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# Roxithromycin Treatment Prevents Progression of Peripheral Arterial Occlusive Disease in *Chlamydia pneumoniae* Seropositive Men

## A Randomized, Double-Blind, Placebo-Controlled Trial

Peter Wiesli, MD; Wolfgang Czerwenka, MD; Alfredo Meniconi, MD; Friedrich E. Maly, MD; Ulrich Hoffmann, MD; Wilhelm Vetter, MD; Georg Schulthess, MD

**Background**—Evidence has been provided that the atherosclerotic process may be associated with chronic infection with *Chlamydia pneumoniae*. The effect of antibiotic treatment on peripheral arterial occlusive disease has not been investigated yet.

**Methods and Results**—Forty *C pneumoniae* seropositive men suffering from peripheral arterial occlusive disease were randomly assigned to receive either roxithromycin (300 mg daily) or placebo for 28 days. During the 2.7-year follow-up, the number of invasive revascularizations per patient, the walking distance before intervention (in patients without intervention at study end), and the change of carotid plaque size were assessed. Five interventions were performed on 4 patients (20%) in the roxithromycin group, and 29 interventions were performed on 9 patients (45%) in the placebo group. Limitation of walking distance to 200 m or less was observed in 4 patients (20%) in the roxithromycin group and in 13 patients (65%) in the placebo group. The effect of macrolide treatment on the number of interventions per patient and on preinterventional walking distance was significant. Possible confounding variables such as classical vascular risk factors were excluded by multiple regression analyses. Carotid plaque areas monitored over 6 months decreased in the roxithromycin group (mean relative value, 94.4%) but remained constant in the placebo group (100.2%). Regression of carotid plaque size observed in roxithromycin-treated patients was significant for soft plaques.

**Conclusions**—This study indicates that macrolide treatment for 1 month is effective in preventing *C pneumoniae* seropositive men from progression of lower limb atherosclerosis for several years. (*Circulation*. 2002;105:2646-2652.)

**Key Words:** atherosclerosis ■ angioplasty ■ carotid artery

The significance of inflammation in the atherosclerotic process has been recognized in the recent years.<sup>1</sup> *Chlamydia pneumoniae* is the infectious agent most convincingly associated with development and progression of atherosclerosis.<sup>2</sup> Several epidemiological studies have demonstrated an association of *C pneumoniae* seropositivity and atherosclerosis, including lower limb atherosclerosis.<sup>3</sup> Additional experimental evidence for this association has been provided in animal models.<sup>4,5</sup> Presence of *C pneumoniae* in atherosclerotic plaques was demonstrated using molecular and immunohistochemical methods and by culturing *C pneumoniae* from atherosclerotic plaques.<sup>6</sup>

Above these considerations, pilot trials have been initiated investigating the effect of antibiotic treatment on *C pneumoniae* seropositive patients with coronary heart disease. A significant reduction of coronary events was found in male survivors of myocardial infarction.<sup>7</sup> In the ROXIS pilot study,

performed on patients with unstable angina or non-Q-wave myocardial infarction, a beneficial effect of antibiotic treatment on clinical events was confirmed.<sup>8</sup> In contrast, the ACADEMIC study showed an effect of antibiotic treatment on markers of inflammation but not on the clinical outcome.<sup>9</sup> In an additional study, antibiotic treatment induced a decrease of plasma fibrinogen in *C pneumoniae* seropositive patients suffering from coronary heart disease.<sup>10</sup> In a recent study, patients with coronary stenting received roxithromycin or placebo for 28 days. Antibiotic treatment revealed no beneficial effect for patients with negative or moderately elevated IgG titers but a preventive effect on coronary restenosis for patients with IgG titers against *C pneumoniae* of 1:128 or greater.<sup>11</sup> Because of controversial results, it is still a matter of debate whether there is a beneficial effect of antibiotic treatment on the course of atherosclerosis in *C pneumoniae* seropositive patients. In the present study, we address this

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question by investigating a small but homogenous population of *C pneumoniae* seropositive, elderly men with peripheral arterial occlusive disease (PAOD) at high risk of undergoing progression of disease.

## Methods

### Study Design

This study was designed as a randomized, double-blind trial of roxithromycin versus placebo in *C pneumoniae* seropositive men with established PAOD. The number of invasive revascularizations per patient (primary parameter), the walking distance before intervention (in patients without intervention at study end), and the change of carotid plaque size as a pathophysiological parameter were assessed. A follow-up period of 2.5 years was planned to achieve statistical power of 80%.

### Eligible Patients

Approval for this project was obtained from the ethical committee of the University Hospital of Zurich. Inclusion criteria were established diagnosis of PAOD, male sex, *C pneumoniae* seropositivity, and at least 1 carotid plaque detectable by ultrasound. Exclusion criteria were diabetes mellitus, malignant neoplasia, chronic inflammatory disorders (eg, chronic infectious diseases and autoimmune disorders), and renal insufficiency (serum creatinine  $>180 \mu\text{mol/L}$ ). Of 100 consecutively recruited patients with diagnosis of PAOD but not diabetes mellitus, 51 tested positive for antibodies recognizing *C pneumoniae*. Of the seropositive patients, 11 were excluded from the study because no carotid plaque was detected by ultrasound (8 patients), bypass surgery of carotid artery was planned (1 patient) or informed consent failed (2 patients). The remaining 40 seropositive patients gave written informed consent to participate in the study.

### Assessment of Baseline Characteristics

PAOD was assessed from typical findings in clinical investigation and oscillography or from history of invasive revascularization of peripheral arteries. Study physicians assessed interventions performed in the year before the study and clinical parameters of PAOD at baseline, such as resting pain, walking distance, and ankle/arm index. Coronary heart disease was defined as history of myocardial infarction or coronary revascularization; occlusive cerebrovascular disease was defined as history of stroke or carotid artery surgery. Actual smoking of several cigarettes per day was recorded as "smoking." Arterial hypertension was taken over from medical records as established diagnosis.

Testing for antibodies against *C pneumoniae* was performed by microimmunofluorescence. The analyses were performed at dilutions of 1:64 and higher for IgG and at 1:32 and higher for IgA. *C pneumoniae* seropositivity was defined as an IgG titer of 1:128 or greater. Some results from testing patients for antibodies against *C pneumoniae* have been reported previously.<sup>12</sup> Fasting homocysteine was determined using HPLC (Bio-Rad). Creatinine, cholesterol and its subfractions, triacylglycerol, C-reactive protein, interleukin 6, and tumor necrosis factor- $\alpha$  were determined routinely at the Institute of Clinical Chemistry of the University Hospital of Zurich using standard methods.

### Randomization and Study Treatment

Aventis Pharma prepared visually indistinguishable tablets containing either 300 mg roxithromycin or placebo. Blinded treatment allocation was obtained by randomization at the pharmacy of the University Hospital of Zurich. All patients were repetitively advised and controlled to take 1 study tablet per day for 28 days; accompanying medication was left unchanged by the study physicians. The randomization code was kept sealed in an opaque envelope unknown to any of the participants of the study until the final results were analyzed.

### Assessment of Outcome Measures

During follow-up, physicians not involved in the study continued the usual management of PAOD, which could include angioplasty or bypass surgery. Clinical parameters of PAOD were determined before revascularization procedures. Study physicians consulted patients and their medical records again at study end. They assessed revascularization procedures performed during the follow-up period as well as actual clinical parameters of PAOD.

Carotid plaque areas were assessed by high-resolution ultrasound at baseline, at the end of treatment, and 6 months after delivering study medication. All ultrasound examinations were done by one investigator (W.C.) using an Acuson 128 XP 10 computed sonography system with a 7.5-MHz linear transducer. Patients were examined following a standardized protocol<sup>13</sup>: common carotid artery, carotid bulb, and proximal 2 cm of internal and external carotid arteries were scanned, and, if available, 2 individual plaque areas were included in the analysis from each side. Plaque areas were calculated from the plaque circumference on the frozen monitor by the duplex system software as the average of 3 consecutive measurements. Plaques were classified into soft or hard (partly calcified) plaques. According to the protocol, total plaque areas were calculated as the sum of all individual plaque areas per patient.

### Statistical Analysis

All data were evaluated by intention-to-treat analyses. Primary parameter was the number of invasive revascularizations per patient observed during the follow-up period. Evaluation was performed on an IBM personal computer using Excel, Statistica (version 4.5) and StatXact (version 5). The variables of the study groups were compared using either Student's *t* test,  $\chi^2$  test, or Mann-Whitney U test for variables with nonparametric distribution. To consider possible confounding variables, additional multiple regression analyses were performed on the outcome measures. Variables with nonparametric distribution were transformed to natural logarithms to approximate normal distribution. Variables with uncertain influence ( $P>0.1$ ) were excluded during the analyses using a stepwise backward elimination procedure. The threshold of significance for the 2-sided treatment comparisons was defined with  $\alpha=0.05$ .

## Results

Forty *C pneumoniae* seropositive men with established PAOD and one or several carotid plaques detectable by ultrasound were randomly assigned to receive either roxithromycin (300 mg daily) or placebo for 28 days. Two patients treated with roxithromycin and 1 patient in the placebo group had slight, transient diarrhea. No additional side-effects were observed, and all patients continued study medication for 28 days. No patient was lost to ultrasound examinations of carotid plaques at the end of treatment and 6 months after delivering study medication. During the 2.7-year follow-up, 1 patient died in the roxithromycin group and 2 patients died in the placebo group. For these patients, outcome measures were assessed from their medical records.

### Baseline Patient Characteristics

The patients' baseline characteristics presented in Table 1 show a homogenous distribution of the variables between the 2 study groups. There was no significant difference of age, body mass index, renal function, risk factors or manifestations of atherosclerosis, antibody titers against *C pneumoniae*, inflammatory markers, or concomitant medication. All patients had either aspirin or coumarin therapy. Only the prescription of statins was not well balanced between the roxithromycin group (35%) and the placebo group (60%). However, this difference was not significant, and multiple

**TABLE 1. Baseline Characteristics of the Study Groups**

	Roxithromycin (n=20)	Placebo (n=20)	P Value*
Age, y	72.4±7.7	70.3±9.1	0.42
Body mass index, kg/m <sup>2</sup>	26.6±2.8	25.1±3.3	0.12
Creatinine, μmol/L	109±21	113±25	0.52
Coronary heart disease (%)	6 (30)	8 (40)	0.51
Occlusive cerebrovascular disease (%)	2 (10)	3 (15)	0.63
Risk factors for atherosclerosis			
Smoking, n (%)	17 (85)	18 (90)	0.63
Arterial hypertension, n (%)	14 (70)	13 (65)	0.74
Total cholesterol, mmol/L	5.70±0.94	5.57±1.07	0.68
LDL cholesterol, mmol/L	3.47±0.75	3.17±0.84	0.23
HDL cholesterol, mmol/L	1.34±0.26	1.36±0.48	0.86
Triacylglycerols, mmol/L	1.96±0.84	2.30±1.24	0.32
Homocysteine, μmol/L	23.8±15.2	22.6±8.2	0.76
Antibody titers and inflammatory markers			
IgG against <i>C pneumoniae</i> , 10 <sup>-1</sup>	256 (128–1024)	256 (128–512)	0.08
IgA against <i>C pneumoniae</i> , 10 <sup>-1</sup>	64 (0–512)	64 (0–256)	0.96
C-reactive protein, mg/mL	5.1±4.6	4.8±3.8	0.82
Interleukin 6, ng/L	10.3 (2.7–21.3)	7.4 (2.5–17.6)	0.16
Tumor necrosis factor-α, ng/L	14.9±9.8	15.0±10.3	0.98
Concomitant administration of drugs (%)			
Aspirin, n	18 (90)	16 (80)	0.38
Coumarins, n	2 (10)	4 (20)	0.38
ACE inhibitors, n	6 (30)	7 (35)	0.74
β-blockers, n	2 (10)	3 (15)	0.63
Calcium antagonists, n	9 (45)	6 (30)	0.33
Diuretics, n	2 (10)	5 (25)	0.21
Statins, n	7 (35)	12 (60)	0.11

Values are mean±SD or median (range).

\*Student's *t* test,  $\chi^2$  square test, or Mann-Whitney U test where median (range) is indicated.

regression analyses revealed no significant association between prescription of statins and outcome measures of this study. Table 2 shows that the study groups were well randomized as well with regard to revascularization procedures performed in the year before the study ( $P=0.91$ ) and walking distance determined at baseline ( $P=0.99$ ). Table 3 shows no relevant difference of total carotid plaque areas ( $P=0.86$ ) or other plaque characteristics between the study groups at baseline.

### Effect of Study Treatment on Atherosclerotic Manifestations

Progression of PAOD requiring invasive revascularization was assessed over 2.7 years. Table 2 shows a clear-cut difference between the 2 study groups: 5 peripheral arterial

**TABLE 2. Effect of Macrolide Treatment on the Walking Distance and Number of Revascularization Procedures**

	Roxithromycin	Placebo	P Value*
Revascularization procedures			
During 1 year before the study (baseline)			
No. of patients (%)	11 (55)	9 (45)	
Total no. of interventions	13	17	0.91†
During follow-up			
No. of patients	4 (20%)	9 (45%)	
Total no. of interventions	5	29	0.049†
Type of intervention			
Angioplasty	5	27	
Bypass surgery	0	2	
Walking distance (no. of patients)			
At entry (baseline) (%)			
<200 m	2 (10)	2 (10)	
200 to 499 m	5 (25)	5 (25)	0.99
500 to 5000 m	5 (25)	5 (25)	
>5000 m	8 (40)	8 (40)	
Preinterventional (%)‡			
Resting pain	0 (0)	2 (10)	
<200 m	4 (20)	8 (40)	
200 to 499 m	0 (0)	3 (15)	0.025
500 to 5000 m	5 (25)	1 (5)	
>5000 m	11 (55)	6 (30)	
Final (at the end of the study) (%)			
<200 m	0 (0)	4 (20)	
200 to 499 m	3 (15)	6 (30)	0.040
500 to 5000 m	6 (30)	3 (15)	
>5000 m	11 (55)	7 (35)	

\*Mann-Whitney U test (†No. of invasive revascularizations per patient).

‡Walking distance determined before revascularization procedures or at study end in patients without intervention.

events requiring angioplasty were observed in 4 patients (20%) in the roxithromycin group, and 29 events requiring angioplasty or bypass surgery were observed in 9 patients (45%) in the placebo group. The study groups differed significantly with regard to the number of interventions per patient ( $P=0.049$ ). Figure 1 shows that macrolide treatment had a marked effect on the number of interventions throughout the follow-up period.

Preinterventional walking distance was defined as walking distance determined before interventions or, in patients without intervention, at study end. Table 2 shows that a limitation of preinterventional walking distance to 200 m or less was observed in 4 patients (20%) in the roxithromycin group, compared with 13 patients (65%) in the placebo group (all 3 patients in the category of 200 to 499 m had a walking distance of just 200 m). The effect of macrolide treatment was significant on preinterventional walking distance ( $P=0.025$ ) as well as on the walking distance assessed at the end of the study ( $P=0.040$ ).

**TABLE 3. Baseline Characteristics and Effect of Macrolide Treatment on Carotid Plaque Size**

	Roxithromycin	Placebo	<i>P</i> Value*
Baseline characteristics of carotid plaques			
No. of individual plaque areas	56	55	
Localization (%)			
Carotid bulb	26 (46)	22 (40)	
Common carotid artery	24 (43)	20 (36)	
Internal carotid artery	4 (7)	6 (11)	
External carotid artery	2 (4)	7 (13)	
Quality (%)			
Soft	44 (78)	39 (71)	
Hard	12 (22)	16 (29)	
Effect of study treatment on carotid plaque areas			
Individual carotid plaque areas, mm <sup>2</sup>	n=56	n=55	
Baseline	15.9±12.0	16.6±10.9	
After 1 month of treatment	15.2±10.8	16.3±10.6	
After 6 months	14.6±10.2	16.5±10.4	
Mean relative value after 6 months, %			
All plaques	94.4±15.6	100.2±12.9	
Soft plaques	93.1±13.5	99.1±10.1	
Total carotid plaque areas, mm <sup>2</sup> †	n=20	n=20	
Baseline	44.4±26.9	45.8±24.0	0.86
After 1 month of treatment	42.6±23.3	44.7±23.9	
After 6 months	40.9±24.0	45.3±22.8	
Mean relative value after 6 months, %			
All plaques	95.6±8.4	99.6±4.8	0.08
Soft plaques	94.8±7.3	99.5±4.4	0.043

Values are count or mean (±SD).

\*Student's *t* test.

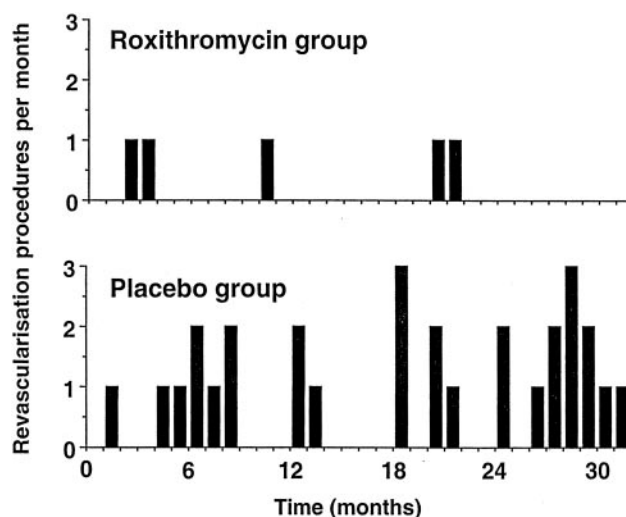
†Sum of all plaque areas per patient.

Mean ankle/arm index remained constant in the roxithromycin group; ie, it was  $0.69 \pm 0.25$  at baseline and  $0.70 \pm 0.23$  before intervention or, in patients without intervention, at study end. In contrast, ankle/arm index decreased from  $0.75 \pm 0.16$  (at baseline) to  $0.58 \pm 0.41$  (before intervention or at study end) in the placebo group. The difference between the study groups was not significant. Values  $>1.5$  were excluded from analysis, because these values strongly indicate a falsely high ankle pressure attributable to calcification of crural vessels.<sup>14</sup>

The study groups were well comparable with regard to additional atherosclerotic manifestations. One stroke and 3 coronary angioplasties were observed in the roxithromycin group; myocardial infarction, coronary bypass surgery, and carotid artery surgery were observed once in the placebo group.

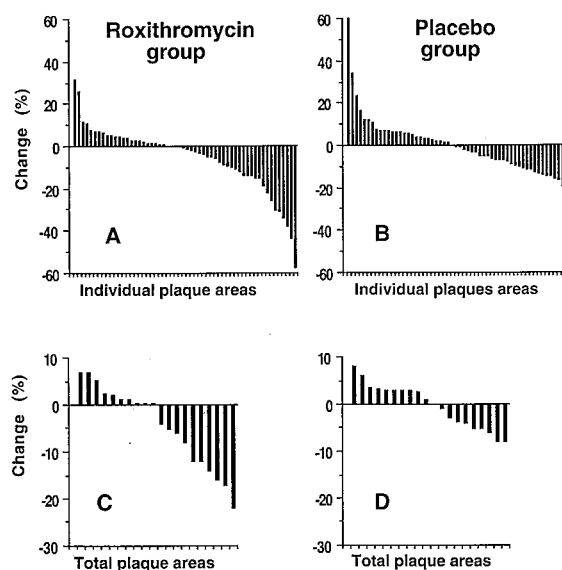
### Effect of Study Treatment on Carotid Plaques and Inflammatory Markers

Carotid plaque areas were monitored over 6 months (Table 3). Mean individual plaque area continuously decreased from



**Figure 1.** Effect of macrolide treatment on the number of revascularization procedures performed during the follow-up period. The patients were treated for the first 28 days with either roxithromycin (300 mg daily) or placebo.

$15.9 \pm 12.0$  to  $14.6 \pm 10.2$  mm<sup>2</sup> in the roxithromycin group (mean relative value after 6 months, 94.4%) but remained constant in the placebo group (100.2%). Plaque regression observed in roxithromycin-treated patients was attributable to decrease of soft plaques (93.1%) rather than hard plaques (99.0%). Mean total plaque area decreased from  $44.4 \pm 26.9$  to  $40.9 \pm 24.0$  mm<sup>2</sup> in the roxithromycin group but remained unchanged in the placebo group. The effect of macrolide treatment on the change of total carotid plaque areas was



**Figure 2.** Effect of macrolide treatment on the change of carotid plaque size monitored over 6 months. Relative change of individual plaque areas (A) and total plaque areas (C) in the roxithromycin group and relative change of individual plaque areas (B) and total plaque areas (D) in the placebo group. The patients were treated for the first 28 days with either roxithromycin (300 mg daily) or placebo. Individual plaque areas were assessed by high-resolution ultrasound; total plaque areas were calculated as the sum of all plaque areas per patient.

**TABLE 4. Multiple Regression Analyses Investigating the Effect of Roxithromycin Treatment on the Number of Revascularization Procedures per Patient, Walking Distance, and the Change of Carotid Plaque Size**

	P Value		
	No. of Invasive Revascularizations	Preinterventional Walking Distance*	Change of Carotid Plaque Areas†
Variables remaining in the model			
Study treatment	0.026 ( $\beta = -0.34$ )	0.009 ( $\beta = 0.38$ )	0.027 ( $\beta = -0.36$ )
Total plaque area at baseline	0.06 ( $\beta = 0.29$ )	0.06 ( $\beta = -0.27$ )	...
Walking distance at baseline	...	0.04 ( $\beta = 0.30$ )	...
Body mass index	...	...	0.06 ( $\beta = 0.30$ )
Variables excluded from the model			
Prestudy revascularizations	0.12	0.64	0.75
Walking distance at baseline	0.99	...	0.95
Total plaque area at baseline	...	...	0.21
Age	0.83	0.93	0.55
Body mass index	0.41	0.99	...
Creatinine	0.81	0.38	0.45
Smoking	0.53	0.51	0.51
Hypertension	0.41	0.39	0.86
Ratio LDL/HDL cholesterol	0.91	0.88	0.39
Triacylglycerols	0.12	0.75	0.94
Homocysteine	0.90	0.99	0.66
IgG titer against <i>C pneumoniae</i>	0.91	0.36	0.43
IgA titer against <i>C pneumoniae</i>	0.45	0.13	0.26
C-reactive protein	0.30	0.86	0.95
Interleukin 6	0.62	0.65	0.90
Tumor necrosis factor- $\alpha$	0.91	0.21	0.56
Prescription of statins	0.19	0.57	0.78

\*Walking distance determined before revascularization procedures or at study end in patients without intervention.

†Relative change of total plaque areas (sum of all plaque areas per patient).

significant for soft plaques ( $P=0.043$ ). Figure 2 shows the relative change of individual and total carotid plaque areas during 6 months. In the placebo group, spontaneous fluctuations of plaque size could be observed (Figures 2B and 2D).

C-reactive protein, interleukin 6, and tumor necrosis factor- $\alpha$  were determined at baseline, after 1 month of treatment, and after 6 months. No significant change and no significant difference between the study groups could be observed with regard to these variables. C-reactive protein determined after 6 months significantly correlated with the number of interventions per patient observed during the follow-up period.

### Possible Confounding Variables

Possible confounding effects were considered by multiple regression analyses (Table 4). The effect of study treatment remained significant on the number of invasive revascularizations per patient ( $P=0.026$ ) and on preinterventional walking distance ( $P=0.009$ ). Total plaque area at baseline remained in the final model as a probable effect on the 2 outcome measures ( $P=0.06$ ). Although not significant in

Student's *t* test (Table 3), the association between study treatment and the change of total plaque areas was significant in multiple regression analysis ( $P=0.027$ ) (Table 4). The body-mass index remained in the final model of this analysis as probable effect ( $P=0.06$ ). Age, creatinine, classical risk factors for atherosclerosis, prescription of statins, IgG and IgA titers against *C pneumoniae*, and inflammatory markers were not significantly associated ( $P>0.1$ ) and, therefore, excluded during the stepwise regression analyses.

No patient received macrolide antibiotics outside study treatment. Additional antibiotic medication was prescribed during follow-up for 3 patients in the roxithromycin group and for 7 patients in the placebo group, mainly short-period Ciprofloxacin or Amoxicillin. The distribution of these antibiotics in favor of the placebo group ruled out a possible beneficial effect in favor of the roxithromycin group.

## Discussion

### Summary of Study Results

This study indicates that macrolide treatment of *C pneumoniae* seropositive men has a beneficial effect on the course

of lower limb atherosclerosis. Prescription of roxithromycin is shown to prevent clinical progression of PAOD and to reduce the number of invasive revascularizations significantly. A remarkable result of this study is that macrolide treatment for 28 days had an effect lasting throughout the follow-up period of 2.7 years. Consistent with the effect on PAOD, a decrease of carotid plaque size was observed in the roxithromycin group. Fluctuations of plaque areas could be observed in the placebo group leading to neither increase nor decrease of mean plaque size. This observation is reasonable considering that spontaneous fluctuations of plaque size have been reported previously.<sup>15</sup> The findings of this study provide good evidence that macrolide treatment had a relevant effect on the course of the atherosclerotic process.

### Study Strengths and Limitations

This is the first study investigating the effect of antibiotic treatment on the course of lower limb atherosclerosis. Elderly men ( $71.3 \pm 8.4$  years) with high prevalence of smoking (>80%) and at high risk of undergoing progression of PAOD were selected as study population. The well-defined and homogenous population was successfully randomized. Only prescription of statins was not well balanced between the study groups, however, in favor of the placebo group. A possible confounding effect was excluded by statistical analysis. During follow-up, the management of PAOD was exclusively in the hands of physicians not involved in the study. Therefore, the decision to perform angioplasty or bypass surgery was made under usual conditions and independent of this study being carried out. Nevertheless, peripheral arterial events requiring intervention could be determined reliably by consulting the patients and their medical records at the end of the follow-up period. In our opinion, it is mostly attributable to selecting the study population according to the above-mentioned criteria that a clear and significant effect of treatment could be observed in the relatively small trial. To corroborate the present findings, we propose to treat *C pneumoniae* seropositive patients suffering from advanced PAOD with the regimen used here in a larger trial and a follow-up of several years.

There is no validated marker indicating chronic endovascular infection with *C pneumoniae*. Based on examinations of vascular specimens, *C pneumoniae* were detected in atherosclerotic plaques using immunohistochemical and molecular methods. Serum immunoglobulins recognizing *C pneumoniae* were used in studies investigating clinical end points<sup>7-10</sup>; however, it is still controversial whether IgG or IgA represents a better marker for persistent endovascular infection. The population selected for the present study had markedly elevated serum concentrations of IgG (median, 1:256) and IgA (median, 1:64).

### Comparisons With Previous Antibiotic Trials

The results of this study are not necessarily consistent with the findings of previous trials, because these were carried out with patients suffering mainly from coronary heart disease. The previous trials were partly performed on study populations with rather low incidence of clinical events or relatively low antibody titers against *C pneumoniae*. This might, at least

in part, explain why these studies provided controversial results with regard to a beneficial effect on the clinical outcome. A recent study showed a preventive effect of roxithromycin treatment on coronary restenosis, however, only for a subgroup with IgG titers against *C pneumoniae* of 1:128 or greater.<sup>11</sup> An IgG titer of 1:128 or greater was an inclusion criterion of the present study.

### Pathophysiological Considerations

Roxithromycin is known to have antibiotic and anti-inflammatory properties.<sup>16</sup> It is not clear whether the results of this study are based on an antibiotic or an anti-inflammatory effect of this drug. We consider an antibiotic effect as more probable because the beneficial effect on PAOD and carotid plaque regression lasted for relatively long periods after discontinuing the medication. Previous investigations have shown that roxithromycin is able to penetrate into atherosclerotic plaques and to eradicate microorganisms in the plaques.<sup>17</sup> In case of an anti-inflammatory effect, we would have expected to find a more temporary effect of the treatment decreasing in the absence of the drug.

It remains unclear whether macrolide treatment preferentially took influence on the spontaneous course of atherosclerosis or rather prevented restenosis after invasive revascularization. Roxithromycin unambiguously had an influence on the spontaneous course of atherosclerosis, as indicated by the carotid plaque regression observed. Regression of plaque size might indicate greater plaque stability going along with a better clinical outcome. However, an effect of roxithromycin on the restenosis process of lower limb atherosclerosis is also probable, because a relevant part of invasive revascularizations were performed on patients who had undergone previous interventions.

### Conclusion

This study indicates that macrolide treatment for 1 month is effective in preventing *C pneumoniae* seropositive men from clinical progression of lower limb atherosclerosis for a period of several years. Provided that our results can be confirmed in additional studies, the regimen is easy to carry out and highly efficient.

### Acknowledgments

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