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A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease

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Summary
Introduction: Macrolides are of unique interest in preventing COPD exacerbations because they possess a variety of antibacterial, antiviral and anti-inflammatory properties. Recent research has generated renewed interest in prophylactic macrolides to reduce the risk of COPD exacerbations. Little is known about how well these recent findings fit within the context of previous research on this subject. The purpose of this article is to evaluate, via exploratory meta-analysis, whether the overall consensus favors prophylactic macrolides for prevention of COPD exacerbations.
Methods: EMBASE, Cochrane and Medline databases were searched for all relevant randomized controlled trials (RCTs). Six RCTs were identified. The primary endpoint was incidence of COPD exacerbations. Secondary endpoints including mortality, hospitalization rates, adverse events and likelihood of having at least one COPD exacerbation were also examined.
Results: There was a 37% relative risk reduction (RR = 0.63, 95% CI: 0.45–0.87, p value = 0.005) in COPD exacerbations among patients taking macrolides compared to placebo.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; RCT, randomized controlled trial; ITT, Intention-to-Treat.

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Furthermore, there was a 21% reduced risk of hospitalization (RR = 0.79, 95% CI: 0.69—0.90, *p*-value = 0.01) and 68% reduced risk of having at least one COPD exacerbation (RR = 0.34, 95% CI 0.21—0.54, *p*-value = 0.001) among patients taking macrolides versus placebo. There was also a trend toward decreased mortality and increased adverse events among patients taking macrolides but these were not statistically significant.

Conclusions: Prophylactic macrolides are an effective approach for reducing incident COPD exacerbations. There were several limitations to this study including a lack of consistent adverse event reporting and some degree of clinical and statistical heterogeneity between studies.
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Introduction

Individuals with Chronic Obstructive Pulmonary Disease (COPD) who suffer recurrent disease exacerbations are likely to see rapid declines in quality of life, lung function and lifespan.[1] As a result, there is a strong interest in developing approaches that can mitigate this substantial problem. While the spectrum of available COPD treatments provide some benefit, they are insufficient. Additional approaches are sorely needed.

As far back as the 1960s, there has been interest in employing prophylactic antibiotics to reduce the incidence of COPD exacerbations. Most of these trials are well summarized in a 2003 Cochrane meta-analysis that concluded the risk reduction (of recurrent exacerbations) with antibiotics was approximately 9%.[2] However, there was a wide degree of heterogeneity in reporting methods and trial design, as well as significant antibiotic-related side effects and drug resistance. So while antibiotics were beneficial in reducing incidence of COPD exacerbations, its associated risks rendered it an ultimately unappealing option. More recently, reports emerged that macrolides, given on a long-term basis, had a beneficial effect in reducing disease progression of diffuse panbronchiolitis[3] and cystic fibrosis.[4] This prompted renewed interest in using specifically macrolides for prevention of COPD exacerbations. Macrolides are of unique interest because, in addition to their antibacterial effects, they possess antiviral and immunomodulatory activity — and all three of these properties seemingly work in concert to prevent and/or treat disease exacerbations.[5] As a result, over the past two decades, several small-scale, well-designed and well-executed trials have been launched, highlighted by the recent study by Albert et al.,[6] which seems to have generated newfound interest in the notion of using prophylactic macrolides to reduce the risk of COPD exacerbations. The purpose of this study is to evaluate via a meta-analysis whether the overall body of research supports the notion that prophylactic macrolides are effective in preventing COPD exacerbations. Furthermore, whether results from the five randomized controlled trials (RCTs) that preceded the Albert et al.[6] study were consistent with each other and in line with findings from that particular groundbreaking study.

Materials and methods

Search strategy

A comprehensive search of MEDLINE, Cochrane Central Register of Controlled Trials and EMBASE was performed. There was no time limit on the search. There were no specific restrictions regarding study length. All English, Spanish and French articles were included. Databases were fully explored for all potential RCTs by conducting a highly sensitive search strategy using the MESH keywords: Chronic Obstructive Pulmonary Disease AND Macrolides or Erythromycin or Clarithromycin or Azithromycin AND randomized controlled trials or controlled clinical trials. A secondary "hand-search" was then pursued — this consisted of individually scanning all abstracts from the 2010, 2011 and 2012 American Thoracic Society Annual Conference, European Respiratory Society Congress as well as the CHEST Annual Conference to identify studies that had not yet been published or accessible on the aforementioned medical databases. Additionally, all selected articles were reviewed for other relevant articles.

Study selection

The initial search strategy yielded 341 studies. Drs Chaudhry and Donath evaluated each study for inclusion in the meta-analysis separately. Dr Hernandez mediated disagreements regarding any specific study. Of these 341 studies, six studies were ultimately selected for inclusion in the meta-analysis (Fig. 1). An additional two cohort studies were also noted, but not included as part of the overall meta-analysis.

Assessment of validity

The methodological quality of all included trials was assessed according to randomization method, concealment of random allocation, eligibility criteria, comparability of baseline characteristics, blinding of outcome assessors, blinding of treatment providers, blinding of patients and whether the trial employed Intention-to-Treat (ITT) Analysis.

Data extraction and synthesis

Data was abstracted from all studies using standardized forms. Of studies selected, a variety of specific trials characteristics were recorded including study design, macrolide dosing/duration, age, sex, smoking history and COPD severity. These trial characteristics were considered the key variables that may have influenced effect size and were explored further via meta regression and subgroup analyses. The primary endpoint was the total number of COPD exacerbations as a function of person-years. A COPD

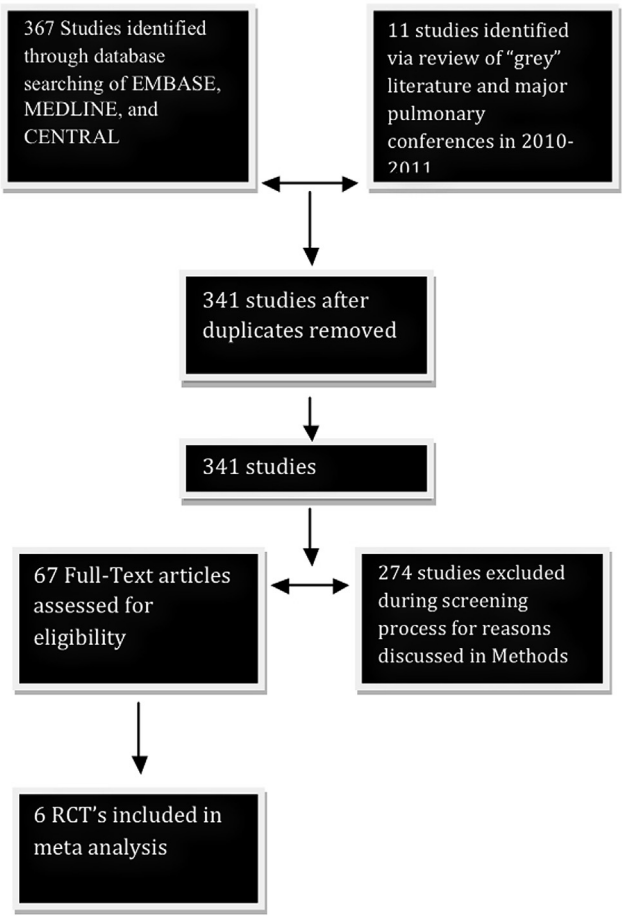

Figure 1 Flow diagram depicting number of studies included at each stage of selection process.

exacerbation was defined as a sudden worsening in respiratory symptoms typically lasting multiple days and characterized by at least two of three symptoms: dyspnea, increased quantity of sputum and purulent sputum. Secondary endpoints included mortality, hospitalization rates, adverse events leading to study withdrawal and likelihood of having at least one COPD exacerbations. Results, extracted specifically from intention-to-treat (ITT) data, were expressed as a relative risk (RR) with accompanying 95% confidence intervals. If RR values weren't explicitly provided by authors, they were calculated using provided study data. Meta-analyses were then pursued using random-effects modeling for the primary endpoint and fixed-effects modeling for the secondary endpoints. The I^2 statistic and forest plots were used to assess the degree of heterogeneity. Causes of heterogeneity were subsequently explored via subgroup analyses and meta regression. Sensitivity analyses were used to assess the impact of excluding studies based on methodological quality. The analysis was performed using Stata 11 (Stata Statistical Software, College Station, TX).

Results

Six studies were identified for inclusion into the meta-analysis.[6–11] These studies were all conducted within the past 10 years. They generally included patients among the ages of 65–75. They were mostly evaluating patients with severe to very severe COPD with baseline FEV_1% values ranging from 20% to 50%. Most patients included in these studies had a history of recurrent COPD exacerbations although only Albert et al.[6] specifically required patients to have had at least one COPD exacerbation in the year prior to study entry (they could also be included if they were using supplemental oxygen at-home without necessarily having had an exacerbation in the prior year). Studies lasted for 3–12 months (Table 1). Two of the six RCTs were not blinded; there were otherwise no major study biases that were consistently identified among included studies (Table 2).

The primary endpoint was the total number of exacerbations as a function of person-years. The comprehensive meta-analysis, involving six studies and 1677 patients, showed that there was 37.3% relative risk reduction (RR = 0.627, 95% CI: 0.452–0.868, p value = 0.005, I-squared 62.8%) in exacerbations among patients taking macrolides compared to those taking a placebo (Fig. 2). An additional two cohort studies, not suitable for inclusion into the meta analysis, were identified that further supported this conclusion.[15,16] As the recent Albert et al. study[6] accounted for a large percentage of the overall effect, a sensitivity analysis was conducted involving the five other RCTs. That meta-analysis, involving 333 patients, found a 48.1% relative risk reduction of exacerbations among patients taking macrolides compared to those taking a placebo (RR = 0.519, 95% CI: 0.315–0.855, p value = 0.01, I-squared 49%).

Additional secondary endpoints were also explored. In terms of mortality risk, three studies addressing that outcome[6,9,11] found a 15% risk reduction in overall mortality among patients taking prophylactic macrolides compared to those taking placebo (RR = 0.85, 95% CI: 0.49–1.46, p-value = 0.55, I-squared 0%) (Fig. 3). In terms of hospitalization risk, three studies addressing that outcome[6,8,9] found a 21% risk reduction in overall number of hospitalizations among patients taking prophylactic macrolides compared to those taking placebo (RR = 0.79, 95% CI: 0.69–0.90, p-value = 0.01, I-squared 0%) (Fig. 4). In terms of likelihood of having at least one COPD exacerbation, two studies addressing that outcome[9,10] found a 68% risk reduction (RR = 0.34, 95% CI 0.21–0.54, p-value = 0.001, I-squared 87%) in having at least one COPD exacerbation among patients taking prophylactic macrolides compared to those taking placebo (Fig. 5). Lastly, in terms of relative risk of having some adverse event leading to study withdrawal, all six studies[6–11] addressing that outcome found a 95% increased risk of withdrawal due to adverse event among patients taking prophylactic macrolides compared to those taking placebo (RR = 1.95, 95% CI 0.92–4.14, p-value = 0.08, I-squared 0%) (Fig. 6).

Several additional study variables including average age, COPD severity and pack-years of smoking were prospectively explored further via subgroup analyses and meta-regression. Through meta-regression, there was a highly statistically significant negative correlation between the mean number of pack-years patients smoked and response to macrolides (i.e. patients with more pack-years of smoking were less likely to respond to macrolides). The adjusted R-squared for this relationship was 96% (p-value = 0.04, I^2 = 0%).

Table 1 Major study characteristics from the six RCTs included in the meta-analysis.

	Banerjee D, Khair OA et al.	Albert R, Connett J et al.	Blasi F, Bonardi D et al.	Seemungal T, Wilkinson T et al.	Suzuki T, Yanai M et al.	He Z, Ou L et al.
Study design	RCT	RCT	RCT	RCT	RCT	RCT
Year of study	2003—2004	2006—2010	2004—2006	2004—2006	1997—1999	2008—2009
Country	United Kingdom	United States	Italy	United Kingdom	Japan	China
Number of patients (treatment:control)	31:36	558:559	11:11	53:56	55:54	18:18
Mean age (treatment: control)	65:68	65:66	72:73	67:68	69.1:71.7	68.8:69.3
Pre-bronchodilator FEV_1 % predicted (treatment:control)	42.5:43.9	39:40	—	49.3:50.6	—	44.3:42.1
Pre-bronchodilator FEV_1/FVC % predicted (treatment:control)	—	42:43	—	48.9:50.9	—	46.9:48.6
Type of macrolide and dose	Clarithromycin 500 mg once daily	Azithromycin 250 mg once daily	Azithromycin 500 mg once 3 days/week	Erythromycin 250 mg twice daily	Erythromycin 200—400 mg once daily	Erythromycin 125 mg 3 times daily
Inclusion in study required one or more COPD exacerbations in past year	No	Yes	No	No	No	No
Duration of treatment	3 months	12 months	6 months	12 months	12 months	6 months
COPD severity	Moderate—severe	Moderate—very severe	Severe	Moderate—severe	—	Moderate—severe
Exacerbations/person-year in treatment group	0.65	1.48	0.80	1.53	0.25	1.22
Exacerbations/person-year in control group	0.22	1.83	3.33	2.23	1.19	2.22
Relative risk (95% confidence interval)	3.27 (95% CI 0.53—34.33)	0.83 (95% CI 0.72—0.95)	0.24 (95% CI 0.05—0.83)	0.65 (95% CI 0.49—0.86)	0.21 (95% CI 0.07—0.65)	0.55 (95% CI 0.31—0.98)

Discussion

COPD exacerbations are generally thought to arise as a result of a complex interplay between bacterial and/or viral invasion associated with an aberrant immune response. Bacteria (most commonly *Haemophilus influenzae*, *Streptococcous pneumoniae* and *Moraxella catarrhalis*) cause airway injury and ultimately restrict airflow by increasing mucus secretion, impeding mucociliary clearance and increasing smooth muscle contraction.[5] Additionally, viruses (most commonly rhinovirus, influenza virus and respiratory syncytial virus) are thought to cause injury to epithelial cells that impair their

Table 2 Ascertainment of study bias from the six RCTs included in the meta-analysis.

	Randomization method	Concealment of random allocation	Eligibility criteria	Comparable at baseline	Blinding of outcome assessors	Blinding of treatment providers	Blinding of patients	ITT analysis
Albert R, Connett J et al.[4]	Yes	Not addressed	Yes	Yes	Not addressed	Not addressed	Yes	Yes
Banerjee D, Khair OA et al.[5]	Yes	Yes	Yes	Yes	Not addressed	Not addressed	Yes	Yes
Seemungal T, Wilkinson T et al.[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blasi F, Bonardi D et al.[7]	Yes	No	Yes	Yes	No	No	No	No
He Z, Ou L et al.[8]	Yes	Not addressed	Yes	Yes	Yes	Yes	Yes	Yes
Suzuki T, Yanai M et al.[9]	Yes	Yes	Yes	Yes	No	No	No	Not addressed

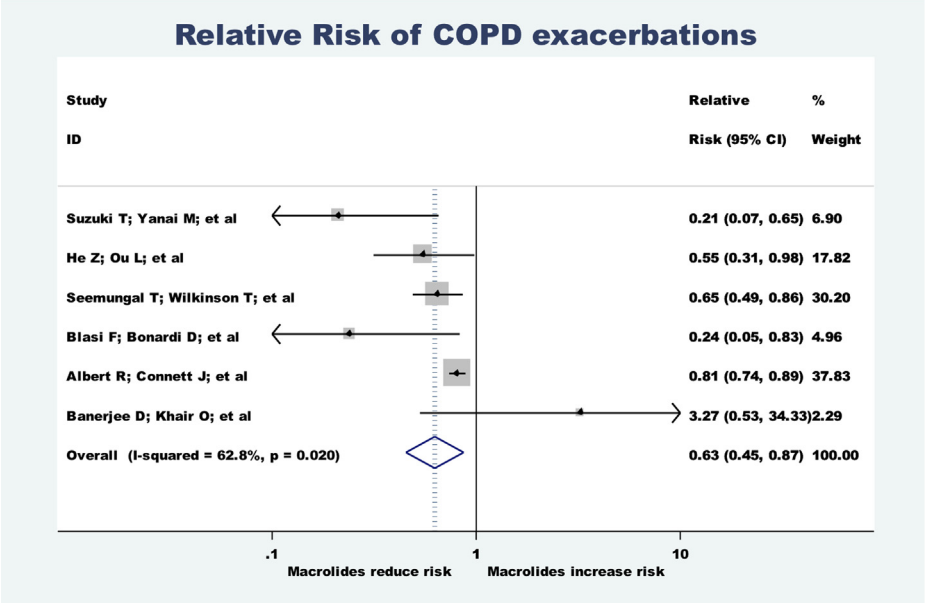

Figure 2 Forest plot from overall meta-analysis, including all six included RCTs, assessing relative risk (RR) of COPD exacerbations as a function of person-years in patients receiving macrolides compared to placebo.

barrier function and lead to epithelial detachment with subsequent pulmonary edema, alveolar destruction and airflow limitation.[5] Lastly, COPD exacerbations seem to be somewhat related to an underlying pro-inflammatory state where an over-activated immune system may egregiously respond to relatively innocuous insults.[12] Macrolides serve as a compelling treatment for prevention of COPD exacerbations by addressing each of these mechanisms separately.[5]

These findings suggest that prophylactic macrolides seem to have a positive net effect among individuals with more severe forms of COPD. This benefit seemed to extend to all outcomes that were assessed — in particular, the incidence of COPD exacerbations, the hospitalization rate and likelihood of having at least one COPD exacerbation all suggested highly statistically significant benefit favoring the use of macrolides versus placebo. This benefit comes at the expense of a variety of adverse events that are inconsistently reported across studies. The one endpoint that was reliably reported for all studies was the likelihood of patients discontinuing the study due to an adverse event — and there was a trend toward high rates of study discontinuation from macrolides, although this was not statistically significant. Of note, it was difficult to capture some of the more large-scale risks associated with macrolide prophylaxis including the development of macrolide resistance. This is becoming an increasing concern worldwide,[13]

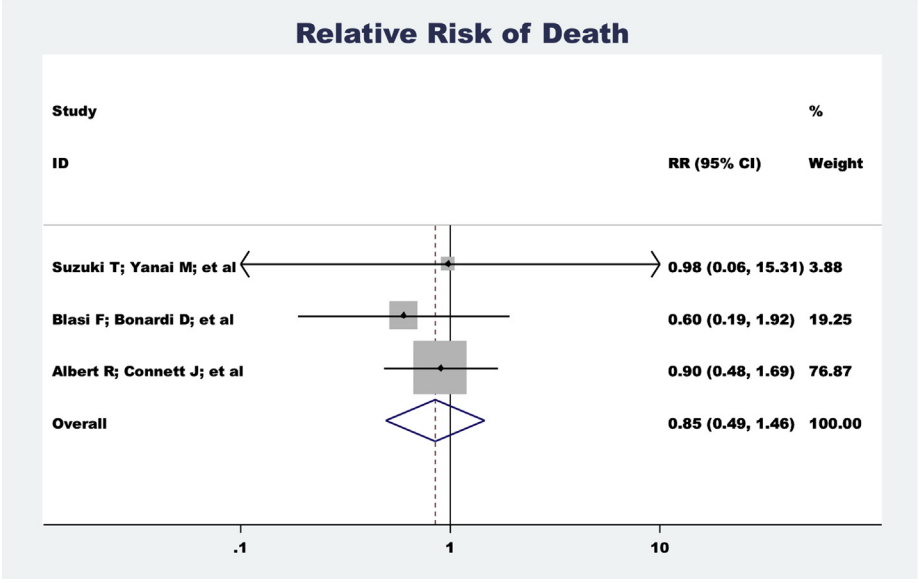

Figure 3 Forest plot assessing relative risk (RR) of death among COPD patients receiving macrolides compared to placebo.

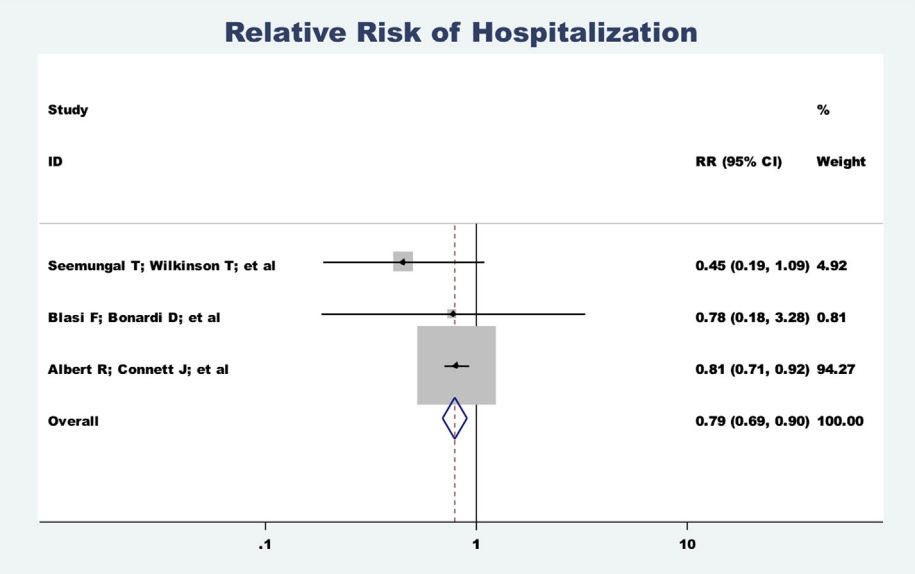

Figure 4 Forest plot assessing relative risk (RR) of hospitalization among COPD patients receiving macrolides compared to placebo.

and particularly in Asia,[14] and the fact that its difficult to characterize in the above studies does not make it any less of a concern. It is probably the most important shortcoming to the widespread implementation of prophylactic macrolides.

Although the overall analysis suggested substantial benefit from prophylactic macrolides, it worth noting that findings from one of the six identified studies was highly inconsistent with the rest. Banerjee D et al.[7] was the one study in which macrolides did not prevent COPD exacerbations. This was likely due to the limited length of the study and the small number of total exacerbations observed - thus limiting the power of the study to detect a true effect. Of note, in addition to the five RCTs which suggest a significant benefit for macrolides, two additional cohort studies showed a statistically significant reduction in COPD exacerbations among patients taking prophylactic macrolides. Yamaya M et al. retrospectively examined hospital records of 131 patients and determined a relative risk reduction of 19% (RR 0.81, 95% CI 0.69—0.95) in COPD exacerbations among those patients taking prophylactic macrolides.[15] Additionally, Gomez J et al. prospectively monitored patients being given prophylactic azithromycin 500 mg daily for three of every 21 days and found that macrolides reduced the risk of COPD exacerbations by 45% (RR 0.55, 95% CI 0.46—0.68).[16]

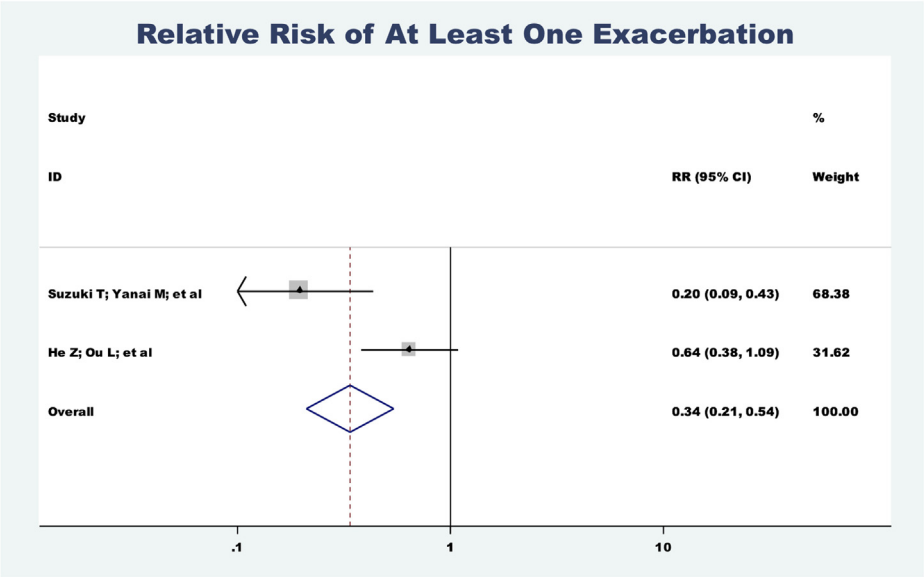

Figure 5 Forest plot assessing relative risk (RR) of at least one COPD exacerbation among patients receiving macrolides compared to placebo.

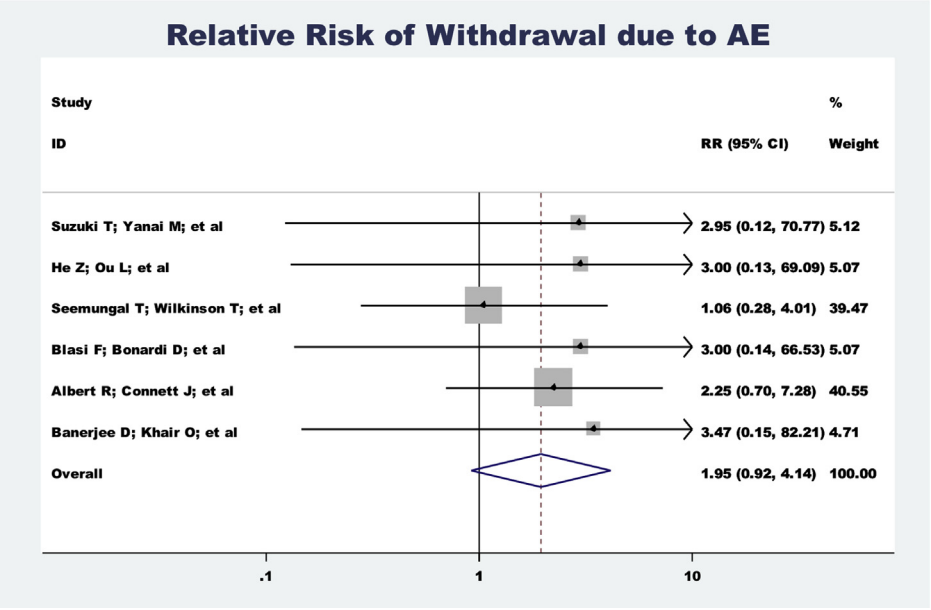

Figure 6 Forest plot assessing relative risk (RR) of withdrawal from study due to an adverse event among patients receiving macrolides compared to placebo.

As there was some degree of heterogeneity in the overall findings, attempts were made to better elucidate that heterogeneity via meta-regression and subgroup analyses. In particular, a meta-regression analysis was employed to detect whether the effect size may have been related to disease severity. There are many variables to consider in evaluating disease severity (including %FEV_1, %FVC, etc…) — the number of pack-years smoked was examined specifically because it was the only variable consistently reported across studies. Interestingly, this analysis revealed that the number of pack-years had an inverse relationship with the likelihood of benefiting from macrolides — which is the opposite of what one may have anticipated. As multiple previous studies have established that COPD severity is directly related to one's smoking history[17,18] this finding belies the widely held notion that prophylactic macrolides should be reserved for individuals with only very severe COPD and suggests a possibly expanded role for macrolides across a wider spectrum of COPD patients. Along these lines, in the study by Albert et al.[6] (in which their subgroup analyses examine benefits across patients with varying COPD severity), they demonstrate the greatest benefit from macrolides is seen in patients with moderate COPD (GOLD Stage 2).

There were several limitations to this analysis. Firstly, there was some degree of clinical heterogeneity between studies in that they originated from different countries, had different grading criteria for COPD severity and employed different macrolides under several dosing regimens. This was the likely reason for the moderate degree of statistical heterogeneity (i.e. elevated *I*-squared values) seen across certain endpoints. Another potential source of heterogeneity was study length (which varied from 3 to 12 months). This was partially controlled for by evaluating the primary outcome as a function of the number of person-years under study (as opposed to the denominator being simply the number of persons). Additionally, adverse events were inconsistently reported between studies and were not fully addressed here. The potential risks associated with macrolide usage have been under recent scrutiny in light of the finding that azithromycin usage may be associated with an increased risk of sudden cardiac death.[19] Thirdly, the overall patient population being studied in this analysis included a disproportionate amount of patients from the recent landmark study by Albert et al.[6] As a result, a sensitivity analysis was performed including only the five studies that preceded Albert et al.[6] and, importantly, there was a statistically significant effect favoring macrolides among those five studies alone. This finding can serve to reinforce the conclusions made by Albert et al.[6] as well as support the overall conclusions from this meta-analysis. Lastly, prophylactic macrolides have become increasingly well established as an important treatment consideration in non-cystic fibrosis bronchiectasis[3] and there were no screening programs in place among these studies to identify patients with underlying bronchiectasis. As a result, it is difficult to tease out how many of the above patients with COPD may have had some component of bronchiectasis and whether the proposed benefit from prophylactic macrolides exists among COPD patients who do not have any underlying bronchiectasis.

It is important to realize that while prior meta-analyses have evaluated the use of prophylactic antibiotics in general for prevention of COPD exacerbations, none have specifically addressed the use of macrolides and none have shown a similar degree of benefit that is being suggested here. These findings serve to bolster the current body of evidence suggesting benefit for prophylactic macrolides among patients with severe to very severe forms of COPD.

Conflict of interest

We certify that all authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication

elsewhere in whole or in part in any language except as an abstract.

The authors of this study would like to declare that no conflicts of interest existed during the development and writing of this manuscript. Furthermore, no funding was provided for this research.

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Dr. Donath was responsible for writing the majority of this paper, aiding in study selection and for performing the statistical analysis. He is the guarantor of this manuscript and takes responsibility for the integrity of this research. Dr Chaudhry was responsible for the study selection process, writing this paper and extracting data from the articles. Dr Hernandez-Aya was responsible for mediating disagreements and assisting with writing of the paper. Dr Lit oversaw the entire project and provided invaluable advice regarding the general tone and direction of the research.

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