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Estimation of atrial fibrillation risk development in patients with metabolic syndrome during atrial extrasystole registration

Glycemic control in diabetes mellitus: review of international studies of glucose-lowering drugs cardiological safety

Relationship between periodontal and cardiovascular diseases

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Contents

Editor's Welcome

Dear colleagues!

In the 11th issue of the International Heart and Vascular Disease Journal, there are leading article, review, original articles and the results of two important scientific events.

The leading article of the issue is dedicated to the review of clinical studies of efficacy and safety of a new group of lipid-lowering drugs – proprotein convertase subtilisin/kexin type 9 inhibitors. European guidelines for dyslipidemia treatment of 2016 give indications for use of this new group of lipid-lowering medicines.

Two articles are included into the «Review articles" section. The first of them discusses the results of international studies of glucose-lowering drugs' cardiological safety. Authors from three Russian scientific schools participated in preparation of this article. The second review article observes the data about relation between periodontal disease and cardiovascular pathology.

In "Original articles" of the 11th issue section we published three papers. In the first article a group of authors estimates the risk of atrial fibrillation development in patients with metabolic syndrome. The second article represents the results of major clinical and experimental study aiming to identify the connection between statins therapy and endothelial dysfunction markers in patients with evident coronary atherosclerosis. One more original work called BASTion is dedicated to the study of complex therapy's safety in patients with chronic heart failure.

The results of two major scientific events are published in the 11th issue of the Journal. Annual congress of the European Society of Cardiology that involved more than 30000 specialists from 106 countries has been successfully held in Rome, Italy, on August 27-31, 2016. It included more than 500 scientific sessions in 150 different fields, including new clinical guidelines and 28 clinical studies "Hot Line".

It is known that annual Russian National Congress of Cardiology was held in Ekaterinburg, Russia, on September 20-23, 2016. Scientific program included 169 meetings. The questions of development strategies and the role of the Society in a new system of medical postgraduate education were discussed during the plenary meeting.

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

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

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LEADING ARTICLE

Opportunities of new lipid-lowering therapy: proprotein convertase subtilisin/kexin type 9 inhibitors' clinical efficacy and safety profile

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Summary

Safe and evident reduction of LDL cholesterol in order to reduce the risk of cardiovascular complications is an important problem of modern cardiology. Results of new clinical placebo-controlled comparative studies investigating proprotein convertase subtilisin/kexin type 9 inhibition with monoclonal antibodies (mAb) indicate high potential of new group of drugs. This review article analyzes clinical efficacy and safety profile of alirocumab and evolocumab as a part of combined statin therapy.

Keywords

Lipid-lowering therapy, proprotein convertase subtilisin/kexin type 9 inhibitors.

Evolution of ideas about lipid-lowering therapy

Impaired lipid metabolism maintains the leading position between cardiovascular disease (CVD) risk factors [1]. The importance of this problem is determined by its high occurrence in population (according with epidemiological studies, up to 55% of adult Russian population) and inadequate control in patients with coronary heart disease (CHD).

In the population of high and very high risk of cardiovascular complications dyslipidemia is caused by several reasons: familial hypercholesterolemia, essential hypercholesterolemia, CHD, stroke, peripheral atherosclerosis, diabetes mellitus type 2, meta-

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bolic syndrome, chronic kidney disease, rheumatic and autoimmune diseases [2].

Nowadays the strategy of lipid-lowering therapy selection is actively discussed. Americal College of Cardiology/American Heart Association recommends combined therapy with two lipid-lowering drugs depending on the level of cardiovascular risk. European guidelines proceed with target therapy in order to achieve target lipid levels [3].

It is known that statins are widely used for hyperlipidemia treatment in different doses. In parallel the search of other effective lipid-lowering drugs is going on and it is determined by the necessity of more intense reduction of total cholesterol (TC) levels, restricted use of statins due to their adverse effects, bad tolerance or contraindications. Often combinations of two and more drugs are used to reach target lipid levels. ezetimibe and in some causes fenofibrate are used in clinical practice for this motivation [1].

Proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitors: mechanism of action

For the first time the relation between PCSK9 and lipid metabolism abnormalities has been shown for patients with familial hypercholesterolemia [4]. In 2003 a new gene PCSK9 mutation of which led to familial hypercholesterolemia development has been identified. Later it has been shown that PCSK9 directly participates in low density lipid (LDL) receptors and apolipoprotein-E 2 type receptors degradation. PCSK9 is mainly expressed in liver, guts and kidney. PCSK9 mutations are linked with the development of both familial hypercholesterolemia (activating mutations) and familial hypobetalipoproteinemia (inactivating mutations). The correlation between PCSK9 plasma levels and TC, triglycerides, LDL cholesterol has been demonstrated in population studies for different ethnic groups. At the same time the correlation between PCSK9 and high density lipids has not been shown in any studies. Patients with familial hypercholesterolemia and PCSK9 gain-of-function(GOF) mutations have no strict correlation between PCSK9 plasma levels and mutation type. At the same time, there is significant correlation between PCSK9 plasma levels with mutation type not depending on LDL cholesterol levels in case of loss-of-function mutations (R46L, Y142X, C679X) that cause hypocholesterolemia [5].

During statins treatment PCSK9 levels increase that in its turn augments TC and LDL cholesterol levels [6]. Several studies demonstrated 14-47% increase of PCSK9 plasma concentrations depending on statins' type and dose. The mechanism of PCSK9 upregulation during statins treatment can be briefly explained like this. Statins administration leads to reduction of intracellular cholesterol levels. As a response to this, sterol regulatory element-binding proteins (SREBP) – transmembrane proteins of endoplasmic reticulum – are cleaved by serine protease 1 and transported by SCAP protein to the Golgi apparatus. Then SREBP undergo further processing by zink-metalloprotease (protease-2) that liberates regulatory domains of SREBP that are translocated into nucleus and consequently activate PCSK9 transcription.

Possible directions of PCSK9 inhibition include suppression of PCSK9 synthesis, blocking of PCSK9 and LDL cholesterol receptors interaction and increase of PCSK9 clearance. Monoclonal antibodies (mAb) are the drugs that currently undergo the investigation for inhibition of PCSK9 synthesis and PCSK9/LDL cholesterol receptor interaction and have successfully passed several stages of clinical trials [4]. Three PCSK9 inhibitors: alirocumab (REGN 727/SAR236553; Regeneron/ Sanofi), evolocumab (AMG-145, Amgen) and bococizumab (REGN 316 / PF-04950615; Pfizer) have reached the phase III of clinical studies and first two of them have been approved by Food and Drug Administration (FDA), two compounds: LGT209 (Novartis) an LY3015014 (Eli Lilly) are on the phase II of clinical trial. RG7652 (Roche/ Genetech) trial had been terminated in 2014.

Review of clinical studies investigating efficacy and safety profile of PCSK9 inhibitors

Creation of pharmacological agents lowering PCSK9 blood levels is one of important directions of lipidology. Use of these drugs in combination with statins seems to be promising because they can potentially increase hypolipidemic effects of statins.

Use of PCSK9 inhibitors, at first, had been considered for patients with familial hypercholesterolemia. The results of several multicenter randomized clinical trials of III phase had been published in 2015. Placebo-controlled trial RUTHERFORD-2 investigated 329 patients who received evolocumab in dose of 140 mg for 2 week or 420 mg per month during not less than 4 weeks during statins therapy [7]. LDL cholesterol levels reduced by 59% and 61% respectively after 12 weeks of therapy comparing with placebo. Target levels of LDL cholesterol have been reached in

more than 60% of cases. In the ODYSSEY FH II study high statin doses and their combination with other lipid-lowering drugs together with alirocumab administration in dose of 74/150 mg each 2 weeks comparing with placebo had led to LDL cholesterol levels reduction by 51-58% averagely after 24 weeks of treatment. Target levels of LDL cholesterol have been achieved in 60-68% of cases. Another study of ODYSSEY HIGH FH series investigated alirocumab efficacy in dose of 150 mg/2 weeks in 106 patients with LDL cholesterol concentration >4mmol/L that remained unchanged after high-dose therapy with statins and other lipid-lowering drugs. Target levels of LDL cholesterol have been reached in 57% of patients [8, 9].

The efficacy of PCSK9 inhibitors has been studied in parallel in patients with high cardiovascular risk during treatment with other lipid-lowering drugs and without them. The results of phase III clinical trials have been present in available literature.

The LAPLACE-2 study included 2067 patients with primary hypercholesterolemia or mixed dyslipidemia during moderate or intense therapy with statins. Patients of main group received evolocumab 140 mg/w weeks or 420 mg per month. In comparison group patients received ezetimibe 10 mg per day or placebo. After 10-12 weeks of observation LDL cholesterol levels reduction in the group of evolocumab therapy has reached 66-75% (140mg/2weeks) and 17-21% during ezetimibe treatment [10]. Another study DESCARTES investigated evolocumab 420mg/4 weeks efficacy in 901 patients with hyperlipidemia during diet with or without lipid-lowering therapy. After 52 weeks of observation the main group comparing with placebo demonstrated LDL cholesterol reduction by 56% during diet and by 62% during atorvastatin administration in 10 mg dose, by 57% - during atorvastatin 80mg, and by49% in the subgroup of atorvastatin 80mg/ezetimibe 10 mg combination.

Clinical efficacy of another PCSK9 inhibitor alirocumab in the dose of 75/150 mg each 2 weeks has been studied in the series of 7 trials with common name ODYSSEY (total number of patients was around 5000). Control groups were made of patients who received placebo or ezetimibe 10 mg per day. Basis therapy in main groups included statins (atorvastatin 20-40 mg per day or rosuvastatin 10–20 mg per day and also higher doses of statins) and in one study – ezetimibe, fenofibrate or diet. Average duration of study was 24 weeks. In the end of observation period LDL cholesterol concentration reduced by 32-68% comparing with placebo group [8, 9].

It is obvious that PCSK9 inhibitors administration additionally potentiates lipid-lowering effect of statins and in prospective it can be considered as a component of combined hypolipidemic therapy.

High attention is paid also to the monitoring of PCSK9 inhibitors safety profile since these drugs target intense reduction of LDL cholesterol levels.

International review articles often present detailed results of clinical studies dedicated to adverse effects of PCSK9 inhibitors. Systematized results about adverse effects are subdivided into several groups: total amount of adverse effects, reasons of therapy termination, severe adverse effects, reaction to injection and neurocognitive consequences [11]. These parameters have been included into clinical study protocols for evolocumab and alirocumab. It is necessary to point out that PCSK9 inhibitors safety has been studied in comparison with placebo or ezetimibe. In both groups statins were used in comparable doses and therapeutic regimens.

During alirocumab therapy with daily dose 75-150 mg and placebo or ezetimibe during 24 weeks any adverse reactions have been registered in 81 and 82,5% of cases and 71,2 and 67,2% of cases, respectively. It has been reported about early termination of therapy in all groups, average amount of registered cases has reached 8%: alirocumab against placebo (7,2% and 5,4%) or ezetimibe (7,5% and 5,4%), respectively. It is worth to notice that these differences were statistically insignificant. Severe adverse actions were described in the first groups in 18,7% and 19,5% of cases. Similar tendencies were observed during alirocumab and ezetimibe comparison: 18,8% and 17,8% of cases, respectively. Specific adverse reactions for example local reactions to subcutaneous injections were registered in 5,9% of alirocumab group cases versus 4,2% of placebo group cases, and in comparative study of alirocumab and ezetimibe these effects were described in 2,5% and 0,8% of cases, respectively. This study investigated also neurocognitive reactions that were registered in 1,2% and 0,5% , and also 0,8% and 1,2% of cases [12].

In clinical placebo-controlled trials investigating evolocumab in 420 mg during 52 weeks total amount of adverse effects was registered in the range of 31-60% of cases in the main group and 24-49% of cases in control group. Early termination of therapy due to adverse reactions was registered in 1-2% and 2-4% of cases respectively. Severe adverse reactions were registered in 0,9–2,7% of cases in evolocumab group and in 1,8–3,6% of cases in placebo group. Local ad-

verse reaction to subcutaneous injections was registered in 0% and 1,3% of cases respectively [13].

Thus, the review of international comparative placebo-controlled clinical trials demonstrated that LDL cholesterol levels reduction by PCSK9 inhibition with mAb is a promising therapeutic strategy due to significant clinical efficacy and good safety profile. Obviously that the spectrum of their use will be expanded from the treatment of familial hypercholesterolemia to indication in case of statins limitations and the necessity of evident lipid-lowering effect in order to reach target cholesterol levels. In future it is reasonable to perform series of clinical studies according with the endpoints and estimation of distant results of therapy.

Conflict of interest: None declared

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REVIEW ARTICLE

Glycemic control in diabetes mellitus: review of international studies of glucose-lowering drugs cardiological safety

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Summary

This review article observes the data about social and medical significance and dynamic prognosis for the next decade. It analyzes modern glucose-lowering drugs, their mechanism of action, efficacy and side effects. Big part of this article is concentrated on the review of clinical studies of lipid-lowering drugs cardiological safety. It demonstrates the results of 5 major international clinical studies dedicated to investigation of cardiological consequences of modern glucose-lowering drugs therapy. In general, not only efficacy but also safety of glucose-lowering drugs is important for their wide use

Keywords

Diabetes mellitus, cardiological safety, glucose-lowering drugs

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Diabetes mellitus: bases of social and medical significance

Diabetes mellitus(DM) is one of serious social and medical problems in developed and developing countries, that can be explained with its high occurrence, significance of complications and high costs of treatment and rehabilitation.

According with the World Health Organization (WHO), in 2014 there were 387 millions of people suffering from diabetes (8,3% of adult population), in 20 years this number is predicted to increase up to 600 millions. The biggest increase of diabetes mellitus frequency is expected for the countries of the South America, Africa, the Middle East, the South-East Asia, Russia and several CIS countries [1]. It is necessary to mention also the increase of risk factors (obesity, metabolic syndrome) that are the predictors of DM.

According with the results of Federal target program "Prevention and management of socially significant diseases in 2007-2012", 3,549 millions of patients with DM have been registered during this period. In 2014 this number had increased up to 3 964 889 persons, 91,4% of whom had DM 2 type [2]. The highest morbidity rate was detected in the Central and Volga federal districts: 224,6 and 227,0 per 100 000 of adult population. The lowest morbidity rate was registered in the North-Caucasian federal districts: 139,9 and 187,8 per 100 000 of adult population, respectively.

The data included in the Atlas of International Diabetes Federation indicate that 13% of total healthcare budged of the Russian Federation are used for the treatment of DM and its complications. In future it would be necessary to increase the costs of DM treatment in case of predicted growth of DM frequency [1].

It is known that the prognosis for the life of patients with DM 2 type depends on their gender, age and the presence of complications and correlates with the degree of disease's control. Cardiovascular diseases are the main cause of disability and mortality in DM patients. In particular, myocardial infarction (MI) is the cause of death of 50% of patients with DM 2 type [3]. frequent development of MI atypical forms like painless or syncopal ones is an important feature of MI course in DM, and it complicates its opportune diagnosis and considerably impairs the prognosis.

Constant growth of DM morbidity and its "rejuvenation" together with the high risk of complications development including the fatal ones highlight the significance of this problem and predetermine the necessity of multilateral approach in treatment and prevention.

Glycemic control: the review of glucose-lowering drugs

According with the results of prospective studies, glycemic control is one of important methods that reduce progression of DM and its complications. During the last years the spectrum of glucose-lowering drugs has significantly widened. Glycemic control drugs can be divided into four groups: 1) drugs stimulating insulin secretion – secretagogues (sulfonylurea derivatives, meglitinides, glucagone-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors); 2) drugs increasing the sensitivity to insulin – insulin sensitizers (biguanides, thiazolidinediones); 3) drugs inhibiting intestinal absorption of glucose (alpha-glucosidases inhibitors); 4) drugs decreasing glucose reabsorption in kidney - Sodium-glucose cotransporter 2 (SGLT2) inhibitors [4].

Sulfonylurea drugs, meglitinides and incretin mimetics (GLP-1 agonists and DPP-4 inhibitors) directly or indirectly increase endogenous insulin secretion. GLP-1 receptor agonists and DPP-4 inhibitors also have additional effects in gastrointestinal tract and brain that affects the sense of satiation (DPP-4 inhibitors have no effect on body weight, GLP-1 receptor agonists promote weight loss). Unlike sulfonylurea and meglitinides administration, in this case stimulation of insulin secretion has distinct glucose-dependent effect that doesn't increase the risk of hypoglycemia development [5].

Pioglitazone (thiazolidinediones group) is PPARg (Peroxisome proliferator activated receptor gamma type) agonist with the effect on PPARa (Peroxisome proliferator activated receptor alpha type) that decreases glucose concentration in blood reducing its production in liver and suppressing insulin-resistance, whereas metformin is a biguanide which reaches the same effects activating AMP-kinase.

Acarbose reduces glucose absorption in gastrointestinal tract (GIT), and SGLT2 inhibitors decrease glucose absorption in kidney's proximal tubules.

In DM 2 type metformin is the drug of the first line, particularly in case of obesity. The main problem of metformin treatment is lactate-acidosis, especially in case of impaired liver or kidney function. But several studies which involved particular cohorts of patients had comparably low frequency of lactate-acidosis [6]. Nevertheless, metformin is not recommended for patients with glomerular filtration rate (GFR) less than 50 ml/min [7]. Still there is no consent about this value that is considered extremely high. Guidelines of British National Institute for Clinical Excellence are

less restricted: it is allowed to use metformin if GFR is higher than 30 ml/min with the reduction of dose starting from GFR 45 ml/min.

Decrease of HbA1c levels is expected to be in the range of 0,5-1% after treatment with each peroral drug or subcutaneous administration of GLP-1 agonists as monotherapy, although it depends on DM duration and other individual factors. Combination of two and three drugs: metformin with one or two drugs that can be chosen from pioglitazone, sulfonylurea, incretin mimetics, meglitinide and glucose absorption inhibitors , is commonly recommended in case of disease progression [8]. In order to reach target glycemic levels, combined use of glucose-lowering drugs is recommended soon after the diagnosis is set. Early aggressive therapy seems to play some role in cardiovascular outcomes decrease, but it is still not investigated enough in prospective protocols.

Cardiovascular safety of glucose-lowering drugs

The question of glucose-lowering drugs safety is actively discussed since the appearance of information about adverse effects of rosiglitazone, especially in combination with other drugs. In general, 10-years observation after the end of the UKPDS study demonstrated that patients who received sulfonylurea drugs and insulin had decrease of MI risk down to 0,85 (95% confidence interval (CI) 0,74–0,97, p=0,01) and mortality risk down to 0,87 (95% CI 0,59–0,89, p=0,002). Although the UKPDS study demonstrated that metformin has advantages from the point of view of cardiovascular outcomes (because of this it obtained the recognition as the first line medicine for obesity and DM 2 type), it is important to notice generally insufficient evidence base of this opinion. There is a possibility that combination of metformin and sulfonylurea can provoke the development of severe consequences influencing morbidity and mortality. Nevertheless, the results of this meta-analysis consider advantages of long-term treatment with this drug in young patients [10].

Pioglitazone reduced the frequency of secondary composite endpoint for general mortality, fatal MI and stroke in the PROActive study (Relative risk (RR) 0,84, 95% CI 0,72–0,98; p=0,027) in patients with DM 2 type and high risk of macrovascular complications [11]. Since the primary outcomes in the PROActive study hadn't reached statistical significance, the interpretation of these results cannot be fully correct. Pioglitazone administration is linked with liquid retention due to indirect effect on kidney, that leads to edema and the worsening of heart failure (HF) functional class in predisposed patients. It is possible to use diuretic therapy to reduce this impact.

In the STOP-NIDDM study acarbose that is prescribed to patients with impaired glucose tolerance (IGT) reduced the number of cardiovascular events, including cardiovascular mortality. Meglitinide have not been studied formally in DM 2 type, but in patients with IGT and high risk nateglinide did not reduce the risk of fatal and non-fatal cardiovascular events [12]. Up to recent time there was no information about outcomes for GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors. Comparative efficacy and safety profile of main peroral glucose-lowering drugs sis present in the Table 1.

Table 1. **Efficacy and adverse effects of glucose-lowering drugs**

Class of drugs	Effects	Body weight change	Hypoglycemia (in case of monotherapy)	Comments
Metformin	Insulin sensitivity	No/loss	No	Side gastrointestinal effects, lactate-acidosis, GFR reduction, hypoxia, dehydration.
Sulfonylurea	Increase of insulin concentration	Increase	Yes	Allergy, hypoglycemia risk, weight gain
Meglitinides	Increase of insulin concentration	Increase	Yes	Frequent administration, hypoglycemia risk
Alpha-glucosidase inhibitors	Inhibition of glucose absorption	No	No	Side gastrointestinal effects, frequent administration
Pioglitazone	Insulin sensitivity	Increase	No	HF, edema, fractures, bladder cancer (?)
GLP-1 agonists	Increase of insulin concentration	Loss	No	Side gastrointestinal effects, pancreatitis, parenteral administration
DPP-4 inhibitors	Increase of insulin concentration	No	No	Pancreatitis
Insulin	Increase of insulin concentration	Increase	Yes	Parenteral administration? risk of weight gain and hypoglycemia
SGLT2 inhibitors	Glucose reabsorption block in proximal convoluted tubules	Loss	No	Urinary tract infections

Analysis of latest clinical studies dedicated to cardiological safety of glucose-lowering drugs

Previously performed large-scale studies of DPP-4 inhibitor (saxagliptin, alogliptin) in patients with DM type 2 demonstrated increased risk of HF that brought anxiety to endocrinogists and cardiologists. The TECOS [13] study estimated cardiovascular safety of another representative of this class – sitagliptin (n=7332) comparing with placebo (n=7339) that had been added to standard therapy of DM 2 type with concomitant cardiovascular diseases (CVD). Sitagliptin did not increase the frequency of combined primary endpoint (cardiovascular death, non-fatal MI, non-fatal stroke, admission to hospital because of unstable angina) in case of 2,9 years observation median (RR 0,98 for 95% CI 0,88–1,09; p<0,001 for "not worse" statement). The frequency of admission to hospital due to HF was 3,1% in groups of sitagliptin and placebo (RR 1,00 for 95% CI from 0,84–1,20; p=0,95), and sum of hospitalization events because of HF or cardiovascular death was 7,3% and 7,2%, respectively (p=0,81). Analysis of subgroup with 2643 patients with previously present HF did not reveal increased risk of cardiovascular events during sitagliptin treatment. These results demonstrated cardiovascular safety of sitagliptin therapy in patients with DM 2 type, including HF.

Mineralocorticoid receptor antagonists spironolactone and eplerenone decrease morbidity and mortality of patients with chronic heart failure (CHF), but their wide use is restricted by the risk of hyperkalemia. Finerenone excels spironolactone in selectivity and eplerenon in the degree of affinity to mineralocorticoid receptors. The ARTS-HF study involved 1055 patients with DM 2 type and/or chronic kidney disease who had been admitted to hospital due to deterioration of systolic HF [14]. Patients were randomized either into 6 groups for treatment with eplerenone, titrating its dose from 25 mg once per 2 days to 50 mg per day or into 5 groups for treatment with finerenone, titrating its dose from 2,5mg to 20 mg per day and trying not to achieve hyperkalemia. Reduction of N-terminal pro-brain natriuretic peptide levels by 30% and more in respect to its initial levels before 90 days of treatment (primary endpoint) was detected with similar frequency in eplerenone and finerenone groups. At the same time finerenone therapy was linked with significant decrease of the frequency of admission to hospital because of cardiovascular reasons (p=0,0229), death because of any cause (p=0,0262) and cardiovascular death (p=0,0108). The biggest reduction of summated unfavorable cardiovascular events was achieved with starting dose of finerenone 10 mg/day (RR 0,56, p=0,0157). Increased potassium plasma levels up to 5,6 mmol/L and more have been registered only for finerenone dose 15-20 mg/day, and if it was safer than eplerenone if it was administered in dose 2,5-15 mg per day.

The ELIXA study involved patients with DM 2 type who survived MI (83% of cases) or admission to hospital due to unstable angina during last 6 months [15]. After randomization subcutaneous injections of GLP-1 receptor agonist lixisenatide (n=3034) or placebo (n=3034) have been added to standard therapy . Primary composite endpoint (cardiovascular death, MI, stroke, unstable angina) has been registered in 13,4% and 13,2% of cases (RR 1,02 for 95% CI 0,89-1,17) of lixisenatide and placebo groups, respectively. Lixisenatide has been considered safe in this category of patients, including HF, but it did not reduce the risk of cardiovascular complications in patients with DM 2 type.

The SCOT study [16] included 7297 patients without cardiovascular diseases who received selective cyclooxygenase-2 inhibitor celecoxib or non-selective nonsteroidal anti-inflammatory drugs (NSAID) (diclofenac, ibuprofen) for the treatment of osteoarthritis or rheumatoid arthritis. Composite primary endpoint included admission to hospital due to non-fatal acute coronary syndrome with elevated levels of myocardial necrosis biomarkers, non-fatal stroke, cardiovascular death and it had been registered during 3,2 years averagely in 1,8% and 2,2% of cases in celecoxib and other NSAID (RR 1,12; p=0,50). The differences in frequency of severe adverse reactions (5,2% in celecoxib group versus 5,8% in other NSAID group) were insignificant. But total number of adverse reactions was higher in patients who received celecoxib (22% versus 16,1% of cases; p<0,001), and its cancellation had been required more frequently than other NSAID (50,9% versus 30,2%; p<0,0001). In general, use of NSAID in patients without severe CVD has not been associated with high risk of cardiovascular complications.

The OPTIDUAL [17] project involved 1799 patients with stable coronary heart disease or acute coronary syndrome, who were implanted with 1 or more drug-eluting stents. After 12 months of double antiplatelet therapy (aspirin and clopidogrel) 1385 patients who did not have severe cardiovascular/cerebrovascular complications or bleedings were randomized for prolonged administration of clopidogrel 75 mg per day (double antiplatelet therapy prolonged for 36 months, n=695) or termination of clopidogrel

treatment (aspirin group, n=690). After a median observation time after stent implanting of 33,4 months the primary composite endpoint (death, MI, stroke or bleeding) had been registered in 5,8% and 7,5% of patients (RR 0,75 for 95% CI 0,50-1,28, p=0,17), death had been registered in 2,0% and 3,5% of cases (RR 0,65, 95% CI 0,34-1,22; p=0,18), bleeding had been registered in 2,0% and 2,0% of cases (p=0,95) in the groups of prolonged double antiplatelet therapy and aspirin, respectively. Although the tendency seems to be promising, it is still impossible to make a categorical statement about efficacy and safety of prolonged double antiplatelet therapy because of insufficient statistical power of the study.

Conclusion

Diabetes mellitus is one of severe and socially significant diseases of XXI century. Primary and secondary prevention of DM significantly increases patients' quality of life and lifespan. Glycemic control is one of important aspects of treatment of patients with DM. Use of new glucose-lowering drugs as monotherapy or combined therapy give new possibilities for glycemic control. But it is necessary to mention that the safety of new drugs is an important aspect of long-term therapy of patients with DM and comorbid diseases. At the same time, there is an opinion that in case of lack of financing there is no need to study precisely cardiologic safety of new glucose-lowering drugs and spend big amount of recourses. In our opinion, it is necessary to reach consensus for this question, since both efficacy and safety of glucose-lowering drugs are important for wide use.

Conflict of interest: None declared

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REVIEW ARTICLE

Relationship between periodontal and cardiovascular diseases

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Summary

Periodontal and cardiovascular diseases share many common risk factors like metabolic syndrome, diabetes, dyslipidemia and arterial hypertension. The review discusses multifaceted relationship between periodontal and cardiovascular diseases.

The data available today demonstrate close relationship between periodontal disease and cardiovascular disease, that makes it necessary to clarify possible dental complaints obtaining medical history and inspect his oral cavity during observation of patients with cardiovascular diseases, diabetes mellitus, metabolic syndrome, and if any of them are found it is necessary to refer person to dentist. On the other hand, to increase the effectiveness of periodontal diseases treatment, it is reasonable to refer dentist's patient to physician to clarify existing somatic pathology.

Keywords

Periodontal disease, cardiovascular disease, risk factors

Chronical inflammatory diseases of periodontium (gingivitis, periodontitis) take the second place of occurrence between dental pathologies after caries. According with the World Health Organization more than 60% of European population and around 50% of the USA population have signs of chronic gums inflammation [1].

Periodontitis is the disease of dentoalveolar system that is characterized with the development of acute or chronic inflammatory process, periodontall tissue destruction and alveolar bone tissue destruction [1]. American Academy of Periodontology considers periodontitis as an inflammatory disease of bacterial genesis [2].

The significance of this problem is determined by long chronic course of inflammatory process, negative influence on patient's organism and lowered life quality. Impaired microcirculation and the presence of periodontopathogenic organisms are the main factors leading to inflammation development in periodontal tissues.

Somatic disorders like cardiovascular diseases (CVD), diabetes mellitus (DM), gastrointestinal tract

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disorders, systemic osteoporosis, respiratory system diseases have significant impact on etiopathogenesis of periodontal diseases [3].

Cardiovascular system diseases are often accompanied with changes of oral cavity organs and tissues. Periodontal diseases and CVD have many common risk factors: metabolic syndrome (MS), DM, dyslipidemia, arterial hypertension (AH).

Close connection between DM and periodontal disease are well known and based on numerous studies that had been performed in the nineties and that allow to consider periodontitis as one of the main DM complications [4]. Big number of reviews and studies indicates the presence of the linkage between MS and periodontal diseases.

In this review we will discuss connection between periodontal diseases and CVD.

Periodontal pathology and AH

Epidemiological data indicate potential connection between periodontitis with elevated blood pressure (BP) and AH prevalence. Results of crossover studies allow to propose that presence of periodontitis in patients with AH can increase the risk and degree of target organs lesions [5, 6]. Elevated BP in patients with periodontal diseases is reported in several studies.

One study performed by Polish scientists (Franek T. et al. (2010)) demonstrated that in the presence of periodontal pathology (periodontitis and gingivitis) patients with DM 2 type had left ventricle hypertrophy (left ventricular myocardial mass index, LVMMI) together with elevated systolic and diastolic BP [7].

Pilot study that had been done in Brazil (Vieira C.L. et al. (2011)) involved 79 patients with heterozygous familial hypercholesterolemia and periodontitis. Patients who had severe periodontitis had elevated diastolic BP, higher cholesterol, triglycerides, glucose levels and values of pulse wave and carotid arteries' intima-media thickness comparing with patients who had moderate periodontitis [8]. Only the connection between severe periodontitis and diastolic BP levels has been proved (Odds ratio (OR)=3,1, confidence interval (CI): 1,1-8,5, P=0,03) after correction and exclusion of common atherosclerosis risk factors. Another Brazilian study (Vidal F. et al. (2011)) demonstrated significant association between AH and severe form of chronic periodontitis (OR=4,04, 95% CI: 1,92–8,49) and common form of chronic periodontitis (OR=2,18, CI:1,04–4,56) [9].

Independent association of periodontitis and AH has been detected in Chinese study (Zhang L. et al. (2011) in adult Uigurs (1415 Uigurs older than 18 years) living in the countryside [10]. Dispersed logistical regression analysis of the results after age, sex, body mass index (BMI) correction, waist circumference, impaired carbohydrate metabolism, dyslipidemia and chronic diseases correction demonstrated that periodontitis was evidently associated with AH (OR=1,75, CI: 1,3–2,36, P<0,01).

Correlation between different characteristics of periodontal condition and AH has been estimated by Iwashima Y. et.al (2014) in Japanese people living in urban zone. This study involved 1643 participants who did not have cardiovascular disease(CVD) (average age 66,6 years, 43,4% of females). Patients with more than three changed periodontal characteristics had AH risk = 1,82 (95% CI: 2,23-2,72; P=0,003) [11].

The presence of periodontal pathology is connected with higher risk of extragenital pathology and unfavorable outcomes of pregnancy, including AH in pregnant women. One Indian study (Pralhad S. et al (2013)) involved 200 pregnant women, 100 of them had AH during pregnancy, 100 women did not have AH during pregnancy [12]. The occurrence of periodontal diseases was 65,5% and it was significantly higher (p<0,0001) in women with AH (relative risk (RR)=1,5, 95% CI: 1,3–1,9).

Swedish study (Zeigler C.C. et al. (2015)) involved patients of 12-18 years with obesity revealed the connection between the presence of pathological periodontal pockets (pocked depth ⩾ 4mm) and diastolic BP (p=0,006). Detected association did not depend on cardiovascular events risk factors or periodontal diseases [13].

German study (Jockel-Schneider Y. et al. (2014)) detected significantly higher pulse wave velocity (p=0,00004), higher augmentation index (p=0,0049) and lowered pulse blood pressure (p=0,028) in patients with severe periodontitis comparing with people without periodontal pathology [14].

Prospective pilot interventional study that involved patients with refractory AH and chronic periodontitis [15] and estimated the influence of therapeutic periodontal treatment on AH, LVMMI and pulse wave velocity. Systolic and diastolic BP values reduced by 12,5 mm Hg. and 10,0 mm Hg., respectively, and LVMMI and pulse wave velocity decreased by 12,9 g and 0,9 m/s, respectively, after treatment of chronic periodontitis (p<0,01).

In order to estimate possible influence of oral cavity hygiene on BP levels, Korean scientists used the data of 19560 adult patients from national represen-

tative survey Korea National Health and Nutrition Examination Survey (KNHANES)in 2008-2010 [16]. Performed analysis demonstrated that people who don't pay enough attention to oral cavity hygiene have higher AH prevalence before periodontitis development. Authors proposed to consider the condition of oral health as an independent predictor of AH hygiene.

Periodontal pathology and stroke

Association between periodontitis and stroke has been investigated in several studies [17, 18].

The link between periodontitis and hemorrhagic stroke has been estimated using multivariate logistic regression analysis taking into account age, gender, income, education, AH, DM, BMI, CVD, family history, smoking and alcohol consumption [17]. The connection between stroke and hemorrhagic stroke has been identified (OR=2,5, 95% CI: 1,1–5,6), with the highest risk for male patients and patients with obesity.

Association between clinical and radiologic markers of periodontal diseases and ischemic stroke has been investigated in another prospective study [18]. Between all studied stomatological parameters the most significant connection has been established for Bleeding on Probing (BOP) index (OR = 1,049; 95% CI = 1,012-1,88, p= 0,009) and bone tissue loss >20% (OR = 1,053; 95% CI = 1,017-1,091, p = 0,004).

Connection between periodontal stomatological parameters and stroke (OR = 1,58; 95% CI 1,1–3,022) had been observed in Senegalese population by Diouf M. et al (2015) [19].

Periodontal pathology and dyslipidemia

Results of numerous studies indicate that dyslipidemia can be related to periodontal pathology in somatically healthy people. For example, in one Iranian study (Golpasand Hagh L. et al. (2014)) average values of total cholesterol (TC) and triglycerides (TG) have been significantly higher in patients with periodontitis (p<0,001), at the same time the frequency of TC and TG pathological levels has been evidently higher in periodontitis group, comparing with patients with healthy periodontium (p=0,002 and p=0,015, respectively) [20]. In Indian study (Sandi R.M. et al. (2014)) patients with chronic periodontits had significant elevation of TC and low density lipids (LDL) cholesterol levels (p<0,05) comparing with patients who had healthy periodontium [21]. Lipid profile characteristics improve after treatment of periodontal diseases in patients with periodontitis [22, 23].

Periodontitis and atherosclerosis

The presence of distinct positive connection of clinical manifestations and inflammatory changes in atherosclerosis, CVD and periodontal diseases is indicated in several studies.

Consensus dedicated to periodontitis and atherosclerotic CVD that had been published in the American Journal of Cardiology and the Journal of Periodontology recommends to inform the patients with moderate and severe periodontitits about possible increased risk of cardiovascular diseases and the necessity to make cardiological examination [24].

Investigation of periodontal diseases occurrence in patients with acute myocardial infarction (AMI) and in patients with coronary heart disease (CHD) without AMI (Kodovazenitis G. et al. (2011)) revealed that periodontal diseases were more frequent in patients with AMI (38,3% and 17,5%, respectively, p=0,03) [25]. In another study Heaton B. et al. (2014) demonstrated the connection between increased marginal bone loss (MBLS) and increased risk of cardiovascular events in patients with CHD [26].

Crossover and analytical study of Marfil-Álvarez R. et al. (2014) investigated blood troponin I and myoglobin levels and estimated the association between severity of chronic periodontitis and occurrence of AMI. Indirect regression analysis demonstrated that the degree (Arbes index) and severity (Periodontal Inflammatory Severity Index) of chronic periodontitis correlated with troponin I levels after controlling influencing social, demographic and clinical factors (R change (2) == 0,041, p <0,02, and R (2) = 0,031, p = 0,04). The Arbes index value was connected with mioglobin levels (R change (2) =0,030, p< 0,01). The results of this study demonstrated that periodontitis degree and severity have positive correlation with acute myocardial infarction and its dimensions in troponin I and mioglobin blood levels.

Intima-media thickness (IMT) of carotid arteries was considered an objective indicator of connection between periodontal diseases and atherosclerosis in numerous studies.

Connection between carotid arteries IMT and flow-mediated dilatation (FMD) with periodontal pathology has been investigated in British meta-analysis (Orlandi M. et al. (2014)). Authors analyzed 2009 abstracts and 101 full-text articles. Meta-analysis demonstrated that periodontitis diagnosis was connected with IMT average growth by 0,08 mm (95% CI: 0,07-0,09) and FMD average difference of 5,1% comparing with the control group (95% CI: 2,08-8,11%). Meta-analysis of

periodontitis treatment influence on FMD has revealed average improvement by 6,64% (95% CI: 2,83-10,44%), that indicated improved endothelial function [28].

Patients with DM 2 type and periodontal diseases (gingivitis and periodontitis) had higher IMT values [29] comparing with the patients without periodontal pathology (0,804 ± 0,112 and 0,772 ± 0,127 versus 0,691 ± 0,151 mm, p <0,01 and p <0,05, respectively, OR = 5,25 for IMT⩾ 0,8 мм; 95% CI: 1,1-25).

In Chinese study (Yu H. et al. (2014)) that involved elderly patients (847 participants in the age of 70,64 ± 9.03 years with ⩾10 teeth remaining) the average dental plaque index reflecting oral cavity hygiene's condition correlated with maximal IMT and atherosclerotic plaque thickness in general (β = 0,068, p <0,001; OR = 2,051, p<0,001) and in patients without impaired carbohydrate metabolism (β = 0,066, p = 0,008; OR = 2.122, p = 0,009). In this study linear and dose-dependent correlation between average value of clinical attachment loss (CAL) index and maximal IMT has been found using multiple linear regression (p=0,006) and multivariate logistic regression analysis (p=0,025) after correction with common atherosclerosis risk factors in patients with impaired carbohydrate metabolism [30]. Each 1 mm CAL corresponded to 0,018 mm IMT increase. The risk of atherosclerotic plaque development increased by 18,3% with each CAL increase by 1 mm. Other parameters of periodontal condition also correlated with IMT and atherosclerotic plaque in patients with hyperglycemia.

The INVEST (Oral Infections and Vascular Disease Epidemiology Study) study has added new results to already big number of epidemiological evidences of CVD and periodontal diseases connections [31]. 420 participants (average age in the beginning of study was 68 ± 8 years) have been observed during 3 years, and the results of this study revealed that average IMT has increased by 0,139 ± 0,008 mm during the observation period. Carotid artery IMT progression used to reduce after improvement of clinical or microbiological condition of periodontium.

Periodontal bacteria and atherosclerosis

Together with this possible mechanisms that determine the association of periodontal pathology and atherosclerosis remain unclear [32]. Periodontal bacteria and systemic inflammation markers are considered to be possible contributing factors. The results of INVEST [31] and several other studies [33, 34] indicate possible participation of periodontal bacteria and their connection with carotid arteries' IMT change. It has been detected that carotid arteries IMT elevates in parallel with the increase of periodontal bacteries number in dentoalveolar pockets [35], and using multiple logistic regression [36] it has been shown that IMT increases in periodontitis (OR=4,22, p<0,05) in case if two subgingival organisms *Prevotella nigrescens* (OR = 4.08; p < 0,05) and *Porphyromonas gingivalis* (OR =7,63; p < 0.01) are present.

The study of Tapashetti R.P. et al. (2014) considered C-reactive protein (CRP) as the main possible mediator for association of periodontal diseases and carotid artery IMT [37]. It has been noticed that average CRP levels were significantly higher in patients with chronic periodontitis (19,58 ± 17,03), comparing with the patients without periodontal pathology (5,54 ± 1,63, p<0,004). The average IMT value was significantly higher in patients with chronic periodontitis (1,09 ± 0,45) than in patients without periodontal pathology (0,57 ± 0,06, p <0,001). Significant correlation between CRP and IMT increase was identified in patients with chronic periodontitis (r = 0,863, p <0,001).

Inflammation is considered to be one of the factors destabilizing atherosclerotic plaque. It is supposed to think that infection with Chlamydia, Helicobacter and viruses can become the cause of inflammatory reaction [3]. Indeed, the relation between acute coronary syndrome and chronic infection with Gram-negative bacteria like *Chlamydia pneumoniae and Helicobacter pylori* has been described in literature.

Epidemiological parallels between oral cavity infections and CVD have been demonstrated in several studies in vitro and in vivo, that allows to propose possible connection between oral cavity bacteria and atherosclerosis. At the same time the interaction between oral cavity bacteria and CVD is very complicated and multifactorial.

Dysbiosis of subgingival biota is common for chronic periodontitis. Periodontitis starts to manifest with gingival inflammation and it is accompanied with periodontal pockets formation, which promotes growth and development of anaerobic Gram-negative bacteria like *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans и Tannerella forsythia* [38].

The INVEST [31] study has revealed the prevalence of bacteria which are traditionally considered as periodontal diseases etiological agents and which are the most tightly connected with atherosclerosis progression. These bacteria have strong relation with periodontitis clinical manifestations and inflammatory markers. Periodontal bacteria, entering blood-

stream, can go inside endothelial cells, induce endothelial dysfunction and activate inflammatory and immune reactions. High titers of antibodies to periodontal bacteria have been detected in serological studies of atherosclerosis and other CVD.

Immune and infectious changes that occur in periodontium can influence the development and severity of CVD. One of these possibilities can be realized through oral cavity bacteria translocation into atherosclerotic plaque [39]. One Canadian-Brazilian joint study [39] estimated the spectrum of microorganisms living in dentogingival pockets and atherosclerotic plaques, and 17 equal plylotypes have been identified that can evidence possible bacterial translocation between periodontal pockets and coronary arteries. Similar possibility has been demonstrated by extraction of viable bacteria *Porphyromonas gingivalis* from atherosclerotic plaque [40]. DNA of periodontal bacteria was identified in 10 out of 17 coronary artery samples: *Porphyromonas gingivalis* was present in 52,9% of cases, *Aggregatibacter actinomycetemcomitans* - in 35,5% of cases, *Prevotella intermedia* – in 23,5%, and *Tannerella forsythia* – in 11,7% of cases [41, 42].

Thus, the presence of periodontal bacteria in coronary and internal thoracic arteries can be connected with development and progression of atherosclerosis and also with valvular lesions, that has been proved by several experimental studies. The results of some of them indicate the role of Porhyromonas gingivalis in CVD pathogenesis in mice: the presence of periodontitis significantly increased the severity of atherosclerotic lesions, and it was possible to extract periodontal bacteria from vascular wall [2].

Periodontitis and systemic inflammation

Response to infection is often accompanied with secretion of proinflammatory cytokines like interleukin (IL) 1 beta (IL-1b), IL6, tumor necrosis factor alpha (TNF-α), that change lipid metabolism and promote hyper- and dyslipidemia. Proinflammatory cytokines like IL-1b, TNF-α , interferone γ induce prostaglandin E2 (PGE2) and matrix metalloproteinases (MMP) – molecules that contribute to the destruction of intercellular matrix of gingival and periodontal ligament and alveolar bone resorption [2].

Apart of this, proinflammatory cytokines cause systemic responses like elevation of CRP and fibrinogen levels. Systemic inflammatory response developing in case of periodontitis can be significant for vascular lesions, but at the same time direct action of periodontal bacteria on vascular wall remains unclear [43].

Periodontitis is considered as a risk factor for systemic inflammation because bacteria and inflammatory/proinflammatory cytokines can enter systemic circulation that can accordingly influence other organs and systems of organs [43, 44].

Numerous studies demonstrate elevated CRP levels in periodontal diseases. In Columbian study Ramirez J.H et al. (2014) revealed higher E-selectin (64,5 ± 30,9 versus 43,8 ± 22,2; p = 0,026) and myeloperoxidase (103 ± 114,5 versus 49,1 ± 35,6; p = 0,032) plasma levels, that also proved systemic character of inflammation [45].

Inflammation and endothelial dysfunction are linked with the development of atherosclerotic diseases. Periodontal infecting and subsequent increase of inflammatory markers' levels can be related to myocardial infarction, diseases of peripheral vessels and cerebrovascular disorders.

Treatment of periodontal diseases and CVD

Bad hygiene of oral cavity, irregular toothbrushing can be linked to endothelial dysfunction [46]. The use of dental floss and interdental toothbrush can reduce the risk of new cardiovascular events in patients with CHD and periodontitis (OR = 0,2, CI 0,06-0,6, p = 0,01), as it was demonstrated in the study of Reichert S. et al. (2015) [47].

In somatically healthy people with periodontitis the treatment of periodontium in the study of Leite A.C. et al. (2014) has been connected with the reduction of C-reactive protein (CRP) levels and high density lipids (HDL) cholesterol serum levels elevation [48]. In the study of Caúla A.L. et al. (2014) CRP, erythrocyte sedimentation rate (ESR), TC and triglycerids levels median has been reduced after 6 months of periodontal treatment (p <0,001, p <0,001, p <0,001, and p= 0,015, respectively) comparing with the patients treatment of whom had been delayed or who did not undergo treatment [49]. CRP levels reduction during periodontitis treatment has been also detected in other studies [7, 50].

In Australian study Cullinan M.P. et al. (2015) estimated TC, HDL cholesterol, LDL cholesterol, triglycerides, CRP, ESR, hemoglobin, white blood cells number, glomerulal filtration rate (GFR) and functional liver tests every year during 5 years [51]. This study involved 283 patients with CVD who had been subdivided into 2 groups: the 1st group (193 patients) used toothpaste with triclosan and the 2nd group (190 patients) used placebo-toothpaste. The use of toothpaste that contained triclosan was accompanied with

TC (p=0,03) and LDL cholesterol (p=0,04) levels reduction comparing with the placebo-toothpaste.

Inflammation markers and clinical parameters of patient's condition have been estimated in Chilean patients with periodontitis initially and then each 3 months up to 12 months after treatment in double blind randomized clinical trial that lasted 1 year. In the main group systemic antibiotics (amoxicillin and metronidazole) had been used for periodontitis treatment together with topical treatment. In the control group only topical treatment and placebo had been used.

Periodontal condition improved significantly 3 months after treatment (p=0,0001) in both groups and remained lower than basal level for 12 months. The main group of patients who received systemic antibacterial therapy demonstrated more significant improvement of periodontal condition (p=0,0001). CRP levels decreased with time, and this reduction was significant 9 and 12 months after therapy (p=0,024 and p=0,001, respectively) in both groups without significant differences between them. Fibrinogen levels reduced significantly only in the main group, 6 and 12 months after the treatment.

Experimental studies evidence that inhibition of vascular inflammation caused by endogenous mediators specifies a new approach for atherogenic events and periodontitis prevention.

Thus, periodontal diseases therapy is important not only for maintaining good health condition, but, possibly, as it is pointed out in several reviews [52. 53], to moderate pathological changes like atherosclerosis and CHD and subsequently AMI and stroke.

Drugs that are used for CVD treatment can influence periodontal condition. The most significant adverse effects negative for periodontium of selective calcium channel blockers (nifedipine, amlodipine, felodipine, lercanidipine, verapamil, diltiazem) are gingival hyperplasia (hemorrhage, painfulness, edema) and hypertrophic gingivitis [3].

Increased gingival hemorrhage can be observed during treatment with acetylsalicylic acid, clopidogrel, ticlopidine, warfarin, unfractionated heparin, low-molecular weight heparin (nadroparin, dalteparin, enoxaparin, bemiparin, repivarin), fondaparinux sodium, rivaroxaban, dabigatran etexilate, abciximab, eptifibatide,. Thrombolytic therapy (streptokinase, alteplase, tenecteplase, prourokinase) can also cause gingival hemorrhage [3].

Positive effects of CVD pharmacological therapy on periodontal condition are connected with the drugs of statins' group. Statins cause the following systemic (pleiotropic) effects: improvement of endothelial functional condition (restoration or improvement of endothelium-dependent dilatation), normalization (improvement) of rheological and reduction of thrombogenic properties of blood.

It is considered to be promising to reduce the activity of all inflammatory markers during therapy with statins, and the intensity of this effect does not depend on statins' action on lipids. It is supposed that anti-inflammatory action of these drugs precedes in time their hypolipodemic effect.

Antiinflammatory effect of lipid-lowering therapy is provided by such mechanisms like improved endothelial function due to increased NO synthase levels, atherosclerotic plaque stabilization, impaired thrombogenesis (due to decreased platelet aggregation and reduced fibrinogen and tissue plasminogen activator 1 type levels). Several studies demonstrated that statins reduce CRP concentration and can decrease secretion of several cytokines: IL-6, TNF-α.

Statins reduce bone resorption by inhibiting osteoclast formation and can lead to increased apoptosis of these cells, according with the results of systematic review that used PUBMED and BIREME [54] databases . Statins' effect on bone formation is related to increased expression of bone morphogenetic protein in osteoblasts. Decreased loss of alveolar bone osteal mass goes along with the reduction of periodontal inflammation clinical manifestations.

High doses of statins (80 mg of atorvastatin) comparing with low ones (10 mg) in the study of Subramanian S. et al. (2013) have led to the reduction of periodontal inflammation according with the results of positron-emission tomography and computer tomography in the beginning of treatment, and after 4 and 12 weeks [55]. There was also significant correlation between the reduction of periodontal inflammatory activity and the changes of carotid arteries (OR = 0,61, p< 0,001).

Conclusion

Discussed relation between CVD and periodontal diseases do not allow to estimate definitely their character. Together with this, all known data indicate the presence of tight connection between periodontal pathology and CVD, that makes it necessary for internal medicine specialists to pay attention to possible stomatological complaints acquiring patient's anamnesis and to perform oral cavity examination, and if any of them are found patient should be referred to stomatologist for consultation and treatment. At the

same time it is reasonable to send stomatological patient to internal medicine specialist in order to obtain more precise information about existing somatic pathology.

Conflict of interest: None declared

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Estimation of atrial fibrillation risk development in patients with metabolic syndrome during atrial extrasystole registration

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Summary

Objective

To estimate atrial fibrillation (AF) risk development in order to determine its long-term and short-term development risks in patients with metabolic syndrome (MS) during atrial extrasystole (AE) registration according with performed prospective study

Materials and methods

1427 patients of the age between 45 and 75 years with MS and registered AE were observed from 1998 to 2012. Apart of general examination, patients underwent hemodynamic monitoring, atrial late potential (ALP) and P-wave dispersion (Pd) measurement and estimation of AE character with quantification of AF development risk index

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(AFDRI). After inclusion into the study patients were observed during the period from 1 to 4-5 years. Presence or absence of AF development during the period of observation was considered the endpoint of this study.

Results

156 (10,93%) of examined patients developed paroxysmal or persistent form of AF during 4–4.5 years of prospective observation. Atrial dilatation and/or ALP detection after single examination in patients above 55 years with MS determine long-term risk of AF development. Short-term risk (during 1–2 years after the first examination) of AF development can be estimated just after dynamic observation of patients: AFDRI reduction to 35% and more during each 3–4 month of observation comparing with initial results determines AF development in patients with MS during 1–2 years, and if AFDRI levels are less than 0,5 units with subsequent reduction to 70% and more each 1–3 months, it determines AF development during 6 months after examination.

Conclusions

Complex examination of MS patients that includes ALP and Pd measurement and AFDRI estimation allows to determine both long-term and short-term risks of AF development.

Keywords

Atrial fibrillation, metabolic syndrome, development risk identification

Indtroduction

Metabolic syndrome (MS) is mentioned as one of atrial fibrillation (AF) frequent causes in international and Russian guidelines for AF treatment. It is recommended to perform pulse screening in patients older than 65 years and in case of irregular pulse make electrocardiogram (ECG) registration to verify the diagnosis [1,2]. During the last years such predictors of AF development like left atrium dilation, mitral valve calcinosis, left ventricular ejection fraction reduction (LVEF), transmitral flow parameters worsening, the presence of atrial late potentials (ALP), increased P-wave dispersion (Pd), etc have been determined [1, 2, 3, 4]. But we were unable to find in available literature an example of prospective study with complex use of ALP, Pd together with the identification of atrial extrasystoles (AE) character aiming to estimate the risk of AF development in patients with MS.

The objective of this work is to estimate AF predictors use for determining long-term and short-term development risks in patients with MS based on performed prospective study.

Materials and methods

1427 patients between 45-75 years (average age 66,3±2,7 years) with MS were observed during the period from 1998 to 2012. MS diagnosis was based on common criteria [3]. The following inclusion criteria were chosen: the presence of sinus rhythm, pathological amount of AE (more than 50 extrasystoles per day) [3] registration, chronic heart failure, I-II NYHA class, no AF registration after 2-3 repeats of 1-3 days of 24 hours ECG monitoring, signed informed consent. Patients with acute coronary syndrome, WPW syndrome, sick sinus syndrome, atrioventricular heart block, artificial cardiac pacemaker, ventricular tachycardia and extrasystoles (II-V classes according with the classification of Rayn), valvular defects, cardiomyopathies, thyroid gland dysfunction, uncontrolled arterial hypertension, severe somatic diseases that could have influenced the results and also patients with LVEF less than 45%, left ventricle aneurism, chronic heart failure III-IV NYHA class [3] were excluded from the study. Essential hypertension was found in 1133 patients (79,40%), 245 patients (17,39%) had the history of myocardial infarction, 914 (64,05%) had diabetes mellitus, 216(15,14%) had chronic bronchitis.

Apart of clinical examination patients underwent the examination of central and intracardiac hemodynamics using echocardiograph Hitachi-EUB-5500 and Doppler-echocardiography according with the common techniques. and such hemodynamic characteristics like LVEF, final diastolic volume of left atrium (laFDV), and the volume more than 28 mL/m^2 was considered as LA dilation [3, 5], left ventricular mass index (LVMI), E (early) and A (late) left ventricle filling velocities and E/A ratio (E/A ratio less than 1,0 was considered as diastolic dysfunction [5]) were determined or quantified for each patient. Determination of signal-averaged ECG characteristics like filtered P-wave duration (FiP-P), duration of signals in the end of P-wave weaker than 5 μV (D_s) and root mean-square amplitude of 20 ms of P-wave (RMS-20), Pd, FiP-P/Pd ratio expressed in relative units have been previously described [6].

All patients received basis hypotensive therapy with angiotensin-converting enzyme inhibitors (enalapril (ednit, renitec, etc)), saluretics (indapamide (arifon), etc) including all patients who survived myocardial infarction, and controlled glucose and lipids concentrations in blood using diet or glucose- and lipid-lowering drugs like statins. In all patients we quantified the risk of AF development index (AFDRI) using formula AFDR=(FiP-P/Pd)*(A/B), where AFDRI is atrial fibrillation development risk index, FiP-P – filtered P-wave duration(ms) in signal-averaged ECG , Pd – P-wave dispersion(ms), determined as the difference between maximal and minimal values of P-wave duration during standard 12-lead ECG registration, A – linear deviation (LD) of corrected pre-ectopic interval (PEIcor) not less than in 20 AE, B – the number of AE used for this study expressed as amount of extrasystoles per 1 hour [7]. PEIcor estimation using not less than 20 extrasystoles excludes false-positive results [8]. It is worth to mention that we used transesophageal ECG registration in case of frequent AE to visualize P-wave more precisely especially when it was difficult to distinguish or it was mixed with T-wave.

After inclusion in the study patients have been observed during the period from 1 to 4-5 years. Presence or absence of AF development during this period was considered as the endpoint of the study. All examinations including ECG monitoring were performed not less frequently than once per 3-4 months, control of patient's state and ECG registrations were done every month. Regular blood pressure and heart rate control were independently measured by patients.

Statistical analysis of results was performed using Student's t-test, χ^2, odds ratio (OR), confidence interval (CI)of mean values and OR and "Statistica 11.0" software.

Results and discussion

After inclusion into the study 156 (10,93%) of 1427 patients demonstrated development of paroxysmal or persistent AF form during 1-4 years of observation. All patients were divided into 2 groups. The first group (I group) included 1271 (89,07%) patients who haven't developed AF, all other patients who acquired AF during the period of prospective observation were included into the second group (group II). 8 patients of the second group (5,13%) underwent examination 3-6 months before they developed AF, 15 (9,62%) were examined 6-12 months before the development of AF, 35(22,44%) – 1-2 years before, and all remaining patients have developed AF 2-4 years after the first examination. No significant differences in gender, frequency of essential hypertension, diabetes mellitus, chronic bronchitis, coronary heart disease (CHD) clinical forms have been found.

The results of clinical examination and laboratory tests in patients of I and II groups are present in Table 1. This table demonstrates that the patients of the II group were older and had significant increase of body mass index (BMI), waist circumference, triglycerids and low density lipids (LDL) cholesterol levels comparing with the I group, at the same time there was no significant difference in other characteristics between two groups. Hemodynamics condition, characteristics of signal-averaged ECG, AFDRI in the II group patients after prospective study are demonstrated in Table 2. It is possible to notice that the II group patients had significant increase of laFDV, LVMI, FiP, D_5, Pd and significant decrease of FiP/Pd, E/A, RMS-20 values and AFDRI comparing with the I group, at the same time there was no significant difference between other compared characteristics. 386 (30,36%) and 94 (60,26%) patients of I and II groups respectively had ALP (p<0,05, sensibility, specificity and prognostic significance were 60%, 95% and 19%, respectively), 254 (19,99%) and 105 (67,31%) had pathological values of Pd (p<0,05, sensibility, specificity and prognostic significance were 67%, 96% and 29%, respectively), 273(21,48%) and 118(75,64%) patients of I and II groups had atrial dilation(p<0,05, sensibility, specificity and prognostic significance were 76%, 97% and 30%, respectively). Estimation of the changes of these characteristics after dynamic observation revealed that the patients of the II group starting from the third year and during subsequent observation had significant increase of laFDV, LVMI, FiP, D5, Pd and significant reduction of FiP/Pd, E/A, RMS-20 in comparison both with the results of ob-

Table 1. **Clinical examination and laboratory tests results in the patients of I and II groups (M±m)**

Groups	I group n = 1271	II group n = 156
Characteristics	M±m	M±m
Body mass index (BMI), kg/m^2	29,4±0,2	33,9±0,5*
Waist circumference, cm	101,2±5,1	125,2±1,5*
Age, years	53,7±3,2	65,9±0,5*
Blood glucose, mmol/L	6,4±0,2	6,8±0,5
Total cholesterol, mmol/L	6,3±0,2	6,9±0,3
LDL cholesterol, mmol/L	3,2±0,2	4,3±0,5*
HDL cholesterol, mmol/L	0,8±0,2	0,9±0,2
Triglycerids, mmol/L	2,1±0,2	3,6±0,5*

Comment: * significant difference comparing with the I group (p<0,05).

Table 2. **Hemodynamics condition, signal-averaged ECG characteristics, AFDRI in patients of II groups after dynamic observation in prospective study (M±m and 95% CI of mean values[1])**

Groups of patients	I group[2] n = 1271	II group n = 156 Observation before AF development (years)				
Characteristics		4-4,5 years[2]	3 years[2]	2 years[2]	1 year[2]	>0.5 years[2]
LVEF, %	58,43±0,23 49-71	57,83±0,76 48-69	56,84±0,77 47-66	56,64±0,76 47-68	57,89±0,85 48-69	58,87±0,97 49-71
E/A, relative units	1,14±0,02 0,96-1,32	1,01±0,02[3] 0,72-1,29	0,95±0,02[3, 4] 0,71-1,23	0,91±0,02[3, 4] 0,66-1,15	0,86±0,02[3, 4] 0,61-1,11	0,85±0,02[3, 4] 0,61-1,09
laFDV, mL/m^2	25,37±0,44 18-33	30,06±0,52[3] 24-38	31,56±0,53[3, 4] 25-39	32,96±0,51[3, 4] 25-41	34,79±0,64[3, 4] 28-43	35,93±0,52[3, 4] 29-45
LVMI, g/m^2	128±0,3 115-143	132±0,3[3] 122-143	134±0,3[3, 4] 123-145	135±0,3[3, 4] 127-148	136±0,3[3, 4] 128-150	138±0,3[3, 4] 128-152
FiP-P, ms	116±0.5 93-134	138±1[3] 125-151	141±1[3, 4] 126-154	142±1[3, 4] 129-155	143±1[3, 4] 130-155	144±1[3, 4] 132-155
D5, ms	25±0,1 10-30	26±0,5[3] 20-32	27±0,4[3, 4] 23-33	31±0,5[3, 4] 26-36	34±0,3[3, 4] 30-38	37±0,3[3, 4] 33-41
RMS-20, μV	4,2±0,04 2,3-5,2	3,3±0,07[3] 2,2-4,3	2,9±0,07[3, 4] 2,0-3,7	2,7±0,07[3, 4] 1,7-3,5	2,6±0,07[3, 4] 1,6-3,3	2,4±0,07[3, 4] 1,4-3,2
Pd, ms	31±1 17-52	42±1[3] 35-59	52±1[3, 4] 39-63	57±1[3, 4] 51-65	65±1[3, 4] 58-78	67±0,6[3, 4] 59-79
FiP-P/Pd, relative units	3,74±0,05 5,39-2,41	3,29±0,03[3] 3,67-2,53	2,71±0,01[3, 4] 3,23-2,34	2,49±0,02[3, 4] 2,59-2,31	2,20±0,02[3, 4] 2,51-2,02	2,15±0,02[3, 4] 2,33-2,01
AFDRI, relative units	24,18±2,34 2,31-54,17	10,25±1,8[3] 1,93-28,57	8,57±1,15[3] 1,28-19,44	0,43±0,09[3, 4] 0,12-1,34	0,29±0,04[3, 4] 0,05-0,7	0,12±0,02[3, 4] 0,01-0,5

Comment:
[1] M±m is above mean values, 95% CI is below mean values, [2] average results during observation period, [3] significant difference of characteristics in comparison with the I group, [4] significant difference in comparison with the results 4-4,5 years before AF development (p<0,05).

servation that had been done 4-4,5 years before and the results of the I group, at the same time no significant difference between other characteristics has been found. Starting from the second year of observation and during follow-up observation patients of the II group had significant reduction of AFDRI (95% and more, in average) comparing both with the precedent results of 3 years before and with the I group (Table 2). AF development correlated (r>0,7 was considered significant) with age above 60 years, BMI>30 kg/m^2, RMS-20<3,1 μV, E/A<0,95, laFDV > 30mL/m^2, Pd > 55ms, FiP > 135 ms, FiP/Pd < 2,5 relative units, AFDRI values less than 0,5 relative units, detection of 1200 and more AE per 24 hours (Table 3). Detection of FiP/Pd ⩽2,5 relative units, together with FiP ⩾ 135 ms and/or laFDV > 30mL/m^2 together with AFDRI reduction by 35% and more during each 3-4 months of observation comparing with initial levels correlated with AF development during 1-2 years (r=0,93, OR=16,2, CI=14,7-17,9), and if AFDRI value was ⩽ 0,5 and its subsequent reduction by 70% and more during 1-3 months of observation correlated with AF development during 6 months after observation (r = 0,95, OR= 17,6, CI = 16,7-18,4).

Nowadays it is known that all cardiovascular diseases including MS can cause progressing structural atrial and ventricular remodeling that leads to electric dissociation, shortening of refractory period and local discontinuity of conduction in atrial myocardium, that in its turn can provoke multiple re-entry waves and AF development [1, 2, 3, 4]. It is worth to notice that the presence of frequent AE and/or short asymptomatic AF episodes increase the risk of stroke and other complications [1, 2, 3, 4]. So prediction of AF development and early primary prevention is an important problem of modern cardiology.

1427 patients of age between 45 and 75 years with MS and AE underwent prospective study. After inclusion each patient had been observed during the period from 1 to 4-5 years, presence or absence of AF development during this period was considered the endpoint of this study. 10,93% of observed patients

Table 3. **Correlation (r > 0,7) and OR of clinical observation and instrumental tests results of AF development in patients with MS**

Characteristics	R	OR	OR CI
Age older than 60 years	0,72	2,8	2,0 - 3,5
BMI > 30 kg/m^2	0,83	3,4	2,4 – 3,9
RMS-20 < 3,1 μV	0,75	6,3	5,6 – 6,8
E/A < 0,95	0,77	3,3	2,6 – 3,8
laFDV > 30 mL/m^2	0,79	6,2	5,1 – 6,8
Pd > 55 ms	0,87	8,4	7,9 – 8,9
FiP > 135 ms	0,91	7,6	6,8 – 8,1
FiP/Pd < 2,5 relative units	0,90	11,3	10,4 – 11,9
AFDRI < 0,5 relative units	0,93	14,8	12,3 – 15,8
⩾ 1200AE during 24h of observation	0,86	6,5	5,6 – 7,1

have developed paroxysmal form of AF during 4-4,5 years of prospective observation.

One of the most frequent causes of this arrhythmia is MS that manifests as abdominal obesity, arterial hypertension, hyperglycemia and/or hyperlipidemia that leads to development of left ventricle dysfunction in the majority of cases, left atrium dilation, transmitral flow parameters worsening, etc [1, 2, 3, 4].

More than that, there are predictors like ALP, pathological Pd values that identify delayed, fragmented conduction of excitation that create anatomic background for development of re-entry loop [6], and the frequency of their detection in patients with MS stays in the range of 10-40% [3 ,4, 6, 8, 9, 10]. Similar results have been obtained in the current study. It is worth to mention that according with Framingham study [11] 10-year risk of AF development in this patients was 25-30% (or 12-15% during 4-5 years). Significantly less frequent development of AF in patients with MS in the current study, possibly, was related to exclusion from this study patients with LVEF < 45%, left ventricle aneurism, valvular defects, chronic heart failure III-IV NYHA class.

Results of this study demonstrated that Af development in patients with MS was registered significantly more frequently at the age above 60 years, in case of BMI ⩾ 30 kg/m^2, elevated blood levels of triglycerides, LDL cholesterol, left atrium hypertrophy, presence of ALP and pathological Pd values. Our results are consistent with the results of other studies [1, 2, 3, 4, 6, 9, 10].

Overdistension of atrial myocardium due to their dilation causes progressing sclerosis of cardiac muscle and electric dissociation between muscle bundles and it leads to irregular shortening of refractoriness, development of inhomogeneous conduction in atria that facilitates development and persistence of AF. Presence of dispersion of conduction that can be detected with signal-averaged ECG and Pd demonstrates potentially possible development of reentrant excitation (re-entry) in atrial myocardium or around anatomic block, for example, during the wave movement around pulmonary veins. It is worse to mention that, although detected ALP , Pd pathological values and atrial dilation have enough high sensitivity and specificity, their prognostic knowledge in AF prediction was not higher than 30%. These results have been obtained in previous studies[3, 4, 6]

Nowadays it's known that AE development can be caused by several mechanisms, for example, the presence of trigger activity (early or delayed postdepolarization), re-entry and some other cellular mechanisms [3, 4]. According with the results of invasive electrophysiological studies, it is not possible to see the difference between trigger mechanisms of ventricular extrasystoles development from re-entry and formation of pathological arrhythmogenic focus [3, 4]

Clinical and experimental assays that have been done previously demonstrated that detection of PEIcor LD ⩽ 10 ms indirectly prove re-entry mechanisms and the presence of pathological ectopic focus, and high variability of this characteristic can indicate trigger mechanisms [8].

In this study we estimated AE character using the ratio of PEIcor LD and the number of extrasystoles used for this study, expressed as number of extrasystoles per hour, and we also used characteristics of signal-averaged ECG, for example Fip-P and Pd, that was reflected in AFRDI determination [7]. Reduction of PEIcor LD, AE together with detection of frequent extrasystoles indirectly indicate the presence of pathological ectopic focus and/or development of reentrant excitation (re-entry) in atrial myocardium, that is reflected in AFRDI values reduction [7].

It is worth to notice that the wide variability of AFRDI values (0,01-54 relative units) detected in this study indirectly indicates the presence of AE with different development mechanisms. At the same time patients demonstrated progressing reduction of AFRDI values (averagely by 35% and more during each 3-4 months of examination) 2 years before they developed AF, that can be possibly explained by formation of pathological ectopic focus and/or development of reentrant excitation (re-entry) in atrial myocardium, and also by formation of organic substrate for this arrhythmia development. It can be proved with the results of this study: during this period we registered increase FiP ⩾ 135 ms together with FiP/Pd ⩽ 2,5 relative units, and laFDV ⩾ 30mL/m^2. From the other side, refractory AE probably can provoke the development of irregular conduction of excitation in atria, contributing in development and persistence of AF, that goes along with the results of current study: detection of ⩾ 1200 AE per 24h of observation has strong correlation with the development of this arrhythmia (r=0,86, OR = 8,5, OR CI =7,8-9,1). After formation of another front of AE excitation wave, for example, in case of ectopic focus or re-entry, this wave can undergo fractionation and decay into daughter waves, each one of them can become independent, and the critical amount of travelling waves necessary for AF development can be formed after division of a bigger wave

in some focus with blocked conduction or in case of active movement in the direction of the other atrium [3,4]. It is worth to notice that it is possible to detect local arrhythmic sites in the majority of patients with paroxysmal AF, and at the same time in patients with persistent AF the sites of increased electric activity are disseminated in all atrial myocardium. [2]. Thus it is possible to propose that detection of AE in patients with persistent AF with different mechanisms of its formation is possible to be an independent predictor of this arrhythmia's relapse development.

These results allow to propose that detection of atrial dilation and/or pathological characteristics of signal-averaged ECG, Pd, AE in patients with MS after single examination can determine long-term risk of possible AF development, for example, during 5-10 years and more, but it doesn't mean that this pathology will manifest in the end. The use of long-term risk category is explained by several reasons. At first, around 90% of patients with MS and potential risk of AF development can be placed into the groups of "low" and "moderate" risk, according with known data. At second, according with the opinion of several authors, correction of potentially modifiable factors like body weight, arterial hypertension, blood glucose and lipids levels normalization that facilitate reverse remodeling of atrial myocardium is recommended for the prevention of AF development in patients with MS [3, 4, 6, 10]. That means that all patients with MS at first instance should actively use correction of modifiable factors for primary AF prevention that in the end will lead to the reduction of number of patients with so-called "high" risk of AF development [12].

According with known results, short-term risk reflecting distinct period during which patients with MS are the most likely to develop AF can be determined only if patients undergo dynamic observation not less frequently than once per 3-4 months. It was proved with the results of our study: FiP/Pd ⩽2,5 relative units detection together with FiP ⩾ 135 ms, and/or laFDV > 30 mL/m2 and together with AFDRI reduction by 35% and more during each 3-4 months of observation comparing with the initial results correlated with af development during 1-2 years (r=0,93, OR=16,2, CI=14,7-17,9), and if AFDRI was ⩽ 0,5 relative units, consequent reduction of this characteristic by 70% and more during 1-3 months of observation correlated with af development during 6 months after observation (r=0,95, OR=17,6, CI=16,7-18,4). It is possible that antiarrhythmic drugs should be prescribed in this category of patients for AF primary prevention apart of modifiable risk factors correction, starting from II class of antiarrhythmics and if these drugs aren't effective medicines of III(I) classes or other treatment methods should be used [12].

Conclusions

1. Patients older than 60 years with MS and BMI⩾30kg/m2, elevated levels of triglycerides, LDL cholesterol are put into the risk group of AF development.

2. Detection of atrial dilation, AE and pathological Pd values of signal-averaged ECG in patients with MS characterize the presence of long-term risk of Af development, for example, in 5-10 years, but it does not imply that this pathology will appear in the end.

3. Short-term risk of AF development in patients with MS reflecting the terms of possible development of this arrhythmia is estimated according with AFDRI not less frequently than once per 3-4 months.

4. Reduction of AFDRI values by 35% and more in patients with MS during each 3-4 months of observation comparing with initial values determines the risk (if OR>16) of AF development during 1-2 years, and if detected AFDRI⩽0,5 relative units with subsequent reduction by 70% and more each 1-3 months it determines the risk (if OR>17) of AF development during 6 months after observation.

Conflict of interest: None declared

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Interrelation between statins and endothelial dysfunction marker in male and female patients with coronary atherosclerosis

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Summary

Objective

To analyze the interrelation between the marker of endothelial dysfunction endothelin and hypolipedemic drugs administration in patients with verified coronary arteries (CA) lesions

Materials and methods

This study included 429 patients (302 males and 127 females) in the age of 62,7±8,8 years with CA lesions verified with coronary angiography. Endothelin levels in serum were measured with immune-enzyme assay ELISA.

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Results

Negative correlation between statins therapy and endothelin levels was identified in male patients (r= -0,11, P=0,04). We revealed that males undergoing statin therapy (n=294) had 1,8 times less endothelin levels comparing with the men who did not receive statins. The interrelation between statin administration and endothelin levels in female patients with CA lesions was not found.

Conclusion

In male patients with CA lesions, as opposed to females, statin administration correlates negatively with endothelin levels and is associated with its 2-fold decrease. Interrelation between endothelin concentration and administration of other drugs was not found.

Keywords

Atherosclerosis, endothelial dysfunction, endothelin, statins.

Introduction

Atherosclerosis that develops asymptomatically during many years underlies many cardiovascular diseases(CVD). Endothelial dysfunction of vascular wall is an initial step of atherogenesis, because of that it is considered to be the marker of early atherosclerosis development [1, 2]. Endothelial dysfunction(ED) is caused by impaired functional activity of vascular endothelium accompanied with unbalanced vasodilators' and vasoconstrictors' production that changes vascular tone. Endothelin is studied better than other known vasoconstrictors produced by endothelium from the point of view of signaling pathways regulation [3]. High endothelin levels are observed in such disorders like acute myocardial infarction, cardiac rhythm abnormalities, myocardial hypertrophy, coronary heart disease (CHD) and it is associated with main cardiovascular disease (CVD) risk factors [4,5]. Thus, misbalanced endothelin production can indicate endothelial dysfunction and other associated abnormalities determining atherosclerosis development.

Big consideration is given to the possibility of ED correction with pharmacological therapy. Wide spectrum of medicines is used for CVD treatment. The most effective groups between them are statins, beta-blockers, anticoagulants, antiaggregants, diuretics, nitrates, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers ets. Particular attention is paid to pleiotropic effects of statins – HMG-CoA reductase inhibitors [6, 7]. Apart of hypolipidemic and antiatherogenic activity positive effect of statins on endothelium can be explained by their antioxidant and endothelium-protective action [8-10]. Investigation of statins pleiotropic effects and particularly their influence on vascular endothelium is of high scientific interest.

The aim of this work was to analyze the interrelation between endothelin as the marker of endothelial dysfunction and administration of statins and other drugs in patients with verified coronary arteries (CA) lesions.

Materials and methods

This study included male and female patients in the age of 30-80 years who were admitted to the National Research Centre for Preventive Medicine for diagnostics and treatment of suspected CHD and who were referred for coronary angiography (CAG) during 2011-2012.

CA lesions verified by CAG were considered as the inclusion criteria for this study. Exclusion criteria for this study were: history of myocardial infarction or stroke less than 6 months ago, any acute inflammatory disease, 3 or more stage of chronic kidney disease (glomerular filtration rate less than 60ml/min/1,73m^2), decompensated diabetes mellitus, both types (glycated hemoglobin levels >7,5%), left ventricle ejection fraction <40%, cancer, hematological diseases including trombocytopathies and coagulopathies, immune system disorders, pregnancy and lactation.

This study was performed according with the principles of Helsinki Declaration. Study protocol was approved by Ethic Committee of the National Research Centre for Preventive Medicine. All patients gave written informed consent for participation in the study and personal data proceeding.

Blood pressure was measured on the right arm in the sitting position after 5-10 minutes of rest twice after 5-minutes break, and the average of 2 measurements was analyzed. Heart rate (HR) was estimated during 60 seconds in the sitting position of patient after rest.

Blood sampling was performed from cubital vein after 12 h of starvation. Blood serum was obtained from blood after centrifugation at 4 ºC degree, 1000 g, for 10 minutes. Blood serum was aliquotated and stored at -26 ºC before analysis.

Then we measured total cholesterol (TC), triglycerides (TG) and high density lipids (HDL) cholesterol levels (after low density lipids (LDL) sedimentation with sodium phosphovolframate and $MgCl_2$) were obtained using enzymatic kits provided by company"Human"(Germany) and automatic analyzer "Konelab 20i" (Finland). LDL lipids concentrations was quantified using Friedewald formula.

Endothelin 1-21 concentration was measured with the kit provided by "Biomedica" (Austria) using solid-phase immunoenzyme assay ELISE according with manufacturer's instruction.

Statistical analysis of the results was performed using Statistica 8.0 software. For each continuous quantity depending on distribution type we measured average value and standard deviation (SD). To estimate the differences between two groups we used non-parametric Mann-Whitney test. To identify correlation between different characteristics we used Spearman's rank correlation analysis. Differences with p-value <0,05 were considered statistically significant.

Results

429 patients (302 males, 127 females) with average age 62,7±8,8 years were included in this study. Main demographic characteristics of cohort and endothelin levels are demonstrated in Table 1.

Age, weight, HR, TC, LDL cholesterol, HDL cholesterol values were different between male and female groups (p<0,05).

Average endothelin concentration in all cohort was 2,90±3,53 fmol/ml, no significant difference in relation with gender was identified.

97% of males and 93% of females received statins in such proportion: atorvastatin (78%), rosuvastatin (12%), simvastatin (10%). We estimated the interrelation between statins therapy and endothelin levels in patients and identified the negative correlation between statins therapy and endothelin levels in males (r=-0,11, p<0,05). More than that, males who were taking statins (n=294) had 1,8 times less levels of endothelin comparing with the males who did not receive them (2,80±3,48 vs 4,98±4,24 fmol/ml, p<0,05, respectively).

We did not observe the interrelation between statins administration and serum endothelin levels in the female patients.

Apart of statins, patients took the following medicines: anticoagulants (Warfarin), antiplatelet drugs (Clopidogrel, Aspirin), ACE inhibitors, calcium channel blockers, angiotensin type II receptor blockers, beta-blockers, nitrogen monoxide donors (organic nitrates), aldosteron antagonists, diuretics. The interrelation between endothelin concentration and administration of other drugs was not identified in both groups of patients.

Discussion

Our results evidence that the interrelation between statins therapy and the marker of endothelial dysfunction endothelin in patients with verified coronary atherosclerosis depends on gender. Statins administration in male patients is associated with almost 2-fold reduction of endothelin concentration in patients who received statins comparing with the ones

Table 1. **Main demographic characteristics, endothelin concentration and lipid profile**

Characteristics	Total (n = 429)	Males (n = 302)	Females (n = 127)
	Means (M) ± SD		
General characteristics			
Age, years	62,7±8,8	59,8±9,1	65,6±8,4*
Weight, kg	83,0±13,8	88,4±15,6	77,5±12,0*
Body mass index, kg/m^2	29,5±4,8	29,1±4,4	29,9±5,1
Systolic blood pressure, mmHg	131,6±15,3	130,3±15,2	132,8±15,3
Diastolic blood pressure, mm Hg	80,3±8,0	80,6±8,7	80,0±7,3
HR, beats per minute	69,9±7,8	68,7±7,8	71,0±7,8*
Biochemical marker of endothelial dysfunction			
Endothelin, fmol/ml	2,90±3,53	2,86±3,50	2,94±3,56
Lipide profile			
TC, mmol/L	5,02±1,33	4,83±-1,20	5,20±1,45*
LDL cholesterol , mmol/L	3,14±1,23	2,99±1,05	3,28±1,40*
HDL cholesterol, mmol/L	1,00±0,25	0,95±0,20	1,06±0,30*
TG, mmol/L	1,93±1,40	1,93±1,25	1,93±1,54

* differences between male and female groups, p<0,05

who did not receive statins. Endothelin concentration reduction after statins therapy goes along with the results of the meta-analysis of 155 independent studies demonstrating that statins reduce plasma endothelin levels [11].

In female patients there is no interrelation between statins therapy and endothelin levels. Females underwent the same pharmacological treatment as males in this study. It is possible that difference in statins action is related to hormonal status of patients. Sexual hormons influence endothelin plasma levels: male hormones (testosterone), unlike female hormones, increase endothelin concentration [12]. The results of meta-analysis proved that statins administration accompanied with testosterone levels reduction [13]. It can be explained with the fact that HGM-CoA reductase inhibition with statins causes the decrease of mevalonate concentration that is the precursor of sterols and isoprenoids that are necessary for steroid hormone synthesis including androgens. Thus, the association of statins with lowered endothelin levels in males is possibly linked with indirect action of statins through the reduction of testosterone levels that, in its turn, increases endothelin levels; otherwise, it can be related to the direct effect of statins on vascular endothelium, that causes endothelin levels reduction. We also cannot exclude the possibility of existence of different mechanisms underlying atherosclerosis development in males and females.

It is necessary to identify if endothelin levels reduction has a positive influence on cardiovascular events. Recent meta-analysis demonstrated that lipophilic statins including atorvastatin and simvastatin can reduce the risk of cardiovascular mortality [14], similar conclusion was obtained in large-scale prospective study of Pauriah, et al. [15]. Thus, it is likely that endothelin levels reduction has positive effect on organism in relation to undesirable cardiovascular events.

Conclusion

Statins obviously have endothelium-protective action. Their endothelium-protective effect can be related to gender. Males with CA lesions, unlike female patients, demonstrate negative correlation between statins administration and endothelin levels that indicate endothelial dysfunction. Male patients who took statins had 2 times less endothelin levels comparing with the males who did not receive statins.

Conflict of interest: None declared.

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Safety of chronic heart failure complex therapy: results of randomized crossover study BASTion

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Summary:

Objective

To estimate the safety of complex therapy of patients with chronic heart failure after adding to treatment diuretics with different influence on potassium excretion.

Matherials and methods

19 patients over 18 years with stable chronic heart failure (CHF), II and III NYHA class, were included in randomized crossover study. All patients were administered with standard CHF therapy: β-blocker, angiotensin-converting enzyme (ACE) inhibitor, mineral-corticoid receptor inhibitor and diuretic. Patients' therapy did not change until one month before randomization. After randomization patients were subdivided into two groups: first group (8 persons) started diurethic therapy with furosemide, second one (11 persons) started diuretic therapy with torasemide. Therapy was estimated after one month and patients who took torasemide started to take furosemide fore one more month and vice versa, patients who previously received furasemide changed it to torasemide. All patients received medicines in necessary doses according with their clinical condition.

Results

Average age of patients included in the study was 68,2±9,5 years. 52,6% of patients were males. Average dose of torasemide in the study was 24,5±7,4 mg per week, and average dose of furosemide was 111,6±16,8 mg per week. Used average doses of four-component therapy did not lead to occurrence of hyperkaliemic conditions. Results of 6-minute walk tests revealed improved tolerability of physical exercise after torasemide treatment. Torasemide was better tolerated by patients.

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Conclusion

Lack of reflex tachycardia in response to torasemide therapy allows to recommend it for the majority of patients with CHF especially to the ones with comorbid pathologies.

Keywords

Torasemide, chronic heart failure, hyperkalemia, hypokalemia, 6-minute walk test

Introduction

It is necessary to use obligatory drugs like ACE inhibitors/sartans, beta-blockers, mineralocorticoid receptor antagonists (MCRA) for the treatment of people with chronic heart failure. It is known that ACE inhibitors and MCRA can lead to body retention of the potassium [1, 2]. Awareness of hyperkalemia development in patients is growing due to the fact that the majority of patients is older than 60 years and they can have impaired kidney function. Nevertheless, the results of R. Pisoni [3] demonstrate that hyperkalemia does not develop frequently in patients with chronic kidney disease receiving spironolacton.

The results of the RALES (Randomized Aldactone Evaluation Study) [4] study demonstrate that spironolacton addition to the therapy had advantages over the therapy without spironolacton in patients with heart failure and reduced glomerular filtration rate.

It is necessary to notice that hipokalemia is more frequent that hyperkalemia. For example, G. C. Liamus and colleagues [12] demonstrated that hypokalemia development was 13,5 times more frequent than hyperkalemia.

Often diuretics like torasemide or furosemide are necessary for the treatment of patients with heart failure. Simultaneous treatment with ACE inhibitors/sartans, MCRA and torasemide can cause apprehension of doctors ddue to possible development of hypokalemic conditions.

The objective of our study was to estimate the safety of complex therapy of patients with chronic heart failure after addition of diuretics differently influencing potassium excretion to the treatment.

Materials and methods

19 patients older than 18 years with stable chronic heart failure, NYHA functional classes II or III, were included in open randomized crossover study. All patients received standard chronic heart failure therapy (CHF): beta-blocker, ACE inhibitor, MCRA and diuretic. Patients received this treatment without changes during at least one month before randomization. After randomization patients were splitted into 2 groups: the first group (8 patients) started diuretic therapy from furosemide and the second one (11 persons) started from torasemide. All patients received the drugs in the doses according with their clinical condition.

Exclusion criteria were: clinically significant diseases of liver and kidney (plasma creatinine levels more 221 mmol/L and/or alanine and/or aspartate aminotransferase levels elevation), initial plasma levels of potassium more than 5 mmol/L or less than 3,5 mmol/L, initial plasma levels of sodium less 135 mmol/L. All patients signed informed consent.

Blood samples were taken in the morning on an empty stomach in the beginning of the study and at the end of each period of the study. Each therapeutic period lasted for 4 weeks without washing period between the periods when patients changed drugs.

Changes of potassium and sodium plasma levels were considered as the primary endpoint of the study. Changes of 6-minute walk test results comparing with the initial ones were taken as the secondary endpoint.

To estimate patient's treatment perception we used visual analogue scale (VAS) of general state. In this scale 0 is considered as a "good general state" and 10 as "very bad general state, it can't be worse". Each patient was asked to estimate his general state according with this 10-points scale. Rate between 6 and 10 points was interpreted as a bad general state. This estimation was made after patient's inclusion into the study and after each stage of the study.

To evaluate patient's satisfaction with diuretic therapy we used VAS. In this scale 0 is considered is "absolutely satisfied" and 10 – as "absolutely unsatisfied". So the less was the rate that patient mentioned the more he was satisfied with diuretic therapy. Estimation was performed according with 10-points scale. Rate between 6 and 10 points was considered as low satisfaction with diuretic therapy. Estimation was performed after patient's inclusion into the study and after each stage of the study.

Statistical methods

Computer analysis of the results was performed with SAS software (Statistical Analysis System,

SAS Institute Inc., USA) using parametric and non-parametric algorithms of variance statistics that take into account scales of each characteristic.

For characteristics measured with interval scale we quantified mean value, standard deviation, error of mean, median, interquartile distance, etc. For characteristics measured with nominal scale ("presence/absence') or rank scale we determined the frequency of registration of different ordinal rates of characteristics in percentage.

for analysis of differences between groups measured with interval scale we performed Student's t-test for independent samples according with suitable formulas in three different modifications taking into account the details of statistical distribution of studied characteristics. Significance of intragroup dynamics of these characteristics during the period of treatment was estimated with appropriate criteria for paired measurements.

In case of "binary" characteristics the significance of difference between frequencies of some factor's detection in two compared groups of patients we estimated also using t-test but with arcsin-modification of Fisher.

Paired correlation connections were estimated with linear Pearson's correlation and Spearman's rank correlation coefficients and Tau-b-Kendall's coupling coefficient and Kramer's contingency coefficient, statistical significance of which was estimated with SAS software using appropriate formulas.

Multiple connections between characteristics were modeled using stepped multivariate regression equations, both linear and logistical ones.

Connection between rank and binary characteristics were estimated with contingency tables, and significance of these connections was evaluated by three different modifications of Pearson's x-squared criterion and Fisher's exact test.

Results

Average age of patients included in the study was 68,2±6,5 years. 52,6% of patients were males. Average dose of torasemide in the study was 24,5±7,4 mg/week and furosemide average dose was 111,6±16,8 mg/week.

After furosemide administration sodium plasma levels significantly decreased from 138,42±10,43 mmol/L to 133,21±10,43 mmol/L, so its concentration decreased by 5,21±9,32 mmol/L (p<0,05). Whereas torasemide administration reduced sodium plasma levels from 139,21±2,64 to 136,21±5,46 mmol/L, so they decreased by 3,00±4,73 mmol/L (p<0,05). There were no statistically significant differences between sodium plasma concentrations in patients who took torasemide and furosemide. At the same time patients who were administered with furosemide has reached sodium plasma levels beyond normal concentration of 135 mmol/L.

Table 1. **Initial characteristics of patients**

Characteristic	Value
Number of patients	19
Gender, number of patients: m f	10 9
Age, years	68,3±9,6
Body mass, kg	84,1±13,0
Body mass index	29,5±4,6
History of diabetes, number of patients	10
History of myocardial infarction	9

Table 2. **Initial characteristics of patients in groups receiving different treatment**

Characteristic	"Torasemide" group	"Furosemide" group
Number of patients	11	8
Gender, number of patients: m f	6 5	4 4
Age, years	67,4±9,0	69,5±10,8
Sodium levels, mmol/L,	139,21±2,64	138,42±2,41
Potassium levels, mmol/L	4,43±0,50	4,51±0,44
6-minute walk test, m	261,1±49,3	290,8±43,4*

* p<0,01 in comparison of torasemide and furosemide groups.

During furosemide treatment potassium plasma levels decreased from 4,51±0,44 mmol/L to 4,43±0,45 mmol/L, so its concentration decreased by 0,08±0,49 mmol/L. Torasemide administration resulted in potassium plasma levels increase from 4,43±0,50 mmol/L to 4,51±0,43 mmol/L, so its concentration increased by 0,08±0,33 mmol/L.

Glomerular filtration rate quantified using MDRD formula changed from 75,6±15,2 to 79,9±17,1 mL/min in patients who received torasemide, so it increased by 4,3±11,2 mL/min. Glomerular filtration rate in patients who were taking furosemide changed from 75,9±15,2 to 80,2±17,1 mL/min, so it increased by 4,3±11,2 mL/min.

Results of 6-minutes walk test demonstrated that patients who received torasemide increased the distance of walk by 35,6±24,9 m (13,6%, p<0,001). Patients who took furosemide decreased their distance by 3,1±31,0 m (1,1%).

There was no significant difference in number of patients who passed the distance more than 300m before the beginning of study. But the number of patients who walked more than 300m in the group who received torasemide increased significantly,

and it was not detected in the group of patients who received furosemide.

One important aspect of therapy is its perception by patient. Torasemide treatment resulted in significant improvement of patients' general state by 21,4% (p<0,001), and furosemide treatment has not led to its significant change. More than that, there was a tendency to the worsening of general state by 11,3% in the group of patients who received furosemide.

General state estimated by patient with the rate of 6 and higher was interpreted as bad general state. After torasemide treatment the number of patients with bad general state lowered from 36,8% to 5.3% (p<0,01). furosemide treatment results were opposite: the number of patients with bad general state increased from 15,8% to 36,8%. Before the start of the therapy there was no significant difference between the number of patients with bad general state. Estimation of results after therapy revealed that number of patients with bad general state between the ones who received torasemide was significantly lower (p<0,01).

Changes of patient's satisfaction with diuretic therapy coincided with patients' general state dynamic. Torasemide administration resulted in significant increase of patient's satisfaction with diuretic therapy by 29,6% (p<0,01). There were no significant changes in it after furosemide treatment. More than that, there was a tendency of the lowering of patient's satisfaction with diuretic therapy by 15,1%.

Rate of 6 points and higher was considered as low satisfaction with diuretic therapy. After torasemide treatment the number of patients with lowered satisfaction with therapy decreased from 31,6% to 10,5% (p<0,05). There were no changes of patient's satisfaction with diuretic therapy after furosemide administration.

In our study we estimated the influence of therapy on different clinical characteristics. So, systolic blood pressure (SBP) has lowered by 7,4±6,9 mm Hg. (5,5%, p<0,001) after torasemide treatment. After furosemide treatment SBP has lowered by 2,6±9,9 mm Hg. (2,0%). Diastolic blood pressure (DBP) has decreased by 5,4±6,6 mm Hg. after torasemide treatment. (6,8%, p<0,01). DBP has decreased by 0,2±9,0 mm Hg. (0,3%) after furosemide treatment.

It is interesting to notice the fact that the heart rate (HR) during torasemide treatment has lowered by 3,7±4,5 beats per minute (5,3%, p<0,01). During furosemide treatment HR has increased by 4,3±4,9 beats per minute (6,3%, p<0,01). There was no difference between HR of two groups of patients before treatment. After the end of the therapy the difference between HR in two groups was 6,7±3,5 beats per minute (p<0,001).

Discussion

The results of our work did not reveal hyperkalemic conditions. Thus, short-term treatment around 2 months from the start of CHF treatment is unlikely to result in development of hyperkalemia. But one recent study revealed the development of hyperkalemic condition in clinical practice with the incidence of 0,92-7,93 episodes for each 100 person-years [8]. It is necessary to take into account that the average age of patients in this study was 75 years. The highest frequency of hyperkalemia was present in elderly patients with diabetes mellitus and kidney diseases. Average age of patients in our study was less.

Another recently finished study [9] revealed 4.3% of hyperkalemic events in patients receiving contemporary CHF therapy.

Thus the risks of hyperkalemia development are possible. Because of this it is necessary to control potassium plasma levels before the start of therapy, and 1 and 3 months after the beginning of CHF therapy.

Addition of diuretics to the complex therapy of patients with CHF aims to stabilize the balance of water and salts. Prevention of exacerbations and admission to hospital depends mostly on the stability of this parameter.

Our results demonstrate the reduction of sodium plasma levels lower than 135 mmol/L during furosemide treatment that can be considered as an unfavorable factor. Taking into account the fact that torasemide did not lead to the decrease of sodium plasma concentration, it can be considered as an advantage of torasemide over furosemide in outpatients with CHF.

Dynamics of potassium plasma levels during furosemide an torasemide treatment had different directions: its increase by 0,08 mmol/L for furosemide and its decrease by 0,08 mmol/L for torasemide. In both cases these changes were insignificant. Cosin J. and coauthors [10] demonstrated that the necessity of hypokalemic conditions correction was significantly less during torasemide therapy comparing with furosemide.

Taking into account all above-mentioned factors, furosemide therapy in outpatients requires additional control of blood electrolytes, that not only creates additional burden for doctors and hospitals but brings also economical problems for healthcare system in general.

Electrolyte abnormalities can lead to impaired cardiac rhythm. The work of Shugushev [11] demonstrated that patients with CHF who took

torasemide had less ventricular heart rhythm abnormalities comparing with patients receiving furosemide. Probably it is related to lower potassium excretion from human organism during torasemide treatment comparing with furosemide.

Glomerular filtration rate increase during the treatment with both diuretics can be considered as a good tendency.

Significant increase of 6-minute walk distance was detected only in patients who received torasemide. These data go along with the results of V.Yu. Mareev [5] study in hospital patients with CHF and the TRIOLYA study of professor F.T.Ageev in outpatients [6].

More significant decrease of SBP and DBP during torasemide treatment allows to think about torasemide prescription to the patients who require more strict control of BP, for example it can be recommended to the patients with concomitant diabetes mellitus.

Heart rate reduction during complex therapy including torasemide as a diuretic demonstrates lack of sympathetic nervous system activation. It was also proved in the study of K. Harada [7]. Thus it can be considered as an additional advantage of torasemide inclusion into complex therapeutic algorithms of comorbid patients.

Conclusion

Four-component therapy of patients with chronic heart failure, NYHA functional classes II or III, consisted of beta-blocker, ACE inhibitor, spironolactone in 25 mg dose and diuretic did not cause significant increase of potassium plasma levels. Hyperkalemic conditions have not been registered.

The results of 6-minute walk test have significantly improved after torasemide treatment and have not changed after furosemide administration. Torasemide was better tolerated by patients.

Lack of reflex tachycardia development during torasemide therapy allows to recommend it to the majority of CHF patients, particularly to the ones with comorbid pathologies.

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Journal of the Cardioprogress Foundation

Short review of new clinical guidelines: report from the European Society of Cardiology Congress 2016

Annual congress of the European Society of Cardiology was successfully held in Rome, Italy, on August 27-31, 2016. It is the biggest international cardiologic scientific event that involved more than 30000 specialists from 106 countries.

At the opening ceremony the Chairman of the program committee, professor Geneviève Derumeaux cheered participants and said: "We warmly welcome everybody at the European Society of Cardiology Congress 2016, which is held in eternal city Rome for a first time. I think that this event can be described with the words of a great Italian director Federico Fellini: "There is no end. There is no beginning. There is only the infinite passion of life"".

The scale of the Congress' scientific program is impressive. It included more than 500 sessions in 150 different fields. More than 11000 abstracts were received and 4594 of them were selected for publication. Apart of them this Congress presented:

- 28 clinical trials "Hot Line"
- 26 updated clinical trials
- Results of 24 international and national registers

One of the main events of the Congress was, undoubtedly, the visit of Pope Francis. During his welcoming speech the Pontifex Maximus applied to the President of the European Society of Cardiology and the Congress' participants and said: "You are responsible for good cardiac performance. How many symbols are hidden in this word! How many hopes are there inside this human organ! You hold in your hands the beating nucleus of human body, and because of it your responsibility is very high. I am sure that you, standing in front of this book of life, will open many pages. With these feelings I show my gratitude for your work. I ask God to bless your investigations and medical help, so everybody would be able to receive the relief from sufferings, life of high quality and growing feeling of hope".

Traditionally there was the workbench of the Russian Society of Cardiology at the exhibition of the European Congress. More than 300 delegates from different regions of Russia took part in the Congress. The works of Russian scientists and young specialists were made in the form of oral and poster presentations. This year our scientists also participated as workshops' chairmen.

New clinical guidelines of the European Society of Cardiology

Five new documents were released during the European Society of Cardiology Congress: guidelines for dyslipidaemia management, atrial fibrillation (AF) management, acute and chronic heart failure diagnostics and treatment, cardiovascular disease prevention in clinical practice and consensus document dedicated to cardiovascular toxicity in cancer treatment. ,

Guidelines for dyslipidaemia management issued by the European Society of Cardiology and European Atherosclerosis Society indicate the necessity of blood lipids levels reduction both in general population and in patients with high risk. It is recommended to prescribe combined therapy including statin and ezetimibe in patients with persistent hypercholesterolemia. Unlike the corresponding guidelines of American societies, according with which statins are recommended

for all the groups of patients with high risk even in case of low cholesterol levels without mentioning aims, updated European document advices target levels of low density lipid (LDL) levels depending on the presence of comorbid pathology and 10-years risk of fatal cardiovascular diseases. It is necessary to reach at least 50% reduction of LDL levels in all cardiovascular risk patients. LDL target levels in patients with high risk is less than 2,6 mM and in patients with very high cardiovascular risk – less than 1,8 mM in case of initial LDL levels around 1,8-3,5 mM.

Special section is dedicated to hypertriglyceridemia treatment.

This guidelines for the first time discuss the use of PSK9 inhibitors: their prescription can be considered in case of persistent high LDL levels during the combined therapy with statin and ezetimibe. It is pointed out that PSK9 inhibitors can be highly effective in the patients with severe familial hypercholesterolaemia. On the other side, high cost of the therapy can restrict the use of this class of drugs in several countries.

This document reviews more precisely the problem of lifestyle change. It includes detailed recommendation in relation to preferable food and the products that should be consumed in moderate or restricted amount.

One more innovation of these guidelines is related to the statement that it is not necessary to determine fasting levels of cholesterol since the results of several studies identified the same levels of lipids after blood tests made on an empty stomach and after food consumption.

Fourteen sections describe the treatment of dyslipidaemia in different clinical situations (familial dyslipidaemia, in children, in females, in elderly people, in diabetes mellitus, in patients with coronary heart disease, after stroke, etc).

The European Society of Cardiology and the European Hearth Rhythm Association **guidelines for the management of atrial fibrillation (AF)** approved by the European Stroke Organization include several new points. They highlight the important role of early detection of asymptomatic AF. It is necessary to perform purposeful electrocardiographic screening for AF diagnostics in all patients older than 65 years or patients who survived stroke/transitory ischemic attack. Anticoagulant therapy should be considered for males with AF and 1 point and females with 2 points of CHA_2DS_2-VASc score, taking into account individual features and preferences of patients. Males with with AF and 2 points and females with 3 points of CHA_2DS_2-VASc score are recommended to receive anticoagulants, particularly, new oral anticoagulants should be the first-line therapy in appropriate patients due to higher safety of these drugs. Moderate/severe mitral stenosis, mechanical heart valves, severe chronic kidney dsease are indications for vitamin K antagonists. Aspirin and other antiplatelet drugs are not recommended for stroke prevention. Bleeding and stroke risk factors in patients with AF overlap, and patients with high risk of bleeding, are likely to have an advantage receiving anticoagulants. System of bleeding risk estimation is not more recommended, and there is a list of modifying risk factors requiring correction to reduce the risk of bleeding.

Strategy for the management of bleeding during anticoagulant therapy is described, it included the question of therapy renewal after bleeding., ischemic stroke or intracranial hemorrhage.

Catheter ablation is recognized as alternative to antiarrhythmic drugs for maintaining sinus rhythm in patients with symptomatic relapses of paroxysmal or persistent AF during pharmacological therapy. Isolation of pulmonary vein ostium is preferable, and extended treatment is recommended as a reserve therapy for patients with recurrent AF.

European Society of Cardiology **guidelines for diagnostics and treatment of chronic heart failure (CHF)** contain new algorithm of CHF diagnostics based on clinical probability of disease (disease history, physical examination, electrocardiography in rest), circulation natriuretic peptids levels and transthoracic echocardiography. New text of the guidelines left ventricle (LV) ejection fraction (EF) less than 40% is considered reduced, 50% and more – preserved, and LV EF in the range of 40-49% is called mid-range.

Treatment of arterial hypetension, administration of statins in case of high risk of coronary heart disease development, angiotensin-converting enzyme inhibitors in case of LV symptomatic disfunction and beta-blockers in case of asymptomatic LV dysfunction and history of myocardial infarction are recommended for CHF prevention.

Sacubitril/valsartan (LCZ696) inhibitor of angiotensin and neprilysin receptors is proposed for the treatment of CHF that demonstrated better results than analapril in mortality risk and hospitalization reduction in patients with CHF with reduced LV EF in the PARADIGM-HF study. It led to the change of CHF

with reduced LV EF management algorithm. At the same time the principles of CHF with LV EF less than 50% treatment that would allow to reduce patients' mortality are still not elaborated.

In the new document implantation of three-chamber cardiac pacemaker. for resynchronization therapy of symptomatic CHF with LV EF less than 35% is contraindicated for patients with QRS duration less than 130 ms.

In case of acute heart failure it is recommended to define immediately the presence of life-threatening clinical conditions and/or provoking factors according with CHAMP abbreviation (acute coronary syndrome, hypertonic crisis, arrhythmia, acute mechanic cause, acute pulmonary embolism) and to perform task-oriented therapy according with the current Guideline. During early stage of acute heart failure it is advised to use the algorithm based on patient's clinical profile, estimating presence of blood congestion and peripheral hypoperfusion.

New quidelines for cardiovascular disease prevention in clinical practice were prepared by the experts of the European Society of Cardiology and European Association of Cardiovascular Prevention and Rehabilitation. Their new chapter is dedicated to the population approach to cardiovascular disease prevention including the measures to popularize healthy life style in all population (healthy food, sufficient physical activity, smoking cessation by economic incentives, prohibition, etc). Population strategy of cardiovascular disease prevention completes the acting principle of "high risk" correction in chosen individuals.

There are recommendations of general risk estimation and a short discussion of the most important cardiovascular disease development risk factors. The main part of these guidelines is dedicated to the ways to modify main risk factors of cardiovascular disease development: arterial hypertension, dyslipidaemia and dysglicemia. New sections are dedicated to the prevention of cardiovascular disease development in particular groups of people: women, young and elderly, ethnic minorities and patients receiving anticancer treatment. This guideline includes key recommendations for prevention of complications in particular clinical situations: heart failure, atrial fibrillation, coronary heart disease and peripheral artery disease.

There is a table in the end of the document that concludes all the main positions of new Guidelines that can improve cardiovascular disease prevention.

Consesus document dedicated to the cardiovascular toxicity in cancer treatment was developed by the expert committee of the European Society of Cardiology. New document covers all aspects of cardiovascular toxicity related to anticancer in conditions of not sufficient amount of data obtained from randomized trials.

The authors concentrate their attention on 9 cathegories of complication in cardiooncology: myocardial dysfunction and heart failure, coronary heart disease, valve pathology, cardiac arrhythmias, arterial hypertension, thromboembolic complications, peripheral artery disease and stroke, pulmonary hypertension, pericarditis, pleuritis and autonomic dysfunction. Vascular spasm, endothelial damage, thrombosis, prolongation of QT interval play the leading role in development of cardiovascular complications in chemotherapy or radiotherapy of cancer.

The major part of the document is dedicated to myocardial dysfunction and heart failure as the consequence of chemotherapy, particularly after anthracycline administration that is accompanied with LV dysfunction averagely in 50% of cases. The time of this drug manifestation varies from the administration of the first dose to several years after chemotherapy. Children survived after cancer treatment with anthracycline and/or mediastinal radiotherapy have 15-fold increased risk of heart failure and reduced life-span. Apart of accumulated anthracycline dose, other risk factors include female gender, kidney failure, other cardiotoxic pharmacological therapy and radiotherapy, concomitant cardiovascular diseases. Cardiotoxicity is considered in case of more than 10% reduction of LV ejection fraction and more than 15% relative change of global longitudinal deformation comparing with its initial levels. It is recommended to correct existing cardiovascular risk factors before the start of therapy and to administer angiotensin-converting enzyme inhibitors and/or beta-blockers soon after cardiac dysfunction is detected.

More detailed information about scientific materials of the European Society of Cardiology Congress 2016 is available on the website www.escardio.org, and full version of clinical guidelines can be found on the page www.escardio.org/guidelines.

The next congress of the European Society of Cardiology will take place in Barcelona on August 26-30, 2017.

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Journal of the Cardioprogress Foundation

Russian National Congress of Cardiology 2016: main results

Annual Russian National Congress of Cardiology was successfully held in Ekaterinburg, Russia, on September 20-23, 2016. The fact that the Congress took part in the capital of the Urals reflects active involvement of regions, one of the main principles of Russian Society of Cardiology (RSC) development. This event was organized by the Ministry of Healthcare of the Russian Federation, Russian society of Cardiology and the government of Sverdlovsk region.

According with the information provided by the Organizing Committee, more than 5000 participants from more than 150 cities of Russsia and 20 countries. During the last day registered participants of the Congress received the certificate of the Ministry of Healthcare with 24 credits of continuous postgraduate education.

E.V. Kuivashev, the governor of Sverdlovsk region, greeted the participants of the National Congress at the Opening ceremony that was held in the Ekaterinburg Opera and Ballet Theatre. This ceremony was highlighted with presentations of the Russian Society of Cardiology president and the member of the Russian Academy of Sciences E.V. Shlyakhto and the European Society of Cardiology ex-president Fausto Pinto.

Scientific program included 169 meetings with participation of lectors from Russia and 17 other countries (featuring Robert Hendel (American College of Cardiology, USA), John Cleland, USA, Thomas Luscher, editor of the European Heart Journal, Switzerland), 3 poster sessions and 2 plenary meetings. Scientific program has covered a wide spectrum of topics varying from epidemiology and diagnostic techniques to the treatment and rehabilitation of patients with cardiovascular diseases. Organizing committee paid particular attention to young scientists. This year RSC allocated 89 grants for participation of young doctors. "The battle of erudite persons" was traditionally held during the Congress. Applications of 50 teams from different regions were received this year. Winner team should have demonstrated not only the knowledge of theory, but also the capability to solve peculiar clinical cases. The winner team received the grant to go to the European Congress of Cardiology.

56 pharmaceutical companies, manufacturers of medical devices and medical publishers and public organizations took part in Forum exhibition.

Social action "March of healthy hearts" with the motto "Movement is life" was organized during the Congress and it involved around 2000 people. Medical persons, students, sportsmen, journalists of regional and federal mass-media walked through the central streets of the Ural's capital.

The photography exhibition "Women of Russia say "Yes" to healthy heart" was held in Ekaterinburg EXPO during the Congress. Many Russian public figures wearing red dresses took part in this project together with cardiologists. Red dress is the symbol of this project that embodies anxiety due to increased number of people with cardiovascular diseases in Russia and in the world.

The questions of RSC development strategies for 2016-2018 and the role of the Society in a new system of medical postgraduate education were discussed during the plenary meeting. Other topics of

this discussion included the ideas about section and working group and also the program of integration of RSC sections into working groups of the European Society of Cardiology associations. Another important problem on the agenda of the meeting was the question of RSC directory group formation dedicated to creation of clinical recommendations and algorithms.

"Cardioprogress" Foundation was present at poster session, round-table discussion and oral presentation. Forthcoming scientific and practical events (VI Caucasus Scientific and Educational Conference of Cardiology and Internal Medicine, VI International Forum of Cardiology and Internal Medicine) were announced at our workbench. We presented Russian and English versions of 10th issue of the International Heart and Vascular Disease Journal and "Cardioprogress" brochures with the comments on new European clinical guidelines.

Next Russian National Congress of Cardiology will be held in Sankt Petersburg in September, 2017. Congress materials can be found on the official RSC website www.scardio.ru.

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Guidelines for authors

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1.14. The Editors recommend that submitted manuscripts conform with the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), and available on the **International Heart and Vascular Disease Journal** website www.cardioprogress.ru, in the 'For Authors' section.

1.15. Adhering to the standards outlined in this document will lead to faster reviewing, editing, and publishing of manuscripts accepted for publication. Manuscripts submitted outside the standards on design and formatting for this journal may not be accepted by the Editors.

2. General recommendations for submission of original scientific works

2.1. The Editors recommend that results of randomized controlled trials conform to the 'Consolidated Standards of Reporting Trials' (CONSORT) guidelines. Information on these standards are available on the CONSORT website: www.consort-statement.org

2.2. A manuscript should be typed using the Times New Roman font (12 points, double spacing; with 2 cm at the top, bottom, left and right margins). The length of a manuscript, including references, schedules, drawings and tables, should not exceed 12 standard typewritten pages (1 page is 1800 letters or symbols, including spaces). A case study should not exceed 6 standard pages. Reviews and lectures should not exceed 25 standard pages.

2.3. Manuscripts should be organized as follows: 1) title page; 2) structured summary and keywords; 3) list of abbreviations; 4) text; 5) acknowledgements (if applicable); 6) references; 7) names and legends of pictures, tables, graphics, and photocopies in the order they appear in the manuscript; 8) drawings, tables, graphics, and photocopies should be submitted on separate pages in the order they appear in the manuscript. Numeration of pages should begin from the title page.

2.4. If the manuscript contains pictures, tables, graphics, or photocopies that have been published previously, reference to the author(s) and publication is necessary. It is the Author's responsibility for determining whether permission is required for the duplication of material, and for obtaining relevant permission.

2.5. Manuscripts based on reviews of original research works should contain the following sections: Introduction (reflecting the urgency of a problem and research goals); Material and methods; Results; Discussion of the obtained results and Conclusion. The text should be clear, brief and without repetition.

3. Publication of uncontrolled trials results

3.1. An uncontrolled trial is a research without a control group.

3.2. Manuscripts based on uncontrolled trials results will be accepted for publication in the 'Practical Experience' column only if the uncontrolled design of the study is described in the Material and methods and Discussion sections. It is important not to exaggerate the significance of results in the Conclusion' section.

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of "good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notifica-

tion that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

4.2. Patients have the right to privacy and confidentiality of their personal data. Therefore, information containing pictures, names, and initials of patients or numbers of medical documents should not be presented in the materials. If such information is needed for scientific purposes, it is necessary to get written informed consent from the research participant (or their parent, their trustee, or a close relative, as applicable) prior to publication in print or electronically. Copies of written consent may be requested by the Editors.

4.3. Animal trials must conform to the 'International Guiding Principles for Biomedical Research Involving Animals', adopted by the *Council for International Organizations of Medical Sciences* (CIOMS) in 1985.

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5.2. If more than 4 authors are indicated in the author's list, it is desirable to describe the contribution of each author in a covering letter. If the authorship is attributed to a group of authors, all members of the group must meet all criteria for authorship. For economy of space, members of the group may be listed in a separate column at the end of the manuscript. Authors can participate in the submitted manuscript in the following ways: 1) contributing to the concept and research design or analyzing and interpreting data; 2) substantiating the manuscript or checking the intellectual content; 3) providing final approval for the manuscript. Participation solely in collection of data does not justify authorship (such participation should be noted in the Acknowledgements section). Manuscripts should be submitted with a covering letter containing the following information: 1) the manuscript has not been submitted to any other media; 2) the manuscript has not been published previously; 3) all authors have read and approved the manuscript's content; 4) the manuscript contains full disclosure of any conflict of interests; 5) the author/authors confirm responsibility for the reliability of the materials presented in the manuscript. The author responsible for the correspondence should be specified in the covering letter.

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7. Manuscript content

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7.1.2. A short title of the article (limited to 45 letters or symbols).

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Periodicals

Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.

Sources in Russian with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabel'nosti serdechnogo ritma pri ispol'zovanii razlichnyh jelektrokardiograficheskih sistem (metodicheskie rekomendacii) [Analysis of heart rate variability using different ECG systems (guidelines)]. Vestnik aritmologii. 2002;24:65-86. Russian.

Please provide initials after the last names of authors. Last names of foreign authors are given in the original transcription. Names of periodicals can be abbreviated. Usually such abbreviations are accepted by the Editors of those

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Chapters in a book

Swanton RH, Banerjee S. Cardiac Failure. In: Swanton RH, Banerjee S., editors. Swanton's Cardiology: A concise guide to clinical practice. 6th ed. Oxford: Blackwell Publishing; 2008. p. 255-309.

Sources in Russian with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In.: Chazov EI, Belenkov YuN., editors. Racional'naja farmakoterapija serdechno-sosudistyh zabolevanij: Rukovodstvo dlja praktikujushhih vrachej [Rationale for drug therapy of cardiovascular diseases: A guide for medical practitioners]. Moscow: Litterra; 2006. p. 431-452. Russian.

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Books

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Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial'naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatel'stvo; 2008. Russian.

Websites

Websites should be provided in the list of references, but not in the text. References to websites should be made only when original text is not available. References should be provided in the following way:

WHO. Severe Acute Respiratory Syndrome (SARS) [Internet]. [place unknown: publisher unknown]; [updated 2010 June 1; cited 2010 June 10]. Available from: http://www.who.int/csr/sars/.

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