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The Role of Macrolide Antibiotics in Increasing Cardiovascular Risk

Yun-Jiu Cheng, MD,* Xiao-Ying Nie, MS,† Xu-Miao Chen, MD,* Xiao-Xiong Lin, MD,* Kai Tang, MD, PhD,* Wu-Tao Zeng, MD, PhD,* Wei-Yi Mei, MD, PhD,* Li-Juan Liu, MD, PhD,* Ming Long, MD, PhD,* Feng-Juan Yao, MD, PhD,* Jun Liu, MD, PhD,* Xin-Xue Liao, MD, PhD,* Zhi-Min Du, MD,* Yu-Gang Dong, MD, PhD,* Hong Ma, MD,* Hai-Peng Xiao, MD, PhD,‡ Su-Hua Wu, MD, PhD*

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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From the *Department of Cardiology, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; †Department of Outpatients, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; and the ‡Department of Endocrinology, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China. This study was supported by National Natural Science Foundation of China grant 81370285, Guangdong Province Science and Technology Program grant 2012B031800091, and Guangzhou City Science and Technology Program grant 201508020057 to Dr. Wu; and National Natural Science Foundation of China grant 81472500 and grant 81272932 to Dr. Xiao. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Cheng, Chen, and Wu and Ms. Nie contributed equally to this work.

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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

of events among patients not taking macrolides. On the basis of population-based cohort studies, I_0 was estimated by weighting the sample size of each study (4). Small study bias, consistent with publication bias, was assessed with funnel plot, by using Begg's adjusted rank correlation test and Egger's regression asymmetry test. Statistical tests were 2-sided and used a significance level of $p < 0.05$.

RESULTS

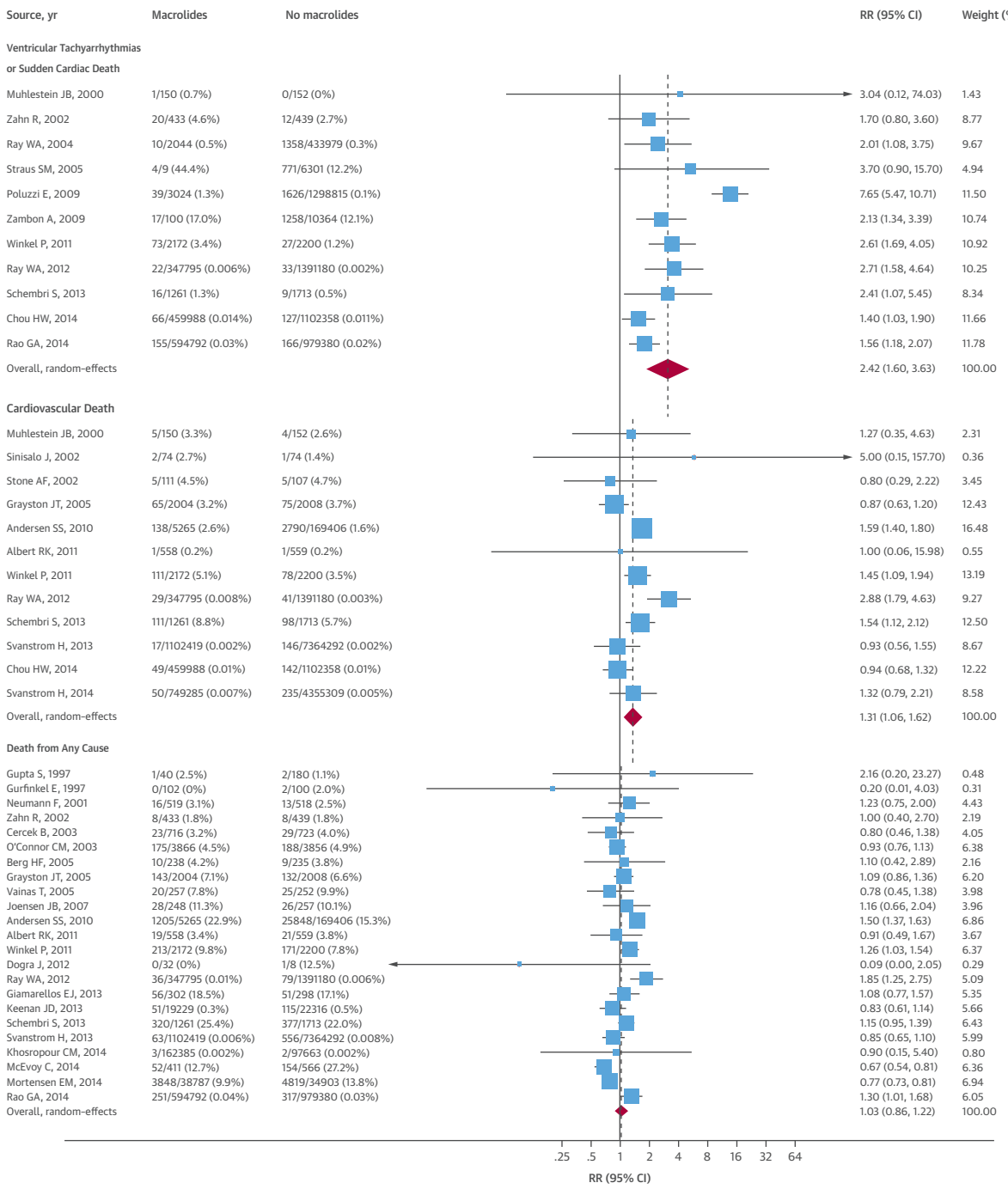
We initially retrieved 1,559 unique citations, eliminating 831 because they provided no information on macrolide antibiotics. Of 728 abstracts remaining, 469 were excluded (401 in vitro, functional, or animal studies; 48 reviews, letters, or editorials; and 20 duplicate reports of the same study population), leaving 259 articles for detailed evaluation. Subsequently, 201 articles were excluded with no relevant outcomes and another 25 articles were excluded because they did not provide enough data to estimate RR (20 were case reports, 2 compared CV risk among different macrolides; 1 compared CV risk between macrolides and fluoroquinolones; 1 assessed sex difference in CV risk associated with macrolides; and 1 reported only the prevalence of arrhythmia in macrolides users), leaving 33 studies for final inclusion in the meta-analysis (Online Figure 1).

A total of 20,779,963 individuals (59.9% women) were included in 33 eligible studies. Sixteen studies were based in Europe, 9 in North America, 2 in East Asia, 1 in South America, 1 in Asia, and 1 in Africa, and 3 were multinational. There were 11 population-based cohorts, 3 case-control studies, and 19 RCTs; 16 studies recruited participants with bacterial infection, and 17 studies were designed to examine whether macrolides could prevent cardiac events in patients with coronary heart disease (CHD) or peripheral artery disease. Study size ranged from 40 to 5,140,594 subjects, with the 6 largest cohort studies each involving more than 1 million participants. Nineteen studies evaluated the endpoints of cardiovascular risk or all-cause death for azithromycin, 12 clarithromycin, 8 roxithromycin, and 4 erythromycin. Duration of treatment across the studies ranged from 3 days to 1 year. Data for daily macrolide doses were reported in 19 RCTs but in none of the observational studies (Online Table 1). In studies reporting baseline patient characteristics, mean age, proportion of women, comorbid condition, and medication use were not systematically different between patients taking and not taking macrolides (Online Table 2). Of the 14 observational studies, the scores of the Newcastle-Ottawa quality assessment scale quality assessment ranged from 5 to 9, and 11 studies had scores of 7 or higher. RCT methodological quality was generally good, with modified Jadad score of 4 or higher in 18 studies (Online Tables 3 to 5).

ASSOCIATION WITH SCD OR VTA. Eleven studies (3 RCTs, 5 cohort studies, and 3 case-control studies) with data for 6,639,411 individuals and at least 5,810 events reported risk estimates for SCD or VTA. Overall, patients taking macrolides experienced a significantly increased risk for developing SCD or VTA compared to those not on macrolide therapy (RR: 2.42; 95% CI: 1.60 to 3.63; $p < 0.001$) (**Figure 1**, **Central Illustration**). There was evidence of high heterogeneity of RRs across these studies (I^2: 85.42%; 95% CI: 75.65% to 91.27%; $p < 0.001$]) (**Figure 1**). Risk estimates changed little after analyses with fixed effects models or inclusion of studies with more than 10,000 participants, yet substantial heterogeneity remained. When the analysis was confined to those studies with propensity-matched cohorts, the overall combined RR did not materially change, but no evidence of significant heterogeneity was observed among the remaining studies (**Table 1**). Of note, in a case-control study by Poluzzi et al., the adjusted risk estimate for macrolide antibiotics (RR: 7.65; 95% CI: 5.47 to 10.71) was much higher than the pooled risk estimate. After excluding this single study, there was no evidence of heterogeneity (I^2: 16.36%; 95% CI: 0% to 57.57%; $p = 0.29$) and the pooled risk estimate still reached statistical significance (RR: 1.89; 95% CI: 1.58 to 2.26) (**Table 1**) (13). Neither funnel plots nor Egger and Begg test results showed evidence of publication bias (Egger test: $p = 0.44$; Begg test: $p = 0.11$) (Online Figure 2).

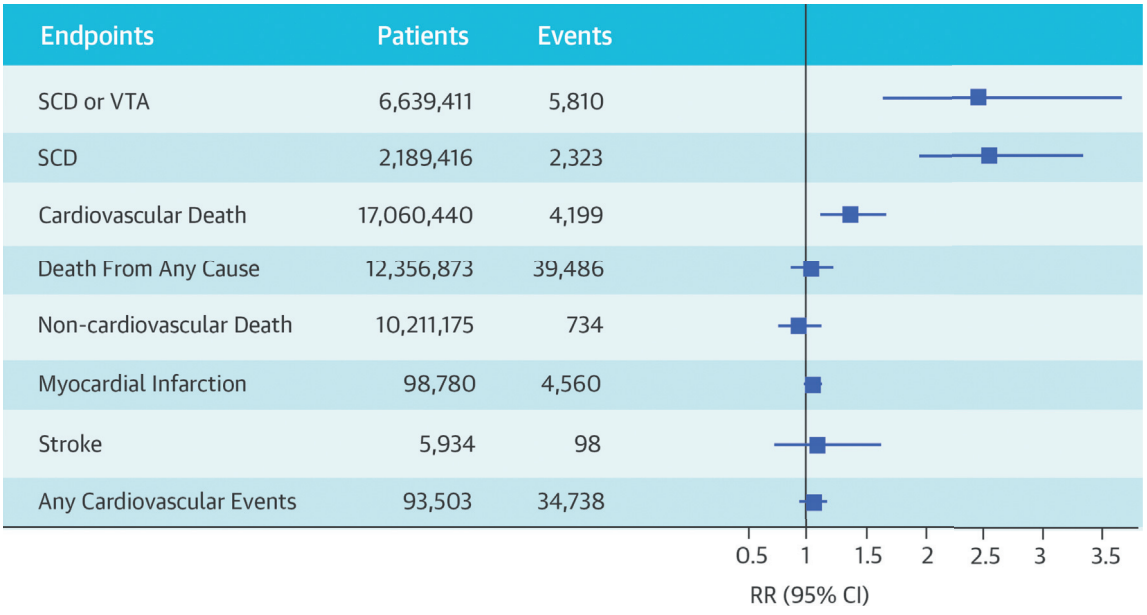
To further explore study heterogeneity, we performed stratified analyses across various key study characteristics and clinical factors; increased risk of SCD or VTA associated with macrolides was consistently observed in most of these analyses (**Table 2**). Number of events, geographical area, baseline disease, average age, publication year, or whether risk profiles were adjusted were not significant sources of heterogeneity. Risk estimates were systematically higher in studies with a higher proportion of females than males compared with studies where <50% of the study population were female, but the difference was not statistically significant. Of note, subgroup analysis showed risk of SCD or VTA was still significantly increased in RCTs for CHD (RR: 2.35; 95% CI: 1.61 to 3.42), with no evidence of significant heterogeneity (I^2: 0%; 95% CI: 0% to 89.60%; $p = 0.62$). Time of macrolide use appeared to be associated with the results; the RR for current use was 2.48 versus 1.52 for

FIGURE 1 Relative Risks of Mortality or VTA



Relative risks (RR) of sudden cardiac death (SCD) or ventricular tachyarrhythmia (VTA), cardiovascular death and death from any cause associated with macrolides were compared to no macrolide use. The **size of each square** is proportional to the study's weight (inverse of variance). **Dotted line** in the forest plot represents random effects summary risk estimate. CI = confidence interval.

CENTRAL ILLUSTRATION **Macrolides Antibiotics and Cardiovascular Risk**



Cheng, Y.-J. et al. J Am Coll Cardiol. 2015; 66(20):2173–84.

Relative risks (RR) of mortality and cardiovascular events. CI = confidence interval; SCD = sudden cardiac death; VTA = ventricular tachyarrhythmia.

former use ($p = 0.03$). A further stratified analysis showed that increased risk of SCD or VTA was observed in users of azithromycin, clarithromycin, and erythromycin, but not roxithromycin (**Table 2**).

In a sensitivity analysis of patients currently taking penicillin or amoxicillin versus those who took no antibiotics, there was no association with increased SCD risk (RR: 0.99; 95% CI: 0.62 to 1.58; $p = 0.96$). However, relative to penicillin or amoxicillin, macrolides were associated with an increased risk of SCD or VTA (RR: 1.69; 95% CI: 1.27 to 2.25; $p < 0.001$) (Online Figure 3).

Five studies used SCD as the endpoint of interest, involving 2,189,416 patients and 2,323 events. Definitions of SCD differed slightly: 3 studies used World Health Organization criteria but 2 did not follow conventional definitions. Cases were determined by multiple sources and adjudicated by a blinded investigator in 4 studies and by death certificates that were not validated in 1 study (Online Table 6). Treatment with macrolides was significantly associated with increased risk of SCD (RR: 2.51; 95% CI: 1.91 to 3.31; $p < 0.001$]), with no evidence of significant between-study heterogeneity ($I^2 = 0\%$; 95% CI: 0% to 79.2%; $p = 0.93$) or publication bias (Egger test, $p = 0.81$; Begg test, $p = 0.56$) (Online Figure 4).

Patients taking no macrolides experienced an average of 79.8 (95% CI: 70.7 to 89.5) cases of SCD or VTAs and 24.1 (95% CI: 16.6 to 32.9) cases of SCDs per 1 million treatment courses. As compared with no macrolide use, current macrolide treatment was associated with an estimated 118.1 (95% CI: 104.6 to 132.4) additional SCD or VTAs and 36.6 (95% CI: 25.2 to 50.0) additional SCDs per 1 million treatment courses.

ASSOCIATION WITH CV DEATH. Twelve studies (6 RCTs and 6 cohort studies) were included for the outcome of CV death, involving 17,060,440 participants and 4,199 events. Overall, macrolide use was associated with an increased risk of CV death (RR: 1.31; 95% CI: 1.06 to 1.62; $p = 0.01$]), with moderate between-study heterogeneity (I^2: 64.8%; 95% CI: 34.84% to 80.99%; $p = 0.001$]) (**Figure 1**, **Central Illustration**). Risk estimates did not materially change after analyses with fixed-effect models, inclusion of the studies with populations >10,000 and with propensity-matched cohort, or exclusion of the largest study and 1 outlier study, with moderate-to-high heterogeneity across studies (**Table 1**) (Egger test, $p = 0.94$; Begg test, $p = 0.10$) (Online Figure 2).

In stratified analyses, there was no significant heterogeneity by study design, number of events,

TABLE 1 Sensitivity and Heterogeneity Analysis of Pooled RRs of Mortality or VTA*

	SCD or VTA				Cardiovascular Death				Death From Any Cause			
	n Studies	RR (95% CI)	I^2 (95% CI)	p Value†§	n Studies	RR (95% CI)	I^2 (95% CI)	p Value§	N Studies	RR (95% CI)	I^2 (95% CI)	p Value§
Statistical model												
Random effects	11	2.42 (1.60–3.63)	85.42 (75.65–91.27)	<0.001	12	1.31 (1.06–1.62)	64.8 (34.84–80.99)	0.001	23	1.03 (0.86–1.22)	89.91 (86.19–92.63)	<0.001
Fixed effects	11	2.33 (2.03–2.68)			12	1.42 (1.30–1.55)			23	0.95 (0.88–1.03)		
Analysis of all studies with												
Propensity–matched cohort	4	1.74 (1.31–2.29)	43.93 (0.00–81.25)	0.15	5	1.46 (1.21–1.76)	76.29 (42.15–90.28)	0.002	5	1.09 (0.82–1.47)	91.45 (83.03–95.69)	<0.001
Large cohort‡	6	2.41 (1.35–4.31)	92.56 (86.55–95.89)	<0.001	5	1.61 (1.13–2.31)	77.08 (44.45–90.54)	0.002	7	1.10 (0.78–1.56)	96.78 (95.09–97.89)	<0.001
Analysis of all studies except												
Largest studies§	6	2.32 (1.77–3.03)	0.00 (0.00–74.62)	0.91	6	1.45 (1.31–1.62)	55.98 (0.00–81.08)	0.03	20	0.99 (0.82–1.19)	90.49 (86.75–93.17)	<0.001
One outlier study‖	10	1.89 (1.58–2.26)	16.36 (0.00–57.57)	0.29	11	1.50 (1.23–1.83)	49.49 (0.00–74.73)	0.03	22	1.02 (0.86–1.21)	90.35 (86.74–92.97)	<0.001

*Compared with no macrolide use. †p value for I^2. ‡Large cohort studies with sample size >10,000. §Studies with populations >1 million. ‖Studies with largest RR by Poluzzi et al. (13) for SCD or VTA; smallest RR by Grayston et al. (30) for cardiovascular death; largest RR by Gupta et al. (31) for death from any cause.

CI = confidence interval; RR = relative risk; SCD = sudden cardiac death; VTA = ventricular tachyarrhythmia.

geographical area, baseline disease, mean age, publication year, or proportion of females. However, stronger associations between macrolides and CV death were found in studies adjusted for cardiovascular risk factors. Additionally, we found evidence for heterogeneity by time of macrolide use, with the risk of CV death stronger for current than for former macrolide use (p = 0.04) (Table 2). Although macrolide type was not a significant source of heterogeneity, azithromycin and clarithromycin but not roxithromycin were associated with increased risk of CV death (Table 2).

In the sensitivity analysis, current use of penicillin or amoxicillin was not associated with an increased risk of CV death compared with no current antibiotic use (RR: 1.03; 95% CI: 0.67 to 1.58; p = 0.89). However, compared with penicillin or amoxicillin, the relative risk associated with current use of macrolides was 1.24 (95% CI: 1.001 to 1.55; p = 0.049); and, compared with no use of macrolides, the relative risk associated with former use of macrolides was 0.94 (95% CI: 0.81 to 1.10; p = 0.46) (Online Figure 5). The average event rate of cardiovascular death in patients not taking macrolides was 51.6 (95% CI: 47.5 to 55.8) per 1 million treatment courses. Using the summary estimates obtained from all studies combined, we estimated that current use of macrolides was associated with an absolute risk increase of 38.2 (95% CI: 35.2 to 41.3) cardiac deaths per 1 million treatment courses.

ASSOCIATION WITH DEATH FROM ANY CAUSE. The endpoint of death from any cause occurred in 39,486 patients among 12,356,873 participants from 23 studies (15 RCTs, 8 cohort studies, and no case-control studies). Overall, use of macrolides was not significantly associated with all-cause death (RR: 1.03; 95% CI: 0.86 to 1.22; p = 0.77 (Figure 1, Central Illustration). There was evidence of considerable heterogeneity of RRs across these studies (Table 1, Figure 1). The findings from the sensitivity analyses showed that risk estimates changed little based on different inclusion and exclusion criteria, but considerable heterogeneity was still present (Table 2). These measures of heterogeneity were likely driven by the extremely large overall number of participants in this analysis (>6 million). Begg test (p = 0.09) and the Egger test (p = 0.26) results provided no statistical evidence for publication bias (Online Figure 2).

In the stratified analyses, little heterogeneity was explained by study design, number of events, type of macrolides, geographical area, baseline disease, average age, proportion of females studied, time of macrolide use, publication year, or whether risk profiles were adjusted. Notably, an increased risk of

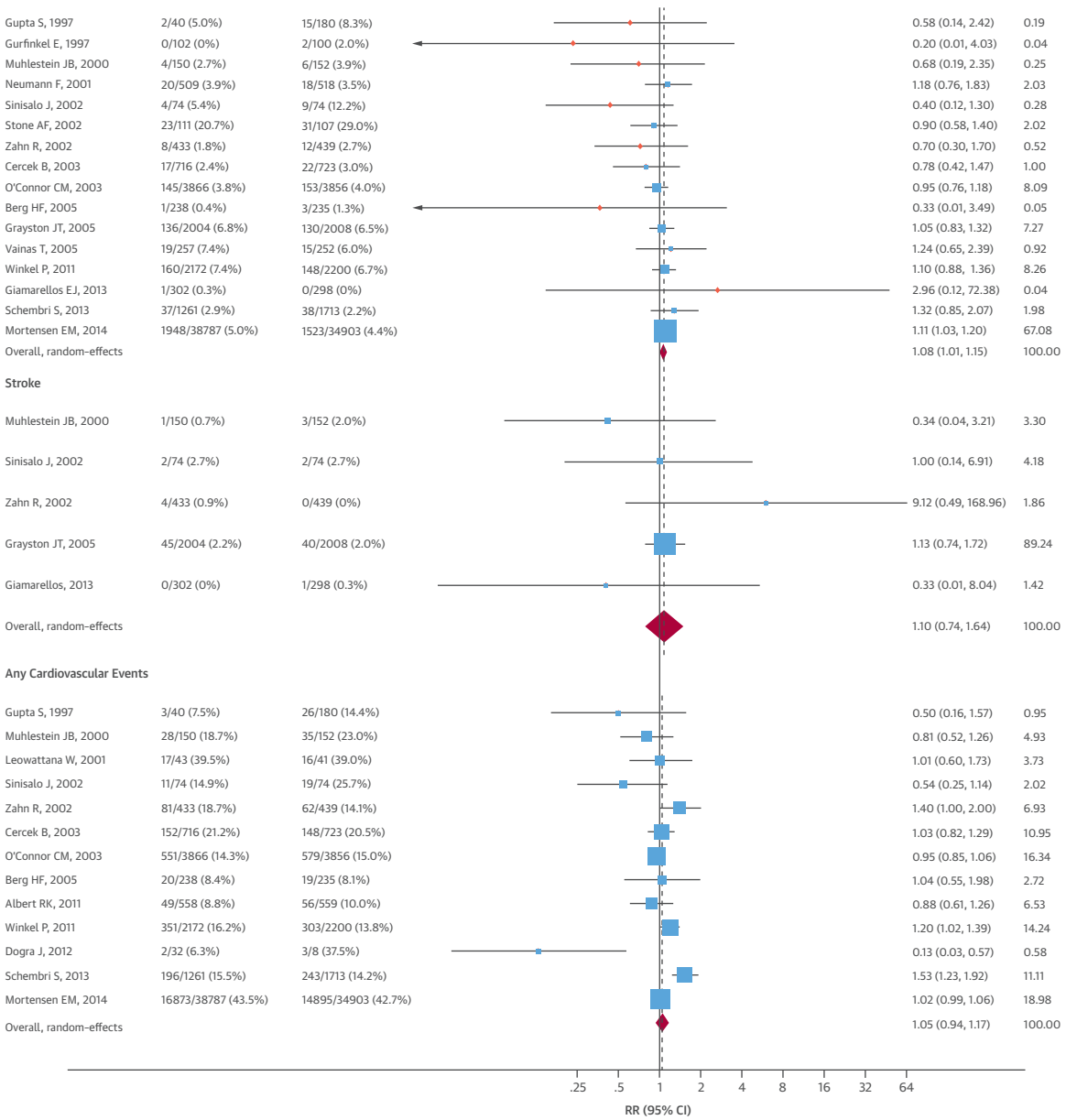
TABLE 2 Stratified Analysis and Heterogeneity Analysis of RRs of Mortality or VTA*

Factors Stratified	SCD or VTA				Cardiovascular Death				Death From Any Cause			
	Events	Patients	RR (95% CI)	p Value†	Events	Patients	RR (95% CI)	p Value†	Events	Patients	RR (95% CI)	p Value†
All studies	5,810	6,639,411	2.42 (1.60–3.63)		4,199	17,060,440	1.31 (1.06–1.62)		39,486	12,356,873	1.03 (0.86–1.22)	
Type of studies												
Case-control	3,715	1,319,375	4.00 (1.44–11.08)	0.02	–	–	–		–	–	–	
Cohort	1,962	5,314,490	1.74 (1.38–2.20)		3,846	17,050,271	1.58 (1.20–2.07)	0.17	37,930	12,292,218	1.07 (0.80–1.45)	0.67
RCT	133	5,546	2.35 (1.61–3.42)		353	10,169	1.12 (0.83–1.52)		1,556	64,655	1.03 (0.94–1.14)	
Events, n												
≧100	5,697	4896288	2.45 (1.45–4.24)	0.86	4,105	15,319,680	1.32 (1.06–1.65)	0.25	39,220	12,090,421	1.06 (0.86–1.30))	0.56
<100	113	1,743,123	2.34 (1.60–3.44)		94	1,740,760	1.71 (0.86–3.39)		266	266,452	0.97 (0.77–1.21)	
Type of macrolide												
Azithromycin	2,204	5,784,391	3.40 (1.68–6.90)	0.84	560	11,380,439	1.54 (1.24–1.90)	0.31	11,125	12,171,177	0.93 (0.80–1.08)	0.02
Clarithromycin	2,665	2,811,858	2.16 (1.70–2.74)		3,540	3,302,883	1.48 (1.32–1.64)		28,260	183,090	1.28 (1.10–1.50)	
Roxithromycin	32	872	1.70 (0.80–3.60)		267	1,869,899	1.04 (0.72–1.51)		101	2,606	1.14 (0.81–1.61)	
Erythromycin	1,843	443,095	3.61 (1.09–11.99)		–	–	–		–	–	–	
Location												
Europe	2,207	25,754	2.31 (1.76–3.03)	0.48	3,787	13,753,688	1.56 (1.39–1.74)	0.48	29,026	8,652,934	1.15 (0.98–1.35)	0.29
North America	1,745	3,749,472	1.85 (1.41–2.44)		221	1,744,406	1.44 (0.61–3.42)		9,876	3,652,991	1.01 (0.78–1.30)	
Asia	193	1,562,346	1.40 (1.03–1.90)		191	1,562,346	0.94 (0.68–1.32)		1	40	0.09 (0.01–2.04)	
Baseline disease												
Infection	5,677	6,643,865	2.48 (1.50–4.12)	0.81	920	16,876,717	1.60 (1.07–2.40)	0.35	10,984	12,159,832	1.04 (0.84–1.28)	0.97
CHD	133	5,546	2.35 (1.61–3.42)		3,279	183,723	1.27 (0.95–1.69)		28,502	197,041	1.02 (0.81–1.27)	
Age												
≧65 yrs	2,175	24,882	2.42 (1.81–3.24)	0.87	3,478	187,364	1.32 (1.04–1.67)	0.32	37,222	262,780	1.07 (0.80–1.43)	0.49
<65 yrs	3,635	6,624,529	2.36 (1.29–4.31)		721	16,873,076	1.83 (0.90–3.72)		2,264	12,094,093	0.99 (0.82–1.18)	
Female proportion												
≧50%	3,306	4,852,157	2.71 (1.26–5.86)	0.46	918	16,875,600	1.73 (1.03–2.93)	0.29	1,967	10,513,269	0.97 (0.77–1.22)	0.45
<50%	2504	1,597,254	1.90 (1.55–2.34)		3,281	184,840	1.27 (0.96–1.67)		37,519	1,843,604	1.06 (0.83–1.34)	
Time periods of macrolides use												
Current‡	5,377	6,643,865	2.48 (1.50–4.12)	0.03	712	14,320,477	1.74 (1.02–2.97)	0.04	11,468	12,165,063	0.98 (0.82–1.16)	0.30
Former§	1,633	493,070	1.52 (0.89–2.58)		3.858	11,201,500	1.12 (0.86–1.45)		28,018	191,810	1.12 (0.92–1.37)	
Adjusted for risk profiles‖												
Yes	5,752	6,645,263	2.50 (1.55–4.04)	0.70	4,038	17,054,791	1.55 (1.25–1.92)	0.04	37,985	12,075,677	1.09 (0.84–1.43)	0.34
No	58	4,148	2.02 (1.17–3.48)		161	5,649	0.88 (0.66–1.19)		1,501	281,196	0.96 (0.81–1.15)	
Publication yr												
≧2010	694	4,882,839	1.91 (1.44–2.54)	0.43	4,037	17,055,760	1.54 (1.24–1.90)	0.06	38,628	12,339,892	1.04 (0.83–1.31)	0.74
<2010	5,116	1,766,572	2.93 (1.44–5.95)		162	4,680	0.89 (0.66–1.20)		858	16,981	0.99 (0.88–1.13)	

*Compared with no macrolide use. †p values test homogeneity between strata. ‡Defined according to days of supply from the day the prescription was filled. §Defined as some use of a study medication that was not current but had occurred within the previous 365 days. ‖Adjusted for age, sex, and cardiovascular risk factors.

CHD = coronary heart disease; RCT = randomized controlled trial; other abbreviations are as in Table 1.

FIGURE 2 Relative Risk of Cardiovascular Events



Relative risks (RR) of myocardial infarction, stroke, and any cardiovascular events associated with macrolides were compared to no macrolide use. The **size of each square** is proportional to the study's weight (inverse of variance). **Dotted line** in the forest plot represents random-effects summary risk estimate. CI = confidence interval.

all-cause death was observed in users of clarithromycin ($p < 0.001$), but not in users of azithromycin and roxithromycin (**Table 2**, Online Figure 6).

We performed further analysis of the endpoint of noncardiovascular death from 4 studies, involving 734 events in 10,211,175 participants. Compared with no macrolide use, macrolide treatment was not associated with an increased risk of noncardiovascular death (RR: 0.94; 95% CI: 0.78 to 1.14; $p = 0.53$), with no evidence of between-study

heterogeneity (I^2: 0%; 95% CI: 0% to 84.69%; p = 0.51) (Online Figure 7).

The average all-cause death rate in patients not taking macrolides was 90.0 (95% CI: 84.2 to 96.1) per 1 million treatment courses. Macrolide treatment was not associated with absolute increased risk of death from any cause: 2.7 (95% CI: −12.6 to 19.8) cases per 1 million treatment courses.

ASSOCIATION WITH MI, STROKE, AND ANY CV EVENTS. For MI, 16 studies were included, reporting 4,560 events among 98,780 participants. The overall RR of MI in patients taking macrolides, compared with those who took no antibiotics, was 1.08 (p = 0.02) (**Central Illustration**) with no significant between-study heterogeneity (p = 0.69) (**Figure 2**). The funnel plot showed evidence of publication bias (Egger, p = 0.34; Begg, p <0.001) (Online Figure 2). When we removed the largest study by Mortensen and colleagues (6), no significant association between macrolides and MI remained (RR: 1.02; 95% CI: 0.91 to 1.14; p = 0.73), but publication bias among the remaining studies was no longer significant (Egger test, p = 0.11; Begg test, p = 0.09). The study by Mortensen et al. (6) demonstrated a significant association between macrolides and MI (RR: 1.11; 95% CI: 1.03 to 1.20). This study was similar in quality and methodology to the remaining studies, except that the participants it enrolled were older patients hospitalized with pneumonia.

Of 5 studies analyzed, there were 98 strokes among 5,934 participants. Evidence synthesis for stroke did not show a statistically significant association with macrolides (p = 0.63), with no significant between-study heterogeneity (p = 0.46) (**Figure 2**).

Thirteen studies involving 93,503 participants were analyzed reporting a total of 34,738 total CV events. Overall, macrolide use was not significantly associated with an increased risk of any CV events (p = 0.42), with moderate heterogeneity between studies (p < 0.001) (**Figure 2**). Similar results were obtained using fixed-effect models (RR: 1.03; 95% CI: 0.996 to 1.06; p = 0.09). There was no statistical evidence of publication bias (Egger test, p = 0.34; Begg test, p = 0.10) (Online Figure 2).

DISCUSSION

The present meta-analysis, involving 20,819,622 individuals from 33 studies, found significantly increased risk of SCD or VTA, cardiovascular death, and MI in users of macrolides. This association with increased CV risk seemed to be present with current use of macrolides and disappeared for former use. In stratified analysis, azithromycin, clarithromycin, and erythromycin were associated with increased risk of SCD or VTA and azithromycin and clarithromycin with increased risk of CV death, but only clarithromycin was associated with increased risk of all-cause mortality. In terms of absolute risk, use of macrolides would account for an estimated 118.1 SCD or VTAs, 36.6 SCDs, and 38.2 cardiac deaths per 1 million courses.

Interpretation of the clinical importance of this finding is delicate. The estimates for additional SCDs and cardiac deaths per 1 million treatment courses are remarkably close, suggesting that most VTA observed in the macrolide groups might not result in fatal outcomes. The absolute risks for SCD and cardiac death are small, so this finding should probably have limited effect on prescribing practice in individual patients. However, given that macrolides are 1 of the more commonly used antibiotic groups in many countries and that millions of patients are prescribed these drugs annually, the total number of excess SCD or VTAs and cardiac deaths may not be negligible.

Results of the study raise the question, why would macrolides be associated with increased risk for cardiac death but not all-cause mortality? Several plausible explanations have been suggested. First, Sligl et al. (14) reported a reduction in any cause death in a subgroup of patients with severe community-acquired pneumonia, indicating an increased risk of CV death might be partly offset by the survival benefit of anti-infection by macrolides. Second, in addition to antimicrobial properties, macrolides have been demonstrated to have immunomodulatory effects in the treatment of diffuse panbronchiolitis, cystic fibrosis, bronchiectasis, and asthma and significantly reduce noncardiovascular death (15). However, among the small number of studies included in our analysis, risk of non-CV death was not significantly decreased in the general population, suggesting these hypotheses need further confirmation.

Another factor may confound the association between macrolides and CV risk. Patients taking macrolides might be sicker and have higher CV risk than patients not taking antibiotics; therefore, the increased risk observed in our study may be related to the acute infection itself. Nevertheless, in the analysis of studies with propensity-matched cohorts that provide more robust control for confounders than adjustment, the results were similar to the main findings. Furthermore, the risk of CV death was similar in patients with no or former macrolide use, indicating that baseline differences between the groups did not likely influence the results significantly. The fact that no significant differences were observed for all-cause death should further lessen concerns about systematic differences in health

status at baseline as an explanation for the observed association with increased CV risk. Additionally, compared with amoxicillin or penicillin, macrolide use was associated with significantly increased risk, indicating that the increased risk was attributable to the prescribed treatment rather than infection effect.

Understanding the mechanisms that underlie the association between macrolides and CV risk will help frame appropriate therapeutic decisions. Our results suggest that association may be largely mediated by an acute toxic mechanism, supported by the higher risk observed in current users of macrolides and that ventricular arrhythmias occurred mainly during short-term therapy. For many drugs with proarrhythmic effects, an elevated serum concentration is a key determinant of increased risk (16), which may be an important reason why increased cardiovascular risk did not persist after macrolide therapy ended.

Blockage of the I_{kr} encoded by human ether-a-go-go-related gene (*HERG*), prolongation of the QT interval, and, thus, increased risk of VTA are thought to be the underlying mechanisms for acute cardiac toxicity with macrolides (17). Therefore, macrolides might increase the risk of severe cardiac arrhythmias in patients with baseline risk factors for QT prolongation, such as hypokalemia, hypomagnesia, and concurrent use of class IA and III antiarrhythmic agents (18). Furthermore, there might be a concomitant, synergistic effect of acute infection on the arrhythmic risk intrinsically associated with macrolide antibiotics (19). Our study indicated that risk of SCD or VTA was increased in patients with bacterial infection, as well as in those with CHD intrinsically burdened by high arrhythmic risk (20). In particular, many basic studies demonstrated that proinflammatory cytokines may promote arrhythmias directly by affecting cardiac electrophysiology (21). Guo et al. (19) previously reported an almost linear increase in HERG block and action potential prolongation by erythromycin over a temperature range of 37°C to 42°C. Clarithromycin and erythromycin also are extensively metabolized by cytochrome P-450 (CYP3A) isozymes, and the serum concentration could be elevated by concomitant use of CYP3A-inhibiting drugs, which may further increase risk of macrolide-associated SCD (3). Of note, our results suggest that macrolide use seems to be associated with a mild increased risk of MI. Macrolides may activate mast cells residing within atherosclerotic lesions, leading to release of vasoactive mediators into the bloodstream, and thus coronary artery vasospasm and platelet activation, resulting in more vulnerable plaques that, over time, might contribute to increased risk of MI or SCD by plaque rupture (22). This hypothesis is inconsistent with the findings in other studies that azithromycin might inhibit activation of monocytes and macrophages and the inflammatory process in vivo, indicating further experimental studies are needed to elucidate the specific pathogenic mechanisms (23,24).

Notably, we observed an increase in risk of SCD or VTA with azithromycin, clarithromycin, and erythromycin but not with roxithromycin. Available mechanistic data comparing individual macrolides suggest that clarithromycin and erythromycin have higher potency of I_{kr} inhibition compared with roxithromycin, and thus higher potential for QT prolongation and proarrhythmic properties (25). Although azithromycin has been considered the safest of the macrolides, as it neither undergoes CYP3A metabolism nor inhibits CYP3A to any clinically meaningful degree, and only shows the weakest blockade of I_{kr} in vitro (26), our results suggest that azithromycin might increase SCD risk similar to clarithromycin and erythromycin. Therefore, the in vitro data about azithromycin's pharmacodynamic property might not truly reflect how it works in vivo. In 2013, the U.S. Food and Drug Administration and pharmaceutical manufacturer issued public safety notifications warning of SCD risk with azithromycin. However, a safety warning of greater CV risk might also apply to erythromycin and, especially, to clarithromycin. Additionally, the absence of an association between roxithromycin and CV risk in our study shows roxithromycin's relative cardiac safety.

STUDY LIMITATIONS. Strengths of this meta-analysis include the strict inclusion criteria, the large number of patients analyzed, the diversity of the study population, and the fact that all subgroup analyses were pre-specified. The absence of important publication bias supports the robustness of the study findings. Still, there were some study limitations. First, a large amount of heterogeneity was observed in the results of the various studies. Although differences in time periods of macrolide use seems to explain this at least partially, heterogeneity still exists in the outcome of any-cause death. However, similar risk estimates were consistently observed in all stratified analyses, indicating heterogeneity might not influence the results significantly. Limited data on macrolide doses in observational studies make it difficult to determine whether differences in doses would be the source of heterogeneity.

Second, because original studies did not report data on electrocardiographic (ECG) monitoring or QT intervals, we could not exclude the possibility of ascertainment bias of VTA, because patients placed on antiarrhythmic agents, with a possible proarrhythmic potential, might be more likely to receive ECG

monitoring, which would bias VTA detection. However, VTA with hemodynamic instability would be easy to degenerate to SCD if untreated. Therefore, episodes of these types of VTA are less likely to be misdiagnosed or undetected. Also, the retrospective, death certificate-based method of surveillance of SCD for 1 study might result in overestimation of SCD incidence (27). However, sensitivity analysis of risk for SCD yielded results similar to the main finding, with no evidence of significant heterogeneity, indicating the method of case determination may not influence the results significantly.

Third, lack of individual participant data may preclude exploring in depth the interaction of CYP3 inhibitors and macrolides and other individual variables that may also influence outcomes. For example, female sex is an independent risk factor for torsades de pointes caused by cardiac drugs due to an intrinsic longer QTc interval compared to males and, indeed, we observed a trend towards higher risk in studies with predominantly female patients (28,29); however, limited data on the sex-stratified analysis of patients in the original studies preclude further sex analysis. Additionally, although a previous report suggests that drug-induced torsade de pointes might be a late phenomenon (29), we could not calculate the mean time interval between treatment with macrolides and cardiac event of interest based on the data available.

Fourth, like all meta-analyses, our study has the limitation of being a retrospective analysis; thus, further large RCTs are warranted to confirm these findings.

CONCLUSIONS

Results of this meta-analysis suggest that macrolides may be associated with significant increased risk for SCD or VTA and cardiovascular death but not all-cause mortality. The observed association with increased CV risk seemed to be largely attributed to current use of macrolides. This calls for large well-designed RCTs to further elucidate the CV safety of macrolides. Lack of significant difference in all-cause death between users of macrolides and no macrolides provide reassurance to clinicians that administration of macrolide antibiotics might be generally safe.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Su-Hua Wu, Department of Cardiology, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan Road #2, Guangzhou, Guandong 510080, China. E-mail: wusuhua@hotmail.com. OR Prof. Hai-Peng Xiao, Department of Endocrinology, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan Road #2, Guangzhou, Guandong 510080, China. E-mail: Xiaohp@mail.sysu.edu.cn.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Meta-analysis suggests that patients taking macrolide antibiotics for treatment of established or presumed bacterial infections experienced increased rates of ventricular tachyarrhythmias, sudden cardiac death, and cardiovascular death. Users of clarithromycin faced an increased risk of death from any cause, but there was no association between roxithromycin and adverse cardiac outcomes.

TRANSLATIONAL OUTLOOK: Large randomized trials are needed to confirm or refute these findings prospectively and identify individual patient features that predict adverse outcomes.

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APPENDIX For supplemental tables, figures, and additional references, please see the online version of this article.