SAŽETAK: Endotelna disfunkcija najranija je vaskularna abnormalnost, a uključena je u sve faze kardiovaskularnog kontinuuma. Osim sposobnosti snizivanja arterijskog tlaka, antihipertenzivni lijekovi u idealnom slučaju trebaju imati dodatna svojstva zaštite endotela. Čini se da među inhibitorima angiotenzin-konvertaze perindopril ima najsnažnije protektivne učinke na endotel. Amlodipin je dobro poznat po svojemu ateroprotektivnom učinku. Klinički dokazi pokazuju da perindopril i amlodipin pojedinačno mogu usporiti progresiju kardiovaskularne bolesti, uz dugoročne blagotvorne učinke liječenja na mortalitet. Taj je učinak jači i širi ako se oba lijeka primjenjuju zajedno. Važnim se doima rano propisivanje perindoprila i amlodipina jer se većina koristi od liječenja obama lijekovima događa u ranim ili srednjim fazama kardiovaskularnog kontinuuma. Klinički dokazi također podupiru blagotvorni učinak na vaskularni endotel kakav pruža trojna kombinacija perindoprila i amlodipina s indapamidom.

SUMMARY: Endothelial dysfunction is the earliest vascular abnormality and it is involved in all stages of the cardiovascular continuum. Antihypertensive compounds should ideally have additional endothelial protective properties beyond their ability to reduce blood pressure. Among angiotensin-converting enzyme inhibitors, perindopril appears to have the greatest endothelial protective effects. Amlodipine is well known for its atheroprotective effect. Clinical evidence has shown that perindopril and amlodipine could individually interrupt and slow the progression of cardiovascular disease with long-term beneficial effects of treatment on mortality. The effect is enhanced and broadened if both agents are used together. Early prescription of perindopril and amlodipine appears to be important, as most of the treatment benefits of both agents occur in the early or middle stages of the cardiovascular continuum. Clinical evidence also supports the beneficial effect on the vascular endothelium offered by the triple combination of perindopril and amlodipine with indapamide.

KEYWORDS: perindopril, amlodipine, endotelna disfunkcija, kardiovaskularni kontinuum.

INTRODUCTION

Funkcionalni integritet endotela bitan je za vaskularno zdravlje. Osim održavanja ravnovesa između vazodilatacije i vazokonstrikcije, endotel ima brojne druge uloge koje su ključne za održavanje vaskularne homeostaze. U prisutnosti kardiovaskularnih (KV) čimbenika rizika, osobito arterijske hipertenzije, hiperkolesterolemije, dijabetesa i pušenja, endotel prolazi kroz funkcionalne i strukturne promjene zbog kojih gubi svoju kardio- i protektivnu ulogu i dobiva pro- aterosklerotska svojstva.

Uvod

Funkcionalni integritet endotela bitan je za vaskularno zdravlje. Osim održavanja ravnovesa između vazodilatacije i vazokonstrikcije, endotel ima brojne druge uloge koje su ključne za održavanje vaskularne homeostaze. U prisutnosti kardiovaskularnih (KV) čimbenika rizika, osobito arterijske hipertenzije, hiperkolesterolemije, dijabetesa i pušenja, endotel prolazi kroz funkcionalne i strukturne promjene zbog kojih gubi svoju kardio- i protektivnu ulogu i dobiva pro- aterosklerotska svojstva.
Endotelna disfunkcija najranija je vaskularna abnormalnost. Uključena je u sve faze KV kontinuuma i pouzdan je prognostički pokazatelj KV događaja. Mogućnost poboljšanja oštećene endotelne funkcije mogao bi biti važan cilj antihipertenzivne terapije. Učinak snizivanja arterijskoga tlaka (AT) sam po sebi nije dovoljan da bi se ispravila endotelna disfunkcija. Ispitivanja su utvrdila da postoji povezanost između poboljšane funkcije endotela s boljim ishodima. Osim učinka snizivanja vrijednosti AT-a, antihipertenzivni lijekovi u idealnom slučaju trebaju imati dodatna svojstva zaštite endotela.

Brojna ispitivanja pružaju uvjerljive dokaze da inhibitori angiotenzin konvertirajućeg enzima (ACEI) mogu obnoviti funkciju endotela. Čini se da među lijekovima iz skupine ACEI-ja upravo perindopril ima najnašnažnije protektivne učinke na endotel, a pokazao je djelotvornost kod brojnih markera endotelne disfunkcije, uključujući arterijsku krutost i progresiju ateroskleroze.

**Od endotelne disfunkcije do kardiovaskularnih događaja**

Vaskularni endotel sada se smatra organom čija je pravilna funkcija presudna za održavanje vaskularnoga zdravlja, odnosno čija je disfunkcija ključna za nastanak, progresiju i kliničke komplikacije vaskularne bolesti. Jednom ko se razvije endotelna disfunkcija, ona predposiroma krvne žile upalnom odgovoru, uključujući vaskularno remodeliranje, nastanak aterosklerotskih lezija u arterijama te u konačnici i rupturu plaka i nastanak krvnih ugrožaka. Endotelna disfunkcija smatra se prvom fazom ateroskleroze i prisutna je mnogo prije aterosklerotskih plakova ili čak i KV događaja. Prikupljeni dokazi upućuju na to da je ona marker faze aterosklerotske progresije, no, isto tako, istina je da ima ulogu markera u obrnutom smjeru: promjene životnog stila i lijekovi kao što su ACEI značajno poboljšavaju endotelnu disfunkciju. Blagotvorni vaskularni učinci perindopril, uključujući poboljšanje endotelne funkcije, opsežno su prepoznati i ispitani. Endotelna disfunkcija smanjuje vaskularnu reaktivnost i krvnu prostučinu, dok ostali bile mehanizmi takve disfunkcije, opaženi su pri bolnim s hipertenzijom, uključujući takve bolesti kao što je hipertenzija (p = 0,0247) u usporedbi s režimom atenolol/diuretik. Srednja vrijednost AT-a u skupini koja je liječena amlodipinom/perindoprilom imala je 1,7 mmHg niža nego u skupini koja je primala beta-blokator/diuretik – što je razlika koja ne može potpuno objasniti razliku u ishodu. Ispitivanje ASCOT (n = 2199) istraživalo je učinke antihypertensivne terapije.

**From endothelial dysfunction to cardiovascular events**

Vascular endothelium is now viewed as an organ whose normal functioning is crucial to maintaining vascular health, and whose dysfunction is key in the initiation, progression, and clinical complications of vascular disease. Once endothelial dysfunction is present, it predisposes the vessel to inflammatory response, including vascular remodeling, formation of atherosclerotic lesions in arteries, and finally plaque rupture and thrombus formation. Endothelial dysfunction is regarded as the first phase of atherosclerosis and is present long before atherosclerotic plaques or even CV events. There is evidence that it marks a stage of atherosclerotic progression but, conversely, its role as a marker also holds true in the reverse direction: lifestyle changes and drugs such as ACEIs measurably improve endothelial dysfunction. The beneficial vascular effects of perindopril, including improvement of endothelial function, have been widely studied and recognized. The CAFE sub-study (n = 2,199) showed that amlodipine therapy also improves endothelial function in patients with hypertension. By attenuating the deleterious effects of cardiovascular disease (CVD) at multiple stages of the CV continuum on top of lowering BP, perindopril and amlodipine could interrupt and slow the progression of CVD – as has been shown by the ASCOT study in which the antihypertensive and vascular effects of both agents have translated into real-life clinical benefits.

The ASCOT study clarified the role of ACE inhibition in the reduction of CV events in patients with hypertension without CVD. In the BP-lowering arm of the trial, patients (n = 19,257) at moderate CV risk were randomized to amlodipine 5-10 mg with the addition of perindopril 4-8 mg as required or atenolol with the addition of diuretic as required. ASCOT was stopped prematurely (after a median of 5.5 years) because the patients in the amlodipine/perindopril group showed an 11% reduction in all-cause mortality (p = 0.0247) compared with the atenolol/diuretic regimen. The mean BP in the amlodipine/perindopril group was 2.7/1.9 mmHg lower than in the beta-blocker/diuretic arm – a difference which could not entirely account for the difference in outcome. The CAFE sub-study (n = 2,199) evaluated the effects of the two ASCOT treatment regimens
Kad dva ljeka nisu dovoljna za kontrolu arterijskog tlaka

Ispitivanja govore da će terapija kombinacijom dvaju ljevaka kontrolirati AT u približno dvije trećine bolesnika. Za bolesnike čiji AT nije stavljen pod kontrolu terapijom kombinacijom dvaju ljevaka, logična je opcija primijetiti kombinaciju triju ljevaka: obično blokator reninsko-angiotenzinskog sustava, dioaura i diuretic. \(^{15}\) Zbog toga je rano istodobno propisivanje perindopril-a i amlodipina pojavilo se kao učinkovita opcija liječenja kombinacijom dvaju lijekova u većini hipertenzivnih bolesnika.

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Metabolički neutralan diuretik indapamid sam iskazuje blagotvorne učinke na ciljne organe jer smanjuje hipertrofiju lijeve klijetke i mikroalbuminuriju, rizik od moždanog udara i ukupni mortalitet. Nadalje, dokazano je da indapamid nema učinak na metabolizam lipida (triglicerida, LDL kolesterola i HDL kolesterola) ni metabolizam ugljikohidrata, što ga čini prikladnim odabirom za vrlo različite bolesnike i kada se koristi u kombinacijama.16-19

Što se tiče perindopila i amlodipina, također postoje klinički dokazi koji podupiru blagotvorni učinak na vaskularni endotel kakav pruža trojna kombinacija ovih dvaju lijekova s indapamidom. U kliničkom ispitivanju koje su proveli Chukayeva i sur.,20 bolesnici (n = 44) koji nisu postigli ciljnu vrijednost AT-a s pomoću prethodne kombinirane terapije prebačeni su na liječenje trojnom kombinacijom perindopril/amlodipin/indapamid (Co-Dalneva®, tablica 1). Mjesečno je podijeljeno na mjesec razinu AT-a od <140/90 mm Hg postiglo je 93% bolesnika. Do kraja ispitivanja svi su bolesnici postigli kontrolu AT-a. Pulinski tlak (PT), koji odražava efikasnost i prohodnost perifernih krvnih žila te funkcionalnost miokarda, smanjio se za 30,3% (p < 0,001).

As for perindopril and amlodipine, there is also clinical evidence supporting the beneficial effect on the vascular endothelium offered by the triple combination of these two drugs with indapamide. In the clinical study by Chukayeva et al. and colleagues, the patients (n = 44) who did not reach their BP targets with the previous combined therapy were upgraded to a treatment with the SPC of perindopril/amlodipine/indapamide (Co-Dalneva®, Table 1). A month after the upgrade of therapy, 47.7% of patients reached the target BP level, whereas after 3 months BP <140/90 mmHg was achieved in 93% of patients. By the end of the study, all patients reached BP control. The pulse BP (PBP), which reflects peripheral vessel elasticity and patency and myocardial functioning, decreased by 30.3% (p<0.001).

| Parameter | Baseline | After 1 month | After 3 months | After 6 months* |
|-----------|----------|---------------|----------------|-----------------|
| SBP, mm Hg | 152±11 | 138.6±8.7 | 129.6±7.1 | 125.1±6.9 |
| DBP, mm Hg | 91±6.7 | 82.6±7.1 | 82±5.7 | 82.2±5 |
| PBP, mm Hg | 61.7±9.1 | 56±9.9 | 47.6±7.0 | 43±7.9 |

Tablica 2 pokazuje promjene u upalnim markerima (СRP, IL-6, IL-10) nakon 6 mjeseci liječenja kombinacijom perindopril/amlodipin/indapamida u jednoj tableti. Razine mar kerorske endotelnine disfunkcije (sVCAM-1) znatno su se smanjile (from 1063.5±442.4 to 898.67±433.5 ng/mL, p < 0.001). Također se postojao trend smanjenja VEGF-a.20

Vrijednost PT-a >60 mm Hg (u starijih osoba) znak je supkliničkog oštećenja ciljnih organa. Postizanje normalne razine BP-a nađe na podjelu oboljelih u regulaciji vaskularnog tonusa. Promjena u endotelnoj funkciji indirektno se koristi za ocjenu organske ochranitve lakova.

Vaskularni endotel je karika u regulaciji vaskularnog tonusa. Promjena u endotelnoj funkciji je direktno prikazana s pomoću upalnih markerima IL-6, IL-10 i sVCAM-1. Promjena u endotelnoj funkciji indirektno se koristi za ocjenu organske ochranitve lijeka.

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If more than 60 mm Hg (in elderly) is a sign of subclinical target organ damage. Achieving the normal level of PBP demonstrates the organ-protective activity of the drug.

Vascular endothelium is an independent link in the regulation of vascular tone. The change in endothelial function was indirectly assessed using inflammation markers and molecular-biological markers of neoangiogenesis, such as the vascular endothelial adhesion molecule and the vascular endothelial growth factor. The peripheral blood concentration of the soluble form of vascular endothelial growth factor (sVCAM-1) increases only with a pathological activation of the endothelium. Change in expression of sVCAM-1 can therefore be used to evaluate the change in the endothelial condition.20

TABLE 2 shows changes in the markers of inflammation (CRP, IL-6, IL-10) after 6 months of treatment with the SPC of perindopril/amlodipine/indapamide. The levels of the sVCAM-1 endothelial dysfunction marker decreased significantly (from 1063.5±442.4 to 898.67±433.5 ng/mL, p<0.001). There was also a trend of VEGF reduction.20

Vascular Health and Cardiovascular Outcomes: Focus on Perindopril and its Combinations

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TABLE 1. Changes in systolic, diastolic, and pulse blood pressure during treatment.

| Parameter | Baseline | After 1 month | After 3 months | After 6 months* |
|-----------|----------|---------------|----------------|-----------------|
| SBP, mm Hg | 152±11 | 138.6±8.7 | 129.6±7.1 | 125.1±6.9 |
| DBP, mm Hg | 91±6.7 | 82.6±7.1 | 82±5.7 | 82.2±5 |
| PBP, mm Hg | 61.7±9.1 | 56±9.9 | 47.6±7.0 | 43±7.9 |

*compared to baseline values

DBP – diastolic BP, SBP – systolic BP, PBP – pulse blood pressure
A significant reduction in sVCAM-1 level after 6 months of treatment along with the achievement of the target BP level demonstrates improvement in endothelial function in the study subjects. The question of whether the improvement in endothelial function is due to a reduction in BP during the treatment or pleiotropic effects of the SPC components is a subject for discussion. However, the improvement of endothelial function is a direct indicator of the organ-protective effect of the drug. Apart from achieving BP control and a significant reduction in PBP, the therapy with a triple SPC of perindopril/indapamide/amlodipine also improved the vascular endothelial state by significantly lowering sVCAM-1. Furthermore, increased patient adherence and improved overall quality of life were also observed during the therapy with the SPC of perindopril/indapamide/amlodipine.

Further information on the action of double and triple SPCs of perindopril/amlodipine (Dalneva®) and perindopril/indapamide/amlodipine (Co-Dalneva®) on BP reduction and vascular health are expected from the international, prospective, interventional study PRECIOS. The study was conducted in 7 countries – Croatia, Slovenia, Serbia, Hungary, Poland, Russia, and Armenia – not only with the aim of assessing the efficacy and safety of the these SPCs in continuous 24-hour BP control but also establishing the correlation between 24-hour central and peripheral BP. The results of interim analysis are available at the moment, presenting the data of 103 patients. They show that the dual SPC of perindopril/amlodipine and the triple SPC of perindopril/indapamide/amlodipine reduce BP effectively, leading to high rates of BP control achieved in a short time with a good safety profile and a very high level of treatment adherence.

### Conclusion

Due to their pleiotropic effects, perindopril and amlodipine with or without indapamide represent a valuable treatment option, slowing the progression of CVD with long-term beneficial effects of treatment on mortality. Early prescription of perindopril and amlodipine appears important, as most of the treatment benefits of both drugs occur in the early or middle stages of the CV continuum. The combination of both is likely to be more effective on outcomes, especially in form of a SPC.

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**TABLE 2. Changes of inflammatory parameters and endothelial dysfunction markers during the treatment.**

| Parameter          | Baseline            | After 6 months of treatment |
|--------------------|---------------------|-----------------------------|
| CRP, mg/L          | 7.78±20.2           | 2.13±3.6                    |
| IL-6, pg/mL        | 1.9±0.5             | 1.8±0.8                     |
| IL-10, pg/mL       | 8.29±7.5            | 6.38±2.7                    |
| sVCAM-1, ng/mL     | 1063.5±442.4        | 898.67±433.5*               |
| VEGF, pg/mL        | 583.14±393.2        | 570.0±468.7                 |

*p<0.001

CRP – C-reactive protein; IL – interleukin, sVCAM – soluble form of vascular endothelial adhesion molecule, VEGF – vascular endothelial growth factor

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Znatno smanjanje razine sVCAM-1 nakon 6 mjeseci liječenja zajedno s postizanjem ciljne razine AT-a pokazuje poboljšanje endotelne funkcije u ispitanika uključenih u ispitivanje. Ostalo je neriješeno pitanje je li za poboljšanje endotelne funkcije zaslužno smanjenje AT-a tijekom liječenja ili pak pleiotropni učinci komponenti kombinacije lijeкова u jednoj tableti. Međutim, poboljšanje endotelne funkcije izravan je pokazatelj organoprotektivnog učinka lijeka. Osim postizanja kontrole AT-a i znatnog smanjenja PT-a, terapija trojnom kombinacijom perindopril/indapamida/amlodipina također je poboljšala stanje vaskularnog endotela jer je znatno smanjila sVCAM-1. Nadalje, također su zabilježene veća adherencija i bolja opća kvaliteta života tijekom terapije trojnom kombinacijom perindopril/indapamida/amlodipina. Očekuju se dodatne informacije o djelovanju dvojnih i trojnih kombinacija perindopril/indapamida (Dalneva®) i perindopril/indapamida/amlodipina (Co-Dalneva®) na smanjenje vrijednosti AT-a i vaskularno zdravlje između našej, perspektivnog, interventionalijskog ispitivanja PRECIOS. Ispitanje je provedeno u 7 zemalja – Hrvatskoj, Sloveniji, Srbiji, Mađarskoj, Poljskoj, Rusiji i Armeniji – ne samo sa svrhom procjene djelotvornosti i sigurnosti navedenih kombinacija lijeкова u jednoj tableti i za kontinuiranu 24-satnu kontrolu vrijednosti AT-a, nego i radi utvrđivanja korelacije između 24-satnog centralnog i perifernog tlaka. Trenutačno su na raspolaganju rezultati privremene analize, koji uključuju podatke za 103 bolesnika. Oni pokazuju da dvojna kombinacija perindopril/indapamida i trojna kombinacija perindopril/indapamida/amlodipina u jednoj tableti učinkovito smanjuju vrijednost AT-a, čime je u kratkome vremenu dovode do viših stopa postignute kontrole AT-a, uz dobar sigurnosni profil i vrlo visoku razinu pridržavanja liječenja.

### Zaključak

Zbog svojih pleiotropnih učinaka, perindopril i amlodipin s indapamidom ili bez njega vrijedna su opcija liječenja jer usporuju progresiju KVB-a i imaju dugoročne blagotvorne učinke liječenja na mortalitet. Doima se važnim ranom proširivanjem lijećniku liječenja zajedno s postizanjem ciljne razine AT-a. Doima se važnim ranom proširivanjem lijećniku liječenja zajedno s postizanjem ciljne razine AT-a. Cijena liječenja u jednoj tableti samlja u velikoj mjeri u vrijednost AT-a, uz dobar sigurnosni profil i vrlo visoku razinu pridržavanja liječenja.
Vascular Health and Cardiovascular Outcomes: Focus on Perindopril and its Combinations

As stated in the 2018 ESC/ESH guidelines for the management of arterial hypertension, the concept of initiating therapy with a two-drug combination for most patients with hypertension is likely to have a major effect on clinical practice and the speed and quality of BP control.

The novel SPC, Predalneva® (perindopril 2.85 mg/amlodipine 2.5 mg), which is also indicated for the initial therapy of hypertension,14 is an additional extension of Krka’s wide portfolio of perindopril-based drugs in Croatia.21

When the combination of amlodipine and perindopril is not enough for reaching BP control, a triple SPC with the addition of the metabolically neutral diuretic indapamide is a logical choice due to its proven protective advantages and suitability in a wide variety of patients.15,19-33,32-36

Krka’s perindopril-based drugs have consistently demonstrated their effectiveness and safety in clinical studies with around 90,000 included patients.10,20,23-34 Physicians in Croatia can now select among 15 alternatives enabling individualized therapy in patients with different needs.22

Kao što navode Smjernice ESC-a/ESH-a za liječenje arterijske hipertenzije iz 2018. godine, koncept uvođenja terapije kombinacijom dvaju lijekova za većinu bolesnika s hipertenzijom vjerojatno će imati važan učinak na kliničku praksu te brzinu i kvalitetu kontrole AT-a.15

Nova kombinacija lijekova u jednoj tableti, Predalneva® (perindopril 2.85 mg/amlodipin 2.5 mg), koja je također indicirana za početnu terapiju protiv hipertenzije,14 dodatno je proširenje Krkina širokog portfelja lijekova na bazi perindopril dostupnih u Republici Hrvatskoj.23

Kad kombinacija amlodipina i perindoprila nije dovoljna za postizanje kontrole AT-a, logičan je odabir trojna kombinacija lijekova u jednoj tableti s dodatkom metabolički neutralnog diuretika indapamida zbog njegovih dokazanih protektivnih prednosti i prikladnosti za vrlo različite bolesnike.15, 20, 22, 23-28

Krkini lijekovi na bazi perindoprila dosljedno su dokazali svoju učinkovitost i sigurnost u kliničkim ispitivanjima s oko 90,000 uključenih bolesnika.20,21,23-34 Liječnici u Hrvatskoj sada mogu odabrati između 15 opcija, što omogućuje individuálnu prilagodbu terapije u bolesnika s različitim potrebama.22

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