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Systematic Review, Meta-analysis, and Network Meta-analysis of the Cardiovascular Safety of Macrolides

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ABSTRACT Studies reporting an increased risk for cardiac toxicities with macrolide antibiotics have raised concern regarding their cardiovascular safety. We sought to assess the cardiac safety of macrolide antibiotics as a class and of the individual agents by conducting a systematic review and network meta-analysis. Medline, Embase, and the Cochrane Library were searched up to February 2018 for studies reporting on cardiovascular outcomes with macrolides. We followed the PRISMA 2009 guidelines for data selection and extraction. Outcomes were pooled using random-effects models and odds ratios (OR), and 95% confidence intervals (CI) were calculated for arrhythmia, cardiovascular death, and myocardial infarction (MI). A total of 33 studies and data on 22,601,032 subjects were retrieved and included in the current meta-analyses. Macrolide use was not associated with the risk of arrhythmia or cardiovascular mortality. In the primary analysis, macrolide use was associated with a small but statistically significant 15% increase in risk for MI (OR = 1.15 [95% CI, 1.01 to 1.30]). In indirect network meta-analysis, erythromycin and clarithromycin were ranked considerably more likely to be associated with a higher risk for MI and significantly associated with increased risk of MI compared to azithromycin (OR = 1.58 [95% CI, 1.18 to 2.11] and OR = 1.41 [95% CI, 1.11 to 1.81], respectively). Our findings indicate that macrolide antibiotics as a group are associated with a significant risk for MI but not for arrhythmia and cardiovascular mortality. Among the macrolides, erythromycin and clarithromycin were associated with a greater risk of MI. However, it is possible that the association between macrolide use and risk of MI is the result of residual confounding.

KEYWORDS arrhythmia, azithromycin, cardiac arrest, cardiac death, cardiovascular, clarithromycin, erythromycin, macrolide, mortality, myocardial infarction, roxithromycin, stroke, torsades de pointes, ventricular tachyarrhythmia

Macrolides are a widely prescribed class of antibiotics, used to treat many common infections, and are considered overall safe, with little risk for severe adverse outcomes. However, in recent years several studies have reported an association between macrolides and cardiotoxicity (1, 2). Reported adverse cardiac outcomes with macrolides include QT interval prolongation, torsades de pointes (TdP), ventricular tachycardia, and sudden cardiac death (1–3).

In previous years, azithromycin was considered relatively free from cardiac toxic effects (4). However, it has since been associated with the risk of cardiovascular death (5). Following these reports, the Food and Drug Administration (FDA) issued a safety communication regarding the risk of potentially fatal arrhythmias with azithromycin (6). In addition to the immediate adverse reactions, a recent FDA communication raised concerns regarding the long-term cardiovascular risk of clarithromycin (7).

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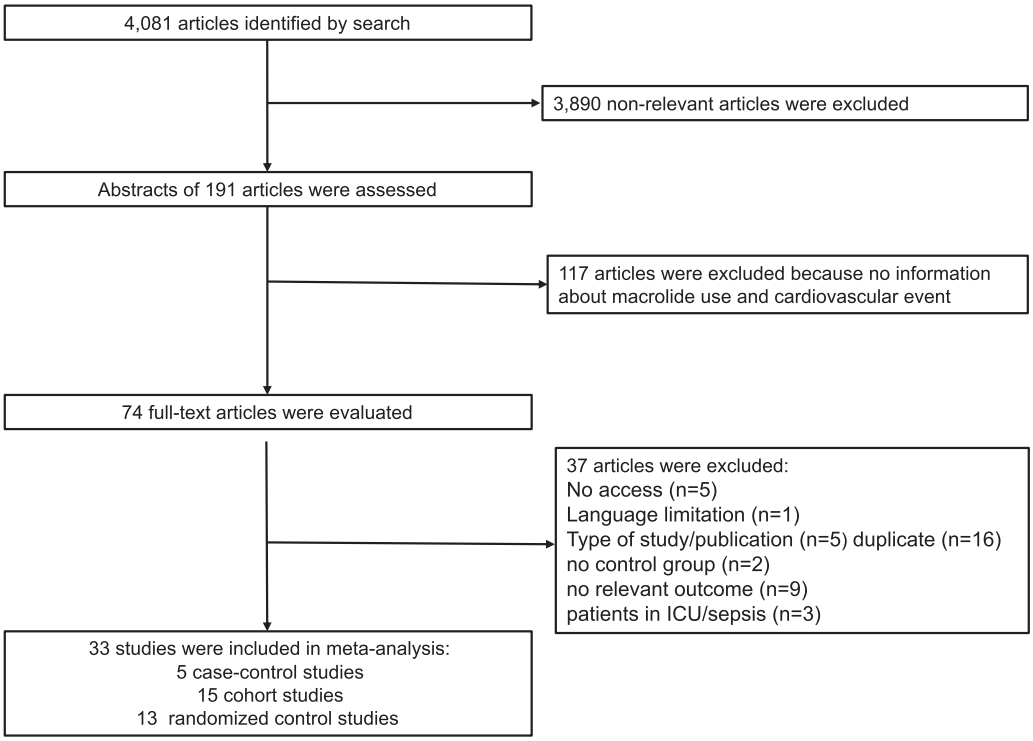

FIG 1 Selection process, including the numbers of articles retrieved, screened, and selected for quantitative analysis.

Previous meta-analyses assessing the cardiovascular risks of macrolides reported conflicting results (3, 8, 9). The first, performed by Cheng et al., found an association between an increased risk for developing sudden cardiac death (SCD) or ventricular tachyarrhythmia (TVA) (3). The second meta-analysis, conducted by Li et al., did not find an association between macrolides and an increased risk for cardiac death compared with nonmacrolide regimens; however, such an association was found in a subgroup of individuals older than 48 years (8). Importantly, none of the published meta-analyses compared individual macrolides (namely, erythromycin, azithromycin, clarithromycin, and roxithromycin) with respect to their relative risk for cardiac toxicity.

Following these meta-analyses, several additional studies have reported cardiovascular outcomes with macrolide antibiotics (10–14, 16, 43).

In light of the conflicting reports and the publication of many additional studies not included in previous meta-analyses, we aimed to perform a systematic review and a network meta-analysis to update the current knowledge regarding the cardiac safety of macrolides as a class, including the risk of arrhythmia, cardiovascular mortality, and myocardial infarction (MI), and to determine the cardiac safety of the specific macrolides.

RESULTS

Description of the selected studies. Our search yielded 4,081 records for evaluation. Records were screened for inclusion by title, resulting in 191 potentially relevant records, which were further evaluated by abstract. After exclusion of irrelevant abstracts, 74 articles were selected for full-text evaluation. The macrolide agent most commonly reported in these studies was azithromycin (17 studies), and the comparator group was most commonly a penicillin-based antibiotic (for observational studies) or a placebo (for randomized controlled trials [RCTs]). Additional characteristics of the included studies are listed in Table S1 in the supplemental material. Thirty-three articles were included in the analysis: 13 RCTs, 15 cohort studies, and 5 case-control studies. The search process is illustrated in Fig. 1. The observational trials' quality assessments by the Newcastle-Ottawa quality assessment scale (NOS) varied from 6 to 9 stars, and

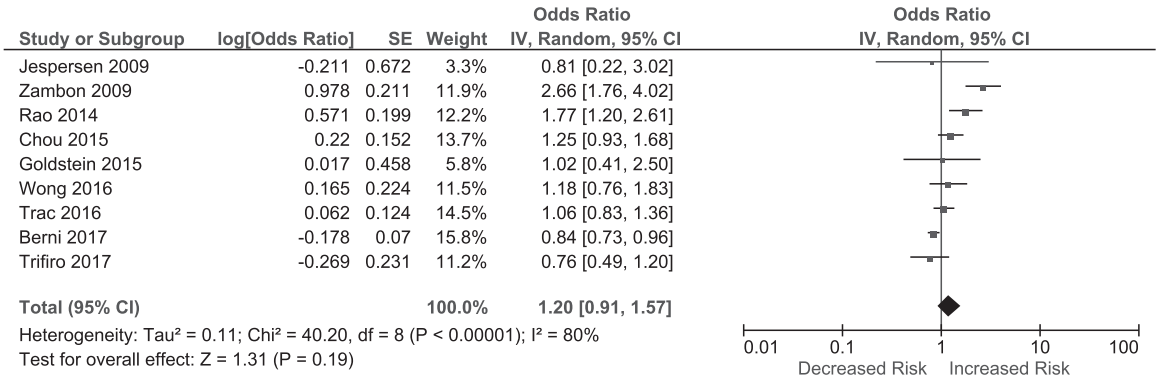

FIG 2 Odds ratios for arrhythmia in macrolide users versus nonusers. The forest plot demonstrates point estimates of risk ratios surrounded by 95% CI calculated by a random-effects model.

the overall risk of bias in the included RCTs was low (see Tables S5 and S6 in the supplemental material).

Meta-analysis. (i) Short-term risk for arrhythmia. Eight studies (1 RCT, 5 cohort studies, 2 case-control studies; the summaries of these studies are illustrated in Table S4 in the supplemental material) evaluated the risk for short-term arrhythmia after exposure to macrolides (11, 12, 14, 16–21). Using a random-effects model, macrolide use was not associated with an increased risk for short-term arrhythmia (OR, 1.20 [95% CI, 0.91 to 1.57]) with high heterogeneity between the studies (P for heterogeneity < 0.00001; $I^2 = 80\%$) (Fig. 2).

Thirty-day cardiovascular mortality. The pooled effect of nine studies (1 RCT, 6 cohort, 2 case-control; summaries of these studies are illustrated in Table S5 in the supplemental material) (1, 5, 11, 13, 18, 21, 24–26) reporting short-term cardiovascular mortality revealed no increase in mortality among macrolide users (OR, 1.22 [95% CI, 0.94 to 1.59]) in a random-effects model with high heterogeneity between the studies (P for heterogeneity < 0.0001; $I^2 = 76\%$) (Fig. 3).

Myocardial infarction. A pooled analysis of 20 studies (13 RCTs, 7 cohort, 1 case-control; summaries of these studies are illustrated in Table S6 in the supplemental material) (10, 11, 21, 27–43) reporting on the risk for MI following macrolide therapy demonstrated a significant 15% increase in risk in the macrolide group (OR = 1.15 [95% CI, 1.01 to 1.30], $P < 0.00001$; $I^2 = 82\%$) (Fig. 4).

Network meta-analysis of risk of myocardial infarction. In network meta-analysis (see the network plot in Fig. S1 in the supplemental material) evaluating the relative risk of MI with individual agents, erythromycin and clarithromycin ranked most likely to

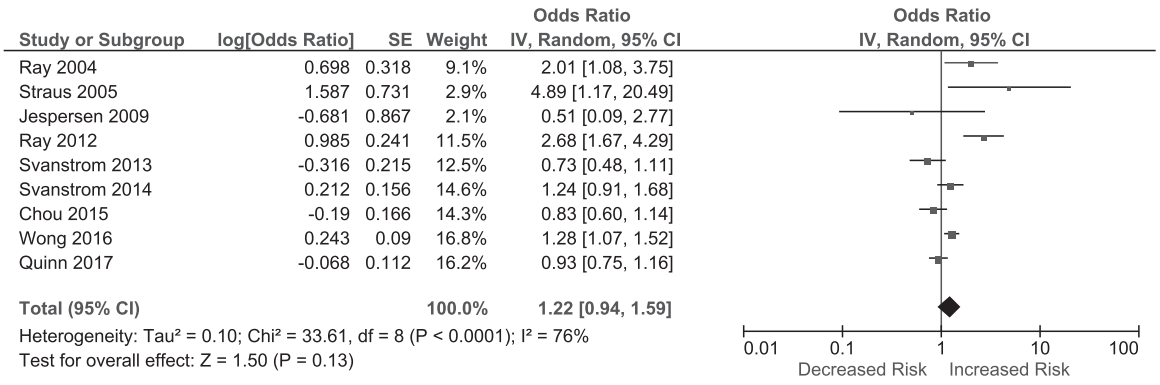

FIG 3 Odds ratios for short-term cardiovascular mortality in macrolide users versus nonusers. The forest plot demonstrates point estimates of risk ratios surrounded by 95% CI calculated by a random-effects model.

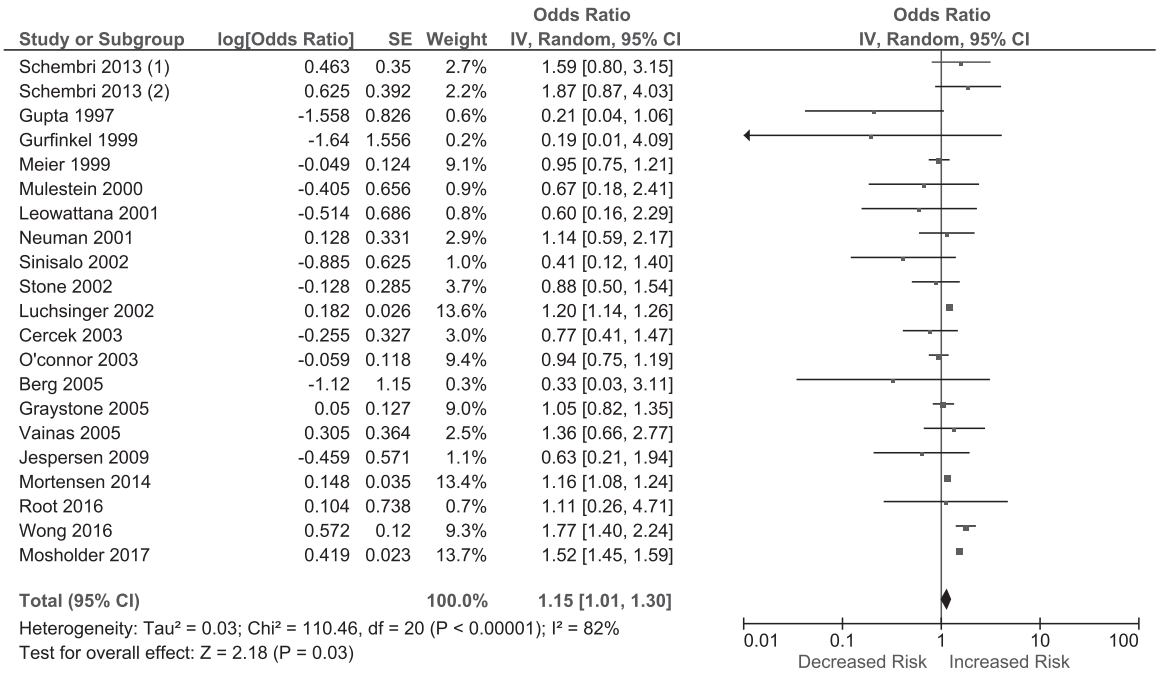

FIG 4 Odds ratios for MI in macrolide users versus nonusers. The forest plot demonstrates point estimates of risk ratios surrounded by 95% CI calculated by a random-effects model.

have the highest risk for MI (P scores [see Materials and Methods], 0.94 and 0.77, respectively [Table 1]). Erythromycin and clarithromycin were associated with a significantly higher risk for MI compared to azithromycin (OR = 1.58 [95% CI, 1.18 to 2.11], and OR = 1.41 [95% CI, 1.11 to 1.81], respectively) and compared to nonmacrolide use (OR = 1.62 [95% CI, 1.27 to 2.1], and OR = 1.45 [95% CI, 1.20 to 1.74] respectively) (Fig. 5). The results of the comparative analysis for MI risk comparing these agents to roxithromycin were not conclusive.

Subgroup analysis. In subgroup analysis, restricting the analysis of the risk of MI with macrolides to RCTs, macrolide use was not associated with an increased risk for MI: the pooled effect showed an OR of 0.95 [95% CI, 0.82 to 1.09] with low heterogeneity among the studies ($P = 0.6$, $I^2 = 0\%$). A small but significant increased risk was observed in the subgroup analysis of observational studies (OR = 1.31 [95% CI, 1.14 to 1.52]) with high heterogeneity among the studies ($P < 0.001$, $I^2 = 91\%$).

Publication bias. Visual inspection of the funnel plots suggested some asymmetry in favor of macrolides and risk of MI; however, Egger's regression test did not reach significance for publication bias in any of the analyses (MI analysis, $P = 0.06$; arrhythmia, $P = 0.25$; cardiovascular mortality, $P = 0.33$) (see Fig. S2 to S4 in the supplemental material).

TABLE 1 Treatment ranked by probability of highest risk of MI

Medication	P score[a]
Erythromycin	0.94
Clarithromycin	0.77
Azithromycin	0.31
Nonmacrolide	0.24
Roxithromycin	0.23

[a]The P score is derived from network meta-analysis and represents the mean extent of certainty that a given treatment has greater risk of MI among the included treatments, measured on a scale from 0 (best) to 1 (worst).

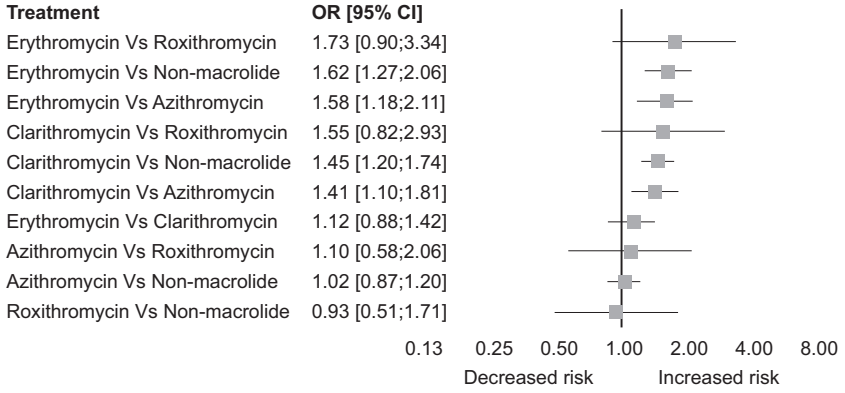

FIG 5 Comparative odds ratio for MI in different macrolides. The forest plot demonstrates point estimates of risk ratios surrounded by 95% CI calculated by a random-effects model.

DISCUSSION

Our meta-analysis found that macrolide use was not associated with the risk of arrhythmia or cardiovascular mortality. In the primary analysis, macrolide use was associated with a small but statistically significant 15% increase in risk for MI (OR = 1.15 [95% CI, 1.01 to 1.30]). In network meta-analysis, erythromycin and clarithromycin ranked most likely to have the highest risk for MI among the treatments included and were associated with a significantly higher risk for MI than azithromycin and nonmacrolide treatment.

The absence of an association between macrolide antibiotics and arrhythmia or cardiovascular death contrasts with earlier reports that raised alarm regarding the cardiovascular safety of macrolides (5, 20). The mechanism suggested by studies reporting increased risk of arrhythmia or cardiovascular death is prolongation of the QT interval and possible increased risk for TdP due to macrolide interference with the delayed rectifier potassium current (I_{Kr}), accumulation of potassium ions in cardiac myocytes, and delayed cardiac repolarization (2, 44). However, even though several macrolides have been documented to prolong QT intervals, our results suggest that their use is not associated with significant clinically related outcomes such as arrhythmia or cardiac mortality. While our results provide reassurance regarding the overall safety of macrolides, we were not able to evaluate whether the risk for arrhythmia may be greater in subpopulations with more advanced age and comorbidity, as some studies have suggested.

Our analysis did find a small but significant association between macrolides and MI, and this risk was more pronounced with clarithromycin and erythromycin use than with other macrolides. This finding is compatible with the recent FDA communication regarding long-term cardiovascular risks with clarithromycin (7). While the association that we detected regarding the risk of MI contrasts with the aforementioned absence of increased cardiovascular death, it should be noted that almost all studies measured and reported only short-term mortality (up to 30 days after the first day of treatment with macrolide), while studies reporting risk for MI provided much longer follow-up.

As various macrolide agents differ from each other in terms of their pharmacokinetic characteristics, drug-drug interactions, and immunomodulatory effects (45, 46), differences in the safety profiles of the different macrolides can be expected. The differences in the risk for MI between macrolides may be explained by the differences in pharmacokinetic characteristics and immunomodulatory effects of the macrolide antibiotics (47). For instance, clarithromycin is a potent inhibitor of cytochrome P450 3A4 and therefore has the potential for many clinically important drug-drug interactions, whereas azithromycin has a lower potential for drug-drug interactions (48). Additionally, treatment with clarithromycin is usually of longer duration than that with azithromycin. However, it should also be noted that the antibiotic indication was not specified

in some of the studies, and it is therefore not possible to rule out indication bias for clarithromycin users. In addition, residual confounding from other unmeasured variables may explain the greater risk observed for clarithromycin and erythromycin.

Importantly, the mechanism behind the link between macrolides and MI is unclear. Studies reporting this association have suggested that macrolides might induce MI via activation of inflammatory macrophages (30). Such an activation could lead to accumulation of lipids and to more-vulnerable plaques in coronary arteries, a continuous process that may leave the plaques permanently weakened. However, this explanation is at odds with anti-inflammatory effects documented in the treatment of respiratory diseases (49). In addition, our subanalyses found that this association was evident only in observational studies (OR = 1.31 [95% CI, 1.14 to 1.52]), and no evidence of increased risk of MI was observed in RCTs. This may reflect the ability of long-term studies in "real-world" settings to detect adverse effects not reported in randomized studies; however, it may also suggest that the association may be the result of residual confounding, often inherent to observational study design. In RCTs, the randomization (if performed correctly) provides assurance that unmeasured confounders are equally distributed between the intervention group and the control group. However, in observational studies, differences in the prevalence of potentially confounding factors between study groups are often present and sometimes difficult to account for. In addition, differences in potential confounders may persist even following rigorous attempts to control for all measured potential confounders, as residual confounding may remain due to unmeasured, or incompletely measured, variables. In addition, the difference between the RCTs and the observational studies may be the result of true differences in effects among the populations included in these studies. The RCTs assessed cardiovascular outcomes among participants with cardiovascular disease, while the observational studies assessed these outcomes in the general population. It is possible that macrolides are a less meaningful risk factor for cardiovascular outcomes in participants who already suffer from cardiovascular disease. Finally, it should also be noted that our analysis of MI risk may be an underestimate of macrolide-associated cardiovascular risk. Our assessment of the studies suggested the presence of publication bias, whereby smaller studies reporting on MI were more likely to be published when they favored macrolides; however, this was not statistically significant ($P = 0.06$).

Our study has several strengths. First, this review and analysis updates the current knowledge regarding macrolide cardiovascular safety according to recently published data. Second, the large number of participants with worldwide coverage using raw data improves the generalizability of the study. Third, we performed a systematic assessment of study quality, subgroup analyses, and evaluation of publication bias. Additionally, to our knowledge, we are the first to conduct an indirect comparison using a network meta-analysis to assess differences between macrolides regarding the risk of MI.

Our analysis also has a number of important limitations. First, the potential of confounding by indication is a possible limitation of the observational studies included in our analysis. We performed subgroup analyses by study design to evaluate the potential impact of study design and excluded articles involving populations with HIV or sepsis and intensive care unit (ICU) patients to reduce heterogeneity and confounding arising from significant differences in disease severity. Second, we detected considerable heterogeneity among the trials included in the analyses. This heterogeneity can be attributed to different indications of antibiotics, coexisting conditions, and participants' age. We used random-effects models in our computations in order to account for the pooling of effect sizes arising from different populations. Third, we had no information regarding important lifestyle factors that influence patients' cardiovascular risk, such as concomitant medications, comorbid conditions, compliance, and antibiotics regimens in many of the studies, and hence we could not rule out the possibility for residual confounding. Furthermore, the diagnosis of arrhythmia is likely not well documented in the medical and administrative databases used in many of the observational studies, and therefore we believe there may be room for additional

prospective studies. Lastly, roxithromycin is not marketed in the United States and only a small number of studies examining roxithromycin safety have been published. The paucity of studies examining roxithromycin use did not allow for conclusive results regarding roxithromycin cardiac risk, and further studies are needed to evaluate the cardiac safety of roxithromycin.

While our study supports the relative short-term cardiovascular safety of macrolides in the general population, we could not rule out a potential risk for specific patient subgroups such as those using interacting drugs or those with preexisting cardiovascular morbidity, since we did not address this population in this study.

Conclusions. Our findings indicate that macrolide antibiotics are likely not associated with a significant risk for arrhythmia and cardiovascular mortality. However, we identified a small but significant association between macrolide use and risk of MI, which was more pronounced with clarithromycin and erythromycin. While this link may be the result of residual confounding, it warrants further investigation, especially with regard to the long-term cardiovascular safety of erythromycin and clarithromycin. Due to the widespread use of macrolides, the findings that we describe in this paper are relevant to practicing health care providers, as well as to clinical researchers.

MATERIALS AND METHODS

Data source and searches. This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-analysis framework guidelines (PRISMA 2009) (50). The systematic review was performed by searching all publications indexed in Medline, Embase, The Cochrane Library, and The Clinical Trials Registry (clinicaltrials.gov) up to February 2018, reporting the outcomes of randomized controlled trials (RCTs), cohort studies, and case-control studies that investigated the association between the macrolide treatment and the risk of cardiovascular events and cardiovascular mortality. No language or date restrictions were applied in the search. Searches were performed using medical subject headings (MeSH) terms and free keywords, including erythromycin, clarithromycin, azithromycin, roxithromycin, macrolide, cardiovascular, cardiac, heart, arrest, death, mortality, tachycardia, ventricular, tachyarrhythmia, arrhythmia, torsades de pointes, myocardial infarction, stroke. A manual search of reference lists of review articles and original studies was performed to identify additional reports. The protocol was registered in the PROSPERO registry (registration number CRD42017080652).

Data extraction and quality assessment. The data were extracted by two independent reviewers (E.G. and R.M.). Disagreements were resolved through consensus or referral to a third reviewer (I.M.) when necessary. Data were extracted for the following characteristics: study details (identifier, study design, geographical location, publication year, duration of follow-up), participants' details (number of participants, study population, age, and gender), intervention characteristics (drug name, dosage regimen), comparator intervention characteristics, primary outcomes, and covariate adjustments.

The quality of the observational studies was assessed using the Newcastle-Ottawa quality assessment Scale (NOS) scoring (51). We considered studies with a NOS score of seven and more to be high-quality studies. We used the Cochrane tool for assessing risk of bias for randomized control trials (Review Manager [RevMan], version 5.3., The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; Copenhagen, Denmark) (52).

Selection criteria. Published studies were considered eligible if they reported on the risk of cardiovascular events in macrolide users versus nonmacrolide users. Cardiovascular events of interest included arrhythmia, 30-day cardiovascular mortality, and MI. We included observational studies and RCTs. When the results of a particular study were reported in more than one publication, the most informative and recent publication was included in the meta-analysis.

Exclusion criteria. Case reports, case series, pharmacokinetic studies in healthy adults, reviews, expert opinion, editorials, letters to the editor, and commentaries were excluded.

Articles were excluded from the analysis if they had insufficient published data for determining an estimate of risk ratio (RR) or odds ratio (OR) and confidence interval (CI). We excluded articles involving populations with HIV or sepsis and ICU patients, to reduce the potential for confounding by indication.

Outcomes. Primary outcomes were (i) short-term arrhythmia (up to 30 days from last use of macrolides), (ii) short-term cardiovascular mortality (up to 30 days from the last use of macrolides), and (iii) myocardial infarction following macrolide use (anytime during follow-up).

Statistical analysis. Raw data from individual studies were extracted, and the pooled ORs and 95% confidence intervals (CI) were calculated for each of the dichotomous outcomes. The heterogeneity of the data was quantified by the Q statistic in combination with the I^2 statistic. High heterogeneity was considered significant when P was <0.1 for the Q statistic or when the I^2 was $>50\%$. For substantial and considerable heterogeneity, we used DerSimonian and Laird random-effects models. This method provides a summary measure of effects observed in the studies while accounting for between-study variations related to specific study characteristics. Study weights calculated using this method are based on a combination of the variance of the study estimate (which is a function of study size and number of events) and the heterogeneity in the estimates between studies. Publication bias was estimated visually by funnel plots and with Egger's regression test to measure funnel plot asymmetry. These

analyses were conducted using CMA (comprehensive meta-analysis) software version 3, and graphs were generated using Review Manager (RevMan), version 5.3.

In addition, for cardiovascular outcomes found to be associated with cardiovascular risk, we performed a network meta-analysis to pool direct and indirect comparisons between specific macrolide agents to provide an estimate of their relative cardiovascular risk. Additionally, the risk of macrolides with the various agents was ranked using P scores derived from network point estimates and standard errors. The P score of a treatment in this analysis can be interpreted as the mean extent of certainty that the treatment has greater risk of MI among the included treatments, measured on a scale from 1 (worst) to 0 (best) (53). These analyses were performed using the package "netmeta" within the R environment (54).

Lastly, we performed a subgroup analysis restricting the analysis of the risk of MI with macrolides to RCTs and observational studies, separately.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00438-18.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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