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Association of Inhaled Corticosteroids with Incident Pneumonia and Mortality in COPD Patients; Systematic Review and Meta-Analysis

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Abstract

Background—Inhaled corticosteroids are commonly prescribed for patients with severe COPD. They have been associated with increased risk of pneumonia but not with increased pneumonia-associated or overall mortality.

Methods—To further examine the effects of inhaled corticosteroids on pneumonia incidence, and mortality in COPD patients, we searched for potentially relevant articles in PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Science and manufacturers' web clinical trial registries from 1994 to February 4, 2014. Additionally, we checked the included and excluded studies' bibliographies. We subsequently performed systematic review and meta-analysis of included randomized controlled trials and observational studies on the topic.

Results—We identified 38 studies: 29 randomized controlled trials and nine observational studies. The estimated unadjusted risk of pneumonia was increased in randomized trials: RR 1.61; 95% CI 1.35-1.93, p<0.001; as well as in observational studies: OR 1.89; 95% CI 1.39-2.58, p<·001. Six randomized trials and seven observational studies were useful in estimating unadjusted risk of pneumonia case-fatality: RR 0.91; 95% CI 0.52-1.59, p=0.74; and OR 0.72; 95% CI 0.59-0.88, p=0.001, respectively. Twenty-nine randomized trials and six observational studies allowed estimation of unadjusted risk of overall mortality: RR 0.95; 95% CI 0.85-1.05, p=0.31; and OR 0.79; 95% CI 0.65-0.97, p=0.02, respectively.

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Contributions of all authors (EF, VB, EG, PDS) include:
Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
Drafting the work or revising it critically for important intellectual content; AND
Final approval of the version to be published; AND
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conclusions—Despite a substantial and significant increase in unadjusted risk of pneumonia associated with inhaled corticosteroid use, pneumonia fatality and overall mortality were found not to be increased in randomized controlled trials and were decreased in observational studies.

Keywords

Case-fatality; drop-out; bias; heterogeneity

Introduction

Inhaled corticosteroids (ICS) are among the most commonly prescribed anti-inflammatory medications. They reduce the incidence of disease exacerbations in COPD patients, which may translate into their improved overall health status. The Global Initiative for Chronic Obstructive Lung Disease recommends ICS for management of patients with severe COPD and those with frequent exacerbations.[1] The TORCH trial[2], published in 2007, was the first to report increased risk of pneumonia in patients using ICS. Since then, numerous prospective randomized trials have reported increased risk of pneumonia with ICS use.[3-7] These trials reported pneumonia events as pre-specified adverse events; however they lacked rigorous diagnostic ascertainment or radiological confirmation of pneumonia. Moreover, the reported increased risk of pneumonia was not uniformly adjusted for the pertinent confounders. We have previously studied and reported that the increased risk of pneumonia is attenuated upon adjustment for demographics, comorbidities and concurrent medications.[8] It is conceivable that the observed increased unadjusted risk of pneumonia can be at least partly explained by higher doses, potency and longer use of ICS, especially in older patients with more severe COPD.[9]

A previous meta-analysis of randomized controlled trials (RCTs) published before June 2008 reported no difference in pneumonia-associated and overall mortality despite significantly increased risk of pneumonia in ICS users, however, the authors noted that the included studies lacked power to detect a difference in pneumonia-associated or overall mortality.[10] Although RCTs carry less risk of inherent bias compared to observational studies, the observed limitations with pneumonia ascertainment, relatively low prevalence rate, reporting bias and confounding limited the ability to interpret RCT's regarding this issue.

Recent, large observational studies have demonstrated either similar or improved mortality in patients using ICS.[8, 11-13] Other improved outcomes have been reported: decreased risk of development of parapneumonic effusion,[14] lesser need for mechanical ventilation[11] and fewer pulmonary complications at admission and during hospitalization.[15] The observational studies did not rely solely on the clinical diagnosis of pneumonia; rather most included confirmatory radiographic assessments. Moreover, the recent observational studies evaluated patients with pneumonia events necessitating admission to the hospital, in comparison to the patients with mostly ambulatory pneumonia events enrolled in RCTs.

Given the discrepancies in estimates of risks of pneumonia, pneumonia-associated and overall mortality in COPD patients utilizing ICS and a number of recently published studies

on the topic, we systematically reviewed all available RCTs and observational studies and pooled the results into two separate meta-analyses.

Materials and Methods

Search strategy

Three authors (E.F., V.B. and E.G.) independently and in duplicate searched PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Science and manufacturers' web clinical trial registries (GlaxoSmithKline, AstraZeneca) with the clinical trial filters using multiple search terms with no language restrictions, from 1994 to February 4, 2014. To identify additional relevant articles, we checked the bibliographies from included and excluded studies, as well as related systematic reviews. All abstracts returned from the preliminary search were reviewed in three combinations of duplicates. Ten random manuscripts were reviewed for eligibility by all three reviewers together to help standardize the selection strategy. Then, the same reviewers each independently assessed approximately two-thirds of all full-text manuscripts for the eligibility. Disagreements regarding eligibility between two reviewers were resolved through consensus and with an input from the third reviewer.

Outcome measures

Among all studies of ICS use in COPD, those which measured pneumonia and reported study-period mortality were analyzed in detail. We considered all pneumonia events irrespective of severity. We also analyzed more reliable overall mortality outcomes, as well as pneumonia-associated mortality (number of pneumonia cases who died divided by number of patients in the ICS versus non-ICS group) and pneumonia case-fatality (number of pneumonia cases who died divided by all pneumonia cases in the ICS versus non-ICS group, respectively). At the outcome level, we assessed risk of bias by using GRADE profiler, version 3.6 (GRADE working group).

Quantitative data synthesis and sensitivity analysis

We used Review Manager Software, version 5.2 (Nordic Cochrane Center, Copenhagen, Denmark), to calculate pooled relative risk (RR) for RCTs and odds ratio (OR) for observational studies with respective 95% confidence intervals (CIs) using a random effects model. We reported the outcomes data according to an "intention to treat" (ITT) analysis. All reported *p*-values are two-sided, with significance set at less than 0.05. The statistical heterogeneity was assessed using the I^2 statistic. Where substantial statistical heterogeneity was present, we explored potential sources of heterogeneity in the subgroup analyses. Sensitivity analyses were performed to explore the influence of statistical models (fixed vs random effects) on the effect size, the influence of individual trials, per protocol analysis and the inclusion of "double-zero" events (zero outcomes in both ICS and non-ICS groups).

Additional details on eligibility, search, data extraction, study characteristics and quality assessment are available in the *Supplemental* file and e-Figures 1-4.

Results

We identified 38 studies, 29 RCTs and nine observational. The flowchart is shown in Figure 1. Twenty-five studies initially fulfilled our inclusion criteria. Thirteen additional studies were identified; four through the reviews of web-based pharmaceutical clinical trial registries and nine through the reviews of bibliographies of the previous meta-analyses.[10, 16] We then investigated why the nine latter studies were not included in our initial search results and discovered that their published versions did not contain either of the specific inclusive terms: “pneumonia” or “pneumoni*”. Study characteristics are shown in Tables 1 (*29 RCTs)*[3-7, 17-40] and 2 (*9 observational studies).*[8, 11-14, 41-44]

The 29 RCTs included 33,472 patients, of whom 18,715 received ICS and 14,757 received control treatment. The duration of trials ranged from 24 weeks to three years, with median duration of 12 months. The most studied ICS was fluticasone with 22,216 participants in 19 trials, followed by budesonide with 8,768 participants in eight trials, and 2 mometasone trials with 2,488 participants. We considered all RCTs as high quality studies based on the sequence generation and double-blinding. At the outcome-level RCTs were judged to be at ‘high’ rather than ‘very high’ risk of bias, as this bias would be expected to be non-differential.

There were nine observational studies, which included 292,430 patients, of whom 76,521 were on ICS and 215,909 were not on ICS. Seven studies were cohort and two were case-control studies. Eight studies assessed risk of pneumonia requiring admission to the hospital and one included patients admitted to either emergency room or hospital. While quality of pneumonia ascertainment was more systematic compared to RCTs, all observational studies were also judged to be at ’very high’ risk of bias due to high heterogeneity and conferred overall lower confidence in pneumonia and mortality outcomes (Table 3).

We attempted to obtain additional unpublished information on 11 trials by contacting corresponding authors by email. Five investigators replied to the first email sent and three were able to provide usable information on three trials. We received no replies to the second email attempts.

Pneumonia

All 29 RCTs were usable for estimating unadjusted increased risk of pneumonia with the use of ICS; RR 1.61; 95% CI 1.35-1.93, p<0.001 *(Figure 2)*. The heterogeneity was deemed acceptable (I^2=37%). Nineteen trials with fluticasone showed significantly increased risk of pneumonia, RR 1.76; 95% CI 1.53-2.02, p<0.001; while eight trials of budesonide and two trials of mometasone showed a non-significant risk, RR 1.27; 95% CI 0.86-1.87, p=0.23; and RR 1.36; 95% CI 0.57-3.22, p=0.49; respectively (e-Figure 5, Online Supplement). However, the difference among these three ICS subgroups was not significant (p=0.27, I^2=23%). Eight trials that allowed use of ICS in the run-in period showed slightly higher risk of pneumonia compared to 13 trials without ICS in run-in period, RR 1.70; 95% CI 1.13-2.55, p=0.01; versus RR 1.59; 95% CI 1.40-1.80, p<0.001; respectively. Two trials with oral corticosteroids used in the run-in period showed even higher risk of pneumonia, RR 2.14; 95% CI 1.29-3.58, p=0.003.

Four observational studies (2 cohort and 2 case-control) allowed estimation of unadjusted risk of pneumonia, which was increased, OR 1.89; 95% CI 1.39-2.58, p<0.001; with the near-maximum heterogeneity noted (Figure 2). Excluding two case-control studies improved heterogeneity somewhat (I^2=62%) and the estimated OR for pneumonia remained similar, OR 1.74; 95% CI 0.97-3.13, p=0.06.

Notably, there was no statistically significant difference (none is singular) between subgroups within any of the subgroup-level analyses.

Pneumonia-associated mortality and case-fatality

Six of 29 RCTs reported mortality experience among patients with pneumonia, hence they were useful in estimating risk of pneumonia-related mortality and fatality. There was no significant differences between ICS and non-ICS arms in either pneumonia-associated mortality; RR 1.50; 95% CI 0.85-2.67, p=0.16, or pneumonia fatality; RR 0.91; 95% CI 0.52-1.59, p=0.74 *(Figure 3)*, with no heterogeneity among these trials, I^2=0%. This suggested that significantly increased risk of pneumonia in ICS group was not proportionately followed by higher risks of pneumonia-associated mortality or pneumonia fatality, which were not significantly different between the ICS and non-ICS groups.

Only two observational studies allowed estimation of pneumonia-associated mortality (number of pneumonia cases who died divided by number of all patients, with or without pneumonia, in the ICS versus non-ICS groups). There was no difference in pneumonia-associated mortality between the ICS versus non-ICS groups; OR 1.09; 95% CI 0.98-1.21, p=0.13, I^2=0% *(Figure 4)*. Seven observational studies allowed estimation of unadjusted risk of pneumonia fatality (number of pneumonia cases who died divided by all pneumonia cases in the ICS versus non-ICS groups). There was a significant difference in pneumonia fatality between the ICS and non-ICS groups; OR 0.72; 95% CI 0.59-0.88, p=0.001, however, substantial heterogeneity was observed (I^2=74%., p<0.001).

Overall mortality

All RCTs allowed estimation of unadjusted risk of overall mortality with ICS use and the risk was not different from the comparison arm, RR 0.95; 95% CI 0.85-1.05, p=0.31; I^2=0% *(Figure 5)*. The risk estimate was similar for all three studied ICS medications. Six estimable observational studies demonstrated decreased unadjusted risk of overall mortality with ICS use but with high heterogeneity, OR 0.79; 95% CI 0.65-0.97, p=0.02, I^2=83% *(Figure 4)*. Exclusion of a single case-control study improved heterogeneity somewhat (I^2=72%) with no change in estimated risk, OR 0.75; 95% CI 0.60-0.94, p=0.01.

Study drop-out rates

All 29 RCTs were assessed for the study drop-out rates. Compared with placebo, use of ICS was associated with a lower relative risk of trial drop-out, RR 0.84; 95% CI 0.81-0.88, p<0.001; I^2=29% (e-Figure 6, Online Supplement).

Sensitivity analyses

Sensitivity analysis on effect size for statistical models showed no appreciable differences for any of the outcomes for fixed vs random effects. Excluding case-control studies decreased the heterogeneity without a change in overall results. Sensitivity analysis of all RCTs by "per protocol" (PP) strategy (excluding patients that did not complete the trial) rather than per ITT, decreased the estimated risks for pneumonia and overall mortality outcomes. This is as expected because the study completion was previously shown to be favored by ICS versus non-ICS arms.[21] For the outcome of overall mortality (e-Figure 7, Online Supplement), a change to PP strategy resulted in a significant decrease in unadjusted risk of overall mortality for patients in ICS arms, RR 0.89; 95% CI 0.81-0.99, p=0.03; I^2=0%). Sensitivity analysis with inclusion of "double-zero" events, and change in risk estimates from RR to OR or vice-versa did not significantly affect any results.

Discussion

Our findings confirm significantly increased unadjusted risk of pneumonia among ICS users in published RCTs as well as observational studies on the topic. Despite this observed risk, pneumonia-associated mortality, pneumonia fatality and overall mortality were not significantly different between the ICS and non-ICS group in RCTs. Surprisingly, observational studies showed significantly decreased risk of pneumonia fatality and overall mortality in the ICS group but with the substantial heterogeneity among these studies. The estimable risk of pneumonia-associated mortality in two observational studies was not different between ICS and non-ICS groups, but it was proportionately lower than the observed higher risk of incident pneumonia in those studies.

In terms of risk of pneumonia associated with ICS use, our results are remarkably similar to the results of a previous meta-analysis on the topic[10], although the total number of patients in the current meta-analysis is twice as large. Therefore, the evidence for increased unadjusted risk of pneumonia with ICS use remains robust. Also, similar to previous reports,[45] in our meta-analysis this risk was more prominent for fluticasone, which has higher corticosteroid receptor affinity compared to budesonide.[46] Although the subgroup analysis showed that the risk of pneumonia was higher in trials where corticosteroids were used in the run-in period, none of the differences among subgroups were statistically significant. A proposed rationale for the observed increased risk of pneumonia with ICS use is combination of immunosuppressive effect of corticosteroids superimposed on an exposed COPD patient with chronically obstructed airways frequently colonized with bacteria.[46] Of note, this risk is not uniform for all patients and is likely dependent on the host characteristics (age, COPD severity, functional status etc.) and medication effects (dose, duration and potency of ICS compounds).

The risk of incident pneumonia was estimated to be higher in observational studies than in RCTs. This could be likely explained by the retrospective inclusion of patients with pneumonia diagnosis without proper adjustment for the duration of preceding respiratory symptoms. A recent major trial showed that a half of all pneumonia events in the fluticasone arm were associated with an ongoing or unresolved COPD exacerbation.[5] The data from this trial's daily record cards showed more unresolved exacerbations preceding pneumonia

events in the ICS-treated patients.[5] While this effect is possible to study and analyze prospectively, the retrospective observational design would not allow this.

Despite an increased unadjusted risk of pneumonia in RCTs, meta-analysis on pneumonia-associated and overall mortality outcomes showed no significant difference between ICS and non-ICS groups. This could be expected if pneumonia events were not severe enough to affect the mortality outcomes. However, both COPD and pneumonia are among the most frequent causes of death, and as such the overall mortality would be expected to be higher in a group of COPD patients with higher rates of serious pneumonia. Moreover, pooling of the observational studies with >75,000 pneumonia events showed similar results. All pneumonia events in observational studies were diagnosed upon the emergency room or hospital admission making these more severe than ambulatory pneumonia events not requiring hospitalization. Therefore, we propose that although ICS might predispose COPD patients to the increased risk of pneumonia, their anti-inflammatory or other mitigating effect might counterbalance the pneumonia risk and result in similar or improved mortality. A recently published RCT on the role of systemic corticosteroids among patients hospitalized for community-acquired pneumonia with high inflammatory response has indicated a protective effect of corticosteroids.[47] This paradoxical beneficial effect of corticosteroids that has been earlier suggested[15, 46] might be further supported by the higher adherence among ICS users in RCTs. A sensitivity analysis by PP strategy, which accounted for the imbalance in drop-out rates in RCTs, showed that patients in ICS arms had significantly decreased unadjusted overall mortality compared to patients in non-ICS arms. Of note, the mortality was assessed completely, regardless of the compliance or drop out from the study protocol.

In view of a recently suggested “double-effect” of ICS,[46, 48] we also analyzed the risk of pneumonia case-fatality between ICS and non-ICS groups. In meta-analyses of both RCTs and observational studies, the estimated risks of pneumonia fatality were in the opposite direction from the observed increased risk for pneumonia, although patients who use ICS tend to be older [9] with more severe disease.

In a recent, population-based study Gershon et al. reported no difference in incidence of pneumonia requiring hospitalization in patients with newly prescribed combination of ICS and long acting beta agonists (LABA) compared to LABA alone.[49] However, patients with new prescriptions for ICS/LABA had decreased risk of overall mortality compared to those using LABA alone. Post hoc addition of this study (with more than 12,000 patients) to our meta-analysis did not change results.

This meta-analysis has several limitations, mostly rooted in the trials and studies we included. As mentioned earlier, many of the trials did not systematically define pneumonia events or require radiographic confirmation for cases of suspected pneumonia. While this specific limitation was largely averted in observational studies, pooling of observational studies resulted in large heterogeneity due to other inherent biases. Although included studies used varying and subjective criteria for the ascertainment of pneumonia diagnosis, this bias was non-differential relative to ICS and non-ICS groups and the expected effect of this bias on the mortality outcomes would not be expected to be different. Indeed, the studies differed widely in their methodologies and only a few of the studies were estimable for the

specific outcomes (e.g. pneumonia mortality), which might have affected the power of the meta-analysis to identify significant differences. Despite the above limitations, the overall similarity in the risk estimates for “pneumonia“ and changes in their direction for the mortality outcomes are considered as important findings. Our meta-analysis was prone to reporting bias as we depended solely on the investigator’s reporting of outcomes. Only about half of contributing authors replied to our enquiry and only a third was able to provide us the required information, hence the possibility for bias remains. Although all but one RCT[17] were sponsored by the pharmaceutical industry, we did not observe evidence for publication bias. We reviewed the clinical trials registry and included both published and unpublished studies. Also, solid evidence for increased unadjusted risk of pneumonia has been the finding in both the non-industry and industry-sponsored studies.

We investigated only the crude outcome risks, both in RCTs and in observational studies. A random enrollment in RCTs and a large number of patients in observational studies likely eased this concern. Although a few observational studies reported adjusted analyses, their selected predictor and outcome variables varied drastically precluding meaningful pooling. Moreover, the available adjusted risk estimates in the individual studies were all very similar to the unadjusted ones. Without individual-patient data, we could not study any differences in pneumonia-associated and overall mortality based on COPD severity or presence of comorbidities. We grouped all patients utilizing ICS into ICS-user group, regardless of ICS being used alone or in combination with other agents. Similarly, those in non-ICS user group were not using ICS regardless of potential use of other pertinent medications. More portioned investigation of ICS alone or in combination with other medications were not done at this stage.

Finally, the grade of confidence in risk estimates from the included studies ranged from low (pneumonia-associated mortality) to high (overall mortality) in RCTs and was lower in observational studies. Previously noted major limitation with ascertainment of pneumonia and associated mortality,[10] still remains. Only future prospective trials of ICS, which would systematically assess and monitor pneumonia as a prespecified outcome using objective pneumonia definitions could clarify this and other above-mentioned concerns.

Conclusion

Despite the fact that most RCTs and observational studies demonstrate increased risk of pneumonia associated with ICS use, the risks of pneumonia fatality and pneumonia-associated as well as overall mortality are, surprisingly, not increased in RCT’s and are reduced in observational studies. This paradox suggests an unexplained “double effect” of ICS in COPD patients and merits further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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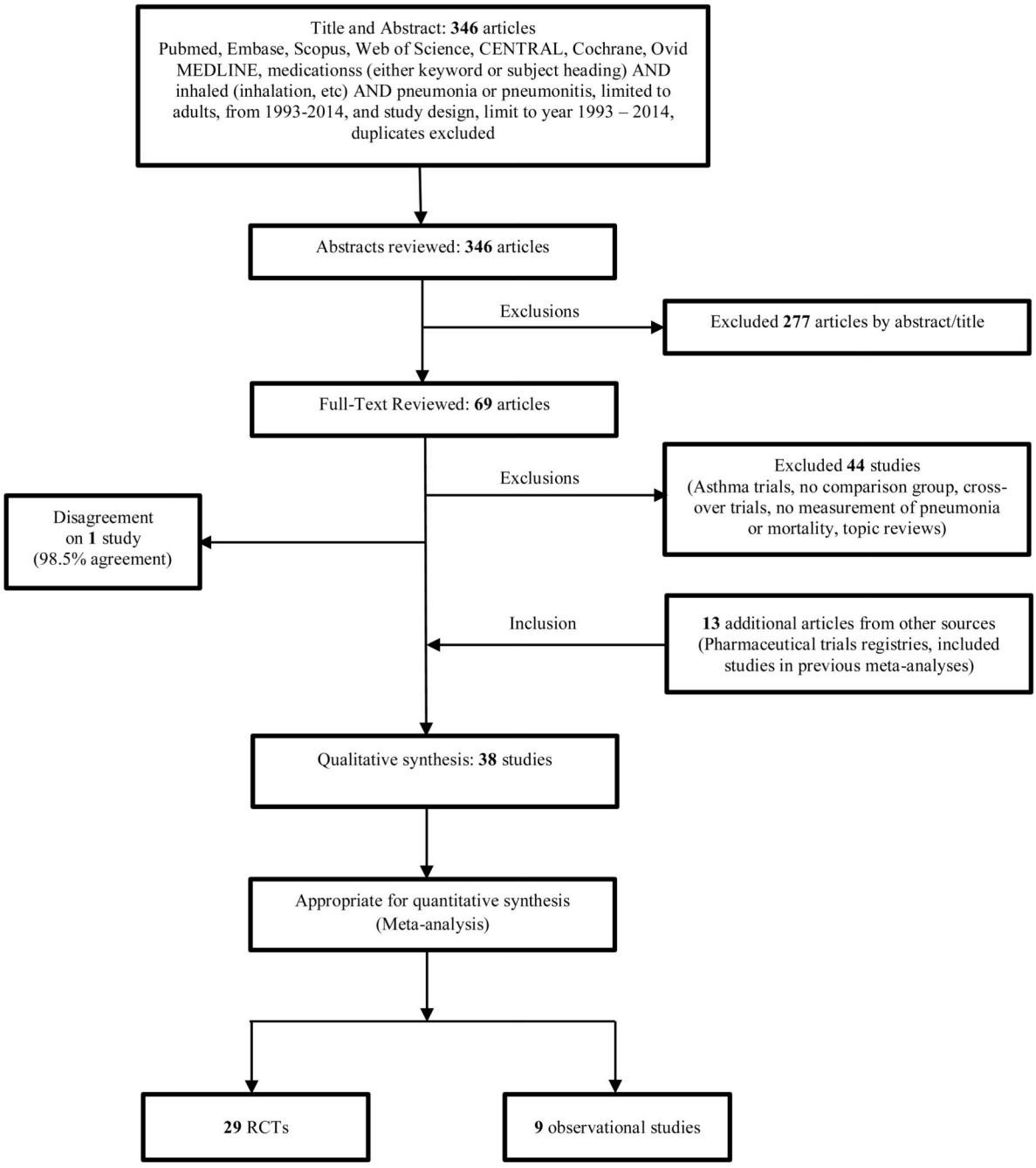
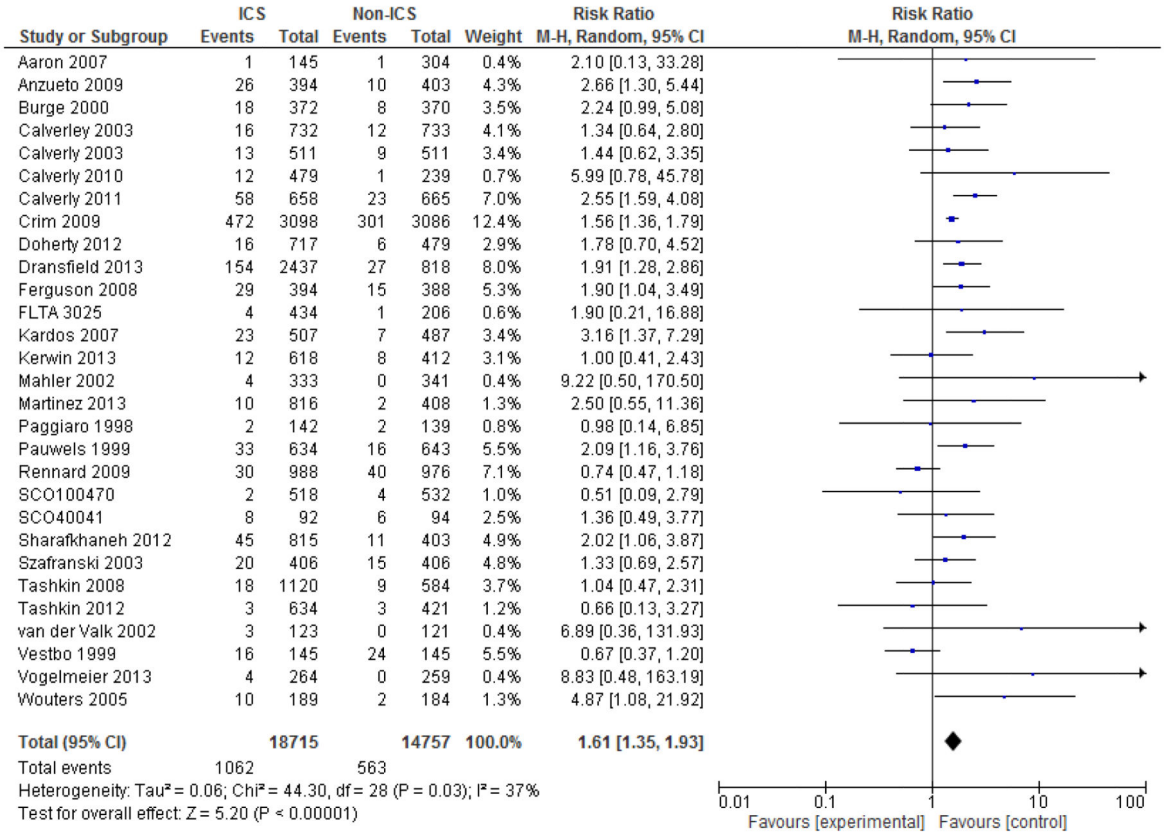


Figure 1. Study flow-chart

RCTs:



Observational:

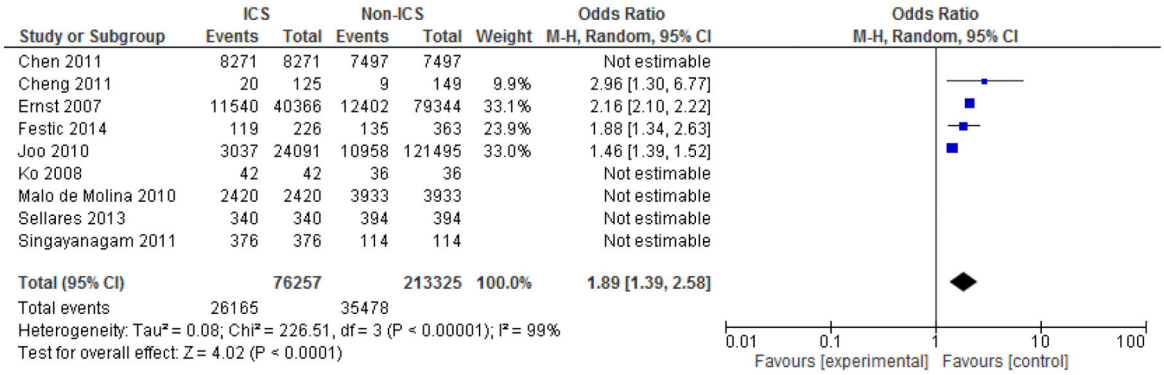
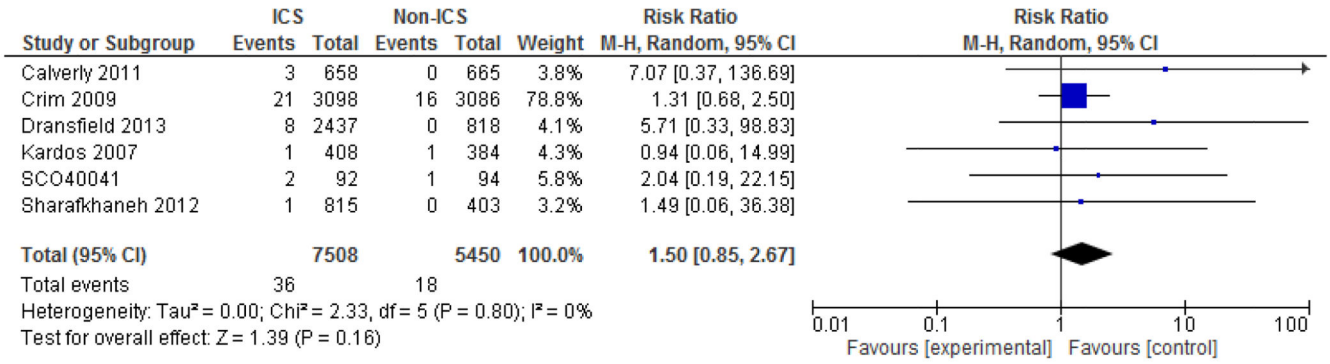


Figure 2. Meta-analysis of RCTs and observational studies for pneumonia. Risk estimates shown are relative risk (RR) for RCTs and odds ratio (OR) for observational studies

a. Pneumonia-associated mortality:



b. Pneumonia fatality:

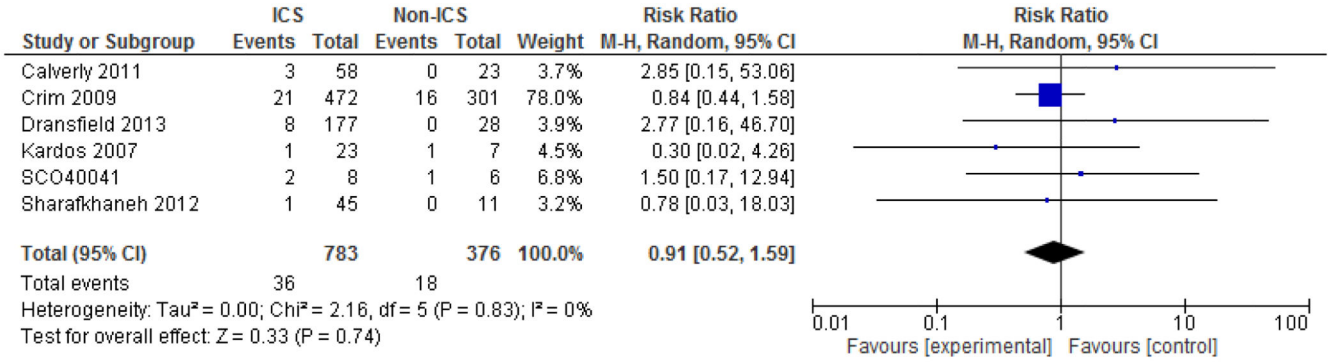
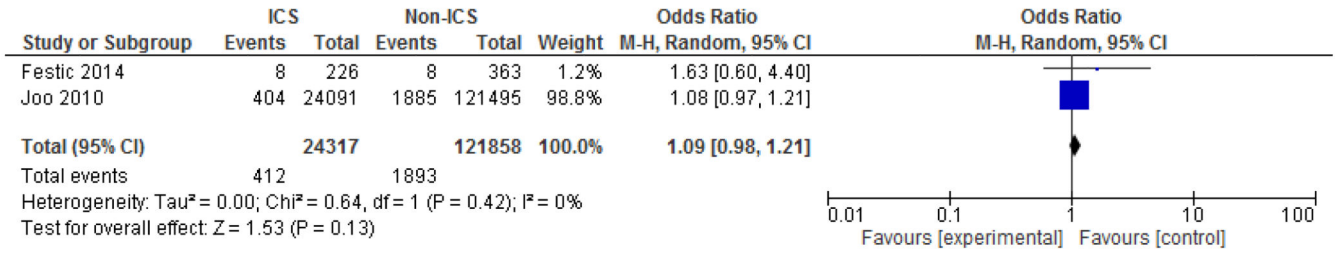


Figure 3. Meta-analysis of RCTs for pneumonia-associated mortality and pneumonia fatality. Risk estimates shown are relative risks (RR)

a. Pneumonia-associated mortality:



b. Pneumonia fatality:

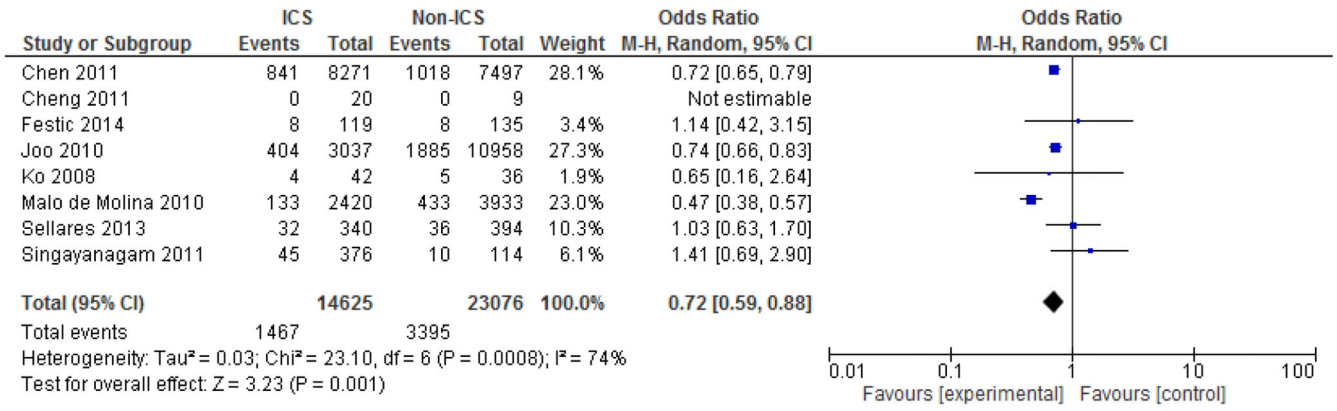
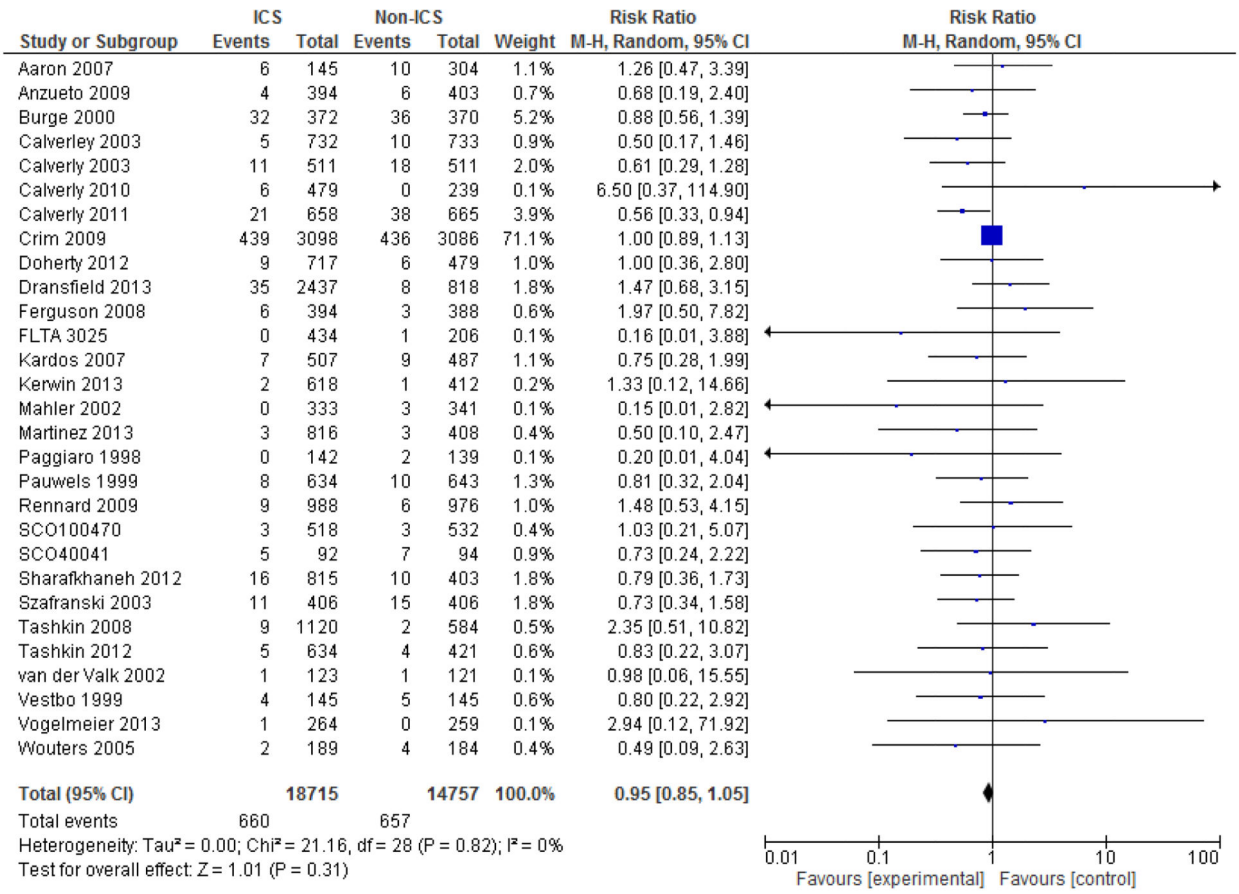


Figure 4. Meta-analysis of observational studies for pneumonia-associated mortality and case fatality. Risk estimates shown are odds ratios (OR)

RCTs:



Observational:

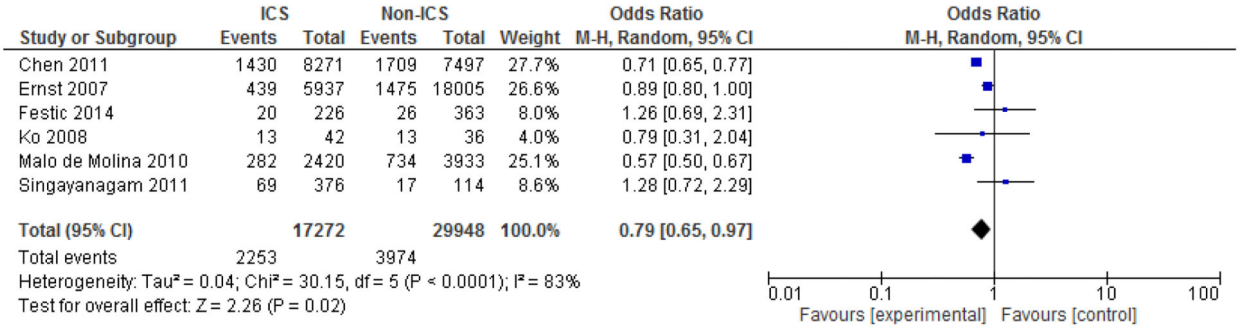


Figure 5. Meta-analysis of RCTs and observational studies for overall mortality. Risk estimates shown are relative risk (RR) for RCTs and odds ratio (OR) for observational studies

Table 1

Characteristics of randomized controlled trials

Source	COPD Patients	Setting	Duration (weeks)	Interventions	Enrolled/ Analyzed	Outcomes	Risk of bias	Funding
Aaron 2007[17]	Moderate to severe COPD	Outpatient	52	Tiotropium 18 μg +placebo Tiotropium 18 μg +salmeterol 25 μg Tiotropium 18 μg +Fluticasone/salmeterol 250/25 μg	156/82 148/84 145/108	Pneumonia Overall mortality	High Low	The Canadian Institutes of Health Research and the Ontario Thoracic Society
Anzueto 2009[4]	Moderate to severe COPD	Outpatient	52	Fluticasone propionate/ salmeterol 250 / 50 μg Salmeterol 50 μg	394/269 403/247	Pneumonia Overall mortality	Low Low	GlaxoSmithKline.
Burge 2000[30]	Moderate to severe COPD	Outpatient	156	Fluticasone propionate 500 μg Placebo	376/212 375/175	Pneumonia Overall mortality	High Low	Glaxo Wellcome Research and Development
Calverley 2003[18] - Maintenance therapy with budesonide and formoterol in COPD	Moderate to severe COPD	Outpatient	52	Budesonide/formoterol 320/9 μg Budesonide 400 μg Formoterol 9 μg Placebo	254/180 257/155 255/144 256/150	Pneumonia Overall mortality	High Low	AstraZeneca, Lund, Sweden
Calverley 2003[19]- Combined salmeterol and fluticasone in the treatment of COPD	Moderate to severe COPD	Outpatient	52	Fluticasone/salmeterol 500/50 μg Fluticasone propionate 500 μg Salmeterol 50 μg Placebo	358/269 374/266 372/253 361/221	Pneumonia Overall mortality	High Low	GlaxoSmithKline
Calverley 2010[20]	Moderate to severe COPD	Outpatient	48	Beclomethasone/ formoterol MDI 100/6μg Budesonide/formoterol DPI 200/6 μg Formoterol DPI 12 μg	237/205 242/212 239/204	Pneumonia Overall mortality	High Low	Chiesi Farmaceutici S.p.A
Calverley 2011[5]	Moderate to severe COPD	Outpatient	104	Salmeterol/fluticasone propionate 50/500 μg Tiotropium bromide 18 μg	658/426 665/386	Pneumonia Pneumonia mortality Overall mortality	Low Low low	GlaxoSmithKline and Nycomed
Crim 2009[21] (TORCH)	Moderate to severe COPD	Outpatient	156	Fluticasone 500 μg Salmeterol 50 μg Salmeterol/fluticasone 50/500 μg Placebo	1534/947 1521/960 1533/1011 1524/851	Pneumonia Pneumonia mortality Overall mortality	High High Low	GlaxoSmithKline
Doherty[22] 2012	Moderate to severe COPD	Outpatient	26	Mometasone /formoterol 400/10 μg Mometasone /formoterol 200/10 μg, Mometasone 400 μg, Formoterol 10 μg, or Placebo	225/190 239/202 253/202 243/193 236/169	Pneumonia Overall mortality	High Low	Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc.

Source	COPD Patients	Setting	Duration (weeks)	Interventions	Enrolled/ Analyzed	Outcomes	Risk of bias	Funding
Dransfield 2013[7]	Moderate to severe COPD	Outpatient	Pooled 2 studies; 104 and 102	Vilanterol 25 μg Fluticasone furoate 50 μg + vilanterol 25 μg Fluticasone furoate 100 + vilanterol 25 μg Fluticasone 200 μg + vilanterol 25 μg	409/294 408/315 403/312 402/301	Pneumonia Pneumonia mortality Overall mortality	Low Low Low	GlaxoSmithKline
Ferguson 2008[3]	Moderate to severe COPD	Outpatient	52	Fluticasone propionate/ salmeterol 250/50 μg Salmeterol 50 μg	394/277 388/239	Pneumonia Overall mortality	High Low	GlaxoSmithKline
FLTA 3025[34]	Moderate to severe COPD	Outpatient	24	Fluticasone propionate 250 μg Fluticasone propionate 500 μg Placebo	216/140 218/147 206/127	Pneumonia Overall mortality	High Low	Glaxo Wellcome Research and Development
Kardos 2007[23]	Moderate to severe COPD	Outpatient	48	Fluticasone propionate/salmeterol 500/50 μg Salmeterol 50 μg	507/408 487/384	Pneumonia Pneumonia mortality Overall mortality	High High Low	Mainly funded by GlaxoSmithKline but also received funds from Altana, AstraZeneca and Novartis
Kerwin 2013[40]	Moderate to severe COPD	Outpatient	24	Fluticasone/vilanterol 100/25 μg Fluticasone/vilanterol 50/25 μg Fluticasone 100 μg Vilanterol 25 μg Placebo	206/151 206/147 206/145 205/142 207/138	Pneumonia Overall mortality	Low low	GlaxoSmithKline
Mahler 2002[39]	Moderate to severe COPD	Outpatient	24	Fluticasone 500 μg Salmeterol 50 μg Fluticasone/salmeterol 500/50 μg Placebo	168/100 160/115 165/113 181/112	Pneumonia Pneumonia mortality Overall mortality	High High High **People who were hospitalized were withdrawn from the study	GlaxoSmithKline
Martinez 2013[24]	Moderate to severe COPD	Outpatient	24	Fluticasone furoate 100 μg Fluticasone furoate 200 μg Vilanterol 25 μg Fluticasone furoate / vilanterol 100/25 μg Fluticasone furoate / vilanterol 200/25 μg Placebo	204/155 203/160 203/161 204/144 205/158 205/146	Pneumonia Overall mortality	Low Low	GlaxoSmithKline
Paggiaro 1998[33]	Moderate to severe COPD	Outpatient	24	Fluiticasone propionate 500 μg Placebo	142/123 139/112	Pneumonia Overall mortality (not specified in article, pooled data from previous meta-analysis)	High High	Glaxo Wellcome Research and Development, Greenford, Middlesex UB6 0HE, UK
Pauwels 1999[32]	Moderate to severe COPD	Outpatient	156	Budesonide 400 μg Placebo	634/458 643/454	Pneumonia Overall mortality	High Low	Astra Draco, Lund, Sweden

Source	COPD Patients	Setting	Duration (weeks)	Interventions	Enrolled/ Analyzed	Outcomes	Risk of bias	Funding
Rennard 2009[25]	Moderate to severe COPD	Outpatient	52	Budesonide/formoterol pMDI 320/9 μg Budesonide/formoterol pMDI 160/9 μg Formoterol DPI 9 μg Placebo	494/360 494/351 495/338 481/306	Pneumonia Overall mortality	High Low	AstraZeneca LP, Wilmington, DE, USA
SCO100470[35]	Moderate to severe COPD	Outpatient	24	Fluticasone propionate/ Salmeterol 250/50 μg Salmeterol 50 μg	518/459 532/458	Pneumonia Overall mortality	High Low	GlaxoSmithKline
SCO40041[36]	Moderate to severe COPD	Outpatient	156	Fluticasone propionate/ Salmeterol 250/50 μg Salmeterol 50 μg	92/56 94/55	Pneumonia Pneumonia mortality Overall mortality	High High Low	GlaxoSmithKline
Sharafkhaneh 2012[6]	Moderate to severe COPD	Outpatient	52	Budesonide/formoterol pMDI 320/9 μg Budesonide/formoterol pMDI 160/9 μg Formoterol DPI 9 μg	407/290 408/290 404/271	Pneumonia Pneumonia mortality Overall mortality	High High Low	AstraZeneca LP, Wilmington, DE, USA
Szafranski 2003[31]	Moderate to severe COPD	Outpatient	52	Budesonide/formoterol 320/9 μg Budesonide 200 μg Formoterol 4.5 μg Placebo	208/149 198/136 201/137 205/115	Pneumonia Overall mortality	High Low	AstraZeneca
Tashkin 2008[27]	Moderate to severe COPD	Outpatient	26	Budesonide/formoterol pMDI 320/9 μg Budesonide/formoterol pMDI 160/9 μg Budesonide pMDI 320 μg + formoterol DPI 9 μg Budesonide pMDI 320 μg Formoterol DPI 9μg Placebo	277/238 281/243 287/239 275/212 284/223 300/223	Pneumonia Overall mortality	High Low	AstraZeneca LP,
Tashkin 2012[26]	Moderate to severe COPD	Outpatient	52; 26-week treatment *, 26-week safety extension	Mometasone/ formoterol 400/10 μg, Mometasone/ formoterol 200/10 μg, Mometasone 400 μg, Formoterol 10 μg, Placebo	217/176 207/169 210/164 209/172 212/159	Pneumonia Overall mortality	Low High	Supported by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc.
Van der valk 2002[37]	Moderate to severe COPD	Outpatient	26	Fluticasone 500 μg Placebo	123/122 121/120	Pneumonia Overall Mortality	High Low	Supported by the Netherlands Asthma Foundation, Amicon Health Insurance Co., Boehringer Ingelheim, and GlaxoSmithKline BV
Vestbo 1999	Moderate to severe COPD	Outpatient	156	Budesonide Placebo	145/109 145/94	Pneumonia Overall Mortality	High Low	ASTRA Denmark A/S, ASTRA Pharmaceutical Production AB Sweden
Vogelmeier 2013[29]	Moderate to severe COPD	Outpatient	26	QVA 149 (LABA indacaterol and the LAMA glycopyrronium in fixed combination) 110/50 μg Salmeterol/fluticasone 50μg/500μg	259/215 264/217	Pmeumonia Overall mortality	High Low	Main funding from Novartis Pharma AG. Authors on advisory board of multiple

Source	COPD Patients	Setting	Duration (weeks)	Interventions	Enrolled/ Analyzed	Outcomes	Risk of bias	Funding
								pharmaceuticals
Wouters 2005[38]	Moderate to severe COPD	Outpatient	52	Salmeterol/fluticasone 50μg/500μg Salmeterol 50μg	189/155 184/138	Pneumonia Overall mortality	High Low	GlaxoSmithKline

* Only the 26-week treatment phase was included in the meta-analysis. The extension phase did not have placebo group and only some patients from the treatment group was randomized to continue in the extension phase.

Table 2

Characteristics of observational studies

Study	Patients Characteristics	Setting	Duration	Exposure	Number of patients	Outcomes	Risk of bias
CASE – CONTROL STUDIES							
Ernst 2007 (Retrospective)	Population-based cohort design with a nested case control analysis for COPD patients 66 years of age or older	Inpatient	14 years (1988-2001)	ICS Non-ICS	40366 79344	Pneumonia (Crude & Adjusted) Overall mortality (Crude)	High* Low
Joo 2010 (Retrospective)	Nested case control study in a cohort of Veterans Affairs (VA) patients with newly diagnosed COPD patients 65 years of age or older	Inpatient	4 years (1998-2002)	ICS Non-ICS	24091 121495	Pneumonia (Crude & Adjusted) Pneumonia (30 day) mortality (Crude)	High* Low
COHORT STUDIES							
Chen 2011 (Retrospective)	Cohort of COPD patients, 65 years of age or older who had a discharge diagnosis of pneumonia	Inpatient	5 years (2002-2007)	ICS Non-ICS	8271 7497	Pneumonia (Crude) Pneumonia (30 day) mortality (Crude & Adjusted) Overall (90 day) mortality (Crude & Adjusted)	High* Low Low
Cheng 2011 (Prospective)	Cohort of moderate to severe COPD patients	Inpatient	2 years (2007-2008)	ICS Non-ICS	125 149	Pneumonia (Crude & Adjusted) Zero pneumonia deaths	Low Low
Festic 2014 (Retrospective)	Cohort of adult patients with pneumonia or other risk factors for ARDS	Inpatient	26 weeks (March 2009– August 2009)	ICS Non ICS	226 363	Pneumonia (Crude & Adjusted) Pneumonia mortality (Crude) Overall (90 day) mortality (Crude)	Low Low Low
Ko 2008 (Prospective)	Cohort of patients with acute exacerbation of COPD with concomitant pneumonia	Inpatient	1 year (2004-2005)	ICS Non ICS	42 36	Pneumonia (Crude) Pneumonia (Deaths during the same hospitalization) mortality (Crude) Overall (Deaths in the following 12 months) mortality (Crude)	Low Low Low
Malo de Molina 2010 (Retrospective)	Cohort of hospitalized patients with diagnosis of pneumonia who had a pre-existing diagnosis of COPD, age 65 or older	Inpatient	1 year (1999-2000)	ICS Non-ICS	2420 3933	Pneumonia (Crude) Pneumonia (30 day) mortality (Crude & Adjusted) Overall (90 day) mortality (Crude & Adjusted)	High* Low Low
Sellares 2013 (Prospective)	Community acquired pneumonia patients admitted through emergency room, age 16 or older	Inpatient	12 years (January 1997 – July 2008)	ICS Non-ICS	340 394	Pneumonia (Crude) Pneumonia mortality (Crude)	Low Low
Singanayagam 2011 (Prospective)	Spirometry-confirmed COPD patients presenting with a primary diagnosis of community acquired pneumonia	Inpatient	4 years (2005-2009)	ICS Non-ICS	376 114	Complicated pneumonia (Crude) Pneumonia (30 day) mortality (Crude & Adjusted) Overall (6 month) mortality (Crude & Adjusted)	Low Low Low

Table 3

Outcome-level GRADE assessment tables

Outcome: Pneumonia											
Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Risk with Non-ICS	Risk difference with ICS (95% CI)
RCTs											
33472 (29 studies) 12 months	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[3]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to risk of bias	563/14757 (3.8%)	1062/18715 (5.7%)	**RR 1.61** (1.35 to 1.93)	**Study population**	
										38 per 1000	**23 more per 1000** (from 13 more to 35 more)
										Moderate	
										16 per 1000	**10 more per 1000** (from 6 more to 15 more)
Observational											
292430 (9 studies)	serious[4]	very serious[5]	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, inconsistency	38063/215909 (17.6%)	26458/76521 (34.6%)	**OR 1.89** (1.39 to 2.58)	**Study population**	
										176 per 1000	**112 more per 1000** (from 53 more to 180 more)
										Moderate	
										1000 per 1000	-

Outcome: Pneumonia fatality											
Quality assessment							Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Risk with Non-ICS	Risk difference with ICS (95% CI)
RCTs											

Outcome: Pneumonia fatality											
Quality assessment							Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Risk with Non-ICS	Risk difference with ICS (95% CI)
1159 (6 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ **LOW**[1,2] due to risk of bias, imprecision	18/376 (4.8%)	36/783 (4.6%)	**RR 0.91** (0.52 to 1.59)	**Study population**	
										48 per 1000	**4 fewer per 1000** (from 23 fewer to 28 more)
										Moderate	
										27 per 1000	**2 fewer per 1000** (from 13 fewer to 16 more)
Observational											
37672 (7 studies)	serious[1]	serious[3]	no serious indirectness	no serious imprecision	undetected	⨁◯◯◯ **VERY LOW**[1,3] due to risk of bias, inconsistency	3395/23067 (14.7%)	1467/14605 (10%)	**OR 0.72** (0.59 to 0.88)	**Study population**	
										147 per 1000	**37 fewer per 1000** (from 15 fewer to 55 fewer)
										Moderate	
										110 per 1000	**28 fewer per 1000** (from 12 fewer to 42 fewer)

Outcome: Overall mortality											
Quality assessment							Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Risk with Non-ICS	Risk difference with ICS (95% CI)
RCTs											
33472 (29 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH**	657/14757 (4.5%)	660/18715 (3.5%)	**RR 0.95** (0.85 to 1.05)	**Study population**	
										45 per 1000	**2 fewer per 1000** (from 7 fewer to 2 more)

Outcome: Overall mortality											
Quality assessment							Summary of Findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Risk with Non-ICS	Risk difference with ICS (95% CI)
										Moderate	
										14 per 1000	**1 fewer per 1000** (from 2 fewer to 1 more)
Observational											
47220 (6 studies)	serious[1]	serious[2]	no serious indirectness	no serious imprecision	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2] due to risk of bias, inconsistency	3974/29948 (13.3%)	2253/17272 (13%)	**OR 0.79** (0.65 to 0.97)	**Study population**	
										133 per 1000	**25 fewer per 1000** (from 3 fewer to 42 fewer)
										Moderate	
										168 per 1000	**30 fewer per 1000** (from 4 fewer to 52 fewer)

[1] No systematic ascertainment of pneumonia outcome

[2] Heterogeneity present but not substantial

[3] Several studies showing non-significant risk and wide confidence intervals represent only 4% of overall weight in RCTs

[4] Unclear length of duration of respiratory symptoms/unresolving exacerbations and step up therapy with ICS prior to admission with pneumonia

[5] Maximum heterogeneity noted

[1] Difficulty with ascertainment of pneumonia-relatedness

[2] Wide confidence intervals in majority of the estimable studies

[3] Substantial heterogeneity

[1] Non-randomized, retrospective, observational design

[2] Substantial heterogeneity