Trostruka kombinacija, dvije bolesti i jedna tableta

Triple Combination, Two Diseases, and a Single Tablet

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SAŽETAK: Nedijagnosticirana ili nedovoljno kontrolirana arterijska hipertenzija (AH) vodeći je neovisni čimbenik kardiovaskularnog (KV) morbiditeta i mortaliteta. Osim toga, grupiranje višestrukih čimbenika rizika u bolesnika s AH-om dodatno pridonosi težini ove „tihe, ali ubojite" bolesti. Procjena ukupnoga KV rizika te liječenje svakoga mogućega rizičnog čimbenika od iznimne je važnosti u smanjenju ukupnoga KV rizika. Primjena fiksnih kombinacija lijekova s dobrim farmakodinamskim, farmakokinetskim, metaboličkim i sigurnosnim profilom dokazano pojednostavnjuje liječenje, a poboljšava ishode i adherenciju bolesnika koja mora biti cjeloživotna. Jedna od takvih kombinacija koja sadržava dugodjelujući ACE inhibitor perindopril, metabolički neutralan dugodjelujući diuretik iz skupine tijazida indapamid, te potentni statin rosuvastatin jest fiksna kombinacija Roxiper® – trostruka kombinacija za dvije bolesti u jednoj tableti.

SUMMARY: Undiagnosed or inadequately controlled arterial hypertension (AH) is the leading independent factor of cardiovascular (CV) morbidity and mortality. In addition, the grouping of multiple risk factors in patients with AH contributes to the severity of this "silent but deadly" disease. Assessment of the total CV risk and treatment of each possible risk factor are extremely important in reducing the total CV risk. The use of fixed-dose combinations of medicinal products with good pharmacodynamic, pharmacokinetic, metabolic, and safety profiles has been proven to simplify the treatment and improve the outcomes and adherence of patients, which must be lifelong. One such combination that contains a long-acting ACE inhibitor – perindopril, a metabolically neutral long-acting diuretic from the thiazide class – indapamide, and a potent statin – rosuvastatin, is the fixed-dose combination Roxiper® – a triple combination for two diseases in a single tablet.

KLJUČNE RIJEČI: arterijska hipertenzija, fiksna kombinacija, adherencija.

KEYWORDS: arterial hypertension, single-pill combination, valsartan, amlodipine, hydrochlorothiazide.

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Uvod

Arterijska hipertenzija (AH) jedan je od najvažnijih promjenjivih čimbenika rizika u nastanku mikrovaskularnih i makrovaskularnih oštećenja te njihovih posljedica. AH je važan javnozdravstveni problem koji posreduje pri nastanku koronarne bolesti srca, srčane insuficijencije, cerebrovaskularne bolesti i periferne arterijske bolesti. Čimbenik je rizika i razvoja kronične bubrežne bolesti te je jedan od glavnih uzroka mortaliteta i morbiditeta u svijetu. Svake godine kardiovaskularne (KV) bolesti uzrokuju 45 % svih smrtnih slučajeva u Europi, odnosno 3,9 milijuna smrti.[1] Barem 80 % KV događaja moglo bi biti spriječeno učinkovitom kontrolom glavnih rizičnih čimbenika.

Introduction

Arterial hypertension (AH) is one of the most important modifiable risk factors for the occurrence of micro-and macrovascular defects and their consequences. AH is an important public health concern involved in the development of coronary heart disease, heart insufficiency, cerebrovascular disease, and peripheral arterial disease. It is a risk factor and a development factor of chronic kidney disease (CKD) and is one of the main causes of mortality and morbidity in the world. Each year, cardiovascular (CV) diseases account for 45% of all deaths in Europe, which means that they cause 3.9 million deaths.[1] At least 80% of CV events are preventable by effectively controlling the main risk factors.

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Procjena ukupnoga kardiovaskularnoga rizika

Pri započinjanja liječenja AH-a potrebno je procijeniti ukupan kardiovaskularni rizik (KVR), komorbiditete i adherenciju svakoga pojedinog bolesnika. Također je veoma važno isključiti sekundarne uzroke AH-a i procijeniti stupanj oštećenja ciljnih organa. KVR možemo procijeniti s pomoću SCORE bodovnog sustava, a on izračunava 10-godišnji kumulativni rizik za prvi fatalni KV događaj na temelju dobi, spola, pušenja i vrijednosti sistoličkoga tlaka. Za izračunavanje KVR-a u Republici Hrvatskoj koristimo se SCORE tablicom za zemlje s visokim KVR-om.

Antihipertenzivno liječenje

Prva linija terapijskoga pristupa jest nefarmakološka intervencija koja uključuje promjene životnih navika u smislu smanjenja unosa soli i alkohola, smanjenja tjelesne mase, redovite tjelesne aktivnosti i prestanka pušenja. Ako se time ne postignu odgovarajući terapijski ciljevi, u većini slučajeva potrebno je uvesti antihipertenzivne i druge lijekove koji smanjuju KVR, ovisno o osobinama samog bolesnika, a pogotovo u bolesnika s visokim KVR-om. Prema Smjernicama za liječenje AH-a Europskoga kardiološkog društva / Europskog društva za hipertenziju (ESC/ESH) iz 2018. godine, preporučuje se, u većine bolesnika, započeti liječenje kombinacijom dvaju različitih lijekova u svrhu postizanja ciljnih vrijednosti arterijskoga tlaka (AT).[2] Monoterapija se preporučuje samo u bolesnika s AH-om 1. stupnja i niskim ukupnim KVR-om ili u vrlo starih i fragilnih bolesnika. S druge strane, primjenom dvaju različitih lijekova djeluje se na više patofizioloških mehanizama te se adekvatno obuhvaća 24-satnu djelotvornost, odnosno kontrole AH-a. S obzirom na manje doze u fiksnim kombinacijama dvaju ili više različitih lijekova, postiže se manja učestalost nuspojava uz učinkovito postizanje ciljnih vrijednosti AT-a. Preporučuje se uporaba lijekova iz skupine ACE inhibitora, blokatora angiotenzinskih receptora (ARB), tijazidskih i tijazidima sličnih diuretika, blokatora kalcijskih kanala i beta-blokatora. U odnosu prema drugim antihipertenzivima posebnu važnost imaju inhibitori enzima koji konvertira angiotenzin (ACE), a prije svega djeluju inhibicijom RAAS sustava. Hiperaktivacija renin-angiotenzin-aldosteronskog sustava (RAAS) povećava AT te posljedično uzrokuje mehaničko naprezanje i oštećenje krvnih žila, zbog čega se aktivira lokalni upalni odgovor. Na taj način RAAS povećava angiogenezu, vazokonstrikciju i broj slobodnih radikala, što pridonosi razvoju AH-a i ateroskleroze. Multicentrično, prospektivno, randomizirano kontrolirano ispitivanje *ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm*) uključivalo je 19 257 bolesnika s AH-om i drugim KV čimbenicima rizika, a pokazalo je kako je fiksna doza (u jednoj tableti) perindoprila i amlodipina učinkovita u snizivanju AT-a te u smanjenju oštećenja ciljnih organa.[3] Ova kombinacija dokazano prevenira veće KV događaje i mortalitet, a s boljim metaboličkim i sigurnosnim profilom u usporedbi s fiksnom dozom beta-blokatora i tijazida.

Arterijska hipertenzija i drugi komorbiditeti

Bolesnici s AH-om često imaju pridruženo oštećenje bubrega, a adekvatna kontrola smanjuje progresiju bubrežne bolesti

Total cardiovascular risk assessment

When starting treatment for AH, total cardiovascular risk (CVR), comorbidities, and adherence should be assessed in each individual patient. It is also very important to rule out any secondary causes of AH and to assess the degree of damage to target organs. CVR can be assessed using the SCORE scoring system, which calculates the 10-year cumulative risk for the first fatal cardiovascular event based on age, sex, smoking status, and systolic blood pressure. To calculate CVR in the Republic of Croatia, we use the SCORE chart for countries with high CVR.

Antihypertensive treatment

The first line of the therapeutic approach is a non-pharmacological intervention that includes lifestyle changes in the form of reducing salt and alcohol intake, reducing body weight, regular physical activity, and quitting smoking. If appropriate therapeutic goals are not achieved, in most cases it is necessary to introduce antihypertensives or other medicinal products that will reduce CVR, depending on individual patient characteristics, especially in patients with high CVR. According to the 2018 ESC/ESH Guidelines for the Management of AH (issued by the European Society of Cardiology and the European Society of Hypertension), in most patients it is recommended to start treatment with a combination of two different drugs in order to achieve target blood pressure (BP).[2] Monotherapy is recommended only in patients with grade 1 AH and low total CVR or in very old and fragile patients. On the other hand, the use of two different drugs acts on several pathophysiological mechanisms and adequately covers the 24-hour period of effectiveness, i.e., AH control. Due to the lower doses in fixed-dose combinations of two or more different medicinal products, lower frequency of side effects is achieved while effectively achieving target BP values. The recommended medications include those from the classes of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), thiazide and thiazide-like diuretics, calcium channel blockers, and beta blockers. In comparison to other antihypertensives, ACEi, which primarily act by inhibiting the RAAS system, are of particular importance. Hyperactivation of the renin-angiotensin-aldosterone system (RAAS) increases BP, consequently causing mechanical strain and damage to blood vessels, which triggers a local inflammatory response. In this way, RAAS increases angiogenesis, vasoconstriction, and the number of free radicals, which contributes to the development of AH and atherosclerosis. The multicentre, prospective, randomized controlled trial *Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm* (ASCOT-BPLA) included 19,257 patients with AH and other CV risk factors, and demonstrated that a fixed dose (a single pill) of perindopril and amlodipine effectively reduces both AP and target organ damage.[3] This combination has been proven to prevent major CV events and mortality, and has a better metabolic and safety profile than a fixed-dose combination of a beta-blocker and a thiazide.

Arterial hypertension and other comorbidities

Patients with AH often have associated kidney damage, and adequate control reduces the progression of kidney disease and mortality. Achieving target BP in patients with CKD can

i smrtnost. Postizanje ciljnih vrijednosti AT-a u bolesnika s kroničnom bubrežnom bolesti (KBB) može biti izazovno. Posebnu važnost ima promjena životnog stila, pogotovo u smislu restrikcije unosa soli, odnosno natrija. Prema KIDGO smjernicama, u bolesnika s KBB-om ciljne su vrijednosti sistoličkoga tlaka manje od 120 mmHg.[4] Kod prisutne albuminurije, koja je poznati pokazatelj oštećenja bubrežne funkcije, odnosno globalnoga mikrovaskularnog oštećenja, preporučuje se uporaba ACE inhibitora ili antagonista receptora angiotenzina II, na temelju njihova učinka redukcije albuminurije. Kombinacija inhibitora RAAS sustava i diuretika jedna je od preporučenih prvih linija liječenja.[2] Važno je naglasiti da se nakon početka liječenja lijekovima ACEi ili ARB snizuje sistemski tlak, smanjuje se vazokonstrikcija eferentnih arteriola bubrega te se, posljedično, smanjuje glomerularna filtracija. U praćenju bolesnika navedeni mehanizam možemo primijetiti kao povišenje razine serumskog kreatinina zbog smanjenja glomerularne filtracije. Važno je naglasiti da povišenje serumskog kreatinina u ovom kontekstu ne znači novo pogoršanje bubrežne funkcije, nego povoljan hemodinamički učinak lijeka na dugoročno smanjenje opterećenja glomerula i očuvanje rezidualne funkcije bubrega. Primjena RAAS inhibitora snizuje AT i smanjuje hiperfiltraciju u glomerulima, za koju je također dokazano da, ako je udružena s albuminurijom, povećava rizik od ukupne i KV smrtnosti, koji odgovara ili je čak veći od rizika opažena za bolesnike s KBB-om u stadiju 3. A ili 3. B bez albuminurije.[5] Primjena antihipertenziva nezaobilazna je stanica u zaštiti ostatne funkcije bubrega.[6] Povećan unos natrija s posljedičnim volumnim opterećenjem potrebno je liječiti diureticima ako to nije moguće postići promjenom životnih navika. U istraživanju *PIANIST* istražena je uloga fiksne kombinacije ACEi perindoprila, tijazidima sličnog diuretika indapamida i amlodipina u liječenju AH-a. Pokazalo se da je ta fiksna kombinacija sigurna te učinkovita u postizanju ciljnih vrijednosti AT-a.[7]

AH je usko povezana s drugim komorbiditetima, kao što je dislipidemija, a istraživanja su pokazala kako se ona često zanemaruje u hipertoničara, pogotovo u onih s visokim KVR-om[8]. U ovom je kontekstu potrebno spomenuti i bolesnike s obiteljskom hiperkolesterolemijom koja se često otkrije tek nakon prvog KV događaja, a u kojih su često potrebne i višestruke primjene kombiniranog liječenja kako bi se smanjio KVR i postigle niske ciljne vrijednost LDL-K.[9] Neovisno o prisutnosti obiteljske hiperkolesterolemije, već i umjereno povišenje vrijednosti LDL-K u bolesnika s AH-om znatno povećava njihov ukupni KVR, što je posebice važno ako se gleda na razini opće populacije. Dislipidemija ima važnu ulogu u patogenezi i progresiji funkcionalnih poremećaja vaskularnog endotela, srca i bubrega. Disfunkcija vaskularnog endotela koja se pojavljuje kao posljedica ovoga stanja pridonosi razvoju ateroskleroze te nastanku KV štetnih događaja. Osnovna terapija u liječenju dislipidemija jesu statini. Prema intenzitetu snizivanja LDL-a statine dijelimo u one visokog intenziteta, među koje svrstavamo atorvastatin i rosuvastatin, i one umjerena intenziteta. Kapacitet redukcije LDL-K u statina visokog intenziteta iznosi oko 50 %. Važno je naglasiti da je rizik od KV štetnih događaja u slučajevima istodobne pojavnosti AH-a i dislipidemije veći nego zbroj rizika pojedinačnih čimbenika. Uz učinak snizivanja lipida, statini imaju i dodatne pleotropne mehanizme u smislu poboljšanja funkcije endotela, smanjenja C-reaktivnog proteina i smanjenja agregacije trombocita. Nekoliko kliničkih istraživanja pokazalo je dobrobiti od dodatka statina an-

be challenging. Lifestyle changes are of particular importance, especially in terms of restricting salt (or sodium) intake. According to the KDIGO guidelines, target systolic pressure should be below 120 mmHg in patients with CKD.[4] In the presence of albuminuria, which is a known indicator of impaired renal function, or global microvascular damage, ACEi or angiotensin II receptor antagonists are recommended due to their effect of reducing albuminuria. The combination of RAAS inhibitors and diuretics is one of the recommended first lines of treatment.[2] It is important to emphasize that when an ACEi or ARB is first introduced, the systemic pressure drops, vasoconstriction of efferent kidney arterioles decreases, and, consequently, glomerular filtration decreases as well. In patient monitoring, this mechanism manifests as an increase in the level of serum creatinine due to a decrease in glomerular filtration. It is important to emphasize that the increase in serum creatinine in this context does not represent a new exacerbation of the renal function, but a favorable hemodynamic effect of the drug on the long-term reduction of glomerular load and preservation of residual kidney function. The use of RAAS inhibitors lowers arterial pressure and reduces glomerular hyperfiltration, which, if associated with albuminuria, has also been shown to increase the risk of total and CV mortality equivalent to or even greater than the risk observed for patients with stage 3A or stage 3B CKD without albuminuria.[5] The use of antihypertensive medicinal products is an unavoidable stop in protecting the remaining kidney function.[6] Increased sodium intake resulting in elevated volume load should be treated with diuretics if this cannot be managed through lifestyle changes. The PIANIST study investigated the role of a fixed-dose combination of the ACEi perindopril, the thiazide-like diuretic indapamide, and amlodipine in the treatment of AH. This fixed combination was demonstrated to be safe and effective in achieving target BP values.[7]

AH is closely related to other comorbidities, such as dyslipidemia, and research has shown that it is often neglected in hypertensive patients, especially in those with high CVR.[8] In this context, it is also necessary to mention patients with familial hypercholesterolemia, which is often detected only after their first CV event, and who require multiple uses of combination therapies to reduce their CVR and to achieve low target values of LDL-C.[9] Regardless of the presence of familial hypercholesterolemia, in patients with AH, even a moderate increase in LDL-C significantly increases their total CVR, which is particularly important when considered at the level of the general population. Dyslipidemia plays an important role in the pathogenesis and progression of functional disorders of the vascular endothelium, heart, and kidneys. Dysfunction of the vascular endothelium that occurs as a result of this condition contributes to the development of atherosclerosis and the occurrence of CV adverse events. Statins are essential drugs in the treatment of dyslipidemia. According to the intensity of their LDL-C lowering effect, statins are classified as high-intensity, including atorvastatin and rosuvastatin, and moderate-intensity drugs. The LDL-C reduction capacity of high-intensity statins is approximately 50%. It is important to emphasize that the risk of adverse CV events in cases of simultaneous occurrence of AH and dyslipidemia is greater than the sum of the risks of individual factors. In addition to their lipid-lowering effect, statins exhibit additional pleotropic mechanisms, such as improving endothelial function, reducing C-reactive protein levels, and reducing platelet

tihipertenzivnoj terapiji u bolesnika s umjerenim do visokim KVR-om. Terapija statinima povezana je s boljom kontrolom AT-a u takvih bolesnika, neovisno o intenzitetu antihipertenzivnih lijekova.[2,10] Čak i kada se ciljne vrijednosti AT-a postignu samo s antihipertenzivnom terapijom, dodatak statina smanjuje rizik od akutnog infarkta miokarda i cerebrovaskularne bolesti. Smjernice preporučuju početak terapije statinima visokog intenziteta. Ako se ne postigne ciljni LDL-K, u terapiju se preporučuje uvesti dodatne lijekove kao što su ezetimib, a potom i inhibitor proprotein konvertaze subtilizin/keksin tipa 9 (PCSK9i).

Imajući na umu važnost liječenja svih čimbenika rizika, s jedne, te potrebu pojednostavnjenja terapijskoga režima, s druge strane, kad god je moguće, potrebno je koristiti se fiksnim kombinacijama lijekova.

Adherencija

Za postizanje dobrih kliničkih ciljeva i učinaka koji su opisani u kontroliranim kliničkim istraživanjima potrebna je adherencija bolesnika. Nakon jedne godine od početka antihipertenzivne terapije samo se pola bolesnika pridržava propisanih mjera liječenja.[11] Loša je adherencija povezana s lošijim ishodom, a pokazalo se da je suradnja bolesnika to lošija što je veći broj propisanih tableta. Čini se da se bolesnici slabije pridržavaju propisane terapije u slučajevima kada imaju složene terapijske režime s više tableta koje se uzimaju više puta na dan. Ovaj je problem moguće premostiti propisivanjem tableta s fiksnim kombinacijama. Fiksna kombinacija uključuje tabletu koja sadržava dvije ili više aktivnih tvari. One pojednostavnjuju liječenje, bolesnici ih bolje prihvaćaju, a time se postiže bolja suradljivost bolesnika te, posljedično, adekvatna kontrola AT-a, kao i smanjenje KV događaja.[12] Trenutačno postoji niz odobrenih kombinacija aktivnih supstancija u jednoj tableti koje se rabe za liječenje AH-a i pridruženih bolesti. U eri individualizirane terapije poseban je naglasak na kliničkoj procjeni čimbenika rizika u bolesnika s AH-om, na temelju koje se odabire najprikladnija fiksna kombinacija lijekova za pojedinog bolesnika.[13]

Zaključak

Učinkovito snizivanje AT-a u bolesnika s AH-om ključno je za sniženje individualnog KVR-a. Kontrola hiperkolesterolemije, po principu „što niže, to bolje“, smanjuje incidenciju KV događaja. Kombinirana terapija temelj je liječenju AH-a u suvremeno doba. Perindopril, ACE inhibitor s povoljnim farmakokinetskim profilom te rosuvastatin, potentni inhibitor HMG-CoA reduktaze poznati su i dobro proučeni lijekovi koji se rabe za liječenje AH-a i dislipidemije. Također je poznato kako imaju angioprotektivni učinak. Indapamid, metabolički neutralan dugodjelujući diuretik, osim toga što potencira učinak ACEi perindoprila te smanjuje rizik od hiperkalemije, svojim pleotropnim vazodilatacijskim učinkom dodatno pridonosi antihipertenzivnom učinku u ovoj fiksnoj kombinaciji.

Kombinacija perindoprila, indapamida i rosuvastatina u jednoj tableti (Roxiper®) terapija je izbora koja zadovoljava sve suvremene kriterije za liječenje bolesnika s AH-om, dislipidemijom, početnim oštećenjem bubrežne funkcije te povećanim ukupnim KVR-om, i njome možemo smanjiti opterećenje brojem tableta koje prosječni hipertoničar mora svakodnevno uzimati.

aggregation. Several clinical studies have shown the benefits of adding statins to antihypertensive therapy in patients with moderate to high CVR. Statin therapy is associated with better AP control in these patients, regardless of the intensity of antihypertensive drugs.[2,10] Even in cases where AP targets can be achieved with antihypertensive therapy alone, the addition of statins reduces the risk of acute myocardial infarction and cerebrovascular disease. Guidelines recommend initiating treatment with high-intensity statins. If the target LDL-C is not reached, it is recommended to introduce additional medicinal products such as ezetimibe, and then also a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i).

Bearing in mind the importance of treating all risk factors on the one hand, and the need of simplifying treatment on the other hand, fixed-dose combinations should be used whenever possible.

Adherence

Patient adherence is necessary for achieving appropriate clinical goals and effects described in controlled clinical studies. One year after staring antihypertensive therapy, only half of the patients still adhere to the prescribed treatment.[11] Poor adherence is associated with a poorer outcome, and it has been shown that patient compliance drops as the number of pills prescribed increases. Patients appear to be less adherent when they have complex therapeutic regimens requiring them to take multiple tablets several times a day. This problem can be overcome by prescribing tablets with fixed-dose combinations. A fixed-dose combination includes a tablet containing two or more active substances. They simplify treatment and are better accepted by patients, thus achieving better patient compliance and, consequently, adequate control of BP and reduction of CV events.[12] Currently, there are a number of approved single-pill combinations of active substances used for the treatment of AH and its associated diseases. In the era of individualized therapy, there is special emphasis on the clinical assessment of risk factors in patients with AH, which is then used to select the most appropriate fixed-dose combination for each patient.[13]

Conclusion

Effective lowering of BP in patients with AH is essential for lowering individual CVR. Control of hypercholesterolemia according to the principle of "the lower the better" reduces the incidence of CV events. Combination therapy is the basis of the modern treatment of AH. Perindopril, an ACEi with a favorable pharmacokinetic profile, and rosuvastatin, a potent HMG-CoA reductase inhibitor, are well-known and well-studied medicinal products used to treat AH and dyslipidemia. They are also known to have an angioprotective effect. Indapamide, a metabolically neutral long-acting diuretic, in addition to potentiating the effect of the ACEi perindopril and reducing the risk of hyperkaliemia, contributes to the antihypertensive effect of this fixed-dose combination with its pleotropic vasodilation effect.

The combination of perindopril, indapamide, and rosuvastatin in a single tablet (Roxiper®) is the therapy of choice that meets all the modern criteria for the treatment of patients with AH, dyslipidemia, initial impairment of renal function, and increased total CVR, enabling us to reduce the burden of pills that the average hypertensive patient must take every day.

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