Cardiovascular outcomes associated with use of clarithromycin: population based study

Journal:	*BMJ*
Manuscript ID	BMJ.2015.027075.R2
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
Complete List of Authors:	Wong, Angel; The University of Hong Kong, Department of Pharmacology and Pharmacy Root, Adrian; London School of Hygiene and Tropical Medicine, Non-Communicable Disease Epidemiology Douglas, Ian; London School of Hygiene and Tropical Medicine, Epidemiology and Population Health Chui, Celine; The University of Hong Kong, Department of Pharmacology and Pharmacy Chan, Esther; University of Hong Kong, Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine Ghebremichael-Weldeselassie, Yonas; The Open University, Siu, Chung Wah; The University of Hong Kong, Division of Cardiology, Department of Medicine Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology and Population Health Wong, Ian; University of Hong Kong, Li Ka Shing Faculty of Medicine
Keywords:	antibiotic, cardiovascular safety

Full title: Cardiovascular outcomes associated with use of clarithromycin: population based study

Angel YS Wong[1*], Adrian Root[2*], Ian Douglas[2], Celine SL Chui[1], Esther W Chan[1], Yonas Ghebremichael-Weldeselassie[3], Chung-Wah Siu[4], Liam Smeeth[2], Ian CK Wong[1,5]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

[3]Department of Mathematics and Statistics, The Open University, Milton Keynes, United Kingdom

[4]Cardiology Division, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[5]Research Department of Practice and Policy, School of Pharmacy, University College London London, London, United Kingdom

*These authors contributed equally to this work.

Correspondence to:

Professor Ian C K Wong

Research Department of Practice and Policy

UCL School of Pharmacy 29-39 Brunswick Square

London WC1N 1AX

Email: i.wong@ucl.ac.uk

Telephone: +44 207 753 5966

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Abstract

Objective To investigate the association between the use of clarithromycin and cardiovascular outcomes.

Design Population based cohort study, self-controlled case series (SCCS) and case-crossover.

Setting The Clinical Data Analysis and Reporting System (CDARS) database, Hong Kong.

Participants Individuals who received clarithromycin (n=108 988) compared with amoxicillin (n=217 793) in cohort analysis and those who received *Helicobacter pylori* eradication therapy in SCCS.

Main outcome measures The primary outcome was myocardial infarction (MI) and the secondary outcomes were arrhythmia, stroke, all-cause, cardiac and non-cardiac mortality.

Results The propensity score adjusted rate ratio of MI 14 days following an initiation of antibiotic treatment was 3.66 (95% confidence interval 2.82 to 4.76) comparing the use of clarithromycin (132 MI occurred, rate 44.4 per 1000 person-years) to the use of amoxicillin (149 MI, 19.2 per 1000 person-years) but no long-term increased risk was observed. Similarly, significantly increased rate ratios of secondary outcomes were only found in current use of clarithromycin versus amoxicillin except stroke. In SCCS, there was an association between current use of triple therapy containing-clarithromycin and cardiovascular events. The risk returned to baseline after treatment had ended. The case-crossover analysis also demonstrated an increased risk of cardiovascular events during current use of triple therapy containing-clarithromycin. The adjusted absolute risk difference for the current use of clarithromycin versus amoxicillin was 1.90 excess MI events (95% confidence interval 1.30 to 2.68) per 1000 patients.

Conclusions This study found an increased short-term risk of MI, arrhythmia and cardiac mortality during current use of clarithromycin but no association with long-term cardiovascular risks among the Hong Kong population.

(260 words)

Article summary

Strengths and limitations of this study: This study used a population based healthcare database with comprehensive data linkages within primary, secondary and tertiary healthcare services and included both cohort and case-only study designs. Channeling bias might arise in the cohort analysis due to differences in the underlying health status between exposure groups.

- Both the cohort and self-controlled case series analysis reported a higher risk of myocardial infarction and arrhythmia with current use of clarithromycin but no evidence of long-term risk.
- The cohort analysis also demonstrates an association between cardiac mortality and current exposure to clarithromycin compared with exposure to amoxicillin, however no long-term effect was observed.

What is already known in this topic:

Previous epidemiological studies suggest that clarithromycin leads to an increased risk of serious cardiovascular outcomes.

The findings on whether the cardiovascular risk associated with clarithromycin is short- or long-term are conflicting.

What this paper adds:

This population-based study suggests a significantly increased risk of myocardial infarction, arrhythmia and cardiac death associated with the current exposure to clarithromycin, however no long-term effect was observed.

Albeit the high overall cardiovascular risk conferred by clarithromycin, such risks are not homogeneous across our patient population. Patients aged 75 or above or with hypertension, and/or diabetes mellitus have a higher absolute risk for myocardial infarction and cardiac death. Thereby, caution should be exercised when selecting antibiotic for these high-risk individuals.

Acknowledgements

We would like to thank the Hong Kong Hospital Authority for access to data and Dr. Michael Mok and Dr. Martijn Schuemie for their expert advice and contribution to our study.

Contributors: AW, AR, ID and IW were responsible for the conception and design of the study. AW and AR had principal responsibility for data analysis, drafting and revising the manuscript, and final approval. AW, AR, ID, CC, EC, YW, CS, LS, IW contributed to the analysis and the drafting, revision, and final approval of the manuscript. All authors were responsible for interpretation of the data. AW and AR are the guarantors.

Transparency declaration: AW and AR affirm that this 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 (and, if relevant, registered) have been explained.

Funding: During the conduct of the study, ID was funded by grants from the Medical Research Council for this project. LS was funded by a grant from the Wellcome Trust. Sponsors played no role in the study design, the collection, analysis and interpretation of the data; the writing of the article; or the decision to submit it for publication.

Competing interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster approved this study (IRB reference number: UW 14-032). Informed consent was not required for research based on routine data.

Data sharing: No additional data available.

Introduction

Clarithromycin is a commonly prescribed macrolide antibiotic, indicated for respiratory tract infections, *Mycobacterium avium* complex disease in patients with human immunodeficiency virus and skin and soft tissue infections.[1 2] Together with amoxicillin or metronidazole and a proton pump inhibitor, it is also used to treat *Helicobacter pylori* infections.[2] Several randomised controlled trials (RCT) were conducted to explore the effects of clarithromycin on the prevention of subsequent cardiovascular outcomes among patients with cardiovascular disease.[3-5] Among these, the first RCT showed that clarithromycin treatment duration of three months appeared to reduce the risk of cardiovascular outcomes in 1.5 years.[3] However, another RCT showed short-term treatment did not significantly reduce the rate of cardiovascular events compared with placebo among patients undertaking coronary artery bypass graft with follow-up of 2 years.[5] On the contrary, a significantly higher risk of cardiovascular mortality was reported over 3 years and also higher all-cause mortality among patients with coronary heart diseases receiving a two week course of clarithromycin once daily versus placebo over 6 years.[4 6 7]

In addition to the randomised trials, a recent cohort study reported a substantially higher risk of cardiac death associated with use of clarithromycin compared with penicillin V in a follow-up of 7 days among the general population.[8] Another cohort study also found a higher risk of cardiovascular events one year after the exposure to clarithromycin compared to other antibiotics among patients with chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia.[9]

Given the uncertain nature of any increased cardiovascular risk with clarithromycin, and the surprising finding of a persistent effect well beyond the period of exposure, further investigation is needed. Therefore, we conducted a cohort study using amoxicillin as comparator, a self-controlled case series (SCCS) and a case-crossover study to eliminate between-person confounding to investigate whether the use of clarithromycin is associated with cardiovascular outcomes among the general population in Hong Kong.

Methods

Data sources

The Clinical Data Analysis and Reporting System (CDARS) is an electronic database managed by the Hospital Authority (HA), which is a statutory body responsible for primary, secondary and tertiary public healthcare services in Hong Kong.[10] There are more than seven million Hong Kong residents who have access to healthcare services provided by the HA. It contains patients' demographic characteristics, and includes history of diagnosis, operation, prescription use, laboratory tests, accident & emergency (A&E), out-patient and in-patient visits since 1993. It also contains data on causes of death through its internal linkage to regional deaths registry, Immigration Department. Anonymous patient identifiers were generated to protect patient confidentiality and used to link all medical information such as diagnostic and prescribing data in CDARS. This database has been used to conduct high-quality epidemiological studies.[11-13]

Cohort analysis

All patients aged 18 years or above and prescribed either oral clarithromycin or amoxicillin (including amoxicillin with clavulanate potassium) between 1 January 2005 and 31 December 2009 were identified. We matched one clarithromycin user to up to two amoxicillin users based on age within 5 years, sex and calendar year at exposure. Patients who had been prescribed clarithromycin up to four years before the date of first antibiotic prescription during the observation period were excluded in both groups. However, amoxicillin users could be classified as being exposed to clarithromycin at a later date.

The observation period commenced from the date of the first antibiotic prescription (index date) and ended at the earliest occurrence of the outcome, death, subsequent exposure of clarithromycin or amoxicillin, or end of study (31 December 2012). We assumed continued treatment course if the gap between scripts was less than or equal to 7 days as the next script was very likely to be prescribed for the same indication during follow-up consultation.

The primary outcome was first recorded myocardial infarction (MI) as principal diagnosis for an A&E or in-patient admission during the observation period in multiple follow-up periods. As the treatment duration of clarithromycin is seven to fourteen days in general, follow-up periods were classified as current use (day 1-14 started on the index date), recent use (day 15-30), and past use (day 31-90, day 91-365, day 366-730, day 731-1095). Secondary outcomes included first recorded principal diagnosis of arrhythmia, stroke, all-cause, cardiac and non-cardiac mortality during observation period. We excluded patients who had previous MI, arrhythmia or stroke before observation period respectively in each analyses. All outcomes were identified using ICD-9 and ICD-10 (International classification of diseases, 9th and 10th revision) (Supplementary material 1).

Self-controlled case series analysis

The SCCS was developed as a method to overcome between-person confounding by comparing the rate of outcomes in different periods within the same individual and gives a relative incidence estimate.[14] The standard SCCS method requires risk windows to be chosen a priori. This method is based on individuals who had both the exposure and the event. We adopted this case-only approach to account for between-person differences. The exposure of interest was *H. pylori* eradication therapy (HPT) containing-clarithromycin. Acute infection is known to be associated with an increased risk of first MI; for this reason *H. pylori* was chosen because it is a chronic infection unlikely to be associated with a period of increased risk of MI, and therefore unlikely to lead to a spurious association between clarithromycin and the risk of MI.[15]

We identified patients who received out-patient HPT of 7 and 14 days duration. HPT is defined as co-prescription of clarithromycin with either amoxicillin or metronidazole, together with one of the proton pump inhibitor with British National Formulary recommended doses (Supplementary material 2). We chose to include patients receiving out-patient therapy only

because it avoids including a selected group of patients with more severe health status at the prescription date. Patients who received a clarithromycin prescription or in-patient HPT before out-patient HPT were excluded. Follow-up was censored if people received a clarithromycin prescription or in-patient therapy after out-patient therapy. Similar to cohort analysis, the event outcomes included MI, arrhythmia and stroke. Within this cohort, patients must also have a first recorded event as principal diagnosis for an A&E or in-patient admission during study period (1 January 2003 and 31 December 2012) to be included as study subjects.

The observation period started from one year after the patients entered the database and follow-up was censored at the earliest of end of the study (31 December 2012), death, or one of the censoring events described above. Patients were ineligible if they had a history of HPT or event before the observation period. Similar to the cohort analysis, several risk windows were defined as follows: current use (day 1-14 from index date), recent use (day 15-30), and past use (day 31-90, day 91-365, day 366-730, day 731-1095). All other periods except 14-day pre-exposure risk window were classed as baseline. As the SCCS requires an assumption that occurrence of event should not alter the probability of subsequent exposure, a 14-day pre-exposure risk window before the use of HPT was removed from the baseline periods. This removes the potential for bias whereby the outcome of interest (MI/ arrhythmia/ stroke) may temporarily alter the likelihood of the exposure being prescribed.[14] Continued treatment course was assumed for treatment gap of less than or equal to 7 days. In addition to the standard SCCS, a non-parametric SCCS was also employed to analyse the data. This method unlike the standard SCCS method does not require pre-defining several risk windows and estimates relative incidence functions that show how the incidence changes with time.[16]

Data validation

To determine the validity of diagnoses recording, we reviewed the original clinical records in the computer-based clinical management system among a sample of patients from the Hong Kong West (HKW) cluster. In Hong Kong, all hospital admissions, outpatient clinic records, laboratory results, and radiological images in the public health system have been recorded in the clinical management system since 1996. The HKW cluster, one of the seven administrative hospital clusters of the HA, provides public healthcare services to 530 000 population (8% of the total Hong Kong population) in that region and allows cross-cluster referrals from other cluster regions.[17] One of the two university teaching hospitals also resides in HKW cluster, the Queen Mary Hospital, providing tertiary and quaternary care to the residents.[17]

For MI and arrhythmia, we identified the cases through CDARS among our study cohort. The patient records including clinical notes, electrocardiograms, laboratory results and X-ray computed tomography were reviewed by a cardiologist (CS). For stroke, we identified the cases from another study cohort. (Lau WCY. The unmet needs of antithrombotic treatment in patients with non-valvular atrial fibrillation in the real-world clinical practice: A population-wide cohort study in Chinese patients, 2015) Clinical notes, results from radiology, computerised tomography

or magnetic resonance imaging of the brain were reviewed. We defined the corresponding positive predictive values (PPV) with binominal exact 95% confidence interval (CI) as the proportion of the number of patients with verified outcomes after review against the total number of patients with the specific diagnosis in CDARS.

Statistical analyses and sensitivity analyses

Poisson regression was used to estimate the rate ratios comparing clarithromycin users with amoxicillin users during current, recent and past use with initial adjustment for age, sex, and history of event of interest. Propensity score adjustment was also used to control for confounding. We derived propensity scores by using conditional logistic regression to represent the conditional probability of exposure given the covariates (Supplementary material 3). We further restricted the cohort to those patients whose propensity scores were within the overlapping region of the distributions of the clarithromycin and amoxicillin groups in order to identify a group within which valid comparisons can be made. To further reduce the potential effects of unmeasured confounding, patients who had extreme scores in upper or lower tail of the propensity score distribution were excluded as those treated contrary to extreme scores may introduce bias due to missing information on important risk factors for adverse outcomes [18]. Therefore, we constructed 20 categories of 5% each for the distribution of scores to allow establishment of the cut-points for trimming.[19] The 1st and 20th propensity score strata were trimmed in the primary analysis (Supplementary material 4). Along with other initial adjustment variables, the estimated propensity score was also used as an adjustment variable in the Poisson regression in the final analysis. With respect to the follow-up periods, we conducted a sensitivity analysis for follow-up periods in current (day 1-7 started on the index date) and recent use (day 8-30). We also performed another sensitivity analysis without trimming any propensity score strata. For the analyses of causes of death, patients with unknown cause of death were censored at the time of death, but were not classified as having an outcome. We also conducted subgroup analysis to evaluate the risk of cardiovascular outcomes with respect to age, sex and history of hypertensive diseases or diabetes mellitus. Moreover, we estimated the propensity score adjusted absolute difference in risk of MI, arrhythmia, stroke and cardiac death for the use of clarithromycin as adjusted rate ratios minus 1, followed by the multiplication of the crude incidence rates among patients using amoxicillin per thousand patients.[20 21] Similarly, we also estimated the propensity score adjusted absolute differences in subgroups. All statistical tests were two–sided and p-values with 5% were considered to be statistically significant.

For the SCCS analysis, incidence rate ratios (IRR) were estimated using the conditional Poisson regression, comparing the rate of events during risk windows with the rate during baseline periods. We further divided all periods in single year bands to adjust for age effect. As MI might increase mortality in short-term, observation period would be censored at random and thus affect the assumption of event independence. As the SCCS analysis might suffer from bias if the outcome leads to observation period censoring, we also performed a post hoc case-crossover analysis which is not vulnerable to this SCCS limitation. The case-crossover design is applied for

studies investigating the association between transient exposure and outcome with abrupt time of onset.[22] Odds ratios were estimated using conditional logistic regression, comparing the exposure status just before the event (current period) with that at other earlier control periods within individual. The length of current and control periods were both 14 days. We used 100 control periods at maximum to improve precision and increase power.[22] We did not adjust time trends in exposure for case-crossover analysis as the prescription temporal trend of HPT containing-clarithromycin was stable throughout the study period (Supplementary material 5).

In the non-parametric SCCS analysis two IRR functions were estimated, using MI as an example to illustrate the IRR over time; a function that represents IRR during the current use of clarithromycin and an IRR function in the washout period up to three years after treatment ended. In this method age effect was also adjusted without pre-specifying age groups.

The statistical analyses were conducted independently by two investigators (AW and CC) to ensure quality assurance and performed with the use of SAS software, version 9.3 (SAS Institute) and R version 3.2.0 (www.R-project.org).

Results

Data validation

A total of 1999 MI and 712 arrhythmia cases were identified in the CDARS from cohort and SCCS analysis. Of these, we identified 151 MI and 44 arrhythmia cases from HKW cluster. In another study cohort, 1054 stroke cases were identified in the analysis. Among these, 90 strokes cases were from HKW cluster. The overall PPVs for MI, arrhythmia and stroke were 85.4% (95% CI 78.8% to 90.6%) (129/151); 45.5% (30.4% to 61.2%) (20/44) and 91.1% (83.2% to 96.1%) (82/90) respectively.

The risk of cardiovascular outcomes

Figure 1 shows the cohort identification and inclusion in the cohort analysis. We matched 108 988 clarithromycin users to 217 793 amoxicillin users. Table 1 and Supplementary material 6 show the baseline characteristics of the full and trimmed cohort respectively. Supplementary material 7 illustrates the propensity score distributions before and after the propensity score trimming. Compared with amoxicillin users, clarithromycin users were more likely to have a medical history of chronic obstructive pulmonary disease, obesity, hepatic problems and heart failure. They were also more likely to have prescriptions for insulin, oral corticosteroids, proton pump inhibitor and H_2 blockers, and were more likely to have had A&E visit in past year compared with amoxicillin users.

Figure 1. Inclusion and exclusion of study subjects in cohort analysis

Table 1. Baseline characteristics of full cohort at index date in cohort analysis

Characteristics	Clarithromycin users	Amoxicillin users
N	108 988	217 793
Median age (years)	60.0	60.0
Male sex, (%)	57 114 (52.4)	114 063 (52.4)
Calendar month at exposure		
January	9387 (8.6)	19 950 (9.2)
February	9046 (8.3)	18 512 (8.5)
March	10 163 (9.3)	20 961 (9.6)
April	9387 (8.6)	18 928 (8.7)
May	9353 (8.6)	18 992 (8.7)
June	8919 (8.2)	18 219 (8.4)
July	9077 (8.3)	18 006 (8.3)
August	9080 (8.3)	17 622 (8.1)
September	8539 (7.8)	16 858 (7.7)
October	8517 (7.8)	16 370 (7.5)
November	8541 (7.8)	16 289 (7.5)
December	8979 (8.2)	17 086 (7.9)
History of : (%)		
Chronic obstructive pulmonary disease	7528 (6.9)	6946 (3.2)
Obesity	339 (0.3)	399 (0.2)
Diabetes	10 761 (9.9)	16 287 (7.5)
Thyroid disorders	1813 (1.7)	3457 (1.6)
Hyperlipidaemia	4348 (4.0)	6749 (3.1)
Hypertensive diseases	17 788 (16.3)	28 067 (12.9)
Coronary heart disease	8200 (7.5)	12 883 (5.9)
Cerebrovascular diseases	8696 (8.0)	13 032 (6.0)
Arterial disease	2132 (2.0)	2970 (1.4)
Cardiomyopathy	382 (0.4)	545 (0.3)
Heart failure	5707 (5.2)	6791 (3.1)
Valve disorders	663 (0.6)	1211 (0.6)
Arrhythmia and conduction disorders	6359 (5.8)	10 404 (4.8)
Hypertensive renal disease	404 (0.4)	475 (0.2)
Renal failure	2675 (2.5)	3146 (1.4)
Esophageal varices	274 (0.3)	192 (0.1)
Hepatic failure, liver fibrosis and cirrhosis	1572 (1.4)	1764 (0.8)
Schizophrenia, delusional disorders and psychosis	2114 (1.9)	4286 (2.0)
Bipolar disorder	226 (0.2)	488 (0.2)
Depression	3096 (2.8)	5386 (2.5)
Prescription in past year:		
ARB/ACE-I	16 573 (15.2)	28 559 (13.1)
Calcium channel blockers	22 098 (20.3)	40 597 (18.6)
Loop diuretics	10 137 (9.3)	12 091 (5.6)
Other diuretics	8989 (8.3)	17 691 (8.1)
Beta-blockers	19 295 (17.7)	36 691 (16.9)
Anti-arrhythmics class I and II	1217 (1.1)	1677 (0.8)
Digoxin	2737 (2.5)	3760 (1.7)
Nitrates	9932 (9.1)	14 492 (6.7)
Platelet inhibitors	17 917 (16.4)	28 159 (12.9)
Anticoagulants	3768 (3.5)	5830 (2.7)
Peripheral vasodilator	974 (0.9)	1455 (0.7)

Lipid lowering drugs	9585 (8.8)	16 979 (7.8)
Insulin	3737 (3.4)	4228 (1.9)
Oral hypoglycemic agent	13 080 (12.0)	23 720 (10.9)
Antidepressants	5536 (5.1)	9359 (4.3)
Antipsychotics	4508 (4.1)	7559 (3.5)
Oral corticosteroids	9945 (9.1)	9600 (4.4)
NSAIDS	18 856 (17.3)	40 139 (18.4)
PPI/H_2 blocker	55 615 (51.0)	44 190 (20.3)
Median number of prescriptions used in past year (Q1-Q3)	17 (4-44)	12 (2-31)
Health care use in past year (Q1-Q3)		
Median number of outpatients visits	5 (2-10)	5 (1-9)
Median number of inpatient stays	1 (0-2)	0 (0-1)
Median number of emergency visits	1 (0-2)	0 (0-1)

Values were corrected to 1 decimal place

After exclusion of propensity score strata 1 and 20, the cohort included 95 797 clarithromycin users and 198 305 amoxicillin users. Among these individuals, 583 clarithromycin users and 1375 amoxicillin users had the primary outcome of MI during follow-up.

Figure 2 and Table 2 show the adjusted rate ratios of all outcomes associated with current, recent and past use of clarithromycin compared with use of amoxicillin. The initial adjusted rate ratio for the association between current use of clarithromycin and MI was 2.72 (2.15 to 3.44), with propensity score adjusted rate ratio of 3.66 (2.82 to 4.76) versus the use of amoxicillin. For the secondary outcomes of arrhythmia and stroke, the initial adjusted rate ratios were found to be 2.13 (1.25 to 3.63) and 1.05 (0.79 to 1.41) respectively. The fully propensity score adjusted rate ratios of arrhythmia and stroke were 2.22 (1.22 to 4.06) and 1.11 (0.80 to 1.54) respectively for current use of clarithromycin compared with amoxicillin. For all-cause mortality, current use of clarithromycin gave an initial adjusted rate ratio of 2.41 (2.27 to 2.56) and a propensity score adjusted rate ratio of 1.97 (1.83 to 2.11) versus the use of amoxicillin. For cardiac mortality, the initial rate ratio was 1.93 (1.61 to 2.30), with propensity score adjusted rate ratio of 1.67 (1.36 to 2.06) versus the use of amoxicillin. With respect to non-cardiac mortality, the initial adjusted rate ratio associated with current use of clarithromycin was 2.59 (2.42 to 2.76), with propensity score adjusted rate ratio of 2.10 (1.94 to 2.27). No significantly increased rate ratios of all outcomes were found in recent and past use of clarithromycin versus use of amoxicillin. In the sensitivity analysis when we included patients with scores in the 1st and 20th 5% strata, similar results were obtained for all outcomes of interest to the primary analysis (Supplementary material 8).

Figure 2. Propensity score adjusted rate ratios of all outcomes in use of clarithromycin versus amoxicillin

Table 2. Adjusted rate ratios of all outcomes in use of clarithromycin versus amoxicillin

	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Myocardial infarction							
Days after treatment	No of patients	Mean follow-up (days)	No of events	Rate ratio* (95% CI)	No of patients	No of events	Rate ratio‡ (95% CI)
Day 1-14 (current use)							
Clarithromycin	102 514	10.6	132	2.72 (2.15 to 3.44)	90 411	117	3.66 (2.82 to 4.76)
Amoxicillin	204 855	13.9	149	---	186 888	132	---
Day 15-30 (recent use)							
Clarithromycin	70 184	15.7	11	1.23 (0.62 to 2.43)	62 803	7	1.06 (0.44 to 2.60)
Amoxicillin	200 770	15.7	34	---	183 379	25	---
Day 31-90 (past use)							
Clarithromycin	67 707	57.8	23	1.31 (0.82 to 2.12)	60 826	19	1.10 (0.63 to 1.92)
Amoxicillin	193 522	57.7	67	---	177 022	59	---
Day 91-365 (past use)							
Clarithromycin	63 155	251.4	67	1.15 (0.87 to 1.52)	57 197	56	0.90 (0.65 to 1.24)
Amoxicillin	180 522	252.2	221	---	165 594	198	---
Day 366-730 (past use)							
Clarithromycin	53 614	339.8	72	1.23 (0.94 to 1.61)	49 126	64	1.17 (0.86 to 1.59)
Amoxicillin	153 426	336.2	223	---	141 460	205	---
Day 731-1095 (past use)							
Clarithromycin	46 586	344.4	62	1.18 (0.88 to 1.57)	42 977	57	1.01 (0.72 to 1.40)
Amoxicillin	130 664	340.7	198	---	120 937	182	---
Arrhythmia							
	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Days after treatment	No of patients	Mean follow-up (days)	No of events	Rate ratio* (95% CI)	No of patients	No of events	Rate ratio‡ (95% CI)
Day 1-14 (current use)							
Clarithromycin	107 200	10.5	23	2.13 (1.25 to 3.63)	94 319	20	2.22 (1.22 to 4.06)
Amoxicillin	214 222	13.9	33	---	195 129	31	---
Day 15-30 (recent use)							
Clarithromycin	72 574	15.7	7	0.97 (0.42 to 2.23)	64 826	5	0.86 (0.31 to 2.37)
Amoxicillin	209 867	15.7	27	---	191 386	24	---
Day 31-90 (past use)							
Clarithromycin	69 933	57.7	17	0.98 (0.58 to 1.68)	62 723	14	0.93 (0.50 to 1.74)

Amoxicillin	202 075	57.7	66	---	184 556	59	---
Day 91-365 (past use)							
Clarithromycin	65 072	250.9	41	1.42 (0.99 to 2.04)	58 854	30	1.00 (0.64 to 1.56)
Amoxicillin	188 113	252.0	110	---	172 294	97	---
Day 366-730 (past use)							
Clarithromycin	55 081	339.6	36	1.28 (0.87 to 1.88)	50 425	28	1.17 (0.73 to 1.86)
Amoxicillin	159 549	335.8	100	---	146 877	88	---
Day 731-1095 (past use)							
Clarithromycin	47 788	344.2	28	1.23 (0.80 to 1.91)	44 042	22	1.17 (0.69 to 2.00)
Amoxicillin	135 506	340.4	81	---	125 218	69	---

Stroke

	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Days after treatment	No of patients	Mean follow-up (days)	No of events	Rate ratio* (95% CI)	No of patients	No of events	Rate ratio‡ (95% CI)
Day 1-14 (current use)							
Clarithromycin	90 225	10.8	63	1.05 (0.79 to 1.41)	80 236	54	1.11 (0.80 to 1.54)
Amoxicillin	180 324	13.9	176	---	164 634	163	---
Day 15-30 (recent use)							
Clarithromycin	63 829	15.7	21	1.20 (0.73 to 1.97)	57 412	18	1.19 (0.67 to 2.12)
Amoxicillin	177 173	15.7	61	---	161 908	55	---
Day 31-90 (past use)							
Clarithromycin	61 804	58.0	79	1.57 (1.20 to 2.05)	55 768	64	1.35 (0.98 to 1.85)
Amoxicillin	171 158	57.9	176	---	156 616	159	---
Day 91-365 (past use)							
Clarithromycin	57 983	252.4	178	1.09 (0.92 to 1.29)	52 658	151	0.97 (0.79 to 1.18)
Amoxicillin	160 206	253.2	573	---	146 937	521	---
Day 366-730 (past use)							
Clarithromycin	49 616	341.0	177	1.12 (0.95 to 1.33)	45 525	154	1.09 (0.90 to 1.34)
Amoxicillin	137 150	337.6	555	---	126 440	505	---
Day 731-1095 (past use)							
Clarithromycin	43 398	345.2	172	1.14 (0.96 to 1.36)	40 064	154	1.17 (0.96 to 1.43)
Amoxicillin	117 679	341.7	524	---	108 918	473	---

All-cause mortality

	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Days after treatment	No of patients	Mean follow-up	No of events	Rate ratio* (95% CI)	No of patients	No of events	Rate ratio‡ (95% CI)

		(days)					
Day 1-14 (current use)							
Clarithromycin	108 988	10.5	1948	2.41 (2.27 to 2.56)	95 797	1471	1.97 (1.83 to 2.11)
Amoxicillin	217 793	13.9	2562	---	198 305	2127	---
Day 15-30 (recent use)							
Clarithromycin	73 526	15.7	569	1.36 (1.24 to 1.50)	65 641	413	0.96 (0.86 to 1.08)
Amoxicillin	213 280	15.7	1611	---	194 421	1352	---
Day 31-90 (past use)							
Clarithromycin	70 820	57.7	659	1.11 (1.02 to 1.21)	63 492	506	0.78 (0.70 to 0.87)
Amoxicillin	205 318	57.7	2283	---	187 445	1920	---
Day 91-365 (past use)							
Clarithromycin	65 875	250.9	836	1.28 (1.18 to 1.39)	59 563	669	0.96 (0.88 to 1.06)
Amoxicillin	191 071	251.9	2563	---	174 938	2251	---
Day 366-730 (past use)							
Clarithromycin	55 750	339.4	505	1.30 (1.18 to 1.44)	51 023	418	1.03 (0.92 to 1.16)
Amoxicillin	161 952	335.8	1544	---	149 045	1392	---
Day 731-1095 (past use)							
Clarithromycin	48 329	344.1	283	1.20 (1.05 to 1.38)	44 534	241	1.03 (0.88 to 1.20)
Amoxicillin	137 515	340.3	954	---	127 043	853	---
Cardiac mortality							
	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Days after treatment	No of patients	Mean follow-up (days)	No of events	Rate ratio[†] (95% CI)	No of patients	No of events	Rate ratio[a] (95% CI)
Day 1-14 (current use)							
Clarithromycin	108 988	10.5	201	1.93 (1.61 to 2.30)	95 797	152	1.67 (1.36 to 2.06)
Amoxicillin	217 793	13.9	315	---	198 305	279	---
Day 15-30 (recent use)							
Clarithromycin	73 526	15.7	55	1.46 (1.07 to 1.99)	65 641	43	1.42 (0.99 to 2.04)
Amoxicillin	213 280	15.7	152	---	194 421	130	---
Day 31-90 (past use)							
Clarithromycin	70 820	57.7	54	1.01 (0.75 to 1.36)	63 492	43	0.80 (0.57 to 1.13)
Amoxicillin	205 318	57.7	219	---	187 445	194	---
Day 91-365 (past use)							
Clarithromycin	65 875	250.9	84	1.15 (0.90 to 1.46)	59 563	70	0.91 (0.69 to 1.20)
Amoxicillin	191 071	251.9	313	---	174 938	273	---
Day 366-730 (past use)							

Clarithromycin	55 750	339.4	53	1.10 (0.81 to 1.49)	51 023	46	0.97 (0.68 to 1.36)
Amoxicillin	161 952	335.8	210	---	149 045	189	---
Day 731-1095 (past use)							
Clarithromycin	48 329	344.1	35	0.94 (0.65 to 1.36)	44 534	29	0.78 (0.51 to 1.19)
Amoxicillin	137 515	340.3	160	---	127 043	144	---

Non-cardiac mortality

	Before PS adjustment				Analysis restricted to patients with comparable propensity scores		
Days after treatment	No of patients	Mean follow-up (days)	No of events	Rate ratio* (95% CI)	No of patients	No of events	Rate ratio‡ (95% CI)
Day 1-14 (current use)							
Clarithromycin	108 988	10.5	1687	2.59 (2.42 to 2.76)	95 797	1271	2.10 (1.94 to 2.27)
Amoxicillin	217 793	13.9	2067	---	198 305	1695	---
Day 15-30 (recent use)							
Clarithromycin	73 526	15.7	490	1.40 (1.26 to 1.56)	65 641	357	0.98 (0.86 to 1.11)
Amoxicillin	213 280	15.7	1335	---	194 421	1112	---
Day 31-90 (past use)							
Clarithromycin	70 820	57.7	555	1.16 (1.05 to 1.28)	63 492	424	0.81 (0.72 to 0.91)
Amoxicillin	205 318	57.7	1808	---	187 445	1492	---
Day 91-365 (past use)							
Clarithromycin	65 875	250.9	655	1.39 (1.27 to 1.53)	59 563	517	1.02 (0.92 to 1.14)
Amoxicillin	191 071	251.9	1799	---	174 938	1561	---
Day 366-730 (past use)							
Clarithromycin	55 750	339.4	387	1.43 (1.27 to 1.61)	51 023	318	1.13 (0.98 to 1.30)
Amoxicillin	161 952	335.8	1052	---	149 045	943	---
Day 731-1095 (past use)							
Clarithromycin	48 329	344.1	195	1.30 (1.11 to 1.53)	44 534	168	1.14 (0.94 to 1.38)
Amoxicillin	137 515	340.3	592	---	127 043	532	---

* Analysis with initial adjustment for age, sex

† Analysis with initial adjustment for age and sex and history of myocardial infarction and arrhythmia

‡ Analysis with full adjustment for age, sex and propensity score

[a] Analysis with full adjustment for age, sex, history of myocardial infarction and arrhythmia, and propensity score

Similar results were obtained for all outcomes of interest to the primary analysis when the sensitivity analysis was conducted, stratifying follow-up periods for current use (day 1-7) and recent use (day 8-30) of clarithromycin versus amoxicillin (Supplementary material 9). The increased cardiovascular risk was largely confined to the current use (day 1-7) of clarithromycin versus amoxicillin. In subgroup analysis, it showed that rate ratios of MI, arrhythmia and cardiac death were comparable in men and women. The highest absolute risk differences were found for MI and cardiac death in patients aged 75 or above and those with history of hypertensive diseases or diabetes. Due to the lack of power, there was no evidence of increased risk of arrhythmia among patients aged 65 or above and those with history of hypertensive or diabetes (Supplementary material 10). The propensity score adjusted absolute risk difference for current use of clarithromycin versus amoxicillin was 1.90 excess MI events (1.30 to 2.68) per thousand patients. There were also excess 0.95 cardiac deaths (0.51 to 1.51) per thousand and 0.20 excess arrhythmia events (0.04 to 0.49) for current use of clarithromycin versus amoxicillin per thousand patients.

In the SCCS analysis, we identified 740 patients who had both out-patient HPT and incident MI during study period. There were 309 patients who had both exposure and incident arrhythmia during observation period. 2279 patients were identified to receive both out-patient HPT and incident stroke. Table 3 presents the IRRs in different risk windows. For the current use of HPT, the IRR of MI and arrhythmia were 3.38 (1.89 to 6.04) and 5.07 (2.19 to 11.72) respectively. In line with the cohort analysis, no increased risk of cardiovascular outcomes was found during all other periods of time after clarithromycin exposure to the end of three years. The case-crossover analysis also gave increased risk of MI and arrhythmia during current use of HPT containing-clarithromycin (Table 3). For stroke, no increased risk was observed in both SCCS and case-crossover studies. Figure 3 presents the IRR functions estimated from the non-parametric SCCS analysis. Panel (a) of the figure shows how the IRR changes with time within the 14-days of current HPT. It can be seen that there is an increased risk of MI during this period and the risk reduces to a baseline rate around the end of treatment. Panel (b) of Figure 3 shows that the IRR of MI after the end of HPT use does not change in time, it rather stays at the baseline rate.

Table 3. Patient characteristics, incidence rate ratios and odds ratios of myocardial infarction, arrhythmia and stroke in self-controlled case series (SCCS) and case-crossover analysis

	SCCS	Case-crossover
Myocardial infarction		
N	740	308
Median age (years)*	65.0	73.3
Male sex, (%)	508 (68.7)	201 (65.3)
	Incidence rate ratio (95% CI)	Odds ratio (95% CI)
Days before treatment		
14	0.81 (0.26 to 2.53)	---
Days after treatment		
1-14 (current use)	3.38 (1.89 to 6.04)	2.20 (1.23 to 3.95)
15-30 (recent use)	0.78 (0.25 to 2.42)	---
31-90 (past use)	0.89 (0.51 to 1.56)	---
91-365 (past use)	1.08 (0.83 to 1.41)	---
366-730 (past use)	1.05 (0.82 to 1.35)	---
731-1095 (past use)	0.96 (0.73 to 1.25)	---
Arrhythmia		
N	309	143
Median age (years)	64.0	71.1
Male sex, (%)	163 (52.8)	86 (60.1)
	Incidence rate ratio (95% CI)	Odds ratio (95% CI)
Days before treatment		
14	2.45 (0.77 to 7.80)	---
Days after treatment		
1-14 (current use)	5.07 (2.19 to 11.72)	2.49 (1.09 to 5.69)
15-30 (recent use)	0.00 (0.00 to INF)	---
31-90 (past use)	1.94 (0.98 to 3.85)	---
91-365 (past use)	1.61 (1.05 to 2.45)	---
366-730 (past use)	1.07 (0.69 to 1.67)	---
731-1095 (past use)	1.02 (0.78 to 1.86)	---
Stroke		
N	2279	852
Median age (years)	66.0	73.0
Male sex, (%)	1295 (56.8)	480 (56.3)
	Incidence rate ratio (95% CI)	Odds ratio (95% CI)
Days before treatment		
14	0.36 (0.13 to 0.96)	---
Days after treatment		
1-14 (current use)	1.49 (0.91 to 2.44)	1.04 (0.63 to 1.71)

15-30 (recent use)	1.25 (0.75 to 2.08)	---
31-90 (past use)	1.21 (0.92 to 1.59)	---
91-365 (past use)	1.06 (0.91 to 1.24)	---
366-730 (past use)	0.94 (0.81 to 1.08)	---
731-1095 (past use)	1.14 (0.98 to 1.31)	---

*Age at study start date for SCCS. Age at event date for case-crossover study.

Figure 3. Incidence rate ratio functions of myocardial infarction (solid lines) estimated by the non-parametric SCCS method and their 95% confidence bands (dotted lines).

Discussion

Principal findings

In this territory-wide cohort study, we did not observe any long-term increased risk of cardiovascular outcomes but a short-term increased cardiovascular risk during and immediately following clarithromycin therapy compared to amoxicillin was suggested. To our knowledge, this is the first study to use a case-only approach to investigate the association for the use of clarithromycin as part of an HPT with cardiovascular outcomes. Similarly, we found that the increased risk of MI and arrhythmia were also only observed during current use of the HPT containing clarithromycin and no long-term increased risk was observed.

Interpretation and comparison with other studies

In the cohort analysis, we selected amoxicillin which is used for similar indications, as the comparator group, attempting to minimise the indication bias. However, we observed the characteristics of clarithromycin users at index date were systematically different from that of amoxicillin users. A higher proportion of patients taking clarithromycin had COPD, diabetes, hepatic problems, coronary heart disease and heart failure. They were also more likely to be using proton pump inhibitors which has been identified as a marker of poor prognosis in previous work.[23] It is possible that physicians tend to opt for clarithromycin in frailer patients. While there seems to imply the presence of channeling bias, the underlying health differences between exposure groups did not appear to fully explain the marked increased short-term cardiovascular risk of clarithromycin based on propensity score adjustment method.

Higher rate ratio of non-cardiac mortality was also found in cohort analysis for current use of clarithromycin versus amoxicillin despite propensity score adjustment, which would not be predicted by the study hypothesis. As a negative control outcome, this may indicate bias. This further suggests that clarithromycin was prone to be prescribed to frailer patients or those with more severe infections compared with amoxicillin. However, it is anticipated that all between person confounding factors that remain stable in cohort study design could be removed over the period of the study with the use of the SCCS methodology. Using this analysis method and focusing on patients treated for *H. pylori* infection which is not an acute infection, an elevated risk of MI and arrhythmia was still found during current use of clarithromycin-containing HPT with no increased risk observed after treatment had ended

Although some patients with *H. pylori* might have severe gastrointestinal bleeding that may precipitate MI[24], it is unlikely to affect this study. We only included patients receiving out-patient HPT containing-clarithromycin who were unlikely to have severe gastrointestinal bleeding. Moreover, if severe gastrointestinal bleeding was the underlying cause, an increased risk of cardiovascular outcomes would also be expected shortly before the start of treatment with clarithromycin; no such increase was observed in the SCCS. Based upon these, we concluded that the short-term increase in cardiovascular risk is not attributable to the infection that

prompted the use of antibiotic treatment, but to the use of clarithromycin. In recent years, case reports have also suggested clarithromycin has pro-arrhythmic potency that leads to QT prolongation, torsades de pointes[26-28], and other arrhythmias.[29] This hypothesis could be explained by blockade of the potassium channel and therefore result in prolonged action potential duration and early after depolarization.[26] Such a mechanism would be consistent with a short lived increased risk of arrhythmia, in keeping with the findings of our cohort and SCCS analysis. Given the increased risk of MI found in our study, QT prolongation alone might not fully explain the cardiac effect, thus requiring further investigation. A recent case report suggested that clarithromycin might cause rupture of coronary plaque resulting from triggering the allergic response.[30] Possibly, arrhythmia may also have a role in plaque rupture leading to MI.

A recent cohort study investigating the association between current use of clarithromycin and cardiac death in Denmark also reported a higher significant rate ratio of 1.76 (95% CI 1.08, 2.85).[8] However, the study outcome was composite causes of death including MI, arrhythmia, heart failure, cardiomyopathy etc. Therefore, given the increased risk of composite causes of cardiac death, we could not exclude the possibility that there may be other mechanism pathways to explain its cardiac effect. Another observational Danish study reported no significant increase in the risk of a composite end point including cardiovascular mortality and MI among patients with ischemic heart disease receiving HPT in follow-up period of 5 years.[31] In addition to cardiac mortality, we chose specific separate outcomes such as MI and arrhythmia to investigate the cardiovascular effect associated with clarithromycin. In line with two Danish studies, our study showed that the risk of all cardiovascular outcomes of interest was increased during the current use of clarithromycin and no long-term risk was observed.[8 31]

In contrast to our study, some observational studies reported long-term cardiovascular risk associated with the use of clarithromycin, which is of great concern due to its widespread use. A significantly higher risk of cardiovascular mortality was observed among the exposed group in the CLARICOR trial in the long follow-up period of 2.6 years, using public registers to ascertain outcomes.[4] Notably, the agreement for hospital discharges and cause of death were 74% and 60% respectively comparing with formal adjudication.[32] Another recent cohort study conducted by Schembri *et al.* also showed the use of clarithromycin increased the risk of cardiovascular events in patients with acute exacerbations of COPD and community acquired pneumonia in one year.[9] In addition, a significant association between the use of clarithromycin and cardiovascular mortality was found in patients with COPD in one year. In these two studies, patients with high baseline cardiovascular risk such as coronary heart diseases, COPD and community acquired pneumonia were recruited. This might reflect the fact that long-term cardiovascular events and mortality associated with the use of clarithromycin merely affect a selected population as our study could not demonstrate any long-term cardiovascular effect among general population. Nevertheless, this might also reflect important underlying co-morbidities between exposure groups that could not be fully addressed in those studies rather than a causal effect. Importantly, it did not report non-cardiovascular mortality as a negative control outcome.[9] Without this

important information, it might be subject to significant residual bias. Therefore, it is highly recommended future studies should also report control outcomes to detect residual confounding.

Study implications

With respect to the absolute risk difference, 0.95 excess cardiac deaths per thousand patients associated with the current use of clarithromycin versus amoxicillin were estimated. Notably, we found that the rate of cardiac mortality was 118.7 per 1000 person-years in patients receiving amoxicillin and aged 75 or above, considerably higher than that of in patients receiving amoxicillin and aged 40-74 (12.9 per 1000 person-years). Moreover, we classified current use as 14 days, which would also double the estimates of absolute risk difference when compared with classifying current use as 7 days. As our study comprised patients aged 75 or above (35% of our cohort) and used longer follow-up period as current use, our estimate was markedly higher than the one estimated by Svanstrom *et al.* (37 per million courses).[8] In our subgroup analysis, 2.63 excess cardiac death and 5.77 excess MI per thousand patients were observed among patients aged 75 or above. In addition, absolute risk differences of cardiac death and MI were also higher among patients with hypertensive diseases or diabetes mellitus. Therefore, cardiovascular risk profile of individual patients, especially the elderly aged 75 or above or with co-morbidities, should be assessed carefully before prescribing clarithromycin.

Strengths and limitations

This study includes both a population-based cohort study with a large cohort size, representative of the Hong Kong population and a case-only design which renders the underlying differences between people less important. Data linkages of CDARS within primary, secondary and tertiary healthcare services and also its connection to death registry allow accurate ascertainment of incident MI and cardiac deaths. The PPV of MI was quite high in which our estimate was similar to most of the high quality validation studies on MI.[33] However, there are several limitations in this study. First, this study did not include lifestyle risk factors such as smoking, alcohol consumption and physical activity in the propensity score modelling. However, we introduced other variables such as COPD, diabetes, and other chronic diseases in the model that might partly represent the effects of these risk factors. Although the absence of this information may affect the performance of propensity score modelling in the cohort analysis, it is unlikely to significantly alter the findings on acute cardiovascular effects in the SCCS analysis. We were unable to obtain data on whether the drug was actually taken or when it was taken. Thus, the true exposure is unknown and this may result in some degree of bias. In addition, we could not determine the causes for patients with unrecorded cause of death in the cause-specific analyses. However, this only affected approximately 10% of deaths in this study and would not have led to substantial bias. Moreover, only the cases from HKW cluster were validated in this study. However, the coding practice is very unlikely to be differential between individual patients and hospitals which are all managed by the same statutory organisation. The PPV of arrhythmia was found to be relatively low, meaning some of the outcomes we included may not have been true

arrhythmias. This error would tend to lead to an underestimate of any genuine causal association, assuming the likelihood of diagnostic inaccuracy was the same for both clarithromycin and comparator patients. It may be due to low incidence of cardiac arrhythmia and less stringent diagnostic criteria comparing with MI and stroke. Similarly, some studies also reported a wide range of PPVs of cardiac arrhythmia or cardiac arrest in different databases.[34-36]

Conclusion

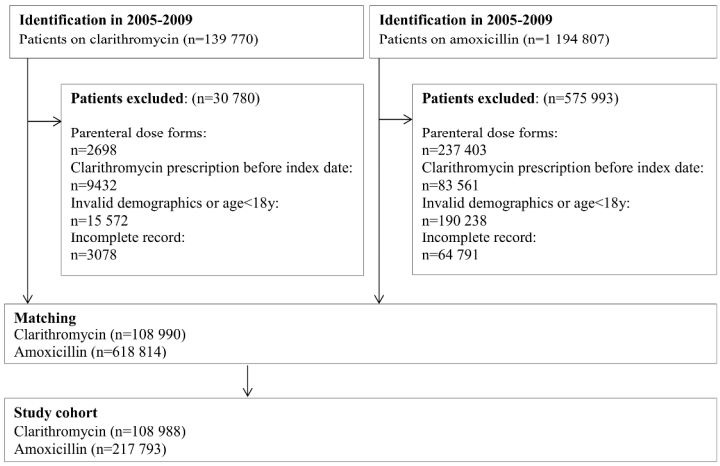
This study confirms no long-term cardiovascular risk associated with clarithromycin but suggests an increased short-term risk of MI, arrhythmia and cardiac death associated with current use of clarithromycin among the Hong Kong population. Given the acute risk, clarithromycin should be prescribed with caution, especially to the patients with high baseline cardiovascular risk.

(Total number of words: 4737)

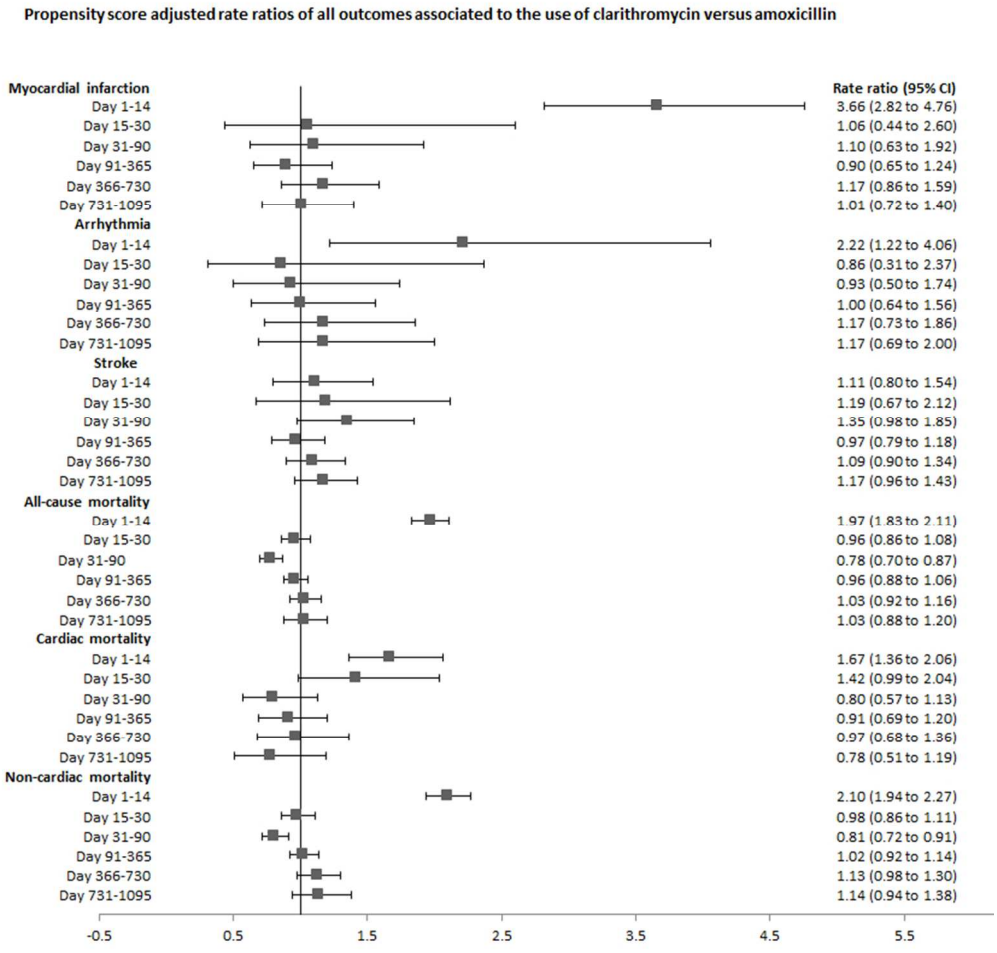
Reference

1. Ho P, Wong S. Fourth Edition: Reducing bacterial resistance with IMPACT: 2012 [updated; cited 14 May 2015]. Available from: http://www.chp.gov.hk/files/pdf/reducing_bacterial_resistance_with_impact.pdf.
2. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. Infect Dis Clin North Am 2004;**18**(3):621-49.
3. Sinisalo J, Mattila K, Valtonen V, et al. Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-q-wave coronary syndrome. Circulation 2002;**105**(13):1555-60.
4. Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. BMJ 2006;**332**(7532):22-7.
5. Berg HF, Maraha B, Scheffer GJ, et al. Treatment with clarithromycin prior to coronary artery bypass graft surgery does not prevent subsequent cardiac events. Clin Infect Dis 2005;**40**(3):358-65.
6. Gluud C, Als-Nielsen B, Damgaard M, et al. Clarithromycin for 2 weeks for stable coronary heart disease: 6-year follow-up of the CLARICOR randomized trial and updated meta-analysis of antibiotics for coronary heart disease. Cardiology 2008;**111**(4):280-7.
7. Winkel P, Hilden J, Hansen JF, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10years in the CLARICOR randomised, blinded clinical trial. Int J Cardiol 2015;**182**:459-65.
8. Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. BMJ 2014;**349**:g4930.
9. Schembri S, Williamson PA, Short PM, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. BMJ 2013;**346**:f1235.
10. HAHO/ITD. Clinical Data Analysis & Reporting System (CDARS) User's Manual. In: Hospital Authority, ed. 2.0 ed. Hong Kong, 2003:3.
11. Chui CS, Man KK, Cheng CL, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. J Antimicrob Chemother 2014;**69**(9):2563-7.
12. Man KK, Chan EW, Coghill D, et al. Methylphenidate and the risk of trauma. Pediatrics 2015;**135**(1):40-8.
13. Chiu SS, Lau YL, Chan KH, et al. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med 2002;**347**(26):2097-103.
14. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;**25**(10):1768-97.
15. Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;**351**(25):2611-8.
16. Ghebremichael-Weldeselassie Y, Whitaker H, Farrington C. Spline-based self-controlled case series method: [updated; cited 14 May 2015]. Available from: http://statistics.open.ac.uk/802576CB00593013/(httpInfoFiles)/DE71C5F9EF48876E80257DEA0052905A/$file/non-parametric-SCCS.pdf.
17. Hospital Authority. Clinical Services Plan for the Hong Kong West Cluster: [updated; cited 23 Jul 2015]. Available from: http://www.ha.org.hk/upload/publication_44/453.pdf.
18. Sturmer T, Rothman KJ, Avorn J, et al. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. Am J Epidemiol 2010;**172**(7):843-54.

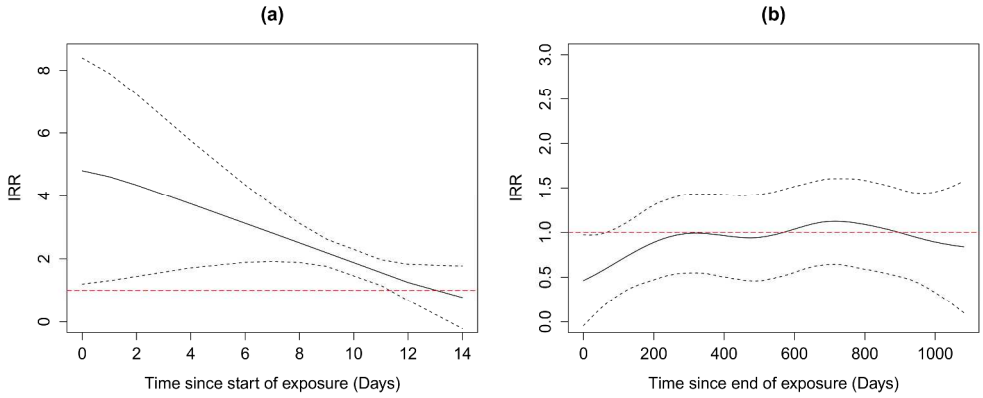
19. Sturmer T, Wyss R, Glynn RJ, et al. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014;**275**(6):570-80.
20. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;**366**(20):1881-90.
21. Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. N Engl J Med 2013;**368**(18):1704-12.
22. Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health 2000;**21**:193-221.
23. Douglas IJ, Evans SJ, Hingorani AD, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. BMJ 2012;**345**:e4388.
24. Cappell MS. Gastrointestinal bleeding associated with myocardial infarction. Gastroenterol Clin North Am 2000;**29**(2):423-44, vi.
25. Douglas IJ, Langham J, Bhaskaran K, et al. Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink. BMJ 2013;**346**:f1936.
26. Lee KL, Jim MH, Tang SC, et al. QT prolongation and Torsades de Pointes associated with clarithromycin. Am J Med 1998;**104**(4):395-6.
27. Hensey C, Keane D. Clarithromycin induced torsade de pointes. Ir J Med Sci 2008;**177**(1):67-8.
28. Kamochi H, Nii T, Eguchi K, et al. Clarithromycin associated with torsades de pointes. Jpn Circ J 1999;**63**(5):421-2.
29. Kundu S, Williams SR, Nordt SP, et al. Clarithromycin-induced ventricular tachycardia. Ann Emerg Med 1997;**30**(4):542-4.
30. Bilgin M, Akyel A, Dogan M, et al. Acute coronary syndrome secondary to clarithromycin: the first case and review of the literature. Turk Kardiyol Dern Ars 2014;**42**(5):461-3.
31. Andersen SS, Hansen ML, Norgaard ML, et al. Clarithromycin use and risk of death in patients with ischemic heart disease. Cardiology 2010;**116**(2):89-97.
32. Kjoller E, Hilden J, Winkel P, et al. Agreement between public register and adjudication committee outcome in a cardiovascular randomized clinical trial. Am Heart J 2014;**168**(2):197-204 e1-4.
33. McCormick N, Lacaille D, Bhole V, et al. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. PLoS One 2014;**9**(3):e92286.
34. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010;**60**(572):e128-36.
35. Joensen AM, Jensen MK, Overvad K, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol 2009;**62**(2):188-94.
36. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;**21 Suppl 1**:148-53.



279x215mm (300 x 300 DPI)



219x210mm (96 x 96 DPI)



348x147mm (300 x 300 DPI)

Appendix: Cardiovascular outcomes associated with use of clarithromycin: population based study

Contents

Supplementary material 1: ICD-9 and ICD-10 codes for outcomes identification

	ICD-9 Codes
Myocardial Infarction	410
Arrhythmia	426.82, 427.0, 427.1, 427.2, 427.41, 427.42, 427.5, 427.60
Stroke	430, 431, 432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, 436, 437.0, 437.1
	ICD-10 Codes
Cardiac death	I11, I13, I20-25, I27, I30-52

Supplementary material 2. Helicobacter pylori eradication therapy regimen containing clarithromycin with appropriate doses

Co-prescription of two antibiotics and one of the proton pump inhibitors:		
Clarithromycin 500mg bd	Amoxicillin 1000mg bd	Esomeprazole 20mg bd Lansoprazole 30mg bd Omeprazole 20mg bd Pantoprazole 40mg bd Rabeprazole 20mg bd
Clarithromycin 250mg bd	Metronidazole 400mg bd	Esomeprazole 20mg bd Lansoprazole 30mg bd Omeprazole 20mg bd Pantoprazole 40mg bd Rabeprazole 20mg bd

Supplementary material 3. List of covariates included in Propensity Score with ICD codes

Parameters	
Demographic factors	
Calendar month at exposure	
Medical history	**ICD9 Codes**
Respiratory related disease	
Chronic obstructive pulmonary disease or related	490-492, 494, 496
Endocrine and metabolic disorders	
Obesity	278.0
Hyperlipidaemia	272.0-272.2, 272.4
Diabetes and related complications	249, 250
Thyroid disorders	242-244
Cardiovascular related disease	
Hypertensive diseases	401-405
Coronary heart disease	410, 411, 412, 413, 414, 429.71, 429.79
Cerebrovascular diseases	430-437
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447, 557
Cardiomyopathy	425
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Valve disorders	424
Arrhythmia and conduction disorders	426-427
Renal disease	
Hypertensive renal disease	403-404
Renal failure	584-586
Liver disease	
Esophageal varices	456.0, 456.1, 456.2
Hepatic failure, liver fibrosis and cirrhosis	570, 571
Psychiatric disease	
Schizophrenia and psychosis	295, 297, 298.3, 298.4, 298.8, 298.9
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.81 296.89
Depression	296.2, 296.3, 296.82, 298.0, 300.4, 311
Prescription drug used in past year	
ARB/ACE-I	
Calcium channel blockers	
Loop diuretics	
Other diuretics	
Beta-blockers	
Anti-arrhythmics class I and II	
Digoxin	
Nitrates	
Platelet inhibitors	
Anticoagulants	
Peripheral vasodilator	
Lipid lowering drugs	
Insulin	
Oral hypoglycemic agent	
Antidepressants	
Antipsychotics	
Oral corticosteroids	
NSAIDS	

PPI/H-2 blocker
Number of drugs used
Health care use
Number of outpatients visits in past year
Number of inpatient stays in past year
Number of emergency visits in past year

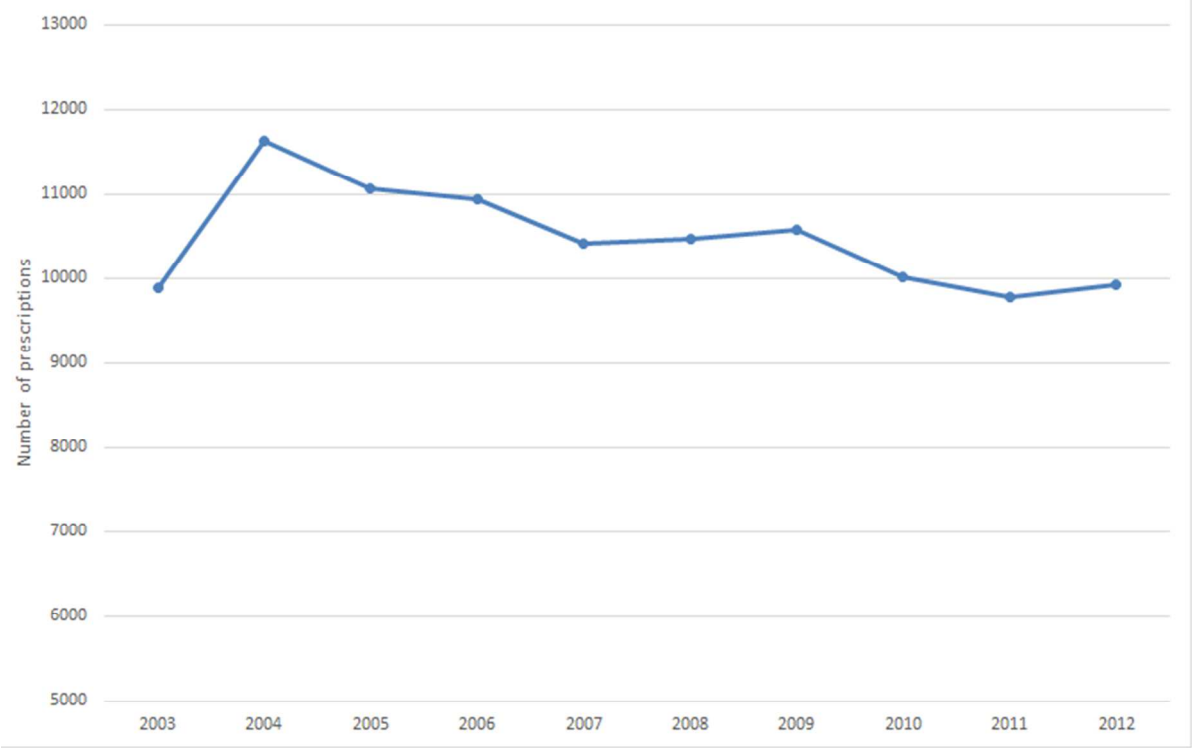
Supplementary material 4. Distribution of propensity scores in 20 strata *†

Propensity score	Clarithromycin users		Amoxicillin users	
	N (%)	Myocardial infarction (%)	N (%)	Myocardial infarction (%)
1	2356 (2.2)	13 (3.5)	13 984 (6.4)	61 (6.8)
2	3284 (3.0)	9 (2.5)	13 055 (6.0)	67 (7.5)
3	3061 (2.8)	18 (4.9)	13 278 (6.1)	85 (9.5)
4	2914 (2.7)	8 (2.2)	13 425 (6.2)	66 (7.4)
5	3074 (2.8)	18 (4.9)	14 344 (6.6)	46 (5.2)
6	2557 (2.4)	9 (2.5)	12 733 (5.9)	40 (4.5)
7	2677 (2.5)	5 (1.4)	13 669 (6.3)	41 (4.6)
8	2925 (2.7)	8 (2.2)	14 165 (6.5)	36 (4.0)
9	2745 (2.5)	7 (1.9)	12 806 (5.9)	35 (3.9)
10	4075 (3.7)	8 (2.2)	12 282 (5.6)	40 (4.5)
11	4935 (4.5)	13 (3.5)	11 638 (5.3)	39 (4.4)
12	6455 (5.9)	16 (4.4)	9634 (4.4)	21 (2.4)
13	5930 (5.4)	7 (1.9)	10 408 (4.8)	39 (4.4)
14	5838 (5.4)	21 (5.7)	10 500 (4.8)	49 (5.5)
15	6414 (5.9)	30 (8.2)	9925 (4.6)	40 (4.5)
16	7612 (7.0)	47 (12.8)	8727 (4.0)	53 (5.9)
17	8860 (8.1)	32 (8.7)	7479 (3.4)	53 (5.9)
18	10 520 (9.7)	32 (8.7)	5819 (2.7)	24 (2.7)
19	11 921 (10.9)	32 (8.7)	4418 (2.0)	27 (3.0)
20	10 835 (9.9)	34 (9.3)	5504 (2.5)	30 (3.4)

* 1 indicates smallest probability of receiving clarithromycin; 20 indicates highest probability of receiving clarithromycin

†Value in (%) was corrected to 1 decimal place

Supplementary material 5. Number of prescriptions for out-patient Helicobacter pylori treatment containing-clarithromycin from 2003-2012



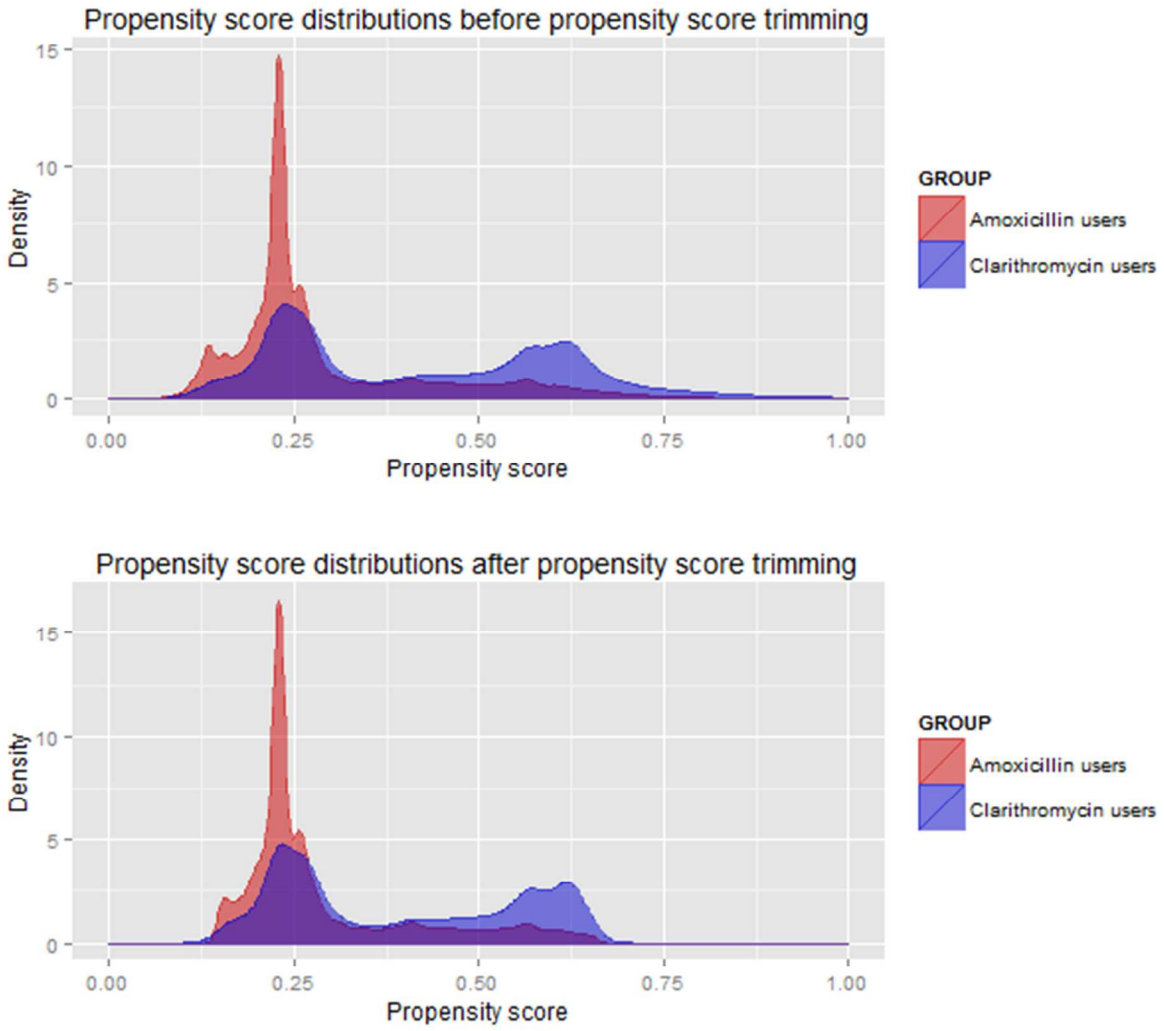
Supplementary material 6. Baseline characteristics of trimmed cohort at index date in cohort analysis

Characteristics	Clarithromycin users	Amoxicillin users
N	95 797	198 305
Median age (years)	59.0	60.0
Male sex, (%)	49 652 (51.8)	104 050 (52.5)
Calendar month at exposure		
January	8247 (8.6)	17 928 (9.0)
February	8025 (8.4)	16 686 (8.4)
March	8996 (9.4)	18 885 (9.5)
April	8293 (8.7)	17 140 (8.6)
May	8269 (8.6)	17 268 (8.7)
June	7897 (8.2)	16 592 (8.4)
July	8023 (8.4)	16 469 (8.3)
August	8009 (8.4)	16 131 (8.1)
September	7452 (7.8)	15 425 (7.8)
October	7449 (7.8)	15 047 (7.6)
November	7401 (7.7)	15 008 (7.6)
December	7736 (8.1)	15 726 (7.9)
History of : (%)		
Chronic obstructive pulmonary disease	4324 (4.5)	5739 (2.9)
Obesity	231 (0.2)	351 (0.2)
Diabetes	8566 (8.9)	14 416 (7.3)
Thyroid disorders	1511 (1.6)	3002 (1.5)
Hyperlipidaemia	3567 (3.7)	5849 (3.0)
Hypertensive diseases	14 290 (14.9)	24 328 (12.3)
Coronary heart disease	6581 (6.9)	10 429 (5.3)
Cerebrovascular diseases	6981 (7.3)	11 459 (5.8)
Arterial disease	1666 (1.7)	2540 (1.3)
Cardiomyopathy	293 (0.3)	461 (0.2)
Heart failure	4078 (4.3)	5724 (2.9)
Valve disorders	537 (0.6)	997 (0.5)
Arrhythmia and conduction disorders	4999 (5.2)	8731 (4.4)
Hypertensive renal disease	296 (0.3)	383 (0.2)
Renal failure	1928 (2.0)	2581 (1.3)
Esophageal varices	133 (0.1)	133 (0.1)
Hepatic failure, liver fibrosis and cirrhosis	1075 (1.1)	1472 (0.7)
Schizophrenia, delusional disorders and psychosis	1739 (1.8)	3775 (1.9)
Bipolar disorder	190 (0.2)	429 (0.2)
Depression	2569 (2.7)	4720 (2.4)
Prescription in past year:		
ARB/ACE-I	13 791 (14.4)	24 758 (12.5)
Calcium channel blockers	18 619 (19.4)	35 205 (17.8)
Loop diuretics	7290 (7.6)	10 189 (5.1)
Other diuretics	7617 (8.0)	15 103 (7.6)
Beta-blockers	16 658 (17.4)	31 485 (15.9)
Anti-arrhythmics class I and II	937 (1.0)	1380 (0.7)
Digoxin	2044 (2.1)	3203 (1.6)
Nitrates	7942 (8.3)	12 008 (6.1)
Platelet inhibitors	14 871 (15.5)	24 069 (12.1)
Anticoagulants	2977 (3.1)	4920 (2.5)
Peripheral vasodilator	775 (0.8)	1258 (0.6)

Lipid lowering drugs	8288 (8.7)	14 468 (7.3)
Insulin	2611 (2.7)	3629 (1.8)
Oral hypoglycemic agent	11 080 (11.6)	21 012 (10.6)
Antidepressants	4549 (4.8)	8091 (4.1)
Antipsychotics	3496 (3.7)	6598 (3.3)
Oral corticosteroids	6516 (6.8)	7796 (3.9)
NSAIDS	15 728 (16.4)	27 525 (13.9)
PPI/H_2 blocker	45 043 (47.0)	38 840 (19.6)
Median number of prescriptions used in past year (Q1-Q3)	14 (4-38)	11 (2-29)
Health care use in past year (Q1-Q3)		
Median number of outpatients visits	5 (1-10)	4 (1-9)
Median number of inpatient stays	1 (0-1)	0 (0-1)
Median number of emergency visits	1 (0-2)	0 (0-1)

Values were corrected to 1 decimal place

Supplementary material 7. Propensity score distributions before and after propensity score trimming



Supplementary material 8. Propensity score adjusted rate ratios of all outcomes without trimming band

Myocardial infarction			
Days after treatment	No of patients	No of events	Rate ratio* (95% CI)
Day 1-14 (current use)			
Clarithromycin	102 514	132	3.64 (2.85 to 4.64)
Amoxicillin	204 851	149	---
Day 15-30 (recent use)			
Clarithromycin	70 184	11	1.06 (0.52 to 2.16)
Amoxicillin	200 766	34	---
Day 31-90 (past use)			
Clarithromycin	67 707	23	1.11 (0.67 to 1.86)
Amoxicillin	193 518	67	---
Day 91-365 (past use)			
Clarithromycin	63 155	67	0.94 (0.70 to 1.27)
Amoxicillin	180 518	221	---
Day 366-730 (past use)			
Clarithromycin	53 614	72	1.17 (0.88 to 1.57)
Amoxicillin	153 423	223	---
Day 731-1095 (past use)			
Clarithromycin	46 586	62	1.03 (0.75 to 1.42)
Amoxicillin	130 661	198	---

Arrhythmia			
Days after treatment	No of patients	No of events	Rate ratio* (95% CI)
Day 1-14 (current use)			
Clarithromycin	107 200	23	2.30 (1.30 to 4.09)
Amoxicillin	214 217	33	---
Day 15-30 (recent use)			
Clarithromycin	72 574	7	0.81 (0.33 to 1.97)
Amoxicillin	209 862	27	---
Day 31-90 (past use)			
Clarithromycin	69 933	17	0.79 (0.45 to 1.40)
Amoxicillin	202 070	66	---
Day 91-365 (past use)			
Clarithromycin	65 072	41	1.10 (0.74 to 1.63)
Amoxicillin	188 108	110	---

Day 366-730 (past use)			
Clarithromycin	55 081	36	1.13 (0.74 to 1.72)
Amoxicillin	159 545	100	---
Day 731-1095 (past use)			
Clarithromycin	47 788	28	1.14 (0.70 to 1.83)
Amoxicillin	135 503	81	---

Stroke

Days after treatment	No of patients	No of events	Rate ratio* (95% CI)
Day 1-14 (current use)			
Clarithromycin	90 225	63	1.13 (0.83 to 1.54)
Amoxicillin	180 320	176	---
Day 15-30 (recent use)			
Clarithromycin	63 829	21	1.13 (0.66 to 1.94)
Amoxicillin	177 169	61	---
Day 31-90 (past use)			
Clarithromycin	61 804	79	1.33 (0.99 to 1.78)
Amoxicillin	171 154	176	---
Day 91-365 (past use)			
Clarithromycin	57 983	178	1.04 (0.87 to 1.25)
Amoxicillin	160 202	573	---
Day 366-730 (past use)			
Clarithromycin	49 616	177	1.12 (0.93 to 1.34)
Amoxicillin	137 147	555	---
Day 731-1095 (past use)			
Clarithromycin	43 398	172	1.16 (0.96 to 1.40)
Amoxicillin	117 677	524	---

All-cause mortality

Days after treatment	No of patients	No of events	Rate ratio* (95% CI)
Day 1-14 (current use)			
Clarithromycin	108 988	1948	1.72 (1.61 to 1.83)
Amoxicillin	217 788	2562	---
Day 15-30 (recent use)			
Clarithromycin	73 526	569	0.89 (0.80 to 0.99)
Amoxicillin	213 275	1611	---
Day 31-90 (past use)			
Clarithromycin	70 820	659	0.68 (0.62 to 0.75)

Amoxicillin	205 313	2283	---
Day 91-365 (past use)			
Clarithromycin	65 875	836	0.89 (0.82 to 0.97)
Amoxicillin	191 066	2563	---
Day 366-730 (past use)			
Clarithromycin	55 750	505	0.99 (0.89 to 1.11)
Amoxicillin	161 948	1544	---
Day 731-1095 (past use)			
Clarithromycin	48 329	283	0.98 (0.84 to 1.13)
Amoxicillin	137 512	954	---

Cardiac mortality

Days after treatment	No of patients	No of events	Rate ratio† (95% CI)
Day 1-14 (current use)			
Clarithromycin	108 988	201	1.71 (1.41 to 2.06)
Amoxicillin	217 788	315	---
Day 15-30 (recent use)			
Clarithromycin	73 526	55	1.30 (0.94 to 1.80)
Amoxicillin	213 275	152	---
Day 31-90 (past use)			
Clarithromycin	70 820	54	0.78 (0.57 to 1.07)
Amoxicillin	205 313	219	---
Day 91-365 (past use)			
Clarithromycin	65 875	84	0.86 (0.66 to 1.11)
Amoxicillin	191 066	313	---
Day 366-730 (past use)			
Clarithromycin	55 750	53	0.96 (0.70 to 1.33)
Amoxicillin	161 948	210	---
Day 731-1095 (past use)			
Clarithromycin	48 329	35	0.77 (0.52 to 1.14)
Amoxicillin	137 512	160	---

Non-cardiac mortality

Days after treatment	No of patients	No of events	Rate ratio* (95% CI)
Day 1-14 (current use)			
Clarithromycin	108 988	1687	1.79 (1.67 to 1.92)
Amoxicillin	217 788	2067	---
Day 15-30 (recent use)			

Clarithromycin	73 526	490	0.89 (0.79 to 0.99)
Amoxicillin	213 275	1335	---
Day 31-90 (past use)			
Clarithromycin	70 820	555	0.69 (0.62 to 0.76)
Amoxicillin	205 313	1808	---
Day 91-365 (past use)			
Clarithromycin	65 875	655	0.92 (0.83 to 1.01)
Amoxicillin	191 066	1799	---
Day 366-730 (past use)			
Clarithromycin	55 750	387	1.05 (0.92 to 1.20)
Amoxicillin	161 948	1052	---
Day 731-1095 (past use)			
Clarithromycin	48 329	195	1.04 (0.87 to 1.25)
Amoxicillin	137 512	592	---

* Analysis with adjustment for age, sex and propensity score

† Analysis with adjustment for age, sex, history of myocardial infarction and arrhythmia, and propensity score

Supplementary material 9. Rate ratios of all outcomes for current and recent use of clarithromycin versus amoxicillin in sensitivity analysis

Myocardial infarction			
Days after treatment	Rate ratio* (95% CI)	Rate ratio‡ (95% CI)	Rate ratio‡ (95% CI)
Day 1-7 (current use)			
Clarithromycin	2.51 (1.95 to 3.22)	3.47 (2.63 to 4.57)	3.34 (2.56 to 4.34)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.63 (1.01 to 2.64)	1.50 (0.82 to 2.73)	1.54 (0.92 to 2.58)
Amoxicillin	---	---	---
Arrhythmia			
Days after treatment	Rate ratio* (95% CI)	Rate ratio‡ (95% CI)	Rate ratio‡ (95% CI)
Day 1-7 (current use)			
Clarithromycin	2.96 (1.57 to 5.60)	3.52 (1.71 to 7.23)	3.41 (1.73 to 6.73)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	0.88 (0.44 to 1.76)	0.77 (0.35 to 1.72)	0.76 (0.36 to 1.58)
Amoxicillin	---	---	---
Stroke			
Days after treatment	Rate ratio* (95% CI)	Rate ratio‡ (95% CI)	Rate ratio‡ (95% CI)
Day 1-7 (current use)			
Clarithromycin	0.93 (0.67 to 1.29)	1.04 (0.72 to 1.50)	1.06 (0.75 to 1.49)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.22 (0.82 to 1.80)	1.11 (0.71 to 1.75)	1.10 (0.72 to 1.69)
Amoxicillin	---	---	---
All-cause mortality			
Days after treatment	Rate ratio* (95% CI)	Rate ratio‡ (95% CI)	Rate ratio‡ (95% CI)
Day 1-7 (current use)			
Clarithromycin	2.67 (2.48 to 2.88)	2.23 (2.04 to 2.43)	1.98 (1.83 to 2.15)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.58 (1.47 to 1.69)	1.17 (1.07 to 1.27)	1.04 (0.96 to 1.12)
Amoxicillin	---	---	---
	Before PS adjustment	**Propensity scores trimming 1st & 20th strata**	**Propensity scores without trimming strata**

Cardiac mortality			
Days after treatment	Rate ratio[†] (95% CI)	Rate ratio[a] (95% CI)	Rate ratio[a] (95% CI)
Day 1-7 (current use)			
Clarithromycin	1.83 (1.48 to 2.26)	1.62 (1.27 to 2.07)	1.62 (1.29 to 2.03)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.62 (1.29 to 2.03)	1.47 (1.13 to 1.92)	1.44 (1.13 to 1.83)
Amoxicillin	---	---	---
Day 1-7 (current use)			
Clarithromycin	2.65 (2.28 to 3.07)	3.29 (2.79 to 3.88)	3.13 (2.67 to 3.66)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.20 (0.93 to 1.54)	0.96 (0.71 to 1.28)	0.99 (0.76 to 1.29)
Amoxicillin	---	---	---
Non-cardiac mortality			
Days after treatment	Rate ratio* (95% CI)	Rate ratio[‡] (95% CI)	Rate ratio[‡] (95% CI)
Day 1-7 (current use)			
Clarithromycin	2.91 (2.68 to 3.15)	2.42 (2.20 to 2.67)	2.10 (1.93 to 2.30)
Amoxicillin	---	---	---
Day 8-30 (recent use)			
Clarithromycin	1.64 (1.52 to 1.77)	1.20 (1.09 to 1.31)	1.04 (0.96 to 1.13)
Amoxicillin	---	---	---

* Analysis with initial adjustment for age, sex

[†] Analysis with initial adjustment for age, sex and history of myocardial infarction and arrhythmia

[‡] Analysis with full adjustment for age, sex, and propensity score

[a] Analysis with full adjustment for age, sex, and history of myocardial infarction and arrhythmia and propensity score

Supplementary material 10. Subgroup analysis of risk of cardiovascular outcomes associated with current use of clarithromycin versus amoxicillin

	Rate ratio (95%CI)*	Absolute risk difference per 1000 (95%CI)*
Cardiac death		
Sex		
Male	1.71 (1.31 to 2.23)	1.15 (0.50 to 1.98)
Female	1.62 (1.16 to 2.25)	0.75 (0.19 to 1.51)
Age		
18-64	2.13 (1.07 to 4.23)	0.20 (0.01 to 0.57)
65-74	1.73 (1.05 to 2.84)	0.87 (0.06 to 2.19)
75+	1.60 (1.25 to 2.03)	2.63 (1.10 to 4.52)
History of hypertensive diseases		
No	1.53 (1.17 to 1.99)	0.57 (0.18 to 1.07)
Yes	1.90 (1.37 to 2.65)	3.47 (1.43 to 6.36)
History of diabetes mellitus		
No	1.57 (1.24 to 1.99)	0.71 (0.30 to 1.24)
Yes	2.03 (1.32 to 3.12)	3.71 (1.15 to 7.63)
Myocardial infarction		
Sex		
Male	3.64 (2.57 to 5.15)	2.13 (1.27 to 3.35)
Female	3.74 (2.51 to 5.56)	1.68 (0.93 to 2.79)
Age		
18-64	5.11 (2.63 to 9.90)	0.63 (0.25 to 1.37)
65-74	2.14 (1.19 to 3.86)	1.15 (0.19 to 2.89)
75+	4.00 (2.89 to 5.54)	5.77 (3.63 to 8.73)
History of hypertensive diseases		
No	3.78 (2.73 to 5.23)	1.51 (0.94 to 2.29)
Yes	3.32 (2.15 to 5.12)	4.78 (2.37 to 8.49)
History of diabetes mellitus		
No	3.76 (2.79 to 5.07)	1.65 (1.07 to 2.43)
Yes	3.12 (1.82 to 5.35)	4.95 (1.91 to 10.15)
Arrhythmia		
Sex		
Male	2.40 (1.17 to 4.91)	0.30 (0.04 to 0.85)
Female	1.92 (0.64 to 5.75)	0.09 (-0.04 to 0.46)
Age		
18-64	3.99 (1.10 to 14.50)	0.13 (0.004 to 0.60)
65-74	2.21 (0.53 to 9.32)	0.18 (-0.07 to 1.27)
75+	1.92 (0.89 to 4.13)	0.40 (-0.05 to 1.36)
History of hypertensive diseases		
No	2.58 (1.26 to 5.27)	0.20 (0.03 to 0.55)
Yes	1.61 (0.55 to 4.75)	0.24 (-0.17 to 1.45)
History of diabetes mellitus		
No	2.49 (1.29 to 4.81)	0.21 (0.04 to 0.53)
Yes	1.25 (0.29 to 5.36)	0.11 (-0.31 to 1.89)

*Adjusted for propensity score with trimming 1st and 20th strata