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

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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 15 702 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.\(^1\)\(^2\) *Chlamydia pneumoniae* has been shown to be present in atherosclerotic tissue.\(^3\) Macrolide antibiotics are anti-inflammatory and eradicate *C pneumoniae* from atherosclerotic plaques.\(^4\)\(^5\) Two small trials showed significant beneficial effects of macrolides on cardiovascular morbidity in patients with acute coronary syndrome,\(^6\)\(^7\) spurring several randomised trials. Most of these have been meta-analysed, showing that antibiotics do not significantly affect mortality.\(^8\) The confidence intervals suggest the true effect of antibiotics to lie between an 11% decrease and a 16% increase in mortality.\(^9\) 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.\(^9\) The code was not broken until all main analyses were completed and a two way main conclusion formulated.

Organisation

The Copenhagen Trial Unit coordinated patient identification, mailings, bookings, randomisation, data entry, and data management. Clean data files were exported to the department of biostatistics, University of Copenhagen, for analyses.

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 informed patients aged 18 to 85 years who were alive in August 1999 about the trial and invited them to visit one of five cardiology centres staffed by a physician and a nurse. At the visit, we gave patients further information about the trial. We completed an electronic record form with information about previous myocardial infarction, angina pectoris, percutaneous transluminal coronary angioplasty, coronary bypass surgery, arterial hypertension, diabetes mellitus, smoking, and treatment with aspirin, β blockers, calcium channel antagonists, long acting nitrates, diuretics, digoxin, statins, and antiarrhythmics. Patients aged 18 to 85 were eligible if they had a history of myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary bypass surgery. Exclusion criteria included myocardial infarction or unstable angina within the previous three months; percutaneous transluminal coronary angioplasty or coronary bypass surgery within the previous six months; New York Heart...
Association class IV cardiac failure; impaired renal or hepatic function; active malignancy; intolerance to macrolides; treatment with methylxanthines, carbamazepine, cisapride, astemizole, terfenadine, or coumarin anticoagulants; participation in other clinical trials within the previous month; incapacity to manage own affairs or sign informed consent; breast feeding; and possible pregnancy.

Randomisation
A computer generated the allocation sequence and served a telephone voice response randomisation system. Eligible patients were randomly assigned to receive oral clarithromycin 500 mg once daily (Klacid Uno) for two weeks or matching placebo, with stratification by sex, previous myocardial infarction, age below 60 years, and centre in blocks of 10 in a 1:1 ratio. Patients could not be randomised before a complete electronic entry record was saved in the computer. If a patient met exclusion criteria, the program refused randomisation. Blood samples were collected for C. Pneumoniae serology. Follow-up
All randomised patients received a numbered tablet container and a report form, on which they were asked to mark each tablet taken and to report all adverse events. At the end of treatment, the report form and the tablet container were to be returned to the coordinating centre. If they were not returned, the patient was reminded.

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, unstable angina, cerebrovascular attack, or peripheral vascular disease. We analysed mortality as part of a composite outcome. 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. Registration is 100% in these registers. On the basis of these registers, the coordinating centre collected death certificates and copies of hospital records during the follow-up period and forwarded each potential event separately to the event committee. As the observed event rate was lower than estimated, the steering committee extended the follow-up period from two to three years without analysing the data.

Evaluation of outcome measures
We used prespecified outcome flowchart forms to search for possible outcomes. We sent copies of hospital records and death certificates to two randomly chosen members of the event committee, which consisted of three cardiologists. In case of disagreement between the two evaluations, we sent both forms together with copies of the record of the event to the third member, who had to select the most likely option. In cases with inadequate information, we classified the cause of death as unknown. If sufficient information was available, we judged death to be due to cardiovascular disease unless a non-cardiovascular cause was present.

Results
Between 5 October 1999 and 15 April 2000, 4373 patients were randomised—2172 to clarithromycin and 2201 to placebo (fig 1)—and started treatment. One placebo patient was HIV positive and was withdrawn at day one. Patients seemed well randomised, although more clarithromycin patients than placebo patients were smokers (table 1).

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; the 90% tablet intake was 90.2% (1950) versus 94.1% (2070), and the 75% tablet intake was 91.0% (1977) versus 94.7% (2083) (all P<0.0001). The potential mean follow-up period was 960 days.

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 2, fig 2).

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 2).
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 2). The number of non-fatal tertiary outcomes was insignificantly increased by 16% in the clarithromycin arm (1.16, 0.97 to 1.39; P = 0.09) (table 2).

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 3, fig 3). Non-cardiovascular mortality and non-classified mortality did not differ significantly (table 3).

Multivariate analyses
None of the prespecified outcome measures was significant in Cox 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 as described in the methods. The non-significant tendency towards increased risk in the clarithromycin group persisted in the multivariate analyses of the primary outcome (1.11, 0.95 to 1.30; P = 0.17), the secondary outcome (1.14, 0.95 to 1.37; P = 0.15), and the tertiary outcome (1.16, 1.00 to 1.35; P = 0.06). All cause mortality was insignificantly increased (1.21, 0.99 to 1.48; P = 0.07), and cardiovascular mortality continued to be significantly increased in the clarithromycin group (1.38, 1.03 to 1.85; P = 0.03).

Chlamydia pneumoniae antibodies
An entry blood sample was available for 4350/4372 (99.5%) 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 (22.4%) and 483/2188 (22.1%) respectively.

Table 1 Entry characteristics of patients randomised to clarithromycin or placebo. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Entry variables</th>
<th>Clarithromycin (n=2172)</th>
<th>Placebo (n=2200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>65.4 (10.3)</td>
<td>65.2 (10.4)</td>
</tr>
<tr>
<td>Male</td>
<td>1514 (69.7)</td>
<td>1519 (69.1)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1470 (68.7)</td>
<td>1484 (67.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>341 (15.7)</td>
<td>337 (15.3)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>878 (40.4)</td>
<td>883 (40.2)*</td>
</tr>
<tr>
<td>Smoking status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>819 (37.7)</td>
<td>753 (34.2)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>981 (45.2)</td>
<td>1012 (46.0)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>372 (17.1)</td>
<td>435 (19.8)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1902 (87.6)</td>
<td>1937 (88.0)</td>
</tr>
<tr>
<td>Statin</td>
<td>896 (41.3)</td>
<td>904 (41.1)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>755 (34.8)</td>
<td>772 (35.1)</td>
</tr>
<tr>
<td>β Blocker</td>
<td>653 (30.1)</td>
<td>681 (31.0)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>604 (27.8)</td>
<td>577 (26.2)</td>
</tr>
<tr>
<td>Long acting nitrate</td>
<td>453 (20.9)</td>
<td>457 (20.8)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>154 (7.1)</td>
<td>126 (5.7)</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>55 (2.5)</td>
<td>51 (2.3)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>773 (35.6)</td>
<td>762 (34.6)</td>
</tr>
</tbody>
</table>


Table 2 Main outcome measures by randomised intervention groups*. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Primary outcome measure†</th>
<th>Clarithromycin (n=2172)</th>
<th>Placebo (n=2200)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>184</td>
<td>159</td>
<td>1.15 (0.99 to 1.34)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction/unstable angina</td>
<td>160</td>
<td>148</td>
<td>1.17 (0.98 to 1.40)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome measure†</th>
<th>Clarithromycin (n=2172)</th>
<th>Placebo (n=2200)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular mortality</td>
<td>88</td>
<td>70</td>
<td>1.20 (1.02 to 1.39)</td>
<td>0.03</td>
</tr>
<tr>
<td>Myocardial infarction/unstable angina</td>
<td>153</td>
<td>144</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
mandatory covariates. All non-fatal events were ignored. *Based on Cox regression model including sex, previous myocardial infarction, and age as

numbers (percentages) unless stated otherwise

Table 3 Mortality according to randomised intervention groups*. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Clarithromycin (n=2172)</th>
<th>Placebo (n=2200)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>111 (5.1)</td>
<td>78 (3.5)</td>
<td>1.45 (1.09 to 1.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>85 (3.9)</td>
<td>84 (3.8)</td>
<td>1.03 (0.76 to 1.41)</td>
<td>0.82</td>
</tr>
<tr>
<td>Non-classified</td>
<td>16 (0.7)</td>
<td>10 (0.5)</td>
<td>1.64 (0.75 to 3.51)</td>
<td>0.22</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>212 (9.8)</td>
<td>172 (7.8)</td>
<td>1.27 (1.03 to 1.54)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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

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. The event committee followed stable criteria uniformly and blindly classified events. These safeguards protected against random errors and systematic errors (bias).10-14

Potential weaknesses include the fact that only 32% of potentially eligible patients were randomised, which may affect the external validity. Furthermore, we cannot exclude chance imbalance at randomisation or after randomisation as a cause of the increased mortality. We would like to know the New York Heart Association class and ejection fraction at randomisation and medical treatment and lifestyle during follow-up. We find it unlikely that these factors would differ substantially between the two groups, which seemed well randomised, but we cannot exclude chance imbalances. Clarithromycin patients were more often smokers. However, 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. Macrolydes possess—apart from their antibiotic characteristics—potassium channel blocker properties,15 which can cause prolonged QT intervals, torsades de pointes tachycardia, and death. This risk is significantly increased by coadministration of macrolydes and drugs metabolised by cytochrome P450 5A isoenzymes.16 We did not 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.17-18 The CLARIFY trial randomised 148 patients to clarithromycin or placebo for three months. The clarithromycin group had an insignificantly raised 1.5 year mortality (odds ratio 4.17, 95% confidence interval 0.46 to 38.2).17 Berg et al randomised 473 patients to clarithromycin or placebo until the day of coronary artery bypass grafting.18 Two year mortality was insignificantly raised in the clarithromycin patients (1.0, 0.44 to 2.76).19 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.1-5 The overall conclusion is that antibiotics have no significant impact on cardiovascular events.6-8 Two of the trials reported a short lived beneficial effect.20 21 We found a gradually increasing outcome rate in the clarithromycin patients (fig 2 and fig 3). If we had stopped follow-up at one year, we would have had a neutral result like most other trials.8 If we pool the data from the Andrews et al meta-analysis,4 the Berg et al trial,18 and our trial, antibiotics irrespective of type and duration of follow-up do not...
Conclusions

Brief intervention with clarithromycin in patients with stable coronary heart disease living in Copenhagen may cause more myocardial deaths. The long term safety of clarithromycin in patients with coronary heart disease needs further examination. We therefore recommend other researchers to assess the long term impact of clarithromycin and other antibiotics. At present, no evidence indicates that antibiotics have protective effects in patients with atherosclerotic cardiovascular disease. Other roads should properly be taken. 25

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

Contributors: HJK had the original idea for the trial. CMJ chaired the steering committee, which consisted of JFH, PH, GBJ, JK, HJK, IL, HL, and CN. CMJ, JFH, PH, GBJ, JK, IL, HL, CN, and GBJ were principal investigators. BA-N, MS, LP, SH, and OHJ were clinical investigators. CMJ and GBJ were coordinating investigators and drafted the protocol and this report. CG is the guarantor. EK was chair of the event committee. JH was a member of the steering group during the planning of the trial.

Funding: The CLARICOR trial was 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).

Papers


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