Long-Term Risk of Acute Myocardial Infarction, Stroke, and Death With Outpatient Use of Clarithromycin: A Retrospective Cohort Study

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In a retrospective cohort study of patients enrolled in the UK Clinical Practice Research Datalink during 2000–2013, we evaluated long-term risks of death, stroke, and acute myocardial infarction (AMI) in adults prescribed clarithromycin. Patients were outpatients aged 40–85 years, who were prescribed clarithromycin (n = 287,748), doxycycline (n = 267,729), or erythromycin (n = 442,999), or Helicobacter pylori eradication therapy with a proton pump inhibitor, amoxicillin, and either clarithromycin (n = 27,639) or metronidazole (n = 14,863). We analyzed time to death, stroke, or AMI with Cox proportional hazards regression. The long-term hazard ratio for death following 1 clarithromycin versus 1 doxycycline prescription was 1.29 (95% confidence interval (CI): 1.21, 1.25), increasing to 1.62 (95% CI: 1.43, 1.84) for ≥5 prescriptions of clarithromycin versus ≥5 prescriptions for doxycycline. Erythromycin showed smaller risks in comparison with doxycycline. Stroke and AMI incidences were also increased after clarithromycin but with smaller hazard ratios than for mortality. For H. pylori eradication, the hazard ratio for mortality following clarithromycin versus metronidazole regimens was 1.09 (95% CI: 1.00, 1.18) overall, and it was higher (hazard ratio = 1.65, 95% CI: 0.88, 3.08) following ≥2 prescriptions in subjects not on statins at baseline. Outpatient clarithromycin use was associated with long-term mortality increases, with evidence for a similar, smaller increase with erythromycin.

Abbreviations: AMI, acute myocardial infarction; CCB, calcium channel blocker; CI, confidence interval; CPRD, Clinical Practice Research Datalink; IPTW, inverse probability of treatment weighting; PH, proportional hazards; PS, propensity score.
doxycycline or erythromycin; and 2) *H. pylori* eradication treatment with or without clarithromycin.

**METHODS**

We conducted a retrospective study of two cohorts in the UK Clinical Practice Research Datalink (CPRD), from January 1, 2000, through December 31, 2013. CPRD, a primary-care database of medical records including >1.3 million patients from UK general practices, is widely used in pharmacoepidemiology studies (10, 11). CPRD’s Independent Scientific Advisory Committee reviewed the study protocol. Subjects in our first cohort received outpatient prescriptions for oral clarithromycin—or antibiotics with generally similar uses, doxycycline or erythromycin—for any indication. Subjects in the *H. pylori* eradication cohort received either: 1) a proton pump inhibitor + amoxicillin + clarithromycin; or 2) proton pump inhibitor + amoxicillin + metronidazole. In UK guidelines, both “triple therapy” regimens are first-line therapies (12), providing a comparison that mitigates confounding by indication. The cohorts were not mutually exclusive.

In both cohorts, subjects were aged 40–85 years, with at least 12 months of prior continuous registration in a CPRD general practice and no stroke or acute myocardial infarction (AMI) during the 90 days before the first prescription date.

Each subject’s follow-up started the day after their first study drug prescription, after 1 year or longer without any study drug prescriptions (for the all-indications cohort, no macrolide or doxycycline prescriptions, and for the *H. pylori* eradication cohort, no macrolide or metronidazole prescriptions).

We analyzed endpoints of death from all causes, stroke, and AMI, as well as the composite of these 3 outcomes. Stroke and AMI were defined in CPRD by Read codes (Web Table 1, available at https://academic.oup.com/aje). Validation studies in this database have reported positive predictive values of 82%–93% for AMI (13, 14), 89% for stroke (15), and 97% for mortality (16).

We adjusted for potential confounding using inverse probability of treatment weighting (IPTW) based on propensity score (PS) (17). This method weights each participant, giving higher weights to participants who are more similar across treatment groups. The weight in IPTW is derived from the PS as the inverse probability of receiving a specific treatment, given baseline characteristics determined over a 1-year look-back period (Table 1). To estimate PSs, in the all-indications cohort we used multinomial logistic regression, a technique for comparisons of more than 2 treatments (18); in the *H. pylori* eradication cohort we used logistic regression because there were only 2 treatment groups. After weighting, we assessed covariate balance by standardized mean differences, the differences between means for each group expressed as proportions of their pooled standard deviation. We interpreted standardized mean differences of <0.1 as indicating adequate balance (19). To check for adequate overlap of PSs and for outlier weights, we examined the distributions of PSs and weights.

To classify indication in the all-indications cohort, we applied an algorithm (Web Appendix 1) to diagnoses recorded up to 29 days before the prescription. We included indication in both the PS and outcome models, categorizing indications as follows: acute bronchitis and bronchiolitis; chronic obstructive pulmonary disease and other chronic pulmonary conditions; pneumonia and influenza; acute respiratory tract infections and diseases; gastrointestinal conditions; respiratory symptoms (with no diagnosis); skin, musculoskeletal, or connective tissue disease; and other infections.

In the primary analysis, patients in the all-indications cohort contributed follow-up time until they were censored for one of the following: 1) a study outcome, 2) end of the study period, 3) end of reporting by their practice, 4) transfer out of the practice, or 5) filling a prescription for a different study antibiotic or another macrolide. The primary analysis adjusted for repeated exposures to the index antibiotic.

In secondary analyses we varied the censoring criteria. We mimicked an intent-to-treat approach by following subjects without regard to subsequent changes in treatment (without censoring on criterion 5, above), and we analyzed events only during exposure to the study drug, estimated by the number of “defined daily doses” (20) in the prescription.

In the *H. pylori* eradication cohort, we censored subjects according to criteria 1–5 above; in addition, we censored subjects

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**Table 1.** Hazard Ratios for Death, With Mimic “Intent-to-Treat” Censoring, in the All-Indications Cohort, Clinical Practice Research Datalink, United Kingdom, 2000–2013

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Unadjusted</th>
<th></th>
<th>IPTW Adjusted</th>
<th></th>
<th>Multivariable Adjusted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR*</td>
<td>95% CI</td>
<td>HR*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Clarithromycin vs. doxycycline</td>
<td>1.94</td>
<td>1.90, 1.97</td>
<td>1.23</td>
<td>1.20, 1.25</td>
<td>1.26</td>
<td>1.24, 1.29</td>
</tr>
<tr>
<td>Clarithromycin vs. erythromycin</td>
<td>1.36</td>
<td>1.34, 1.37</td>
<td>1.13</td>
<td>1.11, 1.15</td>
<td>1.12</td>
<td>1.10, 1.13</td>
</tr>
<tr>
<td>Erythromycin vs. doxycycline</td>
<td>1.43</td>
<td>1.40, 1.45</td>
<td>1.09</td>
<td>1.06, 1.11</td>
<td>1.13</td>
<td>1.11, 1.15</td>
</tr>
</tbody>
</table>

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Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

* Adjusted for age as a continuous variable.

* Adjusted for age as a continuous variable plus the following covariates: age category, alcohol use, body mass index, sex, index year, indication, marital status, region, smoking, medication use (angiotensin-converting enzyme inhibitors, antibiotics, antihyrrthymics, anticoagulants, antplatelet drugs, antipsychotics, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, digoxin, diuretics, estrogen, histamine 2 blockers, nitrates, nonsteroidal antiinflammatory drugs, proton pump inhibitors, QT-prolonging drugs, statins, thiazides, or thyroid replacement), medical history (acute myocardial infarction, ischemic heart disease/coronary heart disease, chronic obstructive pulmonary disease, coronary revascularization, depression, diabetes, heart failure, lipid disorders, peptic ulcer, stroke/cerebral revascularization, or other comorbidities), and practice-level socioeconomic status.

for any use of clarithromycin or metronidazole that was not part of \textit{H. pylori} triple therapy.

In both cohorts, the outcome model was an IPTW-weighted Cox proportional hazards (PH) regression model employing stabilized weights and robust variance estimation to calculate 95% confidence intervals (see Web Appendix 2). We also performed a Cox PH regression analysis without IPTW, adjusting for 41 covariates. We assessed the PH assumption by performing a formal PH test and by inspection of survival function and log-log plots. Because age was a categorical rather than a continuous variable in the PS, we doubly adjusted key analyses for age by including age as a continuous variable in the outcome model, to account for potential residual confounding.

To assess the associations with repeated exposures, the cumulative number of index drug prescriptions was a time-varying covariate with 5 levels of exposure (1, 2, 3, 4, or \geq 5 cumulative prescriptions) in the all-indications cohort, and 2 levels of exposure (1 or \geq 2 cumulative prescriptions) in the \textit{H. pylori} eradication cohort (because of its smaller size). The time-varying model is not a subgroup analysis conditioning on future drug use. Rather, the model can assess whether risk varies with cumulative exposure as follow-up data accrue.

Prospective subgroups analyzed in the all-indications cohort, using the composite outcome of death, stroke, and AMI, were age groups (40–64 years, 65–74 years, and 75–85 years); baseline statin use; indications of chronic obstructive pulmonary disease and pneumonia; prior ischemic heart disease; and baseline calcium channel blocker (CCB) use, because clarithromycin has been reported to increase risk of hospitalization for acute kidney injury and mortality in CCB users (21). In subgroup analyses, we reestimated PS and weights and checked covariate balance after weighting. For age subgroup analyses, age was a continuous variable in the PS model. In the \textit{H. pylori} eradication cohort, we performed a subgroup analysis by baseline statin use. We used SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), for all analyses. The US Food and Drug Administration Research in Human Subjects Committee approved our retrospective use of de-identified CPRD data and did not require review of the study protocol.

**RESULTS**

**All-indications cohort**

There were 287,748 clarithromycin users, 267,729 doxycycline users, and 442,999 erythromycin users meeting selection criteria (Web Figure 1). Baseline subject characteristics and indications are displayed in Web Table 2. There was a slight preponderance of women across groups. Clarithromycin users were slightly older at baseline, had somewhat more cardiovascular comorbidities, and used more cardiovascular medications. Respiratory indications predominated for all 3 antibiotics, although overall, 29% of subjects had no identifiable indication. Web Figure 2 shows the distributions of propensity scores and stabilized weights in the cohort. After IPTW, all covariates in all 3 pairwise comparisons showed standardized mean differences of <0.03 (Web Table 3). Median length of follow-up was 2.4 years, 2.7 years, and 3.9 years for patients receiving clarithromycin, doxycycline, and erythromycin, respectively; Web Table 4 shows the numbers of patients remaining according to time period. Across groups, most patients received only 1 prescription (72%, 72%, and 64% of prescriptions for clarithromycin, doxycycline, and erythromycin, respectively). For patients with 5 or more prescriptions, the median time from the first to the fifth prescription was longest for erythromycin (median, 1,196 days), followed by clarithromycin (median, 943 days) and doxycycline (median, 811 days).

Death from any cause was the most numerous individual outcome by several-fold, occurring in 66,495 patients, representing 7.9%, 4.2%, and 7.3% of the clarithromycin-, doxycycline-, and erythromycin-exposed subjects, respectively (Web Table 5). Accordingly, in presenting the results, we have prioritized results for death.

Weighted time-to-event curves (22) for mortality separated without crossing, with clarithromycin showing the highest rate and doxycycline the lowest (Figure 1). Analyzing cumulative numbers of prescriptions as time-varying covariates showed increasing hazard ratios for death with successive clarithromycin prescriptions (versus corresponding numbers of successive prescriptions for the comparator). The hazard ratio for death with 1 clarithromycin prescription versus 1 doxycycline prescription was 1.25 (95% CI: 1.21, 1.29), and the hazard ratio for death with 5 or more clarithromycin prescriptions versus 5 or more doxycycline prescriptions was 1.62 (95% CI: 1.43, 1.84), adjusted for the time to the fifth prescription (Figure 2). Relative to erythromycin, clarithromycin showed smaller hazard ratios, with similar increase in risk as the number of exposure episodes increased. Erythromycin also showed higher risk versus doxycycline, although with a less robust association with increasing number of treatment episodes. Under mimic intent-to-treat censoring, the hazard ratio for death (using IPTW and adjusted for age as a continuous variable) following clarithromycin treatment was 1.23 (95% CI: 1.20, 1.25) versus doxycycline, and it was 1.13 (95% CI: 1.11, 1.15) versus erythromycin (Table 1). Directly adjusting for the 41 baseline covariates with age as a continuous variable, in a Cox PH model (without IPTW), yielded results consistent with the IPTW mimic intent-to-treat analysis (Table 1) and also with the prescription = 1 exposure condition under the primary censoring method.

![Cumulative hazard for death according to antibiotic used](https://academic.oup.com/aje/article-abstract/187/4/786/4201647/788)
The results suggest a rank order of long-term mortality risk of clarithromycin > erythromycin > doxycycline. An AMI occurred as the first event in 3,622 patients receiving clarithromycin, 2,408 receiving doxycycline, and 6,321 receiving erythromycin (Web Table 5). Overall, hazard ratios for AMI and stroke were lower than for mortality, although as with death the clarithromycin:doxycycline comparison had the numerically highest hazard ratios (Table 2). The term for interaction between exposure and number of prescriptions was not significant in the model, possibly due to lack of power. A composite of death, AMI, and stroke showed hazard ratios similar to death, consistent with death being the most numerous individual outcome (Web Table 6).

In subgroup analyses, we analyzed a composite outcome of death, AMI, and stroke. Results within age strata (Web Figure 3) showed hazard ratios that declined with age. We found increased risks among both statin users and nonusers but with lower hazard ratios in statin users (Web Figure 4), even though statin users had higher cardiovascular event rates than nonusers (data not shown). For indications of chronic obstructive pulmonary disease and pneumonia, clarithromycin:doxycycline hazard ratios were 1.28 (95% CI: 1.14, 1.43) and 1.36 (95% CI: 1.08, 1.72), respectively (Web Table 7); for those two smaller subgroups, the term for interaction between exposure and the number of prescriptions was not significant in the model. Among CCB users, hazard ratios were generally smaller than among nonusers (Web Figure 5). Results were similar in patients with ischemic heart disease at baseline, but hazard ratios were generally smaller compared to those for patients without ischemic heart disease (Web Figure 6).

We analyzed short-term risk of the composite outcome by following patients to the end of their first prescription, finding hazard ratios of 1.97 (95% CI: 1.64, 2.37) for clarithromycin:doxycycline, 1.60 (95% CI: 1.37, 1.88) for clarithromycin:erythromycin, and 1.23 (95% CI: 1.00, 1.52) for erythromycin:doxycycline.

There have been concerns about combining clarithromycin with CCBs (21) and statins (23). Clarithromycin is contraindicated with statins that are extensively metabolized by cytochrome P450 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy and rhabdomyolysis, and caution is advised when coprescribing with atorvastatin or pravastatin (24). We therefore analyzed the composite outcome hazard ratio during the antibiotic prescription according to statin use and CCB use, and we found short-term increased risks for clarithromycin in both users and nonusers of statins and CCBs (Web Table 8).
**Table 2.** Inverse Probability of Treatment–Weighted Hazard Ratios for Acute Myocardial Infarction and Stroke, Adjusted for Age as a Continuous Variable, in the All-Indications Cohort, Clinical Practice Research Datalink, United Kingdom, 2000–2013

<table>
<thead>
<tr>
<th>Comparison</th>
<th>AMI HR</th>
<th>95% CI</th>
<th>Stroke HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin vs. doxycycline</td>
<td>1.13</td>
<td>1.06, 1.20</td>
<td>1.15</td>
<td>1.08, 1.22</td>
</tr>
<tr>
<td>Clarithromycin vs. erythromycin</td>
<td>1.03</td>
<td>0.98, 1.07</td>
<td>1.04</td>
<td>1.00, 1.09</td>
</tr>
<tr>
<td>Erythromycin vs. doxycycline</td>
<td>1.10</td>
<td>1.04, 1.17</td>
<td>1.10</td>
<td>1.04, 1.17</td>
</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio.

**H. pylori eradication cohort**

After applying eligibility criteria (Web Figure 7), there were 27,639 clarithromycin-treated patients and 14,863 metronidazole-treated patients in the *H. pylori* eradication cohort. Nearly two-thirds in both groups were younger than 65 years, with a slight predominance of women (Web Table 9). Ischemic heart disease was present in 18% of patients prescribed clarithromycin and 19% of patients prescribed metronidazole, and roughly a quarter of patients in both groups used statins. Web Figure 2 shows the distributions of propensity scores and stabilized weights in the cohort. Even before IPTW, standardized mean differences for all baseline covariates were <0.1, except for some categories of region and calendar year, consistent with choice of regimen varying mainly by time and geographic location rather than patient characteristics. Median length of follow-up was 3.1 years for clarithromycin regimens and 2.8 years for metronidazole regimens. A total of 1,334 clarithromycin-treated patients (4.8%) and 595 (4.0%) metronidazole-treated patients repeated *H. pylori* eradication treatments. Death from any cause was the predominant individual outcome (Web Table 5), occurring in 5.5% of clarithromycin-regimen patients and 5.2% of metronidazole-regimen patients.

Overall, mortality increased following clarithromycin; the hazard ratio (clarithromycin:metronidazole) for death was 1.09 (95% CI: 1.00, 1.18). The hazard ratio for 1 triple-therapy prescription (1.08, 95% CI: 0.99, 1.18) was close to the overall hazard ratio, while the hazard ratio for ≥2 triple-therapy prescriptions was higher (1.25, 95% CI: 0.77, 2.04, adjusted for time to the second prescription). Similar to the all-indications cohort, patients who received ≥2 triple therapies with clarithromycin and were not on a statin at baseline had an even higher hazard ratio (1.65, 95% CI: 0.88, 3.08) (Table 3). Results for the composite outcome of death, stroke, or AMI were similar (Web Table 10).

**DISCUSSION**

Relative to other antibiotics, outpatient use of clarithromycin increased long-term mortality risk, in both cohorts—patients using it for any indication and patients using it for *H. pylori* eradication. These results recapitulate those of the CLARICOR trial. In what we believe is the first analysis to address multiple exposures, mortality risk was higher with repeated drug exposures. Erythromycin showed a similar, although numerically lower, risk, raising the possibility of a macrolide-class risk; to our knowledge, long-term risks of erythromycin have not been studied. Although recent data on acute cardiovascular risks of clarithromycin have been mixed (25, 26), we found evidence consistent with an acute risk during the time of exposure to clarithromycin relative to doxycycline or erythromycin (and to a lesser degree during erythromycin exposure versus doxycycline). Short-term risks with clarithromycin were present with or without concomitant statins and CCBs.

**Table 3.** Hazard Ratios for Death in the *Helicobacter pylori* Eradication Cohort, Clinical Practice Research Datalink, United Kingdom, 2000–2013

<table>
<thead>
<tr>
<th>Statin Use Subgroup</th>
<th>No. of CLA Triple-Therapy Treated Patients</th>
<th>No. of MET Triple-Therapy Treated Patients</th>
<th>No. of Triple Therapies Received</th>
<th>IPTW-Adjusted HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort</td>
<td>27,639</td>
<td>14,863</td>
<td>Overall</td>
<td>1.09</td>
<td>1.00, 1.18</td>
</tr>
<tr>
<td></td>
<td>1 triple therapy</td>
<td></td>
<td>1.08</td>
<td>0.99, 1.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2 triple therapies</td>
<td></td>
<td>1.25</td>
<td>0.77, 2.04</td>
<td></td>
</tr>
<tr>
<td>No statin use</td>
<td>21,085</td>
<td>11,114</td>
<td>1 triple therapy</td>
<td>1.07</td>
<td>0.96, 1.19</td>
</tr>
<tr>
<td></td>
<td>≥2 triple therapies</td>
<td></td>
<td>1.65</td>
<td>0.88, 3.08</td>
<td></td>
</tr>
<tr>
<td>Statin use</td>
<td>6,544</td>
<td>3,749</td>
<td>1 triple therapy</td>
<td>1.12</td>
<td>0.96, 1.30</td>
</tr>
<tr>
<td></td>
<td>≥2 triple therapies</td>
<td></td>
<td>0.78</td>
<td>0.34, 1.78</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CLA, clarithromycin; HR, hazard ratio; IPTW, inverse probability of treatment weighted; MET, metronidazole.

* Clarithromycin versus metronidazole triple therapy, adjusted for age as a continuous variable.
Similar to CLARICOR, baseline statin users had lower hazard ratios for the composite outcome following clarithromycin use in the all-indications cohort, and they had a lower mortality hazard ratio in the *H. pylori* eradication cohort with repeat clarithromycin treatment. We also found that baseline CCB users showed lower hazard ratios; statin and CCB users were not mutually exclusive subgroups.

Strengths of our study include the length of follow-up, use of outcomes validated for this database, balancing of baseline characteristics after IPTW, consistency of findings across subgroups and sensitivity analyses, and demonstration of a risk for clarithromycin that increased with repeat exposure. Although roughly two-thirds of subjects in the all-indications cohort received only 1 prescription, for those with repeat exposures, the time-varying model accounted for differences in the number of, and time to, subsequent prescriptions.

We note several limitations of our study. We studied outpatient use of clarithromycin, but cardiovascular risks and risk–benefit balances may differ in patients hospitalized for infection; some evidence suggests that macrolides improve short-term mortality among patients hospitalized for pneumonia (27). In the all-indications cohort, the analysis was powered to adjust only for the first prescription’s indication; also, we could not determine indication for over one-fourth of subjects. We cannot be certain that a patient prescribed an antibiotic was actually exposed. The smaller sample limited statistical power in the *H. pylori* eradication cohort. Although fatal AMIs and strokes should be represented as deaths, even if they occurred out of the hospital, we could not analyze specific causes of death.

Most importantly, antibiotic choice could reflect patient factors unaccounted for by our analysis and that influenced long-term risk (i.e., residual confounding by indication); conceivably even the exposure dependency of the risk could reflect sequential confounding. Residual confounding by indication may account for some of the observed association, but it seems unlikely to be the entire explanation. In the *H. pylori* eradication cohort, indication was presumed to be identical across all exposures. There, as in the larger cohort, mortality increased following clarithromycin use, albeit to a lesser degree (hazard ratio = 1.09, 95% CI: 1.00, 1.18). While not a large increase, this was similar to the 10-year increase in all-cause mortality for clarithromycin versus placebo in the CLARICOR trial (hazard ratio = 1.10, 95% CI: 1.00, 1.21) (4). In both cohorts we found the highest hazard ratio in patients with multiple exposures to clarithromycin and no baseline statin use; in CLARICOR, subjects not on statins at baseline had the higher mortality hazard ratio following clarithromycin use (4). While possibly a result of chance or confounding, the similarity argues against these being the complete explanation.

Finally, there is no obvious mechanism by which clarithromycin, or to a lesser degree erythromycin, might induce such long-term risks. Speculatively, inflammatory processes (28) or unfavorable changes in gut microflora influencing cardiovascular risk (29) might be involved, but at present the mechanism is unknown. However, valid associations are sometimes recognized prior to elucidation of an explanatory mechanism.

Our results agree with Schembi et al. (6) and, more importantly, with the CLARICOR study, a randomized, placebo-controlled trial. However, we acknowledge differences between our results and those of other observational studies that failed to identify long-term risks with clarithromycin. Wong et al. (8) compared cardiovascular outcomes over 3 years following use of amoxicillin or clarithromycin in a retrospective cohort study, with an analysis stratified by follow-up time period; they also assessed cardiovascular risks of *H. pylori* eradication treatment with clarithromycin in a self-controlled design. Both analyses found an association between clarithromycin and only short-term risks. With respect to long-term risk, their primary outcome of myocardial infarction, assessed over the period of 2–3 years following exposure, showed adjusted incidence rate ratios of 1.01 (95% CI: 0.72, 1.40) in the clarithromycin versus amoxicillin comparison and 0.96 (95% CI: 0.73, 1.25) in the self-controlled case series of *H. pylori* eradication with clarithromycin. Andersen et al. (7) retrospectively studied ischemic heart disease patients who had received *H. pylori* eradication treatment with clarithromycin, finding no significant difference in mortality relative to nonclarithromycin eradication treatment over 5 years, with hazard ratios numerically favoring nonclarithromycin treatment until year 5 (when the adjusted hazard ratio was 1.09 (95% CI: 0.58, 2.05) for clarithromycin versus nonclarithromycin eradication). However, their analysis had to be stratified by year because the data did not satisfy the PH assumption. Finally, a recent study of recipients of *H. pylori* eradication treatment, also in CPRD, reported evidence of short-term but not long-term cardiovascular risk with clarithromycin regimens (9): This study ended follow-up (censored) at the time of a second clarithromycin prescription. While not necessarily reasons for differing results, our study had larger samples, and a time-to-event analysis (Cox PH) applied to the entire follow-up period (which for many of our subjects extended beyond 5 years). Also, our study examined the influence of multiple exposures on the risk, finding an increased risk with repeated exposures. Results from the triple-therapy cohort suggest that the highest risk applies to repeat clarithromycin exposure in the absence of statin therapy.

In conclusion, relative to comparator treatments, outpatient clarithromycin use was associated with long-term increases in death, stroke, and AMI, with evidence for a similar, smaller long-term risk with erythromycin, and for short-term risks with both macrolides. Because long-term cardiovascular risk has been observed for clarithromycin in two retrospective cohorts (6) and a randomized, placebo-controlled trial (3), evidence is mounting that clarithromycin use potentially carries a poorly understood, long-term hazard. We believe that these data can inform judgments about whether to prescribe an antibiotic, and the choice of antibiotic, particularly for nonserious infections and clinical conditions that an antibiotic may not benefit.
REFERENCES
