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ВЫБОР МЕЖДУ ФИКСИРОВАННЫМИ ДОЗИРОВАННЫМИ КОМБИНАЦИЯМИ АНТИГИПЕРТЕНЗИВНЫХ СРЕДСТВ И ИХ СВОБОДНЫМИ КОМБИНАЦИЯМИ В ЛЕЧЕНИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Choice Between Free Combination of Antihypertensive Agents and Fixed Dosed Combinations in the Treatment of Arterial Hypertension

Резюме

Большинству пациентов с артериальной гипертензией требуется более одного антигипертензивного лекарственного препарата для достижения целевого уровня артериального давления. Некоторым пациентам рекомендуют антигипертензивные схемы, состоящие из нескольких таблеток. Другим — лечение с помощью фиксированных дозированных комбинаций в одной таблетке. Анализ литературы реферативных баз elibrary и PubMed по публикациям в период с 2014 по 2024гг, касающейся выбора двухкомпонентных комбинированных антигипертензивных средств, содержащих ингибитор ренин-ангиотензин-альдостероновой системы (РААС) и тиазидный/тиазидоподобный диуретик или блокатор кальциевых каналов, показал, что использование фиксированных дозированных комбинаций (ФДК) антигипертензивных средств и прием одной таблетки один раз в день улучшает приверженность лечению и ускоряет контроль артериального давления (АД). Хотя стоимость ФДК антигипертензивных средств, содержащих ингибитор РААС и тиазидный/тиазидоподобный диуретик или блокатор кальциевых каналов, чаще выше этих же средств, взятых по отдельности, применение фиксированных комбинаций, повышая приверженность пациента терапии, обладает клиническим преимуществом по критерию эффективности снижения АД. С другой стороны, использование свободной комбинированной терапии в двух разных таблетках, когда их прием разбит в течение суток, иногда может давать более устойчивый антигипертензивный эффект в течение 24 часов. Доказательства эффективности контроля АД для ФДК зачастую экстраполируются с данных о свободных комбинациях. Кроме того, ФДК характеризуются меньшей выявляемостью возможной неэффективности одного из компонентов. Ассортимент ФДК и представленных в них соотношений дозировок компонентов расширяется, но выбор среди свободных комбинаций по-прежнему шире. В перечне жизненно необходимых и важнейших лекарственных препаратов за 2024 год отсутствуют ФДК антигипертензивных средств, что исключает возможность их получения на льготной основе и создает возможность для производителя устанавливать на них произвольные цены. Несмотря на то, что в последнее время научное сообщество рекомендует в качестве стартовой терапии использование ФДК антигипертензивных средств в силу лучшего соблюдения режима применения, а значит клинической эффективности и экономической целесообразности, нельзя сказать, что не осталось места для свободных комбинаций антигипертензивных средств в лечении артериальной гипертензии. Выбор врача, частота назначения, доля закупок ФДК в РФ, обзор их потребления требует дальнейшего анализа.

Ключевые слова: *артериальная гипертензия, фиксированные дозированные комбинации антигипертензивных средств, свободная комбинация антигипертензивных средств*

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Abstract
Most patients with arterial hypertension require more than one antihypertensive drug for blood pressure target achievement. Some patients are recommended for a multi-pill antihypertensive regimen, others — treatment with fixed dosed combinations in one tablet. Analysis of elibrary and PubMed publications in the period mostly from 2014 to 2024 concerning the choice of two-component combined antihypertensive agents containing renin-angiotensin system inhibitor and diuretic or calcium channel blocker, revealed that fixed-dose combinations (FDC) use and taking one tablet once a day improves adherence to treatment and facilitates blood pressure control. Although the cost of FDC containing the renin-angiotensin-aldosterone system inhibitor and a thiazide/thiazide-like diuretic or calcium channel blocker is in most cases higher than the same drugs taken separately, the use of fixed combinations, increasing patient adherence to therapy, has clinical advantage in terms of the effectiveness of lowering blood pressure, which confirms their economic feasibility. On the other hand, the use of free combination therapy in two different tablets, when taken separately during the day, can sometimes provide a more sustained antihypertensive effect over 24 hours. Evidence of the effectiveness of blood pressure control for FDCs is often extrapolated from data on free combinations. In addition, FDCs are characterized by less detection of possible ineffectiveness of one of the components. The range of FDCs and the dosage ratios of the components presented in them is gradually expanding, but the choice among free combinations is still wider. In addition, the list of vital and essential drugs (VED) for 2024 does not contain FDCs for antihypertensive drugs, which excludes the possibility of free receiving them on a preferential basis and gives the opportunity for the manufacturer to set prices for them. Despite the fact that recently the scientific community has recommended the use of FDC antihypertensive drugs as initial therapy due to better compliance with the regimen, and therefore clinical effectiveness and economic feasibility, it cannot be said that there is no space left for free combinations of antihypertensive drugs in the treatment of arterial hypertension. The choice of doctor, frequency of prescription, share of purchases of the FDCs in the Russian Federation, review of their consumption requires further analysis.

Key words: *arterial hypertension, fixed dosed combinations of antihypertensive agents (two-drug single-pill), free-equivalent combination of antihypertensive drugs*

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AH — arterial hypertension, AHD — antihypertensive drug, BP — blood pressure, CCB — calcium channel blocker, ARB — angiotensin II receptor blocker, ACEi — angiotensin-converting enzyme inhibitor, IHD — ischemic heart disease, RAAS — renin-angiotensin-aldosterone system, SBP — systolic blood pressure

Introduction

Control of blood pressure (BP) with achievement of the target levels and prevention of complications is a clinical objective of arterial hypertension (AH) management in adults. According to the World Health Organisation (WHO), the incidence of AH is very high. Over the past 30 years, the number of people with AH has doubled and makes 1.28 billion people [1, 2]. The majority of people with AH are asymptomatic, that is why this pathology is called a silent killer. Without adequate medicinal treatment, AH can affect target organs where BP is elevated: first, it is the heart where the risk of left ventricular hypertrophy, remodelling with myocardium fibrosis and dysfunction, angina, and myocardial infarction exists. Second, the brain with cerebrovascular complications. Third, eye retina with possible retinopathy. Fourth, kidney with progressing renal insufficiency. Annually, AH claims the lives of 9.4 million people. BP is considered elevated if the systolic and diastolic values exceed 140 and 90 mm Hg, respectively. According to the 2022 clinical recommendations for the drug therapy of arterial hypertension, the majority of patients with AH (except for patients with BP < 150/90 mm Hg and patients over 80 years of age, patients with senile

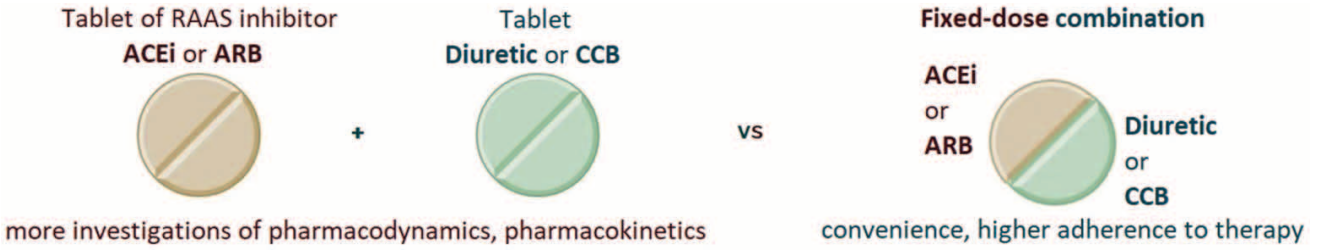

Figure 1. *The choice of combined two-component antihypertensive therapy*
Note: RAAS — renin-angiotensin-aldosterone system, ACEi — angiotensin-converting enzyme inhibitor, ARB — angiotensin II receptor blocker, CCB — calcium channel blocker

asthenia) are prescribed a combination of antihypertensive drugs as their initial treatment [1, 2].

Advantages of combined AH therapy include potentiation of component activity, slowing down counterregulatory mechanisms of BP elevation, better acceptability of the treatment, and efficient prevention of target organ damage [3, 4]. All these aspects are typical of sound combinations of antihypertensive agents, mostly of angiotensin-converting enzyme inhibitors (ACEi) and thiazid/thiazid-like diuretics (TD/TLD) or angiotensin II receptor blockers (ARB) (antagonists) with TD/TLD. Also, these are combinations of ACE inhibitors with calcium antagonists — dihydropyridine calcium channel blockers (CCB) or combinations of ARB and CCB. Once AH has been diagnosed, the physician has to choose between these combinations following the current recommendations; they are first-line therapy [2]. These antihypertensive agent groups can be combined in one tablet and are a part of a majority of fixed-dose combinations (FDC) registered in Russia, or they can be prescribed as two separate tablets (Fig. 1).

A number of recent studies demonstrate that drug therapy compliance and BP control are better in patients taking FDC than in patients taking free combinations of antihypertensive agents [5-7]. At the same time, in the real-life clinical practice, physicians sometimes prefer components of combined antihypertensive drug therapy in two separate tablets. This study seeks to identify whether it is justified for the compliant patients and whether free combinations of antihypertensive agents are still used as the first-line therapy.

Combined antihypertensive therapy

Monotherapy instead of a combined therapy is one of the causes of poor control of BP in the general population of AH patients. An important aspect is selection between fixed (one tablet) and free (two tablets) combinations of antihypertensive agents.

Over the past decades, a number of large-scale randomised studies demonstrated the efficacy of a two-component combination of RAAS inhibitor and a thiazide/thiazide-like diuretic or calcium channel blockers (CCB) in various populations. This choice is challenging; it requires justification and is a common example of the so-called Good Prescribing, when the adequate combined drug therapy prescribed to a specific patient ensures the highest efficacy and safety. The ACCOMPLISH study compared a combination of ACEi benazepril and CCB amlodipine with a combination of benazepril and hydrochlorothiazide (diuretic) in the reduction of the primary combined endpoint of cardiovascular events and cardiovascular mortality. A combination of RAAS inhibitor and CCB demonstrated higher efficacy in reduction of the rate of cardiovascular complications, whereas a combination with a diuretic showed positive results in patients with cardiovascular insufficiency and also in African American patients [9].

When a two-component therapy is insufficient to achieve the target BP values, standard doses of a three-component antihypertensive therapy are used (with possible use of FDC, including ACEi/ARB+CCB+diuretic). According to the State Register of Medicinal Products, four such FDCs are available on the Russian market: two combinations with ACE inhibitors (lisinopril/perindopril) plus amlodipine and indapamide, and two combinations with ARB (valsartan/telmisartan) plus amlodipine and hydrochlorothiazide. Currently, studies are ongoing to evaluate three-component FDCs with low doses of components (telmisartan/amlodipine/indapamide doses (mg): 10/1.25/0.625 and 20/2.5/1.25 vs. two-component FDC of the above antihypertensive agents [10].

In refractory (resistant) hypertension, four-component therapy is possible: a three-component FDC and one antihypertensive agent from the list of second-line drugs. The prospects of using a four-component combination, i. e. very low doses of four antihypertensive agents in one tablet (doses which are four times lower than the average doses of each component): irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and a beta-blocker bisoprolol 2.5 mg [11, 12]) require further studies, since the efficacy of this therapy was

evaluated in the QUARTET study in comparison with irbesartan 150 mg monotherapy; comparison with a two-component FDC is required: irbesartan and indapamide with irbesartan and amlodipine. The study, where irbesartan was replaced with candesartan 2 mg and all other components were the same as in the QUARTET study (amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg), did not demonstrate any significant difference in the clinical efficacy and safety vs. controls (candesartan 8 mg + amlodipine 5 mg daily starting from week 6) [13]. In 2013, a four-component FDC was registered in Russia, which is marketed under the brand name Hypotef (Syntez LLC), containing enalapril 5 mg, vinpocetine 2.5 mg, indapamide 0.75 mg, and metoprolol 25 mg. This FDC contains the average doses of the ACE inhibitor and beta-blocker, while indapamide and vinpocetine are in a lower dose compared to when taken individually. Vinpocetine corrects cerebrovascular disorders, it is not a classical CCB, but its mechanism of action involves calcium antagonism. The FORSAGE study demonstrated comparable efficiency and tolerability of this combination vs. patients who were treated with full doses of antihypertensive agents (ACEi/ARB+diuretic/CCB/beta-blocker), as well as the promising outlook of its use in patients with AH and dyscirculatory encephalopathy [14, 15].

Rate of prescription, share and cost of two-component antihypertensive FDC

Studies conducted in different countries seek to evaluate the rate of prescription by doctors of a drug combination in one tablet as initial combined therapy, according to the recent recommendation of the European Society of Hypertension. Bryan A.S., et al. (2023) report that in the USA only one third of adult patients with AH are treated with FDC [16]. A German study to analyse the use of the current recommendations on the drug treatment of hypertensive patients in 2016–2020 recorded high rates of non-compliance with the recommendations in Germany regarding prescription of antihypertensive FDC. Almost two years after the publication of ESC/ESH 2018 Recommendations on Hypertension Management, in 2020 only 10.9 % of prescribed antihypertensive drugs were FDC, evidencing poor use of the current recommendations on drug treatment of arterial hypertension [17]. At the same time, a cost-benefit analysis of an initial two-component antihypertensive therapy demonstrated that, taking into account direct healthcare costs, quality-adjusted life years (QALY) and 10-year additional economic efficiency coefficient, in 10 years the use of FDC will yield extra 0.028 quality-adjusted life years without any significant investments, vs. monotherapy. A two-component FDC is economically more viable than a free combination of equivalent doses of individual tablets (additional economic efficiency coefficient $57 000/increase in QALY) [16]. Therefore, the more active use of FDCs in routine clinical practice is required in order to improve prognosis for patients with AH.

In Russia, an analysis was performed of the data on antihypertensive agent sales in 2018 in pharmacies across 10 districts of the Far East Federal Region. The study showed that the highest share of FDC was in the Amur Region (15.3 %) and Zabaikalye Territory (13.5 %). The lowest share was recorded in the Sakhalin (5.3 %) and Magadan (6.6 %) Regions. The most popular fixed dose combinations in the Far East Federal Region are balanced combinations of ACEi and diuretics or CCB, as well as ARB with diuretics [18]. For sure, the share of antihypertensive FDC in pharmacies and the rate of prescription by doctors who regularly deal with AH, grows with every passing year, including Russia. A questionnaire survey among primary care providers in the Voronezh Region demonstrated that medical professionals (MP) prefer FDC with ACEi+diuretic (72 % of MPs) vs. the earlier Russian PIFAGOR IV study (2013), where this combination was chosen in 33 % of cases. Compared to the PIFAGOR IV study, healthcare providers preferred ACEi+CCB (46 %) (PIFAGOR IV study: 24 %), ARB+diuretic (36 % vs. 28 %) [19].

According to literature, one disadvantage of free combinations in AH management is higher cost of treatment, since FDC are cheaper than individual agents [20]. However, the opinion that the reduced cost of treatment is partially associated with lower cost of combined products vs. cost of individual components [21] was not confirmed in the majority of cases when we compared retail prices of two-component antihypertensive products in pharmacies (data from at least 5 pharmacies) in Smolensk in May 2024 (Table 1). For instance, the average retail price of FDC containing perindopril and indapamide, marketed under the brand name Noliprel A Forte, is twice as high as the total average price of its components from the same manufacturer (Servier). At the same time, there are FDC (e.g., azilsartan medoxomil with chlortalidone (brand name: Edarbyclor), where the average price is almost the same as the total price of individual components. The cost of AH therapy comprises direct and indirect costs; however, for some patients, the price of drugs in pharmacies can be a deciding factor.

For reference: the annual cost of FDC therapy for one patient in Germany was significantly higher than therapy with the same combinations of two tablet

Table 1. *Comparison of average retail prices for some fixed-dose combinations (FDCs) containing RAAS inhibitor and diuretic or calcium channel blocker with prices for the same combinations in different tablets*

N	FDC: component INN, dosage, number of dosage units, brand name (manufacturer), price per package	Component 1 ACEi or ARB: INN, dosage, number of dosage units, brand name (manufacturer), price per package	Component 2 Diuretic or CCB: INN, dosage, number of dosage units, brand name (manufacturer), price per package
1.	ACEi perindopril 5 mg, diuretic indapamide 1,25 mg, # 30 *Noliprel A Forte (Servier)* Average price: 954,4 RUB	perindopril 5 mg, # 30 *Prestarium A (Servier)* Average price: 259,9 RUB	indapamide 1,5 mg, # 30 *Arifon retard (Servier)* Average price: 211 RUB Average combination price 470,9 RUB
2.	ACEi ramipril 5 mg, diuretic indapamide 1,25 mg, # 30 *Konsilar-D24 (Vertex)* Average price: 672,4 RUB	ramipril 5 mg, # 28 *Ramipril vertex* Average price: 167 RUB	indapamide 1,5 mg, # 30 *Indapamide vertex* Average price: 32 RUB Average combination price 199 RUB
3.	ACEi enalapril 10 mg, CCB lercanidipine 10 mg, #28 *Lerkamen Duo (Berlin-Chemie/Menarini)* Average price: 666,5 RUB	enalapril 10 mg, # 30 *Berlinpril (Berlin-Chemie/Menarini)* Average price: 132,7 RUB	lercanidipine 10 mg, # 28 *Lerkamen (Berlin-Chemie/Menarini)* Average price: 463,8 RUB Average combination price 596,5 RUB
4.	ACEi lisinopril 10 mg, CCB amlodipine 5 mg, # 30 De-kriz (MEDISORB) Average price: 343,6 RUB	lisinopril 10 mg, # 30 *Lisinopril medisorb* Average price: 135,5 RUB	amlodipine 5 mg, # 50 *Amlodipin medisorb* Average price: 80 RUB Average combination price 215,5 RUB
5.	ARB valsartan 80 mg, diuretic hydrochlorothiazide 12,5 mg, # 28 *Co-diovan (Novartis Pharma)* Average price: 2504,8 RUB	valsartan 80 mg, # 28 *Diovan (Novartis Pharma)* Average price: 2035,5 RUB	hydrochlorothiazide 25 mg, # 20 *Gipotiazid (Sanofi Rossija)* Average price: 94,4 RUB Average combination price 2129,9 RUB
6.	ARB azilsartan medoxomil 40 mg, diuretic chlorthalidone 12,5 mg, # 28 *Edarbi-Klo (Takeda Island Limited)* Average price: 1225,4 RUB	azilsartan medoxomil 40 mg, # 28 *Edarbi (Takeda Island Limited)* Average price: 952,2 RUB	chlorthalidone 12,5 mg, # 30 *Dikardplus (Ipca Laboratories Limited)* Average price: 227,8 RUB Average combination price 1183 RUB
7.	ARB candesartan 16 mg, CCB amlodipine 10 mg, # 30 *Giposart A (Akrikhin)* Average price: 618,8 RUB	candesartan 16 mg, # 30 *Giposart (Akrikhin)* Average price: 485,5 RUB	amlodipine 10 mg, # 30 *Amlodipine (Vertex)* Average price: 65 RUB Average combination price 550,5 RUB
8.	ARB telmisartan 40 mg, CCB amlodipine 5 mg, # 28 Telzap AM (Sanofi Russia) Average price: 502,8 RUB	telmisartan 40 mg, # 30 *Telzap AM (Sanofi Russia)* Average price: 464 RUB	amlodipine 5 mg, # 30 *Amlodipine (Vertex)* Average price: 65 RUB Average combination price 528 RUB

(ramipril/ amlodipine: EURO 230 vs. EURO 134; candesartan/amlodipine: EURO 339 vs. EURO 235) [22].

A higher price of antihypertensive FDCs from the same manufacturer in Russia in comparison to the total cost of the same doses of individual components is partially due to a higher demand for FDC, since the doctors are under regulatory pressure to prescribe FDCs. To a greater extent, this is a result of the absence of these FDCs in the list of vital and essential medicines. In the Russian Federation, price control applies only to the drugs which are included in the list of vital and essential medicines (Art. 60 of Federal Law No. 61 as amended on 30/01/2024, On Circulation of Medicines, and Decree of the RF Government No. 865, On State Control of Prices for Vital and Essential Medicines); only medicines in this list are subject to the manufacturer's maximum sale price, specific wholesale and retail mark-ups. The prices for medicines, not included in the list of vital and essential medicines (in this case — antihypertensive FDC), are determined by the manufacturer.

Selection of the most optimal two-component combinations of antihypertensive agents: FDC or free combinations

1) Combination of an ACEi and a diuretic. A combination of an ACEi and TD/TLD is the most common in AH management due to its high efficiency, protection of target organs, adequate safety and tolerability, ability of ACEi to prevent diuretic-mediated hypopotassaemia [23].

An earlier large-scale retrospective study in patients with AH evaluated compliance with ACEi and TD. One year after initiation of hydrochlorothiazide-only therapy, 70 % of patients withdrew from further therapy, whereas when an FDC of TD and ACEi was prescribed, the number of patients withdrawing from antihypertensive therapy was twice as low [24]. In the study, fixed combinations were compared to TD monotherapy; and no comparisons were made with ACEi monotherapy and with a free combination of ACEi and TD in various tablets.

A retrospective cohort study in 13,350 subjects aged 66 years and over in Ontario, with a follow-up period of up to 5 years, compared patients treated with fixed combinations of ACEi and TD/TLD with patients taking individual antihypertensive agents. Comparison of results before the first case of treatment withdrawal (when there were no differences in compliance between groups) did not reveal any significant intergroup difference in clinical results [25]. The use of FDC was associated with better compliance (70 % with FDC vs. 42 % with individual tablets) [25].

A randomised, 8-week prospective cross-section study in two groups, conducted in Nigeria in 2018 in adult patients with AH who were treated with ACEi lisinopril and TD hydrochlorothiazide monotherapy or with FDC, demonstrated that, by the end of week 8, both regimens achieved significant reduction in BP vs. baseline values; there were no cases of proteinuria in both groups; however, compliance was better with the use of FDC [26].

One of the most popular and common FDCs of ACEi with a thiazide-like diuretic is a combination of a lipophilic prodrug perindopril with indapamide. In Russia, this combination is distributed just under 19 trade names, for instance, Noliprel which is presented in three doses: Noliprel A (perindopril/indapamide 2.5 mg/0.625 mg), Noliprel A Forte (perindopril/indapamide 5 mg/1.25 mg), Noliprel A Bi-Forte (perindopril/indapamide 10 mg/2.5 mg), thus making it possible to individually select a dose [27].

In their study, the staff of A. I. Evdokimov Moscow State University of Medicine and Dentistry discuss advantages of the Russian combined medicine — Konsilar-D24, which is a fixed combination of ACEi ramipril 5 mg and TLD indapamide 1.25 mg, primarily better compliance among patients with AH [21]. The study of this FDC continued with the CONSONANCE 2023 program; for the first time, the therapy efficacy was evaluated after home-based BP monitoring, taking into account drug effects for the long-term BP variability and patient well-being using the EuroQol visual and analogue scale. The target clinical BP levels of < 140/90 mm Hg after 2 weeks were achieved in 74.9 % of patients, after 6 months — 99.4 % of patients. The target home-based BP levels of < 135/85 mm Hg after 2 weeks were achieved in 75.7 % of patients, after 6 months — 91.1 % of patients [28].

2) Combination of an ARB and a diuretic. An equally important, and also an alternative, combination with ACEi, especially in case of their individual intolerance (dry cough, angioedema), is ARB with TD/TLD [29].

Telmisartan (ARB) possesses high affinity to AT_1 receptors and more than any other sartans affects peroxisome proliferator-activated receptors γ (PPARγ), at a dose recommended for AH therapy, which can be of importance in case of concomitant insulin resistance, type 2 diabetes mellitus and metabolic syndrome. PPARγ activation boosts adiponectin production and facilitates anti-inflammatory, anti-oxidative effects on vessel walls, thus having angioprotective activity and reducing the risk of atherosclerotic processes.

Currently, the following doses of the FDC of telmisartan and hydrochlorothiazide are marketed in Russia: telmisartan 40 mg+hydrochlorothiazide 12.5 mg, telmisartan 80 mg+hydrochlorothiazide 12.5 mg, telmisartan 80 mg+hydrochlorothiazide 25 mg, as well as the FDC of telmisartan and indapamide: telmisartan 40 mg+indapamide 1.5 mg and telmisartan 80 mg+indapamide 1.5 mg [30].

Also, an FDC containing ARB azilsartan medoxomil with diuretic chlortalidone is of interest [31], which is available only in two doses: azilsartan 40 mg and chlortalidone 12.5 or 25 mg. Chlortalidone is a 1st generation thiazide-like diuretic with a long-lasting effect (24–48 h vs. 6–12 h for hydrochlorothiazide). That is why a comparison of the two combinations of azilsartan medoxomil with chlortalidone (FDC Edarbyclor) and hydrochlorothiazide demonstrated that the combination of azilsartan medoxomil with chlortalidone possesses higher antihypertensive efficiency and comparable safety vs. the combination with hydrochlorothiazide [29]. In a comparative study of the FDC azilsartan medoxomil with chlortalidone (Edarbyclor 40/12.5 mg) and a free combination of azilsartan medoxomil with indapamide retard (Edarb 40 mg+indapamide retard 1.5 mg) in patients with AH, after 12 weeks 88 % of patients in the first group and 72 % of patients in the second group reached target clinical BP; the first group demonstrated higher antihypertensive effects on clinical and 24-hour peripteral BP, as well as normalisation of 24-hour systolic BP [32].

3) Combination of ACEi and CCB. First studies of the combination of fixed doses of ACEi enalapril and dihydropyridine calcium channel blocker lercanidipine showed that the FDC is more potent in BP reduction than enalapril 20 mg monotherapy or lercanidipine 10 mg monotherapy [33].

A comparative analysis of AH management using a free combination of ACEi perindopril and CCB amlodipine and FDC Prestans during 12 months compared changes in BP values, including BP variability, target organ remodelling criteria. By the end of week 4, the target BP values were observed in 87.5 % and 87.1 % of patients in both groups vs. baseline. Diastolic BP and nocturnal systolic BP were lower in patients taking FDC. One year after therapy initiation, the group of patients treated with a free combination of perindopril with amlodipine still demonstrated changes in target organ remodelling parameters: glomerular filtration rate, microalbuminuria, ankle-brachial index, which is a result of poorer compliance, more frequent withdrawals from one of the prescribed antihypertensive agents for 1–3 days, as well as dose modifications by patients [34]. The need for a wider dose range has been satisfied with a fixed dose combination of perindopril with amlodipine sold under the brand name Dalneva, which is available in four perindopril/perindopril dose combinations: 4/5, 8/5, 4/10, and 8/10 mg, which is very useful for the real-life clinical practice [5]. A study by Simonyi G., et al. (2017) comparing the stability of a year-long AH therapy with free combinations and FDC demonstrated that the actual rate of therapy withdrawal was approximately two times higher with free doses vs. FDC [35].

A comparison of the efficacy of FDC and a free combination of ramipril and amlodipine in patients with AH also demonstrated better compliance and the degree of the nephroprotective and angioprotective effects in the FDC group vs. a free combination [36, 37]. A combination of ACEi and CCB is seen as a promising option in the therapy of patients with AH and concomitant COVID-19, it being a result of efficient correction of endothelial dysfunction. It appears that perindopril not only increases the bradykinin levels and boosts the activity of endothelial NO-oxidase, but it also decreases the rate of endothelial cell apoptosis, while amlodipine acts as an antioxidant [5, 38].

4) A combination of ARB and CCB is not indicated in cardiovascular comorbidities with conduction abnormalities: bradycardia, atrioventricular blocks, but is a combination of choice in concomitant ischemic heart disease, myocardial hypertrophy, migraines.

The VICTORY II study assessed the efficacy and safety of an FDC containing valsartan and amlodipine in achievement of target BP levels in newly diagnosed or uncontrolled AH. During a 3-month period with monthly valsartan/amlodipine dose titration, the target AH levels were achieved in a majority of patients with good tolerability. Also, FDCs reduced albuminuria, vascular endothelium dysfunction and improved erectile function and quality of life [39]. The use of medical services and the costs incurred by the patients in the FDC group treated with valsartan/amlodipine, as compared to their free combinations, were 16–20 % lower. In particular, they had fewer hospital admissions, outpatient visits and ambulance calls [40].

In a study conducted at the Kazan Medical University, patients treated with an FDC of losartan and amlodipine showed significantly higher reduction in the values of 24-hour BP monitoring vs. losartan and hydrochlorothiazide. It is assumed that an FDC containing CCB is preferable in patients with reduced nocturnal BP [41].

When an FDC of candesartan and amlodipine and their free combinations were used, the number of patients who were treated with and withdrew from the therapy with these drugs within 2 months after therapy initiation was comparable. However, after 3 months, the

rate of therapy discontinuation was higher in patients taking a combination of two tablets vs. FDC; after 12 months, the difference between the groups was even bigger [42].

A comparison of the comorbidity risk factor (all-cause mortality and all-cause hospitalisation) showed that the FDC regimen, in particular combinations of valsartan/amlodipine, candesartan/amlodipine, had advantages vs. free antihypertensive combinations. Thus, FDC regimens are associated with a lower rate of cardiovascular events and lower all-cause mortality in the clinical practice [43].

Market analysis of two-component antihypertensive FDCs containing a RAAS inhibitor and diuretic/calcium channel blocker

In order to analyse the Russian market of antihypertensive agents, we studied the number of trade names of two-components FDCs, based on the INN of ACEi/ARB in the National Register of Medicines. Below are RAAS inhibitors in descending order of their presence in FDC (in brackets, the first digit means the number of INN combinations with various diuretics and calcium channel blockers; the second digit is the number of their trade names):

1) enalapril (4/16)> lisinopril (3/15)> ramipril (3/7)> perindopril (2/25)>
captopril (1/2)> zofenopril (1/1) ≈ trandolapril (1/1) ≈ fozinopril (1/1) ≈ quinapril (1/1)> spirapril (0/0) ≈ cilazapril (0/0);
2) telmisartan (3/15)> valsartan (3/19)> losartan (2/22)> candesartan (2/6)> olmesartan medoxomil (2/3)> azilsartan medoxomil (2/2) ≈ irbesartan (2/2)> eprosartan (1/1).

In general, prolonged-release antihypertensive FDCs should be preferable in order to ensure a 24-hour effect after a single administration. Less common are products with such diuretics as indapamide; there is only one combination with diuretic chlortalidone (azilsartan medoxomil+chlortalidone). More common are FDCs with a shorter-action diuretic hydrochlorothiazide (especially among 2-component FDCs containing sartans).

The majority of FDCs containing CCB include dihydropyridine derivative amlodipine. There is one FDC containing lercanidipine: enalapril+lercanidipine, and one FDC containing nitrendipine: enalapril+nitrendipine. An FDC with a non-dihydropyridine CCB verapamil is available only in one drug from a non-Russian manufacturer.

An analysis of the market depth, i.e. availability of FDCs with ratios of various component doses, requires a more thorough study. It should also be taken into account that the availability of antihypertensive FDCs mentioned in the National Register of Medicines can significantly differ from the assortment in pharmacies of various constituent territories of the Russian Federation.

Discussion and conclusion

Currently, the most common initial drug therapy of AH is a combination of two products. The recommendations of the International Society of Hypertension (ISH) state that the optimal option is a combination of a RAAS inhibitor (ACEi or ARB) with a CCB in the majority of patients, while a fixed combination of an ACEi or ARB with a diuretic is advisable in elderly people with a history of stroke or transient ischaemic attack, with signs of chronic cardiac failure, and a history of CCB intolerance [39]. Selection of a specific initial regimen of AH therapy depending on the clinical picture is presented in Table 2.

The use of a combined therapy, which is synergetic and complementary, increases a share of patients achieving the recommended target BP values, as well as ensures protection against target organ damage and reduces the risk of side effects and cardiovascular events [46]. An important matter is the selection between a fixed combination in one tablet and a combined therapy in two different tablets.

Combined antihypertensive products in the form of FDCs improve BP control and compliance among patients with AH. Despite the fact that the FDC assortment is gradually growing, a 2-year study in the USA showed that three out of five hypertensive adults treated with 2 classes of antihypertensive agents use a regimen, which as of January 2023 was not commercially available in the form of an equivalent FDC [47]. These results demonstrate that the available FDC assortment does not meet the clinical needs of the target population [48]. On the one hand, the available FDCs are not complete; on the other hand, they overlap and duplicate one another due to a wide range of generic products [47]. Besides, FDCs are not often used as a first-line antihypertensive therapy, despite the increasing volume of evidence and scientific recommendations [49]. According to the literature, patients, whose initial therapy was usually FDCs, were younger and had fewer comorbidities. A multivariate analysis demonstrated that in patients with a history of myocardial infarction or stroke, healthcare providers prefer a more flexible therapy and free combinations of antihypertensive agents [42].

Table 2. *Choice of fixed-dose combinations (FDC) containing RAAS inhibitor and a diuretic or calcium channel blocker for arterial hypertension [2, 7, 44, 45]*

Comorbidities	Preferred FDC	Alternative
angina pectoris	ACEi (primarily perindopril or ramipril) + **CCB**	ARB (primarily valsartan or candesartan) + **CCB**
myocardial infarction	ARB + **CCB**	ACEi + **CCB/TD**
chronic heart failure	ACEi + **TD/TLD**	ARB + **TD/TLD**
left ventricular hypertrophy	ARB + **CCB**	ACEi + **CCB**
atrial fibrillation	ACEi/ARB + **CCB non-dihydropyridine (non-DHP), e.g. verapamil**	ACEi/ARB + **CCB dihydropyridine (DHP)**
coronary and carotid atherosclerosis, dyslipidemia	ACEi + **CCB**	ARB + **CCB**
cerebrovascular disease	ARB + **TLD/ CCB**	ACEi + **TLD**
metabolic syndrome	ACEi/ ARB + **CCB**	ACEi/ARB + indapamide
type 2 diabetes mellitus	ACEi/ ARB + **CCB**	ACEi/ARB + indapamide
proteinuria / microalbuminuria	ACEi/ ARB + **TD/TLD**	ACEi/ARB + **CCB**
chronic kidney disease	ACEi/ ARB + **loop diuretic**	ACEi/ARB + **TD/TLD**
peripheral artery disease	ARB + **CCB**	ACEi + **CCB**
intolerance to ACE inhibitors (dry cough, which is more common for women, patients of the Negroid and Mongoloid races, smokers, patients with concomitant bronchopulmonary pathology)	ARB + **CCB**	ARB + **TD/TLD**
patients with multiple **drug allergies, bronchial asthma, COPD**	ARB + **CCB**	ARB + **TD/TLD**

Note. CCB — dihydropyridine calcium channel blocker, ARB — angiotensin II receptor blocker, ACEi — angiotensin-converting enzyme inhibitor, TD — thiazide diuretic, TLD — thiazide-like diuretic

In addition to the patient convenience, better compliance, ease of prescription and better achievement of target BP values, advantages of a combined antihypertensive drug therapy with FDCs include prevention of the probability of irrational combinations [27]. At the same time, advantages of free combinations of antihypertensive agents include more individualised selection of drug doses (however, the range of FDC doses and assortment grow from year to year), the possibility to cancel or replace one component of the combination with another one, the possibility of taking combination components at various times during the day, which can yield a more stable 24-hour antihypertensive effect (for instance, a RAAS blocker is taken in the morning and a CCB — before bed) [8, 50].

Going back to the main advantage of FDC, that is, better compliance, it is worth mentioning that no therapy will ever be efficient, unless the patient takes the prescribed medicines in a correct order, correct dose and required number of times. FDCs once daily improve compliance. Currently, there are FDCs which contain not only antihypertensive agents, but also components to correct the main risk factors of AH and its complications. For example, in order to simplify the drug therapy regimen in concomitant dyslipidemia and metabolic syndrome, statins were added to one tablet with antihypertensive agents. Two ACEi-containing FDCs are currently available in Russia: lisinopril/perindopril+amlodipine+statin (rosuvastatin/atorvastatin), and one ARB-based combination:

losartan+amlodipine+statin (rosuvastatin). In a study comparing a three-component FDC of olmesartan/amlodipine/rosuvastatin in one tablet at a dose of 20/5/5 mg (group 1) and 20/5/10 mg (group 2) vs. FDC of olmesartan/amlodipine at a dose of 20/5 mg (group 3), the primary endpoint was the difference in the changes in cholesterol and low-density lipoprotein (LDL) levels 8 weeks after the baseline in 3 groups of patients with AH and a low or moderate cardiovascular risk. Achievement of LDL cholesterol of < 5.6 mmol/L after 8 weeks was statistically different between the groups (65.8 %, 86.7 %, and 6.3 %, respectively). Results for total cholesterol, triglycerides, HDL, apolipoprotein B, etc. were better in groups treated with FDCs containing rosuvastatin; no serious adverse drug reactions (ARD) were reported in any group [51]. A meta-analysis of 18 actual clinical studies with the total number of 20,463 subjects revealed a statistically significant correlation between the use of FDCs with statins and improvement in compliance, lower BP and total cholesterol in hypertensive patients in the high-risk group [52].

Generally, an idea of using all required medicines in one tablet to prevent and correct cardiovascular risk factors (not only statins, but also antiplatelets for thrombosis prevention, folic acid for homocysteinemia correction, etc.) has been actively developing [53] and is at the edge of polypharmacy, which brings about sound scepticism. First, there is a risk of taking unnecessary drugs and excessive control of very low levels of BP and LDL cholesterol. Second, there are pharmacokinetic drug-drug interactions in multi-component (4 and more components) FDCs, with subsequent changes in therapy efficacy and unpredictable incidence of ARDs. Third, some healthcare providers want to emphasise a non-drug correction of risk factors.

When evaluating the pharmacoeconomic advantages and reduction in the cost of FDC therapy, it is assumed that the costs for patients treated with adequate FDC regimens is lower than with the use of free combinations. In particular, they have fewer hospital admissions, outpatient visits and ambulance calls [27]. However, in a meta-analysis by Mallat S.G., et al. (2016), analysing 7 randomised clinical studies comparing efficiency of BP control with FDCs and free antihypertensive combinations, the authors concluded that the designs of these studies are not adequate in terms of methodology, that is why their results do not confirm and do not rule out significant difference between a fixed and free combined therapy of AH [39]. Besides, evidences gathered in clinical studies of free combinations are often projected on fixed combined therapy, which is a doubtful extrapolation.

At the same time, the START study analysed data from 57,998 AH patients: 15,349 patients were treated with ramipril/ amlodipine, 10,801 — with valsartan/amlodipine, 1,026 — with candesartan/amlodipine in one tablet or several similar tablets. All groups treated with FDC had reliably lower all-cause mortality, reliably higher therapy tolerability, lower incidence of events with cardiovascular complications vs. a combination of several tablets [56]. These results confirm the recommendations of the European Society of Cardiology/European Society of Hypertension and International Society of Hypertension, recommending using combinations in one tablet and more active introduction of FDC to routine clinical practice.

A systemic review by Parati G., et al. (2016) discusses a number of potential advantages of FDC vs. free combinations of equivalent drugs: lower tablet load, lower healthcare costs and use of resources, reduction in clinical inactivity by healthcare providers and better therapy compliance [54]. However, none of the studies measured compliance through drug monitoring (drug quantification in blood and urine); instead, indirect methods to count tablets were used, such as a share of days covered or drug possession factor, which can overestimate compliance, although, in the long-term, these methods allow for efficient measurements. Also, studies which demonstrated similar compliance between DC and free combinations of two tablets were mostly prospective, and patients were regularly and closely followed-up. Because of better compliance, studies of the positive effect of FDC vs. combinations of two tablets were retrospective.

The 2024 list of vital and essential medicines contains a combination of ARB valsartan with inhibitor neprilysin sacubitril (Uperio), used in the management of chronic cardiac failure. There are no antihypertensive FDCs including a RAAS inhibitor and a diuretic or CCB; patients cannot get them at a discounted price and healthcare providers can choose to prescribe free combinations of antihypertensive agents.

FDCs are associated with some limitations which should be assessed in clinical practice: fewer cases of potential inefficiency of one of the components, a narrower range of component doses, relative limitation of an increase in the dose of one of the drugs irrespective of the other one, or adaptation of the dose of one drug to some circumstances (reduction of the diuretic dose in case of fever or diarrhoea), a higher risk of complications in non-compliant patients [49, 55].

Therefore, optimal fixed dose combinations help both healthcare providers and AH patients to achieve and maintain the life-long target BP. FDCs should be preferable. At the same time, currently there are a number of

circumstances, where combined antihypertensive therapy in two different tablets can be used. Further studies of pharmacoepidemiological and pharmacoeconomic aspects of the two-component antihypertensive therapy in Russia are required.

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Author contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Список литературы / References:

1. World Health Organization. Guideline for the pharmacological treatment of hypertension in adults. 2021 [Electronic resource]. URL: https:// https://www.who.int/publications/i/item/9789240033986. (date of the application: 24.08.2021)
2. Mancia G., Kreutz R., Brunström M. et al. ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). Journal Hypertens. 2023; 41(12): 1874-2071. doi: 10.1097/HJH.0000000000003480.
3. Кобалава Ж.Д., Конради А.О., Недогода С.В. и др. Артериальная гипертензия у взрослых. Клинические рекомендации 2020. Российский кардиологический журнал. 2020; 25(3): 3786. doi: 10.15829/1560-4071-2020-3-3786.
   Kobalava Zh.D., Konradi A.O., Nedogoda S.V. et al. Arterial hypertension in adults. Clinical guidelines 2020. Russian Journal of Cardiology. 2020; 25(3): 3786. doi: 10.15829/1560-4071-2020-3-3786 [in Russian].
4. Морозова Т.Е., Самохина Е.О. Фиксированные комбинации в лечении артериальной гипертензии — реальный путь к повышению приверженности. Российский кардиологический журнал. 2020; 25(11): 177-184. doi: 10.15829/29/1560-4071-2020-4184.
   Morozova T.E., Samokhina E.O. Fixed-dose combinations in the treatment of hypertension to increase adherence. Russian Journal of Cardiology. 2020; 25(11): 177-184. doi: 10.15829/29/1560-4071-2020-4184 [in Russian].
5. Остроумова О.Д., Кочетков А.И., Павлеева Е.Е. и др. Современные представления о выборе фиксированных комбинаций антигипертензивных препаратов: фокус на эффективность и прогноз. Лечебное дело. 2018; (2): 39-48. doi: 10.24411/2071-5315-2018-12001.
   Ostroumova O.D., Kochetkov A.I., Pavleeva E.E. et al. Modern ideas about the choice of fixed combinations of antihypertensive drugs: focus on effectiveness and prognosis. Lechebnoe delo. 2018; (2): 39-48. doi: 10.24411/2071-5315-2018-12001 [in Russian].
6. Banic A., Benkovic V., Knezevic A. Effectiveness of Hypertension Therapy by Using Fixed Combinations and Monocomponent Drugs — A Prospective Study from Croatia. Journal of Pharmacy and Pharmacology. 2018; 4(6): 333-339. doi: 10.17265/2328-2150/2018.04.004.
7. Бойцов С.А., Карпов Ю.А., Недогода С.В. и др. Рациональная фармакотерапия заболеваний сердца и сосудов: Compendium. Москва, Литтерра. 2024; 720 с. doi: 10.33029/4235-0397-0-SSZ-2024-1-720.
   Boytsov S.A., Karpov Yu.A., Nedogoda S.V. et al. Rational pharmacotherapy of heart and vascular diseases: Compendium. Moscow, Litterra. 2024; 720 p. doi: 10.33029/4235-0397-0-SSZ-2024-1-720 [in Russian].
8. Tocci G., Volpe M. Modern clinical management of arterial hypertension: fixed or free combination therapies? High Blood Press Cardiovasc Prev. 2011; 18(10): 3-11. doi: 10.2165/1159615-s0-000000000-00000.
9. Riva N., Lip G.Y. Which is the optimal antihypertensive combination in different diseases, a renin- angiotensin- aldosterone system inhibitor with a diuretic or with a calcium channel blocker? Curr Pharm Des. 2013; 19(21): 3753-3765. doi: 10.2174/1381612813199990299.
10. Rodgers A., Salam A., Cushman W. et al. Rationale for a New Low-Dose Triple Single Pill Combination for the Treatment of Hypertension. Global Heart. 2024; 19(1): 18. doi: 10.5334/gh.1283.
11. Nolde J.M., Atkins E., Marschner S. et al. Effect of Initial Treatment With a Single Pill Containing Quadruple Combination of Quarter Doses of Blood Pressure Medicines Versus Standard Dose Monotherapy in Patients With Hypertension on Ambulatory Blood Pressure Indices: Results From the QUARTET Study. Circulation. 2023; 148(4): 375-377. doi: 10.1161/CIRCULATIONAHA.123.064964.
12. Kovoor J.G., Chow C.K., Salam A. et al. Participants' views of ultra-low dose combination therapy for high blood pressure: a mixed-methods study from the QUARTET trial. Journal of human hypertension. 2024; 38: 516-522. doi: 10.1038/s41371-024-00915-4.
13. Huffman M.D., Baldridge A.S., Lazar D. et al. Efficacy and safety of a four-drug, quarter-dose treatment for hypertension: the QUARTET USA randomized trial. Hypertension Research. 2024; 47: 1668-1677. doi: 10.1038/s41440-024-01658-y.
14. Евдокимова А.Г., Коваленко Е.В., Евдокимов В.В. Клиническая эффективность и безопасность применения многокомпонентной антигипертензивной таблетки (фокус на Гипотэф: обоснование и доказательная база). Медицинский алфавит. 2018; 2(16): 15-21.
   Evdokimova A.E., Kovalenko E.K., Evdokimov V.V. Clinical efficacy and safety of multicomponent antihypertensive tablet use (focus on Gipotef: rationale and evidence base). Medical alphabet. 2018; 2(16):15-21 [in Russian].
15. Шишкова В.Н. Возможности и преимущества четырехкомпонентной антигипертензивной комбинации Гипотэф: клинический разбор. Поликлиника. 2019; 5(2): 40-44.
   Shishkova V.N. The possibilities and advantages of the four-component antihypertensive combination of Hypotef: a clinical analysis. Poliklinika. 2019; 5(2): 40-44 [in Russian].

16. Bryan, A.S., Moran, A.E., Mobley, C.M. et al. Cost-effectiveness analysis of initial treatment with single-pill combination antihypertensive medications. Journal of Human Hypertension. 2023; (37): 985-992. doi: 10.1038/s41371-023-00811-3.
17. Mahfoud F., Kieble M., Enners S., et al. Use of fixed-dose combination antihypertensives in Germany between 2016 and 2020: an example of guideline inertia. Clinical Research in Cardiology. 2023; 112(2): 197-202. doi: 10.1007/s00392-022-01993-5.
18. Soboleva M.S., Loskutova E.E. Analysis of Preferences in the Use of Fixed-Doses Combinations Antihypertensive Drugs in the Regions of Far-Eastern Federal District. Clinico Economics and Outcomes Research. 2020; 27(12): 265-272. doi: 10.2147/CEOR.S251721.
19. Карташова Э.Ш., Батищева Г.А., Жданова О.А. и др. Фармакоэпидемиология назначений антигипертензивных препаратов врачами Воронежской области в сравнении с результатами исследования ПИФАГОР IV. Российский медико-биологический вестник имени академика И.П. Павлова. 2021; 29(4): 475-482. doi: 10.17816/PAVLOVJ64271.
Kartashova E.Sh., Batishcheva G.A., Zhdanova O.A. et al. Pharmacoepidemiology of prescriptions of antihypertensive drugs by doctors in the Voronezh region in comparison with the results of the PYTHAGOR IV study. Rossiiskii mediko-biologicheskii vestnik imeni akademika I.P. Pavlova. 2021; 29(4): 475-482. doi: 10.17816/PAVLOVJ64271 [in Russian].
20. Подзолков В.И., Тарзиманова А.И. Фиксированные комбинации в лечении артериальной гипертензии: новые возможности. Российский кардиологический журнал. 2018; 23(5): 68-73. doi: 10.15829/1560-4071-2018-5-68-73.
Podzolkov V.I., Tarzimanova A.I. Fixed combinations in the treatment of arterial hypertension: new opportunities. Russian Journal of Cardiology. 2018; 23(5): 68-73. doi: 10.15829/1560-4071-2018-5-68-73 [in Russian].
21. Гороховская Г.Н., Мартынов А.И., Васюк Ю.А. и др. Современные возможности фиксированной комбинации ингибитора АПФ и диуретика в лечении артериальной гипертензии мягкой и умеренной степени с точки зрения доказательной медицины. Поликлиника. 2021; (5): 34-38. https://elibrary.ru/download/elibrary_48650928_75747353.pdf
Gorokhovskaya G.N., Martynov A.I., Vasyuk Y.A. et al. Modern possibilities of a fixed combination of an ACE inhibitor and a diuretic in the treatment of mild and moderate arterial hypertension from the point of view of evidence-based medicine. Poliklinika. 2021; (5): 34-38. https://elibrary.ru/download/elibrary_48650928_75747353.pdf [in Russian].
22. Bramlage P., Schmidt S., Sims H. Fixed-dose vs free-dose combinations for the management of hypertension-An analysis of 81 958 patients. The Journal of Clinical Hypertension (Greenwich). 2018; 20(4): 705-715. doi: 10.1111/jch.13240.
23. Галеева З.М., Галявич А.С. Влияние фиксированной низкодозовой комбинации гипотензивных препаратов на клинико-биохимические характеристики больных артериальной гипертензией. Артериальная гипертензия. 2003; 9(6): 221-224. doi: 10.18705/1607-419X-2003-9-6-221-224.
Galeeva Z.M., Galyavich A.S. The influence of a fixed low-dose combination of antihypertensive drugs on the clinical and biochemical characteristics of patients with arterial hypertension. Arterial hypertension. 2003; 9(6): 221-224. doi: 10.18705/1607-419X-2003-9-6-221-224 [in Russian].
24. Motwani J.G. Combining renin-angiotensin-aldosterone system blockade with diuretic therapy for treatment of hypertension. J Renin Angiotensin Aldosterone Syst. 2002; 3(2):72-78. doi: 10.3317/jraas.2002.021.
25. Verma A.A., Khuu W., Tadrous M. et al. Mamdani M.M. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study. PLoS Med. 2018; 15(6): e1002584. doi: 10.1371/journal.pmed.1002584.
26. Ogudu U., Nwaiwu O., Fasipe O.J. A comparative evaluation of fixed dose and separately administered combinations of lisinopril and hydrochlorothiazide in treatment-naïve adult hypertensive patients in a rural Nigerian community. Int Journal Cardiol Cardiovasc Risk Prev. 2022; 5(14): e200144. doi: 10.1016/j.ijcrp.2022.200144.
27. Морозова Т.Е., Самохина Е.О. Фиксированные комбинации в лечении артериальной гипертензии — реальный путь к повышению приверженности. Российский кардиологический журнал. 2020; 25(11): 177-184. doi: 10.15829/29/1560-4071-2020-4184.
Morozova T.E., Samokhina E.O. Fixed-dose combinations in the treatment of hypertension to increase adherence. Russian Journal of Cardiology. 2020; 25(11): 177-184. doi: 10.15829/29/1560-4071-2020-4184 [in Russian].
28. Лопатин Ю.М., Недогода С.В., Галявич А.С. и др. Эффективность антигипертензивной терапии по результатам программы КОНСОНАНС. Только ли достижение целевого уровня артериального давления? Артериальная гипертензия. 2023; 29(4): 419-431. doi: 10.18705/1607-419X-2023-29-4-419-431.
Lopatin Yu.M., Nedogoda S.V., Galyavich A.S. et al. The efficacy of antihypertensive therapy according to the results of the CONSONANCE program: is achieving the target blood pressure level the sole criterion? Arterial Hypertension. 2023; 29(4): 419-431. doi: 10.18705/1607-419X-2023-29-4-419-431 [in Russian].
29. Бакашвили Г.Н. Новая фиксированная комбинация для лечения артериальной гипертонии. РМЖ. 2015; 23(27): 1604-1607. https://www.rmj.ru/articles/kardiologiya/novaya-fiksirovannaya-kombinatsiya-dlya-lecheniya-arterialnoy-gipertonii/#
Bakashvili G.N. New fixed combination for the treatment of arterial hypertension. RMJ. 2015; 23(27): 1604-1607. [in Russian].
30. Саютина Е.В., Буторова Л.И., Туаева Е.М. и др. Телмисартан в комплексной терапии артериальной гипертензии: от фармакологических особенностей к клиническим преимуществам. Кардиоваскулярная терапия и профилактика. 2020; 19(1): 106-117. doi: 10.15829/1728-8800-2020-1-2453.
Sajutina E.V., Butorova L.I., Tuaeva E.M. i dr. Telmisartan in the hypertension treatment: from pharmacological characteristics to clinical benefits. Cardiovascular Therapy and Prevention. 2020; 19(1):106-117. doi: 10.15829/1728-8800-2020-1-2453 [in Russian].
31. Kwon A., Kim G.H. Single-pill Combination Therapy of Azilsartan Medoxomil/Chlorthalidone for Treatment of Hypertension: A Systematic Review. Clinical Therapeutics. 2020; 42(7):1390-1403. doi: 10.1016/j.clinthera.2020.05.015.
32. Кобалава Ж.Д., Кулаков В.В., Горева Л.А. и др. Сравнительные антигипертензивные эффекты хлорталидона и индапамида-ретард в комбинации с азилсартаном медоксомил у пациентов с артериальной гипертонией. Российский кардиологический журнал. 2019; 24(6):122-130. doi: 10.15829/1560-4071-2019-6-122-130.
Kobalava Zh.D., Kulakov V.V., Goreva L.A. et al. Comparative analysis of antihypertensive effects of chlorthalidone and indapamide-retard in combination with azilsartan medoxomil in patients with arterial hypertension. Russian Journal of Cardiology. 2019; 24(6):122-130. doi: 10.15829/1560-4071-2019-6-122-130 [in Russian].

33. Menne J., Haller H. Fixed-dose lercanidipine/enalapril for hypertension. Drugs Today (Barc). 2008; 44(4):261-70. doi: 10.1358/dot.2008.44.4.1164756.
34. Алехина О.Д., Чеснокова И.В. Преимущества контроля за течением гипертонической болезни с помощью фиксированной комбинации амлодипина и периндоприла аргинина. Системные гипертензии. 2018; 15(4):17-23. doi: 10.26442/2075082X.2018.4.180148.
Alekhina O.D., Chesnokova I.V. The advantages of controlling the course of hypertension with a fixed combination of amlodipine and arginine perindopril. Systemic Hypertension. 2018; 15(4):17-23. doi: 10.26442/2075082X.2018.4.180148 [in Russian].
35. Simonyi G., Ferenci T., Medvegy M. et al. Perindopril/amlodipin szabad és fix kombinációk egyéves terápiahűsége [One year persistence of free and fixed dose combinations of perindopril/amlodipine]. Orv Hetil. 2017; 158(36): 1421-1425. doi: 10.1556/650.2017.30851.
36. Максимов М.Л., Обрезан А.Г., Звегинцева А.А. и др. Два препарата — одна цель: рамиприл и фиксированная комбинация рамиприла и амлодипина в лечении артериальной гипертонии. РМЖ. 2022; (9): 22-28. EDN: UVKVEZ.
Maksimov M.L., Obrezan A.G., Zvegintseva A.A. et al. Two drugs — one target: ramipril and a fixed dose combination of ramipril and amlodipine in the treatment of arterial hypertension. RMJ. 2022; 9: 22-28. EDN: UVKVEZ [in Russian].
37. Подзолков В.И., Тарзиманова А.И. Фиксированные комбинации в лечении артериальной гипертензии: новые возможности. Российский кардиологический журнал. 2018; 23(5): 68-73. doi: 10.15829/1560-4071-2018-5-68-73.
Podzolkov V.I., Tarzimanova A.I. Fixed combinations in the treatment of arterial hypertension: new opportunities. Russian Journal of Cardiology. 2018; 23(5): 68-73. doi: 10.15829/1560-4071-2018-5-68-73 [in Russian].
38. Полякова О.А., Кочетков А.И. Остроумова О.Д. Перспективы применения комбинации периндоприла и амлодипина у пациентов с артериальной гипертензией и/или ишемической болезнью сердца и COVID-19: фокус на эндотелий. Российский кардиологический журнал. 2022; 27(3): 92-96. doi: 10.15829/1560-4071-2022-4888.
Polyakova O.A., Kochetkov A.I. Prospects for using a perindopril/amlodipine combination in patients with hypertension and/or coronary artery disease and COVID-19: focus on the endothelium. Ostroumova O.D. Russian Journal of Cardiology. 2022; 27(3): 92-96. doi: 10.15829/1560-4071-2022-4888 [in Russian].
39. Пырочкин А.В. Коморбидный пациент с артериальной гипертензией: фокус на валсартан и фиксированные комбинации. Кардиология в Беларуси. 2023; 15(4): 558-569. doi: 10.34883/PI.2023.15.4.011.
Pyrochkin A.V. Comorbid Patient with Arterial Hypertension: Focus on Valsartan and Fixed Combinations. Cardiology in Belarus. 2023; 15(4): 558-569. doi: 10.34883/PI.2023.15.4.011 [in Russian].
40. Baser O., Andrews L.M., Wang L. et al. Comparison of real-world adherence, healthcare resource utilization and costs for newly initiated valsartan/amlodipine single-pill combination versus angiotensin receptor blocker/calcium channel blocker free-combination therapy. Journal of Medical Economics. 2011; 14(5): 576-583. doi: 10.3111/13696998.2011.596873.
41. Гумеров Ф.Р., Маянская С.Д. Суточное мониторирование артериального давления при лечении различными группами фиксированных комбинаций антигипертензивных препаратов. Российский кардиологический журнал. 2023; 28(S5): 48-48.
Gumerov F.R., Mayanskaya S.D. Daily blood pressure monitoring during treatment with various groups of fixed combinations of antihypertensive drugs. Rossiiskii kardiologi-cheskii zhurnal. 2023; 28(S5): 48-48. [in Russian].
42. Bramlage P., Schmidt S., Sims H. Fixed-dose vs free-dose combinations for the management of hypertension-An analysis of 81 958 patients. The Journal of Clinical Hypertension (Greenwich). 2018; 20(4): 705-715. doi: 10.1111/jch.13240.
43. Wilke T., Weisser B., Predel H.G., Schmieder R., et al. Effects of Single Pill Combinations Compared to Identical Multi Pill Therapy on Outcomes in Hypertension, Dyslipidemia and Secondary Cardiovascular Prevention: The START-Study. Integrated Blood Pressure Control. 2022; 27(15): 11-21. doi: 10.2147/IBPC.S336324.
44. Sarzani R., Laureti G., Gezzi A. et al. Single-pill fixed-dose drug combinations to reduce blood pressure: the right pill for the right patient. Therapeutic Advances in Chronic Disease. 2022; 13. doi: 10.1177/20406223221102754.
45. Kawasoe S., Ohishi M. Regression of left ventricular hypertrophy. Hypertension Research. 2024; 47: 1225-1226. doi: 10.1038/s41440-024-01634-6.38.
46. Leggio M., Fusco A., Loreti C., et al. Fixed and Low-Dose Combinations of Blood Pressure-Lowering Agents: For the Many or the Few? Drugs. 2019; 79(17): 1831-1837. doi: 10.1007/s40265-019-01209-7.
47. Derington C.G., A.P Bress, JS. Herrick, et al. Antihypertensive Medication Regimens Used by US Adults With Hypertension and the Potential for Fixed-Dose Combination Products: The National Health and Nutrition Examination Surveys 2015 to 2020. Journal of the American Heart Association. 2023; 12(11): e028573. doi: 10.1161/JAHA.122.028573.
48. Переверзев А.П., Остроумова О.Д. Рекомендации по артериальной гипертензии 2018 и 2019 годов: остается ли место свободным комбинациям? Consilium Medicum. 2019; 21(12): 118-127. doi: 10.26442/20751753.2019.12.190747.
Pereverzev A.P., Ostroumova O.D. 2018 and 2019 Guidelines for the management of arterial hypertension: is there a place for unfixed drug combinations? Consilium Medicum. 2019; 21(12): 118–127. doi: 10.26442/20751753.2019.12.190747 [in Russian].
49. Laurent S., Bejan-Angoulvant T., Boutouyrie P. Prescription des associations fixes d'antihypertenseurs [Prescription of fixed dose combinations of antihypertensive drugs]. La Revue du praticien. 2019; 69(10):1094-1098. French. PMID: 32237580.
50. Трухан Д.И., Поздняков Ю.М. Актуальные аспекты рациональной фармакотерапии в кардиологии. Плюсы и минусы фиксированных и произвольных комбинаций антигипертензивных препаратов. Consilium Medicum. 2016; 18(1): 25-31. doi: 10.26442/2075-1753_2016.1.25-31.
Trukhan D.I., Pozdnyakov Yu.M. Actual aspects of rational pharmacotherapy in cardiology. Pros and cons fixed and arbitrary combinations of antihypertensive drugs. Consilium Medicum. 2016; 18(1): 25–31. doi: 10.26442/2075-1753_2016.1.25-31 [in Russian].
51. Kim B.J., Cha K.S., Cho W.H. et al. Efficacy and Safety of a Single-Pill Triple Combination of Olmesartan, Amlodipine, and Rosuvastatin in Hypertensive Patients with Low-to-Moderate Cardiovascular Risk: A Multicenter, Randomized, Open-Label, Active-Control, Phase IV Clinical Trial. Journal of Cardiovascular Pharmacology and Therapeutics. 2023; 28:10742484231205204. doi: 10.1177/10742484231205204.
52. Hennawi H.A., Ashraf M.T., Zohaib M. et al. Polypill Therapy in Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials. Current Problems in Cardiology. 2023; 48(8):101735. doi: 10.1016/j.cpcardiol.2023.101735.

53. Birla S., Angural A., Madathumchalil A. et al. Redefining the polypill: pros and cons in cardiovascular precision medicine. Frontiers in Pharmacology. 2023. 14: 1268119. doi: 10.3389/fphar.2023.1268119.
54. Parati G., Kjeldsen S., Coca A. et al. Adherence to Single-Pill Versus Free-Equivalent Combination Therapy in Hypertension: A Systematic Review and Meta-Analysis. Hypertension. 2021; 77(20): 692-705. doi: 10.1161/HYPERTENSIONAHA.
55. Nowak E., Happe A., Bouget J. et al. Safety of Fixed Dose of Antihypertensive Drug Combinations Compared to (Single Pill) Free-Combinations: A Nested Matched Case-Control Analysis. Medicine (Baltimore). 2015; 94(49): e2229. doi: 10.1097/MD.0000000000002229.
56. Schmieder R.E., Wassmann S., Predel H.G. et al. Improved Persistence to Medication, Decreased Cardiovascular Events and Reduced All-Cause Mortality in Hypertensive Patients With Use of Single-Pill Combinations: Results From the START-Stud. Hypertension. 2023; 80(5): 1127-1135. doi: 10.1161/HYPERTENSIONAHA.122.20810.

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