Mounting evidence supports the contention that atherosclerosis is an inflammatory disease. Recently a possible role for infectious microorganisms has gathered attention. Chlamydia pneumoniae is one possible pathogen. If C. pneumoniae is a target organism, antibiotics with antichlamydial activity may be able to ameliorate plaque instability. The WIZARD trial is a secondary prevention study that is assessing the impact of a 3-month course of azithromycin compared with placebo on the progression of clinical coronary heart disease. The study will enroll 3300 patients who have had a prior myocardial infarction and who have a C. pneumoniae IgG titer of \( \geq 1:16 \). The primary end point is a composite of time to either recurrent myocardial infarction, death, a revascularization procedure, or hospitalization for angina. This study is the first of a series of adequately powered clinical trials that will attempt to bridge insights from preclinical investigations to interventions applicable to patient care.

Cardiovascular disease related to atherosclerosis is the most common cause of death in Western society. Recent progress in understanding the pathogenesis of atherosclerosis has uncovered the central role of inflammation in the etiology of this most common affliction [1]. Activated macrophages concentrate modified cholesterol within the arterial wall while releasing a variety of products that impair local cellular function and destabilize the thin fibrous cap covering the atheroma. Subsequent acute rupture of the plaque leads to clot formation with disruption of distal blood flow and infarction of dependent tissue. Circulating inflammatory markers are elevated prior to myocardial infarction and can be predictive of future risk of clinical disease [2]. But what is driving this inflammation? Oxidized low-density lipoprotein alone can stimulate macrophages [3]. Local arterial injury from mechanical trauma or toxins also initiates an inflammatory response [4]. Recently, the role of infectious agents in the pathogenesis of atherosclerosis has gathered attention.

In 1988, it was found that patients enrolled in the Helsinki Heart Study who developed a cardiovascular event were more likely to have elevated titers to Chlamydia pneumoniae than were those who remained event free [5]. Since then, more than a dozen other studies have confirmed and expanded these observations. Histologic examination of atheromatous tissue sections have shown that on average 60% of atheromas contain evidence of C. pneumoniae by either immunohistochemical staining, polymerase chain reaction (PCR), electron microscopy, or culture [6]. Animal models of disease show that intranasal infection with this organism results in a pathologic response in the arterial wall, including cellular infiltration with macrophages and T cells and the accumulation of cholesterol [7]. In addition to this experimental evidence, infection with Chlamydia trachomatis, either in the conjunctiva where it results in blinding trachoma or in the genital tract, results in a chronic inflammatory condition which at face value has pathologic features similar to that described in atherosclerosis. None of these findings provides evidence of a causal role of C. pneumoniae in atherosclerosis but, as a family of observations, the association appears to be more than simply circumstantial.

If it is possible that C. pneumoniae infection of the arterial wall results in an inflammatory state that drives a local accumulation of cholesterol, can intervention with an antibiotic active against this pathogen prevent its clinical sequela? In order to consider such a trial, a number of issues must be addressed.

Given that C. pneumoniae Is Found in Only 60% of Plaques, How Should Patients Be Selected for Antibiotic Therapy?

C. pneumoniae is an organism which, on the basis of serologic data, is likely to have infected most people by the time they are 80 years old [8, 9]. Serology cannot distinguish between previous exposure and active disease so its use as a discriminating tool to identify an actively infected population is limited. Obtaining arterial tissue is also very problematic. It would be logistically impossible to obtain tissue from thousands of subjects with coronary disease, even if it were surgically feasible. Histologic assessments of the target tissue are therefore not possible. Recently, there has been progress in examining tissue...
by PCR, including circulating white blood cells, as a surrogate for active infection with *C. pneumoniae* [10, 11]. While this procedure still needs to be validated and a clinical correlation confirmed, it holds promise as a future method for selecting patients. For the moment, selection of patients will be limited to clinical criteria surrounding the underlying disease.

**As *C. pneumoniae* Is Associated with Chronic Disease and the Organism Sometimes Persists Even after Appropriate Antibiotic Therapy, How Are the Antibiotic Dose and Duration of Therapy Selected?**

A number of antibiotics, including macrolides, tetracyclines, and quinolones, have in vitro activity against *C. pneumoniae* [12–14] and some of these compounds have clinical efficacy for acute disease [9]. Treatment regimens for chronic disease are less well understood and other considerations may be relevant [15]. An intracellular stage of *C. pneumoniae* that persists within the cell after antibiotic use can appear in vitro and may be associated with chronicity of infection [16]. This persistent body exists in a state of low metabolic activity and as a consequence may be less amenable to therapies typically used to inhibit chlamydiae. It is not known how long the organism can remain in this state, but if it does cycle back to a metabolically more active form, antibiotic may need to be present to inhibit critical functions. If, however, the organism remains in this persistent state indefinitely, its eradication may not be possible. In this case, antibiotic therapy may only suppress replication and, possibly, antigenic expression responsible for the local inflammatory state. In either case, longer durations of antibiotic exposure may be needed to maximize clinically relevant activity.

**If Antibiotic Therapy Effectively Reduces the Likelihood of Cardiovascular Events in Persons with Coronary Artery Disease, Will This Be Evidence that *C. pneumoniae* Is Responsible for Atherosclerotic Disease?**

At the present level of understanding of atherosclerosis, an antibiotic intervention study for secondary prevention will have two broad objectives. On one hand, these studies examine the straightforward question of the comparative activity of intervention A relative to intervention B. In addition, these trials will attempt to explore the mechanism behind any observed effect. While clinical trials with antibiotics for treatment of atherosclerotic disease are likely to make clear statements pertaining to the relative efficacy of each intervention, they will be less likely to definitively elucidate the mechanism behind that effect. The tools available to explore the role of chlamydiae in treatment of atherosclerosis include serology, culture, and histologic assessments of tissue by immunohistochemistry and PCR. Given that serologic indices may not resolve with treatment, that obtaining samples of coronary arteries is not feasible and that the antibiotics under consideration have broad antimicrobial activity, it is likely that a positive effect of antibiotics would tighten the association between *C. pneumoniae* without definitively establishing causality.

**The Weekly Intervention with Zithromax (Azithromycin) for Atherosclerosis and its Related Disorders (WIZARD) Trial**

**Study objectives.** The primary objective of this study is to assess the efficacy of azithromycin in preventing the progression of clinical coronary artery disease in subjects who have a myocardial infarction >6 weeks before randomization. Clinical coronary artery disease is defined as a recurrent myocardial infarction, all cause mortality, a revascularization procedure, or a hospitalization for angina.

**Eligibility criteria** (table 1). Patients eligible for inclusion in the study must be >18 years old. Women are to be without childbearing potential or to use contraception considered appropriate by the investigator. Study subjects must have a myocardial infarction >6 weeks before randomization as documented by one set of elevated creatinine phosphokinase MB isoenzymes or by electrocardiography. To be eligible for randomization, patients must have an IgG titer to *C. pneumoniae* >1:16 from the reference laboratory from a blood sample obtained at the screening visit and be expected to survive >6 months. They must provide written informed consent. Patients will be excluded from the trial if they are expected to require a revascularization procedure (e.g., coronary artery bypass grafting or angioplasty) within 90 days or if they have undergone a cardiac artery bypass graft or angioplasty within the prior 6 months.

Study subjects cannot have a history of hypersensitivity to macrolides or azithromycin and must be free of any condition that could be expected to prevent them from completing the trial. Patients with an underlying condition that would require treatment with systemic antibiotics during the study period are not eligible for enrollment nor are those who receive a course of systemic antibiotics within the prior 3 months. Participation in another investigational trial without the consent of the study monitor is prohibited.

**Screening process.** Persons who satisfy the inclusion and exclusion criteria are eligible for a screening visit where informed consent is obtained. Demographic information and a detailed medical history, including a review of pertinent cardiac risk factors, are then obtained. Serum is obtained for *Chlamydia* serologic testing and for banking for future use.

**Randomization.** After an interval not to exceed 30 days, patients are randomized to receive study drug if the *C. pneumoniae* IgG titer is >1:16. Randomization is performed in blocks of drug supplied to each participating site.

**Drug therapy.** Patients are given either azithromycin (Zithromax; Pfizer, New York) 600 mg 4 times a day for the first 3 days then 600 mg once weekly for the next 11 weeks or a
matching placebo. Azithromycin has activity in vitro against chlamydiae and clinical efficacy in treatment of respiratory tract disease. It also demonstrates a unique pharmacokinetics profile. A 600-mg once-weekly dose will provide intracellular levels that exceed the MIC90 of C. pneumoniae by 10-fold for 7 days (figure 1) [17]. It has no significant P450 interactions with medications that are commonly used in patients with cardiovascular disease.

The safety of azithromycin has been extensively studied with different dosing regimens. In phase III trials leading to the registration of the drug for respiratory tract infections and sexually transmitted diseases, including those due to C. trachomatis, 0.7% of patients discontinued dosing for side effects considered related to drug. Side effects noted during these trials include nausea (3%), diarrhea (5%), and abdominal pain (3%). Gastrointestinal side effects are dose-proportional. In subjects given a single 1-g dose, about 17% of subjects note side effects.

Drugs to treat respiratory tract infections, including C. pneumoniae infections, are given as 1.5-g doses over 3–5 days. A single 1-g dose is efficacious for treatment of C. trachomatis. Data obtained from other programs have expanded the safety experience beyond the total 1.5-g dose. In studies of the prophylaxis of disseminated Mycobacterium avium disease in human immunodeficiency virus–infected patients, a single 1200-mg dose was given once weekly for periods up to 2 years. Over the course of about 1 year of dosing, 8.2% of those receiving azithromycin and 2.3% of those receiving placebo discontinued therapy for reasons related to drug, highlighting the mild-to-moderate nature of the majority of side effects experienced. In these long-term prophylaxis studies, the incidence of hearing-related complaints was no higher for subjects receiving azithromycin than those given placebo or the active comparator [18, 19].

Monitoring during the trial. Patients are to be seen at baseline and weeks 4 and 12 while receiving antibiotic therapy and then every 3 months for the rest of the trial. At baseline, all patients undergo an abbreviated physical examination. Laboratory examinations include serum chemistries, a complete blood count, measurement of C-reactive protein, a lipid profile, and a baseline 12-lead electrocardiogram. A listing of concomitant medications is obtained and a health resource utilization questionnaire completed. The visits at weeks 6 and 12 include a review of adverse events, concomitant medications, compliance with study therapy, and the occurrence of any study-dictated end points. Safety laboratory examinations for chemistry and hematology, including measurements of C-reactive proteins, are performed at week 12. After the first 3 months, information is collected on adverse events, concomitant medications, employment status, end points, and health resource utilization. Serum is banked at weeks 12, 24, and 52. Monitors from the sponsor perform site visits to verify source documentation while subjects are on therapy and at the primary end point.

End-point committee. All events that contribute to the primary composite end point are adjudicated by an end-point committee comprised of study investigators to ensure compliance with criteria prespecified in the protocol. This review is done in a blinded fashion.

Duration of trial. The trial duration is based on the occurrence of a prespecified total number of primary end points. Given an anticipated event rate in this patient population on placebo and anticipating a certain reduction in events on the active treatment regimen, the trial is expected to take up to 3 years to complete.

Sample size determination. On the basis of data reported in the literature, the event rate for the primary end point in subjects >=6 weeks after a myocardial infarction is estimated to be 8%. A total of 3000 subjects will provide 90% power, with two-sided 5% significance level, to detect at least a 25% difference in the coronary artery event rates between the placebo and the combined azithromycin groups. Total enrollment will be increased to at least 3300 to allow for a 10% drop-out rate. This calculation is based on the assumptions that the survival

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<th>Table 1. Eligibility criteria for WIZARD Trial.</th>
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<tr>
<td>Criteria</td>
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<tr>
<td>Inclusion</td>
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<tr>
<td>Outpatient men and women &gt;=18 years old</td>
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<tr>
<td>Women must be without childbearing potential or use contraception considered appropriate by investigator</td>
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<td>Definite myocardial infarction &gt;=6 weeks earlier documented by</td>
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<td>(1) 1 set of elevated creatinine phosphokinase-MB isoenzymes or</td>
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<td>(2) electrocardiography</td>
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<td>IgG titer to C. pneumoniae &gt;=1:16 from reference laboratory</td>
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<tr>
<td>Expected to survive &gt;=6 months</td>
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<tr>
<td>Written informed consent required</td>
</tr>
<tr>
<td>Exclusion</td>
</tr>
<tr>
<td>Expected to require revascularization within 90 days</td>
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<tr>
<td>Hypersensitivity to macrolides or azithromycin</td>
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<tr>
<td>Any condition that could be expected to prevent subject from completing trial</td>
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<tr>
<td>Underlying condition that would require subject to take systemic antibiotics during study period</td>
</tr>
<tr>
<td>Cardiac artery bypass graft or angioplasty within prior 6 months</td>
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<tr>
<td>Course of systemic antibiotics within prior 3 months</td>
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<td>Participation in another investigational trial without consent of study monitor</td>
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Reference:

[17] S574 Dunne JID 2000;181 (Suppl 3)
Figure 1. Mean plasma and leukocyte concentrations of azithromycin following 1-h intravenous (IV) infusion and oral administration of 1200 mg to human immunodeficiency virus-positive subjects. Reprinted with permission from [17].

distributions will follow the exponential distribution, a constant accrual rate of about 500 subjects per month over the first 6 months, and a time-to-event comparison using the log-rank statistic.

**Primary outcome variable.** The primary end point for the comparison of azithromycin and placebo is the time to the occurrence of one of the following events: a recurrent myocardial infarction, mortality of any cause, a revascularization procedure, or hospitalization for angina. The selection of this composite end point is based on experience in other large cardiovascular trials of secondary prevention [20–23]. Secondary analyses will be performed around various subgroups and around the occurrence of the individual components of the composite end point, cardiovascular death and sequential combinations of the primary composite, including but not limited to recurrent myocardial infarction and all causes of mortality. Tertiary analyses will be performed around a number of exploratory analyses including the effect on the incidence of respiratory tract infections, systolic and diastolic blood pressure, serum lipid profile, admission for congestive heart failure, cerebrovascular disease, and peripheral artery disease.

**Data analyses.** Interim analyses will be performed when about one-third and two-thirds of the total number of projected end points have occurred. A log-rank statistic calculated at each scheduled interim analysis will be compared to the group sequential boundary, derived from the \( \alpha \)-spending function approach of Lan and DeMets [24]. Each interim safety report will review all aspects of the data collected for each subject.

For the final analysis, the log-rank statistic will be used to compare the time-to-event curves between the placebo and azithromycin groups. The event-free curve estimated by the method of Kaplan-Meier will be summarized for each treatment group. The overall statistical test of significance will be performed at the two-sided 5% significance level with a nominal significance level of 0.049.

**Trial organization.** The 222 centers participating in this trial are located in the United States, Canada, and Europe. This broad geographic distribution of centers may allow for better applicability of results across diverse clinical practice patterns. The institutional review boards affiliated with each center have reviewed and approved the protocol prior to patient enrollment at that site.

**Data support.** Coordination of data collection and management of the database is the responsibility of the sponsor. The Statistical Center at the University of Wisconsin is serving as an independent data management and analysis group in support of the interim analyses under review by the Data and Safety Monitoring (DSM) Board.

**Sponsor’s role.** Pfizer Central Research is the study sponsor. Pfizer provides drug supply to the sites, monitors the case report forms, collects and manages the database, is responsible for the final data analyses, and serves as the liaison to the Food and Drug Administration. Members of the clinical team will remain blinded to drug assignment throughout the course of the trial.

**DSM monitoring.** The DSM Board meets around each of the two interim analyses and as needed to review elements of safety and efficacy related to the clinical trial. The membership of this committee includes individuals with expertise in clinical trials, statistics, infectious diseases, and the pathobiology of atherosclerosis. No members are investigators in the trial. The voting members remain independent of the sponsor. The DSM
Board is charged with monitoring the interim relative safety and efficacy of the trial and with making recommendations regarding the need for sample size readjustment.

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