β-Blockers in Patients With Intermittent Claudication and Arterial Hypertension

Results From the Nebivolol or Metoprolol in Arterial Occlusive Disease Trial

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See Editorial Commentary, pp 138–139

Abstract—The use of β-receptor blockers in peripheral arterial disease is controversial for their impact on vasomotor tone. The β-blocker nebivolol possesses vasodilating, endothelium-dependent, NO-releasing properties that might be beneficial in peripheral arterial disease. The aim of the study was to evaluate the effects and tolerability of nebivolol in comparison with metoprolol in these patients. A total of 128 patients with intermittent claudication and essential hypertension were included and double-blind randomized to receive 5 mg of nebivolol (N=65) or 95 mg of metoprolol (N=63) once daily. End points were changes in ankle-brachial index, initial and absolute claudication distance, endothelial function assessed by flow-mediated dilatation of the brachial artery, blood pressure, and quality of life using the claudication scale questionnaire. End point analysis was possible in 109 patients (85.2%). After the 48-week treatment period, ankle-brachial index and absolute claudication distance improved significantly in both patient groups ($P<0.05$ for both), with no difference across treatments. A significant increase of initial claudication distance was found in the nebivolol group. Adjusted mean change of initial claudication distance was 33.9% after nebivolol ($P=0.003$) and 16.6% after metoprolol ($P=0.12$) treatment. Quality of life was not influenced by either treatment, and there was no relevant change in flow-mediated dilatation in patients treated with nebivolol or metoprolol ($P=0.16$). Both drugs were equally effective in lowering blood pressure. 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. **(*Hypertension*. 2011;58:148-154.)**

Key Words: peripheral arterial disease ■ β receptor blockers ■ intermittent claudication ■ arterial hypertension ■ ankle-brachial index ■ walking distance ■ endothelial dysfunction

The prognosis of patients with peripheral arterial disease (PAD) is mainly determined by cardiovascular events.[1–5] Therapy with β receptor blockers (β-blockers) is associated with an improved clinical outcome in patients with cardiovascular diseases, but there remains some concern that its impact on vasomotor tone can have negative implications, especially in PAD patients with critical limb ischemia.[6–12] On the one hand, β-blockers are contraindicated in the setting of severe PAD, and previous studies reported a worsening in parameters related to quality of life, functional capacity, and clinical symptoms also in stable PAD patients treated with nonvasodilating β-blockers.[13–17] On the other hand, some studies did not show adverse effects of β-blockers in PAD patients.[18–21] In addition, several meta-analyses suggest that β-blockers do not adversely affect walking distance in patients with intermittent claudication.[22–24] In clinical practice, PAD patients often tolerate therapy with β-blockers without worsening of claudication symptoms. Based on this empirical evidence, recent guidelines state that, if indicated as for the treatment of coronary artery disease (CAD), therapy with β-blockers can also be implemented.[11,12]

Newer third-generation β-blockers like carvedilol or nebivolol have vasodilating properties, which might confer these drugs a selective advantage.[25,26] The β-blocker nebivolol possesses unique vasodilating, endothelium-dependent, NO-releasing properties, which might be particularly beneficial in patients with PAD, because an impaired reactivity of the vascular endothelium has been associated with adverse outcome in patients with this condition.[26–29] The issue of the impact of β-blockers in PAD has been addressed by few

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trials, mostly with a small sample size and often only short treatment periods,[13–21] and studies comparing β-blockers with and without vasodilating effects using a double-blind randomized design are lacking.

Therefore, the aim of this clinical trial was to evaluate the effects of the treatment with the endothelium-dependent vasodilating β_1-selective blocker nebivolol, as compared with the nonvasodilating β_1-selective blocker metoprolol, on clinical parameters of PAD and endothelial function, and to compare the tolerability of both drugs in patients with PAD.

Methods

Study Design and Patient Selection

The Nebivolol or Metoprolol in Arterial Occlusive Disease (NORMA) Trial was designed as a prospective, randomized, double-blind, single-center trial. Patients with stable intermittent claudication (Fontaine stage II) for ≥6 months and an ankle brachial index (ABI: ratio systolic blood pressure ankle/arm) of <0.9 were recruited. All of the patients had stage I arterial hypertension (systolic blood pressure 140 to 159 mm Hg and diastolic blood pressure 90 to 99 mm Hg) or a previous diagnosis of stage I arterial hypertension currently under treatment. At time of inclusion, systolic blood pressure must be >100 mm Hg and <160 mm Hg and diastolic blood pressure <100 mm Hg. To exclude effects of female hormones on endothelial function, only postmenopausal women were included. Exclusion criteria were critical limb ischemia with rest pain, leg ulcer, or gangrene; concomitant disease limiting the exercise capacity of the patient (eg, severe angina pectoris or severe heart failure); contraindications for β-blockers (eg, heart rate <50 bpm, sick-sinus syndrome including hearts blocks, and/or atrioventricular block second and third degree; heart failure if not adequately treated or unstable [New York Heart Association class III or IV]; bronchial hyperreactivity; known metabolic acidosis; untreated phaeocromo-cytoma, psoriasis, or family history of psoriasis; treatment with monoamine oxidase inhibitors; or continuous or intermittent treatment with positive inotropic β-sympathomimetics), acute myocardial infarction within 6 months before screening; hyperthyroidism; or poorly controlled diabetes mellitus (hemoglobin A1c >10%). Concomitant treatment with drugs that may influence endothelial dysfunction (eg, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, aspirin, clopidogrel, statins, or estrogens) was only allowed if no change in the dosage had been made in the last 3 months. Previous treatment with nebivolol or carvedilol was not permitted. Previous treatment with other β-blockers was allowed.

The study was approved by the ethics committee of the college of physicians of Rhine Palatinate Mainz, Germany. The investigation was performed according to the Declaration of Helsinki (current version), the recent version of the German Drug Law, and the German Good Clinical Practice decree (GCP-V), and in accordance with the national legal requirements in Germany, as well as the principles of good clinical practice. The study is registered as a randomized clinical trail with the ISRCT number ISRCTN06278310 (http://www.controlled-trials.com/ISRCTN06278310).

Patient Randomization and Study Visits

Patients were randomized in a double-blind fashion to take 5 mg of nebivolol or 95 mg of metoprolol, respectively, once daily. The study consisted of 7 visits. On visit 1, inclusion criteria were screened, and patients were enrolled in the study. Any pre-existing therapy with β-blockers was stepwise withdrawn during a washout period of 2 weeks. On visit 2, baseline measurements including blood pressure, heart rate, treadmill testing, ABI, assessment of endothelial function, and quality of life were performed, and patients were randomized to one treatment group. On visit 3 to 6 (after 2, 12, 24, and 36 weeks of treatment), concomitant medication, vital signs (blood pressure and heart rate), and adverse events were documented. Adverse events were defined as any adverse change in health or any parameter (including laboratory parameters) occurring during the study. After 48 weeks of treatment, all of the measurements initially performed in visit 2 were repeated. In addition, safety laboratory parameters including full blood count, liver enzymes, creatinine, urea, fasting glucose, hemoglobin A1c level, sodium, and potassium were evaluated at visits 2 and 7.

Ankle-Brachial Index

The ABI measurement was performed after ≥15 minutes of rest in the supine position. A standard sphygmomanometer and a Doppler device (cw-Doppler ultrasound device, GE Medical Systems Kretztechnik GMBH & Co) with an 8-MHz continuous wave probe were used. The systolic pressure was measured on both brachial arteries, as well as both anterior and posterior tibial arteries. In accordance with the guidelines of the American Heart Association, the ABI was calculated for each leg as the ratio of the highest ankle blood pressure divided by the highest brachial blood pressure measured in either arm.[12]

Claudication Distance

Treadmill test was performed according to a standardized constant-workload protocol with a constant speed of 3.2 km/h and a constant grade of 12%.[30] Initial claudication distance (ICD) was defined as meters until the onset of limb pain. Maximal or absolute claudication distance (ACD) was defined as the distance beyond which exercise could not be protracted because of claudication pain.

Quality of Life

Quality of life was evaluated using the standardized self-assessed Claudication Scale (CLAU-S) questionnaire for PAD.[31,32] The CLAU-S consists of 47 questions that address 5 dimensions (everyday life, pain, social life, disease-specific fear, and psychic well being) and are answered by the patient either on a 5-point Likert scale or on visual analog scales. The time recall for the questions was the week preceding the interview. The score was analyzed separately for each dimension with a maximum of 100 points for each dimension.

Flow-Mediated Dilatation

Endothelium-dependent flow-mediated dilatation (FMD) was examined according to previous protocols.[33] The right brachial artery was visualized by high-resolution ultrasound using a 7.5- to 12.0-MHz linear array transducer (HDI 5000, Royal Philips). To induce hyperemia, a blood pressure cuff (3,5″) placed at the level of the upper arm was inflated to 50 mm Hg above systolic blood pressure or ≥200 mm Hg. Arterial occlusion was kept for 5 minutes with the ultrasound transducer held in the same position. The diameter of the brachial artery was measured before and 60 seconds after arterial occlusion, and FMD was defined as the maximum percentage increase of brachial diameter during reactive hyperemia. After 15 minutes of recovery, the endothelium-independent dilation (nitrate-mediated dilatation) was assessed as brachial diameter change after sublingual application of 0.8 mg of nitroglycerin. Image acquisition and analysis were performed in a blinded manner.

Data Management and Statistical Analysis

Clinical monitoring, data management, and statistical analysis were performed by the Gesellschaft für Therapieforschung mbH. End points were the change in ABI, ACD, ICD, and FMD and quality of life between baseline and the final visit in response to therapy with nebivolol or metoprolol. Based on previous trials, the study was designed to have an 80% power to demonstrate a difference of 2.0% change of FMD between the treatment groups, with a planned sample size of 51 patients per group. With an estimated dropout rate of 20% after screening, we planned to enroll and randomize a total of 128 patients. The statistical analysis was performed for 2 analysis populations, a safety population including all of the randomized patients who at least once received the double-blind medication and an end point analysis including all of the patients for whom the end point variables were available. The end point analysis was tested for

treatment group differences on a confirmative basis by means of a 2-tailed significance level of $\alpha=0.05$. Quantitative data were analyzed by statistical parameters, such as mean, SD, median, and 95% CI, as appropriate. Qualitative data were presented by absolute and relative frequency distributions. Differences between the 2 treatment groups were tested by 1-way ANOVA test for continuous variables and χ^2 test for categorical variables. An ANCOVA model was applied including the baseline variables as the covariate into the model. Accordingly, adjusted (least-square) means are displayed, and 95% CIs were calculated.

Results

Study Population

A total of 200 prospective patients who presented with stable PAD and essential hypertension were screened for the study. The most frequent reason to fail study enrollment was an ABI at rest of ≤0.9 (N=27) in both legs. In addition, some patients could not be included because of uncontrolled arterial hypertension, contraindications against β-blockers, hyperthyroidism, or elevated hemoglobin A1c. A total of 128 patients were double-blind randomized to receive 5 mg of nebivolol (N=65) or 95 mg of metoprolol (N=63) once daily. End-point analysis was possible in 109 patients (85.2%), 52 patients in the nebivolol and 57 patients in the metoprolol group. Patient characteristics of the end point population are displayed in Table 1. Mean duration of arterial hypertension was 9.0±9.1 years, and mean duration of intermittent claudication was 8.1±6.7 years. In total, 52 patients (47.7%) had previous β-blocker medication; the majority of these patients were treated previously with metoprolol. There was no relevant difference between groups with regard to demographic data, cardiovascular risk factors, cardiovascular comorbidity, or concomitant medication.

Ankle-Brachial Index and Initial and Absolute Claudication Distance

There was no relevant difference between treatment groups in the ABI at baseline ($P=0.67$). In both groups, the ABI significantly improved during therapy with β-blockers: in nebivolol-treated patients, it significantly increased from 0.62±0.16 to 0.68±0.20 after treatment ($P<0.002$); in metoprolol-treated patients the ABI increased from 0.63±0.17 to 0.67±0.21 ($P<0.04$; Figure 1). There was no relevant difference between treatment groups in the ABI measured at the final visit ($P=0.72$).

There was no significant difference between treatment groups in ICD and ACD at baseline. After 48 weeks of treatment, mean ICD significantly increased in the nebivolol group, whereas only a nonsignificant increase of ICD could be found in the metoprolol group (Figure 2). The adjusted mean percentage change (95% CI) of ICD between the baseline and final visit was 33.9% (12.2% to 55.6%) in the nebivolol group ($P=0.0025$) and 16.7% (−4.2% to 37.6%) in the metoprolol group ($P=0.12$; $P=0.26$ for the comparison between treatment groups). We found a significant increase of ACD in both treatment groups (Figure 3). The percentage increase in ACD (95% CI) was 21.7% (1.8% to 41.5%) in nebivolol- ($P=0.03$) and 23.5% (4.7% to 42.3%) in metoprolol-treated ($P=0.01$) patients (P value not significant across treatment groups).

Table 1. Baseline Characteristics of Patients Included in the End Point Analysis According to Treatment Group

Variable	Nebivolol (N=52)	Metoprolol (N=57)	*P*
Men, n (%)	45 (86.5)	41 (71.9)	0.06
Age, y	66.7±8.3	65.9±7.9	0.62
Body mass index, kg/m^2	27.7±3.3	27.5±3.6	0.81
Cardiovascular risk factors, n (%)			
Smoking status			
Current smokers	15 (28.8)	19 (33.3)	0.30
Former smokers	33 (63.5)	29 (50.9)	
Never smokers	4 (7.7)	9 (15.8)	
Diabetes mellitus	17 (32.7)	12 (21.1)	0.17
Dyslipidemia	31 (59.6)	39 (68.4)	0.34
Comorbidity, n (%)			
Coronary artery disease	21 (40.4)	24 (42.1)	0.86
Previous myocardial infarction	7 (13.5)	11 (19.3)	0.41
Carotid artery stenosis	12 (23)	11 (19.3)	0.63
Previous stroke or TIA	7 (13.5)	9 (15.8)	0.73
Previous venous thrombosis or pulmonary embolism	6 (11.5)	5 (8.8)	0.88
Previous PAD treatment, n (%)			
Previous peripheral intervention	15 (28.8)	18 (31.6)	0.76
Previous peripheral bypass operation	15 (28.8)	14 (24.6)	0.61
Concomitant medication, n (%)			
Antithrombotic agents	50 (96.2)	55 (96.5)	0.93
Lipid modifying agents	32 (61.5)	40 (70.2)	0.34
Calcium channel blockers	18 (34.6)	16 (28.1)	0.46
Diuretics	11 (21.2)	17 (29.8)	0.30
ACE inhibitors or AT receptor antagonists	32 (61.5)	44 (77.2)	0.08

TIA, indicates transient ischemic attack; ACE, angiotensin-converting enzyme; AT, angiotensin; PAD, peripheral arterial disease. Data are mean±SD unless otherwise specified.

Claudication Scale

The CLAU-S quality-of-life questionnaire consists of a series of questions addressing 5 dimensions with a scale ranging from 0 (worst) to 100 (best). Results from the questionnaire at baseline and final visit are shown in Table 2. There was no significant change during treatment for any of the 5 dimensions; in addition, there was no significant difference between treatment groups at baseline or at the end of the follow-up period. Notably, for the dimensions "social life," "specific fears," and "psychic well being," very high scores were reached already at baseline. Therefore, it would have been difficult to achieve any additional improvement by either treatment. The only impairment of quality of life was pain, which was slightly affected by therapy with both β-blockers.

Flow-Mediated Dilatation

Baseline FMD of the brachial artery was comparable between groups (FMD at inclusion: nebivolol 6.6±3.1% and metoprolol 6.8±3.5%; $P=0.58$). No relevant change of FMD could be found in either treatment group after the 48-week

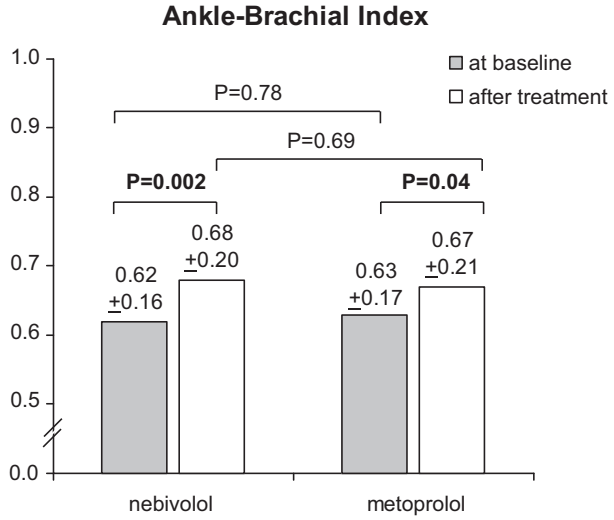

Figure 1. Ankle-brachial index in the 2 treatment groups at baseline and after the 48 week treatment period. Data are presented as mean and accompanying SD.

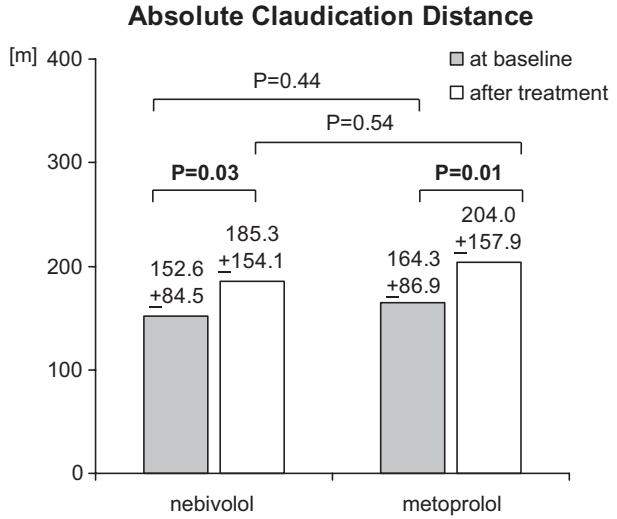

Figure 3. Absolute claudication distance in the 2 treatment groups at baseline and after the 48-week treatment period. Data are presented as mean and accompanying SD.

treatment period (FMD at end of the study: nebivolol 6.5±3.3% and metoprolol 7.3±3.8%; $P=0.14$). At 48 weeks, adjusted mean change (95% CI) of FMD was −0.21 (−0.94% to 0.52%) in the nebivolol group and 0.52% (−0.18% to 1.22%) in the metoprolol group, with no difference between the 2 treatment groups (P value for comparison of adjusted mean change=0.16). Similarly, nitrate-mediated dilatation of the brachial artery was comparable at baseline in both groups and was not affected by either treatment.

Systolic and Diastolic Blood Pressures

Blood pressure was assessed at all of the study visits. There was no relevant difference between treatment groups in mean baseline systolic or diastolic blood pressures (nebivolol: 147.6±6.6/79.6±7.4 mm Hg and metoprolol: 147.6±6.6/81.4±7.6 mm Hg; P value not significant across treatment groups). Blood pressure was significantly lower at the end of the treatment in both treatment groups without relevant differences between drugs. Absolute change of systolic blood pressure (95% CI) was −5.2 mm Hg (−8.2 to −2.1 mm Hg) in the nebivolol group ($P=0.001$) and −3.9 mm Hg (−6.9 to

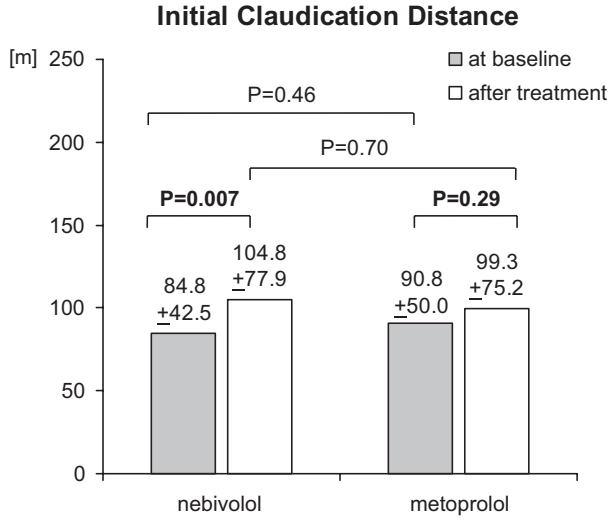

Figure 2. Initial claudication distance in the 2 treatment groups at baseline and after the 48-week treatment period. Data are presented as mean and accompanying SD.

Table 2. Quality of Life Using the Claudication Scale Questionnaire of Patients Included in the End Point Analysis According to Treatment Group (Mean±SD)

Dimensions of the CLAU-S	Nebivolol (N=52)	Metoprolol (N=57)	*P*
Daily life			
Pretreatment	74.0±20.8	74.8±17.1	
Posttreatment	72.4±21.3	73.7±21.8	
Difference between pretreatment and posttreatment	−1.6±18.5	−1.0±16.0	0.83
Pain			
Pretreatment	56.1±19.9	58.7±17.1	
Posttreatment	58.0±22.1	62.1±20.5	
Difference between pretreatment and posttreatment	1.9±14.2	3.4±13.7	0.60
Social life			
Pretreatment	91.9±13.2	92.0±13.1	
Posttreatment	88.3±17.0	91.8±14.7	
Difference between pretreatment and posttreatment	−3.6±17.9	−0.1±16.5	0.25
Specific fears			
Pretreatment	84.1±19.6	81.8±21.4	
Posttreatment	81.8±22.2	84.1±21.0	
Difference between pretreatment and posttreatment	−2.3±20.3	2.3±15.4	0.27
Psychic well being			
Pretreatment	83.9±15.4	81.4±18.5	
Posttreatment	83.0±15.9	81.4±19.6	
Difference between pretreatment and posttreatment	−0.9±15.1	0±13.5	0.94

CLAU-S indicates Claudication Scale.

−1.0 mm Hg) in the metoprolol group ($P=0.01$). Results were similar with regard to diastolic blood pressure with an absolute change (95% CI) of −1.7 mm Hg (−3.3 to −0.1 mm Hg) in nebivolol- ($P=0.04$) and of −2.5 mm Hg (−4.1 to −1.0 mm Hg) in metoprolol-treated patients ($P=0.002$).

Subgroup Analysis of Patients Without Peripheral Intervention

During follow-up, 7 patients underwent peripheral angioplasty (nebivolol N=6 and metoprolol N=1); no patient underwent bypass surgery. To eliminate the confounding effect of revascularization procedures on ABI, ICD, and ACD, an additional analysis was performed after exclusion of these patients. In the subgroup of patients treated with nebivolol who received no vascular intervention during the study, there was still a significant increase of ABI, from 0.64±0.14 at randomization to 0.69±0.19 ($P<0.02$). For the metoprolol-treated patients, ABI improved from 0.62±0.17 to 0.66±0.20, but this difference did not reach statistical significance ($P=0.06$).

After exclusion of patients with peripheral interventions, ICD changed from 81.0±37.0 to 99.6±60.7 m in nebivolol-treated patients and from 91.4±50.3 to 100.2±75.6 m in metoprolol-treated patients (P value not significant across treatment groups). The percentage increase (95% CI) of ICD was still 36.9% (13.6% to 60.3%) in the nebivolol group ($P=0.002$) and 18.5% (−2.7% to 39.8%) in the metoprolol group ($P=0.09$). ACI increased from 148.3±82.5 to 186.4±153.7 m in nebivolol- and from 165.7±87.1 to 206.4±158.3 m in metoprolol-treated patients (P value not significant across treatment groups). The significant increase of ACD also persisted for both treatment groups with a percentage increase (95% CI) of 26.2% (4.6% to 47.7%) in the nebivolol group ($P=0.02$) and 24.4% (5.1% to 43.7%) in the metoprolol group ($P=0.01$; P value not significant across treatment groups). There was no change in the results for FMD, nitrate-mediated dilatation, systolic or diastolic blood pressure, or quality of life after exclusion of patients with peripheral intervention.

Safety Analysis

For safety reasons, vital signs including documentation of adverse events, current medication, and clinical examination, including heart rate, have been documented at each visit. There was no significant difference of heart rate between both treatment groups (heart rate between at baseline: nebivolol 70.8±10.4 bpm and metoprolol 70.6±9.7 bpm; heart rate at final visit: nebivolol 68.3±9.7 bpm and metoprolol 70.6±8.4 bpm).

Recorded adverse effects that could potentially or possibly be associated with β-blocker therapy for all 128 patients who received ≥1 dose of study medication are listed in Table 3. In 18 patients (14.1%), ≥1 adverse effect could be detected, with no significant difference between treatment groups ($P=0.56$).

In 7 patients (5.5%), the study has to be stopped because of adverse effects. In the metoprolol group, 3 patients (4.8%) withdrew study medication because of relevant bradycardia, in the nebivolol group 1 patient also experienced from bradycardia. One patient from the nebivolol group who was treated with metoprolol before randomization experienced uncontrolled arterial hypertension and temporary tachycardia, which required discontinuation of the study medication.

Table 3. Adverse Effects Possibly or Probably Related to Study Drugs

Adverse Effects	Nebivolol (N=65)	Metoprolol (N=63)	*P*
Bradycardia (<50 bpm)*	1 (1.5%)	3 (4.8%)	
Uncontrolled hypertension and tachycardia*	1 (1.5%)	…	
Blurred vision*	1 (1.5%)	…	
Erectile dysfunction*	…	1 (1.6%)	
Edema	…	2 (3.2%)	
Vertigo	…	2 (3.2%)	
Worsening in claudication	…	1 (1.6%)	
Temporary dysesthesia of the hands	…	1 (1.6%)	
Dyspnea	1 (1.5%)	1 (1.6%)	
Skin irritation	3 (4.6%)	…	
Worsening in hypertension	1 (1.5%)	…	
Headache	1 (1.5%)	…	
Moderate diarrhea	1 (1.5%)	…	
Total No. of adverse effects	10 (15.4%)	11 (17.5%)	0.75
No. of patients with any adverse effect	8 (12.3%)	10 (15.9%)	0.56

The table includes all 128 patients who received ≥1 dose of the study drug. Some patients had multiple adverse effects.

*Study drug was stopped because of this adverse effect.

In addition to the 7 patients in which the study was interrupted because of adverse effects, the study was terminated early in 12 patients. In detail, 4 patients died during the treatment period for reasons not related to the study drug (all 4 nebivolol; causes of death: severe pneumonia, after surgery for colon cancer, sudden cardiac death, and stroke); 4 patients withdrew the consent to participate (metoprolol: N=2; nebivolol: N=2) and in 4 patients drugs not permitted in the study protocol because of their known effects on endothelial function had to be added during the follow-up period (all 4 nebivolol).

Discussion

The present trial was designed to prospectively compare nebivolol, a β_1-selective blocker with vasodilating NO-releasing properties, with the nonvasodilating β_1-selective blocker metoprolol in patients with PAD. We observed a significant prolongation of the absolute walking distance and an improvement in the ABI in both treatment groups with a significant improvement of the pain-free walking distance in the nebivolol group only. In contrast, we found no effect on FMD by either medication.

From the clinical perspective, the most important finding of the study was the effect of β-blockade on walking distance. In contrast with the hypothesis of a potential negative effect of β-blockers on PAD symptoms described above, an improvement of walking distance and ABI was observed in both patient groups. Notably, only treatment with nebivolol achieved a statistically significant effect in terms of ICD. Of

importance, this positive result on walking distance remained after exclusion of patients who underwent peripheral interventions, and it was supported by the observation that treatment with both drugs was associated with a small but statistically significant improvement in the ABI. Although the clinical improvements in the nebivolol group are compatible with the peripheral vasodilatation induced by this drug, the mechanism of the positive effects of metoprolol on walking distance is less clear. Whatever the mechanism, our data suggest that the use of either β-blocker improves, rather than worsens, clinical parameters of PAD.

In line with the clinical experience, we found no worsening in symptoms evaluated using the CLAU-S. The CLAU-S is probably the most extensively researched disease-specific quality-of-life questionnaire for intermittent claudication.[31,32] Although mean walking distance was significantly improved in both treatment groups, we established only a minimal trend in improvement of the dimension "pain" in the quality-of-life questionnaire. This could be explained by the high score of our patients, especially in the dimensions "social life," "specific fears," and "psychic well being," but also in the other dimensions already at baseline.

Finally, although nebivolol has been shown to potentiate endothelium-dependent responses in healthy volunteers and patients with essential hypertension, in the present trial FMD was not influenced by either β-blocker treatment at all.[28,34] This lack of efficacy might possibly be explained by the high cardiovascular burden of our patients, such that their endothelial dysfunction is beyond the possibility of pharmacological improvement. In addition, a majority of our patients required treatment with additional antihypertensive drugs with vasodilating properties, such as calcium antagonists or inhibitors of the renin angiotensin system, which have beneficial effects on endothelial function. Likewise, nearly all of the patients were pretreated by antithrombotic drugs and this might improve FMD as well.[33,35]

Patients with PAD have a high prevalence of concomitant CAD and, therefore, a high incidence of cardiovascular events.[1–3,36,37] β-Blockers have been demonstrated to decrease mortality in patients with CAD; therefore, they are often indicated in patients with PAD and concomitant CAD, especially if these patients experience arterial hypertension.[6–8,11,38] The use of some β-blockers in patients with PAD may be complicated by an unopposed increase in α-adrenergic stimulation and subsequently decreased cardiac output.[10,38] Therefore, β-blockers are contraindicated in patients with critical limb ischemia.[11,12] Although biologically plausible, this concept is substantiated by very little clinical evidence. Some studies showed worsening of intermittent claudication in response to therapy with β-receptor blockers, but the number of patients included into these trials was quite small.[13–17] Based on these findings, a recent meta-analysis concluded that, because of lack of large randomized trials, β-blockers should be used with caution in patients with intermittent claudication.[22]

Nevertheless, despite possible adverse effects on clinical symptoms, β-blockers are widely used in PAD patients because of their prognostic impact, clinical experience suggests that β-blockers are often well tolerated in daily practice, and current guidelines recommend their use in PAD patients if indicated in particular in patients with CAD and arterial hypertension.[11,12,24] In this scenario, it remains to be determined whether β-blockers with vasodilating effects should be preferred in patients with PAD. To our knowledge, this was the first prospective double-blind, randomized trial comparing 2 β-blockers with differing hemodynamic profiles in PAD patients.

Limitations of the study should be discussed. The study was double-blind randomized but the absence of a placebo (or "neutral antihypertensive drug") control group must be mentioned. It also needs to be acknowledged that observations based on walking distance might be biased by changes in patient motivation. In previous trials, an improvement of pain-free walking distance has been observed in the placebo group as well.[39] However, it should be noted that the patients have not been included into specific exercise or smoking cessation programs. Finally, the improvement of ABI, although significant, was relatively small. The changes in the ABI, however, a parameter less dependent on patient motivation, suggest that therapy with β-blockers does favorably affect peripheral perfusion in patients with intermittent claudication and arterial hypertension.

Perspectives

β-Blockers improve prognosis in patients with PAD, especially in those with concomitant CAD or arterial hypertension. To our knowledge, this is the first double-blind randomized study to compare a β-blocker with vasodilating properties with a nonvasodilating β-blocker in patients with PAD. We found a significant improvement in the ABI and a prolongation of the ACD in both treatment groups. In addition, a significant improvement of the ICD could be observed in the nebivolol group. Use of β-blockers in patients with intermittent claudication and arterial hypertension appears to be safe. Our observations indicate that nebivolol might have some advantages over metoprolol, but larger studies are needed to prove this concept. However, in the direct comparison, there was no significant difference between nebivolol and metoprolol.

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