Djelotvornost i sigurnost fiksne kombinacije amlodipina/valsartana (Wamlox®) i amlodipina/valsartana/hidroklorotiazida (Valtricom®) u jednoj tableti u bolesnika s arterijskom hipertenzijom 2. ili 3. stupnja – ispitivanje VICTORY II

The Efficacy and Safety of Single-pill Combination of Amlodipine/valsartan (Wamlox®) and Amlodipine/valsartan/hydrochlorothiazide (Valtricom®) in Patients with Grade 2 or 3 Arterial Hypertension – the VICTORY II Study

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SAŽETAK: Arterijska hipertenzija (AH) vodeći je uzrok kardiovaskularnog (KV) morbiditeta i mortaliteta diljem svijeta. Unatoč brojnim različitim preporukama i mjerama za probir i liječenje AH-a, postizanje ciljnih vrijednosti arterijskoga tlaka (AT) i dalje je izazov u kliničkoj praksi. Glavni cilj pri liječenju bolesnika s AH-om i dalje je maksimalno smanjenje rizika od fatalnih i nefatalnih KV komplikacija, cerebrovaskularnih komplikacija i kronične bolesti bubrega. Da bi se taj cilj postigao, potrebno je sniziti AT na ciljne razine. Osim promjena životnoga stila, potrebni su i učinkoviti antihipertenzivni lijekovi. Ispitivanje VICTORY II provedeno je u svrhu procjene djelotvornosti i sigurnosti primjene fiksnih kombinacija amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida u jednoj tableti za postizanje ciljnih vrijednosti AT-a u bolesnika s novodijagnosticiranim i nekontroliranim AH-om 2. ili 3. stupnja. U ovo multicentrično, otvoreno, prospektivno kliničko ispitivanje bilo je uključeno ukupno 100 bolesnika. Svi bolesnici s AH-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana u jednoj tableti od 5 mg/80 mg, koja se po potrebi mogla titrirati naviše, korak po korak do završne opcije, tj. do fiksne kombinacije amlodipina/valsartana/hidroklorotiazida 10/160/12,5 mg u jednoj tableti kako bi se postigle ciljne vrijednosti AT-a. Bolesnici s AH-om 3. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana 5/160 mg u jednoj tableti, koja se po potrebi mogla titrirati naviše, korak po korak, do fiksne kombinacije amlodipina/valsartana/hidroklorotiazida 10/160/25 mg u jednoj tableti kako bi se postigle ciljne razine AT-a. Rezultati ispitivanja VICTORY II pokazali su da fiksne kombinacije amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida u jednoj tableti učinkovito smanjuju AT u bolesnika s AH-om 2. ili 3. stupnja te da imaju dobar profil podnošljivosti.

SUMMARY: Hypertension is the leading cause of cardiovascular (CV) morbidity and mortality worldwide. In spite of many different recommendations and actions related to screening and management of hypertension, reaching target levels of blood pressure (BP) is still a challenge in clinical practice. The main goal of treating patients with hypertension remains the maximum reduction in the risk of fatal and non-fatal CV complications, cerebrovascular complications, and chronic kidney disease. To achieve this goal, it is necessary to lower BP to target levels. In addition to lifestyle changes, effective antihypertensive medication is needed. The VICTORY II study was performed to assess the efficacy and safety of the use of single-pill combinations (SPCs) of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in achieving the target level of BP in newly diagnosed or uncontrolled patients with grade 2 or 3 arterial hypertension. A total of 100 patients were enrolled in this multicenter, open, prospective clinical study. All patients with grade 2 hypertension started the treatment with SPC of amlodipine/valsartan, 5 mg/80 mg, which if necessary could be up-titrated step-by-step to the final option, i.e. SPC of amlodipine/valsartan/ hydrochlorothiazide 10/160/12.5 mg, to achieve target levels of BP. Patients with grade 3 hypertension started the treatment with SPC of amlodipine/valsartan 5 mg/160 mg, which could be up-titrated step-by-step to SPC of amlodipine/valsartan/hydrochlorothiazide 10/160/25 mg if necessary to achieve target levels of BP. The results of the VICTORY II study showed that SPCs of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide effectively reduce BP in patients with grade 2 or 3 hypertension and have a good tolerability profile.

KLJUČNE RIJEČI: arterijska hipertenzija, djelotvornost, sigurnost, fiksna kombinacija lijekova, amlodipin/valsartan, amlodipin/valsartan/hidroklorotiazid.

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

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Uvod

Kardiovaskularne bolesti (KVB) i dalje su vodeći uzrok morbiditeta i mortaliteta u Europi[1] unatoč poboljšanjima u prevenciji, strategijama liječenja i ishodima. U posljednja tri desetljeća više od polovice smanjenja kardiovaskularnog (KV) mortaliteta pripisano je prije svega smanjenju arterijskoga tlaka (AT) te razini kolesterola i pušenja. Arterijska hipertenzija (AH) jedan je od glavnih promjenjivih čimbenika rizika od KV-a te uvelike pridonosi razvoju ateroskleroze.[1]

Unatoč brojnim različitim preporukama i mjerama u vezi s za probirom i liječenjem AH-a, postizanje ciljnih vrijednosti AT-a i dalje je izazov u kliničkoj praksi.[2,3] Prema objavljenim podatcima, manje od 40 % liječenih bolesnika postiže ciljnu vrijednost AT-a izmjerena u ordinaciji.[3]

Smjernice Europskoga kardiološkog društva (ESC; prema engl. *European Society of Cardiology*) i Europskog društva za hipertenziju (ESH; prema engl. *European Society of Hypertension*) za liječenje arterijske hipertenzije iz 2018. godine preporučuju uvođenje antihipertenzivnog liječenja fiksnom kombinacijom dvaju lijekova. Popis preporučenih lijekova prve linije također uključuje blokatore angiotenzinskih receptora (ARB, npr. valsartan) u kombinaciji s blokatorom kalcijevih kanala (BKK) ili diuretikom, po mogućnosti kao fiksna kombinacija lijekova u jednoj tableti. Zanimljivo je da najnovije smjernice Međunarodnoga društva za arterijsku hipertenziju (ISH; prema engl. *International Society of Hypertension*) za liječenje AH-a iz 2020. godine daju prednost primjeni fiksne kombinacije inhibitora reninsko-angiotenzinsko-aldosteronskoga sustava (RAASi) s dihidropiridinskim BKK-om umjesto kombinacije RAASi-a s diureticima u jednoj tableti za početno liječenje AH-a.[4] Koncept početka terapije fiksnom kombinacijom dvaju lijekova za većinu bolesnika s AH-om vjerojatno će imati velik utjecaj na kliničku praksu te brzinu i kvalitetu kontrole vrijednosti AT-a.[1] Za bolesnike čiji se AT ne može učinkovito kontrolirati fiksnom kombinacijom dvaju lijekova, logična je opcija pojačati liječenje na kombiniranu terapiju trima lijekovima koja uključuje RAASi, BKK i diuretik.[1,4]

Kombinirana terapija ima istodoban učinak na razne fiziološke sustave uključene u AT.[5] Osim toga, fiksna kombinacija dvaju ili više lijekova u jednoj tableti može pridonijeti višoj razini pridržavanja zbog jednostavnijeg režima liječenja. Može dovesti i do bolje kontrole AT-a, može poboljšati podnošljivost terapije, jer su nuspojave na određene lijekove slabije kad se primjenjuju zajedno, te može imati dodatne sinergističke vazoprotektivne ili pleiotropne učinke.[6] Ove prednosti nude mogućnost postizanja ciljnih vrijednosti AT-a u najvećega broja bolesnika.

Background

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality in Europe[1] despite improvements in prevention, treatment strategies, and outcomes. In the last three decades, more than half of the reduction in cardiovascular (CV) mortality has been attributed primarily to the reduction of blood pressure (BP), cholesterol levels, and smoking. Hypertension is one of major modifiable CV risk factors and has a major contribution in the development of atherosclerosis.[1]

In spite of many different recommendations and actions related to screening and management of hypertension, reaching target levels of BP is still a challenge in clinical practice.[2,3] According to published data, less than 40% of treated patients achieve target office BP.[3]

The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend initiating an antihypertensive treatment with a two-drug combination. The list of recommended first-line drugs also includes angiotensin receptor blockers (ARBs, e.g. valsartan) in combination with a calcium channel blocker (CCB) or diuretic, preferably in single-pill combinations (SPCs). Interestingly, the most recent 2020 ISH guidelines for the management of hypertension favor the use of SPC of renin-angiotensin-aldosterone system inhibitors (RAASi) with dihydropyridine CCB over SPC of RAASi with diuretics as the initial treatment of hypertension.[4] 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.[1] For patients whose BP cannot be effectively controlled by a two-drug combination therapy, the logical option is to increase treatment to a three-drug combination therapy of a RAASi, CCB, and diuretic.[1,4]

Combination therapy has a simultaneous effect on various physiological systems involved in the control of BP.[5] In addition, a SPC of two or more medications may contribute to a higher level of adherence due to the simplification of the treatment regimen. It may lead to more adequate control of BP, may improve tolerability of therapy by weakening the adverse reactions to certain medications when administered together, and may show additional synergistic vasoprotective or pleiotropic effects.[6] These advantages offer the possibility of reaching the target BP levels in the largest number of patients.

In the management of hypertension, the efficacy of the treatment is mostly assessed by office BP values. Use of out-

Pri liječenju AH-a djelotvornost liječenja uglavnom se procjenjuje vrijednostima AT-a izmjerenima u liječničkoj ordinaciji. U postojećim smjernicama također se preporučuje mjerenje AT-a izvan ordinacije uređajem za 24-satno mjerenje AT-a (ABPM; prema engl. *ambulatory blood pressure monitoring*) i/ili kućnim mjerenjem AT-a (HBPM; prema engl. *home blood pressure monitoring*), kao opcijom za potvrdu dijagnoze AH-a, otkrivanje „fenomena bijele kute" i maskirne hipertenzije te za praćenje vrijednosti AT-a.[2]

Kliničko ispitivanje VICTORY II provedeno je dok su na snazi bile Smjernice ESH-a/ESC-a za liječenje arterijske hipertenzije iz 2013. godine.[7] U ovom članku opisujemo rezultate mjerenja AT-a u liječničkoj ordinaciji, HBPM i ABPM u svrhu procjene djelotvornosti liječenja na bazi fiksne kombinacije amlodipina/valsartana u jednoj tableti u prethodno neliječenih ili prethodno liječenih bolesnika s nekontroliranim AH-om 2. ili 3. stupnja.

Bolesnici i metode

Primarni cilj ispitivanja VICTORY II bio je procijeniti djelotvornost i sigurnost fiksne kombinacije amlodipina/valsartana i fiksne kombinacije amlodipina/valsartana/hidroklorotiazida u jednoj tableti radi postizanja ciljnih vrijednosti AT-a (AT u ordinaciji, HBPM, ABPM) u odraslih bolesnika s AH-om 2. ili 3. stupnja. Sekundarni su ciljevi bili procijeniti učinak terapije na temelju fiksne kombinacije amlodipina/valsartana na erektilnu funkciju u muškaraca, metaboličku neutralnost ispitivanih lijekova, učinak na razinu albumina u urinu bolesnika, na kvalitetu života bolesnika, na praktičnost ispitivane terapije za bolesnike, na elastičnost arterija te na razinu aortalnoga tlaka i endotelnu funkciju. Zbog velikoga broja rezultata dobivenih u ovom ispitivanju, ovaj se članak fokusira na analizu učinka terapije na temelju fiksne kombinacije amlodipina/valsartana na vrijednosti AT-a i opću sigurnost.

Ovo multicentrično, otvoreno, prospektivno kliničko ispitivanje uključivalo je bolesnike starije od 18 godina s esencijalnom AT-om 2. ili 3. stupnja, prethodno neliječene (sistolički tlak u ordinaciji ≥160 mmHg i/ili dijastolički tlak u ordinaciji ≥100 mmHg) ili one s nekontroliranim vrijednostima AT-a mjerenima u ordinaciji usprkos prethodnom liječenju antihipertenzivima. Liječenje je trajalo 16 tjedana. Bolesnici su morali posjećivati klinički centar tijekom razdoblja od 4 tjedna. Svaki je bolesnik morao sudjelovati u 5 posjeta. Za HBPM pri prvom posjetu svim su bolesnicima dani automatski tlakomjeri i dnevnici za samostalno mjerenje vrijednosti AT-a, koje su bolesnici ispunjavali sami, u skladu s preporukama.

Pri prvom posjetu svi bolesnici s AH-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana u jednoj tableti, 5/80 mg, koja se mogla titrirati naviše na fiksnu kombinaciju amlodipina/valsartana/hidroklorotiazida u jednoj tableti, 10/160/12,5 mg, kako bi se postigla ciljna vrijednosti AT-a izmjerena u ordinaciji. Bolesnici s AH-om 3. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana, 5/160 mg, koja se mogla titrirati naviše na amlodipin/valsartan/hidroklorotiazid 10/160/25 mg kako bi se postigao ciljni AT izmjeren u ordinaciji. Na kontrolnim posjetima odluku o korekciji antihipertenzivne terapije donosio je liječnik na temelju analize rezultata mjerenja AT-a u ordinaciji, podataka iz dnevnika o HBPM-u, fizikalnoga pregleda, te bolesnikova općega stanja i njegovih tegoba.

of-office BP measurement with automatic 24-hour BP monitoring (ABPM) and/or home monitoring of BP (HBPM), as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension, and monitoring BP values is also recommended in current guidelines.[2]

The VICTORY II clinical study was conducted at the time of the validity of 2013 ESH/ESC Guidelines for the management of arterial hypertension.[7] In this article, we present office BP measurement, HBPM, and ABPM values to assess the efficacy of the amlodipine/valsartan SPC-based treatment in naïve or previously treated but uncontrolled hypertensive individuals with grade 2 or grade 3 hypertension.

Patients and Methods

The primary objective of the VICTORY II study was to assess the efficacy and safety of SPC amlodipine/valsartan and SPC amlodipine/valsartan/HCTZ in achieving the target levels of BP (office BP, home BP-monitoring data, and 24-h BP monitoring) in adult patients with grade 2 or 3 hypertension. The secondary objectives were to assess the effect of the amlodipine/valsartan-based therapy on erectile function in men, the metabolic neutrality of the tested medications, the effect on the level of albumin in patients' urine, the effect of the therapy on the quality of life of patients, on the convenience of the studied therapy for patients, on the elasticity of the arteries, on the level of central aortic pressure, and endothelial function. Due to the large number of results obtained in the study, this article is focused on the analysis of the effect of amlodipine/valsartan-based therapy on blood pressure parameters and overall safety.

This multicenter, open, prospective clinical study included patients older than 18 years with essential grade 2 or 3 arterial hypertension, previously untreated patients (office systolic BP ≥ 160 mmHg and/or office diastolic BP ≥ 100 mmHg) or those with uncontrolled office BP by previous therapy. The duration of treatment was 16 weeks. Patients were required to visit the clinical center in a 4-week interval. Each patient had to participate in 5 visits. For HBPM, at visit 1 all patients were given automatic BP monitors and diaries for self-monitoring of BP, which patients filled out independently according to the recommendations.

At visit 1, all the patients with grade 2 hypertension started the treatment with SPC of amlodipine/valsartan, 5 mg/80 mg, which could be up-titrated to SPC of amlodipine/valsartan/HCTZ 10/160/12.5 mg to achieve target office BP. The patients with grade 3 hypertension started the treatment with SPC of amlodipine/valsartan 5 mg/160 mg, which could be up-titrated to amlodipine/valsartan/HCTZ 10/160/25 mg to achieve target office BP. At monitoring visits, the decision about the correction of the antihypertensive therapy was made by the doctor based on the analysis of office BP measurement results, data from HBPM diary, physical examination, general condition, and patient's complaints.

The overall clinical effectiveness of the tested medications was evaluated at the end of treatment in accordance with the criteria based on the achieved level of office BP and the presence and severity of adverse events (AE).

Ukupna klinička učinkovitost ispitivanih lijekova procijenjena je na kraju liječenja, u skladu s kriterijima temeljenima na postignutoj razini krvnoga tlaka u ordinaciji te prisutnosti i težini neželjenih događaja.

Rezultati

Ispitivanje je uključivalo 100 bolesnika: 59 žena i 41 muškarca s AH-om 2. stupnja (N = 60) ili 3. stupnja (N = 40). Prosječna dob bolesnika bila je 59,5 ± 10,9 godina, a trajanje AH-a 83,4 ± 8,4 mjeseca. Skupine bolesnika s AH-om 2. ili 3. stupnja bile su usporedive po dobi, spolu, trajanju bolesti i indeksu tjelesne mase.

Pretilost je zabilježena u 32 % bolesnika, a 13 % bolesnika bili su pušači. Ateroskleroza je bila prisutna u 3 % bolesnika u perifernim arterijama te u 11 % bolesnika u aorti ili u brahiocefaličnim arterijama. U 11 % bolesnika bilo je prisutno kronično zatajivanje srca, a 7 % bolesnika imalo je anginu pektoris.

Osim hipertenzije, u 41 % bolesnika zabilježena je i dislipidemija. Hiperglikemija natašte i intolerancija glukoze zabilježene su u 7 %, odnosno u 3 % bolesnika. Dijabetes tipa 2 zabilježen je u 11 % oboljelih.

U vrijeme uključenja u ispitivanje 83 (83 %) bolesnika prethodno su primila antihipertenzivnu terapiju. Od toga su najčešće primjenjivani ARB-i i inhibitori angiotenzin-konvertaze (ACEI) kao monoterapija (16,8 %, odnosno 8,4 %). Čak 58 bolesnika (70%) primilo je dvojnu antihipertenzivnu terapiju, a od toga je samo 25,8 % oboljelih primilo kombinaciju lijekova u jednoj tableti.

Ciljna vrijednost AT-a izmjerena u ordinaciji, prema Smjernicama ESH-a/ESC-a za liječenje arterijske hipertenzije iz 2013. godine (sistolički tlak < 140 mmHg, dijastolički tlak < 90 mmHg, osim u bolesnika s dijabetesom < 85 mmHg), postignuta je u 90 % bolesnika nakon 16 tjedana terapije [95 % CI 81,2 %; 95, 6%] (**Slika 1**).

Results

The study included 100 patients: 59 women and 41 men with grade 2 (N=60) or grade 3 (N=40) hypertension. The average age of the patients was 59.5±10.9 years, with a duration of hypertension of 83.4±8.4 months. The groups of patients with grade 2 or 3 hypertension were comparable in age, gender, duration of hypertension, and body mass index.

Obesity was observed in 32% of the patients; 13% of the patients were smokers. Atherosclerosis was present in 3% of the patients in the peripheral arteries and in 11% of the patients in the aorta or brachiocephalic arteries. As many as 11% of the patients suffered from chronic heart failure and 7% of the patients had angina pectoris.

In addition to hypertension, dyslipidemia was observed in 41% of the patients. Fasting hyperglycemia and impaired glucose tolerance were detected in 7% and 3% of the patients, respectively. Type 2 diabetes was observed in 11% of the patients.

At the time of inclusion in the study, 83 (83%) patients had received previous antihypertensive therapy. Of these, ARBs and angiotensin-converting enzyme inhibitors (ACEIs) were most often used as monotherapy (16.8% and 8.4%, respectively). As many as 58 patients (70%) received a double antihypertensive treatment, of whom only 25.8% were given SPC.

The target office BP, according to the 2013 ESH/ESC Guidelines for the management of arterial hypertension (systolic BP <140 mmHg, diastolic BP <90 mmHg except in patients with diabetes <85 mmHg), was achieved in 90% of the patients after 16 weeks of therapy (95% CI 81.2%; 95.6%) (**Figure 1**).

In all patients, the average change of BP was -32.2 mmHg for systolic blood pressure (SBP) and -16.0 mmHg for diastolic blood pressure (DBP). In patients with grade 2 hypertension, the average change in SBP was -30.7 mmHg and -15.5 mmHg in DBP; the target office BP was reached in 93.8% of the pa-

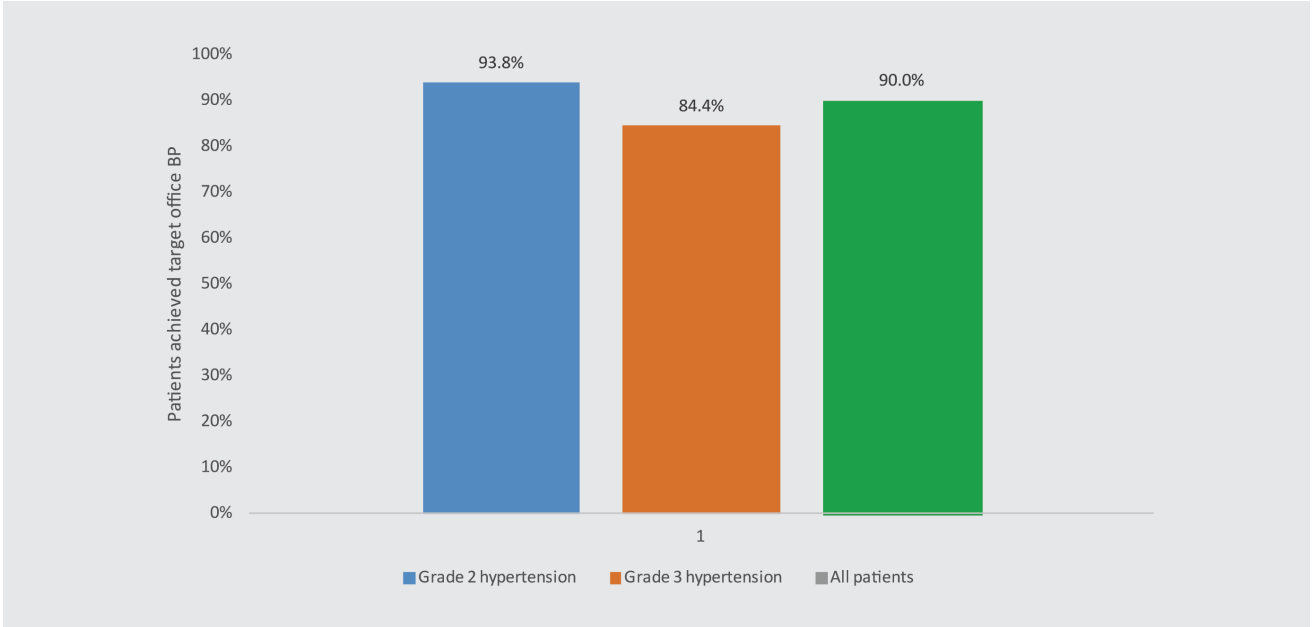

FIGURE 1. Achievement of the target office blood pressure (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, <85 mmHg in patients with diabetes).

U svih bolesnika je prosječna promjena vrijednosti AT-a bila -32,2 mmHg za sistolički te -16,0 mmHg za dijastolički tlak. U bolesnika s AH-om 2. stupnja prosječna promjena sistoličkoga tlaka bila je -30,7 mmHg, a dijastoličkog -15,5 mmHg; ciljna vrijednost AT-a izmjerena u ordinaciji postignuta je u 93,8 % bolesnika. U bolesnika s AH-om 3. stupnja ciljna vrijednost AT-a izmjerena u ordinaciji postignuta je u 84,4 % bolesnika, dok je prosječna promjena sistoličkog tlaka bila -34,6 mmHg, a dijastoličkog tlaka -16,7 mmHg (**Slika 2**).

tients. In patients with grade 3 hypertension, the target office BP was achieved in 84.4% of the patients, while the average change in SBP was -34.6 mmHg and -16.7 mmHg in DBP (**Figure 2**).

The proportion of the patients who reached the target BP levels (SBP/DBP <135/85 mmHg) according to HBPM after 16 weeks of therapy was 40.2% in all patients (95% CI 30.1%; 51.0%), 32.1% (95% CI 20.3%; 46.0%) in the group with grade 2 hypertension, and 52.8% (95% CI 35.5%; 69.6%) in the group with grade 3 hypertension.

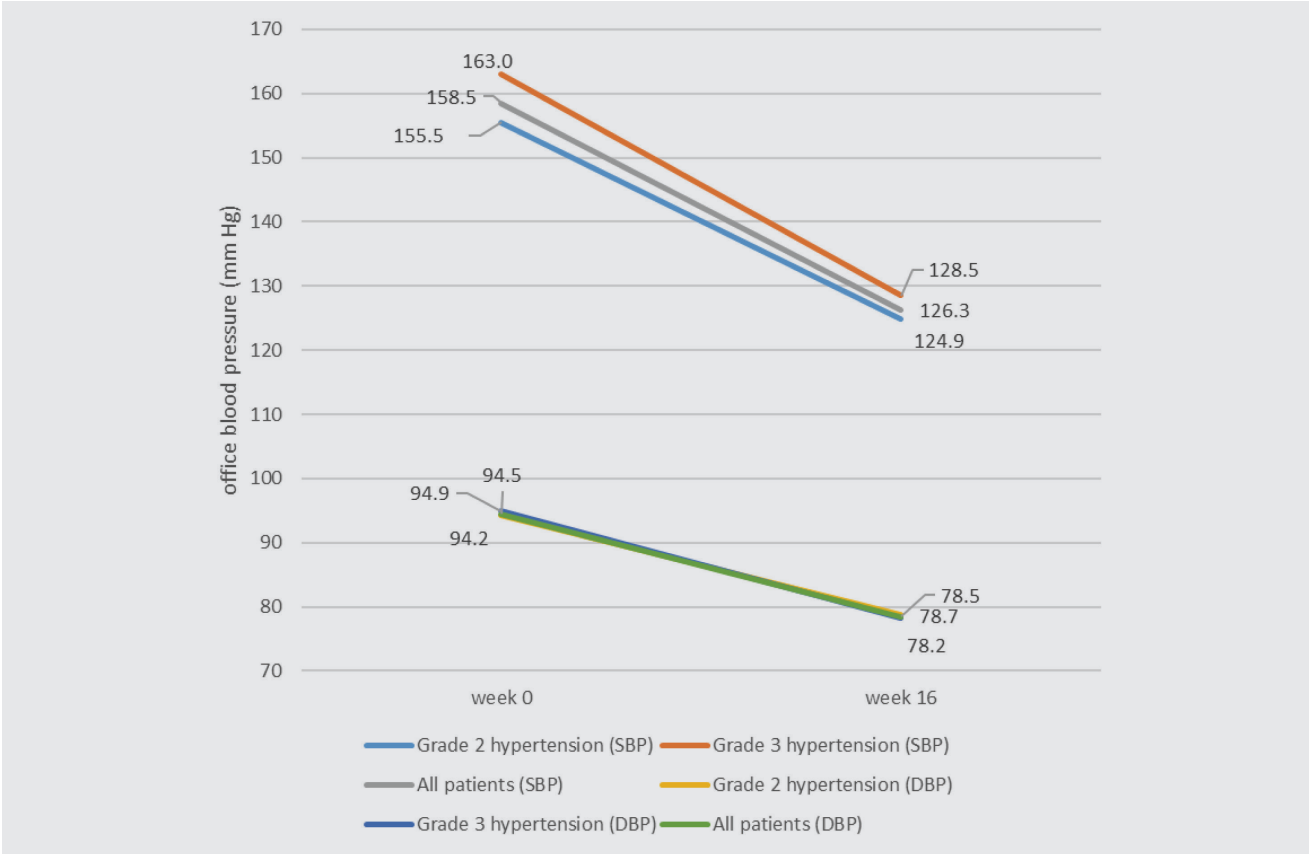

FIGURE 2. Office systolic blood pressure (SBP) and diastolic blood pressure (DBP) during treatment with single-pill combination of amlodipine/valsartan.

Udio bolesnika koji su postigli ciljne razine AT-a (vrijednost <135/85 mmHg), prema HBPM-u, nakon 16 tjedana terapije bio je 40,2 % od svih uključenih bolesnika [95 % CI 30,1 %; 51,0 %], 32,1 % u skupini s AH-om 2. stupnja [95 % CI 20,3 %; 46,0 %] te 52,8 % u skupini s AH-om 3. stupnja [95 % CI 35,5 %; 69,6 %].

Prema rezultatima mjerenja ABPM-om, nakon 16 tjedana terapije 26,5 % bolesnika postiglo je ciljne razine (<125/85 mmHg) dnevnog profila AT-a.

Podatci iz ispitivanja upućivali su na dobru podnošljivost liječenja temeljenog na fiksnoj kombinaciji amlodipina/valsartana u jednoj tableti, što je u skladu s utvrđenim profilom sigurnosti ispitivanih lijekova. Neželjeni događaji povezani s primjenom ispitivanih lijekova uključuju ortostatsku hipotenziju (10 %), periferne edeme (7 %), glavobolju (1 %), omaglicu

According to the 24-hour BP monitoring (ABPM), 26.5% of the patients reached the target levels (SBP/DBP <125/85 mmHg) of the daily BP profile after 16 weeks of therapy.

Concerning the tolerability profile, the study data indicated good tolerability of amlodipine/valsartan SPC-based treatment, which is consistent with the established safety profile of the tested medications. AEs associated with the administration of the tested medications include orthostatic hypotension (10%), peripheral edema (7%), headache (1%), dizziness (1%), asthenia (2%), hypotension (2%). Only six AEs in 5 patients (5%) led to the discontinuation of the study therapy: peripheral edema (3 cases), atrial fibrillation and pneumonia, and allergic dermatitis. Three AEs in two patients (2%) were considered serious, and only one was associated with taking

(1 %), asteniju (2 %) i hipotenziju (2 %). Samo šest neželjenih događaja u 5 bolesnika (5 %) dovelo je do prekida primjene ispitivane terapije: periferni edemi (3 slučaja), fibrilacija atrija i upala pluća te alergijski dermatitis. Tri neželjena događaja u dvoje bolesnika (2 %) smatrana su ozbiljnima, a samo je jedan bio povezan s uzimanjem ispitivanih lijekova. Nije zabilježena nijedna smrt tijekom ispitivanja.

Terapijski učinak liječenja procijenjen je na kraju ispitivanja, nakon 16 tjedana liječenja. Ukupna klinička djelotvornost (gradacije: ekstremno visoka, vrlo visoka, visoka, zadovoljavajuća) postignuta je u 98,8 % [95 % CI 93,2 %; 100 %] bolesnika.

Rasprava i zaključak

Podatci iz kliničkog ispitivanja VICTORY II pokazali su da liječenje temeljeno na fiksnoj kombinaciji amlodipina/valsartana učinkovito smanjuje vrijednosti AT-a na ciljne razine u bolesnika s novodijagnosticiranom ili prethodno liječenom, ali nekontroliranom AH 2. ili 3. stupnja. Početno liječenje ili prelazak na liječenje na osnovi fiksne kombinacije amlodipina/valsartana rezultiralo je postizanjem ciljnih vrijednost AT-a izmjerenog u ordinaciji u 90 % bolesnika nakon 16 tjedana liječenja. Vrijeme potrebno za postizanje ciljnih razina AT-a važna je determinanta kliničkih ishoda. Kraće vrijeme do kontrole povezano je s nižim KV rizikom. Postignute ciljne razine AT-a u ordinaciji bile su slične u bolesnika s hipertenzijom 2. ili 3. stupnja (124,9/78,8 mmHg, odnosno 126,3/78,2 mmHg).

Ovo je ispitivanje provedeno dok su valjane bile Smjernice ESH-a/ESC-a za liječenje AH-a iz 2013. godine. Dizajn ispitivanja bio je ispred svojega vremena jer je početak antihipertenzivnog liječenja temeljen na fiksnoj kombinaciji RAAS-a/BKK-a u jednoj tableti. Ovakva vrsta liječenja preporučuje se kao terapija prve linije u postojećim Smjernicama ESC-a/ESH-a za liječenje AH-a iz 2018. te u Smjernicama ISH-a za liječenje AH-a iz 2020. godine. Rezultati ovoga kliničkog ispitivanja u skladu su i s jednim i s drugim trenutačno valjanim smjernicama te pokazuju da su početno liječenje AH-a kombinacijom dvaju lijekova u jednoj tableti i nadogradnja u trojnu kombinaciju učinkovitije od monoterapije.

Trenutne Smjernice ESC-a/ESH-a za liječenje arterijske hipertenzije iz 2018. godine preporučuju HBPM za dijagnozu i praćenje AH-a.[3] Prema podatcima o HBPM-u, 40,2 % bolesnika u ispitivanju postiglo je ciljne razine AT-a (<135/85 mmHg) nakon 16 tjedana terapije. Postizanje ciljnih razina, prema HBPM-u, utvrđeno je na temelju strogih kriterija, tj. nitko od bolesnika nije smio prekoračiti ciljne razine AT-a tijekom posljednjih sedam dana primjene lijeka prije završnog posjeta nakon 16 tjedana. Pri analizi ovih rezultata važno je uzeti u obzir da HBPM može biti problematično ako tehnologija za mjerenje/bilježenje rezultata i suradljivost bolesnika s primljenim uputama za mjerenje AT-a nisu pažljivo definirane. Pridržavanje smjernica za HBPM unatoč pasivnoj, multimodalnoj intervenciji još uvijek je suboptimalno, što upućuje na nisku pouzdanost podataka.[8] Točnost i reproducibilnost podataka pri uporabi tlakomjera s funkcijom memorije pokazale su se mnogo višima nego u slučaju uporabe dnevnika za HBPM.[9] Naime, pravilno vođenje dnevnika za HBPM te nošenje dnevnika liječniku može činiti problem.[8] Na HBPM tlaka također može utjecati način bolesnikova života: prehrambene navike, ravnoteža tekućina, emocionalna pozadina, konzumacija alkohola itd.[10] Ispitivanje je utvrdilo da HBPM, kao i dothe tested medications. There were no deaths reported during the study period.

The therapeutic effect of the treatment was assessed at the end of the study, after 16 weeks of treatment. The overall clinical efficacy (gradations: extremely high, very high, high, satisfactory) was reached in 98.8% (95% CI 93.2%; 100.0%) of the patients.

Discussion and Conclusion

The data from the VICTORY II clinical study showed that the amlodipine/valsartan-based treatment is effective in reducing BP to target levels in newly diagnosed or previously treated, but uncontrolled patients with grade 2 or 3 arterial hypertension. Initiation of the treatment or change to amlodipine/valsartan SPC-based treatment resulted in the achievement of target office BP in 90% of the patients after 16 weeks of treatment. The time needed to achieve the target BP levels is an important determinant of clinical outcomes. Shorter time to control is associated with a lower CV risk. The achieved levels of target office BP were similar in the patients with grade 2 or 3 hypertension (124.9/78.8 mmHg and 126.3/78.2 mmHg, respectively).

The study was conducted at the time of the validity of 2013 ESH/ESC Guidelines for the management of arterial hypertension. The design of the study was ahead of its time, since the initiation of the antihypertensive treatment was based on the SPC of RAAS/CCB. This kind of treatment is recommended as the first-line therapy by current 2018 ESC/ESH Guidelines for the management of arterial hypertension and also by the most recent 2020 ISH guidelines for the management of hypertension. The results of the clinical study are in compliance with both current guidelines and show that the initial treatment of hypertension with a double SPC and upgrade to a tripple SPC is more effective than monotherapy.

The current 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend HBPM for the diagnosis and follow-up of hypertension.[3] According to HBPM, 40.2% of the patients in the study reached the target BP levels (SBP/DBP <135/85 mmHg) after 16 weeks of therapy. Achievement of target HBPM levels was determined based on strict criteria, i.e. none of the patients exceeding the target BP levels during the last seven days of the administration of the medication before the final visit at week 16. When analyzing these results, it is important to take into account that the HBPM assessment can be problematic if the technology for measuring/recording the results and patient compliance with the received instructions for BP measuring are not carefully defined. Adherence to HBPM guidelines despite a passive, multimodal intervention is still suboptimal, indicating a low reliability of the data.[8] The accuracy and reproducibility of data when using BP measuring devices with a memory function was shown to be much higher than in the case of use of HBPM diaries.[9] Namely, proper maintaining a HBPM diary and bringing to the physician may represent an issue.[8] HBPM measurements may also be affected by the patients' lifestyles: their eating habits, fluid balance, emotional background, alcohol intake, etc.[10] The study identified the assessment of HBPM, along with the proper quality of BP measurements by patients at home, as challenging.[9] Considering the limitations in the evaluation of the study results, this practice needs to be investigated further.

bra kvaliteta mjerenja AT-a koje bolesnici provode kod kuće, znače izazov.[9] S obzirom na ograničenja u procjeni rezultata ispitivanja, ovu je praksu potrebno dodatno istražiti.

U ovom je ispitivanju primjenjivan ABPM za procjenu djelotvornosti liječenja temeljenog na fiksnoj kombinaciji amlodipina/valsartana u snizivanju 24-satnih vrijednosti AT-a u podskupini bolesnika (N = 40). Dvadesetčetirisatno mjerenje AT-a poboljšava točnost dijagnoze AH-a i otkriva bolesnike s nekontroliranom, maskirnom hipertenzijom.[3] Zbog „fenomena bijele kute", AT izmjeren u ordinaciji može biti mnogo viši nego vrijednost AT-a tijekom uobičajenih svakodnevnih aktivnosti u velikoga broja bolesnika. To može dovesti do netočne dijagnoze AH-a u neliječenih osoba.[3] Prosječne vrijednosti AT-a zabilježene 24-satnim mjerenjem niže su od mjerenja AT-s u ordinaciji, što rezultira manjim smanjenjem AT-a tijekom liječenja. U ispitivanju VICTORY II 26,5 % bolesnika liječenih terapijom na osnovi fiksne kombinacije amlodipina/valsartana u jednoj tableti imali su normaliziranu vrijednost AT-a prema 24-satnom mjerenju. Unatoč tomu, sve prosječne promjene AT-a bile su statistički značajne na razini značajnosti od 5 %, uz iznimku prosječnoga sistoličkog tlaka tijekom noći u skupini bolesnika s hipertenzijom 2. stupnja (p = 0,364) i prosječnoga dijastoličkog tlaka tijekom noći u skupini bolesnika s hipertenzijom 3. stupnja (p = 0,086). Prema tome, kao rezultat ovog ispitivanja dokazano je da terapija temeljena na fiksnoj kombinaciji amlodipina/valsartana u jednoj tableti može poboljšati dnevni profil AT-a, što upućuje na dodatni učinak ispitivanoga antihipertenzivnog liječenja na prognozu u bolesnika s hipertenzijom 2. ili 3. stupnja.

Unatoč gore navedenim ograničenjima, rezultati kliničkog ispitivanja VICTORY II pokazuju da liječenje temeljeno na fiksnoj kombinaciji amlodipina/valsartana u jednoj tableti učinkovito smanjuje AT u bolesnika s AH-om 2. ili 3. stupnja jer su zabilježene visoke stope postizanja ciljnih razina AT-a u ordinaciji unutar kratkog razdoblja od 16 tjedana, kao i dobar profil sigurnosti.

In the study, ABPM was used to assess 24-h BP lowering efficacy of the amlodipine/valsartan SPC-based treatment in the subgroup of patients (N=40). ABPM improves the accuracy of diagnosis of hypertension and detects patients with uncontrolled, masked hypertension.[3] Due to white-coat hypertension, the office BP may be substantially higher than BP during normal daily activities in many individuals. This may lead to incorrect diagnosis of hypertension in untreated individuals.[3] The average BP values recorded by ABPM are lower than the office BP readings, which results in smaller reduction of BP during treatment. In the VICTORY II study, 26.5% of the patients treated with amlodipine/valsartan SPC-based treatment normalized BP according to 24-h ABPM measurements. Nevertheless, all average changes of BP were statistically significant at a significance level of 5%, with the exception of the average night-time SBP in the group of patients with grade 2 hypertension (p=0.364) and average night-time DBP in the group of patients with grade 3 hypertension (p=0.086). The results of this study thus demonstrate the possibilities of therapy based on amlodipine/valsartan SPC treatment in improving the BP daily profile, which indicates an additional effect of the studied antihypertensive treatment on the prognosis of patients with grade 2 or 3 hypertension.

Despite the limitations discussed above, the results of the VICTORY II clinical study show that the amlodipine/valsartan SPC-based treatment effectively reduces BP in patients with grade 2 or 3 hypertension, as high rates of achieved office BP target levels in a short 16-week period as well as a good safety profile were observed.

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