Effects of nebivolol versus bisoprolol on endothelial function in hypertensive patients

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OBJECTIVE: To determine the effects of two beta-blockers, nebivolol and bisoprolol, on endothelial function in newly diagnosed hypertensive patients.

METHODS: Twenty-five hypertensive patients with a mean (± SD) age of 45.3±11.5 years were randomly assigned to receive either nebivolol or bisoprolol for eight weeks in an open-label, crossover design. Flow-mediated endothelial-dependent vasodilation (FMD) was measured at baseline and after each eight-week treatment period. At the end of each treatment period, 24 h ambulatory blood pressure (BP) monitoring was performed.

RESULTS: The effect of the two beta-blockers on BP was similar. The mean FMD before initiation of treatment was 4.14±3.55%. After treatment with nebivolol, FMD increased to 8.99±4.21%, with a statistically significant difference from baseline (P<0.001). The effect of bisoprolol treatment on FMD was not as dramatic (3.72±6.84%), with no statistically significant difference from baseline. Comparing FMD after each therapeutic regimen, nebivolol treatment resulted in a marked increase in the reactivity of the brachial artery (ie, improvement of endothelial function) compared with bisoprolol treatment (P<0.001).

CONCLUSION: Nebivolol treatment of untreated hypertensive patients led to a significant improvement in endothelial function compared with bisoprolol treatment, despite the similar effect on BP with either therapeutic agent.

Key Words: *Arterial hypertension; Bisoprolol; Endothelial function; Flow-mediated dilation; Nebivolol*

Arterial hypertension (AH) is considered to be a major risk factor for atherosclerotic cardiovascular disease as well as for diseases that predispose individuals to increased cardiovascular risk. AH has been listed as the number one cause of death worldwide in a World Health Organization report (1). The initiation of antihypertensive treatment leads to a significant reduction in cardiovascular morbidity and mortality.

There are five major classes of antihypertensive agents suitable for initiation and maintenance of AH treatment. The main benefit of therapy is the lowering of blood pressure (BP). The different classes of antihypertensive agents, however, have specific mechanisms of action that can favourably or unfavourably affect different organs or systems. An example of this is the effect of antihypertensive agents on endothelial function.

Endothelial function depends on the ability of endothelial cells to produce and release nitric oxide (NO) – a powerful endogenous vasodilator. Endothelial dysfunction may be defined as the loss of the ability of endothelial cells to respond with vasodilation to pathological vasoconstrictor stimuli (ie, a pathological vasoconstrictor response to a stimulus that, in normal situations, would lead to vasodilation).

Flow-mediated endothelial-dependent vasodilation (FMD) of the brachial artery is a method capable of detecting changes in endothelial function. The method was first described and implemented in clinical practice by Celermajer et al (2). For more than two decades, the method has been used to evaluate early atherosclerotic changes in patients with various risk factors for coronary atherosclerosis.

AH is accompanied by endothelial dysfunction (3) as a consequence of elevated BP (4). The decrease in FMD values is greater in hypertensive patients with established end-organ damage (5) as well as in patients who are defined as 'nondippers' (6).

The objective of the present study was to determine the effects of two different beta-blockers (nebivolol and bisoprolol) on endothelial function (measured as changes in FMD) in newly diagnosed hypertensive patients.

METHODS

Study group

The study group consisted of 25 newly diagnosed hypertensive patients. The demographic characteristics and risk factor distribution of the patients are presented in Table 1. Patients included in the study were 18 years of age and older, with newly diagnosed AH, willing to commence treatment and deemed by a physician to be cooperative and compliant.

Excluded from the study were patients with previously treated AH, individuals with angina pectoris or established coronary artery disease, patients with hemodynamically significant valve heart lesions, as well as patients with other comorbidities that necessitated drug use that could potentially interfere with the estimation of endothelial function.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for inclusion in the study as well as for FMD measurement. The study protocol was approved by the local ethics committee.

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TABLE 1
Demographic characteristics and risk factor distribution of the study group (n=25)

Variable	Distribution
Age, years (mean ± SD)	45.3±11.5
Female sex	7 (28)
Body mass index, kg/m^2 (mean ± SD)	28±5.2
Arterial hypertension*	25 (100)
Systolic blood pressure, mmHg (mean ± SD)	152.4±18.5
Diastolic blood pressure, mmHg (mean ± SD)	99.3±9.3
Diabetes mellitus†	0 (0)
Dyslipidemia‡	7 (28)
Present smokers	7 (28)
Former smokers	4 (16)
Passive smokers§	3 (12)
Family history of coronary artery disease¶	12 (48)

*Data presented as n (%), unless indicated otherwise. *Defined according to the guidelines for the management of arterial hypertension (1); †Defined according the guidelines on diabetes, prediabetes and cardiovascular diseases (7); ‡Defined according to the European guidelines on cardiovascular disease prevention in clinical practice (8); §Defined as exposure to cigarette smoke for 1 h per day for three consecutive years; ¶Defined as first-degree relatives with established coronary artery disease diagnosed before 55 years of age for men and 65 years of age for women*

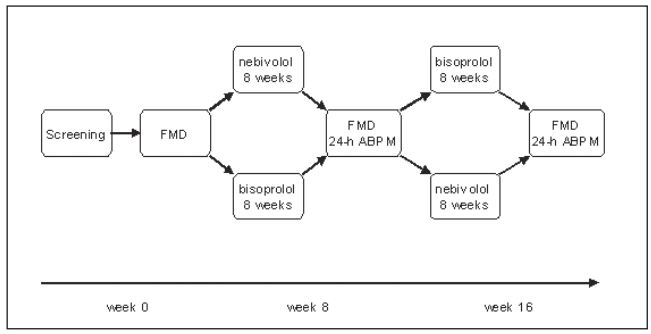

Figure 1) *Flow diagram of the study. FMD Flow-mediated endothelial-dependent vasodilation; 24-h ABPM 24 h ambulatory blood pressure monitoring*

Study design

Before inclusion in the study, patients underwent a medical history evaluation and clinical examination. Special attention was given to the duration of AH, maximal and usual values for systolic BP (SBP) and diastolic BP (DBP) registered by the patient, and the presence of other atherosclerotic risk factors. All patients underwent an electrocardiogram (ECG) and echocardiographic examination.

Ambulatory BP was measured after the patient rested for 15 min. Three measurements were taken at least 5 min apart; mean values for SBP and DBP were calculated using only the second and third measurements.

The next day, the patient was asked to arrive early in the morning for FMD measurement (see below) and was randomly assigned to receive either nebivolol 5 mg or bisoprolol 5 mg in an open-label, crossover fashion. After two weeks of treatment, BP and heart rate measurements were taken, the values of which were defined as the controls. To achieve optimal BP control, the dosage of either nebivolol or bisoprolol was increased, and hydrochlorothiazide (HCT) was added if necessary.

Eight weeks after the first visit, 24 h ambulatory BP was monitored, FMD was measured and the patient was switched to the other active treatment regimen (Figure 1). Another control visit (10th week) and a final visit (16th week) with 24 h ambulatory BP monitoring and FMD evaluation were performed. Patients were asked about the occurrence of medication side effects after each treatment period.

FMD

FMD testing was performed according to the guidelines for ultrasound assessment of endothelial-dependent FMD of the brachial artery (9). The investigator had the experience of 100 supervised FMD scans and measurements before assuming independence, and completed at least 100 scans per year to maintain competency. The inter- and intraobserver variability of the method was evaluated on a sample of 40 patients, with a correlation coefficient of greater than 0.92 and P<0.001 (10).

FMD measurements were performed between 07:00 and 09:00. Patients were asked to refrain from eating, consuming alcohol or smoking after 20:00 the day before. On the morning of the study, the patient was asked not to consume anything but water, refrain from vigorous physical activity and not to smoke. They were also requested to postpone taking the prescribed medication until after FMD measurements were taken.

After 15 min of rest in a quiet and temperate room, the investigation started with BP measurements taken on the dominant arm. The cuff of the sphygmomanometer was placed on the forearm of the same arm with the patient supine. A longitudinal image of the brachial artery with optimal visualization of the intima using a linear array transducer at 3 MHz to 11 MHz and an echocardiograph (Sonos 5500, Philips Medical Systems, USA) was obtained. A 5 s to 10 s recording of the baseline state of the brachial artery was captured on a video cassette recorder. The cuff was inflated to a pressure of 200 mmHg or 50 mmHg above the systolic arterial pressure of the respective patient, whichever was higher, and maintained for 5 min. A new recording during the last 30 s of the ischemic phase (cuff inflated) and at 120 s after cuff deflation was obtained. The entire image was ECG-gated.

Measurement

Data analysis was not performed during image acquisition. The diameter of the brachial artery on different occasions was measured manually. The investigator was blinded to patient identity and medication regimen. Two parameters were considered: the baseline and maximum postischemic diameter of the brachial artery. All measurements were performed in the end-diastole (the beginning of the R on ECG) from endothelial to endothelial surface, along a line perpendicular to the artery's long axis. For the baseline diameter, at least three heart beats were used and the distances between the intimal surfaces of the artery at three different locations along the vessel's axis were measured, from which the mean value for the baseline diameter was calculated. In the reactive hyperemia phase, the diameter of the brachial artery was measured at 10 s intervals, beginning 30 s after cuff deflation and proceeding until 120 s. For every measurement, the diameter was estimated at three different locations along the vessel's axis, with the mean diameter being calculated from these three measurements. The

largest mean diameter of the 10 s interval measurements corresponded to the maximal response of the brachial artery during the reactive hyperemia phase.

The FMD was measured and expressed as a per cent value, derived by the formula:

FMD (%) = [(postischemic diameter of the brachial artery – baseline diameter) / baseline diameter] × 100

24 h ambulatory blood pressure monitoring

Twenty-four hour ambulatory BP measurement was measured with the Oscar 2 system (SunTech Medical, USA) using AccuWin Pro, version 1.5 software. The system requires a patient number, treatment regimen, and an approximate time period during which the patient will be asleep. The device measured BP in 30 min intervals during the day and in 60 min intervals during the night. The target BP levels were set at 140 mmHg for SBP and 85 mmHg for DBP during the daytime, and 120 mmHg for SBP and 80 mmHg for DBP during the nighttime.

The software presented the results graphically as well as exact values regarding the maximal, minimal and mean SBP and DBP, and mean heart rate during the daytime and nighttime period. The percentage of values exceeding the target BP levels was also recorded.

Statistics

The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. All data were normally distributed and presented as mean ± SD. Categorical variables were expressed as a percentage. The FMD and BP values were compared at baseline and after each treatment period, with the paired samples *t* test used for normally distributed data, and the Wilcoxon signed-rank test for non-normally distributed data. A linear regression analysis with stepwise entry criteria was used to determine the variables that independently predicted FMD values. A two-tailed P<0.05 was considered to be statistically significant. All tests were performed with SPSS 13.0 (SPSS Inc, USA) for Windows (Microsoft Corporation, USA).

RESULTS

BP control

Nebivolol was used in 14 of the participants and 11 patients were treated with bisoprolol before the crossover. Optimal BP control was achieved in all patients. During the nebivolol treatment phase, 5 mg nebivolol was required in 19 of the participants, 7.5 mg in three and 10 mg in three (mean nebivolol dose 5.9 mg). HCT was added to the therapeutic regimen in three patients (mean dose 13.3 mg). Optimal BP levels on bisoprolol treatment were achieved with 5 mg and 10 mg of the agent in 16 and nine patients, respectively (mean bisoprolol dose 6.6 mg). The addition of HCT was necessary in three patients (mean dose 13.3 mg).

The mean SBP and DBP during the eight-week nebivolol treatment were reduced from 152.4±18.5 mmHg and 99.3±9.3 mmHg, respectively, to 131.8±11.5 mmHg and 82.4±7.1 mmHg, respectively (P<0.001). The BP values achieved after the eight-week bisoprolol treatment were 129.7±10.2 mmHg and 83.1±7 mmHg for SBP and DBP respectively (P<0.001).

TABLE 2
Mean percentage of values exceeding the target systolic (SBP) and diastolic (DBP) blood pressure during the daytime and nighttime period after each treatment regimen

Variable	Target BP, mmHg	Treatment		P
		Nebivolol	Bisoprolol	
SBP, daytime	140	6.72±7.46	8.4±10.33	0.37
DBP, daytime	85	8.52±11.88	7.92±12.16	0.78
SBP, nighttime	120	4.76±9.43	5.48±10.18	0.8
DBP, nighttime	80	2.52±5.29	2.36±4.5	0.72

Data are presented as % (mean ± SD), unless indicated otherwise

The percentage of values exceeding the target SBP and DBP for the daytime and the nighttime period after each treatment regimen are presented in Table 2. There was no statistically significant difference between the SBP- and DBP-lowering effect achieved with nebivolol and bisoprolol.

Endothelial function

The mean FMD value for the 25 participants in the study before initiation of treatment was 4.14±3.55%. Independent predictors for FMD values in this setting were DBP and patient age. These variables can be combined in a model predicting FMD values, expressed by the following equation:

FMD (%) = 26.17 – 0.17 × DBP (mmHg) – 0.13 × patient's age (years)

The unstandardized coefficients had a significance P<0.01, with an R^2=0.56 (ie, 56% of the variance in FMD values could be explained by the model).

After the eight-week treatment with nebivolol, the mean FMD values increased to 8.99±4.21%, which resulted in a highly statistically significant difference from the mean baseline FMD values (P<0.001). The effect of bisoprolol treatment on FMD values was not as dramatic: FMD after the eight-week treatment was 3.72±6.84%, with no statistically significant difference from the baseline values.

Comparing the FMD values after each therapeutic regimen, nebivolol treatment resulted in a marked increase in the reactivity of the brachial artery (ie, improvement of endothelial function) compared with bisoprolol treatment (P<0.001) (Figure 2).

Patients initially treated with nebivolol (n=14) had a mean FMD value of 9.65±4.51% at the end of the eight-week treatment period. This value decreased significantly after the crossover to bisoprolol (5.02±2.63%; P=0.005).

For the remaining patients initially receiving bisoprolol (n=11), the mean FMD value after the first treatment period was 3.45±4.4%, which increased significantly after switching to nebivolol (8.55±3.77%; P=0.001).

During the treatment period, very few side effects were reported. One of the patients experienced headache, a female patient reported weight gain, and a male patient complained of fatigue and erectile dysfunction. All of these side effects were reported during the bisoprolol treatment period.

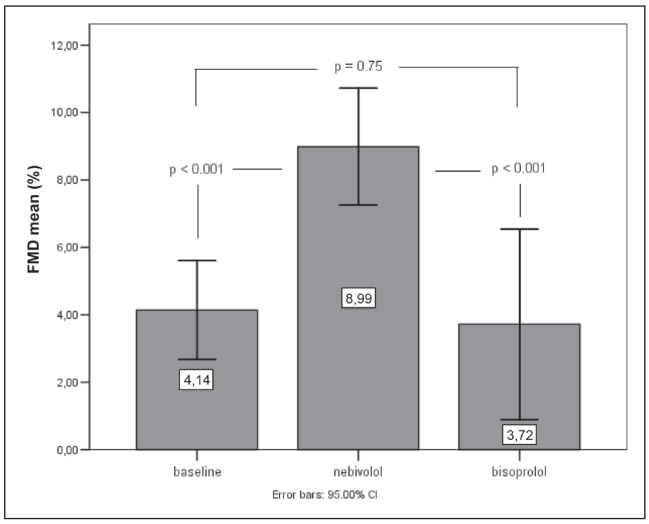

Figure 2) *Mean flow-mediated endothelial-dependent vasodilation (FMD) values with 95% CI at baseline and after eight weeks of treatment with nebivolol and bisoprolol*

DISCUSSION

The effect of nebivolol and bisoprolol treatment on endothelial function in 25 newly diagnosed, untreated, hypertensive patients were evaluated in a randomized, open-label, crossover design. BP control achieved with either of the therapeutic regimens was comparable. Bisoprolol treatment did not lead to a significant change in FMD values, despite the lower BP levels attained at the end of the treatment period. Nebivolol treatment resulted in a statistically significant improvement of baseline endothelial function (ie, increase in FMD) compared with the FMD values attained after bisoprolol treatment.

AH and its treatment have significant social and economic impact, because it involves a considerable number of patients and is lifelong in most of the cases. There is unequivocal evidence that treatment of AH with angiotensin-converting enzyme inhibitors (11), angiotensin receptor blockers (12) and dihydropyridine calcium channel antagonists (13) could lead to an improvement of endothelial function.

The effect of beta-blockers on the reactivity of the brachial artery is, however, not straightforward. In addition to activating alpha receptors, blocking of peripheral $beta_2$-receptors causes one of the major untoward hemodynamic effects of beta-blockers – peripheral vasoconstriction. This could be the reason why the use of conventional beta-blockers does not lead to an improvement in endothelial function. Comparing atenolol with perindopril (14) and with losartan (15), it has been found that the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blocker agents lead to a greater increase in FMD values.

The pharmacodynamic properties of nebivolol, however, differentiate it from the other agents of its class. The beta-1 selectivity of nebivolol surpasses that of atenolol and bisoprolol (16). Moreover, nebivolol has a unique mechanism of action – activating the L-arginine/NO pathway, which leads to vasodilation of resistance vasculature (17). This could explain the results of a study by Lekakis et al (18), in which the authors compared the effect of atenolol 50 mg with nebivolol 5 mg in a four-week treatment regimen. They reported that atenolol had no effect on endothelial function, whereas nebivolol led to a statistically significant increase in FMD values.

Bisoprolol, however, is a beta-blocker with a higher beta-1 selectivity than atenolol (16) and, therefore, causes less vasoconstriction of the resistant vessels. There are no previous studies comparing the effect of bisoprolol and nebivolol on endothelial function; thus, prompting the present investigation. Our finding that nebivolol exerts a more beneficial effect on endothelial function could be explained by its specific mechanism of action. These results were independent from the effects of nebivolol and bisoprolol on BP, which were similar, as reported in other studies (19). Given the well-recognized connection of endothelial dysfunction with untoward cardiovascular events, we suspect that long-term nebivolol treatment would reduce the incidence of such events compared with other beta-blockers.

The effects of nebivolol and bisoprolol on BP were investigated in the Nebivolol, Bisoprolol Multicenter Study (NEBIS) (19). There was no statistically significant difference in the degree of BP control achieved with either therapeutic regimen (5 mg dose) in 273 patients treated for 12 weeks. These results are in accordance with our findings, which were, however, determined with a considerably smaller group and shorter treatment duration.

The FMD values at study initiation were relatively low for patients without angina pectoris or established coronary artery disease (20). This could be the result of untreated AH (3,5,6) – SBP and DBP values at the beginning of the present study were high and DBP was an independent predictor of FMD values in the multiple regression analysis.

We conducted the present study according to the guidelines for ultrasound assessment of endothelial-dependent FMD of the brachial artery (9), which recommend a study group of at least 20 to 30 participants in a crossover design. As limitations of our study, we acknowledge the open-label and single-centre design, manual FMD measurement and the absence of NO-independent vasodilation determination. Despite these limitations, we believe that the present study contributes to the understanding of the differential effects on endothelial function of beta-blockers used in the treatment of AH.

CONCLUSION

In a randomized, open-label, crossover study in hypertensive patients, we found that an eight-week treatment regimen with nebivolol led to an improvement in baseline endothelial function. Such an effect was not found for bisoprolol. FMD values were statistically significantly higher after nebivolol treatment than with bisoprolol, despite the similar effects on BP with either therapeutic agent.

REFERENCES

1. Mancia G, De Backer G, Dominiczak A, et al; European Society of Hypertension; European Society of Cardiology. 2007 ESH-ESC Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16:135-232.
2. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111-5.
3. Ercan E, Tengiz I, Ercan HE, Nalbantgil I. Left ventricular hypertrophy and endothelial functions in patients with essential hypertension. Coron Artery Dis 2003;14:541-4.

4. Millgard J, Lind L. Acute hypertension impairs endothelium-dependent vasodilation. Clin Sci (Lond) 1999;96:217-8.
5. Palmieri V, Storto G, Arezzi E, et al. Relations of left ventricular mass and systolic function to endothelial function and coronary flow reserve in healthy, new discovered hypertensive subjects. J Hum Hypertens 2005;19:941-50.
6. Lee KW, Blann AD, Lip GY. High pulse pressure and nondipping circadian blood pressure in patients with coronary artery disease: Relationship to thrombogenesis and endothelial damage/dysfunction. Am J Hypertens 2005;18:104-15.
7. Ryden L, Standl E, Bartnik M, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guideline on diabetes, pre-diabetes and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88-136.
8. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts), Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Executive summary. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J 2007;28:2375-414.
9. Corretti M, Anderson T, Benjamin E, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257-65.
10. Simova I, Nossikov A, Denchev S. Interobserver and intraobserver variability of flow mediated vasodilatation of the brachial artery. Echocardiography 2008;25:77-83.
11. Hornig B, Arakawa N, Haussmann D, Drexler H. Differential effects of quinaprilat and enalaprilat on endothelial function of conduit arteries in patients with chronic heart failure. Circulation 1998;98:2842-8.
12. Cheetham C, O'Driscoll G, Stanton K, Taylor R, Green D. Losartan, an angiotensin type 1 receptor antagonist, improves conduit vessel endothelial function in type II diabetes. Clin Sci (Lond) 2001;100:13-7.
13. Taddei S, Virdis A, Ghiadoni L, Uleri S, Magagna A, Salvetti A. Lacidipine restores endothelium-dependent vasodilation in essential hypertensive patients. Hypertension 1997;30:1606-12.
14. Ghiadoni L, Magagna A, Versari D, et al. Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension 2003;41:1281-6.
15. Flammer AJ, Hermann F, Wiesli P, et al. Effect of losartan, compared with atenolol, on endothelial function and oxidative stress in patients with type 2 diabetes and hypertension. J Hypertens 2007;25:785-91.
16. Nuttall SL, Routledge HC, Kendall MJ. A comparison of the $beta_1$-selectivity of three beta1-selective beta-blockers. J Clin Pharm Ther 2003;28:179-86.
17. Ritter JM. Nebivolol: Endothelium-mediated vasodilating effect. J Cardiovasc Pharmacol 2001;38(Suppl 3):S13-6.
18. Lekakis JP, Protogerou A, Papamichael C, et al. Effect of nebivolol and atenolol on brachial artery flow-mediated vasodilation in patients with coronary artery disease. Cardiovasc Drugs Ther 2005;19:277-81.
19. Czuriga I, Riecansky I, Bodnar J, et al. For The NEBIS Investigators; NEBIS Investigators Group. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: The Nebivolol, Bisoprolol Multicenter Study (NEBIS). Cardiovasc Drugs Ther 2003;17:257-63.
20. Simova I, Denchev S. Endothelial functional and structural impairment in patients with different degree of coronary artery disease development. Heart and Vessels 2008;23:305-15.