Stručni rad / Professional article

Kombinacijska terapija perindoprilom/amlodipinom — optimalna sinergija u liječenju arterijske hipertenzije i smanjenju kardiovaskularnog rizika

Combination therapy with perindopril / amlodipine — optimal synergy in the treatment of arterial hypertension and cardiovascular risk reduction

Josipa Josipović*, Dajana Katičić, Draško Pavlović
Klinički bolnički centar Sestre milosrnice, Zagreb, Hrvatska
University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

SAŽETAK: Arterijska hipertenzija je vodeći promjenjivi kardiovaskularni čimbenik rizika. U čak 75% bolesnika je potrebna kombinirana antihipertenzivna terapija za postizanje ciljnih vrijednosti arterijskog tlaka (AT). Kombiniranom terapijom postiže se veće snižavanje AT i brže postizanje ciljnih vrijednosti, a primjenom fiksne kombinacije pojednostavljuje se liječenje i poboljšava suradljivost bolesnika. Kombinacija ACE inhibitora i blokatora kalcijskih kanala, osim aditivnog učinka na sniženje vrijednosti AT, donosi dodatnu dobrobit na smanjenje ukupnog kardiovaskularnog rizika.

KLJUČNE RIJEČI: ACE inhibitori, blokatori kalcijskih kanala, arterijska hipertenzija, perindopril, amlodipin.

ABSTRACT: Arterial hypertension is the leading modifiable cardiovascular risk factor. In 75% of patients, the combination antihypertensive therapy is required to achieve target values of blood pressure (BP). The combination therapy leads to greater lowering of BP and faster achievement of target values, whereas the fixed combination simplifies the treatment and improves the patient compliance. The combination of ACE inhibitors and calcium channel blockers, in addition to an additive effect on lowering the value of BP, provides an additional benefit in reducing the overall cardiovascular risk.

KEYWORDS: ACE inhibitors, calcium channel blockers, hypertension, perindopril, amlodipine.

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Srčanožilne bolesti (SŽB) predstavljaju jedan od glavnih javnozdravstvenih problema u svijetu i vodeći su uzrok pobola i smrtnosti.[1] Arterijska hipertenzija (AH) je vodeći promjenjivi čimbenik kardiovaskularnog (KV) rizika s prevalencijom od 25%-35% odrasle populacije, do čak 60%-70% u dobi iznad 70 godina.[2] Rizik od kardiovaskularnog mortaliteta se udvostručuje sa svakim povišenjem arterijskog tlaka (AT) za 20/10 mmHg.[3] Povišeni AT glavni je čimbenik rizika od koronarne bolesti srca (KBS), zatajivanja srca, cerebrovaskularne bolesti, periferne arterijske bolesti, zatajenja bubrega i fibrilacije atrija.[4] Liječenje AH se preporuča odmah u bolesnika s hipertenzijom 3. stupnja, kao i u bolesnika s hipertenzijom 1. i 2. stupnja koji imaju visok ili vrlo visok ukupni rizik od SŽB.

Etiologija hipertenzije je u većini slučajeva multifaktorijalna što otežava, a često čini gotovo nemogućim postizanje kontrole AT djelujući na samo jedan presorni mehanizam. Djelovanje na jednu komponentu u pravilu nakon određenog vremena uzrokuje kompenzatorni odgovor koji smanjuje učinak terapije. Zbog toga je veličina sniženja AT ograničena

Cardiovascular diseases (CVD) are a major public health problem worldwide and the leading cause of morbidity and mortality.[1] Arterial hypertension (AH) is a leading modifiable factor of cardiovascular (CV) risk with a prevalence of 25%-35% of the adult population, up to 60%-70% at the age over 70.[2] The risk of cardiovascular mortality doubles with each elevation of blood pressure (BP) by 20/10 mmHg.[3] Elevated BP is a major risk factor for coronary artery disease (CAD), heart failure, cerebrovascular diseases, peripheral arterial diseases, kidney failure and atrial fibrillation.[4] AH treatment is recommended to be undertaken immediately in patients with grade 3 hypertension, as well as in hypertensive patients of grade 1 and 2 who have a high or very high overall CVD risk.

The etiology of hypertension is multifactorial in most cases, making it difficult and often almost impossible to achieve BP control by acting on only one pressor mechanism. The effect on one component principally causes a compensatory response after a certain time, that reduces the effect of the therapy. Therefore, the size of BP reduction is limited to all indi-

sa svim pojedinačnim skupinama antihipertenzivnih lijekova i prema rezultatima meta analize Law i sur iznosi oko 9,1/5,5 mmHg s minimalnim razlikama obzirom na pojedini razred antihipertenziva.[5]

Više kliničkih istraživanja (ALLHAT, HOT, LIFE) he pokazalo da većina bolesnika treba dva ili više antihipertenziva za postizanje ciljnih vrijednosti AT.[6-9]

Primjenu kombinirane antihipertenzivne terapije podržavaju i aktualne europske smjernice za liječenje AH prema kojima se liječenje može započeti kombinacijom lijekova kod bolesnika s visokim i vrlo visokim KV rizikom. Kombiniranom terapijom postiže se veće snižavanje AT i brže postizanje ciljnih vrijednosti, a primjenom fiksne kombinacije pojednostavljuje se liječenje i poboljšava suradljivost bolesnika.[10] Kombinacijska terapija povezana je s boljom podnošljivosti lijekova naročito kada se nuspojave vezane uz primjenu jednog lijeka neutraliziraju farmakološkim osobinama drugog lijeka. Naime, visoke doze monoterapije nose veći rizik nuspojava.

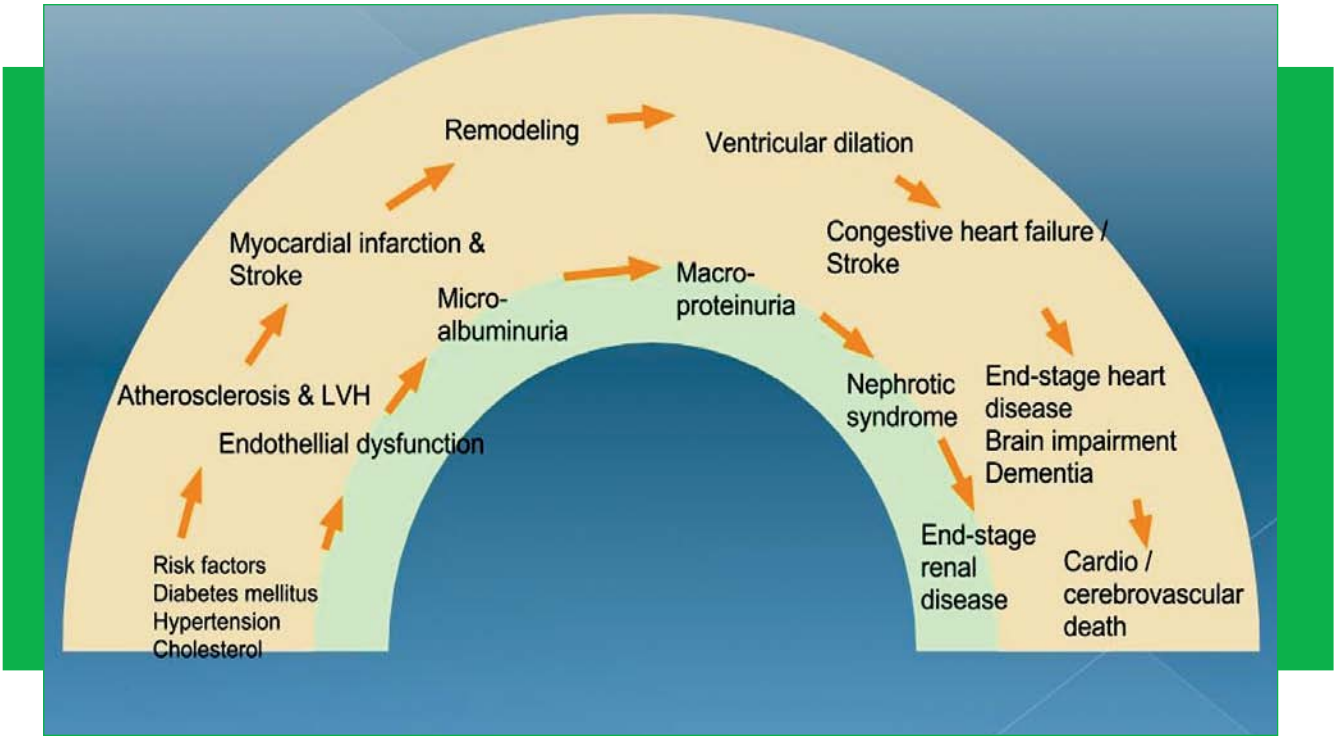
Sedam je glavnih razreda antihipertenzivnih lijekova i broj mogućih kombinacija je velik. Međutim, prema zadnjim smjernicama ESH/ESC iz 2013. i JNC 8 nekim kombinacijama se daje prednost zbog dokazanog sinergističkog učinka na smanjenje ukupnog KV rizika koji nadmašuje dobrobit samog sniženja AT.[10]

vidual classes of antihypertensive drugs and according to the results of the meta-analysis of Law et al it amounts to about 9.1/5.5 mm Hg with minimal differences considering an individual class of antihypertensive drugs.[5]

Large clinical trials (ALLHAT, HOT, LIFE) have shown that the most of the patients need two or more antihypertensive drugs to achieve target BP.[6-9]

The application of the combined antihypertensive therapy is also supported by current European guidelines for the treatment of AH according to which the treatment can begin with a combination of drugs in patients with a high and very high CV risk. The combination therapy leads to greater lowering of BP and faster achievement of target values, while the fixed combination simplifies the treatment and improves the patient compliance.[10] The combination therapy is associated with better tolerability of drugs, especially when the side-effects associated with the use of one drug are neutralized by pharmacological properties of the other drug. The high-doses of monotherapy carry a higher risk of side-effects.

There are seven major classes of antihypertensive drugs and there is a large number of possible combinations. However, according to the latest guidelines of ESH/ESC in year 2013 and JNC 8, some combinations are preferred for the proven synergistic effect on the reduction of the total CV risk outweighing the benefit of BP reduction.[10]



Adapted from: Am Heart J. 1991;121:1244-63.

Figure 1. *Renin-angiotensin-aldosterone system blockers and cardiovascular continuum.*

Mnoge kliničke studije (ADVANCE, ASCOT, EUROPA, PREAMI, PEP CHF, PROGRESS) su pokazale kardiovaskularni i renalni protektivni učinak ACE inhibitora. To se objašnjava protektivnim djelovanjem ACE inhibitora na funkciju endotela i proces ateroskleroze za koje se smatra da su osnovni patofiziološki mehanizmi u procesu tzv. kardiovaskularnog/kardiorenalnog kontinuuma. Koncept tzv. kardiovaskularnog ili kardiorenalnog kontinuuma temelji se na

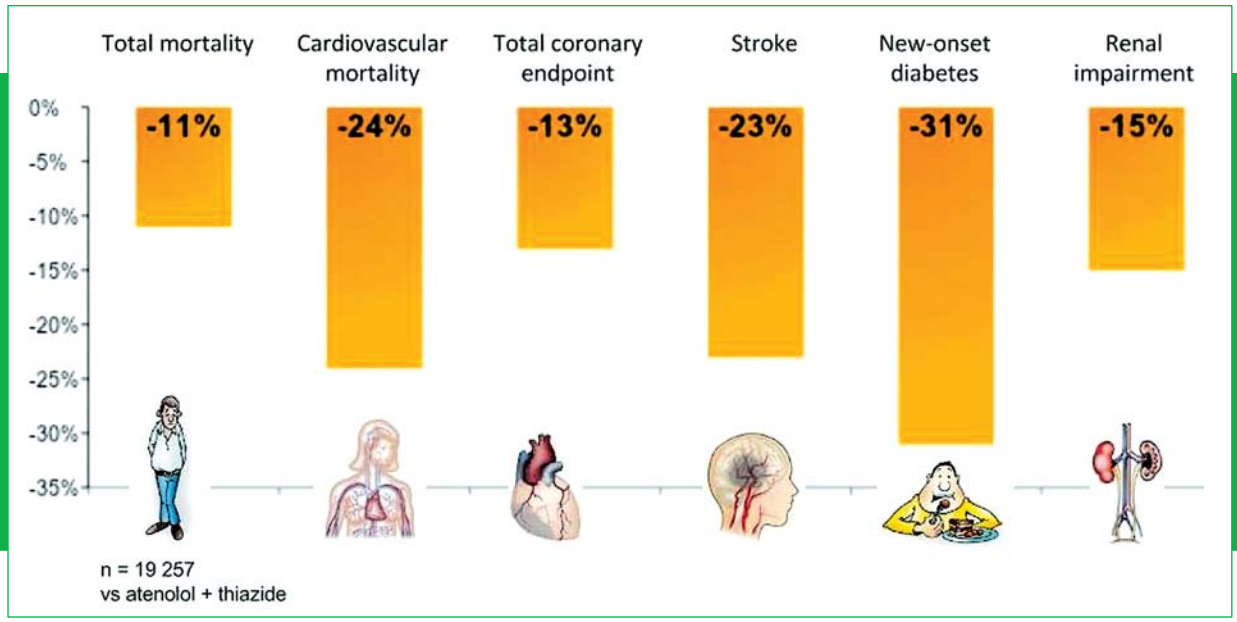
Many clinical trials (ADVANCE, ASCOT, EUROPA, PREAMI, PEP CHF, PROGRESS) showed cardiovascular and renal protective effect of ACE inhibitors. This explains the protective effect of ACE inhibitors on the endothelial function and atherosclerotic process that are considered to be the basic pathophysiologic mechanisms in the process so-called cardiovascular/cardiorenal continuum. The concept of the so-called cardiovascular or cardiorenal continuum is

spoznaji da progresija SŽB počinje već s postojanjem rizičnih čimbenika kao što su AH i dijabetes i vodi kroz KBS do ishemije miokarda (koja se može manifestirati kao angina pektoris, infarkt miokarda ili iznenadna srčana smrt), srčanog zatajivanja i terminalne faze srčane bolesti. Slični princip vrijedi i za nastanak kronične bubrežne bolesti, počevši od mikroalbuminurije kao jednog od najranijih znakova bubrežnog oštećenja, preko jasne proteinurije, sniženja filtracijske funkcije pa sve do terminalnog zatajenja bubrežne funkcije. Čini se da ateroskleroza i endotelna disfunkcija vode glavnu ulogu u ovom procesu. Kronična prekomjerna ekspresija tkivnog ACE dovodi do disbalansa u lokalnoj ekspresiji angiotenzina II/bradikinina što rezultira endotelnom disfunkcijom. ACE inhibitori reduciraju produkciju AT II koji ima glavnu ulogu u oštećenju ciljnih organa te tako smanjuju vazokonstrikciju, adhezivnost molekula, ekspresiju faktora rasta, smanjuju oksidativni stres i apoptozu stanica. Istovremena degradacija bradikinina u sklopu ACE inhibicije podiže razinu kinina što poboljšava vazodilataciju i antiapoptotičko djelovanje. To se najviše pokazalo u EUROPA studiji u kojoj su se određivali markeri endotelijalne funkcije uključujući eNOS, stopa apoptoze i razina vWF u bolesnika s KBS. Kod bolesnika s KBS su izmjerene značajno niže razine eNOS ekspresije i aktivnosti u odnosu na zdrave ispitanike, što se objašnjava prvenstveno prekomjernom tkivnom ekspresijom ACE. Nakon jednogodišnje terapije perindoprilom došlo je do porasta ekspresije eNOS kao i sniženja vWF koji je bazično bio viši kod bolesnika s KBS. Bitno je istaći da ovaj učinak perindoprila na normalizaciju omjera angiotenzina II/bradikinina, smanjenje upalnog procesa i time aptoptoze endotelnih stanica nije tzv. učinak klase ACE inhibitora i prvenstveno ovisi o tkivnom afinitetu lijeka, penetraciji lijeka u aterosklerotski plak i afinitetu za ciljni enzim.[11] Naime, perindopril spada u skupinu ACE inhibitora sa najvećom lipofilnošću i visokim afinitetom za tkivni ACE koji čini gotovo 90% od ukupne distribucije u tijelu i koji je bitan za dugotrajne učinke lijeka.[12] Pored toga, perindopril omogućava gotovo konstatnu 24-satnu kontrolu AT budući da ima T/P (engl. *trough-to-peak*) omjer 75-100% (to znači da će i nakon 24 sata osigurati sniženje 75-100% od maksimalne vrijednosti sniženja tlaka) te dugi poluživot (gotovo 30 sati).[13] Amlodipin je lijek treće generacije blokatora kalcijskih kanala (BKK). Osnovni mehanizam djelovanja jest smanjenje utoka kalcija na razini receptora za kalcij kao i voltažnih kalcijevih kanala u glatkomišićnoj stanici te posljedična vazodilatacija perifernih i koronarnih arterija i arteriola.[14] Tako djeluje i na stanice miokarda i time smanjuje kontrakciju miokarda, pa kod bolesnika sa anginom pektoris smanjuje ishemijsko oštećenje.[15] Prednosti amlodipina u odnosu na ranije generacije BKK su spori i postupni početak djelovanja što za posljedicu ima manje promjene vrijednosti AT, veću vaskularnu selektivnost (više antihipertenzivno, djelovanje, a manje na miokard) i dugotrajno djelovanje (24-satna kontrola AT). Nuspojave amlodipina su uglavnom blage i prolazne. Najčešće nuspojave su posljedica vazodilatacijskog učinka i ovisne su o dozi lijeka, u prvom redu periferni edemi, glavobolja, crvenilo i osjećaj vrućine.

Dodatak ACE inhibitora ili blokatora angiotenzinskih receptora skupini BKK značajno poboljšava toleranciju BKK zbog simpatikolitičkog učinka na renin-angiotenzin-aldosteron sustav (RAAS), kao i djelomičnog neutraliziranja perifernih edema. Naime, uzrok edema je arteriolarna dilatacija uzrokovana BKK s posljedičnim porastom kapilarnog tlaka, a blokatori RAAS svojom prvenstveno venodilatacijom neutraliziraju taj učinak. Pored toga, kombinacija ACE/BKK ima

based on the information that CVD progression begins with the presence of risk factors such as AH and diabetes and leads through CAD to myocardial ischemia (which can be reflected as angina pectoris, myocardial infarction or sudden cardiac death), heart failure and end-stage of the heart disease. A similar principle applies to the development of chronic kidney disease, starting with the microalbuminuria as one of the earliest signs of kidney damage, through clear proteinuria, reduction of the filtration function to the end-stage renal failure. Atherosclerosis and endothelial dysfunction play a main role in this process. Chronic overexpression of tissue ACE leads to imbalance in the local expression of angiotensin II/ bradikinin resulting in an endothelial dysfunction. ACE inhibitors reduce the production of AT II, which plays a major role in damaging target organs and thus reduce vasoconstriction, adhesion of molecules, expression of growth factors, reduce oxidative stress and cell apoptosis. The simultaneous degradation of bradikinin within the ACE inhibition raises the level of quinine which improves vasodilatation and antiapoptotic action. It was best presented in the EUROPA study in which the markers of endothelial function, including eNOS, the rate of apoptosis and vWF levels in patients with CHD were determined. In patients with CAD, significant lower levels of eNOS expression and activity were measured compared to healthy subjects, which is primarily explained by excessive tissue expression of ACE. After one year of the therapy with perindopril, we recorded an increase in eNOS expression and decrease in vWF which was basically higher in patients with CAD. It is important to emphasize that the effect of perindopril on the normalization of the ratio of angiotensin II/bradikinin, reduction of inflammatory process and thus endothelial cell apoptosis is not the so-called effect of the ACE inhibitor class and is primarily dependent on the drug tissue affinity, drug penetration into atherosclerotic plaque and affinity for the target enzyme.[11] Perindopril, namely, belongs to a group of ACE inhibitors with the highest lipophilicity and high affinity for the tissue ACE, which accounts for nearly 90% of the total distribution in the body and which is essential for the long-term effects of the drug.[12] In addition, perindopril allows almost constant 24-hour BP control since it has a through-to-peak ratio of 75-100% (this means that even after 24 hours it will provide a reduction of 75-100% of the maximum value of lowering the pressure) and long half-life (almost 30 hours).[13] Amlodipine is the drug of the third generation of calcium channel blockers (CCB). The main mechanism of action is the reduction of calcium influx at the calcium-sensing receptor level as well as voltage-dependent calcium channels in the smooth muscle cell and consequential vasodilatation of peripheral and coronary arteries and arterioles.[14] This is the way how it acts on the cells of the myocardium thereby reducing the myocardial contraction, and so in patients with angina pectoris it reduces ischemic impairment.[15] The benefits of amlodipine compared to earlier generations of CCB are a slow and gradual onset of action which results in minor changes to BP value, greater vascular selectivity (it has rather antihypertensive action, and less myocardial action) and long-term action (24-hour BP control). The side-effects of amlodipine are mainly mild and transitory. The most common side effects are the consequence of vasodilatation effect and are dependent on the dose of the drug, primarily peripheral edema, headache, flushing and feeling the heat.

The addition of ACE inhibitors or angiotensin receptor blockers to the CCB group significantly improves the tolerance of CBB due to sympatholytic effect on the renin-angiotensin-aldosterone system (RAAS) as well as the partial neutraliza-

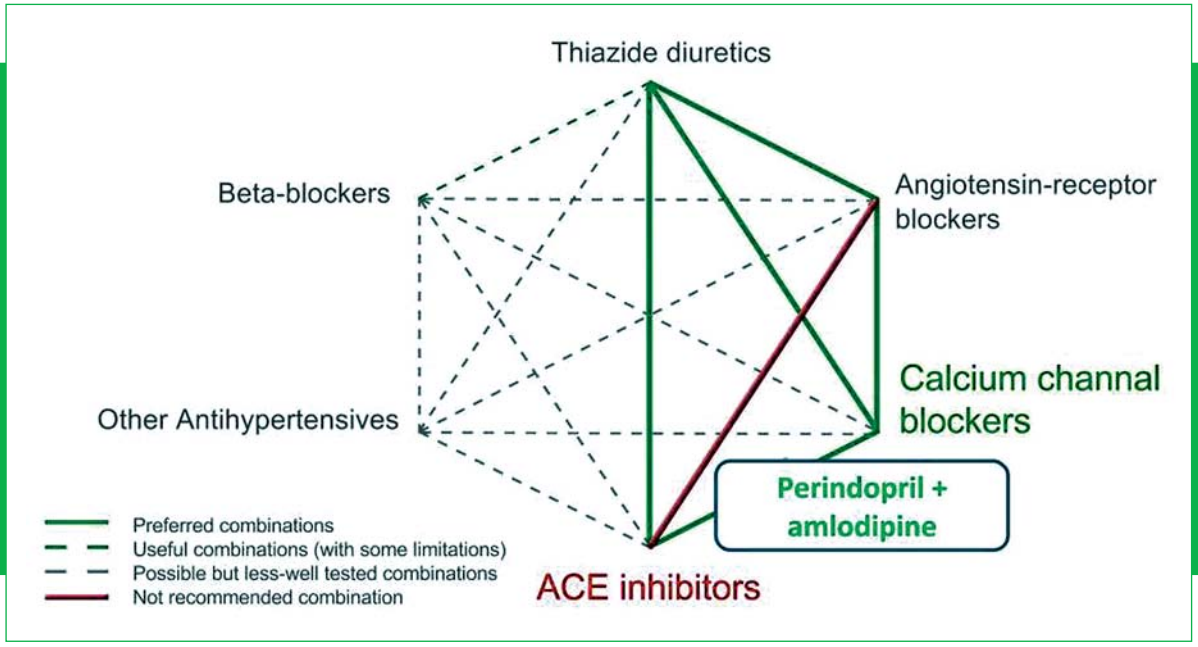


Adapted from Lancet. 2005;366:895-906.

Figure 2. *Combination of perindopril and amlodipine reduces all important CV events and total mortality in hypertensive high risk patients.*

i aditivno djelovanje na sniženje AT. ACE inhibitori induciraju dilataciju dvama različitim mehanizmima: povišenje bradikinina potiče up-regulaciju i ekspresiju aktivnosti eNOS s povećanom proizvodnjom i otpuštanjem NO iz endotela što promovira relaksaciju glatke muskulature putem GMP (gvanozin-monofosfat) — ovisnih kalcijevih kanala. Iz toga slijedi da BKK preveniraju kontrakciju dok ACE inhibitori promoviraju relaksaciju. Nadalje, inhibicijom ACE smanjuje se proizvodnja ATII koji također promovira utok kalcija.[16] Kombinacija perindoprila i amlodipina značajno snižava AT (srednja vrijednost sniženja tlaka čak za 42/23 mmHg) u svih bolesnika s AH neovisno o početnim vrijednostima tla-

tion of the peripheral edema. The cause of the edema is namely arteriolar dilation caused by CCB with a consequential increase in capillary pressure, whereas RAAS blockers neutralize this effect mainly by their venodilatation. In addition, the combination of ACE/CCB has additive effect on lowering BP. ACE inhibitors induce dilation by means of two different mechanisms: the elevation of bradikinin stimulates up-regulation and expression of eNOS activity with an increased production and release of NO from the endothelium which promotes the smooth muscle relaxation via GMP (guanosine monophosphate) — dependent calcium channels. Consequently CCB prevent the contraction, while ACE



Adapted from Eur Heart J. 2013:34;2159-219.

Figure 3. *2013 ESC Guidelines recommend the combination of ACE inhibitor and calcium channel blocker.*

ka, odnosno novodijagnosticiranih, nereguliranih hipertoničara na monoterapiji, nereguliranih hipertoničara na nekoj drugoj kombiniranoj terapiji.[17] U bolesnika s hipertenzijom trećeg stupnja postiže se dodatno sniženje AT (čak za 63/29 mmHg). Primjenom fiksne kombinacije perindoprila i amlodipina postiže se sniženje AT u 74% bolesnika već nakon tri mjeseca terapije. Pored samog sniženja AT, kombinacija perindoprila i amlodipina snižava i sve važne kardiovaskularne incidente i ukupnu smrtnost u hipertenzivnih visoko rizičnih bolesnika (ukupni mortalitet za 11%, kardiovaskularni za 24%, koronarna zbivanja za 13%, moždani udar za 23%, novonastali dijabetes za 31% i bubrežnu insuficijenciju za 15%).[18] Kombinacija perindoprila i amlodipina značajno smanjuje kardiovaskularnu smrtnost u bolesnika sa stabilnom KBS (ukupnu smrtnost za 46%, hospitalizaciju zbog kongestivnog zatajivanja srca za 54%, kardiovaskularni mortalitet za 41%, infarkt miokrda za 28% i zajednički primarni ishod u vidu KV mortaliteta, nefatalnog IM i uspješne resuscitacije srčanog aresta za 34%).18 Osim kod hipertoničara, kombinacija ova dva lijeka smanjuje sve važne kardiovaskularne incidente u bolesnika sa AH i pridruženim drugim dodatnim čimbenicima rizika (za 23% u pušača; za 20% u bolesnika s prethodnom vaskularnom bolesti, za 17% u bolesnika starijih od 60 godina i s oštećenom bubrežnom funkcijom; za 16% u bolesnika s metaboličkim sindromom; za 15% u pretilih i za 13% u bolesnika s tipom 2 šećerne bolesti).[19] Davanje ova dva lijeka u fiksnoj kombinaciji tzv. one-pill povezano je s boljom suradljivošću. ASCOT studija je dokazala da je kombinacija perindopril/amlodipin logična, dobro podnošljiva, isplativa i donosi prognostičku korist, odnosno značajno poboljšava kliničke ishode (kardiovaskularne smrti, infarkta miokarda i moždanog udara za 20%) u visokorizičnih pacijenata (prije svega dijabetičara i bolesnika s već razvijenom ishemijskom bolesti srca) u usporedbi s fiksnom kombinacijom ACE/diuretik.

Na kraju, važno je napomenuti da pojednostavljenje terapije u vidu fiksne kombinirane doze antihipertenziva je samo jedna od strategija za dugoročno održavanje postignutog sniženja AT. Naime, troškovi liječenja također utječu na suradljivost i ustrajnost bolesnika. Stoga, postojanje generičkih lijekova svakako omogućava dostupnost terapije većem broju bolesnika i doprinosi boljoj suradljivosti bolesnika.[20]

Na hrvatskom tržištu u portfelju Krke postoji kombinacija perindoprila i amlodipina pod nazivom Dalneva® u četiri različite doze (4/5 mg, 4/10 mg, 8/5 mg, 8/10 mg) koja je svakako jedna optimalna sinergistička kombinacija za liječenje hipertenzije i ukupnu kardiovaskularnu protekciju.

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Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, HR-10000 Zagreb, Croatia.

Phone: +385-1-3787-526

E-mail: josipa.josipovic01@gmail.com

inhibitors promote relaxation. In addition, due to ACE inhibition, the production of ATII is reduced, which also promotes calcium influx.[16] The combination of perindopril and amlodipine significantly reduces BP (median value of lowering the pressure even by 42/23 mmHg) in all patients with AH regardless of baseline pressure, or newly diagnosed, unregulated hypertensive patients on monotherapy, unregulated hypertensive patients receiving some other combination therapy.[17] Additional lowering of BP is achieved in the hypertensive patients with grade 3 (even by 63/29 mmHg). Lowering of BP is achieved by using the fixed combination of perindopril and amlodipine in 74% of patients already after three months of the therapy. In addition to lowering of BP, the combination of perindopril and amlodipine also lowers all important cardiovascular events and total mortality in high risk hypertensive patients (total mortality by 11%, cardiovascular mortality by 24%, coronary events by 13%, stroke by 23%, new-onset diabetes by 31% and renal failure by 15%).[18] The combination of perindopril and amlodipine significantly reduces cardiovascular mortality in patients with stable CAD (total mortality by 46%, hospitalization for congestive heart failure by 54%, cardiovascular mortality by 41%, myocardial infarction by 28% and the combined primary endpoint such as CV mortality, nonfatal MI and successful resuscitation of cardiac arrest by 34%).[19] The combination of the two drugs reduces all important cardiovascular events not only in hypertensive patients, but also patients with AH and other associated additional risk factors (by 23% in smokers; by 20% in patients with a history of vascular disease, by 17% in patients over 60 years of age and with impaired renal function; by 16% in patients with metabolic syndrome; by 15% in obese people and by 13% in patients with type 2 diabetes).[17] Administering the two drugs in a fixed combination, one-pill, is associated with better compliance. ASCOT study has demonstrated that the combination of perindopril/amlodipine is a logical, well-tolerated, cost-effective combination and provides the prognostic benefit, or significantly improves clinical outcomes (of cardiovascular death, myocardial infarction and stroke by 20%) in high-risk patients (especially in diabetics and patients with pre-developed ischemic heart disease), compared with a fixed combination of an ACE/diuretic.

Finally, it is important to note that the simplification of the therapy in the form of a fixed-dose combination of antihypertensive drugs is just one of the strategies for long-term maintenance of lowered BP. The costs of treatment are also the factor that can affect patient compliance and persistence. Therefore, the availability of generic drugs definitively makes the therapy affordable to a greater number of patients and contributes to better patient compliance.[20]

On the Croatian market, Krka holds in its portfolio a combination of perindopril and amlodipine entitled Dalneva® in four different doses (4/5 mg, 4/10 mg, 8/5 mg, 8/10 mg), which is certainly an optimal synergistic combination for the treatment of hypertension and overall cardiovascular protection.

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