In the Literature

Does a short course of clarithromycin affect mortality in patients with stable coronary artery disease?

Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary artery disease: CLARICOR trial. *BMJ* 2006;332:22-7.

Background: *Chlamydia pneumoniae* DNA is found in human atherosclerotic plaques, and mouse models have shown that *C. pneumoniae* infection leads to arterial inflammation. However, antibiotics have not been shown to reduce cardiovascular events among patients at risk. Recent clinical trials and meta-analyses have failed to show a decrease in cardiovascular events after patients receive courses of antibiotic therapy of variable duration.

Design: These authors examined well patients in Copenhagen with stable coronary artery disease (CAD) (defined as occurrence of myocardial infarction [MI] or angina earlier than 3 months before enrolment or percutaneous transluminal coronary angioplasty or coronary bypass surgery earlier than 6 months before enrolment) for a longer period of follow-up than in other studies. Patients were randomly assigned to receive either clarithromycin by mouth (500 mg once daily) or placebo for 2 weeks. Serologic test results for *C. pneumoniae* antibodies, baseline data of demographic characteristics and known cardiovascular risk factors were collected at study onset. Information on death and fatal and nonfatal hospital admissions were collected from a database over 3 years. The primary outcome was a composite of all-cause death, MI or unstable angina. The secondary outcome was CAD-related death or any nonfatal cardiac outcome.

Results: The clarithromycin and placebo groups were similar at baseline, including the number with *C. pneumoniae* antibody titres reflecting prior exposure (64.3% v. 62.9% respectively). However, there were more current smokers in the clarithromycin group (37.7% v. 34.2%). Public registers of hospital admissions and deaths allowed for outcome data to be analyzed for 99% of the patients.

The composite primary and secondary outcomes did not differ between the 2 groups. However, all-cause death was significantly higher in the clarithromycin group (hazard ratio [HR] 1.27, 95% confidence interval [CI] 1.03–1.54, $p = 0.03$), specifically because of increased CAD-related death (HR 1.45, 95% CI 1.09–1.92, $p = 0.01$) (Table 1). The divergence in the number of deaths began one year after the intervention. After multivariate analysis adjusting for the intervention, sex, previous MI, age and smoking status, all-cause death was insignificantly increased (HR 1.21, 95% CI 0.99–1.48) but CAD-related death significantly increased in the clarithromycin group (HR 1.38, 95% CI 1.03–1.85, $p = 0.03$).

The authors also report that more patients in the clarithromycin group reported at least one adverse event (not defined) during the intervention (39.5% v. 25.1%, $p = 0.001$).

Commentary: For reasons not yet explained, Danish patients with stable CAD had increased mortality 1–3 years after a 2-week course of clarithromycin. Study limitations include a lack of knowledge of the New York Heart Association class and ejection fraction at randomization and potentially relevant factors like medications and lifestyle factors during the follow-up period. Smoking status differed between the groups, but CAD-related mortality remained significant after adjustment for this risk factor.

Why did this study show an increase in mortality when others did not? It is interesting that the 2 groups did not diverge until one year post-intervention, which makes an adverse drug reaction unlikely. Clarithromycin was given for 2 weeks only, even though eradication of *C. pneumoniae* is difficult: the organism may reside in infected monocytes, it may be difficult to penetrate plaques with antimicrobial agents, and one-time eradication of the pathogen does not prevent subsequent infection. The authors argue that when their results are pooled with those of 2 other clarithromycin studies, the increase in mortality among patients receiving clarithromycin is significant (HR 1.28, 95% CI 1.05–1.57). As well, if the results of trials lasting longer than 2 years are pooled with those of this trial, use of antibiotics, regardless of type and duration, is associated with increased mortality (HR 1.20, 95% CI 1.04–1.39).

Practice implications: Since the mechanism of risk remains ambiguous, it seems premature to warn against clarithromycin therapy for patients with stable CAD for whom therapy for acute infection is indicated. However, there is certainly no clinical reason to prescribe antibiotics to reduce the burden of *C. pneumonia* infection in patients with CAD.

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Table 1: Cause of death and hazard ratios by study group

Cause of death	Study group; no. (%)		Hazard ratio (95% confidence interval)*	*p* value
	Clarithromycin *n = 2172*	Placebo *n = 22*		
Cardiovascular	111 (5.1)	78 (3.5)	1.45 (1.09-1.92)	0.01
Noncardiovascular	85 (3.9)	84 (3.8)	1.03 (0.76-1.41)	0.82
Not classified	16 (0.7)	10 (0.5)	1.64 (0.75-2.11)	0.22
All causes	212 (9.8)	172 (7.8)	1.27 (1.03-1.54)	0.03

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*Based on Cox regression model, including sex, previous myocardial infarction, and age as mandatory covariates. Nonfatal events were not included.

DOI:10.1503/cmaj.060011