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

SAŽETAK: Arterijska hipertenzija (AH) vodeći je uzrok kardiovaskularnog (KV) morbidity i mortaliteta diljem svijeta. Unatoč brojnim različitim preporukama i mjerama za probir i liječenje AH-a, postizanje ciljnih vrijednosti arterijskog tlaka (AT) i dalje je izazov u kliničkoj praksi. Glavni cilj pri liječenju bolesnika s AH-om 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 fiksne kombinacije amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida (Valtricom®) i amlodipina/valsartana/hidroklorotiazida (Valtricom®) 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 10/160/25 mg u jednoj tableti. 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 potrošivosti.

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 10/160/25 mg 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 (KV) i dalje su vodeći uzrok morbidity i mortaliteta u Europi\(^1\) unatoč poboljšanjima u prevenci-ji, strategijama liječenja i ishodima. U posljednja tri desetljeća više od polovice smanjenja kardiovaskularnog (KV) mortaliteta pripisano je prije svega smanjenju arterijskog tlaka (AT) te razini kolesterolala i pušenja. Arterijska hipertenzija (AH) jedan je od glavnih promjenjivih čimbenika rizika od KV-a te uvelike pridonosi razvoju ateroskleroze.\(^6\)

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 podacima, manje od 40 % liječenih bolesnika postiže ciljnu vrijednost AT-a izmjerenu 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 receptor (ARB, npr. valsartan) u kombinaciji s blokatorom kalcijskih kanala (BKK) ili diuretikom, po mogućnosti kao fiksn kombinacije 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-aldosteron-skoga sustava (RAAS) s dihidropiridinskim BKK-om omjesto kombinacije RAASI-a s diureticima u jednoj tableti za početno liječenje AH-a.\(^4\) Koncept početne 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.\(^4\) Bolesnici čiji se AT ne može učinkovito kontrolirati fiksnom kombinacijom dvaju lijekova, logična je opcija pojačati liječenje na kombiniranu terapiju tri ma lijekovima koja uključuje RAASI, BKK i diuretik.\(^4\)

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 najvećeg broja bolesnika.

Background

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality in Europe\(^6\) 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 re duction 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.\(^4\)

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

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 10/160/25 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 uspoređive 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 brahiocefalnim 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. Diabete tipa 2 zabilježen je u 11 % oboljelih.

U vrijeme uključenja u ispitivanje 83 (83 %) bolesnika pret hodno su primila antihipertenzivnu terapiju. Od toga su najčešće primjenjivani ARB-i i inhibitori angiotenzin-konver taze (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 Smjer nicama 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).](image-url)
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).

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
Terijski učinak liječenja procijenjen je na kraju ispitivanja, nakon 16 tjedana liječenja. Ukupna klinička djelotvornost (gradacije: ekstremno visoka, vrlo visoka, visoka, zadovoljna, nezadovoljna) postignuta je u 98.8 % [95 % CI 93.2%; 100 %] bolesnika.

**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 (124/78.8 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 triple 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. 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 can be not carefully defined. Adherence to HBPM guidelines despite a passive, multimodal intervention is still suboptimal, indicating a low reliability of the data. 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. Namely, proper maintaining a HBPM diary and bringing to the physician may represent an issue. HBPM measurements may also be affected by the patients’ lifestyles: their eating habits, fluid balance, emotional background, alcohol intake, etc.

The study identified the assessment of HBPM, along with the proper quality of BP measurements by patients at home, as challenging. Considering the limitations in the evaluation of the study results, this practice needs to be investigated further.
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. 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. 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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