

# Polypharmacy in the treatment of arterial hypertension and heart failure

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Due to the development of the pharmaceutical industry, today there are a large number of drugs with similar properties and efficacy, but little-studied pharmacodynamics and pharmacokinetics. Therefore many medicines are prescribed more often and in larger quantities than necessary. That is why patients and doctors often face the problem of polypharmacy in various fields of medicine including cardiology.

The paper presents the results of the analysis of 249 case histories of inpatients with cardiac profile. All patients with underlying cardiac pathology (arterial hypertension, ischemic heart disease) had concomitant diseases. Patients with arterial hypertension had other concomitant diseases, most often gout, diseases of the digestive system, anemia. Chronic heart failure was found in the majority of patients with arterial hypertension, ischemic heart disease, chronic rheumatic heart disease.

We have determined which pharmacological groups of drugs are prescribed to patients with arterial hypertension or chronic heart failure and concomitant diseases: more than 60% of patients are prescribed drugs that are unsuitable for their condition. We analyzed and compared treatment standards in Ukraine and the world and carried out that doctors in Ukraine use modern and effective methods of treatment. The risks of prescribing a large number of drugs to patients are analyzed and the risks of dangerous drug interactions that can threaten the life or health of the patient are identified. In particular, in the treatment of cardiac patients, doctors used combinations of calcium antagonists and beta-blockers, NSAIDs and antithrombotic drugs, corticosteroids and antibacterial drugs of the fluoroquinolone group, ACE inhibitors and potassium-preserving diuretics, antiarrhythmic drugs and highly active diuretics, etc.

We compared medicinal prescriptions for the treatment of cardiovascular diseases with an interval of 10 years and revealed that in 2008 the therapy often did not comply with the international and Ukrainian treatment protocols, however, in 2018, unwanted drug interactions were found 4 times less often. That reflects the trend of doctors' awareness of pharmacology and evidence-based medicine.

**Keywords:** polypharmacy, arterial hypertension, heart failure, treatment, drug interactions, complications.

## Поліфармація в лікуванні артеріальної гіпертензії і серцевої недостатності

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Завдяки розвитку фармацевтичної галузі сьогодні існує велика кількість препаратів з подібними властивостями та ефективністю, але малодослідженою фармакодинамікою і фармакокінетикою. Через це багато ліків призначаються частіше і в більших кількостях, ніж необхідно. Саме тому пацієнти і лікарі часто стикаються з проблемою поліфармації в різних галузях медицини, в тому числі і в кардіології. У статті наведено результати аналізу 249 історій захворювань стаціонарних пацієнтів кардіологічного профілю. Усі пацієнти мали супутні захворювання, окрім основної кардіологічної патології (артеріальна гіпертензія, ішемічна хвороба серця). У пацієнтів із артеріальною гіпертензією були інші супутні захворювання, серед яких найчастіше фіксували подагру, захворювання органів травлення, анемію. Хронічна серцева недостатність була виявлена у більшій частини пацієнтів з артеріальною гіпертензією, ішемічною хворобою серця, хронічною ревматичною хворобою серця.

Визначено фармакологічні групи препаратів, які призначаються хворим на артеріальну гіпертензію або хронічну серцеву недостатність і супутні захворювання: більше ніж 60% пацієнтам призначають ліки, що не є необхідними при даних захворюваннях. Проведено аналіз лікарських призначень відповідно до стандартів лікування в Україні і світі: лікарі в Україні використовують сучасні та ефективні методи лікування. Проаналізовано ризики у разі призначення пацієнтам великої кількості препаратів і виявлено ризики виникнення небезпечних лікарських взаємодій, що можуть загрожувати життю чи здоров'ю пацієнта. Зокрема, при лікуванні пацієнтів кардіологічного профілю лікарі використовували комбінації антагоністів кальцію та бета-адrenoблокаторів, нестероїдних протизапальних лікарських засобів та антитромботичних препаратів, кортикостероїдів та антибактеріальних лікарських засобів групи фторхінолонів, іАПФ та калійзберігаючих діуретиків, антиаритмічних лікарських засобів та високоактивних діуретиків тощо.

При порівнянні лікарських призначень для лікування серцево-судинних захворювань з десятирічним інтервалом виявлено, що в 2008 році терапія частіше не відповідала міжнародним та українським протоколам лікування, проте в 2018 році небажані лікарські взаємодії виявлено у 4 рази рідше, що відображає тенденцію обізнаності лікарів у фармакології і доказовій медицині.

**Ключові слова:** поліфармація, артеріальна гіпертензія, серцева недостатність, лікування, лікарські взаємодії, ускладнення.

## Полифармация в лечении артериальной гипертензии и сердечной недостаточности

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Благодаря развитию фармацевтической отрасли сегодня существует большое количество препаратов с похожими свойствами и эффективностью, но малоисследованной фармакодинамикой и фармакокинетикой. Из-за этого многие лекарства назначаются чаще и в больших количествах, чем необходимо. Именно поэтому пациенты и врачи часто сталкиваются с проблемой полифармации в различных отраслях медицины, в том числе и в кардиологии.

В статье приведены результаты анализа 249 историй болезней стационарных пациентов кардиологического профиля. Все пациенты имели сопутствующие заболевания, кроме основной кардиологической патологии (артериальная гипертензия, ишемическая болезнь сердца). У пациентов с артериальной гипертензией были другие сопутствующие заболевания, среди которых чаще диагностировали подагру, заболевания органов пищеварения, анемию. Хроническая сердечная недостаточность была обнаружена у большей части пациентов с артериальной гипертензией, ишемической болезнью сердца, хронической ревматической болезнью сердца.

Определены фармакологические группы препаратов, которые назначаются больным артериальной гипертензией или хронической сердечной недостаточностью и сопутствующими заболеваниями: более 60% пациентам назначают лекарства, которые не являются необходимыми при данных заболеваниях. Проведен анализ врачебных назначений относительно стандартов лечения в Украине и мире: врачи

в Украине используют современные и эффективные методы лечения. Проанализированы риски при назначении пациентам большого количества лекарств и выявлено риски возникновения опасных лекарственных взаимодействий, которые могут угрожать жизни или здоровью пациента. В частности, при лечении пациентов кардиологического профиля, врачи использовали комбинации антагонистов кальция и бета-адреноблокаторов, НПВП и антитромботических препаратов, кортикостероидов и антибактериальных лекарственных средств группы фторхинолонов, ингибиторов АПФ и калийсодержащих диуретиков, антиаритмических лекарственных средств и высокоактивных диуретиков и др.

При сравнении лекарственных назначений для лечения сердечно-сосудистых заболеваний с десятилетним интервалом выявлено, что в 2008 году зачастую терапия не соответствовала международным и Украинским протоколам лечения, однако в 2018 году нежелательные лекарственные взаимодействия выявляли в 4 раза реже, что отражает тенденцию осведомленности врачей в фармакологии и доказательной медицине.

**Ключевые слова:** полифармация, артериальная гипертензия, сердечная недостаточность, лечение, лекарственные взаимодействия, осложнения.

Despite the achievements of the last decade in the field of studying the pathogenesis, clinic and treatment of chronic heart failure (CHF) and arterial hypertension (AH) these diseases are still one of the most common, severe and predictable complications of all diseases of the cardiovascular system. Due to the fact that these diseases are extremely common among the adult population, often patients have concomitant diseases. Therefore, in the treatment of such diseases, doctors are faced with polypharmacy. The term «polypharmacy» means the simultaneous administration to a patient of a large number (more than 5) of medicines [1]. Therefore, the questions about effective and safe methods of pharmacotherapy, as well as prevention of progression and complications of cardiovascular diseases are very important [2].

## MATERIALS AND METHODS

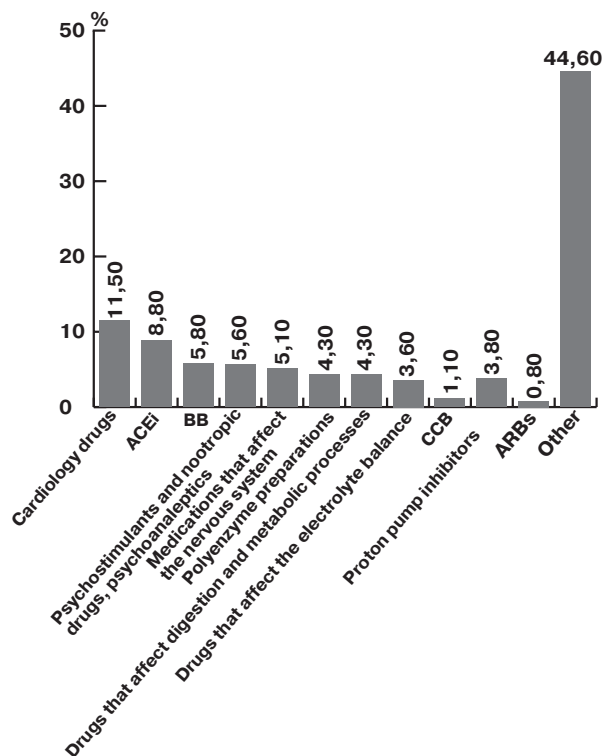
Taking into account treatment protocols [3], we can proceed to practical assignments in daily practice in order to compare protocols with real assignments. In addition, the comparative approach allows to analyze the interaction of the drugs and the volume of prescribed drugs. We analyzed the historic data of patients' diseases of the therapeutic profile in 2008 and 2018 years. The interval of 10 years is chosen for the possibility to analyze changes in the principles of therapy and certain characteristics of patients. In 2008, 100 medical stories (32 patients of male and 68 female) and in 2018, 149 medical stories (72 male patient and 77 female) were analyzed. The average age of patients is  $62,3 \pm 6,0$  years. There is no patient with only one pathology. Patients often have been ill with arterial hypertension and coronary heart disease (CHD). In addition, a large proportion of patients had CHF as a complication of the underlying disease.

The fate of patients with hypertension in 2008 was 31.1% of all pathologies, patients with CHD – 27.1%. Patients with hypertension have had other comorbid conditions, among which there is a common gout, digestive diseases, anemia.

CHF was found in bigger part of patients with hypertension, coronary heart disease, chronic rheumatic heart disease.

So, most patients (93%) with cardiological pathology have had manifestations of chronic heart failure. In 2018, the proportion of patients with hypertension increased 1.45 times and amounted to 46.5% of all hospitalized patients. The patients on CHD amounted to 27.1%, that is, this amount has not changed in 10 years. Manifestations of heart failure were presented in complications of the underlying disease in 46% of patients.

In 2018, there are 6.6 times less patients with hypertension, CHD and CHF than in 2008. In 2018, patients with hypertension and/or CHD with CHF have a large number of different comorbidities, including primary lymphostasis of the lower extremities, chronic gastritis, pathology of the musculoskeletal system, anemia, etc. As in 2008 and in 2018, elderly people account for most of the patients, but in 2018, the number of younger patients with hypertension is bigger.



**Picture 1. The frequency of using different groups of drugs in cardiac patients**

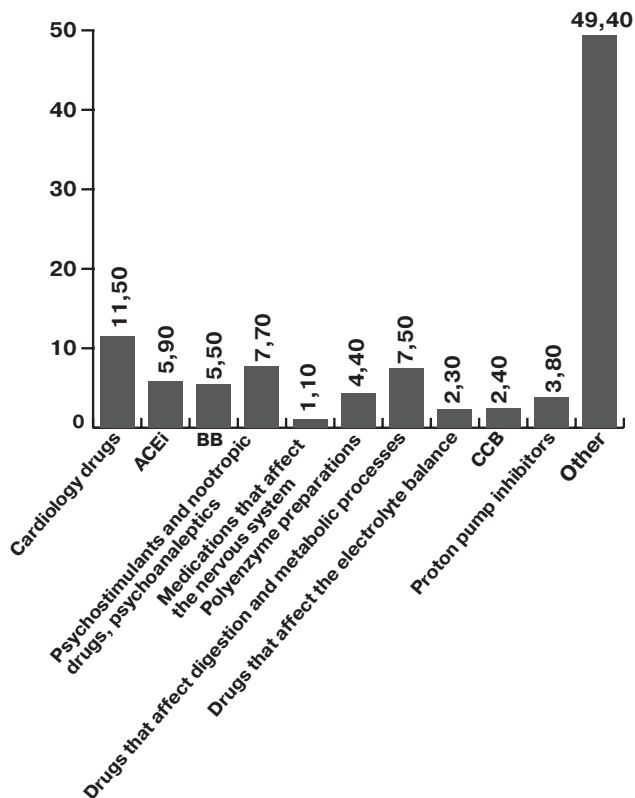
## RESULTS AND DISCUSSION

To identify the risks of drug interactions, the number of drugs that were administered simultaneously to each patient was pre-analyzed.

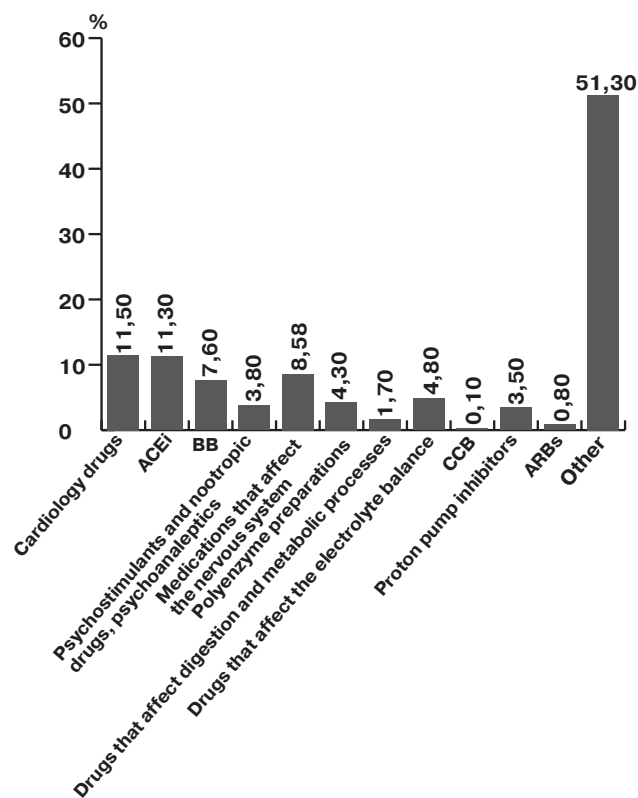
It turned out that doctors prescribe 4 to 15 drugs to patients. With regard to the frequency of use of different groups of drugs, given the major pathology of the cardiovascular system, the first place is occupied by cardiac drugs (Pic. 1).

Thioctic acid or meldonium (received 11.5% of patients) were appointed in most cases. In second place – angiotensin converting enzyme inhibitors (ACEi) (8.8% of patients), and third – beta blockers (BB) (5.8% of patients). Also, a large proportion is occupied by nootropic drug and drugs affecting the nervous system (10.7% of patients), and the drugs affecting the digestive system and metabolic processes (4.3% of patients), as well as polyenzyme preparations (4.3% of patients). The analysis of frequent appointments of certain groups of drugs is analyzed in 2008 and 2018 years (Pic. 2 and 3).

Thioctic acid or meldonium received 11.5% of inpatient patients, ACEi – 5.9%, BB – 5.5%, nootropics, psychostimulants and drugs, that affect the nervous system – 8.9%, polyenzyme preparations – 4.4%, drugs, that affecting metabolic processes – 7.5%.



**Picture 2. The frequency of the use of different groups of drug in cardiac patients in 2008**



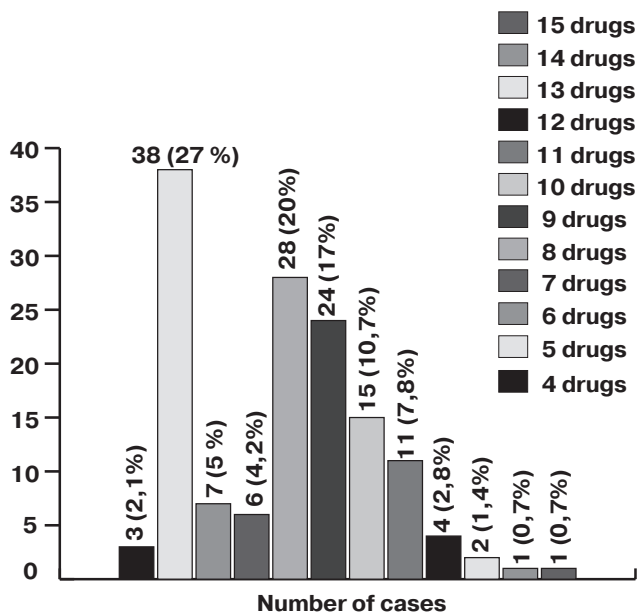
**Picture 3. The frequency of the use of different groups of drugs in cardiac patients in 2018**

In comparison with 2008, the number of patients in hospital settings that received the thioctic acid or meldonium has not changed and takes 11.5%. An ACEi was appointed almost twice more often – in 11.3% of cases, 2.1% of patients received BB, nootropics, psychostimulants and drugs that influence the nervous system – 12.4% of patients, which is 3.5% higher than in 2008 (Pic. 3). The frequency of application of polyenzyme drugs practically did not change, but the number of drugs that influence the metabolic processes was appointed in 4.4 times at least. In addition to the general changes in the frequency of noted groups of drugs, we can also distinguish certain other differences in pharmacotherapy.

Thus, in 2018, the Hydazepam was used more often for patients with hypertension (tranquilizer with anticonvulsant and anxiolytic action), amitriptyline (antidepressants with pronounced hypnotics and anxiolytic action) and emoxypine (active ingredient of ethyl methyl hydroxypyridine succinate), which is not applied in Western countries. This substance does not have enough evidence base for its widespread use [4].

In 2018, the percentage of homeopathic medicines significantly increased in comparison with 2008 year. In 2018, the amino acids were prescribed, but potassium preparations were not prescribed for any patient. The drugs of thioctic acid were used in 2008, but in 2018, patients received meldonium. In an analysis of the quantities prescribed by 140 patients, it was found that on average the patient had averaged 7.9 medications simultaneously (Pic. 4).

4 or 5 medicines received only 41 patients (29.1%). 6 and 7, respectively, received 5% and 4.2% of patients. The great number of patients (20%) had the treatment course out of 8 different drugs. 9 or 10 medicines received in accordance 24 (17%) and 15 (10.7%) patients. More than 10 drugs took 19 (14%) patients. With the increase in the number of products, the risks of development of undesirable medicinal interactions are increasing, which can lead to serious complications.



**Picture 4. The analysis of the number of drugs that were appointed to cardiac patients.**

Analysis of the risks of unwanted drugs interactions in cases of hypertension and/or CHF

We had analyzed all the stories of diseases, and 25 patients were chosen. These patients were ill only with hypertensive disease and heart failure. We conducted an analysis of the number of prescribed drug (Pic. 5).

According to the results obtained, only 9 (37.5%) patients received 5 drugs, the rest of patients simultaneously received from 6 to 11 drugs (an average of 6.8 drugs) that increases the risk of dangerous drug interactions.

So, on average, the doctors prescribe 6.46 drugs, so polypharmacy occurs in 62.5% of all cases.

Analysis of treatment of patients with hypertension and/or HF in accordance with the national protocols [5, 6].

In the analysis of pharmacotherapy of the stationary patients of cardiological profile all prescribed drugs were distributed according to a pharmacological groups (Pic. 6).

From the first line of antihypertensive drugs, patients were prescribed ACEi (100% of patients) and BB (16% of patients). Other first-line drugs were not used. Antithrombotic drug was prescribed only to 4 (16%) of patients. We have noted that there is a high percentage of psychoanalytic and nootropic drugs and drugs that affect the nervous system (70.8% and 66.6% of patients, respectively), which may indicate that the psycho-emotional state of patients is taken into account by physician's, but these drugs are not recommended in the treatment protocols for these nosologies. A group of patients who were advised to take hydazepam from the first day of treatment in the hospital was separately allocated (37.5% of patients).

Irrational combinations of medicinal products in the treatment of arterial hypertension and/or CHF

1. A combination of slow-free calcium channel blockers and beta-blockers lead to a strengthening of the effect of reducing heart rate (pharmacodynamic synergistic) that may lead to cardiac blockade. If necessary, in case of a simultaneous application of BB and calcium channel blockers (CCB), preference is given to dihydropyridine CCB (nifedipine, amlodipine, lerkandipine). Among the 100 analyzed stories of patients treated in 2008, one case was discovered (1% of patients) with irrational interactions. In 2018, this combination was not detected.

2. The simultaneous use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antithrombotic drugs increases the risk of bleeding through pharmacokinetic interactions at the distribution stage. NSAIDs have a high affinity for blood plasma proteins, thereby the free anticoagulant fraction is increasing. In 2008, two patients (2%) and in 2018 one patient (0.7%) were discovered to have this dangerous combination.

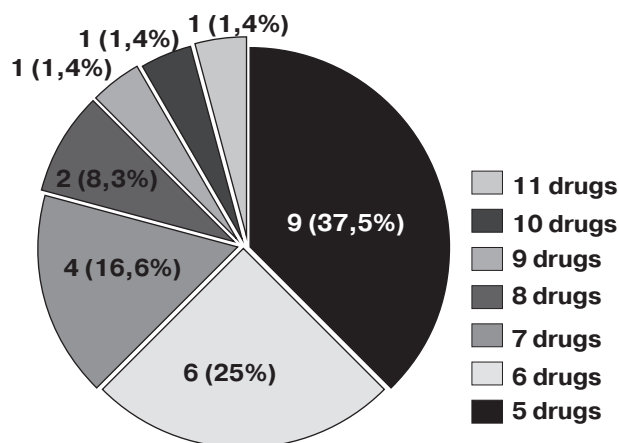
3. Concomitant administration of corticosteroids and antibacterials from the fluoroquinolone group may damage the tendons. This is especially important information for a physiotherapist, who wants to prescribe these medicines to the elderly. In 2008, 3 (3%) patients were identified and in 2018, (2 patients (1.3%) were taking this dangerous combination.

4. ACEi and potassium-sparing diuretics can lead to the development of hyperkalemia, which carries a danger on the development of fatal cardiac arrhythmias. In 2008, 2 (2%) cases were found and in 2018 – 1 case (0.7%) of this drug combination.

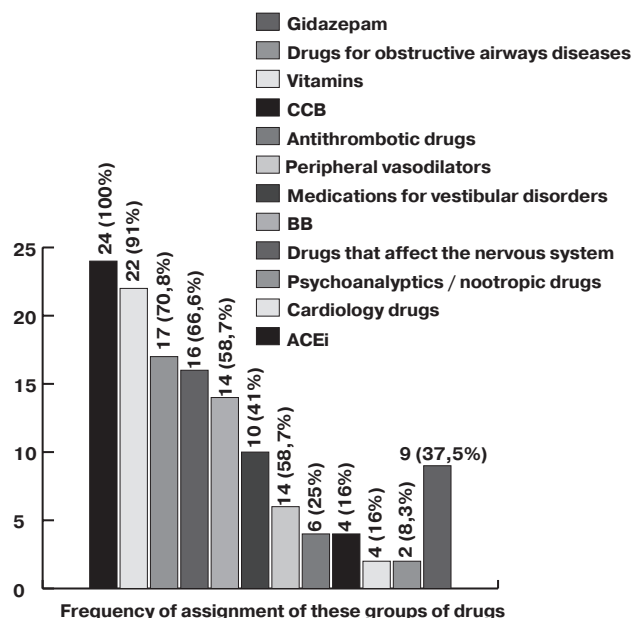
5. ACEi in combination with ARBs have a negative effect on the kidneys. This combination in the short term can lead to the development of kidney failure and since 2013, the simultaneous reception of data of drugs is not recommended. The combination of ACEi and ARBs occurs in one patient (1%), treated in 2008, when there were no data about the danger of this drug interactions. In 2018, there is no such combination of antihypertensive products.

6. Antiarrhythmic drugs and highly active diuretics prolongs the QT interval. QT prolongations is a predictor of fatal cardiac arrhythmias. Antiarrhythmic drugs along with furosemide increase the risk of developing ventricular cardiac arrhythmias, which in turn lead to sudden death of the patient. In 2008, one patient (1%) had this combination of drugs.

Therefore, according to the analysis of pharmacotherapy of patients with hypertension and / or CHF over 10 years, the



Picture 5. The quantity analysis in patients with hypertension and CHF without concomitant pathology



Picture 6. The analysis of the use of different groups in patients with hypertension and/or CHF

number of dangerous combinations of drugs has significantly decreased, but the issue of polypharmacy remains relevant.

## CONCLUSIONS

1. Domestic treatment protocols are in line with international standards.

2. Patients with hypertension and CHF are most often prescribed ACEi (100% of cases) and CCB (16% of patients). Cardiovascular drugs (91% of patients) and drugs that affect the nervous system (66.6%) are often used among other groups of drugs.

3. Polypharmacy is observed in 70.7% of appointments, which increases the risk of complications of treatment due to unwanted drug interactions.

4. In most cases, the prescribed regimens do not comply with the protocol of treatment of nosologies; drugs with unproven efficacy are used.

5. In 2018, dangerous drug combinations were prescribed 3.8 times less often than in 2008 (2.6% vs. 10%), which indicates an increase in physicians' professionalism.

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