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Blokatori beta receptora i erektilna funkcija: nebivolol - svjetlo na kraju tunela

Beta receptor blocker and erectile function: nebivolol - light at the end of the tunnel

Goran Krstačić

Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Zagreb, Hrvatska
Institute for Cardiovascular Diseases Prevention and Rehabilitation, Zagreb, Croatia

SAŽETAK: *Blokatori beta receptora (BB) predstavljaju važnu skupinu lijekova glede svoje kliničke učinkovitosti u nekoliko indikacija. Ipak, nerijetko se naglašavaju nepovoljni učinci lijekova iz te skupine, poglavito na dislipidemiju, metabolizam glukoze ili pak erektilnu funkciju. Noviji, kardioselektivni BB nebivolol ima pozitivne metaboličke učinke, navlastito dokazano protuaterosklerotsko djelovanje i povoljan učinak na erektilnu funkciju. Rezultati nekoliko studija pokazali su da jedino nebivolol ima povoljne učinke na erektilnu funkciju kod hipertenzivnih bolesnika liječenih BB. Pri tome je nebivolol učinkovito snižavao povišeni arterijski tlak uz boljitak funkcije endotela i uopće kvalitete života.*

KLJUČNE RIJEČI: *beta-blokatori, nebivolol, arterijska hipertenzija, erektilna funkcija, dušični oksid.*

ABSTRACT: *Beta receptor blockers (BB) are an important group of drugs with regard to their clinical efficiency in several indications. However, some side-effects of drugs from this group are not rarely mentioned, especially dyslipidemia, glucose metabolism or erectile function. The more recent cardioselective BB nebivolol has positive metabolic effects, some proven anti-atherosclerotic effects or a good effect on the erectile function. The results of several studies have shown that it is only nebivolol that has positive effects on erectile function with hypertensive patients treated with BB. The nebivolol has efficiently lowered high blood pressure improving the function of endothelium and life quality in general.*

KEYWORDS: *beta-blockers, nebivolol, hypertension, erectile function, nitric oxide*

Blokatori beta adrenergičkih receptora (beta-blokatori) predstavljaju važnu skupinu lijekova glede svoje kliničke učinkovitosti u liječenju arterijske hipertenzije (AH), zatajivanja srca (ZS), koronarne srčane bolesti, nekih aritmija i djelotvornosti u sekundarnoj prevenciji infarkta miokarda.

Ipak, nerijetko se naglašavaju neki nepovoljni učinci lijekova iz te skupine, poglavito na dislipidemiju, metabolizam glukoze ili pak erektilnu funkciju. Međutim, neki beta-blokatori imaju i povoljne metaboličke učinke, navlastito dokazano protuaterosklerotsko djelovanje ili pak povoljan učinak na erektilnu funkciju.[1]

Dobar primjer za to je nebivolol. Ovaj lijek je registriran u Hrvatskoj 2002., a na Dopunskoj listi lijekova Hrvatskog zavoda za zdravstveno osiguranje nalazi se od 2007. godine. Nebivolol predstavlja relativno noviji kardioselektivni lipofilni beta-blokator treće generacije bez učinka na β receptore. Smanjuje perifernu vaskularnu rezistenciju i djeluje vazodilatacijski. Ima negativan kronotropni učinak i blag negativan inotropni učinak uz učinkovitu blokadu aktivnosti simpatičkog sustava. Jedno od važnih djelovanja ovog lijeka je poticanje stvaranja i lučenja dušičnog monoksida (NO), tvari koja je ključna u prevenciji poremećaja funkcije endotela koji je presudan za početak poremećaja aterogeneze.[2]

Nebivolol je indiciran u liječenju AH i kroničnog ZS (napomena da za indikaciju liječenja kroničnog ZS nije odobren u SAD[3]). Iz skupine beta-blokatora u terapiji AH danas se primarno preporučuju lijekovi s vazodilatacijskim osobinama, poput karvedilola i nebivolola. Posebna osobitost nebivolola je njegov velik učinak na oslobađanje dušičnog oksida kao potentnog vazodilatatora.

Pored vazodilatacije, NO ima antiagregacijsko djelovanje, smanjuje proliferaciju glatkih mišićnih stanica i mi-

Beta adrenergic receptor blockers (beta-blockers) are an important group of drugs with regard to its clinical efficiency in treatment of hypertension, heart failure (HF), coronary heart disease, some arrhythmias and efficiency in secondary prevention of myocardial infarction.

However, some side-effects of drugs from this group are not rarely mentioned, especially dyslipidemia, glucose metabolism or erectile function. However, some beta-blockers also have good metabolic effects, some proven anti-atherosclerotic effects or a good effect on the erectile function.[1]

Nebivolol is a good example for that. This drug was registered in Croatia in 2002 and it has been in the Supplementary list of drugs of the Croatian Institute for Health Insurance since 2007. Nebivolol is rather a new third generation cardioselective lipophilic beta-blocker with no effect on β receptors. It reduces peripheral vascular resistance and has a vasodilatation effect. It has a negative chronotropic effect and a slight negative inotropic effect with an efficient blockade of sympathetic system activity. One of important effects of this drug is the stimulation of formation and secretion of nitric monoxide (NO), the substance that is a key substance in prevention of the endothelial dysfunction that is crucial for the commencement of the atherogenic disorder.[2]

Nebivolol is indicated in treatment of hypertension and chronic HF (note that it has not been approved for the indication of treatment of chronic HF in the USA[3]). From the group of beta-blockers today the drugs with vasodilatation properties, such as carvedilol and nebivolol are used in the therapy of hypertension. A special characteristic of nebivolol is its effect on release of nitrogen oxide as potential vasodilatator.

Besides vasodilatation, NO has anti-aggregation effect, it reduces proliferation of smooth muscle cells and migra-

graciju leukocita[4]. Na smanjeno oslobađanje NO utječu AH, hiperlipoproteinemija, dijabetes i starenje. To je posebno važno u liječenju sistoličke AH koja se navlastito javlja u osoba starijih od 55 godina. To je čimbenik krvožilnog rizika izravno u svezi sa smanjenim elasticitetom velikih arterija. Jedan od čimbenika koji dovodi do smanjene elastičnosti arterija je disfunkcija endotela i glede toga manje lučenje NO. Nebivolol povećava oslobađanje NO i pogodan je i za liječenje sistoličke AH, poglavito u odnosu na druge beta-blokatore.[5,6]

Problem ZS predstavlja značajan javnozdravstveni problem, unatoč svim poduzetim mjerama prevencije i suvremenog liječenja temeljenog na smjernicama. Jedan je od glavnih razloga za hospitalizaciju, mortalitet je visok, a kvaliteta života bolesnika je urušena. Uvođenjem u terapiju ZS lijekova poput ACE inhibitora i beta-blokatora značajno je poboljšana terapija ove bolesti i povećana duljina prosječnog preživljavanja bolesnika. U terapiji kroničnog ZS do sada su se koristila tri beta-blokatora s dokazanim povoljnim učinkom (karvedilol, metoprolol i bisoprolol), a nakon kliničkog ispitivanja SENIORS u kojem su tijekom tri godine liječenja i dvije godine praćenja nakon toga, uspoređivani učinci nebivolola s placebom u 2.128 bolesnika starijih od 70 godina sa ZS, njima se pridružio i nebivolol. Posebno značenje studije SENIORS je u tome što su u njoj sudjelovali ispitanici koji puno bolje predstavljaju tipičnog prosječnog bolesnika sa ZS. Takav je bolesnik u prosjeku stariji od onih koji su sudjelovali u dosadašnjim kliničkim ispitivanjima beta-blokatora u ZS, te ima češće popuštanje srca s održanom sistoličkom funkcijom lijeve klijetke. Primjena nebivolola u ovih bolesnika dovodi do manjeg broja hospitalizacija, te boljeg preživljavanja, neovisno o veličini istisne frakcije srca na početku ispitivanja.[7]

Nebivolol je stoga beta-blokator s povoljnim farmakološkim profilom i dokazanim povoljnim učinkom u liječenju AH i ZS poglavito u starijih osoba s dodatnim pozitivnim karakteristikama velike $beta_1$ selektivnosti i vazodilatacijskog učinka. Nebivolol je pokazao i zaštitno djelovanje na endotel kao i druga povoljna metabolička svojstva.[8] Nema negativnog učinka na metabolizam ugljikohidrata i lipida, ima povoljan učinak na inzulinsku rezistenciju, a bolesnici koji se liječe nebivololom nisu povećali tjelesnu težinu niti indeks tjelesne mase. Nebivolol povećava koncentraciju adiponektina i smanjuje razinu inzulina u krvi što doprinosi objašnjenju antiaterogenih učinaka ovog blokatora beta adrenergičnih receptora.[9]

No, ono što se često zanemaruje i radi čega se beta-blokatori kao skupina unatoč zornoj indikaciji znaju izbjegavati i glede čega se smanjuje suradljivost i urušava kvaliteta življenja bolesnika je problem erektilne disfunkcije.

Erektilna disfunkcija (ED) po definiciji predstavlja nesposobnost postizanja ili održavanja penilne erekcije dostatne za zadovoljavajući spolni čin. Prevalencija ED u nekim razvijenim zemljama u općoj populaciji iznosi zabrinjavajućih 20-30%, s rastom na više od 50% kod bolesnika s razvijenim čimbenicima krvožilnog rizika, ukazujući na usku svezu između čimbenika kardiovaskularnog rizika i ED, poglavito AH. Primjerice, samo u SAD oko 30 milijuna muškaraca ima ozbiljne smetnje s erektilnom funkcijom. Dušični oksid igra krucijalnu ulogu u fiziologiji penilne erekcije zbog posredovanja u relaksaciji trabekularne muskulature, a važnu ulogu ima i endotelna funkcija pe-

tion of leucocytes[4]. The reduced release of NO is affected by hypertension, hyperlipoproteinemia, diabetes or aging. This is especially important in the treatment of systolic hypertension that especially occurs in persons over 55 years of age. This is a vascular risk factor that is directly connected with reduced elasticity of large arteries. One of the factors that lead to reduced elasticity of arteries is the dysfunction of endothelium and consequently reduced secretion of NO. Nebivolol increases the release of NO and is good for treatment of systolic hypertension, especially compared to some other beta-blockers.[5,6]

The HF problem is a great public health problem despite all undertaken protective measures and modern treatment based on guidelines. It is one of the main reasons for hospitalization, mortality rate is high and the patient's life quality is bad. The introduction of HF drugs such as ACE inhibitors and beta-blockers in the therapy has greatly improved the therapy for this disease resulting in an increased length of average patients' survival. In the therapy of chronic HF, three beta-blockers with proven good effect (carvedilol, metoprolol and bisoprolol) have been used so far, and following clinical study SENIORS when during the period of 3 years and 2 years of monitoring the effects of nebivolol with placebo were compared in 2128 patients over 70 years of age with HF, which were accompanied by nebivolol. A significant importance of the study SENIORS is that respondents who much better represent a typical average patient with HF participated in it. Such a patient is on average older than those who participated in clinical trials of beta-blockers in HF, and more often has heart failure with sustained left ventricular systolic function. The use of nebivolol in these patients leads to a decreased number of hospitalization and better survival rates regardless of the heart ejection fraction rate at the beginning of the questionnaire.[7]

Therefore, nebivolol is a beta-blocker with a favorable pharmacological profile and a proven positive effect in the treatment of hypertension and HF, especially with older patients with additional positive characteristics of high $beta_1$ selectivity and vasodilation effects. Nebivolol has also shown a protective effect on endothelium, as well as other positive metabolic properties.[8] It has no negative effects on carbohydrates and lipid metabolism, it has a positive effect on insulin resistance, and patients treated with nebivolol have neither put on any body weight nor have they increased their body mass index. Nebivolol increases the adiponectin concentration and decreases the blood insulin levels, which helps to explain the antiatherogenic effects of this adrenergic beta-blockers.[9]

However, the thing which is often disregarded and why beta-blockers as a group are often avoided in spite of shown indications and which is why there is a decreased patient cooperation and diminished quality of life is the problem of erectile dysfunction.

Erectile dysfunction (ED) is the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual intercourse. ED prevalence in the general population of some developed countries amounts to a troublesome 20-30%, and increases up to 50% in patients with developed cardiovascular risk factors, indicating a close relationship between the cardiovascular risk factors and the ED, particularly hypertension. For example, only in the US around 30 millions of men have serious problems with ED. Nitrogen oxide plays a crucial role in the physiology of penile erection because of its role in the relaxation of trabe-

nilne arterije i spužvastog tijela. Dušični oksid funkcionira lokalno kao neurotransmiter nonadrenergičkog nonkolinergičkog živca.[10]

Više od 25% ED povezano je s nuspojavama određenih lijekova. Pri tome su antihipertenzivi najčešće izolirana skupina, a beta-blokatori i tijazidski diuretici prema brojnim studijama najviše povećavaju rizik od ED. Točan mehanizam ED uzrokovane beta-blokatorima nije sasvim razjašnjen. Predmnijeva se da je to navlastito posljedica učinka na adrenergički sustav koji je uključen u integracijsku fazu erekcije i ejakulacije. Zanimljivo da je jedna recentna studija pokazala da uloga periferne vazokonstrikcije kao posljedica uzimanja beta-blokatora ipak nema značajan učinak na erektilnu funkciju.

Temeljeno na studijama, niz je primjera kako liječenja AH može negativno utjecati na erektilnu funkciju. Pimjerice, karvedilol, blokator s vazodilatacijskim učinkom značajnije je urušio seksualnu funkciju u usporedbi sa valsartanom, sartanom s također vazodilatacijskim učinkom. Zabilježeno je da je kod bolesnika koji su liječeni propranololom u dozi od 120 mg dnevno ispoljen negativan učinak na erektilnu funkciju. Selektivni beta$_1$ blokator atenolol u dozi od 50-100 mg dnevno znakovito urušava sposobnost održanja erekcije. U dvostruko-slijepoj paralelnoj studiji atenolol je bio inferioran u usporedbi s beta-blokatorom treće generacije celiprololom glede učinka na seksualnu aktivnost.[11] Atenolol je također imao negativan učinak na erektilnu funkciju u odnosu na neke druge antihipertenzive, primjerice lizinopril i valsartan.[12,13] U TAIM studiji (a*nTihypertensive Interventions and Management*), erektilna disfunkcija je bila znakovito češća kod bolesnika koji su uzimali 50 mg atenolola u odnosu na placebo (11% vs 3%), ali ta razlika nije bila statistički značajna.[14] Uopće, ED je kod beta-blokatora receptora dosta ovisna o dozi, a u slučaju atenolola bila je najizraženija kod preporučene doze od 100 mg dnevno koja se i najčešće koristila u liječenju.

Nedavno objavljena studija autora Baumhakela i ostalih o usporedbi učinka dva beta-blokatora koji se koriste u liječenju ZS na endotelnu funkciju kod miševa pokazala je zanimljive rezultate. Učinak 10 mg/kg/dan nebivolola i 90 mg/kg/dan metoprolola bio je podjednak na endotelnu funkciju penilnog i tkiva aorte miševa, ali nebivolol je pokazao znakovito bolji učinak na endotelnu funkciju spužvastog tijela. Taj pozitivan učinak vjerojatno je posljedica smanjenja oksikativnog stresa u spužvastom tijelu.[15]

Studija, koja je nedvojbeno promijenila promišljanje jesu li svi beta-blokatori isti glede učinka na erektilnu funkciju i dala zaključak koji se lijek može preporučiti ako želimo izbjeći ED, je ona čiji su autori Doumas i suradnici iz 2006. godine. U toj prospektivnoj, otvorenoj studiji sudjelovali su mlađi i sredovječni muškarci (dob 31-65 godina) koji su imali AH i liječeni beta-blokatorima: atenololom u dozi od 50-100 mg/d ili metoprololom u dozi od 100 mg ili bisoprololololom u dozi od 10 mg/d dulje od 6 mjeseci (raspon od 6 mjeseci do 22 godine). Bolesnici s bolestima bubrega, jetre, šećernom bolesti ili srčanim pobolom su bili isključeni zbog moguće sveze s ED. Svi ispitanici koji uzimali navedene beta-blokatore ispunili su standardizirani informativni test-upitnik tzv. *Internacionalni indeks za erektilnu funkciju* (IIEF). On sadrži informacije iz različitih područja seksualne funkcije poput upita o erektilnoj funkciji, funkciji orgazma, seksualne želje tijekom odnosa i

cular musculature. Endothelial function of the penile artery and the cancellous tissue also play an important role. Nitrogen oxide functions locally as a non-adrenergic noncholinergic neurotransmitter.[10]

More then 25% of ED are related to side effects of certain drugs. Antihypertensive drugs are commonly an isolated group, while according to numerous studies, beta-blockers and thiazides increase the risk of ED the most. The accurate mechanism of ED caused by beta-blockers has not been completely clarified. It is assumed that it is especially a consequence of effect on the adrenergic system that is included in the integration stage of erection and ejaculation. It should be noted that one recent study has shown that the role of peripheral vasoconstriction is the consequence of taking beta-blockers, but it has no significant effect on the erectile function.

Based on the studies, there is a series of examples showing that the hypertension treatment may negatively affect the erectile function. For instance, carvedilol, the blocker with vasodilatation effect has greatly damaged the sexual function compared to valsartan, sartan that has also vasodilatation effect. It has been recorded that propranolol in dose of 120 mg daily in patients who were treated with, negatively affected their erectile function. Selective beta$_1$ blocker atenolol in dose of 50-100 mg a day greatly damages the ability of erection maintenance. In double-blind parallel study atenolol was inferior compared with third generation beta-blocker celiprolol with regard to effect on sexual activity.[11] Atenolol also had a negative effect on erectile function compared to some other hypertensive drugs, such as lisinopril and valsartan.[12,13] The TAIM study (anTihypertensive Interventions and Management), that ED was much more frequent with patients who were taking 50 mg atenolol compared to placebo (11% vs 3%), but this difference was statistically insignificat.[14] In general, ED with beta-blockers is greatly dependent on a dose, but in the event of atenolol, it was the greatest when taking the drug in recommended dose of 100 mg a day that was most frequently used in treatment.

The recently published study by Baumhakel and others on comparison of the effect of the two beta-blockers used in treatment of heart failure on endothelial function with mice has shown some interesting results. The effect of 10 mg/kg/day of nebivolol and 90 mg/kg/day of metoprolol was the same on endothelial function of penile tissue and aorta tissue in mice, but the nebivolol showed a better effect on the endothelial function of a corpus spongiusum penis. This positive effect was probably a consequence of reduction of oxidative stress in the corpus spongiusum.[15]

The study that undoubtedly changed the attitude as to whether all beta-blockers are the same with regard to erectile function resulting in a conclusion which beta-blocker may be recommended if we wish to avoid ED is the study by Doumas and others in 2006. Younger and middle-aged men (aged from 31 to 65) suffering from hypertension and treated with beta-blockers participated in this prospective and open study. These beta-blockers are the following: atenolol in dose of 50-100 mg/d or metoprolol in dose of 100 mg or bisoprololol in dose of 10 mg/d over 6 months (ranging from 6 months to 22 years). The patients suffering from kidney, liver diseases, diabetes or heart diseases were excluded due to a potential connection with ED. All respondents taking the afore-mentioned beta-blockers completed the standardized information test-questionnaire *International index for erectile function* (IIEF). It contains information from different areas of sexual function such as queries

općenitog zadovoljstva spolnim činom. Erektilna disfunkcija se klasificira prema IIEF skali na značajnu (6-10 bodova), srednje tešku (11-16 bodova), blagu (17-25 bodova) i stanje bez ED (26-30 bodova). Rezultati studije su pokazali da čak 66 % ispitanika s AH koji su uzimali atenolol ili metoprolol ili bisoprolol ima neki oblik ED. Značajna ED je nađena u 18 % ispitanika, srednja ED kod 30% a blaga kod 18% ispitanika. Samo 34% ispitanika nije imala probleme sa erektilnom funkcijom. Nakon prestanka uzimanja navedenih beta-blokatora i razdoblja ispiranja svi ispitanici su prešli na ekvivalentne doze nebivolola (5-10 mg/d). Primjerice, srednja doza atenolola u studiji je bila 63 mg/d, dok je srednja doza nebivolola iznosila 6.45 mg/d. Nakon tri mjeseca uzimanja nebivolola, ispitanici su ponovno ispunjavali IIEF upitnik. Rezultati su bili impresivni. Naime, zabilježeno je statistički značajno poboljšanje erektilne funkcije kod čak 69% ispitanika, a od njih polovice se seksualna funkcija u potpunosti vratila. U svim oblicima ED zabilježen je znakoviti boljitak kod uzimanja nebivolola, primjerice značajna ED (5% vs 18%), srednja ED (27% vs 30%) i blaga ED (9% vs 18%). U zaključku, rezultati studije su pokazali da jedino nebivolol ima povoljne učinke na erektilnu funkciju kod hipertenzivnih bolesnika liječenih navedenim beta-blokatorima. Pri tome je nebivolol učinkovito snižavao povišeni arterijski tlak uz boljitak funkcije endotela i uopće kvalitete života.[16]

Slični rezultati zabilježeni su i u MR NOED studiji (Nitric Oxide Erectile Dysfunction and beta-blocker treatment: benefit of nebivolol vs metoprolol in hypertensive men). Randomizirana, dvostruka slijepa studija trajanja 28 tjedana na 50 muškaraca bez seksualne disfunkcije u dobi od 40-55 godina s prvim stupnjem AH pokazala je podjednaki učinak 5 mg nebivolola i 95 mg metoprolola na sniženje arterijskog tlaka. No, nebivolol je pokazao statistički značajno bolji učinak na erektilnu funkciju. Sve sastavnice IIEF ljestvice, bolesnici tijekom perioda uzimanja nebivolola ocijenili su značajno boljim nego tijekom perioda kada su uzimali metoprolol. Razlika je bila najizraženija kod erektilne funkcije i ukupnog zadovoljstva spolnim činom, ali je bila statistički značajna i kod funkcije orgazma, seksualne želje i zadovoljstva tijekom spolnog čina.[17] U zaključku studije može se kazati da ovi kardioselektivni antagonisti $beta_1$ adrenoreceptora imaju različiti učinak na erektilnu funkciju kod muškaraca s AH. Objašnjenje prednosti nebivolola zasniva se poglavito na vazodilatacijskom učinku posredovanom oslobađanjem NO. Oslobađanje NO uzrokuje koronarnu i sustavnu vazodilataciju te smanjenje perifernog otpora i endotelne disfunkcije. Učinak NO na endotelnu funkciju vjerojatno je posljedica i aktivacije $beta_3$ receptora za koje je dokazano da se nalaze i u spužvastom tijelu. Nebivolol poboljšava erektilnu funkciju i poboljšanjem perfuzije u malim i vrlo malim krvnim žilama što je vrlo slično učinku fosfodiasteraze tip 5 inhibitora sildenafila.[18]

I nešto ranije objavljena studija autora Boydaka i ostalih u kojoj je uspoređivan učinak nebivolola i atenolola s ili bez dodatka klortalidona na seksualnu funkciju pokazala je vrlo slične rezultate kao gore navedene studije. Bolesnici koji su dobivali atenolol kao monoterapiju 12 tjedana imali su znakovito manji prosječni broj zadovoljavajućih seksualnih odnosa mjesečno u odnosu na bazalni period bez uzimanja lijekova (smanjenje sa 7 na 3,7 odnosa mjesečno), dok je u slučaju uzimanja atenolola i klortalidona

about erectile function, function of orgasm, sexual desire during the sexual intercourse and general satisfaction with sexual intercourse. The ED is classified according to IIEF scale for a severe (6-10 points), medium (11-16 credits), mild ED (17-25 credits) and condition with no ED (26-30 credits). The findings of the study have shown that even 66% respondents with hypertension taking atenolol or metoprolol or bisoprolol had some kind of ED. A significant ED was found in 18% of respondents, the medium ED in 30% and mild with 18% of respondents. Only 34% of respondents had no problems with erectile function. After they stopped taking the aforementioned beta-blockers and washout period, all respondents passed on to equivalent doses of nebivolol (5-10 mg/d). For example, the mean dose of atenolol in the study was 63mg/d while the mean dose of nebivolol was 6.45 mg/d. After three months of taking nebivolol, the respondents again completed IIEF questionnaire. The results were impressive. Namely, it was recorded that statistically great improvement of erectile function was recorded in 69% of respondents, while in a half of them the sexual function was re-established. In all forms of ED, a great improvement was recorded in case of taking nebivolol, such as severe (5% vs 18%), medium (27% vs 30%) and mild ED (9% vs 18%). To conclude, the results of the study have shown that it is only nebivolol that has positive effects on erectile function in hypertensive patients treated with afore-mentioned beta-blockers. The nebivolol has efficiently reduced high blood pressure improving the function of endothelium and life quality in general.[16]

Similar results were recorded in the MR NOED study (Nitric Oxide Erectile Dysfunction and beta-blocker treatment: benefit of nebivolol vs metoprolol in hypertensive men). Randomized, a double blind study lasting for 28 weeks conducted on 50 men with no sexual dysfunction aged from 40-55 with the first stage of hypertension has shown the same effect of 5 mg nebivolol and 95 mg of metoprolol on reducing blood pressure. However, nebivolol has shown statistically better effect on the erectile function. All components of the IIEF score were assessed by the patients during the period of taking nebivolol much better than during the period when they were taking metoprolol. The difference was greatest with the erectile function and total satisfaction by sexual intercourse, but it was statistically significant in the orgasm function, sexual desire and satisfaction during sexual intercourse.[17] The conclusion of the study reveals that the cardioselective antagonists $beta_1$ adrenoreceptors have a different effect on the erectile function in men with hypertension. The explanation of advantages of nebivolol is mainly based on vasodilatation effect via release of NO. The release of NO causes coronary and system vasodilatation and reduction of peripheral resistance and endothelial dysfunction. The effect of NO on endothelial function is probably the consequence of activation of $beta_3$ receptors that are proven to be found in corpus spongiosum. Nebivolol improves the erectile function and improvement of perfusion in small and very small blood vessels which is very similar to the effect of the phosphodiesterase type 5 of sildenafil inhibitors.[18]

The previously published study by the author Boydak and others which compared the effect of nebivolol and antenolol with or without an addition of clortalidon on sexual function has shown very similar results as the above mentioned studies. The patients who had been receiving atenolol as mono-therapy for 12 weeks had a much de-

zajedno to smanjenje bilo još izraženije (sa 6,4 na samo 2,8 odnosa mjesečno). Suprotno tome, prosječan broj zadovoljavajućih spolnih odnosa mjesečno bio je konstantan u skupini bolesnika koji su uzimali nebivolol (6,4 bazalno vs 6,0 tijekom zadnjeg mjeseca praćenja). Učinak oba blokatora beta receptora na arterijski tlak i srčanu frekvenciju bio je podjednak.[19]

I studija koja je uspoređivala antihipertenzivni učinak i kvalitetu života tijekom terapije između nebivolola i losartana pokazala je dobre karakteristike nebivolola. Naime, antihipertenzivni učinak na sistolički tlak je bio podjednak dok je nebivolol učinkovitije snižavao dijastolički tlak. Ukupna kvaliteta života procijenjena na osnovu odgovora na 23 pitanja testa, tzv. Quality of Life ljestvice (QOL score) nije pokazala statistički značajnih razlika na seksualnu aktivnost, dok je skupina bolesnika koja je uzimala nebivolol imala značajno manje glavobolja nakon šest tjedana terapije.[20]

U konačnici pregleda učinka beta-blokatora na erektilnu funkciju s naglaskom na pozitivne karakteristike nebivolola, citirajmo riječi L. Ignarro-a, dobitnika Nobelove nagrade za medicinu i istraživanje dušikovog oksida koji drži da "Nebivolol ima potencijal postati nezamjenljivi lijek za liječenje krvožilnih poremećaja što proizilazi iz jedinstvene sposobnosti da pokrene brojne zaštitne mehanizme posredovane dušikovim oksidom".[21]

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E-mail: goran.krstacic@zg.t-com.hr

creased average number of satisfactory sexual intercourses a month compared to basal period when they took no drugs (reduction from 7 to 3.7 sexual intercourses a month), while in the event of taking atenolol and clortalidone together, this reduction was much greater (from 6.4 to only 2.8 sexual intercourses a month). Unlike that, an average number of satisfactory number of sexual intercourses a month was constant in the group of patients who were taking nebivolol (6.4 basally vs 6.0 during the last month of monitoring). The effect of both beta-blockers on blood pressure was the same.[19]

Even the study that compared antihypertensive effect and life quality during the therapy of nebivolol and losartan have shown some good characteristics of nebivolol. Namely, antihypertensive effect on the systolic pressure was the same while nebivolol more efficiently reduced diastolic pressure. Total life quality evaluated on the basis of answers to 23 questions, that is, Quality of Life score (QOL score) neither showed statistically significant differences in effect on sexual activity, while the group of patients that was taking nebivolol had much less headache after six weeks of the therapy.[20]

Finally, reviewing the effects of beta-blockers on the erectile function focusing on positive characteristics of nebivolol, we quote the words L. Ignarro, the Nobel prize winner for medicine and researches of nitrogen oxides who thought that "Nebivolol has a potential to become an irreplaceable drug for the treatment of cardiovascular disorders since it may initiate numerous protective mechanisms via nitrogen oxides".[21]

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