

Long-term Use of Inhaled Corticosteroids and the Risk of Pneumonia in Chronic Obstructive Pulmonary Disease

A Meta-analysis

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Background: Recent studies have suggested a possible association between pneumonia and the use of inhaled corticosteroids. We aimed to ascertain the risk of pneumonia with long-term inhaled corticosteroid use among patients with chronic obstructive pulmonary disease (COPD).

Methods: We performed systematic searches with no date restrictions through June 30, 2008, of MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, regulatory documents, and trial registries. We included randomized controlled trials of any inhaled corticosteroid vs a control treatment for COPD, with at least 24 weeks of follow-up and reporting of pneumonia as an adverse event. Outcomes evaluated included any pneumonia, serious pneumonia, pneumonia-related mortality, and overall mortality.

Results: Eighteen randomized controlled trials (n=16 996) with 24 to 156 weeks of follow-up were included after a

detailed screening of 97 articles. Inhaled corticosteroids were associated with a significantly increased risk of any pneumonia (relative risk [RR], 1.60; 95% confidence interval [CI], 1.33-1.92 [$P < .001$]; $I^2=16\%$) and serious pneumonia (1.71; 1.46-1.99 [$P < .001$]; $I^2=0\%$) but without a significantly increased risk of pneumonia-related mortality (1.27; 0.80-2.03 [$P = .31$]; $I^2=0\%$) or overall mortality (0.96; 0.86-1.08 [$P = .51$]; $I^2=0\%$). Inhaled corticosteroids were associated with a significantly increased risk of serious pneumonia when compared with placebo (RR, 1.81; 95% CI, 1.44-2.29 [$P < .001$]) or when the combination of inhaled corticosteroids and long-acting β -agonists was compared with long-acting β -agonists (1.68; 1.20-2.34 [$P = .002$]).

Conclusion: Among patients with COPD, inhaled corticosteroid use for at least 24 weeks is associated with a significantly increased risk of serious pneumonia, without a significantly increased risk of death.

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INHALED CORTICOSTEROIDS SUCH AS fluticasone propionate, budesonide, and beclomethasone dipropionate are widely used for the treatment of chronic obstructive pulmonary disease (COPD).^{1,2} They are recommended in combination with long-acting bronchodilators to reduce the frequency of exacerbations in symptomatic patients with a forced expiratory volume in the first second of expiration of less than 50% predicted (stage III, severe COPD; stage IV, very severe COPD) and repeated exacerbations.¹

The known adverse effects associated with inhaled corticosteroid use include the development of oropharyngeal candidiasis,² cataracts,³ and fractures.⁴ In a recent trial, patients with COPD who received inhalers containing fluticasone had a higher probability of pneumonia.⁵ Another recent observational study raised the possi-

bility of an association between the use of inhaled corticosteroids and the risk of hospitalization for pneumonia and mortality in elderly patients with COPD.⁶ It is unclear whether the association with pneumonia is specific to the inhaled corticosteroid component or occurs because of an interaction with the long-acting β -agonist component of the combination inhaler. The magnitude and the strength of this potential association, if any, are also unknown. Limited information is currently available to clinicians on the long-term safety of inhaled corticosteroids in COPD.¹

Our primary objectives were to systematically review the current evidence of the risks of pneumonia with long-term use of inhaled corticosteroids in patients with COPD. We also aimed to ascertain the risk of pneumonia-related mortality and overall mortality in these trials as a secondary objective.

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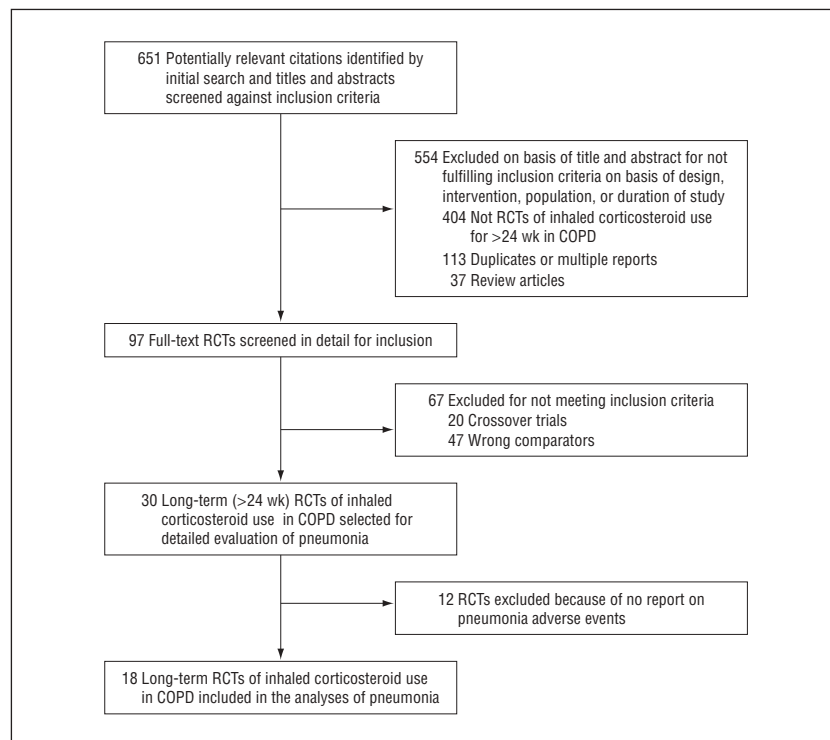


Figure 1. Flowchart describing study selection and excluded studies. COPD indicates chronic obstructive pulmonary disease; RCT, randomized controlled trial.

METHODS

ELIGIBILITY CRITERIA

Our specific inclusion criteria were (1) study design consisting of a randomized controlled trial (RCT) for any inhaled corticosteroid (fluticasone, beclomethasone, or budesonide) with at least 24 weeks of follow-up; (2) study participants with COPD; (3) an inhaled corticosteroid as the intervention drug vs a control treatment, in which the comparison groups consisted of inhaled corticosteroids vs placebo or inhaled corticosteroid in combination with a long-acting β -agonist vs a long-acting β -agonist; and (4) data on the incidence of pneumonia (including 0 events) as an adverse event.

The analysis was restricted to RCTs of more than 24 weeks' duration to evaluate the risk of pneumonia associated with long-term use of inhaled corticosteroids. Randomized controlled trials of inhaled corticosteroids in patients with asthma were ineligible for inclusion. Observational studies susceptible to confounding and channeling bias were also excluded.

SEARCH STRATEGY

Two reviewers (A.V.A. and Y.K.L.) independently and in duplicate searched

PubMed and EMBASE with the clinical trial filters using the search terms *fluticasone* or *budesonide* or *beclomethasone* or *beclomethasone* and *chronic* and *obstructive* with no language or date restrictions through June 30, 2008. Published or unpublished trials were retrieved from the Cochrane Database of Systematic Reviews, Web sites of the US Food and Drug Administration and European regulatory authorities, the manufacturers' product information sheets, and the manufacturers' clinical trials register of fluticasone and beclomethasone (GlaxoSmithKline)⁷ and budesonide (AstraZeneca).⁸ We checked the included and excluded studies lists from systematic reviews and meta-analyses of inhaled corticosteroids in COPD⁹⁻¹⁴ and the bibliographies of included studies and used the Web of Science citation index to identify relevant articles.

STUDY SELECTION

Two reviewers (A.V.A. and Y.K.L.) independently and in duplicate scanned all titles and abstracts that indicated the study was an RCT evaluating the use of inhaled corticosteroids by patients with COPD. After obtaining full reports of potentially relevant trials, the same reviewers independently assessed eligibility from full-text articles. Disagreements regarding eligibility were resolved with a third reviewer through consensus.

STUDY CHARACTERISTICS

A standard protocol was used to record the location and duration of the trial, the criteria used to diagnose COPD in participants, the primary outcome measure, the dose and frequency of inhaled corticosteroid and control interventions, the mean age and sex of participants, the severity of COPD in the participants as mean predicted forced expiratory volume in the first second of expiration, previous inhaled corticosteroid use, and the percentage of current smokers enrolled.

QUALITY ASSESSMENT

The Cochrane Toolkit was used for the assessment of bias in evaluating each trial for the reporting of sequence generation, allocation concealment, the use of blinding of participants and personnel, and information on loss to follow-up.¹⁵ Information was extracted on additional potential sources of bias such as withdrawal rates. The frequency and type of adverse event monitoring during the follow-up period were evaluated as recommended in the Cochrane Handbook for Systematic Reviews of Interventions¹⁵ to determine the strength of adverse event monitoring.

OUTCOME MEASURES

The end points of any pneumonia (pneumonia as an adverse event irrespective of severity) and serious pneumonia (pneumonia as a serious adverse event) were prespecified as the primary outcome measures. Serious adverse events are life-threatening, require hospitalization, or lead to significant disability or death.¹⁶ The end points of pneumonia-related mortality (any death in which pneumonia was the cause of death) and overall mortality were prespecified as secondary outcome measures. The primary outcome of any pneumonia was inclusive of pneumonia reported as a serious adverse event, and the primary outcome of serious pneumonia was inclusive of pneumonia-related mortality.

DATA EXTRACTION

Two reviewers (A.V.A. and Y.K.L.) independently and separately extracted data (including 0 events) on any pneumonia among listings of adverse events, serious pneumonia among listings of pneumonia terms reported as serious adverse events, and pneumonia-related mortality and overall mortality from

Table 1. Characteristics of RCTs of Inhaled Corticosteroid Use Included in the Analysis of Pneumonia Adverse Events

Source	Location	Treatment Duration, wk	COPD Criteria, %	Primary Outcome	Drug	Male, %	Age, Mean (SD), y	Mean (SD) Predicted FEV ₁ , %	% of Subjects	
									Prior ICS Use	Current Smokers
Aaron et al, ²⁰ 2007 ^a	27 Centers in Canada	52	FEV ₁ :FVC ratio, <70	COPD exacerbation	SFC, 50/500 µg BID Sal, 50 µg	57.9 57.4	67.5 (8.9) 67.6 (8.2)	39.4 (11.9) 38.0 (13.1)	70.8 78.8	32.4 24.3
Burge et al, ²¹ 2000	18 UK hospitals	156	FEV ₁ :FVC ratio, <70	Decline in FEV ₁	Flu, 500 µg BID Placebo	75.0 74.2	63.7 (7.1) 63.8 (7.1)	50.3 (14.9) 15.0 (14.9)	51.1 57.0	36.4 39.2
Calverley et al, ²² 2003	196 Centers in 25 countries	52	ERS	FEV ₁	SFC, 50/500 µg BID Sal, 50 µg BID Flu, 500 µg BID Placebo	75 70 70 75	62.7 (8.7) 63.2 (8.6) 63.5 (8.5) 63.4 (8.6)	44.8 (14.7) 44.3 (13.8) 45.0 (13.6) 44.2 (13.7)	50 49 54 52	52 51 53 47
Calverley et al, ²³ 2003	109 Centers in 15 countries	52	GOLD	FEV ₁ and HRQOL	For, 9 µg + Bud, 400 µg BID For, 9 µg BID Bud, 400 µg BID Placebo	78 75 74 75	64 (NA) 63 (NA) 64 (NA) 65 (NA)	36 (10) 36 (10) 36 (10) 36 (10)	47 48 51 46	33 36 39 30
Calverley et al, ⁵ 2007	44 Centers in 42 countries	156	ERS	Mortality	SFC, 50/500 µg BID Sal, 50 µg Flu, 500 µg BID Placebo	75 76 75 76	65 (8.3) 65.1 (8.2) 65 (8.4) 65 (8.2)	44.3 (12.3) 43.6 (12.6) 44.1 (12.3) 44.1 (12.3)	47 45 47 51	43 43 43 43
Ferguson et al, ²⁴ 2008	94 Centers in North America	52	ATS	Rate of exacerbations	SFC, 50/250 µg BID Sal, 50 µg BID	58.3 52.0	64.9 (9.0) 65.0 (9.1)	39.8 (13.9) 50.6 (15.4)	15 18	40 38
FLTA3025, ²⁵ 2005	55 US centers	24	ATS	FEV ₁	Flu, 500 µg BID Flu, 250 µg BID Placebo	66 72 70	63.3 (10) 65.2 (8.7) 64.8 (9.5)	1301 (500) ^b 1240 (486) ^b 1221 (502) ^b	NA NA NA	NA NA NA
Hanania et al, ²⁶ 2003	76 US centers	24	ATS	FEV ₁	SFC, 50/250 µg BID Sal, 50 µg BID Flu, 250 µg BID Placebo	61 58 66 58	63 (NA) 64 (NA) 63 (NA) 65 (NA)	41 (11) 42 (12) 42 (11) 42 (12)	23 20 28 30	43 51 48 47
Kardos et al, ²⁷ 2007	95 Centers in Germany	52	GOLD	COPD exacerbations	SFC, 50/500 µg BID Sal, 50 µg BID	74.0 77.6	63.8 (8.3) 64 (8.2)	40.4 (8.9) 40.3 (8.5)	40.6 44.4	49.7 49.9
Mahler et al, ²⁸ 2002	Multicenter US trial	24	ATS	FEV ₁ and TDI	SFC, 50/500 µg BID Sal, 50 µg BID Flu, 500 µg BID Placebo	62 64 61 75	61.9 (NA) 63.5 (NA) 64.4 (NA) 64 (NA)	41 (NA) 40 (NA) 41 (NA) 41 (NA)	28 31 25 18	46 46 46 54
Paggiaro et al, ²⁹ 1998	13 European centers	24	ERS	Exacerbations	Flu, 500 µg BID Placebo	99 78	62 (NA) 64 (NA)	59 (18) 55 (17)	NA NA	49 49
SCO100250, ³⁰ 2008	98 US and Canadian centers	52	FEV ₁ :FVC ratio, <70	Rate of exacerbations	SFC, 50/250 µg BID Sal, 50 µg BID	51 57	65.4 (NA) 65.3 (NA)	<50 ^c <50 ^c	NA NA	NA NA
SCO100470, ³¹ 2006	135 Centers in Europe and Asia-Pacific	24	GOLD	FEV ₁ and TDI	SFC, 50/250 µg BID Sal, 50 µg BID	78.3 77.2	63.5 (9.3) 63.7 (9.0)	1654 (459) ^b 1681 (465) ^b	NA NA	42 44
SCO40041, ³² 2008	31 US centers	156	GOLD	Bone mineral density	SFC, 50/250 µg BID Sal, 50 µg BID	59.7 62.7	65.4 (8.36) 65.9 (9.52)	<70 <70	NA NA	NA NA
SFCT01/ SCO30002, ³³ 2005	49 Centers in Italy and Poland	52	FEV ₁ :FVC ratio, <88	Time to exacerbations	Flu, 500 µg BID Placebo	83.9 80.0	64.6 (8.7) 65.7 (9.0)	NA NA	NA NA	NA NA
van der Valk et al, ³⁴ 2002	Pulmonary clinics	26	ATS	Exacerbations and HRQOL	Flu, 500 µg BID Placebo	85.4 83.5	64.1 (6.8) 64 (6.7)	57.5 (14.1) 56.1 (14.8)	86.2 80.2	22.0 33
Vestbo et al, ³⁵ 1999	Community in Denmark	156	FEV ₁ :FVC ratio, <70	Rate of FEV ₁ decline	Bud, 400 µg BID Placebo	58.6 62.1	59.0 (8.3) 59.1 (9.7)	86.2 (20.6) 86.9 (21.1)	NA NA	75.9 77.2
Wouters et al, ³⁶ 2005	39 Centers in the Netherlands	52	FEV ₁ :FVC ratio, <88	Rate of FEV ₁ decline	SFC, 50/500 µg BID Sal, 50 µg BID	73 75	63 (7.9) 64 (7.7)	47.4 (13.9) 48.2 (12.9)	85 87	39 35

Abbreviations: ATS, American Thoracic Society; BID, twice daily; Bud, budesonide; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV₁, forced expiratory volume in the first second of expiration; Flu, fluticasone propionate; For, formoterol; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQOL, health-related quality of life; NA, not available; RCT, randomized controlled trial; Sal, salmeterol xinafoate; SFC, combination of salmeterol and fluticasone; TDI, transitional dyspnea index.

^aIndicates treatment with tiotropium bromide, 18 µg/d, in both arms and an additional tiotropium arm. Influenza vaccination was only reported for Aaron et al²⁰ at 75.5% and unavailable for the other studies.

^bReported mean FEV₁ in milliliters as percentage of predicted unavailable.

^cIndicates FEV₁ less than 50% predicted (exact mean and SD data were unavailable).

safety data collected as part of serious adverse event reporting for each study.

Data in the clinical trials register and the regulatory documents were reconciled with that of the published journal article when possible. If there were multiple reports for a particular study, data

from the most recent version were extracted. When specific aspects of the data required clarification, the authors were contacted.

Two reviewers (A.V.A. and Y.K.L.) were independently involved in all stages of study selection, data extraction, and

quality assessment. All discrepancies were resolved with 100% agreement after rechecking the source papers, further discussion among the reviewers, and consultation with a third reviewer (S.S.), with full consensus obtained before drafting the article.

Table 2. Quality Assessment of Included RCTs of Inhaled Corticosteroids in COPD^a

Source	Sequence Generation	Allocation Concealment	Monitoring of AEs	Drug (No. of Subjects)	No. (%)	
					Withdrawal Rates	Lost to Follow-up
Aaron et al, ²⁰ 2007	Adequate, central allocation	Adequate	Captured through monthly telephone interviews and checklist; pneumonia recorded only as SAE leading to hospitalization or death	SFC (145) Sal (148)	15 (10.3) 20 (13.5)	2 (1.4) 2 (1.4)
Burge et al, ²¹ 2000	Adequate, computer generated, stratified by center	Adequate	AEs and SAEs recorded throughout study	Flu (372) Placebo (370)	160 (43.0) 195 (52.7)	16 (4.3) 18 (4.9)
Calverley et al, ²² 2003	Adequate computer generated	Adequate	AE or SAE occurring during therapy	SFC (358) Sal (372) Flu (374) Placebo (361)	89 (24.9) 119 (32.0) 108 (29.0) 140 (38.8)	8 (2.2) 8 (2.2) 8 (2.1) 6 (1.7)
Calverley et al, ²³ 2003	Unclear	Unclear	AEs recorded at 1, 2, 3, 6, 9, and 12 mo of treatment	For/Bud (254) For (255) Bud (257) Placebo (256)	74 (29.1) 111 (43.5) 102 (40.0) 106 (41.4)	4 (1.6) 4 (1.6) 4 (1.6) 6 (2.3)
Calverley et al, ⁵ 2007 ^b	Adequate, schedule generated by system for central allocation	Adequate	AEs reviewed at each visit; no prospective confirmation by radiographs; pneumonia recorded as subset of exacerbations	SFC (1533) Sal (1521) Flu (1534) Placebo (1524)	522 (34.1) 561 (36.9) 587 (38.3) 673 (44.2)	29 (1.9) 15 (1.0) 24 (1.6) 21 (1.4)
Ferguson et al, ²⁴ 2008	Unclear	Unclear	AEs collected at study start and end	FSC (394) Sal (388) Flu (434) Placebo (206)	117 (29.7) 149 (38.4) 147 (33.9) 79 (38.3)	10 (2.5) 10 (2.6) NA NA
FLTA3025, ²⁵ 2005	Unclear	Unclear	AEs and SAEs recorded at each visit	SFC (178) Sal (177) Flu (183) Placebo (185)	53 (30.0) 57 (32.2) 49 (26.8) 59 (31.9)	NA NA NA NA
Hanania et al, ²⁶ 2003	Unclear	Unclear	AE reporting at each visit	SFC (507) Sal (487) SFC (165) Sal (160) Flu (168) Placebo (181)	99 (19.5) 103 (21.1) 52 (31.5) 45 (28.2) 68 (40.5) 69 (38.1)	4 (0.8) 3 (0.6) NA NA NA NA
Kardos et al, ²⁷ 2007	Adequate, centrally generated block	Adequate	AEs and SAEs recorded during trial and follow-up	Flu (142) Placebo (139)	19 (13.3) 27 (19.4)	0 2 (1.4)
Mahler et al, ²⁸ 2002	Unclear	Unclear	AEs and SAEs documented	SFC (394) Sal (403)	125 (31.7) 156 (38.7)	NA NA
Paggiaro et al, ²⁹ 1998	Adequate, computer generated	Adequate	AE defined as untoward medical occurrence during treatment	SFC (518) Sal (532)	59 (11.4) 74 (13.9)	NA NA
SCO100250, ³⁰ 2008	Unclear	Unclear	AEs and SAEs recorded after study medication administration but no later than last date after study medication administration	SFC (92) Sal (94) Flu (131) Placebo (125)	36 (39.1) 39 (41.5) 34 (26.0) 40 (32.0)	NA NA NA NA
SCO100470, ³¹ 2006	Unclear	Unclear	AEs and SAEs recorded at each study visit	Flu (123) Placebo (121)	1 (0.8) 1 (0.8)	0 0
SCO40041, ³² 2008	Unclear	Unclear	AEs and SAEs monitored during therapy	Bud (145) Placebo (145)	36 (24.8) 51 (35.2)	0 0
SFCT01/ SCO30002, ³³ 2005	Unclear	Unclear	All AEs occurring after subject consented to participate until end of follow-up	SFC (189) Sal (184)	34 (18.0) 46 (25.0)	0 0
van der Valk et al, ³⁴ 2002	Adequate, permuted blocks, stratified	Adequate	3- and 6-mo follow-up			
Vestbo et al, ³⁵ 1999	Adequate, computer generated	Adequate	Participants seen every 3 mo			
Wouters et al, ³⁶ 2005	Adequate	Adequate	AE collected at start and end of treatment			

Abbreviations: AE, adverse event; Bud, budesonide; COPD, chronic obstructive pulmonary disease; Flu, fluticasone propionate; For, formoterol; For/Bud, combination of formoterol and budesonide; NA, not available; RCT, randomized controlled trial; SAE, serious AE; Sal, salmeterol xinafoate; SFC, combination of salmeterol and fluticasone.

^aAll RCTs were double blind.

^bData on pneumonia were extracted from the US Food and Drug Administration presentation^{37,38} because the published version provided information on the probability of pneumonia and not the actual number of events.

QUANTITATIVE DATA SYNTHESIS AND SENSITIVITY ANALYSIS

We used Review Manager software, version 5.0.15 (Nordic Cochrane Center, Copenhagen, Denmark), to calculate pooled relative risk (RR) and 95% con-

fidence intervals (CIs) using a random-effects model. Outcome data and data on trial participants were analyzed using a 2 × 2 format according to the intention-to-treat principle. All reported P values are 2 sided, with significance set at less than .05. Statistical heterogeneity was assessed using the I² statistic; values of 50%

or more indicated a substantial level of heterogeneity.¹⁷ If substantial statistical heterogeneity was present (I² > 50%), we planned to explore individual study characteristics and those of subgroups of the main body of evidence.

We performed a sensitivity analysis to explore the influence on effect size for

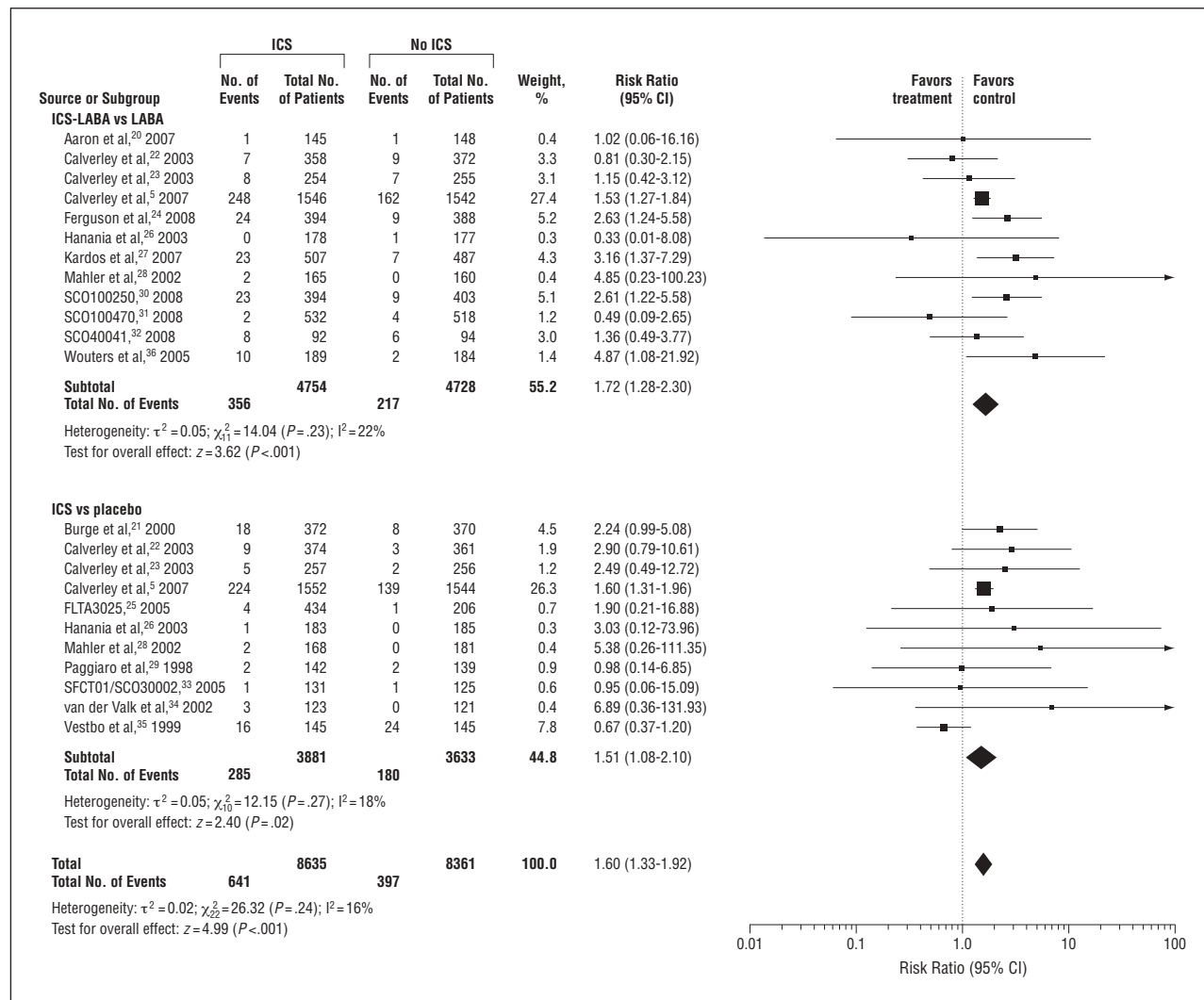


Figure 2. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) use vs control treatment for any pneumonia. CI indicates confidence interval; LABA, long-acting β -agonist.

statistical models (fixed vs random effects), the influence of individual trials, and the risk of bias by restricting the analysis to RCTs considered to be at low risk of bias (adequate sequence generation, allocation concealment, and double blinding, with clear reporting of loss to follow-up). The fail-safe numbers using the Rosenberg method¹⁸ were calculated to assess for the influence of publication bias on the meta-analysis. The fail-safe number represents the number of nonsignificant studies that would need to be added to a meta-analysis to reverse an overall statistically significant result to nonsignificance.

The number needed to harm with inhaled corticosteroids was calculated by applying the pooled RR estimates from the meta-analysis to the control event rate in a large trial population using Visual Rx, version 2.0.¹⁹ The number needed to harm is the number of patients with COPD who needed to be treated with inhaled corticosteroid, rather than with pla-

cebo or active comparators, for 1 additional patient to be harmed by an adverse event of pneumonia.

RESULTS

Of the 651 potentially relevant citations identified, and after a detailed review of 97 of those studies, 18 trials^{5,20-36} fulfilled our inclusion criteria. The flow of the trial is shown in **Figure 1**. Trial characteristics are given in **Table 1**.

The trials included 16 996 patients, of whom 8635 received inhaled corticosteroids and 8361 received control therapy. The trials ranged in duration from 24 weeks to 3 years. The sample size ranged from 186 to 6184 in these trials. Six RCTs^{21,25,29,33-35} compared inhaled corticosteroids with placebo. Seven RCTs^{20,24,27,30-32,36} compared in-

haled corticosteroids and long-acting β -agonist combinations with long-acting β -agonists. Five RCTs^{5,23,26,28,31} had 4 arms that compared inhaled corticosteroids with placebo and the combination of inhaled corticosteroids and long-acting β -agonist with long-acting β -agonists. Ten RCTs^{5,20-22,27-29,33,34,36} evaluated inhaled fluticasone propionate, alone or in combination with salmeterol xinafoate, at a dosage of 500 μ g twice daily, and 6 trials^{24-26,30-32} evaluated inhaled fluticasone propionate at a dosage of 250 μ g twice daily. Two RCTs^{23,35} evaluated inhaled budesonide at a dosage of 400 μ g twice daily.

Trial quality was variable (**Table 2**). Nine RCTs^{5,20-22,27,29,34-36} were judged to be at low risk of bias (adequate sequence generation, allo-

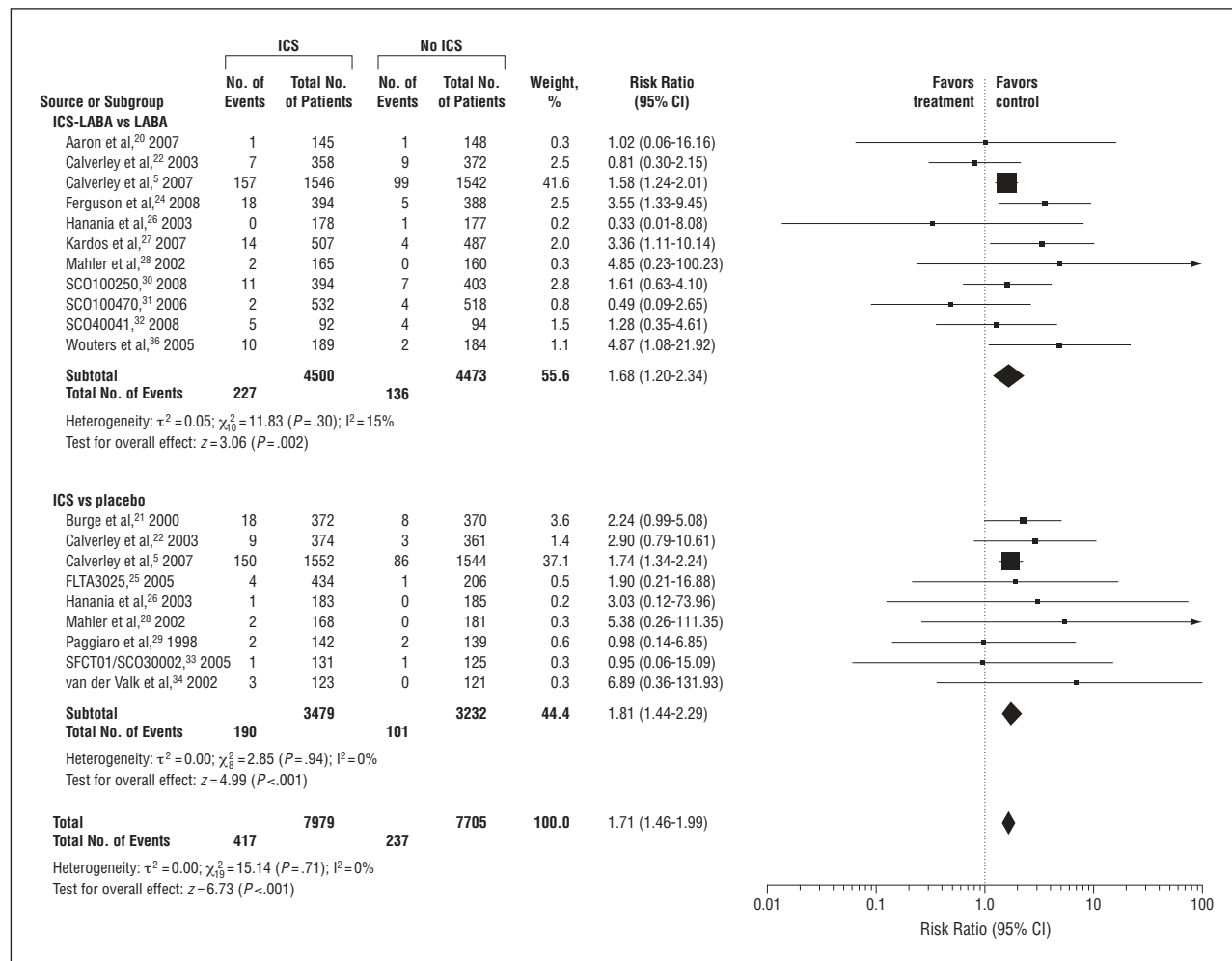


Figure 3. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) use vs control treatment for serious pneumonia. CI indicates confidence interval; LABA, long-acting β -agonist.

cation concealment and double blinding, and clear reporting of loss to follow-up), whereas 9 RCTs^{23-26,28,30-33} were at unclear risk of bias. None of the included trials used objective pneumonia definitions, required radiographic confirmation of pneumonia, or specifically monitored pneumonia as an outcome of interest.

Only 2 trials^{23,35} that evaluated inhaled budesonide reported on pneumonia as an adverse event irrespective of severity. Sixteen trials^{5,20-22,24-34,36} evaluated inhaled fluticasone vs a control and reported on pneumonia as a serious adverse event, with 5 of these trials^{5,24,27,30,32} additionally reporting on pneumonia as an adverse event, irrespective of severity. Only 15 trials^{5,20,22,24-34,36} reported on pneumonia-related mortality, whereas all 18 trials^{5,20-36} provided data on overall mortality.

Data on pneumonia for the Toward a Revolution in COPD Health

(TORCH) Study⁵ were extracted from regulatory documents^{37,38} because the published version reported the probability of pneumonia rather than actual rates.

PRIMARY OUTCOME

Any Pneumonia

Use of inhaled corticosteroids was associated with a significantly increased risk of any pneumonia when compared with controls (641 of 8635 [7.4%] vs 397 of 8361 [4.7%]; RR, 1.60; 95% CI, 1.33-1.92 [$P < .001$]) in a meta-analysis of 18 trials involving 16 996 patients.^{5,20-36} There was evidence of low statistical heterogeneity among the included trials ($I^2 = 16\%$) (**Figure 2**).

Serious Pneumonia

Use of inhaled corticosteroids was associated with a significantly in-

creased risk of serious pneumonia (417 of 7979 [5.2%] vs 237 of 7705 [3.1%]; RR, 1.71; 95% CI, 1.46-1.99 [$P < .001$]) in a meta-analysis of 16 trials^{5,20-22,24-34,36} involving 15 684 patients. There was no evidence of statistical heterogeneity among the trials ($I^2 = 0\%$) (**Figure 3**).

The significantly increased risk of serious pneumonia associated with inhaled corticosteroid use was robust to the choice of comparators. The combination of inhaled corticosteroids and long-acting β -agonists was associated with a significantly increased risk of serious pneumonia when compared with long-acting β -agonists (227 of 4500 [5.0%] vs 136 of 4473 [3.0%]; RR, 1.68; 95% CI, 1.20-2.34 [$P = .002$]) in a meta-analysis of 11 trials* involving 8973 patients. There was evidence of low statistical heteroge-

*References 5, 20, 22-24, 26-28, 30-32, 36.

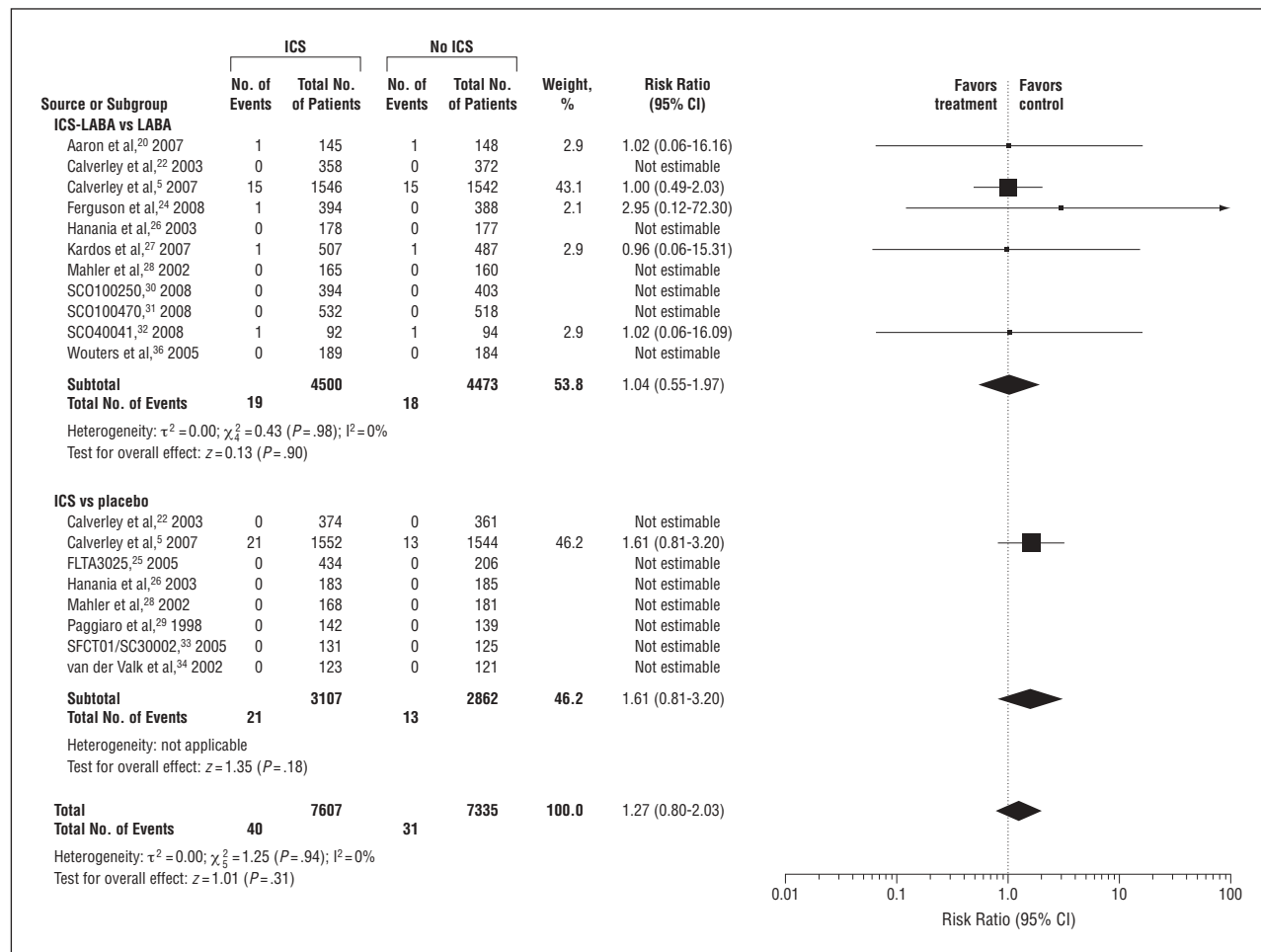


Figure 4. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) vs control for pneumonia-related mortality. CI indicates confidence interval; LABA, long-acting β -agonist.

neity among the included trials ($I^2 = 15\%$). Use of inhaled corticosteroids was associated with a significantly increased risk of serious pneumonia when compared with placebo (190 of 3479 [5.5%] vs 101 of 3232 [3.1%]; RR, 1.81; 95% CI, 1.44-2.29 [$P < .001$]) in a meta-analysis of 9 trials[†] involving 6711 patients. There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$) (Figure 3).

SECONDARY OUTCOMES

Pneumonia-Related Mortality

Use of inhaled corticosteroids was not associated with a significantly increased risk of pneumonia-related mortality when compared with controls (40 of 7607 [0.5%] vs 31 of 7335 [0.4%]; RR, 1.27; 95% CI, 0.80-2.03 [$P = .31$]) in a meta-analysis of

[†]References 5, 21, 22, 25, 26, 28, 29, 33, 34.

15 trials^{5,20,22,24-34,36} involving 14 942 patients. There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$) (Figure 4).

Overall Mortality

Use of inhaled corticosteroids was not associated with a significantly increased risk of overall mortality when compared with controls (525 of 8635 [6.1%] vs 549 of 8361 [6.6%]; RR, 0.96; 95% CI, 0.86-1.08 [$P = .51$]) in a meta-analysis of 18 trials^{5,20-36} involving 16 996 patients. There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$) (Figure 5).

SENSITIVITY ANALYSIS

The fixed-effects analysis of pneumonia from 18 trials yielded effect sizes (RR 1.60; 95% CI, 1.42-1.80 [$P < .001$]) similar in magnitude and

direction to those obtained from random-effects analysis.

The sensitivity analysis of pneumonia limited to the 9 RCTs at low risk of bias^{5,20-22,27,29,34-36} found that the risk of pneumonia (RR, 1.55; 95% CI, 1.19-2.00 [$P = .001$]) associated with inhaled corticosteroid use was similar in magnitude and direction to those from 9 trials in which the risk of bias was unclear (1.88; 1.29-2.75 [$P = .001$]).^{23-26,28,30-33}

After excluding the trial with the largest number of participants and the longest duration of follow-up,⁵ the pooled analysis of pneumonia (RR, 1.69; 95% CI, 1.22-2.33 [$P = .001$]) associated with inhaled corticosteroid use from 17 RCTs was similar in magnitude and direction to those obtained from 18 RCTs.

FAIL-SAFE NUMBER

According to the Rosenberg method,¹⁸ 16 nonsignificant trials of

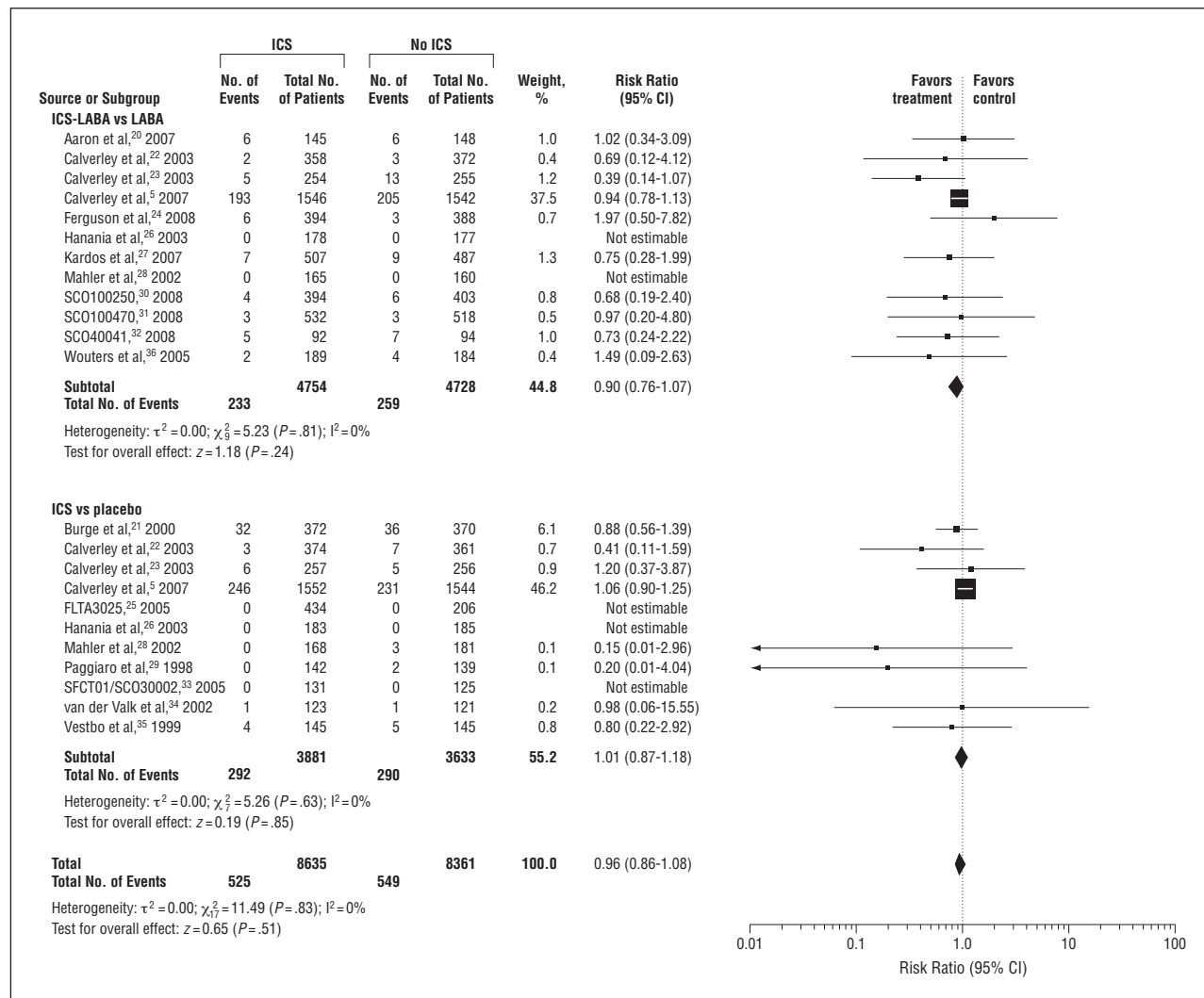


Figure 5. Meta-analysis of randomized controlled trials of inhaled corticosteroids (ICS) vs control for overall mortality. In the Forest plot, the white horizontal line within the black box for Calverley et al⁵ indicates the 95% confidence interval (CI). LABA, indicates long-acting β -agonist.

inhaled corticosteroids with an average sample size of 945 participants each would be required to reverse the significantly increased risk of pneumonia in the random effects meta-analysis.

ESTIMATED NUMBER NEEDED TO HARM

Assuming a baseline event rate of 30 per 1000 person-years for serious pneumonia in adult patients with COPD similar to the control event rate in the trial population of the TORCH Study,³⁸ the annualized number needed to harm for serious pneumonia associated with inhaled corticosteroid use added to long-acting β -agonist therapy is estimated to be 47 (95% CI, 34-73).

COMMENT

The use of inhaled corticosteroids for more than 24 weeks in patients with COPD is associated with a significantly increased risk of any pneumonia (RRs, an approximately 60% increased risk) and serious pneumonia (RRs, an approximately 70% increased risk) without a significant increase in the risk of pneumonia-related death or overall death.

Our findings need to be interpreted in the context of evidence from recent database studies. Use of inhaled corticosteroids was associated with a dose-dependent increased risk of hospitalization for pneumonia (RR, 1.70; 95% CI, 1.63-1.77) and an increase in pneumonia-related mortality in 30 days (1.53;

1.30-1.80) in a case-control study among elderly patients with COPD in Canada.⁶ Another unpublished population-based cohort study in the General Practice Research Database in the United Kingdom reported a doubling in the risk of pneumonia 4 years after inhaled fluticasone exposure (odds ratio [OR], 2.08; 95% CI, 1.01-7.77).³⁹ Another unpublished case-control study based on the General Practice Research Database reported no significant association with pneumonia with inhaled corticosteroid exposure of up to 24 months, with or without long-acting β -agonists, when compared with short-acting β -agonists.⁴⁰ However, the highest risk for pneumonia associated with inhaled corticosteroid use in combination with a long-acting β -agonist

was seen in the 18- to 24-month categories (OR, 1.82; 95% CI, 0.95-3.47 [$P = .07$]).⁴⁰

Our findings must be distinguished from a previous meta-analysis of a limited number of mainly published trials. A Cochrane review of 7 trials^{5,22,23,26-28,31} reported a significantly increased risk of pneumonia with use of inhaled corticosteroids in combination with long-acting β -agonists (OR, 1.58; 95% CI, 1.32-1.88 [$P < .001$]) compared with use of long-acting β -agonists alone.¹⁰ Another pooled analysis of 2 trials^{5,23} showed an increased risk of pneumonia with use of inhaled corticosteroids compared with placebo (RR, 1.55; 95% CI, 1.33-1.80).⁹ Our robust meta-analysis of 18 trials involving 16 996 patients clarifies that the risk of pneumonia reported as an adverse event (and a serious adverse event) can be specifically attributed to the long-term use of the inhaled corticosteroid component because the RRs for serious pneumonia associated with inhaled corticosteroid use are similar when inhaled corticosteroids are compared with placebo (RR, 1.81; 95% CI, 1.44-2.29 [$P < .001$]) or when use of inhaled corticosteroids in combination with long-acting β -agonists are compared with use of long-acting β -agonists alone (RR, 1.68; 95% CI, 1.20-2.34 [$P = .002$]). Our findings also indicate that this increased risk of pneumonia associated with inhaled corticosteroid use is not accompanied by a proportionate increase in pneumonia-related mortality or overall mortality.

Another recent trial⁴¹ showed a significant increase in the rates of serious pneumonia in the inhaled salmeterol-fluticasone combination compared with inhaled tiotropium bromide for 2 years (8% vs 4%; hazard ratio [HR], 1.94; 95% CI, 1.19-3.17 [$P = .008$]), a risk likely attributable to the fluticasone component.

These risks of inhaled corticosteroid use must be weighed against the benefits. The TORCH trial found no reduction of mortality with use of inhaled fluticasone (HR, 1.06; 95% CI, 0.89-1.27 [$P = .53$]).⁵ Inhaled fluticasone use failed to significantly reduce the annual rate ratio of severe COPD exacerbations requiring hos-

pitalization when compared with placebo (0.88; 95% CI, 0.74-1.03 [$P = .10$]) or when the use of inhaled fluticasone in combination with salmeterol was compared with use of salmeterol alone (1.02; 0.87-1.20 [$P = .79$]).⁵ Serious pneumonias, which constituted a subset of exacerbations, were relatively infrequent compared with the number of exacerbations, resulting in an increase in the risk of serious pneumonia with fluticasone use without an increase in the rates of hospitalization for exacerbations in the TORCH trial.⁵ Similarly, the HR of the first exacerbations with inhaled corticosteroid use among those who were not using inhaled corticosteroids before randomization was nonsignificant (1.11; 95% CI, 0.69-1.79 [$P = .68$]) in another trial.^{20,42} Although fluticasone use provided statistically significant improvements in quality-of-life measures, such as the St George Respiratory Questionnaire (SGRQ) (adjusted mean change in SGRQ score for fluticasone vs placebo, -2; 95% CI, -2.9 to -1 [$P < .001$]), these improvements failed to meet the threshold for clinical significance (a decrement of 4 points on this 100-point questionnaire is considered clinically significant).⁵ Thus, the benefits of use of inhaled fluticasone in combination with salmeterol in patients with COPD can be attributed to salmeterol, without any synergistic effect from the use of the combination.⁴²

The precise mechanism underlying the increased risk of pneumonia with inhaled corticosteroid use in patients with COPD is uncertain. Inhaled corticosteroids achieve locally high concentrations in the lung and may increase the risk of pneumonia owing to their immunosuppressive effects.² Inhaled fluticasone propionate at dosages of 1000 $\mu\text{g}/\text{d}$ exerts effects on serum cortisol levels that are equivalent to 10 mg of oral prednisone, a dose that may double the risk of pneumonia in patients with rheumatoid arthritis.⁴³ The limited efficacy of inhaled corticosteroid use in COPD may be due to the progressive reduction in the activity of histone deacetylases, particularly histone deacetylase 2, in the lungs of pa-

tients with increasing severity of COPD.⁴⁴⁻⁴⁶ Histone deacetylase 2 is required by corticosteroids to switch off activated inflammatory genes in COPD.⁴⁴⁻⁴⁶ The contrasting effects of inhaled corticosteroids on pneumonia and exacerbations may possibly be related to a differential effect on viral compared with bacterial infections and needs further investigation.⁴⁷

Although the risk-benefit profile of inhaled corticosteroid use in asthma is clearly favorable, the risk of pneumonia associated with the use of inhaled corticosteroids in patients with severe chronic asthma who have clinical features similar to those of patients with COPD is unknown.

Our meta-analysis has several limitations, which mainly stem from the quality of reported data. The trials did not consistently use an objective definition of pneumonia or require radiographic confirmation. Most of the trials were inadequately powered to detect any significant difference in overall mortality or in pneumonia-related mortality. Nine trials in the analysis were at unclear risk of bias. In the absence of patient-level data, we could not ascertain whether patients with mild COPD were less susceptible to the risk of pneumonia associated with inhaled corticosteroid use. However, the direction of effect for the RRs for pneumonia with inhaled corticosteroid use favors controls in all trials, except for 2 small trials that recruited patients with less severe COPD.^{26,35} We could not determine the onset of pneumonia, dose-response relationships, or the influence of age, body mass index, concomitant systemic corticosteroid use, influenza, and pneumococcal vaccination status on the risk of pneumonia associated with inhaled corticosteroid use. We were unable to discern intraclass differences in the risk of pneumonia.

The manufacturers of inhaled corticosteroids need to make source data available to external academics for independent analysis. Prospective trials of inhaled corticosteroids need to monitor pneumonia as a prespecified outcome using objective pneumonia definitions. Additional cost-benefit analysis may pro-

vide further guidance on optimal use of inhaled corticosteroids among patients with COPD.

Despite these limitations, our findings have potential implications. Our findings suggest the possibility of a risk of pneumonia associated with the long-term use of inhaled corticosteroids in patients with COPD. The magnitude of this risk of serious pneumonia associated with inhaled corticosteroid use in patients with COPD is substantial (RRs, approximately 70% increased risk) and may pose a substantial public health burden. Chronic obstructive pulmonary disease is a known risk factor for the occurrence of pneumonia^{48,49} and for hospitalization for pneumonia.⁵⁰ Patients with COPD and pneumonia also have a higher risk of mortality.⁵¹ Clinicians should remain vigilant for the development of pneumonia with inhaled corticosteroid use because the signs and symptoms of pneumonia may closely mimic those of COPD exacerbations. Clinicians should reevaluate the benefit-harm profile of long-term inhaled corticosteroid use among patients with COPD.

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