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THE STUDY OF DOCTORS' ATTITUDE TO THE USE OF FIXED COMBINATIONS IN THE THERAPY OF ARTERIAL HYPERTENSION

Aim. To study doctors' attitude to the prescription of fixed combinations of antihypertensive drugs by a questionnaire survey, as well as the factors that determine this choice.

Materials and methods. Specially designed questionnaires were used for the study; the data were analyzed using the method of *a priori* ranking, system analysis, mathematical-statistical methods, the analogy and comparison methods.

Results. The questionnaire survey involved 162 doctors, among them cardiologists (45.1 % of the sample) with the work experience from 12 to 40 years dominated. The studies have shown that most doctors prefer to combine angiotensin-converting enzyme inhibitors with a diuretic or a calcium channel blocker. When prescribing fixed combinations, their effectiveness, safety and duration of action of the medicines selected are taken into account.

Conclusions. A sociological study has been conducted among doctors; the groups of combined antihypertensive drugs that are preferred have been identified. It has been found that for the further development of the pharmaceutical provision of the population, doctors see the need to develop new combined medicines. Therefore, according to the interviewed doctors, such combinations of drugs as ramipril with indapamide, bisoprolol with indapamide, metoprolol with ramipril and indapamide; ramipril with amlodipine and indapamide are the most relevant, safe and effective among the new drugs proposed for the development.

Key words: arterial hypertension; antihypertensive drugs; fixed combinations; questionnaire survey; method of *a priori* ranking.

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ДОСЛІДЖЕННЯ СТАВЛЕННЯ ЛІКАРІВ ДО ВИКОРИСТАННЯ ФІКСОВАНИХ КОМБІНАЦІЙ У ТЕРАПІЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

Мета – вивчити ставлення лікарів до призначення фіксованих комбінацій антигіпертензивних лікарських засобів шляхом анкетного опитування, а також факторів, що зумовлюють цей вибір.

Матеріали та методи. Для дослідження використовували спеціально розроблені анкетно-опитувальники, дані аналізували методом апіорного ранжування факторів. Застосовували також системний аналіз, математико-статистичні методи, метод аналогії і порівняння.

Результати дослідження. В анкетному опитуванні взяли участь 162 лікарі, серед яких домінували кардіологи (45,1 % вибірки), зі стажем роботи від 12 до 40 років. Дослідження засвідчили, що більшість лікарів надає перевагу поєднанню інгібіторів ангіотензин-перетворювального ферменту з діуретиком або з блокатором кальцієвих каналів. Призначаючи фіксовані комбінації, враховують їхню ефективність, безпечність та тривалість дії обраного для лікування лікарського засобу.

Висновки. Проведено соціологічне дослідження серед лікарів, визначено групи комбінованих антигіпертензивних лікарських засобів, яким надають перевагу. Виявлено, що для подальшого розвитку фармацевтичного забезпечення населення лікарі вважають за доцільне розробити нові комбіновані лікарські засоби. Отже, на думку опитаних лікарів, такі комбінації ЛЗ, як раміприл з індапамідом, бісопролол з індапамідом, метопролол з раміприлом та індапамідом; раміприл з амлодипіном та індапамідом є найбільш актуальними, безпечними та ефективними серед запропонованих до розробки нових ЛЗ.

Ключові слова: артеріальна гіпертензія; антигіпертензивні лікарські засоби; фіксовані комбінації; анкетне опитування; метод апіорного ранжування.

Statement of the problem. Among cardiovascular diseases, arterial hypertension (AH) is the leading risk factor for mortality and disability, despite the rapid development of medical technologies. An estimated 1.4 billion people worldwide have high blood pressure (BP),

but only 14 % have it under control, even though cost-effective treatment options exist and are quite affordable [1].

The ISH Global Hypertension Practice Guidelines recommend giving preference to the use of combinations of different active ingredients

as separate tablets and in the form of fixed combinations in one dosage form. The advantages of such approaches include achieving optimal BP levels, improving patient adherence to the treatment and preventing cardiovascular complications [2-4].

Practical guidelines for the treatment of AH recommend prescribing a dual fixed combination of drugs for the initial treatment. The next stages of the therapy of hypertension involve the use of a triple combination of drugs [5].

Fixed combinations provide additional benefits for patients and healthcare programs, including simpler dosing regimens, improved adherence, better rates of BP control. They significantly lower frequency of the treatment discontinuation compared to monotherapy. The cost of fixed-dose combination drugs can be the same or lower than the cost of individual monodrugs if they are purchased separately, but the logistic costs are lower [6, 7].

Therefore, conducting sociological research to study the use of combined hypotensive drugs by doctors is necessary, and it will provide an opportunity to implement measures to optimize costs for effective and safe pharmacotherapy.

Analysis of recent research and publications. The issue of providing the population with medicines for the treatment of AH was considered in the scientific publications of B. P. Hromovyk, A. S. Nemchenko, K. L. Kosyachenko, and others. To conduct the research, the authors of the article previously performed a comparative analysis of the range of combined antihypertensive drugs (AHDs) available at the pharmaceutical market of Ukraine in 2022 compared to their availability in 2015 [8].

In December 2022, the pharmaceutical market in Ukraine was saturated with a large number of AHDs. According to the State Register of Medicines of Ukraine, 965 antihypertensive drugs were registered, taking into account the number of doses in the package, 413 of them were combined ones.

The total number of dual combinations of AHDs was 86.37 % of the range. The part of fixed triple combination of active substances that showed antihypertensive effect composed 13.63 % of the drug assortment. The largest number of trade names (TN) contains combinations of angiotensin II receptor blockers (ARB)

with a diuretic (26.63 %), angiotensin-converting enzyme inhibitors (iACE) with a diuretic (19.85 %), as well as iACE with calcium channel blockers (CCB) 14.04 % and CCB with ARB (13.8 %). A smaller number of trade names attributed to such combinations as CCB with ARB and a diuretic (5.33 %), CCB with iACE and a diuretic (4.12 %), β -blockers (β -AB) with iACE (1.94 %), β -AB with ivabridine (1.45 %). The same share of the market belongs to drugs containing a combination of CCB with iACE and a statin, or β -AB with CCB, which is 2.18 % each, as well as CCB with a statin is 1.69 %.

It was found that there was a significant predominance of combined antihypertensive medicines of foreign production, the share of which was 82.71 % of the assortment.

Identification of aspects of the problem unsolved previously. After analyzing the AHDs nomenclature at the pharmaceutical market of Ukraine in 2022 and comparing it with 2015, it was found that the number of fixed combinations of antihypertensive drugs increased. Therefore, the study of doctors' attitude to the choice of fixed combinations of antihypertensive drugs in the AH management becomes relevant. After all, when choosing possible combinations of antihypertensive drugs for the treatment of patients with hypertension, it is necessary to take into account many factors.

Objective statement of the article. To study consumer preferences, to which doctors attach significant importance when prescribing AHDs, the method of expert evaluations was used. This method is the process of determining the quality characteristics of specific medicinal products based on the evaluations of qualified specialists. It is widely used in marketing research and is a complex of logical, mathematical, and statistical measures [9].

The questionnaire templates used to survey doctors contained three blocks of questions. The first block of questions was aimed at studying the list of fixed combinations of AHDs most often prescribed for the treatment of AH. The second block of the questionnaire consisted of questions to study the opinion of doctors regarding potentially possible combinations of AHDs that would be relevant in the treatment. In the third block of the questionnaire, we asked about the doctors' assessment of the factors that were important when

prescribing drugs for the treatment of hypertension. In the process of analyzing questionnaires, we also considered the information about the specialty, work experience, and academic title of the respondents.

To analyze the results of the survey, the method of *a priori* ranking through rank transformation was used.

Presentation of the main material of the research. After the research and comparison of the product range of fixed AHDs combinations at the Ukrainian market, it was decided to conduct a sociological survey to determine doctors' preferences when prescribing medicines.

For our further research, 162 doctors from Ternopil, Ivano-Frankivsk, Uzhorod, Khmelnytsky, Chernivtsi, Kharkiv were selected for the questionnaire survey. The ratio of doctors depending on specialization and the work experience is shown in Table 1.

Doctors with different experience took part in the survey. The doctors' experience ranged from minimum of 5 years to maximum of 47 years.

The questionnaire included three blocks of questions.

The first block of questions aimed at studying the list of fixed AHDs that were most often prescribed for the treatment of hypertension (Table 2).

As a result of the survey, it was found that 26.29 % of doctors preferred the combination of an iACE with a diuretic, indicating the following combinations of active substances: lisinopril with hydrochlorothiazide (HCT), enalapril with HCT, perindopril with indapamide, ramipril with HCT.

20.57 % of doctors indicated that they used combinations of iACE with CCB: enalapril with lercanidipine, lisinopril with nifedipine, ramipril with amlodipine, perindopril with amlodipine, lisinopril with amlodipine.

ARB drugs with diuretics were prescribed by 13.71 % of the surveyed respondents, namely: valsartan with HCT, telmisartan with HCT, azilsartan with HCT. 12.0 % of doctors preferred the triple combination of CCB with iACE and a diuretic, indicating the combination of perindopril with indapamide and amlodipine.

Table 1

THE RATIO OF DOCTORS DEPENDING ON SPECIALIZATION AND THE WORK EXPERIENCE

| Specialty | Percentage | Work experience | Percentage |
|-------------------|------------|-----------------|------------|
| Cardiologists | 45.10 | up to 10 years | 9.80 |
| Therapists | 31.37 | 11-20 years | 41.18 |
| Family doctors | 21.57 | 21-30 years | 26.47 |
| Neuropathologists | 1.96 | 31-40 years | 14.71 |
| | | over 41 years | 7.84 |

Table 2

COMBINATION OF ANTIHYPERTENSIVE MEDICINES PRESCRIBED BY DOCTORS

| Combinations of AHDs groups | Share of prescribed drugs, % |
|---------------------------------------------------------------------------------------|------------------------------|
| Angiotensin-converting enzyme inhibitors with a diuretic | 26.29 |
| Angiotensin-converting enzyme inhibitors with calcium channel blockers | 20.57 |
| Angiotensin II receptor blockers with a diuretic | 13.71 |
| Calcium channel blockers with angiotensin-converting enzyme inhibitors and a diuretic | 12.00 |
| Calcium channel blockers with angiotensin II receptor blockers | 8.00 |
| Calcium channel blockers with angiotensin II receptor blockers and a diuretic | 8.00 |
| β -blockers with angiotensin-converting enzyme inhibitors | 4.57 |
| Calcium channel blockers with a diuretic | 2.86 |
| β -blockers with calcium channel blockers | 1.71 |
| β -blockers with a diuretic | 1.71 |
| Angiotensin-converting enzyme inhibitors with acetylsalicylic acid and a statin | 0.57 |

The shares of prescribing a dual combination of CCB with BRA and a triple combination of CCB with ARB and a diuretic were the same and equaled 8.0 %. Doctors chose the combination of valsartan with amlodipine, telmisartan with amlodipine, olmesartan with amlodipine, and valsartan with amlodipine and HCT.

4.57 % of the interviewed specialists prescribed β -AB with iACE (bisoprolol in combination with perindopril or ramipril, lisinopril). CCB with a diuretic (amlodipine with indapamide, amlodipine with HCT) accounted for 2.86 % of patients. The combinations of β -AB with CCB (nifedipine with bisoprolol (nebivolol), bisoprolol with amlodipine), β -AB with a diuretic (nebivolol with HCT, atenolol with chlorthalidone) accounted for 1.71 % of patients. Only 0.57 % of all interviewed specialists prescribed ACE inhibitors with acetylsalicylic acid (ASA) and a statin (ASA with ramipril and atorvastatin).

The second part of the survey contained questions for studying the doctors' opinions of regarding potentially possible combinations of AHDs that would be relevant in the treatment.

We asked doctors to evaluate the relevance of the creation, effectiveness and safety of the combinations of AHDs proposed. For evaluation, the respondents were presented with AHDs combinations that were not available at the Ukrainian pharmaceutical market, but were registered in other countries:

- metoprolol with amlodipine (X^1);
- metoprolol with ramipril (X^2);
- metoprolol with hydrochlorothiazide (X^3);
- atenolol with indapamide (X^4);
- atenolol with hydrochlorothiazide (X^5);
- amlodipine with hydrochlorothiazide (X^6);
- ramipril with indapamide (X^7);
- bisoprolol with indapamide (X^8);
- metoprolol with ramipril and indapamide (X^9);
- ramipril with amlodipine and indapamide (X^{10}).

Some of the interviewed specialists ranked the factors quite confidently, while other respondents could not separate the degree of influence of the factors and gave them the same ranks. Therefore, the results of the survey were processed using *a priori* ranking through rank transformation [9].

We made conclusions on the distribution of factors into groups based on the comparison

of average values. For this purpose, Linke and Wallace criterion was used. If the tabular value of coefficient is bigger than the calculated value of coefficient $K_{\text{tab}} > K_{\text{calculated}}$, it can be assumed that the average ranks of the considered factors do not differ from each other and they form a single group.

The coincidence of expert opinions was also checked for each analyzed indicator using the Kendall's coefficient of concordance (w) [9, 10].

$$w = \frac{\sum_{j=1}^k S_j^2}{\frac{1}{12} m^2 (k^3 - k) - m \sum_{i=1}^m T_i^2}$$

$$T_i = \frac{1}{12} \sum_{u=1}^m t_u^3 - t_u$$

where form $\sum_{j=1}^k S_j^2$ – is the sum of squared deviations of the sum of the j -th factor from the average sum of ranks;

k – is the number of factors;

m – is the number of specialists;

u – is the number of groups formed by factors of the same rank in the i -ranking

t_u – is the number of identical ranks in the u -th group of the i -ranking.

This indicator can vary from 0 (no agreement) to 1 (complete agreement). Therefore, the concordance coefficient value of 0.42 was set for efficiency. The statistical significance of the concordance coefficient is established using the Pearson test (x_p^2 -criterion). The calculated value is compared with the tabular value of the criterion. Thus, for all the indicators studied when determining the x_p^2 -criterion the significance level is $\alpha = 0.05$, and the number of degrees of freedom is equal to $f = 9$.

The relevance, effectiveness and safety of combined AHDs were evaluated by the value of the sum of the ranks: the lower the rank, the better the criterion was assigned to the combination. According to the results obtained, a chart of ranks was built.

Thus, the division of ranks by drug groups depending on the relevance of the development of new drugs for the treatment of hypertension took the following form (Fig. 1):

- I group: ramipril / amlodipine / indapamide (X^{10}) > ramipril / indapamide (X^7) > metoprolol / ramipril / indapamide (X^9) > bisoprolol / indapamide (X^8);

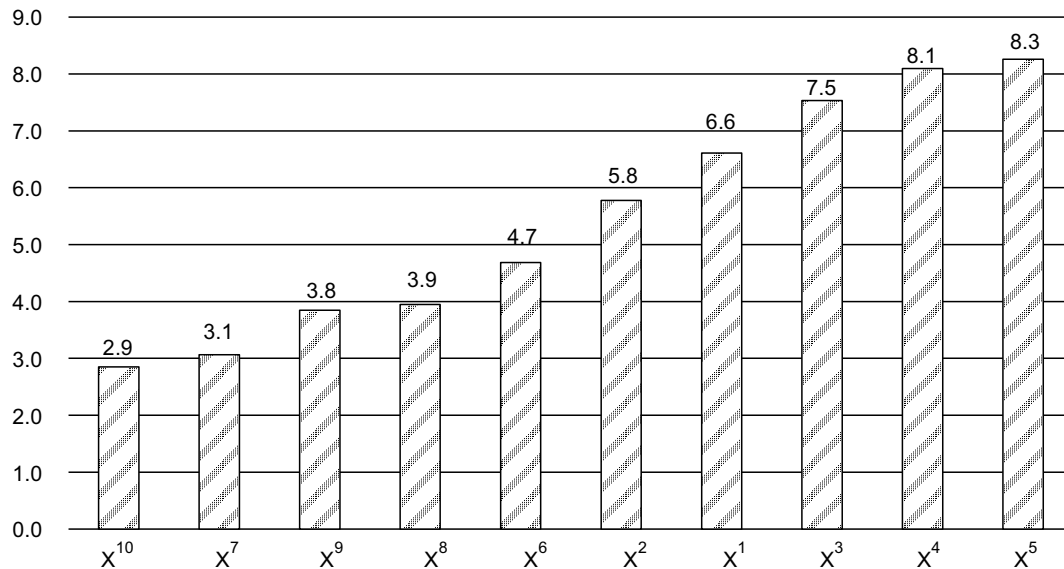


Fig. 1. Division of ranks depending on the relevance of the creation of new combined drugs with the antihypertensive effect

- II group: amlodipine / HCT (X⁶) > metoprolol / ramipril (X²) > metoprolol / amlodipine (X¹);
 - III group: metoprolol / HCT (X³) > atenolol / indapamide (X⁴) > atenolol / HCT (X⁵).
- According to Linke and Wallace criterion, the factors were divided into the following groups depending on the effectiveness of the drug combinations proposed (Fig. 2):
- group I: ramipril / amlodipine / indapamide (X¹⁰) > ramipril / indapamide (X⁷) > metoprolol / ramipril / indapamide (X⁹) > bisoprolol / indapamide (X⁸);
 - group II: amlodipine / HCT (X⁶) > metoprolol / ramipril (X²) > metoprolol / amlodipine (X¹);
 - group III: metoprolol / HCT (X³) > atenolol / indapamide (X⁴) > atenolol / HCT (X⁵).

Evaluating the safety of the proposed drugs and using Linke and Wallace criterion, the following groups of transformations were obtained (Fig. 3):

- I group: ramipril / amlodipine / indapamide (X¹⁰) > ramipril / indapamide (X⁷) > metoprolol / ramipril / indapamide (X⁹) > bisoprolol / indapamide (X⁸);
- II group: metoprolol / HCT (X³) > amlodipine / HCT (X⁶) > metoprolol / ramipril (X²) > metoprolol / amlodipine (X¹);
- III group: atenolol / indapamide (X⁴) > atenolol / hydrochlorothiazide (X⁵).

The summary information on the criteria studied for the selected indicators is given in Table 3.

The small value of the concordance coefficient (moderate correlation) for all indicators

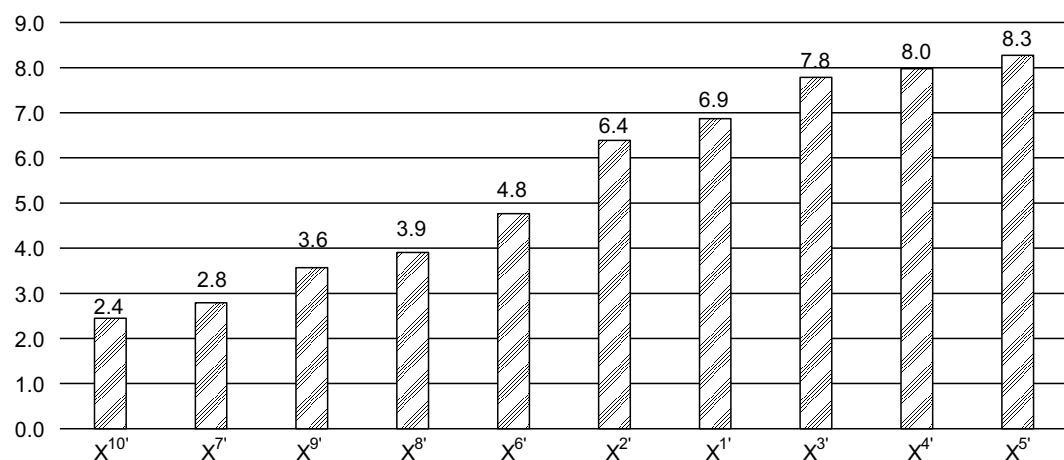


Fig. 2. Division of ranks depending on the effectiveness of the antihypertensive drugs proposed

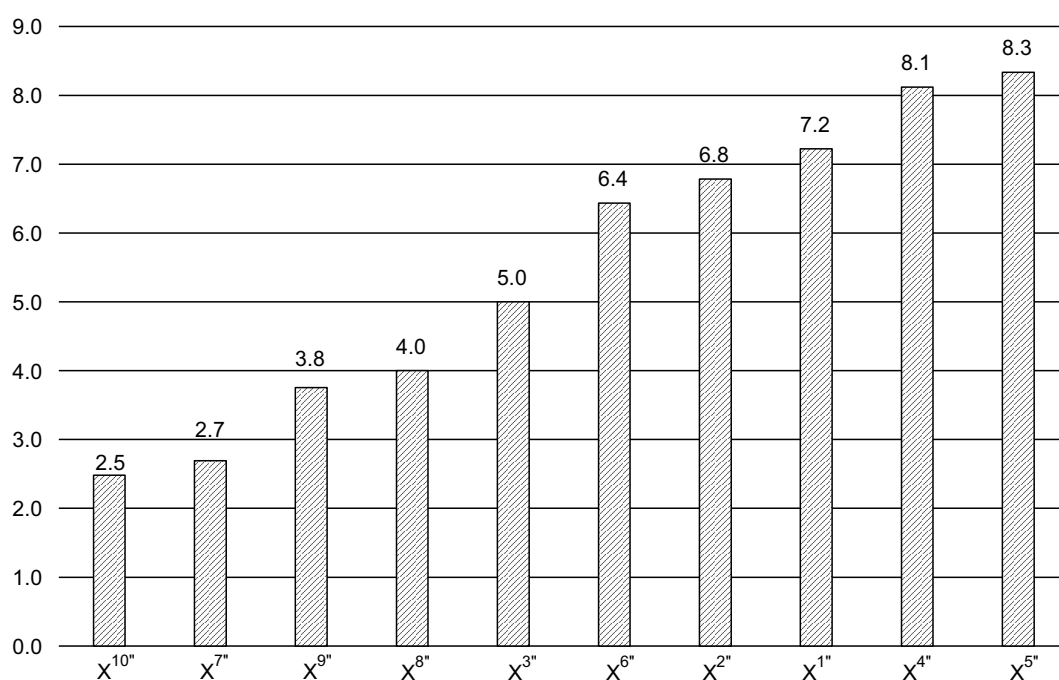


Fig. 3. Division of the ranks regarding the safety of the drugs with the antihypertensive effect proposed

(safety, relevance, effectiveness) is explained by the presence of several optimization factors, which makes it difficult to choose the determining factor.

Therefore, it can be concluded that according to the interviewed doctors, the combinations of such drugs as ramipril with indapamide; bisoprolol with indapamide; metoprolol with ramipril and indapamide; ramipril with amlodipine and indapamide are the most relevant, safe and effective among the new combinations proposed for the development.

At the third stage, the opinions of doctors were studied regarding the factors that were

important when prescribing drugs for the treatment of hypertension.

In the questionnaire, it was suggested to evaluate the factors that, according to doctors, must be taken into account when prescribing combined AHDs. The analysis of the results obtained is presented in Fig. 4.

A significant majority of the doctors interviewed (97.07 %) considered the effectiveness of the selected combined AHDs. The safety of the drug was taken into account by 91.18 % of the respondents, while 84.31 % paid attention to the duration of the drug action. In addition, 72.55 % of the doctors considered the

Table 3

SUMMARY INFORMATION OF THE CRITERIA STUDIED FOR THE SELECTED INDICATORS

| Indicator | Division of ranks | Calculated value of Linke and Wallace criterion $K_{\text{calculated}}$ | Tabular value of Linke and Wallace criterion K_{tabl} | Kendel's concordance coefficient (w) | Calculated value of Pearson's criterion (x_p^2 -criterion) | Tabular value of Pearson's criterion (x_p^2 -criterion) |
|------------|-------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------|
| Relevance | I group | 0.222 | 1.45 | 0.42 | 383.96 | 16.9 |
| | II group | 0.367 | 1.77 | | | |
| | III group | 0.184 | 1.45 | | | |
| Efficiency | I group | 0.332 | 1.45 | 0.50 | 461.92 | 16.9 |
| | II group | 0.407 | 1.77 | | | |
| | III group | 0.127 | 1.45 | | | |
| Safety | I group | 0.323 | 1.45 | 0.37 | 339.47 | 16.9 |
| | II group | 0.804 | 1.45 | | | |
| | III group | 0.040 | 2.23 | | | |

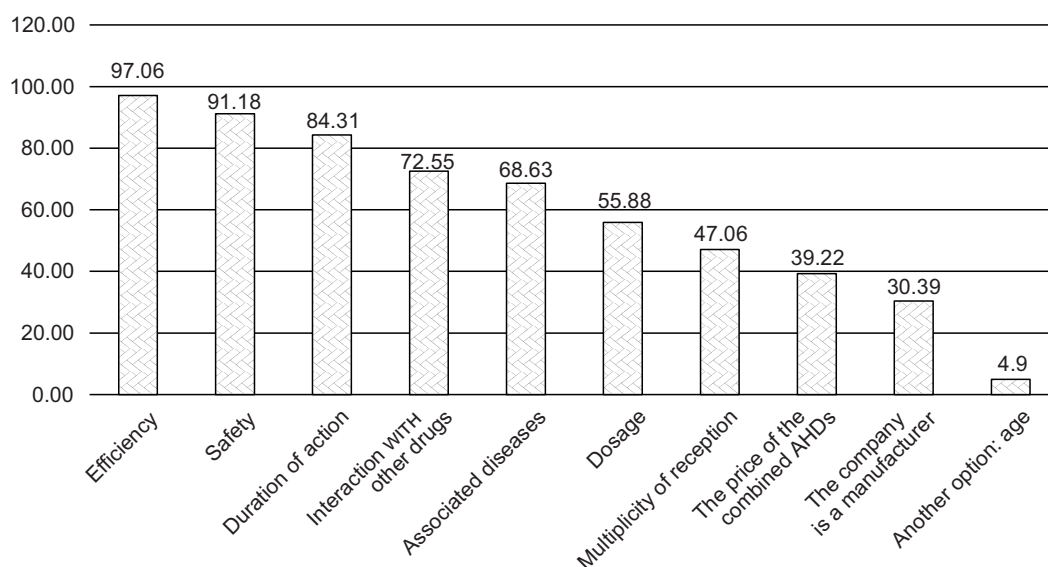


Fig. 4. Factors that are most taken into account by doctors when prescribing combined AHDs

potential interaction of the selected AHDs with other drugs that the patient might use concurrently. The presence of concomitant diseases in patients influenced the prescribing decisions of 68.63 % of the doctors. Dosage and frequency of administration were taken into consideration by 55.88 % and 47.06 % of specialists, respectively. The price of the drug and the manufacturing company were deemed important factors for 39.22 % and 30.39 % of the surveyed respondents, respectively. Furthermore, a small proportion (4.9 %) of physicians indicated that the patients' age played a role in their choice of AHDs for the treatment of hypertension.

When asked about the preferred combinations for the treatment of hypertension, it was found that 61.76 % of specialists chose dual combinations, 37.25 % favored triple combinations, and only 0.98 % indicated their preference for monodrugs. In addition, 62.75 % of the respondents preferred foreign AHDs, while only 37.25 % favored domestic ones. 95.1 % of the surveyed respondents considered it necessary to develop new fixed combinations of AHDs.

Conclusions and prospects of further research. It has been determined that respondents prefer the combination of iACE with a diuretic or combinations of iACE with CCB. ARB drugs with diuretics are prescribed by 13.71 % of surveyed respondents. Only 12.0 % of doctors prefer a triple combination of CCB

with iACE and a diuretic, indicating the combination of perindopril with indapamide and amlodipine.

It has been found that, according to specialists, the most actual, safe and effective among the combinations proposed for the development are: ramipril / indapamide; bisoprolol / indapamide; metoprolol / ramipril / indapamide; ramipril / amlodipine / indapamide.

97.07 % of the interviewed doctors take into account the effectiveness and 91.18 % of the respondents choose the safety of the drugs for the treatment of hypertension, while only 39.22 % of the doctors take into consideration the cost of the drugs, and 30.39 % of the surveyed respondents pay attention to the manufacturer.

The majority of doctors prefer foreign antihypertensive drugs (62.75 %), and only 37.25 % prefer domestic ones. 95.1 % of the surveyed respondents consider it appropriate to create new dual combinations of drugs for the treatment of hypertension.

The survey of doctors conducted regarding the trends in prescribing combined antihypertensive drugs allowed us to determine the relevance of the creation and development of domestic combined antihypertensive drugs in order to expand the range of this market niche.

Conflict of interests: authors have no conflict of interests to declare.

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