Original Study

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2025; 12(2):1682-1691

UDC: 615.225.036(497.11)"2012/2021"

doi:10.5937/hpimj2502682D

# Analysis of The Use of Angiotensin Converting Enzyme Inhibitors In The Republic of Serbia In The Period From 2012 To 2021

Tamara D. Dobrić[1], Nemanja B. Todorović[2], Dragana S. Milijašević[1,3], Mladena N. Lalić Popović[1,4], Boris Ž. Milijašević[5]

[1] Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2] Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[3] Institute for Public Health of Vojvodina, Novi Sad, Serbia
[4] Centre for Medical and Pharmaceutical Investigations and Quality Control (CEMPhIC), Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia
[5] Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

## SUMMARY

**Introduction:** An estimated 1.28 billion people worldwide, aged 30 to 79 years have hypertension, a major risk factor for numerous cardiovascular complications. Adequate therapy can significantly reduce these risks. Today angiotensin converting enzyme (ACE) inhibitors are the drugs of choice in the treatment of hypertension, and are also used in the treatment of heart failure, myocardial infarction and kidney failure, which ranks them among the most commonly prescribed drugs in practice.
**Aim:** The aim of this study was to analyze the consumption of ACE inhibitors in the Republic of Serbia in the period from 2012 to 2021 as well as to examine the relationship between their prices and consumption.
**Material and Method:** Data on medication consumption and pricing were obtained from the official website of the Agency for Medicines and Medical Devices of the Republic of Serbia (ALIMS). Drug utilization analysis was conducted using an internationally established methodology based on the concept of anatomical-therapeutic-chemical classification of drugs (ATC) and defined daily dose (DDD) along with the DU90% method.
**Results:** In the Republic of Serbia higher consumption of monocomponent ACE inhibitors was recorded compared to their fixed-dose combinations. The most frequently used were enalapril and ramipril, which can be related to their lower prices.
**Conclusion:** Given the substantial body of evidence indicating the advantages of perindopril compared to other ACE inhibitors, more frequent use of this drug should be considered. When prescribing ACE inhibitors advantage should also more often be given to fixed-dose combinations because about 75% of hypertensive patients require dual therapy to achieve blood pressure control. The use of fixed-dose combinations has been shown to significantly improve both compliance and adherence.

**Keywords:** Drug Consumption, ACE Inhibitors, Hypertension, Pharmacoeconimics

Corresponding author:
Full Professor Boris Ž. Milijašević, MD, PhD
Specialist in Clinical Pharmacology
Depertment of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine Novi Sad, University of Novi Sad, Hajduk Veljkova 3, 21000, Novi Sad, Serbia
E-mail: boris.milijasevic@mf.uns.ac.rs

## INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACE inhibitors) were introduced into clinical practice as antihypertensive drugs in the 1980s and their use has expanded significantly since then [1]. Today, they are the drugs of choice in the treatment of hypertension and are also used in the treatment of heart failure, myocardial infarction, and renal failure of diabetic and non-diabetic etiology. All of this makes them one of the most commonly prescribed drugs in practice [2].

According to the World Health Organization, 1.28 billion people worldwide between the ages of 30 and 79 have hypertension [3]. At least 3 million people die annually directly from the consequences of high blood pressure, and the condition contributes to many other fatal diseases. Hypertension is a major risk factor for stroke, coronary heart disease, heart failure, and kidney failure [4]. However, the use of antihypertensive medication, regardless of the initial blood pressure or the type of drug used, reduces the risk of adverse events. A reduction in systolic blood pressure by 10 mmHg lowers the risk of coronary heart disease by approximately 25% and the risk of stroke by about 33% [5]. The treatment of uncomplicated essential arterial hypertension can begin with any of the five main classes of antihypertensive drugs: thiazide diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers [6].

ACE inhibitors are effective agents for the treatment of patients with hypertension, and current data indicate that they are even more effective in reducing the morbidity and mortality from cardiovascular events compared with angiotensin receptor blockers [7]. They act through the renin-angiotensin-aldosterone system (RAAS) by blocking angiotensin converting enzyme (ACE) and preventing the conversion of inactive angiotensin I to the active effector hormone angiotensin II. Additionally, ACE inhibitors reduce the degradation of bradykinin and enables its effect - vasodilatation by stimulating the production of nitric oxide and natriuresis via direct tubular action [1,8].

The goal of antihypertensive therapy is to mitigate the risks associated with elevated blood pressure without simultaneously negatively affecting the quality of life. Available data suggest that at least 75% of patients will require combination therapy with multiple antihypertensive drugs to achieve adequate blood pressure control [9]. For adults with hypertension who require pharmacological treatment, the World Health Organization recommends the use of combination therapy, primarily in the form of fixed-dose combinations, which improves patient compliance and adherence [10].

In Serbia, a study analyzing the consumption and pricing of ACE inhibitors in 2009 and 2010 found that these medications were the most widely used among all antihypertensive drugs. The consumption of ACE inhibitors in 2010 was four times higher than in Norway, the country with a developed pharmacotherapeutical practice. This study has also highlighted disproportionately high use of more expensive ACE inhibitors such as monocomponent fosinopril and fixed-dose combinations of diuretics with expensive ACE inhibitors, such as cilazapril and fosinopril, compared to more cost-effective ramipril and enalapril, suggesting that Serbia may have room to improve cost-efficiency in hypertension pharmacotherapy [11]. A study conducted in Novi Sad between 2011 and 2012 analyzed data on the sales and consumption of antihypertensive medications prescribed to outpatients diagnosed with essential arterial hypertension. The data were collected from public pharmacies in Novi Sad. The study found that ACE inhibitors were the most frequently used class of antihypertensive drugs, prescribed three times more often than calcium channel blockers, five times more than beta-blockers, and twenty times more than diuretics [12].

As of 2021, the following monocomponent ACE inhibitors were available in Serbia: captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, cilazapril, fosinopril, trandolapril, and zofenopril. In addition, fixed-dose combinations of ACE inhibitors with diuretics and calcium channel blockers were also in use [13].

## AIM

The aim of the study was to analyze the consumption of angiotensin converting enzyme inhibitors (ACE inhibitors) in the Republic of Serbia in the period from 2012 to 2021, as well as to examine the correlation between the price of individual drugs and their consump-

tion.

## MATERIAL AND METHODS

This study was designed as an academic, retrospective, pharmacoeconomic study.

Data on the consumption and price of angiotensin converting enzyme inhibitors in the Republic of Serbia for the period from 2012 to 2021 were obtained from the official website of the Agency for Medicines and Medical Devices (ALIMS) of the Republic of Serbia [13].

Drug utilization was analyzed using an internationally recognized methodology based on the Anatomical Therapeutic Chemical (ATC) classification system and defined daily doses (DDD), as well as the DU90% method. The consumption of drugs was calculated using the ATC-DDD methodology, where DDD (Defined Daily Dose) serves as a statistical unit of measure for drug use. It represents the average daily dose of a drug for an adult human and it does not depend on the price, size or packaging of the drug. The number of DDD/1000 inhabitants per day provides insight into the number of people (per 1000) who used a certain drug and were exposed to its effects during the day [14]. DU 90% is a method used to measure the effectiveness of drug usage as it ranks drugs by the number of DDD and determines which drugs make up

**Table 1.** Overview of the consumption of monocomponent angiotensin-converting enzyme inhibitors within the DU90% segment, presented as the number of DDD/1000 inhabitants/day (DDD/TID) and as a percentage (%) of total consumption in the C09A group

**INN** - International Nonproprietary Name
**DDD/TID** - number of defined daily doses per 1000 inhabitants per day
**DU90%** - segment of drug use 90%

| 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|
| INN (DDD/TID) | % | INN (DDD/TID) | % | INN (DDD/TID) | % |
| ramipril (72.70) | 37.71% | enalapril (88.14) | 39.61% | enalapril (72.11) | 37.03% |
| enalapril (62.58) | 32.46% | ramipril (72.17) | 32.43% | ramipril (67.42) | 34.62% |
| fosinopril (20.54) | 10.65% | fosinopril (23.46) | 10.54% | fosinopril (17.11) | 8.79% |
| lisinopril (12.27) | 6.36% | lisinopril (10.29) | 4.62% | lisinopril (13.10) | 6.73% |
| cilazapril (8.43) | 4.37% | cilazapril (9.17) | 4.12% | quinapril (7.06) | 3.63% |
| DU90% - 9/5 | 91.55% | DU90% - 10/5 | 91.32% | DU90% - 10/5 | 90.80% |
| **2015** | | **2016** | | **2017** | |
| INN (DDD/TID) | % | INN (DDD/TID) | % | INN (DDD/TID) | % |
| ramipril (98.95) | 38.43% | ramipril (90.01) | 42.40% | ramipril (120.71) | 51.71% |
| enalapril (95.47) | 37.08% | enalapril (60.05) | 28.28% | enalapril (53.47) | 22.91% |
| fosinopril (19.71) | 7.65% | fosinopril (19.41) | 9.14% | lisinopril (19.55) | 8.38% |
| lisinopril (16.56) | 6.43% | lisinopril (15.71) | 7.40% | fosinopril (18.42) | 7.89% |
| perindopril (6.94) | 2.70% | perindopril (7.74) | 3.65% | | |
| DU90% - 10/5 | 92.29% | DU90% - 10/5 | 90.87% | DU90% - 10/4 | 90.89% |
| **2018** | | **2019** | | **2020** | |
| INN (DDD/TID) | % | INN (DDD/TID) | % | INN (DDD/TID) | % |
| ramipril (82.58) | 40.14% | ramipril (115.21) | 47.41% | ramipril (139.80) | 51.91% |
| enalapril (60.10) | 29.22% | enalapril (58.03) | 23.88% | enalapril (44.90) | 16.67% |
| lisinopril (20.75) | 10.09% | lisinopril (23.12) | 9.51% | lisinopril (34.88) | 12.95% |
| fosinopril (18.53) | 9.01% | fosinopril (19.08) | 7.85% | fosinopril (16.82) | 6.25% |
| perindopril (9.73) | 4.73% | perindopril (11.44) | 4.71% | perindopril (15.12) | 5.61% |
| DU90% - 10/5 | 93.19% | DU90% - 10/5 | 93.36% | DU90% - 10/5 | 93.39% |
| **2021** | | | | | |
| INN (DDD/TID) | % | | | | |
| ramipril (81.47) | 45.53% | | | | |
| enalapril (36.42) | 20.35% | | | | |
| lisinopril (18.02) | 10.07% | | | | |
| perindopril (13.95) | 7.80% | | | | |
| fosinopril (13.78) | 7.70% | | | | |
| DU90% - 10/5 | 91.45% | | | | |

90% of total usage [15].

Drug utilization was analyzed using the SPSS version 21.0 package (IBM, Chicago, IL, USA). Changes in the usage of angiotensin-converting enzyme inhibitors and their fixed-dose combinations between 2012 and 2021 were analyzed. Data were expressed as percentages of total consumption for each year. The relative change in usage was calculated as the percentage difference between consumption in 2012 and 2021. To assess the relationship between drug prices and their consumption levels, a correlation analysis was conducted. For each active substance or combination, the Beta coefficient (β) was calculated, representing the slope of the regression line between price and usage over the analyzed period. A negative β value indicates an inverse relationship (i.e., increased price associated with decreased usage), while a positive β value suggests a direct relationship. The statistical significance of the correlation was evaluated using p values, with values of $p<0.05$ considered statistically significant and values of $p<0.01$ considered highly significant.

## RESULTS

Table 1 presents the consumption of monocomponent angiotensin-converting enzyme inhibitors within the DU90% segment in Serbia from 2012 to 2021. In almost all years, 5 out of the 10 available drugs were within DU90%. Additionally, in all observed years, enalapril and ramipril occupied the top two positions in terms of consumption, while fosinopril and lisinopril alternated in third place (Table 1). Regarding fixed combinations of ACE inhibitors, the most commonly used were combinations of angiotensin-converting enzyme inhibitors and thiazide diuretics (C09BA). Two drugs from this group, enalapril-hydrochlorothiazide and ramipril-hydrochlorothiazide, continuously had the highest consumption of all ACE inhibitor combinations from 2012 to 2018. However, a shift was observed in 2019 and 2020, with ramipril-hydrochlorothiazide still maintaining the highest consumption, while perindopril-indapamide took second place. In 2021, the two most used fixed-dose combinations of ACE inhibitors were perindo-

| 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|
| INN (DDD/ TID) | % | INN (DDD/ TID) | % | INN (DDD/ TID) | % |
| ramipril, hydrochlorothiazide (18.42) | 32.38 | enalanpril, hydrochlorothiazide (16.06) | 28.69 | ramipril, hydrochlorothiazide (17.91) | 26.9 |
| enalapril, hydrochlorothiazide (13.41) | 23.57 | ramipril, hydrochlorothiazide (12.74) | 22.76 | enalapril, hydrochlorothiazide (15.33) | 23.03 |
| fosinopril, hydrochlorothiazide (10.06) | 17.68 | fosinopril, hydrochlorothiazide (10.67) | 19.06 | fosinopril, hydrochlorothiazide (10.22) | 15.35 |
| lisinopril, hydrochlorothiazide (5.26) | 9.25 | quinapril, hydrochlorothiazide (7.25) | 12.95 | quinapril, hydrochlorothiazide (9.78) | 14.69 |
| quinapril, hydrochlorothiazide (4.84) | 8.51 | lisinopril, hydrochlorothiazide (5.61) | 10.02 | lisinopril, hydrochlorothiazide (6.86) | 10.3 |
| DU90% - 10/5 | 91.39 | DU90% - 9/5 | 93.48 | DU90% - 10/5 | 90.27 |
| **2015** | | **2016** | | **2017** | |
| INN (DDD/TID) | % | INN (DDD/TID) | % | INN (DDD/TID) | % |
| enalapril, hydrochlorothiazide (18.39) | 28.3 | ramipril, hydrochlorothiazide (22.98) | 31.42 | ramipril, hydrochlorothiazide (31.66) | 38.49 |
| ramipril, hydrochlorothiazide (18.34) | 28.22 | enalapril, hydrochlorothiazide (14.30) | 19.55 | enalapril, hydrochlorothiazide (11.22) | 13.64 |
| fosinopril, hydrochlorothiazide (8.35) | 2.85 | lisinopril, hydrochlorothiazide (9.28) | 12.69 | fosinopril, hydrochlorothiazide (10.08) | 12.25 |
| lisinopril, hydrochlorothiazide (7.14) | 0.99 | fosinopril, hydrochlorothiazide (8.17) | 11.17 | lisinopril, hydrochlorothiazide (9.85) | 12.02 |
| quinapril, hydrochlorothiazide (6.11) | 9.4 | quinapril, hydrochlorothiazide (6.66) | 9.11 | perindopril, indapamide (4.88) | 5.93 |
| cilazapril, hydrochlorothiazide (1.77) | 2.72 | perindopril, indapamide (3.58) | 4.9 | perindopril, amlodipine (3.66) | 4.45 |
| | | perindopril, amlodipine (2.85) | 3.9 | quinapril, hydrochlorothiazide (3.02) | 3.67 |
| DU90% - 10/6 | 92.48 | DU90% - 12/7 | 92.74 | DU90% - 11/7 | 90.45 |

**Table 2a.** Consumption of fixed-dose combinations of ACE inhibitors within the DU90% segment, presented as the number of DDD/1000 inhabitants/day (DDD/TID) and as a percentage (%) of total consumption in the C09B group

**INN** - International Nonproprietary Name
**DDD/TID** - number of defined daily doses per 1000 inhabitants per day
**DU90%** - segment of drug use 90%

**Table 2b.** Consumption of fixed-dose combinations of ACE inhibitors within the DU90% segment, presented as the number of DDD/1000 inhabitants/day (DDD/TID) and as a percentage (%) of total consumption in the C09B group

**INN** - International Nonproprietary Name
**DDD/TID** - number of defined daily doses per 1000 inhabitants per day
**DU90%** - segment of drug use 90%

| 2018 | | 2019 | | 2020 | |
|---|---|---|---|---|---|
| INN (DDD/TID) | % | INN (DDD/TID) | % | INN (DDD/TID) | % |
| ramipril, hydrochlorothiazide (16.95) | 22.87 | ramipril, hydrochlorothiazide (24.08) | 27.73 | ramipril, hydrochlorothiazide (24.67) | 26.08 |
| enalapril, hydrochlorothiazide (13.13) | 17.72 | perindopril, indapamide (11.61) | 13.37 | perindopril, indapamide (14.32) | 15.14 |
| lisinopril, hydrochlorothiazide (9.56) | 12.9 | enalapril, hydrochlorothiazide (11.60) | 13.36 | perindopril, amlodipine, indapamide (11.29) | 11.93 |
| fosinopril, hydrochlorothiazide (9.40) | 12.69 | lisinopril, hydrochlorothiazide (10.25) | 11.80 | lisinopril, hydrochlorothiazide (10.18) | 10.76 |
| perindopril, indapamide (7.84) | 10.58 | perindopril, amlodipine, indapamide (8.97) | 10.33 | enalapril, hydrochlorothiazide (9.91) | 10.47 |
| perindopril, amlodipine, indapamide (5.07) | 6.84 | fosinopril, hydrochlorothiazide (6.70) | 7.72 | fosinopril, hydrochlorothiazide (8.52) | 9.01 |
| perindopril, amlodipine (3.93) | 5.30 | perindopril, amlodipine (4.75) | 5.47 | perindopril, amlodipine (5.37) | 5.68 |
| quinapril, hydrochlorothiazide (3.85) | 5.20 | quinapril, hydrochlorothiazide (3.46) | 3.98 | lisinopril, amlodipine (2.96) | 3.13 |
| DU90% - 12/8 | 94.1 | DU90% - 13/8 | 93.76 | DU90% - 14/8 | 92.2 |

| 2021 | |
|---|---|
| INN (DDD/TID) | % |
| perindopril, indapamide (17.04) | 20.18 |
| perindopril, amlodipine, indapamide (15.14) | 17.93 |
| enalapril, hydrochlorothiazide (11.87) | 14.06 |
| ramipril, hydrochlorothiazide (11.74) | 13.90 |
| lisinopril, hydrochlorothiazide (9.47) | 11.21 |
| perindopril, amlodipine (6.43) | 7.61 |
| fosinopril, hydrochlorothiazide (6.32) | 7.48 |
| DU90% - 13/7 | 92.37 |

pril-indapamide and perindopril-amlodipine-indapamide (Table 2).

In the further course of the study, we observed changes in the consumption of ACE inhibitors and their fixed-dose combinations between 2012 and 2021, as well as the correlation between changes in consumption and the price of the medications which is shown in Table 3. For drugs that were not on the market in 2012, we compared the consumption in the first year they were introduced and in 2021. In both years, the consumption of monocomponent ACE inhibitors was significantly higher than the consumption of their fixed combinations, even though the total consumption of monocomponent ACE inhibitors decreased from 2012 to 2021, while the consumption of fixed combinations increased. Among monocomponent ACE inhibitors the largest increase in consumption was observed for trandolapril, which first appeared on the market in 2013 and, since then, its consumption has increased by 589%, which can be related to a significant drop in its price. The consumption of perindopril from 2012 to 2021 increased by 226.7%. The correlation between the price and consumption of perindopril is strong, negative, and statistically significant. This means that the linear decrease in the price of this drug over the ten-year period was accompanied

by an increase in its consumption. Statistically significant negative correlations between price decreases and consumption increases were also observed for lisinopril and ramipril among the monocomponent ACE inhibitors. Meanwhile, the consumption of enalapril, cilazapril, quinapril, fosinopril, as well as the total consumption of monocomponent ACE inhibitors, declined.

Significant changes were also observed when comparing the use of fixed-dose combinations of ACE inhibitors in the first and last year of the studied period. For example, the consumption of enalapril-hydrochlorothiazide combination decreased by 11.48% in 2021 compared to 2012, and the consumption of ramipril-hydrochlorothiazide decreased by 36.26%, which were the 2 most used medications from this group in years 2012 to 2018. In contrast, the consumption of perindopril-indapamide increased by a remarkable 2562.5% during the same period, which can be attributed to the significant statistical relationship between the decreasing price of this medication and its increased consumption. In contrast, consumption of perindopril-indapamide increased dramatically by 2562.5% during the same period. This increase correlates significantly with the decrease in the medication's price. The most notable growth in consumption was observed for the perindopril-amlodipine combination, which showed a statistically significant correlation between increased use and price reduction. The perindopril-amlodipine-indapamide combination which was first introduced in 2016 saw an increase in consumption of 5121% by 2021. While the correlation between its price and consumption

| INN | 2012 DDD/TID | 2021 DDD/TID | Change in use (%) | Beta | Statistical significance |
|---|---|---|---|---|---|
| captopril | 5.37 | 6.48 | 20.66 | -0.116 | 0.749 |
| enalapril | 62.58 | 36.42 | -41.80 | 0.08 | 0.825 |
| lisinopril | 12.27 | 18.02 | 46.86 | -0.808 | 0.005[B] |
| perindopril | 4.27 | 13.95 | 226.70 | -0.808 | 0.005[B] |
| ramipril | 72.70 | 81.47 | 12.06 | -0.697 | 0.025[A] |
| quinapril | 6.03 | 2.78 | -53.90 | | |
| cilazapril | 8.43 | 2.93 | -65.24 | -0.538 | 0.109 |
| fosinopril | 20.54 | 13.78 | -32.90 | -0.37 | 0.92 |
| trandolapril | 0.18* | 1.24 | 588.89 | -0.869 | 0.002[B] |
| zofenopril | 0.60 | 1.28 | 113.33 | -0.129 | 0.721 |
| **Total for C09A** | **192.80** | **178.95** | **-7.18** | | |
| enalapril, hydrochlorothiazide | 13.41 | 11.87 | -11.48 | -0.20 | 0.956 |
| enalapril, indapamide | 0.18** | 0.06 | -66.67 | | |
| lisinopril, hydrochlorothiazide | 5.26 | 9.47 | 80.04 | -0.896 | 0.001[B] |
| perindopril, indapamide | 0.64 | 17.04 | 2562.50 | -0.642 | 0.045[A] |
| ramipril, hydrochlorothiazide | 18.42 | 11.74 | -36.26 | 0.085 | 0.815 |
| quinapril, hydrochlorothiazide | 4.84 | 2.68 | -44.63 | -0.489 | 0.151 |
| cilazapril, hydrochlorothiazide | 2.89 | 1.12 | -61.25 | 0.112 | 0.759 |
| fosinopril, hydrochlorothiazide | 10.06 | 6.32 | -37.18 | 0.552 | 0.098 |
| **Total for C09BA** | **55.52** | **60.32** | **8.65** | | |
| lisinopril, amlodipine | 0.49 | 1.90 | 287.76 | -0.778 | 0.008[B] |
| perindopril, amlodipine | 0.00 | 6.43 | 91757.14 | -0.964 | 0.001[B] |
| ramipril, felodipine | 0.88 | 2.75*** | 212.50 | -0.741 | 0.036[A] |
| ramipril, amlodipine | 0.05**** | 1.06 | 2020.00 | | |
| trandolapril, amlodipine | 0.0***** | 0.00 | 0.00 | | |
| **Total for C09BB** | **1.37** | **9.39** | **585.40** | | |
| perindopril, amlodipine, indapamide | 0.29***** | 15.14 | 5120.69 | -0.783 | 0.066 |
| **Total for C09BX** | **0.29*****| **15.14** | **5120.69** | | |

**Table 3.** Changes in the usage of ACE inhibitors and their fixed-dose combinations between 2012 and 2021 expressed as percentages, and the correlation between their price and consumption level

**INN** - International Nonproprietary Name
**DDD/TID** - number of defined daily doses per 1000 inhabitants per day
* - calculated from 2013
** - calculated from 2020
*** - calculated until 2020
**** - calculated from 2018
***** - calculated from 2016
[A] - p<0,05
[B] - p<0,01

is strong, it is not statistically significant (table 3).

## DISCUSSION

Based on the obtained results, in the observed period among the monocomponent angiotensin-converting enzyme inhibitors, enalapril and ramipril were the most commonly used, which can be attributed to their low prices. In 2012, the least used drugs from this group were perindopril and zofenopril, which also had the highest prices. Perindopril consumption from 2012 to 2021 increased by 227%. The results show that the linear decline in the price of this drug over a period of ten years was accompanied by an increase in its consumption, which can be considered a progress. Compared to enalapril, perindopril has a longer effect as it provides blood pressure control over 24 hours, so it needs to be taken only once a day, while enalapril is taken twice a day [16]. In addition, perindopril is less likely to cause symptomatic hypotension after the first dose, making it a safer agent for initiating ACE inhibitor therapy, especially in patients with heart failure [17]. Another advantage of perindopril is that it more potently inhibits endothelial cell apoptosis, a process that is one of the important initiating factors in the development of atherosclerosis [18]. Additionally, in the first year after acute myocardial infarction, treatment with enalapril, captopril, fosinopril, and lisinopril was associated with higher mortality compared with treatment with ramipril and perindopril [19]. Despite these advantages, including the significant drop in the price of perindopril, which has been almost equal to the price of enalapril since 2019, as well as numerous studies indicating a greater protective effect of perindopril on the occurrence of acute myocardial infarction, stroke, and death [20], the use of this drug in Serbia remains far behind that of enalapril and ramipril. In fact, it is also surpassed in consumption by both lisinopril and fosinopril.

Among fixed-dose combinations of ACE inhibitors, the most used in the observed period were combinations of angiotensin converting enzyme inhibitors and thiazide diuretics (C09BA). Between 2012 and 2018, enalapril-hydrochlorothiazide and ramipril-hydrochlorothiazide consistently had the highest consumption rates among all ACE inhibitor combinations but by the year 2021 the two most used fixed combinations were perindopril-indapamide and perindopril-amlodipine-indapamide. By far the largest increase in consumption was observed in combinations containing perindopril.

It is important to note that throughout the entire observed period, the consumption of monocomponent ACE inhibitors consistently exceeded that of their fixed combinations. Numerous international guidelines for the treatment of hypertension agree that, in addition to lifestyle changes, the co-prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers with calcium channel blockers and thiazide diuretics in maximum tolerated doses is the most desirable combination in the pharmacotherapy of hypertension [21]. In a large number of patients, monotherapy is not sufficient for successful blood pressure control, so the primary goal of combination therapy is to achieve adequate blood pressure management. In addition, numerous mechanisms are involved in the pathogenesis of hypertension, and monotherapy will often act on only one of them [22]. Combination therapy offers better tolerability and fewer side effects. Given that dose-dependent adverse effects of antihypertensive drugs are very common, combination therapy is often preferable to high doses of individual drugs because it can increase efficacy without significantly increasing the risk of adverse effects and, therefore, has the potential to increase adherence compared to high-dose monotherapy [23]. Initiating therapy with a combination of two drugs allows for faster and better achievement of target blood pressure values, usually with lower doses than if the components of the combination were prescribed separately, while also reducing the frequency of dose-dependent adverse effects. Antihypertensive drugs can be combined by administering two drugs simultaneously or by administering a fixed combination of two drugs in one tablet [6]. The asymptomatic and chronic nature of hypertension affects the adherence and persistence of patients in therapy because there are no symptoms that would remind them of their condition on a daily basis, nor unpleasant effects if they take the therapy incorrectly [23]. Therefore, fixed combinations of drugs should be preferred because in this way the number of tablets that the patient needs to take on a daily basis is reduced, which has been proven to have a positive effect on compliance and ad-

herence [24]. Despite this, the total consumption of monocomponent angiotensin-converting enzyme inhibitors in the Republic of Serbia remained significantly higher than the consumption of fixed-dose combinations of ACE inhibitors across all years. According to the World Health Organization, despite the existence of effective, safe and affordable antihypertensive drugs, the success of hypertension control has been declining in the last 5 to 10 years, both in some low- and middle-income countries and in some high-income countries. A major reason for the above-mentioned poor level of control is the fact that many patients are prescribed only monotherapy, despite clear evidence of the benefits of combining two or more drugs, especially in the form of fixed-dose combinations [10].

Considering the entire C09 group, which includes ACE inhibitors, their fixed-dose combinations, as well as angiotensin receptor antagonists and their fixed-dose combinations, it is evident that ACE inhibitors hold a dominant position in terms of consumption in Serbia. In 2021, the consumption of monocomponent ACE inhibitors accounted for 58.4% of the C09 group, while fixed-dose combinations of ACE inhibitors followed in second place with 27.7%. The consumption of the same groups of drugs in the Republic of Finland was 36% and 3.8%. On the other hand, the consumption of monocomponent angiotensin receptor antagonists and their fixed combinations in Serbia was significantly lower, 9.9% and 4% compared to 47.9% and 12.22% in Finland [13,25]. The higher consumption of angiotensin receptor antagonists in the Republic of Finland, despite their higher prices, could be explained by their more favorable side effect profile compared to ACE inhibitors. These drugs significantly less often cause bradykinin-mediated dry irritating cough. On the other hand, current data suggest that ACE inhibitors are more effective than angiotensin receptor antagonists in reducing morbidity and mortality associated with cardiovascular events [7], which, along with lower prices, could justify their greater use in the Republic of Serbia.

## CONCLUSION

Based on the large number of studies that indicate the advantages of perindopril compared to other ACE inhibitors, more frequent use of this drug should be considered. When prescribing ACE inhibitors advantage should also more often be given to fixed-dose combinations because about 75% of hypertensive patients require dual therapy to control blood pressure and the use of fixed-dose combinations significantly improves compliance and adherence. These findings highlight the importance of continuous national surveillance of drug utilization, physician education, and alignment of prescribing practices with evidence-based guidelines.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## REFERENCES

1. Navis GJ, Faber HJ, de Zeeuw D, DEJONG PE. ACE inhibitors and the kidney - A risk-benefit assessment. Drug Safety. 1996 Sept;15(3):200-11.

2. Odović J, Aleksić M, Trbojević Stanković J. Inhibitori angiotenzin - konvertujućeg enzima - osnovne farmakološke osobine i metode određivanja. Arhiv za farmaciju. 2009;59(1):27-39.

3. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank JK, Cunha PG, Danser AHJ, Pinho RM, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelaković B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Van de Borne P, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023 Dec 1;41(12):1874-2071.

4. Pavlović K. Poremećaji arterijskog krvnog pritiska. In: Popović S, Obradović D, editors. Interna medicina 1. Novi Sad: Medicinski fakultet Novi Sad; 2022. P.159-67.

5. Ivanuša, M. News in Epidemiology of cardiovascular diseases and management of arterial hypertension. Medicus. 2014; 23(1):53-62.

6. Ministry of Health of Republic of Serbia. National guide to good clinical practice for diagnosis and treatment of arterial hypertension. 2012. Available from: https://www.zdravlje.gov.rs/view_file.php?file_id=667&cache=sr

7. Dinicolantonio JJ, Lavie CJ, O'Keefe JH. Not all angiotensin-converting enzyme inhibitors are equal: focus on ramipril and perindopril. Postgrad Med. 2013 Jul;125(4):154-68.

8. Piepho RW. Overview of the angiotensin-converting-enzyme inhibitors. Am J Health Syst Pharm. 2000 Oct;57 Suppl 1:S3-7.

9. Gradman AH, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. J Clin Hypertens (Greenwich). 2011 Mar;13(3):146-54.

10. Hypertension [Homepage on Internet]. Who.int. [cited 2024 Feb 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension

11. Perić DM, Milijašević DS, Tomić NZ, Knežević AD, Bukumirović NR, Milijašević BŽ. Use of ACE-Inhibitors in Serbia in 2009 and 2010. Hospital Pharmacology - International Multidisciplinary Journal . 2014;1(3):122-9.

12. Tomas A , Tomić Z, Milijasević B, Ban M, Horvat O, Vukmirović S, Sabo A. Patterns of prescription antihypertensive drug utilization and adherence to treatment guidelines in the city of Novi Sad. Vojnosanit Pregl2016; 73:531–537.

13. Medicines and Medical Devices Agency of Serbia (ALIMS). Promet i potrošnja lekova za upotrebu u humanoj medicini 2012–2021 [Internet]. Belgrade: ALIMS; [cited 2024 Feb 13]. Available from: https://www.alims.gov.rs/o-agenciji/

14. WHO Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs, 2022 [Internet]. Oslo: WHO Collaborating Centre; [cited 2024 Feb 13]. Available from: https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/

15. Sabo A, Tomić Z, Horvat O, Milijašević B. Osnovi farmakoekonomije i farmakoepidemiologije. Novi Sad; Medicinski fakultet; 2020.

16. Morgan T, Anderson A. Clinical efficacy of perindopril in hypertension. Clin Exp Pharmacol Physiol Suppl. 1992;19:61-5.

17. Vítovec J, Spinar J. First-dose hypotension after angiotensin-converting enzyme (ACE) inhibitors in chronic heart failure: a comparison of enalapril and perindopril. Slovak Investigator Group. Eur J Heart Fail. 2000 Sep;2(3):299-304.

18. Ceconi C, Francolini G, Bastianon D, Gitti GL, Comini L, Ferrari R. Differences in the effect of angiotensin-converting enzyme inhibitors on the rate of endothelial cell apoptosis: in vitro and in vivo studies. Cardiovasc Drugs Ther. 2007 Dec;21(6):423-9.

19. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med. 2004 Jul 20;141(2):102-12.

20. Snyman JR, Wessels F. Perindopril: do randomised, controlled trials support an ACE inhibitor class effect? A meta-analysis of clinical trials. Cardiovasc J Afr. 2009 Mar-Apr;20(2):127-34.

21. Prosser HCG, Azzam O, Schlaich MP. Resistant Hypertension: Which Agent? Heart Lung Circ. 2018 Aug;27(8):911-16.

22. Messerli FH, Combinations in the treatment of hypertension: ACE inhibitors and calcium antagonists. Am J Hypertens.1999;12(S5):86-90.

23. Erdine S. Compliance with the treatment of hypertension: the potential of combination therapy. J Clin Hypertens (Greenwich). 2010 Jan;12(1):40-6.

24. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. Am J Hypertens. 2006 Nov;19(11):1190-6.

25. Finnish Medicines Agency Fimea. Finnish statistics on medicines [Internet]. Helsinki: Fimea; [cited 2024 Feb 13]. Available from: https://fimea.fi/en/databases_and_registeries/consumption

# Analiza upotrebe inhibitora angiotenzin-konvertujućeg enzima u Republici Srbiji u periodu od 2012. do 2021. godine

Tamara D. Dobrić[1], Nemanja B. Todorović[2], Dragana S. Milijašević[1,3], Mladena N. Lalić Popović[1,4], Boris Ž. Milijašević[5]

[1] Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[2] Katedra za farmaciju, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[3] Institut za javno zdravlje Vojvodine, Novi Sad, Srbija
[4] Centar za medicinsko-farmaceutska istraživanja (CEMFIK), Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[5] Katedra za farmakologiju, toksikologiju i kliničku farmakologiju, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija

## KRATAK SADRŽAJ

**Uvod:** U svetu 1,28 milijardi ljudi uzrasta od 30 do 79 godina boluje od hipertenzije, koja predstavlja jedan od glavnih faktora rizika za brojne kardiovaskularne komplikacije. Adekvatna terapija može značajno smanjiti ove rizike. Danas su inhibitori angiotenzin-konvertujućeg enzima (ACE inhibitori) lekovi izbora u terapiji hipertenzije, a koriste se i u lečenju srčane insuficijencije, infarkta miokarda i bubrežne insuficijencije, što ih svrstava među najčešće propisivane lekove u kliničkoj praksi.
**Cilj:** Cilj ovog istraživanja bio je da se analizira potrošnja ACE inhibitora u Republici Srbiji u periodu od 2012. do 2021. godine, kao i da se ispita povezanost njihove cene i potrošnje.
**Materijal i metode:** Podaci o potrošnji lekova i njihovim cenama preuzeti su sa zvanične internet stranice Agencije za lekove i medicinska sredstva Republike Srbije (ALIMS). Analiza potrošnje lekova sprovedena je primenom međunarodno prihvaćene metodologije zasnovane na konceptu anatomsko-terapijsko-hemijske (ATC) klasifikacije lekova i definisane dnevne doze (DDD), kao i metodom DU90%.
**Rezultati:** U Republici Srbiji zabeležena je veća potrošnja monokomponentnih ACE inhibitora u poređenju sa njihovim fiksnim kombinacijama. Najčešće korišćeni lekovi bili su enalapril i ramipril, što se može dovesti u vezu sa njihovim nižim cenama.
**Zaključak:** Imajući u vidu veliki broj studija koje ukazuju na prednosti perindoprila u odnosu na ostale ACE inhibitore, trebalo bi razmotriti češću primenu ovog leka. Prilikom propisivanja ACE inhibitora prednost bi češće trebalo davati fiksnim dozama kombinovane terapije, jer je za oko 75% pacijenata sa hipertenzijom potrebna dvostruka terapija za adekvatnu kontrolu krvnog pritiska, a primena fiksnih kombinacija značajno poboljšava pridržavanje terapiji i adherenciju.

**Ključne reči:** potrošnja lekova, ACE inhibitori, hipertenzija, farmakoekonomija

**Received:** June 1, 2025
**Accepted:** June 14, 2025