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

SAZETAK: Utočak optimizaciji i pojednostavnjenju liječenja arterijske hipertenzije (AH), postizanje kontrole arterijskoga tlaka (AT) i dalje je izazov, a većini je bolesnika potrebno kombinirano liječenje bi postigli ciljev kontrole AT-a. Zbog višefaktorskog učinka AH-a, uz smanjenje vrijednosti AT-a, dodatna prevencija oštećenja cijelih organa te održavanje vaskularnog integriteta postignuto antihipertenzivima korisni su za optimalno smanjenje kardiovaskularnog (KV) rizika. cilj multicentričkog, otvorenog, prospektnog 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 nelijećenih ili prethodno liječenih bolesnika s AH-om 2. ili 3. stupnja u kojih nije postignuta kontrola vrijednosti AT-a. Svi bolesnici sa AH-om 2. stupnja započeli su liječenje fiksom kombinacijom amlodipina/valsartana 5 mg / 80 mg, koja se po potrebi može titrirati u fiksne komezinjacija amlodipina/valsartana/hidroklorotiazida 10/160/25 mg kako bi se postigle ciljev vrijednosti AT-a. Bolesnici sa AH-om 3. stupnja započeli su liječenje fiksom kombinacijom amlodipina/valsartana 5 mg / 360 mg koja se po potrebi može titrirati u fiksne kombinacije amlodipina/valsartana/hidroklorotiazida 10/160/25 mg kako bi se postigle ciljev vrijednosti. Uz postizanje ciljev vrijednosti AT-a mjerenja u ordinaciji, u 90 % bolesnika nakon 16 tjedana liječenja, terapije na bazi kombinacije amlodipina/valsartana tajni su smanjili prevalenciju albuminurne i centralnoga aortalnog tlaka, poboljšale elastnost krvnih žila i pokazale pozitivan učinak na funkciju vaskularnog integriteta putem svoje dejavnja na markeri uključene u funkciju endotel. ZBIRNA RIJEČI: arterijska hipertenzija, fiksna kombinacija, valsartan, amlodipin, hidroklorotiazid.

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

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**Uvod**

Glavni cilj liječenja arterijske hipertenzije (AH) jest smanjiti rizik od fatalnih i nefatalnih kardiovaskularnih (KV), cerebrovascularnih komplikacija i kronične bolesti bubrega. Stoga je važno ne samo smiriti arterijski tlak (AT) na ciljne vrijednosti nego također i smanjiti oštećenje organa uzrokovan hipertenzijom – strukturne i ili funkcionalne promjene na srcu, mozgu, mrežnici, bubrezima i vaskulariti koja izaziva AH.

Smjernice Europskoga kardiološkog društva / Europskog udrženja 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. Medu preporučenim lijekovima prve linije također su i ARB-i (npr. valsartan) u kombinaciji s blokatorom kalcijevednih kanala ili diuretikom, po mogućnosti u obliku fiksne kombinacije. Liječenje fiksnom kombinacijom može dovesti do adekvatnije kontrole AT-a te može pokazati dodatne sinergističke vazoprotektivne ili pleiotropne učinke.

Primarni cilj multicentričnog, otvorenog, prospektivnog kliničkog ispitivanja VICTORY II bio je procijeniti djelotvorno- 
nost i sigurnost fiksnih kombinacija amlodipina/valsartana i amlodipina/valsartana/hidroklorotiazida u postizanju ciljnih razina različitih vrsta AT-a (mjeren u ordinaciji, kod kože te 24-satnim kontinuiranim mjerjenjem) u odraslih bolesni 
ka s AH-om 2 ili 3. stupnja. Sekundarni su ciljevi bili procijeni 
činke liječenja kombinacijom amlodipina/valsartana (amlodipin/valsartan) i amlodipina/valsartana/hidrokloroti 
azida (Valtricom®) na metaboličke parametre, razinu albuminurije, razinu središnje arterijskog tlaka, elastičnost arterija, funkciju endo 
dotela, učinak na erektulinu funkciju, učinak na kvalitetu bo 
lesnikova života i učinak na praktičnost liječenja. Rezultati 
činka ispitivanja liječenje – fiksnih kombinacija amlodipi 
a/valsartana (Wamlox®) i amlodipina/valsartana/hidroklo 
rotiazida (Valtricom®) na AT – već su objavljeni. U ovom se 
članku fokusiramo na procjenu proučavanog dodatnih učin 
aka, osim na kontrolu AT-a, učinak na albuminuriju, central 
arterijski tlak, elastičnost arterija (brzina pulsnog vala i indeks 
augmentacije) i u funkciju endotela (razine faktora nekroze a (TNFα), interleukina 6 (IL-6) i 10 (IL-10), vaskularni stani 
vkišice adhezijske molekule tipa 1 (VCAM-1) i vaskularni endoteli 
ektoral fakta (VEGF-A)).

**Bolesnici i metode**

Kliničko ispitivanje VICTORY II, koje je provedeno dok su vrijedile smjernice ESH/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 diastolički tlak u ordinaciji ≥ 100 mmHg) ili bolesnike s nekontroliranim vrijednostima AT-a mjerena 
i u ordinaciji za vrijeme prethodne terapije. Liječenje je trajalo 16 tjedana. Bolesnici su morali posjetiti klinički centar sredstvom intervala od 4 tjedna. Svaki je bolesnik morao sudjelova 
i u 5 posjetima, s dodatnim posjetom za podskupinu bolesnika. Pri prvom posjetu svi bolesnici s AT-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipina/valsartana (Wam 
x®) 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. 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.

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. Treatment with an SPC may lead to more adequate control of BP and may show additional synergistic vasoprotective or pleiotropic effects.

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 am 
lodipine/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 and amlodipine/valsartan/hydrochlorothiazide (Valtric 
®) were already published. In this ar 
icle, we focus on the evaluation of the additional effects in 
addition to BP control: the effect on albuminuria, central aor 
tic pressure, elasticity of the arteries (pulse wave velocity and 
augmentation index), and on endothelial function (the levels of neocrosis factor α (TNFα), interleukins 6 (IL-6) and 10 (IL-10), type 1 vascular cell adhesion molecules (VCAM-1), and vascul 
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, previous 
ly untreated patients (office systolic BP ≥160 mmHg and/ 
or office diastolic BP ≥100 mmHg), or those with office BP un 
controlled 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 (Valtric®) 10/160/12.5 mg to achieve target of 

**Cardiologia Croatica**

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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 sa AH-om 2. i 3. stupnja bile su u susjednosti po dobi, spolu, trajanju AH-a i inzidentu arterioarterijske bolesti. Najčešće prisutne istodobne KV bolesti u podskupini bolesnika uključivale su dislipidemiju/hiperkolesterolemiju (41% bolesnika), obesinu (32% bolesnika), endokrine poremećaje (12% bolesnika), srčansko ujedinjavanje srca (11% bolesnika), rastnom funkciju (nekrozni faktor 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) ujedno uzimanja ispitivane terapije i nakon 16 tjedana liječenja istraživanja rezultata mjerenja AT-a u ordinaciji, klinička pregleda, općega stanja i tegoba bolesnika.

Za procjenu organoprotektivnih svojstava u svih je bolesnika i posjetom za probleme i pri posjetu određen učinak na centralni (aortalni) tlak i elasticnost arterija i ispitivani liječenje na razinu albumina u urinu. Da bi se procijenio učinak na centralni (aortalni) tlak i elasticnost artetijskih moždina, a dijagnozu liječenja na razinu albumina u urinu bilo je potrebno izvesti u podskupini bolesnika.

Rezultati ispitivanja pokazali su da fiksne kombinacije amlodipina/valsartana/hidroklorotiazida (Valtricom®) 10/160/12,5 mg kako bi se postigla ciljna vrijednost AT-a mjerena u ordinaciji. Bolesnici sa AH-om 3. stupnja započeli su liječenje razini albumina (≥30 mg/dan) na početku ispitivanja za praćenje liječnik u ordinaciji za praćenje liječnik i nakon 16 tjedana liječenja u podskupini bolesnika. Usto, ispitane su razlike razina albumina na (Wamlox®) 10/160/25 mg kako bi se postigla ciljna vrijednost AT-a mjerena u ordinaciji. Pri posjetima za praćenje liječnik cijenio učinak na centralni (aortalni) tlak i elasticnost arterija i ispitivani liječenje na razinu albumina u urinu. Da bi se procijenio učinak na centralni (aortalni) tlak i elasticnost artetijskih moždina, a dijagnozu liječenja na razinu albumina bilo je potrebno izvesti u podskupini bolesnika.

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 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/d) 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 u 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 u arterijsku elastičnost u podskupini bolesnika s dodatnim pregledima zabilježeno je poboljšanje brzine pulsog 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 pulsog vala s 10,37 m/s na početku ispitanja na 9,92 m/s nakon 16 tjedana liječenja (slj. 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).

**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=12) | Visit 5 (n=11) | Visit 5 (n=39) | Visit 5 (n=38) |
| IL-6, median    | 1.26          | 1.17          | 1.46          | 1.25          | 1.42          |
| IL-10, median   | 0.42          | 0.49          | 0.19          | 0.44          | 0.10          |
| sVCAM-1, median | 655.80        | 679.65        | 547.70        | 669.30        | 586.50        |
| VEGF-A, median  | 79.40         | 87.38         | 63.73         | 79.40         | 57.88         |
| TNFa, median    | 0.25          | 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, TNFa – tumor necrosis factor a, 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. i 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 podslike te u 33.3%, odnosno 70% bolesnika iz skupini s AH-om 2. stupnja, 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 uнутar skupine bile su statistički značajne na razini promjene vrijednosti od 5% za IL-6, IL-10, VEGF-A, TNFα, osim za sVCAM-1, u podsliku od 38 bolesnika nakon 16 tjedana liječenja (5. posjet). Zabilježeno je relativno smanjenje vrijednosti ražina 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 razine 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. 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 lijeućih bolesnika s nekontroliranom AH 2. ili 3. stupnja. Metaanalize su pokazale da je u hipertenzivnih bolesnika centralni tlak bolji prediktor CV i HMOD. Također poštujuci učinak antihipertenzivnih lijekova na oštećenje endotela, aorte, a time i brzinu pulsnog vala i centralni tlak.

Tablica 1

| Parametar          | Skupina 1 | Skupina 2 | Skupina 3 |
|--------------------|-----------|-----------|-----------|
| IL-6               | 5%        | 10%       | 15%       |
| IL-10              | 5%        | 10%       | 15%       |
| TNFα               | 5%        | 10%       | 15%       |
| sVCAM-1            | 5%        | 10%       | 15%       |
| VEGF-A             | 5%        | 10%       | 15%       |

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 TNF 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. 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. There is also a different effect of antihypertensive medicines on central BP compared with brachial BP.

The reduction of central BP also decreases CV risk and HMOD. 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.

Many patients included in the VICTORY II study had comitant 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. 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. It has been shown that a treatment strategy that includes an angiotensin-convert-
gija liječenja koja uključuje inhibitor angiotenzin-convertaze (ACE) ili ARB smanjuje albuminuriju i pojavu progresije dija-
betičke nefropatije učinkovitije nego druge skupine lijekova.3 Smanjenje albuminurije liječenjem na bazi fiksne kombinaci-
je amlodipina/valsartana također je zabilježeno i u ispitiva-
nju 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 po-
većati arterijsku krutost. U smjernicama ESC-a/ESH-a za 2018. godinu za liječenje AH-a, katodin-femoralna brzina
pulsnog vala zlatni je standard mjerenja krutosti velikih ar-
terija. Brzina pulsnog vala >10 m/s smatra se konservativnom
procjenom značajnih promjena u aortalnoj funkciji hiperten-
zivnih bolesnika srednje životne dobi.2 Postoje znatni dokazi da je povećana krutost arterija neovisan čimbenik rizika za
KV bolest,3 pa idealan antihipertenzivni lijek treba i sniziti
vrijednosti AT-a i poboljšati arterijsku krutost.4 Prema tome,
smanjivanjem AT-a svi antihipertenzivni lijekovi smanju-
ju arterijsku krutost.5 Metaanalize brojnih randomiziranih
kliničkih ispitivanja upućuju na to da ACE inhibitori i ARB-i,
osićučinika snizavanja AT-a, dugoročno mogu smanjiti i brzi-
u pulsnog vala.6 Pozitivan učinak terapije na osnovi fiksne
kombinacije amlodipina/valsartana također je zabilježen i u
kliničkom ispitivanju VICTORY II. U skupini bolesnika s do-
atnim pregledom, 2 od 3 bolesnika liječenog fiksnom kombi-
nacijom na bazi amlodipina/valsartana imalo je pad brzine
pulsnog vala od barem 5 %, što je nakon 16 tjedana liječenja
do velo srednje vrijednosti brzine pulsnog vala od 10 m/s.
To je pokazivalo istaknuti pozitivan učinak liječenja na ela-
stičnost arterija. Blagotvoren učinak na arterijsku krutost koji se postiže terapijom fiksnom kombinacijom na bazi amlodi-
pina/valsartana može se objasniti potencijalnim učinkom na
vaskularnu stijenku. Valsartan blokira renin-angiotenzin-al-
dosteronski sustav i tako potiskuje proinflamatorne signale
angiotenzina II i smanjuje ozbiljnost oksidativnoga stresa. On
promiče normalizaciju endotela i osigurava pravilnu vazod-
lataciju, što usporjava remodeliranje i restrukturiranje vasku-
larne stijenke. Blokatori kalcijskih kanala mogu blokirati N-
kalcijske kanale na završcima 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

Atheroskleroza je primarno poremećaj lipidnog metaboliz-
ma, ali također postoji i istaknuta kronična učinak kompo-
ponenta koja uzrokuje progresiju atherosklerotske lezije u arterij
skoj stijenici.12 Nakupljanje upalnih stanica unutar arterijske
stijenke dovodi do lokalne proizvodnje upalnih markera,
as što su interleukini (npr. IL-6, IL-10) citokini i proteaz.
Oni pojačavaju ulazak monocita i limfocita, čime pospešju-
ju progresiju atherosklerotskih lezija.13 Vaskularni endoteli
faktor rasta (VEGF) važan je angiogeni faktor. On izaziva
migraciju i proliferaciju stanica endotela, pospešuje vasku-
larnu permeabilnost i modulira trombogenost.14 Abnormalni
deloteli koristi makrofage za razvoj atherosklerotskoga plaka,
u čemu pomaže i endotelnog ekspresija adhezijskih molekula
(npr. vaskularnih staničnih adhezijskih molekula; VCAM).15 Antihipertenzivi kao protuupalni lijekovi mogu imati ključnu
ulogu u atherosklerotskim lezijama. Prethodna su ispitivanja
otkrio da valsartan može inhibirati razvoj atheroskleroze tako
što smanjuje proinflamatorne citokine u serumu.15 U klinič-

ing enzyme (ACE) inhibitor or ARB decreased albuminuria
and the appearance or progression of diabetic nephropathy
more effectively than other medication classes. A decrease
in albuminuria by amlodipine/valsartan SPC-based treat-
ment 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 pa-
tients 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 meas-
uring 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. Significant
evidence suggests that the increase in arterial stiffness is an
independent risk factor for CV diseases, and an ideal anti-
hypertensive medication should both lower BP and improve
arterial stiffness. Thus, all antihypertensive medicines
reduce arterial stiffness by reducing BP. 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. The positive effect of amlodipine/
valsartan SPC-based therapy was also observed in the VIC-
TORY 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, lead-
ing to a mean PWV of 10 m/s after 16 weeks of treatment. This
indicated a positive marked effect of the treatment on arte-
cial elasticity. The beneficial effect of amlodipine/valsartan-
sbased 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 proin-
flammatory angiotsensin II signals and reduces the severity
of oxidative stress. It promotes normalization of the endo-
thelium and ensures proper vasodilatation, which slows down
remodeling and connective tissue restructuring of the vascu-
lar wall.18 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 inhi-
bition 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 compo-
nent that drives atherosclerotic lesion progression in the
arterial wall. 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 lym-
phocytes, thereby promoting the progression of atheroscle-
rotic lesions. The vascular endothelial growth factor (VEGF)
is an important angiogenic factor. It induces migration and
proliferation of endothelial cells, enhances vascular permea-
bility, and modulates thrombogenicity. Macrophage recruit-
ment by abnormal endothelium in developing atherosclerotic
plagues 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 re-
vealed that valsartan may inhibit the development of athero-
sclerosis by lowering serum pro-inflammatory cytokines.15

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kom ispitivanju VICTORY II također je ispitan učinak fiks-
snih kombinacija na bazi amlodipina/valsartana na upalne
parametre. Razine vaskularnoga endotelnog faktora rasta A
(VEGF-A), glavnog regulatora angiogeneze, znatno su se sman-
juile u svih bolesnika u podskupini s dodatnim pregledima, uključujući skupinu bolesnika s AH-om 3. stupnja. Dobiveni
podaci o učinku fiksnih kombinacija na bazi amlodipina/val-
sartana na upalne parametre zahtijeva dodatno ispitivanje jer
su među mnogim parametrima otkriveni promjene koje se
razvijaju u više smjerova. To može biti povezano sa značajka-
dima dajzana ovog ispitivanja, koje je blisko stvarnoj kliničkoj
praksi: otvoreni dizajn, nedostatak randomizacije bolesnika
i kontrolnih skupina, što nije omogućilo usporedbu učinaka
fiksne kombinacije s drugim liječnicima. Primjena fiksne
kombinacije, uključujući dva i više antihipertenziva, nije po-
kazala 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 kombina-
cijama na bazi amlodipina/valsartana djelovanjem na mar-
kere uključene u endotelnu funkciju, osim učinakotog sna-
ženja vrijednosti AT-a, također pruža širok spektar drugih
kliničkih koristi, sličnih od same kontrole AT-a, poput smanjenja
prevalencije albuminurije, smanjenja centralnog aortalnog
tlaka, poboljšane elastičnosti krivih žila i pozitivnog učinka
na funkciju vaskularnog endotela.

The effect of amlodipine/valsartan-based SPCs on inflamma-
tory parameters was also evaluated in the VICTORY II clinical
study. The levels of the vascular endothelial growth fac-
tor 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 iso-
lated 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 elastic-
ity, and a positive effect on the vascular endothelial function
through their effect on the markers involved in endothelial function.

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