

Azithromycin and Risk of Cardiovascular Death: A Meta-Analytic Review of Observational Studies

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Recent evidence, though conflicting, suggests an association between azithromycin use and cardiovascular death. We conducted a systematic review and meta-analysis to evaluate the effect of azithromycin on risk of death. Multiple databases were searched. Authors independently screened and extracted the data from studies. Primary outcome of interest was risk of death (cardiovascular and/or noncardiovascular). Subgroup analyses were conducted to explore the source of a possible heterogeneity. Random effects model meta-analysis and hazards ratio (HR) were used to pool the data and calculate the overall effect estimate, respectively. Eight hundred twenty-eight citations, identified with 5 cohort studies that involved 2,246,178 episodes of azithromycin use, met our inclusion criteria. Azithromycin use was not associated with higher risk of death from any cause, HR = 0.99 [confidence interval (CI), 0.82–1.19], $I^2 = 54\%$, or cardiovascular cause, HR = 1.15 (CI, 0.66–2.00), $I^2 = 64\%$, but there was a moderate degree of heterogeneity. Subgroup analyses have shown no increased risk of death with azithromycin use in younger population with zero degree of heterogeneity, HR = 0.85 (CI, 0.66–1.09), $I^2 = 0\%$. However, current use of azithromycin (within 1–5 days of therapy) was associated with a higher risk of death among older population with mild degree of heterogeneity, HR = 1.64 (CI, 1.23–2.19), $I^2 = 4\%$. In summary, azithromycin use was not associated with higher risk of death particularly in younger population. Nevertheless, older population might be at higher risk of death with current use of azithromycin, and an alternative therapy should probably be considered.

Keywords: azithromycin, cardiovascular death, meta-analysis

INTRODUCTION

Azithromycin is a macrolide antibiotic that is commonly used for treatment of respiratory tract infections and sexually transmitted diseases (STD). It was initially thought that azithromycin is relatively safe and free from cardiovascular toxicities¹ unlike other macrolides, erythromycin and clarithromycin, which are associated with an increased risk of arrhythmia and sudden cardiac death.^{2–5} However, contemporary data showed an increase in cardiovascular and all-cause mortality in an adult population of Medicaid beneficiaries that was treated with azithromycin in comparison with amoxicillin.⁶ As a result, the US Food and Drug Administration issued a public safety warning of

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potentially fatal arrhythmia associated with azithromycin use.⁷ More recently, Rao et al,⁸ in a cohort of US veterans receiving outpatient treatment with azithromycin, found a similarly increased risk of all-cause mortality and arrhythmia in comparison with amoxicillin. In contrast, other studies have failed to show increased cardiovascular or all-cause mortality among patients treated with azithromycin.^{9,10} To complicate the issue further, a newly published study has shown a survival benefit with azithromycin use in elderly patients with pneumonia in comparison with other guidelines—concordant antibiotics—though there was a higher risk of myocardial infarction in azithromycin-treated patients.¹¹

Given the widespread use of azithromycin in the treatment of common infections and the disparate findings of studies regarding its safety, we sought to systematically review the literature and perform a meta-analysis of the available studies that have examined the effect of azithromycin on all-cause mortality and cardiovascular death.

METHODS

A literature review was carried out from the year 1990 (azithromycin was introduced to the market in 1991)

through the first week of June 2014 by a medical reference librarian (P.J.E.). Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)¹² and Meta-Analysis of Observational Studies in Epidemiology¹³ guidelines for reporting systematic review and meta-analysis of observational studies were followed.

Study selection

Studies that assessed the effect of azithromycin as a primary outcome on all-cause mortality or cardiovascular death were considered for inclusion. Three authors (A.B.A., A.H.Q., and S.K.) independently screened the identified studies.

Search strategy

The search strategy was carried out in Ovid MEDLINE, in “Process & Other Non-Indexed Citations” using both the MeSH subject heading “azithromycin” and text words for various formulations: Zentavion or Azitrocin, Zithromax, Sumamed, Goxal, Azadose, Toraseptol, Ultrleon, Azithromycin, Vinzam, and Cp62993. A similar approach combining the MeSH category “Cardiovascular Diseases” and various text words indicating cardiac involvement was created: cardiovascular, heart, cardiac, qt, torsades, arrthymi*, or tachycardia* (asterisk is truncated word). The 2 concepts were combined. The search was then translated

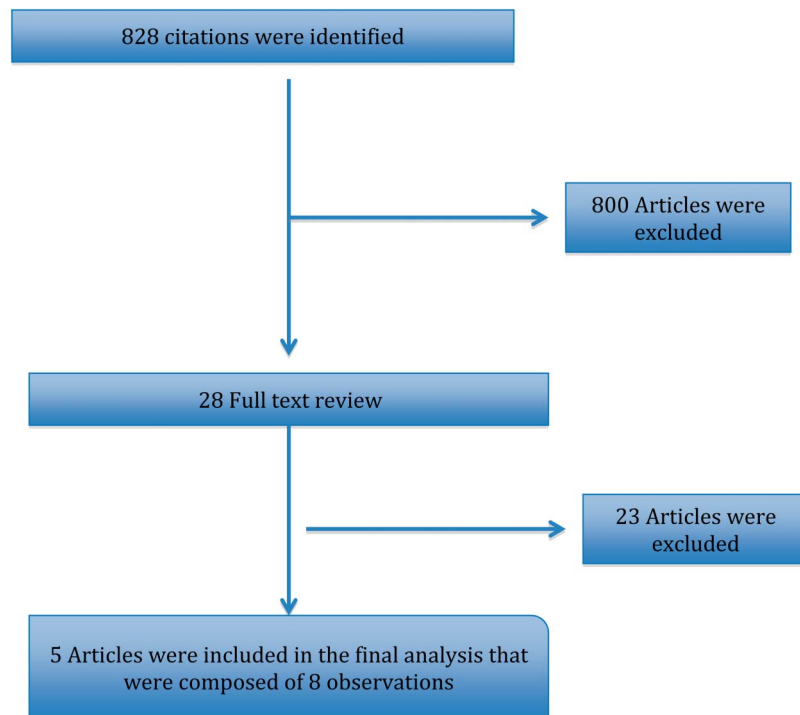


FIGURE 1. Flow diagram of study search.

Table 1. General characteristics of the included studies.

Author	Study design	Setting	Sample size azithromycin	Country of study	Mean age, yr	Male, %	Indications of therapy	Primary outcome
Khosropour et al ¹⁰	Retrospective cohort study	Data from Oregon Public Health Division	162,385	United States	24	35	STD chlamydia; gonorrhea	All-cause mortality within 10 d of therapy
Rao et al ⁸	Retrospective cohort study	Cohort of US veterans (VA Medical Centers)	594,792	United States	56.8	88	ENT/GU infection, pneumonia, COPD	All-cause mortality with current use (1–5 d) and recent use of azithromycin (6–10 d), arrhythmia
Ray et al ⁶	Retrospective cohort study	Tennessee Medicaid cohort	347,795	United States	48.6	22.5	ENT infections bronchitis	Cardiovascular and all-cause mortality with current (1–5 d) and recent use of azithromycin (6–10 d)
Svanström et al ⁹	Retrospective cohort study	Nationwide historical cohort study	1,102,419	Denmark	39.7	35	Respiratory tract infection, STD, SSTI	Cardiovascular death with current (1–5 d) and recent use of azithromycin (6–10 d), noncardiac death with current azithromycin use (1–5 d)
Mortensen et al ¹¹	Retrospective cohort study	Population based	38,787	United States	77.8	92.8	Pneumonia	30- and 90-d mortality; cardiovascular events within 90 d

COPD, chronic obstructive pulmonary disease; ENT, ear, nose, throat; GU, genitourinary; SSTI, skin and soft tissue infection; STD, sexually transmitted diseases.

into Ovid EMBASE, using the same terms, plus categories not available in MEDLINE: cardiovascular risk or heart death. Web of Science and Scopus were also searched using text words.

Data collection and quality assessment

A data collection form was designed to compile study information and included study characteristics (design, year of publication, setting, sample size, country), study population (age, gender, indications for azithromycin therapy), and primary outcome (all-cause mortality, cardiovascular death). Two reviewers (A.H.Q. and S.K.) independently extracted and recorded the data. Disagreements between the reviewers were discussed, and any discrepancy was resolved with consensus.

The Newcastle–Ottawa quality assessment scale (NOS) was used to evaluate the quality of observational studies.¹⁴ NOS scale rates observational studies based on 3 parameters: selection, comparability between the exposed and nonexposed groups, and exposure/outcome assessment. It assigns a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for exposure/outcome assessment. Studies with less than 5 stars are considered low quality, 5–7 stars moderate quality, and more than 7 stars high quality. Two reviewers (A.B.A. and M.G.) assessed the quality of the included studies. Disagreement was resolved by consensus.

Analytical method

Inverse variance method meta-analysis was used to pool studies’ rate ratio, odds ratio, or hazards ratio (HR) into random effects model meta-analysis. The outcome of interest was risk of death (related to cardiovascular and/or noncardiovascular causes) with the use of azithromycin (defined as within 1–10 days of therapy) as reported from individual studies in comparison with other antibiotics. We carried out sensitivity analyses stratifying risk of death with azithromycin use among younger (mean age < 40 years) and older populations (mean age ≥ 40 years) separately, including risk of death with current use of azithromycin (defined as within 1–5 days of start of therapy) and risk of death with recent use of azithromycin (from 6 to 10 days of therapy) among all included studies and stratified by age group. HR, with its 95% confidence interval (CI), was used to calculate the overall effect estimate. Heterogeneity among included studies was assessed using χ^2 and I^2 tests. The I^2 statistic describes the proportion of variation in treatment estimate that is not related to sampling error.¹⁵ A value of zero indicates no heterogeneity, 25%–49% low, 50%–74% moderate, and 75% a high degree of heterogeneity.

Table 2. Modified NOS for the included studies.

References	Selection†					Comparability‡	Outcome§		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Incident disease			Assessment of outcome	Length of follow-up	Adequacy of follow-up
Rao et al ⁸	A*	A*	A*	A*		A**	B*	A*	A*
Svanström et al ⁹	A*	A*	A*	A*		A**	B*	A*	A*
Ray et al ⁶	A*	A*	A*	A*		A*	A*	A*	A*
Khosropour et al ¹⁰	A*	A*	A*	A*		A*	A*	A*	B*
Mortensen et al ¹¹	A*	A*	A*	A*		A**	B*	A*	A*

*Represent the number of stars given for each variable during quality as explained in the text.

†Representativeness of the exposed cohort: A, truly representative of the average patient with exposure to the agent; B, somewhat representative of the average patient with exposure to the agent; C, selected group; D, no description of the derivation of the cohort. Selection of the nonexposed cohort: A, drawn from the same community as the exposed cohort; B, drawn from a different source; C, no description of the derivation of the nonexposed cohort. Ascertainment of exposure: A, secure record (eg, surgical record); B, structured interview; C, written self-report; D, no description. For demonstration that the outcome of interest was not present at the start of the study: A, yes; B, no.

‡For comparability of cohorts on the basis of the design or analysis: A, study controls for comorbidities; B, study controls for any additional factor (eg, age and severity of illness); C, not done.

§Assessment of outcome: A, independent blind assessment; B, record linkage; C, self-report; D, no description. Was follow-up long enough for outcomes to occur? A, yes (ie, in hospital or up to 30 days); B, no. Adequacy of follow-up of cohorts: A, complete follow-up and all subjects accounted for; B, subjects lost to follow-up was unlikely to introduce bias because small numbers were lost (ie, 90% were available for follow-up) or a description was provided of those lost; C, follow-up rate 90% or lower (select an adequate percentage) and no description of those lost; D, no statement.

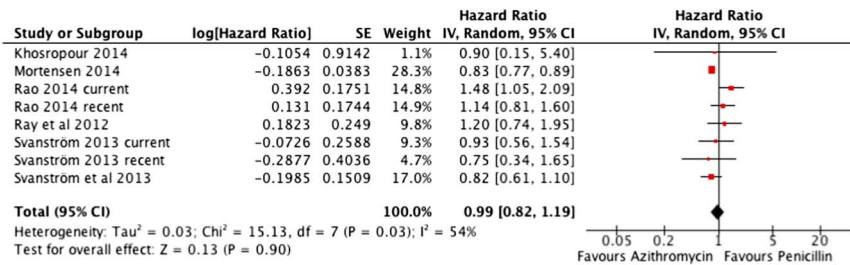


FIGURE 2. Random effects model meta-analysis of risk of death from any cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

Publication bias was assessed by visual assessment of the funnel plot.

The statistical software Review Manager, version 5.2 (The Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen, Denmark), was used for all analyses.

RESULTS

Descriptive and qualitative overview

The initial search strategy yielded 828 citations. Five observational studies, including 2,246,178 episodes of azithromycin use, met inclusion criteria (Figure 1). Out of these 5 studies, there were 8 results included in the meta-analysis of the primary outcome. Khosropour et al¹⁰ reported on cardiovascular death and death from any cause, but the rate ratio of death from any cause was only included as there was no cardiovascular death. Rao et al⁸ reported all-cause mortality with current (within 1–5 days) and recent (from 6 to 10 days) azithromycin use separately, and both results were included in the primary outcome analysis. Ray et al⁶ reported death (from cardiovascular and noncardiovascular causes) with azithromycin use within 10 days. Also, Ray et al⁶ reported on current and recent azithromycin use separately; their results were included in the subgroup analyses. Svanström et al⁹ reported cardiovascular death with current and recent use of azithromycin separately and noncardiovascular

death with current azithromycin use and thus were included as 3 results. Mortensen et al¹¹ reported death within 10, 30, and 90 days of therapy, but we included only odds ratio from death within 10 days. All eligible studies were retrospective cohort studies, 4^{6,8,10,11} from the United States and 1⁹ from Denmark. The US studies were multicentered, and the Danish study used a nationwide historical cohort. Azithromycin was used exclusively for treatment of STD and pneumonia in 2 studies^{10,11} but had variable indications in other studies, including respiratory tract infection, skin and soft tissue infections, STD, ear–nose–throat infections, and genitourinary infections. Study populations differed: Ray et al⁶ used Tennessee state Medicaid beneficiaries, Svanström et al⁹ used a nationwide general adult population, Rao et al⁸ and Mortensen et al¹¹ used data exclusively from US Veteran Administration medical centers, and Khosropour et al¹⁰ reported exclusively on young adults with STD. Table 1 shows the general characteristics of the included studies. All studies were of high quality based on NOS as shown in Table 2.

Meta-analysis

Azithromycin use (within 1–10 days of therapy) was not associated with a statistically significant increased risk of death from any cause, HR = 0.99 (CI, 0.82–1.19), I² = 54%, or cardiovascular cause, HR = 1.15 (CI, 0.66–2.00), I² = 64%, when compared with other antibiotics. However, there was a moderate degree of between-study heterogeneity and possible publication

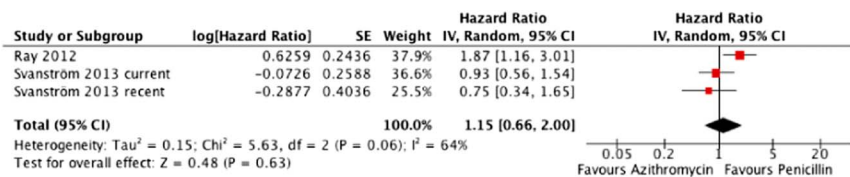


FIGURE 3. Random effects model meta-analysis of risk of death from cardiovascular cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

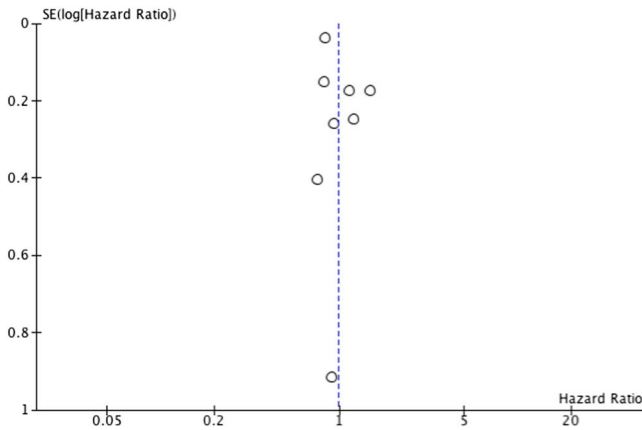


FIGURE 4. Funnel plot of risk of death associated with azithromycin use.

bias as evident by funnel plot asymmetry. Figures 2 and 3 show the contribution of each study, effect estimate, and between-study heterogeneity for risk of death from all cause and cardiovascular cause, respectively. Figure 4 shows funnel plot asymmetry.

Subgroup analyses

In a younger population (<40 years), azithromycin use was not associated with a statistically significant increased risk of death in comparison with other antibiotics with zero degree of heterogeneity, HR = 0.85 (CI, 0.66–1.09), I² = 0%. Similarly, in an older population (≥40 years), azithromycin use was not associated with a statistically significant higher risk of death, but the degree of between-study heterogeneity was high, HR = 1.11 (CI, 0.81–1.050), I² = 81%. Figures 5 and 6 show the forest plot of the meta-analysis in younger and older populations, respectively.

Current use of azithromycin (within 1–5 days of therapy) was not associated with a statistically significant increased risk of death in comparison with other antibiotics, but there was a significant degree of between-study heterogeneity, HR = 1.30 (CI, 0.79–2.15), I² = 81%. Similarly, recent use of azithromycin

(after 6–10 days of therapy) was not associated with a higher risk of death, and the degree of between-study heterogeneity was mild, HR = 0.86 (CI, 0.56–1.33), I² = 46%. Figures 7 and 8 illustrate the contribution of each study, effect estimate, and heterogeneity for current and recent use of azithromycin, respectively.

However, current azithromycin use (within 1–5 days of therapy) in an older population was associated with a statistically significant increased risk of death with a mild degree of between-study heterogeneity, HR = 1.64 (CI, 1.23–2.19), I² = 4%.

DISCUSSION

This meta-analysis shows no overall increased risk of all-cause mortality or cardiovascular death with azithromycin use in comparison with other antibiotics, which have no known adverse effect on mortality (penicillin, amoxicillin, tetracycline), but with a moderate degree of between-study heterogeneity. However, sensitivity analyses showed that current azithromycin use (within 1–5 days of therapy) was associated with a higher risk of death in older populations (40 years or older) and with only a mild degree of between-study heterogeneity.

Azithromycin is a widely used macrolide antibiotic with over 40 million prescriptions in the United States in 2011.⁸ It is primarily used for the treatment of respiratory tract infections and STD. Although azithromycin was previously thought to lack serious cardiovascular side effects,¹ accumulating evidence suggests that the drug might lead to QT prolongation and potentially life-threatening torsades de pointes, particularly in the presence of electrolyte abnormalities, congestive heart failure, prolonged QT, congenital long QT syndrome, history of bradyarrhythmia, coadministration of azithromycin with other drugs known to prolong the QT interval, and in elderly patients.^{7,8,16} Notwithstanding these concerns, the present analysis showed no overall association between azithromycin use and increased risk of death (all cause and

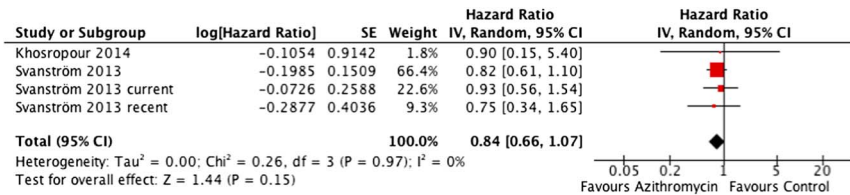


FIGURE 5. Random effects model meta-analysis of risk of death, in the younger population (<40 years), from any cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

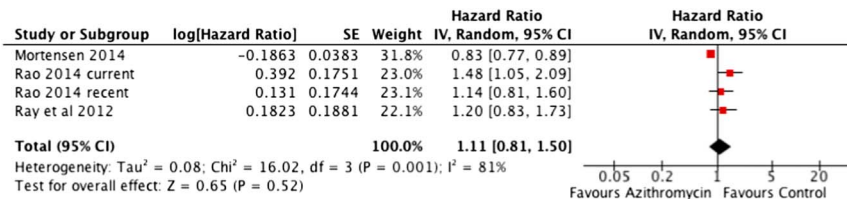


FIGURE 6. Random effects model meta-analysis of risk of death, in the older population (≥ 40 years), from any cause associated with azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

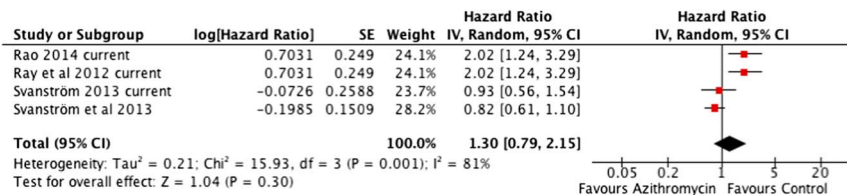


FIGURE 7. Random effects model meta-analysis of risk of death from any cause associated with current (within 1–5 days of therapy) azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

cardiovascular), though the presence of a moderate degree of heterogeneity limits the robustness of this finding.

Subgroup analyses were conducted to explore the source of heterogeneity and showed lack of association between azithromycin use and higher rate of death in a younger population (mean age < 40 years), with zero between-study heterogeneity, but a higher risk of death associated with current use of the antibiotic in an older population (mean age ≥ 40) with no significant heterogeneity.

The pooled estimate and subgroup analysis in the younger population that showed no statistically significant association between azithromycin use and the risk of death are consistent with the result of 2 large studies. Khosropour et al¹⁰ studied the association of azithromycin with risk of death in 162,385 patients with STD with a mean age of 24 years and found no cardiovascular death in the entire cohort and no significant difference in the risk of death from noncardiovascular causes between the azithromycin and nonazithromycin antibiotic groups. Similarly, a nationwide study from Denmark⁹ that involved 1,102,419 episodes

of azithromycin use in a young and middle-aged general population (mean age 39.7 years) showed that azithromycin use was not associated with a higher risk of death from cardiovascular and noncardiovascular causes.

The observed higher rate of death in association with current azithromycin use in an older population as suggested by our subgroup analysis may be a result of proarrhythmic properties of the drug.⁶ However, it might also be related to the specific characteristics of the population under study: older, higher rate of comorbidities, higher baseline risk of death and cardiovascular events, confounding by indications, and the presence of residual unmeasured confounders that could have biased the result toward such association.^{8,9} Ray et al⁶ used data from Medicaid beneficiaries, a population that is known to have multiple comorbidities and a higher rate of mortality, and found a higher rate of cardiovascular deaths among those prescribed azithromycin. Interestingly, there was only one death among the 144,165 patients in the lowest 4 deciles of risk score for cardiovascular disease.¹⁰ Similarly, Rao et al⁸ studied a cohort of

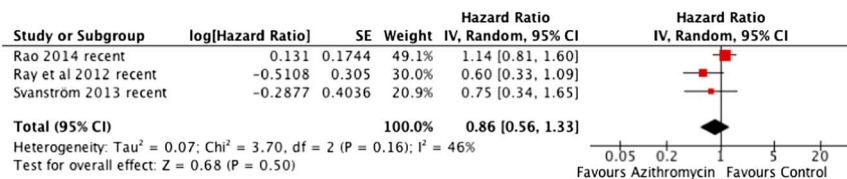


FIGURE 8. Random effects model meta-analysis of risk of death from any cause associated with recent (from 6 to 10 days of therapy) azithromycin use in comparison with other antibiotics. Error bars indicate the CI.

patients who were older and commonly with comorbidities and found a higher rate of death and arrhythmia with current azithromycin use in comparison with amoxicillin. Importantly, both studies used propensity scored matched analysis to minimize the effect of variation in baseline risk between the azithromycin group and the comparison group.

In contrast to the other studies included in the present meta-analysis, Mortensen et al¹¹ found that azithromycin use in an elderly cohort of patients with pneumonia was associated with an improved 30-day mortality. This study, however, excluded death occurring on the first day of therapy and did not report on mortality occurring within the first 5 days of therapy, a period of time during which azithromycin use was associated with a higher risk of mortality in other studies.^{3,6}

Limitations

Data were pooled from observational studies with all the inherent limitations to such study design. Nevertheless, included studies used propensity scored matched analysis to adjust for variations between groups. The findings from the primary analysis were limited by the presence of moderate between-study heterogeneity and possible publication bias. However, we conducted subgroup analyses in an attempt to explore the source of heterogeneity, which was probably related to varying populations with different baseline characteristics. Subgroup analyses by subject age showed no significant between-study heterogeneity.

CONCLUSIONS

In the current meta-analysis, azithromycin was not associated with a significant increase in either all-cause mortality or cardiovascular death, particularly in a younger population. However, older patients at higher baseline risk of cardiovascular events may be at higher risk of death associated with azithromycin use, and an alternative antibiotic therapy should probably be considered for these patients.

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