A meta-analysis of antibiotic use for the secondary prevention of cardiovascular diseases

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BACKGROUND: A number of clinical trials have examined whether antibiotics decrease the incidence of adverse events in patients with cardiovascular diseases. However, results have occasionally been conflicting, and a meta-analysis may provide additional clarification.

OBJECTIVE: To address whether antibiotic use can reduce the risk of future cardiac events among patients with established cardiovascular diseases.

METHODS: PubMed and the Cochrane Central Register of Controlled Trials were searched using the key words "antibiotic" and "cardiovascular diseases". Only randomized, placebo-controlled trials of patients with established cardiovascular disease and reporting cardiovascular outcomes were included. A random effects model was used and a fixed model was applied for sensitivity analysis.

RESULTS: A total of 393 papers published between January 1, 1994, and April 31, 2006, were initially identified. Thirteen trials (12,491 patients in the treatment group and 12,518 patients in the control group) were retained and included in the present meta-analysis. The pooled RR for the composite event end point, including death, myocardial infarction admission and unplanned revascularization procedures, was 0.96 (95% CI 0.90 to 1.04). No associations were seen for the individual outcomes of mortality (RR 1.07, 95% CI 0.96 to 1.19) or myocardial infarction/unstable angina (RR 0.96, 95% CI 0.85 to 1.07). Subgroup analyses based on patient populations (stable or unstable), type of antibiotics, or restricted to those with immunoglobulin G *Chlamydia pneumoniae* antibodies were also negative for a beneficial treatment effect. Similar results were found using a fixed effects model.

CONCLUSIONS: The meta-analysis did not provide evidence of an association between antibiotic use and the secondary prevention of cardiac events. Further research in this area does not appear to be promising.

Key Words: Antibiotic; Cardiovascular diseases; Meta-analysis; Secondary prevention

The increasing burden of cardiovascular diseases and their associated costs have motivated health researchers to investigate novel therapies for the primary and secondary prevention of cardiovascular diseases, particularly among high-risk patients (1,2). Recent investigations have established an association between systemic inflammation and cardiovascular diseases, and this relationship has become an area of active research (3). The biological mechanism of atherosclerosis involves inflammation, endothelial dysfunction and possible plaque instability. Acute inflammation may also alter circulating clotting factors and inflammatory cytokines, thereby intensifying a predisposition to atherothrombosis (4).

If a causal pathway between bacterial infection, inflammation and atherosclerosis exists, antibiotic use may reduce the progression of the atherosclerosis process and, thus, may reduce the risk of subsequent cardiovascular events. Among possible pathogens, the strongest putative association exists between cardiovascular diseases and *Chlamydia pneumoniae* infection. This association has been observed in seroepidemiological studies (5), animal studies (6) and examinations of

Une méta-analyse de l'utilisation des antibiotiques en prévention secondaire des maladies cardiovasculaires

HISTORIQUE : Plusieurs essais cliniques ont analysé si les antibiotiques réduisent l'incidence d'effets indésirables chez les patients atteints d'une coronaropathie. Cependant, les résultats sont parfois contradictoires, et une méta-analyse pourrait clarifier la situation.

OBJECTIF : Vérifier si l'utilisation d'antibiotiques peut réduire le risque de futurs événements cardiaques chez les patients atteints d'une coronaropathie établie.

MÉTHODOLOGIE : Les auteurs ont effectué des recherches dans PubMed et le *Cochrane Central Register of Controlled Trials* à l'aide des mots-clés *antibiotics* et *cardiovascular diseases*. Les auteurs ont seulement inclus dans l'étude les essais aléatoires et contrôlés contre placebo des patients atteints d'une coronaropathie établie et dont l'issue cardiovasculaire était précisée. Ils ont utilisé un modèle d'effets aléatoires et ont appliqué un modèle fixe pour l'analyse de sensibilité.

RÉSULTATS : Au total, les auteurs ont d'abord repéré 393 articles publiés entre le 1^{er} janvier 1994 et le 31 avril 2006. Ils ont retenu et inclus 13 essais (12 491 patients dans le groupe traité et 12 518 dans le groupe témoin) dans la présente méta-analyse. Le RR groupé pour le point limite d'événement composite, y compris la mort, l'hospitalisation pour un infarctus du myocarde et des interventions de revascularisation non planifiées, s'élevait à 0,96 (95 % IC 0,90 à 1,04). Les auteurs n'ont remarqué aucune association avec les issues personnelles de mortalité (RR 1,07, 95 % IC 0,96 à 1,19) ou d'infarctus du myocarde ou d'angine instable (RR 0,96 95 % IC 0,85 à 1,07). Les analyses de sous-groupes fondées sur la population de patients (stables ou instables), sur le type d'antibiotiques ou sur la restriction aux personnes possédant des anticorps aux *Chlamydia pneumoniae* de l'immunoglobuline G étaient également négatives à un effet bénéfique du traitement. Les auteurs ont obtenu des résultats similaires au moyen d'un modèle d'effets fixes.

CONCLUSIONS : La méta-analyse n'a pu démontrer une association entre l'utilisation d'antibiotiques et la prévention secondaire des événements cardiaques. Les recherches supplémentaires dans ce domaine ne semblent pas prometteuses.

human pathology specimens (7). Consequently, anti-*Chlamydia* antibiotics have been the therapy of choice in most randomized controlled trials investigating the use of antibiotics for the prevention of cardiac events. Of note, trials to date have focused on the use of antibiotics for secondary prevention; primary prevention trials are impractical due to the low event rates in this population. Trials examining the use of antibiotics for secondary prevention have provided conflicting results. We have therefore conducted a meta-analysis to determine whether antibiotic use is effective for secondary prevention among patients with cardiovascular diseases.

METHODS

Search strategy

The present meta-analysis was conducted following the guidelines described in the Quality of Reporting of Meta-analyses statement (8). PubMed and the Cochrane Central Register for Clinical Trials databases were searched using the key words "antibiotic" and "cardiovascular disease". The search was limited to journal articles published

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Figure 1) Flow chart for trial selection. RCT Randomized controlled trial

between January 1, 1994, and April 30, 2006. January 1, 1994, corresponds to the initial publication of a hypothetical association between respiratory tract infection and cardiovascular diseases (9), and 3.5 years before the first published secondary prevention trial examining antibiotic use in patients with cardiovascular disease (10). References from relevant studies were also searched for additional trials.

Inclusion and exclusion criteria

Randomized, placebo-controlled, parallel-design clinical studies of patients with established cardiovascular disease were included. The objective was to examine antibiotic use as secondary prevention among patients with cardiovascular diseases. Consequently, only studies reporting cardiac events (death, nonfatal myocardial infarction (MI), angina or unplanned revascularization procedures) were retained. In addition, the meta-analysis was limited to trials published as full-length articles in English.

Nonexperimental studies and interim reports of ongoing trials were excluded. Trials investigating antibiotic-coated drug-eluting stents or antibiotic use in cardiac transplantation were also excluded.

Data abstraction and analysis

Data were extracted by one investigator (ZS) and validated by one of two investigators (JMB or PB). Extracted data included study design, length of follow-up, type of intervention, dosage, patient characteristics and cardiac outcomes. If all relevant information was not available, a search of conference abstracts and secondary publications by the same authors was conducted to obtain the missing data.

Study quality of the identified trials was also assessed (11). The quality assessment included reviewing the following components of each trial: randomization, double-blinding, dropouts and withdrawals, random number generation and allocation concealment. Studies that received a score of at least three out of five were deemed to be of high quality.

In the primary analysis, data were pooled using a random effects model (Review Manager V4.27) (12), which allows for both within- and between-study variability. The risk difference and number needed to treat were also determined. In secondary analyses, subgroup analyses were performed to examine the effect of different antibiotics and patient populations on cardiac events. The primary analysis was repeated using a fixed effects model as part of the sensitivity analyses. Funnel plots were constructed to assess the potential presence of publication bias.

RESULTS

A total of 393 publications were initially identified and 13 randomized controlled trials were finally included in the meta-analysis (Figure 1). These 13 trials randomly assigned a total of 12,491 patients to the

treatment group and 12,518 patients to the control group. A search of the Cochrane Central Register of Controlled Trials databases did not identify any additional studies, nor did the review of references of identified trials. All 13 trials received a quality score of more than three out of five.

Table 1 summarizes the details of trials included in the present meta-analysis. Trial populations were slightly variable. Six trials were conducted among patients with stable coronary artery disease (10,13-17) and six trials involved patients with acute coronary syndromes (18-23). The remaining trial was conducted among patients scheduled to undergo coronary artery bypass graft surgery (24). Three trials (10,13,14) included anti-Chlamydia immunoglobulin (IgG) titres as part of their inclusion criteria. Trials examined the use of one of four different antibiotics: azithromycin (seven trials) (10,13-15,19-21), roxithromycin (two trials) (17,22), clarithromycin (three trials) (16,23,24) and gatifloxacin (one trial) (18).

Antibiotic use was found to be no more effective than placebo for the secondary prevention of cardiac events, defined as a composite end point of death, nonfatal MI, angina or unplanned revascularization procedures (RR 0.96, 95% CI 0.89 to 1.05) (Figure 2). Similar results were obtained while examining the effects of antibiotic use on mortality (RR 1.07, 95% CI 0.96 to 1.19) and MI or unstable angina (RR 0.96, 95% CI 0.85 to 1.07). Similar results were obtained regardless of antibiotic investigated (Figure 3). In subgroup analyses, there remained no association when analyses were restricted to studies that used IgG as an inclusion criterion (RR 0.86, 95% CI 0.64 to 1.16) or to studies involving patients with unstable coronary artery disease (RR 0.92, 95% CI 0.84 to 1.01). Although the proximity of this RR to statistical significance may merely represent a type I error, the absolute risk difference was also calculated between treatment and control groups for patients with acute coronary syndrome to gain insight into any potential clinical benefits. The point estimate of this risk difference was 0.016 (95% CI -0.003 to 0.034), suggesting that 63 patients (number needed to treat) would require treatment for approximately 18 months to avoid one cardiac event. However, because this result was statistically nonsignificant, the CI extends from a number needed to treat as low as 29 to a number needed to harm as low as 333.

In sensitivity analyses, similar results were obtained using a fixed effects model. In addition, our funnel plot suggests that our results may have been affected by publication bias (Figure 4). In particular, small trials with negative (nonprotective) results appear to have been less likely to be published.

DISCUSSION

The present meta-analysis failed to detect a significant association between antibiotic use and secondary prevention of composite cardiovascular events. These results were consistent regardless of the individual cardiac end point examined, antibiotic chosen or baseline clinical status. Even for the specific high-risk acute coronary syndrome population, antibiotic use was not associated with reduced cardiac outcomes.

The association between *C pneumoniae* and cardiovascular diseases was initially noted in serological studies investigating anti-*C pneumoniae* IgG antibody titre (3). However, recent studies suggest that *C pneumoniae* DNA is present in peripheral blood samples of only 8% of cardiovascular patients, while more than 70% of these patients are IgG-positive (25,26). In addition, at least 15 observational studies have failed to find *C pneumoniae* DNA in atherosclerotic lesions using polymerase chain reaction (PCR) (27). Two recent studies (18,28) of cardiovascular patients have confirmed this very low prevalence (lower than 3.5%) of *C pneumoniae*, as assessed by DNA using PCR. This accumulating evidence casts doubt on the hypothesized relationship between *C pneumoniae* infection and cardiovascular disease suggested by IgG titre evidence. Unfortunately, no study to date has avoided this potential misclassification bias by examining the true role of *C pneumoniae* found in peripheral blood monocytes using PCR in this patient population.

Although we believe our findings dispel any positive association between antibiotic use and improved cardiac outcomes, there are a

TABLE 1
List of randomized placebo-controlled trials of antibiotic use among patients with cardiovascular diseases

Trial (year), reference	Inclusion criteria	Intervention	Dosage	Clinical outcomes	Follow-up
Gupta et al (1997), 10 (n=213)*	Acute MI survivors with anti-Chlamydia IgG titres ($\geq 1:64$)*	Azithromycin	1 course of 500 mg once daily for 3 days (n=28) or 2 courses 3 months apart (n=12)	First admission with nonfatal MI; UA, coronary angioplasty, urgent CABG surgery; cardiovascular death	18 months
ROXIS (1999), 22 (n=202)	Patients with UA or non-Q wave MI	Roxithromycin	150 mg twice daily for 30 days	Severe recurrent ischemia, MI and death	6 months
ACADEMIC (2000), 13 (n=302)	Patients with previous MI, bypass surgery, or >50% angiographic stenosis of ≥ 1 major coronary artery and anti-Chlamydia IgG titres ($\geq 1:16$)	Azithromycin	500 mg once daily for 3 days followed by 500 mg once monthly for 3 months	Cardiovascular death, resuscitated cardiac arrest, nonfatal MI, stroke, UA and coronary intervention	18 months
ISAR-3 (2001), 17† (n=1010)	Patients successfully receiving stent placement (random assignment was within 2 h of stenting)	Roxithromycin	300 mg once daily for 28 days	Death and MI‡	12 months
CLARIFY (2002), 23 (n=148)	Patients with UA or non-Q wave MI	Clarithromycin	500 mg once daily for 85 days	Death, MI and UA	18.5 months§
STAMINA (2002), 19¶ (n=325)	Patients admitted with UA or acute MI	Azithromycin	Azithromycin (500 mg daily) + metronidazole (400 mg twice daily) + omeprazole (20 mg twice daily) or placebo for 1 week	Cardiovascular death, readmission with MI or UA, and revascularization	12 months
ANTIBIO (2003), 20 (n=872)	Patients within 5 days of MI	Azithromycin	300 mg once daily for 6 weeks	Death, MI, resuscitation, stroke, readmission for UA	12 months
AZACS (2003), 21 (n=1439)	Patients with chest pain or discomfort consistent with myocardial ischemia lasting at least 5 min and within 24 h of hospital admission, other MI syndromes	Azithromycin	500 mg for one day or 250 mg for 4 days	Death, nonfatal MI and coronary revascularization for recurrent myocardial ischemia	6 months
WIZARD (2003), 14 (n=7747)	Patients with previous MI at least 6 weeks before random assignment and anti-Chlamydia IgG titres ($\geq 1:16$)	Azithromycin	600 mg once daily for 3 days in the first week and 600 mg once weekly for 11 weeks	Death, nonfatal MI, coronary revascularization and readmission with angina	14 months
ACES (2005), 15 (n=4016)	Patients with prior MI documented by enzyme criteria, or past coronary revascularization or angiographic evidence of >50% stenosis	Azithromycin	600 mg once weekly for 1 year	CAD death, MI, revascularization and hospitalized UA	4 years
PROVE-IT (2005), 18 (n=4160)	Patients hospitalized within preceding 10 days with an acute coronary syndrome	Gatifloxacin	Either pravastatin 40 mg or atorvastatin 80 mg once daily; plus gatifloxacin 400 mg once daily for 2 weeks, then 10-day course each month	CAD death, MI, hospitalized UA, revascularization (>30 days after random assignment), stroke	2 years§
Berg et al (2005), 24 (n=473)	Patients scheduled to undergo CABG	Clarithromycin	500 mg once daily for an average of 16 days	Death, MI, UA and unplanned intervention	2 years
CLARICOR (2006), 16 (n=4372)	Patients with stable CAD (MI and/or angina pectoris)	Clarithromycin	500 mg once daily for 14 days	Death, MI and UA	2 years

*Patients (n=213) were stratified by anti-Chlamydia pneumoniae (Cp) status: 59 patients were Cp-negative, 74 had intermediate titres and 80 patients were Cp-seropositive. Patients in the Cp-seropositive group were then randomly assigned to oral azithromycin. The remaining 20 patients were not recruited into the trial (10); †This trial used multiple statistical analyses (comparisons) and obtained one significant result (one interaction term in a secondary analysis); ‡The primary end point of this study was angiographic restenosis, defined as $\geq 50\%$ stenosis of the vessel diameter; §Median follow-up time; ¶The South Thames Antibiotics in Myocardial Infarction and Angina (STAMINA) study (19) had three arms (one placebo arm and two treatment arms), and only patients in the azithromycin and placebo arms were included in this meta-analysis. In the third arm, patients (n=107) received amoxicillin (500 mg) + metronidazole (400 mg twice daily) + omeprazole (20 mg twice daily). Of note, this is the only trial that looked at the combined effects with other anti-infection drugs. ACADEMIC Azithromycin in Coronary Artery Disease Elimination of Myocardial Infection With Chlamydia; ACES Azithromycin and Coronary Events Study; ANTIBIO Antibiotic Therapy After Acute Myocardial Infarction; AZACS Azithromycin in Acute Coronary Syndrome; CABG Coronary artery bypass graft; CAD Coronary artery disease; CLARICOR Clarithromycin for Patients with Stable Coronary Artery Disease; CLARIFY Clarithromycin in Acute Coronary Syndrome Patients in Finland; IgG Immunoglobulin G; ISAR-3 Intracoronary Stenting and Antithrombotic Regimen-3; MI Myocardial infarction; PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy; ROXIS Roxithromycin Ischemic Syndromes; UA Unstable angina; WIZARD Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders

Figure 2) Forest plot of the effects of antibiotic use on the secondary prevention of cardiovascular events. ACADEMIC Azithromycin in Coronary Artery Disease Elimination of Myocardial Infection With Chlamydia; ACES Azithromycin and Coronary Events Study; ANTIBIO Antibiotic Therapy After Acute Myocardial Infarction; AZACS Azithromycin in Acute Coronary Syndrome; CLARICOR Clarithromycin for Patients with Stable Coronary Artery Disease; CLARIFY Clarithromycin in Acute Coronary Syndrome Patients in Finland; ISAR-3 Intracoronary Stenting and Antithrombotic Regimen-3; PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy; ROXIS Roxithromycin Ischemic Syndromes; STAMINA South Thames Antibiotics in Myocardial Infarction and Angina; WIZARD Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders

Figure 3) Forest plot of the effects of antibiotic use on the secondary prevention of cardiovascular events by type of antibiotic. ACADEMIC Azithromycin in Coronary Artery Disease Elimination of Myocardial Infection With Chlamydia; ACES Azithromycin and Coronary Events Study; ANTIBIO Antibiotic Therapy After Acute Myocardial Infarction; AZACS Azithromycin in Acute Coronary Syndrome; CLARICOR Clarithromycin for Patients with Stable Coronary Artery Disease; CLARIFY Clarithromycin in Acute Coronary Syndrome Patients in Finland; ISAR-3 Intracoronary Stenting and Antithrombotic Regimen-3; ROXIS Roxithromycin Ischemic Syndromes; STAMINA South Thames Antibiotics in Myocardial Infarction and Angina; WIZARD Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders

number of other potential explanations that should be considered. First, it is possible that timing of introduction of antibiotic therapy may play a role in its effectiveness. Two animal studies (29,30)

Figure 4) Funnel plot of trials examining the use of antibiotics for the secondary prevention of cardiovascular events

suggested that the early phase of *C pneumoniae* infection may be the optimal time for the introduction of antibiotic therapy for the prevention of the atherosclerotic process. Therefore, restricting the target population to unstable patients with acute coronary syndrome with antibiotics may theoretically increase the likelihood of finding an association. To examine this hypothesis, we conducted a secondary analysis that was limited to patients with unstable coronary artery disease, but the results of this analysis again failed to find an association between antibiotic use and the occurrence of cardiovascular events. Furthermore, only one of seven trials involving acute coronary syndrome patients reported significant results. For example, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial (18), which randomly assigned patients within 10 days of an acute coronary syndrome, failed to demonstrate any significant cardioprotective effects of antibiotic use. Thus, the possibility that we obtained a null result due to the presence of a suboptimal treatment initiation period appears to be unlikely.

Second, it is possible that the type of antibiotic, duration of treatment or dosing regimen can modify the cardioprotective effects of antibiotic use. However, our subgroup analyses found similar results regardless of which antibiotic was used (Figure 3). Furthermore, the Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders (WIZARD) trial (14), which involved three months of continuous azithromycin treatment and, thus, exceeded the known 90% minimum inhibitory concentration for *C pneumoniae*, did not find a protective effect. The PROVE-IT trial (18) (two years of biweekly gatifloxacin [quinolone]) and the Azithromycin and Coronary Events Study (ACES) (15) (one year of monthly azithromycin [macrolide]) were also designed to evaluate the effects of longer duration of treatment. Neither trial found a significant association between antibiotic use and cardiovascular events (15,18). These results suggest that longer duration and higher dosage are unlikely to increase the cardioprotective effects of antibiotics.

A number of previous reviews (31-33) have examined the use of antibiotics for the secondary prevention of cardiovascular events and also failed to find a positive association. However, these reviews were published before completion of the most recent and largest studies. Even more recent reviews (34,35) excluded the large Clarithromycin for Patients with Stable Coronary Artery Disease (CLARICOR) trial (16) (4372 patients). In the review by Danesh et al (35), data for two large trials (ACES and PROVE-IT) were abstracted from presentation data as opposed to the final published data. Other reviews have not explicitly examined for the potential presence of publication bias and have not performed subgroup analyses based on antibiotic type and study population.

Our study does have several limitations. First, our literature search was limited to studies published in English and did not include any studies published in other languages. However, it is unlikely that any large clinical trials were excluded from this analysis. The exclusion of studies

published in languages other than English should have a minimal effect on our conclusions. Second, our funnel plot suggests the potential presence of publication bias. Small trials with negative (nonprotective) results appear to be less likely to be published. Such a bias, if present, would be directed toward the null hypothesis and would merely strengthen the evidence supporting our conclusion that antibiotic use is not effective for the secondary prevention of cardiovascular events.

In summary, our results suggest that the use of antibiotics is not effective in the secondary prevention of cardiovascular events. Our

results suggest that further research in this area is unlikely to be productive.

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