

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 21, 2005

VOL. 352 NO. 16

Azithromycin for the Secondary Prevention of Coronary Events

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ABSTRACT

BACKGROUND

Epidemiologic, laboratory, animal, and clinical studies suggest that there is an association between *Chlamydia pneumoniae* infection and atherogenesis. We evaluated the efficacy of one year of azithromycin treatment for the secondary prevention of coronary events.

METHODS

In this randomized, prospective trial, we assigned 4012 patients with documented stable coronary artery disease to receive either 600 mg of azithromycin or placebo weekly for one year. The participants were followed for a mean of 3.9 years at 28 clinical centers throughout the United States.

RESULTS

The primary end point, a composite of death due to coronary heart disease, nonfatal myocardial infarction, coronary revascularization, or hospitalization for unstable angina, occurred in 446 of the participants who had been randomly assigned to receive azithromycin and 449 of those who had been randomly assigned to receive placebo. There was no significant risk reduction in the azithromycin group as compared with the placebo group with regard to the primary end point (risk reduction, 1 percent [95 percent confidence interval, -13 to 13 percent]). There were also no significant risk reductions with regard to any of the components of the primary end point, death from any cause, or stroke. The results did not differ when the participants were stratified according to sex, age, smoking status, presence or absence of diabetes mellitus, or *C. pneumoniae* serologic status at baseline.

CONCLUSIONS

A one-year course of weekly azithromycin did not alter the risk of cardiac events among patients with stable coronary artery disease.

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N Engl J Med 2005;352:1637-45.
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AN ASSOCIATION BETWEEN *CHLAMYDIA pneumoniae* and atherosclerosis, originally suggested by seroepidemiologic studies,^{1,2} was confirmed by a series of investigations demonstrating the presence of the organism in atherosclerotic lesions by four different methods.³⁻⁶ The etiologic or pathogenic significance of this association needs to be determined. Through basic-science studies of possible mechanisms and animal-model studies of atherosclerosis, data on the role of *C. pneumoniae* in atherosclerosis have accumulated.^{7,8}

The presence of *C. pneumoniae* in atherosclerotic lesions raises the possibility that antibiotic treatment might have a favorable effect on the course of coronary heart disease. A trial of antibiotic treatment in humans would be justified because of the public health importance of coronary heart disease. Moreover, it should be safe for the participants. Prior studies of both short- and long-term administration of macrolide antibiotics, including azalides, have shown few adverse reactions.^{9,10} Chlamydiae have not developed resistance against macrolide antibiotics, but long-term antibiotic therapy could contribute to resistance in other organisms. However, the risk that resistant bacteria might emerge during the trial was offset by the current practice among some physicians of providing antibiotic treatment for coronary heart disease in the absence of any established benefit.¹¹

METHODS

STUDY POPULATION

We conducted a randomized, double-blind, placebo-controlled trial at 28 centers in the United States. Men and women 18 years of age or older who had documented, stable coronary heart disease (defined as a previous myocardial infarction documented on the basis of enzyme-related criteria, angiographic evidence of at least 50 percent stenosis of a coronary artery, or previous coronary revascularization) were eligible. Patients were excluded if during the preceding three months they had had a myocardial infarction, undergone coronary revascularization, or been hospitalized for unstable angina. Additional reasons for exclusion were severe cardiac disease (New York Heart Association class III or IV congestive heart failure or stage III or IV angina), allergy to macrolide antibiotics, clinically significant renal or hepatic dysfunction, cancer, ongoing antibiotic therapy, or immunosuppression.

Written informed consent was obtained from all the participants.

TREATMENT AND FOLLOW-UP

Patients were enrolled in the Azithromycin and Coronary Events Study (ACES) between April 1999 and May 2000, and follow-up concluded on December 31, 2003. Participants were randomly assigned to receive either a 600-mg azithromycin tablet or a matching placebo tablet once weekly for one year. Azithromycin was chosen for treatment because of its proven efficacy against chlamydial infection and its long intracellular half-life, which allowed once-weekly dosing. Participants and all site investigators remained blinded to the treatment assignment through the end of follow-up and data collection.

Participants were interviewed in person or by telephone 3 weeks, 6 weeks, and 3, 6, 9, and 12 months after enrollment to identify adverse events and study outcomes and to ascertain their compliance with the study medication. After the first year, participants were interviewed approximately every six months until the end of follow-up to identify outcomes.

END POINTS

The primary end point was a composite of the first occurrence of any of the following: death due to coronary heart disease, nonfatal myocardial infarction, a percutaneous or surgical coronary revascularization procedure, or hospitalization for unstable angina. The members of a clinical endpoint committee, who were blinded to the treatment-group assignment, adjudicated the end points. Two committee members adjudicated each end point separately, and if there was disagreement, a third member resolved the difference.

Myocardial infarction was defined by hospitalization with a clinical syndrome compatible with infarction and either the development of a new pathologic Q wave or diagnostic elevations in the creatine kinase MB level (or troponin level if creatine kinase MB results were not available) above the upper limit of normal for the treating institution. It was also diagnosed in patients resuscitated after cardiac collapse with creatine kinase MB or troponin levels greater than the upper limit of the normal range. Myocardial infarction was also diagnosed according to the following criteria in patients who had undergone revascularization: within the first 48 hours after coronary bypass surgery in patients with creatine kinase MB levels greater

than five times the upper limit of the normal range; within the first 48 hours after percutaneous revascularization in those with creatine kinase MB levels greater than three times the upper limit of the normal range; and after 48 hours in those who had undergone either procedure and had creatine kinase MB or troponin levels above the upper limit of the normal range.

Unstable angina was defined by hospitalization for new chest pain or changes in the patient's usual chest pain in combination with electrocardiographic ST-T wave changes indicative of ischemia or accompanied by elevations in enzyme markers not diagnostic of myocardial infarction.

Death due to coronary heart disease was defined as death believed to be the consequence of coronary atherosclerotic disease or death not definitively known to be due to a noncoronary cause. Death from cardiac causes included death due to arrhythmias, severe congestive heart failure, cardiogenic shock, or myocardial infarction. Unwitnessed sudden death in the absence of a noncoronary cause was assumed to be death from coronary heart disease. Death within 30 days after coronary revascularization was considered to be due to coronary heart disease, unless another cause unrelated to the procedure or to coronary disease was clearly identified.

Components of the primary end point were analyzed separately. Predefined secondary end points included stroke, cardiac collapse followed by resuscitation, carotid endarterectomy, peripheral revascularization, and death from any cause. Participants who had a nonfatal event were followed to the end of the trial so that the total rate of the individual events constituting the primary end point could be compared between the treatment groups.

LABORATORY TESTS

Blood specimens were obtained from all participants at enrollment. They were tested for the presence of *C. pneumoniae* antibody in the IgG and IgA serum fractions by the microimmunofluorescence test¹² and for total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

STATISTICAL ANALYSIS

Calculations

In the calculation of the sample size, it was assumed that the rate of the primary end point would

be 6.5 percent per year in the placebo group, on the basis of previous trials. With the use of this estimate, the planned sample size of 4000, with an average follow-up of 4.0 years, allowed 98 percent power to detect a 25 percent reduction and 85 percent power to detect a 20 percent reduction in the rate of the primary end point at a two-sided significance level of 0.05.

Data analyses were based on an intention-to-treat approach. In the primary analysis, the time to the primary end point in the azithromycin group was compared with that in the placebo group with use of the log-rank test. Components of the primary end point and secondary end points were similarly analyzed. Participants' data were censored on the date of the last contact or the date of death. Final visits occurred within a three-month period from October 1 through December 31, 2003. The Cox proportional-hazards model was used to compute hazard ratios and the percent risk reduction [$100 \times (1 - \text{the hazard ratio})$]. The curve representing the cumulative rate of the primary end point was estimated by the product-limit (Kaplan-Meier) method.

Safety Monitoring and Stopping Guidelines

The National Heart, Lung, and Blood Institute appointed an independent data and safety monitoring board. The study was conducted under an investigational-new-drug application with the Food and Drug Administration (FDA). The institutional review board at each site approved the protocol.

The data and safety monitoring board monitored the study for safety and efficacy. To preserve the overall type I error, a group sequential approach was used to determine interim monitoring boundaries for stopping the trial owing to a demonstration of the superiority of azithromycin over placebo with use of the log-rank test. Planned interim analyses were performed when approximately one quarter, one half, and three quarters of the expected number of events had occurred, at significance levels of 0.0017, 0.0020, and 0.0023. At each interim analysis, the data and safety monitoring board voted unanimously to continue the study.

Dr. Grayston designed the study with the assistance of Drs. Kronmal and Jackson. The data gathered at the 28 sites (listed in the Appendix) were collected and evaluated at Axio Research, under the direction of Ms. Borrowdale. Dr. Kronmal analyzed the data with assistance from Drs. Grayston and Jackson. Dr. Grayston and all the authors vouch for

the data and the analysis. All the authors contributed to the writing of the manuscript, under the direction of Dr. Grayston.

RESULTS

ACES enrolled 4012 patients; 2004 were randomly assigned to the azithromycin group and 2008 to the placebo group. Of those enrolled, one in the azithromycin group and two in the placebo group did not receive any study drug. Table 1 shows the char-

acteristics of the participants at enrollment. Fifty-six percent of the participants had had a myocardial infarction, and 89 percent had undergone a coronary revascularization procedure. Twenty-nine percent reported angina at rest, 28 percent had angina only on exertion, and 12 percent had congestive heart failure.

Only 86 of the participants (2 percent) withdrew consent or were lost to follow-up. They were divided approximately equally between the azithromycin group (44 participants) and the placebo group (42 participants). Ninety-seven percent of 45,363 scheduled follow-up visits were successfully completed. The median length of observation was 3.91 years in the azithromycin group and 3.92 years in the placebo group. Eighty-eight percent of the participants in the azithromycin group and 93 percent of those in the placebo group completed the one-year period of weekly treatment.

The frequency of the primary end point was 22.3 percent in the azithromycin group and 22.4 percent in the placebo group. There was a reduction of 1 percent in the risk of the primary end point in the azithromycin group (95 percent confidence interval, -13 to 13 percent). The curve representing the cumulative rate of the primary end point in each of the two groups over time is presented in Figure 1.

The proportion of participants with each of the individual events contributing to the primary end point is shown in Table 2. There was no significant difference between the azithromycin group and the placebo group in the frequency of any individual event. Table 3 shows the frequency of all of the primary and secondary outcome events throughout the study, regardless of whether they occurred after the participant had a prior event. Again, there was no difference between the groups with respect to the frequency of primary or secondary end-point events.

Subgroup analyses of the primary end point according to individual baseline characteristics considered to be coronary risk factors are shown in Figure 2. In these analyses, there were no significant differences between the azithromycin group and the placebo group in the risk of the primary end point. There was also no difference between the groups when other baseline characteristics, including angina at rest, angina on exertion, prior revascularization, and prior myocardial infarction were analyzed.

C. pneumoniae antibody status was determined

Table 1. Baseline Characteristics of Participants in ACES, According to Study Group.

Characteristic	Azithromycin (N=2004)	Placebo (N=2008)
Mean age (yr)	65	65
Male sex (%)	80	79
White race (%)*	87	87
Cigarette smoking (%)		
Never	26	28
Former	60	59
Current	14	13
History of hypercholesterolemia	84	81
History of hypertension	67	67
Diabetes mellitus	23	21
Peripheral vascular disease	12	10
Family history of early cardiovascular disease	47	46
Mean total cholesterol at enrollment (mg/dl)†	174.3	175.0
Angina (%)		
At rest	29	30
Only on exertion	28	28
Congestive heart failure	12	11
Percutaneous coronary revascularization	56	57
Coronary-artery bypass surgery	53	50
Any revascularization	90	88
Myocardial infarction	54	58
Medications at enrollment		
Aspirin	87	88
Statins	75	77
ACE inhibitor‡	34	36
Beta-blocker	59	60
Calcium-channel blocker	31	31

* Race was determined according to National Institutes of Health guidelines.

† To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

‡ ACE denotes angiotensin-converting enzyme.

by testing blood specimens obtained at enrollment. Twenty percent of the participants did not have antibody in the IgG serum fraction, and two thirds did not have IgA antibody. Neither IgG antibody nor IgA antibody was significantly associated with the risk of the primary end point in either the azithromycin or placebo group.

Symptoms reported by participants during interviews at intervals during the year of treatment and the number of participants who reported seeking medical care for these symptoms are shown in Table 4. Clinical or laboratory follow-up data on the reported symptoms were not obtained. Although participants assigned to receive placebo reported gastrointestinal symptoms with some frequency, these symptoms were more common among those assigned to receive azithromycin. However, participants who received placebo sought medical care for gastrointestinal symptoms as frequently as did those receiving azithromycin.

Hearing loss was reported more frequently in the azithromycin group. Hearing loss was included among the symptoms discussed during the interviews because of case reports of reversible hearing loss in patients treated with high doses of azithromycin for *Mycobacterium avium* complex infection.^{13,14} Only 12 of the participants reporting hearing loss sought medical care. Two of these participants, both in the placebo group, discontinued the weekly medication (one permanently and one temporarily). Of all the participants reporting hearing loss who either permanently or tempo-

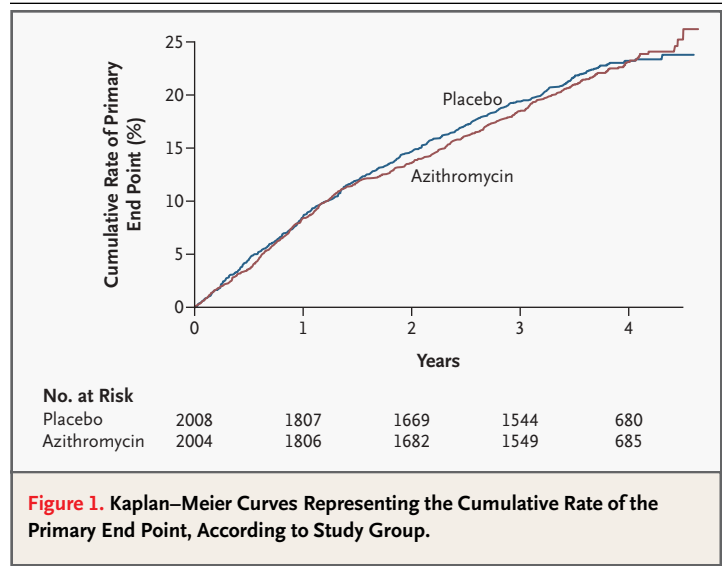


Figure 1. Kaplan–Meier Curves Representing the Cumulative Rate of the Primary End Point, According to Study Group.

rarily stopped taking their assigned medication, six were from the azithromycin group and six were from the placebo group.

Vaginal candidiasis was included among the symptoms discussed during the interviews, because it may be a side effect of long-term antibiotic treatment. Surprisingly, the symptom was more common in the placebo group, and all 12 of the women who reported receiving more than one course of treatment were from the placebo group. Thirty-four serious adverse events (12 in the azithromycin group and 22 in the placebo group) not included in

Table 2. Proportion of Participants with Each Event Contributing to the Primary End Point, According to Event and Study Group.*

Events in the Primary End Point	Azithromycin (N=2004)		Placebo (N=2008)	
	Events	Proportion of Participants	Events	Proportion of Participants
	no. (%)	%	no. (%)	%
Death due to coronary heart disease	46 (10)	2.3	49 (11)	2.4
Myocardial infarction	100 (22)	5.0	98 (22)	4.9
Percutaneous coronary revascularization	192 (43)	9.6	187 (42)	9.3
Coronary-artery bypass surgery	72 (16)	3.6	75 (17)	3.7
Hospitalization for unstable angina	36 (8)	1.8	40 (9)	2.0
Composite primary end point	446 (100)	22.3	449 (100)	22.4

* Because of rounding, percentages may not total 100.

Table 3. Proportion of Participants with Primary or Secondary End-Point Events, According to Type of Event and Study Group.*

Primary or Secondary End-Point Event	Azithromycin (N=2004)	Placebo (N=2008)	Percent Risk Reduction (95% CI)
	no. (%)		
Death due to coronary heart disease	65 (3.2)	75 (3.7)	13 (-21 to 38)
Myocardial infarction	136 (6.8)	130 (6.5)	-5 (-34 to 17)
Percutaneous coronary revascularization	264 (13.2)	259 (12.9)	-2 (-21 to 14)
Coronary-artery bypass surgery	117 (5.8)	110 (5.5)	-7 (-38 to 18)
Hospitalization for unstable angina	50 (2.5)	55 (2.7)	9 (-34 to 38)
Myocardial infarction or death from coronary heart disease	190 (9.5)	186 (9.3)	-2 (-26 to 16)
Death from any cause	143 (7.1)	132 (6.6)	-9 (-38 to 14)
Stroke	45 (2.2)	40 (2.0)	-13 (-73 to 26)
Cardiac collapse followed by resuscitation	13 (0.6)	8 (0.4)	NS
Carotid endarterectomy	37 (1.8)	30 (1.5)	NS
Peripheral revascularization	30 (1.5)	35 (1.7)	NS

* CI denotes confidence interval, and NS not significant.

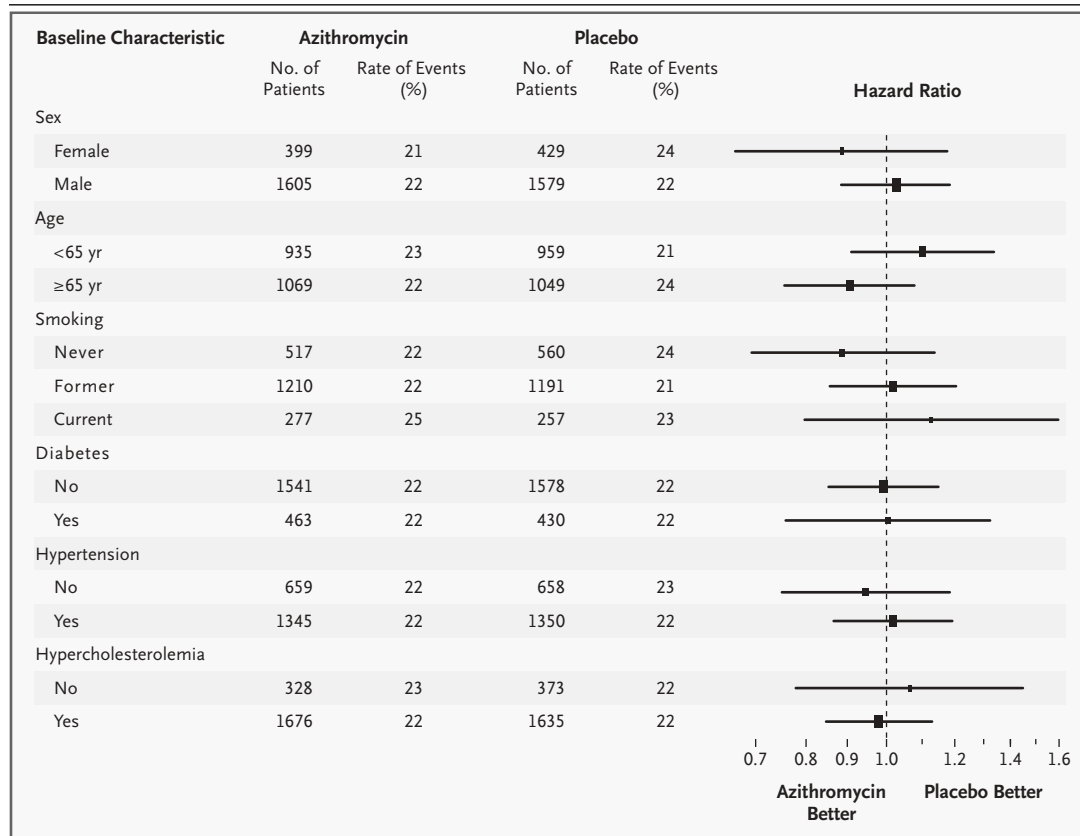


Figure 2. Risk of the Primary End Point Associated with Azithromycin Treatment, Stratified According to Baseline Characteristics Considered to Be Coronary Risk Factors.

The size of the rectangles is proportional to the reciprocal of the variance of the hazard ratio.

Table 4. Symptoms Reported by Participants during the One-Year Treatment Period.*

Symptom	No. of Participants with Symptom		P Value	No. of Participants Seeking Medical Treatment for the Symptom		P Value
	Azithromycin	Placebo		Azithromycin	Placebo	
Nausea	284	198	<0.001	45	37	NS
Abdominal pain	370	216	<0.001	58	62	NS
Diarrhea	724	446	<0.001	76	60	NS
Vomiting	62	63	NS	4	5	NS
Vaginal candidiasis	33	44	NS	16	34	0.01
Hearing loss	38	20	0.02	7	5	NS
Rash	122	116	NS	53	51	NS

* NS denotes not significant.

Table 4 were reported to the FDA because a relation to the treatment could not be ruled out.

DISCUSSION

This trial found that one year of weekly azithromycin therapy was not associated with any clinically significant benefit in the secondary prevention of coronary events. Azithromycin was associated with mild gastrointestinal symptoms. There was a greater number of reports of hearing loss in the azithromycin group, but the available data did not allow clarification of the clinical significance of these reports. More frequent vaginitis was reported in the placebo group, which is the opposite of the expected effect of long-term antibiotic treatment. It is possible that azithromycin provided therapy against bacterial vaginosis, but clinical or laboratory diagnostic data were not available.

Nine other clinical trials testing antibiotics for the secondary prevention of coronary heart disease have been published.¹⁵ Of these, only the WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and Its Related Disorders) trial¹⁶ was adequately powered to give a definite result. The others may be considered pilot trials because of their small sizes and short observation periods. Another deficit of most of the trials was their short treatment periods. Approximately equal numbers of the trials were reported to be positive and reported to be negative. In the WIZARD trial, azithromycin treatment was given once weekly for three months. Its results were similar to the findings of ACES, in that they also failed to support the use of antibiotic therapy for coronary heart disease. The WIZARD tri-

al did report some antibiotic protection from events during the first six months of the trial — a result not seen in ACES.

The ACES protocol required participants to have established coronary heart disease that had been stable for at least three months. Review of the study population revealed that 89 percent of patients had undergone at least one coronary revascularization procedure before the study and that more than half had angina. Most of the participants were receiving vigorous standard treatment for coronary heart disease. Events occurring during the trial might reasonably be attributed to destabilization and rupture of plaques, rather than extension of the atherosclerotic process with vessel narrowing.

What do the findings of the trial tell us about the association between *C. pneumoniae* and atherosclerosis? Assuming that treatment was adequate, they suggest that neither *C. pneumoniae* nor another organism susceptible to azithromycin plays an important role in events associated with late-stage coronary heart disease. However, since ACES was not designed to study the role of *C. pneumoniae* in the pathogenesis of atherosclerosis, the results of the trial do not tell us anything about a possible pathogenic role of *C. pneumoniae* in the early development or acceleration of atherosclerosis.

There have been clinical trials of antibiotic therapy directed at atherosclerotic changes in the carotid artery, peripheral arteries, and the aorta.¹⁷⁻²⁰ These trials were based on noninvasive measurements of changes in the arterial wall. They did not rely on analyses of events, but measurements in the arterial wall in each subject were included in the analysis. Each trial reported that antibiotic therapy

had a significantly favorable effect on the progression of disease. These positive results must be considered preliminary. However, if they can be repeated in studies with larger numbers of subjects, they will offer evidence suggesting that *C. pneumoniae* is involved in the pathogenesis of atherosclerotic occlusive disease.

The limited data available from antibiotic treatment of atherosclerosis in animal models have shown that if the antibiotic is given shortly after the *C. pneumoniae* is inoculated into the lung of the animal, the effect of *C. pneumoniae* on the acceleration of atherosclerosis is greatly reduced or eliminated. If the antibiotic is given later, there is much less or no reduction in the acceleration of atherosclerosis caused by *C. pneumoniae*.²¹⁻²³

Our study has several limitations, including the advanced stage of disease (described above), the possibility that the antibiotic does not reach the microorganism in the chronic lesions of atherosclerosis, the possibility that the treatment was not continued long enough or that the dose of antibiotic given was too small, and the possibility that the antibiotic was not sufficiently effective against *C. pneumoniae*. These limitations do not, for practical purposes, weaken the basic conclusion of this study that antibiotic treatment cannot be recommended for the treatment of chronic coronary heart disease.

This recommendation is confirmed by the results of the PROVE IT (the Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, reported elsewhere in this issue of the *Journal*.²⁴ PROVE IT did not find any significant protection from coronary events with antibiotic treatment. There were important differences between the PROVE IT trial and ACES. A different class of antibiotic, a new fluoroquinolone (gatifloxacin), was used in PROVE IT. The treatment schedule, though also prolonged, was intermittent, consisting of a 10-day course of therapy each month for a mean of 2 years. Moreover, the participants were recruited at the time of an acute coronary syndrome, and they were younger and had had less previous treatment for coronary heart disease than those in ACES. These differences broaden and strengthen the recommendation against antibiotic treatment for coronary heart disease that can be made on the basis of the ACES trial.

Supported by the National Heart, Lung, and Blood Institute and Pfizer.

Presented in part at the annual meeting of the European Society of Cardiology, Munich, August 30, 2004, and at the meeting of the European Society for Chlamydia Research, Budapest, Sept. 2, 2004.

Dr. Grayston reports having received grant support from Pfizer for ACES. Dr. Parisi reports having equity ownership in Pfizer. Dr. Crouse reports having received consulting fees and grant support from Pfizer. Dr. Knirsch is employed by Pfizer and reports having equity interest in the company.

APPENDIX

The ACES investigators are as follows: **Core investigators:** J.T. Grayston (principal investigator), L.A. Jackson (deputy director), R. Kronmal (biostatistician), and W.J. Kennedy (consultant), University of Washington, Seattle. **Investigators at clinical sites:** S. Ghaffari, Cleveland Clinic Foundation, Cleveland; E.G.V. Giardina, Columbia University College of Physicians and Surgeons, New York; J. Varghese, George Washington University, Washington, D.C.; L.A. Jackson, Group Health, Seattle; W. Kussmaul, Drexel University College of Medicine, Philadelphia; M. Alam, Henry Ford Hospital, Detroit; E. Caracciolo, Hospital of St. Raphael, New Haven, Conn.; J.B. Muhlestein, LDS Hospital, Salt Lake City; A.F. Parisi, Miriam Hospital, Providence, R.I.; D. Vorchheimer, Mount Sinai Medical Center, New York; M. Gheorghade, Northwestern University Medical School, Chicago; J.B. Kostis, Robert Wood Johnson Medical School, New Brunswick, N.J.; H. Valantine, Stanford University Medical Center, Palo Alto, Calif.; J.D. Cohen, Saint Louis University, St. Louis; P.F. Cohn, State University of New York, Stony Brook; W.J. Rogers, University of Alabama at Birmingham, Birmingham; G.A. Ewy, University of Arizona Sarver Heart Center, Tucson; C.R. Conti, University of Florida, Gainesville; R.M. Benitez, University of Maryland School of Medicine, Baltimore; B. Hunninghake, University of Minnesota, Minneapolis; S.C. Smith, University of North Carolina, Chapel Hill; M.B. Elam, University of Tennessee Health Sciences Center, Memphis; R. O'Rourke, University of Texas, San Antonio; M. Corson, University of Washington, Seattle; J.R. Crouse, Wake Forest University School of Medicine, Winston-Salem, N.C.; R. Krone, Washington University School of Medicine, St. Louis; J.P. O'Bryan, Southwest Florida Heart Group, Fort Myers; and G. Albin and A.C. Chiu, St. Mary's/Duluth Clinic Health System, Duluth, Minn. **Data coordinating center:** Axio Research, Seattle; S.L. Borrowdale (project director), P. Butler (project coordinator), A. Diaz (project coordinator), and R. Nordfors (programmer). **Executive committee:** S.L. Borrowdale, J. Cohen, J. Thomas Grayston (chair), L.A. Jackson, R. Kronmal, J. B. Muhlestein, A.F. Parisi, W.J. Rogers, and E. Schron. **End-point-adjudication committee:** R.M. Benitez, E. Caracciolo, J.R. Crouse (chair), M. Gheorghade, R. Krone, M.A. Lauer, A.F. Parisi, and D. Vorchheimer. **Central laboratory:** University of Vermont, Colchester; R. Tracy, E. Cornell, and N. Jenny. **Chlamydia laboratory:** C.C. Kuo and L. Campbell, Department of Pathobiology, University of Washington, Seattle. **Data safety and monitoring board:** E. Alderman (chair), J. T. Bigger, G. Byrne, A. Curtis, M. Foulkes, T.C. Quinn, R.M. Robertson, and J.T. Summersgill. **Medical monitor:** K. Gupta.

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