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New opportunities for cardiovascular risk reduction

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Summary
Combined antihypertensive therapies, especially fixed-dosed, have become a major approach in the management of arterial hypertension. angiotensin-converting enzyme (ACE) inhibitor/calcium antagonist combination is among the most effective ones. Statin group drugs involvement into this combination is advisable since almost 70 % of patients have increased serum cholesterol levels . Creation of polypill, fixed combination of 3 and more drugs impacting various risk factors of cardiovascular pathology, is widely discussed last years. fixed combination of Lisinopril (ACE inhibitor), Amlodipin (calcium antagonist) and Rosuvastatin (a hypolipidemic drug from statin group) can be considered as a polypill. It is expected that application of such polypill should increase patient compliance and accordingly improve therapy efficiency in patients with high cardiovascular risk.

Keywords
Arterial hypertension, angiotensin-converting enzyme inhibitors

Risk factors (RF) of cardiovascular disease (CVD) have been well investigated for a long time: first of all it is worth to mention arterial hypertension (AH), dislipidemia and smoking. It has been proved that reducing cardiovascular risk (CVR) factors leads to decrease of cardiovascular disease rate and mortality, unfortunately frequency of drug administration, therapy efficacy and patients' compliance in groups of high and very high CVD remains low. In Russia approximately 40% of adult males suffer from AH, half of them have dislipidemia, more than 60% of males are smokers [1].

At the same time poor patient compliance remains a major health problem [2]. What should be done? In 2003 the strategy of fixed-dose combination drug (Polypill) consisted of antiplatelet drug, statin and an-

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tihypertensive drug had been proposed by N.J. Wald and M.R. Low [3]. Since then the problem of polypill development, ingredients and administration is discussed at international meetings including important ones like annual congress of European Society of Cardiology.

Initially one of polypill's ingredients was folic acid (0.8mg) aimed to reduce such RF as increased homocysteine levels but later folic acid was excluded because of lack of evidence of effective reduction of myocardial infarction and stroke risks [4]. Creators of polypill performed meta-analysis of 15 major clinical trials and found out that polypill administration in all patients older than 55 years allows 80% reduction of CVD frequency. After this meta-analysis the strategy of polypill use for primary prevention of cardiovascular disorders started to develop. According with N.J. Wald and M.R. Low administration of polypill to all patients of the age of 55–64 (independently of RF presence) would protect them from coronary heart disease (CHD) and stroke development during next 10–12 years [3]. Simultaneous reduction of LDL cholesterol levels of 1.8 mM and diastolic BP of 11 mmHg would result in 88% reduction of CHD risk and 80% reduction of stroke risk. These authors consider that the frequency of adverse effects would not exceed 8–15% with necessity of drug withdrawal in 1–2% of cases.

Polypill efficacy depends on initial CVR level. In patients with high level of CVR polypill containing 4 drugs (antiplatelet drug, statin, hydrochlorothiazide, ACE inhibitor) would reduce CHD and stroke development risk by 62% and 60% respectively. At the same time polypill administration in patients with low CVR would result in 44% and 21% reduction of CHD and stroke development risk respectively.

Later in USA it has been demonstrated that wide application of polypills would allow to prevent CHD development in 2 mln people and stroke occurance in 1 mln people for 10 years. According with the authors of meta-analysis polypills usage has distinct economical advantages. It is known that long-term therapy with fixed-dose combinations of antihypertensive drugs increases patient adherence up to 21% comparing with free drug combinations.

Opponents of polypill strategy believe that polypill containing fixed doses of drugs would not allow to reach target levels of LDL, HDL and blood pressure. But it is worth to mention that even 1 mM reduction of LDL cholesterol levels can help to reduce CHD and stroke risk by 40% and 10% respectively, and 10 mmHg reduction of diastolic blood pressure would decrease risk of CHD and stroke by 40% and 60% respectively.

Later clinical researchers started to investigate the use of polypill not only for primary prevention (in patients with various cardiovascular risk) but also for secondary prevention (after myocardial infarction). Polypill components varied in different groups of patients. For example it has been proposed to use polypills containing not only statin and antiplatelet drug but also beta blockers and ACE inhibitors in patients with myocardial infarction because use of three or four drugs significantly increased survival rate comparing with the group of patients after MI who used to receive one or two drugs [5].

According with evaluations made by Word Health Organization combined administration of aspirin, two antihypertensive drugs and one statin to patients with CVR would allow twofold reduction of mortality rate and it would increase the expected lifespan by 2 years. Program of Polypill estimation as a strategy for secondary prevention has been already developed in European Union. Realization of FOCUS project (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) has started in five countries including Argentina, France, Italy, Spain and Switzerland. First stage of this study (FOCUS-1) aimed to investigate adherence of patients receiving standard free drug combinations (separately given drugs). Second stage of this study (FOCUS -2) estimated patient adherence and drug safety in approximately 1500 patients who received polypill containing fixed drug combination of aspirin, ramipril (ACE inhibitor) and simvastatin. As it was expected patient adherence to fixed drug combination was significantly higher comparing with free drug combinations (68% versus 58% respectively, $p<0.049$) [6].

According with TIPS (The Indian Polycap Study) trial polypill costs in developing countries can be reduced up to 20 cents/day (for comparison, in developed countries polypill value is estimated as 1 USD/day) [7]. This value can be achieved with the use of generic drugs, cheap packing, distributor and marketing costs and also with reducing the number of medical appointments and laboratory tests [8–10].

During last decades administration of fixed drug combinations (for example renin-angiotensin system blockers together with thiazide diuretic or calcium channel blockers) for treatment of arterial hypertensia has become common. What is the difference between polypill and usual fixed drug combination

for AH treatment? Majority of antihypertensive drugs contain two active components, whereas polypill should be made from 3 or more drugs. Combination of reserpine, hydralazine, hydrochlorthiazide, metil-ergocristine and potassium chloride can be considered as polypill and it has been used in clinical practice. Nowadays this medication is supposed to be outmoded although in past it has played a certain role in AH treatment.

It is worth to mention that the high occurrence of comorbidity requires creation and usage of polypills, that can contain statins, antiplatelet drugs in addition to effective AH medications. And instead of receiving 3–4 drugs with complicated dosage schedule patient could take one pill for a day. It is expected that polypill usage would allow to solve the problem of patient compliance to therapy.

It is also important to use generic drugs instead of original substances in polypill composition since it would reduce polypill cost and would make it affordable for all segments of society. It is possible to create polypills for coronary heart disease treatment (consisting of aspirin, statin, beta bloker and amlodipine), chronic kidney disease (renin-angiotensin system blockers, statin and antianemic drug), type 2 diabetes mellitus (renin-angiotensin system blockers, indapamide, statin, aspirin and metformin).

Existing connection between AH and dyslipidemia requires simultaneous targeting of both these risk factors. Unfortunately it is not always possible to reduce these risk factors just with the change of lifestyle and it makes the use of medications with proved efficacy in CVD prevention necessary especially knowing that for a lot of patients it can be tough to drastically change diet, to increase physical activity and to refuse smoking. [11].

Fixed drug has been used for secondary prevention of CVD in patients with arterial hypertension and associated hyperlipidemia in Russia and other countries. This drug was created as the realization of an idea of multifactorial prevention - simultaneous targeting several risk factors as the most effective prevention strategy. Efficacy of simultaneous blood pressure (BP) and dyslipidemia targeting has been proved in ASSCOT-LL trial (Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering): administration of 10 mg of atorvastatin together with antihypertensive therapy resulted in additional reducing of total risk of non-fatal myocardial infarction and death from coronary heart disease by 36% and reducing of risk of all cardiovascular complications by 29% [12]. It has been also proved that addition of statin to antihypertensive therapy increases its efficacy [13]. So amlodipine addition to combination of amlodipine and atorvastatin was a good decision, because amlodipine is one of the most effective and well-studied from evidence-based medicine point of view dihydropyridine calcium channel blockers. Amlodipine belongs to III generation of calcium channel blockers, it has the biggest half-life period between all other calcium antagonists (CA) (35-52 h), gradual increase and decrease of plasma concentraton, high antihypertensive efficacy, proved antiischemic and antiatherogenic effect [14, 15]. Both AH and coronary heart disease are indications for amlodipine administration. Amlodipine is one of few CA that are allowed to use in chronic heart failure as antihypertensive or antiischemic drug because it has no negative inotropic effect. Some clinical trials like ASCOT, ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) that investigated efficacy of ACE inhibitors and CA combinations typically used amlodipine. Both trials proved not only efficacy of this combination in BP lowering, but also its influence on frequency of cardiovascular complications in patients with AH. Majority of them had such associated pathologies like coronary heart disease, diabetes mellitus, obesity, so these patients belonged to the group of high cardiovascular risk, In ACCOMPLISH trial patients with the same control level of BP receiving ACE inhibitors and CA amlodipine had 20% lower risk of cardiovascular complications comparing with the group receiving ACE inhibitors and diuretic. Figuratively speaking, it was a competition between amlodipine and thiazide diuretic in which amlodipine has won.

ASCOT and ACCOPLISH trial allowed to conclude that ACE inhibitors and dihydropyridine CA combination is highly effective. After it pharmaceutic companies started to create fixed drug combinations of ACE inhibitors and CA, most frequently with amlodipine. One of these highly effective drug combinations. contains combination of amlodipine and ACE inhibitor lisinopril. This substance has its own unique features. This is the only hydrophilic ACE inhibitor that is administered in active drug form unlike other ACE inhibitors (prodrugs) for which the active form is metabolized one. Because of this reason lisinopril activity doesn't depend on lifer function, and it allows lisinopril to be used as drug of choice in patients with fatty hepatosis, liver cirrhosis etc. In other words, lisinopril effect in case of concomitant liver pathol-

ogies is more predictable, this drug doesn't compete with other drugs for microsomal enzymes of liver and pharmacokinetics interaction with other drugs. doesn't occur. Efficacy of lisinopril doesn't change in smoking patients even if it is well known that nicotine is a potent microsomal enzyme inducing agent and it can accelerate biotransformation of some antihypertensive drugs.

Well-known ALLHAT study (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) involved 42 thousands of patients with AH demonstrated that lisinopril not only reduced BP but also reduced the risk of severe complications development, such as death, stroke, MI, new cases of diabetes mellitus and turned out to be more effective to prevent chronic heart failure than amlodipine [18].

During the last years use of combined antihypertensive therapy especially in the form of fixed drug combination has become common, because of its distinct advantages such as increased efficiency and accordingly the possibility to reach target BP levels in majority of patients, reducing of possible adverse effects and generally good tolerance because of lower doses of medicines in fixed drug combination, increase of adherence to therapy because of maximally simplified drug regimen (in ideal situation, one pill for a day). Patients with high and very high additional risk of complications are recommended to use polypills since the beginning of treatment [19, 20]. In general monotherapy is effective not more than in 30% of patients.

Registration of drug containing amlodipine and lisinopril together with rosuvastatin, one of the safest and the most potent statin drug currently, is expected in the close future. Rosuvastatin not only slows down progression of atherosclerosis. Rosuvastatin not only slows down the progression of atherosclerosis (REVERSAL study (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study)) but also causes regression of atherosclerosis (ASTEROID study (A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound - Derived coronary atheroma burden) [21, 22]. It is important to notice that rosuvastatin not only reduces levels of LDL cholesterol to target levels but also increases HDL cholesterol levels by 8–10% [23]. JUPITER (Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin). is one of the most known studies dedicated to rosuvastatin in primary prevention. In this study patients without apparent dyslipidemia but having high level of C-reactive protein (it is included into the list of cardiovascular complications) received rosuvastatin in the dose of 10mg. Five years after the risk of cardiovascular complications, stroke, need of revascularization and, the most important were significantly lower and general mortality reduced by 20%. More than that, reduction of highly sensitive C-reactive protein levels was achieved [24].

Statins are mainly prescribed to patients with dyslipidemia, but it is worth to mention that it is necessary to administer statins to patients without dyslipidemia in case if they have SCORE risk more than 5%. as it is necessary to administer them to patients with CHD. Therefore it would be possible to administer combination of amlodipine, lisinopril and rosuvastatin to the patients with AH and high additional risk of cardiovascular complications independently from basal level of LDL cholesterol. It is important to remember that statins not only drugs eliminating dyslipidemia but mainly drugs used to increase patients' survivability.

Efficacy and safety of lisinopril, amlodipine and rosuvastatin combination have been investigated in ROZALIA study [25]. Lisinopril and amlodipine were administered as a fixed drug combination (dosage 50mg/5mg, 20mg/5mg, 20mg/10mg) and rosuvastatin (10/20mg) was added to this combination. This trial involved 2452 patients with AH stage 1-2, hypercholesterolemia and high (93.2%) or very high (6.8%) cardiovascular risk that was defined according with presence of diabetes mellitus, metabolic syndrome, peripheral artery disease (Figure 1). After 6 months frequency of reaching target BP and LDL cholersterol levels were estimated (Figure 2 and 3 respectively) , including patients for whom it was impossible to perform before. By the end of the study 91% of patients achieved target levels of BP less than 140/90 mm Hg. and 57% of patients had BP less than 130/80 mm Hg. 94% of patients older than 80 years reached target levels of BP (<150/90 mm Hg.) by the end of the study. There were no differences in the efficacy of antihypertensive therapy in groups of patients with diabetes mellitus, metabolic syndrome and peripheral artery disease and the efficacy didn't depend on preceding therapy.

In one month evident dynamics of total cholesterol and LDL cholesterol levels were detected. By the end of the study (in 6 months) changes increased according with rosuvastatin dose titration, in addition to this triglycerides serum levels decreased significantly (23% decrease, $p<0.05$) and HDL cholesterol levers increased (6% increase, $p<0.05$). In the end of

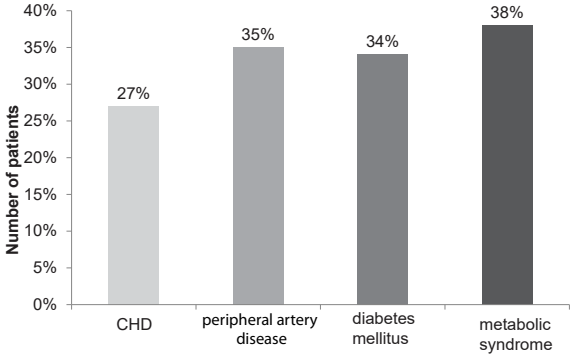

Figure 1. Frequency of concomitant complications in ROZALIA study

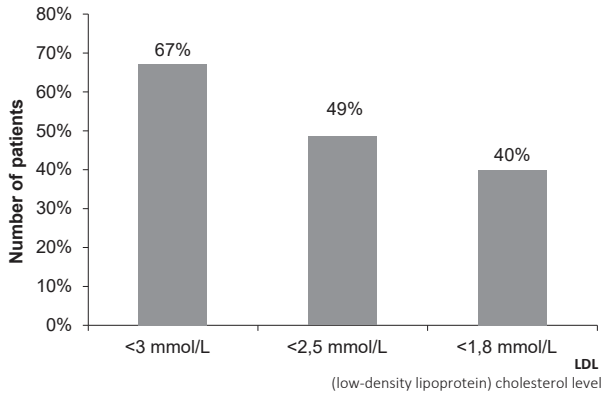

Figure 3. Achievement of target LDL cholesterol levels in the ROZALIA study

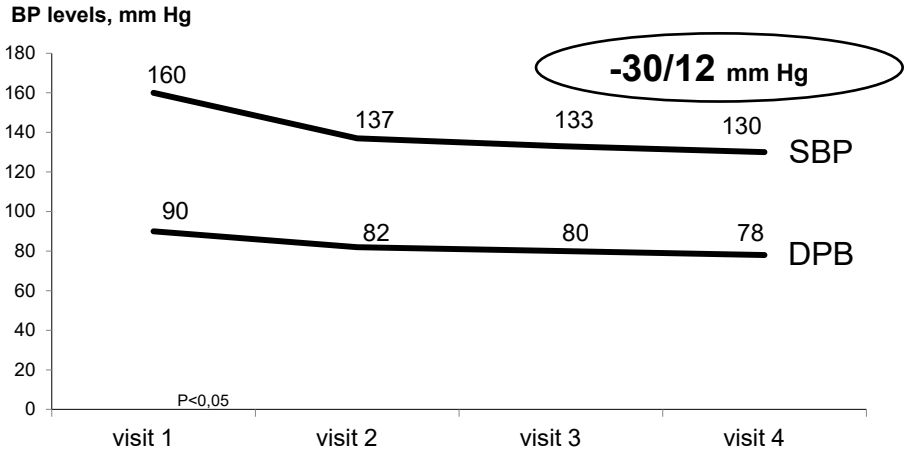

Figure 2. BP dynamics in the ROZALIA trial

the study LDL cholesterol target levels<.3.0 mmol/L, <2.5mmol/L and <1.8 mmol/L were achieved in 67%, 49% and 40% of patients respectively. Efficacy of lipid-correcting therapy didn't change in the groups of patients with diabetes mellitus and metabolic syndrome. It is worth to mention that apparent effect was achieved in 48% of patients who received statins but didn't reach target levels of LDL cholesterol before. In addition, levels of such prognostically important markers like C-reactive protein, uric acid, serum glucose and microalbuminuria were decreased. It is known that combination of ACE inhibitor and dihydropyridine calcium antagonist is able to reduce the frequency of new cases of diabetes mellitus comparing with beta blocker and diuretic combination [16].

Increase of creatine phosphokinase and transaminases levels have been detected in 0.92% and 0.9% of patients, respectively. Majority of patients demonstrated excellent and good tolerability of treatment and observed improvement of life quality. There were no reports about severe adverse effects: dry cough was present in 3.1% of patients, lower leg edema – in 2.2% of patients , muscle pain – in 1.1% of patients. Authors concluded that fixed drug combination of lisinopril and amlodipine together with rosuvastatin is safe and effective for patients with mild and moderate AH, hypercholesterolemia and high/very high CVR.

In Russia the combination of lisinopril/amlodipine together with administration of rosuvastatin was investigated in TRIUMVIRAT study [26–28]. This study pointed out safety and efficacy of fixed combination of amlodipine/lisinopril together with administration of lipid-lowering drug rosuvastatin in patients with uncontrollable AH and hypercholesterolemia in the outpatient setting [28]. This trial involved patients older than 18 years with essential AH both with the new-onset (untreated) AH≥160/100 mm Hg. and with insufficient BP control – BP levels ≥140190 mm Hg. in spite of antihypertensive drug administration including combination of 2 and 3 medicines. Patients involved in this program, received fixed combination amlodipine/lisinopril once per day in the morning in one one of the following doses. Previously untreated patients or patients who received one drug before

were administered with 5/10 mg, patients who previously used to take two or three drugs were administered with 5/20 mg or 10/20 mg respectively. Patients with LDL cholesterol higher than target levels for existing risk degree received also rosuvastatin [29]. Dose of rosuvastatin was chosen according with the target and initial levels of LDL cholesterol. Dose of rosuvastatin varied from 5 mg/day to 40 mg/day in different patients. Rosuvastatin in the dose of 20–40 mg/day reduced LDL cholesterol levels by ⩾ 50%. After three months of treatment target levels of BP (<140/90 mm Hg.) were achieved in 80% of patients. Combined therapy of amlodipine/lisinopril with addition of rosuvastatin not only considerably improved control of BP and lipid levels but also significantly reduced the risk of cardiovascular complications development.

It is well known that in Russia patient adherence to antihypertensive therapy or to statins remains poor. It is reasonable to think that serious simplification of dosage schedule (ideally one pill for a day), reduction of drugs' number and medication's cost due to use of effective generic drugs altogether would help to increase patient adherence.

Clinical practitioners are expecting creation of polypill containing lisinopril, amlodipine, rosuvastatin that are proved to have high efficacy in primary and secondary prevention of cardiovascular disorders and their complications.

Conflict of interest: None declared.

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