Running title: Cardiovascular events following macrolide use

Type of article: ORIGINAL CONTRIBUTION

Title:

Risk of mortality and cardiovascular events following macrolide prescription in chronic rhinosinusitis patients: a cohort study using linked primary care electronic health records

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SUMMARY

***Background*:** Macrolide antibiotics have demonstrated important anti-inflammatory and immunomodulatory properties in chronic rhinosinusitis (CRS) patients. However, reports of increased risks of cardiovascular events have led to safety concerns. We investigated the risk of all-cause and cardiac death, and cardiovascular outcomes, associated with macrolide use.

***Methodology*:** Observational cohort (1997-2016) using linked data from the Clinical Practice Research Datalink, Hospital Episodes Statistics, and the Office for National Statistics. Patients aged 16-80 years with CRS prescribed a macrolide antibiotic or penicillin were included, comparing prescriptions for macrolide antibiotics to penicillin. Outcomes were all-cause mortality, cardiac death, myocardial infarction, stroke, diagnosis of peripheral vascular disease, and cardiac arrhythmia.

***Results*:** Analysis included 320,798 prescriptions received by 66,331 patients. There were 3,251 deaths, 815 due to cardiovascular causes, 925 incident myocardial infarctions, 859 strokes, 637 diagnoses of peripheral vascular disease, and 1,436 cardiac arrhythmias. A non-statistically significant trend towards increased risk of myocardial infarction during the first 30 days following macrolide prescription was observed (fully adjusted hazard ratio 1.60, 95% confidence interval: 0.95, 2.68, p=0.08). No statistically significant short- or long-term risks were observed for macrolide prescription. No significant risks were identified for clarithromycin in particular.

Conclusions: Although not statistically significant, our best estimates suggest an increased short-term risk of myocardial infarction in patients with CRS following macrolide prescription, supporting previous observational evidence. However, confounding by indication remains a possible explanation for this apparent increased risk. We found no evidence of longer term increased risks.

Key words: Macrolides, clarithromycin, cardiovascular events, sinusitis.

INTRODUCTION

Background

Macrolide antibiotics are commonly prescribed in primary and secondary care settings for a wide range of infections. In patients with chronic rhinosinusitis (CRS), macrolides have demonstrated important anti-inflammatory and immunomodulatory properties and currently have an unproven role on the basis of existing trials [1], though there is some promising evidence [2, 3]. Concerns remain about the safety of these antibiotics for this patient group, however previous research assessed the risk in full dose, short-term studies and not in cases of CRS at low doses for longer durations.

Macrolides are known to prolong the QT interval, potentially increasing the short term risk of arrhythmia [4, 5]. A number of studies have explored longer-term associations between macrolide antibiotics, particularly clarithromycin, and a range of cardiovascular events. Some have found increased risks of cardiovascular events that extend at least a year beyond the exposure to the antibiotic [6-9]. In particular a 10-year follow-up of a randomised trial found an increased risk of cardiovascular mortality and other cardiovascular events [9]. In contrast, a number of large observational studies have found no long term effects [10-13], although some found evidence of short term increases in risk of cardiovascular events [11-13]. In particular the recent meta-analysis published by Wong et al [14], demonstrated that the short-term risk of cardiovascular outcomes associated with macrolides in observational studies was estimated at 1.79 excess myocardial infarctions per 1000 patients (95% confidence interval (CI): 0.88 to 3.20). This risk was not observed in RCTs; however, the authors comment that these trials were likely underpowered to detect this. No long-term cardiovascular risk (ranging from 30 days to 3 years) associated with macrolides was observed. A recent drug safety communication released by the U.S. Food and Drug Administration notes the possibility of long-term risks, citing heart problems or death, associated with clarithromycin in patients with heart disease [15].

Objectives

We aimed to explore the association between macrolide prescription, particularly clarithromycin, and a range of cardiovascular outcomes among patients with CRS (all-cause death, cardiac death, myocardial infarction, stroke, arrhythmia, and peripheral vascular disease).

MATERIALS AND METHODS

Study design and setting

An observational cohort study was conducted using linked data from the Clinical Practice Research Datalink, Hospital Episodes Statistics, and the Office for National Statistics.

Ethical approval

Requests to access data provided by the Clinical Practice Research Datalink are subject to approval of the protocol by the Independent Scientific Advisory Committee (ISAC), a non-statutory expert advisory body. Broad scientific and ethical approval for the use of primary

care data, and established data linkages within the Clinical Practice Research Datalink (CPRD) data, was obtained following ISAC application; Protocol number 16_200R.

Participants

A case ascertainment algorithm was developed, using primary and secondary care diagnostic terms and secondary care procedures, to identify patients with CRS (see Appendix A). Patients were included if they were: determined to have CRS; prescribed one or more courses of either a macrolide antibiotic or a penicillin, or both; and aged between 16 and 80 years old at the time of a relevant prescription. Patients with a diagnosis of cystic fibrosis were excluded.

Outcomes

Outcomes studied were: time to all-cause death, cardiac death, fatal and non-fatal myocardial infarction, stroke, diagnosis of peripheral vascular disease, and cardiac arrhythmia. For non-fatal outcomes, patients with a history of the outcome were excluded from those analyses.

All-cause death was defined as a valid date of death, irrespective of cause, recorded in either CPRD or ONS. Date of death was taken to be the earliest recorded date of death from either source. Cardiac death was identified using the primary cause of death only (ICD 10th revision: I00-I99). Prevalent and incident events of all other study outcomes were identified using a combination of CPRD, HES, and ONS data, using previously-validated existing phenotyping algorithms developed in CALIBER [16].

Exposure

All prescriptions for a macrolide antibiotic or a penicillin for CRS cases during follow-up were identified using a clinician-reviewed and curated list of medications (Appendix B). An active comparator – penicillin (the most commonly prescribed antibiotic) – was chosen to minimise selection bias. All durations of prescriptions were included. Secondary analyses restricted the macrolide group to prescriptions of clarithromycin, for comparison with similar studies.

Follow-up

Follow-up of an individual patient began at the date at which the patient was deemed to have a CRS diagnosis, which was necessarily after the last of the following: current registration date of the patient at their general practice, the date at which the general practice was deemed to be providing research quality data, one year of individual research quality data, the patient's 16th birthday, and the study start date (1st April 1997). Follow-up ended at the first of the following: the date of the patient's transfer out of the general practice (defined as the Transfer Out Date in CPRD), the last collection of data from general practice (defined as the Last Collection Date in CPRD), the patient's 80th birthday, the date of death (recorded in either CPRD or ONS), or the study end date (February 29th 2016).

Data sources

We extracted anonymized patient electronic health records from the CALIBER resource described and validated elsewhere [16]. Briefly, CALIBER provides a platform to utilise

longitudinal structured records from three national sources for research: The Clinical Practice Research Datalink (CPRD) [17], Hospital Episodes Statistics (HES), and cause-specific mortality from the Office for National Statistics. CPRD provides anthropometric measurements, laboratory tests, clinical diagnoses, symptoms, prescriptions, and medical procedures, coded with the Read controlled clinical terminology. The primary care practices in CPRD and the subset of linked practices used in the present analysis are representative of the UK primary care setting and have been validated for epidemiological research [17, 18]. HES provides information about diagnoses (coded with the tenth revision of the International Classification of Diseases [ICD-10]) and medical procedures (coded with the 4th revision of the OPCS Classification of Interventions and Procedures [OPCS-4]) related to all elective and emergency hospital admissions across all National Health Service hospitals in England. ONS provides a national mortality registry with physician-certified causes of death (coded using ICD-9 and ICD-10). All data sources were linked with a deterministic algorithm using patients' NHS number (unique ten-digit identifier assigned at first interaction with the healthcare system), date of birth, gender and postcode.

Patients were selected from general practices (CPRD January 2017 version) that were eligible for linkage to HES and ONS, during the study period 1st April 1997 to 29th February 2016. Patients were included if they met the inclusion criteria described above.

Confounders

For each prescription for macrolide antibiotics or penicillin, the most recent information on potential confounders for each participant recorded up to the time of that prescription was obtained; thus values could change over time. Demographic information, including the age and sex of the patient, body mass index (BMI) recorded in primary care, and clinically-recorded smoking status and alcohol consumption, was obtained. For BMI, smoking and alcohol data, the last available measurement prior to the relevant prescription was taken; sensitivity analyses instead used the last measurement only if it was recorded within one year of the relevant date. We additionally included information about the region (Strategic Health Authority) in which the general practice was located, socioeconomic status using the Index of Multiple Deprivation (IMD) score and the frequency of primary care consultations involving clinical contact between the patient and their general practitioner. Missing data for demographic and socioeconomic confounders was handled by including an extra category indicating the information was not available. Phenotyping algorithms previously developed by the CALIBER initiative [16] were used to identify any prior use of: antidepressants, warfarin or digoxin, anti-arrhythmic drugs, anticoagulants, antiplatelet drugs, α-adrenoceptor blockers, lipid regulating drugs, diuretics, nitrates, non-steroidal anti-inflammatories (NSAIDs) and anti-hypertensive drugs including angiotensin-converting enzyme inhibitors. Prior diagnoses of: atrial fibrillation, cancer, COPD, diabetes, dyslipidaemia, hypertension, cardiovascular disease, and asthma, were also identified using existing algorithms [16].

Statistical analysis

Most patients received multiple courses of macrolide antibiotics, penicillin, or both. To handle this, an approach in which the observational data are used to emulate a consecutive series of randomised trials was adopted for the statistical analysis [19]. The study period was split into non-overlapping 30-day periods (giving 219 time intervals). Each of these 30-day intervals was considered the recruitment period for a different observational pseudo-trial. At the first instance during the 30-day interval where a patient was prescribed either a macrolide antibiotic or a

penicillin, the patient was assessed for eligibility. If eligible at that point, the patient entered that pseudo-trial. Instances where both a macrolide antibiotic and a penicillin were prescribed simultaneously were excluded.

Patients were eligible to enter a pseudo-trial if they were, at the time of the relevant prescription of macrolide or penicillin: between 16 and 80 years of age, were deemed to have had a diagnosis of CRS prior to that time, and had no recorded antibiotic prescription of any type in the last four weeks (a washout period). Patients could enter each pseudo-trial only once, but could enter multiple pseudo-trials over the whole study period.

Data on all confounders listed above were recorded for each patient entering each pseudo-trial, with the values of the confounder determined at the date of the relevant prescription; thus confounder data were updated over time for each patient. Follow-up of a patient in a particular pseudo-trial began at the day of the relevant macrolide or penicillin prescription, and ended at the first of: the outcome of interest, death (for outcomes other than all-cause mortality), and end of patient-level follow-up.

Descriptions of the participants, and summaries of outcome data, were performed at the patient level, initially restricting data to the first pseudo-trial each patient participated in. For subsequent analysis, data from the 219 different pseudo-trials were pooled together. Associations of exposure – prescription of macrolide antibiotic or penicillin – with health outcomes was assessed using Cox proportional hazards regression models, with time since entering the relevant pseudo-trial as the timescale. These Cox models adjusted for all confounders listed above. Age at entry into the pseudo-trial was modelled using restricted cubic splines. Differences between pseudo-trials were also modelled by using splines. Robust standard errors, adjusted for clustering by patient, were used due to the fact that patients could enter more than one pseudo-trial and so enter the analysis more than once. Sensitivity analyses censored follow-up at 30 days, to investigate short-term effects following prescription. For analyses of myocardial infarction censoring follow-up at 30 days, number needed to harm (NNH) was calculated by fitting a logistic regression model, approximately equivalent to the Cox model above, and calculating the NNH from the predicted risk under macrolide and no macrolide use, using 100 non-parametric bootstrap samples to obtain percentile confidence intervals.

Public and patient involvement (PPI)

Patients and public have been key to the development of a wider programme in which this study is embedded. Our PPI panel includes 7 patient and 5 lay representatives. A trained PPI facilitator has structured and led the face-to-face group meetings with the panel, ensuring that feedback has been well integrated into the programme of research. The panel has shared experiences of CRS and opinions regarding medical and surgical treatments they have received, and identified where they thought research was most needed to inform optimal patient pathways.

RESULTS

Participants

Of the 88,321 patients who were identified as having CRS in this cohort, 70,369 were prescribed one or more courses of either a macrolide antibiotic (of any type) or penicillin, or both (Figure 1). Among these 70,369 patients, the median number of penicillin and macrolide courses prescribed was 4 (25^{th} to 75^{th} percentile: 2 to 8). A single prescription of either penicillin or macrolide during follow-up was received by 10% of these patients; more than 14 prescriptions were received by 10% of patients. After restricting to prescriptions where the patient was eligible for a pseudo-trial, the final analysis included 66,331 unique patients, 23,465 of whom contributed to the macrolide exposure group and 57,876 to the penicillin group (thus 15,010 entered the analysis both following a macrolide prescription and a penicillin prescription). A total of 320,798 prescriptions were included in the final analysis.

Descriptive data

Of the included 320,798 prescriptions, the most common duration was 1 week: 68% of penicillin prescriptions, 68% of macrolide, and 76% of clarithromycin were for 1 week. Almost all prescriptions were either 250mg or 500mg. For penicillin, 55.4% of prescriptions were for 500mg and 43.5% 250mg. For macrolide prescriptions, 35.6% were 500mg and 64.3% 250mg. Restricting to clarithromycin, 61.2% of prescriptions were for 500mg and 38.8% 250mg. Amoxicillin, Flucloxacillin, and Co-amoxicillin accounted for more than 90% of the included Penicillin prescriptions, with 68% being for Amoxicillin (500 or 250mg), 12% for Flucloxacillin (500 or 250mg), and 10.9% for Co-amoxicillin (500, 250, or 125mg). The data used are collected for clinical care rather than research; as such, the indication the drug was prescribed for is not available.

Recorded characteristics of participants, at the time of their first eligible macrolide or penicillin prescription were very similar (Table 1). Overall, females, patients with prior use of antidepressants, a history of chronic obstructive pulmonary disease or asthma were more likely to receive a macrolide antibiotic, but these differences were fairly small.

Outcome data

Median patient follow-up was 4.24 years (25^{th} to 75^{th} percentile: 2.0 to 7.4 years). Patients receiving a clarithromycin prescription tended to have shorter follow-up (Table 2). Patients included in the analysis participated in a median of 3 of the pseudo-trials (25^{th} to 75^{th} percentile: 2 to 6).

Over the whole follow-up period, 3,251 deaths due to any cause were observed, 815 of which were due to cardiovascular causes (Table 2). There were 925 incident myocardial infarctions, 859 incident strokes, 637 incident diagnoses of peripheral vascular disease, and 1,436 recorded incident cardiac arrhythmias. Of these incident myocardial infarctions, 91 (9.8%) occurred on the date of the cardiac death; 56 (6.5%) of the incident strokes occurred on the date of the cardiac death.

Main results

Table 3 shows estimated hazard ratios (HRs), both unadjusted and adjusted for all confounders listed previously, associated with a prescription of a macrolide antibiotic compared with a prescription for penicillin. At the 5% level, no statistically significant short- or long-term risks were observed after adjustment for confounders.

The unadjusted analysis showed no evidence of increased risk of myocardial infarction following macrolide prescription (crude hazard ratio (HR) 1.10, 95% confidence interval (CI): 0.94 to 1.29, p=0.25). Following adjustment for all confounders above, the estimated hazard ratio for myocardial infarction during the first 30 days following prescription was 1.60, i.e. a 60% increase in risk, with a confidence interval from 0.95 to 2.68, p=0.08. The estimated absolute risk of myocardial infarction within 30 days, per 10,000 patients, is 2.32 (95% CI: 1.84, 2.90) with no macrolide prescription, and 3.75 (95% CI: 2.50, 5.24) with macrolide prescription, corresponding to a number needed to harm (i.e. number of patients needing to be treated with macrolides in order to result in a single extra myocardial infarction) of 7008 (95% CI: 3381, ∞).

No evidence of a longer-term risk of myocardial infarction was seen (fully adjusted HR 1.09, 95% CI: 0.93 to 1.28, p=0.30). Sensitivity analyses using BMI, smoking and alcohol information only if recorded within the last year gave similar results.

Large increased risks were seen in the HRs following clarithromycin prescription, compared with penicillin, in the unadjusted models: all-cause death 1.26 (95% CI 1.12 to 1.42); cardiac death 1.34 (95% CI 1.04 to 1.72). These estimated HRs were greatly diminished following adjustment and were no longer statistically significant: all-cause death 1.09 (95% CI 0.96 to 1.22), and cardiac death 1.15 (0.89 to 1.49).

DISCUSSION

Key results

Looking at a defined population of patients with CRS, we found a trend towards an increase in short-term risk of myocardial infarction in the 30 days following prescription of macrolides that did not reach statistical significance, especially with reference to clarithromycin. Specifically, our best estimates suggest macrolide prescription being associated with a 60% increase in hazard of myocardial infarction; our data are compatible with macrolide prescription being associated with a small reduction in hazard (up to 5% reduction), or with up to a 2.7-fold increase in hazard. No evidence of other short or long-term associations was found. Using contemporary electronic health records from national sources such as the Clinical Practice Research Datalink and Hospital Episode Statistics enabled us to analyse a representative section of the population and therefore our results are generalizable to the UK population more widely.

Limitations

Confounding by indication is a key problem in observational studies like these. Our study population – patients flagged as having CRS – provides a more homogeneous group of individuals which may reduce this bias. Nonetheless, strong confounding was observed in analyses comparing clarithromycin prescriptions to penicillin; large crude associations between clarithromycin prescription and mortality were observed, which were removed after adjustment for potential confounders. Choosing an active comparator, rather than comparing with the absence of a macrolide prescription, minimises such biases; however it is possible that some confounding by indication remains. For example, patients with more severe or recurrent infections may be more likely to be prescribed macrolides rather than penicillin, and severity of infection may itself increase the risk of cardiovascular events, particularly in the short term. Thus the suggestion of a short-term increase in risk of myocardial infarction following macrolide prescription may simply reflect such residual confounding by indication.

Our study was limited by the number of events which occurred during follow-up. Some of the analyses, especially when restricting to prescriptions for clarithromycin versus penicillin, had few events and thus suffered from low statistical power. In particular, uncertainty remains about the possible association between macrolide prescription and risk of myocardial infarction in this patient population.

Diagnoses for chronic rhinosinusitis are not well recorded in electronic health record data. Although we developed an algorithm to determine which patients were likely to have CRS, based on primary and secondary diagnosis data and secondary care procedures, it is possible that the analysis may have omitted some patients with this condition, and included some who did not actually have CRS. This misclassification of case status is unlikely to have biased results, since it is unlikely that cardiovascular effects of macrolide antibiotics differ greatly for patients who have CRS.

As with all analyses relying on electronic health records and administrative data, the quality of the data is a limiting factor. However, sensitivity analyses exploring the impact of missing data showed our results were robust to these missing data.

We were unable to look specifically at longer duration low dose prescriptions of macrolide antibiotics, due to sample size constraints. Future studies are required to assess associations in this setting.

Comparison with other studies

Since 2006, a series of studies have raised concerns about possible cardiovascular risk associated with short term macrolide use. Our results, though not significant at the 5% level, are broadly consistent with those from Root et al. [12], and Wong et al. [13], who found some evidence of a short term association of clarithromycin and incident myocardial infarction but no long-term risks in patients receiving Helicobacter pylori treatment [12] and in the general Hong Kong population [13]. In contrast to other studies [6-9], we found no evidence of increased risks of other events or longer term risks. In particular, unlike other studies, we found no evidence of any increased risk of cardiovascular mortality [6, 8, 9, 11]. One reason for these apparent discrepancies may be that these studies have predominantly investigated associations in populations with pre-existing heart conditions. In contrast, we investigated incident myocardial infarction, stroke, diagnosis of peripheral vascular disease and cardiac arrhythmia,

thus restricting these analyses to populations with lower frequency of pre-existing heart disease. It is possible that these associations truly differ in those different populations.

Previous database studies have tended to be larger than ours, due to our additional restriction to a particular patient subgroup – patients with CRS. This limited our power to look at, for example, analyses restricted to clarithromycin rather than all macrolides.

Clinical implications

In summary, while our results were not statistically significant, our best estimates suggest a possible increased short-term risk of myocardial infarction in patients with CRS following prescription with macrolide antibiotics; this was less so for clarithromycin specifically. This supports prior observational evidence from different patient groups, and fits with physiological data of the impact of macrolides on the heart. However, confounding by indication remains a possible explanation for the apparent increase in risk. We found no evidence of any long-term increased risks.

The MACRO Programme has been funded by the National Institute of Health Research to define best management of adults with CRS and will include a randomised controlled trial comparing a 12 week course of clarithromycin, placebo and sinus surgery starting in September 2018. The trial will screen potential participants for any absolute contraindications to clarithromycin: risk factors including history of ischaemic heart disease, prolonged Q-T interval on ECG, diabetes and age over 65 or any medications known to interact with clarithromycin unless these can be discontinued during the 3 months of clarithromycin/placebo treatment. Based on the findings of this study, we have taken the necessary precautions to screen patients for the forthcoming trial, however, further guidance on when to prescribe clarithromycin and who to select will be forthcoming once the results of the trial are available.

ACKNOWLEDGEMENTS

Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research (PGfAR) Programme (Grant Reference Number RP-PG-0614-20011). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

AUTHORSHIP CONTRIBUTION

CH, CP, HB, AS, JC, SM, SD, PL, VL and MT developed the research question, study design and general analytic approach. EW devised and performed the statistical analysis, based on initial analyses by HE, supervised by JC. SD, CC, KD, and AGI performed data extraction, derivation of codelists, and phenotyping. EW drafted the manuscript. All co-authors critically revised the manuscript. EW is the guarantor.

CONFLICT OF INTEREST

In addition to the NIHR funding for this work acknowledged above, we declare the following interests: Anne Schilder advises on clinical trial design and delivery to a range of biotech companies, and is a member of the Development Advisory Board of Novus Therapeutics. Carl Philpott reports personal fees (Aerin Medical, Navigant, Entellus, Johnson & Johnson) and grants (Sir Jules Thorn Trust, Rosetrees Foundation, Royal College of Surgeons of England, Otorhinolaryngological Research Society), and is a trustee for Fifth Sense and ENT UK. Claire Hopkins has participated in Advisory boards to discuss management of CRS and to advise on design of future trials in this area (Sanofi, GSK, Medtronic). Valerie Lund reports personal fees (Abbott, Hartington, Kyorin, Optinose) and grants from GSK. James Carpenter reports personal fees (Pfizer, GSK), and grants (MRC, Novartis), The remaining authors have nothing to declare.

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FIGURE CAPTIONS

Figure 1. Numbers of patients (n) and antibiotic prescriptions (n_{abx}) included in the observational pseudo-trials

TABLES

Table 1. Characteristics of patients in the first pseudo-trial they were eligible for, by type of antibiotic prescription.

		Penicillin (n=53,498)		Macrolide (n=12,833)		Clarithromycin[a] (n=5,299)	
		Freq.	%	Freq.	%	Freq.	%
Age-group							
	<40	15,149	28.3	3,300	25.7	1,218	23.0
	40-<50	11,369	21.3	2,921	22.8	1,194	22.5
	50-<60	11,563	21.6	2,854	22.2	1,209	22.8
	60-<70	9,687	18.1	2,396	18.7	1,075	20.3
	70-80	5,730	10.7	1,362	10.6	603	11.4
Sex							
	Male	19,919	37.2	4,148	32.3	1,876	35.4
	Female	33,579	62.8	8,685	67.7	3,423	64.6
Smoking							
	Non	24,649	46.1	6,018	46.9	2,393	45.2
	Ex	15,157	28.3	3,679	28.7	1,745	32.9
	Current	9,894	18.5	2,398	18.7	994	18.8
	Unknown	3,798	7.1	738	5.8	167	3.2
Alcohol							
	None	7,353	13.7	1,883	14.7	777	14.7
	Ex	2,529	4.7	686	5.3	322	6.1
	<1/week	10,798	20.2	2,778	21.6	1,172	22.1
	Current	2,256	4.2	513	4.0	207	3.9
	Excess	518	1.0	119	0.9	48	0.9
	Unknown	30,044	56.2	6,854	53.4	2,773	52.3
BMI							
	Underweight	828	1.5	206	1.6	95	1.8
	Normal	18,642	34.8	4,554	35.5	1,798	33.9
	Overweight	16,942	31.7	3,921	30.6	1,683	31.8
	Obese I	7,346	13.7	1,889	14.7	822	15.5
	Obese II	3,869	7.2	1,039	8.1	445	8.4
	Unknown	5,871	11.0	1,224	9.5	456	8.6
Ethnicity							
	White	31,646	59.2	7,856	61.2	3,362	63.4
	Indian	705	1.3	175	1.4	78	1.5
	Black	396	0.7	86	0.7	32	0.6
	China	244	0.5	58	0.5	23	0.4
	Mixed	482	0.9	124	1.0	56	1.1
	Unknown	20,025	37.4	4,534	35.3	1,748	33.0
IMD							
	1 (least deprived)	13,916	26.0	3,352	26.1	1,382	26.1
	2	12,214	22.8	2,974	23.2	1,219	23.0
	3	11,257	21.0	2,691	21.0	1,147	21.6
	4	9,077	17.0	2,186	17.0	918	17.3
	5 (most deprived)	6,984	13.1	1,623	12.6	629	11.9
	Missing	50	0.1	7	0.1	4	0.1
Region							
North East		1,157	2.2	219	1.7	86	1.6
North West		9,393	17.6	2,077	16.2	852	16.1

Yorkshire	2,477	4.6	555	4.3	202	3.8
East Midlands	1,661	3.1	416	3.2	88	1.7
West Midlands	6,693	12.5	1,521	11.9	722	13.6
East	6,490	12.1	1,515	11.8	583	11.0
South West	6,369	11.9	1,468	11.4	651	12.3
South Central	7,184	13.4	1,629	12.7	670	12.6
London	5,934	11.1	1,605	12.5	620	11.7
South East	6,140	11.5	1,828	14.2	825	15.6
Prior use of:						
Antidepressants	23,042	43.1	6,007	46.8	2,603	49.1
Warfarin or Digoxin	1,449	2.7	314	2.4	151	2.8
Antiarrhythmic drugs	5,361	10.0	1,412	11.0	599	11.3
Anticoagulants	1,491	2.8	348	2.7	174	3.3
Antiplatelets	6,567	12.3	1,526	11.9	655	12.4
□□-adrenoceptor blocking drugs	12,052	22.5	2,955	23.0	1,247	23.5
Lipid regulating drugs	8,180	15.3	2,000	15.6	949	17.9
Diuretics	10,308	19.3	2,682	20.9	1,137	21.5
Nitrates	8,700	16.3	2,145	16.7	926	17.5
Non-steroidal anti-inflammatories	37,544	70.2	9,258	72.1	3,889	73.4
Antihypertensive drugs	10,760	20.1	2,604	20.3	1,181	22.3
History of:						
Atrial fibrillation	916	1.7	186	1.4	94	1.8
Cancer	3,540	6.6	947	7.4	460	8.7
Chronic Obstructive Pulmonary	23,550	44.0	6,210	48.4	2,639	49.8
Disease						
Diabetes	2,432	4.5	630	4.9	276	5.2
Dyslipidaemia	5,025	9.4	1,271	9.9	587	11.1
Hypertension	10,988	20.5	2,705	21.1	1,210	22.8
Cardiovascular disease	3,220	6.0	695	5.4	302	5.7
Asthma	13,252	24.8	3,719	29.0	1,543	29.1

[a] subgroup of the macrolide column

Table 2. Outcome and follow-up data for participants in the pseudo-trials, for the first pseudo-trial the patient is eligible for

	All (n=66,321)		Penicillin (n=53,498)		Macrolide (n=12,833)		Clarithromycin[a] (n=5,299)	
	Median ($p25^{th}$, $p75^{th}$)[b]		*Median ($p25^{th}$, $p75^{th}$)[b]*		*Median ($p25^{th}$, $p75^{th}$)[b]*		*Median ($p25^{th}$, $p75^{th}$)[b]*	
Follow-up (years)	5.1 (2.3, 8.8)		5.2 (2.3, 8.9)		4.8 (2.2, 8.6)		3.3 (1.5, 6.0)	
Number of trials participated in	3 (2, 6)		3 (2, 6)		3 (1, 6)		2 (1, 5)	
Outcome events	*Freq.*	*%*	*Freq.*	*%*	*Freq.*	*%*	*Freq.*	*%*
Death by any cause	3,251	4.9	2,653	5.0	598	4.7	207	3.9
Cardiovascular death	815	1.2	694	1.3	121	0.9	34	0.6
Myocardial infarction	925	1.4	742	1.4	183	1.4	52	1.0
Stroke	859	1.3	700	1.3	159	1.2	46	0.9
Ischaemic	498	0.8	410	0.8	88	0.7	27	0.5
Intracerebral haemorrhage	110	0.2	88	0.2	22	0.2	6	0.1
Subarachnoid haemorrhage	94	0.1	74	0.1	20	0.2	4	0.1
Not classified	370	0.6	290	0.5	80	0.6	26	0.5
Peripheral vascular disease	637	1.0	514	1.0	123	1.0	36	0.7
Cardiac arrhythmia	1,436	2.2	1,148	2.1	288	2.2	86	1.6

[a] subgroup of the macrolide column, [b] 25^{th} and 75^{th} percentiles

Table 3. Crude and fully adjusted hazard ratios estimated from Cox models

	Macrolide (vs Penicillin)			Clarithromycin (vs Penicillin)		
	HR	95% CI	P	HR	95% CI	P
Mortality						
Unadjusted	1.04	(0.95, 1.13)	0.446	1.26	(1.12, 1.42)	<0.001
Overall, adjusted[a]	0.99	(0.91, 1.09)	0.865	1.09	(0.96, 1.22)	0.181
Censored at 30 days, adjusted[a]	0.93	(0.70, 1.24)	0.628	0.91	(0.62, 1.34)	0.639
Cardiovascular Mortality						
Unadjusted	1.01	(0.83, 1.23)	0.890	1.34	(1.04, 1.72)	0.023
Overall, adjusted[a]	1.00	(0.82, 1.21)	0.961	1.15	(0.89, 1.49)	0.272
Censored at 30 days, adjusted[a]	0.99	(0.56, 1.77)	0.983	0.65	(0.24, 1.76)	0.394
Myocardial infarction						
Unadjusted	1.10	(0.94, 1.29)	0.252	1.16	(0.91, 1.47)	0.226
Overall, adjusted[a]	1.09	(0.93, 1.28)	0.300	1.04	(0.83, 1.32)	0.713
Censored at 30 days, adjusted[a]	1.60	(0.95, 2.68)	0.077	1.22	(0.55, 2.67)	0.626
Stroke						
Unadjusted	1.09	(0.93, 1.29)	0.280	1.16	(0.91, 1.48)	0.228
Overall, adjusted[a]	1.06	(0.87, 1.29)	0.545	1.01	(0.78, 1.31)	0.947
Censored at 30 days, adjusted[a]	1.11	(0.60, 2.05)	0.735	0.82	(0.33, 2.05)	0.670
Diagnosis of Peripheral Vascular Disease						
Unadjusted	1.09	(0.92, 1.28)	0.309	1.15	(0.90, 1.46)	0.267
Overall, adjusted[a]	0.99	(0.81, 1.22)	0.935	0.80	(0.63, 1.01)	0.060
Censored at 30 days, adjusted[a]	1.03	(0.57, 1.89)	0.915	0.68	(0.24, 1.87)	0.453
Cardiac Arrhythmia						
Unadjusted	1.10	(0.94, 1.30)	0.239	1.15	(0.90, 1.47)	0.250
Overall, adjusted[a]	1.01	(0.88, 1.17)	0.851	0.99	(0.82, 1.19)	0.923
Censored at 30 days, adjusted[a]	0.87	(0.58, 1.30)	0.491	0.85	(0.49, 1.49)	0.573

HR Hazard ratio; CI confidence interval; P Wald-test p-value using robust standard error clustered on patient.
[a] Adjusted for: pseudo-trial (splines), age (splines), gender, region of GP, IMD, smoking status, alcohol consumption, BMI group, contact with GP, prior use of drugs (see list in text), prior comorbidities (see list in text).