Doprinos visokokvalitetnih valsartana liječenju arterijske hipertenzije i drugih bolesti već više od 15 godina

High-quality Valsartans Contributing to the Treatment of Hypertension and Beyond for More than 15 Years

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SAŽETAK: Valsartan je antagonist receptora angiotenzina koji se uporabljuje za liječenje arterijske hipertenzije, zatajivanja srca i nakon infarkta miokarda. Iskazao je učinkovitost i sigurnost, a istodobno omogućio učinke šire od kontrole arterijskoga tlaka u različitim velikim populacijama hipertenzivnih bolesnika. Krka je svojim valsartanom prisutna na tržištima više od 15 godina. Tijekom tog razdoblja izgradili smo snažno povjerenje među liječnicima, ljekarnicima i bolesnicima, što je Krki omogućilo da postane vodeći proizvođač valsartana u Europi na tržištima srednje, istočne i južnoistočne Europe. Naši valsartani, i u monoobliku i u fiksnim kombinacijama s diuretikom i/ili blokatorom kalcijevih kanala i statinom, prepoznatljivi su po svojoj visokoj kvaliteti te na njih nisu utjecali opozivi zbog nečistoća u proizvodima na bazi sartana stoga su uvijek raspoloživi na tržištima bez ograničenja. Štoviše, spomenuti valsartani također su priznati zbog svojih nagrađenih inovacija i ekstenzivnih međunarodnih kliničkih dokaza dobivenih i u kliničkim ispitivanjima i u kliničkoj praksi, što se odražava u povjerenju milijuna hipertenzivnih bolesnika koji svoj arterijski tlak svakodnevno drže pod kontrolom Krkinim valsartanima.

SUMMARY: Valsartan is an angiotensin receptor antagonist used for the treatment of hypertension, heart failure, and post-myocardial infarction. It has demonstrated efficacy and safety, while also providing benefits beyond blood pressure control across broad patient populations with hypertension. Krka has been present in the markets with its valsartan for more than 15 years. During this time, we have built strong trust among physicians, pharmacists, and patients, which has enabled us to become the leading producer of valsartan in Europe (Central, Eastern, and South-Eastern European markets). Our valsartans, both monoform and single-pill combinations with a diuretic and/or calcium channel blocker and a statin, are recognized for their high quality and were not affected by recalls due to impurities issues in sartan-based products. They are therefore continously available in the markets without restriction. Moreover, our valsartans have also been acknowledged for their award-winning innovations and extensive international clinical evidence derived from both clinical trials and real-clinical practice, which is reflected in the trust of millions of patients with hypertension who control their blood pressure with Krka's valsartans every day.

KLJUČNE RIJEČI: valsartan, Krka, visoka kvaliteta, nagrađene inovacije, klinički dokazi, povjerenje.

KEYWORDS: valsartan, Krka, high quality, award-winning innovations, clinical evidence, trust.

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Uvod

Valsartan pripada skupini antagonista receptora angiotenzina (ARB), koji su među lijekovima prve linije za liječenje arterijske hipertenzije (AH).[1,2] U Europi je valsartan odobren 1996. godine za liječenje AH-a u odraslih. Otad su indikacije za val-

Introduction

Valsartan belongs to the group of angiotensin receptor antagonists (ARBs), which are one of the first-line medications for the treatment of hypertension (HT).[1,2] In Europe, valsartan was first approved in 1996 for the treatment of HT in adults.

sartan proširene te također uključuju zatajivanje srca i stanje nakon infarkta miokarda da bi se smanjio kardiovaskularni mortalitet. Djelotvornost valsartana u snizivanju arterijskoga tlaka (AT) i dobra podnošljivost u širokim populacijama bolesnika dokazane su u brojnim kliničkim ispitivanjima koja su uključivala više od 100 000 bolesnika. Nadalje, za valsartan je također dokazano da ima šire učinke od kontrole AT-a, koji pozitivno utječu na kardiovaskularne, cerebrovaskularne, bubrežne i metaboličke ishode.[1]

Priča o Krkinu valsartanu počela je prije više od 15 godina, kad je ponuđen slovenskim liječnicima njegov monooblik. Otad je portfelj valsartana narastao te sada uključuje pet lijekova: monooblik (Valsacor®) i četiri fiksne kombinacije (SPC) s diuretikom i/ili blokatorom kalcijeva kanala i statinom (Valsacombi® – valsartan/hidroklorotiazid (HCTZ), Wamlox® – amlodipin/valsartan; Valtricom® – amlodipin/valsartan/HCTZ i Valarox® – rosuvastatin/valsartan); ovakvi su proizvodi dostupni su u 19 različitih jačina, a mogu se uporabljivati kod svih stupnjeva AH-a te u bolesnika s različitim potrebama.[3-5] Prepoznatljivost po visokoj kvaliteti, nagrađenim inovacijama i ekstenzivnim međunarodnim kliničkim dokazima pridonosi povjerenju milijuna bolesnika s AH-a i čini Krku vodećim proizvođačem lijekova na bazi valsartana u Europi (u područjima srednje, istočne i jugoistočne Europe).[4]

Visoka kvaliteta osigurava stalnu dostupnost bolesnicima

Vertikalno integriran model proizvodnje omogućuje tvrtki potpun nadzor nad cijelim procesom proizvodnje, od djelatne tvari do gotovoga proizvoda, što rezultira proizvodima visoke kvalitete. Godine 2011. godine Krkin je valsartan dobio Certifikat sukladnosti koji izdaje Europska direkcija za kvalitetu lijekova (EDQM), što je najviši standard kvalitete u Europi te potvrđuje da djelatna tvar ispunjava europske farmaceutske standarde.[6,7]

Tijekom posljednjih godina nekoliko proizvođača sartana (uključujući valsartan, losartan i irbesartan) u Europi moralo je povući svoje proizvode s tržišta zbog nitrozaminskih nečistoća. Nakon pregleda Europske agencije za lijekove (EMA-e) EMA je postavila ograničenja maksimalnih razina nitrozaminskih nečistoća u proizvodima koji sadržavaju sartan sa svrhom postizanja nemjerljive razine nečistoća.[8] Tijekom 2021. godine dobivene su nove informacije o potencijalno mutagenim azidnim nečistoćama u određenim proizvodima koji sadrže sartane. Posljedično tomu, EDQM je naredio proizvođačima da poduzmu prikladne mjere kako bi osigurali da je razina azidnih nečistoća ispod praga.[9,10]

Ovi opozivi nisu utjecali na Krkine proizvode s valsartanom s obzirom na znanstvenu procjenu puteva sinteze svih sartanskih djelatnih tvari. Rezultati su pokazali da nema uvjeta za oblikovanje nitrozaminskih nečistoća. Implementirane su sve potrebne mjere i provedena su rigorozna ispitivanja kako bi se dokazalo da se u proizvodima s valsartanom ne nalaze mjerljive razine nitrozamina ili azida. Kao rezultat toga, Krkini valsartani kontinuirano su dostupni već mnogo godina te su ostali na tržištu bez ograničenja.[6,11]

Since then, indications for valsartan have been extended to also include heart failure (HF) and post-myocardial infarction (MI) in order to reduce cardiovascular mortality. Valsartan's efficacy in lowering blood pressure (BP) and good tolerability across broad patient populations have been demonstrated in numerous clinical studies that included over 100,000 patients. Moreover, valsartan has also been shown to possess effects beyond BP control that positively influence cardiovascular, cerebrovascular, renal, and metabolic outcomes.[1]

Krka's valsartan story began more than 15 years ago when we offered Slovenian physicians a monoform version of the medication. Since then, Krka's valsartan portfolio has grown and now includes five medications: monoform (Valsacor®) and four single-pill combinations (SPCs) with a diuretic and/or a calcium channel blocker and a statin (Valsacombi® – valsartan/hydrochlorothiazide (HCTZ), Wamlox® – amlodipine/valsartan; Valtricom® – amlodipine/valsartan/HCTZ; and Valarox® – rosuvastatin/valsartan); these medications are available in 19 different strengths and can be used in all grades of HT and in patients with different needs.[3-5] Krka's valsartan medications are recognized for their high quality, award-winning innovations, and extensive international clinical evidence, which all contribute to the trust of millions of patients with HT, making Krka the current leading producer of valsartan-based products in Europe (Central, Eastern, and South-Eastern Europe).[4]

High quality ensuring continuous availability for patients

Krka's vertically integrated production model allows the company to have complete oversight of the whole production process from the active ingredient to the finished product, resulting in high-quality products. In 2011, Krka's valsartan obtained the Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), which is the highest quality standard in Europe, confirming that its active substance meets European pharmaceutical standards.[6,7]

In recent years, several producers of sartan products (containing valsartan, losartan, and irbesartan) in Europe had to withdraw their products from the markets due to nitrosamine impurities. Following a review by the European Medicines Agency (EMA), EMA set limits on maximum nitrosamine impurity levels in sartan-containing products with a goal of achieving no quantifiable impurities.[8] In 2021, new information about potentially mutagenic azido impurities in certain sartan-containing products emerged. Consequently, EDQM ordered producers to take appropriate actions to ensure that the level of azido impurities is below threshold levels.[9,10]

Krka's valsartan products were not affected by these recalls, since we scientifically evaluated the synthesis routes for all active sartan substances. The results have shown that there are no conditions for the formation of any nitrosamine impurities. We have implemented all necessary measures and conducted rigorous testing to prove no quantifiable levels of nitrosamine or azido impurities are to be found in its valsartan products. As a result, our valsartans have been continuously available for many years and have remained in the markets without restriction.[6,11]

Nagrađene inovacije dokazuju visoku kvalitetu

Krkini proizvodi s valsartanom primili su dvije nagrade za inovaciju od Slovenske gospodarske komore. Godine 2020. proizvodi s valsartanom nagrađeni su u kategoriji najbolje inovacije.

Zlatna nagrada primljena je za zamjenski lijek s trojnom kombinacijom koja sadržava tri djelatne tvari u jednoj tableti – amlodipin, valsartan i hidroklorotiazid. Ova trojna kombinacija omogućuje praktičniji oblik terapije za bolesnike, čime poboljšava kontrolu liječenja AT-a. Spomenuta djelatna tvar neovisna o patentu također omogućuje najviše standarde kvalitete.

Poboljšani proces proizvodnje djelatnog sastojka valsartana primio je srebrnu nagradu. Proces sinteze djelatne tvari optimiran je u različitim tehnološkim fazama, posebice putem inovativnoga pristupa u laboratorijskoj fazi. To je omogućilo povećan kapacitet proizvodnje, ali je i povećalo kvalitetu djelatne tvari, relativno višu iskoristivost procesa i smanjenje otpadnih opasnih otapala.

Obje nagrade imaju i ekološku komponentu jer pomažu smanjiti negativan utjecaj na okoliš zbog optimizacije regeneracije organskih otapala.[12,13]

Ekstenzivni međunarodni klinički dokazi

Krkini proizvodi s valsartanom klinički su dokazani, i u strogoj, kontroliranoj okolini, kakva je karakteristična za klinička ispitivanja, te u stvarnoj kliničkoj praksi (više od 15 godina kliničkog iskustva). Proizvodi s valsartanom ispitani su u dvama glavnim kliničkim ispitivanjima – *VICTORY* i *VICTORY II*. Ta su dva ispitivanja uključivala gotovo 500 bolesnika i dokazala su da je liječenje valsartanom učinkovito i sigurno u bolesnika sa svim stupnjevima AH-a. Nakon 16 tjedana liječenja, 9 od 10 bolesnika postiglo je ciljne vrijednosti AT-a (<140/90 mmHg). Istodobno, više od 90 % bolesnika dobro je podnosilo terapiju. Također je dokazano da proizvodi s valsartanom imaju dodatne učinke povrh kontrole AT-a jer su poboljšali funkciju žila, erektilnu funkciju, kvalitetu života i bubrežnu funkciju te su bili metabolički neutralni.[14-17] Rezultati kliničkog ispitivanja *VICTORY* prikazani su na 26. kongresu Europskoga društva za hipertenziju (ESH 2016).[18]

Ispitivanje *VICTORY* provedeno je da bi se procijenila djelotvornost i sigurnost monooblika valsartana (Valsacor®) i fiksne kombinacije valsartana i HCTZ-a (Valsacombi®) u bolesnika s blagom do umjerenom AH. To je ispitivanje uključivalo ukupno 365 bolesnika, trajalo je 16 tjedana te je bilo međunarodnog, multicentričnog, otvorenog i prospektivnog karaktera. Bolesnici su liječenje započeli s 80 mg valsartana na dan, uz mogućnost titriranja naviše do 320 mg dnevno ili u kombinaciji s HCTZ-om kao fiksna kombinacija da bi se postigla ciljna vrijednost AT-a. Rezultati su pokazali da valsartan i fiksna kombinacija valsartana i HCTZ-a učinkovito snizuju AT i imaju vrlo dobar profil podnošljivosti. Tijekom ispitivanja stabilno su padali i srednji sistolički i dijastolički tlak. Srednja apsolutna smanjenja sistoličkog i dijastoličkog tlaka bila su 26,60 ± 10,41 mmHg, odnosno 14,84 ± 7,57 mmHg, dok su srednja relativna smanjenja bila 16,8 ± 6,1%, odnosno 15,2 ± 7,3 %. Smanjenje srednjega sistoličkoga i dijastoličkoga tlaka između dvaju uzastopnih posjeta bilo je statistički značajno

Award-winning innovations demonstrate high quality

Krka's valsartan products received two awards for innovation from the Slovenian Chamber of Commerce and Industry. In 2020, they received an award in the category of best innovation.

The gold award was received for a substitute medicine with a triple combination that contains three active substances in one tablet (amlodipine, valsartan, and hydrochlorothiazide). This triple combination enables a more convenient form of therapy for patients, thereby improving BP treatment control; this patent-independent active substance also allows us to have the highest quality standards.

The improved production process of valsartan's active ingredient received a silver award. The process of synthesis of the active substance has been optimized at different technological stages, especially through an innovative approach at the laboratory stage. This enabled not only increased production capacity but also improved quality of the active substance, relatively higher process yield, and reduction of hazardous solvent waste.

Both awards have an environmentally friendly component, as they also evaluated reduction of the negative impact on the environment due to the optimization of organic solvent regeneration.[12,13]

Extensive international clinical evidence

The effectiveness and safety of Krka's valsartan products have been clinically demonstrated, both in strict, controlled environments, which are characteristic of clinical trials, and in real-clinical practice (more than 15 years of clinical experience). They were assessed in two main clinical trials – VICTORY and VICTORY II. These two trials included almost 500 patients and demonstrated that valsartan therapies were effective and safe in patients with all grades of HT. After 16 weeks of treatment, 9 out of 10 patients achieved target BP (<140/90 mmHg). At the same time, therapy was well-tolerated by more than 90% of patients. Valsartan products were also shown to have beneficial effects beyond BP control as they improved vessel function, erectile function, quality of life, and kidney function while being metabolically neutral.[14-17] The results of the VICTORY clinical trial were presented at the 26th Meeting of the European Society of Hypertension (ESH 2016).[18]

The VICTORY trial was performed to assess the efficacy and safety of valsartan monoform (Valsacor®) and SPC of valsartan and HCTZ (Valsacombi®) in patients with mild to moderate HT. A total of 365 patients were enrolled in this 16-week, international, multicenter, open-label, prospective trial. The patients started treatment with 80 mg valsartan daily, which could be up-titrated to 320 mg daily or combined with HCTZ as an SPC to achieve target BP. The results showed that valsartan and the SPC of valsartan and HCTZ effectively reduced BP and had a very good tolerability profile. During the trial, the mean systolic BP (SBP) and diastolic BP (DBP) steadily decreased. The mean absolute decreases of SBP and DBP were 26.60 ± 10.41 mmHg and 14.84 ± 7.57 mmHg, respectively, while the mean relative decreases of SBP and DBP were 16.8 ± 6.1% and 15.2 ± 7.3%. The decrease in mean SBP and DBP between two consecutive visits was statistically significant in

(p <0,0001) (**Slika 1**). U 91 % bolesnika zabilježen je vrlo dobar terapijski učinak (AT manji od 140/90 mmHg ili niži od 140/85 mmHg za visokorizične bolesnike i dijabetičare).[14,15]

every case (p<0.0001) (**Figure 1**). A 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.[14,15]

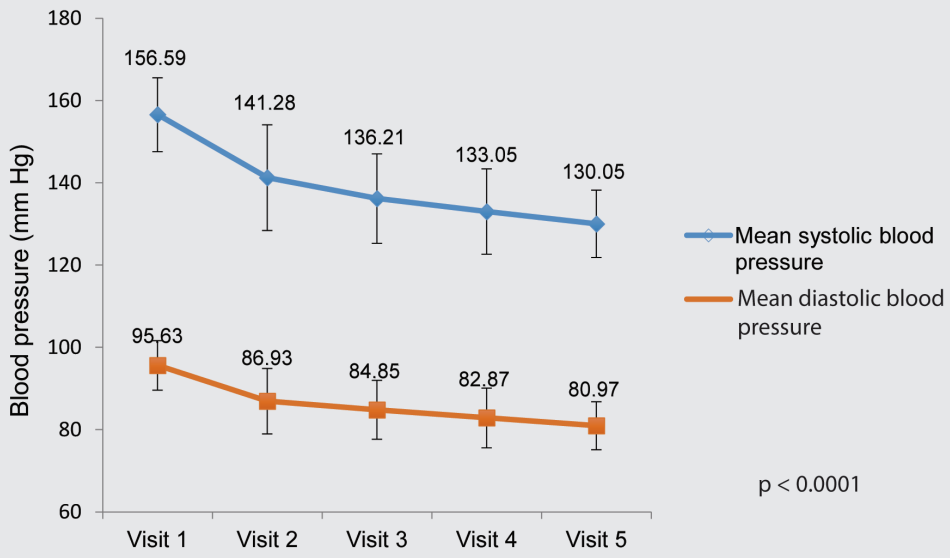

FIGURE 1. Mean systolic blood pressure and diastolic blood pressure during the VICTORY trial (all patients).

Na temelju statistički značajnog smanjenja brzine pulsnog vala (PWV) (**Slika 2**) oba su lijeka pomogla poboljšati i smanjiti aortalnu krutost. Rezultati ispitivanja također su pokazali da su hipertenzivni bolesnici liječeni valsartanom i fiksnom kombinacijom valsartan/HCTZ imali bolju kvalitetu života, uključujući erektilnu funkciju u muškaraca.[14,16]

Furthermore, based on a statistically significant decrease of pulse wave velocity (PWV) (**Figure 2**), both medications helped improve and reduce aortic stiffness. The trial results also showed that patients with HT treated with valsartan and SPC of valsartan/HCTZ had improved quality of life, including erectile function in men.[14,16]

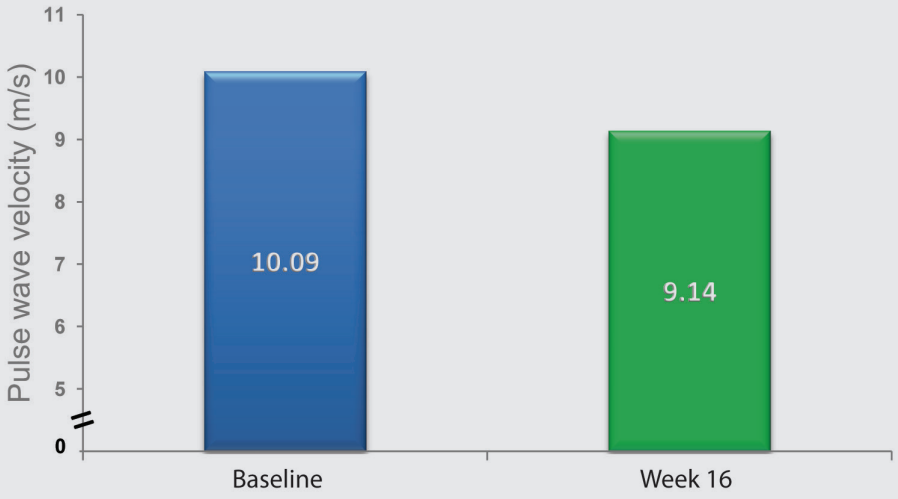

FIGURE 2. Pulse wave velocity (m/s) during treatment with valsartan and single pill combination of valsartan/ hydrochlorothiazide in a subgroup of patients.

Ispitivanje *VICTORY II* provedeno je da bi se ispitale djelotvornost i sigurnost fiksnih kombinacija amlodipin/valsartan i amlodipin/valsartan/HCTZ u postizanju ciljnih vrijednosti AT-a u bolesnika s novodijagnosticiranom ili nekontroliranom bolešću s 2. ili 3. stupnjem AH-a. Ukupno je 100 bolesnika bilo uključeno u ovo 16 tjedana dugo, multicentrično, otvoreno, prospektivno ispitivanje. Bolesnici s AH-om 2. stupnja započeli su liječenje fiksnom kombinacijom amlodipin/valsartan u dozi od 5 mg/80 mg, a bolesnici s AH-om 3. stupnja fiksnom kombinacijom amlodipin/valsartan u dozi od 5 mg/160 mg; u obama je slučajevima bilo moguće titriranje naviše korak po korak do fiksne kombinacije amlodipin/valsartan/HCTZ 10 mg/160 mg/12,5 mg kako bi se postigao ciljni AT. Nakon 16 tjedana terapije u 90 % bolesnika postignut je ciljni AT mjeren u ordinaciji (**Slika 3**) uz dobru podnošljivost. Usto, obje su terapije također smanjile albuminuriju (u 58,8 % bolesnika) i centralni aortalni tlak (smanjenje za najmanje 5 % u 73 % bolesnika), poboljšale elastičnost krvnih žila (brzina PWV-a poboljšana je u 66,7 % bolesnika) te su pokazale pozitivan učinak na vaskularnu endotelnu funkciju, erektilnu funkciju u muškaraca i kvalitetu života.[17,19-21]

The VICTORY II trial was performed to assess the efficacy and safety of SPCs of amlodipine/valsartan and amlodipine/valsartan/HCTZ in achieving target BP in newly-diagnosed or uncontrolled patients with grade 2 or 3 hypertension. A total of 100 patients were enrolled in this 16-week multicenter, open-label, prospective trial. Patients with grade 2 hypertension started treatment with an SPC of amlodipine/valsartan 5 mg/80 mg, and patients with grade 3 hypertension started with an SPC of amlodipine/valsartan 5 mg/160 mg; both could be up-titrated step-by-step to the SPC of amlodipine/valsartan/HCTZ 10 mg/160 mg/12.5 mg to achieve target BP. After 16 weeks of therapy, target office BP was achieved in 90% of the patients (**Figure 3**), with good tolerability. Additionally, both treatments also decreased albuminuria (in 58.8% of patients) and central aortic pressure (at least a 5% reduction in 73% of patients), improved vessel elasticity (speed of PWV was improved in 66.7% of patients), and showed a positive effect on the vascular endothelial function, erectile function in men, and quality of life.[17,19-21]

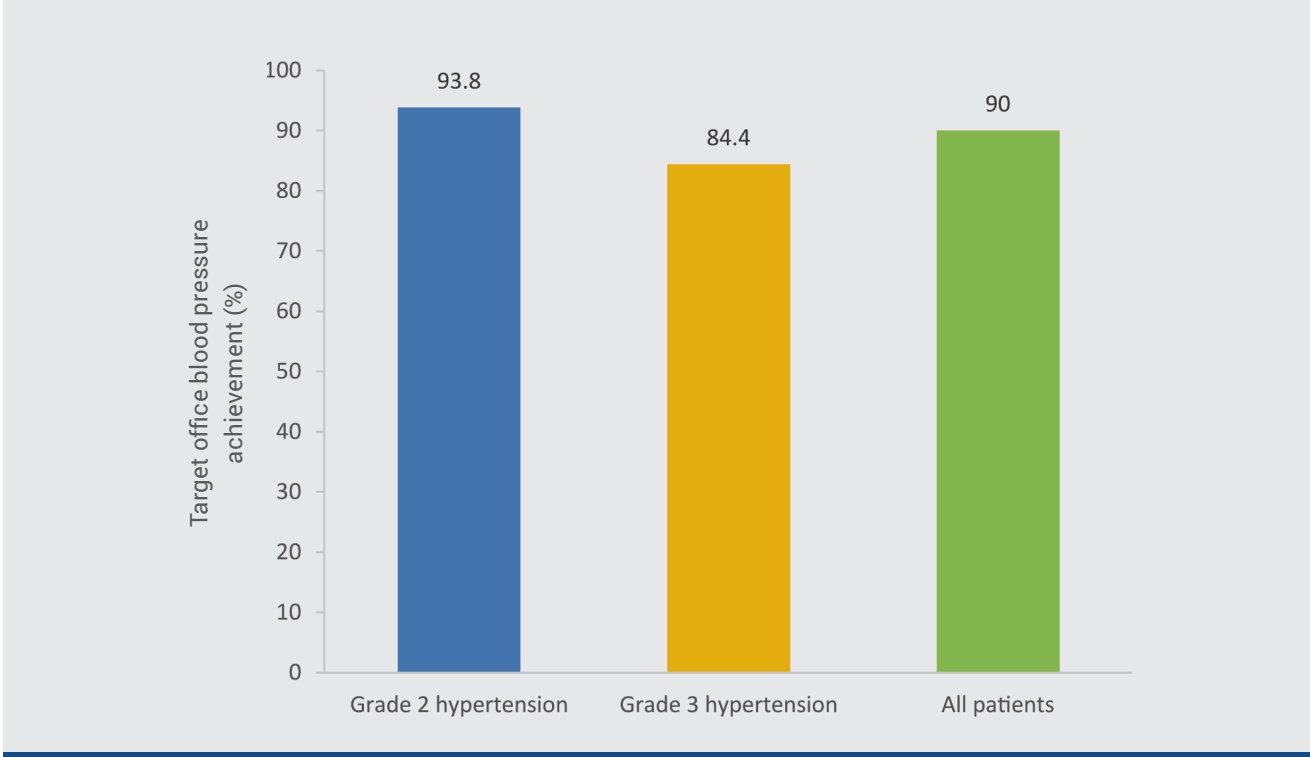

FIGURE 3. Target office blood pressure achievement (BP <140 mmHg/90 mmHg, <140/85 mmHg for high-risk and diabetic patients).

Nadalje, dodatna su ispitivanja dokazala koristi od lijeka Valsacora® u bolesnika sa zatajivanjem srca i u hipertenzivnih bolesnika hospitaliziranih zbog akutnog infarkta miokarda te koristi od lijekova Valsacor® i Valsacombi® u hipertenzivnih bolesnika s oštećenom dijastoličkom funkcijom lijeve klijetke.[22]

Additionally, further studies demonstrated the benefits of Valsacor® in patients with HF and in patients with HT hospitalized for acute MI, and the benefits of Valsacor® and Valsacombi® in hypertensive patients with an impaired left ventricular diastolic function.[22]

Zaključak

Danas Krkini valsartani uživaju veliko povjerenje među liječnicima, ljekarnicima i bolesnicima s hipertenzijom, ali povjerenje u te valsartane nije izgrađeno preko noći. Ono je rezultat više od 15 godina dugog procesa pružanja visoke kvalitete i stalne prisutnosti na tržištima, pružanja kliničkih dokaza putem visoko kontroliranih kliničkih ispitivanja za cijeli asortiman valsartana te u kliničkoj praksi, kao i dobivanja nagrada za inovacije. Kao rezultat toga Krkini valsartani sada su registrirani na više od 50 tržišta diljem svijeta, s četiri milijuna liječenih bolesnika svaki dan. Osim toga, u dvaju od triju europskih bolesnika koji uzimaju valsartan riječ je o Krkinu valsartanu.[4,23]

Conclusion

Today, Krka's valsartans are highly trusted among physicians, pharmacists, and patients with HT, but trust in our valsartans was not built overnight. It is the result of a more than 15 year long process of ensuring high quality and continuous presence in the markets, providing clinical evidence through both highly-controlled clinical trials for the entire valsartan family and real-clinical practice, and receiving awards for innovations. As a result, Krka's valsartans are now registered in more than 50 markets worldwide, with four million patients being treated every day. In addition, two out of three European patients who take valsartan receive Krka´s valsartan.[4,23]

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