Doprinos Krkinih lijekova koji djeluju na renin-angiotenzin-aldosteronski sustav u liječenju arterijske hipertenzije: 25 godina kliničkog iskustva

Contribution of Krka's RAAS-acting Medicines in the Treatment of Hypertension: 25 Years of Clinical Experience

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SAŽETAK: Krka ima više od 25 godina iskustva u proizvodnji visokokvalitetnih lijekova koji djeluju na renin-angiotenzin-aldosteronski sustav (RAAS) te je postala jedan od vodećih proizvođača takvih lijekova u Europi. Otkad je prvi put uvela lijek koji djeluje na RAAS, Krka provodi međunarodna klinička istraživanja kako bi pratila učinkovitost i sigurnost svojih proizvoda unutar opsega primjene, omogućila liječnicima da steknu vlastito iskustvo o njihovom korištenju te dokazala njihovu učinkovitost i sigurnost u kliničkoj praksi. Uz podatke iz istraživanja opisanih u ovom članku, izložit ćemo i dvadesetpetogodišnji doprinos Krkinih lijekova koji utječu na RAAS u liječenju arterijske hipertenzije.

SUMMARY: Krka has over 25 years of experience in the production of high-quality medicines acting on the renin-anigotensin-aldosterone system (RAAS) and has become one of the leading producers of them in Europe. Since its first introduction of a medicine acting on RAAS it has been performing international clinical studies in order to monitor the efficacy and safety of its products within the scope of the doctrine, enable doctors to gain their own experience with them, and prove their efficacy and safety in clinical practice. With the findings of the studies described in this article, we would like to present the contribution of Krka's RAAS-acting medicines in the treatment of hypertension in over 25 years.

KLJUČNE RIJEČI: ACE inhibitori, blokatori angiotenzin II receptora, klinička istraživanja, učinkovitost, sigurnost.

KEYWORDS: ACE inhibitors, angiotensin II receptor blockers, clinical studies, efficacy, safety.

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Renin-angiotenzin-aldosteronski sustav (RAAS) složeni je sustav s ključnom ulogom u održavanju hemodinamske stabilnosti u ljudskom tijelu kroz regulaciju arterijskog tlaka (AT) i ravnoteže vode i elektrolita.[1-4] No, patološka aktivacija RAAS-a, koju treba liječiti, uzrokuje kroničnu hipertenziju i posljedično oštećenje organa.[5] Pretjerana aktivacija RAAS-a može se liječiti inhibitorima angiotenzin konvertirajućeg enzima ili blokatorima angiotenzin II receptora, pri čemu za obje skupine lijekova postoje vrlo dobri podatci što se tiče učinkovitosti i podnošljivosti. Klinička istraživanja s Krkinim lijekovima koji djeluju na RAAS potvrdila su njihovu učinkovitost i visoku podnošljivost u liječenju arterijske hipertenzije u različitim skupinama pacijenata.[6,7] Glavni podatci i rezultati probranih ključnih istraživanja na lijekovima koji djeluju na RAAS

The renin–angiotensin–aldosterone system (RAAS) is a complex system that has a key role in maintaining hemodynamic stability in the human body through regulation of arterial blood pressure (BP) and water and electrolyte balance.[1-4] However, pathological activation of RAAS, which requires treatment, results in chronic hypertension and consequent end organ damage.[5] Excessive RAAS activation can be treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which are both supported by very solid data regarding their safety and tolerability profiles. Clinical studies with Krka's RAAS-acting medicines have confirmed their efficacy and good tolerability in the treatment of hypertension in different groups of patients.[6,7] The main data and results of selected key clinical studies

prikazani su u **tablicama 1 do 4**. U nastavku ćemo ukratko prikazati glavne rezultate.

Prvi Krkin lijek s djelovanjem na RAAS bio je enalapril, uveden na tržište 1988. godine. Od tada je provedeno više od 40 međunarodnih kliničkih istraživanja na lijekovima koji djeluju na RAAS. Istraživanja su provedena za lijekove perindopril (Perineva®), enalapril (Enap®), ramipril (Ampril®), losartan (Lorista®) i valsartan (Valsacor®) te fiksne kombinacije lijekova (FKL) s diuretikom ili amlodipinom. Svrha istraživanja bila je praćenje učinkovitosti i sigurnosti tih lijekova. Dodatna im je vrijednost što uključuju različite populacije pacijenata: od pacijenata s blagom do umjerenom arterijskom hipertenzijom do onih s povećanim kardiovaskularnim rizikom ili drugim stanjima, kao što su zatajivanje srca (ZS), pacijenti s preboljelim infarktom miokarda, dijabetesom, dijastoličkom disfunkcijom lijeve klijetke, hiperuricemijom i gihtom, seksualnom disfunkcijom i drugim stanjima. Raznolikost pacijenata doprinijela je širokom rasponu primarnih ciljeva i kliničkih ishoda koji su daleko veći od sniženja vrijednosti AT.[6,7]

Najnovije istraživanje rađeno je na FKL perindoprila i amlodipina. Ova je kombinacija lijekova prošla istraživanje koje je trajalo četiri mjeseca te je uključilo 2880 pacijenata. Već unutar jednog mjeseca liječenja gotovo pola pacijenata doseglo je ciljnu razinu sniženja AT. Većina je pacijenata dobro podnosila kombinaciju lijekova; 91% pacijenata nije navelo nikakve nuspojave. Pacijenti su se dobro pridržavali liječenja, a doze nije bilo potrebno pretjerano prilagođavati.[8] Perindopril, koji je dosad bio uključen u ukupno četiri istraživanja kao samostalan lijek ili kao FKL s indapamidom ili amlodipinom, korišten je u jednoj od najvećih neinterventnih kliničkih istraživanja u kardiovaskularnoj medicini – u ATRACTIV istraživanju.[6] To je istraživanje potaknulo dobro poznato ASCOT istraživanje, koje je najveće europsko istraživanje arterijske hipertenzije ikad provedeno.[9] ATRACTIV istraživanje, koje se bavilo učinkovitošću suvremenog pristupa smanjenju rizika od kardovaskularnih bolesti u primarnoj skrbi, provedeno je na više od 4400 pacijenata u Češkoj Republici. Bolje liječenje arterijske hipertenzije u ATRACTIV istraživanju povezano je sa značajnim sniženjem vrijednosti AT.[10]

Jedan od najproučavanijih Krkinih lijekova koji djeluju na RAAS svakako je Ampril®, koji je klinički dokazan u 15 kliničkih istraživanja u osam zemalja na gotovo 9000 pacijenata.[11-20] Istraživanja su donijela važne rezultate i veliku bazu podataka kakva nije na raspolaganju za ijedan drugi generički ramipril. Istraživanja s ramiprilom uključivala su pacijente s blagom do umjerenom hipertenzijom, koronarnom bolesti srca, dijabetes melitusom ili metaboličkim sindromom, pacijenata s preboljelim infarktom miokarda i visokorizičnih pacijenata. Ovisno o vrsti populacije, primarni ciljevi su bili, uz evaluaciju smanjenja vrijednosti AT, procjena učinka lijeka na kardiološke i cerebrovaskularne komplikacije i rad bubrega, te poboljšanje elasticiteta arterijskih stijenki nakon smanjenja AT i hipertrofije lijevog ventrikula. Iako je ramipril imao različite pozitivne učinke u određenim situacijama, AT se držao pod kontrolom u svim skupinama pacijenata neovisno o početnim uvjetima.[11-20] Istraživanje CALYPSO također je pokazalo da ramipril, dan unutar prva 24 sata nakon pojave akutnog koronarnog sindroma i tijekom tri mjeseca terapije,

performed with RAAS-acting medicines are presented in **Tables 1, 2, 3 and 4**. In continuation we are briefly summarizing their main results.

Krka's first medicine acting on RAAS was enalapril, which was introduced on the market in 1988. Since then, more than 40 international clinical studies were performed with RAAS-acting medicines. The studies were performed with perindopril (Perineva®), enalapril (Enap®), ramipril (Ampril®), losartan (Lorista®) and valsartan (Valsacor®) and their fixed-dose combinations (FDC) with either diuretic or amlodipine. They were performed with the purpose to monitor the efficacy and safety of these medicines. Their added value is the inclusion of different populations of patients: from patients with mild to moderate hypertension to those with increased cardiovascular risk or with other conditions and risk factors, such as heart failure (HF), post-myocardial infarction (MI) patients, patients with diabetes, left ventricular diastolic dysfunction, hyperuricemia and gout, sexual dysfunction and other conditions. The variety of patients has contributed to a broad setting of primary objectives and clinical outcomes, which were far beyond BP reduction.[6,7]

The most recent study was performed with FDC of perindopril and amlodipine. The use of this combination was studied in a 4-month study in 2,880 patients. Already within 1 month of treatment almost half of the patients reached their target BP values. In most patients, the FDC of perindopril and amlodipine was well tolerated with no adverse reactions being reported in 91% of the patients. Good treatment adherence with little need of dose adjustment to achieve target BP was reported.[8] Perindopril, which has been until now included in altogether 4 studies in either monotherapy or FDC with indapamide or amlodipine, was also used in one of the largest non-interventional clinical studies with cardiovascular medicines, in the ATRACTIV study.[6] The ATRACTIV study simulated the well-known ASCOT study which was the largest European study ever performed in hypertension.[9] The ATRACTIV study, which investigated the efficacy of a complex and modern approach to cardiovascular risk reduction in primary care, was conducted in more than 4,400 patients in the Czech Republic. Improved management of hypertension in the ATRACTIV study was associated with a significant decrease of BP.[10]

One of the most studied Krka's RAAS-acting medicine is certainly Ampril®, which has been clinically proven in 15 clinical studies conducted in eight countries in nearly 9,000 patients.[11-20] The studies yielded important results and an extensive data base, which is not available for any other generic ramipril. Studies with ramipril included patients with mild to moderate hypertension, ischemic heart disease, diabetes mellitus or metabolic syndrome, post-MI patients or high risk patients. Depending on the particular patient population, the primary objectives were, in addition to the evaluation of BP reduction, the influence on the frequency of cardiac and cerebrovascular complications and kidney function and on the improvement of arterial wall elasticity after reduction of arterial pressure and left ventricular hypertrophy. Although ramipril showed different benefits in specific situations, it also kept BP under control in all patient groups regardless of the type of their condition.[11-20] CALYPSO study additionally proved that ramipril, given within

TABLE 1. Key clinical studies with perindopril and/or its fixed-dose combination with either diuretic or amlodipine.

						Study results		
Study	**Primary objective**	**Patient profiles**	**No. of patients**	**Duration**	**Dose**	**Efficacy**	**Safety and tolerability**	**Main conclusion**
Non-interventional clinical study with perindopril and perindopril/indapamide combination[27]	To evaluate the safety and efficacy of perindopril and its FDC with indapamide in the treatment of hypertension.	Patients with mild to moderate hypertension. Mean age: 62 ± 12.3 years.	4574	4 months	• Perindopril: 2 mg, 4 mg or 8 mg • FDC of perindopril and indapamide: 2 mg/0.625 mg, 4 mg/1.25 mg or 8 mg/2.5mg.	SBP and DBP decreased statistically significantly: • SBP by 22.8 mm Hg (from 157.5 to 134.7 mm Hg; mean relative reduction of 14.7%) • DBP by 10.4 mm Hg (from 91.8 to 81.4 mm Hg; mean relative reduction of 11.3%). At the end of the study, 78% of the patients had a BP of 140/90 mm Hg or lower with no adverse reactions observed.	97% of the patients had no adverse reactions.	Perindopril and its FDC with indapamide are effective, safe and well tolerated in patients with hypertension.
Non-interventional clinical study with FDC of perindopril and amlodipine[8]	To evaluate the safety and efficacy of FDC of perindopril and amlodipine in the treatment of hypertension.	Patients with hypertension and/or stable coronary disease. Mean age: 63.9 ± 11.8 years.	2880	4 months	• FDC of perindopril and amlodipine: 4 mg/5mg, 4 mg/10 mg, 8 mg/5 mg or 8 mg/10 mg	SBP and DBP decreased statistically significantly: • SBP by 27.9 mm Hg (from 163.9 to 136.0 mm Hg; mean relative reduction of 17.0%) • DBP by 12.2 mm Hg (from 93.4 to 81.2 mm Hg; mean relative reduction of 13.1%). At the end of the study, 70% of the patients had a BP of 140/90 mm Hg or lower with no adverse reactions observed.	91% of the patients had no adverse reactions.	FDC of perindopril and amlodipine is effective and safe and has a good tolerability profile also in patients who do not reach their target BP with monotherapy.
The ATRACTIV study[10]	To monitor the incidence of risk factors for CVD in high-risk patients on follow-up by GPs and attempt to maximise risk reduction.	Hypertensive patients with dyslipidemia and other risk factors: • type 2 diabetes • abdominal obesity • overweight • smoking and at high risk for CVD. Mean age was 62.9 ± 10 years.	4427	12 months	Atorvastatin was used to treat dyslipidemia. Hypertension was treated with ramipril and perindopril or, if not tolerated, with losartan. In cases of inadequate BP control, amlodipine was added to antihypertensive therapy.	SBP and DBP decreased statistically significantly: • SBP by 20.0 mm Hg (from 152.5 to 132.5 mm Hg; mean relative reduction of 13.1%) • DBP by 10.3 mm Hg (from 90.5 to 80.2 mm Hg; mean relative reduction of 11.4%). Optimisation of dyslipidemia treatment resulted in significant: • decrease of total cholesterol by 23% • decrease of LDL-cholesterol by 28% • decrease of triglycerides by 22% and • increase of HDL-cholesterol by 4.5%.	Pharmacotherapy indicated during the study was well tolerated with minimal adverse reactions.	A comprehensive approach to patients at increased risk for CVD, including lifestyle intervention with effective combinations of lipid-lowering drugs and antihypertensives results in a significant CVD risk reduction.

BP – blood pressure, CVD – cardiovascular disease, DBP – diastolic blood pressure, FDC – fixed-dose combination, HDL – high density lipoprotein, LDL – low density lipoprotein, SBP – systolic blood pressure

TABLE 2. Key clinical studies with ramipril or enalapril and/or their fixed-dose combinaton with diuretic.

Study	Primary objective	Patient profiles	No. of patients	Duration	Dose	Study results		
						Efficacy	Safety and tolerability	Main conclusion
Non-interventional clinical study with ramipril[11,28]	To evaluate the safety and efficacy of ramipril in the treatment of hypertension.	Patients with mild to moderate hypertension who were either newly discovered or previously untreated or unsuccessfully treated with previous therapy.	2798	From 3 to 7 months	Ramipril: 2.5 mg, 5 mg or 10 mg.	SBP and DBP decreased statistically significantly: • SBP by 26.3 mm Hg (from 164.0 to 137.7 mm Hg; mean relative reduction of 16%) • DBP by 12.8 mm Hg (from 96.1 to 83.3 mm Hg; mean relative reduction of 13%). The target BP or lowering of SBP by at least 10 mm Hg and DBP by at least 5 mm Hg was reached in 95% of the patients.	Mild adverse reactions were observed in only 3.5% of the patients. Most adverse reactions were transient.	Ramipril provides effective and safe treatment for patients with hypertension.
The CALIPSO study[13]	To evaluate the influence of early administration of ramipril on the frequency of cardiac and cerebrovascular complications occurrence in MI survivors.	Patients with mild to moderate hypertension and acute coronary syndrome with or without ST segment elevation. Mean age: 62 ± 7 years.	60	3 months	Ramipril group: The initial dosage of ramipril was 2.5 mg twice daily. If a patient did not tolerate the starting dose, the dose was lowered to 1.25 mg. The dose was then increased to 2.5 mg and 5 mg, both taken twice daily. Control group: standard therapy for acute MI using any ACE inhibitor.	Within 3 months ramipril treatment led to significant (65%) reduction of AP frequency in the post-MI period. In the ramipril group, mean level of: • SBP was reduced by 13.2% • DBP was reduced by 9.7%. There was no fatal episode, nonfatal MI or insult registered in the ramipril group. In the control group, 4 cases of recurrent MI were registered, 3 of them had a fatal outcome. 4 other patients were hospitalised due to destabilisation of AP. Ischemic stroke occurred in 1 patient.		Ramipril given within the first 24 hours after acute coronary syndrome occurrence, and administered during the following 3 months, improves the prognosis in patients who survived acute MI.
The GARANT study[29]	To study the effects of FDC of enalapril and HCTZ in treatment of hypertension.	Patients with BP ≥160/95 mm Hg or isolated systolic hypertension and without previous effective antihypertensive therapy. Mean age: > 55 years.	3288	8 weeks	Initial dose: FDC of enalapril and HCTZ 20 mg/12.5 mg. After 3 weeks the therapy changed to FDC of enalapril and HCTZ in a dose of • 10 mg/25 mg for non-responders • 10 mg/12.5 mg for patients whose BP was significantly lowered.	SBP and DBP decreased statistically significantly: • SBP by 31.6 mm Hg (from 166.1 to 134.5 mm Hg; mean relative reduction of 19.0%) • DBP by 14.7 mm Hg (from 97.1 to 82.4 mm Hg; mean relative reduction of 15.1%).	The overall tolerability was very good. Therapy additionally proved to be metabolically neutral, with no negative effects on glucose, cholesterol, creatinine and potassium levels.	FDC of enalapril and HCTZ is effective and well tolerated in patients with hypertension.

ACE – angiotensin-converting enzyme, AP – angina pectoris, BP – blood pressure, DBP – diastolic blood pressure, FDC – fixed-dose combination, HCTZ – hydrochlorothiazide, MI – myocardial infarction, SBP – systolic blood pressure

TABLE 3. Key clinical studies with losartan and/or fixed-dose combination with diuretic.

Study	Primary objective	Patient profiles	No. of patients	Duration	Dose	Study results		
						Efficacy	Safety and tolerability	Main conclusion
The LAURA study[22]	To investigate the correlation between the administration of losartan and its FDC with HCTZ and the dynamics of uricaemia.	Patients with inadequately controlled hypertension (BP ≥ 140/90 mm Hg) or patients with newly diagnosed hypertension. Mean age: 60.9 ± 5.0 years.	505	3 months	• Losartan: 50 mg or 100 mg • FDC of losartan and HCTZ: 50 mg/12.5 mg or 100 mg/25 mg.	SBP and DBP decreased statistically significantly: • SBP by 33.7 mm Hg (from 164.0 to 131.3 mm Hg; mean relative reduction of 20.5%) • DBP by 17.0 mm Hg (from 96.9 to 79.9 mm Hg; mean relative reduction of 17.5%). In patients with normal uricemia, the initial uric acid level did not change significantly. In patients with hyperuricemia, there was a substantial reduction in uric acid concentration in the blood – from 445.7 µmol/l at the beginning of the study to 387.4 µmol/l at the end of the study.	Therapy with losartan and its FDC with HCTZ was accompanied by an insignificant frequency of adverse reaction development. The frequency of cough and vertigo with nausea was comparable to the frequency of these adverse reactions in the placebo group.	Losartan and its FDC with HCTZ have marked antihypertensive activity. It also selectively influences the uric acid level in the blood, reducing it in patients with initial hyperuricemia and having no effect on it in patients with normal uricemia.
Losartan in patients with type 2 diabetes[23]	To study the clinical efficacy and tolerability, the nephroprotective and uricosuric effects of losartan in the treatment of overweight patients with moderate hypertension and type 2 diabetes.	Patients, aged 36-59 years, with • stage II hypertension • diabetes • BMI > 24 kg/m^2 in whom the previous antihypertensive therapy was not effective or they did not take the prescribed antihypertensives regularly.	48	3 months	Group I: losartan 100 mg once daily. Group II: lisinopril 20 mg once daily. Patients in both groups also received the thiazide-like diuretic indapamide in a dose of 2.5 mg once daily.	A significant decrease in: • SBP by 18.3% • DBP by 15.8% • pulse pressure by 26.8% was observed in patients treated with losartan (group I). Treatment with losartan significantly reduced: • microalbuminuria (from 0.238 to 0.116 g/l) • uric acid (from 475 to 403 µmol/l) which was not observed in the lisinopril control group.	No adverse reactions, including cough, were observed during treatment with losartan. Cough was reported in 31.8% of the patients who received lisinopril.	Losartan effectively reduced BP and significantly reduced microalbuminuria in overweight patients with hypertension and type 2 diabetes.

BP – blood pressure, BMI – body mass index, DBP – diastolic blood pressure, FDC – fixed-dose combination, HCTZ – hydrochlorothiazide, SBP – systolic blood pressure

TABLE 4. Key clinical studies with valsartan.

Study	Primary objective	Patient profiles	No. of patients	Duration	Dose	Study results		
						Efficacy	Safety and tolerability	Main conclusion
Valsartan in the treatment of hypertensive patients with erectile dysfunction[24]	To establish the influence of valsartan on the androgen status and erectile function in hypertensive patients.	Men, age 40–65 years and documented hypertension stage I or II for not less than 3 previous years.	60	3 months	Group I: valsartan in a dose of 80 mg, in case of an insufficient BP reduction a dose increase to 160 mg. Group II: other antihypertensives, including ACE inhibitors, beta-blockers, Ca antagonists or a combination of different antihypertensives.	Treatment with valsartan reduced the intensity of the symptoms of erectile dysfunction in hypertensive males by 11.3% versus 2.2% in the control group. The therapy led also to a decrease in androgen deficiency symptoms by 20.2% versus 12.1% in the control group. SBP and DBP reductions were comparable in both groups.	Valsartan was proven as safe, since it reduced the symptoms of androgen deficiency and did not contribute to erectile dysfunction.	Valsartan does not induce erectile dysfunction and leads to an improvement of the androgen deficiency symptoms, which further supports its high efficacy and safety.
Valsartan in the treatment of hypertensive patients with HF[25]	To study the improvement of the tolerance of physical activity, reduction of the severity of dyspnea and edema, the improvement of the parameters of myocardial contractility according to ECG data, the improvement of endothelial function, and the safety and tolerability.	Hypertensive patients with HF class NYHA II or III, aged 45 to 70 years.	53	4 months	Valsartan: • 40 mg twice daily • after 2 weeks a dose increase to 80 mg twice daily with adjustment of concomitant therapy. Allowed concomitant therapy: • furosemide 10-40 mg daily and • digoxin 125-250 mg daily.	Therapy with valsartan resulted in significantly: • increased left ventricular ejection fraction from 36.1% to 42.8% (mean relative increase of 15.0%) • increased left ventricular stroke volume by 12.6 ml (from 60.4 to 73 ml; mean relative reduction of 17%) • reduced end-diastolic volume by 16 ml (from 195 to 179 ml; mean relative reduction of 8%) • reduced end-systolic volume by 23 ml (from 104 to 81 ml; mean relative reduction of 22%) • reduced BNP level in patients with NYHA class II by 90 pg/ml (from 291 to 201 pg/ml; mean relative reduction of 31%) • reduced BNP level in patients with NYHA class III by 188 pg/ml (from 503 to 315 pg/ml; mean relative reduction of 37%).	The frequency of nonsignificant adverse reactions (weakness, headache, sweatiness, cough, dyspepsia) did not exceed 2% and it was observed only in 2 patients.	Valsartan improves the clinical condition of the patients with chronic HF and results in positive changes of the NYHA class.

ACE – angiotensin-converting enzyme, BP – blood pressure, BNP – brain natriuretic peptide, DBP – diastolic blood pressure, HF – heart failure, NYHA – New York Heart Association, SBP – systolic blood pressure

poboljšava prognozu u pacijenata koji prežive akutni infarkt miokarda.[13]

Enap®, aktivna tvar koja je ključni čimbenik u liječenju arterijske hipertenzije, imala je važan doprinos uspjehu kliničkih istraživanja te je korištena kod više od 20.000 pacijenata iz više od 25 država.[21]

Osim što proizvodi ACE inhibitore, Krka je također jedan od vodećih proizvođača blokatora angiotenzin II receptora. Prva je generička tvrtka u Europi koja liječnicima nudi šest blokatora angiotenzin II receptora. Zadnjih je godina provedeno nekoliko kliničkih istraživanja s losartanom (Lorista®) i valsartanom (Valsacor®) na više od 30.000 pacijenata. Oba su lijeka testirana na različitim skupinama pacijenata.[7] Istraživanje LAURA pokazalo je da losartan, uz uspješno smanjenje vrijednosti AT, također uzrokuje značajno smanjenje koncentracije urične kiseline u pacijenata s hiperuricemijom.[22] Nadalje, losartan također znatno smanjuje mikroalbuminuriju u pacijenata s dijabetesom tipa 2.[23] Rezultati kliničkog istraživanja s valsartanom u hipertenzivnih pacijenata sa ZS, nakon infarkta miokarda, s poremećenom dijastoličkom funkcijom lijeve klijetke i onih s erektilnom disfunkcijom jasno opravdava primjenu ovog lijeka kod svih spomenutih skupina pacijenata. Uz smanjenje vrijednosti AT, valsartan poboljšava simptome androgenske deficijencije, kliničko stanje pacijenata s kroničnim zatajivanjem srca i smanjuje mikroalbuminuriju. Podatci iz istraživanja također potvrđuju dobru podnošljivost valsartana.[24-26]

ZAKLJUČAK

Kliničko iskustvo s Krkinim lijekovima koji djeluju na RAAS neprestano raste, a više od 70.000 pacijenata sudjelovalo je ili je trenutno dio kliničkih istraživanja. To obilno kliničko iskustvo predstavlja jasan i uvjerljiv dokaz o uspjehu tih lijekova pri liječenju arterijske hipertenzije i kardiovaskularnih bolesti.

the first 24 hours after acute coronary syndrome occurrence, and administered during the following 3 months, improves prognosis in patients who survived acute MI.[13]

Enap®, an active substance which represents the cornerstone in the treatment of hypertension, provided an important contribution to the success of own clinical studies since it was used in more than 20,000 patients in more than 25 countries.[21]

Apart from producing ACE inhibitors, Krka is also one of the leading producers of ARBs. It is the first generic company in Europe that has offered six ARBs to physicians. With losartan (Lorista®) and valsartan (Valsacor®), several clinical studies were conducted in the recent years in approximately 30,000 patients. Different populations of patients were included in studies with both of them.[7] The clinical study LAURA proved that losartan also provides, in addition to effective BP reduction, a substantial reduction in uric acid concentration in patients with hyperuricemia.[22] Moreover, losartan significantly reduced microalbuminuria in patients with type 2 diabetes.[23] The results of clinical studies with valsartan in hypertensive patients with HF, after MI, with impaired left ventricular diastolic function and in patients with erectile dysfunction clearly support its use in all of these patient populations. In addition to BP reduction, valsartan improved androgen deficiency symptoms, the clinical condition of patients with chronic HF and reduced microalbuminuria. The results also confirmed good tolerability of valsartan.[24-26]

CONCLUSION

Clinical experience with Krka's RAAS-acting medicines is increasing, with more than 70,000 patients treated in completed or on-going clinical studies. This extensive clinical experience provides clear and conclusive evidence of the benefits of these medicines in the treatment of hypertension and cardiovascular disease.

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