Insights Into the Role of Infection in Atherogenesis and in Plaque Rupture

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The potential contribution of infection to the induction and progression of atherosclerosis has been characterized by profound controversy, continuing to the present time. Controversy also surrounds the concept that infection can precipitate plaque rupture, an event complicating the course of atherosclerosis and clinically characterized by acute myocardial infarction and death. The purpose of this article is (1) to review what we believe are the most compelling data that either are compatible with or refute the concept that infection plays a role in atherogenesis or plaque rupture; (2) to present the mechanisms that may contribute to such effects; and (3) to discuss the impact on the infection/atherosclerosis paradigm of the recent negative therapeutic trials examining the effects of macrolide antibiotics on cardiovascular end points in patients with coronary artery disease (CAD).

Evidence Suggesting That Pathogens Contribute to Atherogenesis

Although anecdotal information existed for many years suggesting that acute infection can trigger an acute myocardial infarction,1,2 it was the groundbreaking work by Minick and Fabricant and their coworkers3,4 in the 1970s that began the serious scientific exploration of the relation between infection and atherosclerosis. These investigators demonstrated that Marek’s disease virus, an avian herpesvirus, caused atherosclerotic-like lesions in multiple arteries of chickens and that infection of smooth muscle cells (SMCs) with the virus in vitro caused cholesterol accumulation.

Evidence was subsequently published extending the infection/atherosclerosis paradigm to humans. Thus, pathogens were found to reside in human atherosclerotic vessels,5-8 and seroepidemiological studies demonstrated an association between pathogen-specific antibodies and atherosclerosis. Such associations were found with multiple pathogens, including cytomegalovirus (CMV), herpes simplex virus (HSV) types 1 and 2, Chlamydia pneumonia, Helicobacter pylori, and hepatitis A virus, as well as periodontal pathogens.9-16 However, other studies failed to show such associations,17,18 leading to discussions of the limitations of seroepidemiological studies in evaluating a causal role between infection and atherogenesis.19,20

Adding to the skepticism surrounding the infection/atherosclerosis paradigm, all of the evidence derived from human studies through the late 1990s showing that pathogens reside in atherosclerotic lesions and that anti-pathogen antibodies are associated with atherosclerosis was appropriately considered purely observational and could not be considered as demonstrating a causal role of infection in atherosclerosis. Short of the type of study demonstrating that H pylori causes stomach ulcers (in which the investigator actually ingested H pylori and developed an ulcer21), the only way to prove that pathogens/hoses have the molecular interactive programs that are capable of actually causing atherosclerosis is by demonstrating, in animal studies, that infection does in fact lead to atherosclerosis. Whether such results, even if reproducibly demonstrated, apply to humans would still be problematic. However, it might be argued that the combination of consistent causal studies in animals and compelling mechanistic data could tip the scales. Following is an analysis of such studies. It is obviously up to the reader to determine which way the scales are tipped.

Despite publication of the results by Fabricant and coworkers in the 1970s, a large hiatus followed until their results were confirmed and expanded. Beginning in the late 1990s, however, additional animal studies were performed indicating that pathogens do have the capacity to induce atherosclerosis. Thus, acute infection with CMV in rats caused injury to endothelial cells lining the aorta,22 and acute infection of old (>24 months) apolipoprotein E (apoE) knockout mice with influenza A virus promoted the development of inflammation, SMC proliferation, and fibrin deposition in atherosclerotic plaques; of interest, 1 of the 10 mice infected exhibited a subocclusive platelet and fibrin-rich thrombus.23 Most importantly from a proof-of-concept perspective, chronic infection of apoE knockout mice (which spontaneously develop atherosclerotic lesions) with such pathogens as CMV or C pneumonia actually increased atherosclerotic lesion size.24-27

Mechanisms by Which Pathogens Can Contribute to Atherogenesis

Direct Effects on Cells of the Vessel Wall
Pathogens can either directly infect cells of the vessel wall, where they could persist in a latent state, replicate at a low...
(and possibly intermittent) level, or produce an abortive infection (see below). Alternatively, they can be delivered to the vessel wall by circulating monocytes, which can be infected by both CMV \(^{28–31}\) and \(C\) \(pneumonia\).\(^{32}\) CMV probably infects monocyte precursors in the bone marrow, which then serve as a CMV reservoir. These infected cells could subsequently become a “Trojan horse,” delivering CMV by circulating monocytes to sites of injury or inflammation.\(^{28,33}\) 

Although CMV is quiescent in these cells, once the circulating monocytes enter their target tissue and transform into macrophages, they begin to express their immediate early (IE) viral gene products.\(^{29,30}\) This change is contributed to by the capacity of various constituents of the vessel wall, such as endothelial cells, SMCs, and oxidized LDL, to increase the activity of the major IE promoter of CMV.\(^{31}\) A similar mononuclear-based vector mechanism may exist for \(C\) \(pneumonia\), with the requisite reservoir/vector being pulmonary alveolar macrophages infected by \(C\) \(pneumonia\) during pulmonary infections.\(^{33}\)

Pathogens such as CMV, HSV, and \(C\) \(pneumonia\), when residing in cells of the vessel wall, can cause such “proatherosclerotic” effects as SMC proliferation, increased SMC migration, increased expression of cytokines, chemokines, and cellular adhesion molecules, and development of reactive oxygen species.\(^{30,33–39}\) CMV infection of SMCs increases uptake of oxidized low-density lipoprotein,\(^{40}\) an effect also caused by infection of monocyte-derived macrophages with \(C\) \(pneumonia\).\(^{41}\)

HSV and CMV infection cause phenotypic transformation of endothelial cells from a normal anticoagulant to a procoagulant phenotype, including increases in synthesis of tissue factor and the rate of thrombin generation and decreases in prostacyclin and thrombomodulin generation.\(^{42–45}\) Likewise, \(C\) \(pneumonia\) infection increases expression of adhesion molecules, tissue factor, and plasminogen activator inhibitor.\(^{37,39}\)

Persistent Abortive Infections

Some of the pathogens associated with human atherosclerosis in seroepidemiological studies cause persistent infection, with the pathogen residing in cells for long periods without proliferating. In this regard, some of the atherogenic-related cellular effects of CMV derive from expression of its IE gene products in the absence of early and late gene expression and therefore of viral replication. In this type of infection (an abortive infection), death of the host cell does not occur. Abortive infections are probably of biological relevance. For example, 1 IE gene product of CMV, IE2–84, binds to p53 and inhibits its transcriptional activity.\(^{46}\) Because p53 activity inhibits cell cycle progression and therefore cell proliferation, CMV can, through the p53 inhibitory activity exerted by its IE2–84 gene product, increase proliferation of the cells it infects. In addition, an abortive infection of SMCs with CMV increases the transcriptional activity of the class A scavenger receptor promoter, an action caused, at least in part, by another IE gene product of CMV, IE-72.\(^{40}\) Vascular SMCs abortively infected with CMV exhibit not only increased proliferation but also increased migration.\(^{47}\)

Cells infected with nonreplicating CMV could also contribute to atherogenesis by pathogen-induced molecular mechanisms inhibiting apoptotic pathways. For example, the CMV IE product IE2–84 inhibits the p53-modulated apoptotic program.\(^{46,48}\) If inhibition of apoptosis occurred in abortively infected SMCs located in arteries, such an effect could lead to excessive accumulation of these cells, thereby increasing the mass of atherosclerosis lesions.

During part of its life cycle, \(C\) \(pneumonia\), like CMV, persistently infects cells in a metabolically quiescent nonreplicating state while still expressing certain gene products, including chlamydial heat shock protein (HSP)\(60.49\) Given the fact that \(C\) \(pneumonia\) is present in atherosclerotic lesions,\(^{50}\) it is not surprising that lesions contain chlamydial HSP60. Of potential importance to atherogenesis, this molecule was found to have proatherogenic activity; thus, it induces tumor necrosis factor-\(\alpha\) and matrix metalloproteinase expression by macrophages; increases endothelial cell expression of E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and interleukin-6 (IL-6); and activates nuclear factor-\(\kappa\)B complexes.\(^{50,51}\) Expression of chlamydial HSP60 thus provides another mechanism whereby \(C\) \(pneumonia\) can contribute to atherogenesis and plaque instability.

In Vivo Studies

Acute infection with CMV in rats causes upregulation of adhesion molecules;\(^{22}\) CMV infection of apoE knockout mice and \(C\) \(pneumonia\) infection of apoE3-Leiden mice significantly increase T-lymphocyte influx into atherosclerotic lesions 2 to 4 weeks after infection, and acute infection of apoE knockout mice with CMV causes increased plasma interferon-\(\gamma\) and tumor necrosis factor-\(\alpha\) levels.\(^{26,52}\) Most interestingly, acute CMV infection of apoE knockout and C57BL/6 wild-type mice altered expression of \(>100\) genes in the aortic wall,\(^{53}\) including such genes involved in immune and inflammatory responses as monocyte chemoattractant protein-1, monokine induced by interferon-\(\gamma\), and interferon-\(\gamma\) inducible protein 10. It is not known whether upregulation was caused by virus actually residing in the aorta or from systemic-induced effects (see the next section).

Atherogenic Mechanisms Not Requiring Residence of the Pathogen Within the Vessel Wall

If infection contributes to atherogenesis, its mechanistic contributions are extraordinarily complex, involving not only local effects caused by pathogen actually residing in the arterial wall but also systemic effects. The existence of such systemic effects was demonstrated experimentally in a rat model of acute arterial injury;\(^{54}\) after balloon injury of the carotid artery, rats were infected with CMV and killed 6 weeks later. Infection was associated with significant exacerbation of the neointimal response to injury, despite the fact that virus was essentially absent from the site of injury. Persistent distant infection, associated with systemic cytokine response, was evidenced by isolation of infectious virus from homogenates of both salivary glands and spleen.
That CMV can exert proatherosclerotic effects without the need to replicate was demonstrated in a study in which replication-deficient UV-inactivated CMV virus was injected into apoE knockout mice. Two weeks after injection, no CMV DNA could be detected; nonetheless, mean atherosclerotic lesion area and T-cell number in the atherosclerotic lesions had increased.55

It was also demonstrated that T lymphocytes, derived from the spleens of previously CMV-infected mice, released IL-6 when exposed to CMV antigens,56 and medium bathing the T lymphocytes induced monocyte chemoattractant protein-1 expression in cultured human endothelial cells. Thus, T lymphocytes can locally release IL-6 when presented either with pathogen antigens that may be present in the plaque or with cross-reacting host peptides homologous to the relevant pathogen antigens, thereby triggering monocyte chemoattractant protein-1 release by endothelial cells, which recruits more monocytes and T cells into the vessel wall, thus exacerbating local inflammation and atherogenesis.

Circulating Cytokines
In the aforementioned studies,54,55 CMV-infected rats had higher serum levels of IL-2 and IL-4, and CMV-infected mice had elevated plasma interferon-γ and tumor necrosis factor-α levels. In addition, serum from CMV-infected mice induced monocyte chemoattractant protein-1 expression in cultured endothelial cells,57 an effect partly due to increases in circulating interferon-γ. Each of these effects of infection could exacerbate local inflammatory processes even if the infecting virus was not present in the vascular wall.

Immune-Mediated Mechanisms
Considerable evidence has emerged suggesting that immune-mediated responses targeted to self-antigens importantly contribute to atherogenesis. Thus, Xu, Wick, and their associates58,59 showed that HSPs may serve as targets for autoimmune reactions. HSPs are highly conserved proteins that reside mainly intracellularly; their expression is increased in response to stress. Under certain circumstances (such as exposure to inflammation, infection, and oxidizing agents), HSPs are presented on the cell surface,58,59 and, it was postulated, the surface presentation of these usually intracellular molecules made them appear as “cryptic antigens” recognized as “foreign” by the immune surveillance system. That autoimmune responses targeted to HSP60 play a role in atherosclerosis is suggested by several observations, including that (1) increased expression of human HSP60 occurs on endothelial cells, macrophages, and SMCs in human atherosclerotic lesions,59 and (2) the presence and extent of CAD correlates with the titers of anti-human HSP60 antibodies.60

This autoimmune mechanism provides the basis for a novel mechanism by which infection contributes to atherogenesis: the role of "molecular mimicry" as an inducer of autoimmune responses61–63 (Figure 1). The idea of molecular mimicry, introduced by Oldstone and associates,61,63 is based on the postulated consequences of a host being infected with a pathogen that contains epitopes that are homologous with epitopes of host proteins. The infection would trigger an immune response targeted to the pathogen,58,59 However, because of cross-reacting human epitopes, such as the HSPs, the pathogen-targeted antibodies could cross-react with human HSPs that are overexpressed on endothelial cells, thereby provoking an infection-induced autoimmune contribution to atherogenesis.

Many studies support the validity of this mechanism, including the following: (1) all bacteria encode for HSPs, and atherosclerotic lesions can be induced by immunization of rabbits with mycobacterial HSP6564; (2) serum antibodies to HSP65 are associated with carotid artery thickening65; (3) serum antibodies to HSPs of Escherichia coli and C pneumonia are cytotoxic to endothelial cells66; and (4) increasing...
Evidence Suggesting That Pathogens Play No Role in Atherogenesis: The Macrolide Antibiotic Trials

Early, relatively small trials testing the infection/atherosclerosis paradigm by administering macrolide antibiotics to patients with CAD reported a decrease in cardiovascular events.77–80 These studies, using an antibiotic that targeted *C. pneumonia*, were initiated because of the assumption prevalent in the late 1990s that if infection did play a role in atherogenesis, *C. pneumonia* was the most important pathogen involved; therefore, an antibiotic targeting *C. pneumonia* should exert salutary effects on incident-complicating events (acute myocardial infarction and/or death) in patients with CAD, particularly in CAD patients with an expected high event rate: those with recent acute coronary syndrome. These encouraging results led to larger randomized trials. The results of all of these studies were resoundingly negative77–80 (see the Table in the online-only Data Supplement).

A meta-analysis published in 200478 reviewed the results of 9 prospective, randomized, placebo-controlled trials (6 included only patients with acute coronary syndrome) and confirmed the conclusion that there was no treatment effect on clinical outcome (myocardial infarction and/or death). Another meta-analysis, published in 2005,79 included 11 such trials, containing a total of 19,217 patients; 6 studies, with 7,121 patients, included only patients with acute coronary syndrome. End points included all-cause mortality, myocardial infarction, and a combined end point of myocardial infarction and unstable angina. Antibiotic therapy had no impact on all-cause mortality among treated versus untreated patients, on the rates of myocardial infarction, or on the combined end point of myocardial infarction and unstable angina. Finally, in the most recently published meta-analysis, the investigators analyzed the results of 17 trials (containing 25,271 patients with 1877 deaths) and showed, paradoxically, a small but significant increase in relative risk (1.10) of death in the group treated with antibiotics.80

The conclusions of these studies were carefully circumscribed; for example, Etminan et al78 stated that the results “do not suggest that antibiotic therapy for *Chlamydia pneumonia* is beneficial in the secondary prevention of cardiovascular disease. . . . Thus, routine use of anti-chlamydial therapy for secondary prevention of coronary events is not indicated.” However, the negative results of these trials have often led to more global conclusions not only reflecting the lack of efficacy of macrolide antibiotics on cardiovascular outcome but, by implication, negating a causal role of *C. pneumonia* in atherosclerosis, as well as negating the general concept that infection with any pathogen contributes to atherosclerosis and its complications.

Limitations of the Conclusions Derived From the Antibiotic Trials

However, do such trials indicate, beyond the lack of effectiveness of anti-chlamydial antibiotic therapy, that *C. pneumonia* and other pathogens do not contribute to atherosclerosis? There are several considerations that lead us to the conclusion that the answer to this question is “no.”

First, there is no way to know whether the relatively limited time that patients were on the antibiotic was sufficient to eradicate *C. pneumonia* from the host. Chlamydia is an intracellular pathogen that is highly resistant to treatment during the persistent nonreplicating phase in its life cycle.81 Nonetheless, at this time it still expresses genes that are proinflammatory (as does CMV). In addition, not only is reinfection common, but *C. pneumonia* can be reactivated from its persistent phase at later times.79,81 These factors indicate that if *C. pneumonia* were in fact playing a role in precipitating events in patients with CAD, a single course of antibiotic treatment would not be expected to effectively reduce chlamydia-related complications over the long-term.

Pathogen Burden

An even more important limitation of the antibiotic trials is the consideration that if pathogens contribute to atherogenesis
and its complications, many such pathogens possess this activity. We therefore proposed that if infection plays a role in atherogenesis, it would be likely that (1) not one but many of the pathogens associated with atherosclerosis in epidemiological studies would be causally involved, and (2) the infection-related risk of atherosclerosis and its complications would correlate best with the aggregate pathogen load or what we termed “pathogen burden.”

The pathogens we studied (CMV, chlamydia, hepatitis A virus, HSV1, and HSV2) were selected because each was either an obligate intracellular pathogen known to establish a life-long infection and/or elicited a persistent life-long immune response (as manifest by increased anti-pathogen antibody levels). Employing angiography to document the presence or absence of CAD, we demonstrated in 2 studies with cross-sectional design an association between increasing number of infecting pathogens with increasing CAD risk, increasing C-reactive protein (CRP) levels, and increasing severity of coronary endothelial dysfunction. Moreover, 2 prospective studies were performed in CAD patients that assessed outcome over several years of follow-up. In both studies, it was found that pathogen burden predicted incidence of acute myocardial infarction and death: As the number of pathogens with which an individual had been infected increased, the incidence of acute myocardial infarction/death increased.

The major cause responsible for the end point assessed in these latter 2 prospective studies—acute myocardial infarction/death—is the same end point assessed in the antibiotic trials and undoubtedly predominantly reflects plaque rupture. It is therefore of great relevance that both of the prospective studies demonstrated that seropositivity to C pneumonia was not significantly related to these end points. In addition, most interestingly, the study by Rupprecht et al found that the predictive information for acute myocardial infarction/death was contained in the pathogen burden as related to virus infection: There was no predictive information contained in pathogen burden as it related to bacterial infection. (In a later analysis, these investigators demonstrated that bacterial pathogen burden was related to anatomic severity of CAD but not acute events.) Clearly, additional large trials investigating the role of pathogen burden in atherosclerosis and its complications, in which both bacteria and viruses are studied, need to be performed before definitive conclusions can be drawn. However, the existing data suggest that viruses more commonly than bacteria predispose to plaque rupture, whereas both viruses and bacteria appear to contribute to the initiation and/or progression of atherosclerosis.

It is therefore possible that the particular end point assessed in the antibiotic trials was flawed in that C pneumonia does not seem to be a strong predictor of plaque rupture (and its clinical consequences). Moreover, the results of the prospective studies of Zhu et al and Rupprecht et al strongly suggest that any trial testing the hypothesis that the eradication of a single pathogen might reduce cardiovascular event rate would almost certainly fail because there would be an extremely highly probability that the large majority of patients would have been infected with multiple pathogens. We found, for example, that 75% of patients were seropositive for ≥3 of the 5 pathogens for which we tested. Thus, an antibiotic trial would not necessarily fail because infection did not contribute to plaque rupture (although this could be a reason) but because of the probability that as long as other pathogens that might importantly contribute to disease outcome were not eradicated, an effect on outcome would be unlikely.

Individual Host Factors Leading to Differences in Host Response to Infection

Inflammatory and Immune Responses

There is considerable interindividual variability in a host’s ability to suppress pathogen-induced inflammatory activity. Although the genetic underpinnings for these differences are just beginning to be explored, an example of this derives from a study in which we examined the host response to CMV infection: Only about half of the individuals who were seropositive to CMV had a persistent inflammatory response associated with viral infection, as evidenced by elevated CRP levels. This difference appeared important biologically, as when infection was associated with an inflammatory response, there was a considerably higher risk of the patient having CAD. Thus, the likelihood of CMV contributing to CAD is greatest when the genetic makeup of the host is such that infection elicits an inflammatory response, and such a response is highly variable among different hosts.

Another layer of complexity involving host response to infection is gender-determined variability in the cellular versus antibody immune response. Thus, in a group of men and women being evaluated for CAD by coronary angiography, blood samples were tested for humoral (Ab+) and cellular (Tc+) responses to CMV and for CRP. In men, CMV seropositivity was associated with elevated CRP levels, and an elevated CRP was a significant determinant of CAD. CMV seropositivity was not independently associated with CAD. In contrast, in women, CRP levels were not significantly associated with CAD, whereas CMV seropositivity was independently predictive of CAD. Importantly, compared with CMV Ab+Tc− women, CAD prevalence was higher in Ab+/Tc− and Ab+/Tc+ but not in Ab−/Tc− women (25%). The major determinant of whether CMV infection in men leads to CAD therefore appears to be whether it evokes an inflammatory response. In women, the major determinant appears to be whether infection generates anti-CMV antibodies. An extension of this hypothesis is that women may be more prone than men to autoimmune mechanisms as they relate to the infection/atherosclerosis paradigm.

Genetic Factors

Data now suggest that at least part of the individual variability in susceptibility to pathogen-related CAD relates to genetic factors (ie, risk is modulated by host genotype). Thus, in an important study, C pneumonia seropositivity was most strongly associated with CAD in the subgroup of acute coronary syndrome patients who had specific single-nucleotide polymorphisms present in the inflammatory-related cytokine IL-1 gene (odds ratios for CAD were 1.4 in the group...
with chlamydial seropositivity and no IL-1 single-nucleotide polymorphisms, 1.7 with the single-nucleotide polymorphisms alone, and 3.8 with seropositivity and IL-1 gene polymorphisms. Interestingly, *C pneumonia* was associated with high acute myocardial infarction prevalence (odds ratio 2.8) only in patients with seropositivity and IL-1 gene polymorphisms.

Two other studies, examining the effects of 2 different single-nucleotide polymorphisms involving TLR4, illustrate the importance of genetic polymorphisms in the propensity for infection to influence CAD outcome. The investigators demonstrated that the frequency of the TLR4 polymorphism /H11001896A/G (which attenuates receptor signaling) was significantly lower in patients who had experienced myocardial infarction compared with controls. A second report demonstrated that IL-6 (a proinflammatory cytokine) expression was decreased in response to lipopolysaccharide in a whole blood assay in which cells were genotyped for another TLR4 single-nucleotide polymorphism: ASP299GLY. Like the prior study, the frequency of this polymorphism, which decreases TLR4 signaling, was significantly lower in patients with prior myocardial infarction compared with controls; of interest, the single-nucleotide polymorphism was present at increased frequency in centenarians. The investigators speculated that the interaction between infecting pathogen and host genotype determines the type and intensity of inflammatory responses and that individuals with TLR4 genotypes predisposing to a reduced inflammatory response would be expected to be resistant to pathogen-induced plaque rupture and acute myocardial infarction.

**Time**

Another factor adding to the complexity of any relation between infection and atherogenesis is the factor of time. Thus, if infection causes atherosclerosis, what accounts for the fact that children, who are frequently infected with virus, do not develop complications of atherosclerosis until many years later? This huge time lag can be explained in part by the likelihood that the multiple mechanisms by which pathogens might elicit clinically recognizable disease take decades to actually cause the magnitude of vessel wall changes that result in symptomatic disease. Probably more important is the fact that infection, if it does causally contribute to atherogenesis, is not a sufficient cause but requires the coexistence of multiple risk factors, many of which usually appear in adulthood.

**Summary and Conclusions**

In summary, compelling data indicate that infection does contribute to atherogenesis and to the acute complications of atherosclerosis caused by plaque rupture. What has clearly emerged over the past decade, however, is that there are profound complexities inherent in the interactions that occur between different pathogens and a variety of genetically determined host factors, each of which profoundly alters the host’s response to infection (Figure 2); these include the host’s susceptibility to infection, the magnitude of the host’s inflammatory response to a given infection, and whether the host is predisposed to develop an autoimmune response. Therefore, whether a specific pathogen (or combination of pathogens) will initiate, cause progression of, or precipitate one of the acute complications of atherosclerosis will be determined by these complex factors and their complex interactions. It would thus appear that we need considerably more information about an individual’s genetically based susceptibility to infection, to inflammation, and to immune responses before we can adequately predict how pathogens influence atherogenesis and its complications in the individual patient.

**Disclosures**

None.
References


Key Words: atherosclerosis ■ infection ■ inflammation
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Table. Major antibiotic trials in patients with coronary artery disease.

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<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Antibiotic intervention</th>
<th>Outcome measures</th>
<th>Follow up</th>
<th>Results</th>
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<td><strong>Stable CAD</strong></td>
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<tr>
<td>ACADEMIC¹</td>
<td>2000</td>
<td>302 patients with CAD and CPN titers of ≥1:16.</td>
<td>Azithromycin 500 mg/d for 3 d then 500 mg/wk for 3 mo or placebo</td>
<td>cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction (MI), stroke, unstable angina, and unplanned coronary revascularization</td>
<td>2 y</td>
<td>Negative</td>
</tr>
<tr>
<td>WIZARD²</td>
<td>2003</td>
<td>7747 patients with history of MI ≥ 6 wk ago and CPN titers of ≥ 1:16</td>
<td>Azithromycin (600 mg/d for 3 d then 600 mg/wk for 11 wk or placebo</td>
<td>first occurrence of death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina</td>
<td>14 mo</td>
<td>Negative</td>
</tr>
<tr>
<td>ACES³</td>
<td>2005</td>
<td>4012 patients with stable CAD</td>
<td>Azithromycin 600 mg/wk for 1 y or placebo</td>
<td>composite of death due to CHD, nonfatal MI, coronary revascularization, or hospitalization for unstable angina</td>
<td>3.9 y</td>
<td>Negative</td>
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<tr>
<td>CLARICOR⁴</td>
<td>2005</td>
<td>4373 patients with history of previous (≥3 mo) MI or angina pectoris</td>
<td>Clarithromycin 500 mg/d for 2 wk or placebo</td>
<td>composite of all cause mortality, MI, or unstable angina pectoris</td>
<td>3 y</td>
<td>Negative, Higher mortality in antibiotic arm (p= 0.03)</td>
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<tr>
<td><strong>Acute Coronary Syndromes</strong></td>
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<tr>
<td>ROXIS⁵</td>
<td>1999</td>
<td>202 patients with unstable angina</td>
<td>Roxithromycin 150 mg ×2/d for 30 d or placebo</td>
<td>ischemic death, acute MI, and severe recurrent ischemia</td>
<td>6 mo</td>
<td>Mixed</td>
</tr>
<tr>
<td>CLARIFY⁶</td>
<td>2001</td>
<td>148 patients with acute non–Q-wave MI or unstable angina</td>
<td>Clarithromycin 500 mg/d for 85 d or placebo</td>
<td>Composite of death, MI, or unstable angina</td>
<td>3 mo</td>
<td>Negative</td>
</tr>
<tr>
<td>STAMINA⁷</td>
<td>2002</td>
<td>325 patients with acute MI or unstable angina</td>
<td>Azythromycin 500 mg/d or amoxicillin 500 mg ×2/d, either plus metronidazole 400 mg ×2/d and omperazole 20mg ×2/d for 1 week or placebo</td>
<td>Readmission with, or death from, an acute cardiac event (unstable angina or MI)</td>
<td>12 mo</td>
<td>Positive (RR=0.61, Significant)</td>
</tr>
<tr>
<td>ANTIBIO⁸</td>
<td>2003</td>
<td>872 patients with unstable angina</td>
<td>Roxithromycin 300mg/d for</td>
<td>Total mortality</td>
<td>12 mo</td>
<td>Negative</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Patients/Design</td>
<td>Treatment</td>
<td>Endpoint Description</td>
<td>Duration</td>
<td>Result</td>
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<tr>
<td>AZACS</td>
<td>2003</td>
<td>1439 patients with acute MI or unstable angina</td>
<td>Azythromycin 500 mg on day 1 followed by 250 mg/d for 4 d or placebo</td>
<td>Composite of death, recurrent myocardial infarction, or recurrent ischemia necessitating revascularisation</td>
<td>6 mo</td>
<td>Negative</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>2005</td>
<td>4162 patients with ACS in the preceding 10 d</td>
<td>Gatifloxacin 400 mg/d for 2 wk followed by a 400 mg/d for 10 d/mo for 2 y or placebo</td>
<td>Composite of death from all causes, MI, documented unstable angina requiring rehospitalization, revascularization, and stroke.</td>
<td>2 y</td>
<td>Negative</td>
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<tr>
<td>Other</td>
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<tr>
<td>ISAR-3</td>
<td>2001</td>
<td>1010 patients with CAD and/or ACS after successful coronary stenting</td>
<td>Roxithromycin 300 mg/d for 28 d or placebo</td>
<td>Frequency of restenosis at follow-up angiography</td>
<td>1 y</td>
<td>Negative</td>
</tr>
<tr>
<td>Sander et. al.</td>
<td>2002</td>
<td>272 patients with TIA or minor ischemic stroke with available carotid IMT† measurement within previous 3 y</td>
<td>Roxithromycin 150 mg ×2/d for 30 d or placebo</td>
<td>Reduction of carotid IMT progression after treatment compared with the baseline period</td>
<td>2 y</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* CPN: *Chlamydia pneumonia*
† IMT: Intima-to-media thickness
**References**


