Pregledni članak

Prednosti perindoprila u svim međusobno povezanim kardiovaskularnim zbivanjima: razina dokaza

Review article

Benefits of perindopril all along the cardiovascular continuum: the level of evidence

Aleksandar Knežević*
Opća bolnica Zadar, Zadar, Hrvatska
Zadar General Hospital, Zadar, Croatia

SAŽETAK: *Klinička učinkovitost perindoprila dokazana je velikim kliničkim randomiziranim ispitivanjima u bolesnika s arterijskom hipertenzijom, dijabetesom, cerebrovaskularnom bolesti, stabilnom koronarnom bolesti srca (KBS) i zatajivanjem srca. Stoga ovaj ACE inhibitor ima svoje mjesto u svim vodećim kliničkim smjernicama za liječenje kardiovaskularnih bolesti. Pri tome je kardioprotektivni učinak perindoprila neovisan o njegovom antihipertenzivnom učinku uz povoljan sigurnosni profil. Ovo se objašnjava njegovim farmakološkim osobinama: dugim poluživotom, velikom lipofilnošću i visokim afinitetom za tkivni ACE. Inhibicija ACE perindoprilom dovodi do dva glavna učinka: prevencije stvaranja angiotenzina II te povećanja razine bradikinina. Time je perindopril uz snižavanje vrijednosti povišenog arterijskog tlaka (AT) i kardioprotektivan, obzirom na antiaterosklerotski, antiupalni i antitrombotski učinak. Primjena perindoprila u svakodnevnoj kliničkoj praksi treba se zasnivati, ne samo na antihipertenzivnom učinku, već i na procjeni sveukupnog kardiovaskularnog rizika koji je posebno visok u bolesnika s KBS, dijabetesom i cerebrovaskularnom bolesti.*

KLJUČNE RIJEČI: *perindopril, kardiovaskularna prevencija, kardiovaskularni rizik.*

SUMMARY: *Clinical efficacy of perindopril has been proved by using extensive clinical randomized studies in patients with hypertension, diabetes, cerebrovascular disease, stable coronary heart disease (CHD) and heart failure. Therefore, this ACE inhibitor has found its place in the leading clinical guidelines for the treatment of cardiovascular diseases. The cardioprotective effect of perindopril is independent of its antihypertensive effect with a positive safety profile. This is explained by its pharmacologic properties: long half-life, high lypophility and a high affinity for tissue ACE. ACE inhibition by perindopril causes two main factors: prevention of creation of angiotensin II and increase in bradykinin level. In that way, perindopril does not only lower the high blood pressure (BP), but it is also cardioprotective considering its antiatherosclerotic, antiinflammatory and antithrombotic effect. The use of perindopril in daily clinical practice needs to be based not only on antihypertensive effect, but also on the evaluation of total cardiovascular risk that is very high in patients with CHD, diabetes and cerebrovascular disease.*

KEYWORDS: *perindopril, cardiovascular prevention, cardiovaskular risk.*

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Od pronalaska prvog lijeka u skupini (kaptopril, 1977. god.) ACE inhibitori zauzimaju važno mjesto u farmakoterapiji kardiovaskularnih bolesti. Najviše se upotrebljavaju u liječenju arterijske hipertenzije (AH), njihova je uloga temeljna u liječenju zatajivanja srca, važna u liječenju infarkta miokarda, a sve više se rabe u primarnoj i sekundarnoj kardiovaskularnoj i renalnoj protekciji. Pri tome oni nisu homogena skupina lijekova, razlikuju se prema kemijskoj strukturi, farmakokinetici, a za njihov klinički učinak izgleda da je najvažniji odnos u inhibiciji cirkulirajućeg i tkivnog ACE. Dok kaptopril u svojoj strukturi ima sulfhidrilnu skupinu, a fosinopril fosforilnu skupinu, u ostalih prevladava karboksilna skupina. Prema svojoj farmakokinetici dijele se u tri podskupine: u prvoj je kaptopril koji je djelatan osnovnom supstancom ali i metabolitima, u drugoj su gotovo svi ostali ACE inhibitori koji su predlijekovi te postaju djelatni nakon konverzije u jetri, a treću podskupinu predstavlja lizinopril koji je hidrofilan i ne metabolizira se u jetri već se nepromijenjen izlučuje bubrezima. Najvjerojatnije glavni učinak ACE inhibitori ostvaruju u endotelu krvnih žila koji je dostupan svim ACE inhibitorima bez obzira na njihovu farmakokinetiku[1]. Uz taj učinak dodatne prednosti imaju oni ACE inhibitori koji bolje prodiru u tkiva gdje će dodatno inhibirati tkivni ACE. Tu sposobnost imaju lipofilni ACE inhibitori (ramipril, perindopril, trandolapril i kvinapril) s potencijalno kardioprotektivnim učinkom koji nadilazi njihov učinak u redukciji arte-

Since the discovery of the first drug in the group (captopril, 1977) ACE inhibitors have taken an important role in pharmacology of cardiovascular diseases. They are most used in treatment of hypertension, their role is fundamental in the treatment of heart failure, it is important in treatment of myocardial infarction, and they are more and more used in primary and secondary cardiovascular and renal protection. They are not the homogenous group of drugs and they differ in chemical structure, pharmacokinetics and the relation in inhibition of circulating and tissue ACE seems to be the most important for their clinical effect. Captopril has in its structure sulphydryl group, phosinopryl has phosphoryl group, while carboxyl group prevails in other groups. According to their pharmacokinetics, they are divided in three subgroups: in the first subgroup there is captopril that is effective with its basic substance and metabolites as well, in the second group there are all other ACE inhibitors that are prodrugs and become effective after their conversion in the liver, while in the third subgroup there is lisinopril that is hydrophilic and is not metabolized in the liver, but is excreted in the kidneys in a unchanged form. Most probably, the main effect is achieved by ACE inhibitors in the blood vessel endothelium which is accessible to all ACE inhibitors regardless of their pharmacokinetics[1]. Besides that effect, those ACE inhibitors that better penetrate in tissues where the tissue ACE will be additionally inhibited show additional benefits. Li-

rijskog tlaka (AT). Ipak, ovaj kardioprotektivni učinak treba biti dokazan u velikim kliničkim studijama, a to je do sada uspjelo ramiprilu u HOPE studiji te perindoprilu u EUROPA studiji. Zbog čega to nije dokazano za trandolapril u PEACE studiji te za kvinapril u IMAGINE studiji predmet je diskusije. Moguće je da ti lijekovi uz tkivnu ACE inhibiciju nemaju dodatne učinke na apoptozu ili endotelnu funkciju, ali i da je dizajn studija (broj ispitanika, karakteristike ispitanika te doza lijeka) bio neadekvatan za dokazivanje kardioprotektivne učinkovitosti tih lijekova[2-5].

Postoje mišljenja da ne postoje posebni kardioprotektivni učinci ACE inhibitora kao skupine, a ni tzv. tkivno specifičnih ACE inhibitora kao podskupine, već da se sav njihov kardioprotektivni učinak, a i učinak svih ostalih skupina antihipertenziva svodi tek na snižavanje AT[6].

Ipak uloga ACE inhibitora je prepoznata i priznata od autora smjernica Europskog kardiološkog društva te američkih kardioloških društava (ACC i AHA) te se preporučuju uz liječenje AH i u: liječenju stabilne koronarne bolesti srca (KBS), infarkta miokarda, zatajivanja srca, prevenciji dijabetičke nefropatije. U svim ovim indikacijama imaju I. klasu preporuke, uz razinu dokaza A.

ACE inhibitor perindopril intenzivno je proučavan u nekoliko velikih kliničkih studija: ASCOT, PROGRESS, ADVANCE i EUROPA. Ta ispitivanja su proširila naše znanje o patofiziološkim procesima u kojima ima ulogu RAAS (renin angiotenzin aldosteronski sustav), poglavito podstudije EUROPE u kojima je registrirano da perindopril uz antihipertenzivni učinak poboljšava endotelnu funkciju i neurohumoralnu ravnotežu te smanjuje remodeliranje koronarnih arterija. To postiže svojim velikim afinitetom za cirkulirajući i tkivni ACE te 24-satnom učinkom, uz jednokratno doziranje, čime postiže dobru penetraciju u aterosklerotski plak[7].

Klinička učinkovitost perindoprila u liječenju AH i prevenciji kardiovaskularnih zbivanja ispitivana je u ASCOT kliničkoj studiji, odnosno njenoj podstudiji liječenja AH (BPLA). Tu su ispitivani režim liječenja baziran na kombinaciji blokatora kalcijskih kanala i ACE inhibitora (amlodipin i perindopril) s tzv. konvencionalnim režimom liječenja baziranim na kombinaciji beta-blokator i diuretik (atenolol i bendroflumetiazid) u bolesnika s AH i umjerenim kardiovaskularnim rizikom. Studija je ranije prekinuta jer je skupina bolesnika liječena amlodipinom i perindoprilom imala smanjenje ukupne smrtnosti za 11% u odnosu na drugu skupinu. Ispitivanje je pokazalo da u liječenju AH u skupini bolesnika s umjerenim kardiovaskularnim rizikom kombinacija amlodipina i perindoprila ima prednost u redukciji mortaliteta i kardiovaskularnog rizika u usporedbi s kombinacijom atenolola i tijazida[8].

U ADVANCE studiji ispitivana je pretpostavka da je kontrola AT u dijabetičara bitna za prevenciju makrovaskularnih i mikrovaskularnih komplikacija bolesti. Razina AT nije bila definirana za uključenje u studiju, a primarni ishod studije je bila redukcija zbirnih makrovaskularnih (kardiovaskularni mortalitet, infarkt miokarda i moždani udar) te mikrovaskularnih zbivanja (nefropatija i retinopatija). U studiju je bilo uključeno 11.140 bolesnika s dijabetesom tip II koji su randomizirani u dvije skupine: fiksna kombinacija perindoprila i indapamida ili placebo kao dodatak postojećoj terapiji. Nakon prosječno 4,3 godine praćenja aktivni tretman je smanjio rizik od velikih makro- i mikrovaskularnih događaja za 9%. Pri tome je relativan rizik kardiovaskularne smrtnosti smanjen za 18%, a ukupne

pophilic ACE inhibitors (ramipril, perindopril, trandolapril and quinapril) have this capacity with potential cardioprotective effect that exceeds their effect in reduction of blood pressure (BP). Anyway, this cardioprotective effect needs to be proven in large clinical studies, whereas ramipril in the HOPE study and perindopril in the EUROPA study have been successful in it so far. Why has it not been proved for trandolapril in the PEACE study and for quinapril in the IMAGINE study is the issue to be discussed. It is possible that these drugs with tissue ACE inhibition have no additional effects on apopotosis or endothelial function, but that the design of the studies (number of patients, characteristics and drug dose) was inappropriate for proving cardioprotective effects of such drugs[2-5].

There are opinions that there are no special cardioprotective effects of ACE inhibitors as a group and there are no so-called tissue specific ACE inhibitors as a subgroup, but that their entire cardioprotective effect and the effect of all other groups of antihypertensives is aimed at lowering BP[6].

Anyway, the role of ACE inhibitors has been recognized by the authors of the guidelines of the European Society of Cardiology and American Societies of Cardiology (ACC and AHA) and they are recommended in the treatment of BP and in: treatment of stable coronary heart disease (CHD), myocardial infarction, heart failure, prevention of diabetic nephropathy. In all these indications they have the class of recommendation I with the level A.

ACE inhibitor perindopril has been intensively studied in the several large clinical studies: ASCOT, PROGRESS, ADVANCE and EUROPA. Such studies have broaden our knowledge about pathophysiologic processes where the RAAS (renin-angiotensin-aldosterone system) plays an important role mainly in the EUROPE study which proved that perindopril with antihypertensive effect improves endothelial function and neurohumoral balance and reduces remodeling of coronary arteries. This is achieved by its affinity for circulating and tissue ACE and 24-hour effect with a single dosing, whereas good penetration in atherosclerotic plaque is achieved[7].

The clinical efficacy of perindopril in treatment of hypertension and prevention of cardiovascular events has been tested in the ASCOT clinical study or its sub-study of treatment of hypertension (BPLA). The regime of treatment based on the combination of calcium channel blockers and ACE inhibitors (amlodipine and perindopril) with the so-called traditional regime of treatment based on the combination of beta-blocker and diuretic (atenolol and bendroflumethiazide) in patients with hypertension and moderate cardiovascular risk has been tested. The study was prematurely ended since the group of patients treated by amlodipine and perindopril showed a reduction of total mortality by 11% compared to the other group. The study have showed that in the treatment of hypertension in the group of patients with moderate cardiovascular risk, the combination of amlodipine and perindopril were beneficial in reducing mortality and cardiovascular risk compared to the combination of atenolol and thiazide[8].

The ADVANCE study has tested the assumption that the BP control in diabetic patients is important for the prevention of macrovascular and microvascular disease complications. The BP level was not defined for the inclusion in the study, while the primary outcome of the study was the reduction of cumulative macrovascular (cardiovascular mortality, myocardial infarction and stroke) and microvascular events (nephropathy and retinopathy). The study in-

smrtnosti za 14%. Ova studija je bila još jedna potvrda značenja intenzivne redukcije AT u dijabetičara[9].

Ispitivanje učinka antihipertenzivnog liječenja perindoprilom u bolesnika koji su preboljeli moždani udar i tranzitornu ishemičnu ataku rađeno je u PROGRESS studiji. Ispitivana je monoterapija perindoprilom uz, po potrebi, dodatak indapamida s placebom. U tom ispitivanju nakon 4 godine uzimanja perindoprila, redukcija AT za 9/4 mmHg smanjila je fatalni i nefatalni moždani udar za 28%. Kombinacija perindoprila i indapamida bila je još učinkovitija pa je uz redukciju AT za 12/5 mmHg smanjila rizik moždanog udara za 43%. Kombinirano liječenje s perindoprilom i indapamidom postiže veće smanjenje AT i veće smanjenje rizika nego liječenje sa samim perindoprilom. Kod bolesnika s moždanim udarom liječenje ovom kombinacijom možemo smatrati rutinskom, bez obzira na njihovu vrijednost AT[10].

U kliničkom ispitivanju EUROPA sudjelovala je niskorizična skupina bolesnika sa stabilnom KBS i bez znakova zatajivanja srca. Primarni cilj studije bio je redukcija zbirnog: kardiovaskularnog mortaliteta, infarkta miokarda i aresta srca. Uspoređivani su perindopril 8 mg s placebom kao dodatak postojećoj terapiji. Nakon prosječno 4,2 godine praćenja skupina koja je uzimala perindopril imala je za 20% relativnu redukciju rizika od navedenih zbivanja. Pri tome treba naglasiti da je to bila skupina bolesnika koji su bili dobro liječeni (92% ih je uzimalo antiagregacijske lijekove, 62% beta-blokatore i 58% statine), a učinak terapije bio je neovisan o početnim vrijednostima AT[3].

U bolesnika starijih od 80 godina učinak kombinacije perindoprila i indapamida dokazan je u HYVET studiji. U skupini koja je bila liječena aktivnim tretmanom bilo je 30% manje moždanih udara, 21% manje smrtnih ishoda te 64% manje zatajivanja srca u odnosu na bolesnike liječene placebom[11].

Analize navedenih studija, primarno EUROPA, ADVANCE, i PROGRESS pokazale su učinkovitost i korist liječenja perindoprilom u bolesnika sa stabilnom KBS, dijabetesom i preboljenim moždanim udarom, pri čemu je apsolutna korist liječenja u prevenciji kardiovaskularnih događaja povezana s individualnim rizikom svakog bolesnika. Stoga je važno pri odluci o početku liječenja procijeniti sveukupni rizik svakog bolesnika, a ne samo njegovu pojedinu sastavnicu (npr. visinu AT).

Opažena korist liječenja perindoprilom u navedenim studijama bila je neovisna o početnom AT iz čega se može pretpostaviti da uz hipotenzivni učinak perindopril ima i druge učinke koji pridonose djelotvornosti u kardiovaskularnih bolesnika.

Jedna od pretpostavki je da se to događa i djelovanjem na nastanak bradikinina u tkivima. Zbog svoje lipofilnosti perindopril ima najveću selektivnost za vezna mjesta bradikinina te značajno reducira apoptozu endotelnih stanica u usporedbi s drugim ACE inhibitorima. Bradikinin, povećavajući sintezu dušičnog oksida smanjuje endotelnu disfunkciju, ima antoksidativni učinak, povećava fibrinolizu i smanjuje kardiovaskularno remodeliranje te na taj način snažno antagonozira učinak angiotenzina II. Time se tumači i bolji učinak na prevenciju kardiovaskularnih zbivanja ACE inhibitorima u odnosu na blokatore angiotenzinskih receptora (koji nemaju bradikininski učinak), koji je regi-

volved 11,400 patients with type II diabetes who were randomized in the two groups: fixed combination of perindopril and indapamide or placebo as a supplement to the existing therapy. After 4.3 years on average of follow-up, the active treatment reduced the risk of large macro and microvascular events by 9%. The relative risk of cardiovascular mortality was reduced by 18% and total mortality was reduced by 14%. This study was an additional verification of the importance of intensive reduction of BP in diabetic patients[9].

Testing the effect of antihypertensive treatment with perindopril in patients who suffered from stroke and transitory ishemic attack was performed in the PROGRESS study. The monotherapy with perindopril was tested, as required, with a supplement of indapamide with placebo. During study, after 4 years of taking perindopril, the reduction of BP by 9/4 mmHg resulted in reduction of fatal and non-fatal stroke by 28% The combination of perindopril and indapamide was even more effective, and besides the reduction of BP by 12/5 mmHg it reduced the risk of stroke by 43%. The combined treatment with perindopril and indapamide achieves greater reduction of BP and greater reduction of risk than the treatment with only perindopril. In patients with stroke, the treatment with this combination may be considered a routine treatment, regardless of their value of BP[10].

A low-risk group of patients with stable CHD and with no indications of heart failure participated in the EUROPA trial. The primary goal of the study was the reduction of the cumulative: cardiovascular mortality, myocardial infarction and cardiac arrest. 8 mg perindopril was compared to placebo as a supplement to the existing therapy. After 4.2 years of follow-up on average, the group that was taking perindopril had a relative reduction of the risk from the above incidents by 20%. At the same time, we should emphasize that it was the group of patients who were well treated (92% of them took anti-aggregation drugs, 62% beta-blockers and 58% statins) while the effect of the therapy was independent of the initial values of BP[3].

In patients over 80 years of age, the effect of the combination of perindopril and indapamide was proved in the HYVET study. In the group that was treated by the active treatment, there were 30% less strokes, 21% less deadly outcomes and 64% less heart failures compared to the patients treated with placebo[11].

The analyses of the above mentioned studies, mainly of EUROPA, ADVANCE, and PROGRESS have showed the efficacy and benefit of treatment with perindopril in patients with stable CHD, diabetes and suffered stroke, whereas the absolute benefit of the treatment in prevention of cardiovascular incidents is related with individual risk of every patient. Therefore, when making decision on starting the treatment, it is important to evaluate the total risk for every patient, not only its individual component (such as BP value).

The great benefit of treatment with perindopril in the above studies was independent of the initial BP which makes us conclude that besides the hypotensive effect, perindopril has also other effects that contribute to efficacy in cardiovascular patients.

One of the assumptions is that it occurs by influencing the occurrence of bradykinin in tissues. Owing to its lypophilic properties, perindopril has the greatest selectivity for bradykinin binding sites and greatly reduces apoptosis of endothelial cells compared to the other ACE inhibitors. Bradykinin reduces the endothelial dysfunction by increa-

striran u pojedinim kliničkim ispitivanjima te njihovim metaanalizama[7].

Nuspojave perindoprila (kao i ostalih ACE inhibitora) dobro su poznate. Najčešće su: hipotenzija, kašalj, hiperkalemija, glavobolja, vrtoglavice, omaglice, pogoršanje renalne funkcije. Najčešća nuspojava (oko 10% bolesnika) je perzistentni nadražajni kašalj za koji se predmnijeva da je izazvan djelovanjem bradikinina. Ipak u EUROPA studiji svega je 2,2% ispitanika imalo tu nuspojavu. Za perindopril je poznato da relativno rijetko izaziva hipotenziju pri uzimanju prve doze lijeka zbog svog sporog nastupa djelovanja, a što je relativno česta nuspojava u drugih ACE inhibitora. U velikim studijama EUROPA i PROGRESS svega je 1,0% i 2,1% bolesnika prestalo uzimati lijek zbog te nuspojave[3,10].

Zaključak

Liječenje ACE inhibitorima u koje pripada i perindopril, pokazalo je svoju učinkovitost u nizu kliničkih ispitivanja te se ova skupina lijekova nameće kao prvi izbor u kardioprotektivnom tretmanu bolesnika sa zatajivanjem srca, AH, dijabetesom, moždanim udarom i stabilnom KBS.

Perindopril se od ostalih ACE inhibitora razlikuje po svojim jedinstvenim osobinama kao što su: veliki afinitet za tkivni ACE u usporedbi s drugim lijekovima iz skupine te veliki učinak na razinu bradikinina u odnosu na druge ACE inhibitore. Ima dug poluživot u plazmi te 24-satni učinak što omogućava kontrolu AT noću i u ranim jutarnjim satima. Uz snižavanje AT kao osnovno djelovanje, ACE inhibicija perindoprilom ima i antiinflamatorni, antiaterosklerotski i antitrombotski učinak. Lijek ima dokazan učinak u redukciji kardiovaskularnog rizika u velikog broja bolesnika te može biti prvi izbor u liječenju bolesnika sa: zatajivanjem srca, AH, stabilnom KBS i cerebrovaskularnom bolešću. Reducira kardiovaskularna zbivanja bez obzira na vrstu bolesnika i njihovu razinu rizika.

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*Address for correspondence: Opća bolnica Zadar, Bože Peričića 5 HR-23000 Zadar, Croatia.
Phone: +385-23-505-505
E-mail: aleksandar.knezevic@zd.t-com.hr

sing the synthesis of nitrogen oxide, while it has antioxidant effect, increases fibrinolysis and reduces cardiovascular remodeling and in this way it strongly antagonizes the effect of angiotensin II. This explains better effect of the prevention of cardiovascular events by ACE inhibitors compared to angiotensin receptor blockers (not having bradykinin effect) that is registered in specific clinical tests and their metaanalyses[7].

The adverse effects of perindopril (and other ACE inhibitors) are well known. The most frequent are: hypotension, cough, hyperkalemia, headache, dizziness, vertigo, deterioration of renal function. The most frequent adverse effect (in around 10% of patients) is the persistent irritating cough that is thought to be caused by the bradykinin effect. Anyway, the EUROPA study includes only 2.2% of patients that had this adverse effect. Perindopril is known to relatively rarely cause hypotension when taking the first dose of drug due to its slow start of action, which is a relatively frequent adverse effect in other ACE inhibitors. In the large studies EUROPA and PROGRESS there is only 1.0% and 2.1% of patients who stopped taking the drug because of this adverse effect[3,10].

Conclusion

The treatment with ACE inhibitors now including perindopril as well, has shown its efficacy in a series of clinical tests and this group of drugs is imposed as a first choice drug in cardioprotective treatment of patients with heart failure, hypertension, diabetes, stroke and stable CHD.

Perindopril differs from the other ACE inhibitors in its unique properties such as: great affinity for tissue ACE compared to other drugs from this group of drugs and a great effect on the level of bradykinin compared to other ACE inhibitors. It has a long half-life in plasma and 24 hour effect which enables the BP control at night and early morning hours. While lowering BP as the basis effect, ACE inhibition by perindopril has also antiflammatory, antiatherosclerotic and antiplatelet effect. The drug has a proven effect in reducing cardiovascular risk in a great number of patients and it can be the first choice drug in the treatment of patients with: heart failure, hypertension, stable CHD and cerebrovascular disease. It reduces cardiovascular events regardless of a type of patients and their level of risk.

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