

# Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial

CLARICOR Trial Group

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BMJ 2006;332:22-4

## Abstract

**Objective** To determine if the macrolide clarithromycin affects mortality and cardiovascular morbidity in patients with stable coronary heart disease.

**Design** Centrally randomised multicentre trial. All parties at all stages were blinded. Analyses were by intention to treat.

**Setting** Five Copenhagen University cardiology departments and a coordinating centre.

**Participants** 13 702 patients aged 18 to 85 years who had a discharge diagnosis of myocardial infarction or angina pectoris in 1993-9 and alive in August 1999 were invited by letter; 4373 were randomised.

**Interventions** Two weeks' treatment with clarithromycin 500 mg/day or matching placebo.

**Main outcome measures** Primary outcome: composite of all cause mortality, myocardial infarction, or unstable angina pectoris during three years' follow-up. Secondary outcome: composite of cardiovascular mortality, myocardial infarction, or unstable angina pectoris. The outcomes were obtained from Danish registers and were blindly assessed by the event committee.

**Results** 2172 participants were randomised to clarithromycin and 2201 to placebo. We found no significant effects of clarithromycin on the primary outcome (hazard ratio 1.15, 95% confidence interval 0.99 to 1.34) or secondary outcome (1.17, 0.98 to 1.40). Mortality was significantly higher in the clarithromycin arm (1.27, 1.03 to 1.54;  $P=0.03$ ) as a result of significantly higher cardiovascular mortality (1.45, 1.09 to 1.92;  $P=0.01$ ).

**Conclusions** Short term clarithromycin in patients with stable coronary heart disease may cause significantly higher cardiovascular mortality. The long term safety of clarithromycin in patients with stable ischaemic heart disease should be examined.

**Trial registration** ClinicalTrials.gov NCT00121550.

## Introduction

Inflammation may have a fundamental role in coronary heart disease, and infections may promote atherosclerosis or acute coronary syndrome.<sup>1,2</sup> *Chlamydia pneumoniae* has been shown to be present in atherosclerotic tissue.<sup>3</sup> Macrolide antibiotics are anti-inflammatory and eradicate *C pneumoniae* from atherosclerotic plaques.<sup>4,5</sup> Two small trials showed significant beneficial effects of macrolides on cardiovascular morbidity in patients with acute coronary syndrome,<sup>6,7</sup> spurring several randomised trials. Most of these have been meta-analysed, showing that antibiotics do not significantly affect mortality.<sup>8</sup> The confidence intervals suggest the true effect of antibiotics to lie between an 11% decrease and a 16% increase in mortality.<sup>8</sup> We conducted a large randomised, placebo controlled trial of the effects of

clarithromycin on mortality and morbidity of patients with stable coronary heart disease.

## Methods

CLARICOR is a randomised, placebo controlled, multicentre trial in patients with stable coronary heart disease. It has used central randomisation and blinding of all parties in all phases.<sup>9</sup>

**Patient recruitment**—All patients discharged from wards or outpatient clinics in the Copenhagen area are registered in a database. We identified all patients with a diagnosis of myocardial infarction or angina pectoris (ICD codes 209-219) during the years 1993-9. We invited patients aged 18 to 85 years who were alive in August 1999 to participate in the trial. Patients were eligible if they had a history of myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary bypass surgery.

**Randomisation**—Patients were randomly assigned to receive oral clarithromycin 500 mg once daily for two weeks or matching placebo, with stratification by sex, previous myocardial infarction, age below 60 years, and centre.

**Follow-up**—All randomised patients received a tablet container and a report form, for recording each tablet taken and all adverse events. No follow-up visits were planned. Information about death came from the Danish Central Civil Register, which records the vital status of all inhabitants. Information about fatal and non-fatal admissions came from the Danish National Hospital Register, a database of all somatic hospital admissions.

**Outcome measures**—The primary outcome measure was a composite of all cause mortality, myocardial infarction, or unstable angina. The secondary outcome measure consisted of cardiovascular mortality, myocardial infarction, or unstable angina. The tertiary outcome measure consisted of cardiovascular mortality, myocardial infarction, unstable angina, cerebrovascular attack, or peripheral vascular disease.

**Evaluation of outcome measures**—We sent copies of hospital records and death certificates to two randomly chosen members of the event committee, which consisted of three cardiologists. An elevation of cardiac enzymes and significant ST changes in the electrocardiograph consistent with myocardial ischaemia or myocardial infarction were required for the diagnoses of myocardial infarction. We classified long lasting chest pain or chest pain at rest without major changes in



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enzymes as unstable angina. Stroke was focal cerebral deficit lasting more than 24 hours, and transient ischaemic attack was focal cerebral deficit lasting less than 25 hours. Peripheral vascular event encompassed peripheral arterial thromboembolism, surgery or transluminal angioplasty, and severe claudication.

**Statistical analyses**—For time to event variables, we based the hazard ratio on a regression model. We included sex, previous myocardial infarction, and age as covariates in the model. We searched for covariate-arm interactions. All analyses were intention to treat.

## Results

Between October 1999 and April 2000, 4373 patients were randomised—2172 to clarithromycin and 2201 to placebo—and started treatment. A total of 4330 patients (clarithromycin 2155/2172, 99.2%; placebo 2175/2200, 98.9%) returned the record form. A 100% tablet intake was reported in 90.0% (1954 patients) in the clarithromycin arm and 93.7% (2061) in the placebo arm.

### Composite outcomes

The primary outcome (all cause mortality or non-fatal cardiac outcomes) did not differ significantly between the clarithromycin and placebo arms (15.8% *v* 13.8%; hazard ratio 1.15, 95% confidence interval 0.99 to 1.34; *P* = 0.08) (table 1).

The secondary outcome (cardiovascular mortality or non-fatal cardiac outcomes) did not differ significantly between the clarithromycin and placebo arms (11.5% *v* 9.9%; 1.17, 0.98 to 1.40; *P* = 0.09) (table 1). The tertiary outcome measure (cardiovascular mortality, myocardial infarction, unstable angina, cerebrovascular attack, or peripheral vascular disease) was significantly more frequent in the clarithromycin arm than in the placebo arm (16.2% *v* 13.7%; 1.20, 1.02 to 1.39; *P* = 0.03) (table 1).

### Mortality

All cause mortality was significantly higher in the clarithromycin group (1.27, 1.03 to 1.54; *P* = 0.03), as a result of significantly higher cardiovascular mortality (1.45, 1.09 to 1.92; *P* = 0.01) (table 2). Non-cardiovascular mortality and non-classified mortality did not differ significantly (table 2).

### Multivariate analyses

None of the prespecified outcome measures was significant in regression analyses in which intervention, sex, previous myocardial infarction, age, present smoker status, and ex-smoker status were fixed covariates and other covariates were included.

### *Chlamydia pneumoniae* antibodies

An entry blood sample was available for 4350 (99.0%) patients. We found a *C pneumoniae* IgG antibody titre of 64 or above in 1390/2162 (64.3%) patients in the clarithromycin arm and 1377/2188 (62.9%) in the placebo arm. The corresponding figures for IgA antibody titres of 64 or above were 488/2162 (22.6%) and 469/2188 (21.4%). The serological data did not co-vary significantly with arm, outcomes, or drug effect (data not shown).

### Adverse events

During treatment, 851 (39.5%) clarithromycin patients and 547 (25.1%) placebo patients reported at least one adverse event (*P* = 0.0001).

**Table 1** Main outcome measures by randomised intervention groups\*. Values are numbers (percentages) unless stated otherwise

	Clarithromycin (n=2172)	Placebo (n=2200)	Hazard ratio (95% CI)	P value
<b>Primary outcome measure†</b>				
All cause mortality	184	159		
Myocardial infarction/unstable angina	160	148		
Total	344 (15.8)	307 (13.8)	1.15 (0.99 to 1.34)	0.08
<b>Secondary outcome measure†</b>				
Cardiovascular mortality	89	70		
Myocardial infarction/unstable angina	160	148		
Total	249 (11.5)	218 (9.9)	1.17 (0.98 to 1.40)	0.09
<b>Tertiary outcome measure†</b>				
Cardiovascular mortality	83	65		
Myocardial infarction/unstable angina	153	144		
Stroke	81	68		
Peripheral vascular disease	34	26		
Total	351 (16.2)	303 (13.7)	1.20 (1.02 to 1.39)	0.03

\*Based on a Cox regression model including sex, previous myocardial infarction, and age as mandatory covariates.

†Patients censored after the first event.

## Discussion

We found no beneficial effect of short term clarithromycin for patients with stable coronary heart disease. On the contrary, the significantly increased cardiovascular mortality in the clarithromycin treated patients surprised us.

### Strengths and limitations

The major strengths were the size of the trial, the central randomisation, stratification at randomisation, and the placebo controlled intervention with blinded outcome assessment and intention to treat analyses. Compliance was excellent. We obtained all outcomes from public registers, securing follow-up of more than 99% of patients.

Potential weaknesses include the fact that only 32% of eligible patients were randomised, which may affect the external validity. We do not know the medical treatment and lifestyle of patients during follow-up. However, we find it unlikely that these factors would differ substantially between the two groups. Clarithromycin patients were more often smokers, but our multivariate analyses taking smoking and other entry variables into consideration did not substantially change the results.

### Clarithromycin effects

Why clarithromycin might have an unfavourable effect in patients with coronary heart disease remains unclear. Macrolides possess potassium channel blocker properties,<sup>10</sup> which can cause prolonged QT intervals, torsades de pointes tachycardia, and death. This risk is increased by coadministration of macrolides and drugs metabolised by cytochrome P450 3A isoenzymes.<sup>11</sup> We did not

**Table 2** Mortality according to randomised intervention groups\*. Values are numbers (percentages) unless stated otherwise

Mortality	Clarithromycin (n=2172)	Placebo (n=2200)	Hazard ratio (95% CI)	P value
Cardiovascular	111 (5.1)	78 (3.5)	1.45 (1.09 to 1.92)	0.01
Non-cardiovascular	85 (3.9)	84 (3.8)	1.03 (0.76 to 1.41)	0.82
Non-classified	16 (0.7)	10 (0.5)	1.64 (0.75 to 2.11)	0.22
All cause	212 (9.8)	172 (7.8)	1.27 (1.03 to 1.54)	0.03

\*Based on Cox regression model including sex, previous myocardial infarction, and age as mandatory covariates. All non-fatal events were ignored.

### What is already known on this topic

Studies have shown an association between *Chlamydia pneumoniae* serological markers and cardiovascular events

Randomised trials (mostly under two years in length) have shown variable effects of antibiotics in patients with acute or stable coronary heart disease

A meta-analysis found no significant effects of antibiotics in coronary patients, but the 95% confidence interval indicates an effect between an 11% decrease and a 16% increase in mortality

### What this study adds

Clarithromycin 500 mg/day for 14 days compared with placebo seemed to cause more adverse effects during tablet intake in patients with stable coronary heart disease

Clarithromycin may cause increased mortality (hazard ratio 1.27, 95% confidence interval 1.03 to 1.54) and increased cardiovascular mortality (1.45, 1.09 to 1.92) in patients with stable coronary heart disease followed for up to three years

observe differences in cardiovascular mortality during the first month, and drug interactions cannot readily explain the observed difference in cardiovascular mortality.

#### Comparison with related research

Only two other trials have assessed clarithromycin in patients with coronary heart disease.<sup>12 13</sup> The CLARIFY trial randomised 148 patients to clarithromycin or placebo for three months. The clarithromycin group had a non-significantly increased 1.5 year mortality (odds ratio 4.17, 95% confidence interval 0.46 to 38.2).<sup>12</sup> Berg et al randomised 473 patients to clarithromycin or placebo until the day of coronary artery bypass grafting.<sup>13</sup> Two year mortality was non-significantly increased in the clarithromycin patients (1.10, 0.44 to 2.76).<sup>13</sup> Pooling these data with our results shows a significantly increased mortality in clarithromycin patients (1.28, 1.05 to 1.57).

Several trials on azithromycin, roxithromycin, or gatifloxacin in patients with coronary heart disease have been published.<sup>8 14-20</sup> The overall conclusion is that antibiotics have no significant impact on cardiovascular events.<sup>8 19 20</sup> Two of the trials reported a short lived beneficial effect.<sup>16 17</sup> We found a gradually increasing outcome rate in the clarithromycin patients. If we had stopped follow-up at one year, we would have had a neutral result like most other trials.<sup>8</sup> If we pool the data from the Andraws et al meta-analysis,<sup>8</sup> the Berg et al trial,<sup>13</sup> and our trial, antibiotics irrespective of type and duration of follow-up do not significantly affect mortality (1.09, 0.97 to 1.22). If we pool the data of the three trials following patients for more than two years (PROVE-IT,<sup>14</sup> ACES,<sup>18</sup> and CLARICOR), antibiotics are associated with significantly increased mortality (1.20, 1.04 to 1.39).

#### Conclusions

Brief intervention with clarithromycin in patients with stable coronary heart disease may cause more cardiovascular deaths. The long term safety of clarithromycin in patients with coronary heart disease needs further examination. At present, no evidence

indicates that antibiotics have protective effects in patients with atherosclerotic cardiovascular disease.<sup>20</sup>

We thank Jørn Wetterslev for help during the inspection of the CLARICOR trial.

Contributors: See bmj.com

Funding: The CLARICOR trial is investigator initiated and controlled. This work was supported by grants from non-profit funds (Danish Heart Foundation, Copenhagen Hospital Corporation, Danish Research Council, 1991 Pharmacy Foundation). Abbott Laboratories, IDC, Queensborough, UK, supplied the clarithromycin and placebo tablets. The organisations supporting the trial had no role in design, data collection, data analyses, data interpretation, or writing the report. The steering group had full access to all the data and had final responsibility for the decision to submit the report for publication.

Competing interests: None declared.

Ethical approval: The trial was approved by the local ethics committee (KF 01-076/99), the Danish Medicines Agency (2612-975), and the Danish Data Protection Agency (1999-1200-174).

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(Accepted 17 October 2005)

doi 10.1136/bmj.38666.653600.55