A到Z線上藥學論壇

COPD治療中的生物標記:
如何幫助病患選擇適當的治療方式

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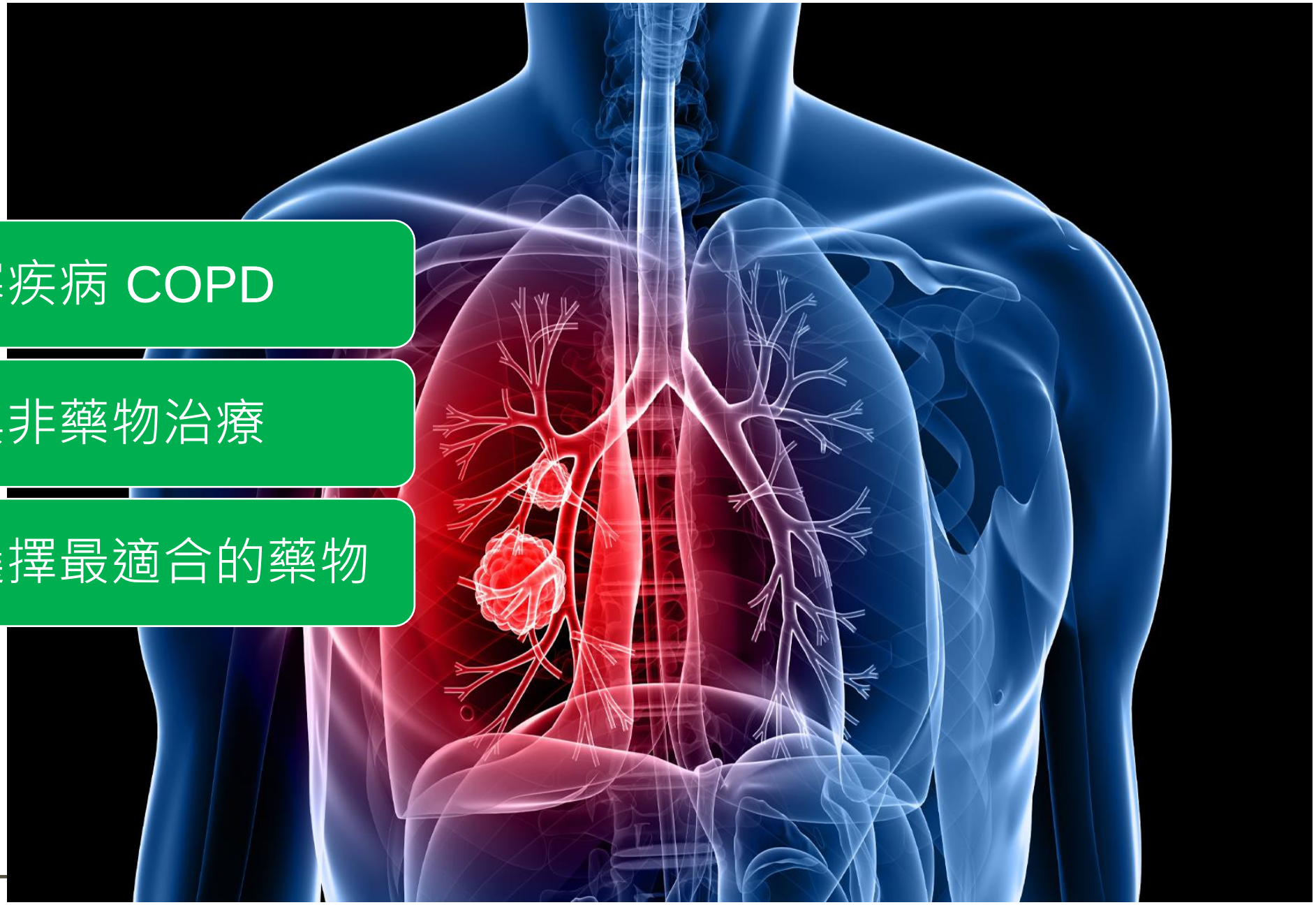
簡介慢性肺阻塞疾病 COPD

肺阻塞的藥物與非藥物治療

應用生物標記選擇最適合的藥物



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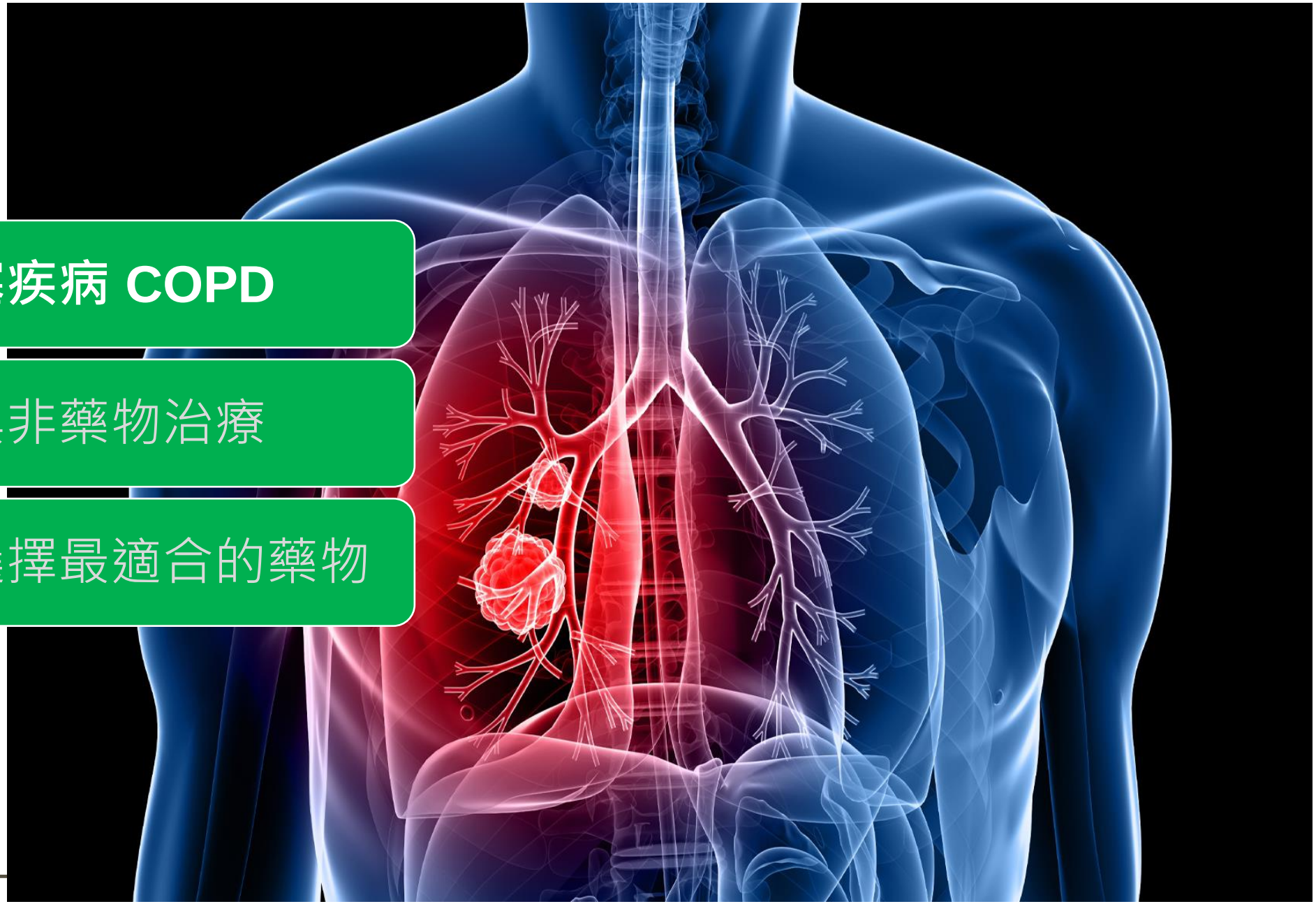
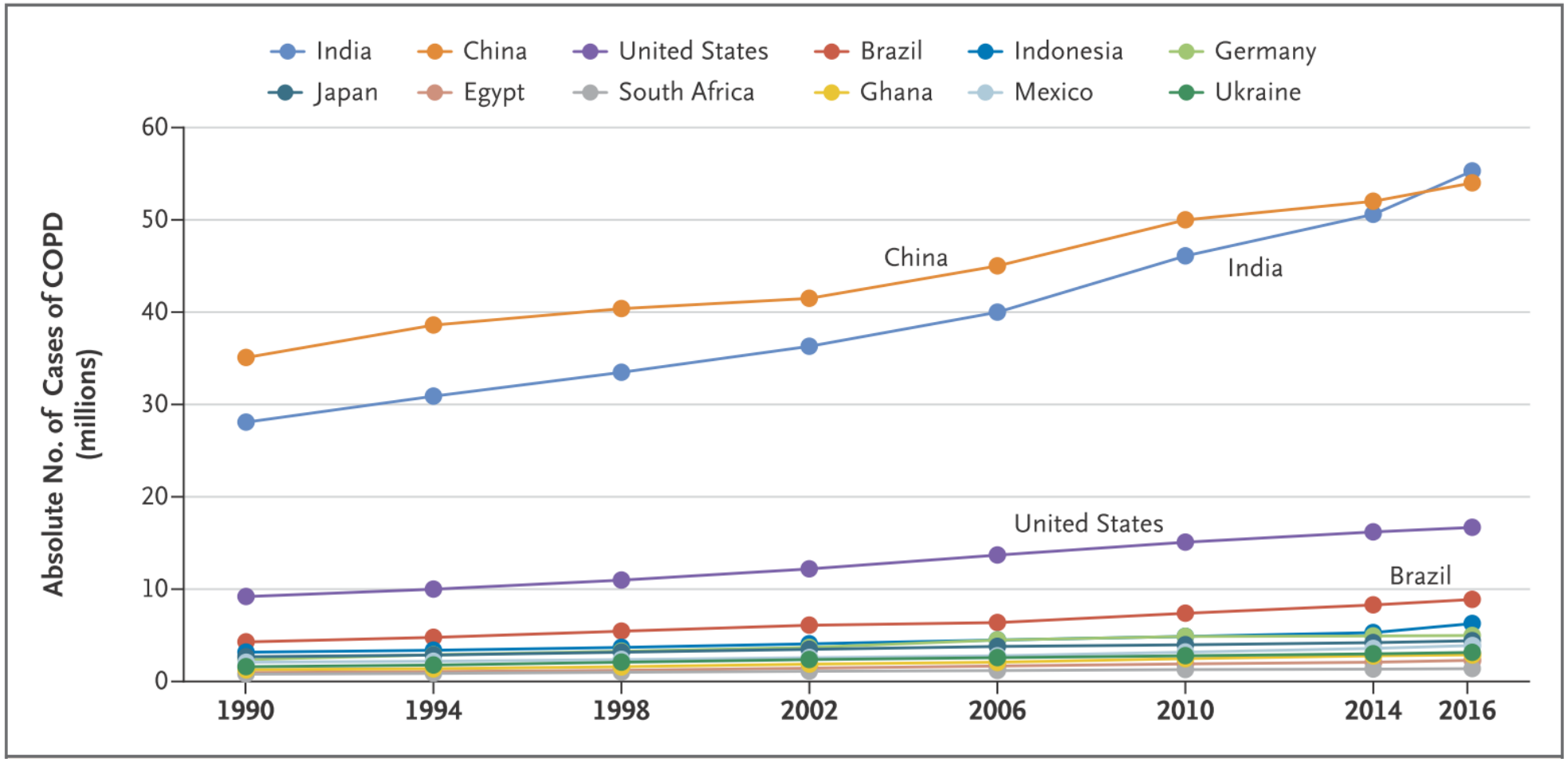
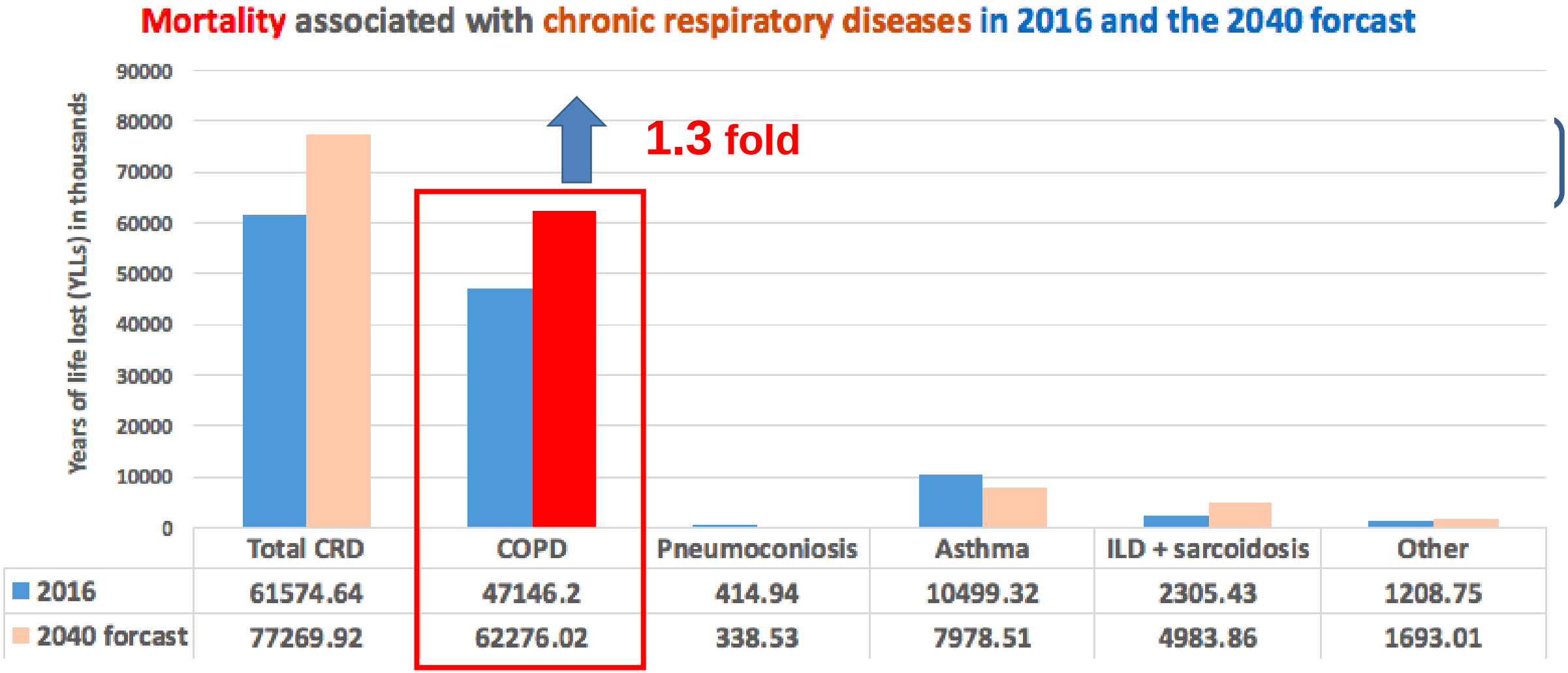


肺阻塞盛行率到現在仍不斷爬升



N Engl J Med 2019;381:1257-66

COPD在2040年死亡率預估仍為升高



	Total CRD	COPD	Pneumoconiosis	Asthma	ILD + sarcoidosis	Other
2016	61574.64	47146.2	414.94	10499.32	2305.43	1208.75
2040 forcast	77269.92	62276.02	338.53	7978.51	4983.86	1693.01

Lancet 2018; 392: 2052–90

台灣慢性肺阻塞現況

盛行率

6.1%

吸入劑錯誤率

≥65%

急性發作

~40%

首年死亡率

22%

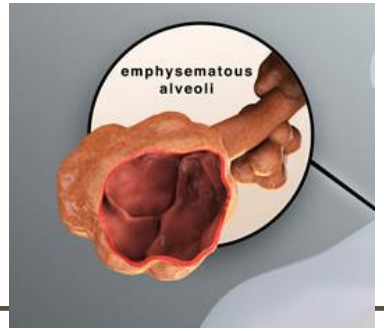
International J of COPD. 2015. PLOS ONE, 2014. Asia Pac Fam Med. 2015 Apr 23;14(1):4. Sci Rep. 2020 Dec 3;10(1):21025.
Int J Chron Obstruct Pulmon Dis. 2018 Sep 25;13:2949-2959. Int J Chron Obstruct Pulmon Dis. 2018; 13: 1309–1316
Modified from Dr. CS Lin

慢性肺阻塞肺病chronic obstructive pulmonary disease

- 呼吸道及肺實質因慢性發炎而導致不可逆的呼吸道阻塞疾病。
- 肺泡因慢性發炎而喪失回彈力(recoil)並且失去對小呼吸道的貼附，而小呼吸道也因為慢性發炎引發黏膜腫脹及呼吸道纖維化，造成阻塞而導致持續的呼氣氣流受阻。

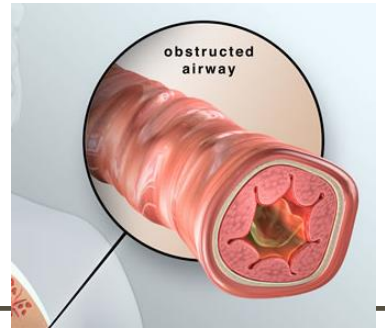
肺實質破壞

肺部的回彈力降低
肺泡失去對小呼吸道的貼附



小呼吸道疾病

呼吸道發炎
呼吸道纖維化
呼吸道阻塞導致阻力上升

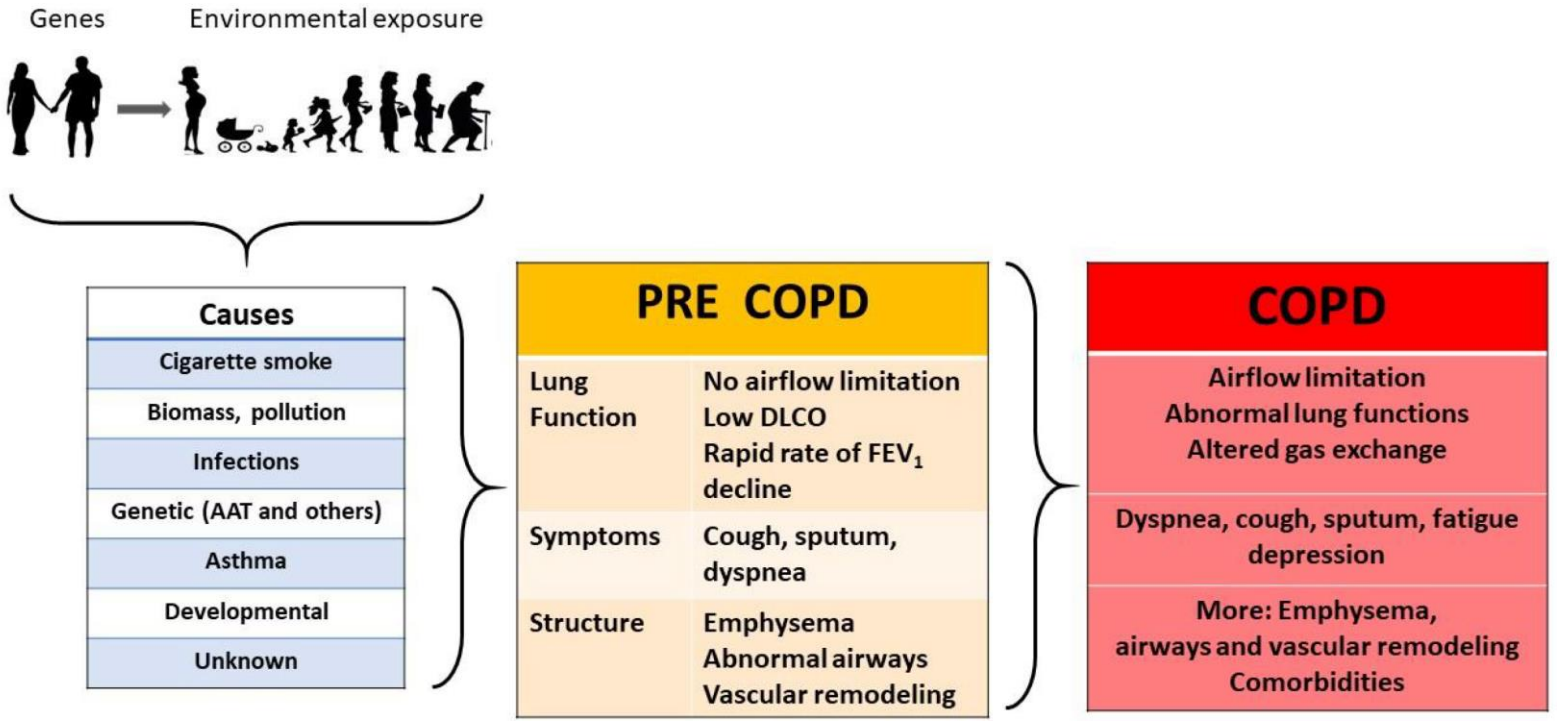


呼氣氣流受阻

胸腔重症學會COPD教材修改

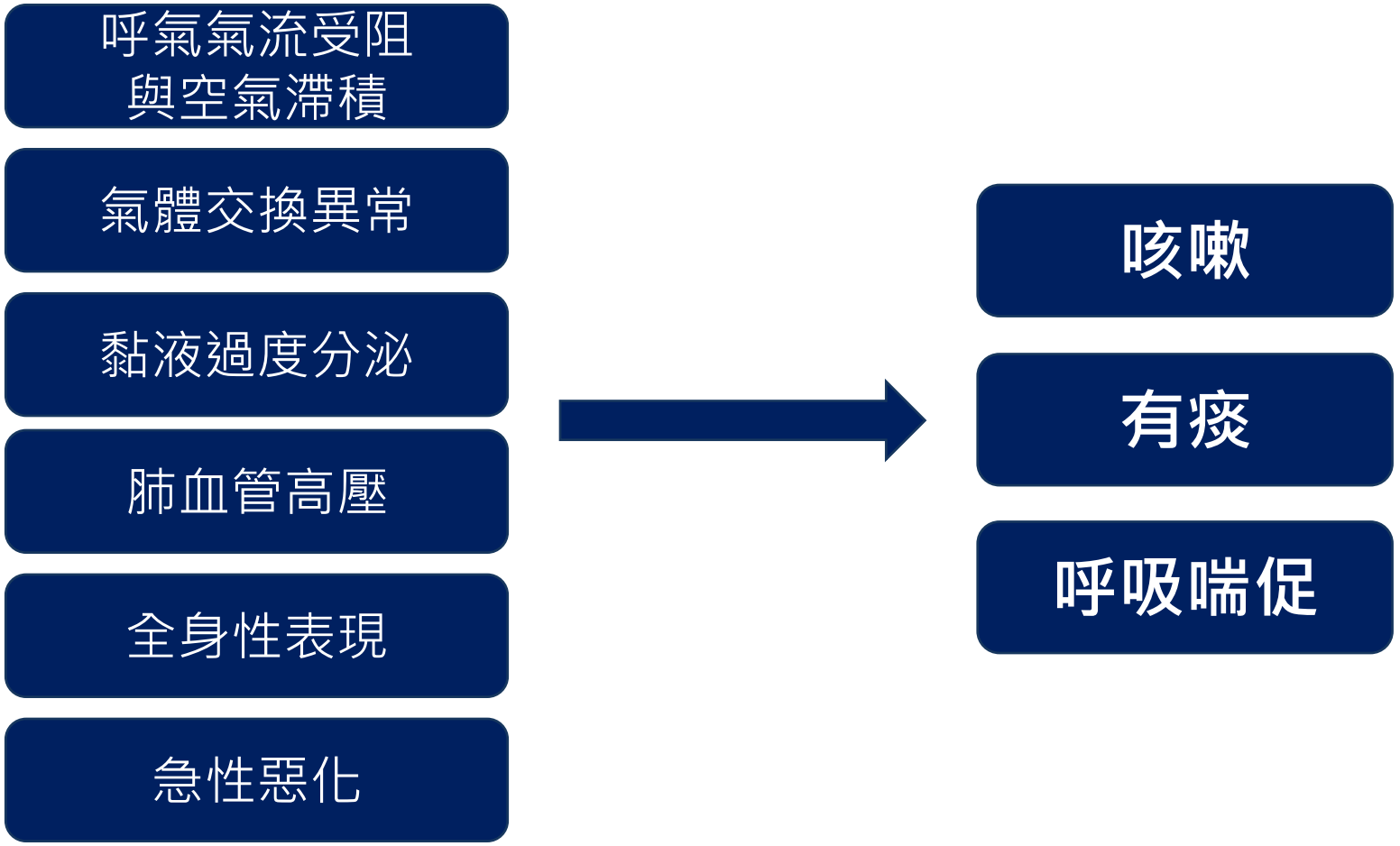
影響肺阻塞惡化及進展的危險因子

- 基因
- 年齡與性別
- 肺部的生長與發育
- 暴露於有害微粒 (如吸菸煙霧、職場的塵埃或化學物質)
- 社經地位
- 氣喘 / 支氣管過度反應
- 慢性支氣管炎
- 感染



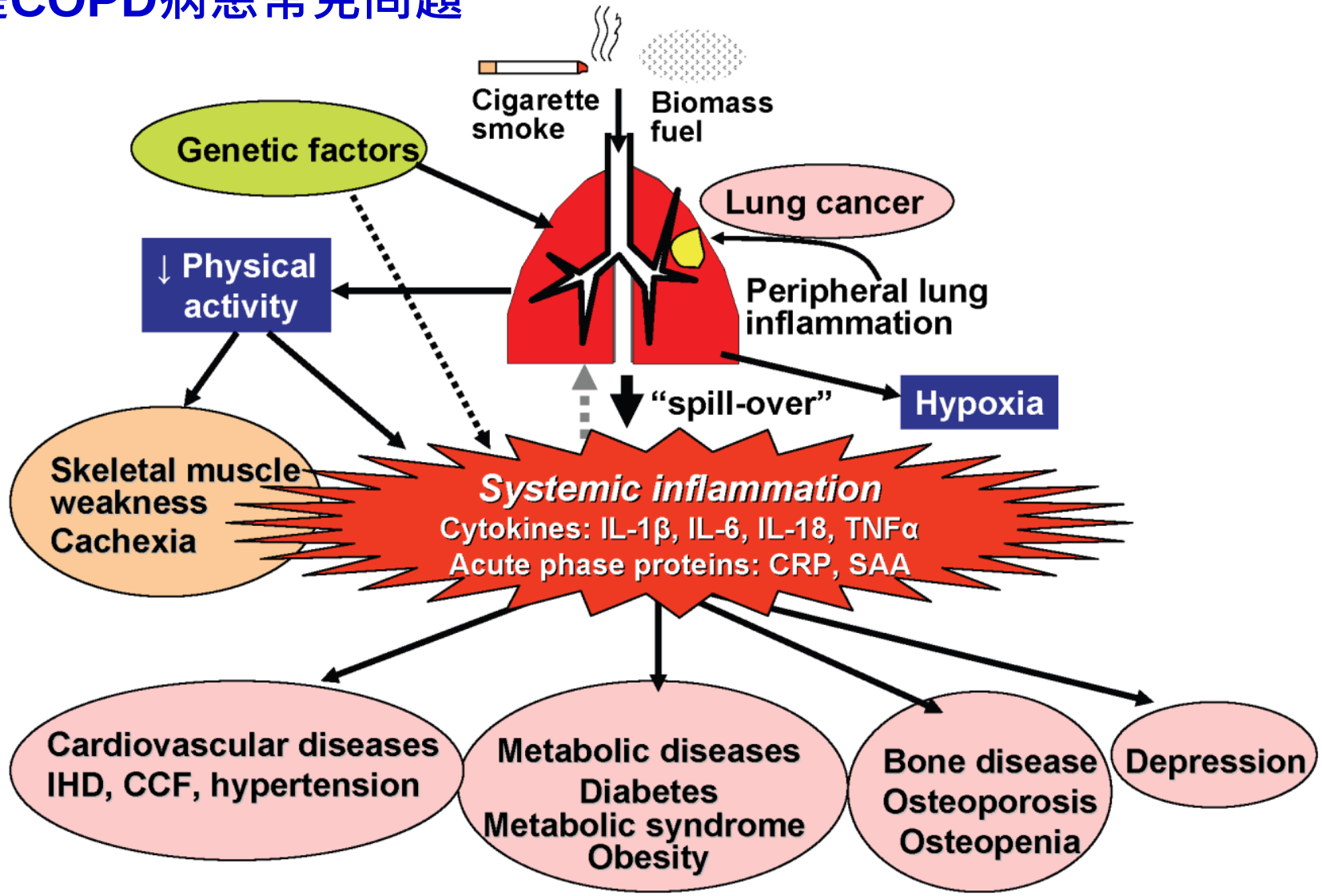
Vestbo J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016); N Engl J Med 2019;381:1257-66.

肺阻塞的病態生理與常見症狀



胸腔重症學會COPD教材修改

多重共病症是COPD病患常見問題



PLoS Med 2010;7(3): e1000220

Asthma vs COPD

	氣喘	慢性肺阻塞
好發年紀	20歲前	40歲後
肺功能	變異度大	阻塞性, FEV/FVC< 70%
緩解期肺功能	可逆	不可逆
危險因子	過敏體質	香菸等
治療	類固醇抗發炎	支氣管擴張劑改善肺功能

肺阻塞的診斷及評估流程

肺功能檢查顯示
呼氣氣流受阻

→

評估氣流受阻
的嚴重度

→

評估病患的症狀及
急性惡化的風險

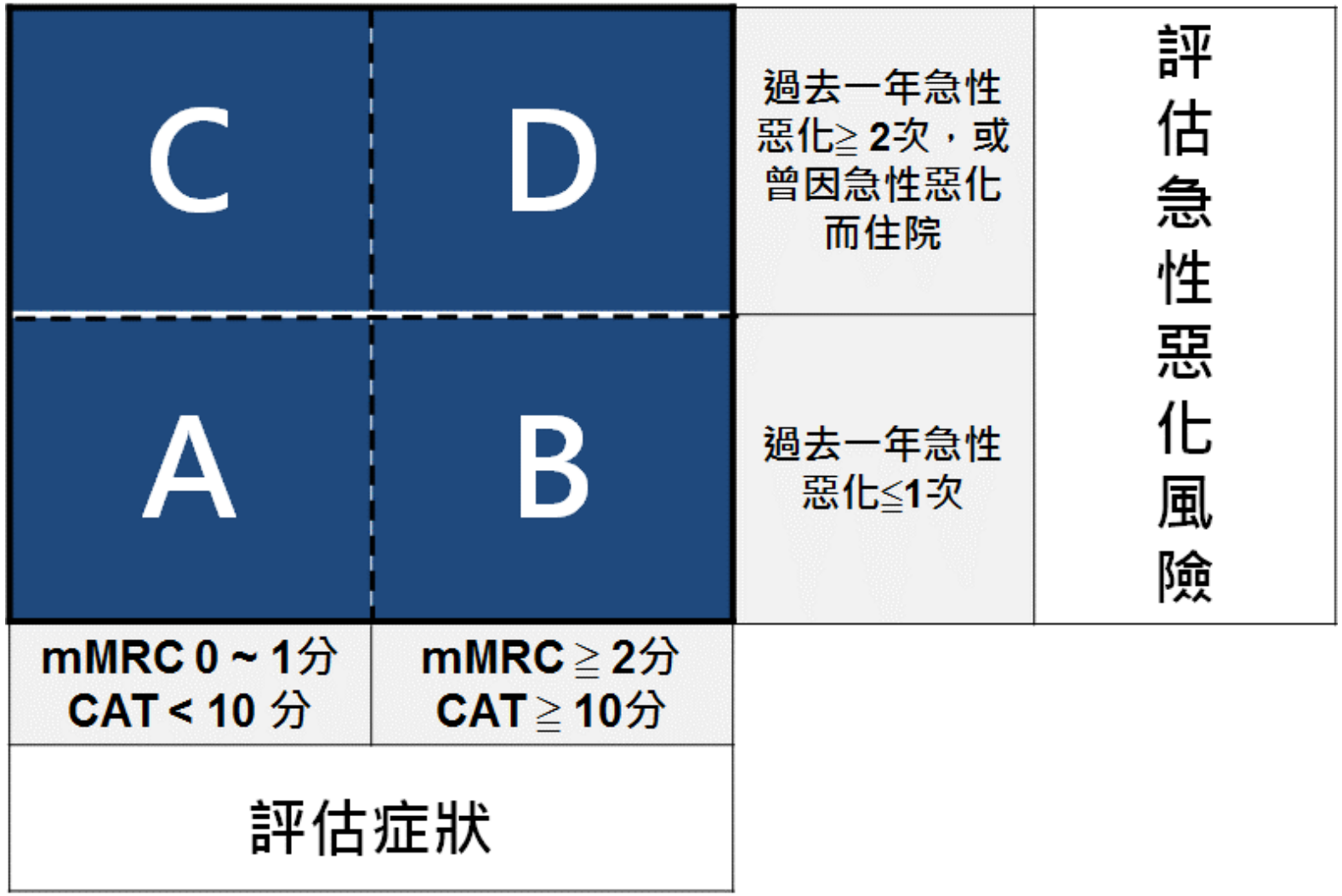
吸入氣管擴張劑後
FEV1/FVC < 0.7

Grade	FEV1 (% of predict)
1	≥ 80%
2	50 ~ 79%
3	30 ~ 49%
4	< 30%

C	D
A	B

胸腔重症學會COPD教材修改

COPD group: 評估病患的症狀及急性惡化的風險



胸腔重症學會COPD教材修改

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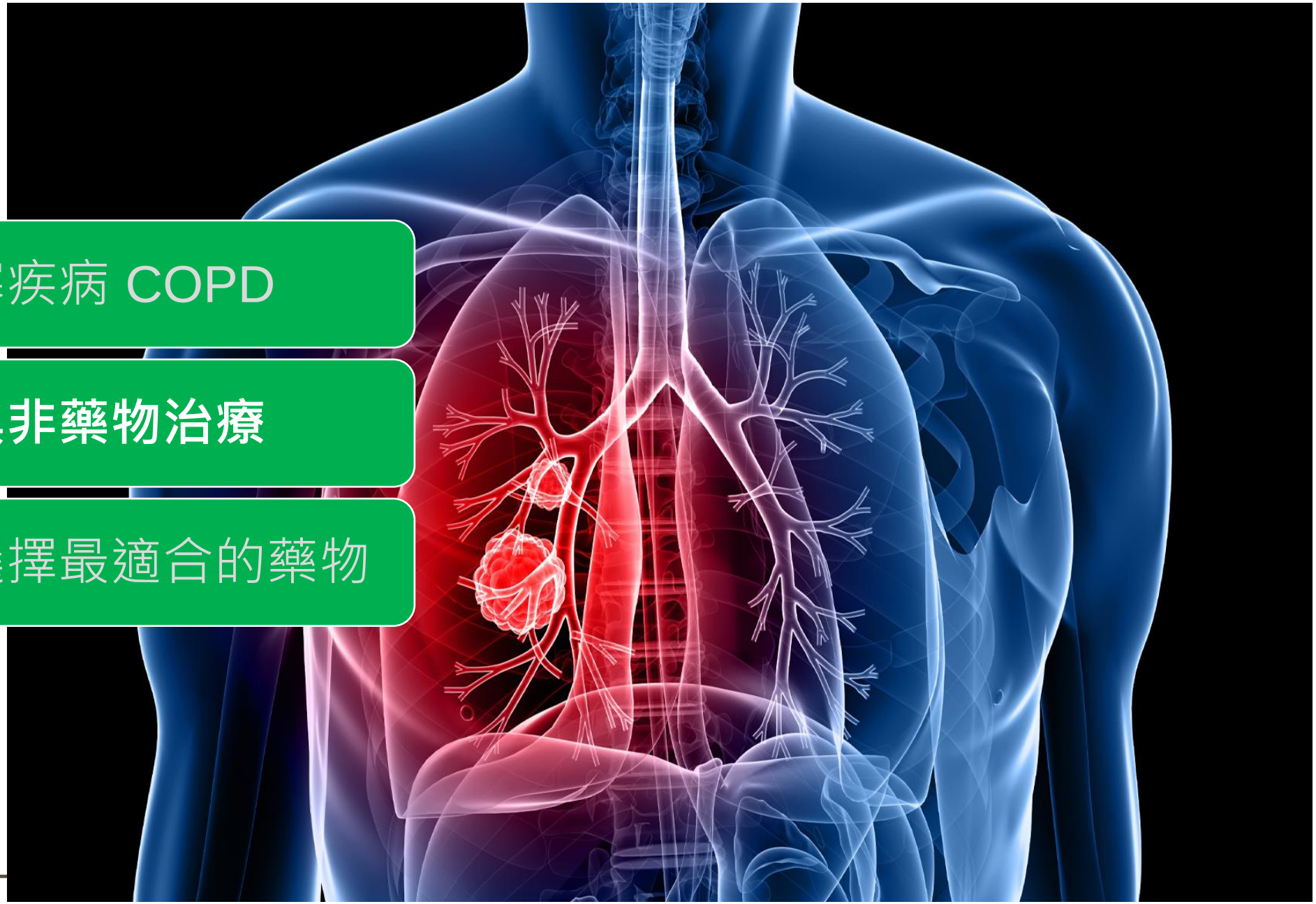
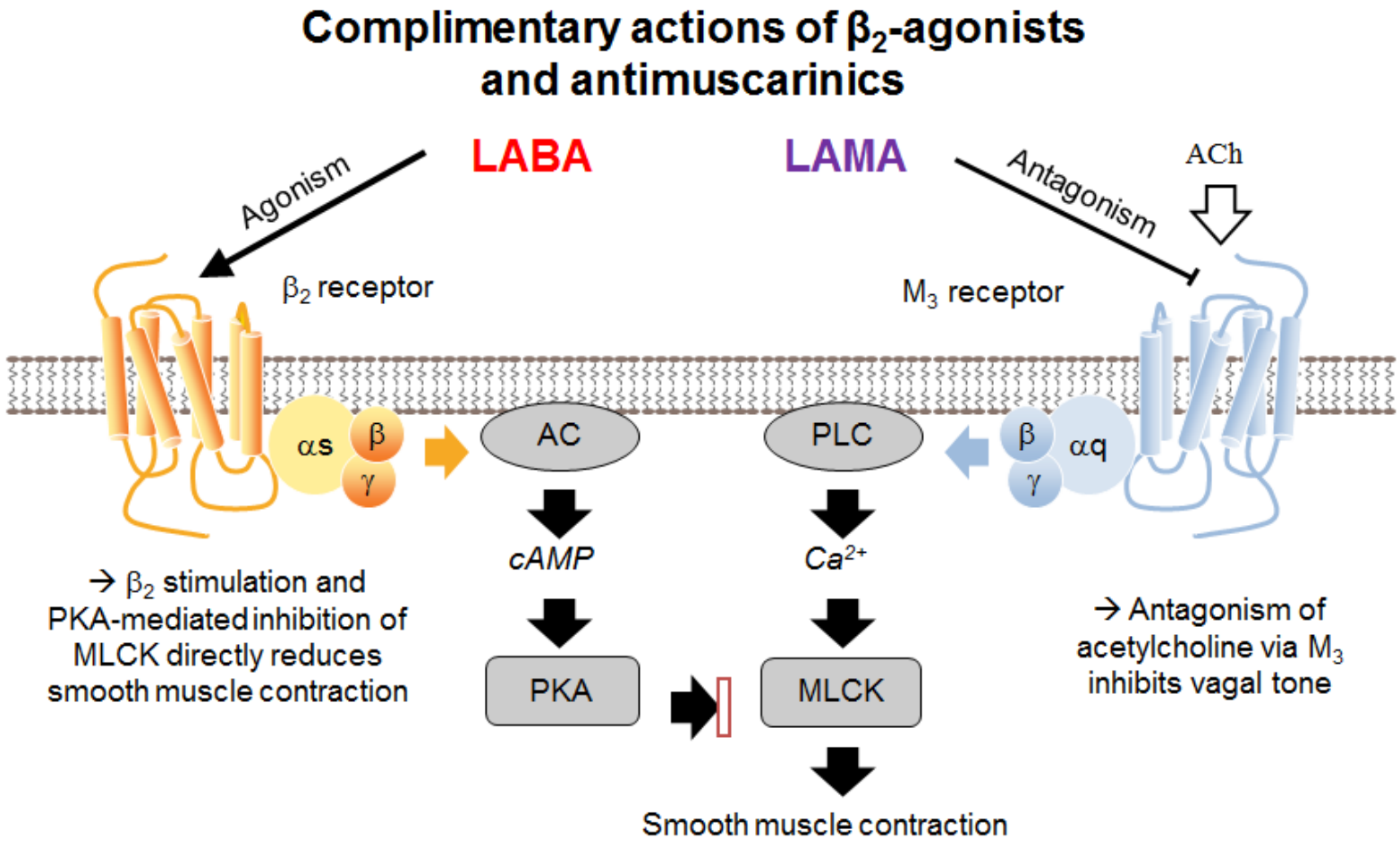


慢性肺阻塞的藥物治療

英文	全名
SABA	Short-acting beta-agonist
SAMA	Short-acting anti-muscarinic agent
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonists
ICS	inhaled corticosteroids
Dual bronchodilators	LABA+LAMA
PDE4 inhibitors	type 4 phosphodiesterase inhibitor
NAC	N-acetylcysteine

Optimizing bronchodilation in COPD



Adapted from Cazzola & Molimard. Pulm Pharmacol Ther 2010

慢性阻塞性肺病起始治療以長效支氣管擴張劑為基石

INITIAL PHARMACOLOGICAL TREATMENT

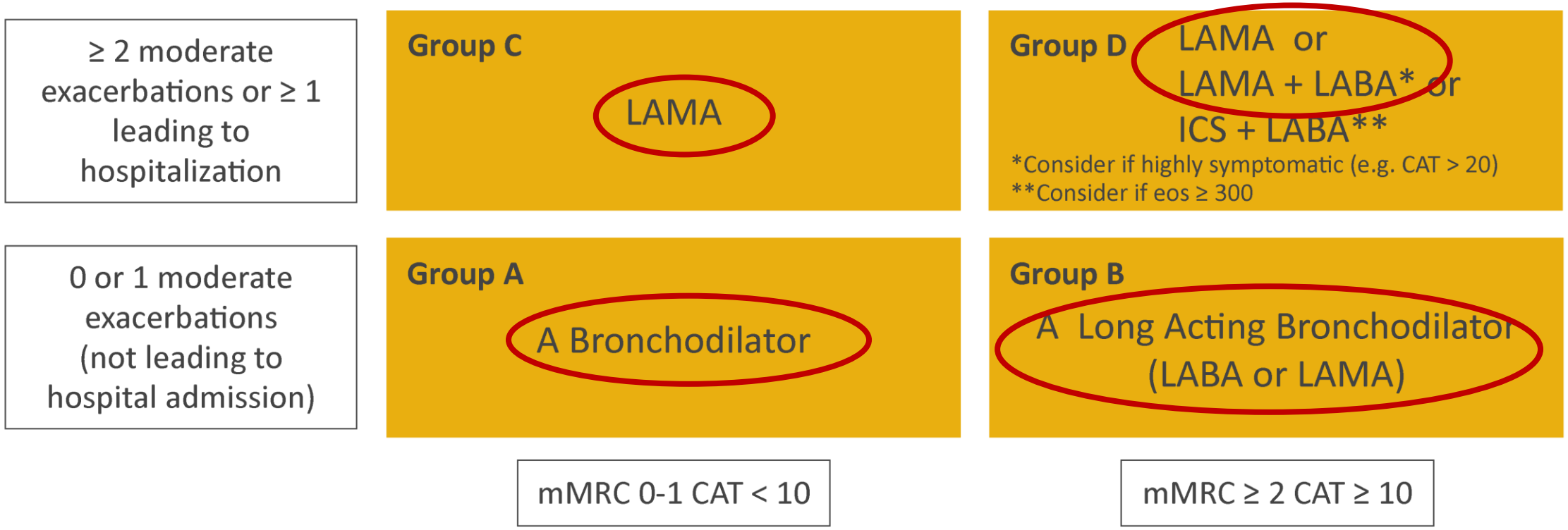


FIGURE 4.1

Dual bronchodilator in COPD

PINNACLE-1, -2, and -4 results demonstrated that FORM/GLY (14.4/9.6 µg) MDI conferred greater benefits vs placebo MDI in patients with moderate-to-very-severe COPD

Peak FEV_1 at Week 24	Primary endpoint: trough FEV_1 at Week 24	Onset of action (FEV_1 at 5 min post-dose on Day 1)
PINNACLE-1: 291 mL **PINNACLE-2: 267 mL** **PINNACLE-4: 298 mL** **(*P*<0.0001)**	**PINNACLE-1: 150 mL** **PINNACLE-2: 103 mL** **PINNACLE-4: 165 mL** **(*P*<0.0001)**	**PINNACLE-1: 187 mL** **PINNACLE-2: 186 mL** **PINNACLE-4: 179 mL** **(*P*<0.0001)**

Results of PINNACLE-3 confirmed the long-term safety and tolerability of FORM/GLY MDI; improvements in Efficacy endpoints were also sustained over 52 weeks

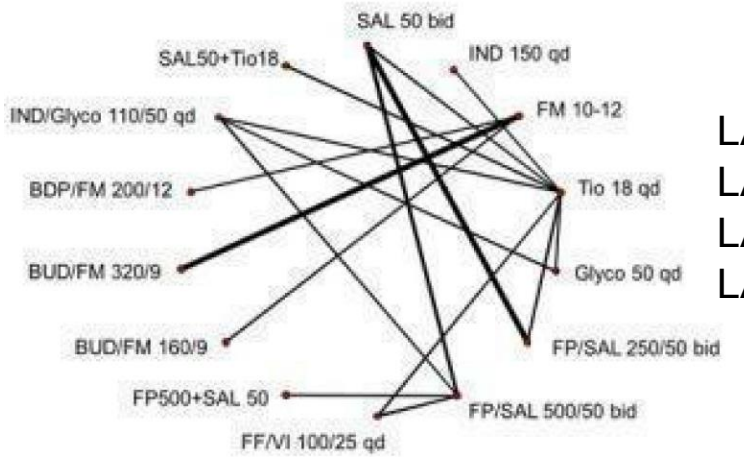
AE, adverse event; ICS, inhaled corticosteroids; CAT, COPD assessment test; FORM, formoterol fumarate; FORM/GLY, glycopyrrolate/glycopyrronium + formoterol fumarate (**Bevespi**); GLY, glycopyrrolate/glycopyrronium; TIO, tiotropium (**Spiriva**)

1. Fernando J Martinez et al. Chest . 2017 Feb;151(2):340-357; 2. Brian J Lipworth wt al. Int J Chron Obstruct Pulmon Dis. 2018; 13: 2969–2984

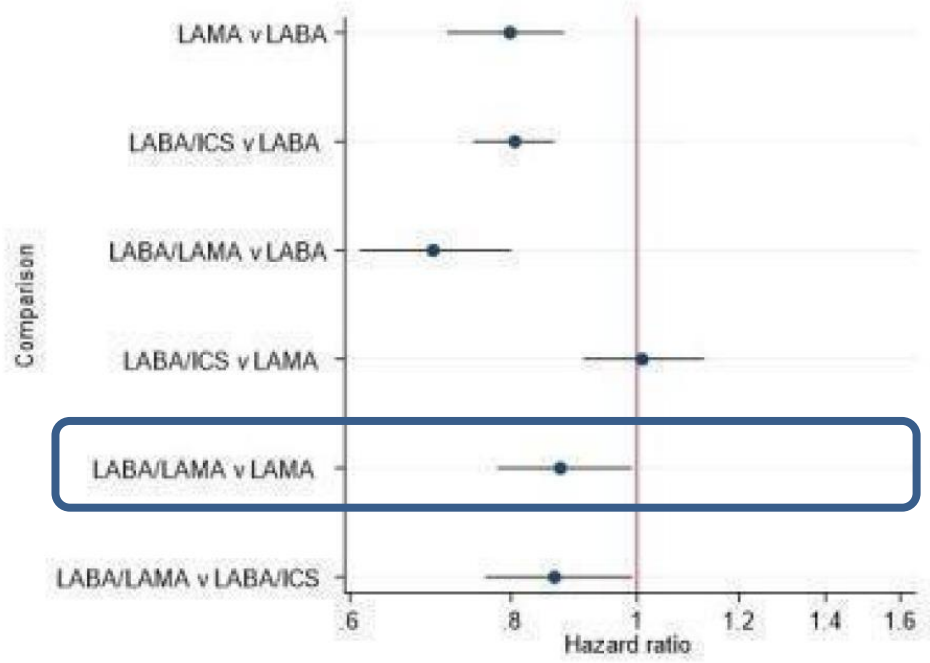
複方支氣管擴張劑比起單方療效更佳

Cochrane network meta-analysis, N=101,311

- The NMAs suggested that the **LABA/LAMA combination** was the highest ranked treatment group to reduce AE. LABA is the worst rank.
- HR against LAMA: **0.87** (95% CI 0.78 to 0.99)



LABA: 10,279,
LAMA: 6376,
LABA/ICS: 8282
LABA/LAMA: 834



Oba Y et al. Cochrane Database Syst Rev. 2018;12:CD01260

Cochrane Library

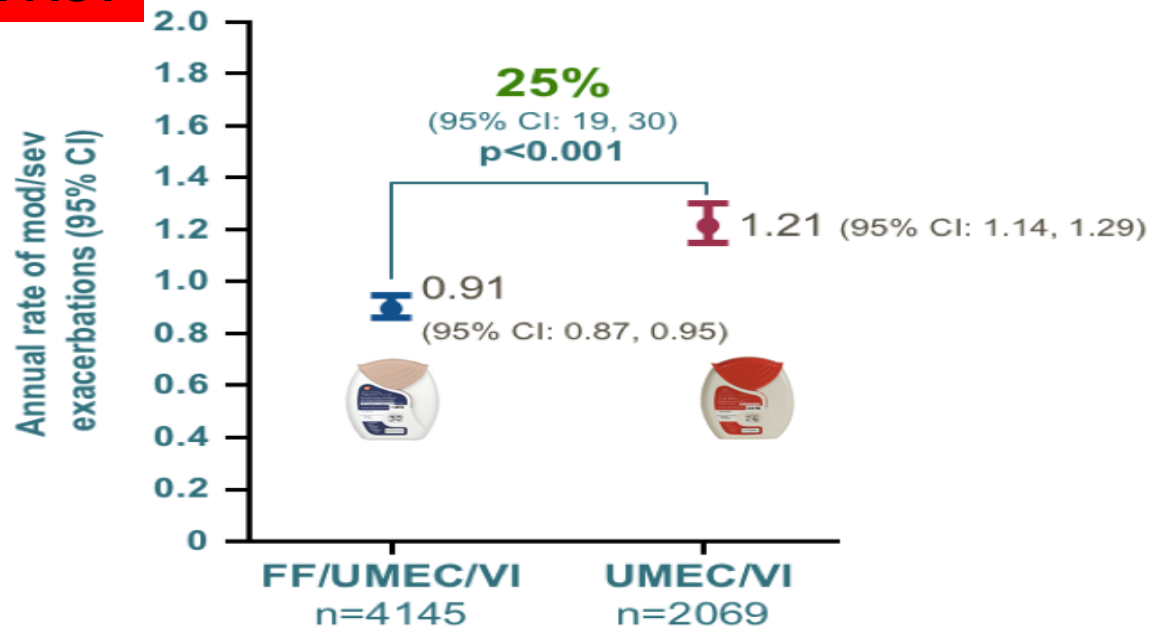
吸入型類固醇（ICS）於肺阻塞病人的使用

- ICS是除了長效吸入型支氣管擴張劑之外，對肺阻塞最重要的治療藥物
- 對於穩定期肺阻塞病人，規則使用吸入型類固醇治療可改善症狀、肺功能、生活品質，同時也可下降急性惡化的風險，但並無法改變長期肺功能（FEV1）下降的趨勢，亦無法減少死亡率

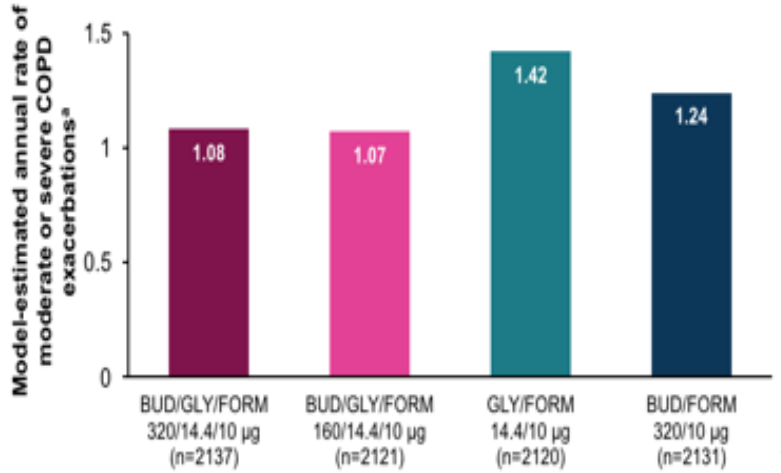
減少急性發作: Triple therapy > Dual BD

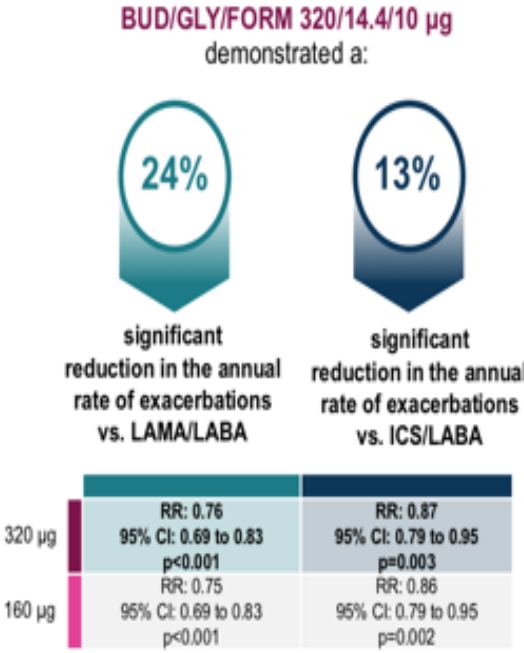
ICS在高風險族群可以減少AE reduction

IMPACT



ETHOS





非藥物性治療

PATIENT GROUP	ESSENTIAL	RECOMMENDED	DEPENDING ON LOCAL GUIDELINES
A	Smoking Cessation (can include pharmacologic treatment) 戒菸	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination Covid-19 Vaccination
B, C and D	Smoking Cessation (can include pharmacologic treatment) Pulmonary Rehabilitation 肺復原	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination Covid-19 Vaccination

*Can include pharmacologic treatment.

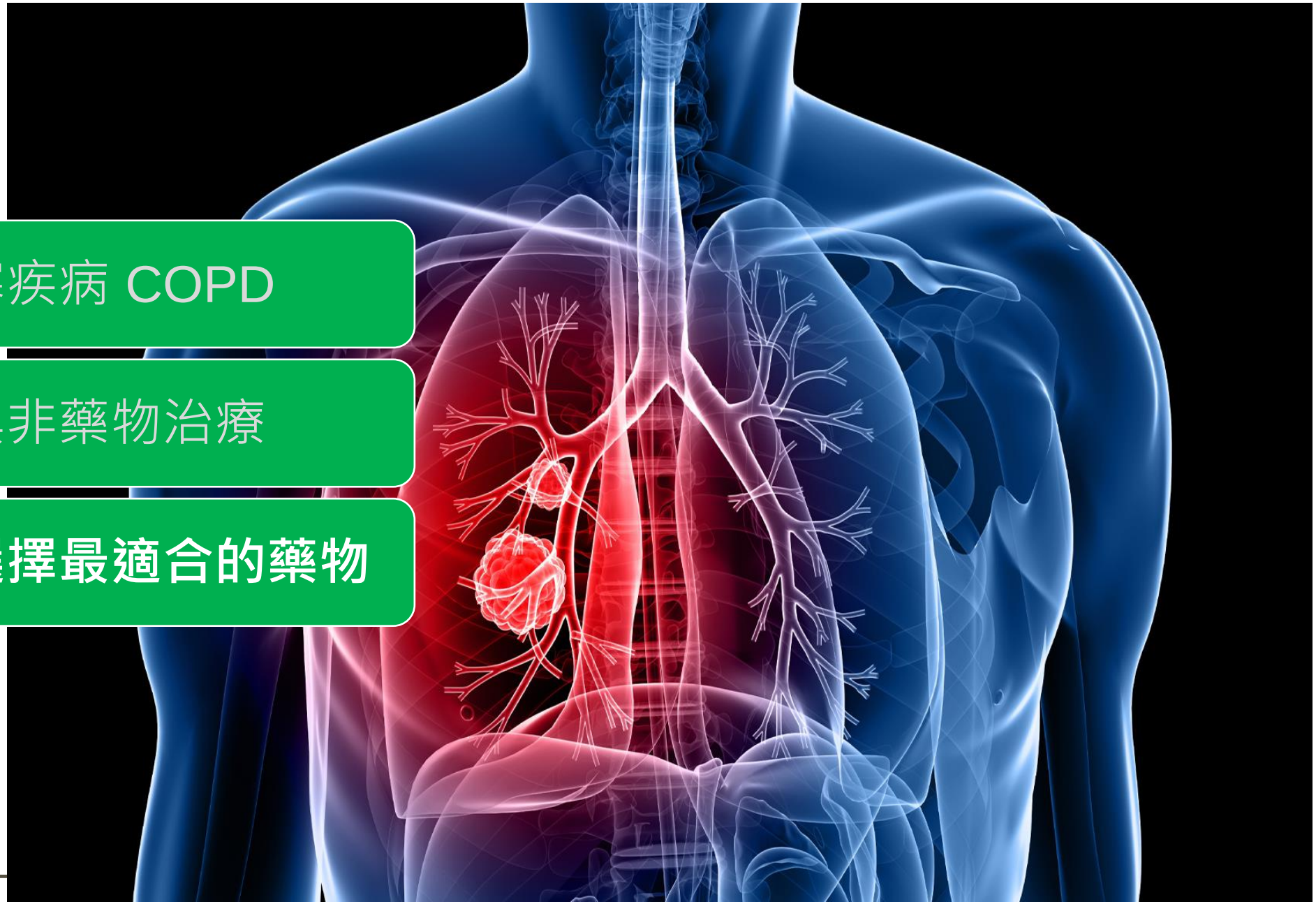
疫苗接種

TABLE 4.8

簡介慢性肺阻塞疾病 COPD

肺阻塞的藥物與非藥物治療

應用生物標記選擇最適合的藥物



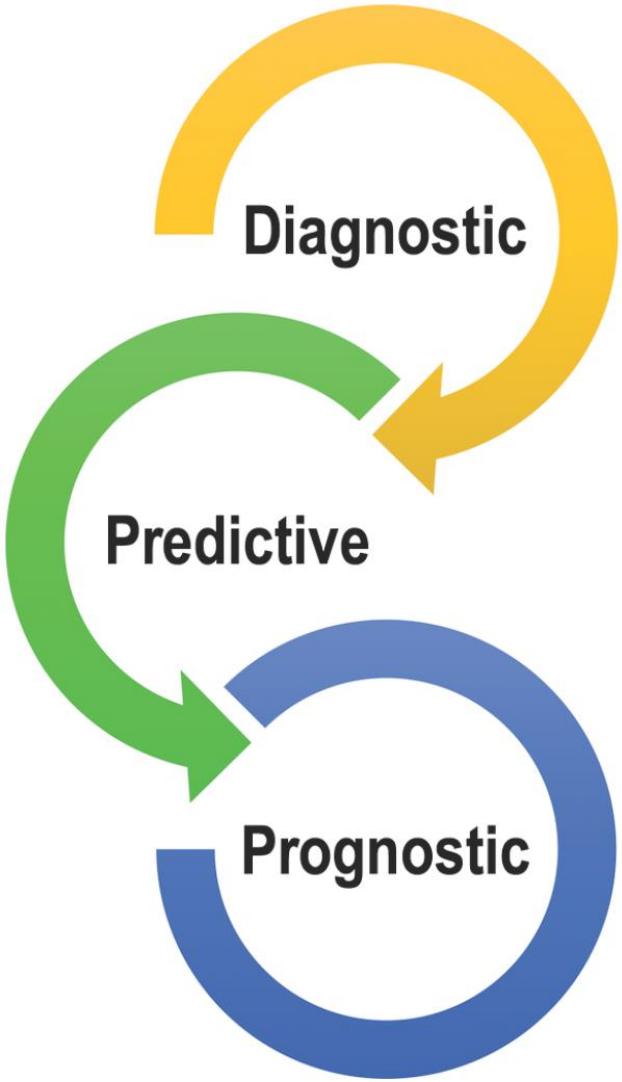
生物標記biomarker

- biological marker
- **Any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease**

  可以在身體內測量到或其產物，並與疾病的產生或預後有影響或相關的物質、結構或過程
- 比如：血壓、心跳

WHO International Programme on Chemical Safety Biomarkers in Risk Assessment: Validity and Validation. 2001
Retrieved from http://www.inchem.org/documents/ehc/ehc/ehc222.htm.

理想的生物標記



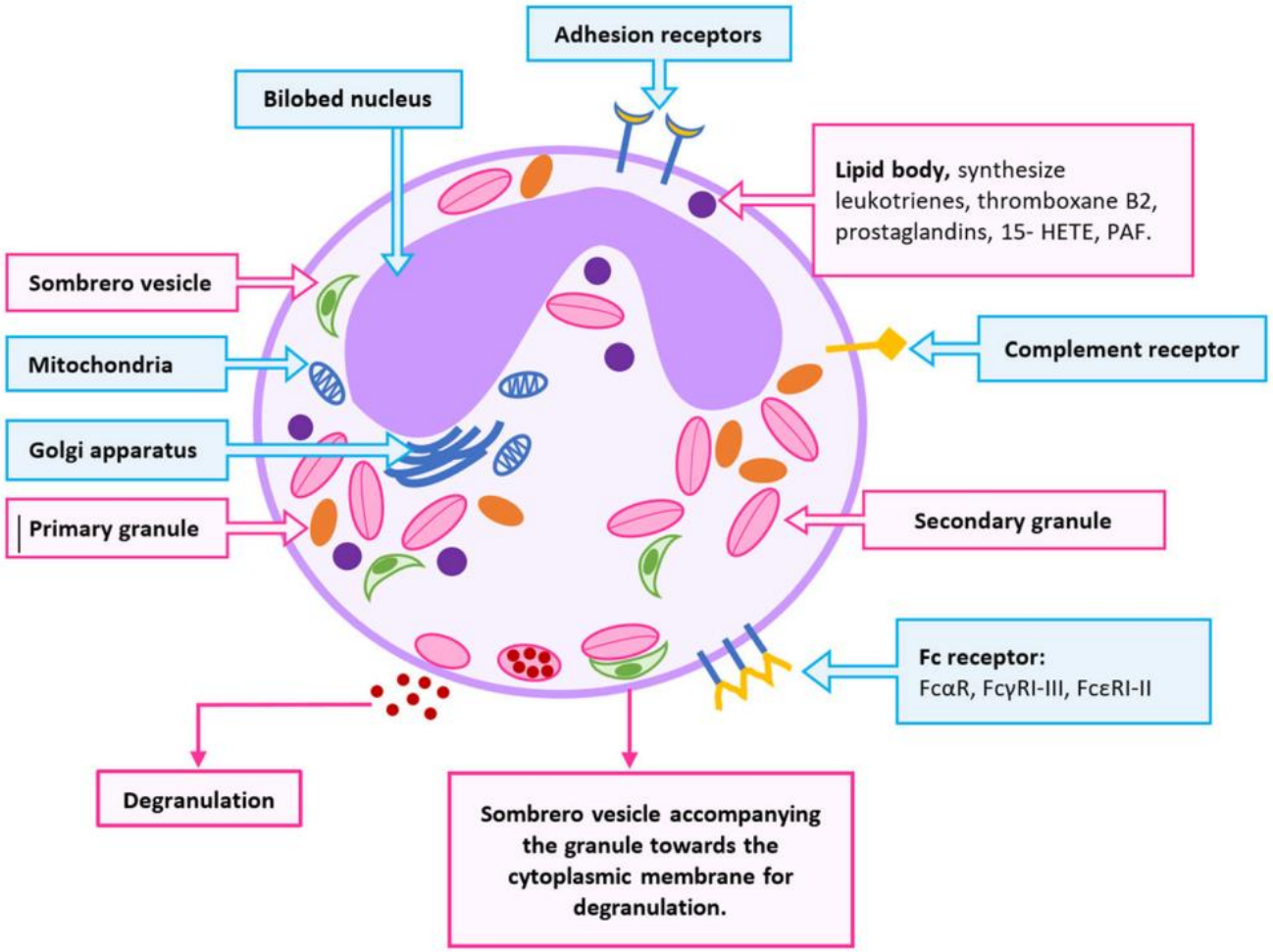
- ✓ Diagnose COPD
- ✓ Define disease severity
- ✓ Define disease endotype
- ✓ Confirm treatment adherence

- ✓ Target treatment effectively
- ✓ Confirm treatment response
- ✓ Avoid inappropriate escalation

- ✓ Reduce exacerbation risk
- ✓ Prevent lung function decline

Respirology 2017;22:430–442

嗜酸性血球



- First described by Paul Ehrlich in 1879
- Up to 6% in bone marrow
- Half life: 18 hours
- Usually less than 500 cells/ul in circulation in healthy person

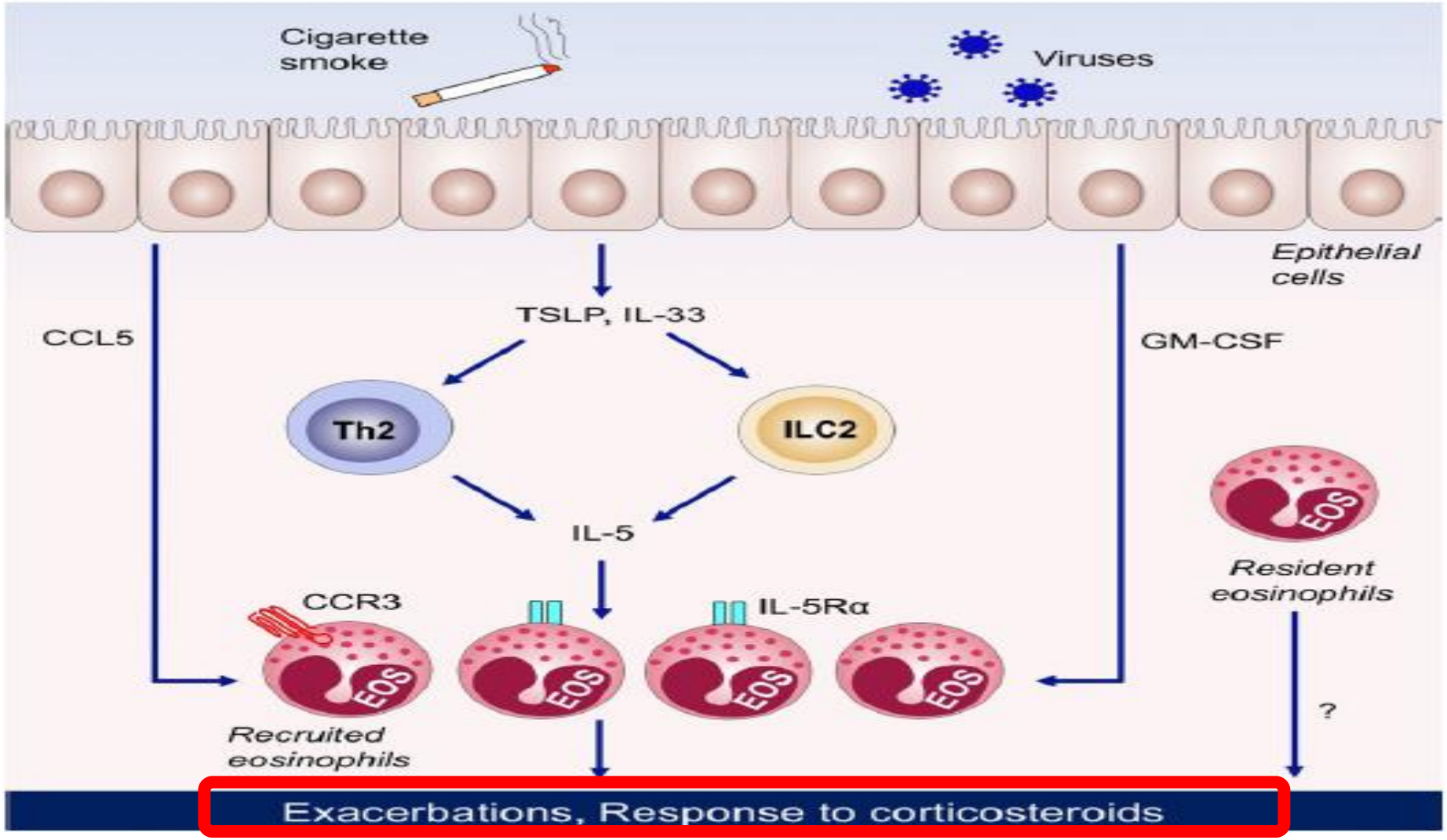
Current Rheumatology Reports 2020;22: 5
BioMed Research International 2018; 9095275

Eosinophil granule proteins 會對人體造成傷害

Granule Protein	Distribution	Mechanism of toxicity
Eosinophil		
CLC	Primary granules	vesicular transport of cationic RNases[26]; requirement for eosinophil granulogenesis[26]; involvement in inflammation[27]
EPO	Primary & secondary granules	oxidative inactivation of pathogens[29–35]; oxidative damage towards host endothelial cells[36]; inhibition of LPS and lipid A in gram-negative bacteria membranes[38]
EDN	Secondary granules	ribonuclease activity against viruses[43–45]; inactivation of extracellular virions[50]; ROS production & induction of apoptosis in keratinocytes[51]
ECP	Secondary granules	antibacterial & antiparasitic properties[39,46–48]; involvement in EETs[5,52,53]; bacterial cell membrane depolarization[54]; neutralization of LPS[55]; formation of amyloid-like fibrils[58]; ROS production & induction of apoptosis in keratinocytes[51]; upregulation of MMP9 expression[51]
MBP	Secondary granules	antibacterial & antiparasitic properties[46,48,59]; cytotoxicity against host tissue[59,60]; causes degranulation of human eosinophils[61]; enhancement of production of proinflammatory IL-8[61]; permabilization of cell membranes[48,59,62]; formation of amyloid-like fibrils[58]; involvement in EETs[5,52,64,65]; non-toxic extracellular deposits[59,63]

Allergology International, https://doi.org/10.1016/j.alit.2020.11.001

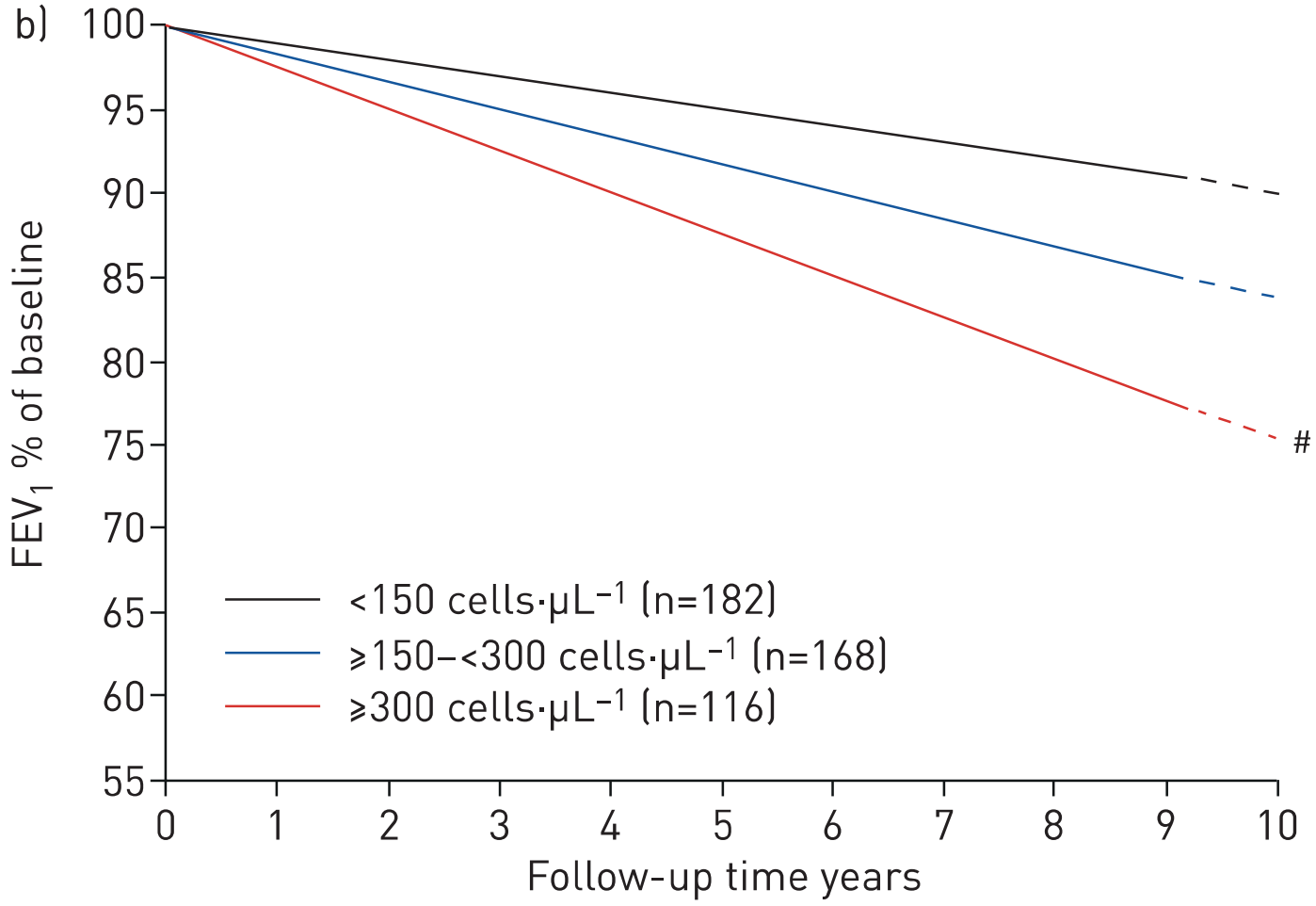
慢性阻塞性肺病與嗜酸性血球造成的呼吸道發炎



Barnes PJ. Inflammatory endotypes in COPD. Allergy. 2019;74:1249–1256

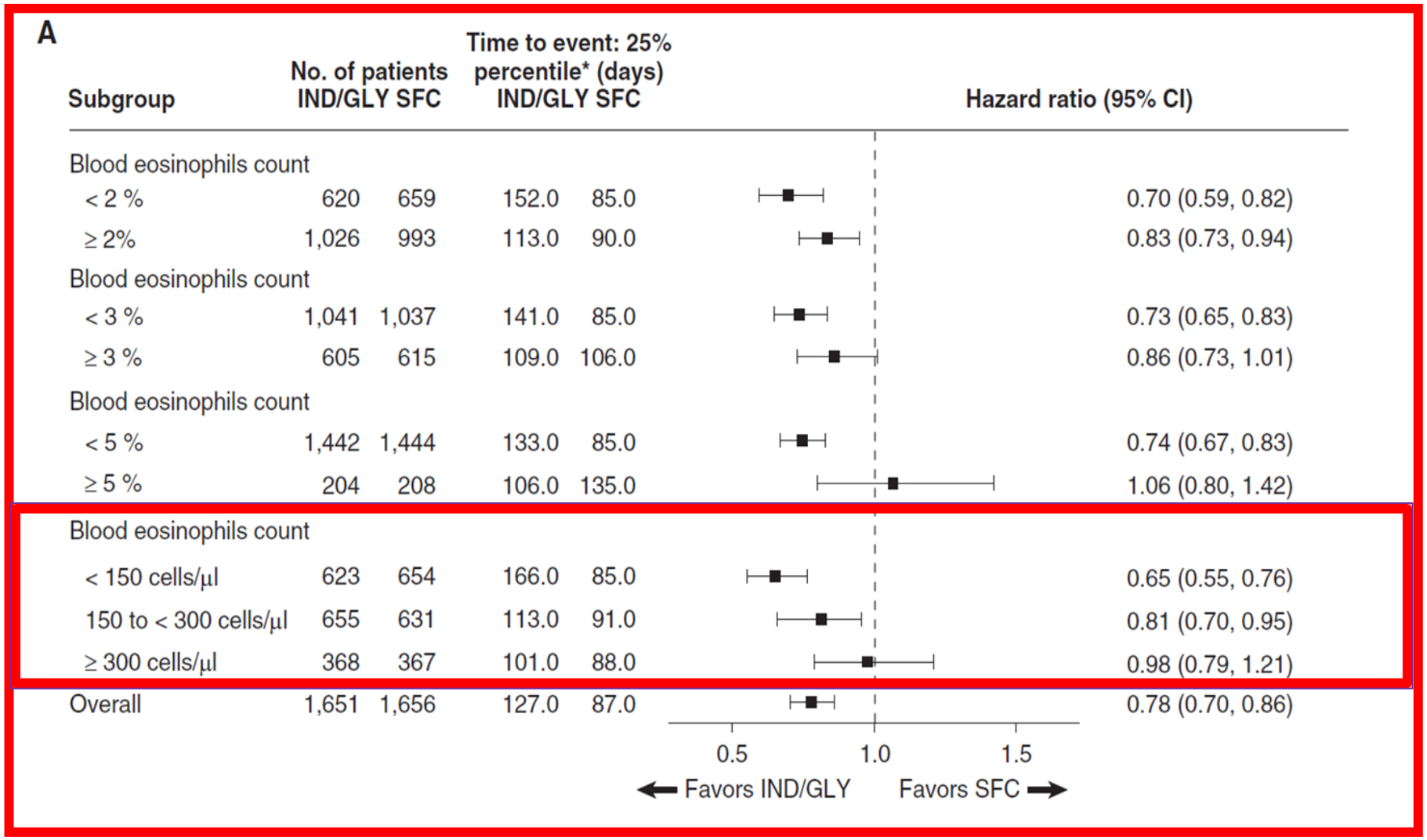
高嗜酸性血球可以預測肺功能FEV1衰退

CanCOLD Study



Eur Respir J 2021; 57: 2000838

Eosinophil Counts 與 AECOPD有正向關聯



A

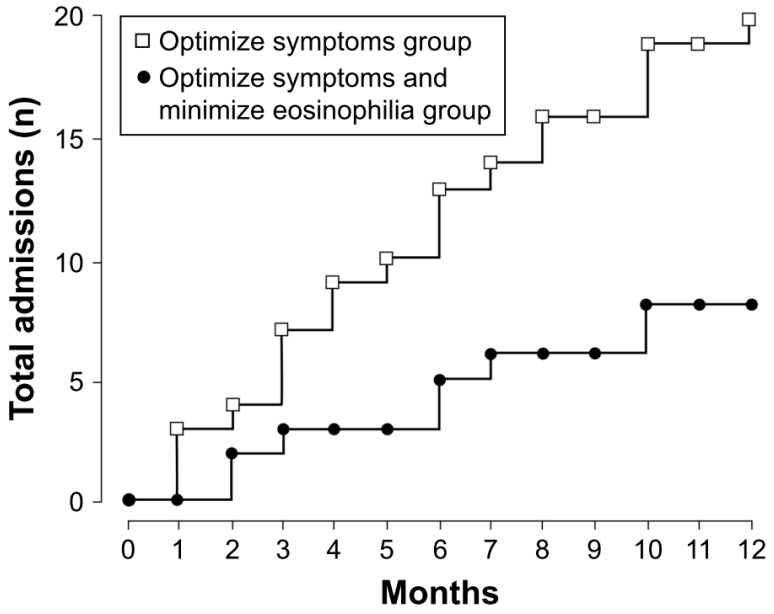
Subgroup	No. of patients IND/GLY	No. of patients SFC	Time to event: 25% percentile* (days) IND/GLY	Time to event: 25% percentile* (days) SFC	Hazard ratio (95% CI)
Blood eosinophils count					
< 2 %	620	659	152.0	85.0	0.70 (0.59, 0.82)
≥ 2%	1,026	993	113.0	90.0	0.83 (0.73, 0.94)
Blood eosinophils count					
< 3 %	1,041	1,037	141.0	85.0	0.73 (0.65, 0.83)
≥ 3 %	605	615	109.0	106.0	0.86 (0.73, 1.01)
Blood eosinophils count					
< 5 %	1,442	1,444	133.0	85.0	0.74 (0.67, 0.83)
≥ 5 %	204	208	106.0	135.0	1.06 (0.80, 1.42)
Blood eosinophils count					
< 150 cells/µl	623	654	166.0	85.0	0.65 (0.55, 0.76)
150 to < 300 cells/µl	655	631	113.0	91.0	0.81 (0.70, 0.95)
≥ 300 cells/µl	368	367	101.0	88.0	0.98 (0.79, 1.21)
Overall	1,651	1,656	127.0	87.0	0.78 (0.70, 0.86)

0.5 1.0 1.5

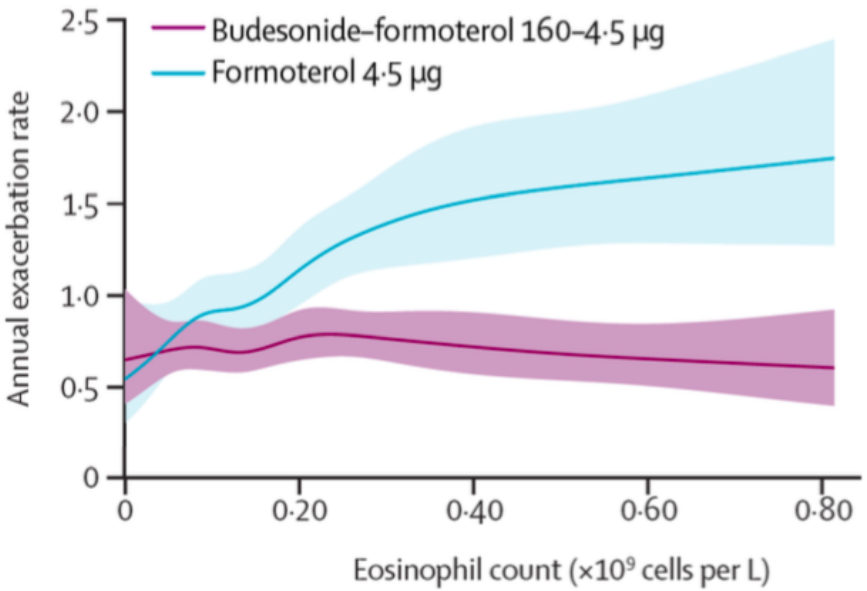
← Favors IND/GLY Favors SFC →

Am J Respir Crit Care Med. 2017 May 1;195(9):1189-1197

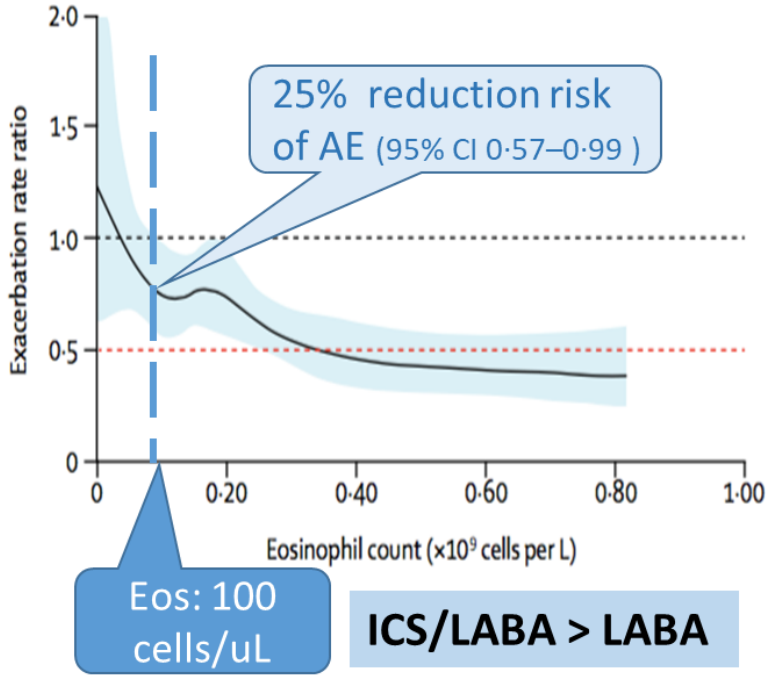
在高嗜酸性血球時使用吸入性類固醇可以減少急性發作



International Journal of COPD 2018:13 335–349



Bafadhel et al. Lancet Respir Med 6(2), 117-126, 2018



ICS/LABA > LABA

FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

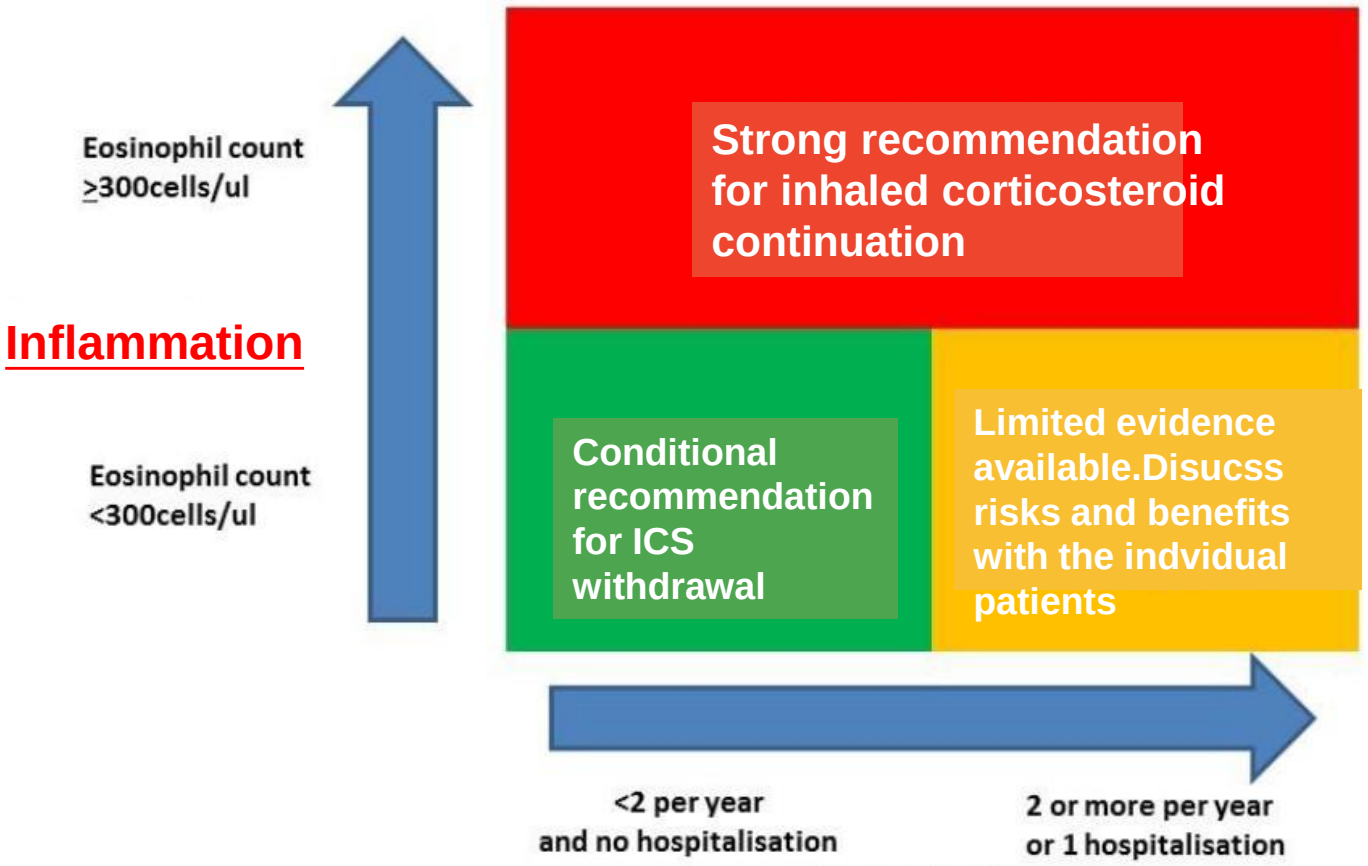
· STRONG SUPPORT ·	· CONSIDER USE ·	· AGAINST USE ·
• History of hospitalization(s) for exacerbations of COPD#	• 1 moderate exacerbation of COPD per year#	• Repeated pneumonia events
• ≥ 2 moderate exacerbations of COPD per year#	• Blood eosinophils 100-300 cells/µL	• Blood eosinophils <100 cells/µL
• Blood eosinophils >300 cells/µL		• History of mycobacterial infection
• History of, or concomitant, asthma		

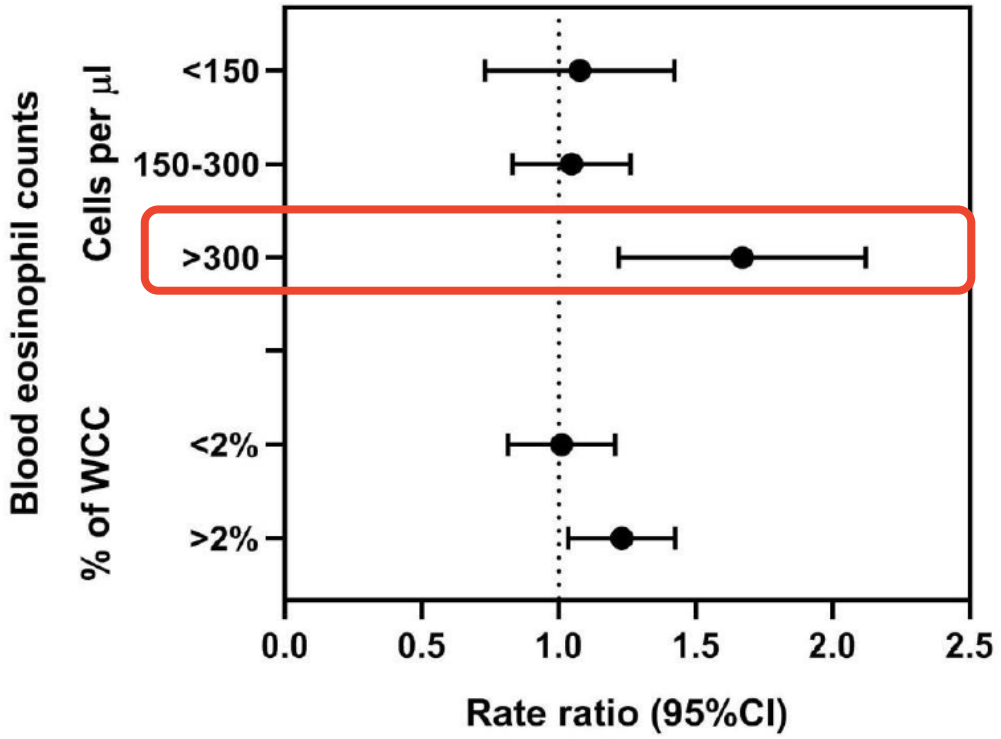
#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

FIGURE 3.1

Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: A European Respiratory Society Guideline

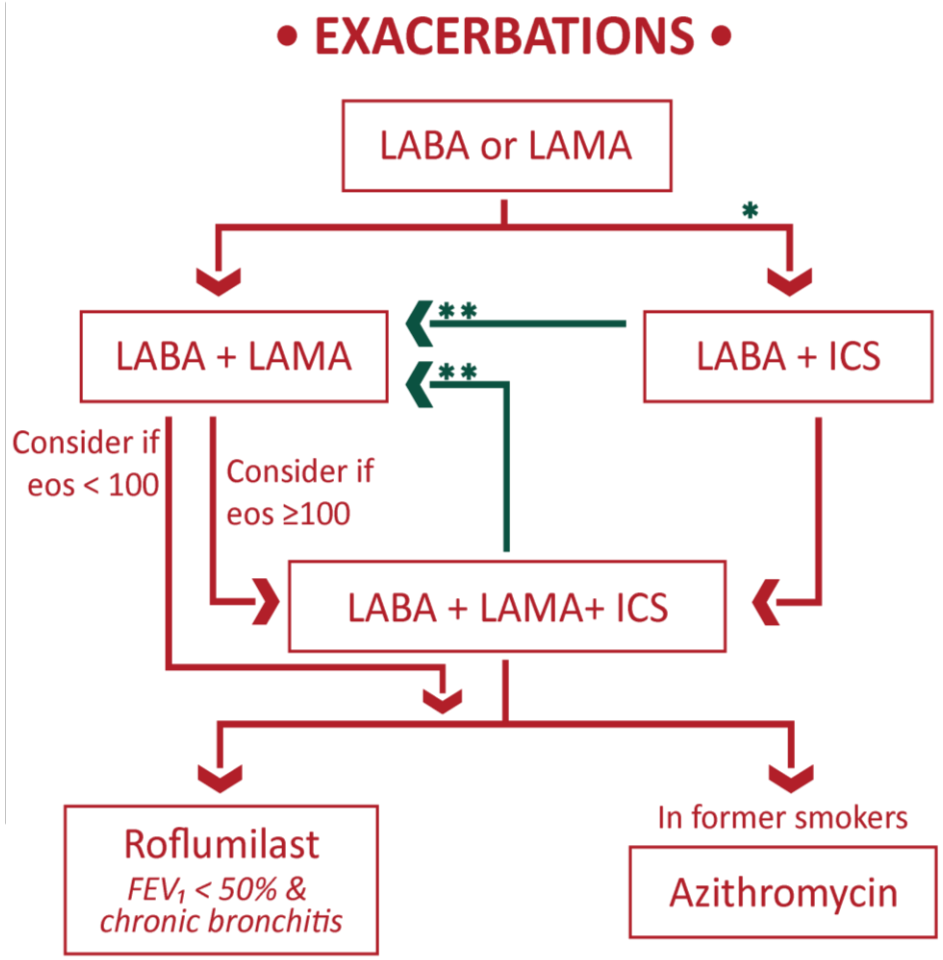




Statistically significant increased AE frequency is observed in patients with BECs > 300 cells/µL−1 or ≥ 2%

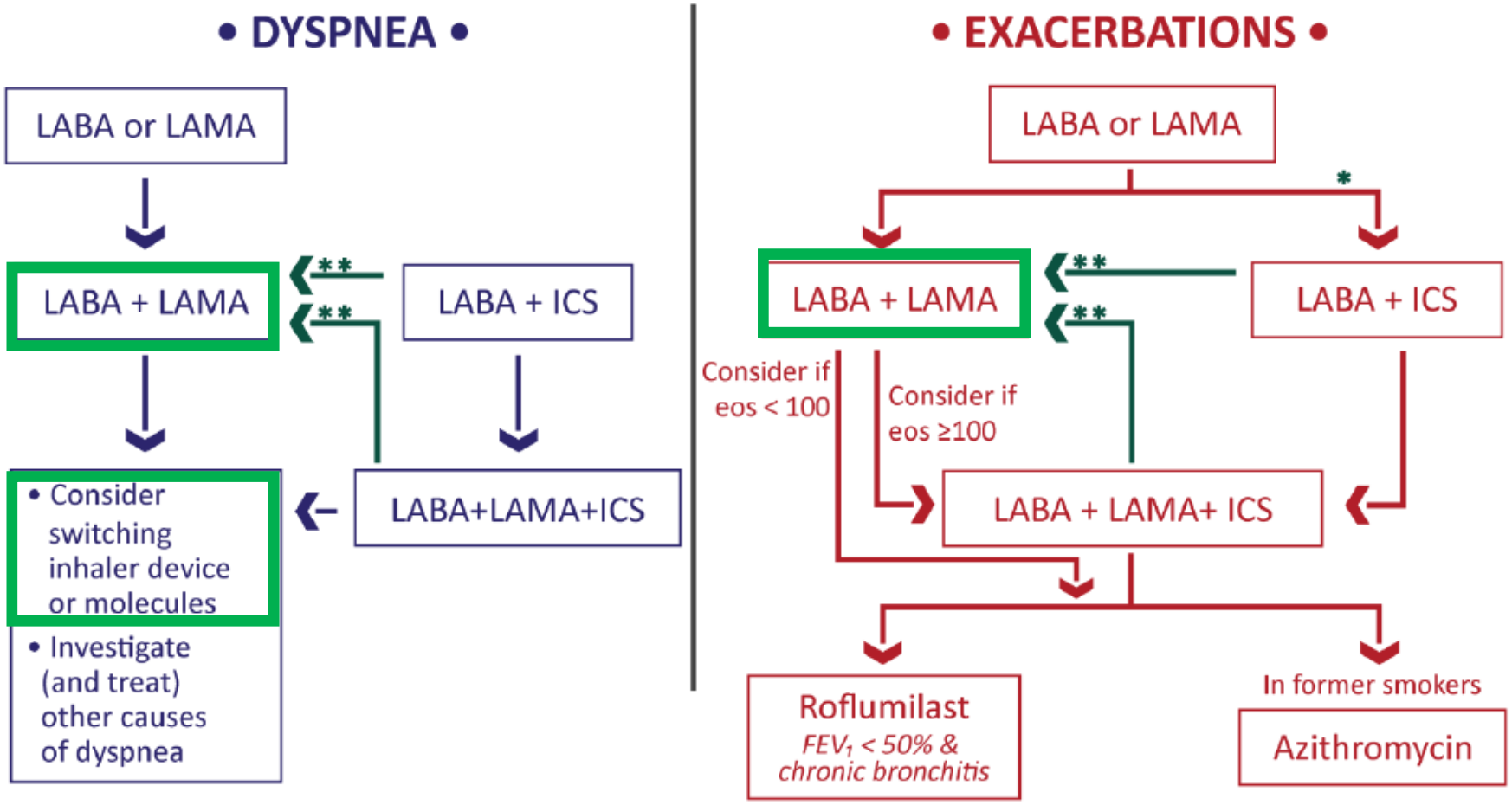
Eur Respir J 2020

Follow-up Management
AE後依據Eos數值判斷是否即早介入ICS



- 原本用單方支氣管擴張劑病患一次AE後
  - Eos<300用Dual
  - Eos≥300 or ≥100但AE>2次(or 1次住院)用ICS/LABA
- 原本用Dual病患一次AE後
  - Eos<100加其他藥物
  - Eos≥100用Triple
- 用ICS/LABA的時機
  - 1次AE後Eos≥300
  - ≥2次AE (or 1次住院)後Eos≥100

追蹤治療時的藥物使用可以根據病情的變化作調整



*Consider if EOS ≥ 300 or EOS ≥ 100 AND ≥ 2 AE/1 hospitalization
**Consider de-escalation of ICS or switch is pneumonia, inappropriate original indication or lack of response to ICS

ICS使用與增加COPD肺炎的機率有相關

UK database, Real world study, N=8853

AE reduction in LABA/LAMA/ICS is better than LABA/LAMA only while:

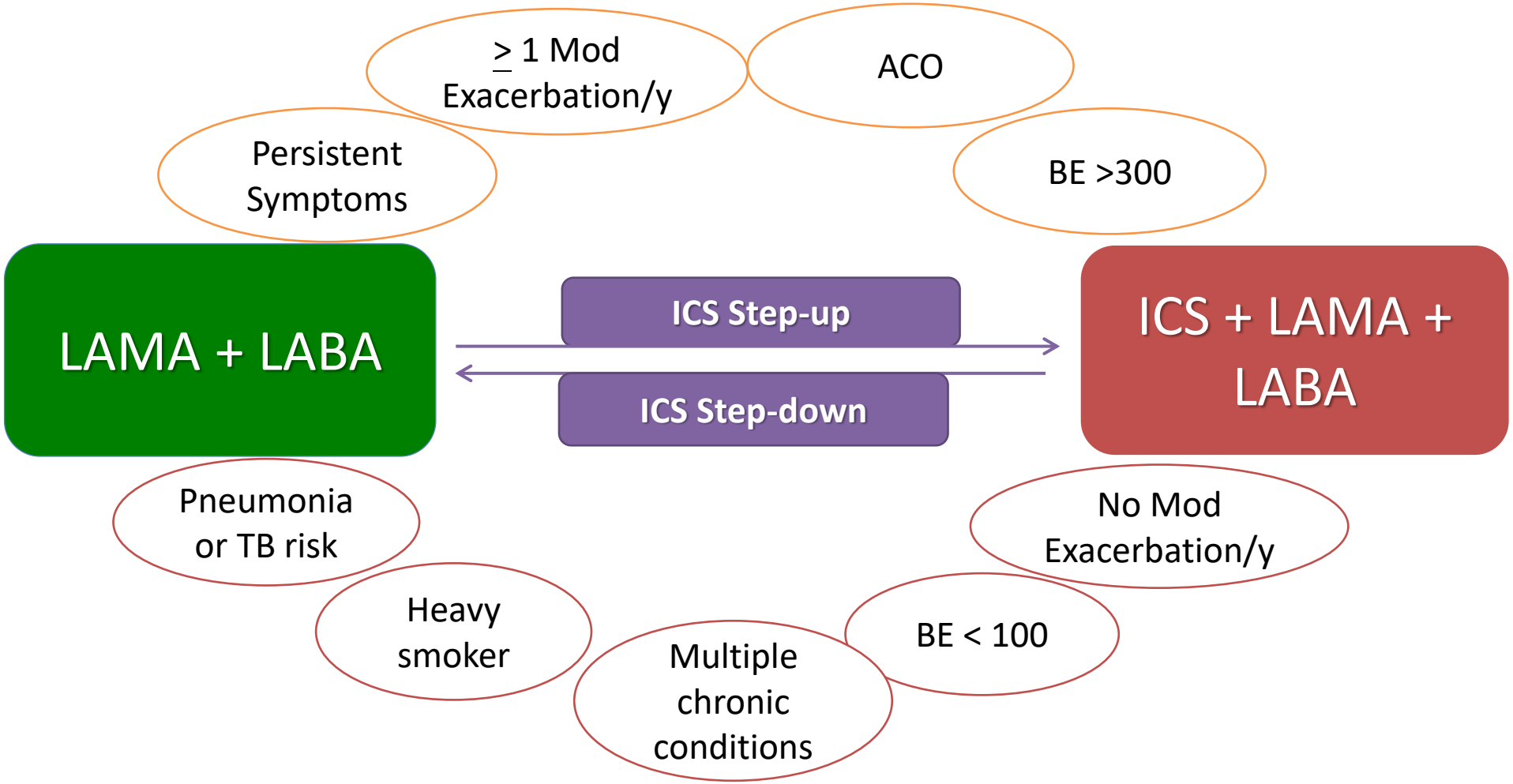
bEos counts > 6%, HR 0.66 (95% CI, 0.46-0.94)

Prior AE>2, HR0.83 (95% CI, 0.70-0.98)

First COPD Exacerbation	No. of Patients	No. With Events	Person- Years	Rate per 100 per Year	Crude[a] HR	Adjusted[b] HR (95% CI)
Moderate or severe exacerbation						
LAMA-LABA-ICS	6,921	1,936	2,487	77.8	1.06	0.97 (0.87-1.08)
LAMA-LABA	1,932	418	542	77.2	1.00	1.00 (Reference)
Severe exacerbation						
LAMA-LABA-ICS	6,921	356	3,074	11.6	1.25	1.04 (0.79-1.37)
LAMA-LABA	1,932	60	630	9.5	1.00	1.00 (Reference)
First severe pneumonia						
LAMA-LABA-ICS	6,921	280	3,099	9.0	1.57	1.46 (1.03-2.06)
LAMA-LABA	1,932	37	634	5.8	1.00	1.00 (Reference)

Chest 2020;157(4):846-855

Dual or triple therapy in COPD management



Real World


HandiHaler®
Boehringer Ingelheim


Spiriva Respimat®


LOT 2579931
MANFD 03-2012
EXP 08-2013
0071424


RELVAR™ ELLIPTA™
100/25 mcg/µg
Inhalation Powder/poudre pour inhalation/
Polvo para Inhalación
fluticasone furoate/vilanterol
furoate de fluticasone/vilanterol
furoato de fluticasona/
vilanterol
30
GlaxoSmithKline
30
0128467


AeroChamber Plus

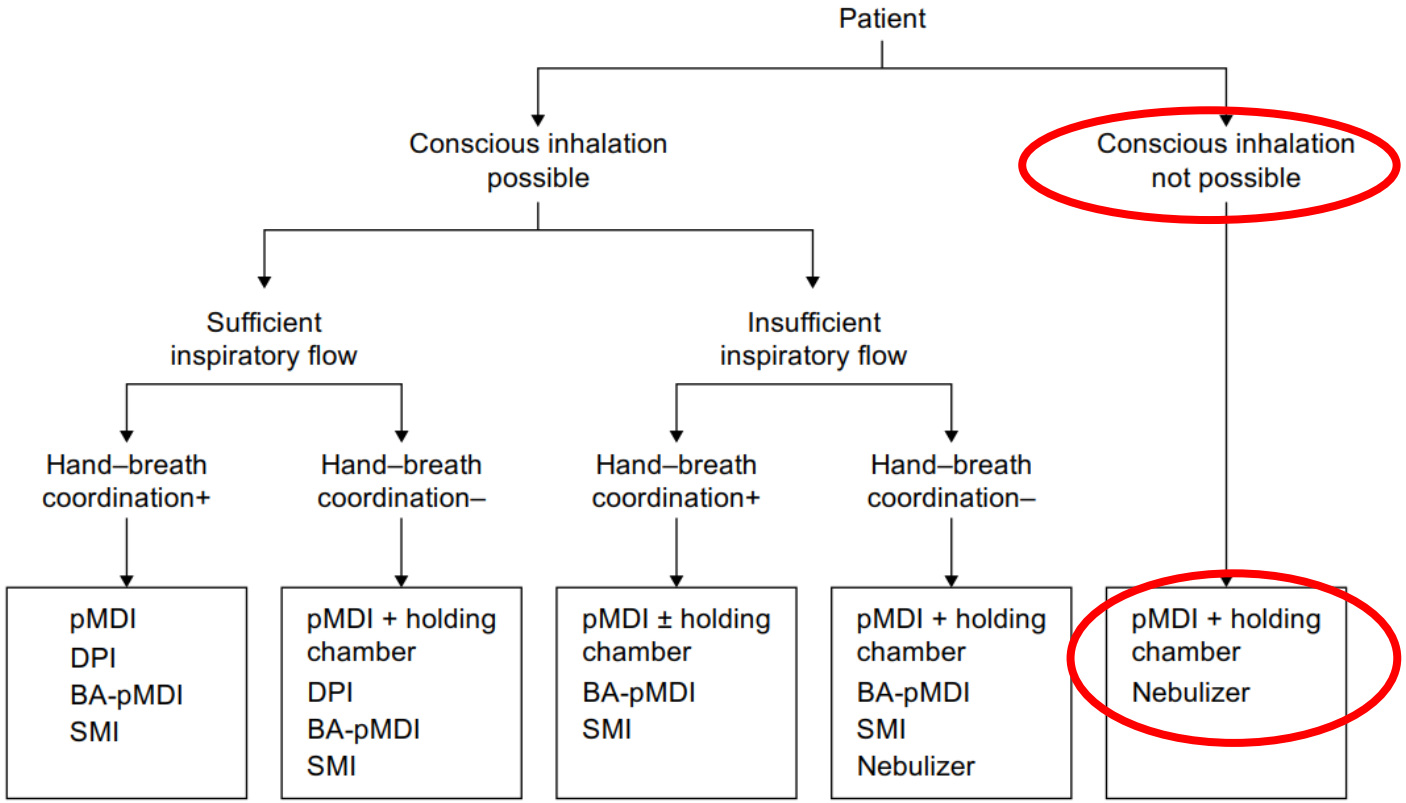

Symbicort
400
Turbuhaler® 400/12
400 microgram budesonide/
12 microgram formoterol-
fumaraatdihydraat per dosis
inhalatiepoeder
60 inhalaties


Symbicort
budesonide 80 mcg/
formoterol fumarate
dihydrate 4.5 mcg
Inhalation Aerosol
120 inhalations
AstraZeneca
80/4.5
Squeeze Sides gently then Pull Out

DRUG ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Ventolin inhaler


onbrez®
breezhaler®
150
300

Rapid and effective choose devices for COPD patients



無法良好配合病人，建議使用pMDI+add-on device

Figure 4 Algorithm for choosing inhaler device according to the patient's inspiratory flow and ability to coordinate inhaler actuation and inspiration.
Note: Reprinted from *Respir Med*, 107/12, Dekhuijzen PN, Vincken W, Virchow JC, et al, Prescription of inhalers in asthma and COPD: towards a rational, rapid and effective approach, 1817–1821, Copyright 2013, with permission from Elsevier.[12]
Abbreviations: BA-pMDI, breath-actuated pressurized metered dose inhaler; DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler; SMI, Soft Mist™ Inhaler.

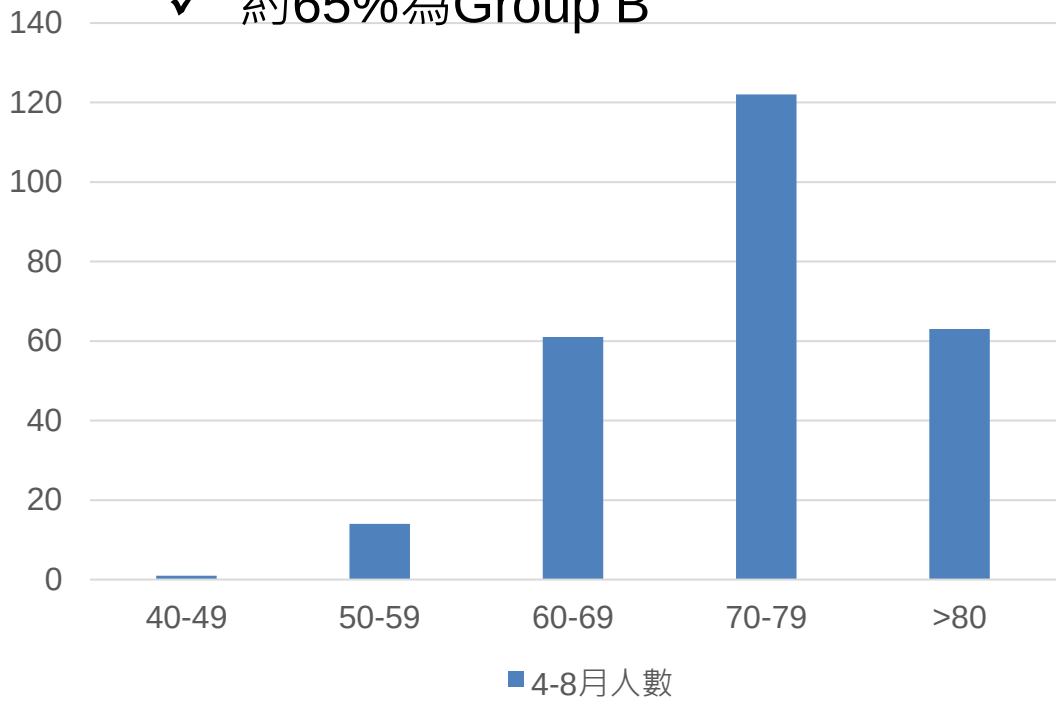
Respir Med. 2013;107(12):1817-21
Patient Prefer Adherence. 2016;10:1561-72

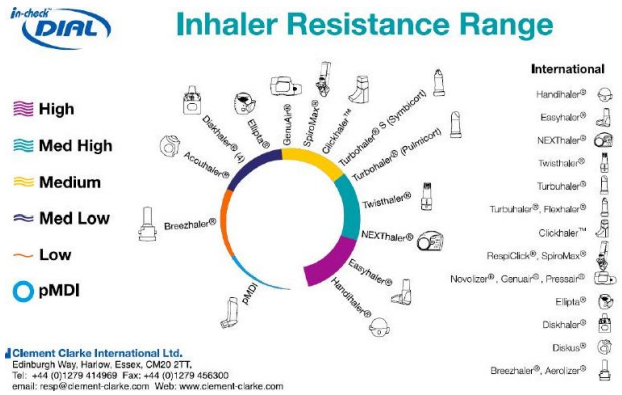
Elderly COPD with comorbidities

COPD device selection in CHGH

CHGH COPD patients' characteristics

- ✓ 70.9%病人年齡超過70歲
- ✓ Post BD FEV1% 62.5%
- ✓ 約65%為Group B

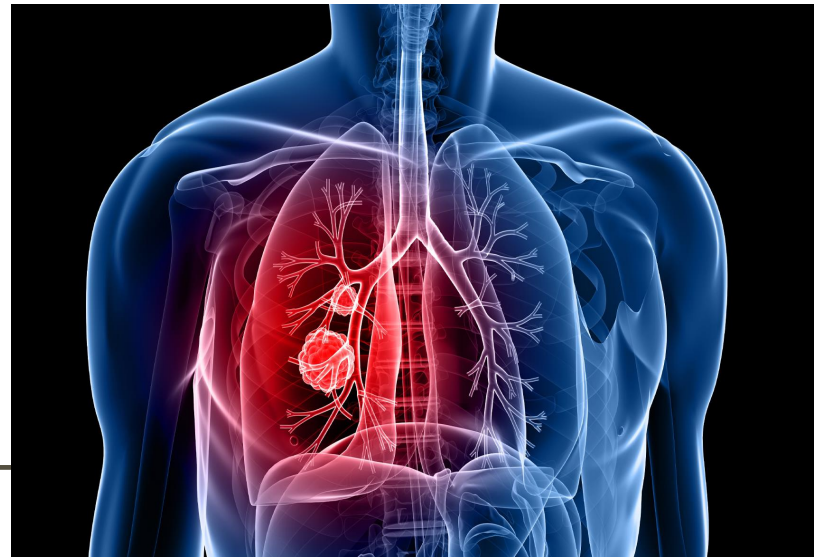




Take Home Message

如何幫助COPD病患選擇適當的治療方式

- 慢性肺阻塞目前仍然為台灣需要加強診斷與治療的疾病之一
- 不可逆的呼吸道損傷、年長、多重共病症與高死亡率
- 長效型支氣管擴張劑為治療慢性肺阻塞的最重要要務之一
- 吸入性類固醇合併長效型支氣管擴張劑的治療在有症狀且常急性發作的病人可以減少急性發作可能
- 運用血中嗜酸性血球可以當作一個可預測治療效果的生物標記



振興醫療財團法人
振興醫院

Thank you for your listening

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