Review Article

Antibiotics in the prevention and management of coronary heart disease- A revisit

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Abstract
Risk factors for acute myocardial infarction other than the well-documented ones such as hyperlipidemia, hypertension, and smoking may account for the incidence of AMI in those with the absence of such traditional factors. Increasing evidence supports the hypothesis of a causal association between certain bacterial infections and increased risk of developing acute myocardial infarction (AMI). Several observational studies previously reported a possible link between bacterial infections and subsequent coronary heart disease or AMI. Some of the findings were refuted by large meta-analyses. We attempt to revisit the topic and throw light on the need for further exploration of the association between infective etiology and AMI.

Introduction:
Atherosclerosis is an active, inflammatory, and thrombotic process rather than a passive infiltrative one. Bacterial vectors as causal factors of atherosclerosis have been postulated and researched. Finding Chlamydia pneumonia and other bacterial antigens and, occasionally, recoverable organisms, within human atherosclerotic plaque further supports this hypothesis. Viral etiology in causation of atherosclerosis was also opined and substantiated by the proof that Marek disease virus in chickens was associated with marked and accelerated atherosclerosis. Herpes simplex 1 and 2, Epstein-Barr virus, human immunodeficiency virus, and influenza A were also believed to exacerbate atherosclerosis.

Evidence for benefit
Macrolide antibiotics have shown benefit in various cardiovascular diseases, such as myocarditis, cardiac transplant rejection and myocardial infarction probably via
alteration of inflammatory factors and controlling the up-regulation of matrix metalloproteinases (MMPs).

In experimental models clarithromycin resulted in a significant reduction of the infarction area:area at risk ratio and preserved fractional shortening ratio after 14 days of reperfusion. Clarithromycin significantly reduced ischemia-reperfusion injury mediated left ventricular fibrosis via increasing MMP activities and controlling macrophage proliferation. Long-term clarithromycin treatment may reduce recurrent cardiovascular events. In the CLARIFY (Clarithromycin in Acute Coronary Syndrome Patients in Finland) trial it was shown that treatment with clarithromycin appears to reduce the risk of ischemic cardiovascular events in patients presenting with acute non-Q-wave infarction or unstable angina.

As per the ACADEMIC (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia) trial Azithromycin use for 6 months significantly decreased Anti–C. pneumoniae titers compared to placebo (43% vs 10%) with modest-to-moderate antibiotic benefit (20%–30% event reduction) in CHD and acute coronary syndromes. Azithromycin also significantly reduced systemic markers of inflammation such as C-reactive protein and interleukin-6. The WIZARD trial (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) suggested a possible benefit during and shortly after treatment with azithromycin (33% reduction in death or myocardial infarction at 6 months). STAMINA (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina), showed that either azithromycin + omeprazole + metronidazole or amoxicillin + omeprazole + metronidazole had a 36% reduction in major coronary events at 12 weeks compared with placebo with benefit lasting through 1 year.

The ROXIS (Roxithromycin in Ischemic Syndromes) study showed that the rates of recurrent ischemia, AMI and ischemic death tended to be lower in the patients treated with roxithromycin. The ISAR-3 (Intracoronary Stenting and Antibiotic Regimen 3) study investigated roxithromycin, for the prevention of restenosis after coronary stent deployment and showed some benefit of roxithromycin in those with high titers of anti-Chlamydia antibodies. Roxithromycin appears to extend the clinical benefit of preventing death and re-infarction for at least 6 months after initial treatment.

Either azithromycin or roxithromycin post-AMI in patients with AMI and elevated anti–C pneumoniae antibody titers had significantly lowered recurrence and cardiac complication rates compared with placebo-treated patients. A population-based case-control analysis showed that cases who had first-time acute myocardial infarction were significantly less likely to have used tetracycline antibiotics or quinolones. Although indirect this shows an association between bacterial infections with organisms susceptible to tetracycline or quinolone antibiotics and the risk of acute myocardial infarction.
Lack of evidence
The Antibiotic Therapy after Acute Myocardial Infarction (ANTIBIO) study showed no significant benefit with use of roxithromycin in reduction of coronary events.\textsuperscript{11}

PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) had a gatifloxacin arm which did not show any benefit in minimizing CHD event risk.\textsuperscript{12} The Azithromycin and Coronary Events Study (ACES) showed that azithromycin did not alter the risk of cardiac events among patients with stable coronary artery disease.\textsuperscript{13} The Azithromycin in Acute Coronary Syndrome (AZACS) study, the largest antibiotic trial to date in ACS showed no benefit of antibiotic therapy (azithromycin) upon ischemic endpoints was observed.\textsuperscript{14} A more recent metaanalysis did not find any association between use of antibiotics in secondary prevention of cardiac events.\textsuperscript{15}

Conclusion
The effect of antibiotics on curbing the risk of AMI as depicted in some studies above is only an indirect marker for an etiologic role of bacterial infections and does not prove the existence of a causal relationship. Although routine clinical use of antibiotics in primary or secondary prevention of coronary heart disease is not supported at this point in time, there may be specific subsets of patients in whom amelioration of infection via antibiotics may be of some benefit. There is a need for large-scale prospective randomized trials to establish universal guidelines as to the role of infections in the etiology of AMI and their treatment if at all.

References


12. Pokrovskaya EV. Final confirmation of inefficiency of antibiotics in secondary prevention of coronary heart disease. Results of PROVE IT (gatifloxacin trial) and ACES. Kardiologiia 2004;44:82-3.

