Is Antibiotic Treatment Effective for Coronary Artery Disease?

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ABSTRACT

Within the last 15 years there has been considerable discussion concerning the multiple contributors to coronary artery disease. With the realization during the late 1990s that atherosclerosis is an inflammatory response, attention has been directed to the possible role of infection. Early research into the role of *Chlamydia pneumoniae* generated interest in pursuing clinical trials using antibiotics to mitigate the effects of *C pneumoniae* and other organisms. Early trials were promising, with reduction in adverse events within months of the initiation of antibiotics and documentation of long-term benefits. However, there were inconsistencies within these small, early trials. Thereafter, larger multicenter trials were conducted but none were able to document long-term benefit. At most, a benefit was shown during the first 6 months of therapy. Since the conclusion of these trials, there has been considerable discussion and critique of the methodologies used. As well, the last 5 years have advanced the biochemical models for inflammation and the role played by infection. This review summarizes the findings of the trials and recommends areas of future research.

INTRODUCTION

Heart disease is the leading cause of death in developed countries. Despite a multi-pronged effort to manage the various contributors of the disease, there appears to be a point of diminishing returns using current therapies. Atherosclerotic disease has been attributed to elevated cholesterol levels and cholesterol deposition upon vessel walls. As described by Ross[1] in a landmark paper, atherosclerotic disease is also defined by elements of chronic and acute inflammation. As biochemical models of plaque formation have developed over the last few years, we are beginning to realize the far-reaching complexity of the process and the role played by infection.

Beginning in 1990, examinations of plaque material revealed frequent seed-

ing by microorganisms such as *Chlamydia pneumoniae*. Studies in the late 1990s first began augmenting current treatment for myocardial infarction (MI) and acute coronary syndrome (ACS) with antibiotics. These studies were small but had promising results.[2]

On a parallel track, research began on other organisms, such as *Helicobacter pylori*, herpes simplex virus, cytomegalovirus,[3] and, most recently, nanobacteria.[4] There may be other organisms involved in the initiation of atherosclerotic disease since improvement due to antibiotic treatment was often noted even with negative immunoassay for the proposed organisms.

Over the last 6 years, several studies have reported conflicting results on antibiotic treatment of patients with demonstrated arteriosclerosis or confirmed cardiac disease. This review compares and critiques these studies and discusses treatment options and future recommendations.

METHODS

A review of current literature was conducted using Internet search engines such as PubMed and Medline using the keywords "antibiotic," "coronary heart disease," "atherosclerosis," "inflammation," "thrombosis," "clinical trials," "prospective trials," "*Chlamydia pneumoniae,*" "*Helicobacter pylori,*" and "nanobacteria." Data from several clinical trials were reviewed for statistical significance and results were compared. The choice of antibiotic, timing of delivery of medication, follow-up period, lab results, and endpoints were gathered and presented.

RESULTS
Current Evidence for the Role of Infection

The most well-researched pathogen in recent studies of coronary artery disease is *C pneumoniae*. These intracellular

bacteria can be rather difficult to eradicate with short courses of antibiotics. It is estimated that 50% of the adult population has been exposed to *C pneumoniae,* as evidenced by immunoassay.[5] *C pneumoniae* or its cellular components have been demonstrated in postmortem examinations of plaques found in cardiac and carotid arteries. In fact, of 50 studies conducted prior to 2000, all but 4 documented the pathogen within atherosclerotic tissue.[6] *C pneumoniae* has been shown in vivo to be sensitive to macrolides, tetracyclines, and fluoroquinolones. Most commonly, azithromycin (Zithromax; Pfizer, New York, NY) is the drug of choice.[7,8]

A second organism proposed to have an impact on atherosclerosis is *Helicobacter pylori*, via seeding of the vasculature.[9] The invasive nature of this bacteria, coupled with its ability to cause gastric ulcer, led to investigations of its vascular impact.

Nanobacteria were first discovered in hot springs in the early 1990s but were not researched until the late 1990s. These bacteria are still controversial in that they are significantly smaller than any known bacteria, and some theorize that they are too small to act as bacteria as we understand it. However, these organisms have been shown to form calcific shells and biofilms. Researchers have demonstrated nanobacteria in calcified arterial plaques.[4,10] Nanobacteria have also been found in renal calculi, billary stones, and other areas of abnormal calcification in vivo. Although treatment trials are just beginning, anecdotal evidence implies that this may be a major cause of arterial calcification that is easily treated.[11]

Both herpes simplex virus and cytomegalovirus have been demonstrated in vitro to cause endothelial damage.[12] They may also cause a generalized immune response promoting a worsening of chronically inflamed arterial

Table 1. Summary of Antibiotic Trials for the Treatment of Cardiovascular Disease

Study, Authors	n	Selection Criteria	Antibiotic Treatment	Short-term Results	Long-term Results
Gupta & Camm[13]	60	MI survivors, seropositive for *C pneumoniae*	Azithromycin 500 mg/d for 3 days	Inflammatory titers fell at 6 months	Reduction of cardiovascular events (OR= 0.2, *P*=0.03)
ACADEMIC, Anderson & Muhlestein[14]	302	Coronary artery disease, seropositive for positive *C pneumoniae*	Azithromycin 500 mg/d for 3 days then weekly for 3 months	Inflammation markers reduced	A trend toward reduction of cardiovascular events after 2 years
STAMINA, Stone et al[15]	325	Acute Coronary Syndrome (ACS)	(1) Azithromycin 500 mg/d, omeprazole 20 mg bid, metronidazole 400 mg bid all for 1 wk, OR (2) amoxicillin 500 mg bid, omeprazole 20 mg bid, metronidazole 400 mg bid all for 1 wk	36% reduction in major events at 12 weeks (*P*=0.02)	Reduction persisted during the 1-yr follow-up
CLARIFY, Sinisalo et al[16]	148	ACS, acute non-q-wave MI or unstable angina	Clarithromycin for 3 months	-	Risk of cardiovascular events reduced (RR=0.49, *P*=0.03)
ANTIBIO, Zahn et al[17]	872	ACS, acute MI	Roxithromycin 300 mg/d for 6 weeks	-	Did not reduce cardiac event rates during 1-yr follow-up
ACES, Grayston[6]	4,012	Stable coronary artery disease and a previous cardiac event	Azithromycin 600 mg/wk for 1 year	-	No significant reduction of cardiac events
PROVE-IT, Wiviott et al[18]	4,162	Acute coronary syndrome	Pravastatin or atorvastatin plus gatifloxacin	-	Late-phase results were similar in the treatment groups
WIZARD, O'Connor et al[19]	7,747	MI and *C pneumoniae* IgG titer of 1:16 or more	Azithromycin 600 mg/d for 3 d for wk 1, then 600 mg/wk for wk 2-12	33% reduction in death or MI at 6 months (*P*=0.03)	No significant reduction in primary event after a median of 14-month follow-up
ISAR-3, Neumann et al[20]	1,010	Successful coronary stenting; assessed for restenosis	Roxithromycin 300 mg/d for 4 wk	No significant benefit in the angiographic restenosis rate	No significant difference in 1-year rates of death or MI
AZACS, Cercek et al[21]	1,439	Unstable angina or acute MI	Azithromycin for 5 days; followed up for 6 mo	No significant difference in rates of death, recurrent MI, or recurrent ischemia needing revascularization	-

MI=myocardial infarction; OR=odds ratio.

plaques.[1] Espinola-Klein and colleagues[3] have demonstrated that high levels of antibodies to either virus are associated with increased risk of disease. Antiviral medications may have some application when infection is demonstrated by antibody titers.

Studies to Date

Table 1 summarizes the data from trials of antibiotics on coronary artery disease outcome. Pilot studies of 60 survivors of acute MI with elevated *C pneumoniae* titers ($\geq$1:64), randomized to placebo or a 3-day course of azithromycin (500 mg/d), showed a reduction of cardiovascular events[13] from 28% to 8% (odds ratio [OR]=0.2, *P*=0.03) compared with placebo-treated patients. The treatment group also showed a reduction in *C pneumoniae* titers at 6 months. Patients receiving a second round of antibiotics at 3 months showed similar results.[7]

A relatively small study, called the ACADEMIC trial (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with *Chlamydia*), was conducted among 302 patients with acute coronary artery disease and seropositivity for *C pneumoniae*.[14] The patients were randomized to placebo or azithromycin 500 mg/d for 3 days, followed by 500 mg/wk for 3 months. At 6 months, there were reductions in systemic markers for inflammation (discussed below). However, there was no statistically significant correlation between antibiotic treatment and reduced endpoints after 2 years of follow-up. Cardiovascular event rates at 2 years did trend toward a reduction (22 vs. 25, hazard ratio=0.9, 95% confidence interval [CI]=0.23-1.5, *P*=0.26), but were not as good as in the pilot study. Given that the study was small, a modest improvement of 20%-30% reduction in the cardiovascular event rate after antibiotic treatment could not be ruled out.

The STAMINA trial (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina) (n=325) addressed both *C pneumoniae* and *H pylori*.[15] Multiple drug therapy using amoxicillin for *H pylori* and azithromycin for *C pneumoniae*, both combined with metronidazole and omeprazole, were found to reduce inflammatory markers. This included C-reactive protein (*P*=0.03) and fibrinogen (*P*=0.06). At 12 weeks of follow up there was a 36% decrease (*P*=0.02) in all end points (cardiac death, revascularization, and readmission). At 1 year there continued to be a significant reduction in end points of cardiac death or readmission with ACS. An interesting finding was that the presence of *C pneumoniae* and *H pylori* antibody was not predictive of outcome.

The CLARIFY trial (Clarithromycin in Acute Coronary Syndrome Patients in Finland) was another small trial conducted with 148 patients.[16] Selection criteria for this trial included acute non-q-wave MI or unstable angina. These patients were randomized to clarithromycin or placebo for 3 months and followed for an average of 555 days (range, 138-924 days). Primary endpoints of death, angina requiring admission, or MI were recorded. At the end of follow-up the relative risk (RR) of a primary event in the treated group was 0.54 (CI=0.25-1.14, *P*=0.10). There was a statistically significant reduction in total cardiovascular events not considered primary end points (RR=0.49, CI=0.26-0.92, *P*=0.03).

The ANTIBIO trial (Antibiotic Therapy for Acute Myocardial Infarction) examined treatment with roxithromycin (a macrolide antibiotic) versus placebo for 6 weeks in 872 patients presenting with acute MI.[17] In this case, the study endpoint was simply death from all causes within 12 months.

The results did not show any reduction in cardiac events (OR=1.1, 95% CI=0.6-1.9, *P*=0.74). Retrospective analysis also found no differences in secondary or combined endpoints.

Following these trials and the conflicting data they produced, several fairly large trials were begun. The ACES trial (Azithromycin and Coronary Events Study) involved 4012 men and women with stable coronary artery disease and a previous cardiac event such as an MI, angioplasty, or bypass surgery.[5,6] This was a double-blind, randomized trial of either azithromycin (600 mg/wk) or placebo for 1 year. Patients were followed for an average of 3.9 years, recording primary endpoints of death due to coronary artery disease, non-fatal MI, unstable angina, or coronary artery bypass surgery. There was no significant reduction of cardiac events among participants receiving antibiotic compared with those receiving placebo. This was shown for all participants regardless of age, gender, smoking status, or presence of *C pneumoniae* antibody.

The PROVE-IT trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy) was a similar effort using statins and the fluoroquinolone gatifloxacin (Tequin; Bristol-Myers Squibb, New York, NY) randomized against placebo among 4162 patients.[18] This study evaluated the use of statin drugs for their anti-inflammatory properties while also treating a proposed infectious model. Selection criteria of the study required presentation with ACS. These patients were followed for 18 months for any major cardiovascular event. Again, no significant difference in outcome was attributable to the use of an antibiotic.

The WIZARD trial (Weekly Intervention with Zithromax for Atherosclerosis and Related Disorders) had a population of 7747 with seropositivity to *C pneumoniae* and history of MI.[19] The control group was treated with placebo while the intervention group received azithromycin 600 mg/d for 3 days for the first week, and then 600 mg/wk from week 2 to week 12. Endpoints were death, MI, unstable angina, or revascularization at 3 years. This was the largest study of antibiotics and atherosclerosis to date, but was only able to show a 7% reduction in endpoints (95% CI=-5%-17%, *P*=0.23) after a median of 14 months of follow-up. However, there was a 33% (*P*=0.03) reduction in death or MI within the first 6 months.

Several other trials, such as ISAR-3 (Intracoronary Stenting and Antibiotic Regimen 3)[20] and AZACS (Azithromycin in Acute Coronary Syndrome),[21] were also unable to demonstrate significant benefit of antibiotics in the rate of restenosis (ISAR-3) and the rates of death, recurrent MI, or recurrent ischemia needing revascularization (AZACS).

The early studies with relatively small sample size showed some positive impact, whereas later, larger studies had generally equivocal results or did not show any significant improvement of cardiac events after treatment with antibiotics. Immunoassay techniques fail to predict efficacy of treatments. This leads one to consider that other organisms may be involved in the atherosclerotic process as well. For example, mild bacteremia from periodontal disease has been proposed as a mechanism. In the STAMINA study, metronidazole was used in combination with other drugs and may have reduced bacteremia from oral or intestinal sources.[15] Of course, viral infections have not been assessed or treated by any of these trials.

The failure of these studies to show an association between antibiotics and improved cardiac event rates caused some in the medical community to rethink the hypothesis that *C pneumoniae* is the primary culprit in atherosclerosis. In 2002 Espinola-Klein and

colleagues[3] published an investigation into exposure to one or more pathogens and their association with atherosclerotic disease. They studied 527 patients and assessed them for prior exposure to herpes simplex virus 1 and 2, cytomegalovirus, Epstein-Barr virus, *Haemophilus influenzae*, *C pneumoniae*, *Mycoplasma pneumoniae*, and *H pylori*. The presence of atherosclerosis was determined by coronary angiography, carotid sonography, and ankle-arm index. After adjusting for age, sex, and cardiovascular risk factors, they found an association between advanced atherosclerotic disease and seropositive tests for *C pneumoniae* (*P*<0.04), *H pylori* (*P*<0.02), cytomegalovirus (*P*<0.05), and herpes simplex virus 2 (*P*<0.01). Further, they found that the risks were additive for coinfections. For example, the odds ratio for advanced atherosclerosis increased by 2.5 (95% CI=1.2-5.1) for those having 6-8 seropositive tests. While testing capitalized on "the usual suspects," a much broader look at all common pathogens may be indicated.

The Use of Azithromycin and Other Analogues

Gieffers and colleagues[22] documented that *C pneumoniae* was resistant to treatment with azithromycin while engulfed within a monocyte. The intracellular *C pneumoniae* remain viable and antibiotics may only have an effect during extracellular reproduction of the parasite. Given that most arterial plaques are laden with monocytes and macrophages, prior treatment trials with azithromycin and its analogues may not have had the intended effects despite the drug having been shown to penetrate into plaques well.

Predictive Value of Cultures and Immunoassay

As stated above, in specific studies antibody titers and blood cultures failed to identify patients at risk and failed to predict the outcome of antibiotic treatment. For example, all cases and controls in the ACADEMIC study[14] were seropositive for *C pneumoniae*. This study failed to show a difference between the treatment group and the controls. However, the STAMINA trial[15] showed success in treatment but found that seropositivity for *C pneumoniae* or *H pylori* had no predictive value. The one exception was the ISAR trial,[7,20] which did show some benefit for treatment in the patient with very high *C pneumoniae* titers (OR, 0.44 for titers ≥1:512). Nanobacteria may be detected by commercially available immunoassay kits, but the usefulness of a positive test may not be significant since 40% of the population will test positive at baseline.

Animal and In Vitro Models

Animal studies and in vitro models have demonstrated a connection between some organisms mentioned earlier and arterial plaque formation. *C pneumoniae* is known to attack arterial endothelial cells and become intracellular, causing damage to the vessel lining without the preexistence of an atheromatous deposit. For example, Muhlestein et al[23] used rabbits receiving bronchial doses or injections with *C pneumoniae* to show the formation of arterial plaques and the use of antibiotic to prevent the process of atherosclerosis. This agrees with published studies showing that the presence of *C pneumoniae* doubles the risk of vascular disease in humans. However, receiving antibiotics after the initial plaque formation does not appear to reverse plaque formation. Less research has been conducted on the vascular impact of seeding by other possible organisms.

Proposed Mechanism of Action

Ross[1] reviewed the evidence that atherosclerosis is an inflammatory disease.

The theory has been well accepted due to the abundance of cell-mediated immune response evident within vascular plaques. Chronic inflammatory process in the artery, which contributes to endothelial dysfunction, may be triggered by a number of factors including elevated and modified low-density lipoproteins (LDL), free radicals caused by cigarette smoking, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations, and infectious microorganisms. As can be seen, this is not a problem with a single answer. Finding the single cause most responsible in any particular patient may not be practical. Regardless of the cause, the inflammatory response is the overriding commonality.

It is generally believed that infection gives rise to inflammation as an early event in atherogenesis, not in developed plaques. Inflammation destabilizes plaques. Plaques rupture at sites of shoulder thinning or from intraplaque hemorrhage. There is no evidence that established plaque is destabilized by acute bacterial infection.

As summarized by Cook,[8] the mechanism for *C pneumoniae*'s atherosclerotic influence is divided into immune response and effects on local lipid metabolism by inflammatory cells. An infection with *C pneumoniae* causes an increase in cholesteryl ester synthesis in human monocyte-derived macrophages incubated in vitro with LDL, producing foam cells usually found in arterial plaques. During the past few years, much has been delineated concerning the biochemical pathways and chemical messengers of inflammation. It has been demonstrated that within the plaque (where *C pneumoniae* has invaded monocytes, macrophages, and smooth muscle cells) there are no less than 20 or so biochemical messengers and pathways involved in the process inherent in endothelial dysfunction. Animal models have shown that *C pneumoniae* tends to accelerate the immune process by influencing many of these pathways and is active from the initial development through the proliferative phases. However, chronic infection does not appear to be directly involved in the final stages of necrosis and plaque rupture.

General inflammatory indicators such as C-reactive protein, erythrocyte sedimentation rate, interleukin-1, interleukin-6, tumor necrosis factor-α and others have been used as proxies to vascular and other inflammatory reaction.[24] There have been several studies demonstrating elevation of these factors during and after a cardiovascular insult as well as cerebrovascular accident. These are in addition to the common cardiac markers such as creatinine kinase isoenzyme MB and troponin fractions. Elevation of these markers may represent a reaction to the insult, or may precede the insult as a reaction to chronic infection. Demonstrating the latter may require a large prospective study; confirmatory data is lacking at this point.

These mechanisms have been advanced for *C pneumoniae*, but one must ask if it is reasonable to assume that other organisms operate by similar means. Our current understanding of the complicated and intertwined biochemistry of this model may be less important than our ability to screen for, and eradicate, offending organisms prior to plaque formation. Additionally, there is some preliminary evidence that a hyperresponse in these pathways is seen in genetically susceptible individuals.[8] This may be advantageous in future screenings. As part of the genetic puzzle, *Chlamydial* heat shock protein has been shown to induce antibodies that cross-react with self-protein and may be important in the genesis of atherosclerosis.[25] Since these heat shock proteins are well conserved across multiple species of

bacteria, the effect may be implied for other organisms as well.

Radiologically demonstrated calcium deposits in major vessels have been used as a marker for cardiovascular disease. As reported by Miller et al[4] nanobacteria have been demonstrated within calcified plaques examined post mortem. These nanobacteria are known to form calcified shells around the cells, followed by calcification of the biofilm containing the cells. It is estimated that 40% of the population has been exposed to nanobacteria and are seropositive. However, a considerably higher percentage (50-70%) of patients with calcific cardiac disease (Monckeberg's medial calcific sclerosis) were positive for nanobacteria. The same is true for renal calculi, with a large percentage of stones estimated to contain nanobacteria.[26] Fortunately, these cells are slow growing, offering an increased window of opportunity for treatment.

Current Treatment Methodologies

Treatment of post-MI or ACS patients using azithromycin alone has been uniformly ineffective for presumed *C pneumoniae*. The addition of metronidazole had improved outcomes in the STAMINA trial.[15] It should also be noted that metronidazole may well contribute to reduction in inflammatory markers. Treatment starting at the time of cardiac compromise has been shown to confer the greatest benefit in the smaller trials. Complete eradication may take 1 year of treatment.[27]

H pylori has been successfully treated in small studies using amoxicillin in combination with metronidazole. As discussed earlier, treatment protocols extending for a prolonged period are indicated, but evidence is lacking on optimum length of treatment.

Nanobacteria infection has been treated using a proprietary protocol developed by the Nanobac company.[10,11]

This largely consists of morning doses of doxycycline followed by an evening ethylenediaminetetraacetic acid (EDTA) suppository. Treatment is usually continued for 3 months.

Treatment for bacteremia of unknown origin is problematic. Metronidazole is known to be effective for the treatment of anaerobic organisms and parasites. However, the PROVE-IT trial using floroquinolones[7,18] should have also treated for bacteremia of oral or intestinal origin but showed no long-term improvements in cardiac events. Multiple organisms such as those cited by Espinola-Klein[3] should be considered. *Staphylococcus*, *Enterococcus* species, *Enterobacteriaceae*, *Pseudomonas* species, unusual gram negative bacteria, and the HACEK organisms (*Haemophilus aphorphilus, Haemophilus paraphrophilius, Actinobacillus actinomycetemcomitans, Cardioacterium hominis, Eikenella corrodens,* and *Kingella kingae*) have been shown to be present in endocarditis and may play a role in vascular inflammation as well.[28]

Lessons Learned and Future Research

As our review has shown, data from the larger trials of antibiotic treatment of coronary artery disease have been disappointing.[18,19,21] Antibiotic treatment appears to cause no significant decrease in long-term adverse outcomes. Therefore, it is difficult to recommend antibiotic treatment after a cardiac event.

Most clinical trials of antibiotic treatment of coronary artery disease have used azithromycin and other macrolides.[13-17,19-21] Gieffers et al[22] showed these to be ineffective against *C pneumoniae* found engulfed within monocytes. Therefore, there is a clear need to evaluate other antibiotic regimens against *C pneumoniae*. The larger studies did not duplicate the successful

smaller studies' choice of antibiotic.[15] Exploration of this option may be helpful.

The in-vitro studies and animal models described above show a distinct connection between *C pneumoniae* and vascular disease, but treating after the fact of a cardiac compromise may simply be too late.[5] As mentioned in the PROVE-IT trial,[18] the best time to treat *C pneumoniae* with antibiotics is before the development of plaques.

C pneumoniae is certainly the most studied organism to date; we have failed to test other organisms in clinical trials. Bacteremia from various sources have been implicated in cardiac valvular disease and may also contribute to vascular inflammation and atherosclerosis.[28-30] Studies cited earlier illustrate that several common pathogens are likely to be involved and that the risk of vascular disease is as much as 2.5 times higher for those with multiple exposures.[3] The antibiotics tested in these trials are fairly broad spectrum but do not cover all plausible organisms.

So what are we left to conclude from the conflicting studies? The smaller studies[13-15] and the large WIZARD study[19] show a short-term benefit of antibiotics. Specifically, the WIZARD trial showed a statistically significant (P=0.03) 33% reduction in death or MI within the first 6 months of treatment. Per the ISAR trial, in patients with a high titer for antibody to *C pneumoniae* there is evidence of long-term benefit in using antibiotics.[20] As antibiotic treatment is generally well tolerated, the benefit of treatment may outweigh risks.

CONCLUSIONS

From what we have seen in the development of the infection/inflammation model since the beginning of these trials, we conclude that antibiotic treatment well prior to a cardiac event should be far superior to post-event treatment.

Within the model, chronic infection of the plaque accelerates the process of atheromatus plaque formation but may not be responsible for plaque rupture. While antibiotic treatment will do nothing to reverse formation of plaques, early eradication should slow progression. The "post-event" 6-month improvement shown in some early trials and the WIZARD trial may be due to halting the rapid progression to maturity of remaining plaques. But these plaques will continue to mature at a normal rate and eventually become problematic.

There is also a genetic link on the horizon.[25] Heat shock protein is genetically conserved across multiple species of bacteria and has been implicated in molecular mimicry. Antibodies to this protein have been shown to also attack self-proteins in genetically predisposed individuals, accelerating atherosclerosis. Screening for individuals with susceptible human leukocyte antigen (HLA) DR makeup may allow targeting for more aggressive treatment.

Evidence for the use of antibiotics in all patients presenting with ACS or acute MI is rather tenuous. The largest study to date, in conflict with slightly smaller studies, has documented a 33% reduction in death and MI during the first 6 months only.[19] No large study has documented improved long-term outcome in terms of reduced need for angioplasty or bypass, lowered risk of angina requiring readmission, or recurrent MI. There are currently no formal protocols outlining clinical indications or methodologies for treatment based on the findings of the larger trials.

There is a high level of confidence that *C pneumoniae* is capable of accelerating the development of vascular plaques. Therefore, early eradication of this organism is important for future cardiovascular health, especially in patients with one or more cardiovascular risk factors. As demonstrated by the

organism's resistance to antibiotics while engulfed within monocytes, treatment may require long-term therapy.

Exposure to other common pathogens has also been correlated with development of advanced atherosclerotic disease. There is some preliminary evidence that molecular mimicry coupled with genetic predisposition may result in autoimmune damage to the vascular endothelium.

By contrast, anecdotal evidence for treatment of nanobacteria is encouraging. Calcific deposits within the vasculature have been shown to be reversible with improvement in exercise tolerance over a period of weeks to months. Multiple centers have begun offering treatment to selected patients and efficacy data are being gathered on this novel approach.

An early intervention before plaque formation may result in a better outcome. More long-term large scale trials of multiple antimicrobials are needed before they are recommended for the prevention of cardiac events.

REFERENCES

1. Ross R. Atherosclerosis— an inflammatory disease. *N Engl J Med*. 1999;340:115-126.

2. Grayston JT. Antibiotic treatment trials for secondary prevention of coronary artery disease events. *Circulation*. 1999;99:1538-1539.

3. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation*. 2002;105:15-21.

4. Miller VM, Rodgers G, Charlesworth JA, et al. Evidence of nanobacterial-like structures in calcified human arteries and cardiac valves. *Am J Physiol Heart Circ Physiol*. 2004;287:H1115-H1124.

5. National Institutes of Health. *New study shows antibiotic treatment does not reduce risk of secondary cardiac events*. Available at: http://www.nih.gov/news/pr/apr2005/nhlbi-20.htm. Accessed February 16, 2007.

6. Grayston JT. Secondary prevention antibiotic treatment trials for coronary artery disease. *Circulation*. 2000;102:1742-1743.

7. Anderson JL, Muhlestein JB. Antibiotic trials for coronary heart disease. *Tex Heart Inst J*. 2004;31:33-38.

8. Cook PJ. Antimicrobial therapy for *Chlamydia pneumoniae*: Its potential role in atherosclerosis and asthma. *J Antimicrob Chemother*. 1999;44:145-148.

9. Patel P, Mendall MA, Carrington D, et al. Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *BMJ*. 1995; 311:711-714.

10. Nano Science and Technology Institute. *Nanobac Life Sciences, Inc. announces detection of nanobacteria-like particles in human atherosclerotic plaques*. Available at: http://www.nsti.org/press/PRshow.html?id=850. Accessed February 16, 2007.

11. Nexus Magazine. *The nanobacteria link to heart disease and cancer*. Available at: http://www.nexusmagazine.com/articles/Nanobacteria.html. Accessed February 16, 2007.

12. Morré SA, Stooker W, Lagrand WK, van den Brule AJ, Niessen HW. Microorganisms in the aetiology of atherosclerosis. *J Clin Pathol*. 2000; 53:647-654

13. Gupta S, Camm AJ. Chronic infection in the etiology of atherosclerosis—the case for *Chlamydia pneumoniae*. *Clin Cardiol*. 1997;20:829-836.

14. Anderson JL, Muhlestein JB. The ACADEMIC study in perspective (Azithromycin in coronary artery disease: elimination of myocardial infection with Chlamydia). *J Infect Dis*. 2000;181:S569-S571.

15. Stone AF, Mendall MA, Kaski JC, et al. Effect of treatment for *Chlamydia pneumoniae* and *Helicobacter pylori* on markers of inflammation and cardiac events in patients with acute coronary syndromes: South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). *Circulation*. 2002;106:1219-1223.

16. Sinisalo J, Mattila K, Valtonen V, et al. Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-q-wave coronary syndrome. *Circulation*. 2002;105:1555-1560.

17. Zahn R, Schneider S, Frilling B, et al. Antibiotic therapy after acute myocardial infarction: A prospective randomized study. *Circulation*. 2003;107:1253-1259.

18. Wiviott SD, de Lemos JA, Cannon CP, et al. A tale of two trials: A comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. *Circulation*. 2006;113:1406-1414.

19. O'Connor CM, Dunne MW, Pfeffer MA, et al. Azithromycin for secondary prevention of coronary heart disease events: the WIZARD Study: A randomized controlled trial. *JAMA*.

2003; 290:1459-1466.

20. Neumann F, Kastrati A, Miethke T, et al. Treatment of *Chlamydia pneumoniae* infection with roxithromycin and effect on neointima proliferation after coronary stent placement (ISAR-3): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2001;357:2085-2089.

21. Cercek B, Shah PK, Noc M, et al. Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet*. 2003;361:809-813.

22. Gieffers J, Füllgraf H, Jahn J, et al. *Chlamydia pneumoniae* infection in circulating human monocytes is refractory to antibiotic treatment. *Circulation*. 2001;103:351-356.

23. Muhlestein JB, Anderson JL, Hammond EH, et al. Infection with *Chlamydia pneumoniae* accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. *Circulation*. 1998;97:633-636.

24. Muhlestein JB, Anderson JL, Carlquist JF, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: Primary clinical results of the ACA-DEMIC study. *Circulation*. 2000;102:1755-1760.

25. Neumann FJ. *Chlamydia pneumonia*–atherosclerosis link: A sound concept in search for clinical relevance. *Circulation*. 2002;106:2414-2416.

26. Ciftcioglu N, Haddad RS, Golden DC, et al. A potential cause for kidney stone formation during space flights: Enhanced growth of nanobacteria in microgravity. *Kidney Int*. 2005;67:483-491.

27. Grayston JT. Antibiotic treatment of atherosclerotic cardiovascular disease. *Circulation*. 2003;107:1228-1230.

28. Calza L, Manfredi R, Chiodo F. Infective endocarditis: A review of the best treatment options. *Expert Opin Pharmacother*. 2004;5:1899-1916.

29. Brodala N, Merricks EP, Bellinger DA, et al. Porphyromonas gingivalis bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. *Arterioscler Thromb Vasc Biol*. 2005;25:1446-1451.

30. Forner L, Nielsen CH, Bendtzen K, Larsen T, Holmstrup P. Increased plasma levels of IL-6 in bacteremic periodontis patients after scaling. *J Clin Periodontol*. 2006;33:724–729.