三軍總醫院
Tri-Service General Hospital

實證醫學競賽

組別：第二組

時間：107 年 5 月 23 日

我們的團隊

徐國峯醫師

張杏怡藥師

陳婉亭醫學實習生

臨床場景

- 55歲陳媽媽平時沒有抽菸，規則運動，最近這幾個月發現運動時變得會喘，回家時，無法一次爬完四樓樓梯。至胸腔科檢查，抽血自體免疫抗體皆呈Negative，痰液培養也無任何細菌， 醫師為她做CT診斷為: 間質性肺病中的特發性肺纖維症(idiopathic pulmonary fibrosis)。治療一陣子後，狀況有改善，鄰居問她要不要加入運動俱樂部？陳媽媽其實本來也喜歡運動，只是發現這個問題後以後變得不大敢運動...

- **陳媽媽的疑問**:

1.這個疾病不用**切片診斷**嗎？
2.如果真的是這個疾病，會不會**容易得到癌症?**
3.使用**新的藥物nintedanib & pirfenidone**，還是用**傳統用藥:秋水仙素 & N-acetylcysteine**治療效果較佳?用新藥可否改善肺功能?會不會有副作用?
4. 運動對於**特發性肺纖維症有沒有幫助?怎樣的運動強度適合她?**
5. 使用氧氣製造機，**氧氣用太多會有不好的影響嗎？**

臨床場景

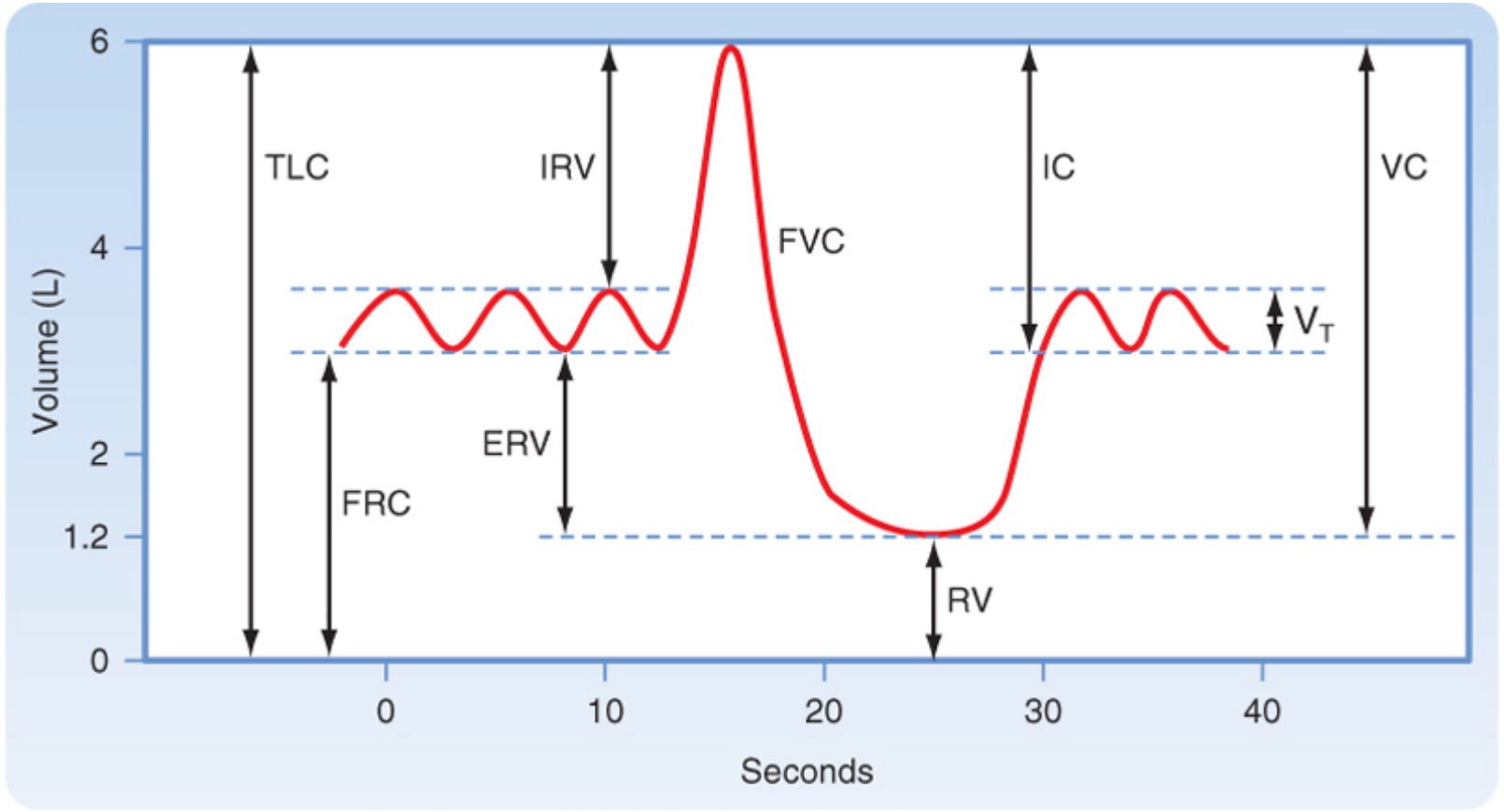
- 她想了解：
  - 傳統是用秋水仙素或是N-actylcysteine治療。兩個新藥物分別是nitedanib和pirfenidone，要用傳統藥物治療還是使用新的藥物呢？
  - 究竟運動對他有沒有幫助？
- 病人期望:
  - 知道何種治療方式對陳媽媽效果好副作用小

背景資訊

- **定義：**
  - 由於各種原因導致肺間質增厚（毛細血管內皮和肺泡上皮之間的空間）。
- **診斷：**
  - 為排除性診斷，經HRCT看到usual interstitial pneumonia (UIP) pattern，搭配病史、症狀，一般不用特別做切片診斷。
- **治療：**
- Oxygen、Corticosteroids、Azathioprine (with prednisolone and N-acetylcysteine)、Cyclophosphamide、Cyclosporine、 Nintedanib 、Pirfenidone
- **併發症：**
  - 心肺衰竭、自發性氣胸、肺癌(common 10%-38%)

背景資訊

- 追蹤：



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

臨床問題

- 我們第一個 PICO 是

	中文	英文
P	55歲女性，無抽菸，有間質性肺病	55 year old woman, non-smoker, interstitial lung disease
I	Nintedanib或pirfenidone	Nintedanib or pirfenidone
C	秋水仙素或N-actylcysteine	Colchicine or N-actylcysteine
O	功能性肺容積改變	Lung Function Tests or Respiratory Function Test or mortality or FVC change

這是一個 ●治療型 ○診斷型 ○預後型 ○傷害型 問題

臨床問題

- 我們第二個 PICO 是

	中文	英文
P	55歲女性，無抽菸，有間質性肺病	55 year old woman, non-smoker , interstitial lung disease
I	運動或肺部復健訓練	Exercise or Pulmonary physical rehabilitation
C	Medicine or placebo	Medicine or placebo
O	功能性肺容積改變	Lung Function Tests or Respiratory Function Test or mortality or FVC change

這是一個 ●治療型 ○診斷型 ○預後型 ○傷害型 問題

關鍵字

- 我們選擇第一個 PICO，使用的關鍵字是：

選擇第一個PICO原因:
臨床問題重要且與病人預後相關

	關鍵字	同義字	中文
P	55 year old woman, non-smoker , interstitial lung disease	Idiopathic Pulmonary Fibrosis : IPF or Fibrocystic Pulmonary or pneumopathy, interstitial	特發性肺纖維化
I	Nintedanib or pirfenidone	Nintedanib or Pirfenidone	Nintedanib , pirfenidone
C	Colchicine or N-actylcysteine	Colchicine , N-actylcysteine or Placebo	Colchicine, N-actylcysteine 安慰劑
O	Lung Function Tests	Lung Function Tests or Respiratory Function Test or mortality or FVC change	肺功能，死亡率

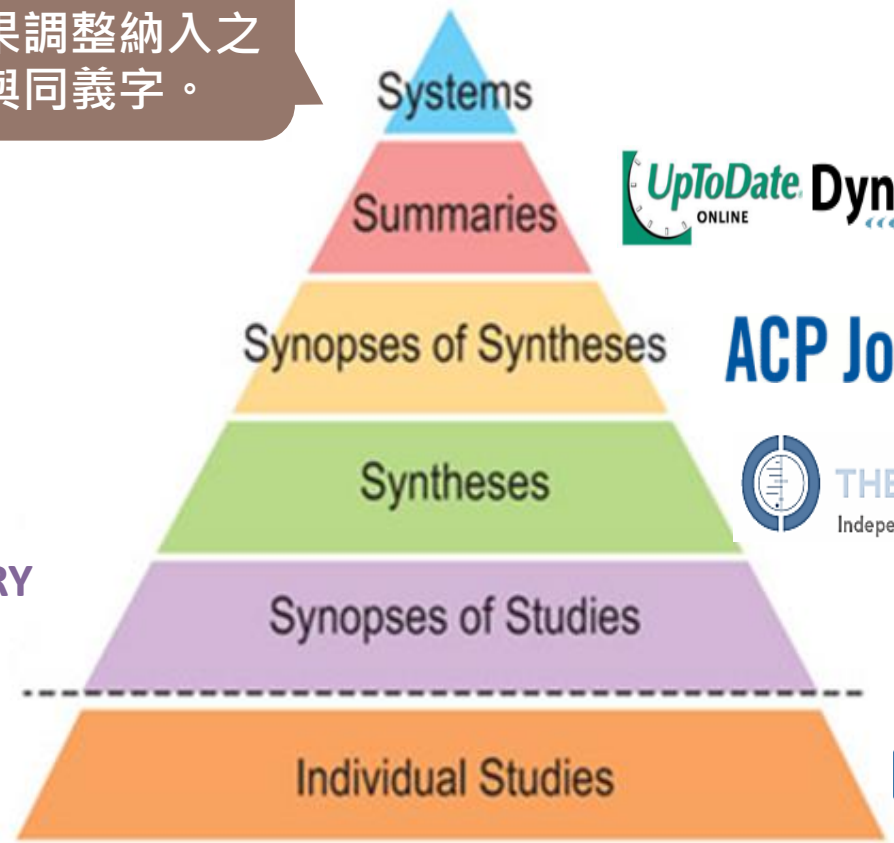
搜尋策略

- 運用布林邏輯 ，先以P、I搜尋，再依結果適當加入關鍵字。

P	I	C	O
Idiopathic Pulmonary Fibrosis : IPF OR Fibrocystic Pulmonary	nintedanib & pirfenidone	Colchicine & N-acetylcysteine	Lung Function Tests OR Respiratory Function Test OR FVC change

搜索策略

以「P & I」搜尋，
再依結果調整納入之
關鍵字與同義字。



SECONDARY DATABASE

PRIMARY DATABASE

UpToDate ONLINE
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THE COCHRANE LIBRARY
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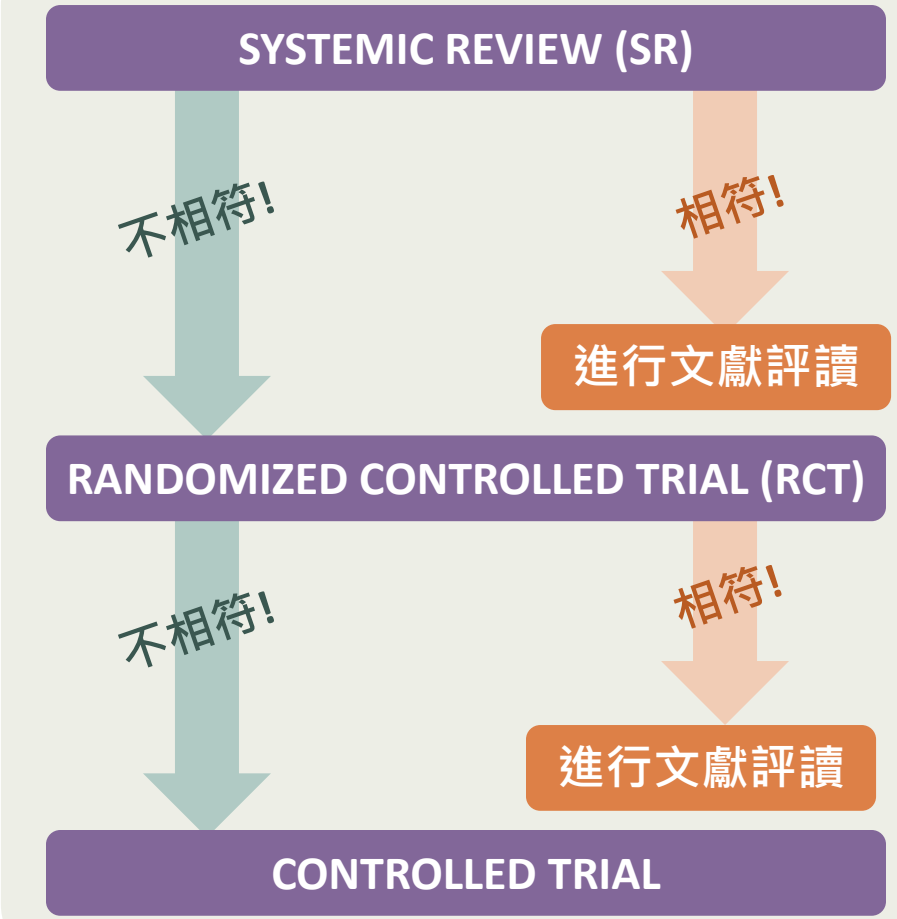
華藝線上圖書館



搜索策略

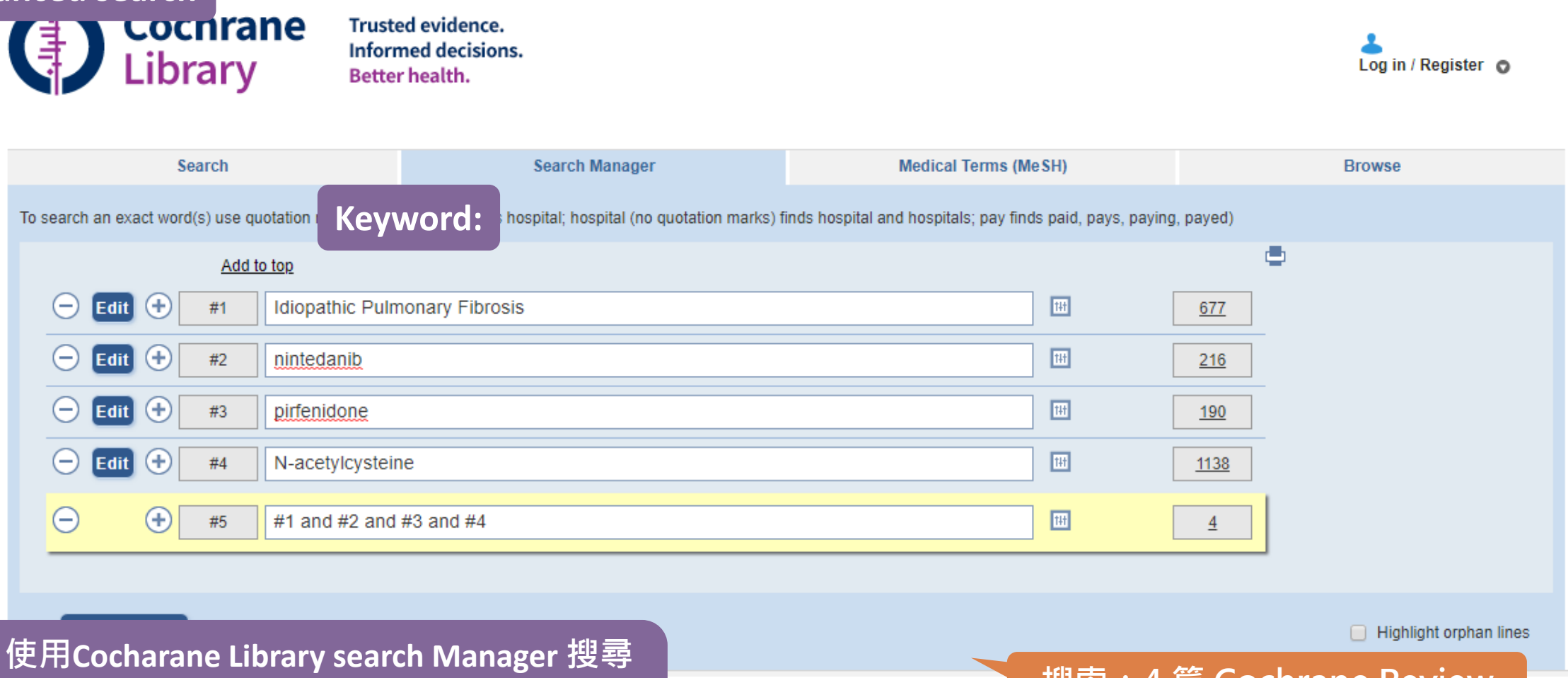
Clinical Queries

Systematic Review(Meta-analysis)→ RCT → Cohort study

Meet our PICO

Secondary Database: Cochrane

Advanced search



1. 使用Cocharane Library search Manager 搜尋
   加入布林邏輯 AND 與 OR 作搜尋連結
2. Search limit: 未限制年份

搜索：4 篇 Cochrane Review

Secondary Database: Cochrane

All Results (4)

- Cochrane Reviews (0)
  - All
  - Review
  - Protocol
- Other Reviews (0)
- Trials (4)
- Methods Studies (0)
- Technology Assessments (0)
- Economic Evaluations (0)
- Cochrane Groups (0)

- All
- Current Issue

- Me Methodology
- Dx Diagnostic
- Ov Overview
- Pg Prognosis
- Qu Qualitative
- Cc Conclusions changed
- Ns New search
- Mc Major change

Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2018

There are **4** results from **1145093** records for your search on **#5 - #1 and #2 and #3 and #4** in **Trials** in the strategy currently being edited

Sort by Relevance: high to low

Select all | Export all | Export selected

Nintedanib cost-effectiveness in **idiopathic pulmonary fibrosis** in the UK
Rinciog C , Watkins M , Chang S , Maher T , LeReun C , Esser D and Diamantopoulos A
Value in health. Conference: ISPOR 19th annual european congress. Austria. Conference start: 20161029. Conference end: 20161102, 2016, 19(7), A553
Online Publication Date: 2017

Treatment of **idiopathic pulmonary fibrosis** : a network meta-analysis
Rochwerg B , Neupane B , Zhang Y , Garcia CC , Raghu G , Richeldi L , Brozek J , Beyene J and Schunemann H
BMC medicine, 2016, 14(1) (no pagination)
Online Publication Date: 2016

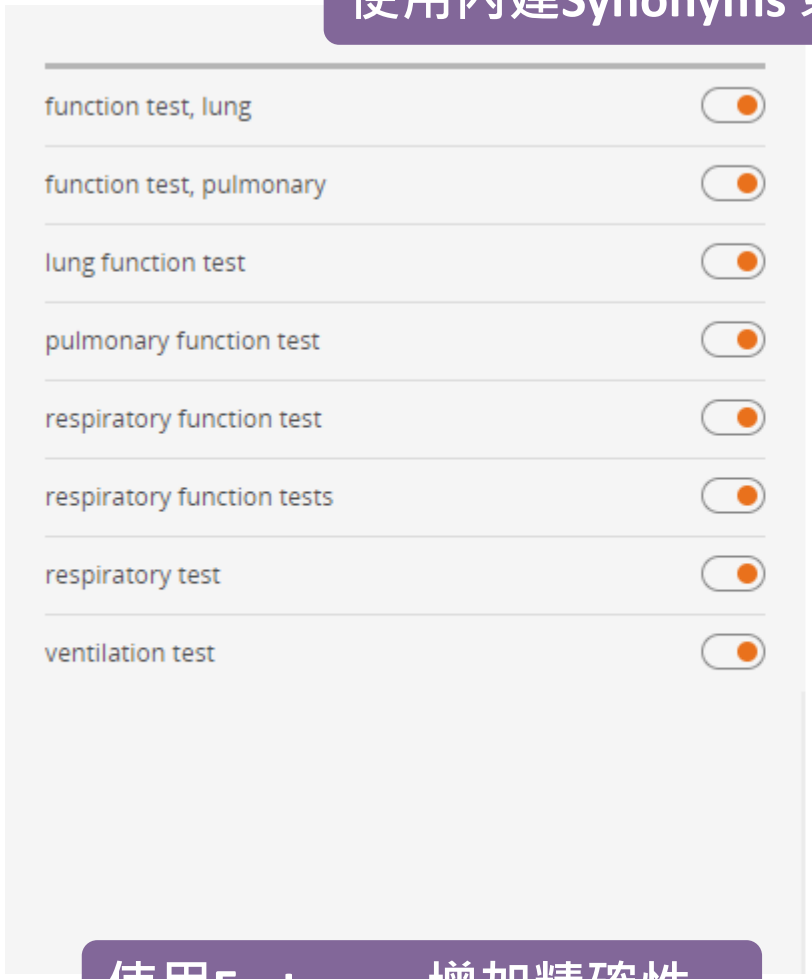
A description of anti-fibrotic therapy prescribing preferences amongst **pulmonary** practitioners for the management of **idiopathic pulmonary fibrosis**
Jablonski R , Frogameni A , Brown KK , Kamangar N , Murgu S , Raparia K , Ryu J , Raoof S , Suh RD , Edell ES , Kamp DW and Raj R
American journal of respiratory and critical care medicine. Conference: american thoracic society international conference, ATS 2017. United states, 2017, 195(no pagination)
Online Publication Date: 2017

Treatment of **idiopathic pulmonary fibrosis** : pharmacological approach
Blin E and Cottin V
Revue des maladies respiratoires actualites, 2016, 8(2), 83
Online Publication Date: 2017

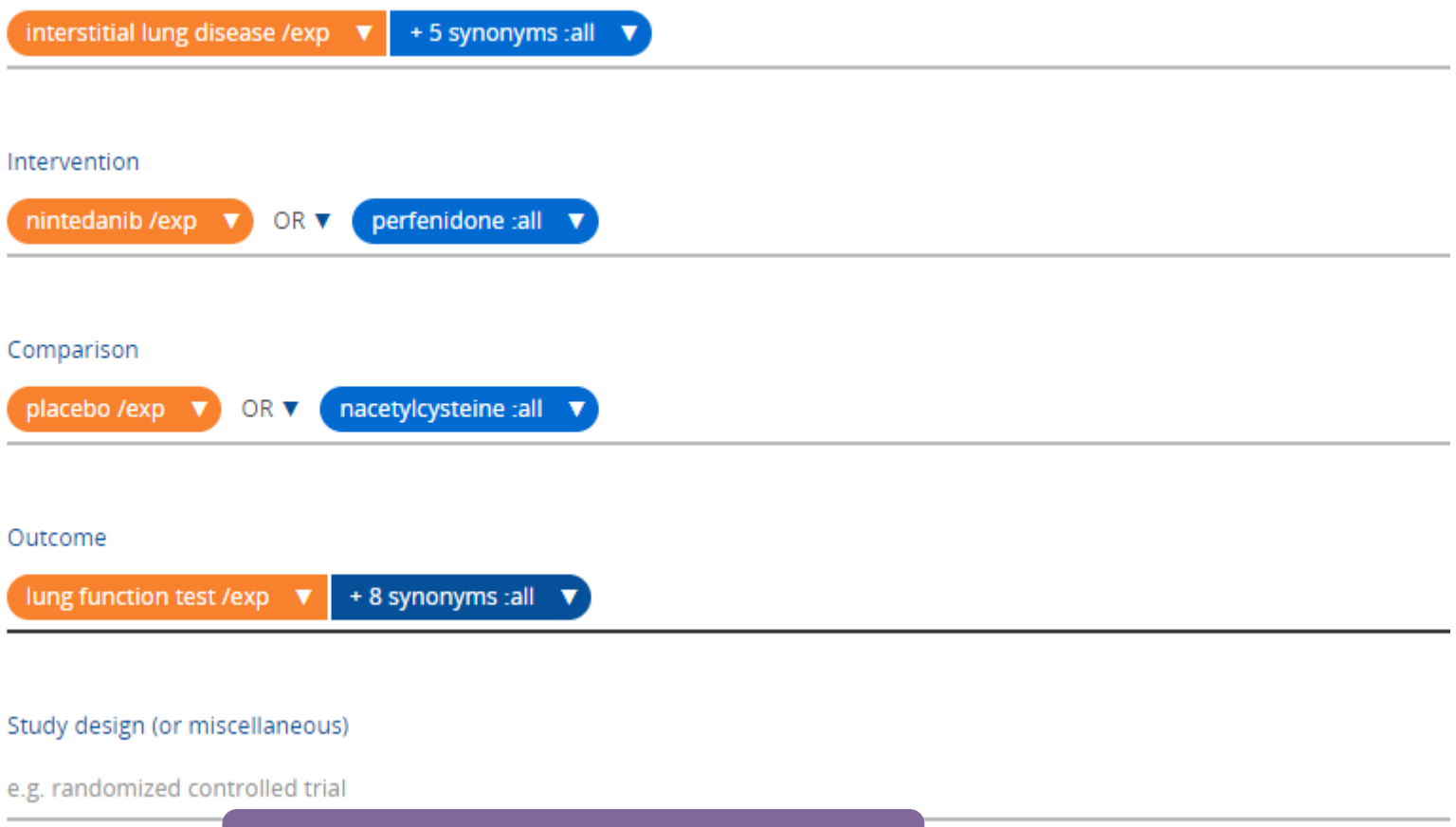
搜索：4 篇 Cochrane Review

Primary Database : Embase

使用內建Synonyms 系統，增加搜尋廣度



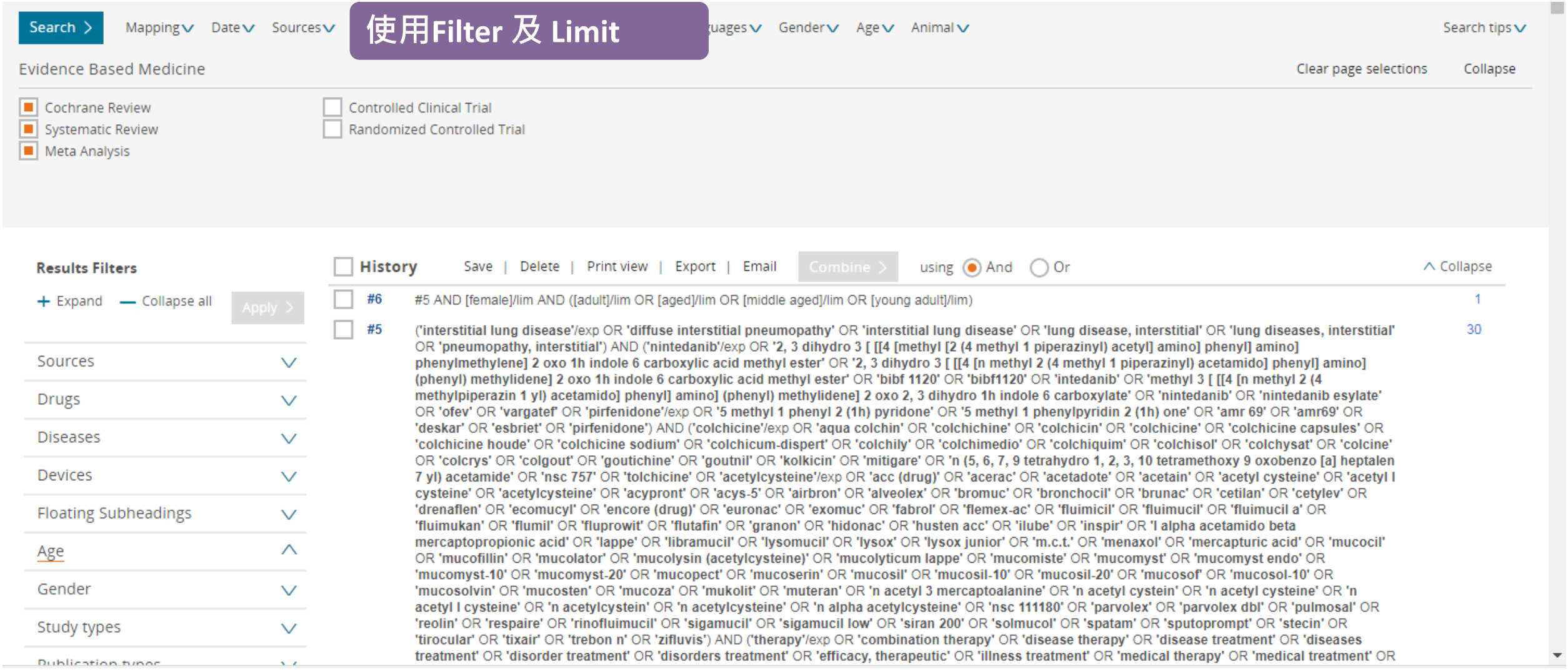
使用Emtree，增加精確性



使用PICO search，增加效率

Primary Database : Embase

使用Filter 及 Limit



Primary Database: PubMed

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

interstitial lung disease AND Nintedanib or pirfenidone AND Colchicine or N-actylcysteine **Keyword:** Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 13

Notable changes in the 2016 update: citalopram, escitalopram, diclofenac added to the list of drugs to avoid.
[No authors listed]
Prescrire Int. 2016 Apr; 25(170):107.

Interventions to improve chronic cyclosporine A nephrotoxicity through inhibiting renal cell apoptosis: a systematic review.
Xiao Z, Li CW, Shan J, Luo L, Feng L, Lu J, Li SF, Long D, Li YP.
Chin Med J (Engl). 2013; 126(19):3767-74.

Novelty in treatment of pulmonary fibrosis: pulmonary hypertension drugs and others.
Correale M, Totaro A, Lacedonia D, Montrone D, Di Biase M, Barbaro Foschino MP, Brunetti ND.
Cardiovasc Hematol Agents Med Chem. 2013 Sep; 11(3):169-78.

Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature.
Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, Koffman J, Riley J.
Thorax. 2013 Sep; 68(9):867-79. Epub 2012 Dec 1.

Decorin and colchicine as potential treatments for post-haemorrhagic ventricular dilatation in a neonatal rat model.
Hogue N, Thoresen M, Aquilina K, Hogan S, Whitelaw A.

Systematic Reviews

Results: 3 of 3

Interventions to improve chronic cyclosporine A nephrotoxicity through inhibiting renal cell apoptosis: a systematic review.
Xiao Z, Li CW, Shan J, Luo L, Feng L, Lu J, Li SF, Long D, Li YP.
Chin Med J (Engl). 2013; 126(19):3767-74.

Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature.
Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, Koffman J, Riley J.
Thorax. 2013 Sep; 68(9):867-79. Epub 2012 Dec 1.

Non-steroid agents for idiopathic pulmonary fibrosis.
Spagnolo P, Del Giovane C, Luppi F, Cerri S, Balduzzi S, Walters EH, D'Amico R, Richeldi L.
Cochrane Database Syst Rev. 2010 Sep 8; (9):CD003134. Epub 2010 Sep 8.

This column displays
analyses, reviews of
consensus developn
information or additio

Medical Genetics

Topic: All

Results: 2 of 2

The effect of antifibrotic drugs in rat precision-cut fibrotic liver slices.
Westra IM, Oosterhuis D, Groothuis GM, Olinga P.
PLoS One. 2014; 9(4):e95462. Epub 2014 Apr 22.

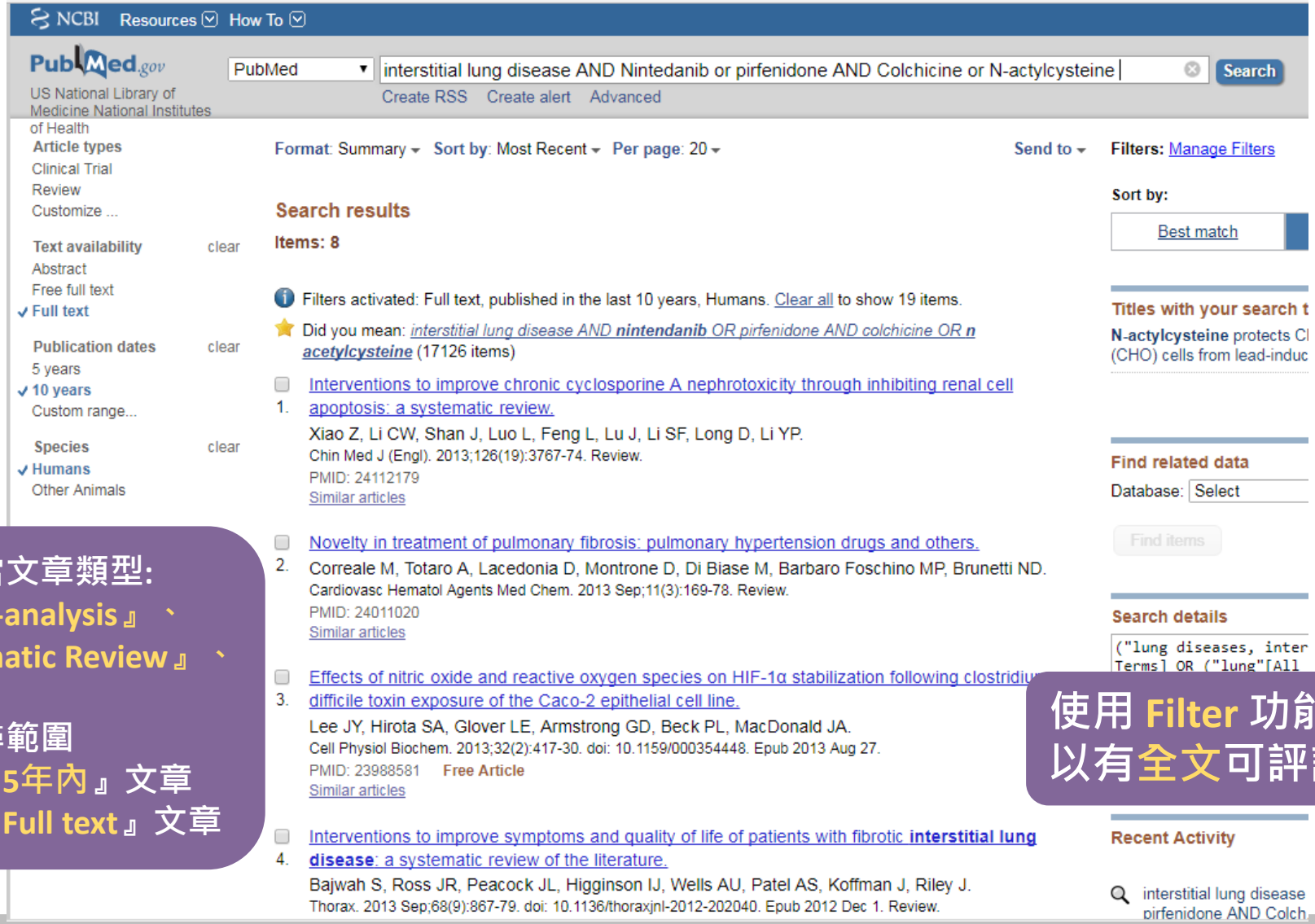
Sialoglycoproteins adsorbed by Pseudomonas aeruginosa facilitate their survival by impeding neutrophil extracellular trap through siglec-9.
Khatua B, Bhattacharya K, Mandal C.
J Leukoc Biol. 2012 Apr; 91(4):641-55. Epub 2012 Jan 11.

See all (2)

This column displays citations pertaining to topics in medical genetics. See more filter information.

1. 將關鍵字輸入透過MeSH找出最適當之Medical Terms
2. 利用布林邏輯 “AND” “OR” “NOT”等語法以免遺漏文獻搜尋分類
3. 使用Clinical Queries檢索分類

Primary Database: PubMed



限定適當文章類型:
『Meta-analysis』、『Systematic Review』、『RCT』
限定搜尋範圍
限定『5年內』文章
限定『Full text』文章

使用 Filter 功能以提升篩選效率
以有全文可評讀， Meta-analysis

Primary Database: 華藝線上圖書館

Keyword: [ALL]:特發性肺纖維化 AND [ALL]:nintedanib AND [ALL]:pirfenidone

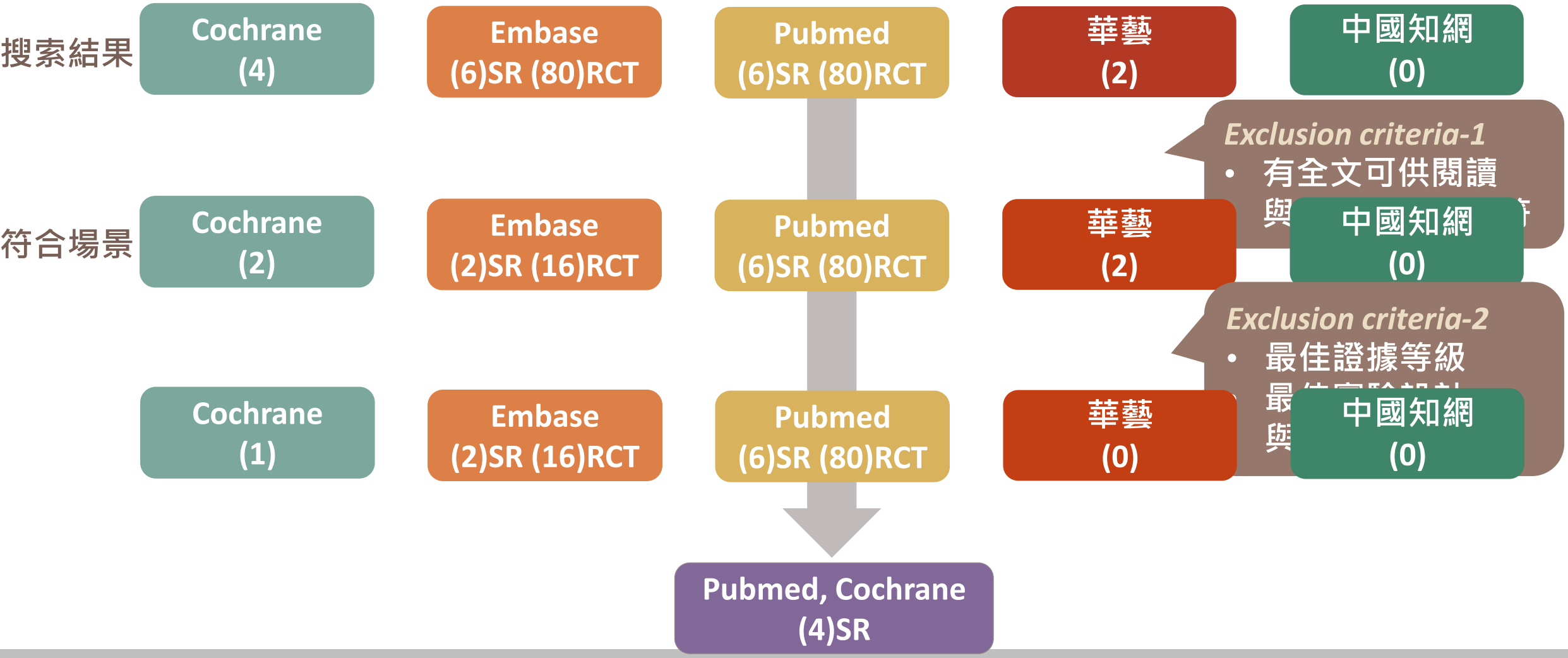
Primary Database: 中國知網Cnki

不遺漏重要亞洲文獻

Keyword:特发性肺纤维化、治疗, 適當使用布林邏輯『並且』、『或者』

限定適當搜尋範圍
限定2年內之文章
限定医药卫生科技之文章
使用同义字扩展 功能，擴大搜尋

篩選結果


搜索結果
Cochrane (4)
Embase (6)SR (80)RCT
Pubmed (6)SR (80)RCT
華藝 (2)
中國知網 (0)
Exclusion criteria-1
• 有全文可供閱讀
符合場景
Cochrane (2)
Embase (2)SR (16)RCT
Pubmed (6)SR (80)RCT
華藝 (2)
中國知網 (0)
Exclusion criteria-2
• 最佳證據等級
Cochrane (1)
Embase (2)SR (16)RCT
Pubmed (6)SR (80)RCT
華藝 (0)
中國知網 (0)
Pubmed, Cochrane (4)SR

各資料庫收納結果

標題	年分
Treatment of idiopathic pulmonary fibrosis: A network meta-analysis BMC Medicine 2016 14:1	2016
Drug treatment of idiopathic pulmonary fibrosis systematic review and network meta-analysis Chest 2016 149:3 (756-766)	2016
Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis Pulmonary Pharmacology and Therapeutics 2016 40 (95-103)	2016
Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments J Manag Care Spec Pharm. 2017 Mar;23(3-b Suppl):S5-S16	2017

篩選結果:選出最佳文獻

	文章
	Treatment of idiopathic pulmonary fibrosis: A network meta-analysis BMC Medicine 2016 14:1
M	August 2015
P	adult patients with IPF
I	nintedanib, pirfenidone, and sildenafil
C	prednisone/azathioprine/N-acetylcysteine triple therapy, and vitamin K antagonist
O	mortality

篩選結果:選出最佳文獻

	文章
	Drug treatment of idiopathic pulmonary fibrosis systematic review and network meta-analysis
M	October 2014
P	IPF
I	pirfenidone and nintedanib
C	Placebo
O	respiratory-specific mortality, all-cause mortality, and decline in percent predicted FVC

篩選結果:選出最佳文獻

	文章
	Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis Pulmonary Pharmacology and Therapeutics 2016 40 (95-103)
M	February 29, 2016
P	IPF
I	Nintedanib or pirfenidone or N-actylcysteine
C	Placebo
O	FVC decline> or ≥ 10%. acute exacerbations, death by respiratory causes, Adverse effects

篩選結果:選出最佳文獻

	文章
	Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments
M	April 2015
P	IPF
I	Nintedanib or pirfenidone or N-actylcysteine
C	Placebo
O	change from baseline in FVC, all-cause mortality

篩選結果:選出最佳文獻

文章	M	P	I	C	O
Treatment of idiopathic pulmonary fibrosis: A network meta-analysis BMC Medicine 2016 14:1	●	●	●	●	●
Drug treatment of idiopathic pulmonary fibrosis systematic review and network meta-analysis Chest 2016 149:3 (756-766)	●	●	●	●	●
Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis Pulmonary Pharmacology and Therapeutics 2016 40 (95-103)	●	●	●	●	●
Systematic Review and Network Meta-analysis of Idiopathic Pulmonary Fibrosis Treatments J Manag Care Spec Pharm. 2017 Mar;23(3-b Suppl):S5-S16	●	●	●	●	●

嚴格評讀

Pirfenidone, nintedanib and *N*-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis

Paola Rogliani [a, b], Luigino Calzetta [a, *], Francesco Cavalli [b], Maria Gabriella Matera [c], Mario Cazzola [a, b]

[a] *University of Rome Tor Vergata, Department of Systems Medicine, Unit of Respiratory Clinical Pharmacology, Rome, Italy*
[b] *University of Rome Tor Vergata, Department of Systems Medicine, Chair of Respiratory Medicine, Rome, Italy*
[c] *Second University of Naples, Department of Experimental Medicine, Unit of Pharmacology, Naples, Italy*

ARTICLE INFO

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Keywords:
IPF
Therapy
Meta-analysis

ABSTRACT

Background: The prevalence of idiopathic pulmonary fibrosis (IPF) is increasing every year. Pirfenidone and nintedanib were approved for treatment of IPF in 2014, but they received only a conditional recommendation for use and, thus, to date no drugs are strongly recommended for IPF. The aim of this study was to assess the effectiveness and safety of the currently approved drugs for IPF and *N*-acetylcysteine (NAC), the most debated drug in the last update of guidelines for IPF treatment.
Methods: RCTs in IPF were identified searching from databases of published and unpublished studies. The influence of pirfenidone, nintedanib and NAC on clinical outcomes, safety, and mortality was assessed via pair-wise meta-analysis.
Results: Ten papers (3847 IPF patients; 2254 treated; 1593 placebo) were included in this study. Our results showed that both pirfenidone and nintedanib, but not NAC, were significantly effective in reducing FVC decline and the risk of FVC ≥10% decline in percent predicted over 12 months. Nintenadib significantly protected against the risk of acute exacerbation and mortality. Pirfenidone and nintedanib showed a similar and good safety profile, whereas NAC provided a signal for increased adverse events.
Conclusions: The rank of effectiveness emerging from this meta-analysis represents an indirect indicator of potential differences between currently approved doses of pirfenidone and nintedanib. Direct comparisons are necessary to assess this matter, and well designed bench-to-bedside studies would permit to understand the potential of combined, sequential, or adjunctive treatment regimens in which perhaps NAC may have a role for specific clusters of IPF patients.

選擇原因

最符合臨床問題
最佳的研究設計
(治療型---RCT)
有全文可供評讀

我們的文獻工具是 NHS **CASP SR critical appraisal tool !!**

1 Did the trial address a clearly focused issue?

此研究是否問了一個清楚明確的問題?

YES NO UNCLEAR

A B S T R A C T

Background: The prevalence of idiopathic pulmonary fibrosis (IPF) is increasing every year. Pirfenidone and nintedanib were approved for treatment of IPF in 2014, but they received only a conditional recommendation for use and, thus, to date no drugs are strongly recommended for IPF. The aim of this study was to assess the effectiveness and safety of the currently approved drugs for IPF and *N*-acetylcysteine (NAC), the most debated drug in the last update of guidelines for IPF treatment.
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I、C O P

評讀 APPRAISAL

1 Did the trial address a clearly focused issue?

此研究是否問了一個清楚明確的問題?

● YES ● NO ● UNCLEAR

此評論文獻研究對象為各年齡層IPF病患，共計3847名；介入措施為使用Nintedanib 或 pirfenidone 或N-actylcysteine；比較組為使用placebo; 結果評量是使用reduce FVC decline，問題清楚且聚焦

	這篇研究	情境	是否相符
P	3,847 IPF patients	55 year old woman, non-smoker, interstitial lung disease	●Yes ○No
I	Nintedanib or pirfenidone or N-actylcysteine	Nintedanib or pirfenidone	●Yes ○No
C	Placebo	Colchicine or N-actylcysteine	●Yes ○No
O	reduce FVC decline	reduce FVC decline	●Yes ○No

2 Did the authors look for the right type of papers?

作者是否收納適當的研究類型？

● YES ○ NO ○ UNCLEAR

此介入型的問題，作者優先收納證據等級較高的 RCT文章，共有12篇。

- ✓ 收納double blind, RCT
- ✓ 清楚定義 inclusion, exclusion

2.2. Study selection

We included RCTs reported in English, lasting at least 6 months and concerning the influence of treatment with pirfenidone, nintedanib and NAC administered in patients suffering from IPF diagnosed by high-resolution computed tomography (HRCT) or biopsy [1,15]. All RCTs regarding IPF patients receiving oral administration of pirfenidone or nintedanib or oral/inhalant administration of NAC were included in the analysis.

3.1. Study characteristics

Overall, results obtained from 3847 IPF patients were selected from 10 published papers including 12 RCTs (Table 1). The studies were assessed as having a Jadad score ≥3, excluded that of Homma et al. [28] that has provided a Jadad score = 2. Data on the 6MWD variable were not suitable for performing an unbiased meta-analysis.

Further details are reported in the Supplemental File.

Table 1
Patient demographics, baseline and study characteristics.

Study and year	ClinicalTrials.gov Identifier	Study characteristics	Duration of study (weeks)	Number of analyzed patients	Drugs (doses)	Administration regimen	Patients characteristics	Age (years)	Male (%)	Current smokers (%)	Time since diagnosis (yr)	FVC or VC (% or L)	6MWD (metres)	DL_{CO} (% or mmol/min/kPa)	Jadad score
Azuma et al., 2005 [34]	NA	A multicentre double-blind, placebo-controlled, randomized clinical trial	39	107	Pirfenidone (1800 mg/die; 200 mg)	3 tablets t.i.d. (oral)	PaO2≥70 mmHg at rest; SpO2 of 90% or less during exertion while breathing air	64.0	86.0	10.0	<1yr 28.0%	81.6%	NA	57.6%	4
Taniguchi et al., 2010 [42]	NA	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	267	Pirfenidone (1800 mg/die; 200 mg); (1200 mg/die; 200 mg)	3 tablets t.i.d.(oral); 2 tablets t.i.d. (oral)	Oxygen desaturation of ≥5% difference between resting SpO2 and the lowest SpO2 during a 6MET; the lowest SpO2 during the 6MET of ≥85% while breathing air	64.7	82.1	9.2	<1yr 35.6%	2.4 L	NA	52.9%	4
Noble et al., 2011 (CAPACITY 04) [37]	NCT00287716	A multicentre double-blind, placebo-controlled, randomized clinical trial	72	435	Pirfenidone (2403 mg/die; 267 mg); (1197 mg/die; 133 mg)	3 tablets t.i.d.(oral); 3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.9	71.5	4.2	<1yr 49.4%	75.5%	4	46.8%	4
Noble et al., 2011 (CAPACITY 06) [37]	NCT00287729	A multicentre double-blind, placebo-controlled, randomized clinical trial	72	344	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d.(oral)	FVC of 50% until 90%; Dlco of 35% until 90%; 6MWD of at least 150 m	66.8	72.0	0.0	<1yr 58.0%	74.9%	378.0	47.8%	4
King et al., 2014 (ASCEND) [44]	NCT01366209	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	555	Pirfenidone (2403 mg/die; 267 mg)	3 tablets t.i.d. (oral)	FVC of 50% until 90%; Dlco of 30% until 90%; FEV1/FVC of 0.80 or more; 6MWD of 150 m or more	68.4	79.9	NA	1.7	67.8%	415.0	43.7%	4
Richeldi et al., 2011 (TOMORROW) [40]	NCT00514683	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	428	Nintedanib (300 mg/die; 150 mg); (200 mg/die; 100 mg); (100 mg/die; 50 mg); (50 mg/die; 50 mg)	1 tablet b.i.d. (oral); 1 tablet b.i.d.(oral); 1 tablet b.i.d. (oral); 1 tablet q.d. (oral)	FVC of ≥50%; Dlco of 30% until 79%	65.2	75.0	NA	1.2	2.8 L	NA	3.8 mmoL/min/kPa	4
Richeldi et al., 2014 (INPULSIS-1) [41]	NCT01335464	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	513	Nintedanib (300 mg/die; 150 mg)	1 tablet b.i.d. (oral)	FVC of ≥50%; Dlco of 30% until 79%	66.9	81.2	6.8	1.7	2.8 L	NA	47.8%	4
Richeldi et al., 2014 (INPULSIS-2) [41]	NCT01335477	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	548	Nintedanib (300 mg/die; 150 mg)	1 tablet b.i.d. (oral)	FVC of ≥50%; Dlco of 30% until 79%	66.4	77.8	2.4	1.6	2.7 L	NA	47.0%	4
Demedts et al., 2005 [43]	NA	A multicentre double-blind, placebo-controlled, randomized clinical trial	52	155	*N*-acetylcysteine (1800 mg/die; 600 mg)	1 tablet t.i.d. (oral)	VC of ≤80%; TLC of <90%; Dlco of <80%;	62.0	69.0	3.8	1.7	2.3 L	NA	3.9 mmoL/min/kPa	4

RCT

評讀
APPRAISAL

3 Do you think the important, relevant studies were included?

作者有沒有可能遺漏掉重要、相關的研究？

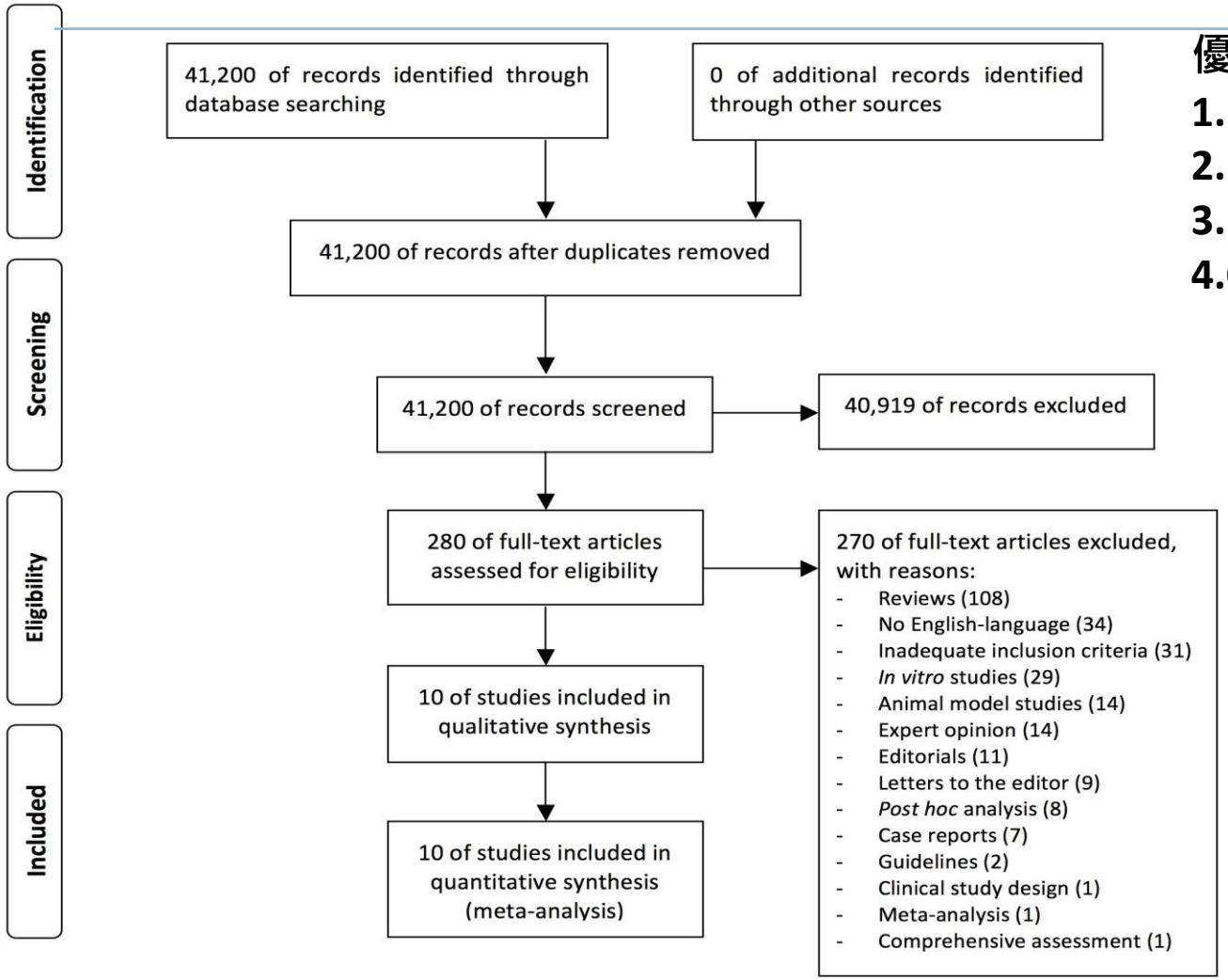
● YES ● NO ● UNCLEAR

2.1. Data sources and searches

The search was performed on PubMed and Google Scholar in order to provide for relevant studies published up to February 29, 2016 [14]. Further search was carried out on clinicaltrials.gov and the EU Clinical Trials Register in order to find potential randomized clinical trials (RCTs) not yet published. Citations of previous published meta-analyses and relevant reviews were examined to identify further pertinent studies, if any [5–11]. The terms "Idiopathic Pulmonary Fibrosis" and the term "treatment" were searched for identify RCTs investigating therapy for IPF.

文獻研究搜尋的關鍵字，包含PICO內措施和結果的醫學辭語或臨床用語。無語言限制。研究員分別在CENTRAL、MEDLINE、等一級及二級資料庫搜尋2016年3月以前的文獻。另外手動搜尋參考文獻的註記和臨床試驗網站的相關RCT文章，以免遺漏重要相關的研究。

搜尋資料庫:	其他文獻:
● MEDLINE/Pubmed	● Unpublished data
● Google scholar	● Original data
● Cochrane	● 學會/會議資料
◌ CENTRAL	◌ 語言(非英文)



優點

1.作者搜尋了重要一級和二級資料庫。

2.列出flow chart，並清楚說明納入及排除理由。

3.沒有研究設計限制。

4.Ongoing trial有搜尋。

4 Did the review's authors do enough to assess the quality of the included studies?

作者是否有評估收納研究的品質？

● YES ○ NO ○ UNCLEAR

2.3. Data extraction and quality assessment

Two reviewers independently checked the relevant RCTs found from literature and databases, and any difference in opinion about eligibility was resolved by consensus.

Data from included studies were extracted and checked for study characteristics and duration, doses of medications, disease characteristics, age, gender, smoking habits, smoking history, sex, forced vital capacity (FVC), carbon monoxide diffusing capacity (DLCO), 6 min walking distance (6MWD), time since diagnosis (years), weight, and Jadad score.

The Jadad score was used to assess the quality of the papers [16], and a score <3 was used as cut-off for subgroup analysis.

The risk of publication bias was assessed by applying the funnel plot and Egger's test [17–19]. Evidence of asymmetry from Egger's test was considered to be significant for $P < 0.1$ [19].

Further details are reported in the Supplemental File.

1.兩位作者獨立地評估研究的合適性。
2.使用Jadad score 評估文章品質，score <3 was used as cut-off for subgroup analysis。
3.內文對於各項的結果皆有清楚的定義。
4.使用Egger's test & Begg's tests 的P<0.1則為有意義

評估方法:

- ◌ Cochrane risk of bias tool
- ● Jadad score

發表誤差:

- ● Funnel plot
- ● Egger's model

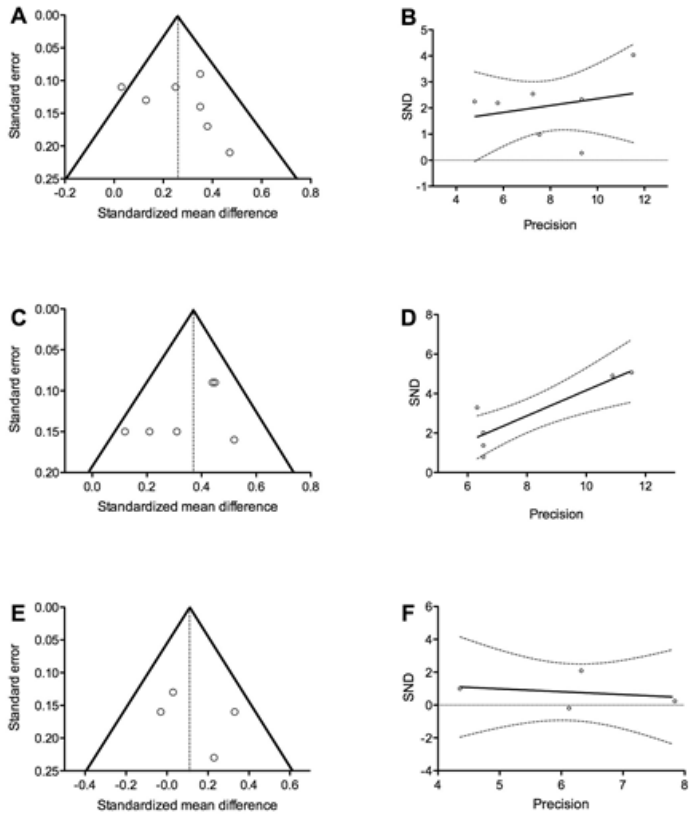


Figure S12. Funnel plots (left panels) and graphical representation of Egger's test (right panels) for the impact on change from baseline in FVC of pirfenidone (A, B), nintedanib (C, D) and NAC (E, F), vs. placebo. SND: standard normal deviate.

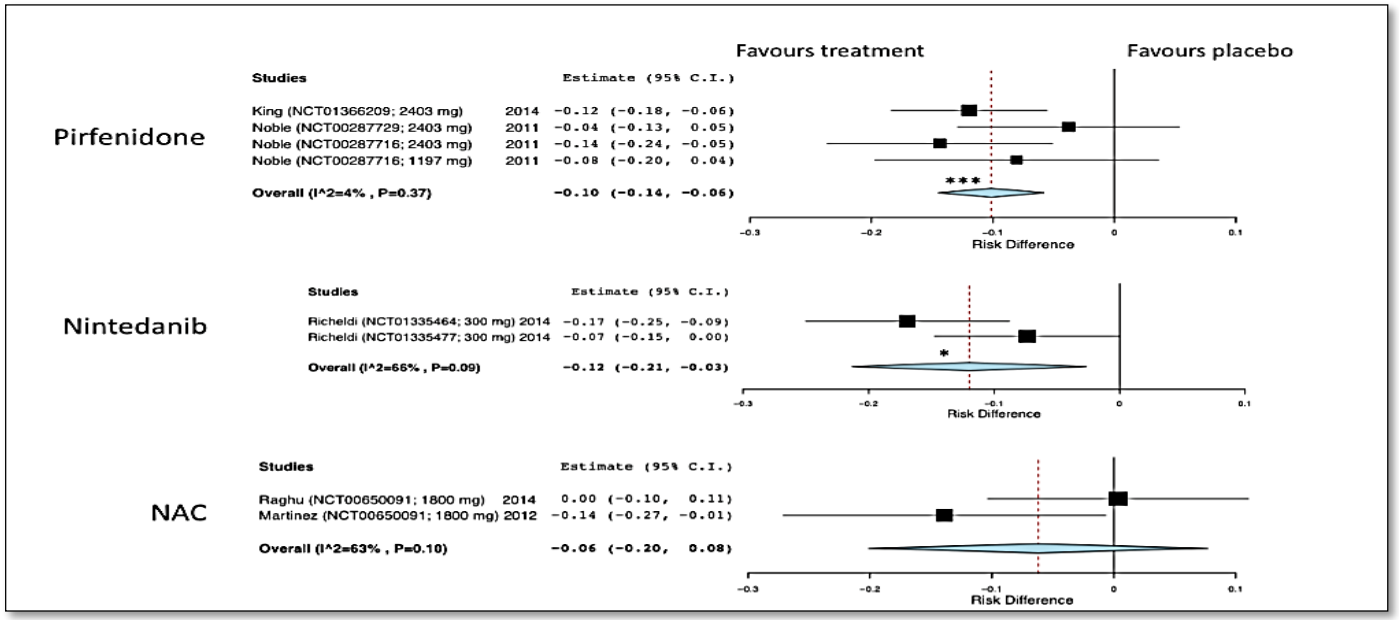
1.由Funnel plot大致算對稱，表示publication bias是可以接受的。
2.於文章內文中有將重要的BIAS和LIMITATION作探討。

評讀 APPRAISAL

5 If the results of the review have been combined, was it reasonable to do so?

作者是否有把各個研究的結果合併起來？這樣的合併是合理的嗎？

● YES ○ NO ○ UNCLEAR



研究員使用Cochrane Review Manager 5 software來分析研究間的異質性(heterogeneity)。而I2值落於30~ 60%，具中度異質性。故研究員選擇隨機效應模式(random-effects model)進行統合分析(meta-analysis)。

FVC decline> or ≥ 10% predicted評讀結果

pirfenidone 95%CI -0.14 to −0.06, I^2 4%(低度異質性,**合理合併**)

nintedanib 95%CI -0.21 to −0.03, I^2 66%(中度異質性,**合理合併**)

NAC 95%CI -0.20 to–0.08, I^2 63%(中度異質性,**合理合併**)

異源性分析:

- ● Cochran's Q statistic
- ● I^2 statistic

合併結果方法為:

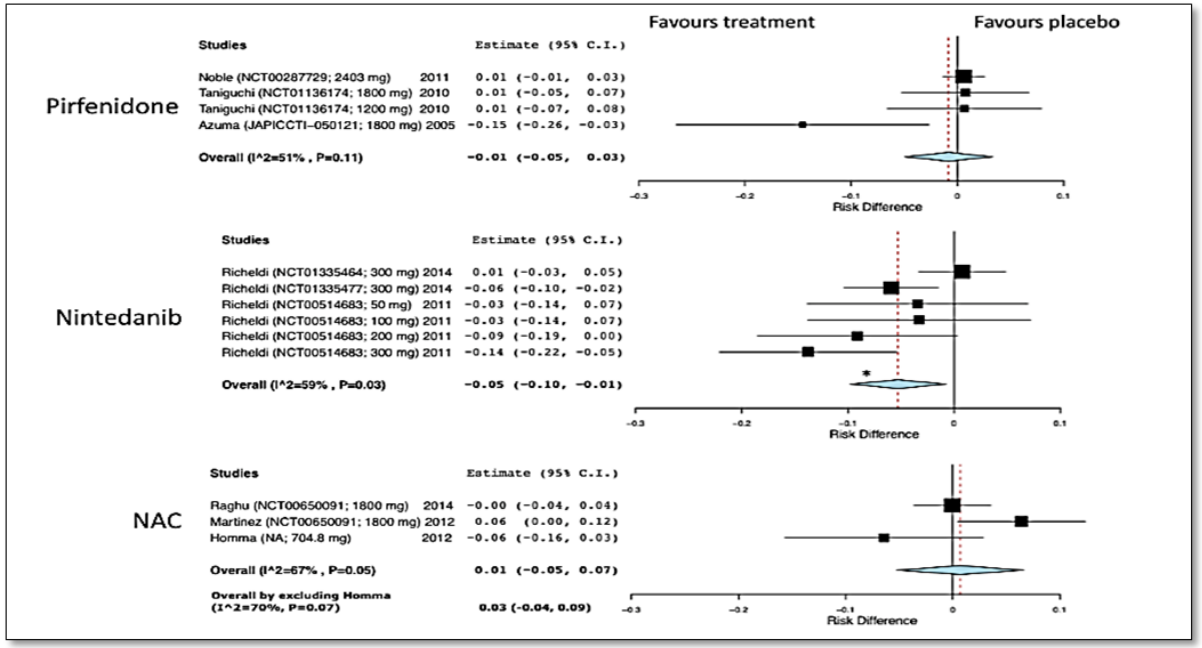
- ◌ Fixed-effect model (異質小)
- ● Random-effect model (異質大)

評讀 APPRAISAL

5 If the results of the review have been combined, was it reasonable to do so?

作者是否有把各個研究的結果合併起來？這樣的合併是合理的嗎？

● YES ○ NO ○ UNCLEAR



研究員使用Cochrane Review Manager 5 software來分析研究間的異質性(heterogeneity)。而I2值落於30~ 60%，具中度異質性。故研究員選擇隨機效應模式(random-effects model)進行統合分析(meta-analysis)。

acute exacerbations評讀結果

pirfenidone 95%CI -0.05 to −0.03, I^2 51%(中度異質性,**合理合併**)

nintedanib 95%CI -0.10 to −0.01, I^2 59%(中度異質性,**合理合併**)

NAC 95%CI -0.05 to–0.07, I^2 67%(中度異質性,**合理合併**)

異源性分析:

- ● Cochran's Q statistic
- ● I^2 statistic

合併結果方法為:

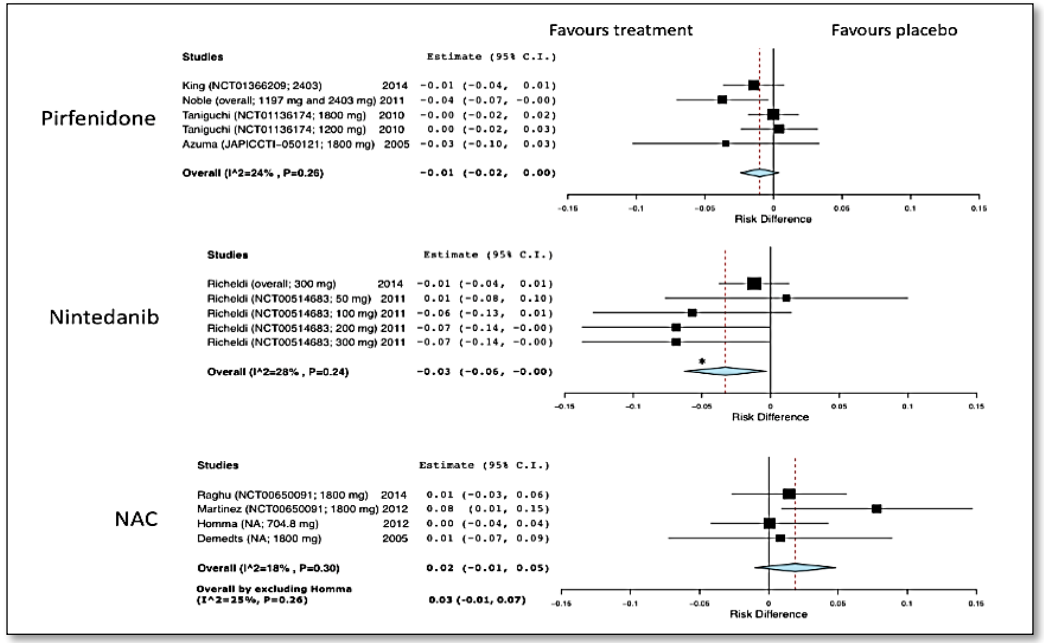
- ◌ Fixed-effect model (異質小)
- ● Random-effect model (異質大)

評讀
APPRAISAL

5 If the results of the review have been combined, was it reasonable to do so?

作者是否有把各個研究的結果合併起來？這樣的合併是合理的嗎？

● YES ○ NO ○ UNCLEAR



研究員使用Cochrane Review Manager 5 software來分析研究間的異質性(heterogeneity)。而I2值落於30~ 60%，具中度異質性。故研究員選擇隨機效應模式(random-effects model)進行統合分析(meta-analysis)。

death by respiratory causes評讀結果

pirfenidone 95%CI -0.05 to −0.03, I^2 24%(低度異質性,**合理合併**)

nintedanib 95%CI -0.10 to −0.01, I^2 28%(低度異質性,**合理合併**)

NAC 95%CI -0.20 to–0.08, I^2 18%(低度異質性,**合理合併**)

異源性分析:

- ● Cochran's Q statistic
- ● I^2 statistic

合併結果方法為:

- ◌ Fixed-effect model (異質小)
- ● Random-effect model (異質大)

6 What are the overall results of the review?

這篇回顧呈現了什麼結果？

(B) What are the results?

評讀
APPRAISAL

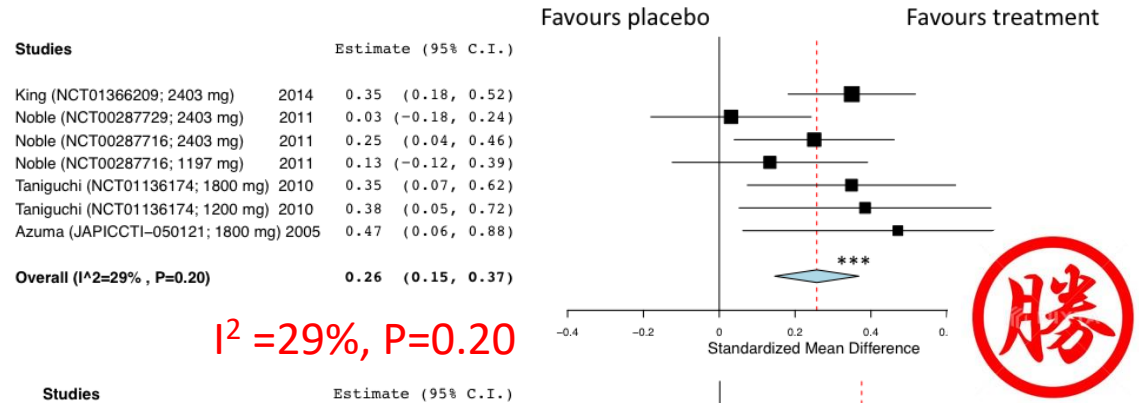
7 How precise are the results?

結果精準嗎？

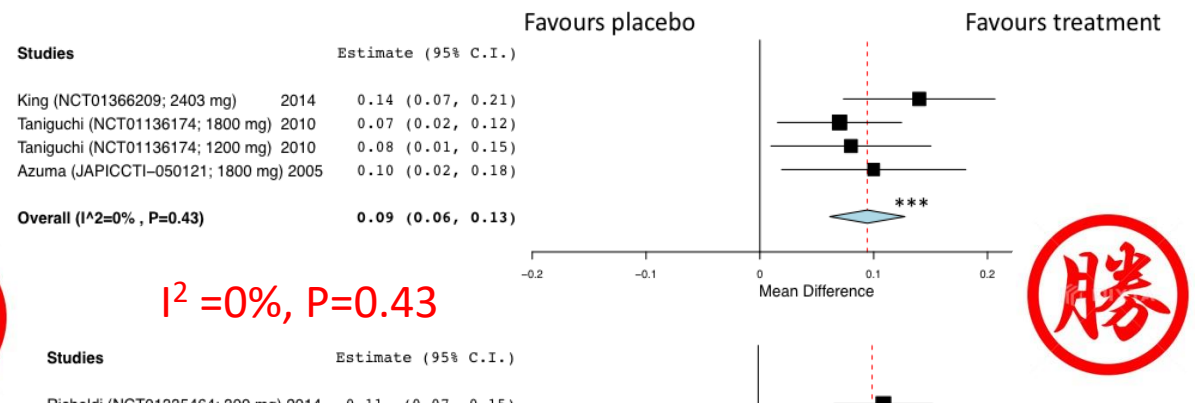
SMD of change from baseline in FVC(%)

MD (L) of change from baseline in FVC

Pirfenidone

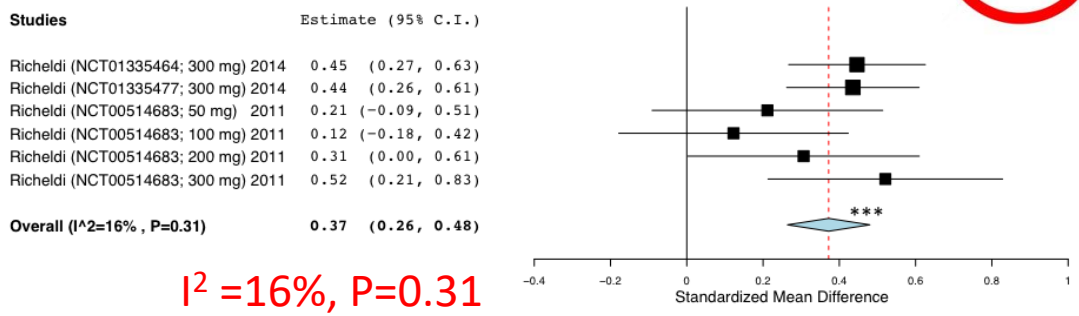


I^2 =29%, P=0.20

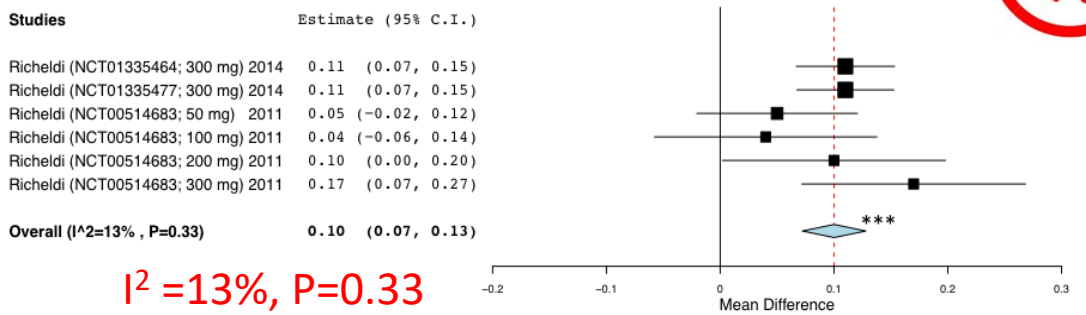


I^2 =0%, P=0.43

Nintedanib

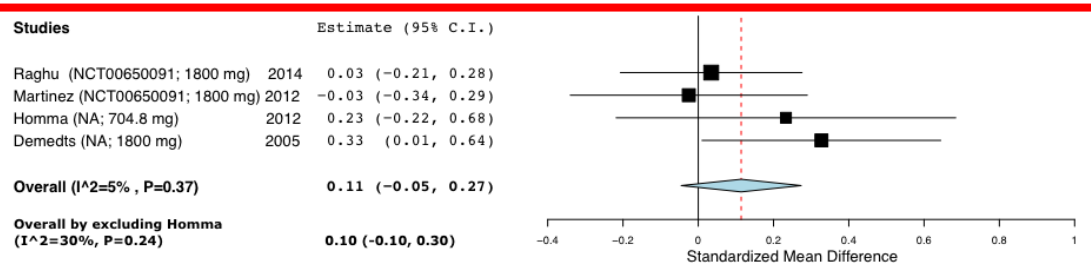


I^2 =16%, P=0.31

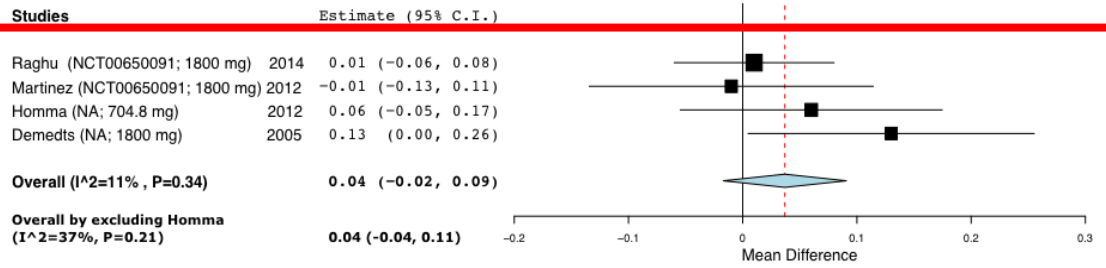


I^2 =13%, P=0.33

NAC



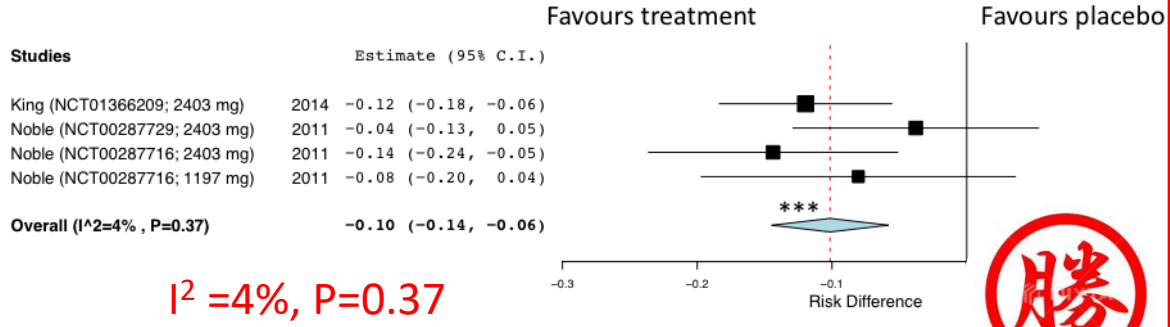
I^2 =5%, P=0.37



I^2 =11%, P=0.34

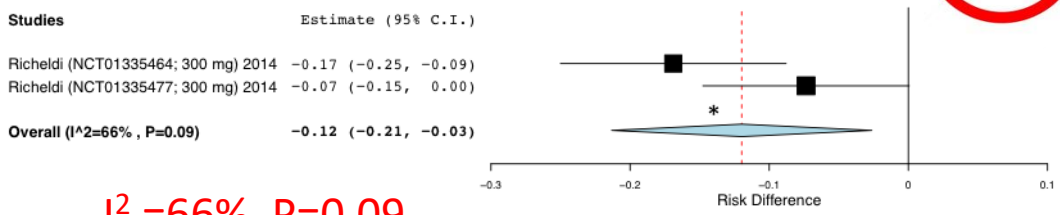
Risk difference of FVC decline > or ≥ 10% predicted

Pirfenidone



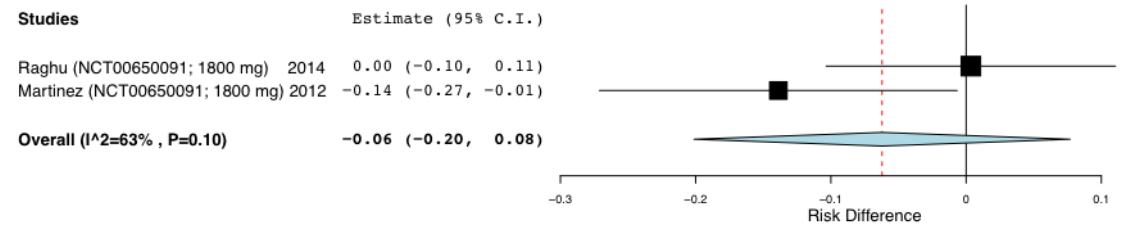
I^2 =4%, P=0.37

Nintedanib



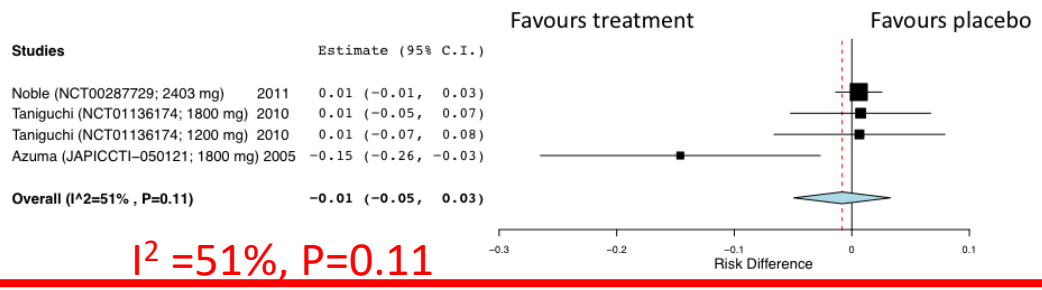
I^2 =66%, P=0.09

NAC

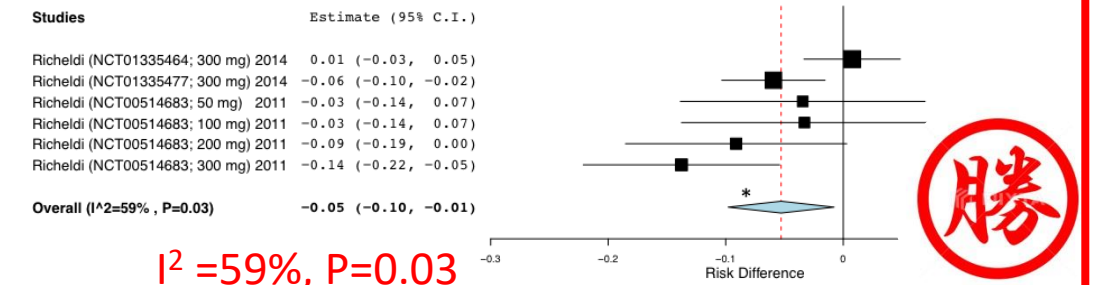


I^2 =63%, P=0.10

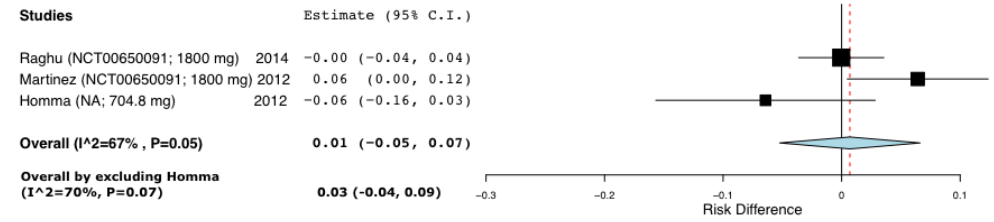
Risk difference of acute exacerbations



I^2 =51%, P=0.11



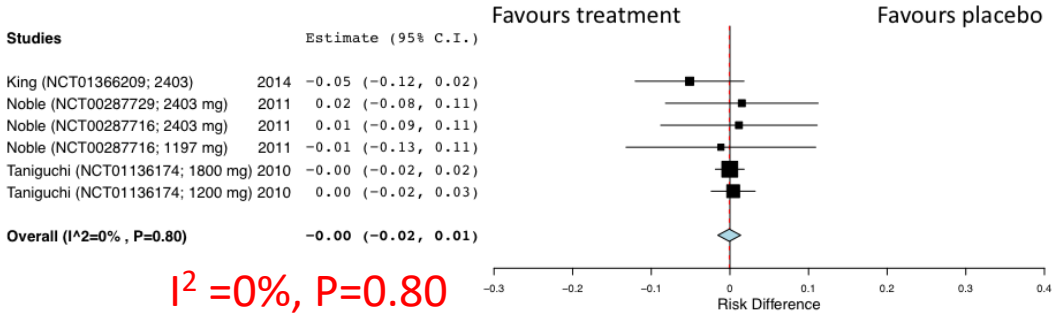
I^2 =59%, P=0.03



I^2 =70%, P=0.07

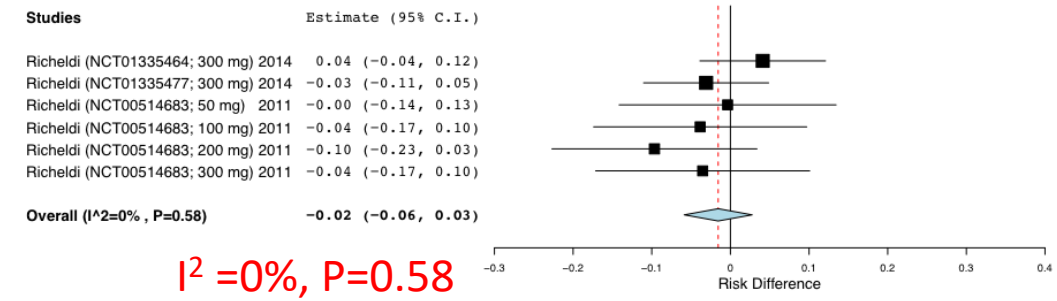
Risk difference of serious adverse events

Pirfenidone



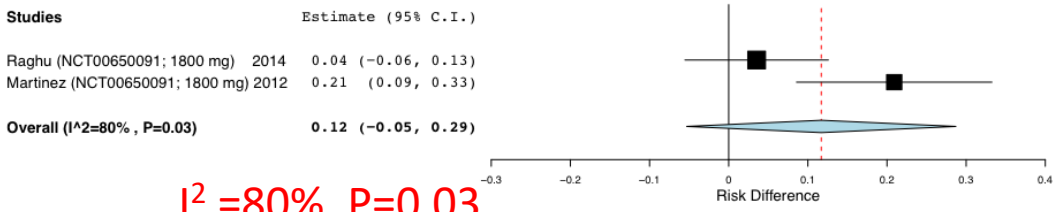
I^2 =0%, P=0.80

Nintedanib



I^2 =0%, P=0.58

NAC



I^2 =80%, P=0.03

- **NAC may increase the risk of adverse events**

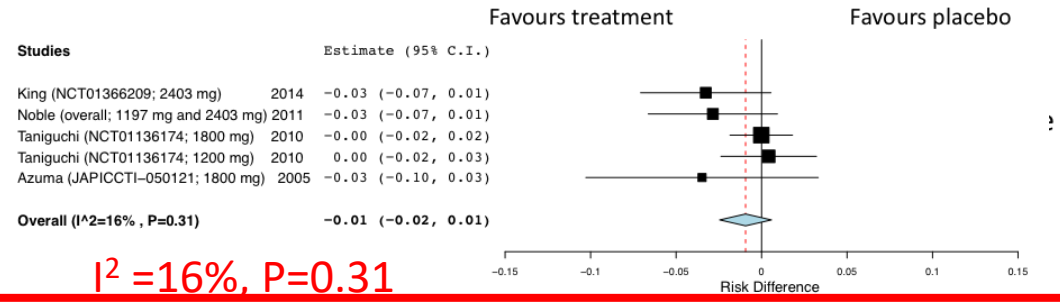
The most frequent adverse events detected in the arms treated with different doses of pirfenidone, nintedanib and NAC and in placebo groups are reported in Table S3. The most common (≥1/10) adverse events associated with the administration of approved dose of pirfeninone were rash (30.34%), nausea (25.68%), cough (19.42%), dizziness (17.98%), headache (16.05%), anorexia (13.00%), dyspepsia (12.68%), dyspnoea (11.08%) and insomnia (10.43), whereas those associated with the approved dose of nintedanib were diarrhoea (60.86%), nausea (24.34%), cough (12.86%), naso-pharyngitis (12.86%), vomiting (11.62%) and decrease appetite (11.07%). However, overall 40% of very common (≥1/10) and 87% of common (≥1/100 to <1/10) adverse events were also observed with similar frequency in the placebo arms.

副作用與劑量有關

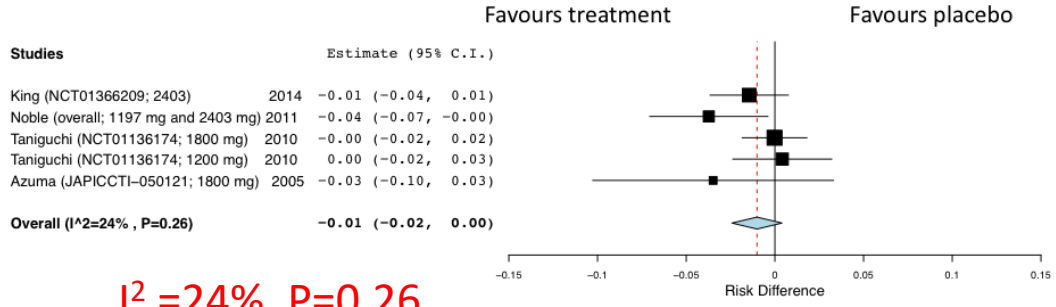
Overall risk difference of death

Specific risk difference of death by respiratory causes

Pirfenidone

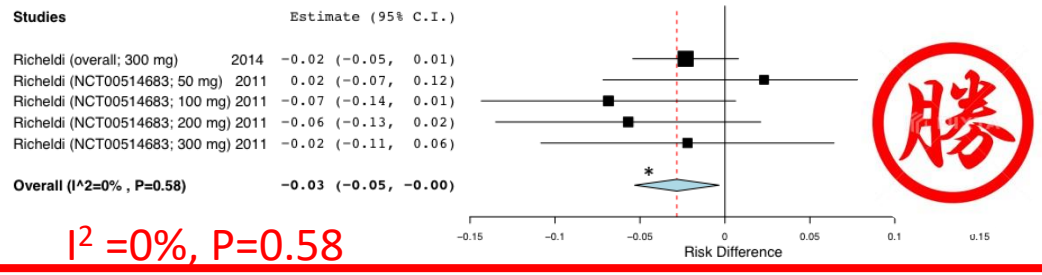


I^2 =16%, P=0.31

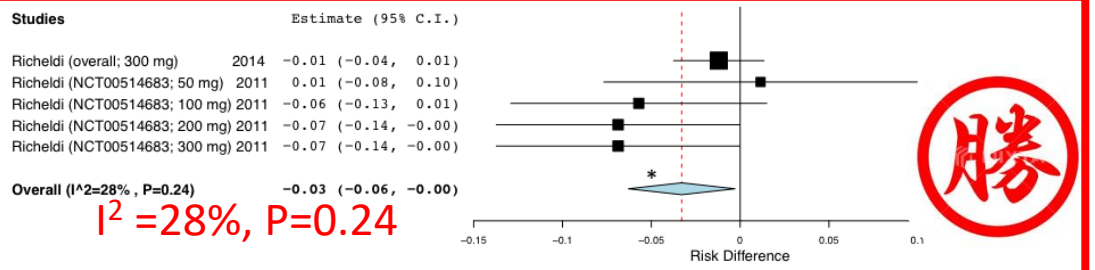


I^2 =24%, P=0.26

Nintedanib

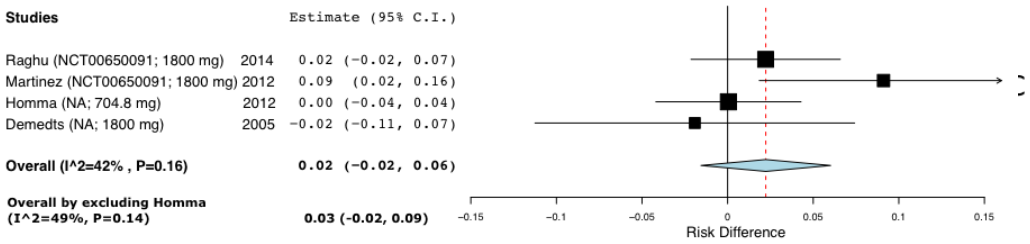


I^2 =0%, P=0.58

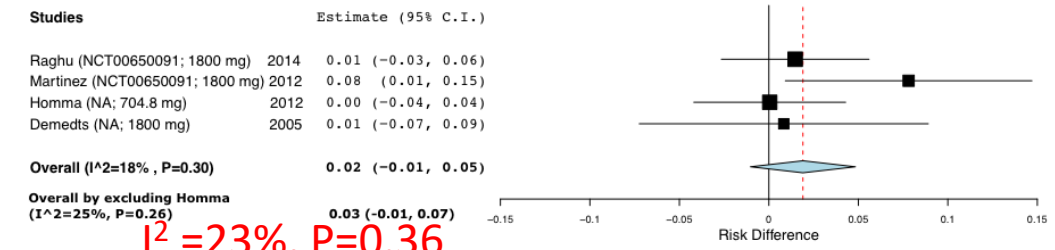


I^2 =28%, P=0.24

NAC



I^2 =49%, P=0.14



I^2 =23%, P=0.36

評讀
APPRAISAL

8 Can the results be applied to the local population?

此研究是否可應用到你的病患？

● YES ○ NO ○ UNCLEAR

2.3. Data extraction and quality assessment

Two reviewers independently checked the relevant RCTs found from literature and databases, and any difference in opinion about eligibility was resolved by consensus.

Data from included studies were extracted and checked for study characteristics and duration, doses of medications, disease characteristics, age, gender, smoking habits, smoking history, sex, forced vital capacity (FVC), carbon monoxide diffusing capacity (DLCO), 6 min walking distance (6MWD), time since diagnosis (years), weight, and Jadad score.

The Jadad score was used to assess the quality of the papers [16], and a score <3 was used as cut-off for subgroup analysis.

The risk of publication bias was assessed by applying the funnel plot and Egger's test [17–19]. Evidence of asymmetry from Egger's test was considered to be significant for $P < 0.1$ [19].

Further details are reported in the Supplemental File.

文獻研究明確定義研究族群年齡(平均62-68.8 歲)、吸菸比率(0.0-10.0%)，診斷為IPF(<1 yr 2 篇，其餘4篇<1 yr約40%)。本個案為55歲女性 ，未抽菸，初診斷為IPF (< 1 yr)故可將本研究應用於本個案上。

9 Were all clinically important outcomes considered?

是否所有重要的臨床結果都被考量到？

● YES ○ NO ○ UNCLEAR

The endpoint of this pair-wise meta-analysis was the influence of pirfenidone, nintedanib and NAC in modulating the change from baseline in FVC, FVC >10% or ≥10% decline in percent predicted, occurrences of IPF exacerbations, safety as serious adverse events (SAE), overall deaths by any causes and by specific respiratory causes, and change from baseline in 6MWD, vs. placebo. Table S2 shows the definition of IPF acute exacerbation and SAE according to the studies included in the meta-analysis.

文獻研究以Change from baseline in FVC, FVC decline > or >= 10 % , Acute exacerbation, safty (serious adverse events), overall deaths作評估藥物(Nintedanib, Pirfenidone, NAC)於IPF治療的結果

其結果聚焦、明確。

10 Are the benefits worth the harms and costs?

這些好處隨之而來的傷害和花費是否值得？

● YES ○ NO ○ UNCLEAR

To better interpret these results, that were obtained from data in which multiple doses were considered in several RCTs, we have carried out a subset analysis that included only the currently approved doses of pirfenidone (2403 mg/day) and nintedanib (300 mg/day) for the treatment of IPF. Only few variables were available for this sub-analysis, but they were adequate to evidence a greater influence of nintedanib in terms of preventing the FVC decline, with an analogous safety profile when compared with pirfenidone. Although some non-serious adverse events were extremely frequent in patient treated with pirfenidone (i.e. rash and nausea) and nintedanib (i.e. diarrhoea and nausea), both these drugs are characterized by a risk–benefit ratio that, in any case, strongly suggests for the prosecution of treatment with possibly no reduction of doses.

效果:

Major outcome: Change from baseline in FVC, FVC decline > or >= 10 %

Pirfenidone, Nintedanib> NAC

Secondary outcome: Acute exacerbation, safety (serious adverse events), overall deaths

Nintedanib> Pirfenidone, NAC

非嚴重副作用:

Pirfenidone: 紅疹、噁心

Nintedanib: 噁心、腹瀉

副作用的發生主要跟劑量有關

此項結果值得應用於臨床個案上。

成本效益

PharmacoEconomics (2017) 35:479–491
DOI 10.1007/s40273-016-0480-2

ORIGINAL RESEARCH ARTICLE

A Cost-Effectiveness Analysis of Nintedanib in Idiopathic Pulmonary Fibrosis in the UK

C. Rinciog[1] · M. Watkins[2] · S. Chang[1] · T. M. Maher[3,4] · C. LeReun[5] · D. Esser[6] · A. Diamantopoulos[1]

Table 6 Incremental cost-effectiveness ratios for pirfenidone and nintedanib versus best supportive care

	BSC (baseline)	Pirfenidone	Nintedanib
Total costs (£)	20,029.23	80,474.37	78,350.71
Drug acquisition costs	0.00	59,121.16	57,582.92
Treatment-related AE costs	589.13	1002.64	702.54
Patient monitoring (liver panel tests) costs	0.00	9.06	8.83
Background follow-up and oxygen use costs	9231.78	10,026.61	10,119.06
Acute exacerbation costs	1265.38	1486.63	1127.31
EoL palliative care costs	8942.94	8828.27	8810.06
Total QALYs	3.0999	3.4509	3.5013
ICER	Baseline	Dominated by nintedanib	£145,310 per QALY gained vs. BSC

AE adverse event, *BSC* best supportive care, *EoL* end of life, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

綜觀評讀結果

問題	結果
清楚的臨床問題	●YES ○NO ○UNCLEAR
收納適當研究	●YES ○NO ○UNCLEAR
搜尋所有相關研究	○YES ○NO ●UNCLEAR
評估收納研究的品質	●YES ○NO ○UNCLEAR
合理地合併結果	●YES ○NO ○UNCLEAR
適當呈現結果	●YES ○NO ○UNCLEAR
精準的結果	●YES ○NO ○UNCLEAR

證據等級 Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

LEVEL 1

評定證據等級—GRADE online

🟢不嚴重 🟡嚴重 🔴很嚴重

		主要結果	次要結果
研究設計		RCT	RCT
降階	1.存在誤差風險	🟡	🟡
	2.結果不一致	🟢	🟢
	3.證據不具直接性	🟡	🟡
	4.結果不精準	🟢	🟢
	5.存在發表誤差	🟢	🟢
升階	1.效果顯著	-	-
	2.降低干擾因素	-	-
	3.具劑量-反應效果	-	-
證據等級		**MODERATE**	**MODERATE**

成本效益

DynaMed Powered by EBSCOhost

衛生福利部中央健康保險署
NATIONAL HEALTH INSURANCE ADMINISTRATION, MINISTRY OF HEALTH AND WELFARE

- 藥物的「選擇」

選擇	好處	壞處	建議等級	價格
Nintedanib (Ofev) 300 mg/day	1. decrease risk of pulmonary function decline 2. reduce acute exacerbations	1. gastrointestinal symptoms and levels of liver aminotransferases 2. moderate-to-severe liver problems, and women should not become pregnant while taking nintedanib due to risk of birth defects or fetal death	Level 2	150 mg: 876 元 52560 元/月
Pirfenidone (Esbriet) 2403 mg/day	1. Reduce mortality 2. Slow disease progression 3. Reduced risk of additional FVC decline	1. gastrointestinal, neurological, and dermatological adverse events 2. Severe liver problems, end-stage kidney disease, or who require dialysis	Level 2	200 mg:139 元 50040 元/月

成本效益

- 藥物的「選擇」

選擇	好處	壞處	建議等級	價格
N-Acetylcystein 1800 mg/day	1. Acetylcysteine monotherapy not recommended in most patients but may be reasonable choice in minority of patients 2. not improve lung function		Level 3	600 mg: 6 元 540 元/月
Colchicine	1. colchicine not recommended 2. colchicine does not appear associated with increased survival		Level 2	0.5 mg: 2 元 120 元/月

成本效益

- 藥物的「其他選擇」

DynaMed Powered by EBSCOhost

衛生福利部中央健康保險署
NATIONAL HEALTH INSURANCE ADMINISTRATION, MINISTRY OF HEALTH AND WELFARE

選擇	好處	壞處	建議等級	價格
Corticosteroids:	急性發作	1. Corticosteroid monotherapy not recommended 2.No adequate controlled trials	Low weak to Strong recommendation, Very low-quality evidence	PREDNISOLONE 5 MG : 1-2 元 30-60 元/月
Azathioprine (with prednisolone and N-acetylcysteine	保持肺容積及carbon monoxide diffusing capacity (level 1)	增加死亡率及住院率(level 2)	Level 1 Level 2	50 MG :25 元
Cyclophosphamide		不會增加死亡率	Level 2	50 MG: 7 元
Cyclosporine		不會預防急性發作	Level 3	25 MG: 43 元 100 MG: 140 元
Thalidomide	improve cough and cough- and respiratory-associated quality of life	constipation, dizziness, and malaise	Level 2	50 MG: 250 元

成本效益

- 非藥物的「治療策略」

選擇	效用	壞處	建議等級	價格
Supplemental oxygen	減輕呼吸困難症狀	不會增加 Survival	Level 2	高壓氧氣筒 (500~1000 元)、氧氣濃縮機(2000-2500 元/月)、液態氧。
Pulmonary physical rehabilitation 1. aerobic conditioning 2.strength and flexibility training 3.educational lectures 4.nutritional interventions 5.psychosocial support	improve short-term walking distance, dyspnea, and quality of life 	Not improve 6-minute walking distance	level 2	0

臨床應用

這篇 Level 2 證據可應用於我們的個案嗎？

✓ 我們的病患與研究是否相仿？ ●YES ○NO ○UNCLEAR

●性別 ●相同疾病 ●種族 ●年齡 ●疾病特徵（症狀/共病症）●使用藥物

✓ 這項治療方式在本地可行嗎？ ●YES ○NO ○UNCLEAR

●醫療政策 ● 技術性 ●風土名情

✓ 是否符合病患主要訴求？ ●YES ○NO ○UNCLEAR

●病患考量點：傳統藥物治療，還是新藥好?副作用?

✓ 此項治療好處是否多於壞處？ ●YES ○NO ○UNCLEAR

●治療效果 ○費用可接受 ● 便利性

臨床應用

病人的想法為何?

病患選擇治療方式會在意的因素有什麼？以及在意的程度 ？				
考量因素	不重要	普通	重要	非常重要
經濟考量因素		✓		
較好生活品質				✓
照護的方便性			✓	
病人的舒適性				✓
病人可存活時間				✓
治療的後遺症				✓

臨床回覆（白話版）

臨床情況
ENVIRONMENT

新藥目前有健保給付但需經事前審查核准後才可使用，每24週需檢送評估資料再次申請。若無申請，自費使用每月約需5萬元。

臨床經驗
EXPERIENCE

特發性肺纖維症診斷主要為HRCT搭配病史、症狀，一般不用特別做切片診斷。日後發生癌症的機率約10-30%，先別過度擔心，先好好治療肺纖維化疾病，如特發性肺纖維症不控制好，危險性反而較癌症可怕，建議定期回診追蹤

最佳證據等級
EVIDENCE

根據目前團隊所搜尋到的最佳證據顯示，新藥(Nintedanib, Pirfenidone) 效果和安慰组比較較傳統藥物(N-acetylcystein)好，但主要效果為在延緩肺功能惡化，減少急性發作比率等，就目前證據建議新藥的使用，目前的新藥作用主要為延緩肺功能的惡化，留意藥品的副作用為腸胃道不適(噁心腹瀉等)，如肺功能持續惡化或無法忍受副作用請回診和醫師溝通

病人期望
EXPECTATION

針對您所關心非藥物問題，如運動及氧氣的使用，研究證據顯示氧氣短期使用可以改善急性發作，但長期使用並無明顯好壞處，此外適度有氧運動可減緩呼吸困難的症狀，建議先從輕度有氧運動開始

Thank You