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Original Article

Effect of clarithromycin versus placebo on risk of atrial fibrillation

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ABSTRACT

INTRODUCTION. The CLARICOR randomised trial of clarithromycin versus placebo in patients with stable ischaemic heart disease found increased all-cause and cardiovascular mortality after a brief clarithromycin regimen, suggesting a possible arrhythmic effect. As atrial fibrillation (AF) is the most common arrhythmia and a major contributor to cardiovascular morbidity and mortality, we compared the AF incidence in the randomisation groups in a post-hoc analysis.

METHODS. In 1999-2000, a total of 4,372 patients with stable ischaemic heart disease were randomised to a two-weeks course of clarithromycin or placebo. Incident AF episodes were followed for ten years through national registers. Using Cox proportional hazard models and some subsidiary analyses, we assessed the effect of clarithromycin on occurrence of AF.

RESULTS. Among participants, 285 (13.5%) patients in the clarithromycin group and 271 (13.3%) patients in the placebo group were recorded to have (at least) one AF period during follow-up. The Cox analysis showed no significant difference in AF incidence between groups (HR = 1.09; 95% CI: 0.92-1.29; p = 0.32), consistent with findings in the subsidiary analyses.

CONCLUSIONS. In this post-hoc analysis, a brief course of clarithromycin did not increase the incidence of new AF in participants with chronic stable ischaemic heart disease.

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TRIAL REGISTRATION. ClinicalTrials.gov, NCT00121550.

Clarithromycin, a macrolide antibiotic, has been widely used in clinical medicine for several decades [1]. The CLARICOR (clarithromycin versus placebo) trial in patients with stable coronary heart disease was initiated after reports of beneficial effects of macrolide treatment in acute coronary syndromes and chronic coronary artery disease [2]. Contrary to expectations, we found a significant adverse effect of clarithromycin on all-cause mortality and stroke [2]. After ten years of follow-up, all-cause mortality remained higher in patients not on statin treatment at entry, but not in those who were on statins at entry [3]. Clarithromycin also increased the risk

of cerebrovascular disease, an effect that also continued in patients not on statin treatment at entry but not in those who were on statin at entry [3]. Furthermore, we showed that clarithromycin versus placebo was associated with an increase in sudden, but not in non-sudden death [4]. This finding suggests an arrhythmic mechanism behind the higher mortality in the clarithromycin group of the trial.

In the present secondary study, we therefore extended our analysis to a non-fatal outcome – atrial fibrillation (AF). AF is the most common arrhythmia [5, 6], resulting in increased cardiovascular mortality and high rates of complications. AF is considered one of the new "epidemics" in cardiology [5], and the lifetime risk of AF is about 40% in persons with many risk factors and 25% in persons with few risk factors [6]. Available data suggest continued increases in AF incidence, which is partly explained by increased longevity, increased survival after acute myocardial infarction, increased attention and diagnostic activity, along with increasing body size (height) in many populations [7]. Risk factors for AF include advanced age, male sex, previous heart disease, height, obesity, hypertension, alcohol use, obstructive pulmonary disease and sleep apnoea, among others [6, 7]. The pathogenesis of AF and the interplay of various risk factors are also gradually becoming clearer. However, much of the increase in AF occurrence cannot currently be explained.

Clarithromycin and other macrolide antibiotics have well-known acute electrophysiological effects. Several reports, including our own analysis, suggest proarrhythmic effects of clarithromycin, particularly in patients with other risk factors such as ischaemic heart disease [4, 8]. A recent meta-analysis suggests that clarithromycin and other macrolide antibiotics may increase all-cause and cardiovascular mortality [9], particularly in connection with digoxin treatment [10]. To the best of our knowledge, no previous studies have examined the possible effect of clarithromycin on the risk of AF. We aimed to examine what the CLARICOR data might contribute to the possible role of antibiotic use in the AF epidemic.

Methods

The CLARICOR trial was an investigator-initiated, randomised, multi-centre superiority trial including 4,372 patients with stable coronary heart disease. It used central 1:1 randomisation and blinding of all parties in all phases, investigating 14 days of clarithromycin versus placebo [2, 3]. The patients were recruited from hospital registers on the basis of a diagnosis of stable coronary heart disease. 40% of the patients were diagnosed with a previous acute myocardial infarction. As participants initiated their experimental treatment right after the entry interview, the drugs used at entry are those they would normally continue to use during the two experimental weeks. AF before inclusion was identified from the Danish Hospital Register and the Danish Death Register [11, 12]. The International Classification of Diseases, eighth version (ICD-8) codes DI 427.93 and 427.94, and ICD-10 code DI48.9 were used.

The AF outcomes were based on the ICD-10 diagnosis code DI48.9 obtained from the National Patient Register or the Cause of Death Register. For each CLARICOR participant, the set of discharge diagnosis codes from all Danish hospital department admissions covering the period from the patient's randomisation in October 1999 through April 2000, and until 31 December 2009, was ordered chronologically and analysed using SAS software (SAS Institute, North Carolina, USA). If patients had not been hospitalised and diagnosed with AF before they died, they were diagnosed using the Cause of Death Register, where the diagnosis code "I48.9" was identified. In many patients, the diagnosis occurred several times due to recurrent events. However, only the first occurrence, marking the incident AF, was used in the present analyses.

The statistical analyses were all predefined in a publicly available detailed statistical analysis plan [13]. Data were handled on the website of the Research Machine (Danish Health Data Agency, Copenhagen, Denmark and all analyses were conducted in R (R Core Team, Vienna, Austria), SAS and Stata (StataCorp LLC, Texas, USA). After

exclusion of participants with past AF, the two intervention groups were compared in two strata: 1) all participants and 2) participants not treated with statins at entry.

The two strata were analysed primarily using the Cox proportional hazard model of time until the first recording of AF after randomisation in the clarithromycin group versus the placebo group. The Cox proportional hazard model included the inclusion site and age group as stratification variables. Assumptions for the Cox proportional hazards model were tested before any analyses were conducted [13]. These analyses were supplemented by Kaplan-Meier plots, log-rank test and restricted mean survival time (i.e., follow-up time until AF) as sensitivity analyses. Subgroup analyses (investigating for interactions) were carried out, investigating sex, use of statins and digoxin. Finally, a post-hoc competing risk analysis was conducted, treating death as a competing rather than a censoring outcome; insofar as the question of the clarithromycin-AF association is concerned, this analysis examines actual AF onsets rather than the number that would have occurred had death not sometimes shortened follow-up. Data were analysed as complete case analysis as there were practically no missing data from entry information in the CLARICOR trial [2]. A significance level of 0.05 is employed. In this post-hoc analysis, all results will be interpreted as hypothesis-generating.

The CLARICOR trial was approved by the local ethical committee (KF 01-076/99), the Danish Medicines Agency (2612-975) and the Danish Data Protection Agency (1999-1200-174). All participants provided informed consent to participate in the trial. The present follow-up study did not require informed consent (regional ethics committee approval: H-B-2009-015).

Trial registration: ClinicalTrials.gov, NCT00121550.

Results

Among the 4,372 patients, 330 had AF before inclusion. Accordingly, a total of 4,042 participants were included in the present analyses (**Table 1**).

TABLE 1 Baseline variables at entry.

	Clarithromycin	Placebo
Participants, N	2,009	2,033
Age, mean (SD), yrs	64.90 (10.26)	64.77 (10.31)
Males, n (%)	1,417 (70.5)	1,406 (69.2)
Previous myocardial infarction, n (%)	1,363 (67.8)	1,389 (68.4)
Diabetes, self-reported, n (%)	310 (15.4)	300 (14.8)
Hypertension, self-reported, n (%)	800 (39.8)	808 (39.8)
Smoking status, n (%)		
Never smoker	337 (16.8)	389 (19.1)
Ex-smoker	899 (44.7)	928 (45.7)
Smoker	773 (38.5)	715 (35.2)
Medication, n (%)		
Aspirin	1,761 (87.7)	1,794 (88.3)
Statin	847 (42.2)	844 (41.5)
Calcium antagonist	694 (34.5)	725 (35.7)
Beta-blocker	596 (29.7)	620 (30.5)
ACE inhibitor	549 (27.3)	517 (25.4)
Long-acting nitrate	407 (20.3)	421 (20.7)
Digoxin	104 (5.2)	83 (4.1)
Antiarrhythmic	42 (2.1)	33 (1.6)
Diuretic	681 (33.9)	674 (33.2)
Biochemistry, concentration, median (IQR)		
High-sensitivity CRP, mg/l	2.79 (1.34; 6.01)	2.80 (1.29; 5.91)
N-terminal-pro-B-type natriuretic peptide, ng/l	203 (88; 483)	178 (76; 441)
High-sensitivity cardiac TnT, ng/l	6.77 (3.36; 12.28)	6.79 (3.44; 11.96)
YKL 40 concentration, µg/l	109 (76; 165)	107 (74; 166)
Pregnancy-associated plasma protein A concentration > 4 mIU/l, n (%)	232 (11.9)	255 (12.9)

ACE = angiotensin-converting enzyme; TnT = troponin T; YKL = chitinase-3-like protein 1.

The two intervention groups were well-matched. During follow-up, AF occurred in 556 (13.7%) participants, 285 (13.5%) in the clarithromycin group versus 271 (13.3%) in the placebo group. On average, participants developing AF during follow-up were older (69 compared with 64 years) and had a slightly more adverse profile regarding N-terminal-pro-B-type natriuretic peptide (356 ng/l compared with 178 ng/l) and other biomarkers, suggesting more subclinical heart failure (**Table 2**).

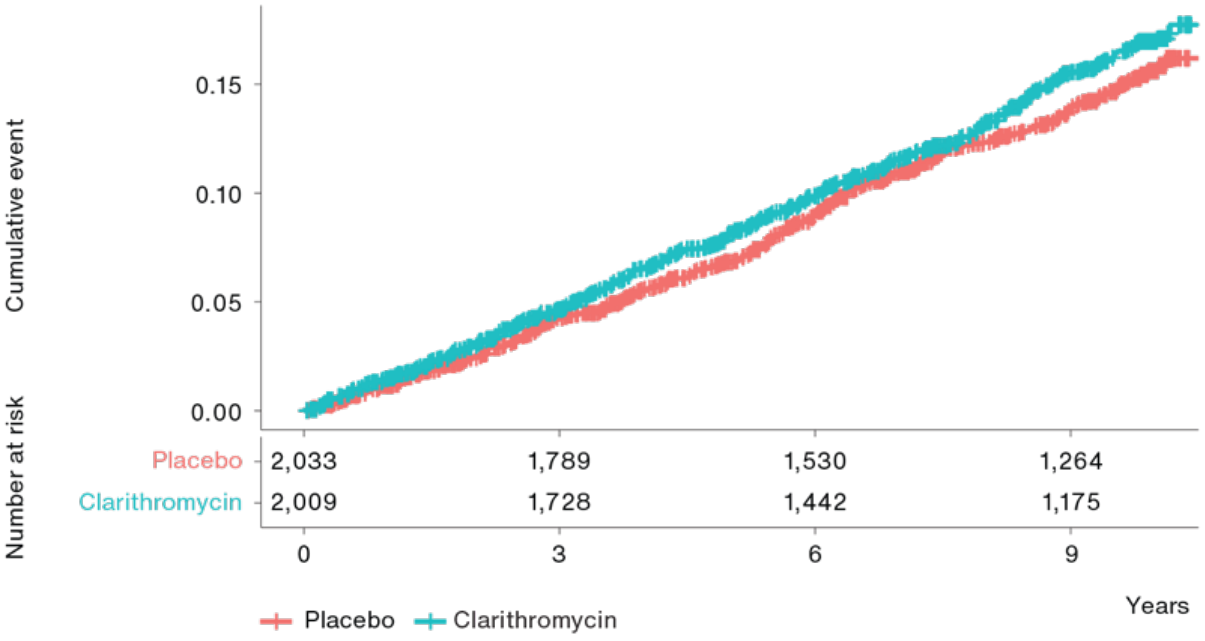
TABLE 2 Baseline variables stratified by occurrence of atrial fibrillation during follow up.

	AF	No AF
Participants, N	556	3,486
Age, mean (SD), yrs	69.05 (9.44)	64.16 (10.26)
Males, n (%)	386 (69.4)	2,437 (69.9)
Previous myocardial infarction, n (%)	377 (67.9)	2,375 (68.1)
Diabetes, self-reported, n (%)	84 (15.1)	526 (15.1)
Hypertension, n (%)	252 (45.4)[a]	1,356 (38.9)
Smoking status, n (%)		
Never smoker	95 (17.1)	631 (18.1)
Ex-smoker	277 (49.9)	1,550 (44.5)
Smoker	183 (33.0)	1,305 (37.4)
Medication, n (%)		
Aspirin	491 (88.5)	3,064 (87.9)
Statin	200 (36.0)	1,491 (42.8)[a]
Calcium antagonist	217 (39.1)	1,202 (34.5)
Beta-blocker	170 (30.6)	1,046 (30.0)
ACE inhibitor	176 (31.7)	890 (25.5)
Long-acting nitrate	117 (21.1)	711 (20.4)
Digoxin	50 (9.0)[a]	137 (3.9)
Antiarrhythmic	15 (2.7)	60 (1.7)
Diuretic	231 (41.6)[a]	1,124 (32.2)
Biochemistry, concentration, median (IQR)		
High-sensitivity CRP, mg/l	3.16 (1.45; 7.20)	2.74 (1.29; 5.75)
N-terminal-pro-B-type natriuretic peptide, ng/l	356 (153; 830)[a]	178 (76; 415)
High-sensitivity cardiac TnT concentration, ng/l	10.25 (5.39; 15.88)	6.37 (3.20; 11.39)
YKL 40 concentration, µg/l	117.5 (79; 177)	107 (74; 163)
Pregnancy-associated plasma protein A concentration > 4 mIU/l, n (%)	79 (14.6)	408 (12.0)

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; TnT = troponin T; YKL = chitinase-3-like protein 1.
a) Pathophysiologically suggestive differences, cf. discussion.

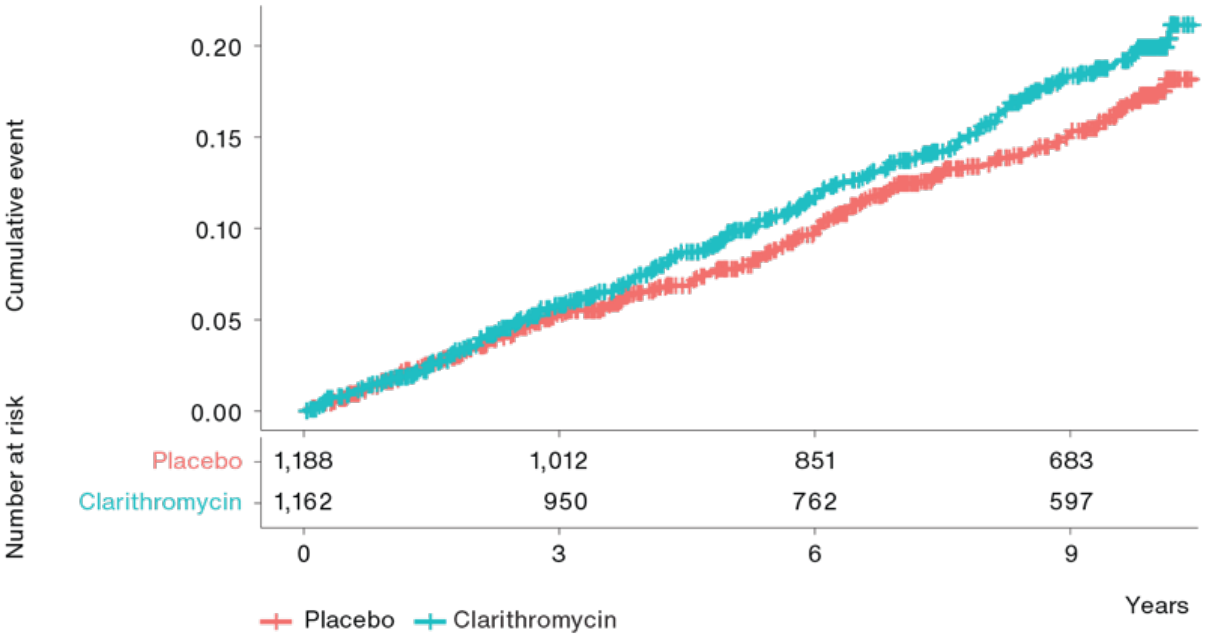
The Cox proportional hazards model for all participants included (n = 4,042) showed no difference between the clarithromycin and placebo groups (HR = 1.09, 95% CI: 0.92-1.29, p = 0.32) (**Figure 1**). Similarly, neither restricted mean survival time (restricted mean survival time difference (ΔRMST) = 0.082 years, 95% CI: &;0.054-0.218 years, p = 0.24) nor the post-hoc competing risk analysis (HR = 1.06, 95% CI: 0.90-1.26, p = 0.47) showed any differences between the groups.

FIGURE 1 Kaplan-Meier plot of atrial fibrillation events in all participants. The plot shows the cumulative frequency of atrial fibrillation over time (x-axis, years), stratified by intervention group (clarithromycin versus placebo).



Of the full cohort of 4,042 participants, 2,350 (58.1%) did not receive statins at randomisation, with 1,162 in the clarithromycin versus 1,188 in the placebo group. AF was observed in 184 (15.8%) of the participants in the clarithromycin-no-statin group and 171 (14.4%) in the placebo-no-statin group, i.e., slightly higher percentages than with statin treatment, in accordance with the suspected protective effect of statin but far from statistical significance. Neither the Cox proportional hazards model (HR = 1.14, 95% CI: 0.92-1.40, p = 0.23, **Figure 2**) nor the restricted mean survival time analysis (ΔRMST = 0.13 years, 95% CI: &;0.06-0.33 years, p = 0.18) showed any differences between the groups.

FIGURE 2 Kaplan-Meier plot of atrial fibrillation events in participants without statin treatment. The plot shows the cumulative frequency of atrial fibrillation over time (x-axis, years) in patients without statin treatment, stratified by intervention group (clarithromycin versus placebo).



The Cox subgroup analysis showed no significant sex difference (p = 0.92) and no association with statin (p = 0.46) or digoxin treatment at entry (p = 0.73).

Discussion

Patients included in the CLARICOR trial were diagnosed with stable ischaemic heart disease and are therefore at high risk of developing AF [14]. The observed AF incidence in the trial was comparable to that in other patient populations [15].

Our previous analyses of the CLARICOR data have suggested an unfavourable cardiovascular effect of clarithromycin. However, to the extent that such an effect exists, the present post-hoc analysis gives no indication that the risk of developing AF is affected. The outcome was similar in several statistical models, including Cox analysis, restricted mean survival time, a competing risk model and Kaplan-Meier plots. We found no interaction with statin treatment or other pharmacological treatments at entry.

Several large-scale randomised clinical trials were initiated after the original observations suggesting beneficial effects on mortality in patients with acute myocardial infarction [9]. The CLARICOR trial was initiated at the same time and with the same aims. Most of the other large-scale trials on antibiotics in ischaemic heart disease have reported a neutral outcome, which may be related to insufficient long-term follow-up. In the CLARICOR trial, we followed the participants for ten years [3]. Contrary to expectations, we observed a significant adverse effect of clarithromycin on all-cause mortality and incidence of stroke [2, 3]. We also had the possibility to determine the long-term effect of clarithromycin on other cardiovascular outcomes.

After ten years of follow-up, all-cause mortality was still significantly increased in patients not treated with a

statin at entry [3]. Patients on a statin at entry had no increased risk of clarithromycin-related mortality [3]. Clarithromycin also increased the risk of cerebrovascular disease in patients not treated with a statin at entry [3]. Recent large-scale retrospective observational evidence supports a protective effect of statins on the increased risks of mortality and of a composite of acute myocardial infarction, stroke and death of clarithromycin compared to doxycycline [16].

The Food and Drug Administration (FDA) amended its product description for clarithromycin based on these findings in 2018 [17]. Unfortunately, the European Medicines Agency (EMA) has not yet found the occasion to act in a similar manner.

The pathophysiology of AF has received extensive attention. Initiation and maintenance of AF requires a substrate and a trigger mechanism; the substrate is left atrial enlargement and fibrosis in the atrial wall (remodelling), allowing multiple re-entry mechanisms. The trigger is supraventricular extrasystoles originating from pulmonary vein sleeves [18]. In contrast, arrythmias associated with macrolide antibiotics occur as ventricular tachycardias secondary to QTc prolongation [8] and occasionally manifest as sudden death, which implies a totally different pathophysiology from the mechanisms leading to AF. The pattern of clinical effects (increased sudden death, no increase in AF) observed in the CLARICOR trial is therefore in line with the putative pathophysiological mechanisms.

The participants in the CLARICOR trial were recruited from the regional hospital register and therefore represent a cohort of real-life patients. As all patients in the register were invited to participate, a sampling bias can be discarded. The proportion participating was about 50% [2]. We have no information on non-attenders.

Coding for a diagnosis of AF is performed after hospital admission or after attending an outpatient clinic. The validity of the AF codes in the registers has been assessed several times by other researchers and found to be high [19].

Electrocardiographic recordings were not collected at randomisation. Patients with AF diagnosed before randomisation were identified from the National Patient Register. However, some patients may have had AF that was not diagnosed in the hospital, and therefore not entered into the register. Due to the randomisation process, we may assume that a similar proportion of patients in either treatment group belongs to this category.

Follow-up was terminated at ten years. Our previous experience suggests that the adverse effect of clarithromycin on mortality was levelling during the last years of follow-up [3].

A recent observational, register-based study of clarithromycin for Helicobacter eradication did not show adverse effects of clarithromycin on cardiovascular outcomes [20]. Register-based studies are subject to biases, in particular, intention-to-treat bias.

The analysis outlined here is prompted by results found previously in the same material. This analysis is a post-hoc analysis, and the interpretation of a result &; no significant effect of clarithromycin on the occurrence of AF &; should be interpreted accordingly.

Data sharing

All de-identified data may be obtained from the Copenhagen Trial Unit upon request.

Conclusions

In this post-hoc analysis, a brief course of clarithromycin did not increase the incidence of new AF in participants with chronic stable ischaemic heart disease.

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