Vaskularno zdravlje i kardiovaskularni ishodi: perindopril i njegove kombinacije

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

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SAŽETAK: Endotelna disfunkcija najranija je vaskularna abnormalnost, a uključena je u sve faze kardiovaskularnog kontinuuma. Osim sposobnosti snizivanja arterijskoga 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.

KLJUČNE RIJEČI: perindopril, amlodipin, endotelna disfunkcija, kardiovaskularni kontinuum.

KEYWORDS: perindopril, amlodipine, endothelial dysfunction, cardiovascular continuum.

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Uvod

Funkcionalni integritet endotela bitan je za vaskularno zdravlje. Osim održavanja ravnoteže između vazodilatacije i vazokonstrikcije, endotel ima brojne druge uloge koje su ključne za održavanje vaskularne homeostaze.[1] U prisutnosti kardiovaskularnih (KV) čimbenika rizika, osobito arterijske hipertenzije, hiperkolesterolemije, dijabetesa i pušenja, endotel prolazi kroz funkcionalne i strukturne promjene zbog kojih gubi svoju kardioprotektivnu ulogu i dobiva proaterosklerotska svojstva.[1]

Introduction

The functional integrity of the endothelium is essential for vascular health. In addition to maintaining a delicate balance between vasodilation and vasoconstriction, the endothelium has numerous other roles crucial for sustaining vascular homeostasis.[1] In the presence of cardiovascular (CV) risk factors, especially hypertension, hypercholesterolemia, diabetes, and smoking, the endothelium undergoes functional and structural alterations that result in it losing its cardioprotective role and becoming proatherosclerotic.[1]

Endotelna disfunkcija najranija je vaskularna abnormalnost.[1] Uključena je u sve faze KV kontinuuma i pouzdan je prognostički pokazatelj KV događaja.[1] Mogućnost poboljšanja oštećene endotelne funkcije mogao bi biti važan cilj antihipertenzivne terapije.[2] Učinak snizivanja arterijskoga tlaka (AT) sam po sebi nije dovoljan da bi se ispravila endotelna disfunkcija.[2] Ispitivanja su utvrdila da postoji povezanost između poboljšane funkcije endotela s boljim ishodima.[3] Osim učinka snizivanja vrijednosti AT-a, antihipertenzivni lijekovi u idealnom slučaju trebaju imati dodatna svojstva zaštite endotela.[2]

Brojna ispitivanja pružaju uvjerljive dokaze da inhibitori angiotenzin konvertirajućeg enzima (ACEI) mogu obnoviti funkciju endotela.[2,4] Čini se da među lijekovima iz skupine ACEI-ja upravo perindopril ima najsnažnije 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.[5] Jednom kad se razvije endotelna disfunkcija, ona predisponira krvne žile upalnom odgovoru, uključujući vaskularno remodeliranje, nastanak aterosklerotskih lezija u arterijama te u konačnici i rupturu plaka i nastanak krvnih ugrušaka.[3,6] 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.[6] Blagotvorni vaskularni učinci perindoprila, uključujući poboljšanje endotelne funkcije, opsežno su prepoznati i ispitani.[1,7,8] S druge strane, amlodipin je dobro poznat po svojemu ateroprotektivnom učinku.[9,10] Ne navodi se često terapija amlodipinom također poboljšava endotelnu funkciju u bolesnika s arterijskom hipertenzijom.[11,12] Utjecajem na štetne učinke kardiovaskularnih bolesti (KVB) štetnih učinaka kardiovaskularne bolesti (KVB) u više faza kardiovaskularnog kontinuuma uz snizivanje vrijednosti AT-a, perindopril i amlodipin mogu usporiti progresiju KVB-a – kao što je pokazalo ispitivanje ASCOT, u kojem su antihipertenzivni i vaskularni učinci obaju lijekova prevedeni u stvarnu kliničku dobrobit.[8]

Ispitivanje ASCOT razjasnilo je ulogu inhibicije ACE-a u smanjenju učestalosti KV događaja u bolesnika s hipertenzijom bez drugog KVB-a. U skupini u kojoj su u ispitivanju snizivane vrijednosti AT-a, bolesnici (n = 19.257) s umjerenim KV rizikom randomizirani su na amlodipin 5 – 10 mg s dodatkom perindoprila 4 – 8 mg po potrebi ili na atenolol s dodatkom diuretika po potrebi. Ispitivanje ASCOT zaustavljeno je prijevremeno (nakon medijana od 5,5 godina) jer su bolesnici u skupini koja je liječena amlodipinom/perindoprilom imali smanjenje od 11 % u ukupnoj smrtnosti (p = 0,0247) u usporedbi s režimom atenolol/diuretik. Srednja vrijednost AT-a u skupini koja je primala amlodipin/perindopril bila je za 2,7/1,9 mmHg niža nego u skupini koja je primala beta-blokator/diuretik – što je razlika koja ne može potpuno objasniti razliku u ishodu.[1] Podispitivanje CAFE (n = 2199) istraživalo je učinke

Endothelial dysfunction is the earliest vascular abnormality.[1] It is involved in all stages of the CV continuum and is a reliable prognostic indicator of CV events.[1] The possibility of ameliorating impaired endothelial function may be an important target for antihypertensive therapy.[2] The blood pressure (BP) lowering effect *per se* is not sufficient to reverse endothelial dysfunction.[2] Outcome studies have established the association of ameliorated endothelial dysfunction with improved hard endpoints in morbidity and mortality.[3] Antihypertensive drugs should ideally have additional endothelial protective properties beyond their ability to reduce BP.[2]

Many studies provide convincing evidence that angiotensin-converting-enzyme inhibitors (ACEIs) can restore endothelial function.[2,4] Among ACEIs, perindopril appears to have the greatest endothelium protective effects and has demonstrated efficacy in a number of markers of endothelial dysfunction including arterial stiffness and progression of atherosclerosis.

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.[5] 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.[3,6] 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.[6] The beneficial vascular effects of perindopril, including improvement of endothelial function, have been widely studied and recognized.[1,7,8] On the other hand, amlodipine is well known for its atheroprotective effect.[9,10] A less frequently mentioned fact is that amlodipine therapy also improves endothelial function in patients with hypertension.[11,12].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.[8]

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 group – a difference which could not entirely account for the difference in outcome.[1] The CAFE sub-study (n = 2,199) evaluated the effects of the two ASCOT treatment regimens

dvaju režima liječenja iz ispitivanja ASCOT na centralni aortalni tlak. Oba pristupa liječenju dovela su do sličnih smanjenja u brahijalnom tlaku, ali centralni aortalni tlak i centralni aortalni pulsni tlak mnogo su više smanjeni kombinacijom amlodipin/perindopril nego režimom atenolol/diuretik (24,3, odnosno 23,0 mmHg, u oba slučaja p = 0,0001), što je koreliralo sa smanjenjima u učestalosti KV događaja ili postupaka.[1,13] Spomenuti lijekovi mogu imati komplementarne učinke na endotelnu funkciju i vazodilataciju koji poboljšavaju KV ishode koji se ne mogu predvidjeti samo na temelju promjena u brahijalnome tlaku.[13]

Ove spoznaje pokazuju da liječenje kombinacijom amlodipin/perindopril utječe na patofiziološki kontinuum i usporuje progresiju KVB-a u hipertenzivnih bolesnika.[1] Dugoročni blagotvorni učinci liječenja režimom amlodipin/perindopril na mortalitet dodatno su potvrđeni rezultatima ispitivanja ASCOT Legacy, u kojemu su sudionici originalnog ispitivanja ASCOT praćeni tijekom medijana od 16 godina.[1] U sudionika iz skupine kojoj nisu snizivani lipidi (n = 3975) bilo je manje KV smrti među bolesnicima koji su primali liječenje temeljeno na režimu amlodipin/perindopril, u usporedbi s liječenjem baziranim na režimu atenolol/diuretik [korigirani omjer hazarda 0,79; 0,67 – 0,93, p = 0,0046].[1]

I perindopril i amlodipin mogu usporiti progresiju KVB-a.[8] Preventivni učinci obaju lijekova šire se na razne faze KV kontinuuma. Oba korigiraju poremećaj odnosa potrebe i opskrbe miokarda kisikom: perindopril tako što povećava koronarnu rezervu i maksimira koronarni krvni protok, a amlodipin tako što smanjuje koronarni vaskularni otpor. Oba mogu smanjiti hipertrofiju lijeve klijetke i ishemiju miokarda.

I perindopril i amlodipin inhibiraju koronarnu trombozu i infarkt miokarda.[8] Fiksna kombinacija (engl. *single pill combination*; SPC) perindopril/amlodipin omogućuje brži odgovor, bolje smanjenje i kontrolu AT-a i adherenciju, nego bilo koji od tih dvaju lijekova kao monoterapija. Ova će kombinacija vjerojatno biti učinkovitija na ishode od perindoprila ili amlodipina pojedinačno, iako djeluje na istom području KV kontinuuma. Osim toga, važno je rano istodobno propisivanje perindoprila i amlodipina jer se većina koristi od liječenja događa u ranim ili srednjim fazama KV kontinuuma.[8]

Od početka svibnja 2020. u Hrvatskoj je dostupna nova niskodozna fiksna kombinacija perindoprila i amlodipina (2,85 mg / 2,5 mg), indicirana za početak antihipertenzivnog liječenja.[14] Kao što navode smjernice Europskoga kardiološkog društva / Europskog društva za hipertenziju (ESC/ESH) za liječenje arterijske hipertenzije iz 2018. godine, koncept uvođenja liječenja kombinacijom dvaju lijekova u većine hipertenzivnih bolesnika vjerojatno će imati važan utjecaj na kliničku praksu te brzinu i kvalitetu kontrole vrijednosti AT-a.[15]

Kad dva lijeka nisu dovoljna za kontrolu arterijskog tlaka

Ispitivanja govore da će terapija kombinacijom dvaju lijekova kontrolirati AT u približno dvije trećine bolesnika. Za bolesnike čiji AT nije stavljen pod kontrolu terapijom kombinacijom dvaju lijekova, logična je opcija primjeniti kombinaciju triju lijekova: obično blokator reninsko-angiotenzinskog sustava, blokator kalcijevih kanala te diuretik.[15]

Kad kombinacija amlodipina i perindoprila nije dovoljna za postizanje kontrole AT-a, trojna kombinacija lijekova u jednoj tableti s dodatkom indapamida vrijedna je opcija liječenja.

on central aortic pressure. Both treatment approaches produced similar reductions in brachial BP, but the central aortic BP and central aortic pulse pressure were reduced significantly more with amlodipine/perindopril vs. the atenolol/diuretic regimen (24.3 and 23.0 mmHg, respectively, both p = 0.0001), which correlated with reductions in CV events or procedures.[1,13] These agents may have complimentary effects on endothelial function and vasodilation that improve CV outcomes that cannot be predicted only by changes in the brachial arterial BP.[13]

These findings suggest that amlodipine/perindopril therapy disrupts the pathophysiological continuum, slowing the progression of CVD in hypertensive patients.[1] The long-term beneficial effects of treatment with amlodipine/perindopril on mortality have been additionally confirmed by the results of the ASCOT Legacy study in which the participants from the original ASCOT study were followed for a median of 16 years.[1] In the participants from the non-lipid-lowering arm group (n = 3,975), there were fewer CV deaths among the patients assigned to amlodipine/perindopril-based treatment compared with atenolol/diuretic-based treatment (adjusted hazard ratio 0.79, 0.67-0.93, p = 0.0046).[1]

Perindopril and amlodipine are both able to slow the progression of CVD.[8] The preventive capability of both agents is extended over various stages of the CV continuum. Both counteract the disruption of myocardial oxygen supply and demand: perindopril by increasing the coronary reserve and maximizing the coronary blood flow, and amlodipine by decreasing coronary vascular resistance. Both are able to reduce left ventricular hypertrophy and myocardial ischemia.

Coronary thrombosis and myocardial infarction are inhibited by both perindopril and amlodipine.[8] A single pill combination (SPC) of perindopril/amlodipine offers a faster response, better BP reduction, BP control, and adherence than either of both agents in monotherapy. The combination is likely to be more effective on outcomes, even though it acts on the same number of the CV continuum stages as perindopril or amlodipine alone. In addition, early concomitant prescription of perindopril and amlodipine appears important, as most of the treatment benefits of both agents occur in the early or middle stages of the CV continuum.[8]

In the beginning of May, a novel low-dose SPC of perindopril and amlodipine (2.85 mg/2.5 mg) was launched in Croatia, indicated for the start of hypertension therapy.[14] 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.[15]

When two agents are not enough to control blood pressure

Studies suggest that a two-drug combination therapy will control BP in approximately two-thirds of patients. For patients whose BP is not controlled by a two-drug combination therapy, the logical option is to increase treatment to a three-drug combination therapy: usually a renin-angiotensin system blocker, a calcium channel blocker, and a diuretic.[15]

When the combination of amlodipine and perindopril is not enough for reaching BP control, a triple SPC with the addition

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 perindoprila 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 vrijednosti AT-a s pomoću prethodne kombinirane terapije prebačeni su na liječenje trojnom kombinacijom perindopril/amlodipin/indapamid (Co-Dalneva®; **tablica 1**). Mjesec dana nakon promjene terapije 47,7 % bolesnika postiglo je ciljnu razinu, a nakon 3 mjeseca razinu AT-a od <140/90 mm Hg postiglo je 93 % bolesnika. Do kraja ispitivanja svi su bolesnici postigli kontrolu AT-a. Pulsni tlak (PT), koji odražava elastičnost i prohodnost perifernih krvnih žila te funkcioniranje miokarda, smanjio se za 30,3 % (p < 0,001).

of indapamide is a valuable treatment option. The metabolically neutral diuretic indapamide itself exerts beneficial effects on target organs, as it reduces left ventricular hypertrophy and microalbuminuria, the risk for stroke, and total mortality. Furthermore, it has been shown that indapamide has no effect on lipid metabolism (triglycerides, LDL-cholesterol, and HDL-cholesterol) and on carbohydrate metabolism, making it a suitable choice for a wide variety of patients also when used in combinations.[16-19]

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[20] 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).

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	153±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±6.9	47.6±7.0	43±7.9

*compared to baseline values

DBP – diastolic BP, SBP – systolic BP, PBP – pulse blood pressure

Vrijednost PT-a >60 mm Hg (u starijih osoba) znak je supkliničkog oštećenja ciljnih organa. Postizanje normalne razine PT-a dokaz je organoprotektivnog djelovanja lijeka.

Vaskularni endotel neovisna je karika u regulaciji vaskularnog tonusa. Promjena u endotelnoj funkciji indirektno je procijenjena s pomoću upalnih markera i molekularno-bioloških markera neoangiogeneze, kao što su vaskularna endotelna adhezijska molekula i vaskularni endotelni faktor rasta. Koncentracija topljivog oblika vaskularnoga endotelnog faktora rasta (sVCAM-1) u perifernoj krvi raste samo kod patološke aktivacije endotela. Prema tome, na temelju promjene ekspresije sVCAM-1 može se procijeniti promjena u stanju endotela.[20]

Tablica 2 pokazuje promjene u upalnim markerima (CRP, IL-6, IL-10) nakon 6 mjeseci liječenja kombinacijom perindoprila/amlodipina/indapamida u jednoj tableti. Razine markera endotelne disfunkcije sVCAM-1 znatno su se smanjile (s 1063,5 ± 442,4 na 898,67 ± 433,5 ng/mL, p < 0,001). Također je postojao trend smanjenja VEGF-a.[20]

PBP > 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]

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

Znatno smanjenje 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 lijekova 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 perindoprila/indapamida/amlodipina također je poboljšala stanje vaskularnog endotela jer je znatno smanjila sVCAM-1.[18] Nadalje, također su zabilježene veća adherencija i bolja opća kvaliteta života tijekom terapije trojnom kombinacijom perindoprila/indapamida/amlodipina.[20]

Očekuju se dodatne informacije o djelovanju dvojnih i trojnih kombinacija perindoprila/amlodipina (Dalneva®) i perindoprila/indapamida/amlodipina (Co-Dalneva®) na smanjenje vrijendosti AT-a i vaskularno zdravlje iz međunarodnog, prospektivnog, intervencijskog ispitivanja PRECIOUS. Ispitivanje je provedeno u 7 zemalja – Hrvatskoj, Sloveniji, Srbiji, Mađarskoj, Poljskoj, Rusiji i Armeniji – ne samo sa svrhom procjene djelotvornosti i sigurnosti navedenih kombinacija lijekova 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 perindoprila/amlodipina i trojna kombinacija perindoprila/indapamida/amlodipina u jednoj tableti učinkovito smanjuju vrijednost AT-a, čime u kratkome vremenu dovode do viših stopa postignute kontrole AT-a, uz dobar sigurnosni profil i vrlo visoku razinu pridržavanja liječenja.[21]

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.[1,8] Doima se važnim rano propisivanje perindoprila i amlodipina jer se većina koristi od liječenja ovim lijekovima događa u ranim ili srednjim fazama KV kontinuuma.[8] Kombinacija obaju lijekova vjerojatno će imati veći učinak na ishode, a posebice ako je u obliku kombinacije lijekova u jednoj tableti.[8,15]

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.[18] Furthermore, increased patient adherence and improved overall quality of life were also observed during the therapy with the SPC of perindopril/indapamide/amlodipine.[20]

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 PRECIOUS. 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.[21]

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.[1,8] 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.[8] The combination of both is likely to be more effective on outcomes, especially in form of a SPC.[8,15]

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 perindoprila dostupnih u Republici Hrvatskoj.[22]

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, 21,23-28]

Krkini lijekovi na bazi perindoprila dosljedno su dokazali svoju učinkovitost i sigurnost u kliničkim ispitivanjima s oko 90,000 uključenih bolesnika.[20,21,28-34] Liječnici u Hrvatskoj sada mogu odabrati između 15 opcija, što omogućuje individualnu prilagodbu terapije u bolesnika s različitim potrebama.[22]

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.[15]

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.[22]

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.[15,20,21,23-28]

Krka's perindopril-based drugs have consistently demonstrated their effectiveness and safety in clinical studies with around 90,000 included patients.[20,21,28-34] Physicians in Croatia can now select among 15 alternatives enabling individualized therapy in patients with different needs.[22]

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