

## EFFICACY AND SAFETY OF FIXED RAMIPRIL + FELODIPINE COMBINATION IN TREATMENT OF ARTERIAL HYPERTENSION: A RETROSPECTIVE STUDY-FORECAST

Ivan Tasić<sup>1</sup> and Gabrijela Stojković<sup>2</sup>

Approximately 30-50% of the world's adult population suffer from arterial hypertension, and only 30-35% is successfully treated. A large number of patients with arterial hypertension require a combination of antihypertensive medications to achieve target blood pressure. The ESH/ESC recommendations suggest the use of fixed dose combinations for treatment simplification and improved adherence to treatment.

The aim of this study was to evaluate efficacy and safety of fixed ramipril + felodipine combination in therapy of essential arterial hypertension.

This multicentric, cross-sectional, non-interventional study evaluated 1.341 adult patients with essential arterial hypertension, defined by systolic and diastolic blood pressure increase (BP $\geq$ 140/90 mmHg), only systolic blood pressure increase or antihypertensive therapy usage. All patients were treated with fixed-dose combination therapy ramipril + felodipine (5+5mg and 2.5+2.5mg) (Triapin® and Triapin mite®) therapy for at least two months. Efficacy was evaluated by proportion of patients who achieved target blood pressure values (<140/90 mmHg and <130/80 mmHg in diabetics) or defined blood pressure reduction ( $\geq$ 15/10mmHg). Safety of ramipril + felodipine therapy was evaluated based on the incidence of adverse events (AE) and therapy discontinuation rate during observational period. Therapy prescription was based on physician decision according to everyday clinical practice and 15 consecutive eligible patients were enrolled by each physician from the cohort of hypertensive patients treated in ambulatory setting.

Patient population consisted of 647 (48.4%) males and 690 (51.7%) females (mean age 60.15 $\pm$ 11.84 and mean duration of hypertension 9.5 $\pm$ 7.34 years). Males were significantly younger (58.74 $\pm$ 15.5 vs. 61.45 $\pm$ 11.04,  $p$ <0.01) without difference in body mass index. There were 47.5% of patients with stage II, 29.2% with stage I and 23.3% with stage III. There was a significant reduction of systolic/diastolic BP and heart rate in patients with ramipril + felodipine combination (162.6 $\pm$ 17/97.2 $\pm$ 9 mmHg and 79.4 $\pm$ 12/min) compared to baseline values prior to treatment (136.9 $\pm$ 17/84.2 $\pm$ 9 mmHg and 73.2 $\pm$ 10 /min,  $p$ <0.01). Group with Triapin mite had lower reduction of systolic/diastolic BP compared to Triapin 21.4 $\pm$ 15.9/11.6 $\pm$ 9.8 vs. 28.9 $\pm$ 19.2/14.1 $\pm$ 11.0 mmHg and lower reduction of heart rate 6.1 vs. 6.3 /min ( $p$ <0.01). In total, 39.3% of patients reached target BP with or without target BP reduction, 30.0% reached only BP reduction and 30.7% did not reach target values. More patients reached target BP (48.4 vs 32.%) and less achieved defined BP reduction (18.8 vs. 38.9%) on Triapin mite therapy compared to Triapin ( $p$ <0.01). The proportion of patients who failed to reach any of these endpoints is similar in both treatment modalities. AEs were present in 34 patients (2.5%); headache in 9 (0.7%), lower leg swelling in 8 (0.6%) and dry cough in 4 (0.2%) cases – these were reported as the most frequent. None of reported adverse events was serious. Therapy continuation was reported in 92.6% of patients. Reasons for therapy discontinuation were insufficient drug efficacy in 29 (2.2%) patients; AE in 28 (2.1%) patients and other reasons in 34 (2.6%) patients. Triapin therapy efficacy and safety evaluated by physicians were: excellent efficacy in 824 (61.4%) patients and excellent safety in 870 (64.9%) patients.

Fixed dose combination of ramipril + felodipine was shown to be an effective antihypertensive therapy in patients with essential arterial hypertension and an alternative approach to monotherapy for the initial management of essential hypertension. Small proportion of patients discontinued from ramipril+felodipine therapy and rare AEs indicate excellent safety profile. *Acta Medica Medianae* 2013;52(1): 16-24.

**Key words:** Ramipril, Felodipine, hypertension, efficacy, safety, treatment, hypertension

Institute for Treatment and Rehabilitation "Niška Banja", Serbia<sup>1</sup>  
Cardiology Unit, Health Center Leskovac, LeskoSerbia<sup>2</sup>

Contact: Ivan Tasić  
Institute for Treatment and Rehabilitation "Niška Banja", Niška Banja, Serbia

### Introduction

Cardiovascular (CV) diseases are the leading cause of death in Europe (over four million

people each year), this number represents about half (47%) of all deaths in Europe and 40% in the European Union. Cardiovascular diseases caused a total of 17.1 million people deaths in 2004 worldwide, or 29% of all deaths in the world. Cardiovascular disease is the main cause of death in women in all countries of Europe and is the main cause of death in men in almost all EU countries (1). With proportion of 57.6%, they were also the leading cause of mortality in Serbia

in 2006, with higher percentage of deaths in females - 53.9% (2).

CV mortality is now decreasing in most European countries, including Central and Eastern European countries which evidenced large increases until the beginning of the 21<sup>st</sup> century (1). The largest percentage of increase is predicted in the eastern Mediterranean region, while the largest increase in the number of deaths is expected in the region of Southeast Asia (3).

Arterial hypertension is still the leading independent risk factor for CV morbidity and mortality. It has been estimated that more than 25% of the world's adult population had hypertension in year 2000 and that this figure is expected to increase by 60% to 1.56 billion by 2025 (4). The risk of CV complications is proportional to increase in blood pressure in both sexes of all age groups. Also, as a CV risk factor, it does not act alone, because consequences of high blood pressure depend on association with other risk factors (age, sex, race, diabetes, presence of previous CV disease, smoking, high blood lipids, and family burden). According to the World Health Organization (WHO), approximately 30-50% of the world's adult population suffer from hypertension, and only 30-35% of them are successfully treated and maintain their blood pressure under control (5). It is estimated that 46.5% of adult population in Serbia are hypertensive (2).

Framingham Heart Study showed a marked benefit from the use of antihypertensive therapy over a longer period of time, with reduced total mortality by 31% and CV mortality by 60% (6).

The ESH/ESC 2009 recommendations confirm instructions from 2007, that is - diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers are eligible for starting the antihypertensive treatment, and sub-sequent treatment (7). The ESH/ESC 2009 recommendations suggest that whenever possible a fixed dose (or one tablet) combinations should be used, as a treatment simplification improves adherence to treatment (8,9). Also, it appears that the vast majority of patients with arterial hypertension requires a combination (at least two drugs) of antihypertensive medications to achieve target blood pressure (7,8). The number of drugs (tablets) is one of the important factors (age, more drugs, drug taking in more daily doses, cost and safety of the drug) that act on compliance. Data show that only one third of patients have good adherence to antihypertensive therapy after six months of therapy. It is well known that fixed combinations of antihypertensive drugs improve therapy adherence up to 24-26% (10).

According to ESH/ESC guidelines, a fixed dose combination with calcium channel antagonist (CCA) and angiotensin converting enzyme inhibitor (ACE) is one of the preferred combination in the treatment of arterial hypertension (7).

### Aim

The aim of this study was to evaluate the efficacy and safety of fixed ramipril+felodipine

combination in therapy of essential arterial hypertension.

### Methodology

#### Study design:

Patients in this multicentric, cross-sectional, non-interventional study were recruited by 95 physicians in 25 cities across Serbia. Study sites were selected according to a number of hypertensive patients treated and their geographic distribution. According to clinical practice and study design, patients observation and data collection were done once during each patient's visit to a physician in a cross sectional manner. The data were collected from patient's records retrospectively and from clinical examination undertaken during the visit. Patients' written informed consent was obtained prior to the conduct of any study-related procedure.

#### Patients:

Study enrolled 1.341 male and female patients aged  $\geq 18$  years, with moderate-to-severe essential hypertension defined by increased systolic and diastolic pressure (BP  $\geq 140/90$  mmHg), only systolic blood pressure increase (isolated systolic hypertension) or antihypertensive therapy application. Baseline characteristics of study patients are described in Table 1.

Patients were selected by physician according to inclusion/exclusion criteria. Each investigator included 15 consecutive hypertensive patients observed in ambulance setting treated with ramipril+felodipine combination for at least two months.

#### Treatment:

At the time of the visit all patients were treated with fixed-dose combination therapy ramipril+felodipine (Triapin® and Triapin mite®) for at least two months. The TRIAPIN mite (2.5 mg+ 2.5 mg) therapy was prescribed in 580 (44.1%) of patients, while 735 (55.9%) patients was using TRIAPIN (5 mg + 5 mg) therapy, Table 2.

Therapy was prescribed by physician according to everyday clinical practice and the assignment of the patient to a particular therapeutic strategy was not decided in advance by the trial protocol.

#### Measurements:

Primary outcome variable is efficacy of fixed dose combined therapy ramipril+ felodipine. Efficacy was estimated by proportion of patients achieving target blood pressure (<140/90 mmHg and <130/80 mmHg in diabetics) or defined blood pressure reduction ( $\geq 15/10$ mmHg) compared to baseline values prior to treatment with fixed-dose combination.

Classification of blood pressure (BP) levels (mmHg) is done according to ESC recommendations (Grade 1 hypertension 140–159 and/or 90–99; Grade 2 hypertension 160–179 and/or

100–109; Grade 3 hypertension  $\geq 180$  and/or  $\geq 110$  mmHg) (11). The BP measured before therapy initiation was used for BP classification.

Safety of ramipril+felodipine therapy was estimated by incidence of adverse events (AE) / adverse drug reaction (ADR) and therapy discontinuation during the observational period.

Date and place:

Study was conducted during the period from September 2010 to October 2011.

Data collection and statistical analyses:

Data was collected on paper case report form (CRF) during regular medical visit and then entered into electronic database. All case report forms were monitored for completeness and accuracy. Baseline data included demographics, medical history, risk factors, physical examination, cardiac parameters. Other collected data included treatments of hypertension, adverse events and efficacy data.

Statistical analyses were performed for all patients who completed the study. Continuous data are presented as mean values with standard deviations or as medians with interquartile ranges (for skewed data). Categorical data are presented by absolute numbers with percentages. Comparisons of mean changes in SBP/DBP and heart rate between starting and final treatment values were performed using a paired t-test. Other parametric examination were done by independent samples t test.

## Results

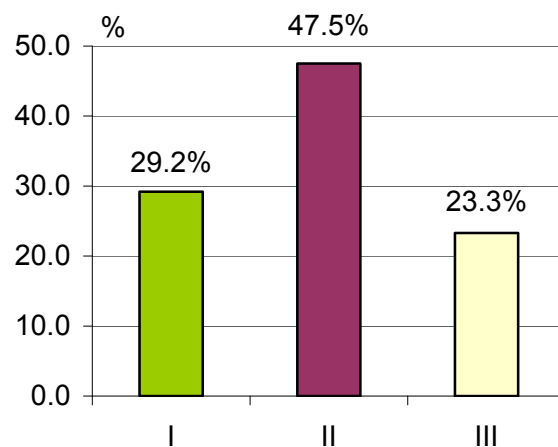
Males enrolled in the study were younger and with shorter duration of hypertension compared to females ( $p < 0.05$ ). There were no significant differences in cardiovascular parameters and BMI

values, except lower heart rate in males (Table 1). The dosage of fixed dose combination is shown in Table 2.

Inadequate hypertension regulation during previous treatment was the most common reason for fixed combination of ramipril + felodipine initiation, in 1.144 (85.3%) patients; compliance improvement in good regulated hypertension, in 348 (26.0%) patients and other reasons in 43 (3.2%) patients.

About half of patients have stage II hypertension, while approximately one quarter of patients have stage I and another quarter stage III (Graph 1).

Efficacy of therapy is measured by reduction of blood pressure, heart rate reduction and achieved target BP values (Graphs 2-4).



Graph 1. Distribution of patients according to hypertension stages determined by starting BP

Stage I (systolic BP 140-159 / diastolic BP 90-99 mmHg); Stage II (systolic BP 160-179 / diastolic BP 100-109 mmHg); Stage III (systolic BP  $> 180$  / diastolic BP  $> 110$  mmHg)

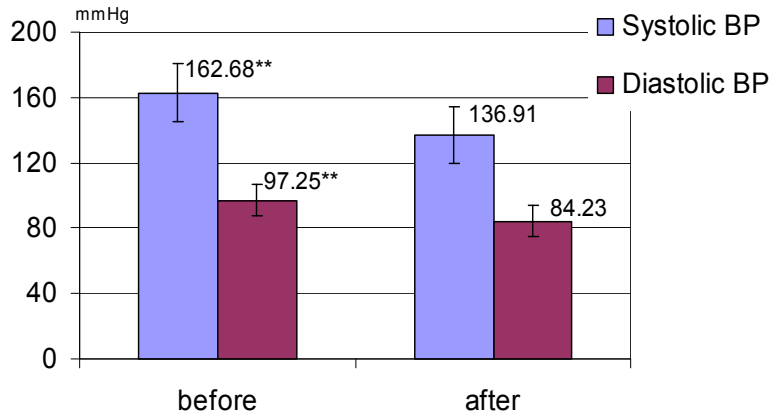
Table 1. Baseline characteristics of study patients

	Males	Females	Total
Number / %	647 / 48.4	690 / 51.6	1337 / 100.0
Age (years)	58.74 $\pm$ 15.5*	61.45 $\pm$ 11.04	60.15 $\pm$ 11.8
BMI (kg/m <sup>2</sup> )	28.3 $\pm$ 3.7	28.0 $\pm$ 4.3	28.1 $\pm$ 4.0
Duration of hypertension (years)	8.9 $\pm$ 7.0*	10.0 $\pm$ 7.5	9.5 $\pm$ 7.3
Waist circumference (cm)	100.02 $\pm$ 11.3*	91.2 $\pm$ 13.2	95.4 $\pm$ 13.2
Systolic BP (mmHg)	161.9 $\pm$ 16.9	163 $\pm$ 18.6	162.7 $\pm$ 17.8
Diastolic BP (mmHg)	97.6 $\pm$ 9.7	93.8 $\pm$ 9.5	97.2 $\pm$ 9.6
Heart rate (/min)	78.3 $\pm$ 12.2*	80.2 $\pm$ 12.3	79.4 $\pm$ 12.3

Data are presented as mean $\pm$ SD; \* $p < 0.05$

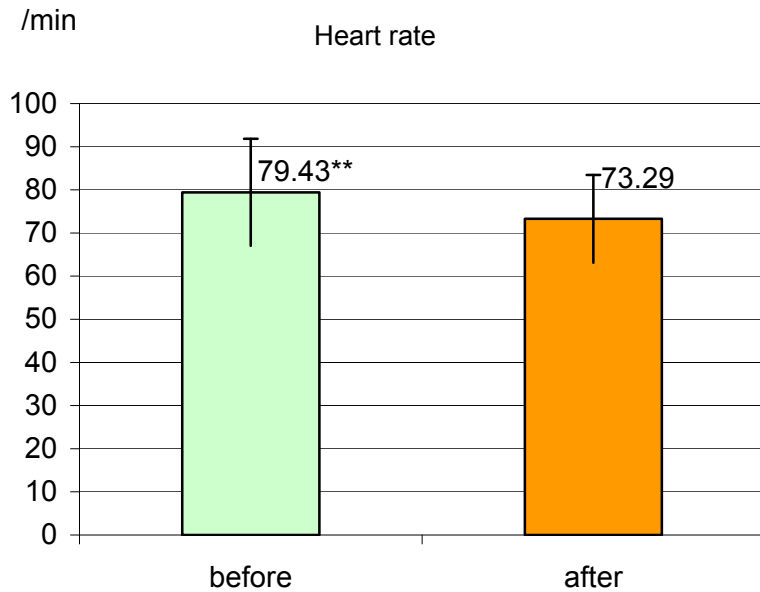
Table 2. Fixed dose combination therapy (ramipril + felodipine) of hypertension: TRIAPIN mite and TRIPIN therapy

	Therapy	Frequency	Percent	Valid Percent
Valid	TRIAPIN mite	580	43.3	44.1
	TRIAPIN	735	54.8	55.9
	Missing	26	1.9	
	Total	1341	100.0	



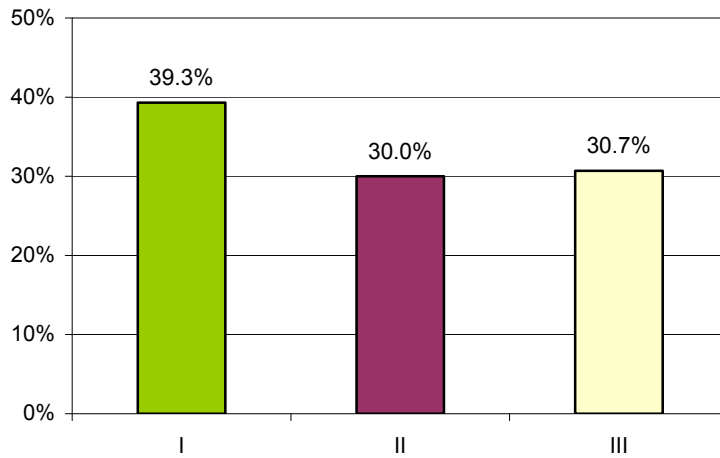
\*\*p<0.01

Graph 2. Therapy efficacy measured by systolic/diastolic BP reduction



\*\*p<0.01

Graph 3. Therapy efficacy measured by heart rate reduction



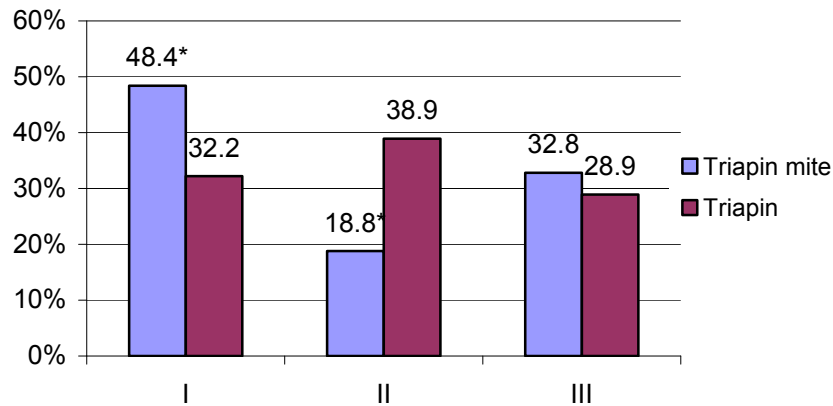
Graph 4. Therapy efficacy measured by achievement of target BP values and/or defined BP reduction.

I - (reached target BP <140/90mmHg in general and <130/80 mmHg in diabetics) with or without reaching defined BP reduction  $\geq 15/10$  mmHg;  
 II - reached only defined BP reduction  $\geq 15/10$  mmHg;  
 III-not reached target BP nor defined BP reduction

Table 3. Therapy efficacy attributed to therapy dose

	ramipril + felodipine 2.5/2.5 mg	ramipril + felodipine 5/5 mg
Age (years)	59.5±12.7*	60.8±11.0
BMI (kg/m <sup>2</sup> )	27.2±3.7*	28.8±4.1
Waist circumference (cm)	92.7±13.1*	97.8±12.6
Duration of hypertension (years)	8.09±6.8*	10.6±7.5
Systolic BP (mmHg)	133.3±14.9*	139.7±18.0
Diastolic BP (mmHg)	82.4±8.9*	85.6±9.9
Heart rate (/min)	72.3±10.0*	74.0±10.1
Previous systolic BP (mmHg)	154.8±13.2*	168.9±18.5
Previous diastolic BP (mmHg)	94.0±8.2*	99.8±9.9
Previous heart rate (/min)	78.6±11.9*	80.1±12.6
Average reduction systolic BP (mmHg)	21.4±15.9*	28.9±19.2
Average reduction diastolic BP (mmHg)	11.6±9.8*	14.1±11.0

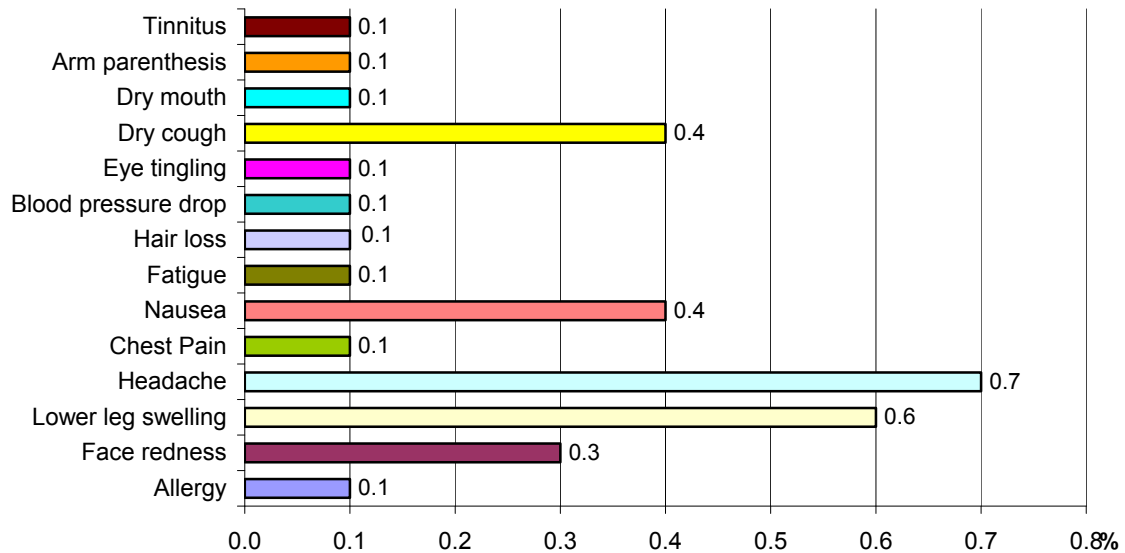
\*p<0.05 vs. ramipril+felodipine 5/5mg



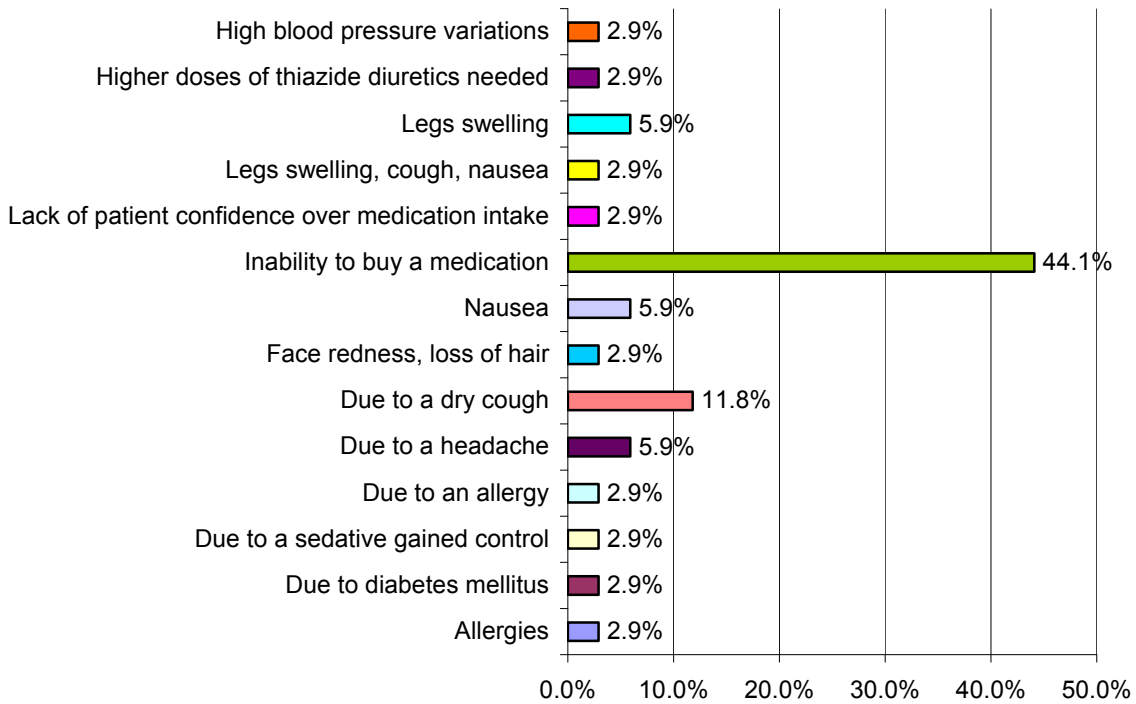
\*p<0.05 vs. Triapin

Graph 5. Therapy efficacy according to dose of ramipril+felodipin fixed combination

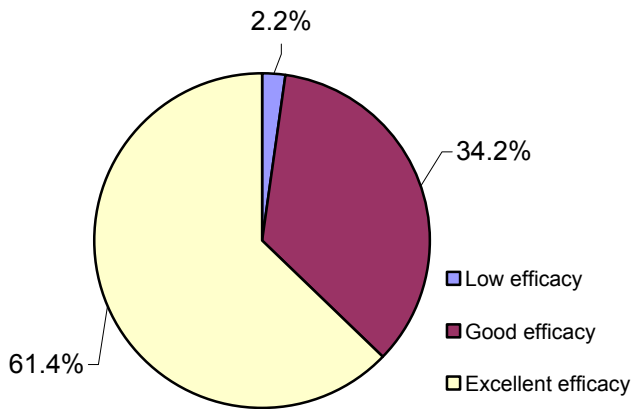
- I- (reached target BP <140/90mmHg in general and <130/80 mmHg in diabetics) with or without reaching defined BP reduction ≥15/10 mmHg;
- II - reached only defined BP reduction ≥15/10 mmHg;
- III-not reached target BP nor defined BP reduction



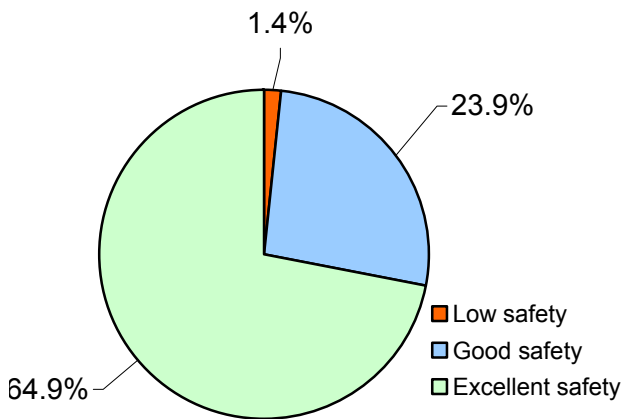
Graph 6. Therapy adverse events



Graph 7. Other reasons for ramipril+felodipin discontinuation in total of 34 patients



Graph 8. Ramipril+felodipin therapy efficacy assessed by physicians



Graph 9. Ramipril+felodipin therapy safety assessed by physicians

Baseline values (systolic and diastolic blood pressure as well as heart rate) were significantly reduced after at least two months of therapy with ramipril+felodipine fixed dose combination ( $p < 0.01$ ) (Graphs 2,3).

The analysis showed that 39.3% of patients from the total number of 1.341 subjects reached the target BP; 30.01% of patients reached defined BP reduction without reaching target BP and 30.7% of patients did not reach the target BP nor defined reduction of BP (Graph 4).

Patients with lower dose of ramipril+felodipin combination were younger, less obese, with better cardiovascular parameters and shorter duration of hypertension. The lower dose ramipril+ felodipin combination also showed a lower average reduction of systolic/diastolic blood pressure ( $p < 0.05$ ) when compared to a higher dose of ramipril+felodipine 5/5mg (Table 3).

The proportion of patients reaching the target BP values or target BP reduction is shown in Graph 5. Patients with lower dose of ramipril+felodipin therapy combination more often reached the target BP values, but less often reached defined BP reduction  $\geq 15/10$ mmHg ( $p < 0.05$ ) (Graph 5).

Therapy continuation: The ramipril + felodipine therapy continuation was reported for 1.242 (92.6%) patients and discontinuation in 99 (7.4%). The main reasons for ramipril+felodipin discontinuation were: insufficient efficacy 29 (2.2%), adverse events 28 (2.1%) and other reasons 34 (2.6%). Adverse events are presented in Graph 6.

Adverse events were reported by 34 patients. Nine patients reported headache (0.7%)

and eight patients reported the lower leg swelling (0.6%) as the most frequent adverse events. None of reported adverse events were serious (Graph 6).

Ramipril+felodipine therapy efficacy and safety are shown in Graphs 8 and 9. Excellent efficacy was reported in 824 (61.4%) patients and excellent safety was reported in 870 (64.9%) patients.

## Discussion

Hypertension is a leading modifiable risk factor for cardiovascular disease. There is a direct relationship between blood pressure and risk of cardiovascular disease. It is shown that reduction of diastolic blood pressure by 2mm Hg reduces the risk of coronary artery disease by 6% and CVD/TIA by 15% (12). Treatment of patients with arterial hypertension varies within a wide range, but it can be generally stated that it is far from the optimal target level. During the period between 2005 and 2008, the overall age-adjusted prevalence of hypertension control among adult hypertension patients was 43.7% (13).

Triapin mite (2.5 mg + 2.5 mg) and Triapin (5 mg + 5 mg) are indicated in patients with blood pressure that cannot be adequately controlled using only felodipine or ramipril. Both components of the drug, calcium antagonist felodipine and angiotensin converting enzyme inhibitor (ACE) ramipril lower blood pressure causing the dilatation of peripheral blood vessels. Calcium antagonists dilate arterial blood vessels, while ACE inhibitors dilate both arterial and venous blood vessels. Vasodilatation and consequent reductions in blood pressure can lead to the activation of the sympathetic nervous system and the renin-angiotensin system. Inhibition of ACE results in a decrease in angiotensin II plasma concentrations (14).

The felodipine+ramipril fixed combination therapy was shown to be more effective than monotherapy with these drugs, even when drugs were administered at higher doses (10 mg) (15-18). Starting values of study patient's blood pressure and heart rate were significantly reduced after at least two months of therapy. This corresponds to the results of other studies where treatment with the fixed dose combination was significantly more effective in reducing systolic and diastolic BP (-15.8/-9.2 mmHg) compared to its monocomponents, ramipril (-7.6/-3.8 mmHg) and felodipine ER (-8.0/-5.0 mmHg) (15,19). It is of interest that reduction observed in the FORECAST study is twice higher.

Patients with higher grade of hypertension are usually with higher therapeutic dose and, as expected, they more often reached the target BP reduction, but less often the target BP value. On the other hand, patients with lower BP grade usually used a mite drug formulation and they

often reached the target values but not the target BP reduction. This result is not only the consequence of the starting BP grade but also it arises from the fact that patients with lower dose ramipril+felodipin combination were younger, less obese, with better cardiovascular parameters and shorter duration of hypertension.

Ramipril+felodipin therapy was discontinued in 7.4% of patients due to insufficient product efficacy in 2.2%, adverse events in 2.1% and other reasons in 2.5% of patients. Slightly lower percentage (5.1%) of discontinuation was reported in Poisson et al. study (16) because of adverse events, but without clear pattern in regard to specific events leading to withdrawal. Bainbridge et al. (18) observed that felodipin attributable headache was not attenuated by co-administration of ramipril. Similar findings indicate that reported adverse events were mild, and smaller number of patients treated with fixed-dose combination reported adverse events (19). Similar study evaluating safety and tolerability of combination therapy showed there were fewer cases of peripheral edema with a combination therapy than with felodipine monotherapy. About 5.1% of patients withdrew from the study because of adverse events, but there was no clear pattern with regard to the specific events leading to withdrawal. All this is in line with the results obtained in FORECAST study (16).

## Conclusion

The fixed dose combination of ramipril+felodipine (Triapin® and Triapin Mite®) was shown to be an effective antihypertensive therapy in patients with essential arterial hypertension and an alternative approach to monotherapy for the initial management of essential hypertension. Ramipril+felodipine appear to be an effective option for the treatment of adults with essential hypertension that is poorly controlled with monotherapy.

Small proportion of patients discontinued ramipril+felodipine therapy and rare AE indicate excellent safety profile. In clinical setting, this therapy showed excellent compliance, efficacy and safety indicated by patients and physicians.

Great incidence of comorbidities, mainly heart disease and presence of cardiovascular risk factors, indicate the pathogenetic role of essential hypertension in target organs damage. The great cardiovascular risk factors load is one of the possible explanations for relatively great proportion of patients with uncontrolled hypertension and indicates the need for multidrug therapeutic approach in therapy of essential hypertension.

## Acknowledgement

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## EFIKASNOST I BEZBEDNOST FIKSNE KOMBINACIJE LEKOVA RAMIPRIL + FELODIPIN U TERAPIJI ARTERIJSKE HIPERTENZIJE: RETROSPEKTIVNA STUDIJA-FORECAST

Ivan Tasić<sup>1</sup> i Gabrijela Stojković<sup>2</sup>

Oko 30-50% ukupne svetske odrasle populacije boluje od arterijske hipertenzije, a samo 30-35% su uspešno lečeni. Veliki broj bolesnika sa arterijskom hipertenzijom zahteva kombinaciju antihipertenzivnih lekova da bi dostigli željeni krvni pritisak. Prema preporukama ESH/ESC koristi se fiksna doza kombinacije za pojednostavljenu i poboljšanu terapiju.

Cilj ove studije bio je da se proceni efikasnost i bezbednost fiksne kombinacije lekova ramipril + felodipin u terapiji esencijalne arterijske hipertenzije.

Ova multicentrična, ukrštena, neintervencionalna studija obuhvatila je 1341 odraslog bolesnika sa esencijalnom arterijskom hipertenzijom, definisanom kao porast sistolnog i dijastolnog krvnog pritiska ( $\geq 140/90$  mmHg), porast samo sistolnog krvnog pritiska ili korišćenje antihipertenzivne terapije. Svi bolesnici su tretirani fiksnom dozom lekova kombinovane terapije ramipril + felodipin (5+5mg and 2.5+2.5mg) (Triapin® i Triapin mite®) najmanje dva meseca. Efikasnost je procenjivana procentom bolesnika koji su dostigli adekvatan krvni pritisak ( $<140/90$  mmHg i  $<130/80$  mmHg in diabetics) ili definisano smanjenje krvnog pritiska ( $\geq 15/10$  mmHg). Procena bezbednosti terapije ramiprilom + felodipinom zasnivala se na incidenci neželjenih efekata i stopi prekida terapije u toku perioda posmatranja. Propisivanje terapije zasnivalo se na odluci kliničara na osnovu svakodnevnog iskustva iz kliničke prakse i 15 bolesnika koje je izabrao i uključio svaki kliničar među mnoštvom bolesnika sa hipertenzijom koji su lečeni u ambulanti.

Grupu bolesnika činilo je 647 (48.4%) muškaraca i 690 (51.7%) žena (prosečna starost  $60.15 \pm 11.84$  i prosečna dužina trajanja hipertenzije  $9.5 \pm 7.34$  godina). Muškarci su bili značajno mlađi ( $58.74 \pm 15.5$  prema  $61.45 \pm 11.04$ ,  $p < 0.01$ ) bez razlike u indeksu telesne mase. U drugom stadijumu bilo je 47.5% bolesnika, 29.2% u prvom i 23.3% u trećem. Uočeno je značajno smanjenje sistolnog/dijastolnog krvnog pritiska i pulsa kod bolesnika sa ramipril + felodipin kombinacijom ( $162.6 \pm 17/97.2 \pm 9$  mmHg i  $79.4 \pm 12$ /min) u poređenju sa vrednostima pre tretmana ( $136.9 \pm 17/84.2 \pm 9$  mmHg i  $73.2 \pm 10$  /min,  $p < 0.01$ ). Grupa sa lekom Triapinom mite imala je manju redukciju sistolnog/dijastolnog krvnog pritiska u poređenju sa Triapinom  $21.4 \pm 15.9/11.6 \pm 9.8$  prema  $28.9 \pm 19.2/14.1 \pm 11.0$  mmHg i manju redukciju pulsa  $6.1$  prema  $6.3$  /min ( $p < 0.01$ ). Ukupno 39.3% bolesnika dostiglo je odgovarajući krvni pritisak, 30.0% dostiglo je samo definisanu redukciju krvnog pritiska, dok 30.7% nije dostiglo odgovarajuće vrednosti. Veći broj bolesnika dostigao je odgovarajući krvni pritisak (48.4 prema 32.%), a manji broj je dostigao definisano smanjenje krvnog pritiska (18.8 prema 38.9%) kod terapije Triapinom mite u poređenju sa terapijom Triapinom ( $p < 0.01$ ). Procenat bolesnika koji nisu dostigli ni jednu od graničnih vrednosti sličan je kod oba modaliteta terapije. Neželjeni efekti bili su prisutni kod 34 bolesnika (2.5%): glavobolja 9 (0.7%), znojenje donjih ekstremiteta 8 (0.6%) i suv kašalj 4 (0.2%) bili su najčešće prijavljivani. Ni jedan od prijavljenih neželjenih efekata nije bio ozbiljan. Nastavak terapije bio je prijavljen kod 92.6% bolesnika. Razlozi za prekidanje terapije bili su nedovoljna efikasnost leka kod 29 (2.2%); neželjeni efekti 28 (2.1%) i ostali razlozi 34 (2.6%). Procenjena efikasnost i bezbednost terapije Triapinom: odlična efikasnost kod 824 (61.4%) i odlična bezbednost kod 870 (64.9%) bolesnika.

Pokazano je da je kombinacija fiksnih doza lekova ramipril + felodipin efikasna antihipertenzivna terapija kod bolesnika sa esencijalnom arterijskom hipertenzijom i alternativa monoterapiji za početno regulisanje arterijske hipertenzije. Ukinuta terapija ramipril+felodipin i retka pojava neželjenih efekata malom broju bolesnika označavaju odličan bezbednosni profil leka. *Acta Medica Medianae* 2013;52(1):16-24.

**Ključne reči:** ramipril, felodipin, hipertenzija, efikasnost, bezbednost, terapija