Dodatni učinci fiksne kombinacije amlodipina/valsartana (Wamlox®) i fiksne kombinacije amlodipina/valsartana/hidroklorotiazida (Valtricom®) osim kontrole arterijskog tlaka u bolesnika s arterijskom hipertenzijom 2. ili 3. stupnja – kliničko ispitivanje *VICTORY II*

Effects of a Single-pill Combination of Amlodipine/valsartan (Wamlox®) and a Single-pill Combination of Amlodipine/valsartan/hydrochlorothiazide (Valtricom®) in Addition to Blood Pressure Control in Patients with Grade 2 or 3 Arterial Hypertension – VICTORY II Clinical Study

Aleša Primožič,
Alenka Glavač Povhe,
Mateja Grošelj,
Breda Barbič-Žagar*

Krka, d. d., Novo mesto, Slovenija
Krka, d. d., Novo mesto, Slovenia

SAŽETAK: Unatoč optimizaciji i pojednostavnjenju liječenja arterijske hipertenzije (AH), postizanje kontrole arterijskoga tlaka (AT) i dalje je izazov, a većini je bolesnika potrebno kombinirano liječenje da bi postigli ciljnu kontrolu AT-a. Zbog višefaktorskog učinka AH-a, uz smanjenje vrijednosti AT-a, dodatna prevencija oštećenja ciljnih organa te održavanje vaskularnog integriteta postignuta antihipertenzivima korisni su za optimalno smanjenje kardiovaskularnog (KV) rizika. Cilj multicentričnog, otvorenog, prospektivnog kliničkog ispitivanja *VICTORY II* u 100 bolesnika uključenih u aktivnu fazu bio je procijeniti sigurnost i djelotvornost fiksnih kombinacija amlodipina/valsartana (Wamlox®) i amlodipina/valsartana/hidroklorotiazida (Valtricom®) u prethodno neliječenih ili prethodno liječenih bolesnika s AH-om 2. ili 3. stupnja u kojih nije postignuta kontrola vrijednosti AT-a. Svi bolesnici s AH-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana 5 mg / 80 mg, koja se po potrebi mogla titrirati naviše korak po korak do konačne opcije – fiksne kombinacije amlodipina/valsartana/hidroklorotiazida 10/160/12,5 mg kako bi se postigle ciljne vrijednosti AT-a. Bolesnici s AH-om 3. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana 5 mg / 160 mg, koja se po potrebi mogla titrirati naviše korak po korak do fiksne kombinacije amlodipina/valsartana/hidroklorotiazida 10/160/25 mg kako bi se postigle ciljne vrijednosti. Uz postizanje ciljne vrijednosti AT-a mjerena u ordinaciji, u 90 % bolesnika nakon 16 tjedana liječenja, terapije na bazi kombinacije amlodipina/valsartana također su smanjile prevalenciju albuminurije i centralnoga aortalnog tlaka, poboljšale elastičnost krvnih žila i pokazale pozitivan učinak na funkciju vaskularnog endotela putem svojeg djelovanja na markere uključene u funkciju endotela.

SUMMARY: In spite of optimization and simplification of arterial hypertension (AH) treatment, achieving blood pressure (BP) control is still challenging, with most patients requiring combination treatment to achieve target BP. Due to the multifactorial effect of AH, additional prevention of hypertension-mediated end-organ damage and the maintenance of vascular integrity achieved by antihypertensive medications in addition to the BP-lowering effect are beneficial for the optimal reduction of cardiovascular (CV) risk. The aim of VICTORY II, a multicenter, open, prospective clinical study with 100 patients included in the active phase was to assess the safety and the efficacy of single-pill combinations (SPC) of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/hydrochlorothiazide (Valtricom®) in naïve or previously treated but uncontrolled patients with grade 2 or 3 AH. All patients with grade 2 AH started the treatment with the SPC of amlodipine/valsartan 5 mg/80 mg, which if necessary could be up-titrated step by step to the final option – the SPC of amlodipine/valsartan/hydrochlorothiazide 10/160/12.5 mg to achieve the target levels of BP. Patients with grade 3 AH started the treatment with the SPC of amlodipine/valsartan 5 mg/160 mg, which could be up-titrated step-by-step to the SPC of amlodipine/valsartan/hydrochlorothiazide 10/160/25 mg if necessary to achieve the target levels of BP. In addition to achieving the target office BP in 90% of the patients after 16 weeks of therapy, the amlodipine/valsartan-based treatments also decreased the prevalence of albuminuria and the central aortic pressure, improved vessel elasticity, and exerted a positive effect on the vascular endothelial function through its effect on the markers involved in the endothelial function.

KLJUČNE RIJEČI: arterijska hipertenzija, fiksna kombinacija, valsartan, amlodipin, hidroklorotiazid.

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

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***ADDRESS FOR CORRESPONDENCE**: Breda Barbič-Žagar, Krka, d. d., Novo mesto, Dunajska 65, SLO-1000 Ljubljana, Slovenia. / Phone: +386-1-4751-339 / E-mail: breda.zagar@krka.biz

ORCID: Aleša Primožič, https://orcid.org/0000-0003-3876-5327 • Alenka Glavač Povhe, https://orcid.org/0000-0001-8846-8596
Mateja Grošelj, https://orcid.org/0000-0002-4035-7691 • Breda Barbič-Žagar, https://orcid.org/0000-0002-1173-7361

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Uvod

Glavni cilj liječenja arterijske hipertenzije (AH) jest smanjiti rizik od fatalnih i nefatalnih kardiovaskularnih (KV), cerebrovaskularnih komplikacija i kronične bolest bubrega.[1] Stoga je važno ne samo sniziti arterijski tlak (AT) na ciljne vrijednosti nego također i smanjiti oštećenje organa uzrokovano hipertenzijom – strukturne i/ili funkcionalne promjene na srcu, mozgu, mrežnici, bubrezima i vaskulaturi koja izaziva AH.[2]

Smjernice Europskoga kardiološkog društva / Europskog udruženja za hipertenziju (ESC/ESH) za liječenje AH-a iz 2018. godine preporučuju da se antihipertenzivno liječenje započne kombinacijom dvaju lijekova, po mogućnosti u obliku fiksne kombinacije, radi boljeg pridržavanja liječenja. Blokatori angiotenzinskih receptora (engl. *angiotensin receptor blockers,* ARB) ubrajaju se u pet glavnih skupina lijekova koji čine osnovu antihipertenzivne terapije. Među preporučenim lijekovima prve linije također su i ARB-i (npr. valsartan) u kombinaciji s blokatorom kalcijevih kanala ili diuretikom, po mogućnosti u obliku fiksne kombinacije.[2] Liječenje fiksnom kombinacijom može dovesti do adekvatnije kontrole AT-a te može pokazati dodatne sinergističke vazoprotektivne ili pleiotropne učinke.[2,3]

Primarni cilj multicentričnog, otvorenog, prospektivnog kliničkog ispitivanja *VICTORY II* bio je procijeniti djelotvornost i sigurnost fiksnih kombinacija amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida u postizanju ciljnih razina različitih vrsta AT-a (mjeren u ordinaciji, kod kuće te 24-satnim kontinuiranim mjerenjem) u odraslih bolesnika s AH-om 2. ili 3. stupnja. Sekundarni su ciljevi bili procijeniti učinke liječenja kombinacijom amlodipina/valsartana (amlodipin/valsartan ili amlodipin/valsartan/hidroklorotiazid) na metaboličke parametre, razinu albuminurije, razinu središnjega aortalnog tlaka, elastičnost arterija, funkciju endotela, učinak na erektilnu funkciju, učinak na kvalitetu bolesnikova života i učinak na praktičnost liječenja. Rezultati učinka ispitivanih lijekova – fiksnih kombinacija amlodipina/valsartana (Wamlox®) i amlodipina/valsartana/hidroklorotiazida (Valtricom®) na AT – već su objavljeni[4]. U ovom se članku fokusiramo na procjenu proučavanih dodatnih učinaka, osim na kontrolu AT-a; učinak na albuminuriju, centralni aortalni tlak, elastičnost arterija (brzina pulsnog vala i indeks augmentacije) i na funkciju endotela [razine faktora nekroze α (TNFα), interleukina 6 (IL-6) i 10 (IL-10), vaskularne stanične adhezijske molekule tipa 1 (sVCAM-1) i vaskularni endotelni faktor rasta (VEGF-A)].

Bolesnici i metode

Kliničko ispitivanje *VICTORY II*, koje je provedeno dok su vrijedile smjernice ESH-a/ESC-a za liječenje AH-a iz 2013., uključivalo je bolesnike s esencijalnom AT 2. ili 3. stupnja, prethodno neliječene bolesnike (sistolički tlak u ordinaciji ≥ 160 mmHg i/ili dijastolički tlak u ordinaciji ≥ 100 mmHg) ili bolesnike s nekontroliranim vrijednostima AT-a mjerenima u ordinaciji za vrijeme prethodne terapije. Liječenje je trajalo 16 tjedana. Bolesnici su morali posjećivati klinički centar u intervalima od 4 tjedna. Svaki je bolesnik morao sudjelovati u 5 posjeta, s dodatnim posjetom za podskupinu bolesnika. Pri prvom posjetu svi bolesnici s AT-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana (Wamlox®) 5 mg / 80 mg, koja se mogla titrirati naviše do fiksne

Introduction

The main goal of arterial hypertension (AH) treatment is to reduce the risk of fatal and non-fatal cardiovascular (CV) complications, cerebrovascular complications, and chronic kidney disease.[1] It is therefore important not only to reduce blood pressure (BP) to the target levels but also to diminish hypertension-mediated organ damage – hypertension-induced structural and/or functional changes in the heart, brain, retina, kidney, and vasculature.[2]

The 2018 European Society of Cardiology / European Society of Hypertension Guidelines for the management of AH recommend that antihypertensive treatment be initiated with a two-medication combination, preferably in the form of a single-pill combination (SPC) to improve treatment compliance. Angiotensin receptor blockers (ARBs) are among the five major classes of medications that form the basis of antihypertensive therapy. ARBs (e.g. valsartan) are also among the recommended first-line medications, administered in combination with a calcium channel blocker (CCB) or a diuretic, preferably in the form of an SPC.[2] Treatment with an SPC may lead to more adequate control of BP and may show additional synergistic vasoprotective or pleiotropic effects.[2,3]

The primary objective of VICTORY II, a multicenter, open, prospective clinical study was to assess the efficacy and safety of SPCs of amlodipine/valsartan and amlodipine/valsartan/ hydrochlorothiazide in achieving the target levels of different types of BP (office BP, home measured BP, and 24-h ambulatory BP) in adult patients with grade 2 or 3 AH. The secondary objectives were to assess the effects of the amlodipine/valsartan-based treatments (amlodipine/valsartan or amlodipine/valsartan/hydrochlorothiazide) on metabolic parameters, albuminuria levels, central aortic pressure levels, elasticity of the arteries, endothelial function, effect on erectile function, effect on patient quality of life, and the effect on the convenience of treatment. The results regarding the BP effect of the tested medication – SPCs of amlodipine/valsartan (Wamlox®) and amlodipine/valsartan/hydrochlorothiazide (Valtricom®) – were already published[4]. In this article, we focus on the evaluation of the additional effects in addition to BP control: the effect on albuminuria, central aortic pressure, elasticity of the arteries (pulse wave velocity and augmentation index), and on endothelial function (the levels of necrosis factor α (TNFα), interleukins 6 (IL-6) and 10 (IL-10), type 1 vascular cell adhesion molecules (sVCAM-1), and vascular endothelial growth factor (VEGF-A).

Patients and Methods

The VICTORY II clinical study, which was conducted when the 2013 ESH/ESC Guidelines for the management of AH were valid, involved patients with essential grade 2 or 3 AH, previously untreated patients (office systolic BP ≥160 mmHg and/or office diastolic BP ≥100 mmHg), or those with office BP uncontrolled 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, with an additional visit for a subgroup of patients. At Visit 1, all the patients with grade 2 AH started the treatment with the SPC of amlodipine/valsartan (Wamlox®) 5/80 mg, which could be up-titrated to the SPC of amlodipine/valsartan/ hydrochlorothiazide (Valtricom®) 10/160/12.5 mg to achieve target of-

kombinacije amlodipina/valsartana/hidroklorotiazida (Valtricom®) 10/160/12,5 mg kako bi se postigla ciljna vrijednost AT-a mjerena u ordinaciji. Bolesnici s AH-om 3. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana (Wamlox®) 5 mg/160 mg, koja se mogla titrirati naviše do fiksne kombinacije amlodipina/valsartana/hidroklorotiazida (Valtricom®) 10/160/25 mg kako bi se postigla ciljna vrijednost AT-a mjerena u ordinaciji. Pri posjetima za praćenje liječnik je odlučivao o korekciji antihipertenzivne terapije na temelju analize rezultata mjerenja AT-a u ordinaciji, kliničkoga pregleda, općega stanja i tegoba bolesnika.

Za procjenu organoprotektivnih svojstava u svih je bolesnika pri posjetu za probir i pri 5. posjetu određen učinak ispitivanih lijekova na razinu albumina u urinu. Da bi se procijenio učinak na centralni (aortalni) tlak i elastičnost arterija, mjerena je brzina pulsnog vala (PWV) i određen indeks augmentacije prije primjene ispitivane terapije te nakon 16 tjedana terapije (pri 5. posjetu) s pomoću uređaja *SphygmoCor* u podskupini bolesnika. Usto, ispitane su razine različitih parametara povezanih s funkcijom endotela [faktora nekroze α (TNFα), interleukina 6 (IL-6) i 10 (IL-10), vaskularne stanične adhezijske molekule tipa 1 (sVCAM-1) i vaskularnog endotelnog faktora rasta (VEGF-A)] prije uzimanja ispitivane terapije i nakon 16 tjedana liječenja u podskupini bolesnika.

Rezultati

Ovo je ispitivanje uključivalo 100 bolesnika: 59 žena i 41 muškarca s AH-om 2. stupnja (n = 60) i 3. stupnja (n = 40). Srednja vrijednost dobi bolesnika bila je 59,5 ± 10,9 godina, s trajanjem AH-a 83,4 ± 8,4 mjeseca. Skupine bolesnika s AH-om 2. i 3. stupnja bile su usporedive po dobi, spolu, trajanju AH-a i indeksu tjelesne mase. Najčešće prisutne istodobne KV bolesti bolesnika uključivale su dislipidemiju/hiperkolesterolemiju (41 % bolesnika), pretilost (32 % bolesnika), endokrine poremećaje (12 % bolesnika), poremećaje provođenja i poremećaje srčanog ritma (11 % bolesnika), kronično zatajivanje srca (11 % bolesnika) i tipa 2 dijabetesa (11 % bolesnika).

Od 60 bolesnika s AH-om 2. stupnja na probiru, koji su liječenje započeli dvojnom fiksnom kombinacijom amlodipina/valsartana 5/80 mg, 17 bolesnika (28,3 %) dovršilo je ispitivanje na početnoj dozi, dok je za ostatak bila potrebna titracija naviše. Trideset bolesnika (50 %) dovršilo je ispitivanje na dozi kombinacije amlodipina/valsartana od 5/160 mg, 11 bolesnika (18,3 %) na dozi amlodipina/valsartana od 10/160 mg, a u samo 2 bolesnika (3,4%) bila je potrebna trojna fiksna kombinacija amlodipina/valsartana/ hidroklorotiazida od 10/160/12,5 mg.

Od 30 bolesnika s AH-om 3. stupnja na probiru, koji su liječenje započeli dvojnom fiksnom kombinacijom amlodipina/valsartana 5/160 mg, samo je 7 bolesnika (17,9 %) dovršilo ispitivanje na početnoj dozi. U 21 bolesnika (53,8 %) terapija je povećana na amlodipin/valsartan 10/160 mg, u 11 bolesnika (28,2 %) terapija je povećana na trojnu fiksnu kombinaciju, od toga u njih 8 (20,5 %) na 10/160/12,5 mg te 3 (7,7 %) na amlodipin/valsartan/hidroklorotiazid 10/160/25 mg.

Rezultati ispitivanja pokazali su da fiksne kombinacije amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida učinkovito smanjuju AT u bolesnika s AH-om 2. ili 3. stupnja i da imaju dobar profil podnošljivosti.

Na početku ispitivanja u 17 bolesnika bila je prisutna povišena razina albumina (≥30 mg/dan). Nakon 16 tjedana liječe-

fice BP. The patients with grade 3 AH started treatment with the SPC of amlodipine/valsartan (Wamlox®) 5/160 mg, which could be up-titrated to amlodipine/valsartan/hydrochlorothiazide (Valtricom®) 10/160/25 mg to achieve target office BP. At monitoring visits, the physician made the decision about the correction of the antihypertensive therapy based on the analysis of office BP measurement results, physical examination, general condition, and the patient's complaints.

The effect of the studied medications on the level of albumin in urine was determined at the Screening visit and at Visit 5 in order to assess organ-protective properties in all patients. The effect on central (aortic) pressure and the elasticity of the arteries was evaluated by measuring pulse wave velocity (PWV) and determining the augmentation index at baseline and after 16 weeks of therapy (at Visit 5) using the SphygmoCor device on a subgroup of patients. Additionally, the levels of different parameters connected to the endothelial function (necrosis factor α (TNFα), interleukins 6 (IL-6) and 10 (IL-10), type 1 vascular cell adhesion molecules (sVCAM-1) and the vascular endothelial growth factor (VEGF-A)) were assessed at baseline and after 16 weeks of treatment in a subgroup of patients.

Results

This study included 100 patients: 59 women and 41 men with grade 2 (n=60) and grade 3 (n=40) AH. The mean age of patients was 59.5±10.9 years, with a duration of AH of 83.4±8.4 months. The groups of patients with grade 2 and 3 AH were comparable in age, gender, duration of AH, and body mass index (BMI). The most frequently present comorbid CV diseases included dyslipidemia/hypercholesterolemia (41% of patients), obesity (32% of patients), endocrine disorders (12% of patients), cardiac conduction abnormalities and heart rhythm disorders (11% of patients), chronic heart failure (11% of patients), and type 2 diabetes mellitus (11% of patients).

Out of 60 patients with grade 2 AH at the screening visit starting the treatment with the dual SPC of amlodipine/valsartan 5/80 mg, 17 patients (28.3%) completed the study on the initial dose, while the rest required up-titration. 30 patients (50.0%) completed the study on the 5/160 mg dose of amlodipine/valsartan, 11 patients (18.3%) on the 10/160 mg amlodipine/valsartan dose, and only 2 patients (3.4%) required the triple SPC of amlodipine/valsartan/hydrochlorothiazide 10/160/12.5 mg.

Out of 30 patients with grade 3 AH at the screening visit starting the treatment with the dual SPC of amlodipine/valsartan 5/160 mg, only 7 patients (17.9%) completed the study on the initial dose. 21 patients (53.8%) up-titrated the therapy to amlodipine/valsartan 10/160 mg, 11 patients (28.2%) up-titrated the therapy to the triple SPC, 8 of them (20.5%) to 10/160/12.5 mg, and 3 of them (7.7%) to amlodipine/valsartan/hydrochlorothiazide 10/160/25 mg. The results of the study showed that SPCs of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide effectively reduced BP in patients with grade 2 or 3 AH and had a good tolerability profile.

At baseline, elevated levels of albumin (≥30 mg/day) were present in 17 patients. After 16 weeks of treatment, amlodipine/valsartan-based therapy significantly decreased albuminuria in 10 (58.8%) studied patients: a change from ≥30 mg/day to less than 30 mg/day was observed in 60.0% and 57.1% of patients in the grade 2 and 3 AH groups, respectively.

nja terapija na bazi kombinacije amlodipina/valsartana znatno je smanjila albuminuriju u 10 (58,8 %) ispitivanih bolesnika: zabilježena je promjena od ≥30 mg/dan na manje od 30 mg/dan u 60,0 % bolesnika u skupini s AH 2. stupnja te u 57,1 % bolesnika u skupini s AH 3. stupnja.

Zabilježeno je minimalno poboljšanje od 5 % u centralnom (aortalnom) sistoličkom tlaku u 73 % svih bolesnika iz podskupine s dodatnim pregledom (n = 38). Centralni (aortalni) sistolički tlak smanjen je za 16,1 mmHg, sa 138,3 na 122,2 mm Hg. Odvojeno, u skupinama s AH 2. i 3. stupnja, zabilježeno je poboljšanje od 5 % u centralnom (aortalnom) tlaku u 66,7 %, odnosno 90 % bolesnika. Najveće smanjenje (sa 147,4 na 122,7 mmHg) zabilježeno je u skupini bolesnika s AH-om 3. stupnja (n = 11). U skupini bolesnika s AH-om 2. stupnja (n = 27) terapija na bazi kombinacije amlodipina/valsartana smanjila je centralni (aortalni) tlak sa 134,6 na 122,2 mm Hg.

Pri procjeni učinka liječenja na bazi fiksne kombinacije amlodipina/valsartana na arterijsku elastičnost u podskupini bolesnika s dodatnim pregledima zabilježeno je poboljšanje brzine pulsnog vala od najmanje 5 % u 57,1 % bolesnika; 48 % u skupini s AH-om 2. stupnja i 80 % u skupini s AH-om 3. stupnja. U skupini bolesnika s AH-om 2. stupnja zabilježeno je smanjenje brzine pulsnog vala s 10,37 m/s na početku ispitivanja na 9,92 m/s nakon 16 tjedana liječenja (**slika 1**).

A minimum improvement of 5% in central (aortic) systolic BP was observed in 73% of all patients from the subgroup with additional examination (n=38). Central (aortic) systolic BP (SBP) was reduced by 16.1 mmHg, from 138.3 mmHg to 122.2 mmHg. In the groups with grade 2 and 3 AH, the 5% improvement of central (aortic) SBP was achieved in 66.7% and 90.0% of patients, respectively. The greatest reduction (from 147.4 mmHg to 122.7 mmHg) of central (aortic) SBP was observed in the group of patients with grade 3 AH (n=11). In the group of patients with grade 2 AH (n=27), amlodipine/valsartan-based therapy reduced central (aortic) SBP from 134.6 mmHg to 122.2 mmHg.

When evaluating the effect of amlodipine/valsartan-based SPC treatment on arterial elasticity in the subgroup of patients with additional examinations, improvement in PWV of at least 5% was observed in 57.1% of patients; 48.0% and 80.0% in groups with grades 2 and 3 AH, respectively. In the group of patients with grade 2 AH, a reduction of PWV from 10.37 m/s at baseline to 9.92 m/s after 16 weeks of treatment was observed (**Figure 1**).

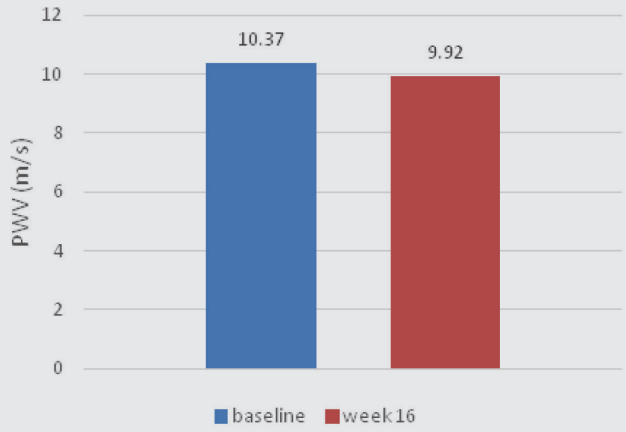

FIGURE 1. Pulse wave velocity (PWV; m/s) during treatment with amlodipine/valsartan-based single-pill combinations in patients with grade 2 hypertension.

TABLE 1. Median values of endothelium function parameters for the subgroup with additional examinations.

Parameter	Grade 2 hypertension group		Grade 3 hypertension group		All patients	
	Visit 5 (n=27)	Visit 5 (n=27)	Visit 1 (n=12)	Visit 5 (n=11)	Visit 1 (n=39)	Visit 5 (n=38)
IL-6, median	1.26	1.39	1.17	1.46	1.25	1.42
IL-10, median	0.42	0.09	0.49	0.19	0.44	0.10
sVCAM-1, median	655.80	723.30	679.65	547.70	669.30	586.50
VEGF-A, median	79.40	57.35	87.38	63.73	79.40	57.88
TNFα, median	0.25	0.68	0.39	1.14	0.25	0.70

IL – interleukin, sVCAM-1 – soluble vascular cell adhesion molecules-1, VEGF-A – vascular endothelial growth factor molecules, TNFα – tumor necrosis factor α, n – number of patients.

Zabilježeno je poboljšanje indeksa augmentacije za ≥5 % u 66,7 % bolesnika te 61,5 %, odnosno 80 % u skupinama s AH-om 2., odnosno 3. stupnja. Najveće je smanjenje zabilježeno u skupini s AH-om 2. stupnja. Kombinirano poboljšanje brzine pulsnog vala i indeksa augmentacije od ≥5 % zabilježeno je u 44,1 % bolesnika iz podskupine te u 33,3 %, odnosno 70 % bolesnika u skupini s AH-om 2., odnosno 3. stupnja.

Razine parametara uključenih u oštećenje endotela (IL-6, IL-10, TNFα, sVCAM, VEGF-A) procijenjene su prije primjene terapije na bazi kombinacije amlodipina/valsartana i nakon 16 tjedana liječenja (**tablica 1**). Apsolutne promjene navedenih parametara unutar skupine bile su statistički značajne na razini promjene vrijednosti od 5 % za IL-6, IL-10, VEGF-A, TNFα, osim za sVCAM-1, u podskupini od 38 bolesnika nakon 16 tjedana liječenja (5. posjet). Zabilježeno je relativno smanjenje vrijednosti razina IL-10 za najmanje 5 – 15 % u 76,3 % bolesnika. Smanjenje razine vaskularne endotelne adhezijske molekule (sVCAM-1) od najmanje 5 % zabilježeno je u 47,4 % bolesnika. Smanjenje razina TNFα za najmanje 5 – 10 % zabilježeno je u 10,5 % bolesnika. Smanjenje razine molekule vaskularnoga endotelnog faktora rasta (VEGF-A) za najmanje 5 % zabilježeno je u 68, 4% bolesnika, za najmanje 10 % u 63,2 % bolesnika, odnosno za najmanje 15 % u 60,5 % bolesnika.

Rasprava

Prvi cilj liječenja AH-a jest postići ciljne vrijednosti AT-a od <140/90 mmHg u svih bolesnika.[2] Rezultati kliničkog ispitivanja *VICTORY II* pokazali su da strategija liječenja fiksnom kombinacijom amlodipina/valsartana ima snažan antihipertenzivni učinak jer snizuje AT na ciljne vrijednosti u 90 % novodijagnosticiranih ili prethodno liječenih bolesnika s nekontroliranom AH 2. ili 3. stupnja. Metaanalize su pokazale da je u hipertenzivnih bolesnika centralni tlak bolji prediktor KV događaja u usporedbi s brahijalnim tlakom.[5] Također postoji i drukčiji učinak antihipertenzivnih lijekova na centralni u usporedbi s brahijalnim tlakom.[2] Sniženjem centralnoga tlaka također se smanjuje i KV rizik i oštećenje ciljnih organa uzrokovano hipertenzijom.[5] Liječenje na bazi fiksne kombinacije amlodipina/valsartana pokazalo je znatno sniženje centralnog (aortalnog) tlaka u gotovo tri četvrtine bolesnika. Zanimljivo je da su slični podatci dobiveni u međunarodnom multicentričnom kliničkom ispitivanju *VICTORY*, u kojem su valsartan i fiksna kombinacija valsartan/hidroklorotiazid u 74 % bolesnika AH-om 1. i 2. stupnja znatno smanjili krutost aorte, a time i brzinu pulsnog vala i centralni tlak.[6]

Mnogi bolesnici uključeni u ispitivanje *VICTORY II* imali su istodobne bolesti koje utječu na progresiju KVB-a pa je stoga odabir antihipertenzivnog liječenja koje ima blagotvoran učinak na usporivanje progresije KVB-a jako važan. Povišen AT i poremećena neurohumoralna regulacija vjerojatno će imati štetan učinak na bubrege. Smanjenje albuminurije, kao ranog markera bubrežne bolesti, također znači i manju pojavu KV i bubrežnih ishoda.[7] Dobro je potvrđeno da ARB-i (npr. valsartan) imaju nefroprotektivne učinke, zajedno s učincima snizivanja vrijednosti AT-a zahvaljujući blagotvornom djelovanju na oštećenje bubrega tijekom razvoja AH-a. K tomu, bubrežna vazodilatacija izazvana ARB-ima rezultira povećanim protokom krvi kroz bubrege, što dovodi do poboljšanja bubrežne ishemije i hipoksije. Lijekovi iz skupine ARB-a učinkovito smanjuju brzinu urinarnog izlučivanja albumina, bez obzira na sniženje vrijednosti AT-a.[8] Dokazano je da strate-

An improvement in the augmentation index of ≥5% was observed in 66.7% of patients; 61.5% and 80.0% in groups with grades 2 and 3 AH, respectively. The largest decrease was observed in the group with grade 2 AH. The combined improvement in PWV and the augmentation index of ≥5% was observed in 44.1% of subgroup patients and in 33.3% and 70.0% in groups with grades 2 and 3 AH, respectively.

The levels of parameters involved in endothelial damage (IL-6, IL-10, TNFα, sVCAM, VEGF-A) were assessed before the administration of the amlodipine/valsartan-based therapy and after 16 weeks of treatment (**Table 1**). Intra-group absolute changes of these parameters were statistically significant at the 5% level of change in values for IL-6, IL-10, VEGF-A, TNFα, with the exception of VCAM-1, in the subgroup of 38 patients after 16 weeks of treatment (Visit 5). Relative decrease in values of IL-10 levels by a minimum of 5-15% was observed in 76.3% of patients. A decrease in the level of vascular endothelial adhesion molecules (sVCAM-1) by a minimum of 5% was observed in 47.4% of patients. A decrease in TNFα levels by a minimum of 5-10% was observed in 10.5% of patients. A decrease in the level of vascular endothelial growth factor (VEGF-A) molecules by a minimum of 5%, 10%, and 15% was observed in 68.4%, 63.2%, and 60.5% of patients, respectively.

Discussion

The first objective of AH treatment is to achieve target BP levels of <140/90 mmHg in all patients.[2] The results of the VICTORY II clinical study showed that the amlodipine/valsartan-based SPC treatment strategy has a strong antihypertensive effect, reducing BP to the target levels in 90% of newly diagnosed or previously treated, but uncontrolled patients with grade 2 or 3 AH. Meta-analyses have shown that central BP is a better predictor of CV events in hypertensive patients compared with brachial BP.[5] There is also a different effect of antihypertensive medicines on central BP compared with brachial BP.[2] The reduction of central BP also decreases CV risk and HMOD.[5] Treatment with amlodipine/valsartan-based SPCs showed a significant reduction of central (aortic) BP in almost three quarters of patients. Interestingly, similar data were obtained in VICTORY, the international multicenter clinical study in which valsartan and a SPC of valsartan/hydrochlorothiazide significantly reduced the stiffness of the aorta and thus PWV and central BP in 74% of patients with grade 1 and grade 2 AH.[6]

Many patients included in the VICTORY II study had concomitant conditions that affect the progression of the CV disease, making and the choice of antihypertensive treatment, which has a beneficial effect on slowing the progression of CV disease, was therefore of great importance. Increased BP and neurohumoral dysregulation are likely to have an adverse effect on the kidneys. Reduction of albuminuria, as an early marker of kidney disease, translates into a decreased occurrence of CV and renal outcomes.[7] It is well-established that ARBs (e.g. valsartan), exert renoprotective effects in addition to their BP-lowering effects due to the benefits on renal injury during the development of AH. Furthermore, ARB-induced renal vasodilation results in an increase in renal blood flow, leading to an improvement of renal ischemia and hypoxia. ARB is effective in reducing the urinary albumin excretion rate independently of BP reduction.[8] It has been shown that a treatment strategy that includes an angiotensin-convert-

gija liječenja koja uključuje inhibitor angiotenzin-konvertaze (ACE) ili ARB smanjuje albuminuriju i pojavu progresije dijabetičke nefropatije učinkovitije nego druge skupine lijekova.[2] Smanjenje albuminurije liječenjem na bazi fiksne kombinacije amlodipina/valsartana također je zabilježeno i u ispitivanju *VICTORY II*, jer je u više od polovice uključenih bolesnika s početnom albuminurijom došlo do poboljšanja albuminurije, čime je poboljšana funkcija bubrega.

U bolesnika s AH-om povišene vrijednosti AT-a mogu povećati arterijsku krutost. U smjernicama ESC-a/ESH-a za 2018. godinu za liječenje AH-a, karotidno-femoralna brzina pulsnog vala zlatni je standard mjerenja krutosti velikih arterija. Brzina pulsnog vala >10 m/s smatra se konzervativnom procjenom značajnih promjena u aortalnoj funkciji hipertenzivnih bolesnika srednje životne dobi.[2] Postoje znatni dokazi da je povećana krutost arterija neovisan čimbenik rizika za KV bolest,[9] pa idealan antihipertenzivni lijek treba i sniziti vrijednosti AT-a i poboljšati arterijsku krutost.[2] Prema tome, smanjivanjem AT-a svi antihipertenzivni lijekovi smanjuju arterijsku krutost.[2] Metaanalize brojnih randomiziranih kliničkih ispitivanja upućuju na to da ACE inhibitori i ARB-i, osim učinka snizivanja AT-a, dugoročno mogu smanjiti i brzinu pulsnog vala.[2,9] Pozitivan učinak terapije na osnovi fiksne kombinacije amlodipina/valsartana također je zabilježen i u kliničkom ispitivanju *VICTORY II*. U skupini bolesnika s dodatnim pregledom, 2 od 3 bolesnika liječena fiksnom kombinacijom na bazi amlodipina/valsartana imalo je pad brzine pulsnog vala od barem 5 %, što je nakon 16 tjedana liječenja dovelo do srednje vrijednosti brzine pulsnog vala od 10 m/s. To je pokazivalo istaknuti pozitivan učinak liječenja na elastičnost arterija. Blagotvoran učinak na arterijsku krutost koji se postiže terapijom fiksnom kombinacijom na bazi amlodipina/valsartana može se objasniti potencijalnim učinkom na vaskularnu stijenku. Valsartan blokira renin-angiotenzin-aldosteronski sustav i tako potiskuje proinflamatorne signale angiotenzina II i smanjuje ozbiljnost oksidativnoga stresa. On promiče normalizaciju endotela i osigurava pravilnu vazodilataciju, što usporuje remodeliranje i restrukturiranje vaskularne stijenke.[10] Blokatori kalcijevih kanala mogu blokirati N-kalcijeve kanale na završetcima simpatičkih živaca, što ima lokalan simpatolitički učinak putem supresije adrenergičkih učinaka na krvne žile. Smanjenje bazalnog tonusa glatkih mišićnih stanica i inhibicija toničke komponente pridonose smanjenju krutosti arterijske stijenke.[11]

Ateroskleroza je primarno poremećaj lipidnog metabolizma, ali također postoji i istaknuta kronična upalna komponenta koja uzrokuje progresiju aterosklerotske lezije u arterijskoj stijenci.[12] Nakupljanje upalnih stanica unutar arterijske stijenke dovodi do lokalne proizvodnje upalnih markera, kao što su interleukini (npr. IL-6, IL-10), citokini i proteaze. Oni pojačavaju ulazak monocita i limfocita, čime pospješuju progresiju aterosklerotskih lezija.[13] Vaskularni endotelni faktor rasta (VEGF) važan je angiogeni faktor. On izaziva migraciju i proliferaciju stanica endotela, pospješuje vaskularnu permeabilnost i modulira trombogenost.[14] Abnormalni endotel koristi makrofage za razvoj aterosklerotskoga plaka, u čemu pomaže i endotelna ekspresija adhezijskih molekula (npr. vaskularnih staničnih adhezijskih molekula; VCAM).[14] Antihipertenzivi kao protuupalni lijekovi mogu imati ključnu ulogu u aterosklerotskim lezijama. Prethodna su ispitivanja otkrila da valsartan može inhibirati razvoj ateroskleroze tako što smanjuje proinflamatorne citokine u serumu.[15] U kliničing enzyme (ACE) inhibitor or ARB decreased albuminuria and the appearance or progression of diabetic nephropathy more effectively than other medication classes.[2] A decrease in albuminuria by amlodipine/valsartan SPC-based treatment was also observed in the VICTORY II clinical study, since there was an improvement in albuminuria, and thus improved kidney function, in more than half of included patients with initial albuminuria.

Increased BP can increase arterial stiffness in patients with AH. In the 2018 ESC/ESH Guidelines for the management of AH, carotid-femoral PWV is the golden standard for measuring large artery stiffness. A PWV >10 m/s is considered a conservative estimate of significant alterations of the aortic function in middle-aged hypertensive patients.[2] Significant evidence suggests that the increase in arterial stiffness is an independent risk factor for CV diseases[9], and an ideal antihypertensive medication should both lower BP and improve arterial stiffness.[2] Thus, all antihypertensive medicines reduce arterial stiffness by reducing BP.[2] Meta-analyses of many randomized clinical trials suggest that ACE inhibitors and ARBs may reduce PWV on a long-term basis in addition to the BP-lowering effect.[2,9] The positive effect of amlodipine/valsartan SPC-based therapy was also observed in the VICTORY II clinical study. In the group of patients with additional examination, 2 out of 3 patients treated with a SPC based on amlodipine/valsartan showed at least a 5% drop in PWV, leading to a mean PWV of 10 m/s after 16 weeks of treatment. This indicated a positive marked effect of the treatment on arterial elasticity. The beneficial effect of amlodipine/valsartan-based SPC therapy on arterial stiffness can be explained by a potential impact of valsartan and amlodipine on the vascular wall that is included in the SPC. Valsartan, by blocking the renin-angiotensin-aldosterone system, suppresses proinflammatory angiotensin II signals and reduces the severity of oxidative stress. It promotes normalization of the endothelium and ensures proper vasodilatation, which slows down remodeling and connective tissue restructuring of the vascular wall.[10] CCBs can block N-calcium channels at the endings of sympathetic nerves, which has a local sympatholytic effect through a suppression of adrenergic effects on blood vessels. A decrease in the basal tone of smooth muscle cells and inhibition of the tonic component contribute to a decrease in the rigidity of the arterial wall.[11]

Atherosclerosis is primarily a disorder of lipid metabolism, but there is also a prominent chronic inflammatory component that drives atherosclerotic lesion progression in the arterial wall.[12] The accumulation of inflammatory cells within the arterial wall leads to a local production of inflammatory markers, such as interleukins (e.g. IL-6, IL-10), cytokines, and proteases. They enhance the influx of monocytes and lymphocytes, thereby promoting the progression of atherosclerotic lesions.[13] The vascular endothelial growth factor (VEGF) is an important angiogenic factor. It induces migration and proliferation of endothelial cells, enhances vascular permeability, and modulates thrombogenicity.[14] Macrophage recruitment by abnormal endothelium in developing atherosclerotic plaques is aided by the endothelial expression of adhesion molecules (e.g. the vascular cell adhesion molecule; VCAM).[14] Antihypertensives as anti-inflammatory agents can play a key role in atherosclerotic lesions. Previous studies have revealed that valsartan may inhibit the development of atherosclerosis by lowering serum pro-inflammatory cytokines.[15]

kom ispitivanju *VICTORY II* također je ispitan učinak fiksnih kombinacija na bazi amlodipina/valsartana na upalne parametre. Razine vaskularnoga endotelnog faktora rasta A (VEGF-A), glavnog regulatora angiogeneze, znatno su se smanjile u svih bolesnika u podskupini s dodatnim pregledima, uključujući skupinu bolesnika s AH-om 3. stupnja. Dobiveni podatci o učinku fiksnih kombinacija na bazi amlodipina/valsartana na upalne parametre zahtijeva dodatno ispitivanje jer su među mnogim parametrima otkrivene promjene koje se razvijaju u više smjerova. To može biti povezano sa značajkama dizajna ovog ispitivanja, koje je blisko stvarnoj kliničkoj praksi: otvoren dizajn, nedostatak randomizacije bolesnika i kontrolnih skupina, što nije omogućilo usporedbu učinaka fiksne kombinacije s drugim liječenjima. Primjena fiksne kombinacije, uključujući dva i više antihipertenziva, nije pokazala izolirani učinak pojedinačnih komponenti terapije, što je važno za procjenu svih sekundarnih parametara, a osobito parametara oštećenja endotela.

Zaključak

Rezultati kliničkog ispitivanja *VICTORY II* pokazali su da u bolesnika s AH-om 2. ili 3. stupnja terapija fiksnim kombinacijama na bazi amlodipina/valsartana djelovanjem na markere uključene u endotelnu funkciju, osim učinkovitog sniženja vrijednosti AT-a, također pruža i širok spektar drugih kliničkih koristi, širih od same kontrole AT-a, poput smanjene prevalencije albuminurije, smanjenoga centralnog aortalnog tlaka, poboljšane elastičnosti krvnih žila i pozitivnog učinka na funkciju vaskularnog endotela.

The effect of amlodipine/valsartan-based SPCs on inflammatory parameters was also evaluated in the VICTORY II clinical study. The levels of the vascular endothelial growth factor A (VEGF-A), a key regulator of angiogenesis, significantly decreased in all patients of the subgroup with additional examinations, including the group of patients with grade 3 AH. The obtained data on the effect of amlodipine/valsartan-based SPCs on inflammatory parameters require further study, since multidirectional changes were detected among the many parameters. This may be associated with the design features of this study that are close to real clinical practice: open design and lack of randomization of patients and control groups, which did not allow for a comparison of SPC effects with other treatments. The use of a SPC, including those with two and three antihypertensives, did not demonstrate an isolated effect of individual components of treatment, which is important in assessing all secondary parameters, especially endothelial damage parameters.

Conclusion

The results of the VICTORY II clinical study showed that therapy with amlodipine/valsartan-based SPCs in patients with grade 2 or 3 AH not only effectively reduces BP but also provides a broad spectrum of clinical benefits in addition to BP control, such as decreased prevalence of albuminuria, decreased central aortic pressure, improved vessel elasticity, and a positive effect on the vascular endothelial function through their effect on the markers involved in endothelial function.

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