Statistical Analysis Plan: Clarithromycin and the Risk of incident Atrial Fibrillation - a secondary analysis of the CLARICOR (clarithromycin for patients with stable coronary heart disease) trial

ABSTRACT

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and AF is a major contributor to cardiovascular mortality and morbidity. The CLARICOR randomised trial of clarithromycin compared with placebo in patients with stable coronary heart disease trial, found increased all-cause and cardiovascular mortality of the brief clarithromycin regimen. Here, we outline an analysis of the relationship between use of clarithromycin and incident AF in the CLARICOR trial.

Methods

The CLARICOR trial randomised 4372 patients with stable coronary artery disease in Copenhagen during October 1999 to April 2000. Outcomes were assessed through validated Danish registers. Here, the outcome of interest is incident AF.

Using Cox proportional hazard method, we will firstly determine the effect of clarithromycin on incidence of AF. Secondly, a competing risk model, by the method of Fine & Gray using mortality as the competing event, will be developed. The analyses will be adjusted for protocol specified stratification variables. Participants with AF occurring before randomisation will both be included and excluded.

Conclusion

This study will potentially contribute to the understanding of development of AF, relative to use of clarithromycin in such patients.

Funding

The Danish Heart Foundation, The Copenhagen Hospital Corporation, The Danish Research Council, and the 1991 Pharmacy Foundation. Abbott Laboratories, IDC, Queensborough, UK, supplied the clarithromycin and placebo tablets.

Trial registration

ClinicalTrials.gov, NCT00121550, 13 July 2005

Introduction

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 originated following reports of beneficial effects of macrolide treatment in acute (ACS) and chronic coronary artery (CAD) disease[2]. Contrary to expectations, we found a significant adverse effect on all-cause mortality and incidence of stroke[2]. After 10 years of follow-up, all-cause mortality was still significantly increased in patients not on statin treatment at entry but not in those on statin at entry. Clarithromycin also increased the risk of cerebrovascular disease an effect that also stayed significant in patients not on statin treatment at entry but not in those on statin at entry[3]. In the present study, we will extend the analysis to a non-fatal outcome, atrial fibrillation (AF).

AF is the most common arrhythmia. Previously, AF was considered a relatively benign condition. However, many studies have revealed a significantly increased CV mortality, and high rates of complications such as embolic stroke, congestive heart failure, and systemic emboli[4,5].

The epidemiology of AF has received extensive attention. AF represents one of the new epidemics in cardiology[6]. Life-time risk of AF is about 40% in persons with many risk factors and 25% in persons with few risk factors[7]. Available data suggest continued increases in the occurrence of AF, which is partly explained by increased longevity, increased survival after acute myocardial infarction (AMI), and increasing body size (height) in many populations[8,9]. Risk factors for AF are: increased age, male sex, previous heart disease, height, obesity, hypertension, alcohol use, obstructive pulmonary disease and others[7–9]. The pathogenesis of AF and the interplay of various risk factors are also

gradually becoming understood. However, much of the increase in the occurrence of AF cannot be explained.

Clarithromycin and other macrolide antibiotics have well-known acute electrophysiological effects. Several reports as well as our own analysis suggest proarrhythmic effects of clarithromycin[10,11]. In this context, it can therefore be hypothesized that the widespread use of macrolide antibiotics including clarithromycin may play a role in the epidemic of AF. As far as we know, there are no previous reports studying a possible effect of clarithromycin on the risk of AF. It is possible that clarithromycin interacts with digoxin, increasing the risk of digoxin toxicity[10], however, others have found macrolides to be safe[11]. Digoxin is widely used for control of heart rate in AF.

In this paper we present the analysis plan for the study of clarithromycin as a risk factor for AF in chronic stable CHD in the CLARICOR trial.

Methods

TRIAL DESIGN AND PATIENT POPULATION

The CLARICOR trial is an investigator initiated, randomised, placebo controlled, multicentre superiority trial including 4,372 patients with stable coronary heart disease, using central 1:1 randomisation and blinding of all parties in all phases[2,3]. The data material includes the baseline data collected at randomisation augmented by clinical outcome data obtained from public registers[12,13].

The patients had all been admitted to hospital and were diagnosed with stable coronary heart disease. Forty percent were diagnosed with a previous AMI.

To identify previous AF before inclusion, we will retrieve data from the relevant Danish register. The ICD-8 code DI 427.93 and 427. 94, and ICD-10 code DI48.9 will be used.

Baseline characteristics include: age, sex, previous AMI, medications: statin and digoxin use at entry, as well as a number of co-variates which will not be studied in the present analysis[12]

OUTCOMES

The clinical outcomes are based on the ICD-10 diagnosis code DI489 obtained from the National Patient Register[13,14]. For each CLARICOR patient the set of discharge diagnosis codes from all Danish hospital department admissions covering the period from the patient's randomisation until Dec. 31, 2009 were ordered chronologically and analysed by a SAS computer program. Among the 4372 patients, the AF disease diagnosis code 'I489' was found after randomisation in 831 (19.0%) patients. In many patients, the diagnosis occurred several times. However, only the first occurrence, marking the incident AF, will be used in the present analyses. If the clarithromycin treatment is associated with a higher incidence of atrial fibrillation (AF) it should be expected that the probability of the occurrence of the AF diagnosis code would be higher in the clarithromycin treated patients than in the placebo treated patients.

STATISTICAL ANALYSIS

The two intervention groups will be compared in two strata: (1) all patients, (2) patients not treated with statins at entry. The distribution of time until first occurrence of an atrial fibrillation diagnosis code following the randomisation will be compared using the Cox proportional hazards model. All

analyses will be adjusted for the protocol specified stratification variables of the CLARICOR trial. As the number of deaths is far larger than the number of AF events, a supplementary competing risk regression analysis will also be reported.

Also, analyses both including and excluding pre-existing atrial fibrillation will be conducted.

Competing risk analyses

The relationship between predictors and incident AF will be analysed in both Cox proportional hazards regression models and in competing risk regression models by the method of Fine and Grey[15]. In the competing risk regression models, incident AF is the event of interest and death the competing event. The standard Cox models estimates the risk of incident AF among those who are alive at the diagnosis; estimates are presented in hazard ratios (HR). The results of the competing risk regression models are presented in subdistribution hazards (subhazards)(sHR) and present the probability (cumulative incidence) of incident AF by groups/ predictor from study inclusion[16].

Main analyses

The primary analysis includes an analysis using the Cox proportional hazard model of the primary outcomes (time until first recording of AF after randomisation) in the clarithromycin group vs. the placebo group after exclusion of participants with previous AF. These analyses will be supplemented by Kaplan-Meier plots and log rank test.

Interaction analyses, and if significant, stratification, will be performed by sex, use of statins and of digoxin. Thus, use of clarithromycin is the predictor, incident AF the outcome, and sex, statin use and digoxin use individually tested for interaction.

Competing risk regression models with death as competing risk will be performed. These includes both incidence rates for death (the competing event) and AF (the event of interest).

Missing values

There are practically no missing data from entry information in the CLARICOR trial[2].

Multiplicity

There is no multiplicity in the primary analysis. A significance level of 0.05 is therefore employed.

Power estimation

The overall frequency of post-trial AF is 830 out of 4370, or 19% (numbers rounded). The number of pre-trial AF records is not known at present, but the frequency must be considerably lower due to the roughly 10 years age difference (1995 vs. 2005 would be typical risk years that a participant contributes, his/her age being then 55 vs. 65 on average), although it may also be larger as a concomitant of the severe (but non-lethal) coronary episodes that serve as entry criterion. Taking 10% as a reasonable guess, some 440 participants with pre-trial AF will be discarded, out of whom many (at least more than 19%) will undoubtedly show post-trial AF, perhaps 30% or 130. By subtraction, some 3930 participants will be available for the main analysis, 700 of them having a post-trial AF record (18%). Under the null hypothesis, half as many will belong to each randomisation group. The ensuing approximate SE of logHR will be 0.756; a HR near 1 will therefore have a 95% confidence interval such as exp(0 ± 1.96X0.0756) = (0.86, 1.16). A hypothetical HR of 0.75 or 1.333 implies a logHR = ± 0.288, which is ±3.81SE removed from zero; the ensuing power, when the two-sided type I error risk is 5%, becomes PHI(3.81 – 1.96) = 97%.

ETHICAL CONSIDERATIONS AND TRIAL REGISTRATION

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). The trial was registered at ClinicalTrials.gov, NCT00121550 at 13 July 2005.

The CLARICOR Trial is investigator initiated and controlled trial. This trial was supported by grants from nonprofit funds including The Danish Heart Foundation, The Copenhagen Hospital Corporation, The Danish Research Council, and the 1991 Pharmacy Foundation. Abbott Laboratories, IDC, Queensborough, UK, supplied the clarithromycin and placebo tablets. Those supporting the trial had no role in design, data collection, data analyses, data interpretation or writing the reports. The CLARICOR steering group had full access to all the data and had final responsibility for the decision to submit the reports for publication. The present analysis was financed by The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet.

Discussion

The patients in the CLARICOR study were recruited from the regional hospital register ("The Green System"), and therefore represent a cohort of real-life patients. As all patients in the register were invited to participate, we consider that a sampling bias can be discarded. Participation rate was about 50%[2]. We have no information about non-attenders. Contrary to expectations, a significant adverse effect of clarithromycin on all-cause mortality and incidence of stroke was observed[2,3]. After 10 years of follow-up, all-cause mortality was still significantly increased in patients not treated with a statin at entry. Patients on a statin at entry had no increased mortality. Clarithromycin also

increased the risk of cerebrovascular disease in patients not treated with a statin[3]. Recent observational evidence support a protective effect of statins on the increased risks of mortality and of a composite of AMI, stroke and death of clarithromycin compared to oxycycline[17].

Coding for a diagnosis of AF is carried out after hospital admittance or attending an outpatient clinic. Our previous assessment of the validity of cardiovascular diagnoses in the National Patient Register and the Register of Causes of Death did not include the AF diagnoses. However, the validity of the AF codes in the registers have been assessed several times and found to be high[18,19].

Follow-up was terminated at 10 years. Our previous experience suggest that the adverse effect of clarithromycin on mortality was levelling after 10 years[3].

Electrocardiographic recordings were not conducted at randomisation. It is likely that some participants had AF at or before randomisation. Such patients will be identified by scrutiny of public registers and excluded from the analysis as previously described. However, some patients may have had AF not diagnosed in hospital, and therefore not entered in the register. Due to the randomisation process, we may assume that a similar proportion of patients in either treatment group belong to this category.

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 (e.g. a significant effect of clarithromycin on the occurrence of AF) should be interpreted accordingly.

It should be noted, that while the Cox model, and the competing risk model may yield different assessment results, neither can be considered more valid than the other.

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