Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10 years in the CLARICOR randomised, blinded clinical trial☆☆☆

Per Winkel a,⁎, Jørgen Hilden b, Jørgen Fischer Hansen c, Jens Kastrup d, Hans Jørn Kolmos e, Erik Kjeller f, Gorm Boje Jensen g, Maria Skoog a, Jane Lindschou a,⁎, Christian Gluud a,⁎, the CLARICOR trial group2

a The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
b Department of Biostatistics, Institute of Public Health Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark
c Department of Cardiology Y, Bispebjerg Hospital, Copenhagen University Hospital, Copenhagen, Denmark
d Department of Cardiology B, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
e Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark
f Department of Cardiology S, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark
g Department of Cardiology, Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark

★ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding: The CLARICOR trial was investigator-initiated and controlled. This work was supported by grants from non-profit funds (The Danish Heart Foundation (grant numbers 01-1-5-21-22894, 99-2-5-103-22773, 99-1-5-87-22712, and 97-2-5-70-22537); The Copenhagen Hospital Corporation (grant date 7 October 1997); The Danish Research Council (grant numbers 9702122 and 22-00-0261); The 1991 Pharmacy Foundation (grant number HPN/id/71-97)) and The Copenhagen Hospital Corporation and the Copenhagen Trial Unit. Abbott Laboratories, IDK, Queensborough, UK supplied the clarithromycin and placebo tablets. Those funds (The Danish Heart Foundation (grant numbers 01-1-5-21-22894, 99-2-5-103-22773, 99-1-5-87-22712, and 97-2-5-70-22537); The Copenhagen Hospital Corporation (grant date 7 October 1997); The Danish Research Council (grant numbers 9702122 and 22-00-0261); The 1991 Pharmacy Foundation (grant number HPN/id/71-97)) and The Copenhagen Hospital Corporation and the Copenhagen Trial Unit. Abbott Laboratories, IDK, Queensborough, UK supplied the clarithromycin and placebo tablets. Those financial supporting the trial had no role in design, data collection, data analyses, data interpretation, or writing the reports. The drafting and revisions were exclusively conducted by the academic authors.

⁎⁎ Trial registration: ClinicalTrials.gov Identifier: NCT00121550.

⁎ Corresponding authors at: The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.

E-mail addresses: pwinkel@ctu.dk (P. Winkel), jl@ctu.dk (J. Lindschou), cgluud@ctu.dk (C. Gluud).

1 Investigators of the CLARICOR trial group are listed at end of article and in references 1 and 2.

1. Introduction

The CLARICOR trial tested the hypothesis that antibiotics active against Chlamydia pneumoniae reduce the clinical manifestations of coronary atherosclerosis [1]. Unexpectedly, the results were that clarithromycin for 2 weeks compared with placebo in patients with stable coronary heart disease increased the all-cause mortality by 27% at 2.6 years and by 20% at 6 years after randomisation [1,2]. Our search...
for explanations of the unexpected harms revealed that cardiovascular death outside hospital was almost doubled by clarithromycin, and this effect was not detected in patients with statin treatment at entry into the trial [1–4].

The long-term effects of clarithromycin versus placebo during 10 years of follow up are presently reported.

2. Methods

2.1. Trial design and participants

The CLARICOR trial is an investigator-initiated, randomised, placebo-controlled, multicentre superiority trial including 4372 patients with stable coronary heart disease, using central 1:1 randomisation and blinding of all participants in all phases [1]. The CLARICOR trial was conducted in compliance with the Declaration of Helsinki, and national laws and regulations (ClinicalTrials.gov NCT0021550; Regional Ethics Committee KF 01-076/99 and HB 2009/015; the Danish Data Protection Agency 1999-1200-174 and 2012-41-0757; and the Danish Medicines Agency 2012-975). All patients in Copenhagen with a hospital diagnosis of myocardial infarction or angina pectoris (International Statis-
tical Classification of Diseases (ICD) codes I20.9 to 21.9) during the years 1993 to 1999 were identified and, if alive, invited by mail in late 1999 to participate in the trial. After providing informed consent, participants were randomised to clarithromycin 500 mg (Klacid Uno®) per day versus placebo for 2 weeks during the period from October 5, 1999 to April 15, 2000. The adjudicated outcomes during the first 2.6 years and the all-
cause mortality during the first 6 years follow up period have been reported [1,2].

Using Danish public registers for outcome assessment, an extended follow up from randomisation until January 1, 2010 (latest update of the National Register of Causes of Death) is now reported, thereby providing a total of 10 years (±3 months) of follow up. Thus, no direct contact post entry data were collected apart from a mailed adverse event form.

2.2. Public register based outcomes

The Danish 10 digit central person registration number is used at all contacts with the health care system. Somatic hospital contact can only be completed with a diagnosis based upon the ICD 10th revision and subsequent notification of the National Patient Register [5, 6]. Each department must issue at least an action diagnosis, describing the main reason for the admission (A diagnosis). Other important diagnoses may be recorded as B diagnoses. Information about vital status was obtained from the Danish Central Civil Register, which, like the National Patient Register, has coverage close to 100%. Information about the underlying cause of death as well as the four putative (direct or indirect) causes of death was obtained from the National Register of Causes of Death [5].

For each recorded A diagnosis and for each underlying cause of death we classified the outcome into a prioritised list of disjoint and exhaustive categories (restrictive diagnosis classification) [7]: acute myocardial infarction (AMI) (I21.0–21.3); unstable angina pectoris (I20.0, I24.8–24.9); cerebrovascular disease (I60.0–64.9 and G45.0–46.8); periph-
eral vascular disease (I70.2–70.9); other cardiovascular diseases (I00.0–99.9 unless already covered); and non-cardiovascular disease (A00.0–T98.3 unless already covered). A more liberal diagnosis classification was based on all A and B codes and the four fields of ICD codes on the form submitted to the Register of Causes of Death, but otherwise based on the same list of disjoint categories [7]. The differences between the results of the two classifications proved to be minor. The Supplementary Appendix compares the restrictive results presented here with the corresponding liberal results.

The date where the outcome was diagnosed was considered the date of the outcome. The primary outcome was time to a composite of death regardless of cause, AMI or unstable angina; the secondary outcome was time to a composite of cardiovascular death, AMI, or unstable angina; and the tertiary outcome was time to a composite of cardiovascular death, AMI, unstable angina, cerebrovascular attack, or peripheral vascular disease [1]. Cardiovascular death outside hospital was used as a proxy for sudden cardiovascular death [4].

2.3. Statistical methods

The distribution of time to outcome was compared between the two intervention groups using Cox regression analysis after testing for proportional hazards [8]. Significant interaction between time and a specified covariate was taken as evidence that the assump-
tion of constancy of hazard ratio (HR) is violated. Linearity of log HR was graphically checked. All biochemical quantities were log transformed to fulfil the linearity assumption [9–12].

The hazards of the first 3 years after randomisation, the next 3 years, and the final 4 years were compared (this analysis is meaningful although intervention groups are no longer comparable at the 3 or 6 year mark). When no time trend was documented, the full 10 year course was analysed. Analyses were either adjusted for the protocol specified stratification variables (sex, previous MI, age below 60 years, and centre) [1] (stratifica-
tion-adjusted analyses) or adjusted for stratification variables plus all design variables re-
corded at randomisation, including clinical variables, medical treatment at entry, and biochemical quantities (see Table 1 for risk factors used for adjustments) (fully adjusted analyses).

All analyses were conducted according to the intention-to-treat principle. P values at or above 5% were regarded as non-significant. As the trial is primarily dealing with harms of an intervention [1,2], it was decided a priori not to adjust our statistical threshold for multiple testing.

All analyses were made using the statistical software SAS 9.3, SPSS 17.1, and STATA13.

3. Results

3.1. 10 year follow up

The CONSORT flowchart is shown in the Supplementary Appendix (Fig 1). Table 1 shows the clinical and biochemical entry characteristics. Table 2 shows the 10 year stratification-adjusted analysis for the composite outcomes and for each single outcome component. For cardio-

vascular mortality the assumption of proportional hazards was signi-
ificantly violated (P < 0.01).

Clarithromycin tended to increase all-cause mortality in all partici-
pants over the 10 years, an effect that was significant in patients not on statin treatment at entry (HR: 1.16, 95% confidence interval (CI) 1.04–1.31, P = 0.010) but not in those on statin at entry (HR: 0.98, 95% CI: 0.83–1.17, P = 0.861) (Fig 1). Clarithromycin increased the HR of cerebrovascular disease (HR: 1.19, 95% CI: 1.02–1.38, P = 0.023), an effect that stayed significant in patients not on statin treat-
ment at entry (HR: 1.25, 95% CI: 1.03–1.50, P = 0.021) but not in those on statin at entry (HR: 1.10, 95% CI: 0.84–1.45, P = 0.46). Other-
wise clarithromycin did not significantly affect any of the outcomes dur-
ing the 10 year period. Fully adjusted analyses gave similar results (Table 5).

3.2. Analyses of the effects of clarithromycin over time

Table 3 examines the time course by contrasting the first 3 years after randomisation with the next 3 year period and the final approxi-
mately 4 year period for the main types of mortality. Clarithromycin in-
creased all-cause mortality during the first 3 years after randomisation in stratification-adjusted and fully adjusted analyses (Table 3). Thereafter, the effect of clarithromycin on all-cause mortality diminished. Clarithromycin increased cardiovascular mortality during the first 3 years after randomisation in stratification-adjusted analysis, but the significance vanished in the fully adjusted analysis (which, amongst other things, takes statin treatment at randomisation into consider-
ation). Thereafter, no significant effect of clarithromycin on cardio-
vascular mortality emerged. There was no demonstrable effect of clarithromycin on cardiovascular mortality at hospital during any of the periods. Clarithromycin did not affect non-cardiovascular mortality.

Clarithromycin increased cardiovascular death outside hospital dur-
ning the first 3 year period in the stratification-adjusted and fully adjust-
ed analyses. During the last 4 years of follow up, this effect was reversed with significantly fewer participants dying a cardiovascular death out-
side hospital in the clarithromycin group in the stratification-adjusted and fully adjusted analyses (Table 3).

During the first 3 years (but not during the next two periods) there was a significant interaction between use of statin and the ex-
perimental intervention (P = 0.004). Clarithromycin increased the HR to 2.36 for cardiovascular death outside hospital in participants not on statin at entry (95% CI: 1.60–3.50, P < 0.0005). This was not the case in the participants on statin at entry (HR: 0.75, 95% CI: 0.38–1.47, P = 0.40).

Table 4 completes the temporal analysis of such deaths. Whilst pa-
tients on statin treatment showed no discernible clarithromycin effects, those not on statin showed a clear time-dependent effect of clarithromycin: the clarithromycin group exhibited a signi-
cantly increased all-cause mortality during the 10 year period. Fully adjusted analyses gave similar results (Table 5).
4. Discussion

In this trial, using data from public registers for follow up, we confirmed the effects of 2 weeks of clarithromycin versus placebo on the increased all-cause mortality, cardiovascular deaths, and cardiovascular death outside hospital in patients with stable coronary heart disease during the first 2.6 years of follow-up. When using public register data for follow-up over a full 10 year period, we found that the effect persisted [1–4, 7]. However, analyses of the effects of clarithromycin over time showed that after the 3rd year, the differences vanished, and during the final 4 years, the effect on cardiovascular death outside hospital was reversed. Here, the placebo-treated participants seemed to catch up with those on clarithromycin. An obvious interpretation is frailty attrition, i.e., sudden cardiac death occurs ‘prematurely’ in a subset vulnerable to the antibiotic, so after some time survivors are on the whole more resistant. The entire reversal turned out to affect a subgroup of patients, viz. patients without statin treatment at randomisation. An alternative interpretation is that the presence of antibodies against C. pneumoniae influences the detrimental effect of clarithromycin. Clarithromycin is concentrated in macrophages, and macrolide antibiotics stimulate the growth of macrophages, which could lead to unstable plaques followed by thrombosis and embolism [19–21]. Sudden cardiac death comprises 33–50% of deaths in patients with chronic ischemic heart disease [22,23]. Such deaths are primarily considered to follow rupture of vulnerable atherosclerotic plaques in the coronary arteries [24,25], but other mechanisms like arrhythmia or coronary spasms may also be involved. Effects on

4.1. Comparison with other studies

The present findings extend our previous results of the CLARICOR trial as well as our meta-analysis of 17 randomised trials assessing the effect of antibiotics for patients with coronary heart disease, as we observed that clarithromycin was associated with increased cerebrovascular disease during the 10 year follow up [1–4].

Our findings during the first couple of years following the 2 week intervention seem in concert with results from previous antibiotic randomised clinical trials [2] as well as most observational evidence assessing clarithromycin [14,15]. Other observational evidence has shown cardiovascular adverse events following erythromycin [16] and azithromycin [17]. A Danish register based observational study concluded that there was no detrimental effect of clarithromycin [18]. Their patient inclusion criteria, treatment duration, and methodology differed from other observational studies and from our evidence, arising (as it is) from a randomised trial.

We do not know the exact mechanism leading to the clarithromycin induced premature sudden cardiovascular deaths. There is no indication that the presence of antibodies against C. pneumoniae influences the detrimental effect of clarithromycin. Clarithromycin is concentrated in macrophages, and macrolide antibiotics stimulate the growth of macrophages, which could lead to unstable plaques followed by thrombosis and embolism [19–21]. Sudden cardiac death comprises 33–50% of deaths in patients with chronic ischemic heart disease [22,23]. Such deaths are primarily considered to follow rupture of vulnerable atherosclerotic plaques in the coronary arteries [24,25], but other mechanisms like arrhythmia or coronary spasms may also be involved. Effects on
myocardial repolarisation causing QT prolongation suggesting potassium channel inhibition are usually short-term events occurring while on macrolides [26,27]. We observed no major effects of clarithromycin on all-cause mortality during the first months following the 2 weeks of clarithromycin administration [1,2], but we observed an increase in out-of-hospital cardiovascular mortality soon after the intervention period [4], extending observational evidence [14,16,17].

### 4.2. Strengths of the trial

The trial’s strengths are the size of the participant population, the strictly concealed central allocation, the few losses to follow up (26/4373 [0.6%] during 10 years), and the blinding of all parties. Risk factors at the start of the trial were comparable in the two intervention groups [1,2,4,9–12]. This was confirmed in the present analyses, which include Table 2

<table>
<thead>
<tr>
<th>Outcomes (restrictive diagnosis classification (see Methods))</th>
<th>HR</th>
<th>95% CI</th>
<th>Stratification-adjusted P (Fully adjusted P)</th>
<th>Number of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (all-cause mortality, AMI, or UAP)</td>
<td>1.06</td>
<td>0.98–1.14</td>
<td>0.17</td>
<td>C: 1238</td>
</tr>
<tr>
<td>Secondary outcome (cardiovascular mortality, AMI, or UAP)</td>
<td>1.05</td>
<td>0.95–1.15</td>
<td>0.35</td>
<td>C: 905</td>
</tr>
<tr>
<td>Tertiary outcome (cardiovascular mortality, AMI, UAP, cerebrovascular disease, or peripheral vascular disease)</td>
<td>1.05</td>
<td>0.96–1.14</td>
<td>0.28</td>
<td>C: 1116</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.10</td>
<td>1.00–1.21</td>
<td>0.054</td>
<td>C: 866</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td>1.07</td>
<td>0.94–1.23</td>
<td>0.30</td>
<td>C: 442</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI or UAP</td>
<td>1.02</td>
<td>0.92–1.13</td>
<td>0.71</td>
<td>C: 690</td>
</tr>
<tr>
<td>AMI</td>
<td>0.99</td>
<td>0.88–1.13</td>
<td>0.93</td>
<td>C: 468</td>
</tr>
<tr>
<td>UAP</td>
<td>1.03</td>
<td>0.90–1.19</td>
<td>0.66</td>
<td>C: 397</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.19</td>
<td>1.02–1.38</td>
<td>0.025</td>
<td>C: 364</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.00</td>
<td>0.79–1.26</td>
<td>0.99</td>
<td>C: 143</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>1.10</td>
<td>1.00–1.21</td>
<td>0.054</td>
<td>C: 1214</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>1.05</td>
<td>0.95–1.15</td>
<td>0.35</td>
<td>C: 905</td>
</tr>
<tr>
<td>Tertiary outcome</td>
<td>1.05</td>
<td>0.96–1.14</td>
<td>0.28</td>
<td>C: 1116</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.10</td>
<td>1.00–1.21</td>
<td>0.054</td>
<td>C: 866</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td>1.07</td>
<td>0.94–1.23</td>
<td>0.30</td>
<td>C: 442</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI or UAP</td>
<td>1.02</td>
<td>0.92–1.13</td>
<td>0.71</td>
<td>C: 690</td>
</tr>
<tr>
<td>AMI</td>
<td>0.99</td>
<td>0.88–1.13</td>
<td>0.93</td>
<td>C: 468</td>
</tr>
<tr>
<td>UAP</td>
<td>1.03</td>
<td>0.90–1.19</td>
<td>0.66</td>
<td>C: 397</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.19</td>
<td>1.02–1.38</td>
<td>0.025</td>
<td>C: 364</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.00</td>
<td>0.79–1.26</td>
<td>0.99</td>
<td>C: 143</td>
</tr>
</tbody>
</table>

---

**Fig. 1.** Kaplan Meier cumulative event curves for all-cause mortality in participants randomised to clarithromycin versus placebo stratified according to statin or no statin treatment at entry into the CLARICOR trial. 2571 participants were without statin treatment at entry (clarithromycin n = 1276; placebo n = 1295) and 1800 participants were with statin treatment at entry (clarithromycin n = 896; placebo n = 904). Apart from 26 participants lost to follow up, there is no censoring until day 3560. HR: hazard ratio. CI: confidence interval.
4.3. Limitations of the trial

We post hoc used death outside hospital as a proxy for ‘sudden cardiovascular death’ [4]. This may be a weakness in a research context, but we had no other means to assess this important outcome. Our present results highlight the problems raised by the use of composite outcomes [36]. We found no detrimental effects of clarithromycin on our three composite outcomes over the 10 years, in spite of the increased occurrence of all-cause mortality, cardiovascular mortality, and cerebrovascular diseases. Moreover, the evidence showing the protective effect of statin treatment on the harmful effects of clarithromycin is observational and should be interpreted as such. However, Danish national prescription statistics show that, if a patient was on statin treatment, then he or she most likely stayed on it, and patients not on statin were not therefore have important public health consequences, as clarithromycin all the serological biomarkers so far assessed [9–12]. These biomarkers all contain significant prognostic information regarding cardiovascular outcomes and mortality but none of them differed noticeably in the two intervention groups at randomisation (Table 1). There is no evidence that systematic errors could have occurred in the trial. The clarithromycin-treated patients exhibited markedly more adverse events such as gastrointestinal complaints during the two week intake of the study drug, which excludes an accidental interchange of codes [28]. The CLARICOR trial surpassed instructions provided in the EU Directive 2001/20/EC [29] and the ICH CCP guidelines [30], having public registration; adequate generation of allocation sequence; adequate allocation concealment; adequate blinding; adequate follow up; adequate reporting of all relevant outcomes; intention-to-treat analyses; and no for profit bias [31–35]. Furthermore, all our analytic results were consistent using two diagnostic classifications [7] and stratification-adjusted and fully adjusted analyses.

4.4. Clinical implications and conclusions

The 10-year ‘number needed to treat for an additional harmful outcome’ was about 35 patients for all-cause mortality and about 52 patients for cardiovascular mortality outside hospital. Our findings may therefore have important public health consequences, as clarithromycin forms part of antibiotic regimens against Helicobacter pylori and is often used antibiotic against a number of infections [16]. The conduct of further randomised clinical trials has been called for [14]. However, with the present evidence such randomised trials should face ethical problems. Considering the potential for harm, we would rather recommend urgent re-analyses of extended follow up of previous randomised clinical trials and observational studies in patients with and without coronary heart disease, taking statin treatment into consideration.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.020.

Conflicts of interest

None declared.

Acknowledgements

We thank the CLARICOR trial participants. We thank the investigators and other staff involved in the first phases of the CLARICOR trial (for full list of named please see references [1,2]). We thank our funders.

Table 3

All-cause mortality and cardiovascular mortality during three follow up periods. Hazard ratio (HR) with 95% confidence interval (CI) of clarithromycin versus placebo. Clarithromycin group n = 2172. Placebo group n = 2200.

<table>
<thead>
<tr>
<th>Outcomes (restrictive diagnosis classification)</th>
<th>HR during 0–3 years</th>
<th>HR during 3–6 years</th>
<th>HR during the 6–10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.26 (1.04–1.53)</td>
<td>1.13 (0.95–1.34)</td>
<td>1.00 (0.87–1.15)</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.10 (0.83–1.45)</td>
<td>0.94 (0.74–1.20)</td>
<td>1.08 (0.81–1.32)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.42 (1.09–1.84)</td>
<td>1.24 (0.96–1.60)</td>
<td>1.06 (0.74–1.13)</td>
</tr>
<tr>
<td>Cardiovascular mortality at hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.92 (0.59–1.44)</td>
<td>1.23 (0.89–1.70)</td>
<td>1.20 (0.91–1.60)</td>
</tr>
<tr>
<td>Cardiovascular mortality outside hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.76 (1.27–2.45)</td>
<td>1.26 (0.82–1.93)</td>
<td>0.91 (0.46–0.88)</td>
</tr>
</tbody>
</table>

**Table 4**

Cardiovascular deaths outside hospital in the two groups (clarithromycin versus placebo) during the three follow-up periods, in participants on statin treatment at entry compared to participants without statin treatment at entry. Clarithromycin group: n = 2172. Placebo group: n = 2200.

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>0–3 years</th>
<th>3–6 years</th>
<th>6–10 years</th>
<th>Total 10 years</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin, n (%)</td>
<td>15 (42.9)</td>
<td>15 (65.2)</td>
<td>24 (38.7)</td>
<td>54 (45.0)</td>
<td>0.088</td>
</tr>
<tr>
<td>Placebo, n (%)</td>
<td>20 (57.1)</td>
<td>8 (34.8)</td>
<td>38 (61.3)</td>
<td>66 (55.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5**

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.020.

Here is the plain text representation of the document:
Appendix A

Contributors: HKJ had the original idea for the CLARICOR trial, JFH, JK, EK, GB) and CG in collaboration with the CLARICOR Trial Group investigators (listed in references [1,2]) conducted the trial. PW, JH, JFH, JK, HJ, EK, GB) and CG conceived and designed the study. PW, JH, JFH, JK, EK, GB) and CG acquired the data. PW, JH, MS, JL and CG conducted the statistical analyses. PW, JH, JFH, JK, EK, GB) and MS, JL and CG analysed and interpreted the data. PW, JH, JFH, JK, EK, GB, MS, JL and CG drafted the manuscript and critically revised the manuscript for important intellectual content. CG obtained funding, PW, JH, MS, JL and CG provided administrative, technical, or material support. PW and JH had access to all of the data in the study and take responsibility for the data analysis. CG is the guarantor.

Ethical approval: This trial was approved by the Regional Ethics Committee of the capital region; the Danish Data Protection Agency and the Danish Medicines Agency.

Data sharing: All de-identified data may be obtained from the Copenhagen Trial Unit.

Transparency: All authors had full access to all of the data in the trial and can take responsibility for the integrity of the data and the accuracy of the data analysis. The guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any disagreements from the study as planned have been explained.

References


