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КЛІНІЧНА ЕФЕКТИВНІСТЬ ЛОСАРТАНУ І РАМІПРИЛУ У ЧОЛОВІКІВ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ЗАЛЕЖНО ВІД ВІКУ, РІВНЯ УРІКЕМІЇ Й ВАРІАНТУ АРТЕРІЙНОЇ ГІПЕРТЕНЗІЇ

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Реферат

Мета. *Дослідити клінічну ефективність лосартану і раміприлу в чоловіків із гіпертонічною хворобою, залежно від віку, рівня урікемії й варіанту гіпертонічної хвороби.*

Матеріал і методи. *Обстежено 90 чоловіків похилого віку, середній вік 72.5 роки з гіпертонічною хворобою II стадії. Більша кількість пацієнтів були високого (54.4%) та дуже високого (22.2%) кардіоваскулярного ризику. Обстежених чоловіків похилого віку було 69,5% та 30,5% - старечого. У 62,2% обстежених реєстрували помірну артерійну гіпертензію (гіпертонічна хвороба II ступеню). Хворі з тяжкою артерійною гіпертензією (гіпертонічна хвороба III ступеню) становили 27,8% і з легкою (гіпертонічна хвороба I ступеню) - лише 10,0%. Найбільшу частку (50,0%) становили пацієнти із тривалістю артерійною гіпертензією від 10 до 20 років і найменшу (8,9%) - із тривалістю > 20 років. Усім пацієнтам призначали стандартну терапію лосартаном або раміприлом із додаванням індапаміда, амлодипіна та доксозазіна при необхідності досягнення контролю артерійного тиску. Окрім антигіпертензійних засобів всім пацієнтам призначали ацетилсаліцилову кислоту 75 мг на добу та розувастатин дозою 10-20 мг на добу. Дозу останнього підбирали під контролем величини холестерину ліпопротеїнів низької щільності, цільовий рівень показника становив <2,5 ммоль/л. Спостереження тривало впродовж 6 місяців. Контроль ефективності лікування проводили за допомогою добового моніторування артерійного тиску. Статистичний аналіз проводили за допомогою пакету прикладних програм [8, 9].*

Результати й обговорення. *У результаті, призначення комбінації раміприлу із індапамідом та амлодипіном у цієї групи пацієнтів показало меншу антигіпертензійну ефективність у порівнянні із групою призначення лосартан із індапамідом та амлодипіном (84.4% і 95.6%). Ми використовували шкалу суб'єктивної оцінки лікування пацієнтом, яка показала майже однакову сприйнятливість лікування в обох групах раміприл - лосартан (4.78 та 6.0 балів, відповідно). Також вивчали ефективність антигіпертензійної терапії у пацієнтів із гіперурікемією та ізольованою артерійною гіпертензією.*

Висновки. *Кращу антигіпертензійну ефективність виявила комбінація лосартан+індапамід у порівнянні із комбінацією раміприл+індапамід впродовж 6 місяців лікування (від 62.2% до 46.7%). Додавання амлодипіну призвело до збільшення антигіпертензійної ефективності комбінацій (95.6% до 84.4%). У зв'язку із побічними явищами було відмінено раміприл у 8.2% пацієнтів та амлодипін у 14.6%. Вищу антигіпертензійну ефективність виявив раміприл у пацієнтів похилого віку, ефект лосартану не залежав від віку. Гіперурікемія та ізольована систолічна артерійна гіпертензія призводила до зниження антигіпертензійної ефективності як раміприла так і лосартана.*

Ключові слова: *антигіпертензійна терапія, чоловіки похилого віку, лосартан, раміприл*

Abstract

CLINICAL EFFICACY OF LOSARTAN AND RAMIPRIL IN MALE PATIENTS WITH HYPERTENSION DEPENDING ON AGE, URICEMIA LEVEL, AND HYPERTENSION TYPE

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Aim. *Aging of population, treatment of cardiovascular diseases in the context of higher longevity, and improving the quality of life are considered among relevant problems of modern medicine. The purpose of our study was to evaluate clinical efficacy of Losartan and Ramipril in men with hypertension (HT), depending on their age, level of uricemia and HT type.*

Materials and Methods. *We examined 90 elderly men of the average age of 72.5 years with Grade II hypertension. Most patients had high (54.4%) and very high (22.2%) cardiovascular risk. 69.5% of examined patients were senior males and 30.5% - elderly males. More than half (62.2%) of the patients were diagnosed with moderate AH (HT Grade II). 27.8% patients had severe AH (Grade III HT) and only 10.0% were mild (Grade I HT) cases. The largest portion (50.0%) were patients with a 10- to 20-year history of AH, and the smallest one (8.9%) - with over 20-year history of the disease. All patients were prescribed standard Losartan therapy or Ramipril in combination with Indapamidum, Amlodipinum and Doxazosin, if blood pressure control was needed. Apart from antihypertensive drugs, all patients were prescribed a daily dose of 75 mg acetylsalicylic acid and Rozuvastatinum at a dose of 10-20 mg per day. The dose of the latter was selected against the controlled value of LDL cholesterol with a target level <2.5 mmol/L. Follow-up lasted for 6 months. The therapy efficacy control was carried out using daily monitoring of blood pressure. A package of*

specialized program applications was used for the statistical analysis [8, 9].

Results and Discussions. *As a result, administration of Ramipril, Indapamidum and Amlodipinum combination in the given group of patients demonstrated less antihypertensive efficacy compared with the group where Losartan, Indapamidum and Amlodipinum were administered (84.4% and 95.6%, accordingly). We used the Patient Impression Scale, which demonstrated almost equal tolerability of treatment in both Ramipril and Losartan groups (4.78 and 6.0 points, respectively). We also studied the efficacy of antihypertensive therapy in patients with hyperuricemia and isolated systolic hypertension.*

Conclusions. *Six months of treatment revealed better antihypertensive efficacy of the Losartan + Indapamidum combination compared with the Ramipril + Indapamidum combination (62.2% and 46.7%, accordingly). Adding Amlodipinum to the regimen resulted in better antihypertensive efficacy of the combinations (95.6% to 84.4%, respectively). Ramipril was discontinued in 8.2% of patients and Amlodipinum - in 14.6% due to side effects. Ramipril appeared to deliver more antihypertensive efficacy in senior patients, whilst the effect of Losartan was independent of age. Hyperuricemia (HU) and isolated systolic hypertension (ISHT) resulted in lower antihypertensive efficacy of both Ramipril and Losartan.*

Key words: *antihypertensive therapy, elderly male patients, Losartan, Ramipril*

Introduction

Aging of population, treatment of cardiovascular diseases in the context of higher longevity, and improving the quality of life are considered among relevant problems of modern medicine. The purpose of our study was to evaluate clinical efficacy of Losartan and Ramipril in men with hypertension (HT), depending on their age, level of uricemia and HT type.

Materials and Methods

The study design is based on a comprehensive examination of 90 men with Grade II HT aged 60 to 89 (average 72.54±0.77) years. The examination of patients was performed at Lutsk Military Hospital within 2011-2015.

The main inclusion criteria were: 1) Grade II HT according to recommendations of the Ukrainian Association of Cardiologists (2009); 2) no history of effective treatment (AT >140/90 mm Hg.) and the need for selection of effective antihypertensive therapy; 3) male gender; 4) senior and elderly age of patients and 5) the informed consent of patients to participate in the study. The exclusion criteria were: 1) female gender; 2) patient`s age <60 and >90 years; 3) Grade III HT and symptomatic AH; 4) concomitant clinically manifested gout according to criteria of the American Rheumatology Association [7]; 5) severe concomitant diseases of the respiratory system, gastrointestinal tract and kidneys, accompanied by organ dysfunction and requiring active treatment; and 6) alcohol abuse and serious neuropsychiatric disorders.

69.5% of examined male patients were senior males and 36 (30.5%) - elderly males. A 2.3 to 1 ratio ($p<0.0001$) suggested a significant predominance of senior patients in the examined population. More than half (62.2%) of patients presented moderate AH (Grade II HT). The patients with severe AH (Grade III HT) amounted to 27.8% and mild AH (Grade I HT) - only to 10.0%. A history of hypertension lasted from 4 to 25 (average 11.34±0.54) years. At the same time, the largest portion (50.0%) of patients with AH had a history of 10- to 20-year long disease and the smallest portion (8.9%) had a history of disease of over 20 years.

Cardiovascular risk (CVR) assessment, carried out according to the AH stratification scale (2009), suggested that 49 (54.4%) patients presented with high, 20 (22.2%) patients - very high, and only 21 (23.4%) patients - with moderate CVR. Therefore, the majority (76.6%) of the surveyed patients had high and very high CVR, which indicated certain problems in patients included in the study.

Selection of antihypertensive therapy. All patients included in the study were administered the initial combined antihypertensive therapy, depending on high and very high risk in the subjects.

The patients, who had not received continuous antihypertensive therapy with blockers of renin-angiotensin-aldosterone system (RAAS), were administered a combination of Ramipril (Ramizes, VAT Farmak, Ukraine) + Indapamidum (Indopres, Borschagovsky HFZ, Ukraine), or Losartan (Lozap®, Zentiva, Slovenia) + Indapamidum. The choice of the combination was carried out randomly.

The patients, who had received continuous antihypertensive RAAS therapy, were subjected to cross substitution - ACE inhibitors were replaced with Losartan, and sartan - with Ramipril. Ramipril and Losartan, as in the previous case, were administered in combination with Indapamidum.

The starting daily dose of Ramipril was 5 mg and

Losartan - 50 mg. For Indapamidum, in all cases, the daily dose was fixed and accounted to 2.5 mg. The antihypertensive effect of all combinations (target blood pressure <140/90 mm Hg) was assessed at Week 3 of the treatment course. In case of insufficient antihypertensive effect, the Ramipril dose was increased to 10 mg and Losartan to 100 mg.

In case of insufficient antihypertensive effect, the above medicines were supplemented (as the third antihypertensive medicine) by Amlodipinum (Ukraine) at a dose of 5-10 mg, and, if necessary (as the fourth antihypertensive medicine), - by Doxazosin alpha-blocker (Zoxon, Zentiva, Czech Republic) at a dose of 4-8 mg.

In case of adverse events associated with administration of Amlodipinum, it was replaced by Doxazosin. After replacement of the medicine, we performed antihypertensive efficacy evaluation following 3 weeks therapy. In case of positive antihypertensive effect, we followed-up patients for 6 months. If no antihypertensive efficacy of the four medicines combination was revealed, or it was impossible to administer medicines according to the above regimen, the patients were excluded from the study.

Besides antihypertensive medicines, all patients were prescribed acetylsalicylic acid at a dose of 75 mg and Rozuvastatinum at daily dose 10-20 mg. The latter dose was selected according to controlled LDL cholesterol levels with target level under 2.5 mmol/L.

The patients were assessed for efficacy of treatment every 3-4 weeks during the 6-month follow-up. We controlled blood pressure using in-house blood pressure monitoring as recommended by the European Society of Hypertension (Parati G., Stergiou G.S., Asmar R. et al., 2008; Parati G., Bil O.G., Kjeldsen S., Mancia G., 2009). The indicators of the in-house blood pressure monitoring were presented as medians, calculated from 4 measurements (at 8:00, 12:00, 18:00 and 22:00) during 5 days before the planned study visit. [6]

Results and Discussions

Clinical efficacy of Losartan and Ramipril was assessed in 90 patients with HT within 6 months of treatment (Table 1). Of them, at the start of the study, Ramipril was administered in 49 (54.4%) male patients at a dose of 5-10 mg (average - 8.9 mg). In 4 (8.2%) of these patients, the medicine was discontinued on 16-45 (average - 32.6±8.4) day of treatment because of dry cough, and replaced by Losartan.

In turn, Losartan at a daily dose of 50-100 mg (average 90.4 mg) was administered at the start

Table 1

Analysis of treatment regimens

1. Antihypertensive medicine (choice: random method)	Ramipril	Losartan
Number of patients the beginning of therapy	49 (54.4%)	41 (45.6%)
Number of patients needing medicine discontinuation	4 (8.2%) – dry cough.	-
Number of patients in final stage	**45 (50.0%)**	**45 (50.0%)**
Variation and average medication dose	5-10 mg/day 8.8±0.1 mg/day	50-100 mg/day 90.4±2.4 mg/day
Reaching target blood pressure in combination with Indapamidum	**In 21 of 45 (46.7%)**	**In 28 of 45 (62.2%)**
2. Antihypertensive medicine (Prescription conditions: ineffective previous combination)	Amlodipinum	Amlodipinum
Number of patients the beginning of therapy	24 (53.3%)	17 (37.8%)
Administration term (days)	Days16–104 52±3.4	Days18–68 39±2.9*
Number of patients needing medicine discontinuation (changed for Doxazosin)	4 (16.7%) – leg swelling	2 (10.5%) – leg swelling
Number of patients in final stage	20 (44.4%)	15 (33.3%)
Variation and average medication dose	5-10 mg/day 6.9±1.2	5-10 mg/day 8.1±1.2
Reaching target blood pressure	**In 38 of 45 (84.4%)**	**In 43 of 45 (95.6%)**
3. Antihypertensive medicine (in case of ineffective previous combination or swelling on Amlodipinum)	Doxazosin	Doxazosin
Number of patients in final stage	7 (15.6%)	2 (4.4%)
Administration term (days)	Days 36–119 79±5.9	Days 38–82 63±4.9
Variation and average medication dose	2–8 mg/day 4.3±1.3	4–8 mg/day 5.9±1.4
Reaching target blood pressure	**In 44 of 45 (97.8%)**	**Un 45 of 45 (100%)**

"" - difference reliability under t-test independent by groups. p=0.003*

of treatment in 41 (45.6%) patients; 4 patients were additionally prescribed the medicine because of dry cough in patients receiving concomitant Ramipril. It should be noted that no case of Losartan administration presented adverse events that would be a reason for discontinuation of therapy. Therefore, at the final phase of the study, the efficacy of Ramipril was assessed in 45 (50.0%) and Losartan - in 45 (50.0%) patients, respectively. As mentioned above, in all cases Ramipril and Losartan were combined with Indapamidum (2.5 mg) only at the start of treatment.

In the whole group (n = 90), positive clinical effect (achieving target BP <140/90 mm Hg) of Ramipril and Losartan in the form of combination with Indapamidum within 6 months of treatment, was reported in 54.4% (49 of 90) of patients. Concomitant Amlodipinum (5-10 mg - an average of 7.6 mg per day - therapy duration ranging from 16 to 104 with an average of 46 days of treatment) provided an opportunity to control blood pressure in 90.0% (81 of 90) of patients, whilst administration of Doxazosin (2-8 mg - an average of 5.1 mg per day - therapy duration ranging from 36 to 119 with an average of 71 days of treatment) was helpful yet for 98.9% (89 of 90) of patients. 66.7% (6 out of 9) of patients were administered Doxazosin in case of leg swelling on the top of already administered Amlodipinum (on Days 16-63, in average on Day 32 of taking medicine) and 33.3% (3 out of 9) of patients - in case of the lack ofefficacy of 3 antihypertensive medicines and development of resistant AH. One patient was excluded from the study due to lack of antihypertensive effect of the proposed treatment and the need for other combinations of antihypertensive medicines, not provided in the study design.

Positive clinical effect of Ramipril in combination with Indapamidum (Table 1) was observed in 46.7% (21 of 45) of patients. The remaining 53.3% (24 of 45) of patients presented a need in concomitant antihypertensive medicines in order to achieve target blood pressure. Thus, 44.4% (20 of 45) of patients were administered Amplodipinum at 5-10 mg per day (average - 6.9 mg) and 15.6% (7 out of 45) of patients - the Doxazosin alpha-blocker at a daily dose of 2-8 mg (average - 4.3 mg) as the third antihypertensive medicine. Doxazosin was administered as the 3-rd, alternative to Amlodipinum, medicine, in 57.1% (4 out of 7) of patients (in the event of leg swelling), and in 42.9% (3 out of 7) of patients - as the concomitant 4-th medicine (in the event of the resistant AH). In this case, administration of 3 medicines (Ramipril + Indapamidum + Amlodipinum) resulted in achievement of the target blood pressure by 84.4% (38 out of 45) patients, while concomitant Doxazosin made it possible to achieve the target blood pressure in 97.8% (44 of 45) of the surveyed male patients. One patient was excluded from the study due to the lack of antihypertensive effect of the proposed treatment and the need for other combinations of antihypertensive medicines, not provided in the study design.

The positive clinical effect of Losartan within 6 months was observed in 62.2% (28 of 45) of patients (difference in comparison with Ramipril had no statistical significance, p=0.13). 37.8% (17 out of 45) of patients, in order to achieve target blood pressure, were prescribed Amlodipinum at 5-10 mg per day (average - 8.1 mg) as a concomitant antihypertensive medicine, and 4.4% (2 out of 45) of patients were subjected to Doxazosin at a daily dose of 4-8 mg (average - 5.9 mg). The latter in one case was administered as the 4-th antihypertensive medicine (in event of resistant AH), and in other case - as a medicine alternative to Amlodipinum (in the event of swelling legs). We noted the significant reduction of Amlodipinum therapy duration on the top of already administered Losartan compared with Ramipril - 39 vs 52 days, p=0.003, in the absence of statistically significant differences in Doxazosin therapy durations. We explained this fact by the phenomenon of departure from the clinical effect, which was largely inherent to Ramipril and led to the need for concomitant Amlodipinum in later dates of treatment.

In this case, a 3-medicine therapy (Losartan + Indapamidum + Amlodipinum) resulted in achievement of target blood pressure by 95.6% (43 out of 45) patients, whilst concomitant administration of Doxazosin made it possible to achieve target blood pressure in all (100%) study subjects.

Normalization of blood pressure by administration of both Ramipril and Losartan therapy, accompanied by significant improvement of subjective and general condition of patients

(disappearance or assuagement ofthe headache episodes, dizziness, shortness of breath, general weakness, and increased tolerance to physical load). For a more informative presentation of changes in the patients` subjective condition associated with normalization of blood pressure, we presented it in a point system, where:

- 3 points is significant deterioration of the general condition;
- 2 points is noticeable deterioration of the general condition;
- 1 point is mild deterioration of general condition accompanied with AT normalization;

0 points is no significant changes in the general condition;

+1 point is slight improvement of the patient's condition;

+2 points is noticeable improvement of the general condition;

+3 points is significant improvement of general condition accompanied with AT normalization.

The choice of points was made independently by patients after their prior informing.

It was noted that no negative points were registered in general by the group (n=90). 0 points were registered in 6 (6.6%), 1 point - in 18 (20.0%), 2 points - in 32 (35.6%), and 3 points - in 34 (37.8%) of patients. Average score of the group as a whole accounted to 2.04±0.10, median - to 2 and interquartile swing - to 1 and 3. We noted that the trend in the subjective (general) condition of patients did not present any significant deviations against the background of administration of different therapy regimens - 2.05±0.11 and 2.18±0.12 for Ramipril and Losartan, respectively, p=0.42.

Moreover, we assessed tolerability of different treatment options by a similar 10-point for self-assessment of prescribed therapies by patients - the Patient Impression Scale - (patients put therapy tolerability marks on the proposed scale on their own). The extreme left limit of the scale (mark 0) indicated extremely poor tolerability, while the extreme right (mark 10) suggested excellent tolerability of prescribed therapy. Only patients who achieved the target blood pressure and were being administered Ramipril + Indapamidum or Losartan + Indapamidum combinations were approved for the study. It should be said that the average score in the group accounted to 5.54±0.29 points. In the Ramipril group (n=21), the treatment tolerability was assessed as 4.78±0.62, while in the Losartan group (n=28) it was 6.00±0.54, and the difference in assessment scores had no statistical significance

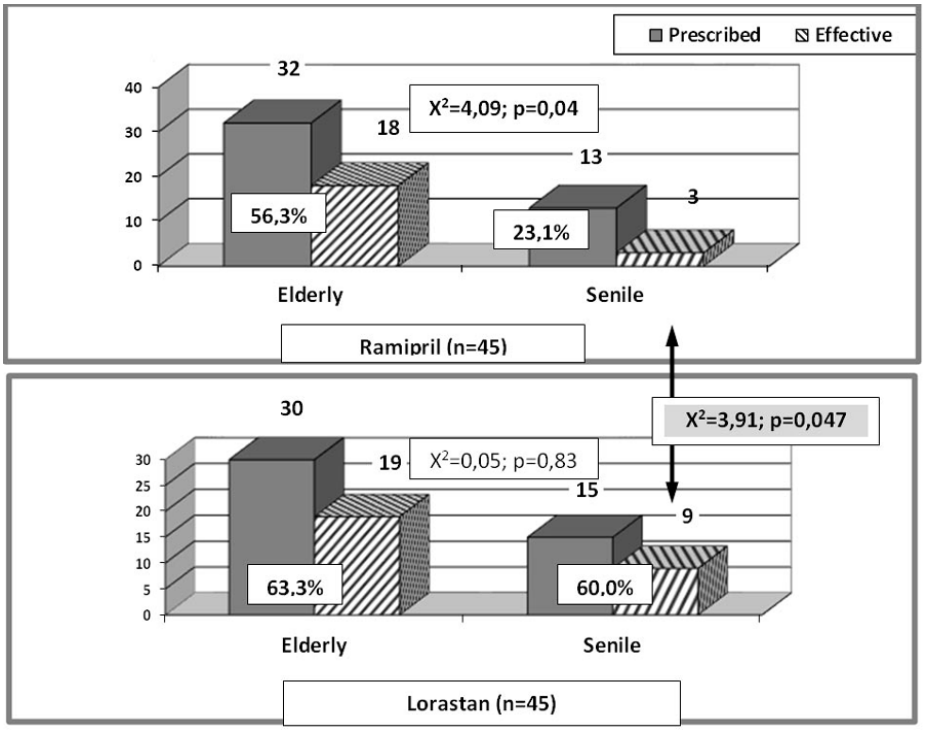

Fig. 1

Clinical efficacy of Ramipril and Losartan in hypertensive men depending on age

Note: reliability of difference % calculated under χ^2 criterion

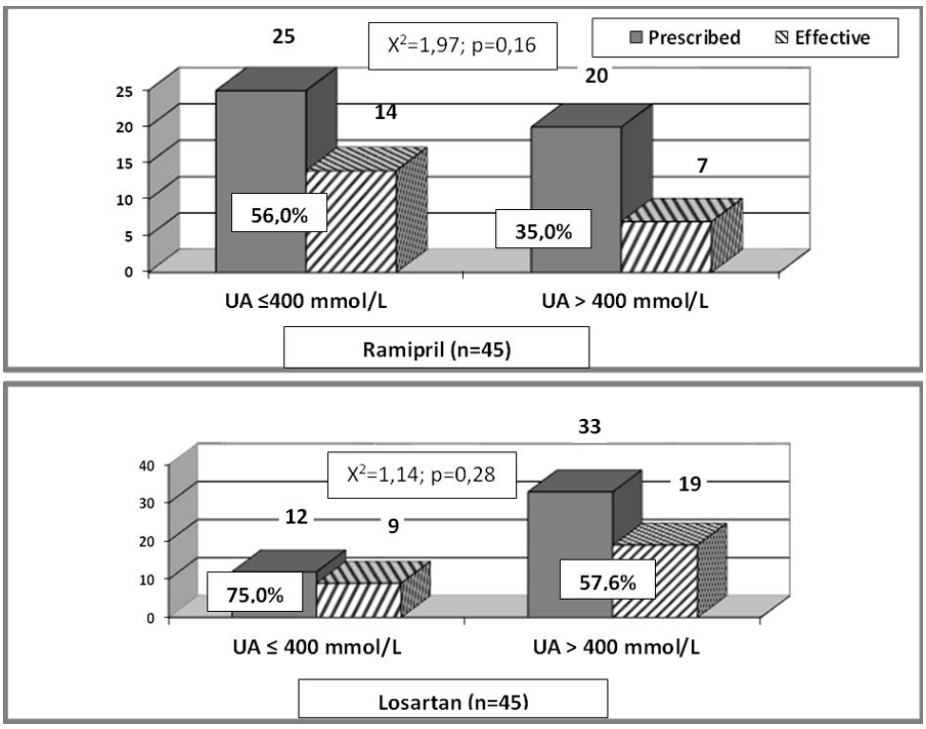

Fig. 2
Clinical efficacy of Ramipril and Losartan in hypertensive men depending on uricemia
Note: UA - uric acid

(p=0.13), indicating almost identical tolerability of subject combinations.

The analysis of clinical efficacy of Ramipril and Losartan (Fig. 1) presented some differences in antihypertensive effects of medicines in different groups of patients, depending on their age. Thus, the antihypertensive efficacy of Ramipril was statistically higher in senior patients, compared with elderly subjects - 56.3% vs 23.1%, p=0.04, while in Losartan group this pattern was not established - 63.3% and 60.0%, respectively, p=0.83.

On the other hand, a comparative analysis of clinical efficacy of Losartan and Ramipril in patients of different age groups showed significantly better efficacy of Losartan in elderly patients (60.0% vs 23.1%, p=0.047). Thus, the data showed that clinical efficacy of Ramipril in HT male patients was associated with the age of the patients - the medicine demonstrated significantly better antihypertensive efficacy in younger patients. Instead, the antihypertensive effect of Losartan did not depend on the age of the patients, which did precondition significantly higher efficacy of the medicine in older patients, compared with Ramipril. This might support the idea that Losartan should be regarded as a medicine of choice for elderly HT patients.

Assessment of clinical efficacy of Ramipril and Losartan in the groups of patients with different levels of uricemia (Fig. 2) demonstrated an upward trend in the effects of both medicines at normal urine concentration (UC≤400 mmol/L) and, consequently, a downward trend for patients with hyperuricemia (UC>400 mmol/L) - 56.0% vs 35.0%, p=0.16 and 75.0% vs 57.6%, p=0.28 for Ramipril and Losartan, respectively.

On the other hand, we noted an upward trend in Losartan antihypertensive efficacy, compared to Ramipril, regardless of the UC level - 75.0% vs. 56.0%, p=0.26 and 57.6% vs 35.0% p=0.11, respectively.

In turn, the analysis of clinical efficacy of Ramipril and Losartan in patients with different types of HT (Fig. 3) presented no specific statistical differences. We noted only a slight downward trend in clinical efficacy of both medicines in ISHT patients - 43,3% vs 53.3%, p=0.52 and 56,5% vs 68.2%, p=0.41 for Ramipril and Losartan, respectively.

Conclusions

1. Senior and elderly male Grade II HT patients demonstrated positive antihypertensive effect of Ramipril (5-10 mg/day) in combination with

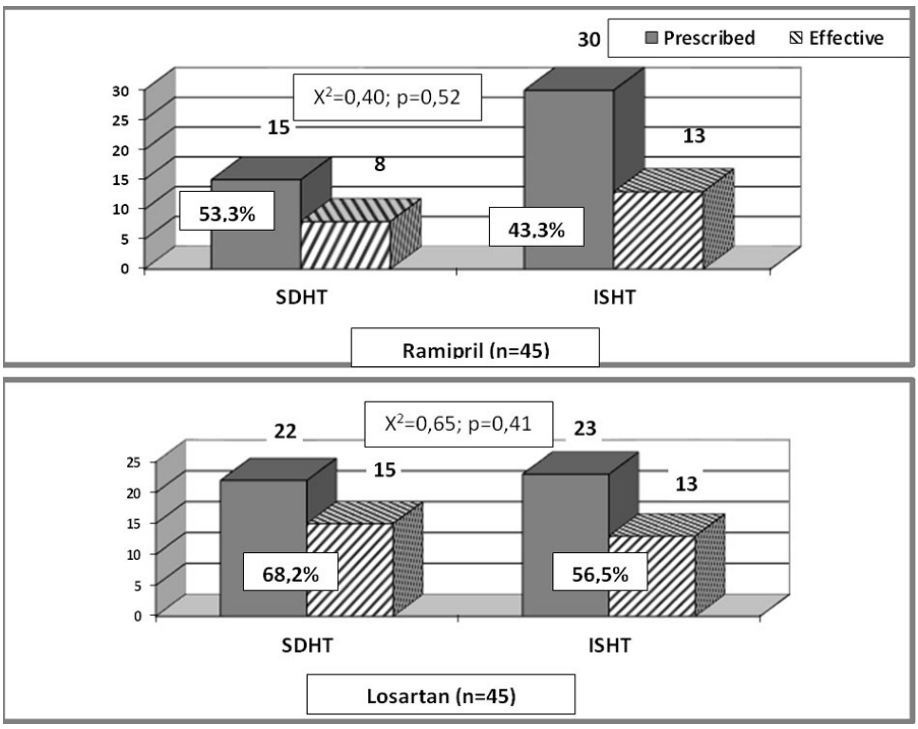

Fig. 3
Clinical efficacy of Ramipril and Losartan in hypertensive men depending on hypertension type
Note: SDHT - systolic-diastolic hypertension; ISHT - isolated systolic hypertension

Indapamidum (2.5 mg/day) over 6 months of treatment in 46.7% of cases. Administration of concomitant Amlodipinum 5-10 mg/day (Ramipril + Indapamidum + Amlodipinum combination) provided the ability to achieve target blood pressure in 84.4% of patients. 8.2% of patients required Ramipril discontinuation due to events of dry cough (average 32.6±8.4 day of treatment).

2. Senior and elderly male Grade II HT patients demonstrated positive antihypertensive effect of Losartan (50-100 mg/day) in combination with Indapamidum over 6 months of treatment in 62.2% of cases. Concomitant Amlodipinum 5-10 mg/day (Losartan + Indapamidum + Amplodipinum combination) provided the ability to achieve target blood pressure in 95.6% of patients.

3. 14.6% of patients required discontinuation of Amlodipinum due to leg swelling on average 32.4±7.7 day of medication.

4. Administration of Ramipril and Losartan was accompanied by significant improvement in subjective status of the patients (2.05 and 2.18 points by the general state evaluation scale, respectively, p=0.41) and satisfactory tolerability (4.78 and 6.00 points by a 10 point Patient Impression Scale (tolerability of treatment), respectively, p=0.13).

5. Clinical efficacy of Ramipril in male HT patients was associated with the age of patients. Significantly higher antihypertensive efficacy of Ramipril was registered in senior patients (56.3% vs 23.1%, p=0.04). Antihypertensive effect of Losartan did not depend on age of the patients; we revealed significantly higher efficacy of the medicine, compared with Ramipril, in elderly patients (60.0% vs 23.1%, p=0.047).

6. Hyperuricemia and ISHT in the HT male patients were associated with a downward trend in antihypertensive effects of Ramipril and Losartan and an increasing need for concomitant antihypertensive medicines.

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