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Treatment of Resistant Hypertension in 2020

Reduced glomerular filtration rate in patients with acute STEMI

Patient-centered management of atrial fibrillation: from guidelines to clinical practice

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Contents

Editor's Welcome

Dear colleagues!

In the 28th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles, as well as the report on the latest congress of European Society of Cardiology.

The leading article section presents the review article of the leading American scientist Wilbert S. Aronow on the resistant arterial hypertension, that includes the pseudohypertension and white coat hypertension. The causes of resistant hypertension and the efficacy of fourth antihypertensive drug are discussed. Poor patient compliance including non-compliance with lifestyle changes are common factors associated with pseudoresistant hypertension.

Four articles are published in the «Original articles» section. The first article is dedicated to the differential therapy of ventricular extrasystoles in patients without cardiac structural changes by screening testing of antiarrhythmic drugs. All patients had potential positive antiarrhythmic effect for 2 and more drugs. Another article aimed to evaluate the characteristics of patients with acute ST-elevation myocardial infarction depending on the glomerular filtration rate (GFR). The authors concluded that it is important to calculate the GFR in order to choose the correct management and assess the risk of complications. A randomized trial aimed to compare the influence of moderate intensity continuous and high-intensity interval cardio-rehabilitation training on blood pressure in athletes with arterial hypertension. Despite similar benefits in cardio-rehabilitation, interval exercise required less time that can significantly affect adherence and exclude some participants of long rehabilitation. Another original article was dedicated to identification of clinical and angiographic characteristics and evaluation of long-term treatment outcomes in young male patients with a history of ST-elevation myocardial infarction registered on an electrocardiogram. Patients had different risk factor profiles and comparable annual survival rates depending on the angiographic picture. Erectile dysfunction was less pronounced with distal coronary blood flow disorders than with proximal occlusions.

The "Review articles" section presents the article on updated European Society of Cardiology Guidelines on diagnosis and treatment of atrial fibrillation and their application in daily patient-centered clinical practice that emphasizes rate and rhythm control.

The" Reports" section is dedicated to the results of the annual congress of the European Society of Cardiology that was held trough virtual mode for the first time. In particular, the highlights of 4 updated clinical guidelines of the European Society of Cardiology are summarized. The results of 13 international clinical trials on the efficacy and safety of pharmacological treatment and identification of factors associated with cardiovascular complications are analyzed.

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

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

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LEADING ARTICLE

Treatment of Resistant Hypertension in 2020

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Abstract

Resistant hypertension is diagnosed if the blood pressure (BP) is not controlled despite optimum doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate BP control needs 4 or more antihypertensive drugs from different classes Pseudohypertension and white coat hypertension must be excluded. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office BP measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension. Secondary hypertension must be excluded and treated. Primary hypertension and hypertension associated with different comorbidities must be treated as recommended by the 2017 American College of Cardiology/American Heart Association hypertension guidelines. Factors contributing to resistant hypertension include obesity, a high-sodium, low-fiber diet, excess alcohol intake, physical inactivity, obstructive sleep apnea, use of cocaine, amphetamines, non-steroidal anti-inflammatory drugs, oral contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills) erythropoietin, licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy. Patient non-adherence to both lifestyle measures and antihypertensive drug therapy are major factors for treatment-resistant hypertension. Treatment of resistant hypertension includes improving compliance with use of medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve BP control. The beneficial effects of thiazide diuretics are reduced when the glomerular filtration rate is reduced to less than 40 ml/minute/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 hours If a fourth antihypertensive drug is needed to control blood pressure in persons treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen. Further research is needed on investigational drugs and device therapy for treating

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resistant hypertension.: Clinical trials are indicated for the treatment of resistant hypertension by sacubitril/valsartan and also by firibastat.

Keywords: *resistant hypertension; antihypertensive drugs; diuretics; mineralocorticoid receptor antagonists; lifestyle measures; device therapy for hypertension.*

Conflict of Interests: None declared.

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Introduction

The 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) hypertension guidelines state that Stage 1 hypertension is a systolic blood pressure (SBP) of 130–139 mm Hg or a diastolic blood pressure (DBP) of 80–89 mm Hg [1]. Stage 2 hypertension is a SBP of≥140 mm Hg or a DBP of≥ 90 mm Hg. [1]. These hypertension guidelines recommend lifestyle measures plus BP lowering drugs for secondary prevention of recurrent cardiovascular disease events in patients who have clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average SBP of≥ 130 mm Hg or an average DBP of≥80 mm Hg. [1–3]. These guidelines recommend treatment with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease≥10 % [4] and an average SBP of≥ 130 mm Hg or an average DBP of≥80 mm Hg. [1,5]. These guidelines recommend treatment with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease of< 10 % [4] and an average SBP of≥140 mm Hg or an average DBP of≥ 90 mm Hg. [1, 5, 6]. These guidelines recommend treatment with antihypertensive drug therapy with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in patients with a BP of≥140/90 mm Hg or with a BP higher than 20/10 mm Hg above their BP target [1, 6]. White coat hypertension must be excluded before using antihypertensive drugs in treatment of patients with hypertension at low risk for atherosclerotic cardiovascular disease [1].

Suspect secondary hypertension if there is new onset or uncontrolled hypertension in adults [1, 7]. Screen for secondary hypertension if there is drug-resistant/induced hypertension, abrupt onset of hypertension, onset of hypertension in a patient younger than 30 years or older than 50 years, exacerbation of previously controlled hypertension, disproportionate target organ damage for the degree of hypertension, accelerated/malignant hypertension, onset of diastolic hypertension in older patients, or unprovoked or excessive hypokalemia [1,7]. Common causes of secondary hypertension include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug-or alcohol-induced hypertension [1]. Uncommon causes of secondary hypertension include pheochromocytoma/paraganglioma, Cushing's syndrome, hypothyroidism, hyperthyroidism, aortic coarctation, primary hyperparathyroidism, congenital adrenal hyperplasia, mineralocorticoid excess syndromes, and acromegaly [1].

The 2017 ACC/AHA hypertension guidelines recommend that the BP should be reduced to< 130/80 mm Hg in patients with ischemic heart disease [1, 3, 8–13], in patients with heart failure with a reduced left ventricular ejection fraction (HFrEF) [1, 14], in patients with heart failure with a preserved left ventricular ejection fraction (HFpEF)[1, 14], in patients with chronic kidney disease[1, 15], in patients after renal transplantation [1], in patients with lacunar stroke [1, 16, 17], in patients with peripheral arterial disease[1, 2], in patients with diabetes mellitus[1, 18–21], in noninstitutionalized ambulatory community-dwelling patients older than 65 years of age [1, 8, 9], and for secondary stroke prevention [1, 22].

Treatment with lifestyle measures

Lifestyle modification should be used to treat hypertension [1, 23]. Weight reduction, consuming a diet rich in fruits, vegetables, and low-fat dairy products with less saturated fat and total fat, sodium reduction to not exceed 1.5 grams daily, smoking cessation, regular aerobic physical activity, avoidance of

excessive alcohol intake, avoidance of excessive caffeine, and avoidance of drugs which can increase BP, including nonsteroidal antiinflammatory drugs, glucocorticoids, and sympathomimetics, are recommended [1, 6, 23].

Antihypertensive drug treatment of primary hypertension

The 2017 ACC/AHA hypertension guidelines recommend for the treatment of white and other non-black patients younger than 60 years of age with primary hypertension that the first antihypertensive drug should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, the second drug a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is necessary, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker should be given [1]. For white and other non-black patients aged 60 years of age and older with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given [1]. For blacks with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given [1].

Antihypertensive drug treatment associated with comorbidities

Patients with stable ischemic heart disease and hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and if a third antihypertensive drug is necessary, a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic or a calcium channel blocker should be given [1, 24–32]. If a fourth antihypertensive drug is indicated to adequately control hypertension, a mineralocorticoid receptor antagonist should be added [1]. In patients with stable ischemic heart disease who have angina pectoris despite beta blocker therapy and persistent uncontrolled hypertension, a dihydropyridine calcium channel blocker should be added [1, 24, 25, 33]. Beta blockers which should be used in treating ischemic heart disease with hypertension include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol [1]. Atenolol should not be given [1, 27]. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are contraindicated if there is left ventricular systolic dysfunction [1]. If there is left ventricular systolic dysfunction, the beta blockers that should be given are carvedilol, metoprolol succinate, or bisoprolol [1, 24, 25, 34].

If hypertension persists after treatment with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with an acute coronary syndrome, a long-acting dihydropyridine calcium channel blocker should be added to the treatment regimen [25]. Aldosterone antagonists should be given to patients treated with beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction and either heart failure or diabetes mellitus if their serum potassium is less than 5.0 meq/L and if their serum creatinine is⩽2.5 mg/dL in men and⩽ 2.0 mg/dL in women [1, 24, 25, 35].

Patients with hypertension who have HFrEF should be treated with a beta blocker (carvedilol, metoprolol succinate, or bisoprolol) plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or preferably an angiotensin receptor-neprolysin inhibitor plus a diuretic and if needed with a mineralocorticoid receptor antagonist [1, 14, 24, 25, 27, 35]. Nondihydropyridine calcium channel blockers are contraindicated in the treatment of patients with HFrEF [1, 14, 24, 25, 36, 37]. Patients with hypertension and HFpEF should have their volume overload treated with diuretics, their other comorbidities treated, and their hypertension treated with a beta blocker plus an angiotensin converting enzyme inhibitor or angiotensin blocker plus a mineralocorticoid receptor antagonist [1, 14, 38, 39].

Patientswith hypertension and chronic kidney disease stage 3 or higher or stage 1 or 2 chronic kidney disease with albuminuria⩾300 mg per day should be treated with an angiotensin-converting enzyme inhibitor to slow progression of chronic kidney disease [1, 40]. If an angiotensin-converting enzyme inhibitor is not tolerated, these patients should be treated with an angiotensin receptor blocker [1]. Patients with stage 1 or 2 chronic kidney disease who do not

have albuminuria may be treated with the usual first-line antihypertensive drugs [1]. If 3 antihypertensive drugs are needed, these patients should be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker. After kidney transplantation, treat hypertension with a calcium channel blocker to improve glomerular filtration rate and kidney survival [1].

Patients with hypertension and a prior stroke or transient ischemic attack should receive treatment with a thiazide diuretic or angiotensin-converting enzyme or angiotensin receptor blocker [1,41]. If a third antihypertensive drug is needed, these patients should be treated with a thiazide diuretic plus an angiotensin-converting enzyme or angiotensin receptor blocker plus a calcium channel blocker.

Patients with hypertension and peripheral arterial disease should be treated with an angiotensin-converting enzyme or angiotensin receptor blocker or a calcium channel blocker or thiazide diuretic or beta blocker [1,42]. There is no evidence that any one class of antihpertensive drugs is better to treat hypertension in patients with peripheral arterial disease [1,42].

Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are effective antihypertensive drugs In patients with hypertension and diabetes mellitus and may be used as initial treatment [1,43]. Angiotensin-converting enzymes or angiotensin receptor blockers should be used for the treatment of diabetics with hypertension and persistent albuminuria [1,44]. Chlorthalidone was better than lisinopril, amlodipine, and doxazosin in decreasing cardiovascular disease and renal outcomes in nondiabetics with hypertension and the metabolic syndrome [1,45].

Beta blockers are the preferred antihypertensive drugs in patients with hypertension and thoracic aortic aneurysm [1,46]. Beta blockers also improve survival in adults with type A and with type B acute and chronic thoracic aortic dissection [1]. If thoracic aorta dissection develops, beta blockers are the initial drug of choice for reducing BP, ventricular rate, dP/dt, and stress on the aorta [46,47]. The SBP should be reduced to 100 to 120 mm Hg, and the ventricular rate should be decreased to less than 60 beats/minute by intravenous propranolol, metoprolol, labetalol, or esmolol [46,47].

Pregnant women with hypertension should not be treated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, or atenolol because these drugs are fetotoxic [1]. Pregnant women with hypertension should be treated with methyldopa, nifedipine, and/or labetalol [1].

Treatment of resistant hypertension

Diagnose resistant hypertension if the BP is not controlled despite optimum doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate BP control needs 4 or more antihypertensive drugs from different classes [1,48–50]. The National Institute for Health ad Clinical Excellence guideline suggests that the 3 drugs should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a calcium channel blocker plus a thiazide-type diuretic [50]. Pseudohypertension and white coat hypertension must be excluded. before diagnosing resistant hypertension.

Pseudo hypertension in elderly patients is a falsely high SBP which results from markedly sclerotic arteries which do not collapse under the BP cuff [1,24]. Confirm pseudohypertension by measuring intra-arterial pressure [1,24]. White coat hypertension is diagnosed if patients have a persistently elevated office BP but a normal home BP or a normal 24-hour ambulatory blood pressure [1,24]. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office BP measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension [1,24,51].

Factors contributing to resistant hypertension include obesity, a high-sodium, low-fiber diet, excess alcohol intake, physical inactivity, obstructive sleep apnea, use of cocaine, amphetamines, non-steroidal anti-inflammatory drugs, oral contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills) erythropoietin, licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy [1,24,50,52].

Patients with resistant hypertension also need screening for secondary causes of hypertension with treatment of these secondary causes [1,24]. Lifestyle measures as previously discussed must be instituted [1,6,23].

Among 205, 750 patients with incident hypertension, 1.9 %, mean age 60.6 years, developed rresistant hypertension within a median of 1.5 years from initial treatment [53]. Over 3.8 years median follow-up, cardiovascular events were 47 % (33 % to 62 %)

higher in the patients who had resistant hypertension [53]. In 53, 380 patients with hypertension and atherothrombotic disease in the International Reduction of Atherothrombosis for Continued Health (REACH) registry, the prevalence of resistant hypertension was 12.7% with 4.6% receiving 4 antihypertensive drugs and 1.9% receiving 5 or more antihypertensive drugs [54]. The patients in this study with resistant hypertension had at 4 years follow-up a higher incidence of cardiovascular death or myocardial infarction, or stroke and a higher incidence of hospitalization for congestive heart failure [54]. Of 614 patients with hypertension followed in a university cardiology or general medicine clinic, 40 patients (7%) were receiving 4 antihypertensive drugs, and 9 patients (1%) were receiving 5 antihypertensive drugs [51]. Of 14.684 patients with hypertension randomized to amlodipine, chlorthalidone, or lisinopril, 11.4%, 9.6%, and 19.7%, respectively, had treatment-resistant hypertension [55]. The 2018 AHA Scientific Statement on resistant hypertension [56] stated that the prevalence of treatment-resistant hypertension among 4.158 US persons with hypertension taking antihypertensive drugs in the 2009 to 2014 National Health and Nutrition Examination Survey was 17.7% using the criteria for diagnosis stated in their 2008 statement [48] and 19.7% using the criteria for diagnosis recommended by the 2017 ACC/AHA hypertension guidelines [1]. Using the 2018 definition [1,56], 3.2% of US adults taking chlorthalidone or indapamide and 9.0% taking spironolactone or eplerenone had resistant hypertension.

Management of resistant hypertension includes improving compliance with use of medication, detection and therapy of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities [1,23]. If a fourth antihypertensive drug is necessary to control BP in patients treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the treatment regimen [1,49].

Patient non-adherence to both lifestyle measures and antihypertensive drug therapy is a major factor for treatment-resistant hypertension [57–62]. Methods for assessing patient non-adherence to antihypertensive drug therapy include clinical impression, questioning of the patient, self-reports, pill counts, refill records, electronic bottle cap monitoring, and measuring concentrations of prescribed antihypertensive drugs in blood and urine[57–62]. The prevalence of non-adherence to antihypertensive drug therapy in patients with treatment-resistant hypertension in a pooled analysis of 24 studies was 31.2% [63].

The prevalence of non-adherence to antihypertensive drug therapy in patients with treatment-resistant hypertension varies from 20.3% to 41.1% depending on the asessment method used [64]. In a study of 76 patients with treatment resistant hypertension prescribed at least 4 antihypertensive drugs who had urine screening for non-adherence, 40 patients (53%) were found to be non-adherent to taking their antihypertensive drugs [62]. Of these 40 patients, 30% had complete adherence and 70% had incomplete adherence to their antihyperensive drugs [62]. An analysis of 62 trials showed that interventions that may improve adherence to self-administered antihypertensive drugs include policy interventions to reduce drug copayments or improve prescription drug coverage, systems interventions to offer case management, and patient-level educational interventions with behavioral support [59].

Antihypertensive drug therapy of resistant hypertension

Antihypertensive drug therapy of resistant hypertension should maximize diuretic therapy [1, 24] Excess sodium and fluid retention is an important cause of resistant hypertension [48, 65, 66]. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve BP control [1,67]. The beneficial effects of thiazide diuretics are decreased when the glomerular filtration rate is less than 40 cc/minute [1, 24, 48, 65, --68]. These patients should be treated with a loop diuretic such as furosemide every 12 hours [1, 24, 65].

Increased activation of the renin-angiotensin-aldosterone system also plays an important role in the development of treatment-resistant hypertension [65, 66, 69). Low dose eplerenone reduces aortic stiffness in patients with resistant hypertension [70]. The data available support the use of an mineralocorticoid receptor antagonist such as spironolactone or eplerenone as the fourth antihypertensive drug to use in patients with treatment-resistant hypertension [1, 24, 50, 65, 66, 69–76]. In the PATHWAY-2 trial, spironolacone was better than placebo, bisoprolol, and doxazosin in treating drug-resistant hypertension [73].

Patients should be treated with appropriate antihypertensive drugs for their comorbidities as discussed earlier in this review. For example, patients

with coronary heart disease or heart failure should be treated with beta blockers. If additional antihypertensive drugs are needed, centrally active alpha agonists such as clonidine or methyldopa or direct vasodilators such as hydralazine and minoxidil are further options [1, 24, 50, 76].

A pooled analysis of 14.094 patients treated for hypertension in the Systolic Blood Pressure Intervention Trial and the Action to Control Cardiovascular Risk in Diabetes trial found that 2.710 patients(19.2%) had resistant hypertension [77]. The optimal SBP goal for decreasing the outcome of myocardial infarction, stroke, cardiovascular death, and heart failure and the same outcomes plus all-cause mortality in patients with and without resistant hypertension was< 120 mm Hg [77].

Investigational drugs for treating resistant hypertension

Investigational drugs for treatment of resistant hypertension include aldosterone synthase inhibitors, activators of the angiotensin-converting enzyme2/ angiotensin (1–7)/ MAS receptor axis, centrally acting aminopeptidase inhibitors, vasopeptidase inhibitors, dual-acting angiotensin receptor-neprilysin inhibitors, dual-acting endothelin converting enzme-neprilysin inhibitors, natriuretic peptide receptor agonists, soluble epoxide hydrolase inhibitors, vasoactive intestinal peptide receptor agonists, intestinal Na+/H+ exchanger 3 inhibitors, and dopamine beta-hydroxylase inhibitors and are discussed elsewhere [69, 78–80]. None of these investigational drugs have been approved in the United States for treating resistant hypertension.

Sacubitril/valsartan was shown in a double-blind, randomized controlled trial to be better than olmesartan in lowering clinic and ambulatory cental aortic and brachial pressures in 454 patients, mean age 67.7 years, with systolic hypertension and stiff arteries [81]. A meta-analysis of 11 randomized controlled trial in 6.028 participants demonstrated that sacubitril/valsartan was better than angiotensin receptor antagonists for treating patients with hypertension [82]. Sacubitril/valsartan merits investigating therapy of resistant hypertension [81–83].

A phase 2, open-label, multicenter, dose-titrating study in 256 overweight or obese hypertensive patients (56% black or Hispanic) demonstrated that firibastat, a first-in-class brain aminopeptidase A inhibitor was effective in reducing BP [84]. Firibastat should also be investigated for treating resistant hypertension.

Device treatment of drug-resistant hypertension

Device therapy being investigated for drug-resistant hypertension includes radiofrequency sympathetic denervation of the renal arteries, baroreflex activation therapy, carotid body ablation, a central arteriovenous anastomosis, carotid artery ablation, and neurovascular decompression [69, 78, 85–92]. None of these device therapies have been approved for treating resistant hypertension in the United States. The device therapy of greatest interest being investigated is sympathetic denervation of the renal arteries [85–90]. A sham-controlled trial of renal artery denervation in 535 patients with resistant hypertension found no significant reduction in SBP 6 months after renal artery denervation compared with the sham procedure [85]. This trial also did not find a benefit of renal artery denervation on reducing ambulatory BP in either the 24-hour or day and night periods 6 months after the procedure compared with the sham procedure [86]. However, an analysis of 6 trials with 977 patients suggested a benefit in lowering BP by this procedure [90]. The 2017 ACC/AHA hypertension guidelines do not recommend any device therapy for treating resistant hypertension [1]. These guidelines state that 2 randomized controlled trials of renal sympathetic nerve ablation have been negative [1, 85, 86, 93].

Conclusion

White coat hypertension and pseudohypertension must be excluded before diagnosing resistant hypertension. Poor patient compliance, inadequate doses of antihypertensive drugs, poor office BP measurement technique, and having to pay for costs of drugs are factors associated with pseudoresistant hypertension. Secondary hypertension must be excluded and treated. Primary hypertension and hypertension associated with different comorbidities must be treated as recommended by the 2017 ACC/AHA hypertension guidelines. Factors contributing to resistant hypertension include obesity, a high-sodium, low-fiber diet, excess alcohol intake, physical inactivity, obstructive sleep apnea, use of cocaine, amphetamines, non-steroidal anti-inflammatory drugs, oral contraceptive hormones, adrenal steroid hormones, sympathomimetic drugs (nasal decongestants and diet pills) erythropoietin, licorice, herbal supplements such as ephedra, progressive renal insufficiency, and inadequate diuretic therapy.Patient non-adherence to both lifestyle measures and antihypertensive drug

therapy are major factors for treatment-resistant hypertension. Treating resistant hypertension includes improving compliance with use of medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treating obesity and other comorbidities. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve BP control. The beneficial effects of thiazide diuretics are less when the glomerular filtration rate is lowered to less than 40 ml/minute/1.73 m^2. These patients should be treated with a loop diuretic such as furosemide every 12 hours If a fourth antihypertensive drug is necessary to control BP in patients treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the drug treatment regimen. Further research is needed for investigational drugs and device therapy for treating resistant hypertension. Clinical trials should be performed investigating treatment of resistant hypertension by sacubitril/valsartan and also by firibastat.

Conflict of interests: None declared.

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The possibility of using screening testing for antiarrhythmic medication for ventricular premature complexes differential therapy selection in patients without cardiac structural changes

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Abstract

Objective

To determine the differential therapy of ventricular extrasystoles (VEs) in patients without cardiac structural changes by screening testing of antiarrhythmic drugs.

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Materials and Methods

The study included 214 patients without cardiac structural changes aged 19 to 45 years with VE III—V classes, according to B. Rayn classification with subjective sensation of arrhythmia and preserved contractile function of the heart. All patients underwent daily electrocardiography monitoring, followed by the selection of potentially effective antiarrhythmic drugs for VEs elimination using screening testing method. The method considered potentially effective when corrected extrasystole index increased by≥ 2 relative units after the third dose of medication compared with the initial data. The accuracy of the choice (AC) was evaluated according to daily electrocardiography monitoring after a short course of therapy for each tested antiarrhythmic medication for at least 5 days. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate ectopic beat. The endpoint of observation was the duration of preserved positive antiarrhythmic effect of the antiarrhythmic medication.

Results

50.47% of patients had positive antiarrhythmic effect of two, 38.32% — of three, and the rest — of four antiarrhythmic medications. AC of potentially effective drugs for eliminating VE in patients without cardiac structural changes was over 90%. In 79.90% of patients, positive antiarrhythmic effect of VE therapy persisted for over 1 year (an average of 3.8±0.08 years). The duration of positive clinical effect for 1 year and higher correlated with the positive results of screening testing of antiarrhythmic drugs (r= 0.94).

Conclusion

All patients without cardiac structural changes with VE had potential positive antiarrhythmic effect for 2 and more drugs. AC of potentially effective drugs for elimination of VE in these patients averaged over 90%.

Key words: *ventricular extrasystole, differential antiarrhythmic therapy selection*

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Introduction

Treatment of ventricular cardiac arrhythmias, including ventricular extrasystoles (VEs), is one of the most difficult issues that may prevent such life-threatening arrhythmias as ventricular tachycardia and ventricular fibrillation [1,2]. Patients with frequent and persistent extrasystoles, should perform differential antiarrhythmic therapy selection**,** which consists of assessment of the frequency and nature of premature complexes before and after the prescription of antiarrhythmic medications, according to the data of daily electrocardiography monitoring, and the effectiveness of each subsequent antiarrhythmic medication determined at least after 5 half-life of the previous one [1]. In general, it takes from 4–5 to 10–12 days to determine the effectiveness of one antiarrhythmic drug [1]. It can be assumed that several antiarrhythmic medications of the same or different classes may be effective in one patient. Recently, method has been proposed for screening testing of antiarrhythmic drugs to determine effective antiarrhythmic therapy in patients with VEs [3]. The method is based on the assessment of the extrasystole index (EI), which was previously used to assess the risk of life-threatening ventricular arrhythmias development. Antiarrhythmic agent was considered effective when this index increased by at least≥2 relative units compared with the initial values after two and / or three doses of the drug [3]. However, differential antiarrhythmic therapy selection for VEs management in patients without cardiac structural changes has not been described in the available literature yet.

Objective of the study was to determine the differential therapy of VEs in patients without cardiac structural changes by screening testing of antiarrhythmic drugs.

Materials and methods

The study included 214 patients aged from 19 to 45 years (33.5±0.95 years). The inclusion criteria were: the absence of cardiac structural changes, sinus rhythm, VEs of IV–V classes according to B. Rayn

classification (1984) [1], subjective arrythmia sensations, left ventricular ejection fraction ⩾ 52 % [4], signed written informed consent to participate in the study. The absence of cardiac structural changes was established after the exclusion of cardiac and extracardiac diseases (chronic rheumatic heart disease, cardiomyopathy, heart defects, mitral valve prolapse, myocarditis, thyrotoxicosis, various clinical forms of coronary artery disease, any form of anemia, chronic lung diseases, nasopharynx, diabetes mellitus, gastrointestinal tract diseases, etc.), electrolyte imbalance, the use of drugs and / or toxic products (primarily diuretics, oral contraceptives, alcohol abuse, etc.), independently or indirectly leading to development of VEs, as well as other criteria, including the use of various stress tests, invasive and non-invasive coronary angiography, contrast magnetic resonance imaging of the heart that have been described previously [5].

All patients, in addition to general clinical examination, underwent 1–3 daily electrocardiography monitoring and echocardiographic examination using the Hitachi EUB-5500 apparatus according to generally accepted methods. The calculation of left ventricular ejection fraction, left ventricular myocardial mass index, etc. were described earlier [5, 6].

After daily electrocardiography monitoring, all patients underwent cardioprotective therapy, including potassium supplements, sedation therapy, polyunsaturated fatty acids, etc. to eliminate VEs [5]. In the absence of an effect, the choice of VEs therapy was based on antiarrhythmic drugs testing: according daily electrocardiography monitoring, the frequency and nature of premature ventricular contractions were assessed before and after average therapeutic dose of antiarrhythmic medication for at least 4–5 days [1, 2]. The criterion for positive effect was the reduction of extrasystoles frequency by over 75 % compared with its initial level, as well as the elimination of paired and group extrasystoles [1, 2]. To identify effective medications, primarily class II antiarrhythmic agents were used, followed by classes I and III. It should be noted that amiodarone was not used in this study, because the main indication for its use in patients without cardiac structural changes is decreased cardiac contractile function [1, 7]. When eliminating VEs in patients without cardiac structural changes, the nature of ectopia, its prognostic assessment, the presence of contraindications, as well as the possible development of adverse effects of antiarrhythmic agents were taken into account [1, 2]. When considering antiarrhythmic therapy, we used 50–100 mg / day of metoprolol, propranolol — 80–160 mg / day, carvedilol — 25–50 mg / day, allapinin — 50–75 mg / day, moricizine — 50–100 mg / day, ethacyzin — 100–150 mg / day, propaphenone — 300–600 mg / day, sotalol — 160–240 mg / day. In all patients, all medications were prescribed twice before reaching the daily dose. Each subsequent drug was tested after at least 5 half-lives of the previous one [1, 2].

The screening testing method to identify effective antiarrhythmic medications for VEs elimination included the following steps. For all patients before and after taking each medication, after a half the period of its half-life, EI was calculated using the following formula: EI= A ÷ B, where EI is the extrasystole index (in units), A is the linear deviation (LD) of the corrected pre-ectopic interval (ms) for at least 20 ventricular extrasystoles, calculated separately for left and right VE, and B — analyzed ventricular extrasystole number (per hour) [3]. Corrected pre-ectopic interval over 20 extrasystoles exclude false positive result in the assessment of this indicator [3,5]. Then the corrected ΔEI (ΔEIcorr.) was calculated according to the formula: ΔEIcorr= [(EIn — EI initial) ÷ EI initial] ÷ √N, where ΔEIcorr.n (in relative units) is the change of EI after each sequential intake of the medication compared with the initial data, EI initial — EI values before using the medication (initial data), EIn — half-life after the first, second, third dose of the medication, N — coefficient corresponding to the amount of dosses, i.e. after first intake of an antiarrhythmic medication this coefficient was «1» (ΔEIcorr.1), after second — «2» (ΔEIcorr.2), after third — 3 (ΔEIcorr.3). The tested medication was considered effective when ΔEIcorr.3 ⩾ 2 relative units [3]. Due to high variability of VEs during the day [1,2], the determination of EI was carried out according to the data of 1–3-day electrocardiography monitoring.

The choice of VE therapy was determined according to daily electrocardiography monitoring compared with potentially effective antiarrhythmic medications based on the VEs changes [3]. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate an ectopic beat. To exclude arrhythmogenic effect of antiarrhythmic therapy, all patients, when taking especially class Ic medications, initially and once every 3–4 days for the first 7–14 days underwent daily electrocardiography monitoring [1,2].

The accuracy of choice (AC) of potentially effective medication was determined according to the following formula: AC= (TP+ TN) ÷ (TP+ TN+ FP+ FN), where AC is the accuracy of the choice of a potentially effective antiarrhythmic drug, determined based on the ΔEIcorr.3≥ 2 relative units (in%), TP — true positive, TN — true negative, FP — false positive, FN — false negative results obtained according to daily electrocardiography monitoring performed before and after a short course of antiarrhythmic therapy.

The endpoint of observation was the duration of preserved positive antiarrhythmic effect of the antiarrhythmic drugs. All studies, including daily electrocardiography monitoring, were carried out at least once in 3–4 months, the examination of patients, ECG registration — once a month. The patients carried out regular arterial pressure and heart rate monitoring independently.

Statistical analysis of obtained results was carried out using Student's t-test, chi-squared test, as well as standard software "Statistica", version 11.0.

Results

The number of VEs per day in included patients ranged from 5570 to 36150 extrasystoles (20850± 1098 extrasystoles on average), left ventricular ejection fraction — from 53 % to 75 % (64.27± 0.79 % on average), which corresponded to the reference values [6]. The percentage of VEs ranged from 6 % to 15 % in 32 (14.95 %) patients of the total ventricular complexes number per day of observation, in the rest — over 15 %. 76 (35.51 %) of patients had episodes of unstable ventricular tachycardia. 106 (49.53 %) of patients had only left ventricular extrasystoles, the rest — right ventricular extrasystoles (p> 0.05), 84 patients (39.25 %) — polymorphic, the rest — monomorphic VEs (p>0.05).

The results of antiarrhythmic drugs testing in included patients are presented in Table 1. As can be seen from the table, the sensitivity, specificity and positive predictive value of ΔEIcorr.3≥2 relative units when assessing potentially effective medications for VEs were over 86 % on average, and AC — 90 %. When analyzing the changes of ΔEIcorr.1–10, it was revealed that in cases of true positive effect of antiarrhythmic therapy index increased after the first and second administrations of medication mostly due to increased LD of corrected pre-ectopic interval (r=0.87), and after the third and subsequent intakes — due to a decreased number of premature ventricular complexes (r=–0.85). Decreased number of VEs after a short course of antiarrhythmic therapy in patients with true positive and false negative results did not differ significantly and amounted to 76 % — 99 % (88.5±0.8 % on average) and 76 % — 96 % (86.2±1.6 % on average), respectively (p>0.05).

In 108 (50.47 %) patients two antiarrhythmic medications had positive effect, in 82 (38.32 %) — three, in the rest — four antiarrhythmic medications. 24 (11.21 %) patients took metoprolol to eliminate VEs, 22 (10.28 %) — propranolol, 12 (5.61 %) — carvedilol, 26 (12.15 %) — allapinin, 34 (15.89 %) — moricizine, 60 (28.04 %) — ethacyzin, 75 (35.05 %) — propafenone, the rest — sotalol.

Positive clinical effect of class II antiarrhythmic medications highly correlated with LD of corrected pre-ectopic interval≥11 ms of polymorphic VE (r=0.88), and for classes I and III — with LD of corrected pre-ectopic interval≤ 10 ms of monomorphic VE (r= 0.84).

43 (20.10 %) patients, had preserved antiarrhythmic effect of VEs therapy for less than 1 year (0.7± 0.04 years on average), the rest — from 1 to 5 years (3.8±0, 08 years on average) (p<0.05). The duration of preserved positive clinical effect of VEs treatment for over 1 year highly correlated with true positive results of screening testing for antiarrhythmic medications (r= 0.94).

Table 1. **Results of testing for antiarrhythmic agents in studied patients***

Medication	Sensitivity, %	Specificity, %	PPV, %	AC, %
Metoprolol, n= 214	90,41 %	94,32 %	89,19 %	92,99 %
Propranolol, n= 212	91,30 %	97,28 %	91,30 %	96,22 %
Carvedilol, n= 214	87,10 %	97,81 %	87,10 %	96,26 %
Allapinin, n= 214	91,67 %	95,45 %	88,79 %	94,39 %
Moricizine, n= 206	90,57 %	97,39 %	92,31 %	95,63 %
Ethacyzin, n= 212	94,92 %	92,71 %	94,12 %	93,93 %
Propafenone, n= 214	93,06 %	94,36 %	89,33 %	93,93 %
Sotalol, n= 204	86,27 %	96,07 %	88,00 %	93,63 %

Comment: * — potential positive effect of tested medication was determined when DEIcorr.3≥ 2 relative units; PPV — positive predictive value (%), AC – accuracy of choice (%).

Discussion

Nowadays it is known that despite positive prognosis of VEs in patients without cardiac structural changes, according to the classification of B. Bigger (1984), antiarrhythmic therapy of premature ventricular contractions should be prescribed in patients with subjective sensation of arrythmia to prevent the development of arrhythmogenic cardiomyopathy and fatal arrythmias [1, 2, 7].

The study included 214 patients without cardiac structural changes aged from 19 to 45 years with VEs of III—V classes, according to B. Rayn classification [1], subjective sensation of arrhythmia, preserved LVEF (≥52 %). 14.95 % of patients had from 6 % to 15 %, the rest — over 15 % of VEs initially of total number of ventricular complexes per day. Episodes of non-sustained ventricular tachycardia were reported in 35.51 % of patients.

According to the latest guidelines, radiofrequency ablation of the arrhythmogenic focus is recommended in patients without cardiac structural changes who have over 10–15 % VEs of the total ventricular complexes, as well as in patients who refuse to take antiarrhythmic pharmacotherapy or in case of its ineffectiveness [2,8]. This statement was the basis for pharmacological antiarrhythmic therapy in included patients.

Nowadays, it is known that VEs can be caused by various cellular mechanisms, including early or delayed after-depolarization, re-entry, and ectopic pacemaker development [1]. For example, progressive hyperpolarization of cardiomyocyte membranes, for example, from –50 to –60 mV, causes local slowdown of excitation with the formation of unidirectional and / or frequency-dependent block of the propagation of excitation with Wenckebach's phenomenon in this area, leading to the development of re-entry [1].

In the current study, in case of ineffectiveness of cardioprotective drugs, the choice of potentially effective medications for the elimination of VEs, screening testing for antiarrhythmic medication was performed based on the changes of EI initially and after their use in medium therapeutic doses [3]. EI was calculated as linear deviation of the corrected corrected pre-ectopic interval (ms) to the analyzed ventricular extrasystole number (per hour) [3]. Due to the wide range in the number of VEs per day of observation and EI values [3], ΔEIcorr.n was determined by comparing the change of EI after each administration of the medication with the initial data related to the number of subsequent doses of the medication [3]. To identify effective medications, primarily class II antiarrhythmic agents were used, followed by classes I and III. Amiodarone was not used in this study, because the main indication for its use in patients without cardiac structural changes is decreased cardiac contractile function [1,7]. In all patients, each medication was used twice before reaching the daily dose. Tested drug was considered effective when after the third dose ΔEIcorr.3≥2 relative units [3].

To exclude false negative and false positive results all tested medications were prescribed as a short course for at least 4–5 days. ΔEIcorr. was calculated after each intake of medication in all patients. The criterion for positive effect is the reduction of extrasystoles frequency by over 75 % compared with its initial level, as well as the elimination of paired and group extrasystoles according to daily electrocardiography monitoring [1,2]. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate ectopic beat.

The results of this study showed that in 50.47 % of patients two medications had positive antiarrhythmic effect, in 38.32 % — three, in the rest — four antiarrhythmic medications. The sensitivity, specificity, and positive predictive value of the ΔEIcorr.3≥2 relative units was over 80 % for the detection of potentially effective medications for VEs elimination.

In recent years, the choice of VEs antiarrhythmic therapy is one of the main issues. Summarizing the known data, there are three main ways to choose VEs antiarrhythmic therapy. First, most common but less effective, is the empirical method that is based on physician's personal experience and research data on the effectiveness of medication. The second way is testing of antiarrhythmic medications using medicinal tests, but there is often a discrepancy between test results and long-term therapy effects [1]. The third method is the selection of antiarrhythmic therapy using 1–3 daily electrocardiography monitoring when each subsequent agent is prescribed no earlier than after five half-lives of the previous one in a short course (for 3–5 days) at an average therapeutic dose [1]. However, the last method of selection is very expensive, requires a rather long time of patient observation and / or the patient's admission to the hospital, as well as the performance of multiple 1–3 daily electrocardiography monitoring.

Current study has also shown that in cases of true positive effect of antiarrhythmic therapy index increased after the first and second administrations of

medication mostly due to increased LD of corrected pre-ectopic interval (r=0.87), and after the third and subsequent intakes — due to a decreased number of premature ventricular complexes (r=–0.85). Therefore, using the proposed method, several potentially effective drugs can be identified even before the onset of clinical effect, by the assessment of the reduction of the number of VEs according to the data of daily electrocardiography monitoring after a short course of therapy. This method allows to evaluate the effectiveness of antiarrhythmic drug only after at least the third intake compared with other methods. It should be noted that the true positive test results obtained using this method were confirmed by 24-hour electrocardiography monitoring data with more than 90 % AC.

11.21 % of patients took metoprolol to eliminate VEs, 10.28 % — propranolol, 5.61 % — carvedilol, 12.15 % — allapinin, 15.89 % — moricizine, 28.04 % — ethacyzin, 35.05 % — propafenone, the rest — sotalol.

Previous clinical and experimental studies have shown that the value of LD of the corrected pre-ectopic interval, for example, ⩽10 ms, indirectly confirmed the presence of "re-entry" and / or the development of pathological ectopic focus, and the large variability of this indicator — the presence of trigger mechanisms [6]. Therefore, after several doses of an antiarrhythmic drug in patients with trigger mechanisms, the hyperpolarization of the cardiomyocyte membrane decreases, and, therefore, corrected pre-ectopic interval increases and VEs frequency decreases. After the development of an excitation wavefront, for example, by the "re-entry" mechanism, it is fractionated, divided into smaller waves, each of which becomes independent, that causes different corrected pre-ectopic intervals on the electrocardiogram — early complexes, followed by complete conduction blockage and elimination of ectopic beats [1, 6].

The results obtained earlier are indirectly confirmed by the data obtained in this study: the positive clinical effect of class II drugs highly correlated with the LD of the corrected pre-ectopic interval ⩾ 11 ms (r=0.88), classes I and III drugs — with ⩽10 ms (r= 0.84).

In 20.10 % of patients, the antiarrhythmic effect of VEs therapy persisted for less than 1 year (0.7±0.04 years on average), in the rest — from 1 year to 5 years (3.8±0.08 years on average) ($p<0.05$). The duration of preserved positive clinical effect of VEs treatment for over 1 year highly correlated with the true positive results of antiarrhythmic drugs screening testing (r=0.94). It is also remarkable that, according to daily electrocardiography monitoring data, the reduction of VEs did not differ significantly between groups with preservation of positive effect for less than 12 months and for over 1 year and averaged 87 %. Similar data were obtained earlier [9]. This fact, apparently, should be taken into account when choosing therapy for VEs in patients without cardiac structural changes.

The duration of positive VEs therapy effect in patients without cardiac structural changes for less than 1 year, may be explained by the following factors. First, the damage of ion channels and / or receptors of cardiomyocytes due to "oxidative stress" [10,11]. Second, premature ventricular complexes can indicate the development of myocarditis, cardiomyopathy, arrhythmogenic right ventricular dysplasia, etc., and in patients with these diseases, pharmacotherapy of arrhythmias is ineffective or less effective, or has very short-term positive effect [1,2]. Therefore, in patients without cardiac structural changes with 10 % or more VEs of the total number of ventricular complexes, predictors of the development of arrhythmogenic cardiomyopathy and life-threatening ventricular arrhythmias, as well as the absence or short-term positive effect of antiarrhythmic therapy radiofrequency ablation of the arrhythmogenic focus is recommended [1, 2, 8].

Conclusion

Thus, the proposed screening testing method for the selection of antiarrhythmic medications allows to determine several potentially effective medications to eliminate VEs in one patient in a fairly short period of time (up to 5–7 days). In current study 50.47 % of patients had positive antiarrhythmic effect of two, 38.32 % — of three, and the rest — of four antiarrhythmic medications. AC of potentially effective drugs for eliminating VE in patients without cardiac structural changes was over 90 %. Therefore, in case of decreased antiarrhythmic effect of medication, selected according to the results of screening testing for long-term VEs therapy, as well as in case of the development of complications, the physician has a number of other potentially effective agents to replace selected therapy, and, if necessary, preform another testing in a short period of time.

We can make several conclusions from our study: AC of potentially effective drugs for eliminating VE using method of screening testing in patients without cardiac structural changes was over 90 %, and positive predictive value — over 80 %.

In 79.90 % of patients, positive antiarrhythmic effect of VE therapy persisted for over 1 year (an average of 3.8±0.08 years). The duration of positive clinical effect for 1 year and higher correlated with the positive results of screening testing of antiarrhythmic drugs (r=0.94).

Conflict of interests: None declared.

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Reduced glomerular filtration rate in patients with acute STEMI

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Abstract

Objective *of this study was to evaluate the characteristics of patients with acute ST-elevation myocardial infarction (STEMI) depending on the glomerular filtration rate (GFR).*

Materials and methods

Patients with STEMI were included. We assessed the changes in their clinical and laboratory characteristics during their hospital stay and evaluated echocardiographic findings depending on the GFR (≥ or<60 ml/min/1.73m^2). In-hospital mortality risk was assessed using the GRACE scale. The statistical analysis was performed using the "Statistica 10.0 for Windows".

Results

Patients with STEMI and reduced GFR comprised 22% of all the patients included, were older, had left atrial and ventricular dilation in the presence of comparable hemodynamic and basic biochemical parameters. Patients with GFR<60 ml/min/1.73m2 were at a higher risk of acute and chronic heart failure and in-hospital mortality according to the GRACE scale. Regardless of GFR the reduction of the concentration of the stimulating growth factor ST2 was noted during inpatient treatment of STEMI. Surgical and pharmacoinvasive STEMI management resulted in the normalization of ST2 concentration in hospitalized patients.

Conclusion

It is important to calculate the GFR in patients with STEMI in order to choose the correct management and assess the risk of complications. The concentration of ST-2 reduced during the hospitalization and returned back to normal values after the percutaneous coronary intervention and pharmacoinvasive therapy regardless of the GFR.

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Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or the loss of kidney function persisting for 3 months or more. In patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 CKD can be diagnosed in the absence of kidney damage markers. In clinical practice, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation is used for GFR estimation.

It is well known that cardiovascular and kidney disease have common risk factors: arterial hypertension (AH); diabetes mellitus (DM); dyslipidemia and obesity. At the same time, patients with kidney disease can have hyperhydration, anemia, phosphate and calcium metabolism disorders, systemic inflammation and hypercoagulation, which, in turn, are the major risk factors for cardiovascular disease (CVD) [1].

Kidney dysfunction is prevalent in 12–17 % of general population, 42.9 % of patients with non-ST-elevation myocardial infarction (NSTEMI) and 30.5 % of patients with ST-segment elevation myocardial infarction (STEMI) [2]. The prevalence of CVD in patients with reduced kidney function is 64 % higher compared with those with preserved kidney function. GFR less than 60 ml/min/1.73 m2 is negatively associated with risk of mortality, cardiovascular complications and hospitalization [3]. The incidence of new cardiovascular complications depends on CKD stage. In patients with CKD stage 2 it was estimated to be 4.8 % and it doubles in patients with CKD stage 3 and 4 [1].

A decline in GFR increases the risk of cardiovascular death in patients with acute coronary syndrome (ACS), acute MI, after thrombolysis, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). In patients with two CVD risk factors the risk of GFR decline to less than 60 ml/min/1.73 m2 increases 3.7-fold compared with the patients without any risk factors. Approximately 30 % of patients are diagnosed with stage 3–5 CKD after acute MI [1, 2]. A decline in GFR is also seen in 30–40 % of patients with ACS and in 70 % of patients with cardiogenic shock. GFR decline to less than 60 ml/min/1.73 m2 is considered a negative mortality predictor in MI, recurrent MI, heart failure (HF), stroke and bleeding in NSTEMI and STEMI [4].

PCI improves the outcomes in patients with ACS. At the same time, the use of contrast dyes can cause kidney injury [5]. The evaluation of kidney function in patients with ACS is an important prognostic factor [6]. In CKD, pharmacological and surgical treatment options are limited. Kidney function decline can lead to bleeding in patients taking antithrombotic agents [7, 8, 9] and poor outcomes after myocardial revascularization. CABG intraoperative mortality in such patients rises more than 7-fold.

We used hospital mortality assessment scales and laboratory markers for outcome prediction. One of the commonly used laboratory markers is a stimulating factor 2 (ST-2). ST-2 is a laboratory predicter that can be used for risk stratification in HF as well as for negative outcomes and cardiovascular events prediction [10]. ST-2 levels are not associated with HF specific causes, weight and age [11], change as a response to treatment and therefore can be used for disease progression and treatment effects monitoring [12]. According to KohliP, et al. (2012), ST-2>35 ng/ml in ACS increase the risk of CVD mortality and HF development 3-fold during the first 30 days and at 1-year follow-up.

We suppose that it would be interesting to study STEMI patients while taking into consideration renal function and ST-2 levels.

Objective of this study was to evaluate the characteristics of patients with STEMI depending on the GFR.

Materials and methods

The current study included 150 patients with STEMI. The study was conducted in accordance with Good Clinical Practice standards and Helsinki Declaration Principles. Informed consents were obtained prior to participation. According to The Russian Society of Cardiology (RSC) 2007 guidelines STEMI diagnosis was based on clinical and instrumental (ECG) findings and the presence of laboratory markers: troponin I and CK-MB (creatine kinase myocardial band). Inclusion criteria were age> 45 years, arterial hypertension, acute heart failure grade II–IV according to T. Killip classification, the first 24-hours of presentation. Exclusion criteria were history of liver dysfunction, severe kidney dysfunction, women of

childbearing age, cancer, type I and II diabetes mellitus, connective tissue disease, infections. We evaluated objective clinical findings such as systolic blood pressure (SBP), diastolic blood pressure (SBP), heart rate. Chemistry panel: AST, ALT, urea, creatinine, lipid profile, cardiac necrosis markers, electrolytes. ST-2 plasma level was also evaluated using the immunoferment analysis (Presage ST2 Assay Critical Diagnostics, UC).

All patients with STEMI were examined twice: at admission to cardiology department (visit 1) and at discharge (visit 2). Patients were treated with pharmacologic agents and infusion therapy: prehospital thrombolysis, primary PCI and pharmacoinvasive therapy (thrombolysis+ PCI).

GFR was estimated using the CKD-EPI formula that is based on age, sex, race and creatinine level. We used The Global Registry of Acute Coronary Events (GRACE) score to estimate the risk of in-hospital mortality:<126 — low risk (<2%), 126–154 — moderate risk (2–5%),>154 — high risk (>5%). ECG and echocardiography (to estimate the size of left atrium (LA), right atrium (RA), left ventricle (LV), right ventricle (RV), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), ejection fraction (EF), pulmonary artery pressure (PAP), the A wave, the E wave, E/A ratio, tricuspid regurgitation, pulmonary regurgitation) were performed in all patients. All patients were divided into groups depending on the estimated GFR (≥ or<60 ml/min/1.73m2).

The statistical analysis was performed using the "Statistica 10.0 for Windows". Mann-Whitney U-test was used to assess the statistical differences between the groups. Spearman's correlation coefficient was used to measure the association between variables. Numerical data are presented as mean M±m. p<0.05 was considered statistically significant.

Results

General characteristics of STEMI patients are: age 61.69±0.96 years, SBP 135.42±2.25 mm Hg, DBP 81.86±1.21, HR 81.61±1.51 beats per minute. Laboratory values: ALT 45.03±2.57 IU/L, AST 86.26±8.73 IU/L, urea 9.76±1.44 mmol/l, creatinine 84.45±2.68 mmol/l, eGFR 81.17±1.98 ml/min/1.73m2. Cardiac necrosis markers: troponin I 13.22±1.40 ng/mL, CK-MB 61.63±14.92 IU/l. Lipid profile: total cholesterol 5.74±0.11 mmol/l, low-density lipoproteins (LDL) 2.87±0.06 mmol/l, high-density lipoproteins (HDL) 1.33±0.02 mmol/l, triglycerides (TG) 1.74±0.09 mmol/l. The mean GRACE risk score was 162.26±2.58, which signifies the high risk of in-hospital mortality for STEMI patients.

Of all STEMI patients, 22% had reduced GFR (n=33) and 78% had preserved GFR (n=117). Patients with GFR<60 ml/min/1.73m2 were older — 69.48±2.01(p<0.05) but had similar hemodynamic characteristics: SBP 132.18±5.54 mmHg, DBP 80.21±3.50 mmHg, HR 81.84±3.45 beats per minute compared with the patients with GFR>60 ml/min/1.73m2: 60.26±1.11 years, SBP 135.77±2.43 mmHg, DBP 82.69±1.21 mmHg, HR 81.89±1.67 beats per minute (p>0.05). Patients with reduced GFR were at a higher risk of in-hospital mortality according to the GRACE risk score (181.15±5.84) compared the patients with preserved GFR (159.83±2.79), p<0.05.

Therefore, patients with STEMI and reduced GFR were older and had a higher risk of in-hospital mortality according to GRACE risk score.

We also studied blood chemistry values in STEMI patients with GFR<60 ml/min/1.73m2 and GFR≥60 ml/min/1.73m2. In patients with reduced GFR the laboratory values were as follows: AST 83.46±24.18 IU/L, ALT 41.17±5.50 IU/l, urea 10.38±2.94 mmol/l, CPK 319.78±90.19 IU/l, CK-MB 101.08±61.57 IU/l. In patients with preserved GFR the laboratory values were as follows AST 87.04±8.99 IU/l, ALT 46.09±2.91 IU/l, urea 9.5±1.64 mmol/l, CPK 320.36±37.89 IU/l, CK-MB 49.94±6.65 IU/l. The differences were not statistically significant (p>0.05). In patients with reduced GFR creatinine level was 118.67±7.57 mmol/l, mean GFR 46.09±1.87 ml/min/1.73m2; in patients with preserved GFR — creatinine 75.01±1.97 mmol/l, mean GFR 90.87±1.54 ml/min/1.73m2 and the differences were statistically significant (p<0.05). Lipid levels in patients with reduced GFR were as follows: total cholesterol 5.89± 0.23 mmol/l, LDL 3.11±0.14 mmol/l, HDL 1.40±0.05 mmol/l, TG 1.51±0.12 mmol/l and were similar to those in patients with preserved GFR: total cholesterol 5.70±0.12 mmol/l, LDL 2.80±0.07 mmol/l, HDL 1.31±0.03 mmol/l, TG 3.67±1.32 mmol/l (p>0.05). Troponin I (13.81±3.51 and 13.05±1.51 ng/ml) and sodium (137.84±4.42 and 140.99±0.38 mmol/l) levels were non-specific in both analyzed groups (p>0.05). Potassium level was higher in patients with reduced GFR compared with the patients with preserved GFR (5.60±1.15 mmol/l versus 4.24±0.05 mmol/l, p<0.05).

Outcome prediction in hospitalized patients is an important problem. We evaluated the correlation between GFR and the risk of ACS, chronic heart failure and GRACE risk score. GFR was inversely correlated

with acute heart failure severity in STEMI patients (r=–0.48, p=0.001), with stage of CHF progression (r=–0.23, p=0.038), in-hospital mortality according to GRACE risk score (r=-0.48, p=0.0001) and with poor outcome during in-hospital treatment (r=-0.40, p=0.043).

We also calculated GFR in patients with different STEMI management approaches: there were no statistical difference between the filtration rate in patients who undergone thrombolysis (75.41±6.25 ml/min/1.73m2) compared with patients who undergone primary PCI (87.04±3.14 ml/min/1.73m2) and with patients who undergone both thrombolysis+PCI (74.85±6.96 ml/min/1.73m2). Patients with PCI had higher GFR compared with those who undergone pharmacoinvasive treatment (thrombolysis+PCI), p<0.05.

As such, GFR estimation plays a major role in choosing the adjust management and medication dosages in STEMI patients and is important for better prognosis in such patients.

Assessment of ST-2 levels in hospitalized patients was also important for outcome prediction. The mean ST-2 level in all the patients with STEMI at admission was 70.48±7.80 ng/ml and 35.25±4.70 ng/ml at discharge (p<0.05). ST-2 concentration was positively correlated with troponin I levels (r=0.21, p<0.05) and inversely correlated with LVEF (r=0.21, p<0.05). These data confirm the association between ST-2 concentration and the extent of myocardial damage. Normalization of ST-2 levels during the treatment period signifies a better prognosis for STEMI patients.

Mean levels of ST-2 in hospitalized patients in STEMI patients with GFR<60 ml/min/1.73m2 and GFR≥60 ml/min/1.73m2 are shown in Figure 1. ST-2 concentrations were similar at the first (p>0.05) and second (p>0.05) visits in both groups of patients with STEMI. At the same time ST-2 levels decreased in groups with GFR<60 ml/min/1.73m2 (p<0.05) and GFR≥60 ml/min/1.73m2 (p<0.05) during hospital stay. Therefore, ST-2 levels decreased in STEMI patients during hospitalization independently from GFR.

STEMI patients were divided into two groups depending on the treatment approach: pharmacologic therapy, primary PCI, prehospital thrombolysis, thrombolysis+ PCI. ST-2 levels were similar at the first 24 hours of treatment in all groups (p>0.05) (Figure 2). ST-2 levels decreased during in-hospital treatment in the pharmacologic therapy group (p<0.05), PCI (p<0.05) and thrombolysis+ PCI groups (p<0.05) groups. The levels of ST-2 normalized in patients in the primary PCI and thrombolysis+ PCI groups and didn't change in thrombolysis group (p>0.05). At the second visit, ST-2 levels were different in patients who have undergone thrombolysis comparing with those who had primary PCI (p<0.05) or thrombolysis+ PCI (p<0.05).

Therefore, normal ST-2 levels were reached during in-hospital treatment in STEMI patients who have undergone primary PCI or thrombolysis+ PCI. Those who only received pharmacologic therapy and prehospital thrombolysis failed to reach normal ST-2 levels while still at the hospital.

Echocardiography findings in STEMI patients with preserved and reduced GFR are presented in Table 1.

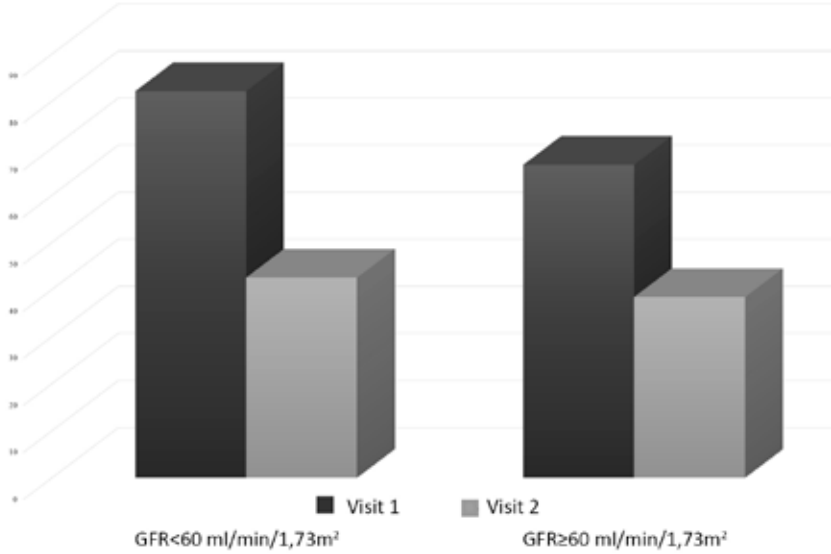

Figure 1. Mean ST-2 levels on visit 1 and 2 in patients with GFR<60 ml/min/1,73m² and GFR≥60 ml/min/1,73m² (p<0,05).

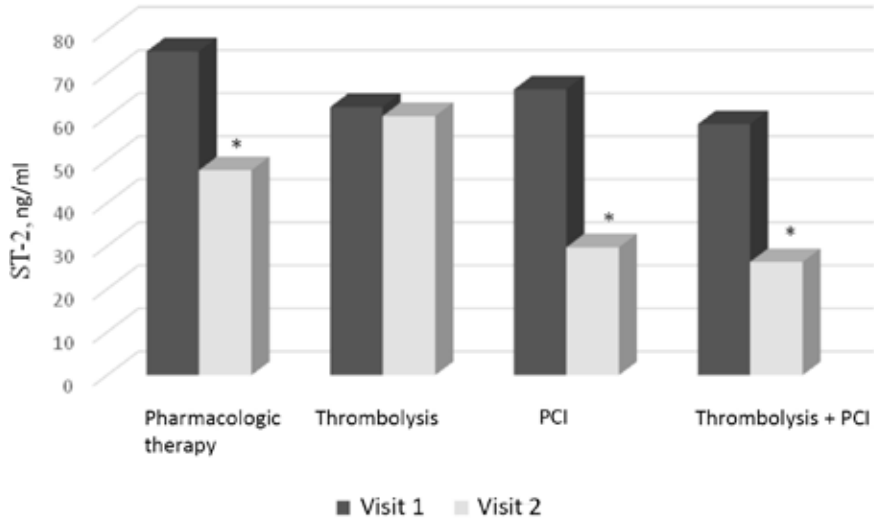

Figure 2. ST-2 levels in STEMI patients with different treatment approaches. **Note:** Visit 1 — ST-2 levels are similar in all groups (p>0,05); * — p<0,05 at visit 2.

STEMI patients with reduced GFR had higher LA, LV end-systolic dimension (ESD), LV end-diastolic dimension (EDD), LV ESV, LV EDV (p<0.05) compared with those with preserved GFR. At the same time, other values of stroke volume and ejection fraction, pulmonary artery pressure, the A wave, the E wave, E/A ratio and RV and RA parameters were similar in both groups. GFR reduction was positively correlated with pulmonary artery pressure (r=–0.20, p<0.02) and E peak decrease (r=0.23, p<0.007). Shortening of early diastolic filling time deceleration (E peak) is considered to be the predictor of increased mortality in patients with acute MI.

Patients with STEMI and reduced GFR also had larger LA and LV, although the sizes of RV and RA were unchanged.

Table 1. **Echocardiography findings in STEMI patients with GFR<60 ml/min/1,73m² and GFR≥60 ml/min/1,73m²**

Value	GFR<60 ml/min/ 1.73m2 M±m	GFR≥60 ml/min/ 1.73m2 M±m	p
LA, mm	45.03±2.20	41.48±0.65	<0.05
LV ESD, mm	44.41± 2.12	40.98±0.64	<0.05
LV EDD, mm	56.41±1.74	53.48±0.52	<0.05
ESV, ml	83.45±3.61	73.14±1.48	<0.05
EDV, ml	148.29±5.25	137.86±1.78	<0.05
SV, ml	67.48±2.24	64.36±0.77	>0.05
LVEF, %	46.32±2.12	47.06±0.74	>0.05
PAP, mmHg	35.96±2.66	32.77±0.90	>0.05
E, cm/sec	48.80±2.72	51.52±1.19	>0.05
A, cm/sec	62.09±2.91	60.68±1.28	>0.05
E/A	4.15±3.29	1.84±0.91	>0.05
RA, mm	35.87±2.32	33.24±0.65	>0.05
RV, mm	32.38±2.4	30.58±0.67	>0.05
TV V max, cm/sec	250.06±7.52	245.38±2.95	>0.05
TR, st	1.06±0.04	1.95±0.90	>0.05
PA, mm	29.16±2.47	27.12±0.76	>0.05
PR, st	0.81±0.07	1.92±0.93	>0.05

Note:
LA — left atrium,
LV ESD — left ventricular end-systolic dimension;
LV EDD — left ventricular end-diastolic dimension;
ESV — end-systolic dimension;
EDV — end-diastolic volume;
SV — stroke volume;
LVEF — left ventricular ejection fraction;
PAP — pulmonary artery pressure;
E — E peak;
A — A peak;
RA — right atrium;
RV — right ventricle;
TV — tricuspid valve;
TR — tricuspid regurgitation;
PA — pulmonary artery;
PR — pulmonary regurgitation.

Discussion

It is well known that in STEMI reperfusion should be performed as early as possible. GFR estimation is an important safety factor for patients with MI. Kidney function assessment can guide physicians when choosing appropriate dosing of antiplatelet agents and contrast agents. Patients with acute MI and CKD often receive high doses of antiplatelet agents during the first 48 hours after the event and that leads to the higher risks of bleeding and other complications [13]. GFR estimation determines if it is possible to perform coronary angiogram, if the drug doses should be changed and what complications are possible.

Our results are similar to those of previous studies reporting that the reduced GFR is a predictor for increased mortality in MI [1]. Contrast-induced nephropathy after PCI are associated with negative outcomes in patients with MI [13]. In our study patients with reduced GFR were at higher risk of in-hospital

mortality according to the calculated GRACE risk score and poor prognosis. Pharmacoinvasive approach had negative influence on GFR compared with primary PCI in patients with STEMI.

GFR depends on a number of clinical and laboratory values [1]. One of the CVD development predictors is ST-2. ST-2 levels are not influenced by gender, age or GFR [11] and its concentration in healthy adults is around 18 ng/ml. Concentration>35 ng/ml is associated with increased risk of CVD complications [14]. Increase in ST-2 correlates with HF severity and doesn't depend on other biomarkers [15]. According to the literature reviewed, ST-2 levels decrease during in-hospital treatment of STEMI patients with both reduced and preserved GFR. The use of primary PCI and pharmacoinvasive leads to normalization of ST-2 levels and improves the prognosis.

Patients with acute MI require the complex assessment of risk factor and objective and laboratory findings for the choice of appropriate safe therapeutic approach. GFR is an outcome predictor in patients receiving pharmacologic and invasive MI treatment [1, 2, 4].

Conclusion

Glomerular filtration rate estimation is necessary for hospitalized patients with acute myocardial infarction as it can guide the choice of appropriate treatment and drug dose changes. STEMI patients with reduced GFR were older, tended to have hyperkalemia with higher in-hospital mortality according to GRACE risk score and dilation of left atrium and ventricle on echocardiography. ST-2 concentration decreased during in-hospital treatment in patients with both reduced and preserved GFR. Surgical and pharmacoinvasive approaches led to ST-2 normalization during in-hospital treatment and thus resulted in better prognosis.

Conflict of interest: none declared.

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A comparative analysis between moderate intensity continuous and high-intensity interval cardio-rehabilitation training in athletes with arterial hypertension: a randomized controlled trial

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Objective

To compare the influence of moderate intensity continuous and high-intensity interval cardio-rehabilitation training on blood pressure in athletes with arterial hypertension.

Materials and methods

The study included 83 athletes of power sports (bodybuilding) with arterial hypertension. The average age of male athletes was 31.2± 4.5 years, and the body mass index was 32.4± 2.8 kg/m^2. The following methods were used: examination, questioning, triple measurement of blood pressure, ergospirometry and methods of mathematical statistics. Athletes were randomized into two groups: the HIIT group (n= 33), the MICT group (n= 30), and the control group RT (n= 20). For 120 days (3 times a week), HIIT and MICT athletes performed simultaneous physical rehabilitation.

Results

120 days after physical rehabilitation systolic blood pressure decreased in HIIT and MICT groups by 8.3 mm Hg and 7.7 mm Hg, respectively. A significant reduction in diastolic blood pressure in HIIT and MICT groups was 7.9 mmHg and 8.3 mmHg, respectively. A decrease of blood pressure in the control group was not statistically significant.

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Conclusion. *Despite similar benefits in cardio-rehabilitation, interval exercise required 38 % less time that can significantly affect adherence and exclude some participants of long rehabilitation.*

Key words: *arterial hypertension, interval training, bodybuilding, physical rehabilitation.*

Conflict of interests: None declared.

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Introduction

According to epidemiological data, cardiovascular diseases (CVDs) are the leading cause of death and disability worldwide [1, 2]. Patients with CVDs do not only have a range of chronic diseases that affect their quality of life, but also increase family and community economic burden. Historically, the "Athletic Heart" hypothesis has encouraged a dichotomous view on heart adaptation to exercising, depending on whether the physical activity is dynamic (runners and swimmers) leading to "cardiomegaly" [3] or isometric (strength athletics) with clear peripheral adaptations, heart enlargement and increased blood pressure [4]. Today, the classification of sports according to its physiological needs recognizes great variety of impacts, depending on physical activity, with the graded transition between the main categories: dynamic and static. Moreover, athletes with predominant static component (strength sports) have higher percentage of CVD, since static contractions stimulate mechanical and metabolic changes in skeletal muscle and sustained changes in blood pressure [5]. Therefore, it is of great practical importance to determine the appropriate, non-pharmacological strategy, to reduce CVD risk factors in strength sports athletes. Moderate-intensity continuous aerobic training (MICT) is considered to be an effective way to reduce CVD risk factors [6,7]. However, in recent years, an aerobic exercise protocol called high-intensity interval training (HIIT) has become more popular, which includes high-intensity intervals of aerobic work (with a heart rate (HR) of 80–100 % HRmax) from 60 to 240 seconds. Many researchers have shown that HIIT is one of the most effective means to improve cardiorespiratory endurance, reduce CVD risk factors [8] and lower blood pressure [9]. However, aerobic training, the «gold standard» for the prevention and treatment of CVDs, is not specific for strength athletics and, therefore, is not included in the training protocols of these athletes. The objective of this study was based on the analysis of mentioned above issues, the data of modern scientific literature and the requests of sports medicine physicians (who use physical rehabilitation methods in patients with arterial hypertension) and strength-trained athletes with arterial hypertension.

Materials and methods

The study was performed on the basis of the Department of Sports Medicine of Russian State University of Physical Education, Sport, Youth with 120-day follow-up. The study involved 83 strength-trained athletes (bodybuilders) with the sports qualifications of candidate to master of sports and mater of sports in heavy weight categories with arterial hypertension (AH), who were recommended aerobic exercises for treatment and prevention of AH. Athletes did not participate in competitions during the study. Athletes were randomized into two main groups: HIIT group (n= 33), MICT group (n=30) and RT control group (n=20). Average age of men was 31.2± 4.5 years, and body mass index was 32.4± 2.8 kg / m^2. All athletes signed written informed consent to participate in the study according to the ethical standards of scientific research in sports and physical activity 2020 (protocol No. 5, meeting of the Ethics Committee of the Russian State University of Physical Education, Sport, Youth and Tourism on 26.10.2017). The study used the following methods: medical examination, three-time measurement of blood pressure (in the morning from 8:00 to 11:00), ergospirometry and methods of mathematical statistics.

Ergospirometry

Aerobic capacity was assessed using MONARK 839 E bicycle ergometer (Monark AB, Sweden), the load was set starting from 20 W and increased for 20 W every 2 minutes. Gasometric analysis was performed using a CORTEX gas analyzer (Meta Control 3000, Germany), which measures oxygen consumption and carbon dioxide emission during each respiratory cycle. The test was performed at the rate of 75 rpm/min^{-1} to determine maximal oxygen consumption, blood pressure (BP) and heart rate at the BP level, and pedal

power at maximal oxygen consumption by the method of Pallarés et al [10].

Mathematical statistics methods

All the results obtained were processed using Microsoft Office Excel 2007 and Statistica 10.0 / W RUS Software, as well as statistical software package for biomedical sciences. Quantitative variables were summarized as mean (M). The significance of differences was determined by the Student's t-test for paired and unpaired samples. Differences were considered statistically significant when $p<0.01$.

Exercise protocols

Athletes from all groups trained for 120 days (3 times a week) according to the following protocols: 1) RT group: strength training — 5 exercises with a weight of 70–90 % of repetition maximum (1RM), 4 approaches with from 2 to 8 repetitions. One cycle of "approach+ rest (until complete recovery)" for 5 minutes. Exercises were performed for all major muscle groups and included: bench press, bar squats, deadlift, barbell forearm flexion, forearms extension. The training session lasted 100 minutes; 2) HIIT group: strength training — 5 exercises with a weight of 70–90 % of 1RM, 3 approaches with from 2 to 8 repetitions. The strength training technique was the same as in the RT group. After the strength protocol, aerobic work on bicycle ergometer was added, included 7 high-intensity intervals (at pedal power of 100 % of maximal oxygen consumption) for 2 minutes and low-intensity intervals with a heart rate of 85 % of anaerobic threshold (AT) for 2 minutes. During the ergospirometry test, the pedal power was set at the level of 85 % of AT, therefore, it was recommended to reduce the load to this level. The training session lasted 103 minutes; 3) MICT group: strength training — 5 exercises with a weight of 70–90 % of 1RM, 3 approaches from 2 to 8 repetitions for bench press exercises and 2 approaches for other exercises. The strength training technique was the same as in the RT group. After the strength protocol, continuous aerobic training on a bicycle ergometer for 45 minutes with an intensity of 60–80 % of pedal power of maximal oxygen consumption was added according to the guidelines of the American College of Sports Medicine (ACSM) 2019 [11] for the participants with arterial hypertension. The training session lasted 100 minutes.

Results and discussion

It has been suggested that HIIT may have positive effect on cardiovascular system. Overall, 33 systematic reviews (including 25 meta-analyzes) that included both healthy and people with various diseases showed that HIIT improved cardiorespiratory endurance, anthropometric parameters, vascular function, heart function, and body mass compared with inactive controls [12] Additionally, recent systematic reviews and meta-analyzes [13, 14, 15] have shown that: 1) HIIT and MICT similarly reduced blood pressure in adults with pre-established arterial hypertension; 2) HIIT was associated with larger increase of maximal oxygen consumption compared to MICT; 3) HIIT significantly decreased nocturnal diastolic blood pressure (DBP) compared with MICT; 4) HIIT significantly decreased daytime blood pressure compared with MICT; 5) the decrease in systolic blood pressure (SBP) after interval exercises did not differ from responses to MICT immediately and 60 minutes after exercise; 6) DBP decreased and

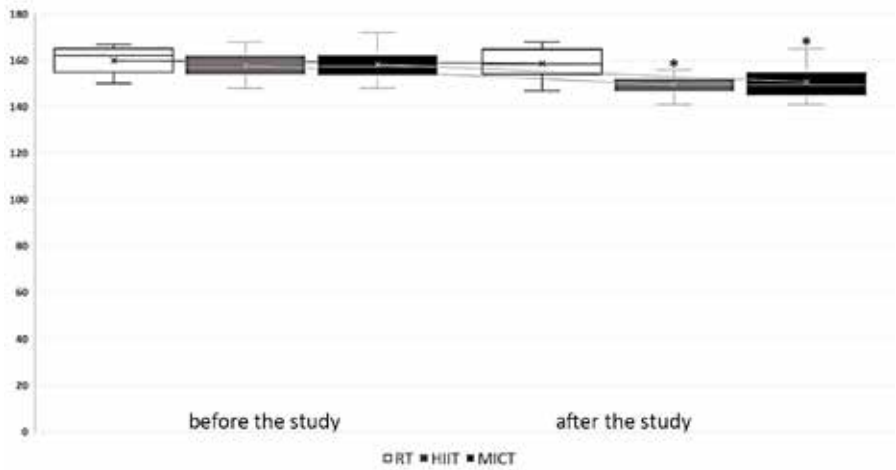

Figure 1. The dynamics of systolic blood pressure changes during different exercise protocols in strength-trained athletes
Comment: (*) statistically significant changes between groups — p<0,01.

Table. **BP dynamics during different exercise protocols in strength-trained athletes**

Group (N=83)	SBP (mmHg)			DBP (mmHg)		
	0 days	120 days	Δ	0 days	120 days	Δ
RT (n=20)	159,9±5,5	158,7±6,2	1,3	96,2±3,5	95,9±4,1	0,3
HIIT (n=33)	157,9±5,1	149,9±4,0	8,3*	96,1±4,8	88,2±4,6	7,9*
MICT (n=30)	158,3±6,3	150,6±6,1	7,7*	97,4±5,3	89,1±5,2	8,3*

Comment: (*) statistically significant changes between groups – p <0,01.

blood flow increased more 10–15 minutes after interval exercise compared with MICT. After 120 days of physical rehabilitation, SBP decreased in HIIT and MICT groups by 8.3 mm Hg and 7.7 mm Hg, respectively (Figure 1).

SBP insignificantly decreased in control RT group (–1.3 mm Hg) that was not statistically significant. According to meta-analysis by Smart and his colleagues [17], isometric exercises (that is common in bodybuilding training programs) alone, without aerobic work, have antihypertensive effect. However, in our study, BP did not decrease in the RT group during 120-day follow-up. The difference between the RT group and MICT and HIIT groups was statistically significant, unlike between aerobic work groups. After 120 days of physical rehabilitation, DBP significantly decreased in HIIT and MICT groups by 7.9 mm Hg and 8.3 mm Hg., respectively (Figure 2), and by 0.3 mm Hg — in the RT group that was not statistically significant. The difference between the decrease of DBP in MICT and HIIT groups was also not statistically significant. It is well known that a decrease in blood pressure by 7.5 mm. Hg. and by 10 mm. Hg. reduces the incidence of strokes by 46 % and 56 % and the incidence of coronary artery disease by 29 % and 37 % [16].

Comparative analysis of blood pressure reduction between the MICT and HIIT groups shows that both methods effectively reduce SBP and DBP (table), however, athletes from the HIIT group spent 38 % less time on exercising.

Conclusion

According to the analysis of modern scientific literature using the following databases: eLibrary, RSCI, PubMed, Cochrane Library, CINAHL, Web of Science, MEDLINE, SPORTDiscus and Scopus, we did not find studies that would prove the effectiveness of any aerobic exercises method in blood pressure lowering in strength-trained athletes with arterial hypertension. 120 days of simultaneous physical rehabilitation using HIIT, MICT and RT showed that: 1) blood pressure did not decrease in the RT group within 120 days; 2) simultaneous combinations of RT+ MICT or RT+ HIIT, similarly reduced SBP within 120 days of physical rehabilitation by 4.9 % and 5.3 %, respectively; 3) simultaneous combinations of RT+ MICT or RT+ HIIT, similarly reduced DBP within 120 days of physical rehabilitation by 8.5 % and 8.2 %, respectively; 4) despite similar effect on blood pressure, athletes from the HIIT group spent 38 % less time that can significantly affect adherence and exclude some participants of long rehabilitation. Further researches are required.

Conflict of interest: none declared.

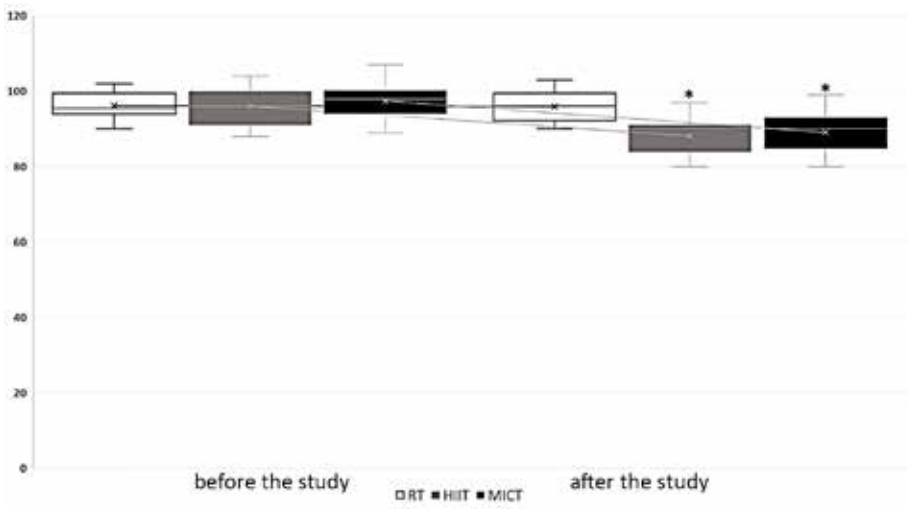

Figure 2. The dynamics of diastolic blood pressure changes during different exercise protocols in strength-trained athletes
Comment: (*) statistically significant changes between groups — p<0,01.

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Coronary "slow-flow" phenomenon in young males with STEMI: clinical features and follow-up

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Abstract

Objective of this study was to identify clinical and angiographic characteristics and evaluate long-term treatment outcomes in young male patients with STEMI.

Materials and methods

Depending on the coronary angiography results we formed two groups of patients aged 25-44 years: the first consisted of 44 men with the angiographic "Y-phenomenon" and the second of 25 men with the typical pattern of a coronary artery occlusion. We analyzed risk factors, laboratory parameters, echocardiographic findings, the severity of depression according to The Beck Depression Inventory (BDI) and the level of androgenic dysfunction according to the Aging Males' Symptoms (AMS) and International Index of Erectile Function (ICEF-5) questionnaires. Survival rates repeated acute coronary events and the prevalence of surgical revascularization after a year of the primary event were evaluated.

Results

There were more men with the higher body mass index (BMI) in the first group. No significant differences in lipid profile were identified. Patients in the second group had higher rates of myolysis (MB-CPK, AST, ALT) and a lower left ventricular ejection fraction at discharge — 52.8% [36; 63] versus 58.1% [20; 69]. These findings were statistically significant. There were no significant differences in the level of the androgen deficiency symptoms according to the AMS scale between the two groups. Depressive symptoms were present in 77.3% of the respondents in the

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first group and in 68% of the respondents in the second group. After 365 days from the indexed event all patients are alive and no large coronary events happened.

Conclusion

Young male patients with STEMI have different risk factor profiles and comparable annual survival rates depending on the angiographic picture. The intensity of the pathological process and inflammatory reaction are more pronounced in the classical MI. Depression, as one of the possible risk factors, turned out to be insignificant in groups with Y-syndrome and with atherothrombosis. Erectile dysfunction was less pronounced with distal coronary blood flow disorders than with proximal occlusions.

Key words: *Y-phenomenon, STEMI, males, risk factors.*

Conflict of interests: none declared.

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Introduction

Myocardial infarction (MI) was traditionally considered a disease of middle aged and older people, but recently MI started to develop more frequently in people under 45 y.o. The potential risk factors (RF) of coronary and myocardial damage vary and often represent a complicated clinical problem. Coronary slow-flow phenomenon, or Y-phenomenon, is one of the poorly understood coronary angiographic characteristics in patients with angina, including those with various types of acute coronary syndrome (ACS). The Y-phenomenon is seen in 1–7% of angiographies performed in patients with stable angina and reflects the presence of microvascular arterial damage caused by increased blood flow resistance [1]. Moreover, it increases the risk of myocardial infarction (MI). The Y-phenomenon is also seen in 1–5% of patients with ACS — typically in young men who are often smokers and obese [1]. As this phenomenon is still poorly recognized and mostly presents in men, the aim of our study is to determine the clinical and angiographical characteristics to evaluate long-term treatment results in young men with a history of ST-elevation myocardial infarction (STEMI) registered on an ECG.

Materials and methods

This study was conducted in the Clinical Cardiologic Healthcare Centre in Perm, Russia in 2019-2020. Male patients who were 25-44 years old, had a history of ST-elevation myocardial infarction less then 12 hours before admission and signed and informed consent for coronary angiography were included. Those with a history of any ACS episodes, prehospital thrombolysis, diabetes, congenital and acquired heart defects, atrial fibrillation or total left bundle branch block (LBBB), implanted pacemaker, genitourinary pathologies, pituitary diseases or cognitive disorders were included. The study was performed in accordance with the Good Clinical Practice guidelines and Helsinki Declaration. Study protocol was approved by E. A. Wagner Perm State Medical University Ethics Committee. Informed consents were obtained prior to participation in the study. Depending on the coronary angiography results two groups of patients were formed: the first consisted of 44 men with the angiographic Y-phenomenon and the second of 25 men with the typical pattern of coronary artery occlusion. Y-phenomenon was determined as slow antegrade progression of contrast agent to normal epicardial coronary arteries. We analyzed the risk factors, laboratory values, echocardiography findings in both groups. We also assessed the presence of depression using The Beck Depression Inventory (BDI) and the level of androgenic dysfunction according to the Aging Males' Symptoms (AMS) and and International Index of Erectile Function (ICEF-5) questionnaires on the 3d day after admission. At one-year follow-up we assessed survival rates, the recurrence of acute coronary events and the frequency of surgical revascularization via phone interviews. Statistical analysis was performed with Statistica 6.0 software. We carried out comparative and correlation analysis. As the data followed non-normal distribution, we used nonparametric tests to compare two groups: Mann-Whitney U test and Kolmogorov-Smirnov two-sample test. We also used Spearman's correlation test (R) to evaluate the associations between two variables. Descriptive statistics for numerical variables are presented as median and interquartile range (Me [25; 75]; for categorical variables — absolute frequencies

and percentages (%). p<0.05 was considered to be statistically significant.

Results

Clinical and demographic characteristics of the participants are presented in Table 1. Men in the first group had higher BMI (p=0.02), but other coronary artery disease (CAD) risk factors (smoking, family history) were more commonly present in the second group. The mean number of the affected coronary arteries (clinically significant stenosis >50%) was 0.3 [0;2] and 2.9 [1; 6] in the first and second groups, respectively. Myocardial bridges were found in 2 patients in the first group. Although the age distribution was similar in two groups, men with classical atherothrombosis had more coronary damage and longer stable angina that explains the differences in the pharmacological treatment before MI. MI localization was similar in both groups.

During the hospital stay apart from standard laboratory and instrumental workup patients filled out the questionaries for additional evaluation of erectile dysfunction and the presence and level of depression. We hypothesized that androgen deficit may cause earlier development of CAD and we also were interested in evaluating the possible differences in men with various MI etiology. Our findings are presented in Table 2. There were no significant differences in lipid profiles although the prevalence of statin therapy differed between the two groups. Moreover, the levels of myocardial necrosis markers (CPK-MB, AST, ALT) were significantly higher in patients from the second group. Left ventricular ejection fraction (LVEF) was also lower in the second group: 52.8% [36, 63] vs 58.1% [20; 69]. The analysis of ICEF-5 questionnaires showed mild erectile dysfunction was present in the majority of patients in the first group (52.3%) and 36.3% of patients didn't have any complaints. In the second group erectile dysfunction was absent in 28% of patients, 64% had only mild symptoms and 8% — moderate symptoms. The level of androgen deficiency assessed by AMS scale didn't differ significantly in the two groups of this age group. Most patients either had mild androgen deficiency symptoms or had none of them. 77.3% of respondents in the first and 68% in the second group didn't have any symptoms of depression and the difference wasn't statistically significant. Somatic and cognitive-affective scales scores were also similar in the two groups of patients.

Table 1. **Clinical and demographic characteristics of patients in the two comparison**

Clinical and demographic characteristics	Group "Y-phenomenon", N=44	Group "Coronary artery thrombosis", N=25	p1–2
Age, years (mean)	42.4 [32; 45]	43.9 [36; 45]	0.4
BMI, kg/m^2	29.8[21.3; 37.9]	26.7 [17.7; 36.1]	0.02
Smoking, absolute number (%)	19 (43.2)	25 (100)	0.001
Regular alcohol consumption, absolute number (%)	6 (13.6)	8 (32)	0.002
Family history of CVD, absolute number (%)	15 (34.1)	19 (76)	0.000
Hemodynamically significant (>50%) coronary stenosis, absolute number	0.3 [0;2]	2.9 [1; 6]	0.01
CAD present> 1 year, absolute number (%)	16 (36.4)	19 (76)	0.000
Statins, absolute number (%)	12 (27.3)	17 (68)	0.00002
ACEi, absolute number (%)	9 (20.5)	18 (72)	0.000
Aspirin, absolute number (%)	12 (27.3)	18 (72)	0.000

Note. CAD — coronary artery disease, CVD — cardiovascular disease, ACEi — Angiotensin-converting enzyme (ACE) inhibitors.

Table 2. **Laboratory and instrumental findings and the survey results**

Values	Group "Y-phenomenon", N=44	Group "Coronary artery thrombosis", N=25	p1–2
Total cholesterol, mmol/l	4.72 [3.9; 6.4]	4.85 [3.7; 6.8]	0.07
HDL cholesterol, mmol/l	1.03 [0.78; 1.12]	1.28 [0.9; 1.3]	0.05
LDL cholesterol, mmol/l	2.90 [2.11; 3.54]	2.96 [2.18; 3.67]	0.4
Triglycerides, mmol/l	1.64 [1.4; 2.1]	1.48 [1.47; 2.08]	0.07
LVEF, (%, Simpson)	58.1% [20; 69]	52.8% [36; 63]	0.02
No erectile dysfunction, absolute number (%)	16 (36.3)	16 (64)	0.01
Mild erectile dysfunction, absolute number (%)	23 (52.3)	7 (28)	0.01
Moderate erectile dysfunction, absolute number (%)	0 (0)	2 (8)	0.3
Depression (BDI)	34 (77.3)	17 (68)	0.08

Note. HDL — low-density lipoprotein, HDL — high-density lipoprotein, LVEF — left ventricular ejection fraction, BDI — The Beck Depression Inventory.

Correlation analysis in patients with Y-phenomenon revealed moderate inverse correlation between the levels of HDL (high-density lipoprotein) cholesterol and band neutrophils (R=0.48, p=0.004) and direct correlation between the number of lymphocytes, BMI and glucose levels (R=0.44; p=0.02; R=0.39; p=0.04 respectively). However, stronger correlations between inflammation markers and lipid profile were found in the second group. The level of total cholesterol and LDL (low-density lipoprotein) strongly correlated with the number of band neutrophils (R=0.84; p=0.00; R=0.69; p=0.00), lymphocytes (R=0.95, p=0.00; R=0.85, p=0.00) and monocytes ((R=0.76, p=0.00; R=0.71, p=0.00 respectively).

Telephone interviews showed that in 365 days after the event all patients were alive and none of all the patients in both groups requires surgical revascularization. None of the patients developed any cardiac rhythm disorders as well. However, unstable angina that stabilized on the II functional class was diagnosed in 3 patients in the second group.

Discussion

Coronary slow flow phenomenon was first described by Tambe et al. in 1972 and termed "cardiac syndrome Y" because of the probable role of neuropeptide Y in the pathophysiology of this condition. This angiographic phenomenon, which is rarely identified, can cause both recurrent chest pain episodes and myocardial infarction [1]. The estimated prevalence of syndrome Y in patients with STEMI who were admitted to Clinical cardiologic Healthcare Centre in 2019-2020 is 3.7% of all angiography studies performed in young men, which is similar to 1%-5.5% in ACS patients worldwide [2]. Recently a number of new studies explored the Y-phenomenon risk factors but data on clinical characteristics and long-term outcomes in such patients is still very sparse. The results of our study are very similar to those described in the majority of works that explore the possible connection between Y-phenomenon development with increased BMI and specific characteristics of chest pain that develops not during physical activity but after it [3]. There is a study that compares the patients with Y-phenomenon and the cardiac syndrome X and those with Y-phenomenon had a significantly lower LVEF [4, 5]. Echocardiography with speckle-tracking detects significant changes in longitudinal and circumferential strain in patients with Y-phenomenon [6]. We performed echocardiography without strain assessment. We couldn't find direct comparisons with classical MI but we determined that LVEF reduction was more prominent in the second group. In general, according to the markers of cardiac myocyte necrosis, LVEF and the levels of neutrophils and lymphocytes, the pathological process seemed to be more severe in patients with classical atherothrombotic MI. The association between the inflammatory markers and lipid profile values was also stronger in the second group.

It is thought today that the Y-phenomenon is caused by increased coronary microvascular resistance that happens at rest, which, in turn, develops due to endothelial dysfunction [1]. At the same time, endothelial dysfunction can be an early sign of CAD and its development can be considered a potential signal of cardiovascular disease.

We didn't find any works on erectile dysfunction in Y-phenomenon and in our study it was less prevalent in this patient group compared with the classical MI. Depression is considered to be one of the risk factors of erectile dysfunction development but its prevalence was low in both groups.

As the pathophysiological process that leads to Y-phenomenon is still not clearly understood, choice of treatment that would improve distal perfusion is also quite challenging. Current data show that dipyridamole and mibefradil improve perfusion in Y-syndrome bur mibefradil was pulled from the market in 1998 [1]. Sparse research explores intracoronary calcium antagonists (nifedipine) infusion followed by oral forms [8, 9]. Nevertheless, it is recommended to use standard pharmacological agents in patients with confirmed MI during acute event and for secondary prevention. Our study showed that the period of in-patient treatment had no significant differences between the two groups. Stenting was more frequently performed in the second group and the difference was statistically significant. Pharmacological treatment recommended at the discharge was similar in both groups. The described clinical observation period ended with a telephone follow-up interview that didn't explore the predictors of benign CAD. We will continue to collect data in order to increase statistical power of various laboratory and instrumental predictors of negative coronary outcomes. According to the available data, the following parameters are the predictors of negative coronary outcomes in patients with Y syndrome: the presence of arterial hypertension at baseline, age>50 years old, hyperhomocysteinemia and dyslipidemia [3, 10]. We suppose that this fact should be taken into consideration in regular follow-ups of this group of patients.

Conclusion

ounger men with STEMI have different risk factors and similar one-year survival depending on the angiography results. Traditional risk factors play a major role in patients with atherothrombosis. Pathological process and inflammatory reaction are more severe in patients with classical MI. Lipid profiles were similar in the two groups but atherosclerosis was significantly different in the two groups that probably explains increased relapses of angina in the second group. Depression, which is one of the probable risk factors, was uncommon in both the Y syndrome group and the classical atherosclerosis group. Erectile dysfunction was less prominent in patients with distal coronary occlusions compared with the proximal occlusions.

Conflict of interest: None declared.

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REVIEW ARTICE

Patient-centered management of atrial fibrillation: from guidelines to clinical practice

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Abstract

The current article discusses the updated European Society of Cardiology (ESC) Guidelines on diagnosis and treatment of atrial fibrillation and their application in daily patient-centered clinical practice that emphasizes rate and rhythm control.

Keywords: *atrial fibrillation, rate control, rhythm control.*

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The estimated prevalence of atrial fibrillation (AF) is around 2–4 % [1], which makes it the most common stable arrythmia in adult population. The number of patients with AF is expected to rise partly due to the better diagnosis of asymptomatic forms, longer life expectancy and to the development of diseases that increase the risk of AF [2, 3, 4]. It was previously estimated that AF developed in 1 in 4 people over 55 years, and now the estimated risk in the European population is 1 in 3 people [5]. AF is associated with increased mortality, stroke, heart failure (HF), cognitive decline, vascular dementia, depression, decreased quality of life, increased number of hospitalizations and therefore is a great burden for patients, physicians and healthcare system worldwide. Large resources are required annually for research related to new and ef-

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fective AF prevention and treatment approaches, its mechanisms and predictors. New scientific data is constantly generated and evaluated in order to create new evidence-based clinical guidelines. On the August 29th 2020 the European Society of Cardiology (ESC) presented the updated guidelines for the diagnosis and management of AF developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). The guidelines emphasize the need of multifaceted and multidisciplinary approach to AF management that requires active patient collaboration with the physicians. The "Atrial Fibrillation Better Care — ABC" pathway that was proposed in the guidelines aims to further improve the management of AF patients concentrating on their interests and improving the treatment outcomes [6].

The current article discusses the updated 2020 ESC guidelines on diagnosis and treatment of atrial fibrillation and their application in daily patient-centered clinical practice that emphasizes rate and rhythm control.

Diagnosis and structured characteristics of atrial fibrillation

Atrial fibrillation diagnostic approach was extended with a requirement to document an electrocardiogram (ECG) finding in patients with diagnosed AF. A 12-lead ECG or a single-lead ECG tracing of≥30 s showing heart rhythm with no discernible repeating P waves is required for diagnosis of AF, which is the 2007 consensus of Heart Rhythm Society (HRS), European Heart Rate Association (EHRA) and European Cardiac Arrhythmia Society (ECAS) (Class I) [7]. This is the first step of the proposed "CC to ABC" pathway, according to which the first step is to confirm the presence of AF. Then, AF is characterized, which includes the assessment of stroke risk, symptom severity, severity of AF burden and substrate severity in all patients with AF. Such a structured characterization simplifies clinical evaluation of patients with AF and helps to make right decisions concerning the optimal clinical management (Class IIa). The 4 characteristics that were mentioned previously make up the "4S-AF" (("Stroke risk", "Symptom severity", "Severity of AF burden", "Substrate severity") [8]. The existing tools used for risk assessment are currently integrated into a scheme, but as new technologies are constantly emerging the best instruments will be determined later. Severity of AF burden (Sb) means the AF clinical form (paroxysmal, persistent, longstanding persistent, permanent). Substrate severity (Su) is associated with the AF pathophysiology severity and includes both the simple clinical patient characteristics (age, cardiovascular risk factors) and the comorbidities, the presence and extent of left atrial distention, atrial malfunction and atrial myocardial fibrosis. Transthoracic echocardiography is widely available in everyday clinical practice and provides the main information about atrial size and function. More complicated methods include transesophageal echocardiography, computed tomography or magnetic resonance imaging and allow to evaluate the additional parameters and structural changes of the atria including the level of fibrosis and the presence of epicardial adipose tissue. These parameters can be used as prognostic values and taken into consideration when making the decision about, for instance, the optimal ablation strategy.

Integrated management of patients with atrial fibrillation

Integrated management of AF patients requires a coordinated and agreed patient-individualized care pathway to deliver optimized treatment by an interdisciplinary team. In the 2020 document the class of the recommendations that promote patient-centered approach was increased. Treatment options should be discussed with the patient, and the patient should also be informed about the pros/cons and risks/benefits of certain options and the management plan should be agreed in discussion with the patient and healthcare professionals (Class I). Regular collection of "PRO" ("patient-reported outcomes") is recommended for evaluation of treatment effects and improvement of patient care (Class I). International Atrial Fibrillation Patients and Healthcare Workers Consortium selected the following important PRO: health-related quality of life, physical and emotional functioning, cognitive functions, symptom severity, exercise tolerance and working capacity. Incorporation of PRO in the process of AF treatment is discussed in the special document developed by the EHRA in collaboration with patients' representatives [9].

"ABC" pathway in treatment of atrial fibrillation

"ABC" pathway was developed to make the integrated AF patient care more effective on all levels of healthcare and in all providers. It includes three most crucial aspects of atrial fibrillation treatment: "A" — Anticoagulation/Avoid stroke, "B" — Better symptom

management, "C" — Cardiovascular and Comorbidity optimization.

Anticoagulation and stroke avoidance

This crucial aspect of atrial fibrillation treatment was expanded with several new points. In order to officially assess bleeding risk in patients with AF taking oral anticoagulants it is necessary to calculate HAS-BLED score. That can help eliminate the modifiable bleeding risk factors and reveal the patients at a very high risk of bleeding (HAS-BLED score≥3) who require earlier and more frequent follow-up (Class II). The decision on starting anticoagulation therapy in patients with atrial fibrillation shouldn't be based on the calculated risk of bleeding alone in the absence of absolute contraindications to oral anticoagulation for stroke prevention. Regular stroke and bleeding risk reassessment is recommended for optimal management decisions (e.g. starting oral anticoagulation in patients who don't have low stroke risk anymore) and elimination of modifiable bleeding risk factors (Class I). In patients with AF who had low stroke risk at the first place, the first reassessment should be performed in 4–6 months (Class IIa). For patients taking warfarin in whom the INR (International Normalized Ration) was in the therapeutic range less then 70 % of time (time in therapeutic range (TTR)<70 %) the following options are recommended: switching to oral anticoagulants that are not vitamin K antagonists (for patients without mechanical valves or with moderate or severe mitral stenosis but with good adherence to treatment (Class I)) or efforts to improve TTR (e.g. education/counselling and more frequent INR checks) (Class IIa).

Better symptom control

Rate control

In the 2020 ESC Guidelines the current approach stayed unchanged: rate control is still considered to be sufficient to improve AF-related symptoms. Clinical studies didn't produce any evidence of the best type and intensity of rate control [10–12]. The optimal heart rate target range in patients with AF is still unknown. Of all the studies on this topic, the randomized controlled RACE (Race Control Efficacy in Permanent Atrial Fibrillation) II trial is still the key one. In the RACE II trial there was no difference in clinical events, Ney York Heart Association (NYHA) class or hospitalizations between the strict [target heart rate<80 beats per minute. (bpm) at rest and<110 bpm during moderate exercise] and mild (<110 bpm at rest) heart rate control [13, 14]. Similar results were reported earlier in the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) и RACE trials [15]. Therefore, in accordance with the results of these studies, mild heart rate control (<110 bpm according to a standard 12-lead ECG) is an acceptable initial approach (Class IIa, level B) regardless of HF status (with the exception of tachycardia-induced cardiomyopathy), unless symptoms require stricter rate control.

According to our studies [16, 17], in the patient-centered approach the optimal heart rate target range can be selected with the intention to balance cardioprotection and sufficient peripheral hemodynamics in order to avoid local, primarily cerebral, prothrombotic state. In one randomized prospective study we assessed the levels of high-sensitivity cardiac troponin I (cTnI-hs), mean blood flow velocity and the pulsality index using the high-frequency power doppler ultrasound with fluorescence in 150 patients with stable AF aged 74±8 years, randomized into 2 groups depending on the target heart rate range at rest: 60–79 bpm (first group, n=75) and 80–100 bpm (second group, n=75). Patients who completed the study protocol were included into the analysis. The level of cTnI-hs was significantly reduced in both treatment groups, but the reduction was more profound in the 60–79 bpm group — 2.1 (1.6; 3.9) ng/L — median (25^{th} percentile; 75^{th} percentile) versus 1.1 (0.7; 2.4) ng/L in the second group ($p<0.001$) that represents the reduction in the chronic myocardial damage. Spearman's correlation coefficients between the levels of heart rate reduction and cTnI-hs concentration were 0.45 ($p<0.001$) and 0.44 ($p<0.001$) in the first and second groups respectively. Mean blood flow velocity increase and the pulsality index reduction was noted in both groups but was more profound in the second treatment group (80–100 bpm) that signified the better tissue perfusion. Therefore, the level of chronic myocardial damage that is assessed by the cTnI-hs levels, and the tissue perfusion markers can become the basic values for heart rate target range determination in the patient-centered AF treatment approach.

In the 2020 ESC guidelines beta-adrenoblockers or non-dihydropyridine calcium channel blockers (CCBs) are recommended as the first-line agents for heart rate control in patients with AF and left ventricular ejection fraction (LVEF)≥40 % (Class I). This recommendation is based on the results of the Ulimoen SR, et al. (2013) [18], Scheuermeyer FX, et al. (2013) [19],

Tisdale JE, et al. (1998) [20] and Farshi R, et al. (1999) [21] studies. Digoxin is still considered to be the second-line agent in this patient cohort. In patients with AF and LVEF<40 % beta-blockers and/or digoxin are still recommended for heart rate control (Class I) according to the Nikolaidou T, et al. (2009) [22], Kotecha D, et al. (2014) [23], Ziff OJ, et al. (2015) [24], Darby AE, et al. (2012) [25], Khand AU, et al. (2003) [26], Lewis RV, Irvine N & McDevitt DG (1988) [27] and Mulder BA, et al. (2014) [28] studies. Currently a major randomized trial DIGIT-HF (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure) that studies digoxin in chronic CHF patients is in progress [29].

Rhythm control

According to the 2020 ESC guidelines, the main indication for the sinus rhythm control in patients with AF is the improvement of AF-related symptoms and quality of life in symptomatic patients. These beneficial effects were demonstrated in the leading randomized controlled trials. The results of EAST-AFNET 4 (Early treatment of Atrial fibrillation for Stoke prevention Trial) [30, 31] trial that evaluated the effects of early sinus rhythm control on the clinical outcomes in patients with newly diagnosed AF were presented on the ESC 2020 Congress and are further discussed in the current article.

An attempt to restore the sinus rhythm can also be performed for evaluation of treatment response in patients without clear connection between symptoms and the presence of AF. Rhythm control is preferred in the presence of the following factors: young age; first AF episode of short AF history; tachycardiomyopathy; normal or moderately increased left atrial volume; normal or moderately decreased atrial conduction (the signs of left atrial remodeliing); absence or a low number of comorbidities; difficulties with rate control; AF precipitated by a temporary event (e.g. acute disease); patient's preference.

Pharmacological cardioversion is indicated only in hemodynamically stable patients and the pulmonary emboly risk should be taken into consideration (Class I). Pharmacological cardioversion shouldn't be performed in patients with sick sinus syndrome, reduced atrioventricular conduction or QT prolongation (>500 ms) until the risks of proarrhythmic effects and bradycardia are considered (Class III). It is recommended to emphasize the importance of the treatment adherence and the need of oral anticoagulation both before and after cardioversion (Class I). In patients with AF>24 hours who undergo cardioversion therapeutic anticoagulation should be continued for at least 4 weeks even after successful cardioversion with sinus rhythm restoration (after 4 weeks the decision about the anticoagulation continuation should be made based on the stroke risk factors) (Class IIa). Patients with AF⩽24 hours who are at a very low risk of stroke (CHA2DS2-VASc 0 points in men or 1 points in women) anticoagulation in the 4 weeks after cardioversion can be neglected (Class IIb).

In the long-term AAD rhythm control the following aspects are important: AAD is only moderately effective for maintaining sinus rhythm; effective antiarrhythmic therapy only recuses but doesn't eliminate fibrillation relapses; proarrhythmic and other adverse events are often seen and the choice of AAD therapy should be based primarily on the safety profile. Sotalol can be considered for the long-term rhythm control in patients with normal LV function or with coronary artery disease with the control of QT interval, plasma potassium concentration, creatinine clearance and other proarrhythmic risk factors (Class IIb). The recommendation to use amiodarone for rhythm control in patients with AF (also in patients with HFrEF) was improved to Class I, but other AAD should be considered when feasible because of the extracardiac toxicity of amiodarone.

In the 2020 ESC guidelines catheter ablation (CA) still remains the treatment option for symptomatic AF except for patients with high risk of tachycardia-induced cardiomyopathy when this procedure is recommended for LV function correction (Class was increased to I) independently from the presence of symptoms. AATAC (Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device) and CASTLE-AF (Catheter Ablation vs Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) [32, 33] as well as the CABANA (Catheter ABlation vs ANtiarrhythmic Drug Therapy for Atrial Fibrillation) [34] trials showed that CA had some effects on the morality and hospitalization frequency in patients with AF and HFrEF. Therefore, the 2020 ESC guidelines note that CA should be considered in certain patients with HFrEF and AF for survival benefits and the reduction of hospitalizations (Class IIa). CASTLE-AF and CABANA [35] studies are known to have certain limitations and AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) [36] trial hasn't shown CA to improve LVEF in patients with LVEF⩽35 %. compared to pharmacological therapy.

For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient (Class I). AF catheter ablation means ablation for pulmonary veins isolation (PVI). According to the CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) [37] trial results, the guidelines now state that AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (Class IIa) or persistent AF without major risk factors for AF recurrence as an alternative to AAD class I or III, considering patient choice, benefit, and risk (Class IIb). Catheter ablation after unsuccessful treatment with AAD class I or III to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (Class I). Each if these approaches emphasize the central role of the patient. Catheter ablation in patients taking oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban or edoxaban) is recommended without OAC interruption. Risk factors for atrial fibrillation relapse after ablation include: left atrial size, AF duration, age, kidney dysfunction, substrate severity according to the MRI. All scales that estimated the risk of AF relapse showed the same effectiveness [38]. Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI (Class IIa). Strict control of risk factors and avoidance of triggers are recommended as part of rhythm control strategy Class I). This new recommendation was added in the 2020 guidelines because the effects of strict RF control and trigger avoidance have been shown to affect CA outcomes. Effective treatment of arterial hypertension, diagnosis and treatment of obstructive sleep apnea, reduction of excessive alcohol consumption, hyperlipidemia control, smoking cessation, BMI reduction if the patient is overweight or obese (<27 kg/m^2) and hyperglycemia control.

Cardiovascular risk management and concomitant diseases treatment in patients with AF

Cardiovascular risk management and treatment of concomitant chronic diseases are crucial in patients with AF (Class I). Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity. Opportunistic screening for AF is now recommended in patients with arterial hypertension (Class I) and obstructive sleep apnea (Class IIa). Recommendation class of exercise was decreased to Class IIa. Physical activity should be promoted in patients with AF in order to decrease the risk of relapse. Excessive exercise should be avoided as they can precipitate AF. Recommendation class of obstructive sleep apnea treatment was also decreased to IIb. Optimal treatment of OSA can be considered for the reduction of AF prevalence, progression and relapse frequency as well as symptom severity.

Specific clinical states

New recommendations were presented for patients with AF and acute or chronic coronary syndromes and for those who undergo percutaneous coronary intervention (PCI). In AF patients with ACS undergoing an uncomplicated PCI, early cessation (<_1 week) of aspirin and continuation of dual therapy with an OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespectively of the type of stent used (Class I). After uncomplicated PCI, early cessation (<_1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespectively of the type of stent used (Class I).

EAST-AFNET 4 study

The EAST-AFNET 4 project results were presented on August 29, 2020 simultaneously with the new 2020 ESC guidelines and therefore couldn't be taken into consideration when the guidelines were developed. The results of this study can influence treatment choices. In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, 2789 patients who had early atrial fibrillation (diagnosed≤1 year before enrollment) and cardiovascular conditions were randomized to receive either early rhythm control or usual care [30]. Early rhythm control included treatment with AAD (flecainide, amiodarone, dronedarone, propafenone) or catheter ablation after randomization. Usual care included the management of AF–related symptoms. Two primary endpoints were determined: the first primary endpoint was a composite of death from cardiovascular

causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary endpoint was the number of nights spent in the hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated. The trial was stopped for efficacy after a median of 5.1 years of follow-up per patient. The patients in the early rhythm control were at a lower risk of primary-outcome event (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; P=0.005) and certain events such as death from cardiovascular causes (HR 0.72; 95% CI 0.52–0.98) and stroke (HR 0.65; 95% CI 0.44–0.97). Length of hospital stay did not differ significantly between the groups. Adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control, the majority of adverse events included pharmacologically induced bradycardia.

Of note, patients with persistent AF made up only 26.0 and 27.3% of participants in the early rhythm group and usual care group respectively. Median days since AF diagnosis to the study inclusion was 36 days. Therefore, the results of this study can't be used in patients with long-standing AF. Information about AF relapses was not collected in both groups. The analysis of AAD used showed that the majority of patients didn't have structural heart disease in the rhythm control group. EAST-AFNET 4 differed from earlier studies, e.g. AFFIRM, as the patients showed significantly higher treatment adherence — 91.2% and 89.7% in the early rhythm control and usual care groups respectively. Also, important factors included rhythm control together with structured patients follow-up, optimal rate control, thorough risk factor modification and treatment of concomitant diseases. As such, both EAST-AFNET 4 and 2020 ESC guidelines describe that integrated approach towards AF management is highly effective.

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REVIEW ARTICE

The congress of European Society of Cardiology 2020: contribution to the new era of virtual communications

The report presents the results of the annual congress of the European Society of Cardiology that was held trough virtual mode for the first time. In particular, the highlights of 4 updated clinical guidelines of the European Society of Cardiology are summarized. The results of 13 international clinical trials on the efficacy and safety of pharmacological treatment and identification of factors associated with cardiovascular complications are analyzed.

Key words: *congress, clinical guidelines, international research.*

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The next congress of the European Society of Cardiology was held from August 29 to September 1, 2020. Due to epidemiological situation, the congress was held trough virtual mode. Over 500 scientific and educational sessions have been organized using about 1000 mobile studios around the world. Approximately 58.000 users joined the conference that was 80 % more compared with the number of participants of European Society of Cardiology Congress in Paris in 2019. The website of the European Society of Cardiology contains over 4000 presentations and electronic posters with congress materials.

Traditionally, the Congress presented updated guidelines and the results of new clinical trials.

This year 4 new clinical guidelines were presented:

1. The management of acute coronary syndromes in patients without persistent ST-segment elevation (chairs: Jean-Philippe Collet and Holger Thiele).

2. The diagnosis and management of atrial fibrillation (chairs: Gerhard Hindricks and Tatiana Potpara).

3. The management of adult congenital heart disease (chairs: Helmut Baumgartner and Julie De Backer)

4. Sports and exercise in patients with cardiovascular diseases (chairs: Antonio Pelliccia nd Sanjay Sharma).

A wide range of cardiologists are interested in changes in the guidelines on the management of acute coronary syndromes in patients without persistent ST-segment elevation and atrial fibrillation.

For the rapid diagnosis of acute coronary syndrome, it is recommended to use high-sensitivity cardiac troponin assay immediately and after 1 (optimal) or 2 hours. Once myocardial infarction (MI) has been excluded, invasive coronary angiography should be considered in patients with very high clinical likelihood of unstable angina. Imaging stress testing or computed tomography of the coronary arteries is the best diagnostic option for patients with low to moderate clinical risk. Stress testing with imaging or coro-

nary computed tomography angiography will be the best option in patients with low-to-modest clinical likelihood of unstable angina.

An early routine invasive approach within 24 hours of admission is recommended for patients without ST-segment elevation according to high-sensitivity cardiac troponin assay, GRACE risk score>140, and dynamic new, or presumably new, ST-segment changes as it improves major adverse cardiac events and possibly early survival. A selective invasive approach after positive ischemic testing or cardiac obstruction according to computer tomography is recommended for patients at low risk. Routine pre-treatment with a P2Y12 receptor inhibitor in patients with acute coronary syndrome without ST-segment elevation in whom coronary anatomy is not known and an early invasive management is planned is not recommended given the lack of established benefit. Dual antiplatelet therapy (P2Y12 receptor inhibitor and aspirin) is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. However, its duration can be shortened (<12 months) or extended (>12 months). The therapy can also be modified by switching P2Y12 receptor inhibitor or de-escalation of dual antiplatelet therapy depending on patient's individual characteristics and the availability of the respective drugs.

The new guidelines on the management of patients with atrial fibrillation suggests that at least a short course of triple therapy (≤7 days) would be desirable in such patients before dual antiplatelet therapy. Only in patients with high risk of ischemic events triple antiplatelet therapy can be prescribed for 4 weeks.

The guidelines emphasize that the diagnosis of AF needs to be confirmed by a conventional 12-lead electrocardiogram tracing or rhythm strip showing atrial fibrillation for≥30 s. Structured characterization of AF, including stroke risk, symptom severity, severity of AF burden, and AF substrate, helps improve personalized treatment of AF patients. The ABC pathway streamlines integrated care of AF patients across healthcare levels and among different specialties (includes A (avoid stroke and anticoagulation), B (better symptom control), and C (cardiovascular risk factors and comorbid conditions management)). The realization of such approach will significantly improve outcomes of patients with AF.

Patient values need to be considered in treatment decision making and incorporated into the AF management pathways; the structured assessment of patient-reported outcome measures is an important element to document and measure treatment success.

Catheter ablation with pulmonary vein isolation is recommended to maintain sinus rhythm after ineffective use or intolerance of a class I or III antiarrhythmic drugs in patients with paroxysmal or persistent AF, regardless of the underlying risk factors. Overall, guidelines emphasize that weight loss, strict control of risk factors, and avoidance of triggers for AF are important strategies to improve outcomes.

Full versions of clinical guidelines are posted on the official website of the European Society of Cardiology: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines.

The summary of the results of the new large international clinical trials are presented below.

The RATE-AF study: the role of digoxin for heart rate (HR) control in patients with permanent AF

The RATE-AF study showed that digoxin can be used as first-line treatment in elderly patients with permanent AF and heart failure symptoms. Authors followed up 160 patients with 76 mean patient age with permanent AF and heart failure symptoms for 12 months. Patients were randomized into 2 groups: the first group received low dose of digoxin, the second — beta-blocker bisoprolol. Heart rate reduction was similar between treatment groups at 12 months: from 100 beats per minute initially to 70 beats per minute after 6 and 12 months. According to Short Form–36 form, both medications similarly affected life quality. Both medications were well-tolerated. For example, at 12 months, the digoxin group scored significantly higher than the beta-blocker group on several domains of the Short Form–36 physical component score, including vitality, physical function, and global health. Heart failure symptoms in the digoxin group improved from a mean baseline New York Heart Association class of 2.4 to 1.5 at both 6 and 12 months; the improvement was more modest in the beta-blocker group, going from NYHA 2.4 at baseline to 2.0 at both 6 and 12 months. N-terminal of the prohormone brain natriuretic peptide levels improved in the digoxin group from a baseline of 1.095 pg/mL to 1.058 at 6 months and 960 at 12 months from 1.041 to 1.209–1.250 pg/mL at 12 months in the beta-blocker group. It is notable that study limitations included small sample size as well as the fact that digoxin is more effective for the heart rate control at rest but not during physical activity.

ATPCI: trimetazidine is not effective in patients with angina pectoris having been treated by percutaneous coronary intervention (PCI)

Routine use of oral trimetazidine added to guideline-recommended medical therapy did not improve patient outcomes following a successful percutaneous coronary intervention (PCI), based on findings from the ATPCI trial. The study included 6.007 patients with myocardial infarction (MI) who had undergone successful planned or urgent PCI at 365 centers in 27 countries. After randomization patients additionally to standard recommended therapy (aspirin and P2Y12-receptor inhibitor in 97% of cases, hypolipidemic medications in 96.6% of cases, renin-angiotensin-aldosterone inhibitors in 82.2% and beta-blockers in 83.9% of cases), as well as calcium channel blockers (in 27.6% of cases) received modified-release trimetazidine 35 mg twice daily or placebo. The majority of patients (77% of all patients were men) suffered from angina pectoris III / IV functional classes according to the Canadian Cardiovascular Society classification (58%). 2517 patients underwent emergency, and 3490 — planned PCI. The duration of follow-up was 47.5 months. The primary outcome occurred in 23.3% of the trimetazidine group compared with 23.7% of the placebo group. Trimetazidine was not superior to placebo in the prevention of several cardiovascular events including cardiovascular death (2.1% versus 2.6%), hospitalization for cardiac events (13.4% versus 13.4%), recurrent/persistent angina leading to adding, switching, or increasing antianginal therapy, or coronary angiography (16.9% versus 16.6%).

According to experts, this result may be due to the fact that all patients received beta-blockers or calcium channel blockers, and had successful PCI. At the same time, 2019 European Society of Cardiology guidelines on the chronic coronary syndrome recommended trimetazidine as a second-line therapy after beta-blockers and calcium channel blockers in patients with chronic coronary syndrome.

DAPA-CKD: the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors in chronic kidney disease patients without type 2 diabetes

The trial enrolled 4.304 patients with chronic kidney disease (estimated glomerular filtration rate from 25 to 75 mL/min/1.73m2; urinary albumin to creatinine ratio over 200 mg/g). Patients were randomly allocated to dapagliflozin 10 mg or placebo once daily in addition to standard of care (renin-angiotensin-aldosterone system receptor blocker in 97% of cases). The average age of participants was 61.8 years and 66.9% were male. A total of 2.906 (67.5%) patients had type 2 diabetes. The primary composite endpoint was worsening kidney function, defined as>50% sustained decline in estimated glomerular filtration rate or onset of end-stage kidney disease, or death due to kidney disease or cardiovascular disease.

During a median follow-up of 2.4 years, there were 197 primary endpoint events with dapagliflozin and 312 with placebo (p=0.000000028 for the dapagliflozin benefit in patients with and without type 2 diabetes). Dapagliflozin reduced all three secondary endpoints compared with placebo: 1) worsening renal function or death from kidney failure (0.56 hazard ratio; p<0.0001) ; 2) hospitalization for heart failure or cardiovascular death (0.71 hazard ratio; p=0.0089) ; and 3) all-cause mortality (0.69 hazard ratio; p=0.0035).

The safety and tolerability of dapagliflozin was in keeping with its established profile. In the placebo group, the proportion of patients who discontinued the study drug due to an adverse event or experienced a serious adverse event were 5.7% and 33.9%, respectively. The proportion of patients with these events was similar in the dapagliflozin group — 5.5% and 29.5% respectively. Diabetic ketoacidosis was not reported in any patient randomized to dapagliflozin and occurred in two patients in the placebo group. Neither diabetic ketoacidosis nor severe hypoglycemia were observed in patients without type 2 diabetes.

DAPA-CKD showed that dapagliflozin reduced the risk of worsening kidney function or death from cardiovascular or kidney disease in patients with chronic kidney disease with and without type 2 diabetes. The results highlight the medicine's potential to benefit patients with chronic kidney disease who are in need of improved treatment options.

Aspirin alone was preferential as antithrombotic therapy in patients after TAVI

Ischemic and hemorrhagic complications after transcatheter aortic valve implantation are relatively common and are associated with increased mortality. The goal of the POPular TAVI trial was to evaluate aspirin alone compared with aspirin plus clopidogrel for 3 months among patients who underwent TAVI. Patients with implantation of a drug-eluting stent within the last 3 months or bare-metal stent within

the last month before TAVI were excluded from the study.

The primary co-outcome included all bleeding (including associated with medical procedures). Bleeding at 12 months, occurred in 15.1 % of the aspirin alone group compared with 26.6 % of the aspirin plus clopidogrel group (p= 0.001). Nonprocedure-related bleeding at 12 months, occurred in 15.1 % of the aspirin alone group compared with 24.9 % of the aspirin plus clopidogrel group (p= 0.005).

Secondary outcomes included bleeding and thromboembolic complications (including cardiovascular death, nonprocedure-related bleeding, thromboembolic events stroke, or myocardial infarction) at 12 months occurred in 23.0 % of the aspirin alone group compared with 31.1 % of the aspirin plus clopidogrel group (p<0.001). Cardiovascular death, stroke, or myocardial infarction at 12 months occurred in 9.7 % of the aspirin alone group compared with 9.9 % of the aspirin plus clopidogrel group (p= 0.004).

Therefore, aspirin alone significantly reduced the rate of bleedings compared with aspirin and clopidogrel with absolute decrease of 10 %. At the same time aspirin alone compared with aspirin and clopidogrel did not increase the risk of thromboembolic events. Thus, aspirin alone is recommended in patients after TAVI who does not receive peroral anticoagulants and did not undergo coronary revascularization.

Safety and effectiveness of evolocumab in the treatment of familial hypercholesterolemia in children

HAUSER-RCT is first randomized double blinded placebo-controlled study of PCSK9 inhibitor in pediatric patients with heterozygous familial hypercholesterolemia. The study included 157 patients aged from 10 to 17 years with heterozygous familial hypercholesterolemia from 23 countries from 5 continents. Before the study patients took statins with or without ezetimibe, but the level of low-density lipoprotein cholesterol (LDL-cholesterol) was over 130 mg/dl.

Patients will be randomized in a 2:1 ratio to receive 24 weeks of monthly 420 mg evolocumab or placebo. At week 24, the mean percent change from baseline in LDL cholesterol level was 44.5 % in the evolocumab group and 6.2 % in the placebo group, for a difference of 38.3 % (P<0.001). The absolute change in the LDL cholesterol level was –77.5 mg per deciliter in the evolocumab group and –9.0 mg per deciliter in the placebo group, for a difference of 68.6 mg per deciliter (P<0.001).

Monoclonal antibody directed against PCSK9 (evolocumab) were well tolerated and effectively decreased the level of LDL-cholesterol compared with placebo in pediatric patients with heterozygous familial hypercholesterolemia who already took statins with or without ezetimibe.

EMPEROR-Reduced: the efficacy of empagliflozin in patients with heart failure with reduced ejection fraction with or without type 2 diabetes

The trial enrolled 3.730 patients with heart failure and a left ventricular ejection fraction of 40 % or less, with or without diabetes. Patients were randomly assigned to empagliflozin 10 mg once daily or placebo. The primary endpoint was the composite of cardiovascular death or hospitalization for heart failure.

During a median follow-up of 16 months, the primary endpoint occurred in 361 patients in the empagliflozin group and in 462 patients in the placebo group (p<0.0001). Empagliflozin reduced total hospitalizations for heart failure (p<0.001). The effect of empagliflozin did not depend on the presence of type 2 diabetes mellitus. Empagliflozin reduced total hospitalizations for heart failure (p<0.001). Patients with SGLT inhibitors had lower risk of renal outcomes. Uncomplicated genitourinary tract infections were more common in the empagliflozin group.

The SGLT2 inhibitors have strengthened their role as the new primary treatment for patients with heart failure with low ejection fraction with or without type 2 diabetes mellitus. The results of the second large randomized controlled trial showed significant efficacy and safety of SGLT2 inhibitors in this patient population.

The effect of low-dose colchicine in patients with stable coronary artery disease

Anti-inflammatory pharmacotherapy can significantly decrease the risk of atherothrombosis on a background of standard therapy and secondary prophylaxis.

LoDoCo2 is a double-blind controlled trial in which 5522 patients with stable coronary artery disease have been randomized to colchicine 0.5 mg daily or matching placebo. The median follow-up was 28.6 months. The primary endpoint (cardiovascular death, spontaneous myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization) occurred in 187 patients (6.8 %) in the colchicine group

compared with 264 patients (9.6 %) in the placebo group (p<0.001).

Ischemic events (cardiovascular death, spontaneous myocardial infarction, or ischemic stroke) occurred in 4.2 % of patients from the colchicine group and in 5.7 % of patients (p=0.007) from the placebo group. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (0.7 vs. 0.5 events per 100 person-years).

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.

The REALITY trial: the impact of restrictive blood transfusion strategy for MI patients with anemia

Restricting blood transfusion in myocardial infarction patients with anemia to those with very low hemoglobin levels saved blood and did not have a negative impact on clinical outcomes, according to findings from the REALITY trial.

According to statistics, 5–10 % of patients with acute myocardial infarction have anemia. Cardiologists does not accept restricting blood transfusion strategy without the evidence of its safety and due to concerns about the effect of low hemoglobin on ischemic myocardium.

The REALITY trial was first large randomized study on the restricting blood transfusion compared with standard therapy in myocardial infarction patients. The study included 668 patients hospitalized at 35 centers in France and Spain with acute myocardial infarction and anemia (hemoglobin 7–10 g/dL). Patients were randomly allocated to either a restrictive transfusion strategy (transfusion withheld unless hemoglobin dropped to 8 g/dL) or a liberal transfusion strategy (transfusion given as soon as hemoglobin was 10 g/dL or below). The target level of hemoglobin was 8–10 g/dL for the restrictive transfusion strategy, and over 11 g/dL for the liberal transfusion strategy. Restrictive transfusion strategy group used 414 blood units less.

The primary clinical endpoint was a composite of major adverse cardiac events (all-cause mortality, MI, stroke or emergency PCI due to myocardial ischemia) at 30 days. The primary clinical outcome occurred in 11 % of cases in the restrictive strategy group compared with 14 % of patients in the liberal strategy group.

The risk of infection between restrictive strategy group and liberal strategy group (0 % vs. 1.5 %), acute lung injury (0.3 % vs. 2.2 %), length of stay (7.0 vs. 7.0 days) did not differ significantly. In terms of cost effectiveness, researchers noted the restrictive strategy had an 84 % probability of being cost-saving while improving clinical outcomes.

The HOME-PE trial: the identification of patients with pulmonary embolism for home management

The HOME-PE trial is randomized, open-label trial that was conducted in 26 hospitals in France, Belgium, the Netherlands and Switzerland. 1.974 patients with normal blood pressure presenting to the emergency department with acute pulmonary embolism were included in the study. The possibility of outpatient treatment was assessed with HESITIA criteria (all 11 criteria were negative; in 39 % of patients) or with the PESI scale (the score was 0; in 48 % of patients).

The frequency of serious adverse events was low in both groups of patients managed at home. Through 30 days of follow-up, there were few adverse events, which included recurrent venous thromboembolism, major bleeding, and death among the patients receiving treatment at home, with a rate of 1.3 % in the HESTIA group and 1.1 % in the PESI group.

The researches also highlighted that both studied methods of prognosis assessment in patients with pulmonary embolism were imperfect and that the physician in charge to make final management decision. Among the patients initially deemed eligible for home treatment, physicians overruled that assessment less frequently in the HESTIA arm (3 % vs 29 %). Thus, the proportion of patients ultimately managed in the outpatient setting was similar in the HESTIA and PESI arms of the trial (38 % versus 37 %). The HESTIA criteria were as safe as Pulmonary Embolism Severity Index (PESI) for the selection of patients for home management.

THEMIS-PAD trial: the combination of ticagrelor and aspirin among patients with stable coronary artery disease, type 2 diabetes and peripheral artery disease

The goal of previously performed randomized THEMIS trial was to evaluate ticagrelor/aspirin compared with placebo/aspirin among patients with stable coronary artery disease and type 2 diabetes. The THEMIS-PAD study included 1687 patients with peripheral arterial disease. Ischemic limb events (acute limb

ischemia; major amputation of vascular etiology; peripheral revascularization) occurred in 1.3 % of cases in the ticagrelor/aspirin group compared with 1.6 % of cases in placebo/aspirin (p=0.022).

Elevated troponin T levels were associated with significantly higher rates of COVID-19 complications

A study from the United States showed that patients admitted with COVID-19 have high incidence of cardiovascular disease and its complications. An earlier French study also demonstrated that high levels of troponin and brain natriuretic peptide were independent predictors of COVID-19 complications.

About 1200 patients were included in the study, and the results of treatment of the first 485 patients were presented at the congress (average age 68 years, 46 % women, 49 % — white, 27 % — African American and 16 % — Latin Americans). The results demonstrated high prevalence of cardiovascular diseases (46 %) and cardiovascular risk factors (over 40 % suffered from arterial hypertension, hyperlipidemia and diabetes mellitus) in patients admitted with COVID-19.

Elevated troponin T levels at admission were associated with death and serious adverse cardiovascular events, which were higher than expected based the experience of other respiratory infections management.

The effectiveness of antihypertensive treatment in patients with normal blood pressure (BP)

The meta-analysis of 48 studies on the effectiveness of antihypertensive treatment included 348 854 patients. Patients were divided into seven subgroups based on systolic blood pressure at study entry (less than 120, 120–129, 130–139, 140–149, 150–159, 160–169, 170 and above mmHg). Over an average four years of follow-up, each 5-mmHg reduction in systolic blood pressure lowered the relative risk of major cardiovascular events by about 10 %. The risks for stroke, ischemic heart disease, heart failure and death from cardiovascular disease were reduced by 13 %, 7 % and 14 % and 5 %, respectively. Neither the presence of cardiovascular disease nor the level of blood pressure at study entry modified the effect of treatment.

According to the researchers, blood pressure lowering with antihypertensive drugs reduces the risks of cardiovascular events, even in patients with normal or slightly elevated blood pressure. However, the fact that the relative effects are similar for everyone does not mean that everyone should be treated. This decision will depend on an individual's likelihood of suffering cardiovascular disease in the future.

Gut microbes are associated with cardiovascular and other diseases

Previous researches have shown that the human gut microbiome is associated with many diseases, but the level of this association is still unclear.

In order to identify diseases associated with microbiome, the study included 422 417 unrelated individuals in the UK Biobank who had undergone genotyping to identify their genetic make-up. The average age of participants was 57 years and 54 % were women.

The researchers assessed possible associations, including 35 single nucleotide polymorphisms that affect human gut microbiome. 7 single nucleotide polymorphisms were significantly associated with 29 diseases, including arterial hypertension, heart failure, hypercholesterolemia, type 2 diabetes, renal failure, and osteoarthritis.

According to experts, the composition of human gut microbiome, including genetic and environmental factors, can be associated with certain diseases, including cardiovascular diseases, as well as its progression and outcomes. Clarification of this risk factor may lead to the development of new personalized risk stratification strategies and preventive measures.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

III. Registration on the Website and information about the authors.

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

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

If the author has several places of work, it is written: 1. "The name of the institution..." 2. "Name of institution."... The name of the institution is written in abbreviated form, for example, Moscow state University, Moscow. Brackets are not put.

How to fill in the article metadata: all data that is entered in the "article metadata" must exactly match the data specified in the text of the article!

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

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

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

IV. Manusctipt submision check-list

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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).

All Russian-language sources of literature should be presented in the transliterated version of the model given below.

The author (s) are responsible for the correctness of the data given in the references.

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:

Article citation:

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 pa-

tient 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.

VI. Preparation of manuscript.

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.

For more information on placing articles on the website you can read http://cardiovascular.elpub.ru/jour/announcement

VII. Copyright and publishing policy.

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").

The author, by sending the article to the Editor, agrees that the editorial Board of the journal shall be transferred to the exclusive property rights to use the manuscript (transferred to the Editorial Board of the journal material, including such protected objects of copyright as photos of the author, drawings, diagrams, tables, etc.), including the reproduction in print and on the Internet; distribution; translation into any languages of the peoples of the world; export and import of copies of the journal with the article of the Author for distribution, to bring to the public.

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.

When using the article, the editors have the right to supply it with any illustrated material, advertising and allow third parties to do so.

The editorial Board has the right to assign the rights received from the Author to third parties and has the right to prohibit third parties from any use of materials published in the journal for commercial purposes.

The author guarantees that he has exclusive rights to use the submitted material. In case of violation of this guarantee and the presentation of claims to the editorial Board, the Author independently and at his own expense undertakes to settle all claims. The editorial Board is not responsible to third parties for violation of the Author's guarantees.

The Author retains the right to use the published material, its fragments and parts for personal, including scientific and teaching purposes.

The Author transfers the above rights to the Editors without limitation of their validity period, in the territory of all countries of the world without limitation, including the territory of the Russian Federation.

The rights to the manuscript are considered to be transferred By the author of the editorial Office from

the moment of sending an information letter about the acceptance of the manuscript to the press.

Reprinting of materials published in the journal by other individuals and legal entities is possible only with the written permission of the editorial Board, with the obligatory indication of the journal name, number and year of publication.

The editors are not responsible for the accuracy of the information provided by the Author.

The author, sending the manuscript to the Editor, gives permission to use and process personal data.

The editorial Board reserves the right to reduce and correct the articles, to change the design of graphs, figures and tables to comply with the standard of the journal, without changing the meaning of the information provided. In case of untimely response of the author (s) to the request of the editorial Board, the editorial Board may at its discretion make changes to the article or refuse to publish.

Sending to the editor of works that have already been sent to other publications or printed in them is absolutely not allowed. The editors are not responsible for the accuracy of the information provided by the authors. Articles sent in violation of the rules of registration are not accepted by the editorial Board for consideration.

VIII. The procedure for rewiewing manuscripts

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.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

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 article 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.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

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.

11. The decision to publish a manuscript is made solely on the basis of its significance, originality, clarity of presentation and compliance of the research topic with the direction of the journal. Reports on studies in which negative results are obtained or the provisions of previously published articles are challenged are considered on General grounds.

12. Original reviews are kept in the Editorial office for 5 years from the date of publication.

13. In case of a decision to refuse to publish an article, its archive copy remains in the electronic system of the editorial Board, but access to it by editors or reviewers is closed.

IX. The manner of publication of manuscripts

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.

2. Each issue of the journal is formed by a separate Executive editor appointed by the editor-in-Chief and/or editorial Board. It is the responsibility of the editor-in-charge to select high-quality articles for publication, and he can be guided by both thematic principles and a separate scientific direction.

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.

Editors of journals should consider the concerns, if:

they received information about the authors ' inappropriate actions, but there is no clear evidence of such behavior; there are arguments that the results of the work are unreliable, and the institution in which the authors work is not going to find out the truth; they believe that the investigation into the alleged violations committed by the authors in connection with the publication has either not been or will not be fair, impartial and convincing; the authors ' violations are being investigated, but the results are not expected soon enough.

Journal editors should consider making amendments if:

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:

authorship needs to be changed, but there is no reason to doubt the validity of the findings.

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.

All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

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

Editorial office:

Room 213, Building 2, Prospect Gostinichny 6, Moscow 127106, Russia

e-mail: editor.ihvdj@gmail.com

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The manuscripts are accepted if has not been published or submitted for publication elsewhere.

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