

ORIGINAL ARTICLE

Marketing research of combined drugs for treatment of cardiovascular diseases

Marketingový výzkum kombinovaných léčivých přípravků pro léčbu kardiovaskulárních onemocnění

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Received August 1, 2022 / Accepted January 10, 2023

Summary

The work is devoted to the results of complex marketing research of all combined cardiovascular drugs. The market of combined drugs from group C according to the ATC classification in 41 countries of the world during 2019–2022 was analyzed. Segment markets of the 27 European Union countries, Albania, Belarus, Bosnia and Herzegovina, Canada, Colombia, Great Britain, India, Moldova, Norway, Russian Federation, Switzerland, and Ukraine, were studied. The pharmaceutical market of Australia and the United States were also studied. The structure of this group of drugs was characterized, and the most common combinations in the analyzed markets were identified. It was found that group C09 is the most filled with combined drugs, and the number of combinations is most diverse in C09 drug groups that act on the renin-angiotensin system, C10 hypolipidemic drugs, C07 beta-blockers, and C03 diuretics, which are the drugs of the first choice for arterial hypertension and coronary heart disease. There are two promising areas for expanding the range of drugs that affect the cardiovascular system.

Key words: cardiovascular diseases • arterial hypertension • combined cardiovascular drugs • marketing research • directions of assortment expansion

Souhrn

Práce je věnována výsledkům komplexního marketingového výzkumu všech kombinovaných kardiovaskulárních léčivých přípravků. Byl analyzován trh s kombinovanými léčivými přípravky ze skupiny C podle ATC klasifikace ve 41 zemích světa v letech

2019–2022. Analyzovány byly segmentové trhy 27 zemí Evropské unie, Albánie, Běloruska, Bosny a Hercegoviny, Kanady, Kolumbie, Velké Británie, Indie, Moldavska, Norska, Ruské federace, Švýcarska a Ukrajiny. Byl také sledován farmaceutický trh Austrálie a Spojených států amerických. Byla charakterizována struktura této skupiny léčivých přípravků a byly identifikovány nejběžnější kombinace na analyzovaných trzích. Bylo zjištěno, že skupina C09 je nejvíce naplněna kombinovanými léčivými přípravky a počet kombinací je nejrozmanitější ve skupinách C09 léčivé přípravky působící na renin-angiotenzinový systém, C10 hypolipidemika, C07 betablokátory a C03 diuretika, která jsou léky první volby u arteriální hypertenze a ischemické choroby srdeční. Existují dvě perspektivní oblasti pro rozšíření nabídky léčivých přípravků ovlivňujících kardiovaskulární systém.

Klíčová slova: kardiovaskulární onemocnění • arteriální hypertenze • kombinované kardiovaskulární • léčivé přípravky • marketingový výzkum • směry rozšiřování sortimentu

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and one of the most common diseases affecting a person's whole life. In 2011, the United Nations formally recognized noncommunicable diseases, including CVD, as a major global health problem^{1, 2}. These diseases accounted for more than 17 million deaths in 2008, and the World Health Organization estimates that about 23.6 million people will die from CVD in 2030. The equivalent contribution of prevention initiatives, pharmaceutical development, and technological initiatives has significantly reduced CVD mortality in some Western countries. However, increased life expectancy, incomplete adherence to guidelines, and difficulties in persuading the public to support and adhere to prevention measures still make the burden of CVD extremely high.

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Hypertension is the strongest or one of the strongest risk factors for almost all different CVD acquired during life, including coronary heart disease, left ventricular hypertrophy and valvular heart diseases, cardiac arrhythmias including atrial fibrillation, cerebral stroke, and renal failure. The continuous relationship between blood pressure and cardiovascular and renal events distinguishes between high normal blood pressure and hypertension based on arbitrary cut-off values for blood pressures³. The pathophysiology of high blood pressure suggests that the onset of changes should be due to increased cardiac output, increased peripheral vascular resistance, or a combination of both. Each of these mechanisms is regulated, in turn, by hemodynamic, nervous, humoral, and renal processes, all of which differ in their contribution from one person to another. According to updates to the European ESH / ESC (2018) guidelines, the higher the overall risk for the patient's cardiovascular system, blood pressure should be more strictly monitored, and treatment should be initiated urgently to reduce blood pressure to less than 140/90 mmHg⁴.

Drug treatment of hypertension can be started with one drug or a drug combination⁵. In the updated joint guideline, ESC and ESH recommend that most patients take two antihypertensive drugs at the start of pharmacotherapy, preferably in combination in a single tablet⁶. The recommended first-line treatment consists of medicines comprising the following four groups of drugs: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (sartans), calcium channel blockers dihydropyridine type, and thiazide-like diuretics.

Although beta-blockers are inferior to these classes of cardiovascular agents⁷, they are considered an appropriate component of first-line treatment in some countries. Beta-blockers are used in patients with angina who have suffered a myocardial infarction or had a failure or heart rate monitoring⁶.

Patients are best suited to drugs with a long half-life that can be administered once daily. Due to the circadian rhythms of blood circulation regulation, it is preferable for patients to take long-acting antihypertensives in the evening⁸. Still, a positive effect on CVD remains unclear.

Many drugs are used to treat CVD worldwide, and each market has unique medicines for treatment. Marketing studies of specific groups of antihypertensive drugs are common, but comprehensive analyses of all combination cardiovascular drugs have not yet been conducted, which was the aim of our study.

Experimental part

The experiment involved researching the market of combined drugs from group C according to the anatomical-therapeutic-chemical (ATC) classification in the world register of medicines in 41 countries found on the Internet and available literature from 2019–2022.

While doing an experiment, a market segment of the 27 European Union countries, Albania, Belarus, Bosnia and Herzegovina, Canada, Colombia, Great Britain, India, Moldova, Norway, Russian Federation, Switzerland, and Ukraine, were studied. The pharmaceutical market of Australia and the United States were also analysed^{9–51}.

For our research, 27 countries that are part of the European Union (EU) were selected. In addition, the USA, UK, Canada, and Switzerland were included as the world market leaders, Ukraine as the domestic market, Moldova, Russia, and Belarus as the countries geographically closest to the domestic market, and India and Colombia representing countries with emerging pharmaceutical markets. Finally, Albania, Bosnia, Herzegovina, and Norway were covered as non-EU countries.

Since the Ukrainian pharmaceutical market is a domestic market, we focused on its analysis on a broader scale. We investigated which combined medicines from group C according to the ATC classification occupy the largest market share regarding patient sales.

Comprehensive marketing research was conducted in two areas: operational and strategic. Operational analysis was aimed at assessing market conditions, and at the strategic level, an in-depth analysis was conducted to identify promising areas of development. For a more detailed study of the Ukrainian market, the Pharmxplorer program was used.

The methods of grouping, comparison, analysis, mathematical-statistical, graphic, and generalization are used in the study.

Results

According to the ATC classification, cardiovascular drugs belong to group C Medicines affecting the cardiovascular system. Their characteristics are shown in Table 1.

C01 Cardiac drugs

Cardiac drugs enhance the contractile activity of cardiomyocytes and eliminate the phenomenon of heart failure, which can be defined as systolic and (or) diastolic myocardial dysfunction. It leads to remodelling of the heart and blood vessels and impaired hemodynamics and homeostasis.

Most combinations of this group are found in Germany (68 combinations), Ukraine (27 combinations), and Switzerland (27 combinations). In other countries, there are up to 10 combinations.

The most common combination drugs are based on plants. The most popular combinations are preparations based on *Crataegus* herb in combination with other herbal infusions that have a cardiac effect, such as lemon balm, valerian, peppermint, and others (Ukraine, Germany, Switzerland, Moldova, Austria).

In Ukraine, preparations based on *Crataegus* occupy a market share of less than 5% (realization in money).

Table 1. Number of combined cardiovascular drugs according to ATC classification

| Country* | Number of drugs in group C | Number of combined drugs in group C | Percentage of combined drugs in group C, % | Number of combined drugs | | | | | | | | |
|------------------------|----------------------------|-------------------------------------|--|--------------------------|-----|-----|-----|-----|-----|-----|------|-----|
| | | | | C01 | C02 | C03 | C04 | C05 | C07 | C08 | C09 | C10 |
| Albania | 219 | 59 | 26.94 | 0 | 2 | 0 | 0 | 1 | 3 | 0 | 53 | 0 |
| Austria | 2006 | 783 | 39.03 | 8 | 0 | 8 | 5 | 31 | 31 | 5 | 511 | 73 |
| Belgium | 1381 | 455 | 32.95 | 0 | 0 | 4 | 0 | 8 | 40 | 0 | 336 | 67 |
| Belorussia | 155 | 40 | 25.80 | 0 | 0 | 0 | 0 | 0 | 2 | 6 | 19 | 13 |
| Bosnia and Herzegovina | 922 | 271 | 29.39 | 0 | 0 | 3 | 0 | 19 | 8 | 2 | 221 | 18 |
| Bulgaria | 1961 | 312 | 15.90 | 0 | 0 | 2 | 0 | 0 | 23 | 7 | 234 | 46 |
| Canada | 2473 | 438 | 17.71 | 6 | 1 | 13 | 0 | 62 | 8 | 0 | 316 | 32 |
| Colombia | 9480 | 1922 | 20.27 | 0 | 25 | 14 | 0 | 61 | 136 | 0 | 1586 | 122 |
| Croatia | 787 | 244 | 31.00 | 0 | 0 | 0 | 0 | 9 | 13 | 4 | 185 | 42 |
| Cyprus | 827 | 265 | 32.04 | 0 | 0 | 1 | 0 | 2 | 23 | 0 | 176 | 63 |
| Czech Republic | 12256 | 5158 | 42.10 | 0 | 0 | 23 | 2 | 49 | 148 | 12 | 4119 | 805 |
| Denmark | 1536 | 363 | 23.63 | 0 | 0 | 16 | 0 | 2 | 9 | 0 | 282 | 58 |
| Estonia | 996 | 365 | 36.65 | 0 | 0 | 1 | 0 | 8 | 8 | 4 | 305 | 47 |
| Finland | 1057 | 278 | 26.30 | 0 | 0 | 7 | 0 | 1 | 13 | 0 | 244 | 13 |
| France | 3980 | 1075 | 27.01 | 0 | 0 | 25 | 0 | 0 | 105 | 12 | 811 | 122 |
| Germany | 2087 | 828 | 39.67 | 68 | 0 | 76 | 6 | 34 | 33 | 14 | 522 | 73 |
| Great Britain | 879 | 115 | 13.08 | 0 | 0 | 14 | 0 | 7 | 4 | 0 | 86 | 4 |
| Greece | 890 | 302 | 33.93 | 0 | 0 | 6 | 0 | 20 | 26 | 0 | 186 | 65 |
| Hungary | 1822 | 641 | 35.18 | 0 | 0 | 4 | 0 | 3 | 47 | 2 | 454 | 131 |
| India | 2640 | 727 | 27.54 | – | – | – | – | – | – | – | – | – |
| Ireland | 1040 | 354 | 34.04 | 0 | 0 | 7 | 0 | 0 | 11 | 0 | 335 | 0 |
| Italy | 2556 | 638 | 24.96 | 0 | 0 | 8 | 0 | 19 | 33 | 0 | 527 | 50 |
| Latvia | 2300 | 1075 | 46.74 | 5 | 1 | 0 | 1 | 14 | 59 | 16 | 932 | 66 |
| Lithuania | 9691 | 3407 | 35.16 | 0 | 0 | 9 | 4 | 14 | 96 | 24 | 2995 | 267 |
| Luxembourg | 834 | 265 | 31.77 | 0 | 0 | 9 | 0 | 0 | 26 | 2 | 343 | 32 |
| Malta | 1096 | 205 | 18.70 | 1 | 0 | 3 | 0 | 23 | 32 | 2 | 106 | 37 |
| Moldova | 1392 | 332 | 23.85 | 4 | 0 | 2 | 0 | 52 | 34 | 0 | 213 | 27 |
| Netherlands | 2601 | 836 | 32.14 | 0 | 0 | 18 | 0 | 4 | 54 | 6 | 637 | 120 |
| Norway | 1152 | 232 | 20.14 | 0 | 0 | 3 | 0 | 7 | 9 | 0 | 189 | 24 |
| Poland | 3087 | 674 | 21.83 | 5 | 5 | 2 | 1 | 29 | 35 | 5 | 463 | 93 |
| Portugal | 3420 | 1159 | 33.89 | 5 | 0 | 13 | 1 | 14 | 24 | 2 | 929 | 166 |
| Romania | 7040 | 2705 | 38.42 | 0 | 0 | 7 | 0 | 39 | 197 | 24 | 2127 | 310 |
| Russia | 3540 | 557 | 15.73 | – | – | – | – | – | – | – | – | – |
| Slovakia | 972 | 335 | 34.47 | 0 | 0 | 0 | 0 | 11 | 25 | 0 | 261 | 38 |
| Slovenia | 1500 | 170 | 11.33 | 0 | 0 | 11 | 0 | 26 | 25 | 2 | 50 | 56 |
| Spain | 3910 | 763 | 19.51 | 1 | 5 | 8 | 4 | 16 | 18 | 1 | 647 | 53 |
| Sweden | 4388 | 800 | 18.23 | 0 | 0 | 13 | 9 | 12 | 23 | 25 | 624 | 106 |
| Switzerland | 1299 | 445 | 34.26 | 27 | 0 | 9 | 0 | 39 | 29 | 2 | 289 | 51 |
| Ukraine | 1795 | 491 | 27.35 | 27 | 1 | 2 | 1 | 56 | 19 | 2 | 353 | 34 |

* Pharmaceutical markets of Australia and USA do not provide the division of drugs according to ATC classification in their electronic drug registers. Therefore, they are not included.

For example, preparations based on *Crataegus* L. + *Leonurus cardiaca/quinquelobatus* gilib. + taurin are 2.02 %, and *Crataegus* L + *Valeriana officinalis* + *Leonurus cardiaca/quinquelobatus* gilib are 1.6 %.

The C01 group also includes combinations based on potassium and magnesium asparaginate (Ukraine, Germany), combinations of ivabradine with carvedilol (Portugal), and ivabradine with metoprolol (Poland).

C02 Antihypertensive drugs

Antihypertensives are drugs of different pharmacological groups and chemical structures that can lower blood pressure.

Group C02 Antihypertensives are characterized mainly by combinations of reserpine with other substances in this group or other agents that affect the cardiovascular system. The most common are combinations of reserpine with bendroflumethiazide (Albania, Netherlands), clopamide and dihydroergocristine (Latvia, Netherlands, Poland, Russia, and Ukraine), hydrochlorothiazide (Canada, Slovenia, USA), hydrochlorothiazide and dihydralazine (Russia), hydralazine and hydrochlorothiazide (USA). The combination of hydrochlorothiazide with methyldopa was also observed in Colombia and clopamide with dihydroergocristine in Ukraine.

In Ukraine, the drug based on reserpine + clopamide and dihydroergocristine is called Normatens®, manufactured by IC Polfa Rzeszow JSC, Poland. The market share of this preparation was 9.58 % in 2019 and gradually decreased. In 2022, it was 5.97 %.

C03 Diuretics

Diuretics increase the excretory function of the kidneys and the amount of urine.

Group C03 is characterized mainly by combinations of hydrochlorothiazide with other substances in this group or other agents that affect the urinary system. Hydrochlorothiazide is combined with amiloride hydrochloride (21 countries), spironolactone (Greece, Italy, Canada, Colombia, Moldova, Portugal, USA), triamterene (Canada, Colombia, Germany, Russia, USA, Ukraine), butizide (Colombia). In Ukraine, the combination of hydrochlorothiazide + triamterene is registered under the trade name Triampur® composite, AVD Farma GmbH & Co. KG/PLIVA Hrvatska d.o.o., Germany/Croatia. The drug is not popular among diuretics, and the share of the drug is 0.36%.

The combination of furosemide with spironolactone is popular in the world. This combination can be found in 11 countries, including Ukraine. Spironolactone is also combined with butizide (Austria, Germany) and altizide (Iceland, Portugal).

Furosemide is combined with amiloride hydrochloride (UK, India, Ireland, Malta, Luxembourg, Greece), and triamterene (Iceland, Italy).

Chlortalidone is combined with metoprolol tartrate (Slovakia), amiloride hydrochloride (Czech Republic), atenolol (Russia), and azilsartan medoxomil (Russia).

The C03 group is also filled with a combination of potassium-sparing agents with altizide (Luxembourg), epitizide (Netherlands), butizide (Italy), and bendroflumethiazide (Greece, Ireland, Norway, Sweden).

C04 Peripheral vasodilators

This group includes drugs used to treat cerebrovascular or peripheral circulatory disorders.

Group C04 has a tiny number of combinations of active pharmaceutical ingredients (APIs), which enhance the contractile activity of cardiomyocytes and eliminate the phenomena of heart failure.

This group includes the following combinations: bendazole hydrochloride + papaverine (Ukraine, Russia), papaverine + platyphylline (Russia), and buflomedil + cilostazol (Colombia).

According to research data, the drug under the trade name Papazol-Darnytsia® (Ukraine), based on bendazole hydrochloride in combination with papaverine, is not the first choice for treating cerebrovascular or peripheral blood circulation disorders. This product accounted for a 3% market share in 2019–2022.

C05 Angioprotectors

Angioprotectors are a group of drugs that improve microcirculation, normalize vascular permeability, reduce tissue swelling and improve metabolic processes in the walls of blood vessels. Angioprotectors also show antispasmodic activity, cause vasodilation, normalize the rheological properties of blood and vascular permeability, and increase the resistance of capillaries.

The largest number of combinations (more than 30) between different APIs in the C05 group are found in Austria, Canada, Colombia, Moldova, Germany, Romania, Ukraine, and Switzerland.

The most common combinations among the analyzed markets are based on heparin sodium in combination with dexpanthenol (Austria, Germany), allantoin + dexpanthenol (Moldova, Switzerland) dimethylsulfoxide + dexpanthenol (Moldova, Switzerland), vennorutanol + dexpanthenol (Moldova, Ukraine), diclofenac sodium (Moldova), hydroxyethyl salicylate + menthol (Austria, Colombia), benzocaine (Moldova, Ukraine), benzocaine + benzyl nicotinate (Moldova), prednisolone acetate + lauromacrogol 400 (Moldova), prednisolone + polidocanol (Moldova, Ukraine), dexpanthenol + troxerutin (Moldova), hippocastani semen (Auszug) + arnica flower (Auszug, Germany), menthol + hydroxyethyl salicylate (Germany), escine + diethylamine salicylate (Romania), hippocastani semen with extract spissum (Romania), escine (Ukraine), hydrocortisone acetate + framycetin sulfate + esculoside + benzocaine + butamben (Ukraine), escine + epikuron (Ukraine), allii cepae extract + hyoscyami maceratum oleosum + allantoin + avobenzene + 3-(4-methyl)benzylidene-borane-2-on (Switzerland).

This group includes a combination that is registered in most of the analyzed countries. It is a combination of diosmin with hesperidin. It is used as a venotonizing agent.

There are many combinations with troxerutin. This API is combined with hippocastani semen (auszug), hamamelidis folium (auszug) + meliloti herba (auszug) + hippocastani semen (auszug), hippocastani semen (auszug) + crataegi folium cum flore (auszug) + hamamelis folium (auszug) + meliloti herba (auszug), menthol + hippocastani semen (auszug) + hamamelis folium (auszug) + benzocaine + zinc oxide, crataegi folium cum flore (auszug) + hippocastani semen (auszug), indomethacin, carbazochrome etc.

The C05 group also includes drugs used to treat haemorrhoids. These drugs are often combined based on prednisolone, tribenoside, local anesthetics such as cincocaine and lidocaine, and plant extracts.

In Ukraine, by the number of sales, the top three are drugs based on diosmin + hesperidin, troxerutin, and L-lysine aescinat. The market share in 2022 is 37.20%, 9.25%, and 8.50%, respectively. The sales leader is the Detralex® drug based on diosmin + hesperidin, manufactured by Les Laboratoires Servier Industrie, France.

C07 Beta-blockers

Beta-blockers are a class of pharmacological drugs designed to block the function of the beta-subtype of adrenoceptors in the body. Beta-blockers have antianginal, antiarrhythmic and antihypertensive effects. Beta-blockers exhibit positive effects in cardiology due to the blockade of beta-adrenoceptors. They reduce the strength of heart contractions, heart rate (negative inotropic and chronotropic effect), reduce excitability, and myocardial conduction (negative dromotropic and bathmotropic effects). Due to this depressant effect, myocardial oxygen demand is reduced. The reduction of blood pressure is owed by a reduction in cardiac output due to a decrease in heart rate and a reduction of stroke volume of the heart. When using non-selective beta-blockers, peripheral vascular resistance is moderately increased.

Of all the analyzed combined drugs in this group, the most significant number is based on atenolol. Atenolol is combined with the following APIs: chlortalidone (19 countries), nifedipine (Austria, Luxembourg, Germany, France, India), amlodipine besylate (Belarus, Ukraine, Russia, India), chlortalidone + nifedipine (Ukraine, Moldova), hydrochlorothiazide + amiloride hydrochloride (Belarus, Spain), bendroflumethiazide (Spain).

In Ukraine, atenolol + chlortalidone + nifedipine preparations also lead among all combination medicines. The sales study showed that these drugs occupy the fourth place in the C07 group, and their market share in the last 3 years is 8%.

The second place in the number of combinations belongs to metoprolol. Among the countries analyzed, the following combinations can be singled out: metoprolol tartrate + ivabradine hydrochloride (15 countries), metoprolol succinate + felodipine (Belgium, Belarus, Iceland, Spain, Luxembourg,

Sweden, Russia, Switzerland), metoprolol succinate + hydrochlorothiazide (Austria, Belarus, Netherlands, Germany, USA), metoprolol tartrate + chlortalidone (Switzerland, USA) and vinpocetine + indapamide + metoprolol + enalapril maleate (Russia). Metoprolol-based combination products are not registered in Ukraine.

The third place went to bisoprolol and timolol. Bisoprolol is combined with hydrochlorothiazide (26 countries), amlodipine besylate (19 countries), acetylsalicylic acid (11 countries), and perindopril (Belarus, Russia). In Ukraine, preparations based on bisoprolol + amlodipine besylate are sold in small volumes, as the market share in 2022 was 3 %. Timolol maleate is combined with the following APIs: hydrochlorothiazide + amiloride (Belarus, Portugal), bendroflumethiazide (Ireland, UK), hydrochlorothiazide (Canada, Colombia), amiloride (Colombia).

Combination preparations based on propranolol hydrochloride include diazepam (India), alprazolam (India) or hydrochlorothiazide (Canada, USA).

Combining nebivolol hydrochloride with other APIs is common: hydrochlorothiazide (26 countries) and amlodipine besylate (India).

Carvedilol is combined with ivabradine hydrochloride (13 countries) and hydrochlorothiazide (Austria, Germany). In Ukraine, carvedilol is registered as a single-component drug.

In addition, there are combinations of acebutolol hydrochloride + hydrochlorothiazide (Belgium, Belarus, Luxembourg, USA, Colombia), pindolol + hydrochlorothiazide (Canada, USA), labetalol hydrochloride + hydrochlorothiazide (USA), sotalol + hydrochlorothiazide (Belarus, Netherlands), pindolol + clopamide (Belarus, Slovenia, Russia), nadolol with bendroflumethiazide (Canada, USA, Colombia).

A diagram of the combined drug ratio from group C07 is shown in Figure 1.

C08 Calcium antagonists

Calcium channel antagonists are a heterogeneous group of drugs with antianginal and antihypertensive properties. They exhibit the same mechanism of action based on blocking slow L-type calcium channels in the myocardium, conduction system, and vascular smooth muscle. They differ in chemical structure, pharmacokinetics, and pharmacodynamics, including effects on vasodilation, cerebral vessels, and conduction and contractile function of the myocardium.

Of the analyzed countries, this group includes mainly single drugs. There are only a very few combinations. Registered combined drugs are based on amlodipine besylate + indapamide (17 countries), trandolapril + verapamil hydrochloride (Australia, Belarus, Bulgaria, Latvia, Netherlands, Portugal, Poland, Croatia), amlodipine besylate + bisoprolol (Russia), amlodipine besylate + nebivolol (Russia), amlodipine besylate + celecoxib (USA), acetylsalicylic acid + nifedipine (Canada), and amlodipine besylate + hydrochlorothiazide (Colombia).

In Ukraine, drugs based on amlodipine besylate + indapamide take fourth place in sales volume; before, there were only single-component drugs. One drug based on amlodipine besylate +

indapamide is registered on the Ukrainian market under the trade name Arifam®, Servier (Ireland) Industries Ltd. In 2021, this drug had sales of \$ 1 million 653 thousand.

Combined drugs from group C07

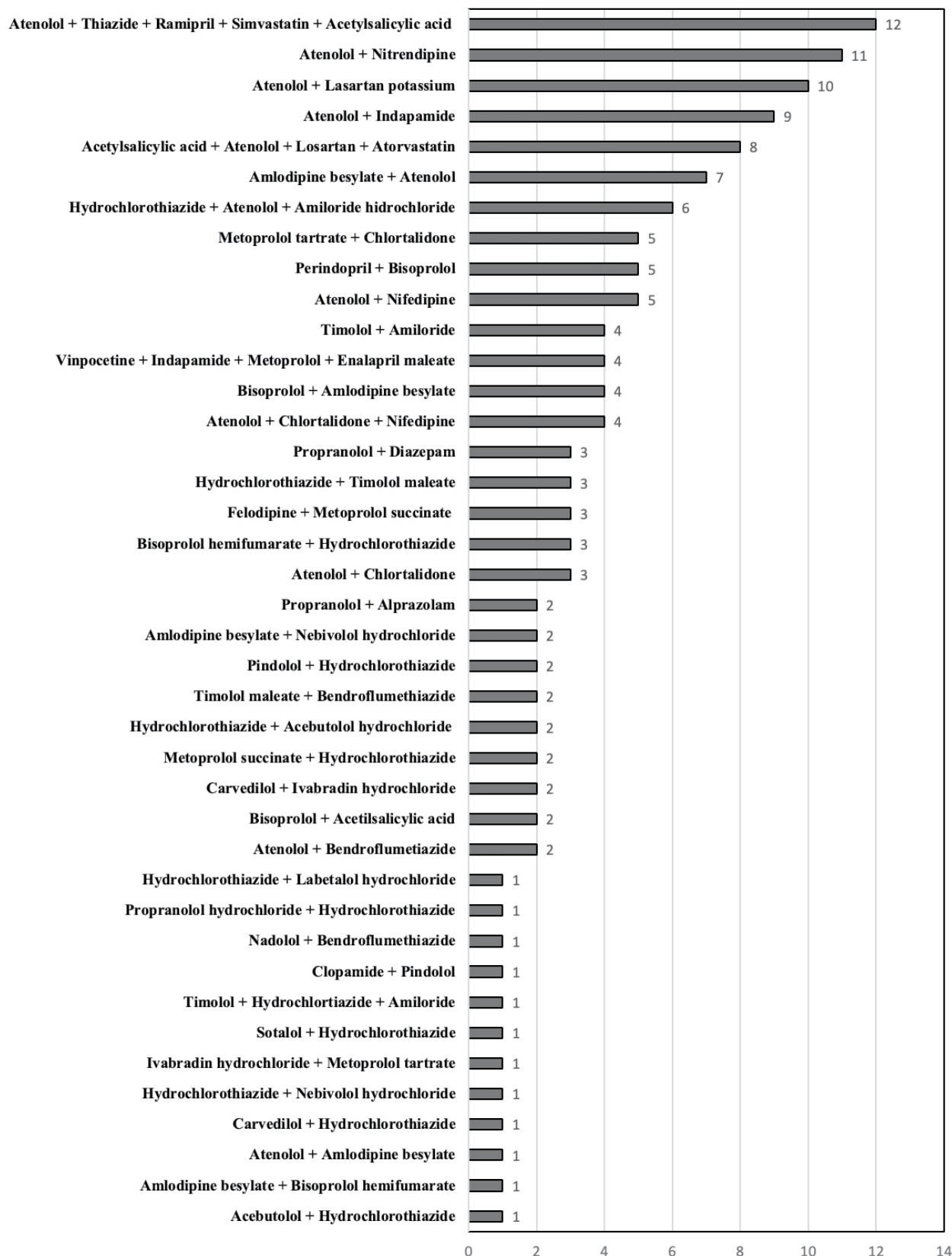


Fig. 1. Diagram of the ratio of combined drugs from group C07

There are more combinations based on amlodipine besylate in India also. These are combinations with atenolol, enalapril, lisinopril, ramipril, valsartan, benazepril, atorvastatin, losartan, nebivolol, telmisartan + hydrochlorothiazide.

C09 Drugs acting on the renin-angiotensin system

ACE inhibitors depress the action of angiotensin-converting enzyme, which converts biologically inactive angiotensin I into angiotensin II, which has a vasoconstrictive effect. In the mechanism of their antihypertensive action, the ability to block the angiotensin-converting enzyme plays the role, followed by inhibition of angiotensin II production from angiotensin I. This, in turn, reduces the synthesis of aldosterone in the adrenal cortex, accompanied by increased excretion of sodium and water from the body. The influence of ACE inhibitors improves renal blood flow and filtration processes in the kidneys. Drugs increase the synthesis of vasodilators such as prostacyclin, nitric oxide, depressant prostaglandins, and atrial natriuretic hormone and reduce the inactivation of bradykinin. ACE inhibitors reduce the sympathetic-adrenal system's activity and inhibit the development of hypertrophy of the myocardium and smooth muscle of the vascular wall. They are one of the most effective modern antihypertensive agents.

This group has a very large number of combined drugs. Group C09 includes combinations based on subgroups of ACE inhibitors, angiotensin II receptor antagonists, and direct renin inhibitors (Table 2).

The most popular combinations, found in 30 countries, are based on the following substances: amlodipine besylate + perindopril arginine, amlodipine besylate + valsartan, candesartan cilexetil + hydrochlorothiazide, enalapril maleate + hydrochlorothiazide, hydrochlorothiazide + irbesartan, hydrochlorothiazide + losartan, hydrochlorothiazide + telmisartan, hydrochlorothiazide + valsartan, indapamide + perindopril arginine, and sacubitril + valsartan.

Popular combinations found in 20 of the analyzed countries are based on the following APIs: aliskiren + hydrochlorothiazide, amlodipine besylate + hydrochlorothiazide + valsartan, amlodipine besylate + olmesartan medoxomil, amlodipine besylate + ramipril, amlodipine besylate + telmisartan, bisoprolol hemifumarate + perindopril arginine, enalapril maleate + lercanidipine hydrochloride, hydrochlorothiazide + amlodipine besylate + olmesartan medoxomil, hydrochlorothiazide + fosinopril sodium, hydrochlorothiazide + lisinopril, hydrochlorothiazide + olmesartan medoxomil, hydrochlorothiazide + quinapril hydrochloride, and hydrochlorothiazide + ramipril, indapamide + perindopril arginine + amlodipine besylate.

In Ukraine, there are 30 combinations with different APIs. The most popular of all drugs of the C09 group is a combination based on amlodipine besylate + indapamide + perindopril arginine. The market share of these products in 2022 was 17.7%. Indapamide + perindopril and hydrochlorothiazide + valsartan

occupy the second and the fourth place (the third place belongs to enalapril maleate) with a market share of 12.3% and 5.0%, respectively.

There are also unique combinations that are registered in a particular country. Only in the USA are the following combinations available: diltiazem maleate + enalapril maleate and enalapril maleate + felodipine. In addition, the following combinations were found in individual countries: in the Czech Republic – amlodipine besylate + perindopril erbumin, in Russia – amlodipine besylate + lisinopril + rosuvastatin and amlodipine besylate + indapamide + lisinopril, hydrochlorothiazide + irbesartan, in India – amlodipine besylate + enalapril maleate, amlodipine besylate + telmisartan, hydrochlorothiazide + losartan potassium, enalapril maleate + losartan potassium, ramipril + losartan potassium and ramipril + hydrochlorothiazide, in Netherlands – azilsartan medoxomil + hydrochlorothiazide, in Spain – delapril hydrochloride + manidipine hydrochloride and valsartan + dihydrochlorothiazide, in Italy – delapril + indapamide, and in Austria – perindopril + tert-butylamine and perindopril arginine + amlodipine besylate.

C10 Hypolipidemic drugs

Hypolipidemic drugs (antihyperlipidemic, antiatherosclerotic) prevent the development or promote regression of the atheromatous process. In the basics of the development of atherosclerosis – lipid metabolism disorders, mainly cholesterol. Lipids in blood plasma form complexes with proteins – lipoproteins that can penetrate the arteries' inner lining.

This group includes a combination of statins with APIs from other groups that affect the cardiovascular system. The most common are combinations based on atorvastatin. It is combined with amlodipine besylate (27 countries), ezetimibe (26 countries), amlodipine besylate + perindopril arginine (21 countries), perindopril arginine (16 countries), acetylsalicylic acid + ramipril (13 countries), acetylsalicylic acid (Belgium, Ukraine, Russia, India), fenofibrate (India), nicotinic acid (India), fenofibrate + ezetimibe (India), methylcobalamin + folic acid + pyridoxine (India), and amlodipine besylate + simvastatin + ezetimibe (Australia).

In Ukraine, combined drugs based on atorvastatin + acetylsalicylic acid + ramipril take fourth place in market share. Before, there were single-component drugs with significantly higher sales volumes. The market share of these drugs was 2.25% in the last three years.

Rosuvastatin-based drugs are also popular. Combinations include ezetimibe (29 countries), amlodipine besylate (20 countries), valsartan (10 countries), tert-butylamine perindopril + indapamide (Estonia, Latvia, Lithuania, Portugal, Slovenia), lisinopril + amlodipine besylate (Moldova), and acetylsalicylic acid (Russia).

Simvastatin is frequently combined with ezetimibe (27 countries), fenofibrate (16 countries), and sitagliptin

Table 2. Extended description of combined drugs from group C09

| Subgroup C09 | Pharmacotherapeutic group | API | Number of countries | Notes |
|----------------|--|---|---------------------|---|
| ACE inhibitors | ACE inhibitors + diuretics | captopril + hydrochlorothiazide | 14 | |
| | | enalapril maleate + hydrochlorothiazide | 36 | |
| | | enalapril maleate + indapamide | 2 | Ukraine, Russia |
| | | lisinopril + hydrochlorothiazide | 31 | |
| | | lisinopril + torasemide | 2 | Lithuania, Poland |
| | | perindopril + indapamide | 33 | |
| | | ramipril + hydrochlorothiazide | 29 | |
| | | ramipril + furosemide | 3 | Austria, Germany, Canada |
| | | ramipril + piretanide | 2 | Ireland, Switzerland |
| | | quinapril hydrochloride + hydrochlorothiazide | 26 | |
| | | fosinopril sodium + hydrochlorothiazide | 24 | |
| | | zofenopril calcium + hydrochlorothiazide | 17 | |
| | | cilazapril + hydrochlorothiazide | 13 | |
| | | benazepril hydrochloride + hydrochlorothiazide | 9 | Bulgaria, Spain, Luxembourg, Netherlands, Portugal, France, Italy, Switzerland, USA |
| | | delapril + indapamide | 1 | Italy |
| | ACE inhibitors + calcium channel blockers | enalapril maleate + lercanidipine hydrochloride | 27 | |
| | | enalapril maleate + nitrendipine | 9 | Austria, Greece, Spain, Germany, Portugal, Romania, Ukraine, Russia, Moldova |
| | | enalapril maleate + felodipine | 1 | USA |
| | | enalapril maleate + diltiazem malate | 1 | USA |
| | | enalapril maleate + amlodipine besylate | 1 | India |
| | | lisinopril + amlodipine besylate | 17 | |
| | | perindopril + amlodipine besylate | 33 | |
| | | ramipril + amlodipine besylate | 24 | |
| | | ramipril + felodipine | 14 | |
| | | trandolapril + verapamil hydrochloride | 18 | |
| | | benazepril hydrochloride + amlodipine besylate | 2 | USA, India |
| | | delapril hydrochloride + manidipine hydrochloride | 2 | Spain, Italy |
| | ACE inhibitors + beta-blockers | perindopril arginine + bisoprolol hemifumarate | 21 | |
| | ACE inhibitors + calcium antagonists + diuretics | perindopril + amlodipine besylate + indapamide | 24 | |
| | | lisinopril + amlodipine besylate + indapamide | 1 | Russia |
| | | lisinopril + amlodipine besylate + indapamide | 1 | Russia |
| | ACE inhibitors + calcium antagonists + statin | lisinopril + amlodipine besylate + rosuvastatin | 1 | Russia |

| | | | | |
|----------------------------------|---|---|----|--|
| Angiotensin receptor blockers II | Angiotensin II receptor blockers + diuretics | losartan potassium + hydrochlorothiazide | 37 | |
| | | valsartan + hydrochlorothiazide | 36 | |
| | | irbesartan + hydrochlorothiazide | 36 | |
| | | candesartan cilexetil + hydrochlorothiazide | 33 | |
| | | telmisartan + hydrochlorothiazide | 35 | |
| | | olmesartan medoxomil + hydrochlorothiazide | 28 | |
| | | azilsartan medoxomil + hydrochlorothiazide | 1 | Netherlands |
| | | azilsartan medoxomil + chlorotalidone | 5 | Ireland, Portugal, Ukraine, Russia, USA |
| | | eprosartan mesilat + hydrochlorothiazide | 15 | |
| | Angiotensin II receptor blockers + calcium channel blockers | losartan potassium + amlodipine besylate | 15 | |
| | | valsartan + amlodipine besylate | 32 | |
| | | irbesartan + amlodipine besylate | 2 | Ukraine, Russia |
| | | candesartan cilexetil + amlodipine besylate | 17 | |
| | | telmisartan + amlodipine besylate | 28 | |
| | | olmesartan medoxomil + amlodipine besylate | 24 | |
| | Angiotensin II receptor blockers + calcium channel blockers + diuretics | losartan potassium + amlodipine besylate + hydrochlorothiazide | 4 | Italy, Russia, USA, India |
| | | valsartan + amlodipine besylate + hydrochlorothiazide | 25 | |
| | | telmisartan + amlodipine besylate + hydrochlorothiazide | 1 | India |
| | | olmesartan medoxomil + amlodipine besylate, and hydrochlorothiazide | 23 | |
| | Angiotensin receptor blockers II + ACE inhibitors | losartan potassium + perindopril | 2 | Belarus, India |
| | | losartan potassium + enalapril maleate | 1 | India |
| | | losartan potassium + ramipril | 1 | India |
| | Angiotensin II receptor blockers + ACE inhibitors + diuretics | losartan potassium + ramipril + hydrochlorothiazide | 1 | India |
| | Angiotensin II receptor blockers + neprilysin inhibitors | valsartan + sacubitril | 31 | |
| | Angiotensin II receptor blockers + direct renin inhibitors | aliskiren + valsartan | 3 | Russia, USA, Colombia |
| Direct renin inhibitors | Direct renin inhibitors + diuretics | aliskiren + hydrochlorothiazide | 21 | |
| | Direct renin inhibitors + calcium channel blockers | aliskiren + amlodipine besylate | 7 | Estonia, Lithuania, Lithuania, USA, Portugal, Sweden, Russia |
| | Direct renin inhibitors + calcium antagonists + diuretic | aliskiren + amlodipine besylate + hydrochlorothiazide | 3 | Portugal, Sweden, USA |

ACE inhibitors – angiotensin-converting enzyme inhibitors, API – active pharmaceutical ingredient

phosphate (USA). Pravastatin sodium is combined with fenofibrate in 15 countries and acetylsalicylic acid only in the USA. In Canada, a combination of lovastatin and nicotinic acid can be found. A variety of nicotinic acid with laropiprant is used in Australia, Ireland, Estonia, Portugal, Romania, and Russia.

A graphic representation of the ratio of combined drugs of group C10 is shown in the form of diagrams in Figure 2.

An analysis of the pharmaceutical market for drugs affecting the cardiovascular system in 41 countries revealed that some drugs are registered in only one country (Table 3).

Discussion

Drugs affecting the cardiovascular system are most abundant in Lithuania, Colombia, Romania, Sweden, Spain, Portugal, and Poland markets. The highest share of combination medicines is in Latvia (46.74%), the Czech Republic (42.10%), Germany (39.67%), Austria (39.03%), Romania (38.42%), Estonia (36.65%), and Hungary (35.18%).

Among all the drugs affecting the cardiovascular system, group C09 – medicines acting on the renin-angiotensin system is the most filled with combined pharmaceutical products. In the groups of C09

medications acting on the renin-angiotensin system, C10 hypolipidemic drugs, C07 beta-blockers, and C03 diuretics, the most significant number of combinations was found. These are drugs of the first choice in treating cardiovascular and renal diseases, including heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, and hypertension.

Group C01 (Cardiac drugs) includes mainly preparations based on Crataegus extract. Crataegus extract contains many pharmacologically active substances, the most abundant compounds being flavonoids, triterpenic acids, and phenol carboxylic acids. Crataegus preparations are currently being marketed as an alternative treatment for hypertension, arrhythmia, and early stages of congestive heart failure by regulating the whole organism at multiple levels and targets⁵². Medicinal preparations based on Crataegus extracts are combined with other plant-origin materials with cardiac action to enhance the hypotensive, cardioprotective, and anticonvulsant effects⁵³.

The most common combined drugs of the C02 group (hypotensive drugs) are drugs based on reserpine. Reserpine is an indole alkaloid extracted from Rauwolfia serpentine roots, an Indian climbing shrub. Reserpine was FDA-approved and is one of the first agents developed to treat hypertension in clinical practice. Reserpine is prescribed alone or combined

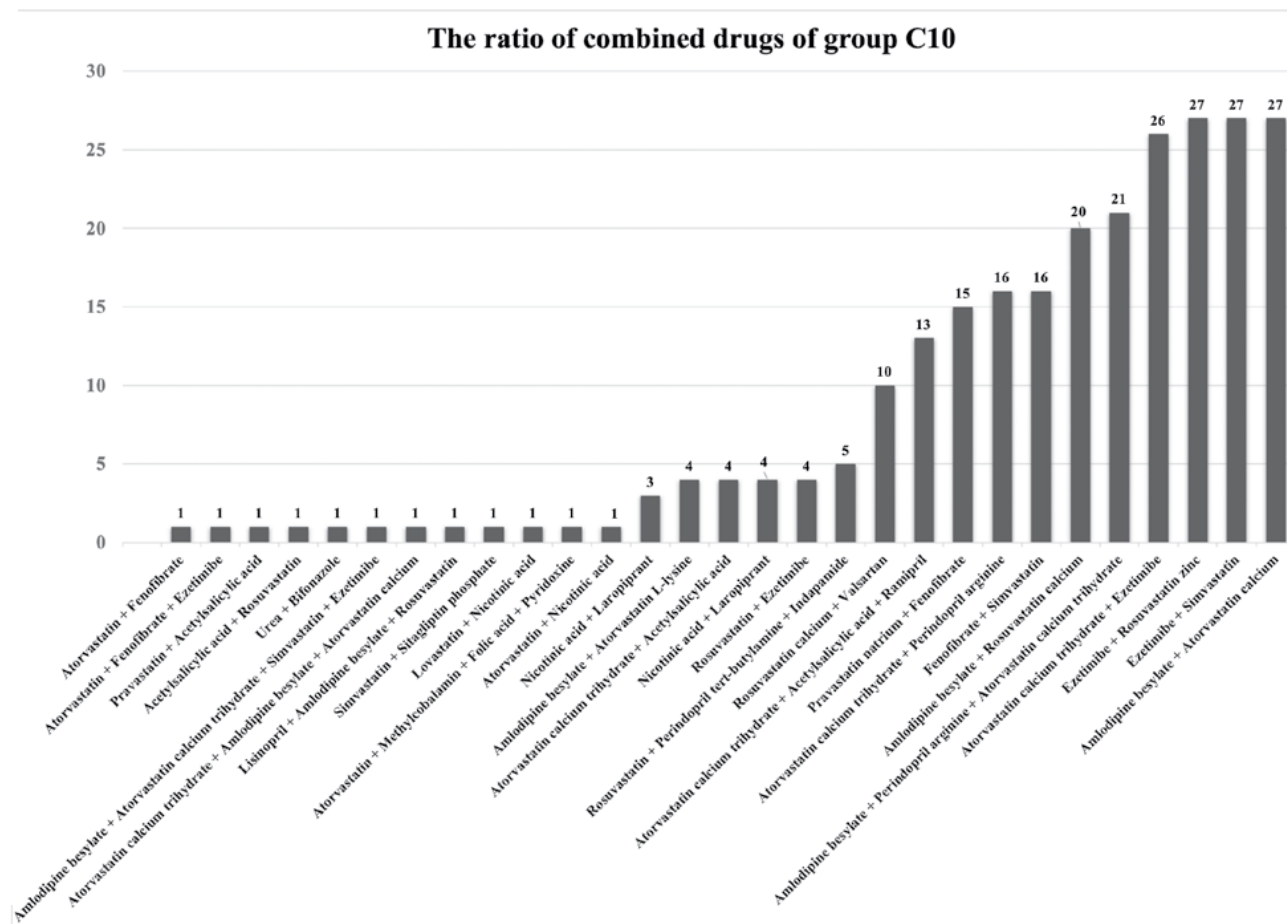


Fig. 2. Diagram of the ratio of combined drugs of group C10

Table 3. List of medicinal products registered in one country

| Country | Medicines |
|----------------|--|
| Canada | Acetylsalicylic acid with nifedipine |
| Colombia | Hydrochlorothiazide with methyldopa |
| | Butizide with hydrochlorothiazide |
| | Buflomedil with cilostazol |
| | Timolol with amiloride hydrochloride |
| | Amlodipine besylate with hydrochlorothiazide |
| Czech Republic | Chlortalidone with amiloride hydrochloride |
| India | Amlodipine besylate with atenolol |
| | Acetylsalicylic acid, atenolol, losartan, and atorvastatin |
| | Atenolol with indapamide |
| | Atenolol with losartan potassium |
| | Atenolol with nitrendipine |
| | Atenolol, thiazide, ramipril, simvastatin and acetylsalicylic acid |
| | Propranolol with alprazolam |
| | Propranolol with diazepam |
| | Amlodipine besylate with enalapril maleate |
| | Amlodipine besylate, telmisartan and hydrochlorothiazide |
| | Losartan with enalapril maleate |
| | Losartan with ramipril |
| | Losartan, ramipril and hydrochlorothiazide |
| | Atorvastatin with fenofibrate |
| | Atorvastatin with fenofibrate and ezetimibe |
| | Atorvastatin, methylcobalamin, folic acid, and pyridoxin |
| | Atorvastatin with nicotinic acid |
| Italy | Delapril hydrochloride with indapamide |
| Netherlands | Azilsartan medoxomil and hydrochlorothiazide |
| Portugal | Dyhydroergocristin mesylate, esculin with rutoside |
| Russia | Hydrochlorothiazide, hydralazine and reserpine |
| | Chlortalidone with azilsartan medoxomil |
| | Chlortalidone with atenolol |
| | Papaverine with platyphylline |
| | Vinpocetine, indapamide, metoprolol and enalapril maleate |
| | Amlodipine besylate, indapamide, and lisinopril |
| | Rosuvastatin with acetylsalicylic acid |
| Slovakia | Chlortalidone with metoprolol tartrate |
| Spain | Atenolol with bendroflumetiazide |
| Ukraine | Clopamide with dyhydroergocristine |
| USA | Hydralazine hydrochloride, hydrochlorothiazide and reserpine |
| | Reserpine with trichlormethiazide |
| | Hydrochlorothiazide with labetalol |
| | Amlodipine besylate with celecoxib |
| | Diltiazem with enalapril maleate |
| | Enalapril maleate with felodipine |
| | Pravastatin with acetylsalicylic acid |
| | Simvastatin; sitagliptin phosphate |

with a vasodilator or thiazide diuretic, such as reserpine-hydrochlorothiazide. Reserpine was initially introduced as a first-line antihypertensive therapy but is currently considered a second-line treatment. This change in status is due to newer and more favorable antihypertensive medications with reduced side effects⁵⁴.

Diuretics (C03) are the first-line therapy for widespread cardiovascular and non-cardiovascular diseases. Traditional diuretics are commonly prescribed for treatment in patients with hypertension, edema, heart failure, and many kidney problems. The use of several classes of diuretics currently available for clinical use exhibits an overall favorable risk/benefit balance⁵⁵. Hydrochlorothiazide remains the most popular of the thiazide diuretics, and furosemide is the loop diuretic. They are often combined with potassium-sparing diuretics to minimize side effects and improve blood pressure control. Hydrochlorothiazide is usually combined with amiloride hydrochloride, spironolactone, triamterene, and other potassium-sparing agents. Furosemide is combined with amiloride hydrochloride and spironolactone. The hydrochlorothiazide and amiloride hydrochloride combination is the most popular in the studied countries⁵⁶. Non-thiazide diuretic API chlorthalidone is often combined with selective beta-receptor blockers, allowing better blood pressure control if monotherapy is ineffective⁵⁷.

The C04 group is mainly filled with single-component drugs, but combinations can be found based on the myotropic antispasmodic agent papaverine. It reduces tone and smooth muscle contractile activity, resulting in a vasodilating and antispasmodic effect. Papaverine is combined with bendazole and platyphylline to enhance the antispasmodic action of smooth muscles and blood vessels⁵⁸.

The results of our studies have shown that heparin (the C05 group according to the ATC classification) is included in the highest number of combinations. Heparin has an anti-edematous, anti-exudative, anti-inflammatory, and anti-coagulation effect. Heparin is combined with various drugs to expand the therapeutic effect, such as dexpanthenol (stimulates granulation and epithelization of tissues), allantoin (an anti-inflammatory, adstringent effect), diclofenac sodium, benzocaine, diethylamine salicylate, butamben (analgesics), lauromacrogol 400, polidocanol (a sclerosing agent), prednisolone acetate (a corticosteroid), or framycetin sulfate (an antibiotic for local use). There are also combinations with bioflavonoids such as vennorutinol and troxerutin. Heparin is also combined with pro-drugs (dimethyl sulfoxide and benzyl nicotinate) and biologically active substances (escin, esculin).

A combination of diosmin + hesperidin is most often used to treat chronic venous disorders. This drug is found in most countries we investigated^{59, 60}. The study showed that troxerutin is combined mainly with herbal preparations.

The C07 group counts a sufficient number of combinations, which makes it possible to choose an effective medicine. The market analysis showed that the included top three combined drugs are atenolol, metoprolol, and bisoprolol. Most of the registered drugs were based on atenolol with chlortalidone. This combination has an antihypertensive effect due to the impact on beta-blockers and the action of a thiazide-like diuretic⁶¹. Metoprolol tartrate is most often combined with ivabradine hydrochloride. This drug is prescribed for the symptomatic treatment of chronic stable angina pectoris. The drug has a therapeutic effect due to the impact of beta-blockers and the effect on heart rate⁶². The combination of bisoprolol with hydrochlorothiazide is registered in many world countries. This drug is used for arterial hypertension. The therapeutic effect is achieved due to the beta-blockers and thiazide diuretic effects⁶³.

Group C08 is filled with combined drugs based on amlodipine besylate. Those medicines are combined with drugs with different mechanisms of action. According to our research, these are diuretics (indapamide and hydrochlorothiazide), beta-blockers (atenolol, bisoprolol, and nebivolol), and nonsteroidal anti-inflammatory drugs (celecoxib), ACE inhibitors (benazepril, enalapril, lisinopril, ramipril), hypolipidemic drugs (atorvastatin), antiplatelet drugs (acetylsalicylic acid), angiotensin II receptor antagonists (valsartan, losartan, telmisartan).

According to our research, the most significant number of combined drugs in the C09 group is found with enalapril maleate. Given the pharmacological properties of ACE inhibitors⁶⁴, combining them with diuretics, beta-blockers, and calcium channel blockers having a different mechanism of action is advisable⁶⁵.

Studies have shown that the most common combinations are enalapril maleate with hydrochlorothiazide. Moreover, it has been clinically proven that this combination is one of the best for treating arterial hypertension^{66, 67}. The most common combinations are enalapril maleate with hydrochlorothiazide, presented in such trade names, for example, in Austria Co – Renitec®, Co-Enac Hexal®, Co-Enalapril 1A Pharma®, Co-Mepril®, Co-Renistad®⁶⁹. Albania – CO-ME-PRIL®¹⁰. Ireland – Innozide®²². Poland – Enap H®, Enap HL®³⁹. Every country on the market has its own generic drugs. Representatives of the combination of enalapril maleate with lercanidipine are Coripren®, Elernap®, Enalapril/Lercanidipine Accord®, Lercaprel®, and others. The following trade names represent ramipril with hydrochlorothiazide on the world market: Hypren plus HCT forte®, Lannaprilplus®, Lannapril plus forte®, Ramicomp Genericon mite®, Ramicomp Genericon®, Ramipril HCT Krka®, Ramipril-HCT Sandoz®, Ramipril/HCT Actavis®, Ramipril/HCT Hexal®, and others. Indapamide with perindopril – Bipreterax-arginine®, Preterax arginine®, Indixcombi®, Noliprel®, Co-prenessa®, Panoprist®, Perindopril + indapamide krka®, Tertensifbi-kombi®. Sacubitril with valsartan is

available under the brands Entresto®, Neparvis®, Yuperio®, and others.

In Ukraine, enalapril maleate as a single-component drug takes third place, which proves its popularity among ACE inhibitors. Its combination with hydrochlorothiazide is a leader, which coincides with studies in 41 countries.

Our studies have shown that the C10 group (hypolipidemic medicines) has many combinations. Fixed-dose combinations of hypolipidemic agents are useful and safe for managing hyperlipidemia. They combine important characteristics of each compound, such as established efficacy and a favorable safety profile. Furthermore, their complementary mechanism of action may result in enhanced hypolipidemic and pleiotropic effects. The most common drugs, such as atorvastatin and rosuvastatin, are combined with antihypertensive drugs since patients with a combination of hypertension and dyslipidemia have a triple risk of death from CVD⁶⁸. Atorvastatin, rosuvastatin, and simvastatin are combined with ezetimibe. Ezetimibe is often used as an add-on therapy to statins to decrease LDL-C levels further. Fibrates can be crucial in managing dyslipidemia, especially in patients with obesity, metabolic syndrome, or diabetes who usually have residual CVD risk. Fibrates (fenofibrate) are combined with atorvastatin, simvastatin, pravastatin⁶⁹.

A more extensive analysis of the Ukrainian pharmaceutical market showed that the most common drugs worldwide are not always the best sellers.

To overcome the global problem of CVD mortality, expanding the range of drugs that affect the cardiovascular system is advisable. It can take place in two promising directions. The first direction is to create new combinations that have proven themselves well in other countries⁷⁰ or to develop combined drugs, including drugs often used simultaneously as single-component drugs⁷¹. It will help the individual approach prescribing pharmacotherapy and reduce the risk of adverse reactions. The second direction is implemented by registering generic drugs in the same market. It will ensure lower prices and, consequently, accessibility to all social spheres of the population and increase the likelihood of continued treatment. As a result, compliance and treatment efficiency will increase, and cardiovascular mortality will decrease^{72, 73}.

Conclusion

A comprehensive marketing study of combined drugs of group C according to the ATC classification was conducted in 41 countries. The structure of each subgroup is analyzed, and the most common combinations are highlighted. The most common combination drugs belong to group C9. It was found that group C09 is most filled with combination drugs. The drug combinations are most diverse in groups

C09 drugs that act on the renin-angiotensin system, C10 hypolipidemic drugs, C07 beta-blockers, and C03 diuretics, which are first-line drugs for the treatment of hypertension and coronary heart disease.

We conducted a more extensive analysis of the pharmaceutical market of Ukraine. The results showed which combinations from group C are the leaders and have the highest sales.

We selected drugs found in unique combinations and registered only in one country. There are two promising areas for expanding the range of drugs that affect the cardiovascular system.

Conflict of interests: none.

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