Annals of Biomedical and Clinical Research

Original article

ABCR Vol 4; No 2; 2025;84-91

Lisinopril – Proven Antihypertensive Efficacy and Safety over Time

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ABSTRACT

Background: The aim of this study was to investigate the effectiveness, tolerability, and safety of using lisinopril tablets in the treatment of essential hypertension for a period of 12 weeks.

Methods: A multicenter, observational, non-interventional, postmarketing clinical trial was conducted on adult patients older than 30 years with a diagnosis of hypertension and blood pressure values ≥ 140/90 mmHg. Patients taking lisinopril were monitored for 12 weeks, during one initial and three control examinations.

Main findings: The study included 334 patients: group A – aged 30 to 59 (n=167) and group B – aged 60 and older (n=167). In the group of younger respondents, the systolic/diastolic pressure before therapy was on average 150/95 mmHg, and with the use of lisinopril therapy, decreased to an average of 130/80 mmHg after four weeks. For the older respondents, the systolic/diastolic pressure before therapy was on average 155/95 mmHg, while after starting the lisinopril therapy, it dropped to an average of 135/80 mmHg. The differences in systolic/diastolic pressure were assessed as very good, namely 70.9% in the older and 87.4% in the younger group. More patients from the elderly group (34 patients) had adverse events compared to the younger group (24 patients). Adherence was generally good. Comparison of the two groups showed better results in the younger group compared to the older one, 82.6% vs. 69.3%.

Principal conclusion: Lisinopril showed good efficacy and safety in reducing essential hypertension in patients. Tolerability and high adherence to lisinopril therapy was observed.

Key words: lisinopril, hypertension, systolic blood pressure, diastolic blood pressure

Article processing history:
Received February 21, 2025
Revised June 10, 2025
Accepted September 1, 2025

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Cite this article as: Kulić M, Šehić-Lihovac A, Šukalo A, Mehić M, Skopljak A, Tanović Avdić A. Lisinopril – Proven Antihypertensive Efficacy and Safety over Time. Annals of Biomedical and Clinical Research. 2025;4:84-91.
https://doi.org/10.47960/2744-2470.2025.2.4.84

INTRODUCTION

Hypertension is defined as the presence of increased pressure, at a level where the patient is exposed to an enlarged risk of damage to target organs in several vascular areas, including the retina, brain, heart, and kidneys, as well as large blood vessels. Hypertension is defined by blood pressure values that are higher than 140/90 mmHg (1).

The highest prevalence of hypertension is in developed countries, namely in Europe and North America: 20% of the total population and 60% of people over the age of 65 have hypertension (1). Hypertension is one of the most common causes of rises in cardiovascular diseases today (2). According to a report by the Federal Ministry of Health of Bosnia and Herzegovina, based on a study on the health of the adult population, 42.1% of adults in Bosnia and Herzegovina have blood pressure values above 140/90 mmHg, or are already taking antihypertensive therapy, which makes hypertension the most common chronic illness (3).

Along with smoking and hypercholesterolemia, hypertension is an important factor in the development of cardiovascular diseases and cardiovascular mortality. Each increase in systolic pressure by 20 mmHg or diastolic pressure by 10 mmHg doubles mortality from ischemic heart disease and stroke (1). The primary goal of hypertension treatment is to reduce the risk of cardiovascular morbidity and mortality. Recommended classes of drugs in the treatment of hypertension are diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II antagonists (ARBs), and beta blockers (1–3).

According to the American Heart Association/ American College of Cardiology (AHA/ACC) Guidelines for the treatment of hypertension, one of four drug classes (thiazide diuretics, calcium antagonists, ACEIs, or ARBs) are considered as the first choice (4). The data show that lisinopril is one of the most frequently prescribed antihypertensive drugs in the world. This is demonstrated by the fact that in the United States in 2018, lisinopril was the first on the list of antihypertensive drugs prescribed (5). In the guidelines of the National Institute for Health and Clinical Excellence (NICE) from 2019, initial treatment with certain groups of antihypertensive drugs was recommended depending on age. Thus, the guidelines recommend the use of ACEIs or (if this group is not tolerated or contraindicated) one of the ARBs as the first choice in people under the age of 55. In people over 55 years of age, the first choice of treatment is a calcium channel blocker (6, 7).

Lisinopril is an active form of the drug that does not depend on hepatic metabolism. In patients with liver failure, it is not necessary to adjust the dose of lisinopril (8). The objectives of our study were to examine its effectiveness and tolerability as well as the cooperation of patients during therapy with lisinopril in the treatment of hypertension over 12 weeks.

PARTICIPANTS AND METHODS

Participants

The study included 334 adult patients older than 30 years with a diagnosis of hypertension (blood pressure values ≥ 140/90 mmHg) that required pharmacological treatment. The patients were monitored for 12 weeks, during one initial and three control examinations. The initial examination included taking a detailed personal, family, and socio-epidemiological history, identifying risk factors, and measuring blood pressure and pulse.

The inclusion criteria were: proven hypertension with blood pressure values >140/90 mmHg, renovascular hypertension with or without heart failure, and age over 30 years.

The exclusion criteria were: hypersensitivity to ACE inhibitors, as well as a positive history of angioneurotic syndrome and associated conditions that may affect the pharmacokinetics of lisinopril.

The withdrawal criteria were: worsening of the underlying disease, or development of serious side effects that required discontinuation of therapy, or of a disease that may affect the course of the study. The investigation used the medicine Lopril from the Bosnian-Herzegovinian manufacturer Bosnalijek d.d., in the form of 5 mg, 10 mg, and 20 mg tablets.

Methods

A multicenter, observational, non-interventional, postmarketing clinical trial was conducted from December 2014 to December 2015 in 18 centers in Bosnia and Herzegovina. Blood pressure was measured on an outpatient basis, by a doctor, using a mercury manometer, after five to 10 minutes of rest. The upper arm was freed from clothing, placed at the height of the heart, and rested on a hard surface. The manometer cuff covered 80% of the circumference of the upper arm. The cuff was inflated quickly, 20 mmHg above the systolic blood pressure. The membrane of the stethoscope was placed in the cubital fossa. After that, air was gradually released from the cuff, 2–3 mmHg per second, and the occurrence of noise was monitored on the stethoscope. The appearance of the first noise on the stethoscope indicated the value of the systolic blood pressure, which was read from the mercury column. The disappearance of noise indicated the value of diastolic blood pressure, which was taken from the mercury column.

The pulse was also measured on an outpatient basis, by a doctor, after the patient had rested for five to 10 minutes. The pulse was measured on the brachial artery by multiplying the measured number of beats in 15 seconds by four to obtain the number of beats in one minute.

After meeting the criteria, patients started the lisinopril therapy. The initial and maintenance dose was prescribed according to health care professionals (summary of product characteristics, SmPC) (9). The first control examination was two weeks after the start of the therapy. The last, third control examination was 12 weeks after inclusion in the study.

Control examinations included measurement of blood pressure and pulse. During the control examinations, the patient's cooperation and the clinical picture were assessed, and if necessary, the dose was titrated. At the final examination, in addition to measuring blood pressure and pulse, the tolerability of the therapy, the cooperation of the patients, and side effects that occurred during the therapy were noted.

The working hypothesis was that by using lisinopril for 12 weeks, 65% of patients aged 30 to 59 and 50% of patients aged 60 and over would achieve target blood pressure values (<140/90 mmHg).

Statistical analysis

Testing was performed using a two-sided test, with an alpha value set at a significance level of 95% ($\alpha = 0.05$) and statistical power of the test of 80% ($ß = 0.20$). The chi-squared test was used to analyze differences in proportions after assessing the effect of therapy on blood pressure control over a period of 12 weeks. Values of a significance level at $p<0.05$ were considered statistically significant. Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) program, version 23.0.

RESULTS

A total of 334 respondents were included in the research, divided into two groups according to age: group A (the group of younger respondents), which included respondents aged 30 to 59 (n=167), and group B (the group of older respondents), which involved respondents aged 60 and older (n=167). The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of patients included in the study

Parameter	All patients (n=334)	Younger patients 30–59 (n=167)	Elderly patients 60 and older (n=167)	p-value of younger compared to older respondents
Age (years)	334	167	167	
Gender, w	188	95 (56.9)	93 (55.7)	0.825
Hypertension	320	158	162	0.275
Newly diagnosed hypertension	123	89 (53.3)	34 (20.4)	<0.001
Smoker	113	65 (38.9)	48 (28.7)	0.049
BMI				0.5
<25	70	40 (24.1	30 (19.2)	
26–30	154	79 (47.6)	75 (48.1)	
31 +	98	47 (28.3)	51 (32.7)	
Diabetes mellitus	75	24 (14.4)	51 (30.5)	0.001
Hyperlipidemia	161	68 (40.7)	93 (55.7)	0.006
Angina pectoris	43	11(6.6)	32(19.2)	0.001
Systolic blood pressure (mmHg)		150 (145–160)	150 (145–165)	<0.001
Diastolic blood pressure (mmHg)		95 (90–100)	95 (85–100)	0.001

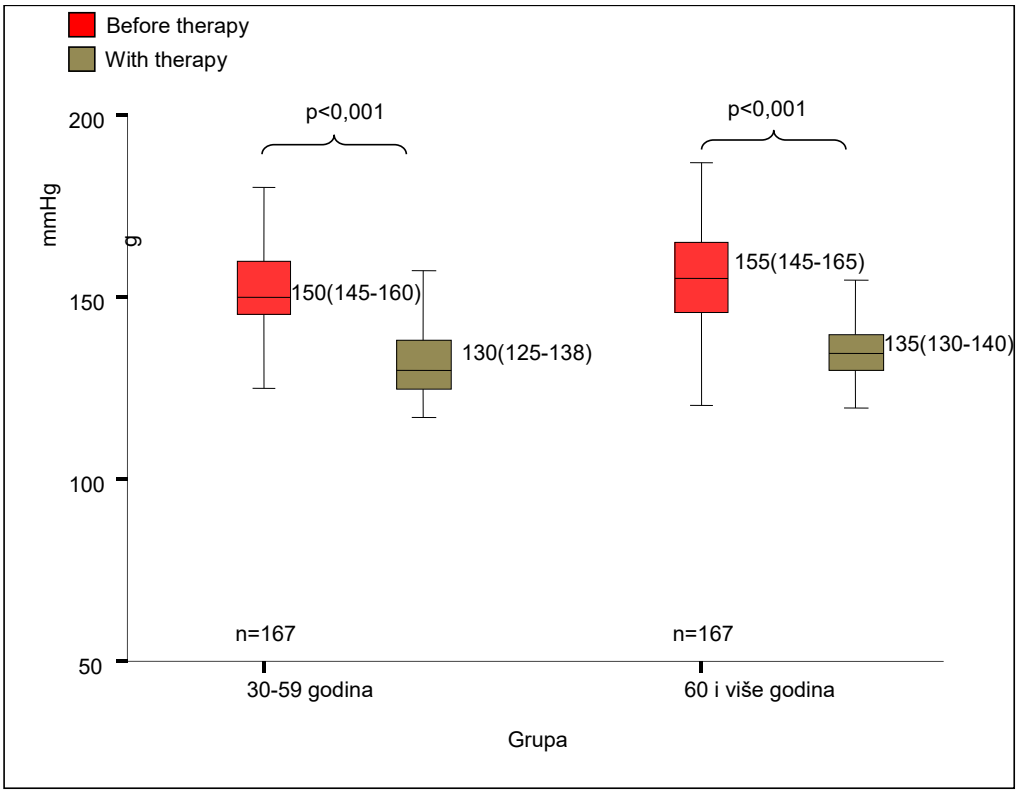

Figure 1. Average values of systolic pressure in both groups before using the therapy and with the use of lisinopril therapy

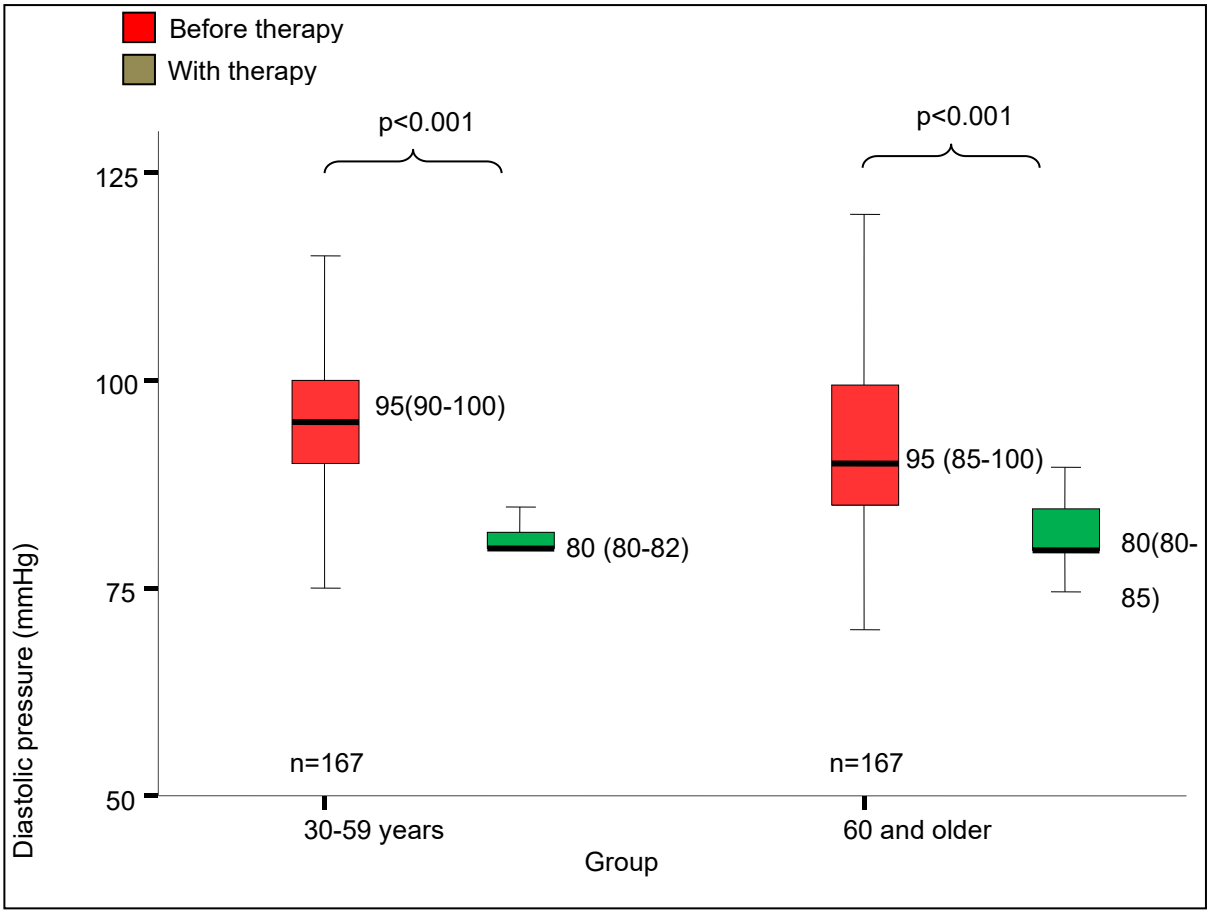

Figure 2. Average values of diastolic pressure in both groups before using the therapy and with the use of lisinopril therapy

In the group of younger respondents, the systolic pressure before using the therapy was on average 150 mmHg, i.e., it ranged from 145 to 160, and with the use of lisinopril therapy, the systolic pressure decreased to an average of 130 mmHg, i.e., it ranged from 125 to 138. In the group of older respondents, the systolic pressure before lisinopril therapy was on average 155 mmHg, i.e., in the interval 145–165, while after starting the lisinopril therapy, the systolic pressure reduced to an average of 135 mmHg, i.e., in the interval 130–140 mmHg. The difference in the drop in systolic pressure was statistically significant (p<0.001) (Figure 1).

The diastolic pressure before using the therapy was on average 95 mmHg, i.e., it ranged from 90–100 mmHg, and with the use of lisinopril therapy, the diastolic pressure decreased to an average of 80 mmHg, i.e., in the interval 80–82 mmHg. With the older respondents, the diastolic pressure before lisinopril therapy was on average 95 mmHg, i.e., in the interval 85–100 mmHg, while after starting lisinopril therapy, the diastolic pressure reduced to an average of 80 mmHg, i.e., in the interval 80–85 mmHg. The difference in the drop in diastolic pressure was statistically significant (p <0.001) (Figure 2).

The Wilcoxon signed-rank test showed that the differences in systolic and diastolic pressure between the two measurements (mmHg) in younger respondents were statistically significant p<0.001. Systolic pressure decreased by an average of 20 mmHg (from 14 to 30 mmHg), while diastolic pressure showed a smaller difference and declined by an average of 12 mmHg (from 10 to 20 mmHg). The differences in systolic and diastolic pressure between the two measurements (mmHg) in

older respondents were statistically significant p<0.01. Systolic pressure dropped by an average of 20 mmHg (from 10 to 30 mmHg), while diastolic pressure showed a smaller difference and diminished by an average of 10 mmHg (from 5 to 17 mmHg).

More than 65.0% of respondents rated the drug as "very effective", 79.0% in the younger group, and 65.5% in the older group. The rating "effective" was awarded by 29.7% in the older group and 21.0% in the younger group. In the older group of respondents, 4.8% rated the effectiveness as "bad", while there were no such cases in the younger group. Effectiveness had a weak correlation (rho=0.162, p=0.003) with the age of the respondents.

According to these percentages, it can be said that the drug was somewhat more effective in the younger group of respondents than in the older group of respondents (Table 2).

Table 2. Evaluation of the effectiveness of the therapy according to the tested groups

Groups	Drug efficacy			Total
	Very good	Good	Bad	
30–59 years of age	132 (79)	35 (21)	0 (0)	167
60 years and older	108 (65.5)	49 (29.7)	8 (4.8)	165
Total	240 (72.3)	84 (25.3)	8 (2.4)	332

The tolerability of the drug was assessed as very good by the majority of respondents in both age groups, namely 70.9% in the older and 87.4% in the younger group.

Fisher's exact test showed that the percentage of adverse events did not depend on the age of the patients. In the older patient group, adverse events were recorded in 34 respondents, of which the majority (29 patients) were expected and five were related to concomitant therapy. In the younger group, side effects were recorded in 23 respondents, and all were expected (Table 3).

Table 3. Adverse events according to the tested groups

Groups (n=334)	Adverse events	
	Expected	Associated with concomitant therapy
30–59 years (n=167)	23 (13.17)	0
60 and older years (n=167)	29 (85.3)	5 (14.7)
Total	52 (15.7)	5 (1.5)

Regarding adherence, there was very good cooperation in both groups of subjects, although it was better in the group of younger patients at 82.6% compared to the group of older patients at 69.3%.

DISCUSSION

In this study, the ACEI lisinopril demonstrated efficacy, safety, and adherence in the treatment of hypertension in both age groups. We can state that lisinopril therapy is effective in reducing systolic and diastolic pressure in both age groups, with slightly greater effectiveness in the younger group of respondents.

This can be explained by the fact that, in comparison with older people with hypertension, younger people often have higher levels of renin in their blood (meaning they are more sensitive to renin), which increases the level of the angiotensin-converting enzyme, consequently raising blood pressure. Since ACEIs inhibit the activity of the angiotensin-converting enzyme and directly reduce blood pressure, it can be said that younger people benefit more from ACEIs (10).

Our results regarding efficacy in the treatment of essential hypertension in both younger and older groups are in accordance with other trials. In four large multicenter investigations conducted on 807 younger and older hypertension patients treated for eight to 12 weeks, lisinopril proved to be effective in reducing blood pressure. Furthermore, elderly patients had an equal or slightly greater reduction in blood pressure, although a low

level of renin activity in the plasma is more frequent in the elderly (11). In a 10-week, prospective, single-blind study on 23 patients with mild to moderate essential hypertension, lisinopril was effective and safe in reduction of hypertension. When comparing older and younger patients, the results did not differ significantly (12). In a double-blind, parallel-group investigation of eight weeks' duration with 219 patients, lisinopril showed significantly better efficacy in comparison to extended-release felodipine in lowering systolic and diastolic blood pressure. This was especially pronounced in the reduction of systolic pressure in the younger group compared to the group older than 65. Furthermore, lisinopril showed better tolerability (13).

In our study, adverse reactions were expected and mild, occurring in 17.6% of patients. Out of this percentage, 10.1% refers to the older group. This implies that patients aged 60 and over are at greater risk for developing adverse events.

These findings are consistent with other studies conducted. In several controlled clinical trials on a total of 1,015 hypertension patients, lisinopril showed its safety and tolerability equally. The most common adverse reactions were headache, dizziness, cough, and diarrhea (14).

Although tolerance was very good in both age groups in our study, it was observed that the percentage was higher in the group of younger patients (87.4%) in comparison to the older ones (70.9%). We conclude that the drug was more tolerable in the younger than in the older group of respondents. Furthermore, it should be emphasized that there were no subjects who poorly tolerated the drug.

Lisinopril has shown good tolerance in other studies as well. In another work conducted on patients with essential hypertension, lisinopril showed better results regarding safety as well tolerability compared to a placebo and to felodipine (13).

Furthermore, in our investigation, the adherence rate was very good in both groups. A higher adherence rate was noted in the group of younger patients (82.6%) compared to 69.3% in the older one. This is in line with the results of other works. According to a retrospective observational study including 142,945 hypertensive patients, lisinopril showed a high adherence rate at 89.9% in comparison with other antihypertensive drugs. These results place it in second position, immediately after valsartan (90.1%) in terms of adherence (15). It is estimated that approximately 50% of hypertension patients stop therapy after one year. This is influenced by several factors, such as efficiency, tolerability, and understanding of the importance of therapy (16).

According to some authors, patients often wrongly conclude that a symptom that occurs is the result of antihypertensive drugs. The results of a study conducted on 249 patients showed that non-adherence to antihypertensive drugs among hypertensive patients is influenced by adverse reactions (16).

CONCLUSION

On the basis of the results of a multicenter, observational study of the effectiveness of lisinopril in the treatment of essential hypertension, we conclude that the drug was effective and well tolerated in the treatment of essential hypertension in both test groups: a group of younger individuals and one of older respondents. Patients' adherence to lisinopril was very good.

ACKNOWLEDGMENTS
None.

FUNDING
Bosnalijek d.d.

CONFLICT OF INTEREST
Aziz Šukalo, Meliha Mehić, and Amna Tanović Avdić disclose the following relationships – they are employees of Bosnalijek d.d., a pharmaceutical company producing the drug lisinopril in Bosnia and Herzegovina.

Bosnalijek d.d. had a role in the design of the study, in the collection, analyses, and interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

AUTHORS' CONTRIBUTIONS

Conception and design: AŠ, MM, AS, and ATA; acquisition, analysis, and interpretation of data: AŠ, MM, and MK; drafting the article: MM, AŠL, and ATA; revising it critically for important intellectual content: AŠ, MK, AŠL, and AS; approving the final version of the manuscript: Mehmed Kulić, Anela Šehić-Lihovac, Amira Skopljak, Aziz Šukalo, Meliha Mehić, and Amna Tanović Avdić.

ETHICAL BACKGROUND

Institutional review board statement: The study was conducted according to the criteria set by the Declaration of Helsinki of 1975, as revised in 2000, and each patient signed informed consent before enrolment in the study.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials, and associated protocols.

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