Stručni rad

Učinkovitost i sigurnost ramiprila kao monoterapije i u fiksnoj kombinaciji s hidroklorotijazidom u liječenju različitih skupina hipertenzivnih bolesnika i njegov učinak na kardiovaskularnu prevenciju

Professional article

The efficacy and safety of ramipril as monotherapy and in fixed-dose combination with hydrochlorothiazide in the treatment of different groups of hypertensive patients and its effect on cardiovascular prevention

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SAŽETAK: *Arterijska hipertenzija predstavlja vodeći zdravstveni problem u svijetu. Jedna od tri osobe ima visoke vrijednosti arterijskog tlaka (AT). Previsoka vrijednost pritiska na stijenke arterija uzrokovana visokim vrijednostima AT može uzrokovati oštećenje krvnih žila, kao i organa u tijelu. Nekontrolirano visoke vrijednosti AT mogu uzrokovati različite komplikacije. Hipertenzija je najmanje u dvije trećine svih slučajeva praćena čimbenicima kardiovaskularnog rizika poput dijabetesa, preboljelog infarkta miokarda ili moždanog udara, dislipidemije, pretilosti ili dokazane vaskularne bolest. Današnje liječenje hipertenzije je vrlo izazovno, posebno u bolesnika s povećanim kardiovaskularnim rizikom, pri čemu se od višestrukog farmakološkog pristupa zahtijeva da se postigne prihvatljiva ciljna vrijednost AT. Ramipril je lipofilni ACE inhibitor pogodan za primjenu jednom dnevno. On učinkovito smanjuje perifernu vaskularnu rezistenciju regulirajući tako visoki AT. U kombinaciji s hidroklorotijazidom ima sinergistički učinak koji povećava učinkovitost i sigurnost oba lijeka. Ramipril je istraživan u brojnim kliničkim studijama. Također je istraživana i učinkovitost te sigurnost Krkinog ramiprila (Ampril®) u nekoliko kliničkih i postautorizacijskih studija o sigurnosti i učinkovitosti. Krkin ramipril dostupan je u različitim jačinama i pakiranjima, uz fiksne kombinacije.*

KLJUČNE RIJEČI: *arterijska hipertenzija, inhibitori angiotenzin konvertirajućeg enzima, ramipril.*

SUMMARY: *Hypertension is a major health problem in the world. One in every three adults has high blood pressure (BP). The excessive pressure on the artery walls caused by high BP can damage blood vessels, as well as organs in the body. Uncontrolled high BP can lead to different complications. Hypertension is accompanied by cardiovascular risk factors, such as diabetes, previous myocardial infarction or stroke, dyslipidemia, obesity or proven vascular disease, in at least two-thirds of all cases. Today's treatment of hypertension is very challenging, especially in patients with enhanced cardiovascular risk, where a multiple pharmacological approach is often required to achieve an acceptable BP goal. Ramipril is a lipophilic ACE inhibitor suitable for once-daily administration. It effectively reduces peripheral vascular resistance, thus regulating high BP. In combination with hydrochlorothiazide, it produces a synergetic effect, which increases the efficacy and safety of both drugs. Ramipril has been studied in numerous clinical studies. Also the efficacy and safety of Krka's ramipril (Ampril®) have been studied in several clinical and post-authorisation safety and efficacy studies. Krka's ramipril is offered in a variety of dosage forms, strengths and fixed-dose combinations.*

KEYWORDS: *hypertension, angiotensin-converting enzyme inhibitor, ramipril.*

CITATION: *Kardio list. 2011;6(9-10):257-261.*

Arterijska hipertenzija predstavlja vodeći zdravstveni problem diljem svijeta. Visoke vrijednosti arterijskog tlaka (AT) doprinose približno polovici od svih kardiovaskularnih bolesti, a jedna od tri odrasle osobe ima visoke vrijednosti AT[1]. Previsoka vrijednost pritiska na stijenke arterija uzrokovana visokim vrijednostima AT može uzrokovati oštećenje krvnih žila, kao i organa u tijelu. Što je viša vrijednost i što duže AT nije kontroliran veće je oštećenje[2]. Hipertenzija je praćena drugim čimbenicima kardiovaskularnog rizika poput dijabetesa, prethodnog infarkta miokarda ili moždanog udara, dislipidemije, pretilosti ili dokazane vaskularne bolesti u najmanje dvije trećine svih bolesnika[3]. Današnje liječenje hipertenzije je vrlo izazovno, posebice u bolesnika s povećanim kardiovaskularnim rizikom, pri čemu se od višestrukog farmakološkog pristu-

Hypertension is a major health problem in the world. High blood pressure (BP) contributes to around half of all cardiovascular diseases, and one in every three adults has high BP[1]. The excessive pressure on the artery walls caused by high BP can damage blood vessels, as well as organs in the body. The higher the BP is and the longer it goes uncontrolled, the greater is the damage[2]. Hypertension is accompanied by other cardiovascular risk factors, such as diabetes, previous myocardial infarction or stroke, dyslipidemia, obesity or proven vascular disease, in at least two-thirds of all patients[3]. Today's treatment of hypertension is very challenging, especially in patients with enhanced cardiovascular risk, where a multiple pharmacological approach is often required to achieve an acceptable BP goal. Since the goals of antihypertensive therapy in pa-

pa zahtijeva postizanje prihvatljive ciljne vrijednosti AT. Budući da su ciljevi antihipertenzivne terapije u bolesnika s kardiovaskularnom bolešću postali sve intenzivniji, farmakološke kombinacije često sadrže različite klase antihipertenziva (uključivo i ACE inhibitore) i rezultiraju poboljšanom učinkovitosti i podnošljivosti[3].

Ramipril je lipofilni ACE inhibitor pogodan za primjenu jednom dnevno. On učinkovito smanjuje perifernu vaskularnu rezistenciju regulirajući tako visoku vrijednost AT. Ramipril se može koristiti u kombinaciji s različitim lijekovima, uglavnom s hidroklorotijazidom (HCTZ), diuretikom koji povećava bubrežno izlučivanje natrija i klorida. Zajedno daju sinergički učinak koji za rezultat ima bolje sniženje vrijednosti AT te u isto vrijeme nudi visoku sigurnost (manje doze oba lijeka uzrokuju manje neželjenih reakcija). Antihipertenzivni učinak ove kombinacije traje do 24 sata[4].

Ramipril je istraživan u brojnim studijama. Jedno od najznačajnih istraživanja bila je HOPE (Heart Outcomes Prevention Evaluation) studija. HOPE je bila velika, jednostavna, faktorijalnog dizajna, dvostruko slijepa, placebom kontrolirana studija kojom se odredio rizik kardiovaskularnih događaja kod preko 9.500 bolesnika u 267 centara iz 19 zemalja[5]. Bolesnici uključeni u studiju su smatrani visokorizičnom skupinom za budući vaskularni smrtni ishod ili drugi događaj zbog dobi jer su bili stariji od 55 godina ili su imali dijabetes ili su preboljeli neki vaskularni događaj ili su imali postojeću vaskularnu bolest. Pacijenti s dijabetesom trebali su imati poznatu vaskularnu bolest ili jedan od čimbenika rizika kardiovaskularnih bolesti, kao što su pušenje cigareta, AT iznad 140/90 mmHg, ili povišenu vrijednost kolesterola u serumu (>5,2 mmol/L). Dijabetičari su bili uključeni u ovu studiju jer čak i bez prepoznatljive koronarne bolesti srca (KBS) oni imaju približno isti rizik od koronarnih događaja kao pacijenti bez dijabetesa s utvrđenom KBS. Ispitanici su bili randomizirani na ramipril ili placebo, počevši s fazom titriranja od 2,5 mg dnevno tijekom prvog tjedna, a zatim 5 mg dnevno tijekom 3 tjedna. Nakon toga liječeni su s 10 mg dnevno do završetka studije. Praćenje je bilo nakon 1 mjesec i zatim svakih 6 mjeseci. Svi bolesnici su primali vitamin E (400 IU) ili placebo. Predviđeno trajanje studije bilo je 5,5 godina. Primarni ishod je bio definiran kao kombinacija kardiovaskularne smrti, nefatalnog infarkta miokarda i nefatalnog moždanog udara[5]. Rezultati su prikazani na **Slici 1**.

tients with cardiovascular disease have clearly become more intensive, combinations of pharmacological modalities that lead to improved efficacy and tolerability often will include different classes of drugs, and angiotensin-converting enzyme (ACE) inhibitors are one of them[3].

Ramipril is a lipophilic ACE inhibitor suitable for once-daily administration. It effectively reduces peripheral vascular resistance, thus regulating high BP. Ramipril can be used in combination with different drugs, mostly with hydrochlorothiazide (HCTZ), a diuretic that increases the renal excretion of sodium and chloride. Together, they produce a synergetic effect that results in better BP reduction, and at the same time offer good safety (lower doses of both drugs are causing fewer adverse reactions). The antihypertensive effect of the combination lasts for up to 24 hours[4].

Ramipril has been studied in numerous studies. One of the milestone studies was HOPE (Heart Outcomes Prevention Evaluation) study. The HOPE study was a large, simple, factorial-design, double-blind, placebo-controlled study that determined the risk of cardiovascular events in over 9500 patients in 267 centres in 19 countries[5]. Patients included in the study were considered at high risk of future vascular death or morbidity by virtue of age, in that they were required to be older than 55 years of age, or because they had either diabetes or evidence of a prior vascular event or existing vascular disease. Diabetics were required to have either known vascular disease or one other risk factor for cardiovascular disease, such as cigarette smoking, BP over than 140/90 mmHg, or elevated serum cholesterol (>5.2 mmol/L). Diabetics were included in this study because even without recognisable coronary artery disease (CAD) they have about the same risk for coronary events as non-diabetic patients with established CAD. Subjects were randomised to ramipril or placebo, beginning with a titration phase of 2.5 mg/day for 1 week, followed by 5 mg/day for 3 weeks. Thereafter, patients received 10 mg/day until study completion. Follow-up was at 1 month and thereafter every 6 months. All patients received either vitamin E (400 IU) or matching placebo. The study was predicted to last up to 5.5 years. The primary endpoint was defined as a combination of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke[5]. The results are presented in **Figure 1**.

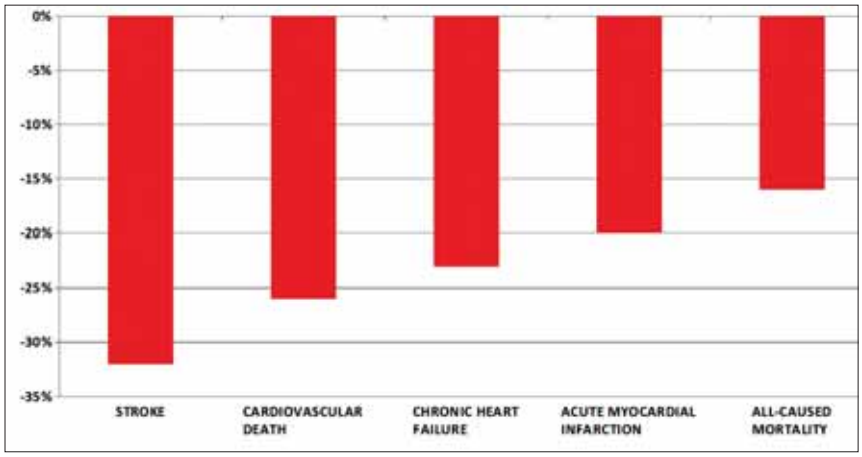

Figure 1. *Reduction of risk for different clinical endpoints in the HOPE study.*

U istraživanju HOPE većina bolesnika je dobro podnosila ramipril i nastavila je uzimati punu dozu od 10 mg. Registrirano je 7,3% prekida terapije zbog kašlja povezanog s ramiprilom. Istraživanje je prekinuto oko godinu dana ranije nego što je bilo planirano, nakon 4,5 godine liječenja prema savjetu Odbora za praćenje podataka i sigurnosti, budući su dostupni rezultati snažno ukazivali na povoljniji ishod skupine liječene ramiprilom. Pojedinačne komponente sveukupnog krajnjeg ishoda su bile također značajno smanjene: 32% za moždani udar, 26% za kardiovaskularnu smrt i 20% za infarkt miokarda. Ramipril je također smanjio rizik nekoliko drugih kliničkih krajnjih ishoda, uključujući kronično zatajivanje srca za 23% i postupke revaskularizacije za 15%, dok je ukupna smrtnost smanjena za 16% (**Slika 1**). Neočekivan rezultat HOPE studije bilo je 33% smanjenje novonastalog dijabetesa u skupini liječenoj ramiprilom tijekom razdoblja od 4,5 godina studije, što ukazuje u korist izrazito povoljnog učinka ramiprila na liječenje hipertenzije i njezinih komplikacija. Rezultati HOPE studije[5] su bili dovoljni da potaknu Američko udruženje za bolesti srca da ovu studiju uključi na svoju listu vodećih deset istraživanja tijekom 1999. godine. U narednim godinama, nekoliko naknadnih studija su predstavile dodatne dugoročne prednosti ramiprila, a mnoge druge neovisne studije su dokazale njegovu učinkovitost i sigurnost kod različitih skupina bolesnika.

Otkako je Krka uvela vlastiti ramipril u mono obliku (Ampril®) i kombinaciji s HCTZ (Ampril®HL, Ampril®HD) različitih doza[6], njegova učinkovitost i sigurnost su dokazani u nekoliko vlastitih kliničkih i postautorizacijskih studija sigurnosti i učinkovitosti koje su uključile više od 8.500 bolesnika različitih profila[4,7-16]. Rezultati nekih istraživanja[4,7-12] su prikazani u **Tablici 1** na stranici 260.

Rezultati HOPE studije su pokazali značajne prednosti primjene ramiprila na smrtnost i pobol u velikoj skupini visokorizičnih ispitanika. Studije Krke su dokazale učinkovitost i sigurnost Krkinog ramiprila u nekoliko skupina bolesnika sa zajedničkom karakteristikom — arterijskom hipertenzijom. Iako je ramipril pokazao različite prednosti u pojedinim situacijama, kontrolirao je AT kod svih skupina bolesnika bez obzira na njihovu različitost. Postizanje ciljnih vrijednosti AT predstavlja jedan od najvažnijih ciljeva antihipertenzivne terapije u Hrvatskoj za kojeg je na hrvatskom tržištu dostupno više različitih antihipertenziva. Između ostalih tu je i Krkin ramipril koji je dostupan u različitim jačinama i pakiranjima te u fiksnim kombinacijama različitih jačina koje omogućavaju prilagođavanje liječenja potrebama bolesnika.

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The HOPE study showed that ramipril was well tolerated, with the large majority of patients continuing on the full 10-mg dose. There was only a 7.3% excess dropout rate because of ramipril-related cough. The study was stopped about 1 year earlier than scheduled, after 4.5 years of treatment, on the advice of the Data and Safety Monitoring Committee, since the weight of the available evidence strongly supported a more favourable outcome in the ramipril-treated group. The individual components of the composite endpoint also were significantly reduced: by 32% for stroke, 26% for cardiovascular death, and 20% for myocardial infarction. Ramipril also reduced the risk of several other clinical endpoints, including chronic heart failure by 23% and revascularisation procedures by 15%, while all-cause mortality was reduced by 16% (**Figure 1**). An unexpected finding in the HOPE study was that ramipril-treated patients experienced a 33% reduction in the onset of new diabetes during the 4.5 years of the study, which speaks in favour of an extremely beneficial effect of ramipril on the treatment of hypertension and its complications. The results of the HOPE study[5] were of sufficient significance to prompt the American Heart Association to include this study in its top ten list of research advances for the year 1999. In the years to come, several follow-up studies presented additional long-term benefits of ramipril, and many other independent studies proved its efficacy and safety in different patient profiles.

Since Krka has introduced its ramipril in mono-form (Ampril®) and combination with HCTZ (Ampril®HL and Ampril®HD) of different strengths[6], its efficacy and safety have been proven in several own clinical studies and post-authorisation safety and efficacy studies that included more than 8,500 patients of different profiles[4,7-16]. The results of some of them[4,7-12] are presented in **Table 1** (page 260).

The HOPE study results showed substantial benefits in mortality and morbidity with the use of ramipril in a large group of subjects at a high risk of future cardiovascular events. Krka's studies proved the efficacy and safety of Krka's ramipril in several patient groups with a common feature — hypertension. Although ramipril showed different benefits in specific situations, it kept BP under control in all patient groups regardless of their differences. To achieve target BP levels is one of the most important goals of antihypertensive therapy in Croatia, and for reaching this goal several different antihypertensives are available on the Croatian market, among them Krka's ramipril which is offered in a variety of dosage forms, strengths and fixed-dose combinations that enable adjustment of the treatment to the patient's needs.

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Table 1. *Krka's studies with ramipril and their results.*

Patient profiles	No. of patients included in the study	Results	Safety and tolerability of Krka's ramipril during the study
Hypertensive patients[7]	2798	**≥74%** of patients reached the target BP level (140/90 mm Hg or less)[7]	Very well. 3.5% of patients had mild adverse reactions. It was concluded that more than 95% of patients, included in this study were successfully treated[7]
Hypertensive patients after acute myocardial infarction[8, 9]	60	CRP level was reduced by **87.6%** and frequency of angina pectoris was decreased by **82%** in post-infarction period. Prognosis of these patients was also improved[8, 9]	During the 3 months of treatment there was no fatal episode, nonfatal MI, or insult registered in the ramipril group[8, 9]
Hypertensive patients with ischemic heart disease[10]	30	In **63.3%** of patients there was improvement of endothelial functional state[4, 10]	No serious adverse effects reported
Hypertensive patients with type II diabetes[11]	30	**44%** of diabetic patients, whose BP was not controlled in previous multicomponent treatments, reached target BP levels and also had improved endothelial function[11]	Only 2 patients experienced adverse effects connected to drug intake. Adverse effects were mild and temporarly[11]
Hypertensive women with metabolic syndrome in post menopausal period[12]	80	**100%** of patients reached target BP level (≥130/80 mm HG) with Krka's ramipril in combination with Krka's amlodipine (Tenox)[12]	The tolerance of the drug was evaluated by all patients as good[12]

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Ispravak

Errata corrige! U članku "Knežević A. Prednosti perindoprila u svim međusobno povezanim kardiovaskularnim zbivanjima: razina dokaza. (*Kardio list.* 2011;6(7-8):112-116.)" u tiskanoj inačici lista pogreškom nisu otisnuti literaturni navodi.

Uredništvo lista ispričava se autoru i čitateljima, a popis literaturnih navoda slijedi u nastavku.

Erratum

Correction notice to the article: In the article, "Knežević A. Benefits of perindopril all along the cardiovascular continuum: the level of evidence. (*Kardio list.* 2011;6(7-8):112-116.)" literature references were erroneously not indicated in the printed version.

The Editorial board apologizes to the author and readers, while the list of literature references is indicated below.

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