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## USAGE OF THE FIXED-DOSES COMBINATIONS FOR DRUG THERAPY OF ARTERIAL HYPERTENSION IN NORTHERN REGIONS OF THE FAR EASTERN FEDERAL DISTRICT

DOI 10.25789/YMJ.2018.64.28

### ABSTRACT

**Aim.** To analyze the usage of the fixed-doses combinations for treatment of arterial hypertension in three northern regions of the Far Eastern Federal District.

**Material and methods.** The pharmacoepidemiological study of realization of antihypertensive drugs in the pharmaceutical organizations of the Magadan region, Kamchatka Krai, the Sakha Republic (Yakutia). The studied period was 2013-2017. Total sales were calculated based on the amount of drugs and defined daily doses, acquired by patients. The range of international nonproprietary names has been divided into therapeutic classes. Further calculation of indicators in group for each combination was carried out. The analysis was performed with usage of Microsoft Office of Excel 2015.

**Results.** In a therapeutic class of combinations  $\beta$ -blockers with diuretics or calcium channel blockers the combination atenolol+chlortalidone remained the leader in three regions. Shares of sales of other international nonproprietary names were insignificant, and did not exceed totally 10%. Valsartan+amlodipin had the greatest indicators of realization in the therapeutic class of angiotensin II antagonists with calcium channel blockers. Among combinations of angiotensin II antagonists and diuretics, the combination of losartan+hydrochlorothiazide had more than a half of the acquired defined daily doses. Since 2017 in the Sakha Republic (Yakutia) were more actively used valsartan+hydrochlorothiazide, azilsartan medoxomil+chlortalidone. In a therapeutic class of angiotensin-converting-enzyme inhibitors with calcium channel blockers in the Magadan region and in the Sakha Republic (Yakutia) the leader of the market was the combination of lisinopril+amlodipine, in Kamchatka Krai - perindopril+amlodipine. Acquisition of the drugs containing ramipril and amlodipine has increased in all three regions. In a therapeutic class of combinations of angiotensin-converting-enzyme inhibitor with diuretics, the redistribution of preferences from drugs containing enalapril+hydrochlorothiazide in favor of perindopril+indapamid was observed. The combinations lisinopril+hydrochlorothiazide had the considerable share of sales in the Sakha Republic (Yakutia). Usage of a combination of hydrochlorothiazide+triamterene and drugs of a reserpine is characteristic of the Magadan region and Kamchatka Krai. In the Sakha Republic (Yakutia), in comparison with other explored regions, triple-component drugs are more actively applied.

**Conclusions.** The greatest part of realization of the defined daily doses of the modern antihypertensive fixed-doses combinations was the share of only seven international nonproprietary names, on condition of presence in the pharmaceutical market of 43 variants. Current situation proves expediency of prescription of the applied schemes of drugs therapy, taking into account the available range of drugs in the pharmaceutical organizations of regions.

**Keywords:** arterial hypertension, fixed-doses combinations, pharmaceutical market, Far Eastern Federal District, defined daily dose, epidemiology.

#### List of reductions:

$\beta$  – AB –  $\beta$ -blockers

AH – arterial hypertension

BP – arterial blood pressure

AC – calcium channel blockers

ARA – angiotensin II antagonists

D – diuretic

FEFD – the Far Eastern Federal District

ACE inhibitor – angiotensin-converting-enzyme inhibitor

INN – international nonproprietary name

FDC – the fixed-dose combination

**Introduction.** The high morbidity of cardiovascular system, risk of development of fatal complications, results of modern randomized studies, data of meta-analyses, registration in the pharmaceutical market of new drugs and improvement of their forms of usage, cause need of systematic revision of the existing recommendations, standards, other regulations regulating approaches of experts to drugs therapy [1]. The Far Eastern Federal District (FEFD) is also characterized by high rates of presence of cardiological pathology among the population. In northern regions heavy climate, low temperatures and small duration of light day complicate the situation. Difficult geographical conditions can negatively influence on epidemiological situation in

districts (figure1) [4].

The main in structure cardiovascular nosologies are circulatory system diseases. Indicators in Kamchatka Krai till 2016 remain higher in comparison with Russian and Far East. The tendency to their decrease can be explained with implementation of federal and regional target programs, medical examination of the population, promoting of a healthy lifestyle, improvement of diagnostics and treatment.

The Arterial Hypertension (AH) is one of the most widespread chronic diseases. Around the world, researches on optimization of therapy are actively conducted [14]. According to the last recommendations of the European Society of Cardiology, the target level of the arterial blood

pressure (BP) has to be reached no later than in 3 months after an initiation of treatment. At the same time less than 50% of the patients receiving antihypertensive therapy reach the level of systolic BP<140 mmHg. It proves relevance of a problem of increase in compliance of patients. One of the easiest ways of growth of this is use of the multicomponent drugs. In the recommendations of 2018 the class and level of validity of initiation of therapy from the double fixed-dose combination is raised to IB. There are recommended combinations of inhibitors of – angiotensin-converting-enzyme inhibitor (ACE inhibitor) or the angiotensin II antagonists to blockers (ARA) with calcium channel blockers of a dihydropyridine structure (AC) or thia-

zide diuretic (D), it is preferable in «one tablet» (IA) [2].

In the Russian Federation researches of features of a current of AH [1,6,9] are also actively conducted. The recommendations of the All-Russian scientific organization of cardiologists and the Russian Medical Society of Arterial Hypertension [12] are revised. The combinations of ACE inhibitors+AC/D [5,8,10,11,13] are the most studied. Advantages of use of combinations of ACE inhibitors and  $\beta$ -blockers ( $\beta$  – AB) [7], three-component antihypertensive drugs are analyzed [3].

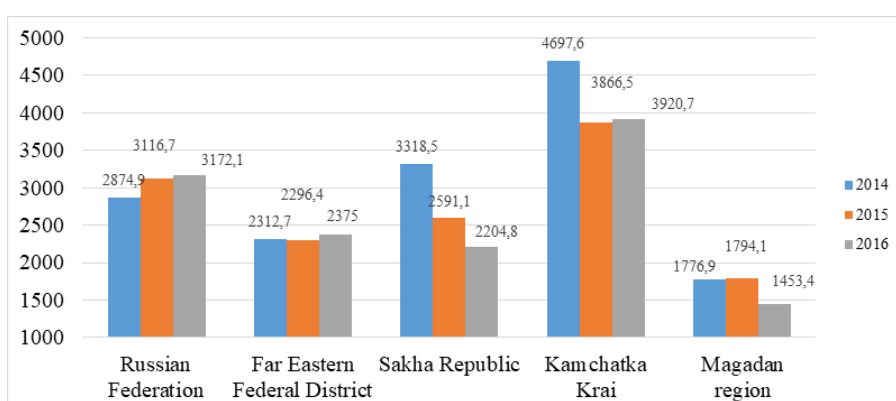
The analysis of the pharmaceutical market is one of the most reliable ways of assessment of introduction of the existing regulations in real clinical practice and also usage by patients of antihypertensive medicines. The **purpose** of the conducted research: comparison of approaches to drugs therapy of AH with use of the fixed-doses combinations in three northern regions of the FEFD.

**Material and methods.** The epidemiological research was conducted based on data on realization of antihypertensive medicines in the pharmaceutical organizations (n=17) during 2013-2017 in the Magadan region, in Kamchatka Krai, in the Sakha Republic (Yakutia). Based on the obtained data the general base of sales in a quantity equivalent (by the number of packing's) has been carried out with use of Microsoft Office of Excel 2015. Injection medicines, in connection with their use, generally in a hospital segment have been excluded from the list. At the following study phase the total indicators of sales of the established daily doses (DDD) all international non-proprietary name (INN), were calculated on the basis of DDD, presented on the website of World Health Organization. In the analysis of the fixed-doses combinations, the rule is followed: 1 tablet - DDD for the combinations applied once a day; 2 tablets - DDD for the combinations applied twice a day and 3 tablets DDD for the combinations applied three times a day, etc. This principle means what the DDD of fixed-doses combination can differ from the DDD of its active ingredients [15]. Further the average indicator of realization of each INN in the specific region on 1 drugstore sold for a year (for alignment of differences of population density in regions) was calculated. The "Analysis of Data" and "Intermediate Results" package was used.

**Conflict of interests:** authors declare lack of the obvious and potential conflicts of the interests connected with the publication of the present article.

**Financing source:** authors declare lack of financing.

**Compliance to the principles of ethics:** research work conforms to the ethi-



**Fig.1.** Indicators of incidence of circulatory system diseases on 100000 all population of northern subjects of the FEFD (with the diagnosis established for the first time in life)

cal standards developed according to the Helsinki declaration of the World medical association "Ethical Principles for Medical Research Involving Human Subjects" with amendments of 2000. The epidemiological research was conducted without participation of people and animals.

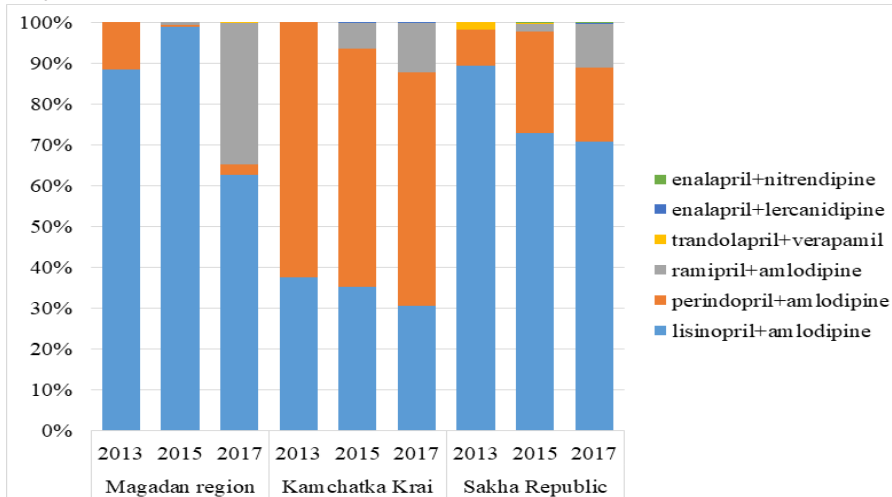
**Acknowledgements:** none.

**Results and discussion.** In a therapeutic class of combinations  $\beta$ -AB+AC/D more than 90% of realized amount by DDD were from the leader - an atenolol with chlortalidone in all three analyzed districts. Only in 2017 the share of sales bisoprolol+amlodipine in the Sakha Republic (Yakutia) has increased to 11,11%. Indicators of acquisition of INN bisoprolol+hydrochlorothiazide in Yakutia and the Magadan region were less than 3%. Patients in northern regions of the FEFD did not demand combinations atenolol + amlodipine, metoprolol + felodipine, nebivolol + amlodipine for the studied period. The narrow list of the fixed-doses combinations acquired by patients characterizes therapeutic group of the ARA+AC. The leader of the market is the combination valsartan+amlodipine. More than 95% of an intra-group indicator of realization are the share of this INN. Only since 2017, losartan+amlodipine

and telmisartan+amlodipine have begun to be applied by patients in Kamchatka Krai and in the Sakha Republic (Yakutia). At the same time, totally their share has made less than 5%.

Changes that are important in the data of sales were observed in a therapeutic class of combinations the ARA+D. More than 80% of realization intra-group remains the leader - INN losartan+hydrochlorothiazide. Since 2017 patients buy combination INN valsartan+hydrochlorothiazide were: in the Magadan region - 4,8%; in Kamchatka Krai - 7,8%; in the Sakha Republic (Yakutia) - 11,02%. Shares of sales kandesartan/telmisartan+hydrochlorothiazide in the Magadan region have increased to 3,4% in 2017, and combinations azilsartan medoxomil+chlortalidone to 12,18% in the Sakha Republic (Yakutia).

The therapeutic group of combinations of ACE inhibitors+AC is one of the most demanded in the pharmaceutical market in regions. The structure of realization of these fixed combinations for the studied period in three districts is presented in the figure 2. In the Magadan region more than 50% of intra-group volume acquired by DDD were the share of a combination of lisinopril with amlodipine, and sales



**Fig.2.** Structure of realization of the DDD fixed-doses combinations ACE inhibitors+AC

of perindopril+amlodipine decreased. In 2017 was increased to 35% the indicator of sales of rather new fixed-doses combination ramipril+amlodipine and has occurred come a redistribution of preferences. The share of this INN in the Sakha Republic (Yakutia) in 2017 has made more than 10%. In general, the structure of realization in regions was similar. At the same time, patients in Sakha Republic (Yakutia) actively bought the fixed combinations of a perindopril+amlodipine. Their share has made about 25% in 2016 and 18% in 2017.

Preferences of experts and patients in Kamchatka Krai differed from the regions described above. The leader of the therapeutic group of ACE inhibitors+AC was perindopril+amlodipine. More than 50% of sales were the share of this INN in the district. Since 2015 there is a market redistribution - realization of a combination lisinopril+amlodipine decreases to 30% in favor of INN ramipril+amlodipine – his indicator increases to 10%. Combinations of trandolapril+verapamil and also rather new drugs, which containing enalapril+lercanidipine and enalapril+nitrendipine, were not demanded among patients in regions. In general, decrease in demand for drugs of an enalapril is noted. It can be connected with feature of pharmacokinetics of the substance (applied twice a day). It reduces at patients commitment to treatment, while there are effective, long acting ACE inhibitors (perindopril, ramipril, fosinopril) in the market.

Dynamics of realization of the fixed doses combinations in the ACE inhibitors+D group is presented in the figure 3. The leader was the combination perindopril+indapamide. The share of its sales varied from 20% (in 2015 in the Magadan region) up to 60% (in 2017 in Kamchatka Krai). Indicators of sales of INN enalapril+indapamide were insignificant (no more than 10%) and decreased in three studied districts. Use by patients of a combination enalapril+hydrochlorothiazide was also decreased in the Magadan region and in Kamchatka Krai. Shares of other representatives of this therapeutic class remained insignificant - totally no more than 10%. The increase in realization was also observed for combinations of ramipril+hydrochlorothiazide and lisinopril+hydrochlorothiazide in the Sakha Republic (Yakutia).

At the following study phase the sales of the fixed-doses combinations of drugs from various therapeutic classes have been analysed. Dynamics of realization is presented in the figure 4. In the Magadan region the most acquired there were combinations hydrochlorothiazide+triamterene

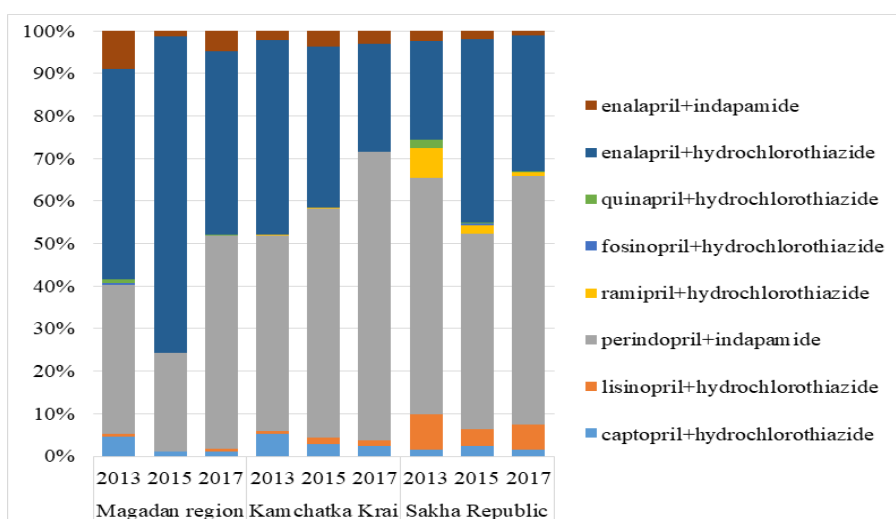


Fig.3. Structure of realization of the DDD fixed-doses combinations ACE inhibitors+D

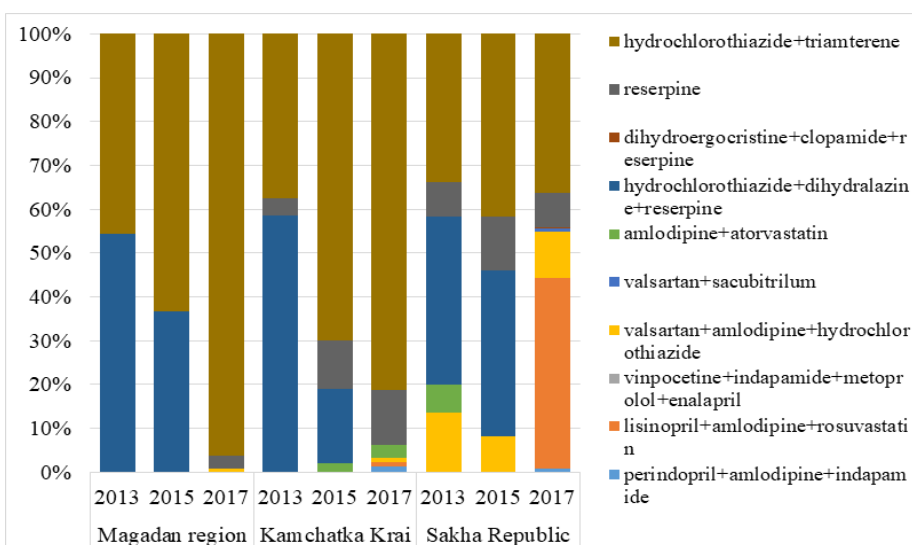


Fig.4. Structure of realization of the DDD fixed-doses combinations of antihypertensive drugs of other therapeutic classes

and hydrochlorothiazide+dihydralazine+reserpine. Despite emergence of modern multicomponent medicines ACE inhibitors+AC+D, ACE inhibitors+AC+statins, the ARA+ AC+D, AC+D, AC+statins, ACE inhibitors+D+ $\beta$ -AB+nootropic in the pharmaceutical market, their total share made no more than 10%. The situation in Kamchatka Krai was similar, but at the same time, high rates (over 60% intragroup in 2013 year) characterized sales of alkaloids of a *Rauwolfia serpentina* (trade name "Rau-natine").

The pharmaceutical market of the Sakha Republic (Yakutia) also differed in view of considerable acquisition of combinations of a reserpine with hydrochlorothiazide. At the same time, market redistribution nevertheless happened, and an intra-group share of a combination lisinopril+amlodipine+rosuvastatin by 2017 has made more than 40%. At INN valsartan+amlodipine+hydrochlorothiazide indica-

tors of sales have increased to 10%.

Despite existence in the pharmaceutical market of combinations of more selective  $\beta$ -AB (bisoprolol, metoprolol, nebivolol), till 2017 year the most acquired by patients there is an atenolol combination. It can be explained with the accumulated experience of its clinical application, presence duration in the regional pharmaceutical markets and also rather low cost of the concrete trade name «Tenoric».

The significant proportion of realization of INN valsartan+amlodipine among combinations of the ARA+AC can be caused by recent registration and, respectively the entry to the regional pharmaceutical markets, trade names of combinations of an irbesartan, losartan, olmesartan medoxomil and telmisartan with amlodipine. Till 2017 in drugstores this group has been presented, generally by the trade name «Exforge».

In the therapeutic class ARA+D redistribution of preferences from a com-

bination of a losartan with hydrochlorothiazide, in favor of rather new INN was observed. Current situation can be a consequence of increase in interest of specialists and patients to group of sartans in general, an active promotion, acquisition of practical experience of use of medicines by doctors and patients in northern regions of the FEFD.

In group of the fixed-doses combinations ACE inhibitors+AC remained high a share of realization lisinopril+amlodipine. It can be caused by the fact that this combination was one of the first in the regional pharmaceutical markets. Nevertheless, entry of new options of combinations has attracted interest of specialists. This can be connected with a later registration (only in 2015 year) of a full-doses combination «Ekvator» (20 mg +10mg), and also the increase in number of researches devoted to efficiency and safety of a combination perindopril+amlodipine [5,8,10,11,13]. The lack of sales of INN enalapril+nitrendipine/lercanidipine can be explained with recent registration of medicines (2016-2017) and need of accumulation of practical experience of usage in the form of single component drugs.

In a therapeutic class of combinations of ACE inhibitors+D considerable and stable share of sales at a perindopril+indapamide what can be explained with synergism of action due to vasodilating properties, additional at diuretic. Decrease in demand for combinations of enalapril can be caused by registration and entry into the pharmaceutical market of combinations of a ramipril, a fosinopril and quinapril and also growth of interest in combinations of ACE inhibitors+AC and ARA+D and ARA+AC.

Traditional preference of acquisitions by patients of combinations of diuretics and medicines with reserpine shows need of informing doctors about new double-component, triple-component drugs, effective for treatment of patients with an arterial hypertension, according to National clinical guideline (2018).

**Conclusion.** In general sales of antihypertensive combinations are characterized by concentration around several INN. The most realized fixed combinations in northern districts of the FEFD are atenolol+chlortalidone, valsartan+amlodipine, losartan+hydrochlorothiazide, lisinopril+amlodipine, perindopril+amlodipine, perindopril+indapamide. Leaders of therapeutic groups can vary considerably depending on the specific regions of the FEFD. Despite registration and availability in drugstores of regions of modern multicomponent drugs, acquisition by patients of medicines of a reserpine in

2013-2017 years and insignificant usage of the drugs containing three and/or four active ingredients, except for the Sakha Republic (Yakutia), still takes place. Results of a research prove slow introduction of recommendations in real practice of the antihypertensive therapy, which is appointed to patients, in the remote northern regions of the Russian Federation. The structure and dynamics of development of the pharmaceutical market shows need actions for expansion of knowledge of doctors about new standards of therapy, about the registered multicomponent drugs with the fixed-doses, which allow increasing compliance of patients to the appointed treatment.

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## ASSOCIATION OF ACE GENE POLYMORPHISM WITH HYPERTENSION AND RISK FACTORS AMONG INDIGENOUS PEOPLE OF THE NORTHERN TERRITORY OF YAKUTIA

DOI 10.25789/YMJ.2018.64.29

#### ABSTRACT

A study of the association of insertion-deletion (ID) polymorphism of the ACE gene with arterial hypertension and risk factors of cardiovascular diseases in the indigenous people of the northern territory of Yakutia was conducted. The obtained data show that the representatives of the indigenous population with the ID genotype of the ACE gene are associated with a level of systolic blood pressure, abdominal obesity. Carriers of this genotype of the ACE gene have the greatest chance of developing hypertension, metabolic syndrome. The heterozygous DD genotype is associated with lipid metabolic disorders both in hypertensive patients and persons without hypertension. Therefore, the research confirms influence of the D allele ACE gene polymorphism onto genetic mechanisms of cardiovascular diseases development.

**Keywords:** polymorphism, ACE gene, arterial hypertension, indigenous people, risk factors.

**Introduction.** Hypertension (HTN) is one of the main cardiovascular disease risk factors and the main reason for a high mortality among adult population in

the world [3, 6]. The prevalence of HTN is rather high in the world: it is on the average by 22% among adult population, according to WHO data [16]. Rising of

arterial blood pressure is a multifactorial disease which development is defined by the difficult mechanism of interaction of genetic and not genetic risk factors and