Djelotvornost i sigurnost valsartana i kombinacije valsartana i hidroklorotiazida u liječenju bolesnika s blagom do umjerenom arterijskom hipertenzijom – kliničko ispitivanje VICTORY

The efficacy and safety of valsartan and the combination of valsartan and hydrochlorothiazide in the treatment of patients with mild to moderate arterial hypertension — the VICTORY trial

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SAŽETAK: Povišeni arterijski tlak (AT) vodeći je globalni čimbenik rizika za kardiovaskularne bolesti i kronične bubrežne bolesti. Stoga su uz promjene u životnome stilu očito potrebni i djelotvorni antihipertenzivni lijekovi kako bi se bolesnicima pružilo ne samo ublažavanje simptoma nego i kardiovaskularna zaštita. Kliničko ispitivanje VICTORY provedeno je kako bi se procijenila djelotvornost i sigurnost monoterapije valsartanom (Valsacor®) i liječenja kombinacijom fiksnih doza (KFD) valsartana i hidroklorotiazida (Valsacombi®) u široj populaciji bolesnika s blagom do umjerenom arterijskom hipertenzijom. Ukupno je 365 bolesnika bilo uključeno u šesnaestotjedno međunarodno, multicentrično, otvoreno, prospektivno ispitivanje. Bolesnici su počeli liječenje s 80 mg valsartana na dan, što se zatim moglo titrirati do 320 mg dnevno ili kombinirati s hidroklorotiazidom u KFD kako bi se postigla ciljna vrijednost AT-a. Rezultati kliničkog ispitivanja VICTORY pokazali su da valsartan i KFD valsartana i hidroklorotiazida djelotvorno smanjuju AT u bolesnika s blagom do umjerenom arterijskom hipertenzijom te imaju vrlo dobar profil podnošljivosti.

SUMMARY: Raised blood pressure (BP) is the leading global risk factor for cardiovascular disease and chronic kidney disease. Thus, in addition to lifestyle changes effective antihypertensive medication is clearly needed to provide not only symptomatic relief but also cardiovascular protection. The VICTORY trial was performed to assess the efficacy and safety of valsartan monotherapy (Valsacor®) and therapy with the fixed-dose combination (FDC) of valsartan and hydrochlorothiazide (Valsacombi®) in a broad population of patients with mild to moderate arterial hypertension. A total of 365 patients were enrolled in this 16-week, international, multicentre, open-label, prospective trial. The patients started the treatment with 80 mg valsartan daily, which could be up-titrated to 320 mg daily or combined with hydrochlorothiazide (HCTZ) in a fixed-dose combination to achieve target BP. The results of the VICTORY trial showed that valsartan and the FDC of valsartan and hydrochlorothiazide effectively reduce BP in patients with mild to moderate arterial hypertension, and have a very good tolerability profile.

KLJUČNE RIJEČI: arterijska hipertenzija, arterijski tlak, djelotvornost, sigurnost, valsartan.

KEYWORDS: hypertension, blood pressure, efficacy, safety, valsartan.

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Uvod

Kad je Steven Hales prvi put izmjerio arterijski tlak (AT) budnoga konja 1733. godine,[1] nije bio svjestan činjenice da pojedini ljudi mogu imati povišeni AT i da to može biti loše za njihovo zdravlje. Dapače, do početka 20. stoljeća većina je liječnika smatrala da bi povišena vrijednost AT-a bio odgovor na potrebe organa u organa u bolesnika s arterijskom hipertenzijom. Danas je zahvaljujući Framinghamskoj studiji te mnogim drugim velikim epidemiološkim istraživanjima očito da je visoki AT doista temeljni uzrok infarkta miokarda i moždanog udara u milijuna hipertenzivnih bolesnika.[2]

Introduction

When Steven Hales, for the first time, measured blood pressure (BP) in an awake horse in 1733,[1] he was not aware of the fact that some individuals may have elevated BP and that this may be bad for their health. Indeed, until the beginning of the 20th century most physicians felt that elevated BP would be a response to a requirement of the organs in hypertensive patients. Today, thanks to the Framingham trial and many other large epidemiological surveys, it is obvious that high BP is indeed the underlying cause of myocardial infarction and stroke in millions of hypertensive patients.[2]

Procjenjuje se da se broj odraslih osoba s povišenim vrijednostima AT-a povećao s 594 milijuna u 1975. godini na 1,13 milijardi u 2015., zahvaćajući 597 milijuna muškaraca i 529 milijuna žena. Na globalnoj je razini to povećanje pripisivo rastu i starenju populacije. U 2015. godini prevalencija povišenog AT-a standardizirana po dobi bila je 24,1% u muškaraca i 20,1% u žena. Prema najnovijim podatcima, povišeni AT trajan je zdravstveni problem u srednjoj i istočnoj Europi.[3]

Promjene u prehrani i načinu života mogu poboljšati kontrolu AT-a i smanjiti rizik od komplikacija, no farmakološko je liječenje često ipak prijeko potrebno u osoba kod kojih promjene u načinu života nisu dovoljne ili djelotvorne.[4]

Blokatori angiotenzinskih receptora (ARB, npr. valsartan) u prvoj su liniji antihipertenzivnih lijekova. Mogu se rabiti i samostalno i u kombinaciji s drugim antihipertenzivnim lijekovima (npr. hidroklorotiazid, HCTZ).[5] Provedena su mnoga klinička ispitivanja s valsartanom na području arterijske hipertenzije, no podatci su o djelotvornosti i sigurnosti generičkih lijekova rijetkost. Ovaj članak izlaže glavne rezultate kliničkog ispitivanja VICTORY[6], koje je prethodno objavljeno u časopisu *Kardiologia Polska* te je također uključivalo bolesnike iz Hrvatske.

Pacijenti i metode

Ukupno je 365 bolesnika (196 žena i 169 muškaraca) sudjelovalo u ovome međunarodnom, multicentričnom, otvorenom, prospektivnom kliničkom ispitivanju četvrte faze, nazvanom VICTORY. Hipertenzivni bolesnici iz 25 centara u pet zemalja – Slovenija, Ruska Federacija, Ukrajina, Češka Republika i Hrvatska – bili su uključeni u kliničko ispitivanje između svibnja 2013. i lipnja 2015. godine. Bolesnici su uključeni na osnovi indikacija u sažetku opisa svojstava lijeka za ispitivane lijekove. Pri prvome posjetu svaki je bolesnik dobio detaljno objašnjenje ciljeva i postupaka ispitivanja te je bio zamoljen da potpiše formular za informirani pristanak prije no što je proveden bilo kakav postupak. Protokol je kliničkog ispitivanja predan i potvrdila su ga sva nacionalna povjerenstva za medicinsku etiku u zemljama koje su sudjelovale u njemu.[6]

Tijekom razdoblja od 16 tjedana bolesnici su liječnika posjetili pet puta: prvi put pri uključivanju u ispitivanje, drugi put nakon mjesec dana liječenja, treći nakon 2 mjeseca, četvrti put nakon 3 mjeseca i peti put nakon 16 tjedana liječenja. Liječenje je započeto jednom tabletom valsartana od 80 mg na dan u svih bolesnika (i neliječenih i prethodno liječenih). Samo su u Rusiji prethodno liječeni bolesnici pri prvome posjetu dobili dozu od 160 mg (na zahtjev etičkog povjerenstva), što nije utjecalo na rezultate ispitivanja. Nakon četiri tjedna liječenja doza je promijenjena na jednu tabletu valsartana od 160 mg na dan u pacijenata čija se vrijednost AT-a nije snizila na 140/90 mmHg ili niže. Nakon daljnja četiri tjedna doza je povećana na 320 mg valsartana ili 160/12,5 mg kombinacije fiksnih doza (KFD) valsartana i HCTZ u bolesnika s nezadovoljavajućim odgovorom. Ako ciljne vrijednosti AT-a nisu bile postignute ni nakon dodatna četiri tjedna, doza je povećana na 320/12,5 mg KFD valsartana i HCTZ.[6]

Pri procjeni sigurnosnoga profila rabljeni su anamneza i klinički pregled. Bolesnika se pitalo o bilo kakvim simptomima koje su doživjeli od prethodnog posjeta, a provođenjem kliničkoga pregleda identificirali su se znakovi mogućih neželjenih događaja (ND). Svi zamijećeni ND stratificirani su

The estimated number of adults with raised BP increased from 594 million in 1975 to 1.13 billion in 2015, affecting 597 million men and 529 million women. At the global level, this increase was attributable to population growth and ageing. In 2015, age-standardised prevalence of elevated blood pressure was 24.1% in men and 20.1% in women. According to the latest data, elevated BP is a persistent health issue in Central and Eastern Europe.[3]

Dietary and lifestyle changes can improve BP control and decrease the risk of health complications, although medication therapy is still often necessary in people for whom lifestyle changes are not enough or not effective.[4]

Angiotensin receptor blockers (ARBs, e.g. valsartan) are among the first-line medications for hypertension. They can be used either alone or in combination with other antihypertensive agents (e.g. hydrochlorothiazide).[5] Many trials with the valsartan in the field of hypertension have been performed; however data about efficacy and safety of generic medications are scarce. The present article highlights the main results of the VICTORY trial[6], which was previously published in *Kardiologia Polska* and in which also patients from Croatia were included.

Patients and Methods

A total of 365 patients, 196 females and 169 males, were enrolled in this international, multicentre, open-label, prospective, phase IV trial named VICTORY. Hypertensive patients in 25 centres in five countries – Slovenia, Russian Federation, Ukraine, Czech Republic and Croatia – were included in the trial from May 2013 to June 2015. The patients were included according to indications in the summaries of product characteristics of the investigated medicines. At the initial visit, each patient received a detailed explanation of the objectives and procedures of the trial and was asked to sign an informed consent form before any procedure was performed. The protocol of the trial was submitted to and approved by all national medical ethics committees in the participating countries.[6]

During the 16-week period, the patients had five visits: the first visit upon inclusion in the trial, the second after one month of the treatment, the third after 2 months, the fourth after 3 months and the fifth after 16 weeks of the treatment. The treatment was initiated with one 80 mg tablet of valsartan daily in all patients (naïve and previously treated). Only in Russia, previously treated patients received valsartan at the first visit in a dose of 160 mg (request by ethical committee), which did not have any influence on trial results. After four weeks of treatment, the dose was changed to one 160 mg tablet of valsartan daily in patients whose BP was not lowered to 140/90 mm Hg or lower. After the following 4 weeks, the dose was increased to 320 mg valsartan or 160/12.5 mg FDC of valsartan and HCTZ in patients with unsatisfactory response. If target BP levels were not achieved after additional 4 weeks, the dose was increased to 320/12.5 mg FDC of valsartan and HCTZ.[6]

To assess the safety profile, an interview and physical examination were used. The patients were asked about any signs or symptoms they had experienced since the last visit and a physical examination was carried out to identify any signs of possible adverse events (AEs). All recorded AEs were stratified according to time of occurrence, frequency, relatedness to treatment, severity, therapeutic measures required and outcome.[5]

prema vremenu pojave, učestalosti, povezanosti s liječenjem, ozbiljnosti, potrebnim terapijskih zahvatima i ishodu.[5]

Rezultati

Među 365 bolesnika bilo je 196 (54,0 %) žena. Prosječna je dob bila 54,6 ± 12,0 godina. Analiza primarnih i sekundarnih ishoda uključivala je 365 bolesnika. Četiri su bolesnika obustavila liječenje zbog ND-a vezanih za liječenje.[6]

Prosječni početni sistolički arterijski tlak (SAT) i dijastolički arterijski tlak (DAT) bili su 156,59 ± 8,98 mmHg i 95,63 ± 6,01 mmHg. U prethodno liječenih bolesnika početni AT izmjeren je nakon jednoga tjedna "ispiranja" od lijeka. Pri posljednjemu posjetu nakon 16 tjedana aktivnoga liječenja, prosječni SAT i DAT bili su 130,05 ± 8,18 mmHg i 80,97 ± 5,84 mmHg. Prosječni SAT i DAT postojano su bili snizivani tijekom razdoblja kliničkog ispitivanja. Prosječna relativna sniženja SAT-a i DAT-a iznosila su 16,8 ± 6,1% i 15,2 ± 7,3%. Snizivanje prosječnoga SAT-a i DAT-a između dvaju uzastopnih posjeta u svim je slučajevima bilo statistički značajno (p < 0.0001), (**slika 1**).[6]

Postizanje ciljnog AT-a prema Smjernicama ESH/ESC za zbrinjavanje arterijske hipertenzije iz 2013. pratilo se pri svakome kontrolnom posjetu. Pri zadnjem pregledu u 91 % oboljelih bila je registrirana željena ciljna vrijednost AT-a. Stopa postizanja vrijednosti ciljnog AT-a bila je veća pri svakom uzastopnom posjetu, što se može vidjeti na **slici 2**.[6]

Sveukupno, 230 bolesnika uključeno je u analizu ciljnog AT-a prema protokolu. Pedeset ih je liječeno KFD-om valsartana i HCTZ pri barem jednom kontrolnom posjetu, a 180 ih je bilo na monoterapiji tijekom cijelog ispitivanja. Liječenje KFD-om valsartana i HCTZ započeto je u bolesnika koji nisu postigli ciljne vrijednosti AT-a pri trećemu i četvrtomu posjetu liječniku. Razlika u prosječnom apsolutnom i relativnom sniženju SAT-a i DAT-a od trećeg do petog posjeta između monoterapije i kombinacijske terapije bila je statistički značajna (p < 0.0001). Bolesnici na kombinacijskoj terapiji bili su oni koji nisu imali ciljni AT pri trećem i/ili četvrtom posjetu, a bolesnici na monoterapiji bili su uglavnom pacijenti sa zadovoljavajuće kontroliranim KT (**slika 3.**).[6]

Terapijski učinak liječenja procjenjivao se pri zadnjemu posjetu u sklopu kliničkog ispitivanja. Vrlo dobar terapijski učinak (vrijednost AT-a manja od 140/90 mmHg ili niža od 140/85 mmHg u bolesnika s visokim rizikom i šećernom bolesti) uočen je u 91 %

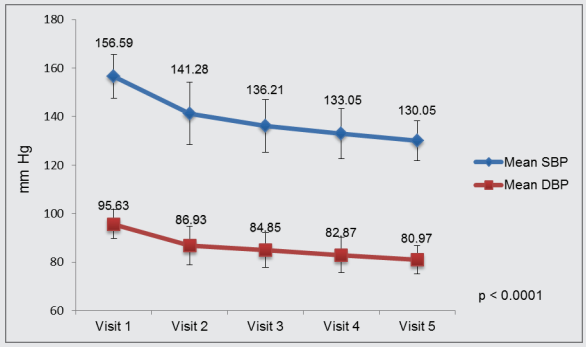

FIGURE 1. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg) during the trial for all patients.[6]

Results

Among 365 patients, 196 (54.0%) were females. The mean age was 54.6 ± 12.0 years. An intention-to-treat (ITT) analysis of primary and secondary outcome measures included 365 patients. Four patients discontinued the treatment due to AEs related to the treatment.[6]

The mean baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 156.59 ± 8.98 mmHg and 95.63 ± 6.01 mmHg, respectively. In previously treated patients, the baseline BP was measured after 1 week of a wash-out period. At the final visit after 16 weeks of active treatment, the mean SBP and the mean DBP were 130.05 ± 8.18 mmHg and 80.97 ± 5.84 mmHg, respectively. During the trial, the mean SBP and DBP were steadily decreasing. The mean absolute decreases of SBP and DBP were 26.60 ± 10.41 mmHg and 14.84 ± 7.57 mmHg, respectively. The mean relative decreases of SBP and DBP were 16.8 ± 6.1% and 15.2 ± 7.3%. The decrease of mean SBP and DBP between two consecutive visits was in every case statistically significant (p<0.0001) (**Figure 1**).[6]

Achievement of the target BP according to the 2013 ESH/ESC Guidelines for the management of arterial hypertension was monitored at each control visit. At the last visit, 91% of the patients who appeared at the last visit had their BP lowered to the target BP. The rate of achieving target BP was higher at each subsequent visit, which can be seen in **Figure 2**.[6]

Overall, 230 patients were included into per protocol analysis of target BP control. Fifty of them were on combination therapy with valsartan and HCTZ FDC at at least one control visit and 180 of them were on monotherapy throughout the trial. The combination therapy was initiated in patients who did not reach the target BP at visit 3 and visit 4. The difference in mean absolute and relative decreases of SBP and DBP from visit 3 to visit 5 between monotherapy and combination therapy was statistically significant (p < 0.0001). Patients on combination therapy were patients who did not have the target BP on visit 3 and/or visit 4 and patients on monotherapy were mostly patients with adequately controlled BP (**Figure 3**).[6]

The therapeutic effect of the treatment was assessed at the last visit of the trial. Very good therapeutic effect (BP below 140/90 mmHg or below 140/85 mmHg for high-risk and diabetic patients) was observed in 91% of the patients. In the remaining 9% of the patients the therapeutic effect was good (if the SBP was reduced by at least 10 mmHg, and the DBP by at

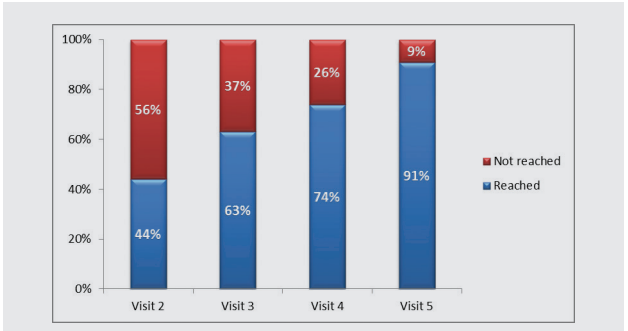

FIGURE 2. Blood pressure reduction to target blood pressure during the trial.[6]

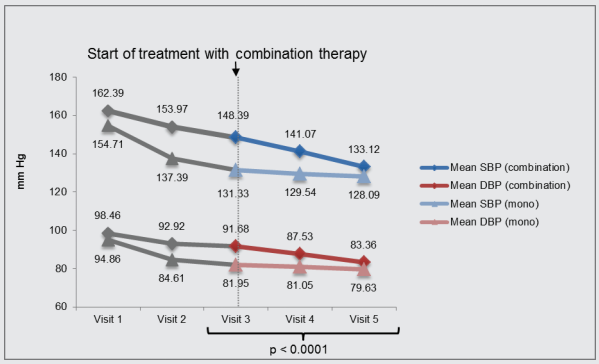

FIGURE 3. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg) at each control visit for patients treated with monotherapy (valsartan) or combination therapy (fixed-dose combination of valsartan and hydrochlorothiazide).[6]

bolesnika. U preostalih je 9 % oboljelih terapijski učinak bio dobar (ako je SAT bio snižen za ≥ 10 mmHg i DAT za ≥ 5 mmHg), zadovoljavajući (ako su ili vrijednosti SAT bile snižene ≥ 10 mmHg ili DAT za ≥ 5 mmHg), ili nezadovoljavajući (ako su vrijednosti SAT-a bile snižene za < 10 mmHg i DAT također za < 5 mmHg). Učinak je bio nezadovoljavajući u samo 1,4 % pacijenata.[6]

Učinak liječenja na kvalitetu života (QoL) bolesnika procijenjen je na temelju jednostavnog upitnika. Na kraju kliničkog ispitivanja 73, 7 % bolesnika izjavilo je da se osjećaju dobro ili bolje nego na prethodnoj antihipertenzivnoj terapiji. U većini je slučajeva liječenje poboljšalo QoL. U 22,3 % bolesnika liječenje nije pogoršalo QoL. Ovi rezultati jasno pokazuju da se QoL popravila u pacijenata liječenih valsartanom i bolesnika liječenih KFD valsartana i HCTZ.[6]

Glede profila podnošljivosti, bolesnici su vrlo dobro podnosili valsartan i KFD valsartana i HCTZ. Analiza je pokazala da je incidencija neželjenih događaja tijekom 16 tjedana liječenja bila niska, jer je tijekom kliničkoga ispitivanja samo 7,1% bolesnika dobilo ND vezane uz liječenje. Učestalost uočenih ND-a bila je niska. Od ND koje su bolesnici naveli, glavobolja (1,9 %), palpitacije (1,6 %), vrtoglavica (1,6 %) i umor (1,6 %) bili su najčešći. Samo 4 (1,1 %) bolesnika prekinula su liječenje zbog vezanih ND-a.[6]

Zaključak

Rezultati kliničkog ispitivanja VICTORY potvrdili su da valsartan (Valsacor®) i KFD valsartana i HCTZ (Valsacombi®) djelotvorno smanjuju vrijednost AT-a u bolesnika s blagom do umjerenom arterijskom hipertenzijom. Bitan je podatak da je ciljno smanjenje AT-a, definirano Smjernicama ESC/ESH 2013., postignuto u 91 % bolesnika. Tijekom kliničkog ispitivanja stopa je prevalencije prijavljenih neželjenih događaja bila niska. Valsartan i KFD valsartana i HCTZ čine se kao povoljna opcija za djelotvornu kontrolu vrijednosti AT-a u blago do umjereno hipertenzivnih bolesnika, što je od ključne važnosti za poboljšanje kardiovaskularnih ishoda.

least 5 mmHg), satisfactory (if only the SBP was reduced by at least 10 mmHg, or only the DBP by at least 5 mmHg) or unsatisfactory (if the SBP was reduced by less than 10 mm Hg, and the DBP by less than 5 mmHg). Only in 1.4% of the patients the therapeutic effect was unsatisfactory.[6]

The effect of treatment on the patients' quality of life (QoL) was assessed with a simple questionnaire. At the end of the trial, 73.7% of the patients answered that they were feeling well or better than with previous antihypertensive therapy. In most cases, the treatment improved QoL. In 22.3% of the patients, the treatment did not aggravate the patients' QoL. These results clearly show that QoL improved in patients treated with valsartan and patients treated with valsartan and HCTZ FDC.[6]

Concerning the tolerability profile, valsartan and the FDC of valsartan and HCTZ were very well tolerated. An analysis revealed that the adverse event incidence rate during 16 weeks of treatment was low, as during the course of the trial only 7.1% of the patients experienced AEs related to the treatment. The frequency of the observed AEs was low. Among all reported AEs, headache (1.9%), palpitations (1.6%), dizziness (1.6%) and fatigue (1.6%) were most common. Only 4 (1.1%) patients discontinued the treatment because of treatment-related AEs.[6]

Conclusion

The results of the VICTORY trial confirmed that valsartan (Valsacor®) and the FDC of valsartan and HCTZ (Valsacombi®) effectively decrease BP in patients with mild to moderate arterial hypertension. Notably, the target BP reduction, as defined by the ESC/ESH 2013 guidelines, was achieved in 91% of the patients. During the course of the trial, the incidence rate of reported AEs was low. Valsartan and the FDC of valsartan and HCTZ seem to be a beneficial option for effective BP control in mildly to moderately hypertensive patients, which is of key importance for improved cardiovascular outcomes.

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