A randomized trial to evaluate the effect of azithromycin in patients with unstable angina or non-Q-wave MI

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A. Study purpose and rationale

Coronary artery disease is one of the largest causes of morbidity and mortality worldwide. It has been estimated to account for 1.5 million hospital admissions and 900,000 deaths annually in the United States alone[1]. There are several well-known risk factors for coronary artery disease that are modifiable by changes in behavior or medication, including tobacco use, hypertension, hypercholesterolemia, and diabetes mellitus. Others, such as age, male gender and family history of premature coronary artery disease, are unmodifiable. These multiple risk factors do not account for all coronary artery disease, however; they are absent in up to 30% of patients with myocardial infarction. It is not known what predisposes patients without these classical risk factors to develop ischemic heart disease. Some studies have shown that infection with certain common organisms may contribute to coronary disease, the most well studied of which is *Chlamydia pneumoniae*.

Chlamydia pneumoniae is an intracellular bacterium found throughout the world, and is a common cause of respiratory infections. The most common illnesses associated with this organism are pharyngitis, sinusitis, bronchitis and atypical pneumonias, although symptoms can be quite mild, and only about 10% of infections with *Chlamydia pneumoniae* may lead to a clinical diagnosis. In spite of this low rate of recognized disease, large numbers of people are infected by this organism one or more times during their lifetime: prevalence studies of antibody to *Chlamydia pneumoniae* have shown that half of the population has had an infection with this organism by the age of 20, and two-thirds by the age of 50[4].

There is insufficient data to state at this time that *Chlamydia pneumoniae* definitively causes coronary artery disease or acute myocardial infarcts, but many studies have suggested an association between them. The majority of these studies have been of two types: seroepidemiologic studies measuring antibody levels to *Chlamydia pneumoniae* in different populations, and pathologic studies examining tissue for the presence of the organism. The initial study linking *Chlamydia pneumoniae* with coronary artery disease was a seroepidemiologic study from Finland, in which a case-control study showed that 68% of patients after acute myocardial infarction had a significant antibody response to *Chlamydia pneumoniae*, but only 3% of people in the control group (without MI) had antibodies[2]. Later retrospective studies showed that patients with current MI were more likely to have had elevated antibody titers in the three to six months prior to the event, a finding more temporally consistent with a causative relationship[3].

Numerous pathologic studies have also shown evidence for *Chlamydia pneumoniae* localization to atherosclerotic plaques. These studies have used as specimens cardiovascular plaques from both animals and humans, obtained by endarterectomy, coronary atherectomy, heart transplants and autopsies; they have used a variety of techniques, including immunostaining, electron microscopy, polymerase chain reaction (PCR) and culture of viable organisms from the plaque. These have provided more direct evidence for the possible role of *Chlamydia pneumoniae* in atherosclerotic disease.

It is not clear how *Chlamydia pneumoniae* might be involved in the development of atherosclerotic disease – some researchers argue that it may just be an "innocent bystander", that the organism may be present in atherosclerotic plaques but may not be harmful. However, it is known that other Chlamydia species are involved in low-grade chronic infections. It is thus thought by some researchers that infection with *Chlamydia pneumoniae* may induce a chronic immune activation mediated by cytokines; this may lead to the progression of atherosclerotic lesions by direct chronic endothelial damage, and/or by an enhanced procoagulant state with an increased risk of local or distant thrombosis.

Recent animal and clinical studies have investigated the role of antibiotics in altering the risk for cardiac events. In one study, rabbits were fed high-cholesterol diets, with one group being inoculated with

Chlamydia pneumoniae intranasally; half of the infected animals were then treated with intramuscular azithromycin; three months later the animals were sacrificed, and it was found that the aortic atherosclerotic lesions in the infected and treated animals were similar in thickness and extension as those in the non-infected animals[5]. In another study, patients who survived their first MI and had high antibody titers to *Chlamydia pneumoniae* were randomized to azithromycin or placebo. After two years follow-up, the group with high titers that received placebo were four times as likely as those with low antibody titers to have an adverse cardiovascular event, whereas the group with high titers that received antibiotic were at equal risk as those with low titers for adverse outcomes[6]. In another clinical study, patients hospitalized with unstable angina or non-Q-wave MI were randomized to roxithromycin or placebo, and followed for six months for ischemic events; those randomized to placebo were significantly more likely to have adverse events than those that had received antibiotic[7].

These last two studies have supported the idea that antibiotic use may reduce the risk of cardiac events in patients. However, there are some difficulties with both study protocols. The study by Gupta et al[6] did not examine the effect of antibiotic in patients with low antibody titers (given the potential anti-inflammatory effect of some antibiotics, this may have some impact on their outcome). The study by Gurfinkel et al[7] did address this issue by randomizing all patients to treatment or placebo, but did not examine any possible differential effect in patients with high titers or low titers.

The purpose of this study is to determine whether azithromycin given to patients at the time of hospitalization for unstable angina or non-Q-wave MI will affect incidence of subsequent recurrent ischemic events, and to assess whether there is a differential effect on patients with high anti-*Chlamydia pneumoniae* titers.

B. Study design and statistical analysis

The study will be a randomized, double-blinded, placebo-controlled clinical trial. Patients will be randomized to receive either azithromycin or placebo. Prior to the study, a table will be prepared by an independent party, whereby numbered patients will be assigned to receive either study drug or placebo. Vials of the drug or an identical-appearing and identically-packaged placebo will be prepared by the research pharmacy. As patients are enrolled, they will be assigned a number in sequential order, and this number will determine the type of pill given. The person enrolling the patient will give the pills to the patient, and instruct them how to take the pills; both the person dispensing the pills and the patient will be blinded to the identity of the pills in the vial. The estimated needed number of patients is 650 in each arm (1300 patients total); this was determined by estimating an event incidence rate of 20% and an expected decrease in incidence of 30% in patients receiving the study drug. Using 650 patients in each group will provide 80% power to detect a difference between the treated and the placebo group, when testing statistical significance at the 0.05 level. Patients will not be crossed over from one group to another.

The primary outcomes to be measured are as follows:

- Severe recurrent ischemia – chest pain lasting at least 5 min with ST-T wave changes in at least two contiguous leads (ST elevation or depression and/or T-wave inversion), and/or prompting emergent PTCA or CABG.
- Acute myocardial infarction – creatine kinase-MB elevated above normal, and creatine kinase or troponin above normal limits.
- Death – due to cardiac ischemia.

Possible confounding effects to be measured are cholesterol levels; tobacco use; presence of diabetes mellitus, hypertension or family history of premature coronary artery disease; use of beta-blockers or aspirin; and anti-Chlamydia antibody titers (immunoglobulin G microimmunofluorescence assay, SmithKline Laboratories). These will be assessed by the patient's primary physician and by blood tests every three months for one year.

The primary analysis of the results will be performed using a chi-square analysis. Kaplan-Meier survival curves will be constructed, to determine whether any benefit is early or late in the follow-up period. Multiple regression analysis will be performed to control for possible confounding effects.

C. Study procedures

At the time of enrollment and every three months thereafter, subjects will have 10cc of blood drawn in a standard serum separator tube. This can be done concurrently with other blood draws. The risk of phlebotomy is that of discomfort at the needle-stick site.

D. Study drug

The study drug will be azithromycin, a drug that is commercially available from Pfizer, Inc. (trade name, "Zithromax"). It is a member of the macrolide group of antibiotics; it is available in intravenous and oral forms, but only the oral formulation will be used in this study. The standard dose will be used (500 mg on the first day, 250 mg per day for the next four days). This drug seldom causes serious adverse reactions; fewer than 5% of patients taking it experience diarrhea, nausea or abdominal. The drug is FDA pregnancy risk category B. No in vivo studies of drug efficacy against *Chlamydia pneumoniae* have been performed, but in vitro studies have shown it to be effective[9].

Patients will be provided with a vial containing six pills; they will be instructed to take two pills on the first day and one pill daily for the next four days, on an empty stomach.

E. Medical devices

None

F. Study questionnaires

None.

G. Study subjects

Patients to be enrolled will come from patients admitted to the Cardiac Care Unit or to the Cardiology Service at both Milstein and the Allen Pavilion Hospitals of New York Presbyterian Hospital.

a. Inclusion Criteria

- Age >21 years.
- Episode of angina at rest lasting at least 10 min in the previous 48 hr.
- Evidence of ischemic heart disease on EKG: ST segment depression, transient ST elevation (<15 min) of >0.1 mV, or T-wave inversions, in at least two contiguous leads.
- Cardiac enzyme elevation: total creatine kinase (CK) above the upper limit of normal, total CK isoenzyme MB above 15mg/dL, or troponin above the upper limit of normal.

b. Exclusion Criteria

- Evidence of evolving Q-wave MI.
- Left bundle branch block.
- Hepatic or renal failure.
- Congestive heart failure.
- Contraindications to macrolide therapy, including treatment with drugs known to interact with macrolides.

Vulnerable populations will not be included. The study will not be restricted by gender, race or primary language.

H. Recruitment of subjects

All patients on the Cardiology and Coronary Care Unit services will be reviewed on a regular basis; potential subjects will be identified, and their primary physicians approached for approval. Written, informed consent will be obtained prior to commencement of the protocol.

I. Confidentiality of study data

Research records will be kept confidential. Patients will be identified by a code number, which will be stored in a secured and locked location accessible only to the researchers.

J. Potential conflict of interest

None.

K. Location of the study

The study will be conducted in the Coronary Care Unit and the Cardiology Services of the Milstein Hospital and the Allen Pavilion.

L. Potential risks

The major risks associated with participation in the study are discomfort at the needle-stick site, and the small risk of adverse side effects from azithromycin (<5% of patients are expected to experience diarrhea, nausea or abdominal pain).

M. Potential benefits

The immediate benefit of this study to the patients taking the medication is the potential reduction of recurrent myocardial ischemia. There are no immediate benefits to the patients of the control group. However, the results of this research may benefit other patients with myocardial ischemia in the future by helping to understand the role of *Chlamydia pneumoniae* and antibiotics in the prevention of recurrent ischemia.

N. Alternative therapies

If a patient chooses not to participate in this study, he or she will continue to receive standard medical treatment.

O. Compensation to subjects

No compensation will be provided to patients during this study.

P. Costs to subjects

There will be no additional costs to the subjects as a result of participating in this study.

Q. Minors as research subjects

This study does not involve participation of minors.

R. Radiation or radioactive substances

This study does not involve the use of radiation.

S. References

1 American Heart Association. 1997 Heart and stroke statistical update. 1996; 3-10.

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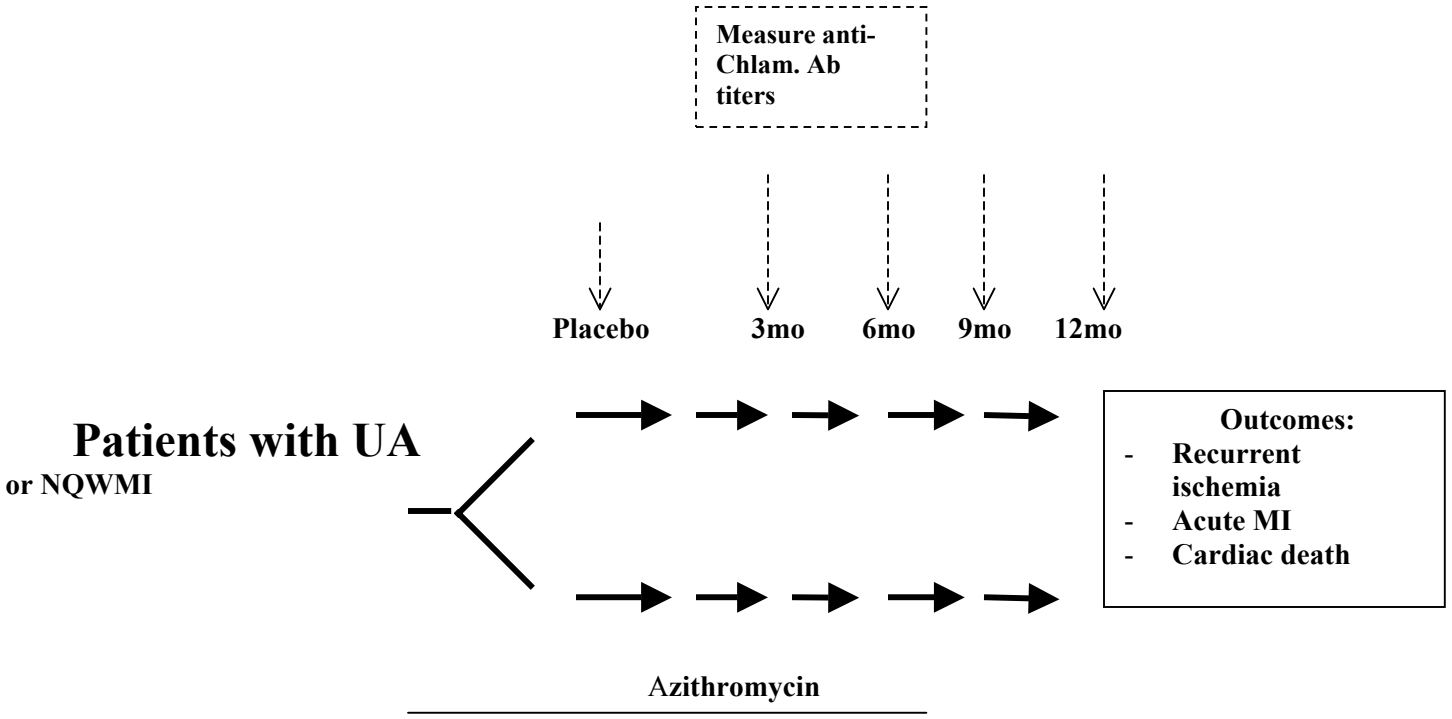
5 Muhlestein JB, Anderson JL, et al. Infection with *Chlamydia pneumoniae* accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. Circulation 1998; 97:633-36.

6 Gupta S, Leatham EW, et al. Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. Circulation 1997; 96:404-07.

7 Gurfinkel E, Bozovich G, et al. Randomized trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS pilot study. Lancet 1997; 350:404-07.

8 Meier CR, Derby LE, et al. Antibiotics and risk of subsequent first-time acute myocardial infarction. JAMA 1999; 281(5):427-31.

9 Hammerschlag MR, Khaldoon KQ, et al. In vitro activities of azithromycin, clarithromycin, L-ofloxacin, and other antibiotics against *Chlamydia pneumoniae*. Antimicrobial Agents and Chemotherapy, 1992; 36(7):1573-74.



Inclusion criteria:
- **age >21yo**
- **angina >10min**
- **EKG changes**
- **CK, MB or troponin ↑**

Exclusion criteria:
- **evolving QWMI**
- **LBBB**
- **Hepatic/renal failure**
- **CHF**
- **Contraindications to macrolides**