JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 20, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.09.029

The Role of Macrolide Antibiotics in Increasing Cardiovascular Risk

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ABSTRACT

BACKGROUND Large cohort studies provide conflicting evidence regarding the potential for oral macrolide antibiotics to increase the risk of serious cardiac events.

OBJECTIVES This study performed a meta-analysis to examine the link between macrolides and risk of sudden cardiac death (SCD) or ventricular tachyarrhythmias (VTA), cardiovascular death, and death from any cause.

METHODS We performed a search of published reports by using MEDLINE (January 1, 1966, to April 30, 2015) and EMBASE (January 1, 1980, to April 30, 2015) with no restrictions. Studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) for the associations of interest were included.

RESULTS Thirty-three studies involving 20,779,963 participants were identified. Patients taking macrolides, compared with those who took no macrolides, experienced an increased risk of developing SCD or VTA (RR: 2.42; 95% CI: 1.61 to 3.63), SCD (RR: 2.52; 95% CI: 1.91 to 3.31), and cardiovascular death (RR: 1.31; 95% CI: 1.06 to 1.62). No association was found between macrolides use and all-cause death or any cardiovascular events. The RRs associated with SCD or VTA were 3.40 for azithromycin, 2.16 for clarithromycin, and 3.61 for erythromycin, respectively. RRs for cardiovascular death were 1.54 for azithromycin and 1.48 for clarithromycin. No association was noted between roxithromycin and adverse cardiac outcomes. Treatment with macrolides is associated with an absolute risk increase of 118.1 additional SCDs or VTA, and 38.2 additional cardiovascular deaths per 1 million treatment courses.

CONCLUSIONS Administration of macrolide antibiotics is associated with increased risk for SCD or VTA and cardiovascular death but not increased all-cause mortality. (J Am Coll Cardiol 2015;66:2173–84)

Macrolides are one of the most widely used antibiotic groups and have an expanding role in treating a broad range of common bacterial infections, including upper and lower respiratory infections and certain sexually transmitted diseases. Although considered generally free of adverse effects, including cardiovascular (CV) toxicity, several of these agents were recently reported to have arrhythmia-related cardiac effects, including QT interval prolongation, torsades de pointes, ventricular tachycardia, and sudden cardiac death (SCD) (1).

Although numerous case reports support this notion, evidence from large cohort studies to assess a potential increase in serious cardiac events is conflicting (2). Two cohort studies of Medicaid patients in Tennessee reported increased risk of SCD and CV death associated with erythromycin and azithromycin,

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Manuscript received February 9, 2015; revised manuscript received August 24, 2015, accepted September 2, 2015.

ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CI = confidence interval

CV = cardiovascular

OR = odds ratio

RCT = randomized controlled trial

RR = relative risk

SCD = sudden cardiac death

VTA = ventricular tachyarrhythmias

respectively (3,4). However, other studies failed to detect a significant relationship between macrolides and CV risk (5,6). These inconsistencies among studies could be partly explained by different types of macrolide antibiotics, study designs, population characteristics, and different baseline levels of CV risk and/or disease outcomes. Furthermore, cardiovascular risk may be underestimated due to lack of distinction between former and current macrolide use.

Given this background, the cardiac safety profiles of individual macrolides need to be better elucidated to help guide clinical treatment decisions. Therefore, we conducted a meta-analysis to examine the link between macrolides and CV risk, including SCD or ventricular tachyarrhythmias (VTA), cardiovascular death, death from any cause, myocardial infarction (MI), stroke, and any cardiovascular events.

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METHODS

We searched MEDLINE (source, PubMed; January 1, 1966, to April 30, 2015) and EMBASE (January 1, 1980, to April 30, 2015) using the following text and key words in combination, both as MeSH terms and text words: macrolides, azithromycin, erythromycin, clarithromycin, roxithromycin, cardiac, cardiovascular, death, mortality, ventricular tachycardia, ventricular arrhythmia, torsades de pointes, sudden cardiac death, and cardiac arrest. We searched articles published in any language and scrutinized references from these studies to identify other relevant studies.

To minimize differences, studies were required: 1) to contain the minimum information necessary to estimate the relative risk (RR) associated with macrolides and a corresponding measure of uncertainty (i.e., 95% confidence interval [CI], SE, variance, or p value); 2) to be cohort studies, case-control studies, or randomized controlled trials (RCTs) published as original articles (case reports and prevalence studies were excluded); and 3) to be independent. In case of multiple publications/reports on the same population or subpopulation, we considered the estimates from the most recent or informative reports.

Three authors (Y-J.C., X-M.C., and X-Y.N.) independently extracted the data, which included the first author's name, publication year, geographical location, sex, mean age, study size, study design, sampling framework, study population, number of CV events, categories of macrolides, covariates adjusted for in the multivariable analysis, and relative risks and associated measures of variance for all categories of macrolides. Primary authors were contacted if the study did not report data amenable to the creation of 2×2 tables. We used the Newcastle-Ottawa quality assessment scale (7) to evaluate the quality of cohort and case-control studies and modified Jadad score (8) to evaluate the quality of RCTs. We developed the evaluation criteria with score ranges from 0 to 9 points for cohort and case-control studies and 0 to 7 points for RCTs, with a higher score indicating higher study quality.

The primary study endpoint was SCD or VTA, as defined by International Classification of Diseases-10th revision codes as ventricular tachycardia, torsades de pointes, ventricular fibrillation, ventricular flutter, sudden cardiac arrest, and SCD. The secondary endpoint was CV death, because we hypothesized that the incidence of cardiac death should be increased if macrolides were pro-arrhythmic. Additionally, we included an analysis of death from any cause to examine whether the risk for cardiac death would be offset by the survival benefit of anti-infection by macrolides. We also analyzed MI and any CV events that might precipitate SCD or VTA.

STATISTICAL ANALYSIS. RR was used as a measurement of the association between macrolides and cardiovascular risk. For case-control studies, the odds ratio (OR) was used as estimates of the RR because CV events are sufficiently rare (9).

When RR were available, we used the most comprehensively adjusted risk estimates reported in the original manuscript. When the actual RR was not available, we calculated RRs and 95% CIs by using Stata version 11.0 software (used for all analyses; StataCorp LP, College Station, Texas). For studies that had endpoints with zero events in a treatment arm, RRs and 95% CI values were calculated using a 0.5 cell correction (10). We used random rather than fixed effects models to estimate pooled RRs to account for heterogeneity, however small, of the risk estimates and, therefore, to be more conservative. Pooled RRs were expressed with 95% CIs. We calculated the I^2 (95% CI) statistic to assess heterogeneity across studies, applying the following interpretation for I^2 <50%, low heterogeneity; 50% to 75%, moderate heterogeneity; >75%, high heterogeneity (11,12). Subgroup analyses and metaregression models were carried out to investigate potential sources of between-study heterogeneity. We calculated absolute difference in risk per 1 million treatment courses with macrolides as: $[(RR - 1) \times I_0]$, where RR indicates pooled RRs and I_0 was the cumulative incidence