
Jespersen CM, Als-Nielsen B, Damgaard M, Hansen F, Hansen S, Helo OH, et al. Randomized placebo controlled multicenter trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ*, doi:10.1136/bmj.38666.653600.55 (published 8 December 2005)

Background: Cardiovascular disease is one of the most common causes of morbidity and mortality worldwide. Major risk factors include diabetes, hypertension, hyperlipidemia, obesity, and physical inactivity. Recently, the presence of *Chlamydia pneumoniae* antibodies has been linked to coronary heart disease as well. *C. pneumoniae* infections have been associated with the initiation and progression of atherosclerosis in some patients. It is reasonable to assume that antibiotic administration will eradicate *C. pneumoniae* in infected patients and subsequently decrease cardiovascular morbidity and mortality.

Study Objective: To determine what effects short term clarithromycin use has on mortality and cardiovascular morbidity in patients with stable coronary heart disease.

Study Design: A centrally randomized, placebo-controlled, multicenter trial involving five Copenhagen University cardiology departments.

Study Population:

- 13,702 males and females 18-85 years of age who were diagnosed with a myocardial infarction or angina pectoris in 1993-1999.
- Of the 13,702 patients invited to participate, only 4,373 were randomized.

Inclusion Criteria:

- Males and Females 18-85 years of age with a history of myocardial infarction, angina, percutaneous transluminal coronary angioplasty, or coronary bypass surgery.

Exclusion Criteria:

- Myocardial infarction or unstable angina in the past 3 months.
- Percutaneous transluminal coronary angioplasty or coronary bypass surgery in the past 6 months.
- NYHA class IV cardiac failure
- Impaired renal or hepatic function, active malignancy
- Macrolide intolerance
- Use of methylxanthines, carbamazepine, cisapride, astemizole, terfenadine, or coumarins.
- Participation in other clinical trials in the previous month.
- Possible pregnancy or breast feeding.

Treatment Regimen: 2,172 participants were randomized to receive clarithromycin 500mg q day for 2 weeks and 2,201 were randomized to receive the equivalent placebo.

Study Endpoints:

Primary

- Composite of all cause mortality, myocardial infarction, or unstable angina.

Secondary

- Cardiovascular mortality, myocardial infarction, or unstable angina.

Tertiary

- Cardiovascular mortality, myocardial infarction, unstable angina, cerebrovascular attack, or peripheral vascular disease.

Statistical Analysis:

- Cox regression model
- Hazard ratio and 95% CI
- Multivariate Cox analysis
- Intent to treat
- Kaplan-Meier estimate

Results:

- No significant difference between the clarithromycin and placebo groups for the primary outcome. (15.8% vs. 13.8%, HR 1.15, 95% CI 0.99 – 1.34; P =0.08)
- No significant difference between the clarithromycin and placebo groups for the secondary outcome. (11.5% vs. 9.9%, HR 1.17, 95% CI 0.98 – 1.40; P =0.09)
- The tertiary outcome occurred significantly more frequently in the clarithromycin group vs. placebo. (16.2% vs.13.7%, HR 1.20, 95% CI 1.02 – 1.39; P = 0.03)
- All cause mortality was significantly higher in the clarithromycin group compared to placebo (HR 1.27, 95% CI 1.03 – 1.54; P=0.03) because cardiovascular mortality was higher for clarithromycin vs. placebo (HR 1.45, 95% CI 1.09 – 1.92; P=0.01)
- No differences in non-cardiac mortality and unclassified mortality were detected.
- IgG antibodies for *C. pneumoniae* were present in 1,390(64.3%) of the patients in the clarithromycin group and in 1,377(62.9%) of the placebo patients. IgA antibodies were present in 488(22.6%) of the clarithromycin patients and in 469(21.4%) of the placebo patients.
- Significantly more clarithromycin patients reported at least one adverse event during treatment. 851(39.5%) vs. 547(25.1%) P = 0.0001
- Multivariate analysis demonstrated similar results.

Authors Conclusions:

- Short term clarithromycin use did not show beneficial effects in patients with stable coronary heart disease.
- Clarithromycin increased morbidity and mortality in patients with coronary heart disease.
- Long term safety trials are needed for the use of clarithromycin and other macrolides in patients with coronary heart disease.

Strengths:

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| • Randomized, placebo controlled | • Multiple endpoints |
| • Multicenter | • Methods well explained |
| • Length of study | • ITT |
| • Reasonable clarithromycin dose | • Drop-outs accounted for |
| • Compliance | • Similar demographics |

Limitations:

- 32% of potential patients participated
- Smoking habits worse in clarithromycin group
- No follow up visits
- Authors calculated a need for 2,302 patients in each group
- Study involved 70% males
- Not all patients were positive for *C. pneumoniae* antibodies.

Other Pertinent Literature:

Sinisalo J, Mattila K, Valtonen V, Anttonen O, Juvonen J, Melin J, et al. Effect of 3 Months of Antimicrobial Treatment With Clarithromycin in Acute Non-Q-Wave Coronary Syndrome. *Circulation* 2002; 105:1555-1560.

- Randomized, double-blinded, placebo-controlled study involving 148 patients with non-Q-wave infarction or unstable angina.
- Patients were randomized to receive either clarithromycin 500mg q day for 85 days (n=74) or placebo (n=74)
- Primary endpoint was the composite of death from any cause, myocardial infarction, or unstable angina during the 3 month treatment period.
- 16 patients in the clarithromycin group vs. 27 in the placebo group experienced the primary outcome. (95% CI 0.26-0.92; P=0.03)
- There were 4 deaths in the clarithromycin group(IHD) compared to 1 death in the placebo group (cancer)
- Author concluded that clarithromycin appears to reduce the risks of cardiac events in patients with non-Q-wave infarction and unstable angina.
- Limitations include small study sample and limited follow up period.

O'Connor CM, Dunne MW, Pfeffer MA, Muhlestein JB, Yao L, Gupta S, et al. Azithromycin for the secondary prevention of Coronary Heart Disease. The WIZARD Study: A Randomized Controlled Trial. *JAMA* 2003; 290(11):1459-1466.

- Randomized, multicenter, placebo-controlled trial of 7,747 adults with previous myocardial infarction that occurred at least 6 weeks previously.
- Patients were randomized to receive either azithromycin 600mg/week (3,879) or placebo (3,868) for 12 weeks.
- Endpoints were death from any cause, myocardial infarction, coronary revascularization, or hospitalization for angina.
- After a 14 month follow up there was no significant risk reduction in the likelihood of a primary event. (95% CI -5% - 17%; P = 0.23)
- No significant difference in other individual outcomes were detected.
- Authors concluded that a 3 month course of azithromycin did not significantly decrease the risk of recurrent coronary events.
- This was a well designed trial with an adequate number of participants and 14 month follow up period.

Andraws R, Berger JS, Brown DL. Effects of Antibiotic Therapy on Outcomes of Patients with Coronary Artery Disease: A Meta-analysis of Randomized Controlled Trials. *JAMA* 2005; 293(21):2641- 2647.

- A meta-analysis of randomized, placebo controlled trials of antichlamydial antibiotic therapy in patients with CAD that report all-cause mortality, myocardial infarction, or unstable angina.
- Involved 11 studies and 19,217 patients.
- Concluded that antibiotic therapy had no impact on all-cause mortality among treated vs. untreated patients (4.7% vs. 4.6% P=0.83), on the rates of MI's (5% vs. 5.4% P=0.19), or the combined endpoint of MI and unstable angina (9.2% vs. 9.6% P=0.25).

My Conclusion: I agree with the author's conclusion that clarithromycin does not have a beneficial effect in patients with coronary heart disease. This trial shows that short term clarithromycin therapy may increase the risk of cardiovascular mortality and morbidity. However, more trials are needed before any definite relation can be assumed. Although the multivariate analysis did not show a difference, it is possible that differences in lifestyle may have adversely affected the clarithromycin group (especially smoking, diet and exercise). At this point, clarithromycin should not be used to prevent recurrent cardiovascular events and patients should not refrain from using clarithromycin because of cardiovascular risk.