

Effect of Nebivolol on Microalbuminuria in Hypertensive Patients with or without Type 2 Diabetes Mellitus

Padma Latha Merugu, Thrilok Chander Bingi¹

Department of Pharmacology, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, ¹Department of General Medicine, Gandhi Medical College/ Hospital, Secunderabad, Telangana, India

Abstract

Objective: To evaluate the effect of nebivolol on microalbuminuria (MA) in hypertensive patients with or without type 2 diabetes mellitus. **Materials and Methods:** This was an open-label, prospective study. Drug naive patients with stage I hypertension with or without type 2 DM with MA (urine albumin: creatinine ratio [UACR] between 30–300 mg/g) were enrolled in the study and were started on nebivolol 5 mg orally once daily. Efficacy parameters UACR, blood pressure (BP) were measured at baseline and 24 weeks. Paired *t*-test was used to analyze efficacy endpoints. $P < 0.05$ was considered to be statistically significant. **Results:** A total of 30 participants completed the study. Participants who received nebivolol showed a significant decrease in mean UACR, systolic BP, and diastolic BP at 24 weeks compared to baseline ($P < 0.001$). No participant discontinued the study because of adverse events. **Conclusion:** Nebivolol has a favorable effect on MA in addition to its antihypertensive effect in hypertensive patients. Further studies with large samples are required to characterize this effect of nebivolol on clinical outcomes.

Keywords: Endothelial dysfunction, hyperglycemia, mean arterial blood pressure, oxidative stress, proteinuria

INTRODUCTION

Microalbuminuria (MA) is a well-known predictor of poor renal and cardiovascular events in patients with essential hypertension and type 2 diabetes mellitus (DM).^[1] The National Kidney Foundation's Outcomes Quality Initiative guidelines define MA as an abnormally increased excretion of albumin in the specific range of 30–300 mg in 24 h urine collection or albumin to creatinine ratio of 30–300 mg/g in a spot urine specimen or albumin concentration of >3 mg/dl in a spot urine specimen using an albumin-specific dip stick.^[2]

Several studies have shown the prevalence of MA in hypertensive patients between 6.7% to 51% depending on the selection criteria, the severity of hypertension, age, and ethnic group.^[1,3] The advent of more sensitive methods to quantitate urinary albumin excretion has revealed a higher frequency of MA. Indian study by Aggarwal *et al.*, have shown a prevalence of 47% of MA in Indian hypertensive patients.^[4] The prevalence of MA in people with both hypertension and diabetes, as would be expected, is alarmingly high at 58.6%.^[5]

The exact pathogenesis of MA in patients with essential hypertension has not been established. Putative mechanisms include: increased glomerular hydrostatic pressure due to defect in autoregulation, increased permeability of glomerular basement membrane, overactivation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), oxidative stress, inflammation, and endothelial dysfunction. RAAS and SNS activation are crucial in the pathogenesis of hypertension, cardiovascular and renal disease. Reactive oxygen species (ROS) are an important mediator of adverse RAAS-induced renal and cardiovascular effects. Increased level of ROS reduces the production of endothelium-derived nitric oxide (NO) through inhibition and/or uncoupling of nitric oxide synthase (NOS) enzymes.

Address for correspondence: Thrilok Chander Bingi,
Flat No: 605, Namita Everest, Bahadurguda, L.B. Nagar, Ranga Reddy,
Hyderabad - 500 074, Telangana, India.
E-mail: thrilok73@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Merugu PL, Bingi TC. Effect of nebivolol on microalbuminuria in hypertensive patients with or without type 2 diabetes mellitus. *J Pharmacol Pharmacother* 2020;11:13-8.

Received: 06-10-2019

Revised: 27-12-2019

Accepted: 06-05-2020

Web Publication: 12-09-2020

Decreased production of NO leads to endothelial dysfunction and associated glomerular injury and early proteinuria.^[6,7]

Numerous studies show that early detection and treatment of MA is essential for the prevention of micro and macrovascular complications of hypertension and diabetes. Lowering blood pressure (BP) by different antihypertensive agents has been shown to be able to reduce urinary protein excretion in patients with essential hypertension with or without diabetes. Recent guidelines recommended RAAS blockers as the agents of first choice for the management of hypertension in patients with MA and proteinuria, because of the significant renal-protective effects of this class of drugs.^[8,9] However, these agents are associated with cough, angioedema, hyperkalemia and are contraindicated in renovascular hypertension.^[10] Recent studies have reported that vasodilatory beta-blockers like nebivolol have adequate antihypertensive efficacy and less harmful effects on the metabolic profile, and also exert beneficial effects on endothelial function and renal protection.^[11-14]

Nebivolol is a third-generation beta-blocker, has a unique profile among antihypertensive drugs. It is a highly selective antagonist of β_1 -adrenergic receptors and agonist of β_3 receptors and induces vascular production of NO, the primary endothelial vasodilator. The specific mechanism of nebivolol is particularly pertinent in hypertension, where NO dysfunction occurs.^[15] Studies in animal models have shown that nebivolol has the ability to reduce the levels of ROS, attenuate oxidative stress and endothelial dysfunction.^[7,16] Further nebivolol have shown beneficial effects on renal hemodynamics, it increased renal plasma flow and glomerular filtration rate (GFR) in a dose dependent manner.^[15] At recommended doses, nebivolol decreased plasma renin and aldosterone levels in hypertensive and normotensive patients.^[17] In addition, clinical studies have shown that nebivolol provides significant BP and MA reductions with neutral or beneficial effects on metabolic parameters (lipid, glucose, insulin) in patients with diabetes and hypertension.^[12] This evidence suggests that nebivolol could offer a favorable effect on proteinuria in addition to its antihypertensive effect in hypertensive patients with or without diabetes. There have been limited clinical studies^[12,13] exploring the effects of nebivolol treatment in states of MA. Hence, this study was undertaken to evaluate the effect of nebivolol on MA in hypertensive patients with or without type 2 DM.

MATERIALS AND METHODS

An open-label, prospective study was conducted in the Department of Pharmacology in collaboration with the Department of Medicine in Gandhi Medical College, Secunderabad after taking approval from the Institutional Ethics Committee (IEC/GMC/2011/dated 07-11-2011). Written informed consent was taken from all the patients prior to participation in the study. The participants were enrolled from the general medicine outpatient department (OPD) and the study was conducted for 13 months from November 2011 to November 2012.

Drug naïve patients of either gender, aged 30–70 years, having stage-I hypertension (systolic BP [SBP] between 140–159 mmHg or diastolic BP [DBP] 90–99 mmHg according to Joint National Committee VII guidelines^[18]) or stage-I hypertension with type 2 DM with MA (urine albumin: creatinine ratio [UACR] between 30–300 mg/g) were included in the study.

Patients with overt proteinuria, Type-1 DM, urinary tract infection, Stage 2 hypertension (BP $\geq$ 160/100 mmHg), secondary hypertension, chronic obstructive pulmonary disease, bronchial asthma, hepatic and renal diseases, significant peripheral vascular disease, sinus bradycardia, sick sinus syndrome, A-V block greater than first degree were excluded from the study. Further, subjects with a history of unstable angina, myocardial infarction, heart failure, cerebrovascular accidents and sensitivity or significant adverse reactions to β -blocker therapy were also excluded. Pregnant and lactating women were not included in the study.

Drug naïve adult patients with stage-I hypertension with or without type 2 DM attending the medicine OPD were first screened for urine albumin by Albustix dipstick method. Morning mid-stream urine sample, negative for proteinuria by Albustix was used to test for MA. A total of 34 participants with MA satisfying the inclusion and exclusion criteria were enrolled in the study and were started on nebivolol 5 mg orally once daily. Participants' demographic details, the past and current medical and drug history, personal history, pulse, BP were recorded in a structured case record form. Participants were followed up with BP recording every 2 weeks until the end of the study. Urine albumin to creatinine ratio was performed in the early morning urine samples of all the selected patients at the start of the study and repeated at the end of 24 weeks. All these patients were advised health-promoting lifestyle modifications and in participants with coexistent diabetes, increased blood glucose levels are controlled with diet, oral hypoglycemic drugs or insulin. Participants were enquired for the presence of adverse drug reaction (ADR) at every visit, and any reported ADRs were recorded in the case report form. Compliance with therapy was assessed by pill count method.

Five milliliter of first-morning midstream urine sample was collected in a sterile container and analyzed for MA. All participants were afebrile at the time of the collection of urine. The participants were asked to avoid exercise or exertion before urine collection. In the women, urine was collected during the nonmenstrual phase of their cycles. The estimation of urinary albumin was carried out by immunoturbidimetry assay using the Tina-quant Albumin Gen. 2 kit (Roche Diagnostics Indianapolis USA cat. no. 190) method on Roche Hitachi 917 chemistry analyzer. Urinary creatinine was estimated by Buffered kinetic Jaffe's reaction by using Creatinine Jaffe Gen. 2 kits (Roche Diagnostics Indianapolis USA cat. no. 190).

BP was measured on the right arm of the participants by the auscultatory method using a sphygmomanometer with an

appropriate cuff size in the sitting position after 5 min of rest. The 1st and the 5th Korotkoff's sound were used to determine the SBP and DBP measurements, respectively. The median value of two consecutive measurements taken at 5 min interval was used for the study.

Efficacy parameters

The primary efficacy endpoint was the mean change in urine albumin to creatinine ratio (MA) from baseline to the end of 24 weeks and secondary efficacy endpoint was the mean change in SBP and DBP from baseline to the end of the 24 weeks.

Statistical analysis

Data were presented as mean $\pm$ standard deviation. Paired *t*-test was done to determine the changes in urine albumin to creatinine ratio and BP within the group. A $P < 0.05$ was considered to be statistically significant. The statistical analysis was done using the Graph Pad Prism software, version 4 (Graph Pad Software, La Jolla, CA, USA).

RESULTS

A total of 34 eligible participants were enrolled in the study. Out of 34 enrolled participants, three participants were excluded from the study because of noncompliance and one subject lost the follow-up. A total of 30 (20 males, 10 females) participants completed the study and were included in the analysis. The mean age of the study population was 55.6 ± 8.54 years. Of

the 30 subjects, 11 subjects (8 males and 3 females) had stage I hypertension, 19 participants (12 males, 7 females) had both hypertension and type 2 DM. The participant's disposal has been depicted in the consort study flow chart [Figure 1].

Urine albumin to creatinine ratio was calculated to determine MA. The effect of nebivolol on urine albumin to creatinine is shown in Figure 2. In the present study, it was observed that nebivolol significantly reduced urine albumin creatinine ratio from 87.12 ± 28.79 to 70.5 ± 31.41 at the end of the 24 weeks compared to baseline ($P < 0.001$). Further mean percentage change was also calculated, and the observed mean percentage decrease in UACR was 21% from baseline to the end of the 24 weeks.

The effect of nebivolol on BP has been shown in Figures 3 and 4. It was found that nebivolol significantly decreased mean SBP from 150.93 ± 5.03 to 128.53 ± 5.22 mmHg [Figure 3] and mean DBP from 93.13 ± 2.66 to 81.27 ± 2.85 mmHg [Figure 4] at the end of the 24 weeks compared to baseline ($P < 0.001$). The observed mean percentage reduction was 14.84% in SBP and 12.74% in DBP.

All participants tolerated therapy well. There were no serious adverse events recorded in the study. Two participants complained of headaches which got resolved with symptomatic treatment. None of the patients discontinued the study prematurely because of adverse events.

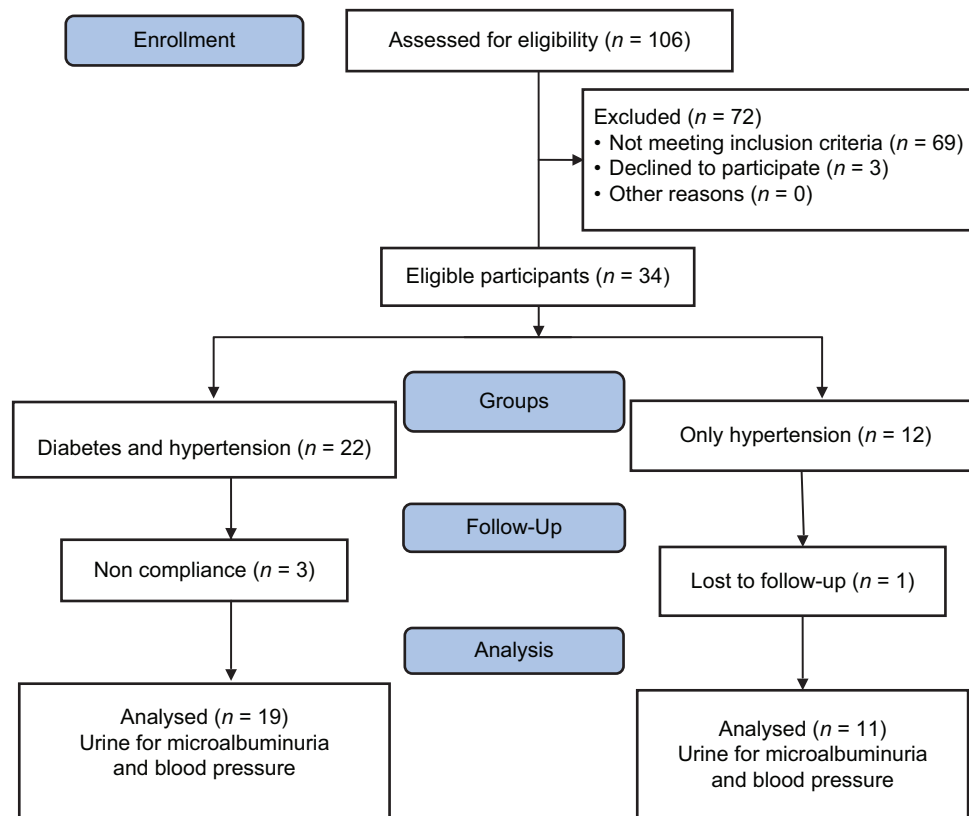


Figure 1: The participant's disposal in the study (CONSORT flow chart)

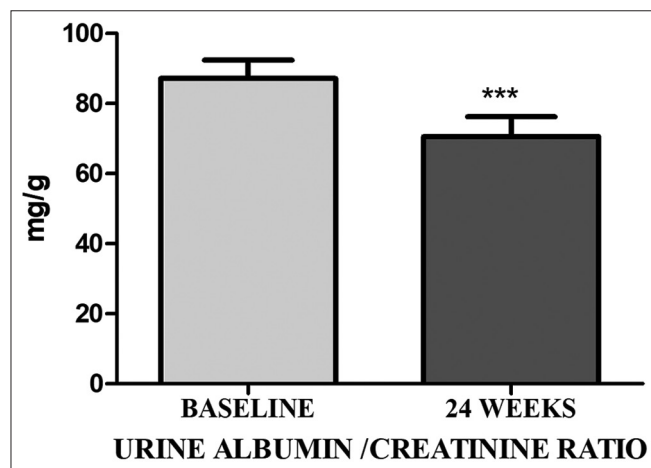


Figure 2: The effect of nebivolol on urine albumin to creatinine ratio (mg/g) at baseline and 24 weeks (mean $\pm$ SE). Baseline versus at 24 weeks $P < 0.001$. Error bars represent standard error (SE)

DISCUSSION

In this prospective study, participants who received nebivolol 5 mg/day for 6 months have shown a significant reduction in MA ($P < 0.001$) in addition to substantial reductions in SBP and DBP ($P < 0.001$).

MA is an early predictor of both renal and cardiovascular events in hypertensive and diabetic patients. Prevailing preclinical and clinical data suggest that generalized endothelial dysfunction frequently characterized by decreased NO bioavailability, actually precedes the development of MA. One of the key factors in endothelial dysfunction is overproduction of ROS which cause injury to both renal and systemic vascular beds.^[19] The modulation of MA and endothelial function might provide beneficial effects on future cardiovascular and renal outcomes.

Nebivolol is a third-generation selective β_1 -blocker with vasodilator activity. The vasodilator effect is attributed largely to the activation of endothelial NOS and increased NO release. In addition, nebivolol also possesses free radical scavenging activity with promising antioxidant properties. Tzemos *et al.* in a randomized, double blind, crossover trial in hypertensive patients with endothelial dysfunction showed that nebivolol reverses endothelial dysfunction through increased basal and stimulated endothelial NO release.^[20] Mason *et al.* demonstrated that nebivolol prevented eNOS uncoupling and restored NO bioavailability in endothelial cells. The investigators also reported that the most beneficial action of nebivolol on endothelial function is the reduction of oxidative stress by the inhibition of NAD(P)H oxidase activity and/or direct antioxidant properties of nebivolol.^[21] Sendur *et al.*, investigated the effects of olmesartan or nebivolol treatment on BP and endothelial function biomarkers (flow-mediated vasodilatation, NO and plasminogen activator inhibitor-1) in newly diagnosed patients with stage 1 essential hypertension. The investigators concluded that olmesartan and nebivolol causes similar improvement in BP response and endothelial function biomarkers.^[22]

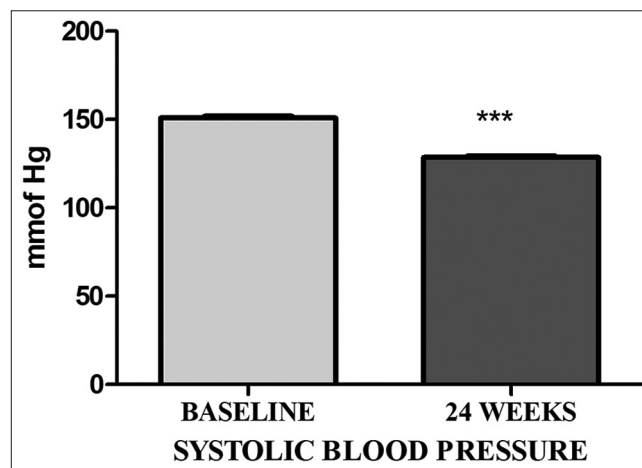


Figure 3: The effect of nebivolol on systolic blood pressure (mm of Hg) at baseline and 24 weeks (mean $\pm$ SE). Baseline versus at 24 weeks $P < 0.001$. SBP: Systolic blood pressure, Error bars represent standard error (SE)

The beneficial effect of nebivolol on proteinuria was demonstrated in an animal study done by Whaley-Connell *et al.* The investigators reported that nebivolol treatment results in reductions in proteinuria in the Transgenic Ren2 Rat model of RAAS activation that demonstrates hypertension, insulin resistance, and proteinuria. Whaley-Connell *et al.*, also reported that treatment with nebivolol helps maintain the integrity of podocyte-specific proteins in concert with a reduction in NADPH oxidase/ROS formation and increases eNOS levels in renal cortical tissue.^[7]

Clinical studies demonstrating the beneficial effect of nebivolol on MA in patients with hypertension are limited. In a pilot study of 33 patients with severe renal artery stenosis who underwent revascularization, nebivolol ($n = 17$) significantly increased the estimated GFR and decreased proteinuria ($P = 0.04$) as compared with the control group.^[13] A study done by Fogari *et al.* in hypertensive subjects with type 2 diabetes demonstrated that nebivolol in a dose of 5 mg/day given for 24 weeks significantly reduced mean SBP and DBP ($P < 0.001$). Besides, Fogari *et al.* also demonstrated nebivolol caused a decreasing trend in proteinuria in the study population.^[14] Yestono study,^[12] a prospective, open-label, multicenter, postmarketing surveillance study was conducted in 2838 patients in Germany with arterial hypertension and concomitant type 2 diabetes for 3 months. This study showed that nebivolol has a good antihypertensive effect, with positive changes in metabolic parameters including MA, lipid levels and glycosylated hemoglobin. A recent study (2017) done in Russia by Krivonos and Kolomiets reported that addition of nebivolol at a dose of 5 mg/day to ongoing antihypertensive therapy with lisinopril in the dose of 10 mg and amlodipine 5 mg in type 2 diabetic hypertensive patients caused a significant reduction in the MA, creatinine and improvement in lipid metabolism.^[23]

In our study, we observed that nebivolol in a dose of 5 mg/day for 6 months, significantly reduced MA ($P < 0.001$) in addition

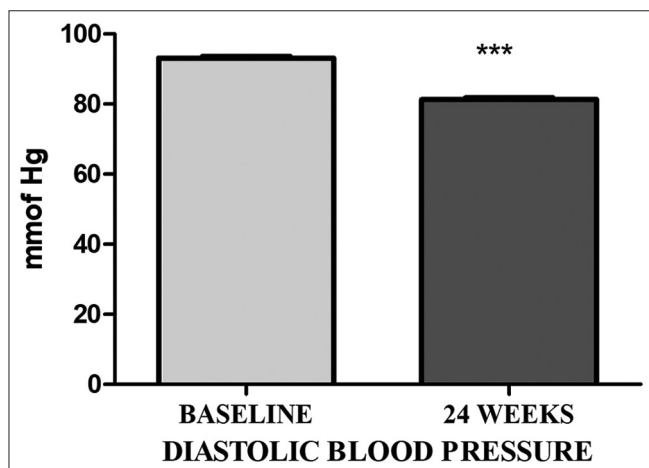


Figure 4: The effect of nebivolol on diastolic blood pressure (mm of Hg) at baseline and 24 weeks (mean $\pm$ SE). Baseline versus at 24 weeks $P < 0.001$. DBP: Diastolic blood pressure, Error bars represent standard error (SE)

to its antihypertensive effects. Our study results were similar to those of Yestono study and Fogari study.

In the present study, the significant reduction in MA levels in participants of essential hypertension on nebivolol treatment may be explained by its unique dual mechanism of action and its antioxidant properties. Beneficial change in MA with nebivolol might be partly due to improved BP control and partly due to significant improvement in endothelial dysfunction through restoration of NO bioavailability and reduced oxidative stress by nebivolol.

An advantage of the present study was that it was a prospective longitudinal design. Limitations of the study were small sample size; short duration and lack of control subjects.

CONCLUSION

In the present study, nebivolol significantly reduced MA in addition to BP in hypertensive patients with or without type 2 diabetes. Thus, it is suggested that nebivolol has a favorable effect on MA in addition to controlling BP. Further studies with large samples are required to characterize this effect of nebivolol on clinical outcomes.

Acknowledgments

We are grateful to Dr. R. Prahlad, Former Professor, Department of Medicine, Gandhi Hospital, Secunderabad for his clinical support. We are thankful to Dr. Usha Sree, former Professor & H.O.D of Pharmacology, Gandhi Medical College for her guidance. We are thankful to the study participants and general medicine department post graduates.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Basi S, Fesler P, Mimran A, Lewis JB. Microalbuminuria in type 2 diabetes and hypertension: A marker, treatment target, or innocent bystander? *Diabetes Care* 2008;31 Suppl 2: S194-201.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39: S1-266.
- Poudel B, Yadav BK, Nepal AK, Jha B, Raut KB. Prevalence and association of microalbuminuria in essential hypertensive patients. *N Am J Med Sci* 2012; 4:331-5.
- Aggarwal HK, Jain D, Mor S, Yadav RK, Jain P. Prevalence and clinical correlates of microalbuminuria in patients with essential hypertension – A tertiary care center cross sectional study. *J Assoc Physicians India* 2018; 66:30-4.
- Wu AY, Kong NC, de Leon FA, Pan CY, Tai TY, Yeung VT, *et al.* An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: The MicroAlbuminuria Prevalence (MAP) Study. *Diabetologia* 2005; 48:17-26.
- Maggon RR, Malik R, Jain N, Isser HS. Study of the prevalence of microalbuminuria in patients of essential hypertension and its correlation with left ventricular hypertrophy and carotid artery intima-media thickness. *J Clin Prev Cardiol* 2018; 7:11-6.
- Whaley-Connell A, Habibi J, Johnson M, Tilmon R, Rehmer N, Rehmer J, *et al.* Nebivolol reduces proteinuria and renal NADPH oxidase-generated reactive oxygen species in the transgenic Ren2 rat. *Am J Nephrol* 2009; 30:354-60.
- National Kidney Foundation. KDIGO Blood PressureWork Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;2:337-414.
- Verbeke F, Lindley E, Van Bortel L, Vanholder R, London G, Cochat P, *et al.* A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in nondialysis-dependent chronic kidney disease: An endorsement with some caveats for real-life application. *Nephrol Dial Transplant* 2014;29:490-6.
- Hilal-Dandan R. Renin and angiotensin. In: Brunton LB, Lazo JS, Parker KL, editors. *Goodman's Gilman's The Pharmacological Basis of Therapeutics*. 13th ed.. New York, NY: McGraw-Hill; 2018. p. 483-5.
- Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, *et al.* Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA* 2004;292:2227-36.
- Schmidt AC, Graf C, Brixius K, Scholze J. Blood pressure-lowering effect of nebivolol in hypertensive patients with type 2 diabetes mellitus: The YESTONO study. *Clin Drug Investig* 2007;27:841-9.
- Duranay M, Kanbay M, Akay H, Unverdi S, Sürer H, Altay M, *et al.* Nebivolol improves renal function in patients who underwent angioplasty due to renal artery stenosis: A pilot study. *Nephron Clin Pract* 2010;114:c213-7.
- Fogari R, Zoppi A, Lazzari P, Mugellini A, Lusardi P, Preti P, *et al.* Comparative effects of nebivolol and atenolol on blood pressure and insulin sensitivity in hypertensive subjects with type II diabetes. *J Hum Hypertens* 1997;11:753-7.
- Maffei A, Lembo G. Nitric oxide mechanisms of nebivolol. *Ther Adv Cardiovasc Dis* 2009; 3:317-27.
- Mollnau H, Schulz E, Daiber A, Baldus S, Oelze M, August M, *et al.* Nebivolol prevents vascular NOS III uncoupling in experimental hyperlipidemia and inhibits NADPH oxidase activity in inflammatory cells. *Arterioscler Thromb Vasc Biol* 2003;23:615-21.
- Chan TY, Woo KS, Nicholls MG. The application of nebivolol in essential hypertension: A double-blind, randomized, placebo-controlled study. *Int J Cardiol* 1992;35:387-95.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003;289:2560-72.
- Ochodnický P, Henning RH, van Dokkum RP, de Zeeuw D. Microalbuminuria and endothelial dysfunction: Emerging targets for primary prevention of end-organ damage. *J Cardiovasc Pharmacol*

- 2006;47 Suppl 2:S151-62.
20. Tzemos N, Lim PO, MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: A randomized, double-blind, crossover study. *Circulation* 2001;104:511-4.
 21. Mason RP, Kalinowski L, Jacob RF, Jacoby AM, Malinski T. Nebivolol reduces nitroxidative stress and restores nitric oxide bioavailability in endothelium of black Americans. *Circulation* 2005;112:3795-801.
 22. Sendur MA, Güven GS, Yorgun H, Ateş AH, Canpolat U, Sunman H, *et al.* Effect of antihypertensive therapy on endothelial markers in newly diagnosed stage 1 hypertension: A randomized single-centre study. *Anadolu Kardiyol Derg* 2014;14:363-9.
 23. Krivonos NY, Kolomiyets VV. Nephroprotective effect of nebivolol in patients essential hypertension combined with sugar type 2 diabetes. *Univer Clin* 2017;3:131