Što nam donosi fiksna trojna kombinacija u liječenju arterijske hipertenzije?

What does fixed-dose triple-combination treatment for arterial hypertension bring us?

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SAŽETAK: Prevalencija arterijske hipertenzije (AH) i dalje je visoka. AH je najvažniji promjenjivi kardiovaskularni (KV) čimbenik rizika te je znatno povezana s visokim morbiditetom i mortalitetom od KV i cerebrovaskularnih (CV) bolesti. Stoga je AH velik javnozdravstveni problem. Ona je multifaktorijalna te je pristup njezinu liječenju zasnovan na kombiniranoj terapiji. Kombinirana se terapija sastoji od dvaju ili više antihipertenziva različitih skupina, različita mehanizma djelovanja, čime se brže postižu ciljne vrijednosti arterijskoga tlaka (AT). Prema smjernicama za liječenje arterijske hipertenzije koje su izdali Europsko društvo za hipertenziju (ESH) i Europsko kardiološko društvo (ESC), preporuka je da se kombinirana terapija može uvesti već u 1. stupnju bolesti, kao prva crta liječenja u slučaju visokog KV rizika i komorbiditeta, ili u slučaju neuspješnog liječenja jednim lijekom. Nažalost, uzimanjem više tableta tijekom dana smanjuje se adherentnost u liječenju. Svrha je suvremenog liječenja AH-a da se fiksnim kombinacijama antihipertenziva komplementarnog i sinergističkog djelovanja, postigne što učinkovitije liječenje AH-a. Arterijski tlak se mnogo bolje kontrolira već manjim dozama djelotvornih komponenti u kombinaciji, a time se smanjuje i incidencija nuspojava. Uzimanjem terapije jednom na dan, koja je djelotvorna i ne opterećuje bolesnika, znatno se povećava adherentnost u liječenju. Krajnji cilj ovakvoga uspješnog liječenja AH-a jest smanjenje morbiditeta i mortaliteta od KV i CV bolesti. Prema smjernicama ESH/ESC-a za liječenje hipertenzije, optimalna je kombinacija antihipertenziva triju skupina: inhibitori renin-angitenzin-aldosteronskog sustava, antagonisti kalcijevih kanala i diuretici.

SUMMARY: The prevalence of arterial hypertension (AH) is still high. Hypertension is the most important changeable cardiovascular (CV) risk factor and is significantly associated with high morbidity and mortality from cardiovascular and cerebrovascular (CBV) diseases. AH thus represents a significant healthcare problem. It is multifactorial, and the treatment approach is based on combination treatment. Combination treatment consist of two or more antihypertensives of different groups with different mechanisms, which results in faster achievement of target blood pressure (BP) values. According to the guidelines for the treatment of arterial hypertension published by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), it is recommended to introduce the combination therapy already in the first stage of the disease as the first line of treatment in case of high CV risk and comorbidity or in case of failed treatment with a single medication. Unfortunately, prescribing multiple tablets to be taken during the day reduces treatment adherence. The goal of modern AH treatment is to use fixed-dose combinations of antihypertensives with complementary and synergistic effects in order to achieve the most effective treatment. Management of BP is significantly improved even at smaller doses of the active components in the combination, which also reduces the incidence of side-effects. Receiving a treatment which is effective, does not burden the patient, and is taken once per day significantly increases patient adherence. The ultimate goal of such successful treatment of AH is the reduction of CV and CBV morbidity and mortality. According to the ESH/ESC guidelines for the treatment of hypertension, the optimal combination is that of three groups of antihypertensives: renin-angiotensin-aldosterone system inhibitors, calcium channel antagonists, and diuretics.

KLJUČNE RIJEČI: arterijska hipertenzija, fiksne kombinacije antihipertenziva, adherentnost.

KEYWORDS: arterial hypertension, fixed antihypertensive combinations, adherence.

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Uvod

Arterijska hipertenzija (AH) glavni je promjenjivi rizični čimbenik kardiovaskularnog (KV) i cerebrovaskularnog (CV) morbiditeta i mortaliteta. Jedan je od najvećih javnozdravstvenih problema (64 milijuna DALY – *disability adjusted life years*; 4,4%)[1]. Osim za KV i CV bolesti, AH je čimbenik rizika i razvoja kroničnih bubrežnih bolesti[2]. Prema studiji EH-UH, prevalencija hipertenzije u Hrvatskoj je 37,5%. Pedeset devet posto hipertoničara uzima antihipertenzivnu terapiju, a samo 19,4 % njih ima dobru kontrolu arterijskog tlaka[1]. Američko kardiološko društvo predvidjelo je da će do 2030. godine godišnji ekonomski trošak zbog KV bolesti uvjetovanih hipertenzijom porasti na oko 200 milijardi američkih dolara[3,4]. Unatoč sve većemu broju antihipertenzivnih lijekova i njihovoj dostupnosti, kontrola liječenih hipertoničara i dalje je relativno mala. U većini zemalja oko polovice hipertoničara, koji su pod terapijom, i dalje nema arterijski tlak (AT) pod nadzorom[5].

Važnost kontrole arterijskoga tlaka

Mnoge su kliničke studije i metaanalize dokazale da se boljom kontrolom arterijskoga tlaka (AT) reduciraju KV i CV morbiditet i mortalitet[6,7]. U kliničkim studijama VALUE, ACCOMPLISH i Syst-Eur dokazano je da rana dijagnoza i liječenje AH-a dovode do redukcije infarkta miokarda, moždanog udara, morbiditeta i mortaliteta od KV-a[3,8-10]. Pedesetak posto hipertoničara treba dva ili više antihipertenziva, a barem 25 % njih treba trojnu kombinaciju lijekova kako bi se postigle ciljne vrijednosti AT-a[3,11]. ALLHAT, INVEST, SCOPE, HOT, MDRD, AASK primjeri su kliničkih studija koje dokazuju da je u većine bolesnika nužna kombinirana antihipertenzivna terapija[3]. Slijedom toga, smjernice Europskoga društva za hipertenziju (ESH) i Europskoga kardiološkoga društva (ESC) za liječenje AH-a godine 2007. prvi put su uvrstile kombinaciju antihipertenziva u prvu crtu liječenja pri izoliranoj sistoličkoj AH, kod brzo progresivne AH, u bolesnika s AT-om <140/90 mmHg u svrhu prevencije oštećenja ciljnih organa (dijabetičari, kronična parenhimna bubrežna bolest)[11,12]. Prema zadnjim ESH/ESC smjernicama iz 2013. godine, izbor liječenja AH-a ovisi o visini AT-a, procijenjenom KV riziku, komorbiditetima, oštećenju ciljnih organa i dobi pa se liječenje može započeti jednim antihipertenzivom ili kombinacijom dvaju njih[13].

Najučestaliji je 1. stupanj AH-a. Približno 2/3 koronarnih smrti povezano s hipertenzijom pojavljuje se u bolesnika s 1. stupnjem AH-a[14]. Upravo ta skupina bolesnika čini velik javnozdravstveni problem. To je potvrdila studija *MRFIT* u kojoj je praćeno 122 086 hipertoničara. Tijekom 15 godina praćenja 6293 bolesnika umrla su zbog koronarne bolesti srca[14]. Već u 1. stupnju AH-a i prehipertenziji pojavljuju se oštećenja ciljnih organa, kardijalno remodeliranje, pad udarnog volumena, ubrzanje frekvencije srca. Stoga je važno pravodobno liječenje AH-a i što ranije postizanje ciljnih vrijednosti AT-a[14]. U toj, ranoj fazi bolesti većina se bolesnika osjeća dobro, nema subjektivnih tegoba, ne smatraju se bolesnima i često ih je teško uvjeriti u nužnost liječenja[14]. Smjernice ESH/ESC preporučuju kombinirano liječenje kod AH-a 1. stupnja s visokim KV- rizikom od KV-a, AH-a 2. i 3. stupnja[13]. Ovakav oblik liječenja ima višestruke prednosti: ima manje nuspojava, zbog čega se bolje podnosi, skraćuje se vrijeme traženja učinkovite terapije kod visokih vrijednosti AT-a, a fiksne kombinacije pojednostavnjuju način liječenja (uzimanje jednom na dan) i obično imaju nižu cijenu od pojedinačnih komponenti lijekova. Time se po-

Introduction

Arterial hypertension (AH) is the most important changeable risk factor for cardiovascular (CV) and cerebrovascular (CBV) morbidity and mortality. It is one of the most significant public health problems (64 million disability adjusted life years (DALY); 4.4%)[1]. In addition to CV and CBV diseases, AH is also a risk factor for the development of chronic kidney diseases[2]. According to the EH-UH study, the prevalence of AH in Croatia is 37.5%. 59% of hypertensive patients receive antihypertensive therapy, and only 19.4% achieve good blood pressure (BP) management[1]. The American Heart Association has estimated that the annual economic cost of CV diseases conditioned by AH will grow to approximately 200 billion US dollars by 2030[3,4]. Despite the growing number of antihypertensive drugs and their availability, AH control for treated patients is still relatively poor. In most countries, about half of such patients who receive treatment still do not achieve BP control[5].

The significance of blood pressure control

Many clinical studies and meta-analyses have shown that better BP control reduces CV and CVB morbidity and mortality[6,7]. The clinical studies VALUE, ACCOMPLISH, and Syst-Eur have demonstrated that early diagnosis and treatment of AH lead to a reduction in the incidence of myocardial infarction, stroke, and CV morbidity and mortality[3,8-10]. Approximately 50% of hypertensive patients require 2 or more antihypertensives, and at least 25% require a triple combination of drugs to achieve target BP values[3,11]. ALLHAT, INVEST, SCOPE, HOT, MDRD, and AASK are examples of clinical trials demonstrating that combined antihypertensive therapy is necessary in most patients[3]. Consequently, the 2007 guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) for AH treatment were the first time treatment with antihypertensive combinations was included in the first line of treatment for isolated systolic hypertension, rapidly progressive hypertension, and for patients with BP <140/90 mmHg, with the goal of preventing damage to target organs (diabetics, chronic parenchymal renal disease)[11,12]. According to the latest ESH/ESC guidelines from 2013, the treatment of choice for AH depends on BP values, estimated CV risk, comorbidities, damage to target organs, and age; treatment can be started with one or with a combination of 2 antihypertensives[13].

The first stage of AH is the most common. Approximately 2/3 coronary deaths associated with hypertension happen in patients with stage 1 AH[14]. It is this group of patients that represents a significant public health issue. This was confirmed by the MRFIT study, which followed 122 086 hypertonic patients. During 15 years of follow-up, 6 293 patients died due to coronary heart disease[14]. Damage to target organs, cardiac remodeling, reduced stroke volume, and elevated heart frequency can occur even in stage 1 AH and in pre-hypertension. Timely AH treatment and the earliest possible achievement of target BP values is thus of the utmost importance[14]. In this early stage of the disease, most patients feel well, do not report subjective difficulties, do not consider themselves sick, and are often hard to convince of the necessity of treatment[14]. The ESH/ESC guidelines recommend combined treatment in stage 1 AH in cases of high CV risk and in stage 2 and 3 AH[13]. This type of treatment offers multiple advantages: it has less side-effects and is thus better tolerated, the time searching for effective treatment is reduced for high BP values, and fixed

boljšava adherentnost bolesnika u uzimanju terapije, što dovodi do brže i bolje kontrole AT-a[12,15]. Adherentnost u uzimanju terapije veoma je važna u liječenju. Na nju utječe niz čimbenika: broj tableta koje se uzimaju tijekom dana, zaboravljivost, pojava nuspojava, suradnja s liječnikom. Prema nekim metaanalizama mnogo je bolja adherentnost u liječenju postignuta uzimanjem fiksnih doza antihipertenziva s obzirom na slobodne kombinacije pojedinih antihipertenziva[3]. Bolja adherentnost dovodi do bolje kontrole AT-a, smanjenja morbiditeta od KV-a i CV-a, smanjuje se stopa bolovanja i hospitalizacija zbog KV i CV bolesti, a time se smanjuje i ekonomski trošak[3].

Racionalni pristup kombiniranoj antihipertenzivnoj terapiji znači izbor lijekova koji imaju komplementaran, ali različit mehanizam djelovanja. Prema ESH/ESC smjernicama za liječenje AH-a najveća se prednost daje kombinaciji inhibitora renin-angitenzin-aldosteronskog sustava (RAAS), diuretika i antagonista kalcijevih kanala[13].

Studija ACCOMPLISH dokazala je učinkovitost liječenja fiksnom kombinacijom dvaju antihipertenziva (amlodipina – antagonist kalcijskih kanala i benazeprila – ACE inhibitor) i njihovu superiornost s obzirom na kombinaciju benazeprila i hidroklortijazida u hipertoničara s visokim KV rizikom[10,15]. U studiji ADVANCE bolesnici s dijabetesom tipa 2 koji su uzimali fiksnu kombinaciju perindoprila (ACE inhibitor) i indapamida (diuretik), imali su redukciju KV događaja od 18 % i bubrežnih događaja od 21 %[15,16].

Važnost kombinirane terapije

Kombinirana terapija uključuje dvije vrste liječenja: propisivanje različitih lijekova odvojeno ili fiksnih kombinacija različitih lijekova u jednoj tableti. Uzimanje fiksne kombinacije pojednostavnjuje režim liječenja (većinom jednom na dan), što je osobito važno u bolesnika koji zbog komorbiditeta uzimaju više lijekova i u starijih bolesnika. Prema Smjernicama ESH/ESC[13], kombinirano liječenje treba zadovoljavati sljedeće uvjete:

- komplementaran mehanizam djelovanja
- antihipertenzivni učinak djelovanja treba biti veći od svake pojedinačne komponente kombinacije
- kombinacija treba imati bolju podnošljivost
- komplementaran mehanizam djelovanja komponenti može umanjiti njihove pojedinačne nuspojave.

Liječenje kombinacijama dovodi do većega smanjenja AT-a i bržeg postizanja ciljnog AT-a, a smanjuje se rizik od KV događaja i mortaliteta. Fiksna kombinacija smanjuje broj tableta u dnevnoj terapiji, poboljšava suradljivost bolesnika i razinu kontrole AT-a[13].

Osim aditivnog učinka, treba postići i učinkovitije liječenje nižim dozama pojedinih komponenata lijeka u kombinaciji, brže postizanje ciljnog AT-a te bolju podnošljivost (smanjenje incidencije nuspojava). Poželjne kombinacije trebaju imati komplementaran i sinergistički učinak.

ACE inhibitori imaju protektivan učinak na funkciju endotela i proces ateroskleroze, čime postižu renalnu i KV protekciju (kliničke studije ADVANCE, ASCOT, EUROPA, PREAMI, PEPCHF, PROGRESS, HOPE), smanjuju oštećenje ciljnih organa, kao i morbiditet i mortalitet[17,18]. U EUROPA studiji nakon godinu dana uzimanja perindoprila uočeni su smanjenje upalnih procesa, apoptoza endotelnih stanica te normaliza-

combinations simplify the treatment (intake once per day) and usually have a lower price than the individual components. This increases patient adherence to treatment, which leads to faster and better BP control[12,15]. Treatment adherence is very important in AH. It is influenced by a number of factors: the number of tablets to be taken per day, forgetfulness, the appearance of side-effects, and cooperation with the physician. According to some meta-analyses, significantly better adherence is achieved by prescribing fixed doses of antihypertensives than by free combinations of individual antihypertensives[3]. Better adherence leads to better BP control, reduced CV and CVB morbidity, reduced sick days and hospitalization for CV and CVB, and consequently a reduced economic burden[3].

The rational approach to combined antihypertensive therapy entails choosing drugs that have a complementary, but different mechanism of action. According to ESH/ESC guidelines for the treatment of AH, the highest recommendation goes to the combination of renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics, and calcium channel antagonists[13].

The ACCOMPLISH study demonstrated the effectiveness of treatment with fixed-dose combinations of two antihypertensives (amlodipine – a calcium channel antagonist –and benazepril – an ACE inhibitor) and their superiority in comparison with the combination of benazepril and hydrochlorothiazide in hypertensive patients with high cardiovascular risk[10,15]. In the ADVANCE study, patients with type 2 diabetes receiving a fixed dose of perindopril (ACE inhibitor) and indapamide (diuretic) had an 18% reduction in CV events and a 21% reduction in renal events[15,16].

The significance of combined therapy

Combined therapy comprises two types of treatment: prescribing different medications separately or prescribing fixed combinations of different drugs in a single tablet. Taking a fixed combination simplifies the treatment regimen (usually once per day), which is especially important in elderly patients and in patients taking multiple medications due to comorbidity. According to the ESH/ESC[13] guidelines, combined treatment should satisfy the following conditions:

- Complementary mechanisms of action.
- The antihypertensive effect should be larger than that of each component individually.
- The combination should have better tolerability.
- The complementary mechanisms of action can reduce the side-effects of the individual drugs.

Treatment with drug combinations leads to greater BP reduction and more rapid achievement of target BP values and reduces the risk of CV events and mortality. Fixed-dose combinations reduce the number of tablets in daily treatment and improve patient compliance as well as the level of BP control[13].

In addition to the additive effect, combination treatment should also achieve more effective treatment with lower doses of the individual component drugs, more rapidly achieve target BP, and provide better tolerability (reduced incidence of side-effects). Desirable combinations should have a complementary and synergistic effect.

ACE inhibitors have a protective effect on endothelial function and the atherosclerosis process which achieves renal and CV protection (clinical trials ADVANCE, ASCOT, EUROPA, PREAMI, PEPCHF, PROGRESS, HOPE), reduce damage to target organs, and reduce morbidity and mortality[18]. In the EUROPA study, after a year of receiving perindopril, there was a reduction in in-

cija omjera bradikinina/angiotenzina II. Perindopril ima visoku lipofilnost, visok afinitet za tkivni ACE, a *trough-to-peak* omjer mu je 75 – 100 %[18]. Stoga perindopril osigurava 24-satnu kontrolu AT-a, odgađa progresiju ateroskleroze, obnavlja endotelnu disfunkciju, djeluje antitrombotski i protuupalno[19]. Perindopril time pridonosi boljemu liječenju hipertoničara i u KV bolesnika.

Antagonisti kalcijevih kanala heterogena su skupina antihipertenziva. Najpropisivaniji je amlodipin koji pripada skupini dihidropiridina. Smanjenjem utoka kalcija u stanice dolazi do vazodilatacije perifernih i koronarnih arterija i arteriola. Ne postoji veći negativni inotropni učinak i ne utječe na atrioventrikularnu kondukciju. Ima antiaterosklerotska i antioksidativna svojstva te dugotrajan antihipertenzivni učinak[18,20].

Kombinacija perindoprila i amlodipina ispitivana je u studiji ASCOT te su rezultati pokazali da je ova kombinacija dobro podnošljiva, znatno snizuje AT i reducira KV događaje u usporedbi s fiksnom kombinacijom beta-blokatora i tijazida[21].

Diuretici i danas zauzimaju ravnopravno mjesto među ostalim skupinama antihipertenziva. Najčešće se u liječenju AH-a rabe tijazidski diuretici, većinom u kombinaciji s drugim skupinama antihipertenziva. Osobito se preporučuju u liječenju starijih bolesnika s izoliranom sistoličkom hipertenzijom i AH-om s dekompenzacijom srca[22]. Oni pospješuju filtraciju, apsorpciju i sekreciju elektrolita u bubrezima i djeluju vazodilatacijski. Među njima se ističe indapamid zbog niza prednosti: uz navedene učinke, inhibira kalcij u stijenci krvnih žila (vazodilatacija i smanjenje perifernog otpora), što dodatno snizuje AT[22]. On je metabolički neutralan, djeluje kardioprotektivno, smanjuje ukupni mortalitet, pruža 24-satnu kontrolu AT-a i ima nisku incidenciju nuspojava[23-25]. U kliničkoj studiji PROGRESS kombinacija indapamida i perindoprila smanjila je za 43 % rizik od moždanog udara u usporedbi s placebo skupinom[26]. Njihova kombinacija kao početna terapija AH-a smanjuje KV i CV ishode u usporedbi s monoterapijom[27].

Osnova suvremenog liječenja AH-a jest kombinacija antihipertenziva. Svaki četvrti bolesnik u svrhu kontrole AT-a prima 3 antihipertenziva[13]. Međutim, uzimanje više tableta na dan uvjetuje slabiju adherentnost bolesnika prema liječenju. Fiksnim kombinacijama antihipertenziva postiže se odlična adherentnost u liječenju zbog redukcije količine tableta, bolje podnošljivosti i bolje učinkovitosti, što sve motivira bolesnika u liječenju. Prethodno navedeni perindopril, amlodipin i indapamid primjer su lijekova čija fiksna kombinacija ima odličnu farmakodinamiku zbog različitih, ali komplementarnih mehanizama djelovanja, a sinergistički učinak na AT prisutan je tijekom 24 sata svih triju komponenata u kombinaciji. Ova, fiksna kombinacija ima i odličnu podnošljivost: perindopril smanjuje edeme koje može uzrokovati amlodipin; amlodipin smanjuje incidenciju kašlja uzrokovanu perindoprilom; indapamid ima povoljne učinke na metaboličke parametre (glukoza, lipidi). Ova fiksna trojna kombinacija antihipertenziva svoju izvrsnu djelotvornost i sigurnost potvrdila je u prospektivnoj, opservacijskoj, „open label" kliničkoj studiji PETRA (**slika 1**)[28]. Tijekom 3 mjeseca praćen je učinak kontrole AT-a u 11 209 hipertoničara obaju spolova koji su jednom na dan primali fiksnu trojnu kombinaciju perindopril/indapamid/amlodipin. Doza je prilagođivana tlaku (AT je mjeren ambulantno, u kućnim uvjetima i 24-satnim kontinuiranim mjerenjem). Prije uvođenja te kombinacije bolesnici su bili na dvojnoj kombiniranoj terapiji. Kao sekundarni ishodi liječenja praćeni su sigurnost, podnošljivost i laboratorijski parametri.

flammatory processes, endothelial cell apoptosis, and a normalization in the bradykinin/angiotensin II ratio. Perindopril has a high lipophilicity, high affinity for tissue ACE, and a trough-to-peak ratio of 75-100%[18]. Consequently, perindopril guarantees 24-hour BP control, delays progression of atherosclerosis, alleviates endothelial dysfunction, and has an antithrombotic and anti-inflammatory effect[19]. Perindopril thus contributes to better treatment for hypertensive and CV patients.

Calcium channel antagonists are a heterogeneous group of antihypertensives. The most commonly prescribed is amlodipine, which belongs to the dihydropyridine group. Reducing calcium flow to cells leads to vasodilatation of the peripheral and coronary arteries and arterioles. It does not have a large negative inotropic effect and does not affect atrioventricular conduction. It has anti-atherosclerotic and anti-oxidative properties as well as a long-lasting antihypertensive effect[18,20].

The combination of perindopril and amlodipine was examined in the ASCOT study, and the results showed that this combination is well-tolerated, significantly reduces BP, and reduces CV events in comparison with a fixed combination of beta blockers and thiazide[21].

Even today, diuretics are still equal to other groups of antihypertensives. Thiazide diuretics are the ones most commonly used in AH treatment, mostly in combination with other groups of antihypertensives. They are especially recommended in the treatment of elderly patients with isolated systolic hypertension and hypertensive patients with heart failure[22]. They improve filtration, absorption, and secretion of electrolytes in the kidneys and have a vasodilatory effect. Indapamide stands out due to a number of advantages: in addition to the above-mentioned effects, it inhibits calcium in the blood vessel walls (vasodilatation and a reduction in peripheral resistance), which provides an additional reduction in BP[22]. It is metabolically neutral, has a cardioprotective effect, reduces total mortality, provides 24-hour BP control, and has a low incidence of side-effects[23-25]. In the PROGRESS clinical trial, the combination of indapamide and perindopril reduced stroke risk by 43% in comparison with the placebo group[26]. As an initial treatment for AH, this combination reduces CV and CBV outcomes in comparison with monotherapy[27].

Antihypertensive combinations are the basis of modern AH treatment. Every fourth patient receives 3 antihypertensives with the goal of controlling BP[13]. However, taking multiple tablets per day leads to poorer patient adherence to treatment. Fixed antihypertensive combinations achieve excellent treatment adherence due to the reduction in the number of tablets, better tolerability, and better effectiveness, all of which motivate the patient to adhere to the treatment. The above-mentioned perindopril, amlodipine, and indapamide are examples of drugs where their fixed combination has excellent pharmacodynamics due to different, but complementary mechanisms of action, and the synergic effect on BP is present over 24-hours for all three components in the combination. This fixed combination also has excellent tolerability: perindopril reduced edema that can be cause by amlodipine; amlodipine reduces the incidence of cough caused by perindopril; indapamide has beneficial effects on metabolic parameters (glucose, lipids). This fixed triple combination confirmed its excellent efficacy and safety in the PETRA prospective, observational, open label clinical trial (**Figure 1**)[28]. The study monitored the effectiveness of BP control over 3 months in 11 209 hypertonic patients of both sexes who received a fixed-dose triple-combination of perindopril/indapamide/amlodipine once per day. The dose was adjusted to the pressure (BP was measured in the clinic, at home, and with

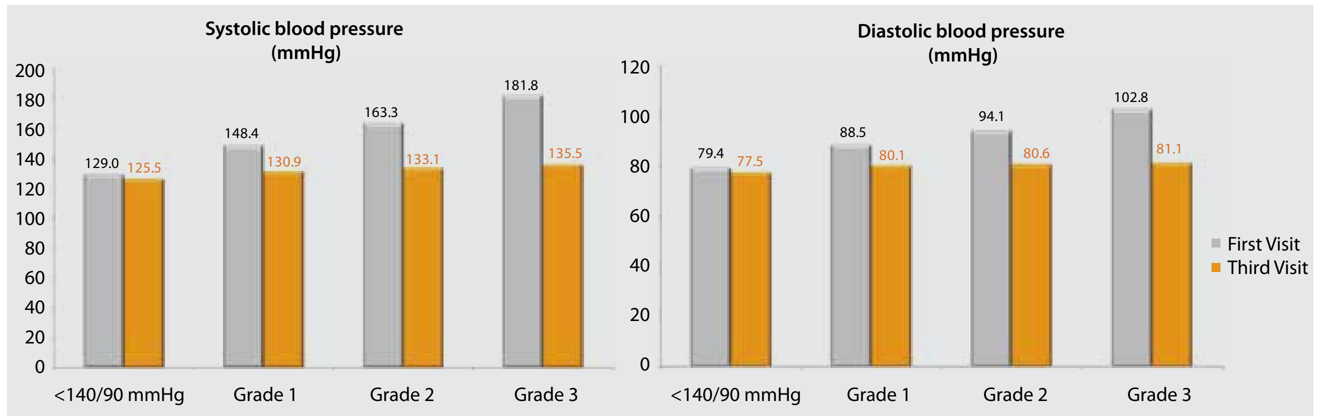

FIGURE 1. The results of PETRA study.

Adapted from Abraham G. The antihypertensive efficacy of the triple fixed combination of perindopril, indapamide and amlodipine: The results of PETRA study. Adv Ther 2017.

Rezultati su pokazali znatna sniženja AT-a: 73 % prethodno nekontroliranih hipertoničara postiglo je ciljne vrijednosti AT-a. Poboljšali su se i metabolički parametri (sniženje glukoze i lipida u krvi). Ova je kombinacija pokazala i izvrsnu podnošljivost: nuspojave su nastale u samo 0,5 % bolesnika (edem gležnjeva, suhi kašalj, tahikardija, omaglica, hipotenzija)[28].

Samo je 50 % opće populacije u razvijenim zemljama adherentno u pridržavanju kronične terapije te da se 70 % podignutih lijekova nikada i ne uzme[29]. Više je čimbenika odgovorno za adherenciju pri uzimanju terapije: dob, spol, razina obrazovanja, zaboravljivost, učestalost uzimanja, broj lijekova, neadekvatna suradnja s liječnikom. Adherencija se može poboljšati boljom edukacijom i informiranošću bolesnika, ali jedna od najvažnijih mjera koja može poboljšati adherentnost i suradljivost bolesnika u liječenju jest uvođenje fiksnih kombinacija lijekova. Kod fiksnih kombinacija antihipertenziva smanjuje se za 24 % loša suradnja. Najbolja se adherencija postiže doziranjem jednom na dan[29].

Zaključak

Prema dosadašnjim istraživanjima, 94 % novootkrivenih hipertoničara treba započeti liječenje kombiniranom terapijom dvaju antihipertenziva. Kombinirana terapija trima antihipertenzivima komplementarnog učinka nužna je u liječenju 30-ak % bolesnika kako bi se postigla dobra kontrola AT-a i smanjilo oštećenje ciljnih organa. Kombinirana terapija temelj je suvremenog liječenja AH-a, a izbor antihipertenziva ovisi o hemodinamskim i metaboličkim kriterijima. Kako bismo ostvarili što bolju suradnju i adherentnost u liječenju, treba smanjiti broj tableta u svakodnevnoj terapiji, smanjiti incidenciju nuspojava, povećati učinkovitost i djelotvornost liječenja kao i smanjiti trošak liječenja. Dosadašnja iskustva dokazuju nam da fiksnom kombinacijom triju antihipertenziva – perindopril/indapamid/amlodipin – ostvarujemo sve te ciljeve. To je kombinacija koju preporučuju i zadnje Smjernice ESH/ESC za liječenje hipertenzije. Opservacijska klinička studija PETRA dokazala je da ova fiksna kombinacija u različitim dozama djelatnih tvari brzo postiže ciljne vrijednosti AT-a u bolesnika s nereguliranom AH, pokazuje dobru podnošljivost, metabolički je neutralna i znatno povećava adherentnost prema liječenju.

24-hour ambulatory BP measurement). Before the introduction of this combination, the patients had been receiving dual combined therapy. The monitored secondary outcomes of the treatment were: safety, tolerability, and laboratory parameters. The results showed significant reduction in BP: 73% of patients with previously uncontrolled BP achieved target values. Metabolic parameters also improved (reduced glucose and blood lipids). This combination also demonstrated excellent tolerability: side-effects manifested in only 0.5% of patients (ankle edema, dry cough, tachycardia, dizziness, hypotension)[28].

Only 50% of the general population in developed countries adheres to chronic treatment, and 70% of the drugs that are picked up are never even taken[29]. Multiple factors determine adherence to treatment: age, sex, level of education, forgetfulness, dose frequency, the number of prescribed medications, and inadequate cooperation with the physician. Adherence can be improved by providing patients with better education and information, but one of the most important measures that can improve adherence and patient compliance to treatment is introducing fixed drug combinations. Fixed antihypertensive combinations reduce poor compliance by 24%. The best adherence is achieved by prescribing a single dose per day[29].

Conclusion

According to current studies, 94% of newly-diagnosed hypertensive patients should initiate treatment with a combination of two antihypertensives. Combined therapy with three antihypertensives with a complementary effect is invaluable in the treatment of approximately 30% of these patients in order to achieve good BP pressure and reduce target organ damage. Combined therapy is the basis of modern AH treatment, and the choice of antihypertensives depends on hemodynamic and metabolic criteria. In order to achieve the best possible compliance and adherence to treatment, the number of tablets in daily therapy and the incidence of side-effects should be reduced, while increasing the efficacy and effectiveness of the treatment and reducing treatment costs.

Our experience so far has demonstrated that the fixed-dose combination of three antihypertensives, perindopril/indapamide/amlodipine, achieves all these goals. This is also the combination recommended by the most recent ESH/ESC guidelines for the treatment of AH. The PETRA observational clinical trial

has demonstrated that this fixed combination in different doses of active ingredients rapidly achieves target BP values in patients with unregulated AH, shows good tolerability, is metabolically neutral, and significantly increased treatment adherence.

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