Anti-Chlamydial Antibiotic Therapy for Symptom Improvement in Peripheral Artery Disease

Prospective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication and Other Endpoints in *Chlamydia pneumoniae* Seropositive Patients (PROVIDENCE-1)

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Background—A potentially strong association exists between *Chlamydia pneumoniae* and atherosclerosis, but the clinical benefits of antibiotic therapy have not been demonstrated. Preliminary studies of antibiotic therapy in peripheral artery disease have shown a decreased need for revascularization and improved walking ability. The objective of this phase-III trial was to assess the effect of a potent anti-Chlamydial agent, rifalazil, on peak walking time in patients with symptomatic peripheral artery disease.

Methods and Results—Patients with intermittent claudication secondary to peripheral artery disease who were seropositive for *C pneumoniae* were randomized to 25 mg rifalazil once weekly for 8 weeks or matching placebo. Two hundred ninety-seven patients were enrolled from 3 countries and were followed up for 1 year. The mean±SD ankle brachial index at baseline was 0.63±0.16. The primary end point, change from baseline in log peak walking time on a graded treadmill, was assessed 180 days after randomization. Secondary end points included changes in claudication onset time and quality of life, assessed with the Walking Impairment Questionnaire and the Short Form Medical Outcomes 36. No benefit of rifalazil therapy was found in the primary or any secondary end point among this cohort of patients with peripheral artery disease. The group treated with rifalazil improved their peak walking times by 23% (95% confidence interval, 15 to 31) from baseline to day 180, whereas the placebo group improved by 18% (95% confidence interval, 11 to 26; $P=0.38$). Peak walking time, claudication onset time, Walking Impairment Questionnaire, and Short Form Medical Outcomes 36 showed no treatment-by-time interaction during the 360-day study period. Thirty-two adjudicated cardiovascular events occurred, 16 in each treatment group.

Conclusions—Rifalazil did not improve exercise performance or quality of life in patients with intermittent claudication. No safety concerns were identified. Given the very small effect size, it is unlikely that larger studies would demonstrate a symptomatic benefit of this therapy in peripheral artery disease. **(*Circulation*. 2009;119:452-458.)**

Key Words: claudication ■ infection ■ peripheral vascular disease

Peripheral artery disease (PAD) is a common atherosclerotic disease, affecting up to 29% of patients who have risk factors for PAD.[1] Intermittent claudication is one of the most common symptoms of patients with PAD.

Clinical Perspective p 458

The association of chronic infection with *Chlamydia pneumoniae* and atherosclerosis has been postulated for 2 decades; however, results of clinical trials seeking to determine whether anti-Chlamydial therapy reduces atherosclerotic events have been contradictory. Most of these trials have involved patients with coronary artery or cerebrovascular disease. Studies have demonstrated that high titer seropositivity to *C pneumoniae* is greater in PAD patients than in coronary disease patients, with most studies demonstrating 50% to 78% of PAD patients seropositive with immunoglobulin G (IgG) antibodies against the pathogen.[2]

C pneumoniae is postulated to contribute to the pathophysiology of atherosclerosis, including an increase in intima-media thickness and plaque size and a progressive reduction in luminal diameter.[3] In animal models, *C pneumoniae* infection causes a profound increase in intima-media thick-

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ness and atherosclerosis but does not increase the frequency of plaque rupture or thrombogenicity.[4] Therefore, PAD might represent a better population in which to study the impact of antibiotic therapy directed against *C pneumoniae*. Progression of PAD and luminal diameter reduction is more likely to result in leg symptoms, and measurement of physiological benefit is easier in patients with PAD. The graded treadmill test is a validated test for assessing treatment effect in patients with claudication.[5]

Rifalazil is a second-generation rifamycin antibiotic, the site of action of which is the DNA-dependent RNA polymerase of bacteria. Rifalazil is a potent anti-Chlamydial agent compared with other rifamycins. This agent has been well tolerated in dose-ranging studies for the treatment of nongonococcal urethritis.[6] Because vascular infection with *C pneumoniae* is likely to require prolonged courses of therapy, the ability of rifalazil to promote long-term eradication of infection may be beneficial in the treatment of patients with PAD.[7]

Accordingly, the goal of this study was to determine whether rifalazil would be effective in patients with symptomatic PAD. The Prospective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication and Other Endpoints in *Chlamydia pneumoniae* Seropositive Patients (PROVIDENCE-1) study was designed to test the hypothesis that this potent anti-Chlamydial agent would improve peak walking time (PWT) relative to placebo in PAD patients with intermittent claudication.

Methods

Overview of Study Design

The PROVIDENCE-1 trial was a prospective, randomized, double-blind study conducted at 44 clinical sites in 3 countries. The protocol was reviewed and approved by all participating Institutional Review boards, and written informed consent was obtained from each patient in the study. This study abided by rules governed by the Helsinki doctrine, met all guidelines of good clinical practice, and was registered at http://www.clinicaltrials.gov/.

A Steering Committee was responsible for the oversight of the study, its implementation, and the analysis of data. The committee's charter defined its role and independence, as well as the sponsor's commitment to publish the data in a timely manner. An independent Safety and Monitoring Committee regularly reviewed unblinded adverse events and provided formal reports to the Steering Committee. Cardiovascular end points were adjudicated by an independent Clinical End Point Committee.

Patient Inclusion and Exclusion Criteria

Men and women between 40 and 80 years of age with stable intermittent claudication caused by PAD for the previous 6 months with a resting ankle brachial index of <0.90 in at least 1 limb were eligible for the study. PAD was defined as atherosclerotic stenosis of arteries of the lower extremity, involving the iliac and/or infrainguinal arteries.

Treatment with lipid-lowering agents, aspirin, clopidogrel, pentoxifylline, or cilostazol was allowed if dose and duration of therapy were stable for the previous 6 months. Patients were excluded from the study if they had signs of critical limb ischemia as evidenced by ischemic rest pain, ulceration, or gangrene; had planned surgical or endovascular revascularization; or were unable to complete the screening treadmill protocols for other reasons.

Screening

At screening, patients underwent a history and physical examination, ECG, exercise treadmill test, and an ankle brachial index assessment. All patients had to have PWTs between 1 and 12 minutes on a screening graded treadmill test. Blood samples were obtained for hematology and serum chemistry tests and for the *C pneumoniae* IgG antibody titer. An IgG *C pneumoniae* immunofluorescence titer $\geq$1:128 was required to be eligible for further participation in this study. The same assay kit (Chlamydia MIF IgG, Focus Diagnostics, Cypress, Calif) for determination of *C pneumoniae* titer was used in all participating countries. The test results were read in central laboratories in each country.

Baseline Measurements

If the screening tests indicated that the subject had PAD and the *C pneumoniae* IgG antibody titer was $\geq$1:128, participants were asked to return for up to 3 baseline treadmill visits. Subjects with 2 consecutive baseline PWTs between 1 and 12 minutes, with variability of $<25\%$, and maximal effort limited only by claudication symptoms were qualified for randomization. The average walking times from the 2 qualifying treadmill tests were used as the baseline values for PWT and claudication onset time (COT), respectively. Patients also completed the Short Form Medical Outcomes 36 (SF-36) and the Walking Impairment Questionnaire (WIQ) at a baseline visit.

Treatment and Follow-Up Phase

Patients were randomized to receive either 8 once-weekly doses of rifalazil, 25 mg orally, or matching placebo. Study drug and placebo were packaged in randomized blocks of 4 and sent to the site with instructions that they be given to eligible subjects in numerical order. This dosing scheme was devised from prior human data on the eradication of Chlamydia with rifalazil in other disorders. Patients were followed up for 360 days after the initial dose of rifalazil. Return visits occurred at 30, 60, 90, 180, and 360 days after randomization, during which efficacy and safety assessments were obtained. Treadmill assessments were obtained during visits on days 60, 90, 180, and 360. Assessment of physical function from the SF-36 and walking impairment from the WIQ were obtained at days 90, 180, and 360. Safety information and laboratory studies were collected at every follow-up visit. Subjects were called every week during the treatment phase and every other week during the follow-up phase to assess treatment compliance and safety between visits.

Treadmill Measurements

PWT and COT were quantified with a graded treadmill exercise test using the Gardner protocol.[5] The treadmill speed was maintained at 2 mph with an initial treadmill grade of 0%. At each subsequent 2-minute interval, the grade was increased by 2%. The onset time of limb discomfort noted by the subject was recorded as the COT. Subjects terminated exercise when limb discomfort prevented them from continued walking, which was designated as the PWT. A quality control program overseen by the Colorado Prevention Center, the Academic Research Organization for the trial, was in place at each site to ensure that the exercise performance testing was applied in a consistent and reproducible manner according to the protocol.

Primary End Point

The primary efficacy end point was the change in log PWT from the average of 2 qualifying baseline visits to day 180 in patients randomized to rifalazil compared with the change in log PWT in patients randomized to placebo.

Secondary End Points

Secondary end points included the treatment-by-time interaction for all time points through day 360 for log PWT, log COT, walking distance, and walking speed as measured by the WIQ and physical functioning as assessed by the Physical Component Score of the SF-36.

Determination of Sample Size and Statistical Analysis

The sample size estimate was calculated for the primary efficacy end point of the change in log PWT at baseline to day 180. The placebo

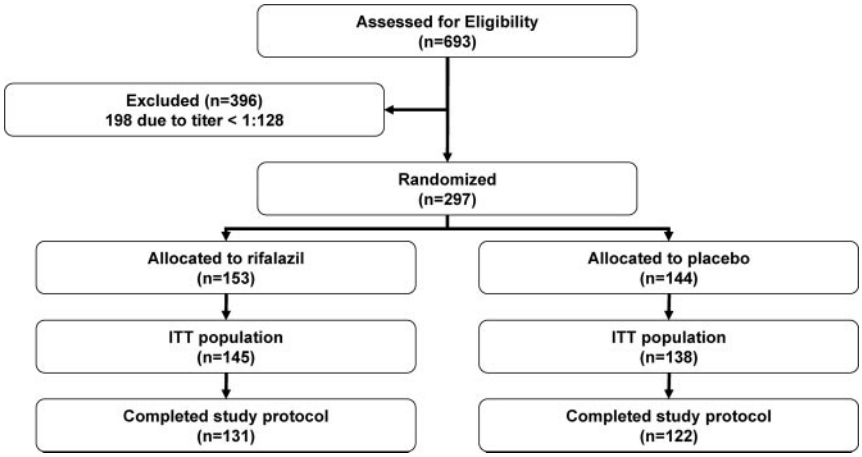

Figure 1. Flow diagram of study participants. ITT indicates intention-to-treat.

effect and pooled SD estimates were based on unpublished data from a separate clinical trial using a Gardner graded treadmill protocol in a similar patient population. One hundred thirteen patients per arm would provide 90% power at $\alpha=0.05$, based on a 2-sided 2-sample equal-variance *t* test, to detect a treatment difference in change in log PWT at day 180 of 25%. The placebo effect and pooled SD estimates were based on unpublished data from a clinical trial testing a different drug in a similar patient population using a Gardner graded treadmill test. A pooled SD on the change in log PWT of 0.46 was used. To account for a 17% dropout rate, enrollment of 137 patients per arm (n=274 total) was planned.

For the primary analysis, missing data were handled as the last postbaseline PWT value carried forward to day 180. The analysis was based on a 2-sample equal-variance *t* test of the null hypothesis that the difference between treatment groups in the change from baseline to day 180 in log PWT was equal in the 2 groups. Natural logarithm transforms of PWT were used because of the known skewed distribution of PWTs. The log-transformed data were back-transformed to geometric means for data presentation in units of seconds. The percent change in geometric mean from baseline to day 180 is presented for each group with a 95% confidence interval (CI).

Secondary end points, including log PWT, log COT, SF-36, and WIQ, were analyzed with mixed models. This allowed the inclusion of all data obtained throughout the 360-day trial and testing of the overall treatment-by-time interaction. Random subject effects and an autocorrelation term were included in the model. The treatment-by-time-by-country interaction on log PWT was modeled for exploratory analysis.

Adverse event and serious adverse event patient rates were presented and compared between treatment groups with relative risks and 95% CIs. Kaplan-Meier analysis was conducted on the population to determine whether rifalazil compared with placebo altered the time to a combined cardiovascular end point as adjudicated by the Clinical End Point Committee. The combined cardiovascular end point comprised vascular death, nonfatal clinically apparent or silent myocardial infarction, nonfatal stroke, revascularization, or readmission to hospital for a vascular or atherosclerosis-related complication. The time to the first end point per patient was used in the analysis.

Study results were analyzed with SAS version 9.1 (SAS Institute Inc, Cary, NC). Efficacy analyses were conducted on the intent-to-treat population, defined as subjects who had at least 1 postbaseline treadmill test. Safety data are reported for all subjects who received at least 1 dose of study medication. Categorical variables were summarized using frequency and percent per group, and baseline values were compared by use of χ^2 tests or Fisher exact test when appropriate. Continuous variables were summarized by total number, mean, and SD; baseline values were compared by use of *t* tests. All statistical tests were 2 sided with an α level of 0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Demographics and Baseline Characteristics

Between November 2005 and September 2006, 693 patients were screened for inclusion from 3 countries. Three hundred ninety-six subjects did not meet eligibility requirements, but of note, 71% of patients (484 of 682) screened for the *C pneumoniae* antibody titer inclusion criterion had values ≥1:128. Two hundred ninety-seven patients were randomized into the study at 44 study sites: 129 subjects from the United States, 126 from Russia, and 42 from Brazil. Figure 1 is a flow diagram of subjects participating in the study.

The majority of patients were men (81.4% on rifalazil, 79.0% on placebo). The mean age of the rifalazil-treated patients was slightly older (66.6 years) than that of the placebo-treated patients (64.1 years). In the entire cohort, 26.3% of participants had diabetes mellitus (43.4% of US subjects, 5.6% of Russian subjects, 35.7% of Brazilian subjects). The mean ankle brachial index was 0.63 in each group. The geometric mean of the average baseline PWT was 232.4 seconds in the rifalazil-treated patients and 262.8 seconds in the placebo-treated patients. Five randomized subjects had *C pneumoniae* antibody titers <1:128 as a result of laboratory error. Table 1 lists key demographic features of the randomized patients by treatment group.

Primary and Secondary Efficacy

The primary efficacy end point data are presented in Table 2. No statistical difference could be found in the change in log PWT from baseline to day 180 between the rifalazil- and placebo-treated patients. The change in log PWT was 0.20±0.39 on rifalazil and 0.16±0.37 on placebo ($P=0.38$). These data converted to the geometric mean scale show that walking time increased by 23% (95% CI, 15 to 31) in the rifalazil group and by 18% (95% CI, 11 to 26) in the placebo group.

Figure 2 shows the log-transformed PWT values by treatment group for each time point during the trial. PWT increased in both the rifalazil and placebo groups from baseline to day 60; thereafter, little change occurred in PWT. The treatment-by-time interaction, tested as a secondary end point, was not significant ($P=0.48$). Treatment effect on log PWT by high and low *C pneumoniae* IgG antibody titer (<1:256 and ≥1:256) was tested in an exploratory analysis.

Table 1. Demographics of Intention-to-Treat Population

Characteristic	Rifalazil (n=145)	Placebo (n=138)	*P*
Age, mean±SD, y	66.6±8.0	64.1±8.7	0.01
Gender, n (%)			
Male	118 (81.4)	109 (79.0)	0.66
Female	27 (18.6)	29 (21.0)	
Race/ethnicity, n (%)			
White	133 (91.7)	126 (91.3)	0.27
Black	6 (4.1)	10 (7.2)	
Hispanic or Latino	3 (2.1)	2 (1.4)	
Other	3 (2.1)	0 (0.0)	
Body mass index, mean±SD, kg/m^2	27.7±5.3*	27.3±4.6	0.59
Current smoking status, n (%)			
None	17 (11.7)	21 (15.2)	0.21
Former	78 (53.8)	60 (43.5)	
Current	50 (34.5)	57 (41.3)	
Ankle brachial index, mean±SD	0.63±0.17	0.63±0.15†	0.71
PWT, Gmean (95% CI), n	232.4 (212.7–254.0)	262.8 (239.0–289.0)	0.06
COT, Gmean (95% CI), s	105.4 (95.5–116.4)	113.2 (102.2–125.3)	0.33
C pneumoniae titer, n (%)			
<1:256	38 (26.2)	37 (26.8)	0.91
≥1:256	107 (73.8)	101 (73.2)	

Gmean indicates geometric mean. Continuous variables were compared by use of 2-sample *t* tests; categorical variables were compared by use of Fisher exact tests.

*n=143; †n=137.

No evidence was found of a treatment effect on log PWT in either subgroup (P=0.71, P=0.43, respectively).

No difference was found in walking distance assessed by WIQ (P=0.46) or SF-36 physical functioning scores (P=0.10) between treatment groups during the study (Table 3). Both treatment groups had higher walking distance and physical functioning scores at the end of the study than at baseline. No difference was found in COT between the rifalazil- and placebo-treated patients (P=0.48).

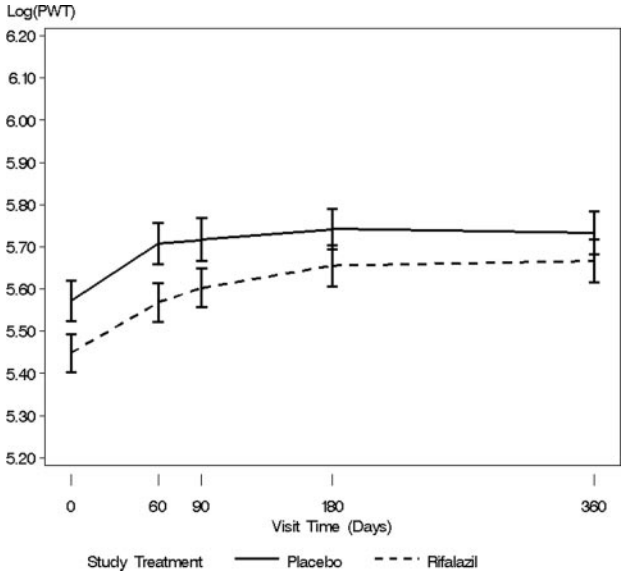

Figure 2. Primary end point: log-transformed PWTs. Least-squares mean±SE, intention-to-treat population (n=283). P=0.48.

Figure 3 shows the log-transformed PWT by country. Although no evidence was found that treatment influenced the time course of PWT for any of the countries (P=0.92), country was a significant predictor of PWT (P<0.01). The 41 subjects from Brazil had the longest PWT; the subjects from Russia had the shortest PWT.

Safety

A total of 955 adverse events were reported during the 360-day trial, with 53% of these occurring in rifalazil-treated patients. Table 4 shows the most frequent adverse events and serious adverse events reported by study subjects in the first 180 days of the trial.

Thirty-two combined cardiovascular events were adjudicated during the trial, 16 in each treatment group. Figure 4 shows a Kaplan-Meier plot of the time to combined cardiovascular events for the safety population. No difference was found in the time to event as assessed by the log-rank statistic (P=0.91) during the 360-day follow-up. Sensitivity analyses conducted on the intent-to-treat population, for best- and worst-rank scenarios and assessed at day 180, confirmed this result.

Discussion

This study did not demonstrate a benefit of rifalazil on PWT or questionnaire-assessed functional status in patients with inter-

Table 2. Primary End Point: PWT From Baseline to Day 180

	Rifalazil (n=145)		Placebo (n=138)		
	Natural Log (SD)	Gmean (95% CI), s	Natural Log (SD)	Gmean (95% CI), s	*P**
Baseline	5.45 (0.54)	232.4 (212.7–254.0)	5.57 (0.56)	262.8 (239.0–289.0)	
Day 180 (LOCF)	5.65 (0.58)	285.1 (259.2–313.7)	5.73 (0.56)	308.5 (280.4–339.4)	
Change in Gmean, %		23 (15–31)		18 (11–26)	
Change in log	0.20 (0.39)		0.16 (0.37)		0.38

Gmean indicates geometric mean; LOCF, last postbaseline observation carried forward to day 180.

*From a *t* test comparing the change in log value from baseline to day 180 between rifalazil and placebo.

Table 3. SF-36 and WIQ Quality-of-Life Scores for the Intention-to-Treat Population

	Walking Distance (WIQ)			Physical Functioning (SF-36)		
Visit	Rifalazil (n=145)	Placebo (n=138)	*P*, Treatment-by-Time Interaction	Rifalazil (n=145)	Placebo (n=138)	*P*, Treatment-by-Time Interaction
Baseline						
n	143	137	0.46	145	137	0.10
LS mean±SE	29.8±2.0	29.3±1.9		47.7±1.5	50.5±1.5	
Day 90						
n	137	124		137	124	
LS mean±SE	35.8±2.2	37.8±2.5		53.2±1.5	52.0±1.6	
Day 180						
n	136	124		136	124	
LS mean±SE	35.8±2.2	39.2±2.4		51.5±1.4	52.1±1.5	
Day 360						
n	129	121		130	122	
LS mean±SE	37.2±2.3	39.5±2.3		52.6±1.6	52.1±1.6	

LS mean indicates least-squares mean from mixed model.

mittent claudication. The study had >90% power to detect a 25% difference in PWT between groups. Furthermore, the lack of difference in the effect of treatment on the time course of PWT across countries reflects the homogeneity of the primary outcome measure in this international trial. No major safety concerns were raised, but the study was underpowered to detect any difference in cardiovascular events between groups.

Treatment options for patients with intermittent claudication are limited. The American College of Cardiology/American Heart Association guidelines for the management of PAD advise supervised exercise rehabilitation and cilostazol.[8] Supervised exercise rehabilitation may increase PWT by 180%[9] but is not reimbursed by the Center for Medicare and Medicaid Services and is not widely available. Cilostazol, a phosphodiesterase III inhibitor, improves PWT by ≈50%.[10] In a meta-analysis of 6 randomized trials, the mean improvement in walking distance ranged from 50 to 70 m in patients treated with cilostazol.[11] Endovascular and surgical revascularization may be considered in patients with disabling claudication who are not responsive to exercise therapy and cilostazol (American College of Cardiology/American Heart Association guidelines).[8] However, endovascular interventions, particularly for patients with disease affecting femoropopliteal and tibioperoneal arteries, suffer from limited durability. Surgical revascularization is associated with significant morbidity that does not justify its use in patients with stable claudication symptoms. Thus, a need exists to identify novel and safe medical therapies for treatment of patients with intermittent claudication.

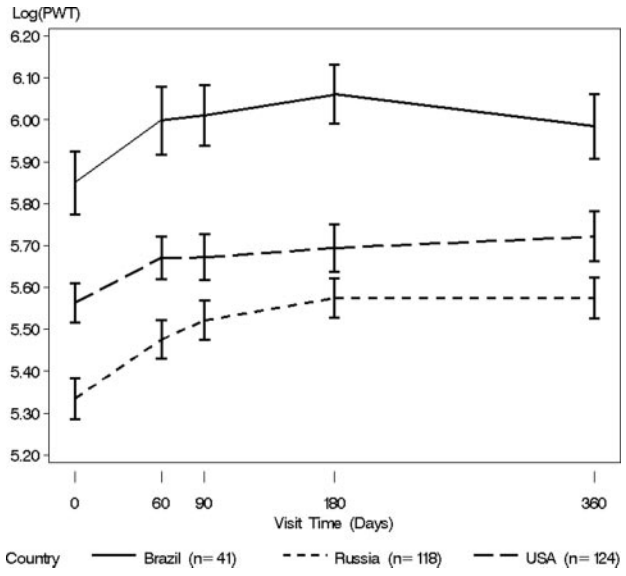

Figure 3. Primary end point reported by country of origin. Least-squares mean±SE, intention-to-treat population (n=283). Country *P* value <0.01.

The association of chronic infection with *C pneumoniae* and atherosclerosis was first described in 1988.[12] Seroepidemiological studies established the association between this pathogen and coronary artery disease.[13,14] It has been shown that *C pneumoniae* invades the arterial wall and can be found in the vascular intima and plaque, residing in monocytes within the vessel wall.[15] There, it produces a multitude of effects that may contribute to the progression of atherosclerosis, including alterations in endothelial function, increases in low-density lipoprotein oxidation and plaque burden, and vascular smooth muscle proliferation through upregulation of intracellular adhesion molecules and inflammatory cytokine production.[16–20] Thirty-five clinical studies have been published in this area, predominantly evaluating whether antibiotic therapies directed at *C pneumoniae* may result in a positive impact on atherosclerosis burden and clinical events. The results of these studies have been contradictory.

Several large multicenter studies in patients with coronary artery disease, including the Antibiotic Treatment of *Chlamydia pneumoniae* After Acute Coronary Syndromes (PROVE-IT),[21] Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders (WIZARD),[22] and Azithromycin for the Secondary Prevention of Coronary Events (ACES)[23] trials, which collectively involved almost 16 000 patients, have found no clinical benefit. PROVE-IT evaluated patients with acute

Table 4. Most Frequent Adverse Events and Serious Adverse Events by Treatment Group From Randomization to Day 180*

MedDRA Preferred Term	Rifalazil (n=153), n (%)	Placebo (n=144), n (%)	Relative Risk (95% CI)
Adverse event			
Headache	17 (11.1)	8 (5.6)	2.00 (0.89–4.49)
Pyrexia	12 (7.8)	3 (2.1)	3.76 (1.08–13.07)
Pain in extremity	10 (6.5)	13 (9.0)	0.72 (0.33–1.60)
Back pain	10 (6.5)	8 (5.6)	1.18 (0.48–2.90)
Arthralgia	10 (6.5)	5 (3.5)	1.88 (0.66–5.37)
Diarrhea	8 (5.2)	7 (4.9)	1.08 (0.40–2.89)
Dizziness	8 (5.2)	6 (4.2)	1.25 (0.45–3.53)
Muscle spasms	7 (4.6)	3 (2.1)	2.20 (0.58–8.33)
Rash	7 (4.6)	2 (1.4)	3.29 (0.70–15.60)
Fatigue	7 (4.6)	2 (1.4)	3.29 (0.70–15.60)
Nausea	6 (3.9)	6 (4.2)	0.94 (0.31–2.85)
Influenza	5 (3.3)	2 (1.4)	2.35 (0.46–11.94)
Nasopharyngitis	5 (3.3)	2 (1.4)	2.35 (0.46–11.94)
Asthenia	5 (3.3)	1 (0.7)	4.71 (0.56–39.80)
Paresthesia	2 (1.3)	6 (4.2)	0.31 (0.06–1.53)
Serious adverse event			
PAD	2 (1.3)	2 (1.4)	0.94 (0.13–6.59)
Carotid artery stenosis	2 (1.3)	0 (0.0)	
Angina, unstable	1 (0.7)	2 (1.4)	0.47 (0.04–5.13)
Arteriosclerosis, coronary artery	1 (0.7)	1 (0.7)	0.94 (0.06–14.91)
Chest pain	1 (0.7)	1 (0.7)	0.94 (0.06–14.91)
Postoperative wound infection	1 (0.7)	1 (0.7)	0.94 (0.06–14.91)

MedDRA indicates *Medical Dictionary for Regulatory Activities*. Data are the number and percent of patients per treatment group with reported event. Relative risk is calculated as risk in the rifalazil group divided by the risk in the placebo group.

*Day 180 visit may have occurred up to 3 weeks after the nominal visit day (ie, up to 201 days after randomization).

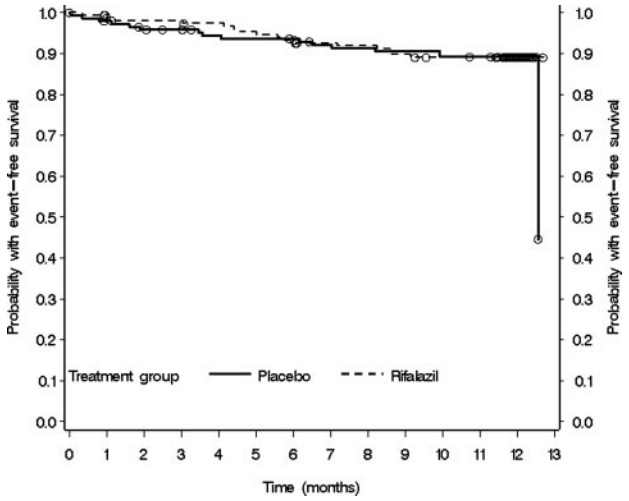

Figure 4. Time to combined adverse cardiovascular end point based on randomized patient group. Safety population (n=297). Log rank P=0.9098.

coronary syndromes within 10 days of randomization with gatifloxacin versus placebo for 2 years. WIZARD studied patients with previous myocardial infarction 6 weeks before randomization with azithromycin or placebo for 3 days. ACES evaluated patients with stable coronary artery disease randomized to once-weekly therapy with azithromycin versus placebo for 1 year. These studies assessed the impact of antibiotic therapy on major adverse cardiac end points of death, myocardial infarction, stroke, unstable angina, revascularization, or readmission to the hospital. Despite antibiotic therapy, all 3 trials demonstrated no reduction in coronary events.

Several trials have specifically addressed the impact of anti-Chlamydial antibiotic therapy in patients with PAD. Some have demonstrated a positive impact of antibiotic therapy on end points.[24] Krayenbuehl et al[25] studied 97 male PAD patients and randomized 40 with antibody titer–positive *C pneumoniae* infection to either daily roxithromycin treatment or placebo for 1 month. After a mean follow-up of 2.7 years, a reduction was seen in the number of subsequent peripheral arterial interventions in the antibiotic treatment group. In addition, absolute walking distance had improved at the end of the trial in those patients who did not undergo an intervention. Recently, Joensen et al[26] evaluated 507 patients with PAD randomized to roxithromycin or placebo for 28 days who were followed up for a mean of 2 years. The primary composite end point of progression of PAD, need for revascularization, or amputation was not different between the roxithromycin and placebo groups. Only 55% of actively treated patients were seropositive for *C pneumoniae* infection. Vainas et al[27] studied 509 patients with PAD (88% with intermittent claudication) randomized to 3 days of azithromycin or placebo. Fifty-two percent of the cohort were seropositive for *C pneumoniae*. In this series, seropositive patients had a significantly higher risk of adverse cardiovascular events (other than mortality). Patients treated with azithromycin experienced similar cardiovascular events and death rates compared with the placebo-treated group.

In view of these conflicting data, the PROVIDENCE-1 trial was designed to assess the efficacy of a potent anti-Chlamydial antibiotic, rifalazil, on walking distance and quality of life among patients with intermittent claudication who are seropositive to *C pneumoniae*. Treatment of PAD patients who are seropositive for *C pneumoniae* with rifalazil did not improve their PWT compared with placebo. In addition, no relationship was found between treatment of *C pneumoniae* infection and walking ability or quality of life in patients with PAD.

From these results and those of previous trials of antibiotic therapy directed against *C pneumoniae*, no compelling reason exists to study this antibiotic class of agents further in patients with atherosclerotic vascular disease. The body of evidence demonstrates a lack of benefit on cardiovascular event reduction or functional outcomes.

Source of Funding

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CLINICAL PERSPECTIVE

This study provides data from an international, multicenter, randomized clinical trial assessing the impact of anti-Chlamydial therapy on walking distance among patients with peripheral artery disease. Several studies have suggested that anti-Chlamydial therapy may reduce the need for peripheral arterial revascularization; however, Prospective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication and Other Endpoints in *Chlamydia pneumoniae* Seropositive Patients (PROVIDENCE-1) is the first large-scale randomized prospective study to evaluate the effect of this therapy on exercise walking distance. No benefit was found in rifalazil-treated patients compared with placebo-treated patients. In addition, no benefit was observed in any subset of patients. Therefore, PROVIDENCE confirms the lack of therapeutic benefit of anti-Chlamydial therapy as treatment of patients with intermittent claudication caused by peripheral artery disease.

Anti-Chlamydial Antibiotic Therapy for Symptom Improvement in Peripheral Artery Disease: Prospective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication and Other Endpoints in Chlamydia pneumoniae Seropositive Patients (PROVIDENCE-1)

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