Research Article

Cost-effectiveness analysis of nebivolol and metoprolol in essential hypertension: A pharmacoeconomic comparison of antihypertensive efficacy of beta blockers

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ABSTRACT

Objective: To estimate and compare the cost-effectiveness and safety of nebivolol with sustained-release metoprolol in reducing blood pressure by 1 mm of Hg per day in hypertensive patients.

Materials and Methods: This was a prospective, randomized, open label, observational analysis of cost-effectiveness, in a questionnaire-based fashion to compare the cost of nebivolol (2.5 mg, 5 mg, 10 mg) and sustained released metoprolol succinate (25 mg, 50 mg, 100 mg) in hypertensive patients using either of the two drugs. A total of 60 newly detected drug naïve hypertensive patients were considered for the comparison, of which 30 patients were prescribed nebivolol and the other 30 were prescribed metoprolol succinate as per the recommended dosage. Based on the data, statistical analysis was carried out using GraphPad Prism 5 and MS Excel Spreadsheet 2007.

Result: The cost of reducing 1 mm of Hg blood pressure per day with nebivolol was 0.60, 0.70, and 1.06 INR, whereas that of metoprolol succinate was 0.93, 1.18, and 1.25 INR at their respective equivalent doses, hence significantly lower with the nebivolol group as compared to the metoprolol group ($P < 0.05$).

Conclusion: This pharmacoeconomic analysis shows that nebivolol is more cost-effective as compared to metoprolol when the cost per reduction in blood pressure per day is considered. This may affect the patients economically during their long-term use of these molecules for the treatment of hypertension.

KEY WORDS: Cost-effectiveness, hypertension, metoprolol, nebivolol, pharmacoeconomics

Introduction

Hypertension is an increasingly prevalent chronic condition that is associated with serious morbidity and mortality. It is an important risk factor for the development and progression of cardiovascular disease (CVD), which is predicted to become the leading cause of death and disability worldwide by 2020.[1] As per the Registrar General of India and Million Death Study investigators (2001-2003), CVD was the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually.[2] In India, 23.10% men and 22.60% women over the age of 25 years suffer from hypertension.[2] Treating systolic blood pressure (SBP) and diastolic blood pressure (DBP) to targets that are <140/90 mmHg is associated with a decrease in CVD complications.[3] Blood pressure (BP) reductions of 10 mmHg systolic or 5 mmHg diastolic are associated with a 33-48% reduction in stroke and a 17-27% reduction in coronary heart disease (CHD) events.[4] The co-morbidities, high prevalence rates, and the chronic nature of hypertension generate substantial economic burden for both the patient and the healthcare system.[5] Previous research has shown that systematic control of blood pressure can result in considerable cost savings.[6,7]

Carlberg *et al.* described in their meta-analysis that the efficacy and effectiveness of atenolol was found to be as good as that of placebo. Moreover, they challenge the use of atenolol as a reference drug in outcome trials of hypertension.[8] Van Bortel LM *et al.* performed meta-analysis of efficacy and tolerability of the novel highly cardio-selective nebivolol compared with

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other anti-hypertensive drugs. This meta-analysis suggests that nebivolol 5 mg is likely to have advantages over existing antihypertensive drugs and may have a role in the treatment of hypertension.[9] However, majority of the patients are currently prescribed extended release metoprolol succinate for reduction of blood pressure.

Therefore, this study was conducted in order to compare the cost-effectiveness of standard doses of nebivolol and metoprolol in terms of reduction in mm of Hg of blood pressure per day with the secondary objective of comparing the overall efficacy and safety of the two drugs in order to determine the better drug in totality.

Materials and Methods

This was a prospective, randomized, controlled (RCT), open label, observational analysis of cost-effectiveness carried out to compare the cost of nebivolol (2.5 mg, 5 mg, 10 mg) and sustained released metoprolol succinate (25 mg, 50 mg, 100 mg) in drug naïve newly diagnosed hypertensive patients. They were given either of the two drugs based on randomization. The protocol was approved by the Institutional Ethics Committee beforehand. A total of 60 patients were considered for the comparison and written informed consent was obtained from them. Thirty patients were evaluated in either of the drug groups for the study.

Patients of either sex, between 18-65 years, with hypertension (defined as supine SBP and/or DBP more than 140 mmHg and 90 mmHg, respectively) and written signed informed consent of the patient/relative were included in this study.

Patients with pregnancy and/or lactation, patients with anuria, progressive and severe oliguria, hepatic coma, hypernatremia (sodium <135 mEq/ml), hypokalemia (K^+<3.5 mEq/ml), hyperuricemia (uric acid >6 mEq/ml), systemic lupus erythematosus, bronchial asthma, diabetes, thyrotoxicosis, peripheral vascular disease, bradycardia (heart rate <60 bpm), heart block greater than first degree, cardiogenic shock, decompensated cardiac failure or sick sinus syndrome, hepatic and/or renal dysfunction, any other serious concurrent illness or malignancy, continuing history of alcohol and/or drug abuse were excluded from the study.

A standardized pre-tested pre-coded questionnaire under "Case Report Form" was used to collect data on demographics, socio-economics, morbidity, healthcare, and the use of drugs. The questionnaire was reviewed by the supervising consultant cardiologist. The study was carried out in a total of three visits: V1 (Day 1), V2 (Day 29), and V3 (Day 57). On V1, patients eligible for the study were interviewed and the blood pressure was measured after obtaining signed informed consent from them. The three readings of blood pressure and pulse rate were measured using a digital sphygmomanometer during each visit and the mean of these readings was considered for each visit. A total of 60 patients were divided into six groups consisting of ten patients. Patients in groups I, II, and III were given nebivolol in doses of 2.5 mg, 5 mg, and 10 mg, respectively and those in groups IV, V, and VI were given sustained released metoprolol succinate in doses of 25 mg, 50 mg, and 100 mg, respectively.

The patients were called for follow-up visits, V2 and V3, after 28 days and 56 days, respectively. On both occasions, the blood pressure was measured using a digital sphygmomanometer and the patients were asked for any adverse effects observed. Data as mentioned in the Case Report Form, which included demographic details of patient, blood pressure readings and pulse rate measurements, was collected from all the three visits and subjected to further analysis.

The collected data was entered in Microsoft Excel 2007 and analyzed using GraphPad Prism 5 for calculation of statistical parameters. The result of this analysis was used to provide the final comparison of data to finalize the study results. Parameters like the Level of Significance were calculated based on the data related to drug efficacy using paired and unpaired T-test. Safety Percentage was evaluated based on data on CRF directly in the MS Excel Spreadsheet 2007. Also, the comparison of the cost as per the efficacy was carried out in MS Excel Spreadsheet 2007.

Results

A total of 60 patients, who met all the inclusion criteria and none of the exclusion criteria, were enrolled for the study. Among these, 30 patients were given nebivolol and the other 30 patients were given sustained released metoprolol succinate. None of the patients were lost during the follow-up period.

As shown in Table 1, in the nebivolol groups (namely, groups I, II, and III), the mean (± SD) age of patients was determined to be 45 ± 8.34 years and the mean (± SD) body mass index (BMI) value was 23.6 ± 1.33 kg/m^2 and in the metoprolol groups (namely, groups IV, V, and VI), the mean (± SD) age of patients was 48 ± 9.47 years and mean (± SD) BMI value was 23.18 ± 1.91 kg/m^2. According to the BMI scale both group most of the patients were matched and in the normal range.

During the screening, that is, on Day 1, the baseline characteristics, including systolic blood pressure, diastolic blood pressure, pulse rate, were recorded in both the drug groups. As presented in Table 2, no statistically significant difference was observed between the nebivolol groups and sustained released metoprolol succinate groups, that is, between group I and group IV, group II, and group V and between group III and group VI.

The change in SBP and DBP was statistically significant in the comparison of groups taking 2.5 mg of nebivolol and 25 mg of sustained released metoprolol succinate, both on week 4 and week 8 [Table 3]. Similarly, the change in SBP and DBP was statistically significant in the comparison of groups taking 5 mg of nebivolol or 50 mg of sustained released metoprolol succinate on both week 4 and week 8 [Table 3]. It was found to be higher than that found in the pair of groups taking lower doses of both the drugs. Likewise, the change in SBP and DBP was statistically significant in the comparison of groups taking 10 mg nebivolol or 100 mg of sustained released metoprolol succinate on week 4 and week 8 [Table 3]. It was somewhat higher than that found in the pair of groups taking moderate doses.

Evidently, an equivalent reduction in both systolic and diastolic blood pressure was brought about by nebivolol in a shorter duration of time than that required by metoprolol to cause the same amount of reduction in blood pressure.

The comparative cost evaluation of different equivalent doses of the two drugs is presented in Table 4. The cost of nebivolol per tablet was 4.80 INR at 2.5 mg daily dose, whereas that of sustained released metoprolol succinate was 4.50 INR

Table 1:

Demographic characteristics of hypertensive patients

Parameter	Nebivolol	Metoprolol
Male	20 (67%)	21 (70%)
Female	10 (33%)	9 (30%)
Age, mean±SD (years)	45±8.34	48±9.47
BMI, mean±SD (kg/m^2)	23.6±1.33	23.18±1.91

BMI=Body mass index, SD=Standard deviation

Table 2:

Baseline characteristics of the hypertensive patients

Comparative groups	Measured parameter	Mean (±SD)		P value
		Nebivolol	Metoprolol	
Group I and Group IV	SBP (mmHg)	147.2±2.87	147.2±3.19	0.9421 (NS)
	DBP (mmHg)	87±2.58	87.9±3.14	0.4931 (NS)
	Pulse rate (per min)	85±2.71	86.8±2.70	0.1539 (NS)
Group II and Group V	SBP (mmHg)	156.8±3.52	154.6±3.50	0.1783 (NS)
	DBP (mmHg)	91.1±3.21	94.9±2.13	0.0810 (NS)
	Pulse rate (per min)	83.6±1.58	83.6±3.63	1.0000 (NS)
Group III and Group VI	SBP (mmHg)	160.3±3.71	161.2±2.90	0.5533 (NS)
	DBP (mmHg)	96.7±2.26	96.5±2.27	0.8459 (NS)
	Pulse rate (per min)	87.2±2.53	90±3.77	0.0670 (NS)

SBP=Systolic blood pressure, DBP=Diastolic blood pressure, SD=Standard deviation

at 25 mg daily dose. Cost comparison and evaluation showed that the cost required for a 1 mmHg reduction in systolic blood pressure for nebivolol group I was 0.60 INR, whereas the same for metoprolol group III was 0.93 INR. The cost needed for a 1 mmHg reduction in diastolic blood pressure was 0.83 INR for the nebivolol group I, whereas the same for the metoprolol group IV was 1.15 INR. Thus, at low equivalent doses, the cost for an equivalent reduction in blood pressure per day was less for the nebivolol group as compared to the sustained released metoprolol succinate group. Similarly, at moderate as well as high equivalent doses, the cost for an equivalent reduction in blood pressure per day was less for the nebivolol group as compared to the sustained released metoprolol succinate group.

From the questionnaire filled during the follow up visits that is after 4 weeks and after 8 weeks the quality of life was estimated for each patient using either nebivolol or metoprolol. Total 66.66% (n = 30) of patients taking nebivolol were found improved overall condition of disease, whereas it was 60% (n = 30) of patients taking metoprolol were found improvement. Also, 53.33% (n = 30) of patients taking nebivolol found no change in their routine activity, 30% (n = 30) patients found little bit change in their daily routine and 16.66% (n = 30) patients found moderate decrease in their routine activities. Among the patients taking Metoprolol it was found out that total 43.33% (n = 30) patients found no change in their routine, 23.3% (n = 30) patients felt the little change in their daily activities, and 33.33% (n = 30) patients found over all moderate change in their routine schedule because of hypertension.

Table 3:

Changes in the systolic blood pressure and diastolic blood pressure in the three pairs of groups of patients

Parameter	Mean (±SD) (n=10)		P value (A)
	Nebivolol	Metoprolol	
Changes in SBP and DBP in Group I and Group IV			
SBP			
Baseline	147.2±2.87	147.2±3.19	0.9421#
After week 4	141.7±2.11	144.6±3.10	0.0249*
After week 8	139.3±1.70	142.4±2.99	0.0106*
P value (B)	<0.0001*	<0.0001*	
DBP			
Baseline	87±2.58	87.9±3.14	0.4931#
After week 4	83.3±2.06	86.2±3.33	0.0307*
After week 8	81.2±1.93	84±3.43	0.0373*
P value (B)	<0.0001*	<0.0001*	
Changes in SBP and DBP in Group II and Group V			
SBP			
Baseline	156.8±3.52	154.6±3.50	0.1783#
After week 4	147.9±2.88	150.8±2.97	0.0400*
After week 8	146.1±2.64	148.7±2.41	0.0336*
P value (B)	<0.0001*	<0.0001*	
DBP			
Baseline	91.1±3.21	94.9±2.13	0.0810#
After week 4	85.1±2.73	90.9±3.14	0.0003*
After week 8	83.7±2.58	89.4±2.07	0.0001*
P value (B)	<0.0001*	<0.0001*	
Changes in SBP and DBP in Group III and Group VI			
SBP			
Baseline			
After week 4	160.3±3.71	161.2±2.90	0.5533#
After week 8	154.0±3.94	157.4±3.06	0.0451*
P value (B)	148.3±3.65	153.6±2.88	0.0020*
DBP	<0.0001*	<0.0001*	
Baseline	96.7±2.26	96.5±2.27	0.8459#
After week 4	91.2±2.04	93.4±2.22	0.0333*
After week 8	87.4±2.41	89.9±2.69	0.0419*
P value (B)	<0.0001*	<0.0001*	

P value (A)=Unpaired *T*-test, *P* value (B)=Paired *T*-test, *=*P*<0.05 statistically significant, #=*P*>0.05 statistically not significant, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, SD=Standard deviation

It was found out from this study that there was somewhat better Quality of Life in patients taking nebivolol than the patients taking metoprolol. The overall condition of disease was much improved in case of patients with nebivolol than patients taking metoprolol. Also, the most common adverse events were fatigue, headache, and nausea. A total of 10% (n = 30) of the metoprolol users suffered such adverse effects, whereas only 3.33% of the nebivolol users (n = 30) suffered adverse effects [Figure 1].

Metoprolol users reported to have experienced fatigue, nausea, dizziness, headache, and insomnia, whereasmild fatigue was reported by patients using nebivolol. Overall, nebivolol was found to give rise to lesser adverse effects than metoprolol, though occurrence of adverse drug reactions with

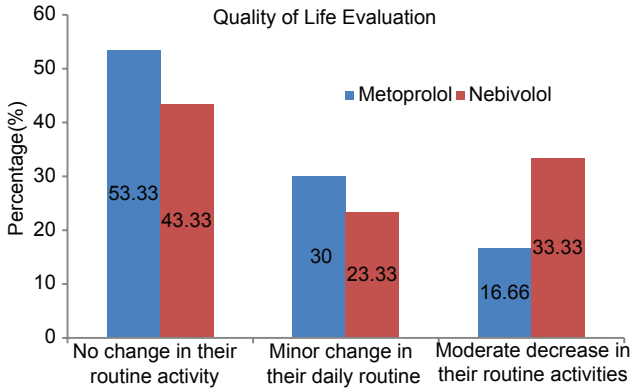
Table 4:

Cost evaluation at different doses of nebivolol and metoprolol in hypertensive patients

Treatment	Cost for reducing 1 mmHg		Per day cost per mmHg	
	SBP (INR)	DBP (INR)	SBP (INR)	DBP (INR)
Nebivolol (2.5 mg) vs	33.60	48.00	0.60	0.83
Metoprolol (25 mg)	52.65	63.00	0.93	1.15
Nebivolol (5 mg) vs	37.5	60.00	0.70	1.01
Metoprolol (50 mg)	63.00	77.00	1.18	1.40
Nebivolol (10 mg) vs	64.00	76.8	1.06	1.37
Metoprolol (100 mg)	66.50	76.00	1.25	1.44

SBP=Systolic blood pressure, DBP=Diastolic blood pressure, INR=Indian rupee

Figure 1: Quality of life evaluation of hypertensive patients on β-blockers (nebovolol and metoprolol)



use of either drug was not statistically significant due to smaller sample size ($P = 0.3006$).

Discussion

Hypertension is defined as a SBP of 140 mmHg or more or a DBP of 90 mmHg or more or taking antihypertensive medication.[10] Hypertension is classified as either essential hypertension (EH) or secondary hypertension, and EH accounts for about 90-95% of the cases characterized by high blood pressure with no obvious underlying medical causes.[11] In developing countries, it is a major medical concern that the high rate of undetected and untreated EH.[12] In clinical trials, antihypertensive therapy has been associated with reductions in (1) stroke incidence, averaging 35-40%; (2) myocardial infarction (MI), averaging 20-25%; and (3) HF, averaging >50%.[13] It is estimated that in patients with stage 1 hypertension (SBP 140-159 mmHg and/or DBP 90-99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death.[14] Numerous classes of antihypertensive agents are available, and B-blockers were among those previously recommended as a first-line treatment option in patients with uncomplicated, mild to moderate essential hypertension.[15-18]

Metoprolol is the cardioselective beta-1-adrenoreceptor blocker conventionally used to treat hypertensive patients particularly in developing countries such as India. Nebivolol is a potent, highly cardioselective beta-blocker with a unique hemodynamic profile compared with other cardioselective beta-blockers, such as metoprolol. The blood pressure lowering effects of nebivolol could be attributed to b1 adrenoceptor antagonism, modulation of the endothelial Nitric Oxide (NO) system, increasing the liberation of NO, resulting in coronary and systemic vasodilation and, thereby, a reduction in peripheral resistance and counteraction of endothelial dysfunction and additionally, an increase in stroke volume, associated with a reduction in vascular resistance, resulting in a maintained cardiac output despite reduced heart rate.[19-23]

Christine Espinola-Klein *et al.* carried out a study to evaluate the effects and tolerability of nebivolol in comparison with metoprolol in these patients. In conclusion, β-blocker therapy was well-tolerated in patients with intermittent claudication and arterial hypertension during a treatment period of ≈ 1 year. In the direct comparison, there was no significant difference between nebivolol and metoprolol.[24] Furthermore, Van Bortel LM *et al.* performed a meta-analysis of efficacy and tolerability of nebivolol compared with other anti- hypertensive drugs. Twelve randomized controlled studies were included in which nebivolol 5 mg once daily was compared with the recommended clinical doses of other antihypertensive drugs ($n = 9$), placebo ($n = 2$), and both ($n = 1$). Although not definitive, this meta-analysis suggests that nebivolol 5 mg is likely to have advantages over existing antihypertensives and may have a role in the treatment of hypertension.[9] In another study, 16 of 82 (20%) and 25 of73 (34%) patients reported adverse events while receiving nebivolol 5 mg once daily or metoprolol 100 mg twice daily, respectively.[25] However, the cost of nebivolol per tablet is higher than that of metoprolol per tablet, a factor that discourages the preference of the former over the latter.

This pharmacoeconomic study was carried out for a comparative evaluation of the cost effectiveness of nebivolol and sustained released metoprolol succinate in hypertensive patients. There was a statistical as well as clinically significant difference in the efficacy of both the molecules. As per this comparative analysis, it was found that nebivolol has better efficacy than metoprolol in terms of reducing both systolic as well as diastolic blood pressure. In this study, it was evident that nebivolol produces less adverse effects and ensures a better quality of life than metoprolol.

The study results showed significant differences in the cost of both the molecules. The cost per reduction in systolic blood pressure in mm of Hg per day was found to be 0.60, 0.70, and 1.06 INR by nebivolol at different doses respectively the same being 0.93, 1.18, 1.25 INR by sustained released metoprolol succinate at different equivalent doses respectively. The cost per reduction in diastolic blood pressure in mmHg per day was found to be 0.83, 1.04, and 1.37 INR for nebivolol at different doses respectively the same being 1.15, 1.40, 1.44 INR for different equivalent doses of sustained released metoprolol succinate, respectively.

This analysis shows that nebivolol is more cost-effective than extended release metoprolol succinate in the treatment of hypertensive also offering a favorable adverse effect profile and

quality of life in comparison to the latter. Hypertension, given its chronicity and associated morbidity and mortality, constitutes a significant disease burden to the society, both in terms of the health-related repercussions as well as financial costs incurred due to morbidity and the cumulative cost of drug therapy. As neither the symptoms of hypertension nor the beneficial effects of lowering blood pressure are readily apparent to patients, it is important to administer drugs that are cost-effective and have minimal adverse effects. This is particularly important in a developing country like India, where, the accretive cost of long-term therapy is often a significant deterrent to patient compliance. The results of this study contribute towards decision making involved in formulary management and by clinicians treating patients with hypertension.

The limitations of the study include the small sample size and recall bias commonly associated with survey-based studies. Similar studies on a larger scale would help eliminate this error and help make a categorical conclusion about the superiority of nebivolol over metoprolol.

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References

1. Boos CJ, Beevers GD, Lip GY. Assessment of platelet activation indices using the adviatm 120 amongst 'high-risk' patients with hypertension. Ann Med 2007;39:72-8.
2. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-92.
3. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the hypertension optimal treatment (hot) randomised trial. HOT Study Group. Lancet 1998;351:1755-62.
4. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
5. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, *et al*. American Heart Association Advocacy Coordinating Committee, Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Arteriosclerosis, Thrombosis and Vascular Biology, *et al.* Forecasting the future of cardiovascular disease in the united states: A policy statement from the American heart association. Circulation 2011;123:933-44.
6. Ormond BA, Spillman BC, Waidmann TA, Caswell KJ, Tereshchenko B. Potential national and state medical care savings from primary disease prevention. Am J Public Health 2011;101:157-64.
7. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. Am J Manag Care 2010;16:568-76.
8. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366:1545-53.
9. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: A meta-analysis. Am J Cardiovasc Drugs 2008;8:35-44.
10. 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.
11. Carretero OA, Oparil S. Essential hypertension. Part I: Definition and etiology. Circulation 2000;101:329-35.
12. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007;370:1929-38.
13. Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ace inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. Lancet 2000;356:1955-64.
14. Ogden LG, He J, Lydick E, Whelton PK. Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the jnc vi risk stratification. Hypertension 2000;35:539-43.
15. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46.
16. Chalmers J, Zanchetti A. The 1996 report of a World Health Organization expert committee on hypertension control. J Hypertens 1996;14:929-33.
17. Chalmers J. Treatment guidelines in hypertension: Current limitations and future solutions. J Hypertens Suppl 1996;14:S3-8.
18. Chalmers J. Round table 2. First-line drugs: The position of the World Health Organization-International Society of hypertension. J Hypertens Suppl 1993;11:S381-3.
19. Brehm BR, Bertsch D, von Fallois J, Wolf SC. Beta-blockers of the third generation inhibit endothelin-1 liberation, mrna production and proliferation of human coronary smooth muscle and endothelial cells. J Cardiovasc Pharmacol 2000;36:S401-3.
20. Dessy C, Saliez J, Ghisdal P, Daneau G, Lobysheva II, Frerart F, Belge C, *et al*. Endothelial beta3-adrenoreceptors mediate nitric oxide-dependent vasorelaxation of coronary microvessels in response to the third-generation beta-blocker nebivolol. Circulation 2005;112:1198-205.
21. Ignarro LJ. Experimental evidences of nitric oxide-dependent vasodilatory activity of nebivolol, a third-generation beta-blocker. Blood Press Suppl 2004;1:2-16.
22. Kamp O, Sieswerda GT, Visser CA. Comparison of effects on systolic and diastolic left ventricular function of nebivolol versus atenolol in patients with uncomplicated essential hypertension. Am J Cardiol 2003;92:344-8.
23. Nodari S, Metra M, Dei Cas L. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. Nebivolol. Eur J Heart Fail 2003;5:621-7.
24. Espinola-Klein C, Weisser G, Jagodzinski A, Savvidis S, Warnholtz A, Ostad MA, *et al*. Beta-blockers in patients with intermittent claudication and arterial hypertension: Results from the nebivolol or metoprolol in arterial occlusive disease trial. Hypertension 2011;58:148-54.
25. Uhlíř MF, Havránek K, Lefflerová J, Vojáček J, Widimský J, Winterová KZ. Nebivolol versus metoprolol in the treatment of hypertension. Drug Investig 1991;3:107-10.

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