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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☆,☆☆

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ABSTRACT

Background: The CLARICOR trial reported that clarithromycin compared with placebo increased all-cause mortality in patients with stable coronary heart disease. This study investigates the effects of clarithromycin versus placebo during 10 years follow up.
Methods: The CLARICOR trial is a randomised, placebo-controlled trial including 4373 patients with stable coronary heart disease. The interventions were 2 weeks of clarithromycin 500 mg a day versus placebo. 10 year follow up was performed through Danish public registers and analysed with Cox regression.
Results: Clarithromycin increased all-cause mortality (hazard ratio (HR): 1.10, 95% confidence interval (CI): 1.00–1.21) and cerebrovascular disease during 10 years (HR: 1.19, 95% CI: 1.02–1.38). The increased mortality and morbidity were restricted to patients not on statin at entry (HR: 1.16, 95% CI: 1.04–1.31, and HR: 1.25, 95% CI: 1.03–1.50). The assumption of constant HR during the 10 years was violated for cardiovascular death ($P = 0.01$) and cardiovascular death outside hospital ($P < 0.0005$). Analyses of the effects over time showed that clarithromycin increased cardiovascular mortality during the first three years (HR: 1.42, 95% CI: 1.09–1.84) due to increased cardiovascular mortality outside hospital in patients not on statin (HR: 2.36, 95% CI: 1.60–3.50). During the last 4 years, cardiovascular death outside hospital was lower in the clarithromycin group (HR: 0.64, 95% CI: 0.46–0.88).
Conclusion: Clarithromycin increased mortality due to cardiovascular death outside hospital and cerebrovascular morbidity in patients with stable coronary heart disease who were not on statin. The increased cardiovascular mortality was years later compensated, likely through frailty attrition.

1. Introduction

The CLARICOR trial tested the hypothesis that antibiotics active against *Chlamydophila 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

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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 parties in all phases [1]. The CLARICOR trial was conducted in compliance with the Declaration of Helsinki, and national laws and regulations (ClinicalTrials.gov NCT00121550; 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 2612–975). All patients in Copenhagen with a hospital diagnosis of myocardial infarction or angina pectoris (International Statistical 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 year 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) (I21.0–23.9); unstable angina pectoris (I20.0, I24.8–24.9); cerebrovascular disease (I60.0–64.9 and G45.0–46.8); peripheral 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 assumption 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] (stratification-adjusted analyses) or adjusted for stratification variables plus all design variables recorded 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 (S 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 cardiovascular mortality the assumption of proportional hazards was significantly violated ($P < 0.01$).

Clarithromycin tended to increase all-cause mortality in all participants 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, $P = 0.025$), an effect that stayed significant in patients not on statin treatment 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, $P = 0.46$). Otherwise clarithromycin did not significantly affect any of the outcomes during the 10 year period. Fully adjusted analyses gave similar results (S 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 approximately 4 year period for the main types of mortality. Clarithromycin increased 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 consideration). Thereafter, no significant effect of clarithromycin on cardiovascular 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 during the first 3 year period in the stratification-adjusted and fully adjusted analyses. During the last 4 years of follow up, this effect was reversed with significantly fewer participants dying a cardiovascular death outside 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 experimental 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 patients 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 significantly increased risk during the first 3 years as compared with the placebo group; a correspondingly lower proportion died during the final period; cf. the absolute numbers of deaths in the table.

Table 1
Entry characteristics of participants randomised to clarithromycin versus placebo in the CLARICOR trial.

Entry variables		Clarithromycin (n = 2172)	Placebo (n = 2200)
Age in years	Mean (SD)	65.4 (10.3)	65.2 (10.4)
Males	n (%)	1514 (69.7)	1519 (69.1)
Previous myocardial infarction	n (%)	1470 (67.7)	1494 (67.9)
Diabetes	n (%)	341 (15.7)	337 (15.3)[a]
Hypertension	n (%)	878 (40.4)	883 (40.2)[a]
Smoking status			
Smoker	n (%)	891 (37.7)	753 (34.2)
Ex-smoker	n (%)	981 (45.2)	1012 (46.0)
Never smoked	n (%)	372 (17.1)	435 (19.8)
Drugs			
Aspirin	n (%)	1902 (87.6)	1937 (88.0)
Statin	n (%)	896 (41.3)	904 (41.1)
Calcium antagonist	n (%)	755 (34.8)	772 (35.1)
β-blocker	n (%)	653 (30.1)	661 (31.0)
ACE inhibitor	n (%)	604 (27.8)	577 (26.29)
Long acting nitrate	n (%)	453 (20.9)	457 (20.8)
Digoxin	n (%)	154 (7.1)	126 (5.7)
Antiarrhythmic	n (%)	55 (2.5)	51 (2.3)
Diuretic	n (%)	773 (35.6)	762 (34.6)
Biochemical quantities in plasma[b]			
High sensitivity C-reactive protein, mg/L	Mean (median)	5.85 (2.84)	5.29 (2.76)
	min–max	0.03–96.9	0.10–87.8
	N	2128	2159
N-terminal-pro-B-type natriuretic peptide, ng/L	Mean (median)	509 (212)	476 (195)
	min–max	4.4–19,303	8.5–31,040
	N	2123	2149
High sensitivity cardiac TnT, ng/L	Mean (median)	10.4 (7.0)	11.5 (7.0)
	min–max	3–397	3–1966
	N	2086	2111
YKL40, μg/L	Mean (median)	151 (111)	149 (109)
	min–max	18–3047	15–2808
	N	2135	2163
Pregnancy associated plasma protein A, n ≥ 4 mIU/L	n (%)	261 (12.4)	288 (13.5)
	N	2102	2141

[a] Missing data for one placebo participant.
[b] Missing data mainly due to storage and thawing problems of serum samples for at least one biochemical quantity in 91 (4.2%) clarithromycin participants and in 91 (4.1%) placebo participants.

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 more frequent, accelerated, cardiovascular symptoms during the first periods lead to more coronary revascularisations or more attentive medication, both of which could explain the improved cardiovascular survival during the final 4 years.

As a further new observation, clarithromycin increased the risk of cerebrovascular diseases by about 20% versus placebo during the 10 year period in the stratification adjusted analysis. This observation rests on more than 600 outcomes [13] and the findings were robust to whether a restrictive or liberal diagnosis classification was used. Furthermore, the harmful effect was again only observed in patients not on statin at entry.

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

Table 2
Hazard ratio (HR) and 95% confidence interval (CI) of clarithromycin versus placebo for participants with stable coronary heart disease in the CLARICOR trial according to outcomes. Clarithromycin group, n = 2172. Placebo group n = 2200.

Outcomes (restrictive diagnosis classification (see Methods))	HR	95% CI	Stratification-adjusted P (Fully adjusted P)[a]	Number of outcomes
Primary outcome (all-cause mortality, AMI[b], or UAP[c])	1.06	0.98–1.14	0.17 (0.52)	C[d]: 1238 Pl[e]: 1214
Secondary outcome (cardiovascular mortality, AMI, or UAP)	1.05	0.95–1.15	0.35 (0.80)	C: 905 Pl: 897
Tertiary outcome (cardiovascular mortality, AMI, UAP, cerebrovascular disease, or peripheral vascular disease)	1.05	0.96–1.14	0.28 (0.65)	C: 1116 Pl: 1108
All-cause mortality	1.10	1.00–1.21	0.054 (0.16)	C: 866 Pl: 815
Non-cardiovascular mortality	1.07	0.94–1.23	0.30 (0.41)	C: 442 Pl: 426
Cardiovascular mortality	Period dependent[f]	Period dependent	Period dependent	C: 424 Pl: 389
AMI or UAP	1.02	0.92–1.13	0.71 (0.87)	C: 690 Pl: 700
AMI	0.99	0.88–1.13	0.93 (0.42)	C: 468 Pl: 488
UAP	1.03	0.90–1.19	0.66 (0.63)	C: 397 Pl: 399
Cerebrovascular disease	1.19	1.02–1.38	0.025 (0.074)	C: 364 Pl: 321
Peripheral vascular disease	1.00	0.79–1.26	0.99 (0.47)	C: 143 Pl: 148

[a] Value in parenthesis is P value of corresponding adjusted analysis (see Table 1 for adjustment factors, i.e., all entry variables).
[b] AMI: acute myocardial infarction.
[c] UAP: unstable angina pectoris.
[d] C: clarithromycin group.
[e] Pl: placebo group.
[f] Proportional hazards assumption not fulfilled (see S Table 3).

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

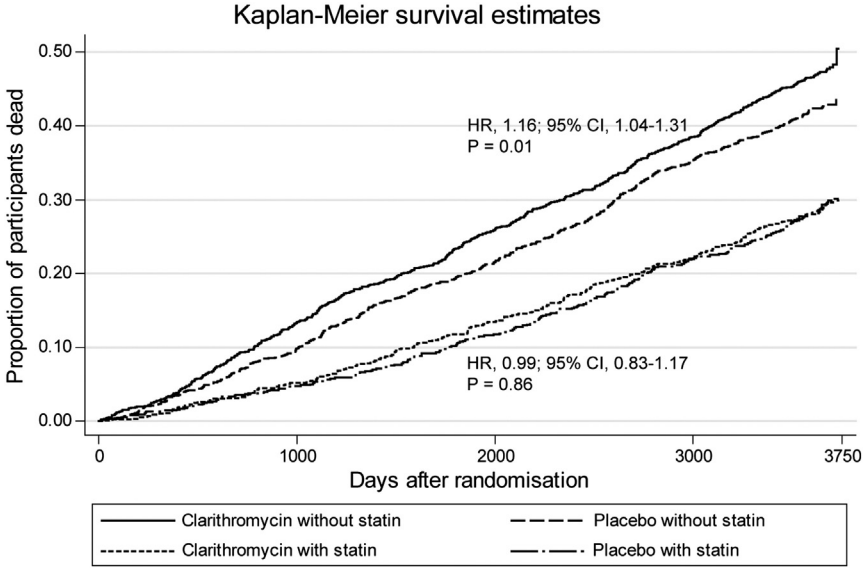

Fig. 1. Kaplan Meier cumulative event curves for all-cause mortality in participants randomised to clarithromycin versus placebo stratified according to statin or no statin treatment at entry into the CLARICOR trial. 2571 participants were without statin treatment at entry (clarithromycin n = 1276; placebo 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.

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.

Outcomes (restrictive diagnosis classification (see Methods))	HR during 0–3 years[a] HR (95% CI)	Stratification-adjusted P (Fully adjusted P)[b]	Deaths	HR during 3–6 years HR (95% CI)	Stratification-adjusted P (Fully adjusted P)[b]	Deaths	HR during the 6–10 years HR (95% CI)	Stratification-adjusted P (Fully adjusted P)[b]	Deaths
All-cause mortality	1.26 (1.04–1.53)	0.017 (0.04)	C[c]: 237 Pl[d]: 192	1.13 (0.95–1.34)	0.18 (0.12)	C: 260 Pl: 240	1.00 (0.87–1.15)	0.99 (0.31)	C: 369 Pl: 383
Non-cardiovascular mortality	1.10 (0.83–1.45)	0.52 (0.40)	C: 102 Pl: 95	0.94 (0.74–1.20)	0.94 (0.47)	C: 134 Pl: 134	1.08 (0.81–1.32)	0.43 (0.77)	C: 206 Pl: 197
Cardiovascular mortality	1.42 (1.09–1.84)	0.008 (0.053)	C: 135[e] Pl: 97	1.24 (0.96–1.60)	0.11 (0.06)	C: 126 Pl: 106	0.91 (0.74–1.13)	0.39 (0.14)	C: 163 Pl: 186
Cardiovascular mortality at hospital	0.92 (0.59–1.44)	0.73 (0.51)	C: 37 Pl: 41	1.23 (0.89–1.70)	0.22 (0.20)	C: 80 Pl: 68	1.20 (0.91–1.60)	0.20 (0.31)	C: 104 Pl: 90
Cardiovascular mortality outside hospital	1.76 (1.27–2.45)	0.001 (0.006)	C: 97 Pl: 56	1.26 (0.82–1.93)	0.30 (0.14)	C: 46 Pl: 38	0.64 (0.46–0.88)	0.006 (0.002)	C: 59 Pl: 96

[a] Period after randomisation.
[b] Value in parenthesis is P value of fully adjusted analysis (see Table 1 for adjustment factors, i.e., all entry variables).
[c] C: clarithromycin group.
[d] Pl: placebo group.
[e] One death could not be classified.

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 GCP 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.

4.3. 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 likely to get the treatment [37]. Another potential weakness is the large number of outcomes analysed and the repetitive analyses. However, we decided not to adjust for multiplicity in our protocol for this report because we are dealing with harms.

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.

Intervention Group	0–3 years[a]	3–6 years	6–10 years	Total 10 years	P[b]
Participants on statin treatment at entry					
Clarithromycin, n (%)	15 (42.9)	15 (65.2)	24 (38.7)	54 (45.0)	0.088
Placebo, n (%)	20 (57.1)	8 (34.8)	38 (61.3)	66 (55.0)	
Participants not on statin treatment at entry					
Clarithromycin, n (%)	82 (69.5)	31 (50.8)	35 (37.6)	148 (54.4)	<0.0005
Placebo, n (%)	36 (30.5)	30 (49.2)	58 (62.4)	124 (45.6)	

[a] Period after randomisation.
[b] Chi^2 test of independence between intervention group and period.

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 an 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.

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Appendix A

Contributors: HJK had the original idea for the CLARICOR trial. JFH, JK, EK, GBJ and CG in collaboration with the CLARICOR Trial Group investigators (listed in references [1,2]) conducted the trial. PW, JH, JFH, JK, HJK, EK, GBJ and CG conceived and designed the study. PW, JH, JFH, JK, HJK, EK, GBJ, MS, JL and CG acquired the data. PW, JH, MS, JL and CG conducted the statistical analyses. PW, JH, JFH, JK, HJK, EK, GBJ, MS, JL and CG analysed and interpreted the data. PW, JH, JFH, JK, HJK, EK, GBJ, 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 discrepancies from the study as planned have been explained.

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