Kontrola vrijednosti arterijskog tlaka donosi zdravstvenu dobrobit u svim stupnjevima arterijske hipertenzije

Blood Pressure Control for Health Benefits in all Grades of Hypertension

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SAŽETAK: Svaka treća odrasla osoba ima visoke vrijednosti arterijskoga tlaka (AT), a zbog starenja populacije i nezdravog načina života očekuje se daljnji porast prevalencije arterijske hipertenzije. Usprkos povećanoj svijesti javnosti i dostupnosti širokog raspona antihipertenzivnih lijekova, kontrola vrijednosti AT-a i dalje je neostvareni cilj. Podatci pokazuju da znatni udio bolesnika s arterijskom hipertenzijom ostaje neidentificiran i neliječen ili pak usprkos liječenju ne uspijeva sniziti vrijednosti AT-a do preporučene razine (niže od 140/90 mmHg). Nedavno objavljeni sažetci iz Smjernica Europskoga kardiološkog društva i Europskoga društva za hipertenziju o zbrinjavanju arterijske hipertenzije 2018. naglašavaju da bi prvi cilj liječenja trebao biti snizivanje vrijednosti AT-a na manje od 140/90 mmHg u svih bolesnika. Ako se liječenje dobro podnosi, ciljni bi se AT trebao spustiti do 130/80 mmHg u većine bolesnika kako bi se u najvećoj mogućoj mjeri smanjio rizik od kardiovaskularnih događaja, što je glavna svrha liječenja arterijske hipertenzije. U ovom ćemo članku raspraviti o mogućnostima koje mogu poboljšati kontrolu vrijednosti AT-a.

SUMMARY: One in three adults suffers from high blood pressure (BP), and the prevalence is expected to rise in the future due to population ageing and unhealthy lifestyles. Despite increased public awareness and access to a variety of antihypertensives, BP control remains an unmet objective. The data suggest that a significant proportion of patients with hypertension are not identified and treated, or despite the therapy do not have BP lowered to the recommended values (below 140/90 mmHg). Recently published extracts from the 2018 European Society of Cardiology and European Society of Hypertension Joint Guidelines for the Management of Arterial Hypertension emphasize that the first objective of treatment should be to lower BP below 140/90 mmHg in all patients. If the treatment is well-tolerated, BP should be targeted to 130/80 mmHg in most patients in order to maximally reduce the risk of cardiovascular events, which is the main goal of hypertension treatment. Some solutions which may help improve the BP control are discussed below.

KLJUČNE RIJEČI: arterijska hipertenzija, kontrola vrijednosti arterijskog tlaka, liječenje, perindopril, erbumin.

KEYWORDS: hypertension, blood pressure control, treatment, perindopril, erbumine salt.

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Uvod

Arterijska hipertenzija, koja zahvaća svaku treću odraslu osobu, i dalje je jedan od vodećih uzroka smrtnosti, jedan od najrelevantnijih čimbenika rizika za kardiovaskularne (KV) bolesti te jedan od glavnih uzroka prerane smrti.[1,2] Snizivanje vrijednosti arterijskog tlaka (AT) primarna je odrednica smanjenja KV rizika.[3] Rezultati sistematskog pregleda i metaanalize 123 velika klinička ispitivanja o snizivanju vrijednosti AT-a s uključenih 613 815 ispitanika donose snažnu potporu snizivanju vri-

Introduction

Hypertension, which affects every third adult, remains one of the leading causes of mortality, one of the most relevant risk factors for cardiovascular (CV) disease, and a major cause of premature death.[1,2] Blood pressure (BP) reduction *per se* is the primary determinant of CV risk reduction.[3] The results of a systematic review and meta-analysis of 123 large-scale BP lowering trials with 613,815 participants provide strong support for lowering BP, i.e. systolic blood pressure, to less than 130

jednosti AT-a, poglavito sistoličkog, na niže od 130 mmHg koji donosi snizivanje rizika od velikih KV događaja (**slika 1**).[4] To se odražava i u Smjernicama Europskoga kardiološkog društva (ESC) i Europskog društva za hipertenziju (ESH) o zbrinjavanju arterijske hipertenzije 2018. koje naglašavaju da bi prvi cilj liječenja trebao biti snizivanje vrijednosti AT-a na niže od 140/90 mmHg u svih bolesnika. Ako se liječenje dobro podnosi, ciljni bi AT trebalo sniziti na 130/80 mmHg u većine bolesnika.[5] Usprkos povećanoj svijesti javnosti o važnosti snizivanja vrijednosti AT-a na niže od 140/90 mmHg, taj je cilj još uvijek neostvaren. Nedavno je objavljena analiza probira vrijednosti AT-a u više 1,2 milijuna osoba uključenih u globalnu inicijativu *Mjesec mjerenja* tijekom svibnja 2017. godine. Gotovo 20 % osoba s hipertenzijom nije liječeno antihipertenzivnim lijekovima, a čak 50 % liječenih nisu postigli kontrolu vrijednosti AT-a.[6] Rana identifikacija i liječenje hipertenzije kako bi se postigle ciljne vrijednosti od ključne je važnosti u skrbi za svakog bolesnika s hipertenzijom kako bi se spriječilo oštećenje ciljnih organa koje može uzrokovati KV bolesti, moždanog udara ili zatajenja bubrega.[7-9]

Smjernice ESH/ESC-a za hipertenziju iz 2013.[10] preporučuju sljedeće pristupe, koji mogu dovesti do poboljšanja vrijednosti AT-a:

- mjerenje AT-a tijekom dolaska u ordinaciju nevezanih za hipertenziju ili probleme KV prirode
- skrb za hipertenziju 1. stupnja
- početna primjena kombinacijske terapije u visokorizičnih bolesnika i onih sa znatno povišenim vrijednostima AT-a
- pojednostavnjenje liječenja primjenom kombinacija lijekova u jednoj tableti (SPC; prema eng. *single-pill combinations*) kako bi se smanjilo opterećenje bolesnika lijekovima i poboljšala adherencija, što ima presudnu ulogu u postizanju pozitivnih učinaka liječenja
- nadogradnja terapije u slučaju nedovoljne kontrole vrijednosti AT-a.

Hipertenzija 1. stupnja: liječiti ili ne liječiti?

Arterijska hipertenzija označuje progresivan KV sindrom koji proizlazi iz složenih i međusobno povezanih etiologija. Rani biljezi tog sindroma često su prisutni i prije trajnog povišenja vrijednosti AT-a.[11] Blago povišenje vrijednosti AT-a, tj. hipertenzija 1. stupnja, najzastupljeniji je oblik hipertenzije (71 %) te zbog svoje učestalosti ima velik učinak na javno zdravlje. Učestalost hipertenzije 1. stupnja toliko je visoka da je usprkos razmjerno niskom riziku za pojedinca ta vrsta hipertenzije odgovorna za gotovo 60 % koronarnih smrti. Hipertenzija počinje rano, a vrijednost AT-a raste eksponencijalno s vremenom. Oštećenje ciljnih organa, koje hipertenziju čini važnim čimbenikom rizika za KV pobol i smrtnost, može se primijetiti već u hipertenziji 1. stupnja. Ranim liječenjem hipertenzije 1. stupnja mogu se spriječiti KV oštećenja uzrokovana visokim vrijednostima AT-a, sprečavajući time i razvoj visokorizične hipertenzije i smanjujući učestalost KV događaja.[12]

Kombinacije dvaju lijekova kao početna terapija u većine bolesnika

Više od 80 % bolesnika s hipertenzijom ima dodatne čimbenike rizika (npr. muški spol, dob, pušenje, abnormalne razine lipida i glukoze, pretilost, pozitivna obiteljska anamneza preuranjenog nastupa KV bolesti) koji otežavaju regulaciju vrijednosti AT-a.[10] Neovisno o primijenjenom lijeku, monoterapija može učinkovito smanjiti vrijednost AT-a u manje od 25 % bolesnika s hipertenzi-

mmHg in terms of reducing the risk of major CV events (**Figure 1**).[4] This is also reflected in the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Joint Guidelines for the Management of Arterial Hypertension, which suggest that the first objective of the treatment should be to lower BP below 140/90 mmHg in all patients. If the treatment is well-tolerated, BP should be targeted to 130/80 mmHg in most patients.[5] Despite increased awareness of the importance of lowering BP below 140/90 mmHg, this target remains unmet. An analysis of BP screening results for more than 1.2 million patients included in the May Measurement Month 2017 global action has been published recently. Almost 20% of hypertensive individuals were not receiving any antihypertensive treatment and almost 50% of individuals receiving treatment did not have BP controlled.[6] Early identification of hypertension and its treatment for achieving target values are critically important in the management of every patient with hypertension in order to prevent target organ damage, which may result in CV disease, stroke, and kidney failure.[7-9]

The 2013 ESH/ESC Hypertension Guidelines[10] recommend the following approaches, which can result in improved overall BP control:

- BP measurements at visits not related to hypertension or problems of a CV nature;
- Management of grade 1 hypertension;
- Initial combination therapy in high-risk patients and in patients with markedly elevated BP;
- Therapy simplification by using single-pill combinations (SPCs) in order to decrease pill burden for the patient and improve adherence, which has a determinant role in achieving favorable treatment outcomes;
- Therapy upgrade in case of an insufficient BP control.

Grade 1 hypertension: To treat or not to treat?

Hypertension is a progressive CV syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before BP elevation is sustained.[11] Mild BP elevation, i.e. grade 1 hypertension, is the most prevalent form (74%) of hypertension and due to its frequency has a large impact on public health. The prevalence of grade 1 hypertension is so high that despite a relatively low individual risk this type of hypertension accounts for nearly 60% of all coronary deaths. Hypertension starts early and with time BP rises exponentially. Target organ damage, which makes hypertension a major risk factor for CV morbidity and mortality, is observed already in grade 1 hypertension. Early treatment

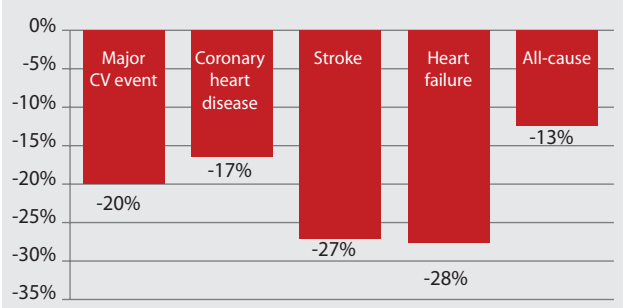

FIGURE 1. Results of meta-analysis of 123 large-scale blood pressure (BP) lowering trials with 613,815 participants. The graph shows how much a 10 mm Hg reduction in systolic BP reduced the risk of cardiovascular (CV) disease and death.

jom.[3,10] Prednosti početne primjene kombinacijske terapije jesu brža reakcija na liječenje, veća vjerojatnost postizanja ciljnih vrijednosti AT-a i niža vjerojatnost loše adherencije bolesnika zbog mnogobrojnih promjena terapije.[10] Početno liječenje kombinacijskom terapijom također je povezano s 34 %-tnim smanjenjem rizika od KV događaja i smrti u usporedbi s monoterapijom i kasnijim prelaskom na kombinacijsku terapiju.[13] Smjernice ESC/ESH-a o zbrinjavanju hipertenzije iz 2018. potvrđuju primjenu strategije početnog liječenja kombinacijskom terapijom u većine bolesnika, pri čemu su SPC terapija izbora jer dodatno poboljšavaju adherenciju.[5]

Krka je predstavila svoj perindopril (*Perineva*®) u 2005. kao prvi generički perindopril.[14] Dvije godine poslije popratila ga je SPC-om s indapamidom (*Co-Perineva*®) kao prvim kombiniranim generičkim lijekom.[15] Klinička studija s Perinevom i Co-Perinevom[16] koja je uključivala 4574 ispitanika s blagim do umjerenim stupnjem hipertenzije dokazala je statistički značajno snizivanje vrijednosti sistoličkog (prosječno za 22,8 mmHg) i dijastoličkog tlaka (prosječno za 10,4 mmHg) nakon četiri mjeseca liječenja. Na kraju istraživanja 78 % bolesnika imalo je vrijednost AT-a 140/90 mmHg ili niže. To je bilo popraćeno odličnom adherencijom jer se 72,5 % bolesnika potpuno pridržavalo preporuka za liječenje. Ovo se također može pripisati dobroj podnošljivosti jer 97 % bolesnika nije imalo nikakve nuspojave. Devet od 10 bolesnika bilo je više nego zadovoljno liječenjem Perinevom i Co-Perinevom.

Nekontrolirani arterijski tlak: rezistentna hipertenzija ili bolesnik koji se ne pridržava liječenja?

Zbog multifaktorijalne etiologije arterijske hipertenzije, uspješna kontrola vrijednosti AT-a često zahtijeva liječenje kombinacijom molekula s različitim djelovanjima.[9] Istodobno liječenje dvama antihipertenzivima iz dvaju razreda potrebno je u otprilike 50 % bolesnika s hipertenzijom, a trostruka je kombinacija potrebna u otprilike 25 % kako bi se postigla dugoročna kontrola vrijednosti AT-a.[3,17] S druge strane, polifarmacija je također veliko opterećenje bolesnicima jer mnogi od njih istodobno primaju lijekove za druge kronične bolesti.[18] To uzrokuje lošu adherenciju, što je jedan od glavnih uzroka za slabu kontrolu AT-a. Podatci pokazuju da nakon jedne godine oko polovice bolesnika s hipertenzijom prekine s liječenjem.[10] Smjernice ESC/ESH-a za hipertenziju iz 2018. preporučuju primjenu SPC-a kad god je moguće kako bi se terapija pojednostavnila, što dovodi do bržeg postizanja ciljnih vrijednosti AT-a i bolje adherencije.[10,19] Usto, liječenje je SPC-ima i bolje podnošljivo zbog komplementarnih mehanizama djelovanja koji se pripisuju molekulama kombiniranima u jednoj tableti.[20]

U 2011. godini Krka je stavila na tržište prvi generički SPC perindoprila s amlodipinom (*Dalneva*®).[21] Zbog pozitivnih karakteristika u smislu smanjenja KV događaja i smrtnosti te brzog i učinkovitog snizivanja vrijednosti AT-a, kombinacija perindoprila i amlodipina među najprimjenjivanijim je kombinacijama u liječenju hipertenzije.[22,23] Klinička studija s Dalnevom (COMPLIANT)[24] koja je uključivala 3821 bolesnika dokazala je statistički značajno snizivanje vrijednosti AT-a nakon četiri mjeseca u svih bolesnika, neovisno o prvotnome stupnju hipertenzije. Do završetka istraživanja bolesnici su postigli prosječnu razinu AT-a od 135,7/81,3 mmHg. Uvođenje Dalneve dovelo je do dodatnoga snizivanja AT-a u usporedbi s prethodno primjenjivanim liječenjem ACE inhibitorima, blokatorima kalcijskih kanala, kombiniranim liječenjem ACE

of grade 1 hypertension may prevent vascular damage caused by high BP, thus preventing the development of high-risk hypertension and reducing the incidence of CV events.[12]

Two-drug combination as initial therapy in most patients

More than 80% of patients with hypertension have additional risk factors (e.g. male sex, age, smoking, abnormal lipids and glucose levels, obesity, family history of early CV disease), that make BP difficult to regulate.[10] Regardless of the medication used, a monotherapy can effectively reduce BP in no more than 25% of patients with hypertension.[3,10] Advantages of using a combination therapy from the beginning are: prompter treatment response, a greater probability of achieving target BP, and lower probability of discouraging patient adherence with many treatment changes.[10] Additionally, an initial combination therapy is associated with 34% risk reduction of CV events and deaths compared with an initial monotherapy and subsequent switch to a combination therapy.[13] The 2018 ESC/ESH Hypertension Guidelines confirmed the strategy of initial treatment with a combination therapy for most patients, where SPCs are a preferred choice as these additionally improve adherence.[5]

Krka introduced its perindopril (*Perineva*®) in 2005 as the first generic perindopril.[14] Two years later, Krka's SPC with indapamide (*Co-Perineva*®) followed as the first generic.[15] A clinical study with Perineva and Co-Perineva[16], which included 4,574 patients with mild to moderate hypertension, demonstrated statistically significant reduction in systolic BP (mean reduction of 22.8 mmHg) and diastolic BP (mean reduction of 10.4 mmHg) after four months of treatment. At the end of the study, 78% of patients had a BP of 140/90 mmHg or lower. The treatment was associated with excellent treatment adherence, since 72.5% of the patients completely adhered to the treatment. This can also be attributed to good tolerability, since 97% of the patients had no adverse reactions. Nine out of 10 patients were more than satisfied with the treatment with Perineva and Co-Perineva.

Uncontrolled blood pressure: Resistant hypertension or a non-adherent patient?

Due to multifactorial etiology of hypertension, successful BP control often requires treatment with a combination of molecules acting on different targets.[9] Simultaneous treatment with two antihypertensives from different classes is required in approximately 50% of patients with hypertension, while a triple combination is required in approximately 25% of them in order to achieve long-term BP control.[3,17] On the other hand, polypharmacy represents a heavy burden for the patients, considering that many of these patients also concomitantly receive medications for other chronic diseases.[18] This results in poor adherence, which is one of the main causes for low BP control. The data show that after one year, about one half of patients with hypertension stop their treatment.[10] The 2018 ESC/ESH Hypertension Guidelines recommend the use of SPCs whenever applicable to simplify the therapy, resulting in faster achievement of the target BP and better adherence to the treatment.[10,19] Additionally, the treatment with SPCs is better tolerated due to complementary mechanisms of action attributed to molecules combined in a single tablet.[20]

In 2011, Krka launched the first generic SPC of perindopril and amlodipine (*Dalneva*®).[21] Because of its beneficial properties in terms of reducing CV events and mortality, as well as fast and effective BP reduction, the combination of perindopril and amlodipine is among most favored combinations in the treatment of

inhibitorima i blokatorima kalcijskih kanala u odvojenim tabletama ili kombiniranim liječenjem ACE inhibitorima i diureticima.

U 2014. Krka je proširila svoj portfolio perindoprila uvođenjem trostrukog SPC-a perindoprila, indapamida i amlodipina (*Co-Dalneva*®) kao prva farmaceutska tvrtka koja je ponudila takvu kombinaciju u Europi.[2,25]

Krkina perindoprilska obitelj: učinkovito i sigurno liječenje za sve bolesnike s hipertenzijom

Krkin složeni portfolio perindoprila sastoji se od 15 različitih doza i omogućuje liječenje prilagođeno pojedincu kod svakog stupnja hipertenzije. Započinjanje liječenja perindoprilom ili SPC-om perindoprila i indapamida omogućuje kasniju nadogradnju terapije u slučaju nedovoljne kontrole vrijednosti AT-a.[26] U više od deset godina kliničke uporabe, Krkin je perindopril postojano dokazao svoju učinkovitost i sigurnost kao monoterapija te kao dio SPC-ova u kliničkim studijama više od 55 000 bolesnika i u svakodnevnoj kliničkoj praksi.[14,16,24,27-30] Široko iskustvo i povjerenje učinili su Krkin perindopril i njegove SPC-e najpropisivanijim generičkim perindoprilskim proizvodima u Europi, s gotovo 2,5 milijuna liječenih bolesnika.

Perindopril erbumin ili perindopril arginin: koji izabrati?

Aktivna tvar perindopril kemijski je vezana ili za erbumin (s nižom molekularnom težinom) ili za arginin (s višom molekularnom težinom). To je razlog zbog kojeg se doze od 2, 4 i 8 mg perindopril erbumina razlikuju od 2,5, 5 i 10 mg doza perindopril arginina. No perindopril erbumin i perindopril arginin imaju jednake koncentracije aktivne tvari u plazmi te time i jednak učinak liječenja. Terapijska ekvivalentnost tih lijekova potvrđena je bioekvivalencijskim studijama. Registracija izvornog perindopril arginina bila je temeljena na njegovoj bioekvivalenciji s perindopril erbuminom.[31-35] Za svoju vlastitu inovativnu formulaciju perindopril erbumina Krka je nagrađena zlatnim priznanjem te je dobila patentnu zaštitu.[36] Sva klinička ispitivanja na više od 50 000 bolesnika (npr. EUROPA, PROGRESS, PREAMI, ADVANCE, ASCOT-BPLA, PEP-CHF) koja su potvrdila pozitivne kliničke učinke perindoprila na različitim skupinama bolesnika, koristila su se s perindopril erbuminom.[37-42]

Zaključak

Većina KV bolesti može se prevenirati kroz pravodobnu eliminaciju ili kontrolu glavnih čimbenika rizika.[43] Još uvijek imamo prostora za poboljšanje dijagnosticiranja i liječenja arterijske hipertenzije kao dominantnoga promjenjivog predispozicijskog čimbenika za KV bolesti.[2,6] Čak i mala snizivanja vrijednosti AT-a dovode do značajnih pozitivnih učinaka u smanjenju bolesnikova rizika od KV komplikacija.[4] Dostupnost naprednih antihipertenziva, konkretno perindoprila, koji posjeduju pozitivne učinke (24-satno djelovanje na normalizaciju AT-a, prevencija/regresija oštećenja ciljnih organa, smanjenje učestalosti KV događaja) i SPC-a koji poboljšava pridržavanje liječenju, mogli bi olakšati postizanje ciljnih vrijednosti AT-a.[10,44,45] Učinkovita kontrola AT-a i sigurnost dokazana u kliničkim istraživanjima zajedno s pozitivnim iskustvima u svakodnevnoj kliničkoj praksi učinili su to da je od generičkih perindoprila u Europi, Krkin perindopril prvi izbor liječnika.[14,16,24,27-30]

hypertension.[22,23] A clinical study with Dalneva (COMPLIANT)[24], which included 3,821 patients, demonstrated statistically significant BP reductions after four months in all patients, irrespective of the initial grade of hypertension. By the end of the study, the patients achieved an average BP level of 135.7/81.3 mmHg. Introduction of Dalneva resulted in additional BP reduction compared with previous therapies with 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.

In 2014, Krka widened its perindopril portfolio with a triple SPC of perindopril, indapamide and amlodipine (*Co-Dalneva*®) as the first pharmaceutical company to offer such combination in Europe.[2,25]

Krka's perindopril family: Effective and safe treatment for any patient with hypertension

Krka's complex perindopril portfolio includes 15 strengths and allows for an individually-tailored treatment of any hypertension grade. Initiating therapy with perindopril or SPC of perindopril and indapamide makes it possible to subsequently upgrade the therapy in case of insufficient BP control.[26] In more than ten years of clinical use, Krka's perindopril has consistently demonstrated its effectiveness and safety as a monotherapy and in SPCs in clinical studies with more than 55,000 patients as well as in everyday clinical practice.[14,16,24,27-30] Wide experience and trust have made Krka's perindopril and its SPCs the most prescribed generic perindopril products in Europe with almost 2.5 million treated patients.[30]

Perindopril erbumine or perindopril arginine: Which one to choose?

The active substance perindopril is chemically bound either to erbumine (with lower molecular weight) or arginine (with higher molecular weight). This is why the 2, 4 and 8 mg dosages of perindopril erbumine differ from the 2.5, 5 and 10 mg dosages of perindopril arginine. However, perindopril erbumine and perindopril arginine provide the same plasma concentrations of the active substance, resulting in the same therapeutic effect. The therapeutic equivalence of the two has been confirmed by bioequivalence studies. The registration of the originator's perindopril arginine was based on its bioequivalence with perindopril erbumine.[31-35] For own innovative formulation of perindopril erbumine, Krka was awarded a gold recognition and granted patent protection.[36] All major clinical trials in more than 50,000 patients (e.g. EUROPA, PROGRESS, PREAMI, ADVANCE, ASCOT-BPLA, PEP-CHF), which confirmed clinical benefits of perindopril in wide groups of patients, were performed with perindopril erbumine.[37-42]

Conclusion

The majority of CV diseases can be prevented through timely elimination or control of their main risk factors.[43] There is still potential to improve the diagnosis and treatment of hypertension as a dominant modifiable predisposing factor for CV diseases.[2,6] Even small BP reductions provide significant benefits in reducing risk of experiencing CV complication.[4] The accessibility of advanced antihypertensives, e.g. perindopril, possessing favorable properties (24-hour BP normalization, prevention/regression of target organ damage, reduction of CV events), and SPCs, which improve adherence, might facilitate the achievement of BP targets.[10,44,45] Effective BP control and safety, demonstrated in clinical studies, together with positive experiences in daily clinical practice have made Krka's perindopril the physician's first choice for generic perindopril in Europe.[14,16,24,27-30]

LITERATURE

1. World Health Organisation. A global brief on hypertension: silent killer, global public health crisis. Available at: http://www.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf (June 18, 2018).
2. Yang MH, Kang SY, Lee JA, Kim YS, Sung EJ, Lee KY, et al. The effect of lifestyle changes on blood pressure control among hypertensive patients Korean J Fam Med. 2017 Jul;38(4):173-180. https://doi.org/10.4082/kjfm.2017.38.4.173
3. Gradman AH, Basile JN, Carter BL, Bakris GL, Materson BJ, Black HR, et al. Combination therapy in hypertension. J Am Soc Hypertens. 2010 Mar-Apr;4(2):90-8. https://doi.org/10.1016/j.jash.2010.03.001
4. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016 Mar 5;387(10022):957-967. https://doi.org/10.1016/S0140-6736(15)01225-8
5. ESC-ESH: 2018 guidelines for the management of arterial hypertension [internet]. Barcelona: European Society of Cardiology-European Society of Hypertension; 28th European Meeting on Hypertension and Cardiovascular Protection; June 8-11, 2018. Available at: https://www.youtube.com/watch?v=dL2IRxK11FM (June 18, 2018).
6. Beaney T, Schutte AE, Tomaszewski M, Ariti C, Burrell LM, Castillo RR, et al; MMM Investigators. May Measurement Month 2017: an analysis of blood pressure screening results worldwide. Lancet Glob Health. 2018 Jul;6(7):e736-e743. https://doi.org/10.1016/S2214-109X(18)30259-6
7. Lackland DT. Early-life detection of hypertension risks. Implications for clinical practice and research. Hypertension. 2017 Sep;70(3):486-487. https://doi.org/10.1161/HYPERTENSIONAHA.117.09529
8. Schmieder RE. End organ damage in hypertension. Dtsch Arztebl Int. 2010 Dec;107(49):866-73. https://doi.org/10.3238/arztebl.2010.0866
9. Ábrahám G, Dézsi CA.The antihypertensive efficacy of the triple fixed combination of perindopril, indapamide and amlodipine: The results of the PETRA study. Adv Ther. 2017 Jul;34(7):1753-1763. https://doi.org/10.1007/s12325-017-0572-1
10. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013 Jul;34(28):2159-219. https://doi.org/10.1093/eurheartj/eht151
11. Giles TD, Materson BJ, Cohn JN, Kostis JB. Definition and classification of hypertension: an update. J Clin Hypertens (Greenwich). 2009 Nov;11(11):611-4. https://doi.org/10.1111/j.1751-7176.2009.00179.x
12. Julius S. Need for fixed-dose combination therapy in the early phases of hypertension. Medicographia 2010;32:262-268. Available at: https://www.medicographia.com/2011/01/need-for-fixed-dose-combination-therapy-in-the-early-phases-of-hypertension/ (June 20, 2018).
13. Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients. Hypertension. 2013 Feb;61(2):309-18. https://doi.org/10.1161/HYPERTENSIONAHA.112.201566
14. Krka, d.d., Novo mesto, Annual report 2006. Available at: http://www.krka.biz/media/doc/en/for_investors/2012/AR_2006_full.pdf (June 18, 2018).
15. Krka, d.d., Novo mesto. Annual report 2007. Available at: http://krka.biz/media/doc/en/for_investors/2012/LP_2007_EN.pdf (June 18, 2018).
16. Final report. Postmarketing surveillance study of the efficacy and safety of perindopril (Prenessa®) or perindopril and indapamide (Co-Prenessa®) in the treatment of arterial hypertension. Data on file. Krka, d.d., Novo mesto, Slovenia, 2010.
17. Gradman AH. Rationale for triple-combination therapy for management of high blood pressure. J Clin Hypertens (Greenwich). 2010 Nov;12(11):869-78. https://doi.org/10.1111/j.1751-7176.2010.00360.x
18. Hagendorff A, Freytag S, Müller A, Klebs S. Pill burden in hypertensive patients treated with single-pill combination therapy - an observational study. Adv Ther. 2013 Apr;30(4):406-19. https://doi.org/10.1007/s12325-013-0018-3
19. Iellamo F, Werdan K, Narkiewicz K, Rosano G, Volterrani M. Practical applications for single pill combinations in the cardiovascular continuum. Card Fail Rev. 2017 Apr;3(1):40-45. https://doi.org/10.15420/cfr.2017:5:1
20. Mancia G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, et al. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine J Hypertens. 2015 Feb;33(2):401-11. https://doi.org/10.1097/HJH.0000000000000409
21. Krka, d.d., Novo mesto. Annual report 2011. Available at: http://www.krka.biz/media/doc/en/for_investors/2012/KRKA 2011 Annual report link.pdf (June 18, 2018).
22. Bertrand ME, Ferrari R, Remme WJ, Simoons ML, Deckers JW, Fox KM; EUROPA Investigators. Clinical synergy of perindopril and calcium-channel blocker in the pervention of cardiac events and mortality in patients with coronary artery disease. Post hoc analaysis of the EUROPA study. Am Heart J. 2010 May;159(5):795-802. https://doi.org/10.1016/j.ahj.2009.12.042
23. Mp G, Bahl VK, Jadhav UM, Thacker H, Kumar S. Blood pressure control of fixed dose, perindopril/amlodipine combination treatment in hypertensive patients uncontrolled on monotherapy or on two drug combination therapy: PP.5.167. J Hypertens. 2010;28(e-Suppl A):e98. https://doi.org/10.1097/01.hjh.0000378491.10769.a7
24. Final report. Non-interventional follow-up of efficacy and safety of treatment with fixed-dose combination of perindopril and amlodipine (Amlessa®) in patients with arterial hypertension and the impact of additional risk factors for cardiovascular diseases on patient compliance (COMPLIANT). Data on file. Krka, d.d., Novo mesto, Slovenia, 2016.
25. Co-Dalnessa (perindopril/indapamide/amlodipine, 2/0.625/5 mg) Marketing Authorisation No: OGYI-T-22577/01-09, Co-Dalnessa (perindopril/indapamide/amlodipine, 4/1.25/5 mg) Marketing Authorisation No: OGYI-T-22577/10-18, Co-Dalnessa (perindopril/indapamide/amlodipine, 4/1.25/10 mg) Marketing Authorisation No: OGYI-T-22577/19-27, Co-Dalnessa (perindopril/indapamide/amlodipine, 8/2.5/5 mg) Marketing Authorisation No: OGYI-T-22577/28-36, Co-Dalnessa (perindopril/indapamide/amlodipine, 8/2.5/10 mg) Marketing Authorisation No: OGYI-T-22577/37-45, Hungary.
26. Summary of product main characteristics of Prenessa, Co-Prenessa, Amlessa and Co-Amlessa.
27. Hribar V, Milovanović Jarh D. Contribution of Krka's ACE inhibitors to the treatment of hypertension: 25 years of experience. Krka Med Farm. 2014;26 (38):14-25.
28. Drapkina OM. Combination therapy of high-risk patients in real clinical practice. Results of SYNERGY study. Part 1. Antihypertensive branch. Rational Pharmacotherapy in Cardiology. 2017;13(2):155-163. https://doi.org/10.20996/1819-6446-2017-13-2-155-163
29. Data on file, Krka, d.d., Novo mesto, 2017.
30. Sekundarna prodaja: ePharma Market, IQVIA, Quintiles IMS, MEDICUBE, PHARMSTANDARD, PharmaZOOM, INTELLIX, CEGEDIM 2017
31. Guideline On Clinical Development Of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1). European Medicines Agency. London, 19 February 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf (June 18, 2018).
32. Public Assessment Report, FR/H/325-326-327/01-04/DC, Perindopril arginine – Amlodipine, Servier, July 2009.
33. Public Assessment Report, FR/H/130/03-04/E/01, perindopril arginine/indapamide, Servier, April 2009.
34. Single-dose, 3-way pharmacokinetic study of three perindopril tablet formulations in healthy volunteers under fasting conditions. Krka, d. d., Novo mesto, Data on file. Krka d. d., Novo mesto, Slovenia 2009.
35. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. Curr Med Res Opin. 2007 May;23(5):953-60. https://doi.org/10.1185/030079907X182158
36. European Patent Office. Available at: http://worldwide.espacenet.com/ (June 18, 2018).
37. Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003 Sep 6;362(9386):782-8. https://doi.org/10.1016/S0140-6736(03)14286-9
38. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001 Sep 29;358(9287):1033-41. https://doi.org/10.1016/S0140-6736(01)06178-5
39. The PREAMI Investigators. PREAMI: Perindopril and Remodelling in Elderly with Acute Myocardial Infarction: study rationale and design. Cardiovasc Drugs Ther. 2000 Dec;14(6):671-9. https://doi.org/10.1023/A:1007879201470
40. Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40. https://doi.org/10.1016/S0140-6736(07)61303-8
41. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005 Sep 10-16;366(9489):895-906. https://doi.org/10.1016/S0140-6736(05)67185-1
42. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006 Oct;27(19):2338-45. https://doi.org/10.1093/eurheartj/ehl250
43. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;37(29):2315-2381. https://doi.org/10.1093/eurheartj/ehw106
44. Taddei S. RAS inhibitors` dose-dependent efficacy: myth or reality? Curr Med Res Opin. 2015;31(7):1245-56. https://doi.org/10.1185/03007995.2015.1053047
45. Ferrari R. Angiotensin-converting enzyme inhibition in cardiovascular disease: evidence with perindopril. Expert Rev Cardiovasc Ther. 2005 Jan;3(1):15-29. https://doi.org/10.1586/14779072.3.1.15