實證醫學文獻查證：

COPD病人長期使用吸入型類固醇是否會增加罹患肺炎風險

胸腔內科　許育彰醫師

背景

- GOLD guideline, 2009，建議第三期(severe) COPD 及第四期(very severe)的COPD病人，若有反覆急性發作時，使用吸入型類固醇以減少急性發作的頻率。
- 問題：

慢性阻塞性肺病的病人長期使用吸入型類固醇是否會增加罹患肺炎機會？

實證醫學(Evidence Based Medicine)五大步驟

第一步驟:提出可回答的臨床問題

第二步驟:搜尋最佳實證文獻資料

第三步驟:謹慎的文獻評讀

第四步驟:臨床應用

第五步驟:評估改善

一、提出可回答的臨床問題

Patient or Problem	COPD (chronic obstructive pulmonary disease)
Intervention or exposure	Inhaled corticosteroid (fluticasone, budesonide)
Comparison	Placebo
Outcome	Pneumonia

二、搜尋最佳實證文獻資料

- 搜尋策略：

Seconday database □ Primary database

Design: Systemic review or Meta-analysis

- Primary Database：

PubMed

- Secondary Database:

Cochrane Collaboration and Library

二、搜尋最佳實證文獻資料: 證據等級

表1-1 英國的Oxford Centre證據應用等級 (Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998)

Level		Therapy/Prevention, Aetiology/Harm
1	a	將隨機對照臨床試驗研究 (RCT) 以系統性評論 (systematic review, SR) 後的結果。
	b	具有嚴格的信賴區間的個別RCT研究。
	c	無論使用何種研究方法，但其研究結果為完全正面、完全負面或完全無效果 (all or none) 的研究報告。
2	a	將同質性的世代研究 (cohort studies) 以系統性評論後的結果。
	b	個別世代研究或質量較不足的RCT研究（例如低於80% follow-up）。
	c	以多數結果為基礎的研究，及生態學的研究 ("outcomes" research; ecological studies)。
3	a	將同質性的個案對照研究 (case control studies) 以系統性評論後的結果。
	b	個別的個案對照研究 (individual case control study)。
4		病例統計報告，以及質量較不足的個案對照研究。
5		未經嚴謹評估的專家意見，或者基礎生理學、一般實驗室研究及必要原則。

Secondary Database: Cochrane Collaboration

Primary Database: Pub Med

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed | Limits | Details | Help

#5 AND #6 AND #7 AND #8 | Search | Preview | Clear

Advanced Search

COPD AND ("inhaled corticosteroid" OR fluticasone OR budesonide) AND pneumonia AND ("systemic review" OR meta-analysis)

Query #9 deleted.

Search Builder

Search History

Search	Most Recent Queries	Time	Result
#8	Search "systemic review" OR "meta-analysis"	15:28:44	39773
#7	Search Pneumonia	15:28:11	93542
#6	Search "Inhaled corticosteroid" OR fluticasone OR budesonide	15:27:39	6713
#5	Search COPD	15:26:51	28483

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed

RSS Save search Limits Advanced search Help

#5 AND #6 AND #7 AND #8

Search Clear

Display Settings: Summary, 20 per page, Sorted by Recently Added

Send to:

Results: 8

1. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update.
Singh S, Loke YK.
Curr Opin Pulm Med. 2010 Mar;16(2):118-22.
PMID: 19926996 [PubMed - in process]
Related articles

2. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data.
Sin DD, Tashkin D, Zhang X, Radner F, Sjöbring U, Thorén A, Calverley PM, Rennard S.
Lancet. 2009 Aug 29;374(9691):712-9.
PMID: 19716963 [PubMed - indexed for MEDLINE]
Related articles

3. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis.
Singh S, Amin AV, Loke YK
Arch Intern Med. 2009 Feb 9;169(3):219-29. Review.
PMID: 19204211 [PubMed - indexed for MEDLINE]

相同作者

Reference 8

Reference 4

Filter your results:

All (8)

Review (5)

Free Full Text (2)

Manage Filters

Find related data

Database: Select

Find items

Search details

Turn Off

#5 AND #6 AND #7 AND #8

Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis.

4. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E.
JAMA. 2008 Nov 26;300(20):2407-16. Review. Erratum in: JAMA. 2009 Mar 11;301(10):1024.
PMID: 19033591 [PubMed - indexed for MEDLINE]
Related articles Free article

Reference 9

Benefits and risks of adjunctive inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis.

5. Sobieraj DM, White CM, Coleman CI.
Clin Ther. 2008 Aug;30(8):1416-25.
PMID: 18803985 [PubMed - indexed for MEDLINE]
Related articles

Reference 11

Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease.

6. Nannini LJ, Cates CJ, Lasserson TJ, Poole P.
Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006829. Review.
PMID: 17943918 [PubMed - indexed for MEDLINE]
Related articles

Reference 12

Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease.

7. Nannini LJ, Cates CJ, Lasserson TJ, Poole P.
Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006826. Review.
PMID: 17943917 [PubMed - indexed for MEDLINE]
Related articles

Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease.

8. Nannini L, Cates CJ, Lasserson TJ, Poole P.
Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003794. Review.
PMID: 17943798 [PubMed - indexed for MEDLINE]

三、謹慎的文獻評讀

- 在文獻評讀方面最主要有三個主要步驟，即為VIP：V（Validity/Reliability）效度/信度

I（Importance/Impact）重要性

P（Practice/Applicability）臨床適用性

三、謹慎的文獻評讀: 使用評讀工具

- **Users' Guides to the Medical Literature:** *JAMA 1994; 272: 1367-*

- **University of Oxford, 2005: -** *Systematic Review Appraisal Sheet*

- CAT maker (software)

- **Public Health Resource Unit, England (2006):** Critical Appraisal Skills

- **University of Birmingham: CASP (critical appraisal skill programme)**

三、謹慎的文獻評讀: 使用評讀工具

SYSTEMATIC REVIEW: Are the results of the review valid?

What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The *Title, Abstract or final paragraph of the Introduction* should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	

F – Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The *Methods* section should describe the search strategy, including the terms used, in some detail. The *Results* section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	

A – Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The *Methods* section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	

A – Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up)	The *Methods* section should describe the assessment of quality and the criteria used. The *Results* section should provide information on the quality of the individual studies.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	

T – Were the results similar from study to study?	
What is best?	Where do I find the information?
Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored.	The *Results* section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present.

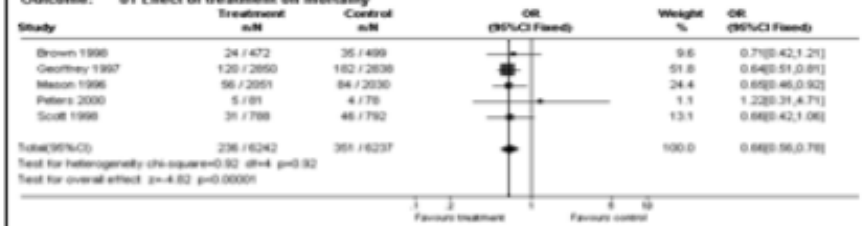
This paper: Yes ☐ No ☐ Unclear ☐

Comment:

What were the results?

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a forest plot.



The forest plot depicted above represents a meta-analysis of 5 trials that assessed the effects of a hypothetical treatment on mortality. Individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to "no effect" of treatment - an odds ratio of 1.0. When the confidence interval includes 1 it indicates that the result is not significant at conventional levels (P>0.05).

The diamond at the bottom represents the combined or pooled odds ratio of all 5 trials with its 95% confidence interval. In this case, it shows that the treatment reduces mortality by 34% (OR 0.66 95% CI 0.56 to 0.78). Notice that the diamond does not overlap the 'no effect' line (the confidence interval doesn't include 1) so we can be assured that the pooled OR is statistically significant. The test for overall effect also indicates statistical significance (p<0.0001).

Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for overlap of the confidence intervals of the trials with the summary estimate. In the example above note that the dotted line running vertically through the combined odds ratio crosses the horizontal lines of all the individual studies indicating that the studies are homogenous. Heterogeneity can also be assessed using the Cochran chi-square (Cochran Q). If Cochran Q is statistically significant there is definite heterogeneity. If Cochran Q is not statistically significant but the ratio of Cochran Q and the degrees of freedom (Q/df) is > 1 there is possible heterogeneity. If Cochran Q is not statistically significant and Q/df is < 1 then heterogeneity is very unlikely. In the example above Q/df is <1 (0.92/4 = 0.23) and the p-value is not significant (0.92) indicating no heterogeneity.

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity.

三、謹慎的文獻評讀: 使用評讀工具

SYSTEMATIC REVIEW: Are the results of the review valid?

What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The ***Title, Abstract*** *or final paragraph of the* ***Introduction*** should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes □ No □ Unclear □ Comment: p.118 title, abstract; p. 119 introduction 皆有明白地指出本篇文章所針對的臨床問題	

Current Opinion in Pulmonary Medicine 2010,16:118–122

Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update

Sonal Singh[a] and Yoon K. Loke[b]

[a]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA and [b]School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

Correspondence to Sonal Singh, MD, MPH, Department of Medicine, Johns Hopkins University

Purpose of review

The aim was to determine the effects of long-term inhaled corticosteroid use on pneumonia in patients with chronic obstructive pulmonary disease (COPD) via systematic searches of *MEDLINE*, *EMBASE*, *ISI*, regulatory documents and manufacturers' trial registries.

Introduction

Inhaled corticosteroids are widely used in patients with chronic obstructive pulmonary disease (COPD). The commonly used inhaled corticosteroids include inhaled fluticasone, inhaled budesonide and inhaled beclometasone.

According to the Chronic Obstructive Pulmonary Disease Global Obstructive Lung Disease Guidelines, inhaled corticosteroids are indicated in combination with long-acting bronchodilators such as β-agonists to reduce the frequency of exacerbations in symptomatic patients with severe COPD [forced expiratory volume in 1 second (FEV1) reported a higher probability of having pneumonia reported as an adverse event among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group of salmeterol 50 μg/fluticasone 500 μg and 18.3% in the group of fluticasone only 500 μg) than in the placebo group (12.3%; $P < 0.001$ for comparisons between these treatments and placebo) among nearly 6112 participants with COPD for a period of 3 years [2,3•]. Our aim is to critically review, analyze and update the current evidence on the risk of pneumonia associated with the long-term use of inhaled corticosteroids in patients with COPD.

Current Opinion in Pulmonary Medicine 2010,16:118–

三、謹慎的文獻評讀: 使用評讀工具

F - Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The ***Methods*** section should describe the search strategy, including the terms used, in some detail. The ***Results*** section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.

This paper: Yes □ No □ Unclear □

Comment:

1. *Current Opinion in Pulmonary Medicine 2010,16:118–122*

p.118 ~ p.119 “Literature search and methodology”

2. *Arch Intern Med. 2009;169(3):219-229*

p.220 “SEARCH STRATEGY” “STUDY SELECTION” “RESULTS”

Recently, several studies have raised the possibility of pneumonia with inhaled corticosteroid therapy in COPD.

Literature search and methodology

As part of our previous meta-analysis [4••], we set up an automated search on *PubMed* to provide weekly notifica-

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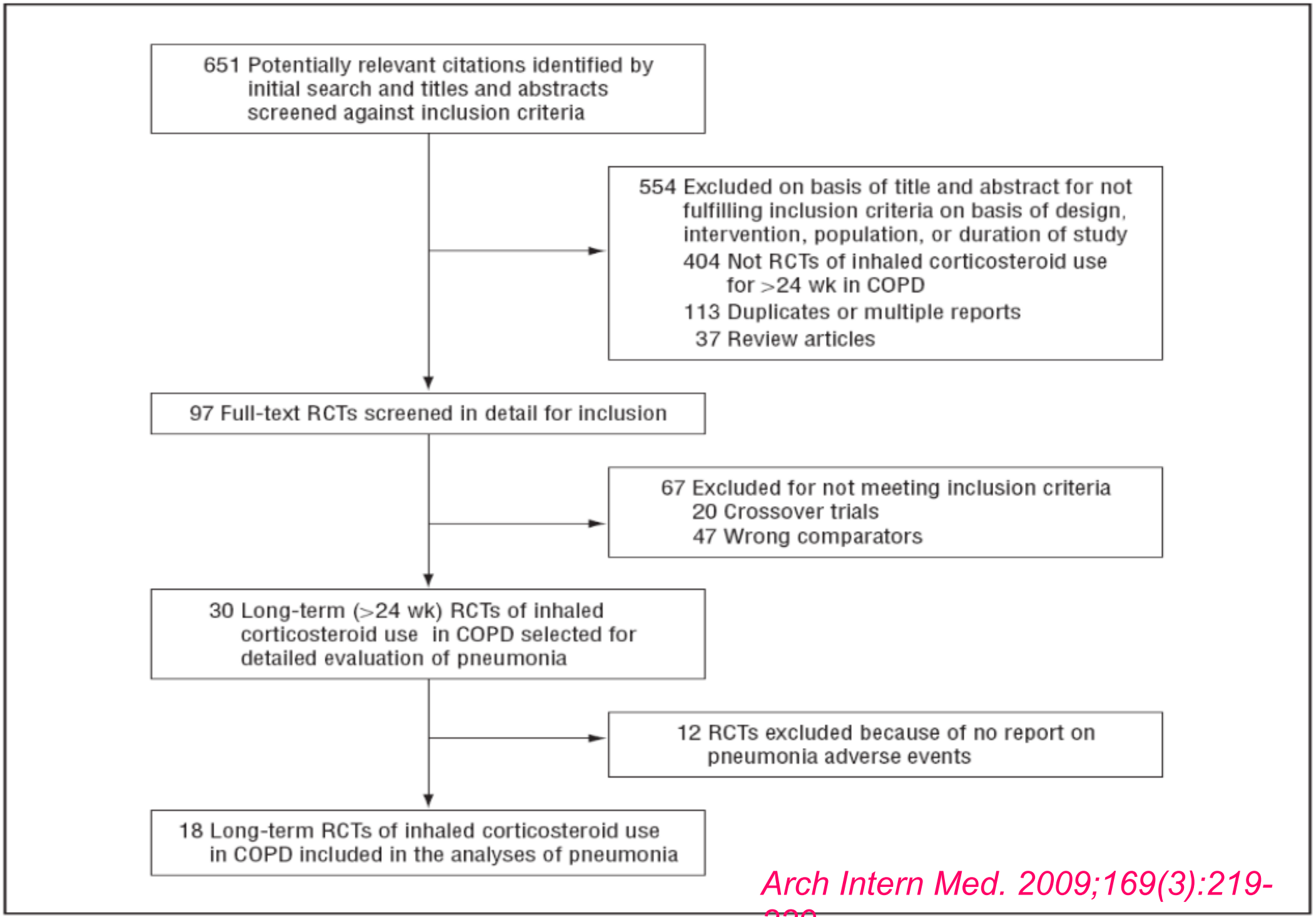
Current Opinion in Pulmonary Medicine 2010,16:118–122

tions on any new publications of trials of budesonide, beclometasone, fluticasone or triamcinolone in COPD, and inhaled corticosteroids and pneumonia. Details of the search strategy and methods are outlined in our previous meta-analysis on this topic [4••]. These searches were updated in October 2009. We checked the study registries of GlaxoSmithKline and AstraZeneca. We extracted data from the published study manuscript when available and from pharmaceutical company reports when published data were unavailable.

Both these studies were limited by the recruitment focusing on incident (newly diagnosed) COPD cases and the uncertainty around whether the diagnosis of pneumonia was validated by chest radiographs in the GPRD.

Meta-analysis of randomized controlled trials

Our previous systematic review and meta-analyses [4••], another industry-supported pooled analysis [8••], have



Arch Intern Med. 2009;169(3):219-229

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 COPD[9-14] 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.

Arch Intern Med. 2009;169(3):219-

三、謹慎的文獻評讀: 使用評讀工具

A - Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The ***Methods*** section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes □ No □ Unclear □ Comment: p.220 "**ELIGIBILITY CRITERIA**"	*Arch Intern Med. 2009;169(3):219-229*

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.

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Inclusion criteria

Inclusion criteria

Arch Intern Med. 2009;169(3):219-

三、謹慎的文獻評讀: 使用評讀工具

A - Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up)	The ***Methods*** section should describe the assessment of quality and the criteria used. The ***Results*** section should provide information on the quality of the individual studies.

This paper: Yes □ No □ Unclear □

Comment:

p.220 "**QUALITY ASSESSMENT**",

1. 應用"Cochrane Toolkit"來評估每篇trial有關於分派序列的產生、隱匿分配、盲性作
業、及失落到追蹤(loss to follow-up)資訊的bias。

2. 不良事件監控的頻率和種類是應用"Cochrane Handbook for Systematic Reviews of Interventions"的建議來評估其效力。

p. 223 "**RESULTS**", 有九篇RCT的bias風險性較低, 另九篇bias的風險性不清楚, 沒有一篇trial用客觀的肺炎定義。

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 Interventions[15] to determine the strength of adverse event monitoring.

Arch Intern Med. 2009;169(3):219-229

RESULTS

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, allocation 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.

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

Arch Intern Med. 2009;169(3):219-

有九篇RCT的bias風險性較低，另九篇bias的風險性不清29

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

三、謹慎的文獻評讀: 使用評讀工具

T - Were the results similar from study to study?	
What is best?	Where do I find the information?
Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored.	The ***Results*** section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present.

This paper: Yes □ No □ Unclear □

Comment:

p.222 “Statistical heterogeneity was assessed using the I^2 statistic; values of 50% or more indicated a substantial level of heterogeneity.”

此篇文章因heterogeneity數據為0%或於低值，所以無再更進一步討論heterogeneity的相關問題。

Any Pneumonia

Source or Subgroup	ICS No. of Events	ICS Total No. of Patients	No ICS No. of Events	No ICS Total No. of Patients	Weight, %	Risk Ratio (95% CI)
ICS-LABA vs LABA						
Aaron et al,[20] 2007	1	145	1	148	0.4	1.02 (0.06-16.16)
Calverley et al,[22] 2003	7	358	9	372	3.3	0.81 (0.30-2.15)
Calverley et al,[23] 2003	8	254	7	255	3.1	1.15 (0.42-3.12)
Calverley et al,[5] 2007	248	1546	162	1542	27.4	1.53 (1.27-1.84)
Ferguson et al,[24] 2008	24	394	9	388	5.2	2.63 (1.24-5.58)
Hanania et al,[26] 2003	0	178	1	177	0.3	0.33 (0.01-8.08)
Kardos et al,[27] 2007	23	507	7	487	4.3	3.16 (1.37-7.29)
Mahler et al,[28] 2002	2	165	0	160	0.4	4.85 (0.23-100.23)
SCO100250,[30] 2008	23	394	9	403	5.1	2.61 (1.22-5.58)
SCO100470,[31] 2008	2	532	4	518	1.2	0.49 (0.09-2.65)
SCO40041,[32] 2008	8	92	6	94	3.0	1.36 (0.49-3.77)
Wouters et al,[36] 2005	10	189	2	184	1.4	4.87 (1.08-21.92)
Subtotal		**4754**		**4728**	**55.2**	1.72 (1.28-2.30)
Total No. of Events	**356**		**217**			
Heterogeneity: $\tau^2=0.05$; $\chi^2_{11}=14.04$ ($P=.23$); $I^2=22\%$						
Test for overall effect: $z=3.62$ ($P<.001$)						
ICS vs placebo						
Burge et al,[21] 2000	18	372	8	370	4.5	2.24 (0.99-5.08)
Calverley et al,[22] 2003	9	374	3	361	1.9	2.90 (0.79-10.61)
Calverley et al,[23] 2003	5	257	2	256	1.2	2.49 (0.49-12.72)
Calverley et al,[5] 2007	224	1552	139	1544	26.3	1.60 (1.31-1.96)
FLTA3025,[25] 2005	4	434	1	206	0.7	1.90 (0.21-16.88)
Hanania et al,[26] 2003	1	183	0	185	0.3	3.03 (0.12-73.96)
Mahler et al,[28] 2002	2	168	0	181	0.4	5.38 (0.26-111.35)
Pagglaro et al,[29] 1998	2	142	2	139	0.9	0.98 (0.14-6.85)
SFCT01/SCO30002,[33] 2005	1	131	1	125	0.6	0.95 (0.06-15.09)
van der Valk et al,[34] 2002	3	123	0	121	0.4	6.89 (0.36-131.93)
Vestbo et al,[35] 1999	16	145	24	145	7.8	0.67 (0.37-1.20)
Subtotal		**3881**		**3633**	**44.8**	1.51 (1.08-2.10)
Total No. of Events	**285**		**180**			
Heterogeneity: $\tau^2=0.05$; $\chi^2_{10}=12.15$ ($P=.27$); $I^2=18\%$						
Test for overall effect: $z=2.40$ ($P=.02$)						
Total		**8635**		**8361**	**100.0**	1.60 (1.33-1.92)
Total No. of Events	**641**		**397**			
Heterogeneity: $\tau^2=0.02$; $\chi^2_{22}=26.32$ ($P=.24$); $I^2=16\%$						
Test for overall effect: $z=4.99$ ($P<.001$)						

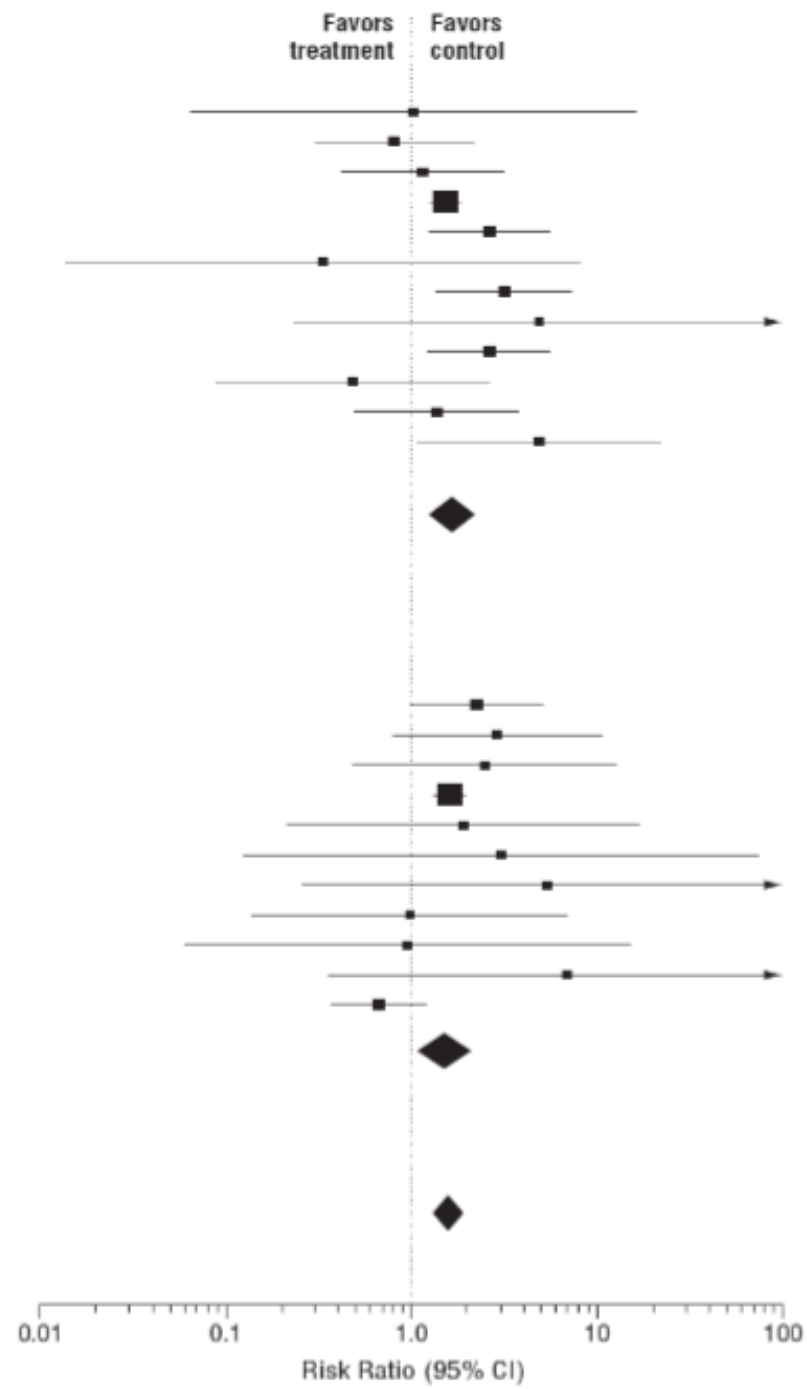

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Figure 2. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) use vs control treatment for any pneumonia. CI indicates confidence interval; LABA, long-acting β-agonist.

Serious Pneumonia

Source or Subgroup	ICS No. of Events	ICS Total No. of Patients	No ICS No. of Events	No ICS Total No. of Patients	Weight, %	Risk Ratio (95% CI)
ICS-LABA vs LABA						
Aaron et al,[20] 2007	1	145	1	148	0.3	1.02 (0.06-16.16)
Calverley et al,[22] 2003	7	358	9	372	2.5	0.81 (0.30-2.15)
Calverley et al,[5] 2007	157	1546	99	1542	41.6	1.58 (1.24-2.01)
Ferguson et al,[24] 2008	18	394	5	388	2.5	3.55 (1.33-9.45)
Hanania et al,[26] 2003	0	178	1	177	0.2	0.33 (0.01-8.08)
Kardos et al,[27] 2007	14	507	4	487	2.0	3.36 (1.11-10.14)
Mahler et al,[28] 2002	2	165	0	160	0.3	4.85 (0.23-100.23)
SCO100250,[30] 2008	11	394	7	403	2.8	1.61 (0.63-4.10)
SCO100470,[31] 2006	2	532	4	518	0.8	0.49 (0.09-2.65)
SCO40041,[32] 2008	5	92	4	94	1.5	1.28 (0.35-4.61)
Wouters et al,[36] 2005	10	189	2	184	1.1	4.87 (1.08-21.92)
Subtotal		**4500**		**4473**	**55.6**	1.68 (1.20-2.34)
Total No. of Events	**227**		**136**			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_{10} = 11.83$ ($P = .30$); $I^2 = 15\%$						
Test for overall effect: $z = 3.06$ ($P = .002$)						
ICS vs placebo						
Burge et al,[21] 2000	18	372	8	370	3.6	2.24 (0.99-5.08)
Calverley et al,[22] 2003	9	374	3	361	1.4	2.90 (0.79-10.61)
Calverley et al,[5] 2007	150	1552	86	1544	37.1	1.74 (1.34-2.24)
FLTA3025,[25] 2005	4	434	1	206	0.5	1.90 (0.21-16.88)
Hanania et al,[26] 2003	1	183	0	185	0.2	3.03 (0.12-73.96)
Mahler et al,[28] 2002	2	168	0	181	0.3	5.38 (0.26-111.35)
Paggiaro et al,[29] 1998	2	142	2	139	0.6	0.98 (0.14-6.85)
SFCT01/SCO30002,[33] 2005	1	131	1	125	0.3	0.95 (0.06-15.09)
van der Valk et al,[34] 2002	3	123	0	121	0.3	6.89 (0.36-131.93)
Subtotal		**3479**		**3232**	**44.4**	1.81 (1.44-2.29)
Total No. of Events	**190**		**101**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 2.85$ ($P = .94$); $I^2 = 0\%$						
Test for overall effect: $z = 4.99$ ($P < .001$)						
Total		**7979**		**7705**	**100.0**	1.71 (1.46-1.99)
Total No. of Events	**417**		**237**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{19} = 15.14$ ($P = .71$); $I^2 = 0\%$						
Test for overall effect: $z = 6.73$ ($P < .001$)						

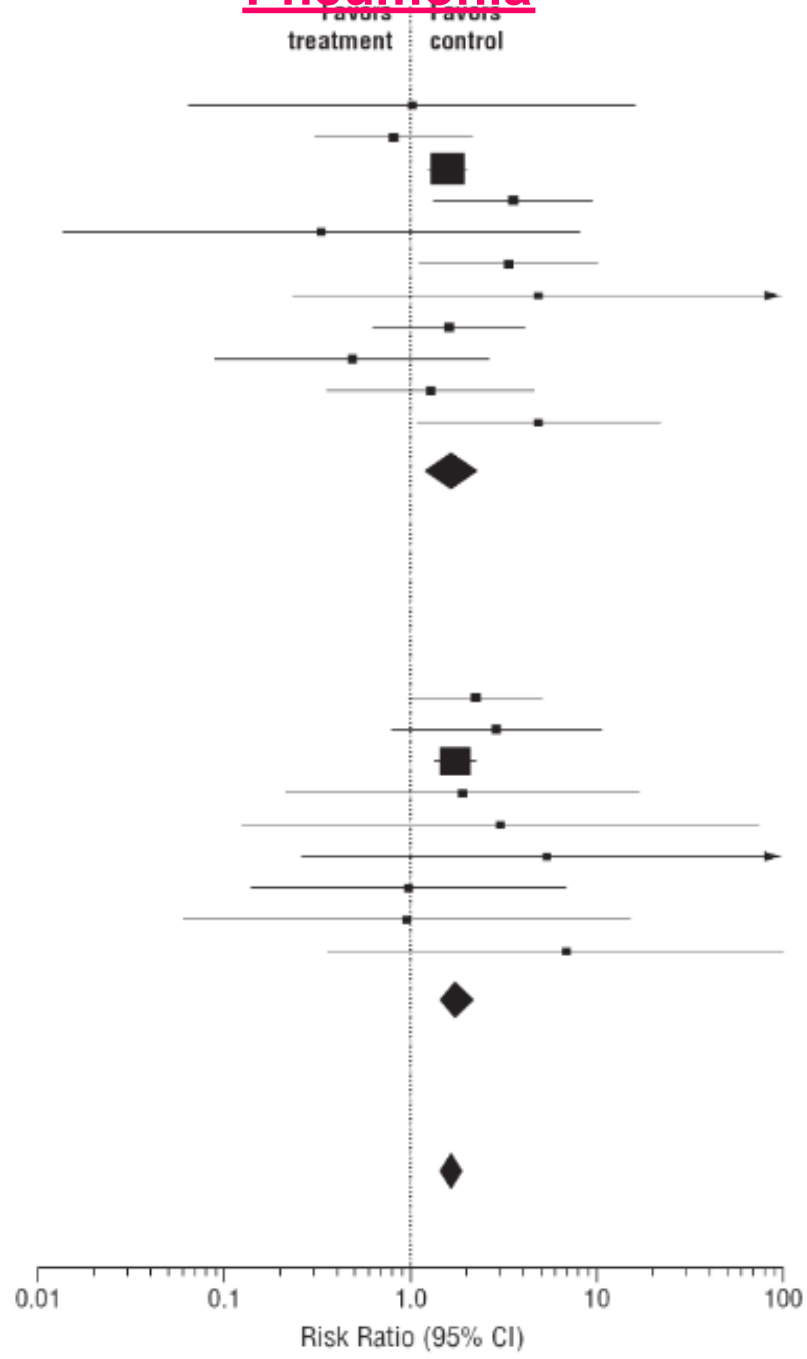

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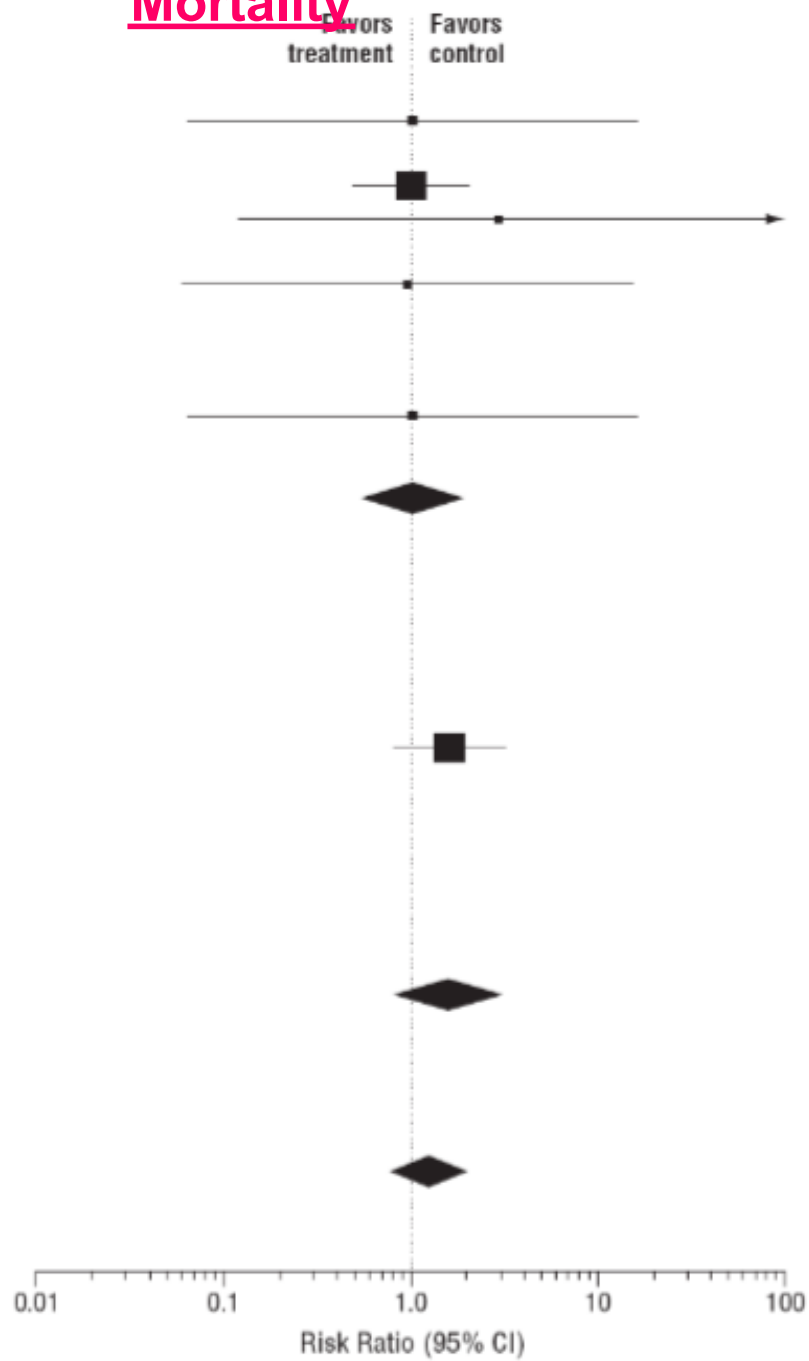
Figure 3. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) use vs control treatment for serious pneumonia. CI indicates confidence interval; LABA, long-acting β-agonist.

Pneumonia related Mortality

Source or Subgroup	ICS No. of Events	ICS Total No. of Patients	No ICS No. of Events	No ICS Total No. of Patients	Weight, %	Risk Ratio (95% CI)
ICS-LABA vs LABA						
Aaron et al,[20] 2007	1	145	1	148	2.9	1.02 (0.06-16.16)
Calverley et al,[22] 2003	0	358	0	372		Not estimable
Calverley et al,[5] 2007	15	1546	15	1542	43.1	1.00 (0.49-2.03)
Ferguson et al,[24] 2008	1	394	0	388	2.1	2.95 (0.12-72.30)
Hanania et al,[26] 2003	0	178	0	177		Not estimable
Kardos et al,[27] 2007	1	507	1	487	2.9	0.96 (0.06-15.31)
Mahler et al,[28] 2002	0	165	0	160		Not estimable
SCO100250,[30] 2008	0	394	0	403		Not estimable
SCO100470,[31] 2008	0	532	0	518		Not estimable
SCO40041,[32] 2008	1	92	1	94	2.9	1.02 (0.06-16.09)
Wouters et al,[36] 2005	0	189	0	184		Not estimable
Subtotal		**4500**		**4473**	**53.8**	1.04 (0.55-1.97)
Total No. of Events	**19**		**18**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_4 = 0.43$ ($P = .98$); $I^2 = 0\%$						
Test for overall effect: $z = 0.13$ ($P = .90$)						
ICS vs placebo						
Calverley et al,[22] 2003	0	374	0	361		Not estimable
Calverley et al,[5] 2007	21	1552	13	1544	46.2	1.61 (0.81-3.20)
FLTA3025,[25] 2005	0	434	0	206		Not estimable
Hanania et al,[26] 2003	0	183	0	185		Not estimable
Mahler et al,[28] 2002	0	168	0	181		Not estimable
Paggiaro et al,[29] 1998	0	142	0	139		Not estimable
SFCT01/SC30002,[33] 2005	0	131	0	125		Not estimable
van der Valk et al,[34] 2002	0	123	0	121		Not estimable
Subtotal		**3107**		**2862**	**46.2**	1.61 (0.81-3.20)
Total No. of Events	**21**		**13**			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.35$ ($P = .18$)						
Total		**7607**		**7335**	**100.0**	1.27 (0.80-2.03)
Total No. of Events	**40**		**31**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 1.25$ ($P = .94$); $I^2 = 0\%$						
Test for overall effect: $z = 1.01$ ($P = .31$)						



Arch Intern Med. 2009;169(3):219-229.

Figure 3. 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.

三、謹慎的文獻評讀: 使用評讀工具

What were the results?

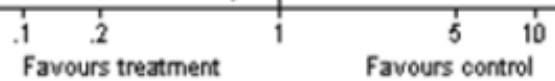
How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a **forest plot.**

Comparison: 03 Treatment versus Placebo
Outcome: 01 Effect of treatment on mortality

Study	Treatment n/N	Control n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Brown 1998	24 / 472	35 / 499		9.6	0.71[0.42,1.21]
Geoffrey 1997	120 / 2850	182 / 2838		51.8	0.64[0.51,0.81]
Mason 1996	56 / 2051	84 / 2030		24.4	0.65[0.46,0.92]
Peters 2000	5 / 81	4 / 78		1.1	1.22[0.31,4.71]
Scott 1998	31 / 788	46 / 792		13.1	0.66[0.42,1.06]
Total(95%CI)	236 / 6242	351 / 6237		100.0	0.66[0.56,0.78]

Test for heterogeneity chi-square=0.92 df=4 p=0.92
Test for overall effect z=-4.82 p<0.00001



三、謹慎的文獻評讀: 使用評讀工具

The forest plot depicted above represents a meta-analysis of 5 trials that assessed the effects of a hypothetical treatment on mortality. Individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment - an odds ratio of 1.0. When the confidence interval includes 1 it indicates that the result is not significant at conventional levels (P>0.05).

The diamond at the bottom represents the combined or pooled odds ratio of all 5 trials with its 95% confidence interval. In this case, it shows that the treatment reduces mortality by 34% (OR 0.66 95% CI 0.56 to 0.78). Notice that the diamond does not overlap the 'no effect' line (the confidence interval doesn't include 1) so we can be assured that the pooled OR is statistically significant. The test for overall effect also indicates statistical significance (p<0.0001).

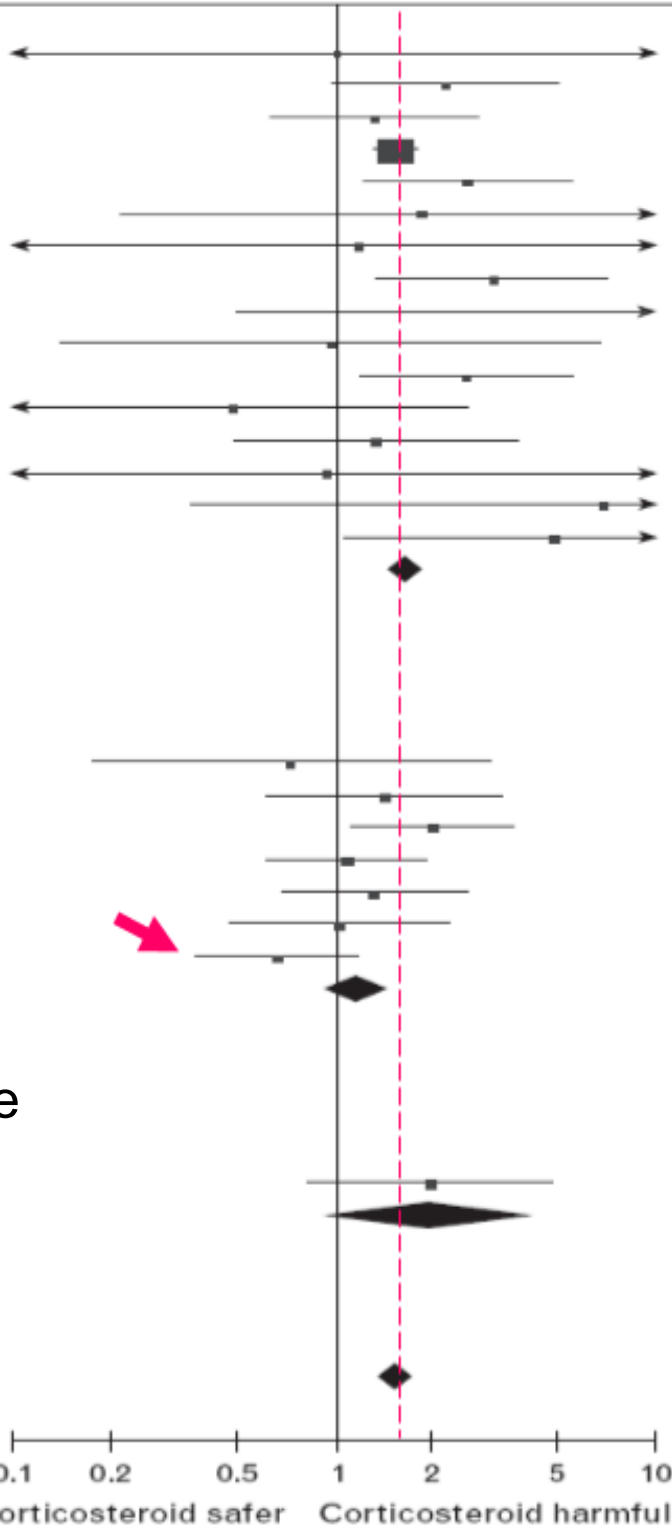
Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for overlap of the confidence intervals of the trials with the summary estimate. In the example above note that the dotted line running vertically through the combined odds ratio crosses the horizontal lines of all the individual studies indicating that the studies are homogenous. Heterogeneity can also be assessed using the Cochran chi-square (Cochran Q). If Cochran Q is statistically significant there is definite heterogeneity. If Cochran Q is not statistically significant but the ratio of Cochran Q and the degrees of freedom (Q/df) is > 1 there is possible heterogeneity. If Cochran Q is not statistically significant and Q/df is < 1 then heterogeneity is very unlikely. In the example above Q/df is <1 (0.92/4= 0.23) and the p-value is not significant (0.92) indicating no heterogeneity.

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity.

Study or subgroup	Inhaled corticosteroid Events	Total	Control Events	Total	Weight	Risk ratio M.H, fixed, 95% CI
6.1.1 Fluticas-one exposure						
Aaron 2007	1	145	1	148	102%	1.02 [0.06, 16.16]
Burge 2000	18	372	8	370	1.7%	2.24 [0.99, 5.08]
Calverley (a) 2003	16	732	12	733	2.5%	1.34 [0.64, 2.80]
Calverley 2007	472	3098	301	3086	63.2%	1.56 [1.36, 1.79]
Ferguson 2008	24	394	9	388	1.9%	2.63 [1.24, 5.58]
FLTA3025 2005	4	434	1	206	0.3%	1.90 [0.21, 16.88]
Hannania 2003	1	301	1	362	0.2%	1.20 [0.08, 19.15]
Kardos 2007	23	507	7	487	1.5%	3.16 [1.37, 1.29]
Mahler 2002	4	333	0	341	0.1%	9.22 [0.50, 170.50]
Paggiaro 1998	2	142	2	139	0.4%	0.98 [0.14, 6.85]
SCO100250 2008	23	394	9	403	1.9%	2.61 [1.22, 5.58]
SCO100470 2006	2	532	4	518	0.9%	0.49 [0.09, 2.65]
SCO40041 2008	8	92	6	94	1.2%	1.36 [0.49, 3.77]
SFCT01 2005	1	131	1	125	0.2%	0.95 [0.06, 15.09]
Van der Valk 2002	3	123	0	121	0.1%	6.89 [0.36, 131.93]
Wouters 2005	10	189	2	184	0.4%	4.87 [1.08, 21.92]
Subtotal (95% CI)		7919		7705	76.8%	1.67 [1.47, 1.89]
Total events	612		364			
Heterogeneity: Chi² = 13.68, df = 15 (P = 0.55); I² = 0%						
Test for overall effect: Z = 8.14 (P < 0.00001)						
6.1.2 Budesonide exposure						
Bourbeau 2001	3	38	4	37	0.9%	0.73 [0.18, 3.04]
Calverley (b) 2003	13	511	9	511	1.9%	1.44 [0.62, 3.35]
Pauwels 1999	33	593	16	582	3.4%	2.02 [1.13, 3.64]
Rennard 2009	37	988	17	495	4.8%	1.09 [0.62, 1.92]
Szafranski 2003	20	406	15	406	3.1%	1.33 [0.69, 2.57]
Tashkin 2008	18	1120	9	584	2.5%	1.04 [0.47, 2.31]
Vestbo 1999	16	145	24	145	5.0%	0.67 [0.37, 1.20]
Subtotal (95% CI)		3801		2760	21.5%	1.19 [0.92, 1.53]
Total events	140		94			
Heterogeneity: Chi² = 7.83, df = 6 (P = 0.25); I² = 23%						
Test for overall effect: Z = 1.30 (P = 0.19)						
6.1.3 Mometasone exposure						
Calverley (mometasone) 2008	25	616	6	295	1.7%	2.00 [0.83, 4.81]
Subtotal (95% CI)		616		295	1.7%	2.00 [0.83, 4.81]
Total events	25		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
Total (95% CI)		12336		10760	100.0%	1.57 [1.41, 1.75]
Total events	777		464			
Heterogeneity: Chi² = 27.21, df = 23 (P = 0.25); I² = 15%						
Test for overall effect: Z = 8.04 (P = 0.00001)						

Chi²/df (7.83/6)> 1, possible heterogeneity



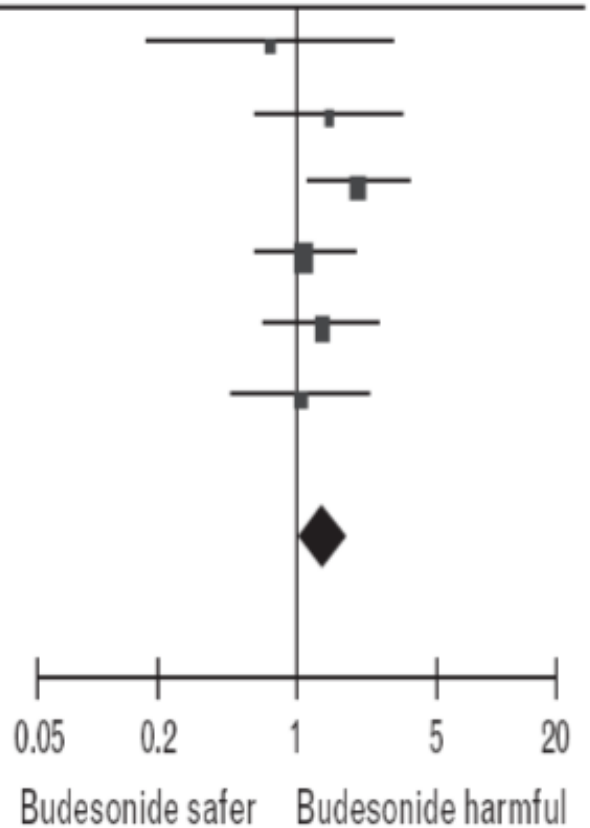
- Vestbo 1999因病人選擇不適切，病情嚴重度太輕，FEV1接

Figure 2 Sensitivity analysis of inhaled budesonide and the risk of pneumonia in chronic obstructive pulmonary disease

Study or subgroup	Budesonide Events	Budesonide Total	Control Events	Control Total	Weight	Risk ratio M.H, fixed, 95% CI
Bourbeau 2001	3	38	4	37	5.2%	0.73 [0.18, 3.04]
Calverley (b) 2003	13	511	9	511	11.4%	1.44 [0.62, 3.35]
Pauwels 1999	33	593	16	582	20.5%	2.02 [1.13, 3.64]
Rennard 2009	37	988	17	495	28.8%	1.09 [0.62, 1.92]
Szafranski 2003	20	406	15	406	19.1%	1.33 [0.69, 2.57]
Tashkin 2008	18	1120	9	584	15.0%	1.04 [0.47, 2.31]
Total (95% CI)		3656		2615	100.0%	1.34 [1.01, 1.79]
Total events	124		70			

Heterogeneity: $Chi^2 = 3.53$, $df = 5$ ($P = 0.62$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P < 0.04$)



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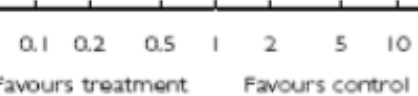
Analysis 1.3. Comparison 1 Combined inhalers versus Placebo (Primary Outcomes), Outcome 3 Pneumonia.

Review: Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

Comparison: 1 Combined inhalers versus Placebo (Primary Outcomes)

Outcome: 3 Pneumonia

Study or subgroup	Combined inhalers n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 FPS				
Barnes 2006	1/67	0/73		3.32 [0.13, 82.80]
Hanania 2003	0/178	0/185		0.0 [0.0, 0.0]
Mahler 2002	2/165	0/181		5.55 [0.26, 116.46]
O'Donnell 2006	0/62	1/64		0.34 [0.01, 8.47]
SCO100540	12/297	0/148		13.00 [0.76, 221.16]
TORCH	303/1546	190/1544		1.74 [1.43, 2.12]
TRISTAN	7/358	3/361		2.38 [0.61, 9.28]
Subtotal (95% CI)	**2673**	**2556**		**1.80 [1.48, 2.18]**
Total events: 325 (Combined inhalers), 194 (Placebo)				
Heterogeneity: Chi² = 3.85, df = 5 (P = 0.57); I² =0.0%				
Test for overall effect: Z = 5.98 (P < 0.00001)				
2 BDF				
Calverley 2003	8/254	2/256		4.13 [0.87, 19.64]
Subtotal (95% CI)	**254**	**256**		**4.13 [0.87, 19.64]**
Total events: 8 (Combined inhalers), 2 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.78 (P = 0.075)				
Total (95% CI)	**2927**	**2812**		**1.83 [1.51, 2.21]**
Total events: 333 (Combined inhalers), 196 (Placebo)				
Heterogeneity: Chi² = 4.98, df = 6 (P = 0.55); I² =0.0%				
Test for overall effect: Z = 6.19 (P < 0.00001)				



文獻結論

Conclusion

The consistency of the available clinical, biological and epidemiological evidence suggests that long-term inhaled corticosteroid use in patients with COPD is associated with a significantly increased risk of pneumonia. The evidence for any intraclass differences in the risk of pneumonia remains inconclusive.

Robust head-to-head trials of sufficient duration, sample size and active ascertainment of pneumonia events along with radiologic and microbiologic confirmation are required to address these uncertainties. Clinicians should remain particularly vigilant for the development of pneumonia with inhaled corticosteroids in these patients, as the signs and symptoms of pneumonia may closely mimic that of COPD exacerbations. They should discuss the risks and benefits of long-term inhaled corticosteroid therapy with their patients.

四、臨床應用

- 證據等級: Level 1 A (Oxford center, Nov. 1998)
- 長期使用(>24 weeks)吸入型類固醇的COPD病人明顯增加罹患肺炎之風險。
- COPD疾病嚴重度同等級內的罹患肺炎風險機會未有定論。
- 必須更進一步解決以下不確定的事物:是否有足夠的追蹤期、病人數、和明確的肺炎定義(包含影像學、微生物學上的確認)。
- 臨床醫師對使用吸入型類固醇的病人需提高警覺是否有發生肺炎, 因肺炎的症狀徵兆與COPD with AE時很相似。