unfolding 'ischaemic cascade' leads to biochemical disturbances, the steps of which are described as follows:

- decreased blood flow and oxygen content;
- cyclic nucleotide formation and oxygen utilisation;
- eicosanoid release, calcium accumulation, protease activation;
- development of oxidative stress and local inflammatory reactions;
- endotheliocyte dysfunction and development of microcirculation block.

These steps in the pathological "cascade" in the conditions of ischaemia/hypoxia that develop in DEP lead to CD, a progressive condition that will eventually turn into dementia. Thus, if a patient is diagnosed with moderate CD, 5–15 % of patients will develop dementia within one year and 100 % of patients will develop dementia within 5 years [1]. It is therefore very important to detect CI in patients with CVD at an early stage.

Possibilities of organ-protective therapy in the field of cardioneurology

Metabolic therapy, aimed at improving the efficiency of oxygen use by the heart muscle and brain in condi-

tions of developing ischaemia, has recently received special attention in cardioneurology. It is known that in physiological conditions FRO is necessary for normal functioning of the organism. In case of increased oxidative stress, DE develops, cells are damaged and processes of oxidative phosphorylation and tissue respiration are dissociated, enzymatic systems are inhibited, DNA is depolarised, cell membranes are damaged and their permeability is disturbed, loss of elastic properties is observed, up to rupture and cell death. Oxidative stress plays an important role in the pathogenesis of atherosclerosis, CHD, CHF, ischaemic and haemorrhagic stroke and other CVDs.

Thus, the underlying cause of the disorders caused by increased lipid peroxidation (LPO) activity in many CVDs is hypoxia; therefore, it is desirable to prescribe drugs with multi-organ and pleotropic properties in complex therapy. The use of renin-angiotensin-aldosterone system blockers (ACEi, sartans), long-acting dihydropyridine calcium channel blockers (DCCB), beta-adrenergic blockers of the II (bisoprolol, metoprolol succinate) and III (nebivolol, carvedilol) generations — in sympathicotonia; Mineral corticoid receptor antagonists (MCRAs) with the ability to exert antifibrotic effects in the heart and vasculature, inhibitors of glucose sodium cotransporter type 2 (iSGLT-2), imidazoline receptor agonists may have a beneficial effect on CI. Neuroprotective therapy should be added at all stages of CI, taking into account the correction of all CVD risk factors.

Neurologist's view of CDs and their correction

Depending on the severity of the CR, it is usually divided into the following categories:

- **Moderate (MCD, pre-dementia stage, DEP 1–2 stages):** obvious cognitive dysfunction, usually noticed by the patient, not very noticeable to others, interfering with professional activity (although our patients are more likely to be retired by this time), but practically not affecting daily activity and independence. Mild forgetfulness, often confused with natural age-related memory loss. The MCD stage lasts for several years.
- **Mild dementia:** occupational activities, complex household activities are impaired, but self-care skills are preserved. This is a fairly common and underrecognised stage of dementia, and it is at this stage that patients attend neurologists: Treatment is aimed at maintaining preserved functions. The patient needs outside help (often a little) to organise their life, hints, reminders.
- **Moderate dementia:** all household activities are affected (problems with cooking, personal hygiene, needing almost constant help from others). The impairment is quite obvious to others, but is still underestimated even at this stage. Moderate dementia is often associated with psychotic and affective disorders, which make life even more difficult for others.
- **Severe dementia:** the patient's activity is bedridden, constant nursing care is required.

It is important to note that dementia does not always mean irreversible cognitive impairment. It is very important not to overlook cases of pseudodementia (cognitive decline associated with depression, less often with other mental illnesses, regressing on therapy with antidepressants and other specific drugs). Another case is the potentially reversible dementia, in which identification of the cause and its elimination contribute to a significant improvement in cognitive status with a reduction in the severity or regression of the patient's maladaptation (e.g, correction of glycaemia, vitamin B12 and folic acid deficiency, surgical treatment of intracranial hemaetomas and hydrocephalus).

Thus, the most common cause of dementia in people over the age of 60 is Alzheimer's disease. In our country, especially among psychiatrists (these are purely personal observations), Alzheimer's disease is traditionally understood more as a presenile form of the disease (dementia with early onset, rapid progression, malignant course, and a clear clinical picture). At the same time, studies have shown the complete morphological identity of presenile and senile dementia, which justifies identical therapeutic approaches and leads us to reconsider the historically established classification.

The basis of Alzheimer's disease is a progressive central acetylcholinergic defect that spreads from the entorhinal cortex to the hippocampus and on to the temporal, parietal and occipital lobes. Memory problems are the first and foremost complaint of both patients and family members. However, it is worth noting that the early symptoms are much more likely to go unnoticed or ignored, as they are explained by the natural age-related decline in cognitive function of the CNS. As the disease progresses, problems with language, counting, visual-spatial orientation and

practical skills appear and increase. Emotional (behavioural) and psychotic disorders such as depression, agitation, delusions, hallucinations may occur at any time from the onset of the disease. Neurological examination findings, excluding mental status evaluation (testing), are often normal.

The diagnosis of **AD** is confirmed by the following signs:

- The undetected onset and progression of dementia;
- The prevalence of memory disturbances (especially recollection and recall of new material) in the early stages of the disease (e.g. when the patient is ready to tell in great detail about their youth, but cannot remember what happened to them the day before);
- The onset after the age of 60;
- Absence of focal neurological symptoms and gait disturbances, especially in the early stages of the disease;
- The absence of any other cause of dementia.

Vascular dementia (the most common type of dementia) can result from diffuse damage in the deep white matter caused by changes in small vessels under the influence of various factors (AH, hyperlipidaemia, hyperglycaemia, hyperhomocysteinaemia) or from focal (more often multifocal) brain damage caused by stroke. Vascular dementia is characterised by a sudden onset of impairment in one or more cognitive domains; gradual progression of the process; the presence of focal neurological symptoms, including limb weakness, strong deep tendon reflexes, positive extensor plantar reflexes, and gait disturbance; and anamnestic or neuroimaging evidence of stroke. However, gradual progression and/or the presence of focal neurological symptoms are not found in all cases of vascular dementia. Affective disorders, psychotic symptoms and depression may occur in vascular dementia.

The combination of **vascular and neurodegenerative pathology** is particularly noteworthy. These processes can coexist in several ways. On the one hand, vascular RFs themselves potentiate the development of neurodegeneration, thus making it partially possible to prevent this from occurring. On the other hand, vascular and neurodegenerative processes may have different contributions to the clinical picture. In our country, the prevalence of different forms of dementia differs somewhat from that observed in Western countries. Thus, if purely neurodegenerative forms of dementia are more characteristic of Western Europe and America, in Russia the majority of patients with dementia have a mixed or vascular genesis, which is determined by the higher prevalence and poorer control of the corresponding RFs.

Delirium in patients with CD is a problem in its own right. Delirium can be caused by a variety of somatic conditions, such as latent pneumonia or other infection, CVD decompensation, etc., which, if corrected, will resolve and the patient will return to normal state. Delirium is characterised by a sudden onset and fluctuation of symptoms during the day (e.g. yesterday an elderly patient was alert and active, today he does not recognise anyone and sees enemies everywhere); short duration, change in activity level from drowsiness, stupor to agitation, psychomotor agitation, presence of hallucinations and distorted visual perception.

Recommendations for patient evaluation:

The examination of the patient should aim to identify factors that cause or worsen the course of dementia.

1) Assessing the cardiovascular system (presence of AH or hypotension, atherosclerosis of the main head arteries, CHF, arrhythmias). Ultrasound of the neck vessels, ECG (possibly Holter ECG, daily blood pressure monitoring), ECHO-CG are recommended among the instrumental methods.

2) Blood tests (general blood count, glycated hemoglobin (HbA1c), liver and kidney function, thyroid function, vitamin B12, homocysteine, vitamin D, blood lipids, coagulation indices) and urinalysis (urine may be tested for heavy metals, etc. if history relevant).

3) Neuroimaging. Neuroimaging is an important diagnostic tool, although it is by no means mandatory in typical cases. MRI is usually used to clarify the severity of diffuse and focal changes, to exclude damage in brain areas strategic for cognitive activity, and to assess the degree of atrophy (coronal slices through the hippocampus area may even suggest Alzheimer's disease).

When neuroimaging is mandatory: suspected tumour or trauma, especially if there is a dramatic deterioration in condition and an evidence of a previous fall or hit to the head (e.g. abrasions on the head, patient may have amnesia about the time of injury; CT scan to rule out intracranial haematoma is standard), suspected history of stroke, hydrocephalus, brain infection.

4) Assessment of medication history. Patients may be taking medications that contribute to the worsening of CF, a list of which and their pathogenetic mechanisms are presented in the literature [9]. In addition, patients may make medication errors due to poor memory (relatives should be made aware of the need for total control of what the patient is taking). In severe cases, a carer is needed; in mild cases, a timer and a pillbox with a metered dose are required).

5) Ideally, neuropsychological assessment of cognitive status is recommended. When in doubt, it is reasonable to administer brief cognitive scales: MMSE (Mini-mental State Examination, sensitivity 83–100 % for MCD, 94–100 % for AD, specificity 35–87 %) is not well suited to "vascular patients" as it is mainly focused on speech and memory impairment, which is more characteristic of AD.

The MoCA is a more modern questionnaire, but a little more time consuming. It is well suited to all types of dementia and has a standardised form in Russian. Clock Drawing Test — illustrates visual-spatial functions and regulatory disorders. Word List Memorisation Test (3 to 12) — very illustrative of Alzheimer's disease.

CD treatment

Thus, the treatment of cognitive and other neuropsychiatric disorders associated with dementia will depend to some extent on the aetiology, the associated RFs and the stage of the disease.

MCD stage: correction of blood pressure, cholesterol, glucose, homocysteine (not clinically proven, but theoretically sufficiently justified), vitamin D, vitamin B12 and folic acid levels, normalisation of thyroid function, reduction of body weight, lifestyle modification including regular physical and mental exercise, promotion of life activity and socialisation, correction of depressive/anxiety disorders (if necessary, consultation with a psychotherapist). By western international standards, no other medication is required. Therefore, metabolic and vascular drugs, which are popular in our country, are justified only at this stage and only if all other factors are balanced. It is important to remember that all vascular and metabolic drugs have side effects (vinpocetine can have a negative effect on heart rhythm, ginkgo preparations can cause epileptic seizures in sensitive people, cinnarizine is associated with a risk of Parkinson's disease, etc.).

Dementia: treatment, taking into account the pathogenesis based on acetylcholinergic deficiency, consists in the use of drugs that improve acetylcholine transmission — acetylcholinesterase (AChE) inhibitors. Another type of disturbances observed in dementia are disturbances in the regulation of nervous activity and the speed of mental processes (patients poorly able to switch from one subject to another, often fragmentary in their perception, impulsive). It is thought that memantine, an NMDA receptor blocker, has an influence on this link in the pathogenesis. In fact, the mechanism of action of memantine is quite complex, ranging from a mild dopaminergic effect, which allows its use as an adjuvant in Parkinson's disease, to the effects of modulating glutamatergic transmission, similar to magnesia, by modifying the functional activity of NMDA receptors. Memantine is thought to negate the "white noise" of nerve impulses that disorganise the CNS in case of diffuse lesions of the deep white matter.

AChE inhibitors are indicated in all stages of dementia. In Russia, the most commonly used drugs are galantamine (Reminyl) or rivastigmine (Exelon). Among the problems — most often gastrointestinal disorders (to some extent facilitated by the use of transdermal system in the form of patches) and disorders of the cardiovascular system (conduction disorders, etc.). The dosage should be increased slowly, depending on the clinical effect and side effects. According to international standards, memantine is added at the stage of moderate dementia, when the effect of AChE inhibitors becomes insufficient. At the same time, in the last decade the hypothesis of neuroprotective effect of memantine has been discussed in the literature, which creates conditions for its prescription at any stage of cognitive disorders (almost from the stage of MCD, but this is only a hypothesis, not a guide to action). Memantine is much better tolerated than AChE inhibitors. The effect is not so obvious, but it is undoubtedly present in a significant proportion of patients.

Treatment for behavioural and affective disorders

Behavioural problems are often secondary to CD. For example, the "doppelganger" symptom, where patients mistake their reflection in a mirror for a stranger in the room, is not a true hallucination but a visual perception disorder. Anxiety and depression

have a very significant impact on the progression of behavioural and psychotic disorders. Therefore, first of all, such patients need non-drug measures consisting of a strict daily regime, no change of the usual environment. E.g., moving to a new place is often the trigger for a decompensation. Insults and harsh criticism are not allowed, because due to the impairment of speech understanding, patients are oriented not on the meaning of what is said, but on the intonation).

Now to antipsychotics. Studies have clearly shown that the use of traditional neuroleptics is associated with increased patient mortality. It is interesting to note that very often the prescription of basic anti-dementia therapy makes it possible to eliminate (or at least weaken) psychotic disorders. Therefore, if the situation allows, we start treatment with these drugs rather than with neuroleptics. The effectiveness of the initial treatment is assessed every 6–8 weeks. If the effect is sufficient, then every six months. If absolutely necessary, in case of delirium, hallucinations, aggression, psychomotor agitation, the drugs of choice are (in descending order): quetiapine, risperidone, olanzapine, aripiprazole.

In case of aggression, irritability, impulsiveness: valproic acid, followed by carbamazepine, propranolol.

In case of agitation, depression, anxiety: escitalopram, sertraline, fluoxetine, citalopram.

For insomnia and other sleeping disorders: first of all, non-pharmacological methods — restricting sleep during the daytime, exclude emotional events in the evening, add walks in the fresh air, introduce a daily regime, avoid stress. Medication: melatonin, trazadone, mirtazapine, correction of restless legs syndrome. All doses should be started at the lowest adult starting dose and titrated at the lowest interval, with no more than one dose increase per week.

In case of apathy/abulia: AChE inhibitors, memantine, dopaminergic agents, low-dose levodopa, low-dose stimulant antidepressants (fluoxetine).

Conclusion

The presented concepts of cognitive disorders and Alzheimer's disease with various manifestations have been formed within the framework of modern achievements on this problem, controversial and not fully understood mechanisms of developing cardio-cerebral interrelations, experience of treating such patients in real clinical practice.

COVID-19 causes marked deterioration in the course of CVDs and in various cognitive spheres, up to rapid, lightning-fast development of dementia. Timely administration of vasotropic, neurotropic, neurometabolic drugs, cholinesterase inhibitors, memantine, anticoagulant and antiplatelet therapy is necessary to prevent and treat cognitive impairment.

Obviously, further large-scale clinical trials are needed to determine the extent of the interrelationships and to further clarify the mechanisms in preventing the development of Alzheimer's disease, in early diagnosis and in optimising the treatment of cognitive impairment in patients with CVD, especially those associated with new coronavirus infections.

Conflict of interest: none declared.

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The role of cardiac adipose tissue depots in assessing the risk of paroxysmal atrial fibrillation in patients with coronary heart disease and arterial hypertension

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The aim of the study was to investigate the influence of the severity of local cardiac depots of adipose tissue on the development of paroxysmal atrial fibrillation (AF) in patients with coronary heart disease (CHD) and arterial hypertension (AH).

Materials and Methods. The study included 82 patients (49 men and 33 women) with CHD aged 37–88 years (mean age — 62 [60; 75] years). Paroxysmal form of AF was diagnosed in 27 patients who constituted the main group.

All patients had anthropometric parameters measured: body mass index, waist circumference, hip circumference. Structural and functional state of myocardium was assessed by echocardiography (EchoCG).

Statistical data processing was performed using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium). The nature of the data distribution was assessed using the Kolmogorov-Smirnov criterion. In case of normal distribution, data were presented as mean (M) and standard deviation

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(SD). Nonparametric indicators were represented as median and interquartile range (Me [Q25; Q75]). The correlation between the two quantitative characteristics was assessed using Spearman correlation analysis (r). ROC analysis was performed to determine the threshold value of the studied attribute. Binary logistic regression method was used to assess the possibility to predict the risk of AF development. Differences were considered statistically significant at p<0.05.

Results. There was a correlation between interatrial septal thickness (IST) and waist circumference (WC) (r = 0.5; p = 0.0003), hip circumference (HC) (r = 0.6; p < 0.0001), and epicardial fat thickness (EF) (r = 0.7; p < 0.0001).

ROC analysis showed that IST > 0.7 cm (p<0.001) and EF thickness > 0.6 cm (p < 0.001) were indicative of paroxysmal AF.

Determination of threshold values of IST and EF thickness separately among men and women with the regard to the presence/absence of abdominal obesity (AO) showed that in men without AO, IST thickness > 0.5 cm and EF thickness > 0.7 cm, as well as IST > 0.7 cm in men with AO had a high diagnostic value for determining the probability of AF development.

Conclusion. Epicardial adipose tissue thickness > 0.6 cm (p < 0.001) and IST > 0.6 cm (p < 0.001) may serve as markers of AF in patients with CHD, and determination of EF thickness and IST together with WC measurement may serve as prognostic criteria of AF risk in men with CHD (model significance p = 0.0062).

Thus, the assessment of IST and EF thickness in patients with CHD can be recommended for determination during EchoCG.

Keywords: obesity, atrial fibrillation, epicardial adipose tissue, interatrial septal lipomatosis, predictors.

Conflict of interest: none declared.

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Data from modern epidemiological studies indicate a high prevalence of atrial fibrillation (AF) in the population (approximately 33 million people worldwide). Furthermore, a significant proportion (35%) of cardiovascular disease (CVD) mortality is caused by this arrhythmia [1–3].

Age, arterial hypertension (AH), diabetes mellitus (DM), coronary heart disease (CHD), chronic kidney disease (CKD) and obesity are the main risk factors (RFs) for the development of AF, with obesity being one of the most important RFs (incidence of 25%) [4–6].

Currently, obesity should be understood as a complex multifactorial condition with excessive deposition of adipose tissue leading to the formation of different metabolic phenotypes of obesity [7–9]. In addition, there is evidence in the literature that there is an inverse relationship between body mass index and risk of death — the "obesity paradox" [10].

A number of studies evaluating adipose tissue distribution as a measurable cardiovascular risk factor in a group of patients with AH have found that epicardial fat thickness (EF) > 0.4 cm is associated with the risk of developing AH [11–13]. In addition to the already known mechanisms leading to cardiac remodeling in patients with CHD and AH, the negative effect of EF leading to the formation of local fibrosis in the atrial myocardium and its pathogenetic association with the formation of "re-entry" foci has also been described [11, 14]. In the work of Mitrofanova L.B. et al, devoted to the search for the morphological substrate of AF, the role of fatty infiltration of the interatrial septum (IAS) was demonstrated [15, 16].

The aim of the study was to investigate the influence of the local cardiac adipose tissue depots on the development of paroxysmal form of AF in patients with CHD.

Methods

The study has been carried out by the Cardiologic Department of the "City Clinical Emergency Hospital", Ryazan. The study included 82 patients. The proportion of men was 60% (n = 49), the proportion of women was 40% (n = 33). The mean age of the patients was 62 [60; 75] years.

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The study included patients with CHD represented by unstable angina pectoris, myocardial infarction localised in the anterior wall of the left ventricle (31 %), posterior basal wall (13 %), inferior wall of the left ventricle (19 %), anterolateral wall of the left ventricle (37 %). All patients had a history of AH and chronic heart failure (HF). 21 % of patients had type 2 DM, one patient had a history of diffuse toxic goiter.

The main group (group 1) included 37 patients with paroxysmal form of AF documented by electrocardiography (ECG) or by the daily Holter monitoring. The duration of AF in group 1 patients was 4.3±1.2 years. A first-ever paroxysm of AF was recorded in 30 % (n=11). In patients with MI, paroxysms occurred within the first 24 hours in 75 % of patients and on the second day in 15 % of patients. The duration of the paroxysms did not exceed 48 hours. Emergency sinus rhythm restoration was achieved by a pharmacological cardioversion. 45 patients without AF formed the comparison group (group 2). Comparative characteristics of the patient groups are shown in Table 1.

Table 1. **Clinical characteristics of patients in comparison groups**

Parameter	1 group	2 group
Number of patients, n	37	45
Mean age, years	67.7 [61; 70]	64.2 [58; 72]
Gender: Male, n (%) Female, n (%)	 25 (67 %) 12 (33 %)	 25 (56 %) 20 (44 %)
CHD, n (%) Unstable angina, n (%) Postinfarction cardiosclerosis, n (%) MI, n (%)	37 (100 %) 27* (74 %) 6 (16 %) 4 (10 %)	45 (100 %) 11 (26 %) 22** (48 %) 12 (26 %)
AH, n (%)	37 (100 %)	45 (100 %)

Note. * p < 0.001; ** p = 0.0008.

All patients were treated according to current clinical guidelines [17–20]. Patients with AF received anticoagulant therapy and oral antiarrhythmic drugs were prescribed to maintain sinus rhythm after the cardioversion. Patients hospitalised with non ST-elevation acute coronary syndrome received anticoagulant therapy with unfractionated heparin in the acute phase, acetylsalicylic acid, P2Y12 inhibitors and new oral anticoagulants after the acute phase. 15 % of patients underwent percutaneous transluminal coronary angioplasty with stent implantation. All patients also received drug treatment for secondary prevention: hypolipidaemic therapy, antihypertensive therapy, β-blockers, and diuretics.

The study was conducted in accordance with good clinical practice and the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee of Ryazan State Medical University (extract from protocol #3 dated 11.11.2020). Written informed consent was obtained from all patients prior to enrolment.

Study exclusion criteria:

— heart defects with significant haemodynamic abnormalities;

— cardiomyopathies;

— acute renal failure;

— liver failure;

— severe respiratory failure;

— present malignancy;

— pregnancy;

— severe mental illness.

Anthropometric study was performed: measurement of height and body weight with subsequent calculation of body mass index (BMI), waist circumference (WC) and hip circumference (WC).

EchoCG was performed in all patients after control of AF episode using ultrasound diagnostic medical system HS60-RUS, Korea, Samsung Medison CO., LTD. All examinations were performed by a single specialist. Interatrial septum (IAS) thickness was measured in atrial diastole at the periphery of the fossa ovalis through a subcostal approach. EF thickness was measured in diastole from the parasternal position along the long and short axes of the left ventricle. EchoCG results are shown in Table 2.

Table 2. **Echocardiography data**

Parameter	1 group	2 group
Number of patients, n	37	45
Left ventricular end-diastolic dimension, cm	5.5 [5.1; 5.7]	5.4 [5.1; 5.6]
left ventricular end-systolic dimension, cm	4.03 [3.7; 4.3]	3.8 [3.4; 3.8]
Interatrial septum, cm	1.1 [1.05; 1.25]	1.2 [1.0; 1.3]
Left ventricle posterior wall, cm	1.1 [1.05; 1.2]	1.1 [1.02; 1.2]
Right ventricle anterior-posterior dimension, cm	2.7 [2.5; 2.8]	2.7 [2.4; 2.8]
IST, cm	0.8±0.1 (CI от 0.7 до 0.9)	0.6*±0.2 (CI от 0.5 до 0.6)
EF, cm	0.9±0.1 (CI от 0.8 до 1.0)	0.6**±0.1 (CI от 0.5 до 0.7)

Note. *p = 0.0001; **p < 0.0001

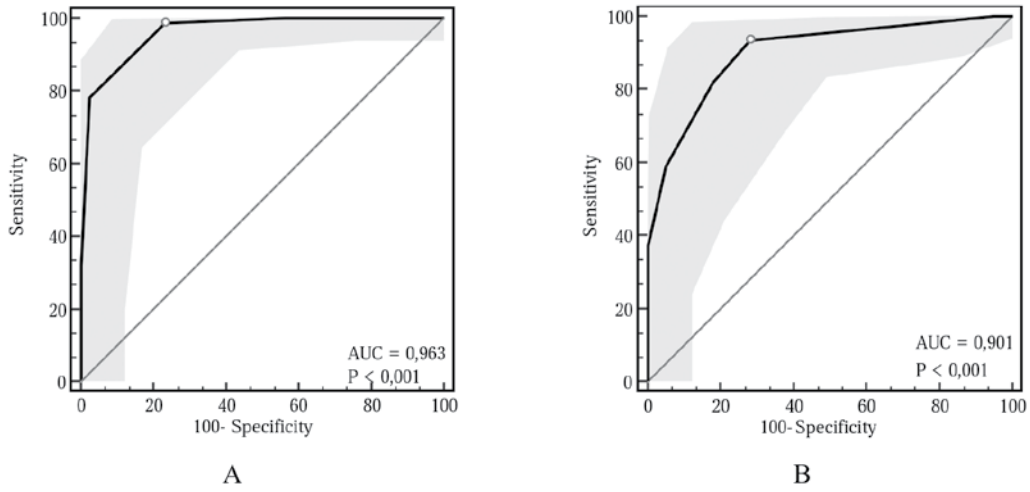

Fig. 1. ROC curves of IAS thickness (A) and EF thickness (B) in patients with CHD

Statistical data processing was performed using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium). The nature of the data distribution was assessed using the Kolmogorov-Smirnov criterion. In case of normal distribution, data were presented as mean (M) and standard deviation (SD). Nonparametric indicators were represented as median and interquartile range (Me [Q25; Q75]). The correlation between the two quantitative characteristics was assessed using Spearman correlation analysis (r). ROC analysis was performed to determine the threshold value of the studied attribute. Binary logistic regression method was used to assess the possibility to predict the risk of AF development. Differences were considered statistically significant at $p < 0.05$.

Results

The anthropometric study in the groups showed the following results: BMI was 30.5 [25; 34] kg/m^2 in group 1 and 29.8 [26; 33] kg/m^2 in group 2. HC was 106.8 [98.5; 111.5] cm in group 1 and 102.5 [97.2; 112] cm in group 2. The WC in group 1 was 114±5.5 cm and was significantly greater (p=0.02) than the WC in group 2 (107.5±2.6 cm). No significant differences in BMI and HC were found between the groups compared.

In all subjects, IAS thickness correlated with WC (r = 0.5; p = 0.0003), with HC (r = 0.6; p < 0.0001), and with EF thickness (r = 0.7; p < 0.0001).

In patients with CHD and paroxysmal AF, a positive correlation was found between IAS thickness and EF (r=0.7; p<0.0001).

Multivariate analysis was performed to demonstrate a statistically significant influence of EF thickness and IAS thickness on the probability of detecting AF in patients with CHD and AH. Odds ratio (OR) and confidence interval (CI) were calculated for each parameter: for EF thickness — OR = 5.8; 95 % CI: 0.8–5.6; for IAS thickness — OR = 3.9; 95 % CI: 1.2–6.3.

ROC analysis was performed to determine thresholds for local cardiac adipose depot thickness (Fig. 1). It was found that IAS thickness > 0.7 cm (AUC=0.963; p<0.001, sensitivity — 98.7 %, specificity — 76.9 %) and EF thickness > 0.6 cm (AUC = 0.901; p < 0.001, sensitivity — 93.6 %, specificity — 71.8 %) indicated the presence of the paroxysmal form of AF. Thus, the increase in IAS and EF thickness above the specified thresholds can serve as markers for the presence of AF in patients with CHD and AH.

In addition, ROC analysis of the curves was performed separately in the men's group and in the women's group with and without AF within the gender group (Table 3).

In the group of men without AF (Fig. 2), the threshold for IAS thickness was > 0.5 cm and for EF thickness was > 0.7 cm. In the group of men with AF (Fig. 3), the threshold for MPP thickness was > 0.7 cm. The data obtained were statistically significant and therefore have a high diagnostic value for determining the likelihood of AF development.

Similar analysis of ROC-curves in the group of women did not show statistically significant results.

The binary logistic regression method was used to assess the possibility of predicting the risk of AF development (Nagelkerke R-square was 0.524 (R2 = 0.5750); model significance p = 0.0062).

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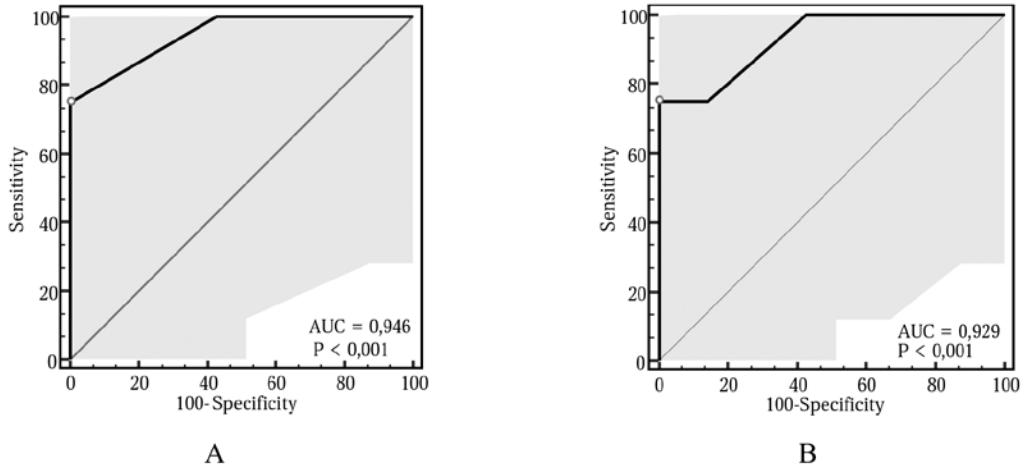

Fig. 2. ROC curves of IAS thickness (A) and EF thickness (B) in men without AO

Table 3. **ROC analysis of IAS and EF thickness thresholds in patients with CHD and arterial hypertension**

Gender	Measured parameter	No AO					AO				
		Parameter value, cm	Area under the curve	p	Sensitivity%	Specificity, %	Parameter value, cm	Area under the curve	p	Sensitivity, %	Specificity, %
Male	IAS	>0.5	0.946	<0.0001	75	100	>0.7	0.838	0.0237	75	100
	EF	>0.7	0.929	<0.0001	75	100	>0.8	0.688	0.3694	75	95
Female	IAS	>0.6	0.623	0.5	62	52	>0.7	0.595	0.4996	66	64
	EF	>0.7	0.541	0.456	58	41	>0.6	0.524	0.8971	33	43

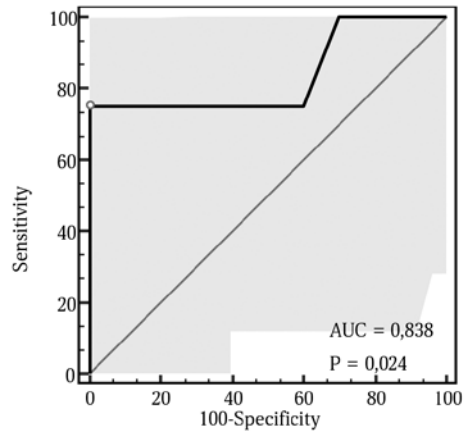

Fig. 3. ROC curves of IAS thickness in men with AO

The obtained model can be used to predict the risk of AF in men using as diagnostic criteria the thickness of EF and IAS thickness measured in diastole, as well as the presence or absence of AO.

Discussion

The conducted study showed that EF thickness in CHD patients with paroxysmal form of AF has significantly higher values compared to patients with CHD without arrhythmias (p = 0.0026). IAS thickness > 0.8 cm indicates the presence of paroxysmal form of AF, which is consistent with the already available data in the work of Czerny A. et al. devoted to the study of the role of EF in the development of AF in patients with AH [11].

In our study, we found that in patients with CHD, IAS thickness > 0.65 cm indicated the presence of a paroxysmal form of AF, which is also confirmed in a number of works [15, 21].

The ROC analysis, based on the comparison of patients within group 1 by sex and by the presence or absence of AO, showed that IAS thickness > 0.5 cm and EF thickness > 0.7 cm in CHD men without AO, and IAS thickness > 0.7 cm in men with AO can be used to assess the likelihood of developing AF. No such correlation applied to women.

According to the literature, the role of EF in the aetiopathogenesis of AF is not only due to a systemic influence, but also due to local effects associated with an increase in the amount of proinflammatory and profibrotic biologically active substances. The disruption of the structure and function of adipose tissue, regardless of its amount or total body weight,

may contribute to an increase in cardiovascular risk [22]. However, more detailed studies (also regarding the activity of fibrosis markers) are needed to address the role of lipomatous hypertrophy of IAS in AF.

Conclusion

The data obtained suggest the existence of a direct correlation between the expression of cardiac adipose tissue depots and the risk of developing the paroxysmal form of AF in patients with CHD.

EF thickness > 0.6 cm ($p<0.001$) and IAS thickness > 0.6 cm ($p < 0.001$) can serve as markers for the presence of AF in patients with CHD, and determination of EF thickness and IAS thickness together with WC measurement can serve as prognostic criteria for the risk of AF in men with CHD (model significance $p = 0.0062$).

Therefore, assessment of IAS and EF thickness during echocardiography can be recommended in CHD patients.

Conflict of interest: none declared.

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Comparison of the prognostic significance of the complications according to short-term scales in patients with Non-ST-segment elevation acute coronary syndrome without percutaneous coronary intervention

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Abstract
This study aimed to compare the short-term prognosis of fatal and nonfatal complications using GRACE (Global Registry of Acute Cardiac Events risk score), TIMI (Thrombolysis In Myocardial Infarction), PREDICT (PREdicting risk of Death In Cardiac disease Tool), PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and RECORD scales in patients with Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) without percutaneous coronary intervention (PCI).
Methods. 122 patients admitted to the Mordovian Republican Central Clinical Hospital" with a referral diagnosis of NSTE-ACS were examined. The peculiarity of this sample is the absence of primary PCI while the patient was in the hospital. Absence of primary PCI was explained in 14 (11.5%) patients by the refusal of coronary angiography (CAG) (due to age), in 8 (6.5%) patients due

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to intolerance of contrast agent or analgesic medication. All other 100 patients from this group underwent CAG, where intact coronary vessels were detected in 27 (27%) patients, in 42 (42%) patients the degree of stenosis was less than 50% and in 31 (31%) patients (all patients with type 2 diabetes) a distal type of coronary lesion was detected.

Results. When comparing the effectiveness of prognostic significance of short-term fatal and nonfatal complications, as well as the prognosis assessment regardless of the type of adverse outcome in ACS patients without PCI, GRACE scale showed the highest sensitivity and specificity compared with short-term RECORD, PREDICT, TIMI and PURSUIT scales used in this study. The TIMI and RECORD scales showed efficacy of short-term prognosis only for fatal complications in this category of patients.

Conclusion. Taking into account the results of this study in NSTE-ACS patients without PCI, the GRACE scale was recommended to assess the prognostic significance of short-term complications regardless of the type of adverse outcome.

Keywords: NSTE-ACS without PCI, short-term prognostic scales — GRACE, RECORD, PREDICT, TIMI, PURSUIT.

Conflict of interest: none declared.

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Introduction

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a common emergency medical condition [1, 2]. Not only is the number of cases of this form of coronary heart disease (CHD) increasing, but patients also tend to get younger [3, 4].

Considering the variety of clinical variants that characterise the instability of the atherosclerotic plaque of the coronary arteries, analysing the prognosis of the development of fatal and non-fatal complications, both on the patient's admission to hospital and those delayed to occur within the first 30 days, is of particular importance. Special attention should be paid to the situation of NSTE-ACS without percutaneous coronary intervention (PCI).

In order to assess the development of short-term complications in patients with NSTE-ACS and to select the optimal scale, the results of comparative studies of the available risk prediction scales GRACE, TIMI, PURSUIT, RECORD, PREDICT are presented [5, 6]. However, the comparative effectiveness of these scales in patients with NSTE-ACS in the absence of PCI during emergency hospitalisation remains controversial, indicating the need for more in-depth study of this issue.

The aim of this study was to compare the short-term prognosis of fatal and non-fatal complications using GRACE (Global Registry of Acute Cardiac Events risk score), TIMI (Thrombolysis In Myocardial Infarction), PREDICT (PREdicting risk of Death In Cardiac Disease Tool), PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and RECORD in patients with non-PCI NSTE-ACS ST.

Methods

The patient sample was formed in 2 years (2017-2019) and consisted of 122 patients admitted to "Mordovian Republican Central Clinical Hospital" with the referral diagnosis "NSTE-ACS". The absence of primary PCI during the patient's hospitalisation is a unique feature of this sample. The study was in accordance with the standards of good clinical practice and the requirements of the Declaration of Helsinki. The study protocol was approved by the local ethics committee of the National Research Ogarev Mordovia State University on 17 June 2017 (protocol #40). All participants gave written informed consent to be examined before the study.

Non-inclusion criteria: acute coronary syndrome with ST-segment elevation, myocarditis, pericarditis, arrhythmias not related to NSTE-ACS.

Exclusion criteria: incomplete laboratory and instrumental data.

The mean age of the patients was 62.2 ± 8.9 years (min age 36 years, max age 83 years), including 35 fe-

males (28.6 %) and 87 males (71.4 %). The mean age of the women was older (65.3 ± 8.1 years) compared to the mean age of the men (61.7 ± 9.4 years).

According to electrocardiogram (ECG) data in the group of NSTE-ACS patients, ST-segment depression corresponding to subendocardial myocardial infarction (MI) was detected in 41 patients (33.6 %) and T inversion in 36 patients (29.5 %). A positive troponin test was obtained in 25 patients (20.5 %). The same group included 8 % of patients with recurrent MI. In addition, 36.9 % of patients were diagnosed with unstable angina.

9 (7.4 %) patients were admitted with a complicated course of NSTE-ACS: pulmonary oedema in 6 (4.9 %) patients and cardiogenic shock with due to atrial fibrillation (AF) paroxysms in 3 (2.5 %) patients. Rhythm disturbances were recorded in 22 patients: in 7 patients (5.7 %) the first diagnosis of AF was registered on the ECG, in 12 (9.8 %) patients a permanent form of AF was detected and in 3 (2.5 %) patients ventricular extrasystole of 4–5 Laun gradations.

Signs of chronic heart failure (CHF) stage II A — III were detected in 28 (22.9 %) patients (stage II A — 17 people (13.9 %), stage II B — 7 people (5.7 %), stage III — 4 people (3.3 %).

Comorbidities were common in NSTE-ACS patients: hypertension (AH) was present in 52 (42.6 %) patients and 31 (25.4 %) patients had compensated type 2 diabetes mellitus (DM).

Chronic kidney disease (CKD) with a glomerular filtration rate (GFR) below 40ml/min/1.73m^2 was found in 11 patients (9.0 %), 4 (3.2 %) patients had anaemia. No lung diseases such as bronchial asthma or chronic obstructive pulmonary disease were found in this group.

All patients at the pre-hospital stage and in the hospital were treated in accordance with the clinical protocol for the treatment of patients with STEMI of the Ministry of Health of the Russian Federation (2016) [7].

The absence of primary PCI was explained by refusal of coronary angiography (CAG) (age restrictions) in 14 (11.5 %) patients, and intolerance of contrast or anaesthetic in 8 (6.5 %) patients.

All the other 100 patients in this group underwent CAG. 27 (27 %) patients had intact coronary vessels, 42 (42 %) patients had a stenosis with severity of less than 50 %, and 31 (31 %) patients (all patients with type 2 DM) had a distal type of coronary stenosis.

The GRACE, TIMI, RECORD, PREDICT and PURSUIT scales were used to predict the risk of short-term complications in patients with NSTE-ACS without PCI.

The study design consisted of an initial assessment of the prognosis of fatal and non-fatal complications in patients with NSTE-ACS without PCI on hospital admission.

The study endpoint was then assessed 30 days after the admission. After the discharge, the development of complications (fatal and non-fatal) and repeat hospitalisations were assessed by outpatient clinic staff.

Statistical analysis

The results obtained were processed using the StatSoftStatistica 10.0 programme. For the assessment of the normality of the distribution of quantitative data Kolmogorov-Smirnov, Shapiro-Wilk criterions were used. Qualitative data are presented as relative indices (fractions, %). To analyse intergroup differences in quantitative characteristics, descriptive statistics were used with the Student's t-test and the Mann-Whitney rank U criterion, depending on the normality of the distribution. The χ^2 test, and Fisher's exact test when the number of observations was small, was used to identify differences in the frequencies of values of qualitative indicators between groups and to assess their statistical significance.

To assess the prognostic significance of the above-mentioned scales and their criteria, sensitivity (Se) and specificity (Sp) and relative risk (RR) with 95 % confidence interval (CI) were calculated.

The results were considered reliable at a significance level of $p < 0.05$.

Results

The analysis of the initial examinations and data from the short-term scales in NSTE-ACS patients without PCI showed an unclear distribution of the number of patients in relation to the degree of prognosis for complications (Table 1).

A high risk of complications was found in all five short-term scales, but the number of patients at this risk ranged from 1.6 % (PREDICT) to 36.9 % (TIMI).

The moderate risk of complications in NSTE-ACS patients without PCI was reported for the four scales, ranging from 23.8 % (PURSUIT) to 61.5 % (TIMI), except for the RECORD scale (where this risk level is

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Table 1. **Distribution of NSTE-ACS patients without PCI by risk stratification according to the scores of short-term prognostic scales**

Risk	GRACE, %	RECORD, %	PREDICT, %	TIMI, %	PURSUIT, %
High	20.5	18	1.6	36.9	7.4
Moderate	42.6	–	54.1	61.5	23.8
Low	36.9	82	44.3	1.6	68.8

Table 2. **Relationship of primary prognostic short-term scales to in-hospital mortality in NSTE-ACS patients without PCI**

Scales	Ratio	High risk		Moderate risk		Low risk	
		Assigned	Died	Assigned	Died	Assigned	Died
GRACE	absolute number n=	25	4	52	–	45	–
RECORD	absolute number n=	22	3	–	–	100	1
PREDICT	absolute number n=	2	1	66	3	54	–
TIMI	absolute number n=	45	4	75	–	2	–
PURSUIT	absolute number n=	9	2	29	1	84	1

not reported). Diametrically, the number of patients classified as low risk ranged from 1.6 % (TIMI) to 82 % (RECORD).

The development of fatal complications was only recorded on the first day of hospitalisation. During the two years of the study, 4 (3.3 %) NSTE-ACS patients without PCI died.

Given the presence of mortality in NSTE-ACS patients without PCI, we analysed the comparability of mortality and risk score as assessed by short-term prognostic scales at first admission (Table 2).

All 4 dead patients (100 %) were included in the high-risk category according to the GRACE and TIMI scales. However, the number of patients classified as high risk according to these scales is remarkable; according to the TIMI scale, there are 2 times more of these patients than according to the GRACE scale (45 patients and 25 patients, respectively).

Looking at the data on the risk distribution according to the RECORD scale, 3 patients (75 %) were included in the high-risk category and one patient was classified as being at low risk on admission.

Regarding the PURSUIT scale, two patients (50 %) were classified as high risk, with one patient classified as moderate and one as low risk.

On the PREDICT scale, as only two patients were in this category at the initial risk assessment for prognosis of complications, one patient (25 %) entered the high risk category. The remaining three patients were classified as moderate risk at the initial assessment.

Given the variation in the number of patients assigned to a particular risk category for fatal complications, sensitivity, specificity, and relative risk with 95 % CI were calculated to assess the prognostic significance of the above-mentioned scales (Table 3).

When determining the ratio of sensitivity and specificity for predicting fatal complications, the GRACE, TIMI and RECORD scales had higher prognostic values for this category of patients than the PREDICT and PURSUIT scales (Table 3).

Complications occurred in 16 patients (13.5 %) with NSTE-ACS without PCI during the hospitalisation and up to 30 days in the outpatient setting. Two patients (1.7 %) were hospitalised for the recurrent MI.

Table 3. **Comparative analysis of scales in sensitivity and specificity in patients with NSTE-ACS without PCI regarding the development of fatal complications**

Death	Se	Sp	RR (95 % CI)	X^2	p
GRACE	1.000	0.805	*	16.0461	0.0003
RECORD	0.750	0.839	13.636 (1.487-125.009)	9.07998	0.0025
PREDICT	0.250	0.992	20.00 (3.372-118.628)	15.9314	0.0003
PURSUIT	0.500	0.941	12.556 (1.997-78.953)	11.3423	0.0034
TIMI	1.00	0.695	*	7.07646	0.0290

Note. *RR was not calculated due to the absence of events in one of the groups.

Table 4. **Ratio of NSTE-ACS patients without PCI classified into risk groups for developing non-fatal complications**

Scales	Ratio	High risk		Moderate risk		Low risk	
		Assigned	Complications	Assigned	Complications	Assigned	Complications
GRACE	absolute number n=	21	8	52	7	45	1
RECORD	absolute number n=	19	4	–	–	99	12
PREDICT	absolute number n=	1	1	63	8	54	7
TIMI	absolute number n=	41	7	75	8	2	1
PURSUIT	absolute number n=	7	3	28	5	83	8

The paroxysmal form of AF was observed in 4 (3.4%) patients. Early postinfarction angina manifested in 5 (4.2%) patients and episodes of cardiac asthma due to hypertensive crisis were also recorded in 5 (4.2%) patients.

A comparative analysis of patients with non-fatal complications and risk classification at initial hospital assessment was performed, taking into account the development of non-fatal complications in this group of patients during the first 30 days and including patients who died (Table 4). There were significant discrepancies in the number of patients with non-fatal complications and the risk categories obtained at the initial assessment of prognosis.

For example, according to the PREDICT scale, only one patient was at high risk of complications, while the rest were at moderate and low risk (see Table 4). According to the RECORD scale, out of 16 patients with non-fatal complications, 4 patients had a high risk of complications and 12 patients had a low risk. The GRACE (8 patients) and TIMI (7 patients) scales had the highest number of patients with a high risk of non-fatal complications, but at the same time up to 50% of patients had a moderate risk of complications according to these scales.

We analysed the sensitivity and specificity of the presented scales in determining the prognosis of non-fatal complications in NSTE-ACS patients without PCI (Table 5), taking into account the revealed discrepancies between the number of patients classified in the complication prognosis categories and the number of patients who developed complications.

When determining the ratio of the sensitivity and specificity values of the short-term scales in relation to the prognosis of non-fatal complications in NSTE-ACS patients without PCI, the data obtained from the RECORD and TIMI scales did not reach the criterion of reliability. The PURSUIT and PREDICT scales showed high specificity but low sensitivity for the development of non-fatal complications in this group of patients. Only the GRACE scale showed high values of sensitivity and specificity regarding the prognosis of non-fatal complications in NSTE-ACS patients without PCI, compared to other scales studied.

Taking into account the obtained data of sensitivity and specificity of the short-term scales used in this study regarding the development of fatal and non-fatal complications, it is possible to use a unified scale for short-term prognosis in NSTE-ACS patients without PCI for the practical work of a physician. For this purpose, the ratio of all patients with complications to those with initial risk stratification was assessed (Table 6).

When analysing the distribution of NSTE-ACS patients without PCI, the majority of patients who developed complications, regardless of the outcome, were in the high-risk category according to the GRACE (60%) and TIMI (55%) prognostic scales. The lowest number of patients who developed complications were classified in the primary prognosis of complication development according to the PURSUIT (25%) and PREDICT (10%) scales.

According to the RECORD scale, 35% of patients who experienced complications of varying severity were classified in the high-risk category.

Table 5. **Comparative analysis of scales in sensitivity and specificity in patients with NSTE-ACS without PCI regarding the development of non-fatal complications**

Complications	Se	Sp	RR (95% CI)	X^2	p
GRACE	0.500	0.851	6.059 (3.113-11.792)	15.6084	0.0004
RECORD	0.250	0.851	1.719 (0.620-4.765)	1.04581	0.3064
PREDICT	0.063	1.000	7.733 (4.823-12.401)	6.37324	0.0413
TIMI	0.438	0.663	1.442 (0.579-3.588)	3.15078	0.2069
PURSUIT	0.188	0.960	3.626 (1.339-9.820)	6.53129	0.0381

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Table 6. **Ratio of NSTE-ACS patients without PCI matched by risk group regarding the development of fatal and non-fatal complications**

Scales	Ratio	High risk		Moderate risk		Low risk	
		Assigned	Any compications	Assigned	Any compications	Assigned	Any compications
GRACE	absolute number n=	25	12	52	7	45	1
RECORD	absolute number n=	22	7	–	–	100	13
PREDICT	absolute number n=	2	2	66	11	54	7
TIMI	absolute number n=	45	11	75	8	2	1
PURSUIT	absolute number n=	9	5	29	6	84	9

Table 7. **Comparative analysis of scales in terms of sensitivity and specificity in patients with NSTE-ACS without PCI in the development of complications regardless of outcome**

Complications	Se	Sp	RR (95 % CI)	X^2	p
GRACE	0.600	0.873	5.820 (2.670-12.685)	22.918	<0.001
RECORD	0.350	0.853	2.448 (1.106-5.417)	4.659	0.031
PREDICT	0.100	1.000	6.667 (4.354-10.207)	10.370	0.002
TIMI	0.550	0.667	2.091 (0.939-4.657)	3.372	0.067
PURSUIT	0.250	0.961	4.185 (1.976-8.866)	10.873	<0.001

Considering the search for the most informative short-term scale for the purpose of risk stratification regardless of the outcome of complication development in NSTE-ACS patients without PCI, a comparative analysis of the scales was performed according to the criteria of sensitivity and specificity (Table 7).

The values of the TIMI scale obtained in this study did not meet the criterion of validity in terms of sensitivity and specificity for the development of all categories of complications in patients with NSTE-ACS without PCI. The RECORD, PREDICT and PURSUIT scales generally have high specificity but low sensitivity. In patients with NSTE-ACS without PCI, the GRACE scale was the most informative scale for prognosis of complications regardless of outcome.

Discussion

All of the short-term scales presented in this study have an evidence base for their ability to predict complications in patients with ACS [8]. However, it should be taken into account that the algorithms of these scales were developed in the context of heterogeneous clinical situations with heterogeneous medical approaches and patients belonging to different ethnic groups.

Scales such as GRACE, RECORD and PREDICT have been developed and proposed for ACS situations regardless of ST segment changes and have a single set of values. TIMI scale is also developed and proposed for ACS with and without ST elevation, but has two variants of set of values specifically for each ACS situation. The prognostic value of these scales lies in the assessment of the risk of death, mortality and the development of MI. Only the PURSUIT scale estimates the risk of death, MI in NSTE-ACS patients for the period of monthly follow-up in patients without PCI [9].

There is insufficient information in the literature to compare the short-term prognostic scales GRACE, RECORD, PREDICT, TIMI and PURSUIT in NSTE-ACS without PCI.

However, in routine clinical practice, it is necessary to have a unified scale for risk stratification of the development of short-term complications, which will allow a quicker decision on treatment, due to the daily need of the physician to make a decision on the tactics of patient management.

In our study, we are particularly interested in the prognostic significance of the TIMI and PURSUIT scales, which have a specific set of markers for NSTE-ACS patients.

Regarding the TIMI scale, Antman E. M. et al. developed a comprehensive approach to determine the risk of death, MI, recurrent angina and/or the need for urgent revascularisation in patients with NSTE-ACS.

In our study of NSTE-ACS and non-PCI patients, this model showed high sensitivity and specificity only for the prediction of fatal complications (Se = 1.00 Sp = 0.695 at $X^2 = 7.07646$, p = 0.0290) in contrast to the prediction of non-fatal complications (Se = 0.438 Sp = 0.663 95 % CI = 1.442 (0.579–3.588) at $X^2 = 3.15078$, p = 0.2069). Similarly, this model did not demonstrate reliability in predicting short-

term complications as a function of outcome (Se = 0.550 Sp = 0.667 95 % CI = 2.091 (0.939-4.657) X^2 = 3.372, p = 0.067).

The prognostic significance of the short-term PURSUIT scale is based on Platelet Glycoprotein IIb-IIIa in unstable angina: Receptor Suppression Using Integrilin Therapy study. It assesses the risk of death and MI in NSTE-ACS patients over a one-month follow-up period in patients without PCI.

In our study of NSTE-ACS patients without PCI, we did not find a superior prognostic performance of this scale compared to other short-term scales studied. Both in the prediction of fatal complications (Se = 0.500 Sp = 0.941 95 % CI = 12.556 (1.997–78.953) X^2 = 11.3423 at p = 0.0034) and non-fatal complications (Se = 0.188 Sp = 0.960 95 % CI = 3.626 (1.339 – 9.820) X^2 = 6.53129 at p = 0.0381), and in predicting complications independent of outcome (Se = 0.250 Sp = 0.961 95 % CI = 4.185 (1.976-8.866) X^2 = 10.873 at p < 0.001) showed not only high specificity but also low sensitivity.

The PREDICT scale was proposed as a risk stratification for short-term prognosis after hospitalisation for ACS (acute MI and unstable angina).

The analysis of the prognostic efficacy with regard to the development of complications in NSTE-ACS patients without PCI showed that this scale had not only a high specificity but also a low sensitivity in all three risk assessment categories, regardless of the outcome of the complications development. Fatal complications (Se = 0.250 Sp = 0.992 95 % CI = 20.00 (3.372-118.628) X^2 = 15.9314 at p = 0.0003); non-fatal complications (Se = 0.063 Sp = 1.000 95 % CI = 7.733 (4.823-12.401) X^2 = 6. 37324 at p = 0.0413); when assessing the development of complications regardless of outcome (Se = 0.100 Sp = 1.000 95 % CI = 6.667 (4.354–10.207) X^2 = 10.370 at p = 0.002).

In order to create the RECORD prognostic scale, the ACS registry was created in domestic hospitals, which suggests its relevance for the Russian population and characterises its prognostic efficacy in relation to the development of mortality and MI in the hospital period.

In the study carried out, the RECORD scale showed high values of sensitivity and specificity while determinating the prognosis of fatal complications (Se = 0.750 Sp = 0.839 95 % CI = 13.636 (1.487–125.009) X^2 = 9.07998 with p = 0.0025), surpassing the ability to predict non-fatal complications (Se = 0.250 Sp = 0.851 95 % CI = 1.719 (0.620–4.765) X^2 = 1.04581 with p = 0.3064) and to predict any complications (Se = 0.350 Sp = 0.853 95 % CI = 2.448 (1.106-5.417) X^2 = 4.659 with p = 0.031).

A comparative analysis of the GRACE scale in predicting short-term complications in patients with NSTE-ACS without PCI showed high sensitivity and specificity in predicting the development of fatal (Se = 1.000 Sp = 0.805 95 % CI = X^2 = 16.0461 at p = 0.0003) and non-fatal (Se = 0. 500 Sp = 0.851 95 % CI = 6.059 (3.113–11.792) X^2 = 15.6084 at p = 0.0004) complications, and in predicting complications regardless of outcome (Se = 0.600 Sp = 0.873 95 % CI = 5.820 (2.670–12.685) X^2 = 22.918 at p < 0.001), compared to all other scales examined in this study.

Conclusion

Thus, in NSTE-ACS patients without PCI, only the GRACE scale showed higher sensitivity and specificity than the short-term scales used in this study (RECORD, PREDICT, TIMI and PURSUIT), when comparing the ability to predict the short-term fatal and non-fatal complications, as well as any type of adverse outcomes. At the same time, scales such as TIMI and RECORD showed significantly higher values of sensitivity and specificity in predicting the development of fatal complications in this category of patients compared to the PREDICT and PURSUIT scales.

Conflict of interest: none declared.

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Acute myocardial infarction: biological role of postinfarction tissue

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Abstract

This study aimed to analyze morphological changes of postinfarction tissue during the restorative period after acute myocardial infarction (AMI), which, in our opinion, can change the perception of AMI in terms of its biological significance.

Methods. Objects of the study were cardiac biopsy specimens from 27 AMI patients who died in the hospital within 7 to 34 days after the onset of AMI, as well as heart biopsy specimens from 8 people aged 45 to 61 years old who deceased due to an unnatural cause (car accident) and whose autopsies revealed large foci of postinfarction tissue. The deceased patients had history of coronary heart disease (CHD) and arterial hypertension (AH).

Results. During the autopsy we diagnosed extensive intramural myocardial infarctions localized in the anterior-lateral walls of the left ventricle with the infarction zone spreading to the apex and the anterior part of the interventricular septum. All deceased patients had a severe atherosclerotic lesion in left anterior descending artery; thrombotic masses were revealed in the upper third of coronary artery in 19 deceased patients (11 men and 8 women). Postinfarction fibrous tissue was detected at the infarction site on average by 29 to 30 days after the onset of AMI. The special feature was that its fibers were oriented parallel to the preserved muscle fibers, and the remains of the preserved muscle tissue fibers, breaking on the border with the infarction site, were continued by the fibers of newly formed postinfarction connective tissue. There was a small amount of glycogen and oxidation-reduction enzymes present in the postinfarction tissue, which were also present in the preserved cardiomyocytes.

Conclusion. Thus, according to the results obtained, AMI is a compensatory-adaptive process aimed at correcting the anatomical-physiological mismatch between

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hypertrophied myocardium and the state of coronary vessels affected by atherosclerotic process in postnatal (often late) ontogenesis.

Key words: myocardial infarction, regeneration, compensatory-adaptive process, vascular atherosclerosis.

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Introduction

Myocardial infarction (MI) is one of the clinical forms of coronary heart disease, and is characterised by an ischemic necrosis of myocardial area due to atherosclerotic vascular lesions [1, 2]. Due to prolonged ischemia of myocardial area, a focus of necrosis with leukocyte shaft formation occurs [3]. The pathogenesis of acute myocardial infarction (AMI) is based on the following mechanisms: destruction of atherosclerotic plaque, due to sudden increase of sympathetic nervous system activity (as a result of elevated blood pressure (BP), sudden increase of HR and intensification of coronary circulation) [1, 2]. The thrombus formation in the area of ruptured atherosclerotic plaque [3, 4] and vasoconstriction are also key components. Analyzing AMI morbidity and mortality [5, 6], the authors have concluded that after acute stage of the disease and in rehabilitation period — the greatest importance is given to the state of preserved myocardial tissue, and the role and state of postinfarction area is often neglected.

The aim is to analyze morphological changes occurring in postinfarction tissue during the restorative period after AMI, which, in our opinion, can change the perception of AMI in terms of its biological significance.

Methods

Objects of the study were cardiac biopsy specimens from 27 AMI patients who died in the hospital within 7 to 34 days after the onset of AMI (14 males, 13 females), as well as heart biopsy specimens from 8 people aged 45 to 61 years old (5 men, 3 females) who died due to an unnatural cause (car accident) and whose autopsies revealed large foci of postinfarction tissue (without confirmed AMI history). The deceased patients had history of coronary heart disease (CHD) and arterial hypertension (AH).

For histopathology, 10 slices were cut from the infarct areas and at the border with the preserved muscle tissue. The prepared paraffin sections (6 μm) were stained with standard hematoxylin and eosin, van Gieson and Heidenhain's iron hematoxylin. Part of the material was examined for redox enzymes: tetrazolium method to detect succinate dehydrogenase, lactate dehydrogenase and NAD-diaphorase [1].

Significance relative to control: Mann-Whitney U criterion ($p < 0.001$).

The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki.

Results

Autopsy diagnosed the extensive intramural myocardial infarctions localized in the anterior-lateral walls of the left ventricle with infarction zone spreading to the apex and the anterior part of the interventricular septum. All deceased patients had a severe atherosclerotic lesion in left anterior descending artery; thrombotic masses were found in the upper third of coronary artery in 19 deceased (11 men and 8 women).

The healing process of AMI went according to the classical course described in the available literature. The formation of postinfarction tissue drew our attention.

During the muscle detritus resorption, many different cellular elements gradually accumulated in the necrotic focus. These included macrophages and lymphocytes as well as a significant number of spindle cells containing oval or oval elongated large nuclei with soft clumps of chromatin (unlike coarse, clumpy chromatin of fibroblast nuclei) evenly distributed along the nucleus. The cytoplasm of such cells was stained pale pink. According to morphological parameters, such cells corresponded to myoblasts. Specific large nuclei with serrated chromatin

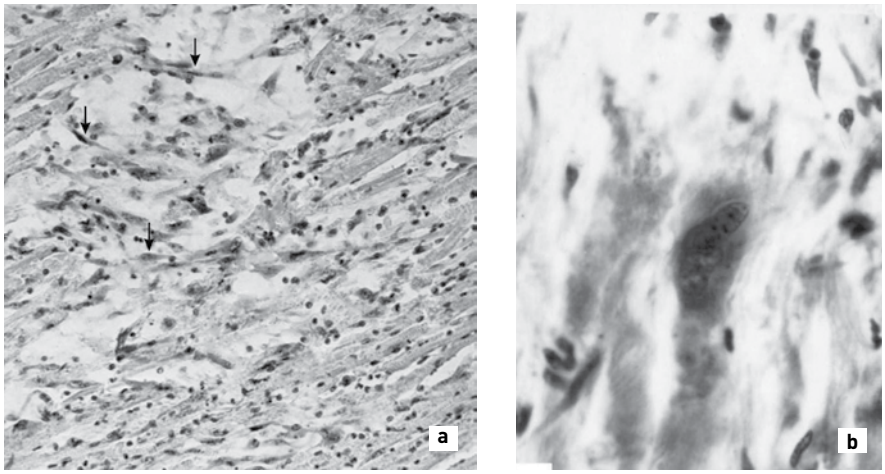

Fig. 2. The pattern of mutual arrangement of muscle fibers and postinfarction tissue. Autopsy data: continuation of the fibers of the newly formed tissue by the stumps of muscle fibers and their parallel course to the preserved muscle fibers. Van Gieson staining, x 400

arrangement were detected, which corresponded to the criterion of cardiomyocyte mitosis. A small ring of cytoplasm, which was stained pale pink with eosin, was often detected around such nuclei, which gave them similarity to myoblastic-like structures.

Postinfarction fibrous tissue was detected at the infarction site on average by 29 to 30 days after the onset of AMI. The special feature was that its fibers were oriented parallel to the preserved muscle fibers, and the remains of the preserved muscle tissue fibers, breaking on the border with the infarction site, were continued by the fibers of newly formed postinfarction connective tissue.

Due to the significant cardiomyocyte hypertrophy in the myocardium, the formation of large foci of tissue arisen in the place of the dead myocardium was observed. When analyzing the newly formed tissue, low-differentiated myogenic elements — myoblasts and muscle buds along with the connective tissue elements participated in its formation (Fig. 1). The structure of the mutual compound of the preserved muscle and fibers of the newly formed postinfarction tissue was noteworthy — the stumps of the muscle fibers at the border with the postinfarction tissue were cut off and continued by the fibers of the newly formed postinfarction tissue. At the same time, its fibers continued their course, parallel to the preserved muscle fibers (Fig. 2). The postinfarction tissue showed a small amount of glycogen and redox enzymes, which were also present in the preserved cardiomyocytes.

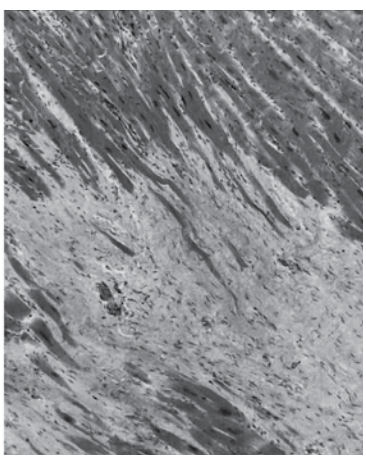

Fig. 1. Low-differentiated muscle elements in the forming postinfarction tissue: a) muscle bud at the border with postinfarction cardiosclerosis, x Immersion; b) myoblasts in the zone of postinfarction tissue formation. Hematoxylin and eosin staining, x 400

Discussion

It is known from the literature that in the majority of cases, people who have suffered an AMI gradually improve their state of health [1-5], haemodynamics stabilise and electrophysiological parameters normalise. The majority of people, especially young and middle-aged people, return to work. The explanation for this is the restoration of functional activity of the heart due to regenerative hypertrophy (intracellular regeneration). In our opinion, taking into account the results of the present work, the restoration of cardiac activity is associated with the development of a specific tissue at the infarct site.

There are reports in the literature that connective tissue is involved in the contractile activity of a number of muscular organs: skeletal muscle [7, 8], in the heart during diastole [5]. Data from an experimental study showed the contraction of tissue formed in place of dead myocardium as a result of ligation of the descending coronary artery.

The ability of the connective tissue to contract was explained by the fact that it contains myofibroblasts — cells containing smooth muscle myosin with a contractile apparatus. Especially noteworthy is the discovery of a specific protein in fibroblasts called caldesmon, which is similar in structure to the tro-

pomyosin complex and is involved in the interaction between actin and myosin in heart and skeletal muscle [7].

In the studied heart biopsy specimens, a peculiar tissue appeared in the place of the dead heart muscle, with the main characteristics of a fibrous component, but with the participation of the heart muscle elements in its formation. A kind of myofibrous tissue with the ability of contractile activity was formed. When studying histological preparations of the deceased heart, there was an evidence that the fibres of the newly formed tissue, being a continuation of the stumps of muscle fibres, continued their parallel course, participating in the contractile activity of the heart. Indirect evidence of this is the presence in the newly formed tissue of all the components present in cardiomyocytes (glycogen, redox enzymes).

During the contractile activity of the normal heart, the interstitial connective tissue contracts together with the muscle fibres. On this basis, it is difficult to imagine that post-infarction tissue remains intact outside the contractile rhythm. If this is the case, the role of myocardial infarction as a pathological process is questionable.

Several factors contribute to the aetiology of AMI: atherosclerotic lesions of the coronary arteries and hypertrophic changes in the left ventricular myocardium. In our opinion, the occurrence of AMI in these conditions can be regarded as a compensatory adaptive process aimed at eliminating the discrepancy between hypertrophic myocardial mass and altered vessels incapable of providing adequate blood supply to the myocardium. After AMI, the dead tissue is replaced by undemanding tissue that is resistant to hypoxia and, at the same time, participates to some extent in the contractile activity of the heart. Thus, the formation of post-infarction myofibrous tissue in the heart leads to an optimisation of the ratio between pathologically altered vessels and left ventricular muscle mass.

Conclusion

On the basis of the evidence presented here, indicating the potential involvement of post-infarct tissue in cardiac contractility, AMI is a compensatory and adaptive process designed to correct the anatomical and physiological mismatch between the hypertrophied myocardium and the state of the coronary arteries affected by the postnatal atherosclerosis process.

Conflict of interest: none declared.

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The use of antiplatelet agents in patients with new coronavirus infection exampled by acetylsalicylic acid

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Abstract

The outbreak of the new coronavirus infection, which subsequently led to the pandemic, negatively affected preventive and treatment measures in patients with acute and chronic noncommunicable diseases, including cardiovascular diseases (CVDs). Arterial hypertension, diabetes mellitus, chronic kidney disease, coronary heart disease, obesity are the most prevalent diseases in the structure of multimorbidity that aggravate the outcomes in patients with COVID-19.

Patients with COVID-19 and in the absence of CVDs may develop cardiovascular complications, including life-threatening ones. In addition, some therapeutic agents administered at the beginning of the pandemic in experimental settings, such as antimalarial and antiviral drugs, may cause cardiovascular adverse events.

The severe course of COVID-19 is accompanied by the development of inflammatory alveolar lesions. Moreover, endothelial dysfunction also occurs, which leads to micro- and macrothrombosis in the blood vessels. Activation of thrombosis contributes to the development of thrombotic/thromboembolic complications.

Since activated platelets may contribute to the pathogenesis of thrombotic complications, the feasibility of using antiplatelets (acetylsalicylic acid, P2Y12 receptor blockers, dipyridamole) in COVID-19 is currently being studied. The available clinical and scientific data demonstrates the need for a comprehensive approach to the prevention and treatment of new coronavirus infection, which should

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include viral replication management, blocking the release of cytokines and other biologically active substances, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function.

Keywords: antiplatelet drugs, acetylsalicylic acid, COVID-19.

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Introduction

An outbreak of novel coronavirus infection (COVID-19), first reported on 8 December 2019 in Hubei Province, China, was defined as a pandemic by World Health Organization (WHO) experts on 11 March 2020. The pandemic has had a negative impact on a range of preventive and treatment interventions for patients with acute and chronic non-communicable diseases (CNCDs), including cardiovascular diseases (CVDs). Evidence from prospective and retrospective studies continues to shape our understanding of the long-term effects of COVID-19 and demands further study. It is extremely important to analyse the information on the characteristics of the endothelial thrombo-inflammatory syndrome in COVID-19 and the complex therapy of patients with this disease and high cardiovascular risk, with a focus on the appropriate use of acetylsalicylic acid, which is the subject of this article.

The burden of CVDs in the COVID-19 pandemic era

Arterial hypertension (AH), diabetes mellitus (DM), chronic kidney disease (CKD), coronary heart disease (CHD), and obesity are the most common comorbidities in the structure of multimorbidity and further exacerbate the adverse outcomes of COVID-19 [1]. To date, many investigators have reported that patients with CVDs have an increased risk for a more severe course of COVID-19 and the development of life-threatening complications.

According to Pranata R. et al. AH was associated with an increased combined adverse outcomes, including death, severe COVID-19, acute respiratory distress syndrome (ARDS), intensive care unit (ICU) treatment, and progression of CVD in patients with COVID-19 (odds ratio (OR) 2.11, 95% confidence interval (CI) 1.85-2.40, $p < 0.001$) [2].

A meta-analysis of 30 studies published between February and April 2020, involving 6389 patients with COVID-19, showed that acute myocardial injury and symptomatic heart failure (HF) occur in 15.7% and 11.5% of patients, respectively [3].

The burden of CVD in the COVID-19 pandemic era should be viewed from several perspectives. Patients with cardiovascular risk factors and pre-existing CVDs have a high risk of adverse outcomes; patients with COVID-19 and in the absence of CVDs may develop cardiovascular complications, including life-threatening ones; some therapeutic agents administered early in the pandemic under experimental conditions, such as antimalarials and antivirals, may cause cardiovascular adverse events [4].

The above-mentioned factors contribute to the formation of new phenotypes of major CVDs and related complications, which, among other things, can develop even after a certain period of time after infection, even if the bronchopulmonary system is not involved in the pathological process (Fig. 1).

When talking about the long-term consequences of COVID-19, it is impossible not to mention such a term as "long-term COVID", which confirms the fact that the patient continues to suffer after the acute phase of the disease and clinical recovery. The WHO proposes define the post-COVID-19 state as the persistence of symptoms beyond 3 months after acute SARS-CoV-2 infection, lasting at least 2 months and not explained by another disease [6]. The mechanisms of persistent cardiovascular damage after acute illness are poorly understood. One possible explanation may be a chronic inflammatory response, which in turn may be exacerbated by obesity-related inflammatory signalling, partially controlled by perivascular adipose tissue through the release of adipokines and chemokines, exacerbating endothelial dysfunction through dissociation of endothelial nitric

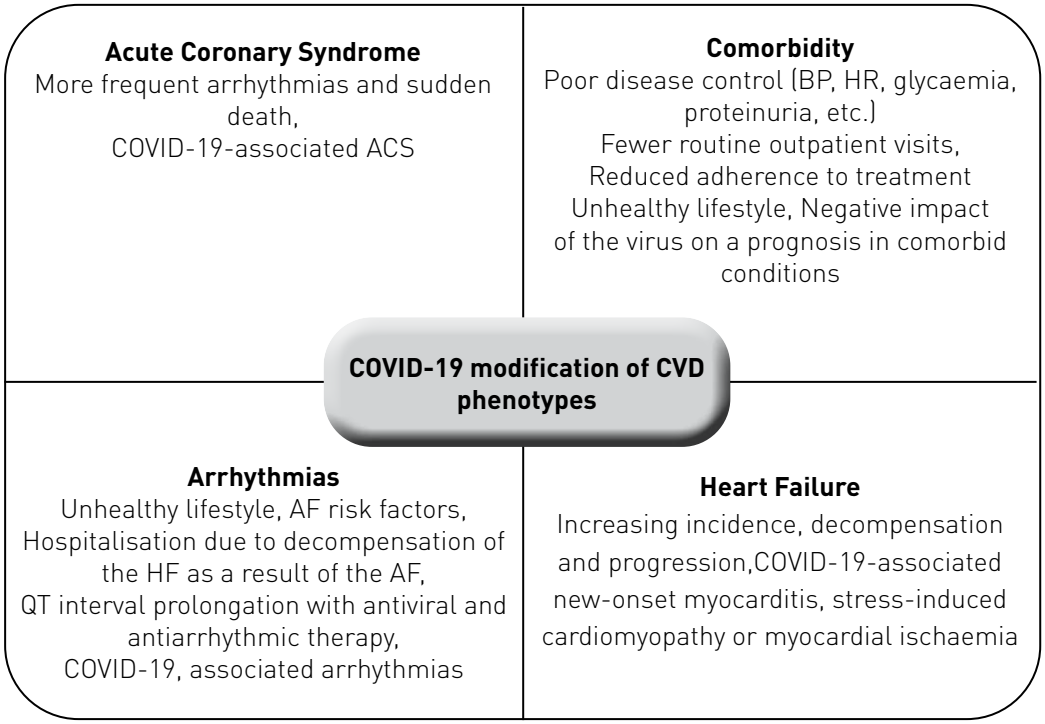

Fig. 1. New CVD phenotypes in the COVID-19 era

oxide synthetase and reactive oxygen species production [7].

COVID-19-associated endothelial thrombo-inflammatory syndrome

To date, sufficient data have been collected to demonstrate the different pathophysiological features and severity of COVID-19 disease in patients, which depend on age, leading risk factors and the presence of comorbidities.

In the severe course of COVID-19 associated with the development of pneumonia, hypoxaemia develops not only due to inflammatory alveolar damage, but also due to endothelial dysfunction leading to micro- and macrothrombosis in the vascular bed [8, 9].

Activation of thrombosis contributes to the development of thrombotic/thromboembolic complications. In addition, the development of microangiopathy with the presence of inflammation and thrombosis at the level of the microcirculatory bed without signs of thromboembolism has been observed, which is explained not only by the activation of thrombosis, but also by the direct effect of the SARS-CoV-2 virus on the endothelium and the rapidly progressing systemic immune inflammation. This results from an imbalance of T-cell activation with unregulated release of pro-inflammatory interleukins (ILs): IL-6, IL-7, IL-22, IL-17, etc., the cytokine storm triggers the processes of "immunothrombosis" leading to multiple organ failure and death [10, 11].

The pathobiology of coronavirus infection involves binding of the SARS-CoV-2 virus to the host angiotensin-converting enzyme 2 (ACE-2) receptor for entering into target cells. In this context, ACE-2 is considered to be an important modulator not only of the pathophysiological processes of several CVDs, including AH, CHD and HF, but also of the severity of symptoms associated with SARS-CoV2 virus infection.

ACE-2 receptors are found throughout the human body, on the airways cells, kidney, oesophagus, bladder, ileum, heart and central nervous system. ACE-2 is a key regulator of the renin-angiotensin system (RAS) and converts angiotensin II to angiotensin 1-7, which has protective vasodilatory and anti-inflammatory properties and counteracts the vasoconstrictive effects of angiotensin II [12, 13].

The SARS-CoV-2 virus binds to the catalytic site of the ACE-2 receptor and interferes with its ability to convert angiotensin II to angiotensin 1-7. As a result, the angiotensin II type 1 (ATR1) receptor, which is normally associated with ACE-2, is dissociated by the SARS-CoV-2 virus, allowing ATR1 to act freely and cause vasodilation, increased vascular permeability,

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oedema and ultimately the severe respiratory and cardiovascular manifestations of SARS-CoV-2 seen in some patients [14].

Evidence of disseminated intravascular coagulation (DIC) and pulmonary embolism is common in COVID-19. In a study by Tang N. [15] of 183 patients, the overall mortality rate was 11.5%; 71.4% of the patients who died and 0.6% of the surviving patients had evidence of disseminated intravascular coagulation during their hospital stay.

The intact endothelium of the vascular bed has so-called thromboresistance, which is caused by a number of factors, including negative surface charge and secretion of the antiaggregant prostacyclin, binding of thrombin by thrombomodullin and inactivation of other procoagulants (plasma factors V, VIII, IX and X), activation of the fibrinolytic system by synthesis of tissue plasminogen activator, production of nitric oxide, etc. [16].

It is important to note that damaged endothelium acts as a procoagulant factor. Adrenaline release and endothelin-1 secretion lead to transient vasospasm at the site of injury, which slows down blood flow and improves the interaction between platelets, coagulation factors and the site of injury. It also contributes to the decreased production of the physiological antiplatelet prostacyclin and increased release of platelet activators, stimulators of platelet adhesion and aggregation: adrenaline, ADP, Willebrand factor, thromboxane A2, platelet aggregation factor, etc. The anticoagulant activity of the endothelium is weakened; thrombomodulin activity, protein S synthesis, antithrombin III activation, tissue factor pathway inhibitor synthesis are reduced.

The work of Bois M. et al. seems to support the concept of microthrombi caused by COVID-19 [17]. In a small group of 15 individuals, the authors observed that postmortem fibrin microthrombi were more common (80%) than acute ischaemic injury (13%) and myocarditis (33%), suggesting a role for thrombosis in aggravating myocardial injury.

Elevated levels of cytokines (IL-1, IL-6, IL-17, IL-22, interferon-γ, tumour necrosis factor-α) may also contribute to myocardial damage, causing endothelial dysfunction, platelet activation, neutrophil recruitment and ultimately a hypercoagulable state [18].

Given the strong association of COVID-19 with increased thrombosis, the renaming of COVID-19 to MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) is being considered. The authors believe that in predisposed individuals, alveolar viral injury is followed by an inflammatory response and progressive endothelial thromboinflammatory syndrome with further multiorgan failure and death [19].

Issues in the complex management of patients with COVID-19

One of the main issues discussed in the resolution of the International Expert Council of the Eurasian Association of Therapists and the Russian Society of Cardiology on rehabilitation after COVID-19 was devoted to risk factors (RFs) for thrombosis formation in the post-hospital stage [20].

According to the results of the expert meeting, it was decided to consider COVID-19 as an independent risk factor for thrombosis formation and to include patients with the development of new diseases (CHD, HF, AH, type 2 DM) in the post-hospital period (up to 6 months, according to the available data) in a separate risk group for thrombotic events.

As activated platelets may also be involved in the pathogenesis of thrombotic complications, the appropriate use of antiplatelet drugs (acetylsalicylic acid, platelet P2Y12 receptor blockers, dipyridamole) is currently being investigated in COVID-19. Canzano P. therefore hypothesised that the cytokine storm described in COVID-19 patients may lead to sequential activation of cellular tissue factor (TF)-mediated coagulation, release of procoagulant microvesicles (MVs) and massive platelet activation. COVID-19 plasma added to the blood of healthy volunteers induced platelet activation similar to that observed in vivo. This effect was attenuated by a pre-incubation with tocilizumab, aspirin or a P2Y12 inhibitor [21].

The answer to this question cannot be clear, as antithrombotic therapy in COVID-19 may not only prevent the development of thrombosis and/or thromboembolism, but may also be the part of the pathogenetic treatment of the disease, reducing the severity of clinical manifestations and improving the prognosis. However, it should be noted that COVID-19 is associated with an increased risk of bleeding, which increases with the severity of the disease.

One of the most commonly recommended agents in cardiovascular and cerebrovascular pathology for primary and secondary prevention is acetylsalicylic acid (ASA). The action of ASA is based on the inacti-

vation of cyclooxygenase-1 (COX-1) and COX-2, which influence platelet activation and the action of prostanoids. COX-1 is involved in the conversion of arachidonic acid to prostaglandins and subsequently to thromboxane A2, a potent vasoconstrictor and stimulator of platelet activation and aggregation. COX-1 suppression is an irreversible process and persists throughout the life of the platelet. In addition, ASA acts through the acetylation mechanism to inactivate platelets by inhibiting glycoprotein P-selectin, preventing thrombin generation and increasing fibrinolysis [22, 23].

ASA suppresses the expression of genes involved in the activation of pro-inflammatory cytokines (tumour necrosis factor-α and interleukin-1β) and other mechanisms other than antiaggregation [24]. In particular, interleukin-1ß is the major mediator of platelet-induced activation of endothelial cells, causing enhanced release of chemokines and upregulation of endothelial adhesion molecules, which promotes adhesion of neutrophils and monocytes to the endothelium. The efficacy and safety of ASA administration have been confirmed in numerous trials and meta-analyses, allowing ASA to be considered as a standard of antithrombotic therapy [25-27].

The objective of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was to evaluate the efficacy and safety of aspirin (at a dose of 150 mg/day in addition to standard therapy) in patients hospitalised for COVID-19. The trial was conducted in 177 clinics in the UK, two clinics in Indonesia and two clinics in Nepal. The primary outcome was the occurrence of death within 28 days. The trial was registered on ClinicalTrials.gov (NCT04381936) [28].

Previous searches of the major bibliographic databases such as MEDLINE, Embase, bioRxiv, medRxiv and WHO using the search terms "coronavirus infections", "SARS-CoV-2. mp", "coronavirus" or "CORONAVIRUS.mp", "COVID.mp", "COVID-19.mp", "2019-nCoV.mp", "COVID19.mp", "SARS-CoV2.mp" or "SARS-Cov2. mp" and "aspirin.mp", "aspirin/" or "acetylsalicylic acid/", and for the medRxiv and bioRxiv systems, the term "aspirin" was not found in published randomised controlled trials evaluating the effect of aspirin in the treatment of patients with COVID-19, which prompted the RECOVERY study.

The characteristics of the patients included in the trial are shown in Table 1.

Table 1. **Baseline characteristics of patients**

	Prescribed treatment	
	Aspirin (n = 7351)	**Standard treatment (n = 7541)**
Age, (years)	59.2 (14.1)	59.3 (14.3)
< 70	5658 (77 %)	5786 (77 %)
70–79	1163 (16 %)	1165 (15 %)
⩾ 80	530 (7 %)	590 (8 %)
Gender		
Males	4570 (62 %)	4631 (61 %)
Females*	2781 (38 %)	2910 (39 %)
Ethnicity		
Europeoids	5474 (74 %)	5655 (75 %)
Negroids, Mongoloid and ethnic minorities	1176 (16 %)	1202 (16 %)
Unknown	701 (10 %)	684 (9 %)
Number of days since the onset of the symptoms	9 (7–12)	9 (6–12)
Number of days since hospital admission	1 (1–3)	2 (1–3)
Respiratory support		
None or oxygen therapy	4936 (67 %)	5036 (67 %)
Non-invasive ventilation	2057 (28 %)	2133 (28 %)
Invasive ventilation	358 (5 %)	372 (5 %)
Biochemical parameters		
C-reactive protein, mg/l	88 (47–146)	91 (47–150)
Creatinine, μmol/l	76 (63–93)	76 (62–92)
D-dimer, ng/ml	475 (205–1088)	489 (210–1083)
Pre-existing conditions		
Diabetes mellitus	1588 (22 %)	1659 (22 %)
Cardiovascular diseases	776 (11 %)	788 (10 %)
Chronic pulmonary diseases	1425 (19 %)	1411 (19 %)
Tuberculosis	20 (< 1 %)	21 (< 1 %)
HIV	25 (< 1 %)	21 (< 1 %)
Severe liver diseases†	67 (1 %)	53 (1 %)
Severe kidney failure‡	214 (3 %)	251 (3 %)
Any of the above-mentioned conditions	3154 (43 %)	3247 (43 %)
Use of corticosteroids		
Yes	6906 (94 %)	7109 (94 %)
No	441 (6 %)	425 (6 %)
No data	4 (< 1 %)	7 (< 1 %)
Test result for SARS-CoV-2		
Positive	7140 (97 %)	7327 (97 %)
Negative	87 (1 %)	86 (1 %)
Unknown	124 (2 %)	128 (2 %)

Notes. Data are presented as n (%), mean (SD) or median (IQR).
* Including 58 pregnant women.
† Requiring a constant supervision by a specialist.
‡ Glomerular filtration rate less than 30 ml/мin/1.73 м².

Aspirin (in combination with standard therapy) was not associated with a reduction in mortality compared with standard therapy. Within the first 28 days of hospitalisation, the mortality rate in the aspirin and standard of care groups was 17 % (p = 0.35), and the

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Table 2. **Effect of aspirin prescription on study outcomes**

	Prescribed treatment		OR (95% ДИ)	p
	Aspirin (n = 7351)	Standard treatment (n = 7541)		
Primary outcome				
Mortality within 28 days	1222 (17%)	1299 (17%)	0.96 (0.89–1.04)	0.35
Secondary outcome				
Discharge mean time of a living patient (interquartile range), days	8 (от 5 до > 28)	9 (от 5 до > 28)	—	—
Hospital discharge within 28 days	5496 (75%)	5548 (74%)	1.06 (1.02–1.10)	0.0062
Transition to invasive mechanical ventilation or death*	1473/6993 (21%)	1569/7169 (22%)	0.96 (0.90–1.03)	0.23
Invasive mechanical ventilation	772/6993 (11%)	829/7169 (12%)	0.95 (0.87–1.05)	0.32
Death	1076/6993 (15%)	1141/7169 (16%)	0.97 (0.90–1.04)	0.39
Secondary clinical outcomes				
Use of artificial ventilation	1131/4936 (23%)	1198/5036 (24%)	0.96 (0.90–1.03)	0.30
Non-invasive ventilation	1101/4936 (22%)	1162/5036 (23%)	0.97 (0.90–1.04)	0.36
Invasive mechanical ventilation	296/4936 (6%)	325/5036 (6%)	0.93 (0.80–1.08)	0.35
Successful cessation of invasive mechanical ventilation	135/358 (38%)	135/372 (36%)	1.08 (0.85–1.37)	0.54
Renal replacement therapy	273/7291 (4%)	282/7480 (4%)	0.99 (0.84–1.17)	0.93

Note. RR — The rate ratio for the incidence of death and discharge from hospital within 28 days, and the rate ratio for the transition to invasive mechanical ventilation or death (and its components).
* Excluding patients already on invasive mechanical ventilation at randomisation.

event rates did not differ between the pre-specified subgroups.

However, there was a small but statistically significant increase in the proportion of patients discharged within the first 28 days in the aspirin group (75% vs 74%; OR 1.06; 95% CI 1.02-1.10; p = 0.0062) (Table 2).

Thus, it was concluded that aspirin has a small advantage in the complex therapy of patients with COVID-19, which is not a sufficient reason to include aspirin in the scheme of routine therapy of patients with COVID-19.

Russian scientists analysed the efficiency of interaction of the aspirin molecule with the active centres of a number of proteins of the SARS-CoV-2 virus using the molecular docking method, and it was shown that aspirin is able to inhibit the activity of some of them, which may affect the design of further studies on this drug. The results of this study were published in the Journal of Molecular Structure in March 2022 [29].

The available clinical and scientific data demonstrates the need for a comprehensive approach: to the prevention and treatment of new coronavirus infection, which should include viral replication management, blocking the release of cytokines and other biologically active substances, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function.

Therefore, ASA, as an inexpensive, widely available, safe and time-tested anti-inflammatory, antithrombotic drug, can be considered as an additional therapeutic option for COVID-19 treatment, especially in the group of patients with cardiovascular pathology. In addition, experts of the European Society of Cardiology confirm the fact of necessity of continuation of ASC intake in persons with chronic coronary syndrome on COVID-19 background for secondary prevention.

Conclusion

Taking into account the available scientific evidence, a comprehensive approach to the prevention and treatment of new coronavirus infections is reasonable, which should include an impact on all pathogenetic mechanisms of the disease development: viral replication, blocking cytokine release, endothelial dysfunction, coagulation, fibrinolysis and, most importantly, platelet function. These data allow us to consider ASC as one of the possible additional treatment options for COVID-19, especially in the group of patients with cardiovascular pathology and high cardiovascular risk.

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Ventricular arrhythmias and prevention of sudden cardiac death

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Abstract
This review article presents updated European guidelines for the management of patients with ventricular arrhythmias (VA) and prevention of sudden cardiac death (SCD). New understanding of SCD epidemiology, modern concepts on genetics, imaging and a large volume of clinical data for stratification of VA and SCD risk, as well as advances in diagnostic assessment and therapeutic strategies contributed to the revision of the previous recommendations. In the given recommendations the leading role is given to genetic analyses, invasive and noninvasive methods of diagnostics, such as electrophysiological examination, programmed electric stimulation of heart, magnetic resonance imaging (MRI). In terms of preventive treatment, recommendations on expanding general education of the population, the principles of first aid to persons with sudden cardiac arrest and ensuring the availability of out-of-hospital cardiac defibrillation have been prioritized. The indications for beta-blockers, flecainide, implantable cardioverter-defibrillators, catheter ablation, implantable programmed antitachycardia stimulation devices, and left-sided sympathetic cardiac denervation have expanded considerably.
Keywords: prevention, genetic risk factors, ventricular arrhythmias, sudden cardiac arrest, sudden death.

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Introduction

Sudden cardiac death (SCD) accounts for about 50 % of all deaths from cardiovascular disease (CVD), with 50 % of SCDs occurring as the first manifestation of heart disease, i.e. as a cardiac cause of sudden death [1, 2]. Regardless of gender, the incidence of CHD increases significantly with age. With a very low incidence in infancy and childhood (1 per 100.000 person-years), the incidence of CHD in middle-aged people (in the fifth to sixth decade of life) is approximately 50 per 100.000 person-years [3]. In the eighth decade, the incidence is at least 200 per 100.000 person-years. At every age, and even after the correction of the risk factors for coronary heart disease (CHD), men have a higher rate of CHD than women[4]. CHD accounts for 75–80 % of all cases of CHD. Studies by various authors suggest that there is a correlation between age and the cause of CHD. In 20–30 years, primary electrical diseases and cardiomyopathies, as well as myocarditis and coronary anomalies [5]; in 30–40 years, 50 % of cases of VSS are associated with CHD, especially acute coronary syndrome [6]. In the 40–50 year age group, CHD is associated with potentially inherited electrical or structural non-ischemic heart disease [7]. Chronic structural diseases such as acute coronary events or chronic coronary artery stenoses, heart defects and heart failure (HF) are prevalent in the elderly. 10–20 % of all deaths in Europe are SCDs. Over the course of a year, 300.000 people in Europe experience episodes of out-of-hospital cardiac arrest requiring emergency medical care [8].

Let us briefly review the current definition of sudden cardiac arrest (SCA) and SCD:

- SCA is the sudden cessation of normal cardiac activity with haemodynamic collapse.
- SCD is sudden natural death presumed to be due to cardiac disease, witnessed and occurring within 1h of symptom onset or, in the absence of witnessing, within 24 h of the last time the deceased was seen alive. SCD at autopsy is defined as sudden death from unknown or cardiac causes.

Updates

Here are the key updates for 2022 on VA prophylaxis in SCD. The new guidelines call for the optimisation of implantable cardioverter defibrillator (ICD) programming and algorithms for the management of patients with the "electrical storm" type sustained ventricular tachycardia (SVT). This term refers to SVT occurring three or more times within 24 hours (at least 5 minutes apart), each requiring emergency intervention. New sections on diagnostic evaluation are described in detail, including pharmacological provocation tests, genetic testing and systematic screening of probands and relatives with primary electrical heart disease. Detailed flowcharts and guidelines for the diagnostic evaluation of VA in patients with no known heart disease are presented. ICD guidelines are updated and algorithms for the management of patients with SVT and frequent recurrent ICD discharges are proposed.

New sections and concepts are covered in detail, such as provocative diagnostic tests, genetic testing, diagnostic evaluation at first presentation with ventricular tachycardia (VT) in patients without known cardiac disease, management of patients with electrical storm, and features of device therapy. The focus is on the universal availability of basic life support and access to automated external defibrillators (AEDs). The primary requirements in this regard are the public availability of AEDs in locations with the highest probability of SCA [9] and the increase of emergency out-of-hospital cardiopulmonary resuscitations (CPRs) by bystanders. It is recommended that life support education be promoted in the community for the later[10]. It is important to use all means of alerting bystanders who have received basic life support training.

General aspects of the VA treatment

General aspects of the treatment of UA emphasise that optimal drug therapy (ODT), including angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin receptor blockers and neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), beta-blockers (BBs) and SGLT2 inhibitors, is indicated in all patients with HF with reduced left ventricular ejection fraction (LVEF). Direct current cardioversion (DC) is recommended as a first-line therapy for patients with sustained monomorphic VT (SMVT) with high tolerance to therapy. ICD implantation is recommended for patients with an estimated survival of > 1 year. In patients with haemodynamically tolerable SMVT and high risk of SCD, intravenous (IV) procainamide (novocainamide) should be administered, and IV amiodarone may be discussed in the absence of an established diagnosis. In SMVT/non-sustained

polymorphic VT (NPVT)/ventricular fibrillation (VF) caused by premature ventricular complexes (PVCs), catheter ablation may be considered as an alternative to ICDs. In the early phase after myocardial infarction (MI), the use of a portable cardioverter defibrillator is recommended in some patients.

CHD patients

Catheter ablation is preferable to escalating antiarrhythmic drug (AAD) therapy in patients with CHD despite ongoing amiodarone therapy for the persistence of recurrent symptomatic SMVT or recurrent ICD discharges. In CHD patients with an abnormal aortic bifurcation of the coronary artery and a history of prevented SCAs, postoperative cardiac imaging under exercise conditions is recommended as an adjunct to cardiopulmonary exercise testing [11]. ICD is recommended in patients with coronary artery spasm, survivors of SCAs, CHD patients with LVEF ⩽ 30 % despite ODT for ⩾ 3 months [12], and CHD patients with LVEF ⩽ 40 % and non-sustained VT (NVT) converting to SMVT during programmed electrical stimulation (PES). Catheter ablation can replace ICDs in CHD patients with well-tolerated SMVT and LVEF ⩾ 40 % [13], as well as augment ICDs when treatment with BB or sotalol is ineffective, manifested by recurrent symptomatic SMVT or recurrent ICD discharges.

Idiopathic VT or PVCs

Catheter ablation is recommended as first-line therapy for symptomatic idiopathic VT or PVC from the right ventricular outflow tract (RVOT) or left bundle branch of the His [14]. BBs, non-dihydropyridine calcium channel blockers (CCBs) or flecainide are only prescribed when catheter ablation is not possible or undesirable. The same applies to symptomatic idiopathic PVC/VT from other parts of the heart [15]. In patients with non-idiopathic PVC/VT, even with normal echocardiography (ECHO), even in patients with unexplained EF reduction with a PVC rate of at least 10 %, if PVC-induced cardiomyopathy is suspected, cardiac MRI should be scheduled[16]. Catheter ablation is also important in patients who are tolerant to resynchronisation therapy (RST) and who, despite medical therapy, have frequent, predominantly monomorphic PVCs that limit optimal biventricular pacing, and may be used for idiopathic PVC/VT in asymptomatic patients with a PVC frequency > 20 % per day [16, 17]. Amiodarone is not recommended as first-line therapy in patients with idiopathic PVC or VT.

Dilated cardiomyopathy (DCMP) or hypokinetic non-dilated cardiomyopathy (HNDC)

Genetic testing (including at least the LMNA, PLN, RBM20 and FLNC genes) is recommended in patients with DCMP or HNDC with atrioventricular (AV) conduction slowing under the age of 50 years, or with a history of first-degree relatives with DCMP/HNDC or SCD (age < 50 years) [18]. Prescription of MRI with delayed gadolinium enhancement (DGA) should be discussed to assess the aetiology and risk of VA/SCD. ICD implantation is required both in symptomatic patients with LVEF < 50 % and in the presence of ⩾ 2 risk factors (syncope, DGA on MRI, SMVT in PES, pathogenic mutations in LMNA, PLN, FLNC and RBM20 genes) and in patients with DCMP/HNDC with haemodynamically tolerable SMVT. Electrocardiography (ECG) and echocardiography are desirable in close relatives of patients with apparent sporadic DCM/HNDC. Participation in high-intensity exercise, including competitive sports, is not recommended for individuals with DCM/HNDC and the LMNA gene mutation [19].

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

MRI, genetic counselling and testing are recommended in patients with suspected ARVC [20]. BBs treatment may be considered in all patients diagnosed with ARVC. ICD implantation should be considered in symptomatic patients with moderate RV or LV dysfunction or NVT or PES-inducible SMVT. If ICDs are contraindicated, antitachycardia pacing (ATC) should be considered [21]. PES may be used for risk stratification in patients with suspected UA [22]. Carriers of ARVC-associated pathogenic mutations should avoid high-intensity exercise.

Hypertrophic Cardiomyopathy (HCMP)

MRI with DGA is recommended for the diagnostic evaluation of patients with HCMP, with genetic counselling and testing being an essential feature for the diagnosis and further follow-up of these patients [23]. ECG and EchoCG are recommended for the first-degree relatives. ICD implantation is important primarily in patients with HCMP aged ⩾ 16 years with

an intermediate 5-year risk of SCD (4-6 %) and with significant DGA on MRI (usually ⩾ 15 % of LV mass), or LVEF < 50 %, or abnormal blood pressure response during exercise testing, or LV apex aneurysm, or the presence of a sarcomeric pathogenic mutation. ICD should also be discussed in children < 16 years of age with an estimated 5-year risk of SCD ⩾ 6 % (based on the HCM Risk-Kids score) and in patients with stable haemodynamics on SMVT [24]. Patients with recurrent symptomatic VA or recurrent ICD discharges should be prescribed with antiarrhythmic drugs (AD). ICD implantation may be considered in patients with HCMP aged ⩾ 16 years with a low estimated 5-year risk of SCD (< 4 %) but significant DGA on MRI (usually ⩾ 15 % of LV mass) or LVEF < 50 % or LV apex aneurysm [25]. Catheter ablation is indicated in selected patients with recurrent, symptomatic SMVT or recurrent ICD discharges in whom AD treatment is ineffective. Asymptomatic adult patients without the above-mentioned risk factors can participate in high-intensity exercise [26].

Left ventricular noncompaction (LVNC) and restrictive cardiomyopathy (RCMP)

The diagnosis of LVNC and RCMP is based on MRI or echocardiography. To prevent SCD in patients with LVNC and RCMP, as well as in patients with light-chain or transthyretin-associated cardiac amyloidosis and haemodynamically intolerable VT, the decision to implant an ICD is made according to the guidelines regarding DCMP/HNDC.

Myotonic dystrophy

Invasive electrophysiological evaluation is recommended in patients with myotonic dystrophy and palpitations or syncope associated with VA, or in patients who have survived SCA. This method of evaluation is also acceptable in patients with myotonic dystrophy and a PR interval ⩾ 240 m/s on ECG or a QRS complex duration ⩾ 120 m/s, or in patients older than 40 years with supraventricular arrhythmias or significant DGA on MRI. ICD implantation is recommended in patients with myotonic dystrophy and SMVT or prevented SCA not caused by reentrant VT. ICD should also be discussed in patients with myotonic dystrophy without atrioventricular conduction slowing and syncope, where there is a reasonable suspicion of VA [27]. In addition, an ICD may be considered in patients with limb-girdle type 1B or Emery-Dreyfus muscular dystrophy with an indication for electrocardiostimulation, in patients with significant DGA on MRI, and over a permanent pacemaker in patients with myotonic dystrophy and additional risk factors for VA and SCD[28]. In patients with myotonic dystrophy, frequent electrophysiological assessment of AV conduction and arrhythmia induction is not recommended in the absence of suspected arrhythmias or progressive conduction disturbances.

Myocarditis

In patients with haemodynamically intolerable SVT or ventricular fibrillation (VF) in the acute or chronic phase of myocarditis, ICD implantation should be considered before hospital discharge or during outpatient follow-up [29]. In post-myocarditis patients with recurrent symptomatic VT, treatment with ADs should be considered and, if ineffective, catheter ablation should be discussed. In patients with haemodynamically well-tolerated SMVT in the chronic phase of myocarditis, with preserved LV function and an expected small post-ablation scar, catheter ablation may be used as an alternative to ICD therapy.

Cardiac sarcoidosis

In patients with cardiac sarcoidosis with LVEF > 35 % but significant DGA on MRI, ICD implantation should be considered after resolution of the acute inflammation [30]. In the case of small DGA on MRI, PES should be discussed for risk stratification and ICD implantation should be considered in the case of induced SMVT. In patients with Chagas cardiomyopathy with symptomatic PVCs or VT, AD treatment with the possibility of amiodarone should be the first line of treatment [31]. If ADs are ineffective, catheter ablation should be considered.

Congenital heart defects (ConHD)

In patients with ConHD and persistent VA, evaluation for residual lesions or new structural abnormalities is recommended. Treatment of supraventricular tachycardia with delayed intraventricular conduction should be discussed in selected patients with ConHD (including atrial septal repair for transposition of the main arteries, Fontaine surgery and Ebstein's anomaly) presenting with SCA [32]. In patients with corrected tetralogy of Fallot requiring surgical or transcatheter pulmonary valve replacement, pre- or intra-operative catheter mapping and crossing of an-

atomical isthmuses that induce VT can be discussed. If biventricular function is preserved in patients with symptomatic SMVT, catheter-based or concomitant surgical ablation may be considered as an alternative to ICD therapy [33]. In the absence of arrhythmia but in the presence of its risk factors, electrophysiological study including PES may be considered.

Idiopathic VF

It is recommended that idiopathic VF in SCA be diagnosed, preferably with documented VF, after exclusion of underlying structural changes of canalopathic, metabolic or toxicological etiology. In idiopathic VF with "electrical storm" or recurrent ICD discharges, emergency infusion of isoproterenol, verapamil or quinidine followed by long-term quinidine therapy is preferred [34]. In patients with idiopathic VF, genetic testing for canalopathy and cardiomyopathy genes and clinical evaluation (history, ECG and high thoracic ECG, exercise testing, echocardiogram) in first-degree family members is desirable [35].

Long QT syndrome (LQT)

Genetic counselling and testing is recommended in patients with clinically diagnosed LQT. Non-selective BBs (nadolol or propranolol) are recommended to reduce the risk of arrhythmias in patients with LQT with documented QT prolongation. Mexiletine is indicated in patients with type 3 LIQT[36]. The risk of arrhythmia, which depends on genotype and QT interval length, should be calculated before starting treatment for LIQT. ICD implantation can be used in asymptomatic LQT, in patients with a high risk profile (on a scale of 1-2-3 on the LQT risk calculator), as an adjunct to genotype-specific therapy[37]. Routine diagnostic testing with adrenaline provocation is not recommended in patients with SUIQT.

Andersen-Tawil syndrome

Genetic testing is recommended for all patients suspected of having Andersen-Tawil syndrome. In the absence of structural heart disease, Andersen-Tavila syndrome is suspected in patients with at least two of the following features: prominent U teeth with/without QT prolongation, bidirectional and/or polymorphic premature ventricular complexes/VT, dysmorphic features, periodic paralysis, and a pathogenic loss-of-function mutation of KCNJ2 [38, 39]. For unexplained syncope, implantation of an implanted loop recorder (ILR) should be discussed. ICD implantation is used in patients with prevented SCA or intolerable SVT and a history of unexplained syncope or tolerable SVT. Prescription of BB and/or flecainide with or without acetazolamide should be considered as an AD therapy.

Brugada syndrome (BrS)

Genetic testing for the SCN5A gene is recommended for probands with BrS[40]. The diagnosis of BrS is made in patients without other heart disease and induced type 1 BrS on ECG if at least one of the following features is present: arrhythmic syncope or nocturnal agonal breathing, family history of BrS, family history of SCD (< 45 years) with negative autopsy and presence of situations suspicious for BrS. In cases with unexplained syncope, implantation of an ILR should be considered. BrS can be suspected in patients with an induced ECG pattern of type 1 BrS without other cardiac disease [41]. PES can be used to detect VA in asymptomatic patients, with spontaneous manifestation of type 1 BrS on ECG. A test with sodium channel blockers is not recommended in patients with a previous episode of type 1 BrS. Catheter ablation is also not necessary in asymptomatic patients.

Early repolarisation syndrome (ERS)

It is recommended that ERS be diagnosed as J-point elevation ⩾ 1 mm in the two adjacent inferior and/or lateral ECG leads and in patients with the above-mentioned ECG features with unexplained VF/PVCs [42]. The diagnosis of ERS is made in a case of SCD with a negative autopsy result if the physical examination and pre-mortem ECG show ERS. In patients with suspected ERS, genetic testing for ERS is desirable [43]. First-degree relatives of the patient should be clinically evaluated for additional risk factors. For the diagnosis of arrhythmias, ILR should be considered in individuals with at least one risk factor or arrhythmic syncope [44]. ICD implantation is recommended for all patients who have experienced SCA. Intravenous infusion of isoproterenol is required for the medical management of patients with electrical storm. In recurrent VF, the use of quinidine in addition to an ICD should be discussed. PVC ablation is required in patients with recurrent episodes of VF caused by similar ventricular extrasystoles (VEs) that do not respond to medical therapy [45]. ICD implantation or quinidine treatment is used in selected individuals

with arrhythmic syncope and additional risk factors, and in the absence of symptoms in individuals with high-risk ERS and a family history of unexplained juvenile SCD [46]. Routine clinical evaluation and ICD implantation is not recommended in asymptomatic individuals with ERS [47].

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Genetic counselling and testing is indicated in all patients with a clinical diagnosis of CPVT. If physical stress testing is not possible, provocation with adrenaline or isoproterenol may be considered to diagnose this condition. In terms of treatment, BBs, preferably non-selective, are recommended for all patients [48].

Short QT syndrome (SQT)

Genetic testing is required in SQT patients when the QTc duration is ⩽ 320 m/s[49]. In arrhythmic syncope, the diagnosis of SQT is suspected when the QTc duration is between 320 m/s and 360 m/s. In addition, this diagnosis may be considered in patients with a QTc of 320–360 m/s if there is a family history of SCD before the age of 40 years. In younger patients, implantation of an ILR should be discussed, and an ICD should be considered in patients with arrhythmic syncope. In some cases, quinidine may be used if the patient refuses an ICD or in asymptomatic patients with a family history of SCD [50]. In the case of "electrical storm", intravenous isoproterenol is preferred [51].

Some population groups

Athletes with CVD and at risk of SCD are treated according to current eligibility guidelines. In women with ARVC, the continuation of BB during pregnancy should be considered. Metoprolol, propranolol or verapamil are preferred for long-term treatment of idiopathic sustained VT during pregnancy. In women with symptomatic recurrent SMVT refractory to ADs, it is advisable to consider catheter ablation after the first trimester of pregnancy using neuroimaging techniques [52]. ICD implantation may be discussed in selected patients with vasculopathy of the transplanted heart or who are taking immunosuppressants. ICD implantation for primary prevention of SCD in elderly patients may be discouraged because of the lack of expected defibrillator benefit associated with age and comorbidities [53].

Conclusion

Prevention of ventricular arrhythmias and SCD therefore requires an individualised approach to each case, taking into account the nosology of CVD, arrhythmia characteristics, results of genetic counselling and testing, imaging data and appropriately selected treatment.

Measures to prevent SCD through out-of-hospital emergency cardiopulmonary resuscitation with universal availability of defibrillation are an integral task not only for health authorities, but also for the all state structures in general.

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in the International heart and vascular disease journal

Edit from December, 2021

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1. Authors ' names (you can not write in full, the format of the journal provides for the publication of names and initials. Therefore, in the "Windows", where the name and patronymic of the authors are written in capital letters with a dot (example: A.).

2. Names of institutions (write the official name. At the same time — there is a reduction of Federal, STATE, etc.; the quotation marks are placed; Ministry of health of Russia, a city without the letter G.

3. Positions and titles (using traditional abbreviations: PhD, senior researcher, leading researcher, PhD, C.b.N., MD), head reduces to the head., then write the full name of the laboratory/Department / Department; Director, head, Professor — is not reduced.

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.

5. Summary. Sections of the abstract should exactly match the sections prescribed In the rules for authors. If the sections are not correct, the Editors will ask to correct them. What the authors are currently publishing on the site will then be included in all systems after the final publication. Be careful!

6. Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors "forget" and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks,

the Editors will not start with the article to eliminate errors.

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.

6. Information on overlapping publications (if available).

7. Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

8. Information about the obtained consent in patients for the study.

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 compar-

ative control group, studies the interaction between interventions to improve health or the results obtained. The world health organization offers the primary register: International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html). The clinical study is considered to be reliable in a group of more than 20 patients.

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

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

IV. Manusctipt submision check-list

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Making graphs, diagrams and drawings — tables and figures should provide the reader with visual information, be interesting and educational. They should be placed after the text of the article, as the reviewer and editor look at the manuscript as a whole. However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

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

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

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

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

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

Each first mention of a figure or table in the text is highlighted with a yellow marker. If a reference to a figure or table is included in the sentence, the full spelling of the word «figure 1», «table 1» is used; if the words are enclosed in brackets, the abbreviation is used (Fig. 1), (table. 1).

Providing the main file of the manuscript with the names of the authors or institutions is the basis for refusal to accept the manuscript for consideration.

V. The list of references.

In the form to fill in when submitting the article provides a list of cited literature (section — Literature).

Literary references are listed in the order of citation in the manuscript. The text refers to the serial number of the cited work in square brackets [1] or [1, 2]. Each link in the list is on a new line. All documents referred to in the text should be included in the list of references.

References to works that are not in the list of references and Vice versa, references to unpublished works, as well as to works of many years ago (>10 years) are not allowed. The only exceptions are rare highly informative works. Especially close attention to this item, please pay to those authors who submit "literature Review".

The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate "et al.", for foreign — "et al." When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

If you want to make a quotation of the authors ' names in the text, you must specify the name of the first author with the initials, the year of work. Example design: Smith AA, et al. (2018).

With the purpose of increase of citation in the journal is the transliteration of Russian sources with the use of the official languages in the following order: the authors and the journal title is transliterated in the Latin alphabet, and the name of the article is semantic transliteration (translation into English). The name of the source where the work is published is transliterated in Latin if the source (journal) does not have an official name in English).

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The list of references should correspond to the format recommended by the American National organization For information standards (national Information Standards organization — NISO), adopted by the National Library of Medicine (NLM) for databases (Library's MEDLINE/PubMed database) NLM: http://www.nlm.nih.gov/citingmedicine Oh? The names of periodicals may be abbreviated. Usually this

form of writing is accepted by the publisher; it can be found on the website of the publisher, or in the list of abbreviations Index Medicus.

Mandatory all articles DOI specified, all books ISBN. References to dissertations, patents, theses and any collections without output and ISBN are not accepted.

Examples of link design:

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Smith A, Jones B, Clements S. Clinical translation of tissue-engineered airway. Lancet. 2008;372:1201-09. DOI:10.00000/0000-0000-.

Russian-language sources with transliteration:

Bart BYa, Larina VN, Brodskyi MS, et al. Cardiac remodelling and clinical prognosis in patient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. DOI:10.15829/1560-4071-2011-6-4-8.

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)

All sources of literature are checked for correctness through the system of the Russian electronic library. Significant errors in citation or duplication of the source are the reason for the return of the manuscript to the authors for revision.

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The author prepares the following documents to upload the manuscript to the site:

The main file Is the text of the article (the system renames it after loading, so it does not matter how it is called).

Additional files-Directional (accompanying) letter, Information file with the Title page, information about the authors and disclosure of conflicts of interest, files with pictures.

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This section regulates the relationship between the editorial Office (Publisher) of *International heart and vascular disease journal* (the "editorial Office") and the author or group of authors who submitted their manuscript for publication in the *International heart and vascular disease journal* (the "Author").

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The editorial Board reserves the right to reduce and edit the materials of the manuscript, to carry out scientific editing, to reduce and correct articles, to change the design of graphs, drawings and tables to bring into line with the design of the journal, without changing the meaning of the information provided.

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1. The manuscript should be sent in electronic form to the Editor through the website — http://www.heart-vdj.com. The manuscript should be drawn up in accordance with these requirements for scientific articles submitted for publication in the journal.

2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

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5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

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10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

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1. According to the requirements of the Higher attestation Commission, the journal provides priority for post-graduate and doctoral works, the period of their publication depends on the expected date of protection, which the authors must specify in the primary documents attached to the manuscript.

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3. All selected articles are submitted to the scientific editor and proofreader. After creating the layout of the article and editing it, the article will be available to the Author through the site. At this stage, it will be possible to send comments on the text of the article. The author is obliged to send his / her consent to the publication or his / her comments within the established time specified in the cover letter.

4. The editorial office does not send the author's copy by mail or PDF of the article by e-mail, access to the published numbers is open.

Subscription to the printed version is carried out by half a year (through subscription agencies).

X. After the publication in the journal

1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

XI. Revocation or correction of articles

The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) — http://www.publicationethics.org.uk. in cases:

Editors of journals should consider the opinion of the publication, if:

they have clear evidence of the unreliability of the information published, either as a result of conscious actions (for example, falsification of data), or due to good faith errors (for example, errors in calculations or experiments); the findings have been previously published in another publication and there is no proper reference, authorization and justification for re-publication (i.e. duplicate publication).); it is plagiarism; describes unethical research.

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a small part of the rest of the high-quality publication is unreliable (especially because of conscientious errors); the list of authors / sponsors contains errors (i.e., it does not contain someone who is worthy to be an author, or a person who does not meet the authorship criteria).

In most cases, a review is not appropriate if:

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XII. Position E-log backup (if journal is no longer published)

The purpose of backup is to prevent loss of information in case of hardware, software, critical and crisis situations, etc.

Information of the following main categories is subject to backup: — personal information of authors (personal directories on file servers); — pdf of published articles; — information about literary links to the article in the DOI system.

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XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

Official sites where information about the journal is placed:

http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

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

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3.The cited literature is presented in full, framed by the Rules for the authors and does not contain duplicates. All references are indicated in the text of the article.

4. Text should be typed with an interval of one line spacing, font Times New Roman, 12 pt; to highlight the accents it is recommended to use italics rather than underlining (except Internet links). All images, graphics and tables are placed within the text according to the meaning of the particular part of text (and not at the end of the document).

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