

## Važnost valsartana u liječenju hipertoničara s erektilnom disfunkcijom

### The Importance of Valsartan in the Treatment of Hypertonic Patients with Erectile Dysfunction

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**SAŽETAK:** Eretilna se disfunkcija, prema više autora, pojavljuje u više od 50 % muškaraca, napose srednje i više dobi, koji boluju od arterijske hipertenzije. Arterijska hipertenzija, ali i neki lijekovi koji se upotrebljavaju u njezinu liječenju, mogu nizom patofizioloških mehanizama (ateroskleroza na krvnim žilama koje opskrbljuju tkiva odgovorna za erekciju, simpatikotonija i disregulacija vaskularnog tonusa erektilnog aparata, loša remodelacija i sniženje elastičnosti krvnih žila erektilnog aparata, promjene u strukturi kavernoznog tijela te povećanje koncentracije slobodnih radikala i peroksidacije lipida u penilnome tkivu) uzrokovati poremećaje erekcije. Nasuprot tomu, ima više istraživanja u posljednjih petnaestak godina koja dokazuju pozitivan utjecaj valsartana u poboljšanju erektilne disfunkcije, pa i orgazmične funkcije, spolne želje i zadovoljstva spolnim odnosom te u povećanju njihova broja u bolesnika koji boluju od arterijske hipertenzije. Osnovni mehanizam toga djelovanja jest inhibicija lokalnog angiotenzin-konvertirajućeg enzima, ali postoje i drugi posredni mehanizmi. Stoga se može zaključiti da valsartan, uz dobru antihipertenzivnu učinkovitost, tolerabilnost i organoprotektivni učinak, ima naglašeni proerektilni učinak te je dobar izbor u bolesnika s arterijskom hipertenzijom i erektilnom disfunkcijom, osobito ako je riječ o pretilim bolesnicima i bolesnicima sa šećernom bolešću. Istraživanjima na životinjskom modelu pokazano je da bi valsartan mogao biti i dobro terapijsko sredstvo za erektilnu disfunkciju u dijabetičara, no za potvrdu takve tvrdnje potrebna su dodatna istraživanja na humanom modelu.

**SUMMARY:** According to multiple authors, erectile dysfunction manifests in over half of the male population with arterial hypertension, especially in middle-aged or older men. Arterial hypertension, but also some of the medication used to treat it, can lead to erectile dysfunction through a number of pathophysiological mechanisms (atherosclerosis in the blood vessels supplying the tissue responsible for the erection, sympatheticotonia and dysregulation of the vascular tonus of the erectile organ, poor remodeling and lowered elasticity of blood vessels in the erectile organ, changes in the structure of the cavernous body, and increased concentration of free radicals and lipid peroxidation in the penile tissue). On the other hand, several studies over the recent 15 years have found a positive influence of valsartan on the improvement of erectile dysfunction, as well as orgasmic function, sex drive, and intercourse satisfaction and frequency in patients with arterial hypertension. The basic mechanism that leads to these effects is inhibiting the local angiotensin converting enzyme, but other indirect mechanisms are at play as well. We can thus conclude that valsartan, in addition to good antihypertensive effectiveness, tolerability, and organoprotective effects, has a pronounced pro-erectile effect and is a good treatment choice in patients with arterial hypertension and erectile dysfunction, especially in patients with obesity and diabetes; confirming this hypothesis, however, will require further studies in a patient model.

**KLJUČNE RIJEČI:** valsartan, arterijska hipertenzija, erektilna disfunkcija.

**KEYWORDS:** valsartan, arterial hypertension, erectile dysfunction.

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#### Uvod

Sartani su skupina lijekova koja svoje antihipertenzivno djelovanje i ostale pozitivne učinke zahvaljuju selektivnoj blokadi receptora angiotenzina II tipa 1 prije svega antagoniziranjem

#### Introduction

Sartans are a group of drugs that has an anti-hypertensive effect as well as other positive effects due to selective blocking of angiotensin II type 1 receptors, primarily through antagoniz-

njegova vazokonstriktornog učinka i smanjenjem retencije natrija i tekućine u tijelu. Spomenuti su lijekovi povoljni za liječenje bolesnika s arterijskom hipertenzijom (AH), osobito onih s povećanim rizikom od razvoja kardiovaskularnih bolesti, hipertrofijom lijeve klijetke, nakon infarkta miokarda, bolesnika sa zatajavanjem srca (ZS), dijabetesom tipa 2 i mikroalbuminurijom.<sup>1-9</sup> Prema posljednjim smjernicama Europskoga društva za hipertenziju i Europskoga kardiološkog društva za liječenje arterijske hipertenzije<sup>10</sup>, skupina sartana jedna je od pet skupina antihipertenziva povoljna za započinjanje antihipertenzivne terapije i njezino održavanje. Ako se monoterapijom ne uspiju optimirati vrijednosti bolesnikova arterijskoga tlaka (AT), sartani se mogu kombinirati i s drugim antihipertenzivima, najčešće s hidroklorotiazidom. Ako je pak riječ o kombinacijama u jednoj tableti, tada, osim višestruko boljšeg sniženja AT-a, možemo očekivati i znatno sniženje kardiovaskularnog rizika te povećanu suradljivost bolesnika.<sup>11-12</sup>

Valsartan je jedan od sartana s 24-satnom djelotvornošću uz jednokratnu primjenu dokazanom u više studija.<sup>13-14</sup> Ispitivanje valsartana u akutnom infarktu miokarda (*VALsartan In Acute myocardial iNfarctiOn trial*; VALIANT)<sup>15</sup> uključivalo je pacijente s akutnim infarktomiokarda kompliciranim ZS-om i/ili disfunkcijom lijeve klijetke. Organizirano je radi ocjenjivanja povećava li valsartan ili kombinacija valsartana i kaptoprila učestalost preživljenja nakon infarkta miokarda i smanjuje li incidenciju kardiovaskularnih nuspojava u usporedbi s monoterapijom ACE inhibitorom. Rezultati su pokazali da su stope smrtnosti svih uzroka bile slične u trima liječenim skupinama. Dodatna je analiza pokazala da je monoterapija valsartanom sačuvala 99,6 % pozitivnih učinaka na mortalitet dokazanih u terapiji ACE inhibitorom uz superiornu podnošljivost. Rezultati ispitivanja valsartana (*Valsartan Heart Failure Trial*; Val-HeFT)<sup>16</sup> u pacijenata sa ZS-om, prema NYHA, stupnja II. do IV., pokazalo je znatna smanjenja pobola/smrtnosti uz valsartan u usporedbi s placebo u pacijenata koji su primali preporučenu standardnu terapiju za ZS. Pokazalo se smanjenje od 13,2 % rizika od pobola/smrtnosti te smanjenje od 27,5 % rizika od prve hospitalizacije zbog ZS-a. Najveći su pozitivni učinci valsartana primijećeni u pacijenata sa ZS-om koji istodobno ne uzimaju ACE inhibitore. Drugi pozitivni učinci primijećeni uz valsartan u ispitivanju Val-HeFT uključuju poboljšanje funkcije lijeve klijetke, promjenu u remodeliranju lijeve klijetke, smanjenje vrijednosti moždanih natriuretskih peptida i aldosterona u plazmi, prevenciju povećanja norepinefrina u plazmi i smanjenje učestalosti fibrilacije atrijske. Istraživanje *Valsartan Antihypertensive Long-Term Use Evaluation* (VALUE)<sup>17</sup> ispitivalo je zaštitne učinke valsartana u hipertenzivnih pacijenata pod visokim kardijalnim rizikom. Istraživanje je bilo organizirano za usporedbu kardijalnog morbiditeta i mortaliteta terapije bazirane na valsartanu u usporedbi s terapijom baziranom na amlodipinu. Rezultati su pokazali da nije bilo statistički značajne razlike između liječenih skupina u primarnoj ishodnoj točki kardijalnog pobola i smrtnosti, usprkos većemu sniženju AT-a uz amlodipin u prvih 6 mjeseci ispitivanja. Štoviše, liječenje temeljeno na valsartanu dalo je smanjenje od 23 % u incidenciji nastupa dijabetesa. Kao i ostali sartani, i valsartan ima malo nuspojava i dobru podnošljivost, osobito u usporedbi s ACE inhibitorima.<sup>18</sup>

ing the vasoconstrictive effect and reducing sodium and fluid retention in the body. Sartans are a good treatment choice for patients with arterial hypertension, especially in patients with increased risk of cardiovascular disease, left ventricular hypertrophy, previous myocardial infarction, heart failure (HF), diabetes type 2, and microalbuminuria.<sup>1-9</sup> According to current guidelines of the European Society of Hypertension & European Society of Cardiology<sup>10</sup>, the sartan group is one of five groups of antihypertensive drugs appropriate for initial antihypertensive treatment and maintenance. If monotherapy fails to optimize blood pressure (BP) values in the patient, sartans can be combined with other antihypertensive drugs, most commonly hydrochlorothiazide. If the treatment comes in the form of single-tablet combinations, we can expect, a significant reduction in cardiovascular risk as well as improved patient compliance in addition to significantly better reduction of BP.<sup>11-12</sup>

Valsartan is one of the sartans with a 24 hour effect from a single dose, as shown in multiple studies.<sup>13-14</sup> VALsartan In Acute myocardial iNfarctiOn (VALIANT) trial<sup>15</sup> included patients with acute myocardial infarction complicated by HF and/or left ventricular dysfunction. The aim of the study was to determine whether valsartan or a combination of valsartan and captopril improves survival rates after myocardial infarction and whether it reduces incidence of cardiovascular side-effects in comparison with angiotensin-converting enzyme (ACE) inhibitor monotherapy. The results showed that all-cause mortality was similar in the three patient groups. Further analysis showed that valsartan monotherapy maintains 99.6% of the positive effects on mortality shown for ACE inhibitor treatment, while having superior tolerability. Valsartan Heart Failure Trial (Val-HeFT)<sup>16</sup> for HF patients with NYHA classes II to IV, showed a significant decrease in morbidity/mortality for the valsartan group in comparison with placebo in patients receiving standard recommended HF treatment. A reduction of 13.2% in morbidity/mortality and a 27.5% reduction in first hospitalization for HF were found. The greatest positive effects of valsartan were found in patients with HF that were not simultaneously receiving ACE inhibitors. Additional positive effects related to valsartan noted in the Val-HeFT trial included improved left ventricular function, changes in left ventricular remodeling, reduction of brain natriuretic peptide levels and plasma aldosterone concentration, preventing increase of plasma norepinephrine levels, and a reduction in atrial fibrillation frequency. The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)<sup>17</sup> trial evaluated the protective effects of valsartan in hypertensive patients at high cardiovascular risk. The trial compared cardiac morbidity and mortality under valsartan treatment with that of patients under treatment based on amlodipine. The results showed no statistically significant difference between the treated groups in the primary endpoint of cardiac morbidity and mortality, despite a greater reduction in BP from amlodipine during the first 6 months of the trial. Furthermore, treatment based on valsartan showed a 23% reduction in the incidence of diabetes onset. As with other sartans, valsartan has few side-effects and good tolerability, especially in comparison with ACE inhibitors.<sup>18</sup>

## Erektilna disfunkcija u bolesnika s arterijskom hipertenzijom

Osim u bolesnika koji boluju od šećerne bolesti i metaboličkog sindroma, erektilna je disfunkcija problem i nemaloga broja bolesnika s AH-om. Zanimljivo je na tome polju istraživanje Giuliana i suradnika<sup>19</sup> iz 2005. godine, koji su u 7689 ispitanika s AH-om, šećernom bolešću ili objema bolestima proučavali učestalost i neke druge parametre erektilne disfunkcije. Prosjek dobi ispitivanih bolesnika bio je oko 59 godina života, a erektilnu je disfunkciju definirao *International Index of Erectile Function (IIEF)*, najčešće primjenjivani indeks u ovom tipu istraživanja. Indeks se izračunava jednostavnim upitnikom od šest pitanja kojim se procjenjuje erektilna funkcija u posljednjih šest mjeseci.<sup>20</sup> Erektilna disfunkcija, definirana kao zbroj manji od 21, pronađena je u 67 % hipertoničara te u 71 % njih s dijabetesom. Učestalost i razina erektilne disfunkcije bile su to više što je bolesnik bio stariji, imao dulje AH i što je bolest bila lošije regulirana.<sup>19</sup> Artom i suradnici<sup>21</sup> 2015. godine u 270 talijanskih hipertoničara u dobi od 40 do 70 godina nalaze nešto niži postotak erektilne disfunkcije (51 %), no također ovisan o dobi, pušenju, o razini sistoličkoga tlaka i frekvencije srca te o liječenju statinima i funkciji bubrega.

Arterijska hipertenzija dovodi do erektilne disfunkcije putem nekoliko patofizioloških mehanizama. Prvi je pojava i progresija ateroskleroze na krvnim žilama pa tako i onima koje opskrbljuju tkiva odgovorna za erekciju. Povišena razina simpatikotonije, karakteristična za AH, uzrokuje poremećaj regulacije vaskularnog tonusa, pa tako i erektilnog aparata. Loša remodelacija i sniženje elastičnosti krvnih žila erektilnog aparata, promjene u strukturi kavernoznog tijela te povećanje koncentracije slobodnih radikala i peroksidacije lipida u penilnome tkivu dodatni su mehanizmi nastanka erektilne disfunkcije u hipertoničara.

Proučavajući kliničke smjernice izdane od 2000. godine u smislu navođenja utjecaja antihipertenzivnih lijekova na spolnu disfunkciju, Al Khaja i suradnici<sup>22</sup> zaključuju da se tek u polovici njih navode tiazidski diuretici, beta-blokatori i centralni inhibitori simpatikusa kao mogući uzroci spolne disfunkcije. Osim toga, uglavnom se ne spominje treća generacija beta-blokatora ili diuretici nalik na tiazide koji bi mogli povoljno utjecati na spolnu funkciju, podtipovi spolne disfunkcije (gubitak libida ili orgazma, poremećaj ejakulacije, prijavizam), potreba za evaluacijom spolne funkcije prije uvođenja lijekova, kao i mogućnost kombinacije lijekova s inhibitorima 5-fosfodiesteraze. Chrysant<sup>23</sup> ističe da AH, koronarna bolest srca i ZS, kao i neki lijekovi kojima se te bolesti liječe (tiazidski diuretici, beta-blokatori, antagonisti aldosteronskih receptora) mogu uzrokovati erektilnu disfunkciju. To treba imati na umu i saznati od bolesnika o postojanju toga problema te ga odgovarajuće liječiti. Prema *American Heart Association*<sup>24</sup>, inhibitori 5-fosfodiesteraze mogu biti korisni u liječenju erektilne disfunkcije u bolesnika sa stabilnim kardiovaskularnim bolestima, a jedina jasna kontraindikacija jest terapija nitratima koji se ne bi smjeli uzimati 24 sata nakon uzimanja sildenafilila ili vardenafila, tj. 48 sati nakon tadalafile.

## Erectile dysfunction in patients with arterial hypertension

As in patients suffering from diabetes and metabolic syndrome, erectile dysfunction is a common problem for patients with hypertension. An interesting study in that field by Giuliano et al.<sup>19</sup> from 2005 on 7689 patients with hypertension and/or diabetes looked at the incidence and some other parameters of erectile dysfunction. The average patient age was about 59 years of age, and erectile dysfunction was defined using the International Index of Erectile Function (IIEF), the most commonly applied index in this type of research. The index uses a simple six-question questionnaire that evaluates erectile dysfunction for the last 6 months.<sup>20</sup> Erectile dysfunction, defined as a score less than 21, was found in 67% of hypertensive patients and 71% of those with diabetes. The likelihood and severity of erectile dysfunction increased with age, duration of hypertension, and how poorly the disease had been regulated.<sup>19</sup> In 2015, Artom et al.<sup>21</sup> examined 270 Italian patients with AH between 40 and 70 years of age, and found a somewhat lower incidence of erectile dysfunction (51%) that was still dependent on age, smoking habits, BP, heart frequency, statin therapy and kidney function.

Arterial hypertension leads to erectile dysfunction due to several pathophysiological mechanisms. The first is onset and progression of atherosclerosis in blood vessels supplying blood to tissue responsible for the erection. Increased sympathetic levels typical of hypertension disrupts the regulation of vascular tone, and consequently the erectile function as well. Poor remodeling and reduced elasticity of the blood vessels of the erectile organ, changes in the structure of the cavernous body, and increased concentration of free radicals and lipid peroxidation in the penile tissue are further mechanisms that cause erectile dysfunction in hypertensive patients.

In 2000, Al Khaja et al.<sup>22</sup> examined clinical guidelines for mention of the influence of antihypertensive drugs on sexual dysfunction, concluding that only half of them listed thiazide diuretics, beta-blockers, and central sympathetic inhibitors as potential causes of sexual dysfunction. There was also little mention of third-generation beta-blockers or thiazide-like diuretics that could have a positive effect on sexual function, of sex dysfunction subtypes (loss of libido or orgasm, ejaculation disorders, priapism), the need to evaluate sexual function before introducing drug treatment, and of the option of combining medication with 5-phosphodiesterase inhibitors. Chrysant<sup>23</sup> noted that AH, coronary heart disease, and HF as well as some of the drugs used to treat these conditions (thiazide diuretics, beta-blockers, and aldosterone receptor antagonists) can cause erectile dysfunction. This must be kept in mind, and patients should be evaluated for this condition and treated if necessary. According to the American Heart Association<sup>24</sup>, 5-phosphodiesterase inhibitors can be useful in treating erectile dysfunction in patients with stable cardiovascular diseases, and the only clear contraindication for their use is nitrate therapy that should not be taken 24 hours after taking sildenafil or vardenafil, and 48 hours after taking tadalafil.

## Važnost valsartana u erektilnoj disfunkciji

Lokalni angiotenzin-konvertirajući enzim regulira tonus glatkih mišićnih stanica angiotenzinom II (stimulira kontrakciju glatkih mišićnih stanica kavernoznog tijela). Valsartan, osim toga što inhibira taj mehanizam, značajno smanjuje promjene u kavernožnom tijelu. Postoji više istraživanja u posljednjih petnaestak godina koja dokazuju taj pozitivan patofiziološki utjecaj valsartana na erektilnu disfunkciju na kliničkoj razini. Fogari i suradnici<sup>25</sup> 2001. godine objavljuju studiju usporedbe dviju skupina novootkrivenih hipertoničara liječenih karvedilolom ili valsartanom (ukupno 160 njih) s obzirom na broj spolnih odnosa mjesečno. Dok u prvo vrijeme, kada su bolesnici uzimali placebo, autori prate pad učestalosti spolnih odnosa, nakon uvođenja terapije u karvedilolnoj skupini taj se broj dodatno smanjuje, a u valsartanskoj počinje rasti čak iznad početne razine, tako da autori zaključuju da valsartan ne samo da ne pogoršava nego i poboljšava spolnu aktivnost. Slični porast broja spolnih odnosa uz terapiju valsartanom u odnosu prema smanjenju toga broja uz konvencionalnu antihipertenzivnu terapiju prikazuju i švicarski istraživači<sup>26</sup> 2003. godine. Treba naglasiti da je u objema studijama i u valsartanskim i u kontrolnim skupinama postignuto sniženje AT-a. Iste godine Dusing<sup>27</sup> objavljuje statistički značajno pozitivne rezultate pri uvođenju valsartana kao prvog antihipertenziva ili zamjene prethodne antihipertenzivne terapije u više od 3500 hipertoničara na erektilnu i orgazmičnu funkciju, spolnu želju i zadovoljstvo spolnim odnosom.

Nakon navedenih rezultata istraživanja s valsartanom Chen i suradnici<sup>28</sup> na animalnom modelu pokazuju da bi valsartan mogao biti dobro terapijsko sredstvo za erektilnu disfunkciju dijabetičara. Zbog svoje antihipertenzivne učinkovitosti, tolerabilnosti i organoprotektivnih učinaka, uz naglasak na proerektilni učinak, valsartan se navodi kao lijek osobito indiciran u bolesnika s AH-om, debljinom, šećernom bolešću i erektilnom disfunkcijom.<sup>29,30</sup> Ruski istraživači<sup>31</sup> u relativno manjoj studiji pokazuju, uz pozitivan učinak valsartana na erektilnu disfunkciju, i smanjenje androgenog deficita u bolesnika s AH-om u terapiji tim lijekom. Amlodipin je lijek s relativno malim brojem nuspojava, ako se izuzmu perimaleolarni edemi, i praktički se ne povezuje s erektilnom disfunkcijom, no metaanaliza iz 2015. godine pokazuje i tu prednost valsartana, kako u prevenciji hipertrofije lijeve klijetke, tako i pri klinički relevantnim nuspojavama, uključujući erektilnu disfunkciju.<sup>32</sup>

## Zaključak

Eretilna je disfunkcija čest problem u muškaraca, napose srednje i više dobi, koji boluju od AH-a, a neki ga antihipertenzivni lijekovi mogu i potencirati. Valsartan je lijek koji uz dobru antihipertenzivnu učinkovitost, tolerabilnost i organoprotektivni učinak ima naglašeni proerektilni učinak te je dobar izbor u hipertenzivnih bolesnika s erektilnom disfunkcijom.

## The importance of valsartan in erectile dysfunction treatment

Local angiotensin-converting enzymes regulate the tone of the smooth muscle cells with angiotensin II, which stimulates the contraction of smooth muscle cells in the cavernous body. Valsartan, in addition to inhibiting this mechanism, significantly reduces changes in the cavernous body. There have been multiple studies over the last 15 years that have demonstrated this positive pathophysiological effect of valsartan on erectile dysfunction at the clinical level. In 2001, Fogari et al.<sup>25</sup> published a study that compared monthly intercourse frequency between two groups of newly-diagnosed hypertensive patients treated with carvedilol or valsartan (for a total of 160 patients). At first, while the patients were given placebo medication, the authors noted a drop in monthly intercourse frequency; after treatment initiation this number dropped further in the carvedilol group but increased even beyond initial levels in the valsartan group, leading the authors to conclude that valsartan not only does not inhibit, but actually stimulates sexual activity. A similar increase in intercourse frequency under valsartan treatment in comparison with a reduction under conventional antihypertensive treatment was also found by Swiss researchers<sup>23</sup> in 2003. It is important to note that both the valsartan and control groups achieved a reduction in BP. Also in 2003, Dusing<sup>27</sup> found statistically significant effects on erectile and orgasmic function, sexual drive, and sexual satisfaction when introducing valsartan as first-line treatment or as a replacement for previous antihypertensive therapy in a study on over 3500 patients.

In addition to the aforementioned results, Chen et al.<sup>28</sup> used an animal model to show that valsartan could be an effective treatment for erectile dysfunction in diabetics. Due to its antihypertensive effectiveness, tolerability, and organoprotective effects, with an emphasis on its pro-erectile effects, valsartan is noted as a drug especially indicated in patients with hypertension, obesity, diabetes, and erectile dysfunction.<sup>29,30</sup> In a smaller study, Russian researchers<sup>31</sup> showed that valsartan, in addition to its positive effect on erectile dysfunction, also reduces androgen deficiency in patients with hypertension when treated with valsartan. Amlodipine is a drug with relatively few side-effects, perimaleolar edema aside, and is rarely associated with erectile dysfunction. However, a meta-analysis from 2015 found valsartan had the advantage here as well, both in preventing left ventricular hypertrophy and in relation to clinically relevant side-effects, including erectile dysfunction.<sup>32</sup>

## Conclusion

Erectile dysfunction is a common problem in patients with hypertension, especially in middle-aged or older men, and some antihypertensive medication can exacerbate it. Valsartan is a drug that combines good antihypertensive effectiveness, tolerability, and organoprotective effects with a pro-erectile effect and is a good treatment choice in hypertensive patients with erectile dysfunction.



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