Postizanje ciljnih vrijednosti s perindoprilom: arterijska hipertenzija i dodatni učinci

Reaching the targets with perindopril: hypertension and beyond

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SAŽETAK: Među 67 analiziranih čimbenika visoki arterijski tlak (AT) identificiran je kao glavni čimbenik rizika za smrtni ishod i invalidnost. Kontrola vrijednosti AT-a još je uvijek daleko od razine koja bi bila nužna za smanjenje kardiovaskularnog rizika, a liječenje bolesnika s arterijskom hipertenzijom i dalje je izazov u svakodnevnoj kliničkoj praksi. Smanjenje učestalosti kardiovaskularnih događaja tijekom liječenja perindoprilom potkrepljuje koncept dodatnih zaštitnih kardiovaskularnih učinaka perindoprila i uz snizivanje vrijednosti AT-a. Učinkovita kontrola AT-a, kao što je to dokazano u kliničkim studijama s Krkinim perindoprilom i njegovim fiksnim kombinacijama doza s indapamidom I amlodipinom, zajedno s dobrom podnošljivošću i pogodnim jednodnevnim doziranjem, u pacijenata dovodi do pozitivnog učinka na ustrajnost liječenja, što je ključan korak prema postizanju ciljnih vrijednosti AT-a.

SUMMARY: High blood pressure has been identified as the leading risk factor, among 67 studied, for death and disability. Blood pressure control is still far from what would be necessary to reduce the cardiovascular risk. The treatment of hypertensive patients remains a challenging issue in daily clinical practice. The reduction in cardiovascular events with perindopril supports the concept of cardiovascular protective effects of perindopril beyond blood pressure lowering. Effective blood pressure control, as demonstrated in clinical studies with Krka's perindopril and its fixed-dose combinations with indapamide and amlodipine, together with good tolerability and convenient once-daily dosing, have a positive impact on patients' adherence to the treatment – which is a crucial step towards reaching the blood pressure targets.

KLJUČNE RIJEČI: perindopril, arterijska hipertenzija, arterijski tlak, učikovitost, sigurnost, ustrajnost.

KEYWORDS: perindopril, hypertension, blood pressure, efficacy, safety, adherence.

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Uvod

Visoki arterijski tlak (AT) među 67 analiziranih čimbenika identificiran je kao glavni rizični čimbenik za smrtni ishod i invalidnost.[1] Kontrola vrijednosti AT-a još je daleko od onoga što bi bilo nužno za smanjenje kardiovaskularnog rizika.[2] Klinička su ispitivanja pokazala da liječenje arterijske hipertenzije smanjuje rizik od neželjenih ishoda kardiovaskularnih bolesti, uključujući novonastale moždane udare (za 35 do 40 %), infarkt miokarda (za 15 do 25 %) i zatajivanje srca (do 64 %).[1] Na globalnoj razini, normalizacija AT-a na vrijednosti < 140/90 mmHg postiže se u manje od 50 % hipertoničara.[2] To upućuje na to da je liječenje bolesnika s arte-

Introduction

High blood pressure has been identified as the leading risk factor, among 67 studied, for death and disability.[1] Blood pressure (BP) control is still far from what would be necessary to reduce the cardiovascular risk.[2] Clinical trials have shown that treatment of hypertension reduces the risk of cardiovascular disease outcomes, including incident stroke (by 35 to 40%), myocardial infarction (by 15 to 25%), and heart failure (by up to 64%).[1] On the global level, BP normalization to below 140/90 mmHg is achieved in no more than 50% of hypertensive patients.[2] This suggests that despite comprehensive guide-

rijskom hipertenzijom i dalje izazov u svakodnevnoj kliničkoj praksi usprkos iscrpnim smjernicama i brojnim kliničkim ispitivanjima.[2]

Pri optimizaciji učinkovitosti antihipertenzivnog liječenja, ključni su ciljevi sljedeći:[2]
- normalizacija vrijednosti AT-a tijekom 24 sata
- prevencija/regresija oštećenja ciljnih organa
- smanjenje neželjenih kardiovaskularnih događaja.

Učinci perindoprila nisu ograničeni na smanjenje vrijednosti arterijskoga tlaka

Perindopril je lipofilni ACE inibitor s dugim djelovanjem uz izraženi učinak smanjenja vrijednosti AT-a tijekom 24 sata, a uzima se jedanput na dan.[2,3] Ima bolje dokumentiranu vaskularnu penetraciju u usporedbi s lijekovima iste klase te najbolje dokumentiranu djelotvornost s obzirom na više parametara za procjenu vaskularne disfunkcije ili strukturnih promjena u različitim segmentima arterijskoga stabla.[2] Također pokazuje visok afinitet za tkivni angiotenzinkonvertirajući enzim i organoprotektivne učinke, pogotovo pri primjeni većih doza.[2] Poboljšanje u ravnoteži angiotenzin II – bradikinin koju postiže perindopril ima više pozitivnih učinaka na kardiovaskularni sustav, uključujući antihipertenzivne i antiaterosklerotske učinke.[3] Velike kliničke studije, poput istraživanja EUROPA i PROGRESS, analizirale su učestalost neželjenih kardiovaskularnih ishoda i dokazale da primjena perindoprila smanjuje učestalost kardiovaskularnih događaja u velikoga broja bolesnika. Smanjenje u učestalosti neželjenih kardiovaskularnih događaja bilo je i veće nego što bi se moglo očekivati na temelju opaženoga smanjenja vrijednosti AT-a primjenom perindoprila, što upućuje na specifične antiaterosklerotske i protuupalne učinke te učinak na disfunkciju endotela.[3] Ishodi spomenutih i drugih kliničkih studija potkrepljuju hipotezu da perindopril ima dodatne protektivne kardiovaskularne učinke, osim smanjenja vrijednosti AT-a.[3]

Normalizacija vrijednosti arterijskoga tlaka Krkinim perindoprilom

Učinkovitost i sigurnost liječenja Krkinim perindoprilom[4] ili primjena dvostruke fiksne kombinacije doza perindoprila s indapamidom bile su predmet istraživanja u 4574 pacijenta s blagom do umjerenom arterijskom hipertenzijom (srednja dob 62 ± 12,3 godine; 49 % muškaraca i 51 % žena). Sudjelovalo je 1726 (37,7 %) pacijenata koji dotad nisu primali antihipertenzive. Od 2814 pacijenata koji su već bili liječeni antihipertenzivima, njih 81,4 % bilo je liječeno drugim ACE inhibitorima. Nakon 4 mjeseca liječenja uočeno je statistički značajno smanjenje vrijednosti sistoličkoga arterijskog tlaka (SBP) i dijastoličkoga arterijskog tlaka (DBP). Prosječno smanjenje vrijednosti SBP-a bilo je 22,8 mmHg (sa 157,5 na 134,7 mmHg; prosječno relativno smanjenje 14,7 %) te 10,4 mmHg za DBP (s 91,8 na 81,4 mmHg; prosječno relativno smanjenje 11,3 %). Na kraju studije 80 % pacijenata imalo je normalne vrijednosti AT-a od 140/90 mmHg ili niže. Promjene u vrijednostima SBP-a i DBP-a prikazane su na **slici 1**.

lines and numerous clinical trials, the treatment of hypertensive patients remains a challenging issue in daily clinical practice.[2]

When optimizing the efficacy of antihypertensive treatment, the crucial goals are:[2]
- BP normalization lasting 24 hours;
- prevention/regression of target organ damage;
- reduction of cardiovascular events.

Effects of perindopril are not limited to blood pressure reduction

Perindopril is a long-acting once-daily lipophilic ACE inhibitor with a pronounced 24-hour BP lowering effect.[2,3] Perindopril has greater documented vascular penetration than other medicines of the same class and the best documented efficacy with respect to several parameters assessing vascular dysfunction or structural alterations in different segments of the arterial tree.[2] It exhibits high affinity for the tissue angiotensin-converting enzyme and organ-protective effects, especially when used in higher dosages.[2] Improvement in the angiotensin II-bradykinin balance, achieved by perindopril, has a number of beneficial effects on the cardiovascular system, including antihypertensive and antiatherosclerotic effects.[3] Large morbidity-mortality clinical studies, such as EUROPA and PROGRESS, have shown that antihypertensive treatment with perindopril reduces or prevents cardiovascular disease in a wide range of patients.[3] The reduction in cardiovascular events was higher than could have been expected from the observed reduction in BP achieved with perindopril. These findings suggest specific anti-atherosclerotic and anti-inflammatory effects, as well as effects on endothelium dysfunction.[3] The outcomes of these and other clinical studies support the concept of cardiovascular protective effects of perindopril beyond blood pressure lowering.[3]

Blood pressure normalization with Krka's perindopril

The efficacy and safety of treatment with Krka's perindopril[4] or the fixed-dose combination of perindopril and indapamide were assessed in 4,574 patients with mild to moderate arterial hypertension (mean age 62±12.3 years; 49% of male and 51% of female patients). There were 1,726 (37.7%) patients who had not been treated for hypertension before inclusion in the study. Among the 2,848 patients who had previous antihypertensive therapy, 81.4% had been treated with other ACE inhibitors. After 4 months of treatment, a statistically significant reduction in both SBP and DBP was observed in the patient population. The mean decrease in systolic blood pressure (SBP) was 22.8 mmHg (from 157.5 to 134.7 mmHg; mean relative reduction 14.7%) and in diastolic blood pressure (DBP) 10.4 mmHg (from 91.8 to 81.4 mmHg; mean relative reduction 11.3%). At the end of the study, 80% of the patients had a normalized BP of 140/90 mmHg or lower. The changes in SBP and DBP values are shown in **Figure 1**.

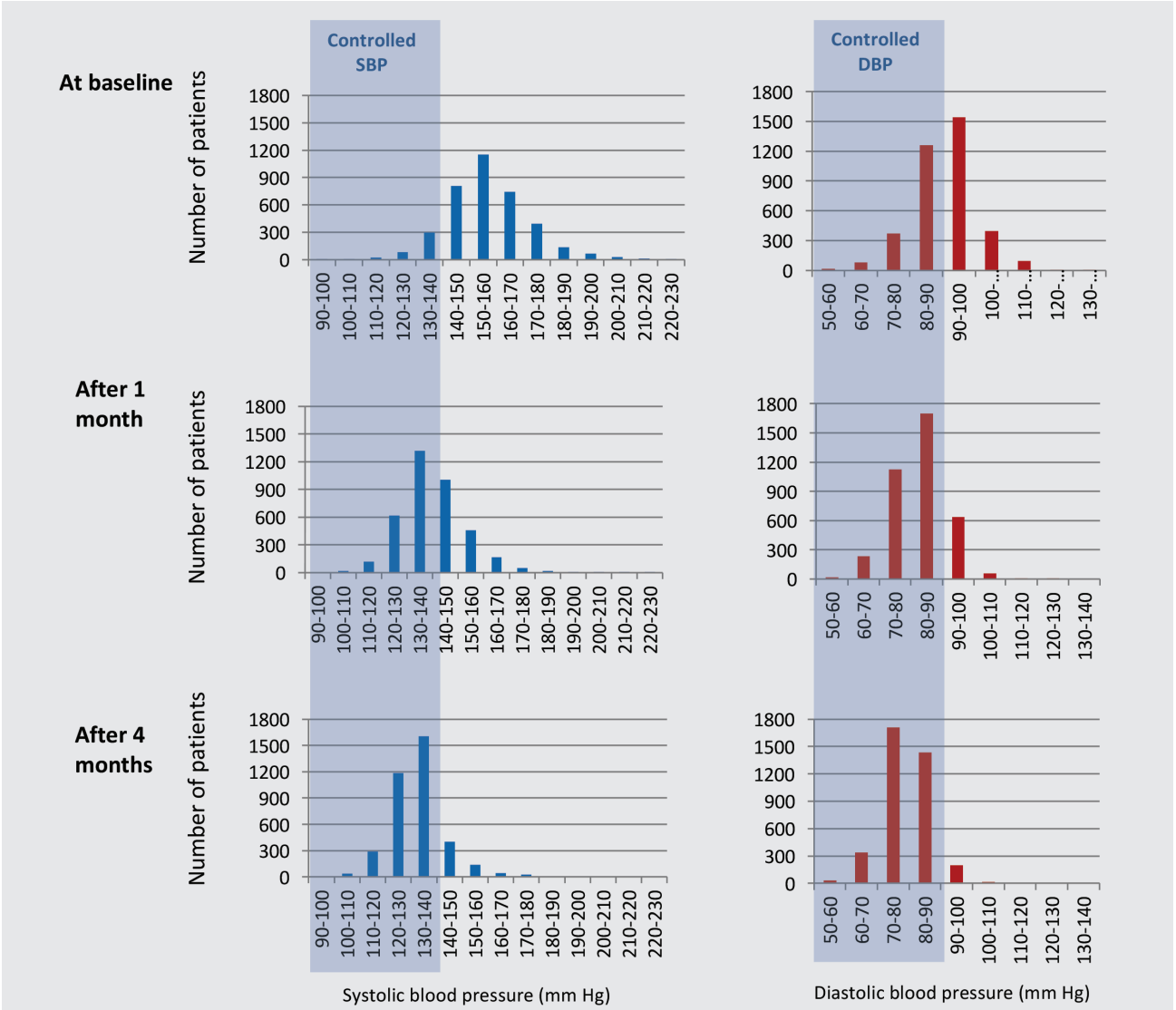

FIGURE 1. The number of patients with substantially lowered blood pressure increased already in the first month after introduction of perindopril or perindopril/indapamide therapy. The majority of patients moved into the controlled blood pressure zone, which was even more obvious after 4 months of treatment.

Najčešće primjenjivane doze bile su sljedeće: Perineva* 4 mg i Co-Perineva* 4 mg/1,25 mg. U većine pacijenata nije bilo potrebno titrirati dozu tijekom istraživanja.

Liječenje Krkinim perindoprilom i fiksnom kombinacijom doza perindoprila i indapamida bilo je povezano s odličnim ustrajnošću u pacijenata: 72,5 % pacijenata potpuno se pridržavalo terapijskoga protokola te uzelo sve propisane doze, 17,5 % pacijenata jednom je zaboravilo uzeti lijek, a samo 9,6% zaboravilo ga je uzeti dvaput. To se također može pripisati visokoj podnošljivosti lijeka u studiji, jer u 97 % pacijenata nisu registrirane nuspojave.

Tijekom studije oko polovice pacijenata redovito je kod kuće pratilo i dokumentiralo svoje vrijednosti AT-a. Vrijednosti AT-a bile su znatno smanjene ($p < 0,0001$) u objema skupinama pacijenata. U skupini koja je sama pratila svoje vrijednosti prosječ-

The most commonly used doses were Perineva* 4 mg and Co-Perineva* 4 mg/1.25 mg. In most patients, no adjustment of dosage was necessary during the study duration.

The treatment with Krka's perindopril and the fixed-dose combination of perindopril and indapamide was associated with an excellent adherence: 72.5% of the patients completely adhered to the treatment protocol and took all prescribed doses, 17.5% of the patients forgot to take the medicine once and only 9.6% forgot to take it twice. This can also be attributed to good tolerability of the study medicine, since 97% of the patients had no adverse reactions.

During the study approximately half of the patients regularly monitored and recorded their home BP values. The BP levels were significantly reduced ($p < 0.0001$) in both groups of patients. In the self-monitoring group, the mean SBP reduc-

no je smanjenje SBP-a bilo 25,6 mmHg, a prosječno smanjenje DBP-a bilo je 11,8 mmHg. U skupini bez samostalnog praćenja prosječno je smanjenje SBP-a bilo 23,2 mmHg, a prosječno smanjenje DBP-a bilo je 11,1 mmHg. Razlike u smanjenju vrijednosti između sistoličkih i dijastoličkih vrijednosti među dvjema skupinama bile su statistički značajne.

Iz gore navedenih rezultata može se zaključiti da samostalno praćenje AT-a također može pridonijeti dobroj stopi normalizacije AT-a u pacijenata.

Fiksna kombinacija doza perindoprila s amlodipinom za pacijente s povišenim vrijednostima arterijskoga tlaka i dodatnim čimbenicima rizika

Djelotvornost perindoprila u liječenju hipertenzije dokumentirana je u nekoliko velikih kliničkih studija u kojima su dokazani poželjni učinci na smanjenje neželjenih kardiovaskularnih događaja i smrtnih ishoda, osobito u kombinaciji antagonistom kalcija (amplodin) ili diuretikom (indapamid).[5] Perindopril primijenjen u fiksnoj kombinaciji s amlodipinom ili indapamidom izrazito je djelotvoran i u kontroli vrijednosti AT-a i kardiovaskularnoj prevenciji,[5] što je osobito važno u bolesnika s dodatnim kardiovaskularnim čimbenicima rizika.[6]

Ukupno je 3821 pacijent s arterijskom hipertenzijom bio uključen u neintervencijsku kliničku studiju COMPLIANT.[7] Od svih pacijenata 88% je imalo dodatne kardiovaskularne čimbenike rizika. Dislipidemija je bila najčešći čimbenik rizika i bila je prisutna kod 55 % oboljelih, nakon čega slijedi abdominalna pretilost koja je bila prisutna u 45 % pacijenata. Trećina oboljelih imala je dva dodatna čimbenika rizika uz hipertenziju, a 26 % imalo ih je tri ili više. U studiju su bila uključena i 752 (20 %) pacijenta koji prije uključivanja u studiju nisu bili liječeni antihipertenzivima. Među 3069 (80 %) pacijenata koji su već bili liječeni zbog hipertenzije, većina ih je već primala RAAS inhibitore (n = 2497), i to pretežno ACE inhibitore te antagoniste kalcija (n = 849), dok su ostali pacijenti (n = 1257) primali druge antihipertenzive. Pri uključivanju u studiju, 55 % pacijenata dobilo je Krkinu fiksnu kombinaciju perindoprila s amlodipinom Dalneva* 4 mg/5 mg. Na kraju istraživanja 37 % ispitanika imalo je početnu dozu. Veća doza perindoprila od 8 mg započeta je u 42 % pacijenata na početku istraživanja. Tijekom studije doza se mogla titrirati, tako da je do kraja istraživanja 55 % pacijenata primilo višu dozu perindoprila (**tablica 1**). U slučaju titriranja doze, liječnici su se većinom odlučivali na više doze obiju aktivnih tvari.

tion was 25.6 mmHg and the mean DBP reduction 11.8 mmHg. In the group without self-monitoring, the mean SBP reduction was 23.2 mmHg and the mean DBP reduction 11.1 mmHg. The differences in SBP and DBP reduction between both groups were statistically significant.

From the above results it can be concluded that patients' self-monitoring of BP could also have contributed to good rates of BP normalization.

Fixed-dose combination of perindopril and amlodipine for patients with higher blood pressure levels and additional risk factors

The efficacy of perindopril in the treatment of hypertension has been documented in several large-scale clinical studies, particularly in combination with the calcium antagonist amlodipine or the diuretic indapamide, showing beneficial effects in reducing cardiovascular events and mortality.[5] Perindopril in the fixed-dose combination with amlodipine or indapamide is highly effective for both BP control and cardiovascular prevention,[5] which is especially important in patients with additional cardiovascular risk factors.[6]

A total number of 3,821 patients with arterial hypertension were included in the non-interventional clinical study COMPLIANT.[7] Of these, 88% had additional cardiovascular risk factors. Dyslipidemia as the most frequent risk factor was present in 55% of the patients, followed by abdominal obesity in 45% of the patients. A 33% portion of the patients had 2 additional risk factors apart of hypertension, and 26% had 3 or more additional risk factors. The population included 752 (20%) patients who had no antihypertensive therapy prior to inclusion. Among 3069 (80%) patients who had been previously treated for hypertension, the majority had therapy with RAAS inhibitors (n=2497), mainly ACE inhibitors, and calcium antagonists (n=849), the rest of the patients (n=1257) received other antihypertensive therapies. At inclusion, the patients were prescribed Krka's fixed-dose combination of perindopril and amlodipine; Dalneva* 4 mg/5 mg was prescribed to 55% of the patients. At the end of the study, 37% of the patients still had the same dose. The higher dose of perindopril, 8 mg, has been introduced in 42% of the patients at the beginning of the study. During the study, the dose could be adjusted if necessary, so by the end of the study 55% of the patients received the higher dose of perindopril (**Table 1**). In case of dose adjustment, physicians mostly decided to prescribe higher doses of both active ingredients.

TABLE 1. Dosing of Krka's fixed-dose combination of perindopril and amlodipine during the study. At the end of the study, 37% of the patients were still treated with perindopril/amlodipine 4 mg/5 mg. The higher dose of perindopril, 8 mg, which offers better blood pressure reduction and organ protection, was not taken advantage of to an optimal extent.

Perindopril / Amlodipine	1st visit	2nd visit	3rd visit
4 mg / 5 mg	52%	40%	37%
4 mg / 10 mg	7%	8%	7%
8 mg / 5 mg	28%	31%	30%
8 mg / 10 mg	14%	21%	25%

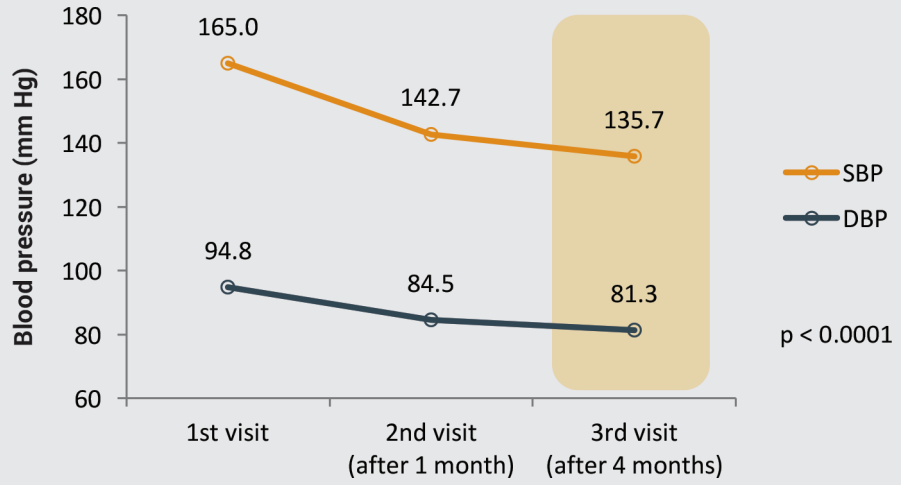

FIGURE 2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were statistically significantly reduced already after the first month of treatment with Krka's fixed-dose combination of perindopril and amlodipine. After 4 months, the patients reached an average SBP of 135.7 mmHg and an average DBP of 81.3 mmHg.

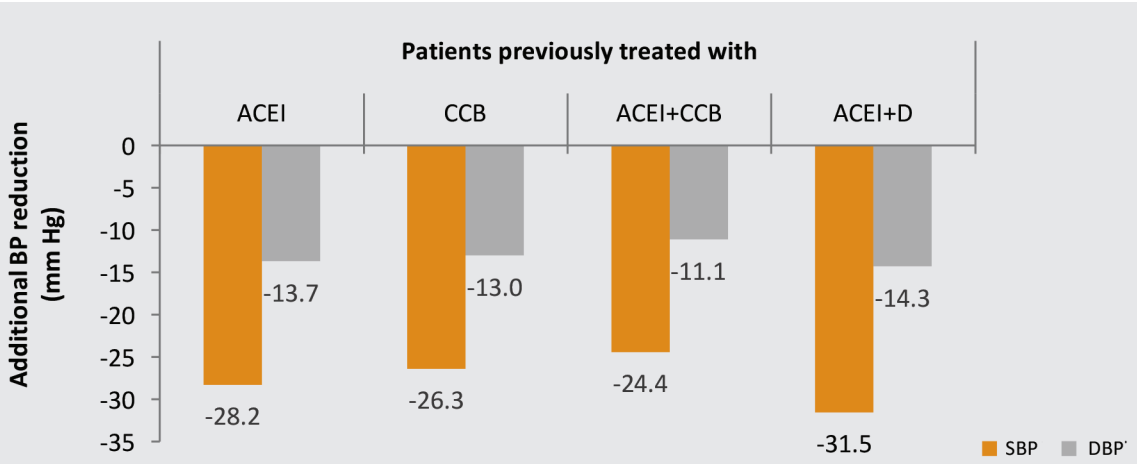

FIGURE 3. Blood pressure was further reduced after introduction of the fixed dose combination of perindopril and amlodipine in patients previously treated with other antihypertensive drugs.

ACEI = ACE inhibitor; CCB = calcium channel blockers; D = diuretic; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolica blood pressure.

Nakon četiri mjeseca liječenja vrijednosti AT-a u svih su bolesnika bile statistički značajno smanjene, neovisno o početnome stupnju arterijske hipertenzije. Do kraja studije pacijenti su imali prosječnu vrijednost AT-a od 135,7/81,3 mmHg (**slika 2**).

Uvođenje Krkine fiksne kombinacije perindoprila s amlodipinom dovela je do daljnjega smanjenja vrijednosti AT-a u usporedbi s prijašnjim liječenjem, uključujući ACE inhibitore, antagoniste kalcija, kombinaciju ACE inhibitora s antagonistom kalcija i kombinaciju ACE inhibitora s diuretikom (**slika 3**).

Podnošljivost liječenja s Krkinom fiksnom kombinacijom perindoprila s amlodipinom bila je dobra: 94 % pacijenata nije imalo nikakve nuspojave. Najčešće nuspojave vezana uz liječenje tije-

After four months of treatment, the BP levels were statistically significantly reduced in all patients, irrespectively of the initial stage of hypertension. By the end of the study the patients had an average BP level of 135.7/81.3 mmHg (**Figure 2**).

The introduction of Krka's fixed-dose combination of perindopril and amlodipine resulted in further BP reduction if compared to previous therapies, including an ACE inhibitor, a calcium antagonist, a combination of an ACE inhibitor and a calcium antagonist or a combination of an ACE inhibitor and a diuretic (**Figure 3**).

Treatment with Krka's fixed-dose combination of perindopril and amlodipine was well tolerated: 94% of the patients experienced no adverse reactions. The most common treat-

kom studije bili su periferni edemi (3,2 %), kašalj (0,8 %) te eritremi (0,5 %). Hipotenzija je bila primijećena u 10 (0,3 %) pacijenata.

Prema mišljenju liječnika, ustrajnost je porasla s 90,6 % pacijenata koji su se pridržavali liječenja nakon jednog mjeseca na 94,5 % nakon 4 mjeseca. Udio pacijenata koji su sami za sebe rekli da se pridržavaju uputa vezanih za liječenje bio je još i veći, čak 98,3%, nakon 4 mjeseca liječenja Krkinom fiksnom kombinacijom perindoprila s amlodipinom.

Zaključak

Klinička je djelotvornost perindoprila dokazana, kao i njegova sigurnost i dobra podnošljivost.[5] Viša se doza preporučuje za veću kontrolu vrijednosti AT-a i kardiovaskularnu zaštitu hipertoničara.[5] Primjena Liječenja fiksnim kombinacijama doza važna je mogućnost za učinkovitu kontrolu vrijednosti AT-a u kliničkoj praksi, a perinodpril davan u fiksnoj kombinaciji doza s diuretikom indapamidom i antagonistom kalcija amplodinom veoma je učinkovit i u kontroli AT-a i u kardiovaskularnoj prevenciji.[5]

Rezultati kliničkih studija s Krkinim perindoprilom i njegovim kombinacijama s indapamidom i amlodipinom dokazuju da se ti lijekovi mogu učinkovito primjenjivati u liječenju hipertenzije.[4,7] Dobar profil podnošljivosti te pogodno doziranje jedanput na dan imaju pozitivan učinak na pridržavanje uputa vezanih za liječenje[4,7] – što je ključan korak prema postizanju ciljnih vrijednosti arterijskoga tlaka.[8]

*Krkin se perindopril zbog zakonskih razloga prodaje pod različitim imenima. Lijekovi iz opisanih kliničkih studija bili su perindopril koji je proizvela Krka, koji se u Sloveniji prodaje pod imenom Prenessa®, a u Hrvatskoj kao Perineva®, fiksna kombinacija doza perindoprila s indapamidom koji je proizvela Krka, koja se u Sloveniji prodaje pod imenom Prenewel®, a u Hrvatskoj kao Co-Perineva® te fiksna kombinacija doza perindoprila s amlodipinom koji je proizvela Krka, koja se u Sloveniji prodaje pod imenom Amlessa®, a u Hrvatskoj kao Dalneva®.

ment-related adverse events observed during the study were peripheral edema (3.2%), cough (0.8%) and erythema (0.5%). Hypotension was observed in 10 (0.3%) patients.

In the physicians' opinion, adherence to treatment increased from 90.6% of adherent patients after 1 month to 94.5% after 4 months. The patients evaluated themselves as adherent in an even higher number, reaching 98.3% after 4 months of treatment with Krka's fixed-dose combination of perindopril and amlodipine.

Conclusion

The clinical efficacy of perindopril was demonstrated, as well as its safety and good tolerability.[5] The higher dosage is suggested for a greater BP control and cardiovascular protection in hypertensive patients.[5] The combination therapy is an important option for effective BP control in clinical practice, and perindopril in the fixed-dose combination with the diuretic indapamide and the calcium antagonist amlodipine is highly effective in both BP control and cardiovascular prevention.[5]

The results of clinical studies with Krka's perindopril and its combinations with indapamide and amlodipine demonstrate that can effectively be applied in hypertension management.[4,7] The good tolerability profile of these medicines and convenient once-daily dosing have a positive impact on patients' adherence to the treatment[4,7] – which is a crucial step towards reaching the blood pressure targets.[8]

*Krka's perindopril is marketed under different brand names due to regulatory reasons. The study medicines in the presented clinical studies were perindopril produced by Krka, which is marketed in Slovenia under the brand name Prenessa® and in Croatia under the brand name Perineva®, the fixed-dose combination of perindopril and indapamide produced by Krka, which is marketed in Slovenia under the brand name Prenewel® and in Croatia under the brand name Co-Perineva® and the fixed-dose combination of perindopril and amlodipine produced by Krka, which is marketed in Slovenia under the brand name Amlessa® and in Croatia under the brand name Dalneva®.

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