The scourge of coronary disease in diabetic patients: will antibiotics sweeten the pill?

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Diabetes is a major and increasing public health problem and this is reflected in the growing proportion of diabetics presenting with coronary artery disease[1]. In this issue, Erkens et al. present data that suggest a potential role for antibiotics in the prevention of coronary heart disease in diabetic patients. While the results are provocative, the authors readily admit that they should be regarded as hypothesis-generating rather than definitive.

Although the hypothesis that chronic infection plays a role in the pathogenesis of coronary heart disease (CHD) is far from new, few studies have looked specifically at the diabetic population[2–5]. The infectious agent for which the link with atherosclerosis is the strongest is Chlamydia pneumoniae, a Gram-negative obligatory intracellular bacterium, and we will only discuss this pathogen, which is also the focus of the paper by Erkens et al.[1].

*Chlamydia pneumoniae* is the second most prevalent bacterial cause of atypical pneumonia[4]. It is also responsible for acute pharyngitis, sinusitis, and bronchitis. About half of the adult population have positive *C. pneumoniae* antibodies titres. There is no definitely reliable laboratory test, and some of these tests are technically demanding (e.g. microimmunofluorescence)[5].

More than 30 seroepidemiological studies have looked at the relationship between *C. pneumoniae* antibodies and CHD[2,5]. In most of these studies, the odds ratio was at least two. In some of them, the odds ratio increased with increasing antibody titres. The results appear consistent from one study to another, thus the relation between *C. pneumoniae* and CHD may be real. But there may be biases: the populations differed, as did the design of the studies (case-control, prospective), the criteria for cases, the method of detection of antibodies, the cut-off for defining seropositivity, the degree of adjustment for potential confounders (e.g. smoking), publication bias favouring positive results; only very few studies were prospective. Recently, Danesh et al., in a meta-analysis of 15 prospective studies, found only a weak association between *C. pneumoniae* IgG titres and CHD: the odds ratio was 1.15 (95% confidence interval: 0.97–1.36)[6].

Multiple pathological studies have shown the presence of *C. pneumoniae* in human atherosclerotic specimens, by different techniques (immunochemistry, polymerase chain reaction, electron microscopy, culture), at various stages of the atherosclerotic process[3,5]. In 13 studies of *C. pneumoniae* in human pathology samples, infection was present in 52% of atheromatous lesions and in only 5% of control arterial samples[2]. Supportive evidence for a role of *C. pneumoniae* in the pathogenesis of atherosclerosis from animal models is less clearcut[3,4,7].

Of course, a link between *C. pneumoniae* and CHD does not necessarily imply that a causal relationship exists. According to the ‘innocent bystander’ hypothesis, *C. pneumoniae* could be carried by circulatory monocytes from the site of infection and remain dormant in atheromatous lesions[5,8].

Some potential mechanisms by which *C. pneumoniae* might promote atherosclerosis are its replication in macrophages and in other cells (e.g. endothelial cells, smooth muscle cells), triggering of the clotting cascade, stimulation of the release of stimulators of the inflammatory process (e.g. interleukin-1, interleukin-6, TNF-α, interferon-α), or an autoimmune reaction involving heat shock proteins (e.g. HSP60)[4].

Three trials of antibiotics (macrolides) active against *Chlamydia* in patients with CHD have been published[9–13]. In the United Kingdom, 220 male survivors of myocardial infarction were screened for anti-Chlamydia antibodies[9]. Sixty patients with persisting seropositivity of ≥1/64 were randomized to oral azithromycin, 500 mg day<sup>−1</sup> for 3 days, 500 mg day<sup>−1</sup> for 6 days or placebo. After a mean follow-up of 18 ± 4 months, the adjusted odds ratio for cardiovascular events was 2.0 (0.6–6.8) in patients with titres of 1/8 to 1/32 dilution, 4.2 (1.2–15.5) in patients receiving placebo or with titres of 1/64 dilution but not randomized and 0.9 (0.2–4.6) in patients receiving azithromycin (reference: patients with no detectable antibodies; adjustment on age, diabetes...
mellitus, smoking, hypertension, hyperlipidemia and previous resvascularization).

The ROXIS trial tested the effect of roxithromycin in 202 patients with unstable angina or non-Q-wave myocardial infarction\[10\]. In this double-blind randomised controlled trial performed in Argentina, the patients received either oral roxithromycin 150 mg twice a day for 30 days or placebo. Between 72 h and day 31, the rate of recurrent ischaemia, myocardial infarction and ischaemic death was 5%, 2% and 2% in the placebo group and 2%, 0% and 0% in the roxithromycin group, respectively; the rate of the triple endpoint was 9% in the placebo group and 2% in the roxithromycin group (unadjusted \(P=0.032\); \(P\) after Bonferroni correction for multiple comparisons = 0.064). At 3 and 6 months, there was no difference between the roxithromycin group and the placebo group\[11\].

In the ACADEMIC randomized trial, 302 patients with CHD and seropositive to \(C.\ pneumoniae\) (IgG titres \(\geq 1/16\)) received either oral azithromycin, 500 mg \(\times\) day\(^{-1}\) for 3 days then 500 mg \(\times\) week\(^{-1}\) for 3 months or placebo. At 6 months and 2 years, there was no reduction in the rate of cardiovascular events\[12,13\].

One must remember that, besides their antimicrobial effects, macrolides, also have antiinflammatory and plaque-stabilizing effects\[14,15\].

The study of Erkens was a nested case-control study in type 2 diabetics in the Netherlands\[1\]. Two-hundred and forty-four patients hospitalized for CHD were matched to 686 patients without CHD. The use of antibiotics during 3 years prior to the event was determined via a database of pharmacy drug-dispensing records. The use of fluoroquinolones for more than 2 weeks was associated with a lower risk of CHD (odds ratio: 0.30; 95% CI: 0.12–0.75). There was no association between CHD and other antibiotics, i.e. tetracyclines, macrolides, lincosamides, penicillins, cephalosporins, sulphonamides and trimethoprim. While provocative, the findings are subject to multiple caveats such as the design of the study (retrospective, case control), and the possibility that they may be related to the presence of unidentified confounding factors. Nevertheless, they open another potential avenue for research.

We now know that several ‘non-infectious’ diseases are linked to microorganisms, e.g. peptic ulcer disease and \(Helicobacter pylori\) or Whipple’s disease and \(Tropheryma whippleii\). Erkens work adds another element to the infectious theory of CHD. Nevertheless, as yet we do not have any firm evidence that \(C.\ pneumoniae\) is causally related to CHD. The negative results of one eagerly awaited trial, the WIZARD (Weekly Intervention with Zithromax in Atherosclerosis-Related Disorders) study, presented orally at the recent Annual Scientific Sessions of the American College of Cardiology, is a major setback for expectations that azithromycin might have clinical benefit in atherosclerosis. However, several other large-scale trials of anti-Chlamydia antibiotics in patients with infection and CHD, including a total of nearly 20 000 patients, are ongoing: ACES (Azithromycin and Coronary Events Study), MARBLE (Might Azithromycin Reduce Bypass List Events), and PROVE-IT (Pravastatin or atorvastatin evaluation and infection therapy). Their results are eagerly awaited. Erkens work suggests that studies in primary prevention, perhaps in patients without CHD, but with cardiovascular risk factors, such as diabetes mellitus may also be worthwhile.

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**References**


Homocysteine, smoking and vascular disease

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Cigarette smoking has long been recognised as a major risk factor for vascular disease, while the role of homocysteine, a relatively ‘new boy on the block’ is still unclear. Homocysteine, a sulphur-containing amino acid, was first linked to a human disorder in 1963. This was with the identification in Ireland[1] and in the U.S.A.[2] of a new inborn error of metabolism associated with the urinary excretion of homocystine, the oxidised form of homocysteine. Homocystinuria was later shown to be due to a deficiency of the enzyme cystathionine β-synthase, which mediates the conversion of homocysteine to cystathionine in the metabolism of the essential amino acid, methionine. Untreated, this defect is associated with elevated plasma methionine, very high levels of circulating total homocysteine (150–300 μmol.l⁻¹), commonly a marfanoid bodily habitus and dislocation of the ocular lens and, importantly, with precocious vascular disease. It was McCully who first postulated that even mild elevation of circulating homocysteine might also contribute to the aetiology of vascular disease came from a recognition of the difficulty of explaining the totality of the occurrence and extent of coronary artery disease solely in terms of the recognised standard risk factors[7]. Indeed, we were only able to account for about 50% of the variance in severity of angiographically-determined coronary disease in patients aged less than 65 years, in terms of the hierarchy of circulating lipid variables and other clinical factors known to be predictive of vascular disease[8]. Many studies have now confirmed the presence of an association between modest homocysteine elevation and the occurrence of vascular disease[9], and most recently also with Alzheimer disease[10], perhaps emphasising the importance of a vascular component in its development.

The very large Hordaland total plasma homocysteine and cardiovascular risk profile study conducted in Norway identified a positive association between elevated plasma total homocysteine levels and a number of cardiovascular risk factors including, particularly, smoking[11]. The results of the study by O’Callaghan and colleagues in the present issue provide compelling support for this observation but show further that cardiovascular risk in smokers is markedly increased when plasma homocysteine is also increased[12]. In the comprehensive analysis now reported from the large European Concerted Action Project case control study, O’Callaghan and colleagues provide convincing evidence for an amplifying effect of cigarette-smoking on homocysteine-associated cardiovascular risk[13]. Smokers with plasma homocysteine levels above 12 μmol.l⁻¹ had, in this study, a 12-fold increase of cardiovascular risk when compared with the risk in non-smokers with plasma homocysteine less than 12 μmol.l⁻¹. B vitamins, particularly folic acid, tended to be lower in the smokers, as expected, but importantly the amplification of risk persisted after controlling for the levels of B-vitamins. The mechanisms mediating this synergy between homocysteine and smoking remain unclear.