



## Nebivolol — novi beta-blokator na raspolaganju našim bolesnicima

## Nebivolol — a new beta-blocker available for our patients

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**SAŽETAK:** Premda je registriran u Hrvatskoj još 2002. godine, a na Dopunskoj listi lijekova Hrvatskog zavoda za zdravstveno osiguranje se nalazi od prije godinu dana, Nebilet® (nebivolol) je tek odnedavno dostupan našim bolesnicima. Nebivolol je istovremeno visokoselektivni blokator beta-1 receptora, ali i vazodilatator, pretežito preko oslobađanja dušičnog oksida. Stoga je indiciran u liječenju arterijske hipertenzije i kroničnog zatajivanja srca. U liječenju zatajivanja srca temeljem SENIORS studije, indiciran je za liječenje osoba starijih od 70 godina. Posebna osobina nebivolola je njegov velik učinak na oslobađanje dušičnog oksida (NO) kao snažnog vazodilatatora. Pored vazodilatacije NO ima antiagregacijsko djelovanje, smanjuje proliferaciju glatkoćelijskih stanica i migraciju leukocita. Na smanjeno oslobađanje NO utječu: arterijska hipertenzija, dislipidemija, dijabetes i starenje. To je posebice važno u liječenju sistoličke hipertenzije, koja se primarno javlja u osoba starijih od 55 godina i sada se smatra čimbenikom kardiovaskularnog rizika. Taj je rizik izravno povezan sa smanjenom elastičnošću velikih arterija. Jedan od čimbenika koji dovodi do smanjene elastičnosti arterija je i disfunkcija endotela, te zbog toga manjeg lučenja NO. Nebivolol kao lijek koji povećava oslobađanje NO stoga je vrlo pogodan za liječenje sistoličke hipertenzije, daleko više od atenolola, koji tih svojstava nema. Također zbog visoke selektivnosti na beta-1 receptore (koja je veća od bisoprolola i karvedilola), izaziva i manje nuspojave (poglavito bronhospazmatični učinak), a ima i povoljan metabolički učinak s neutralnim ili povoljnim djelovanjem na inzulinsku rezistenciju, te razinu glukoze i lipida u plazmi.

**KLJUČNE RIJEČI:** nebivolol, arterijska hipertenzija, zatajivanje srca, dušični oksid, beta-blokatori

**SUMMARY:** Although registered in Croatia since 2002, and it has been accessible on the Complementary List of Medicines by the Croatia Bureau of Health Insurance for almost a year, Nebilet® (nebivolol) has only recently become available to our patients. Nebivolol is a highly-selective blocker of beta-1 receptors and also a vasodilator, mostly through the release of nitrous oxide. It is therefore recommended in treating arterial hypertension and chronic heart failure. In treating heart failure based on the SENIORS study, persons older than 70 years of age are recommended for such treatment. A special effect of nebivolol is its great impact on releasing nitric oxide (NO) as a strong vasodilator. Besides vasodilatation, NO possesses antiaggregation effects, reduces proliferation of smooth muscle cells and migration of leukocytes. A reduction in releasing NO is influenced by: arterial hypertension, dyslipidemia, diabetes and aging. This is especially important in treating systolic hypertension, which appears primarily in persons over 55 years of age and is now considered a cardiovascular risk. This risk is directly related to a reduction in the elasticity of large arteries. One of the factors that leads to a reduction in elasticity in arteries is dysfunction of endothelium, and therefore leading to less secretion of NO. Nebivolol as medication that increases release of NO is therefore very suitable for treating systolic hypertension, much more so than atenolol, which does not possess these characteristics. Also, due to a high selectivity of beta-1 receptors (which is greater than bisoprolol and carvedilol), it causes fewer side-effects (mainly broncho-obstructive effects), and has a favourable metabolic effect with neutral or appropriate action on insulin resistance, and on the level of glucose and lipids in plasma.

**KEYWORDS:** nebivolol, arterial hypertension, heart failure, nitrogen oxide, beta-blockers.

Premda je registriran u Hrvatskoj još 2002. godine, a na Dopunskoj listi lijekova Hrvatskog zavoda za zdravstveno osiguranje se nalazi od prije godinu dana, Nebilet® (nebivolol) je tek odnedavno dostupan našim bolesnicima.

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Brojnim kliničkim ispitivanjima dokazano je da je dobra kontrola arterijskoga tlaka (AT) bitan čimbenik, kako u prevenciji kardiovaskularnih bolesti, tako i u njihovom liječenju. Unatoč novim i raznovrsnim terapijskim mogućnostima, prema brojnim izvorima, još uvijek velik broj bolesnika nema reguliran AT na odgovarajući način.

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Numerous clinical tests have proven that a good control of blood pressure (BP) is an important factor not only in the prevention of cardiovascular diseases, but also in its treatment. Despite new and various therapeutical possibilities, in accordance with many sources, still a large number of patients do not have a regulated BP in an acceptable manner.



Prema posljednjim Europskim smjernicama, za inicijalno liječenje preporuča se odabrati jedan od lijekova iz sljedećih skupina: diuretik, beta-blokator, kalcijски antagonist, ACE inhibitor ili antagonist angiotenzinskih receptora. Beta-blokatori se preporučuju u bolesnika s koronarnom bolesti srca, preboljelim infarktom miokarda, zatajivanjem srca, tahiaritmijama i u trudnoći. U provedenim kliničkim ispitivanjima nebivolol je pokazao istu učinkovitost kao i drugi beta-blokatori, te antihipertenzivi iz ostalih farmakoterapijskih skupina.

Ipak, u posljednje vrijeme uloga beta-blokatora kao prvoga antihipertenziva postaje upitna, poglavito atenolola. Prema nekim autorima, njegova se primjena uopće ne preporuča, dok se iz skupine beta-blokatora u terapiji AH primarno preporučuju lijekovi s vazodilatatornim osobinama, a to su karvedilol i nebivolol. Posebna osobina nebivolola je njegov velik učinak na oslobađanje dušičnog oksida (NO) kao snažnog vazodilatatora. Pored vazodilatacije, NO ima antiagregacijsko djelovanje, smanjuje proliferaciju glatkomišićnih stanica i migraciju leukocita. Na smanjeno oslobađanje NO utječu: AH, dislipidemija, dijabetes i starenje. To je posebice važno u liječenju sistoličke hipertenzije, koja se primarno javlja u osoba starijih od 55 godina i koja se sada smatra čimbenikom kardiovaskularnog rizika, a taj je rizik izravno povezan sa smanjenom elastičnošću velikih arterija. Jedan od čimbenika koji dovodi do smanjene elastičnosti arterija je i disfunkcija endotela, te zbog toga manjeg lučenja NO. Nebivolol kao lijek koji povećava oslobađanje NO vrlo je pogodan za liječenje sistoličke hipertenzije, svakako puno više od atenolola koji tih svojstava nema. Također zbog visoke selektivnosti na beta-1 receptore (koja je veća od bisoprolola i karvedilola) izaziva i manje nuspojave (poglavito bronhospastični učinak), a ima i povoljan metabolički učinak s neutralnim ili povoljnim djelovanjem na inzulinsku rezistenciju, te razinu glukoze i lipida u plazmi.

Zatajivanje srca je bolest koja je i dalje u porastu, unatoč svim do sada poduzetim mjerama na njezinoj prevenciji i liječenju. Jedan je od glavnih razloga za hospitalizaciju, mortalitet je još uvijek visok, a kvaliteta života bolesnika je mala. Uvođenjem u terapiju zatajivanja srca ACE inhibitora i beta-blokatora, značajno je poboljšana farmakoterapija ove bolesti, te je poglavito povećana dužina prosječnog preživljavanja bolesnika. U terapiji kroničnog zatajivanja srca do sada su se rabila tri beta-blokatora s dokazanim učinkom (karvedilol, metoprolol i bisoprolol), a nakon kliničkog ispitivanja Seniors, njima se pridružio i nebivolol. Posebno značenje ove studije je u tome što su u njoj sudjelovali ispitanici koji puno bolje predstavljaju prosječnoga bolesnika sa zatajivanjem srca. Takav je bolesnik u prosjeku stariji od onih koji su sudjelovali u dosadašnjim kliničkim ispitivanjima beta-blokatora u zatajivanju srca, te ima češće popuštanje srca s očuvanom sistoličkom funkcijom lijeve klijetke, entitet za čije liječenje su dosadašnji dokazi iz kliničkih ispitivanja bili ograničeni. Primjena nebivolola u ovih bolesnika dovodi do manjeg broja hospitalizacija, te većeg preživljavanja, neovisno o veličini istisne frakcije srca na početku ispitivanja.

According to the most recent European guidelines, as regards the initial treatment, one of the following medicines from the following groups is recommended: diuretic, beta-blocker, calcium antagonist, ACE inhibitor or antagonist of angiotensin receptors. Beta-blockers are recommended to patients with coronary heart diseases, those recovering from myocardial infarction, heart failure, tachyarrhythmia and during pregnancy. In undertaken clinical testing, nebivolol has shown the same effectiveness as other beta-blockers, and antihypertensive drugs from the other pharmacotherapy groups.

However, during recent times, the role of beta-blockers as a first hypertensive has become questionable, especially atenolol. According to some authors, its use is generally not recommended, while from the beta-blocker group in therapy AH primarily recommended are medicines with vasodilator characteristics, such as carvedilol and nebivolol. A particular characteristic of nebivolol is its strong effect on the release of nitrogen oxide (NO) as a strong vasodilator. Besides vasodilatation, NO has an antiaggregation effect, reducing the proliferation of smooth muscle cells and migration of leukocytes. Reduction in release of NO is affected by: AH, dyslipidemia, diabetes and aging. This is especially important in treating systolic hypertension, which primarily appears in persons over 55 years of age and which is considered to be a cardiovascular risk, with the risk exceptionally related to reduced elasticity of large arteries. One of the factors leading to reduced elasticity of arteries is a dysfunction of endothelium resulting thus in less secretion of NO. Nebivolol as a medicine increasing the release of NO and is very appropriate for treating systolic hypertension, much more so than atenolol which does not possess such characteristics. Also, due to its high selectivity of beta-1 receptors (which is greater than bisoprolol and carvedilol) it causes fewer side-effects (especially broncho-obstructive effects), but it also possesses a favourable metabolic effect with neutral and appropriate results on insulin resistance, and the level of glucose and lipids in plasma.

Heart failure is an illness which is still increasing, despite all measures undertaken for its prevention and treatment. It is one of the main reasons for hospitalization, mortality is still always high, while the patients' quality of life is low. By introducing therapy for heart failure using ACE inhibitors and beta-blockers, pharmacotherapy of such a disease has been significantly improved, and the expected life average of the patient has been generally increased. Therapy for chronic heart failure has up till now included three beta-blockers with proven results (carvedilol, metoprolol and bisoprolol), and following testing Seniors, nebivolol has now joined them. Of special significance to this study is that examinees who much better represent an average patient with heart failure participated. Such a patient is on average older than those who had participated in previous clinical testing of beta-blockers for heart failure, and suffers from a more frequent failure of the heart with preserved systolic functioning of the left ventricle, an entity for which treatment previous evidence from clinical testing were limited. Administration of nebivolol in such patients leads to less hospitalization, and a greater chance



Iz svega navedenoga, vidljivo je da je nebivolol beta-blokator s vrlo povoljnim farmakološkim profilom, te dokazanim učinkom u liječenju AH, kao i zatajivanja srca u osoba starijih od 70 godina, koji i čine pretežit broj oboljelih od ove bolesti. Zbog njegova farmakološkog profila (velika beta-1 selektivnost i vazodilatacijski učinak), nebivolol je lijek koji se sve više preporučuje kao beta-blokator izbora u liječenju AH i zatajivanja srca.

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### Literature

1. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.
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3. Zanchetti A. Clinical pharmacodynamics of nebivolol: new evidence of nitric oxide-mediated vasodilating activity and peculiar haemodynamic properties in hypertensive patients. *Blood Pressure* 2004;13(Suppl 1):18-33.
4. Mattace-Raso FUS, Van der Cammen TJM, Hofman A, Van Popele NM, Bos ML, Schalekamp MADH et al. Arterial stiffness and risk of coronary heart disease and stroke. The Rotterdam Study. *Circulation* 2006;113:657-63.
5. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a beta-adrenoceptor antagonist with unique characteristics. *Drugs* 2007;67:1097-107.

## 4. kongres Hrvatskog društva za ultrazvuk u medicini i biologiji s međunarodnim sudjelovanjem

Zagreb, hotel Westin, 3. i 4. travnja 2008.

### Sekcija iz ehokardiografije - Ultrazvuk u kardiologiji i hitnoj medicini

Petak, 4. travnja 2008. godine, 14.30 - 17.30 sati  
 Voditelj sekcije: V. Nikolić Heitzler, Zagreb  
 Predsjedavajući : D. Štajer, Ljubljana; D. Planinc, Zagreb  
 14.30-14.42 (+3) M. Vrsalović: Ehokardiografija u procjeni kardiovaskularnog rizika  
 14.45-14.57 (+3): K. Štambuk: Ehokardiografija kod bolesnika s dijabetesom  
 15.00-15.12 (+3): I. D. Gabrić: Ehokardiografija kod plućnih bolesnika  
 15.15-15.30 (+3): A. Šmalcelj: Ehokardiografska evaluacija atrijske morfologije i funkcije u aritmijama  
 15.33-15.48 (+3): D. Štajer: Ehokardiografija u hemodinamskoj procjeni kritičnog bolesnika  
 15.51- 16.20 Pauza za kavu  
 16.20-16.35 (+3): D. Planinc: Ishemijska mitralna regurgitacija  
 16.38-16.53 (+3): B. Starčević: Aortna stenoza sa značajnom disfunkcijom lijevog ventrikula  
 16.56-17.11 (+3): V. Nikolić Heitzler: Miokarditis  
 17.14-17.27 (+3): D. Delić-Brkljačić: Transezofagijska ehokardiografija kao nadopuna i metoda u rješavanju transtorakalnih ehokardiografskih enigma

of survival, independent of the size of ejection fraction of the heart at the start of testing.

From what has been stated, it is evident that nebivolol is a beta-blocker with a very good pharmacological profile, and proven effect in treating AH, as well as heart failure in persons older than 70 years, that make for those mainly suffering from such a disease. Due to its pharmacological profile, (large beta-1 selectivity and vasodilatation effect), nebivolol is a medication increasingly recommended as a beta-blocker, a choice in treating AH and heart failure.

## 4<sup>th</sup> Congress of the Croatian society for ultrasound in medicine and biology with international participation

Zagreb, Westin hotel, 3<sup>rd</sup> and 4<sup>th</sup> April 2008

### Session in echocardiography - Ultrasound in cardiology and emergency medicine

Friday, 4<sup>th</sup> April 2008, 14.30 - 17.30  
 Host of the session: V. Nikolić Heitzler, Zagreb  
 Chairpersons : D. Štajer, Ljubljana; D. Planinc, Zagreb  
 14.30-14.42 (+3) M. Vrsalović: Echocardiography in assessing cardiovascular risks  
 14.45-14.57 (+3) K. Štambuk: Echocardiography in patients suffering from diabetes  
 15.00-15.12 (+3) I. D. Gabrić: Echocardiography in patients suffering from lung diseases  
 15.15-15.30 (+3) A. Šmalcelj: Echocardiographic evaluation of atrial morphology and functions in arrhythmias  
 15.33-15.48 (+3) D. Štajer: Echocardiography in haemodynamic assessment of critical patients  
 15.51- 16.20 Coffee break  
 16.20-16.35 (+3) D. Planinc: Ischemic mitral regurgitation  
 16.38-16.53 (+3) B. Starčević: Aortic stenosis with a significant dysfunction of the left ventricle  
 16.56-17.11 (+3) V. Nikolić Heitzler: Myocarditis  
 17.14-17.27 (+3) D. Delić-Brkljačić: Transesophageal echocardiography as a supplement and a method in resolving transthoracic echocardiographic enigmas