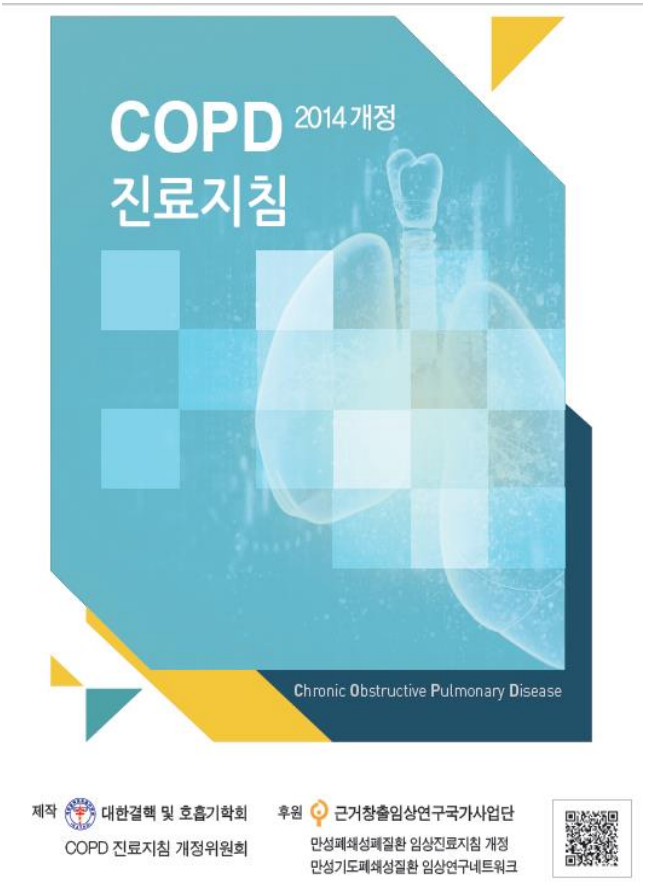
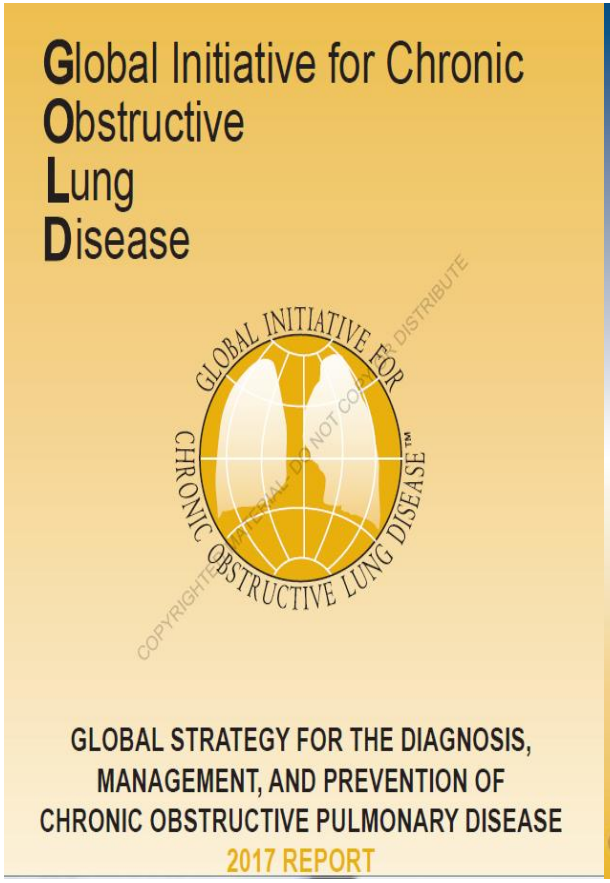
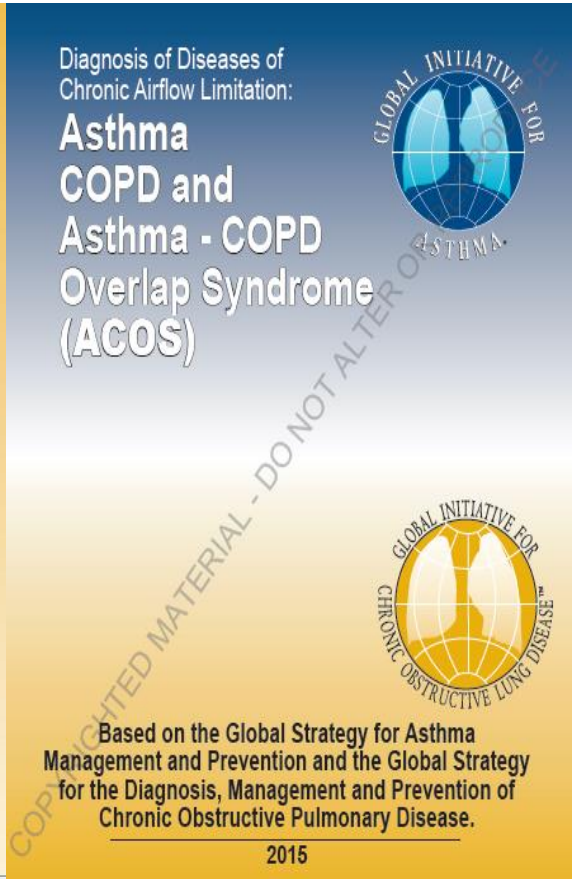
COPD Phenotypes/Endotypes for Clinical Practice

전남대병원 내과
김유일

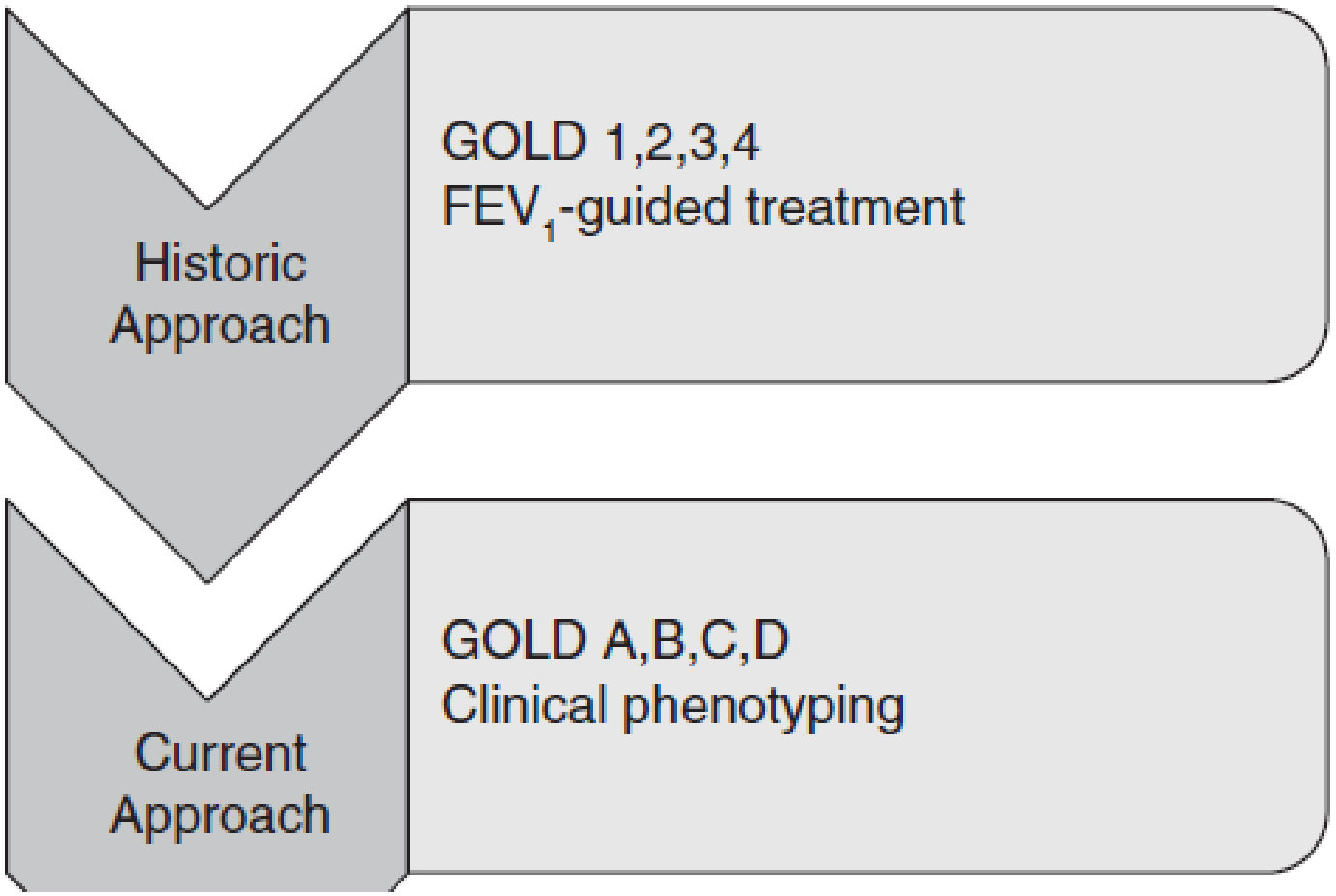


kaim.or.kr/pds/guide02.php





goldcopd.org

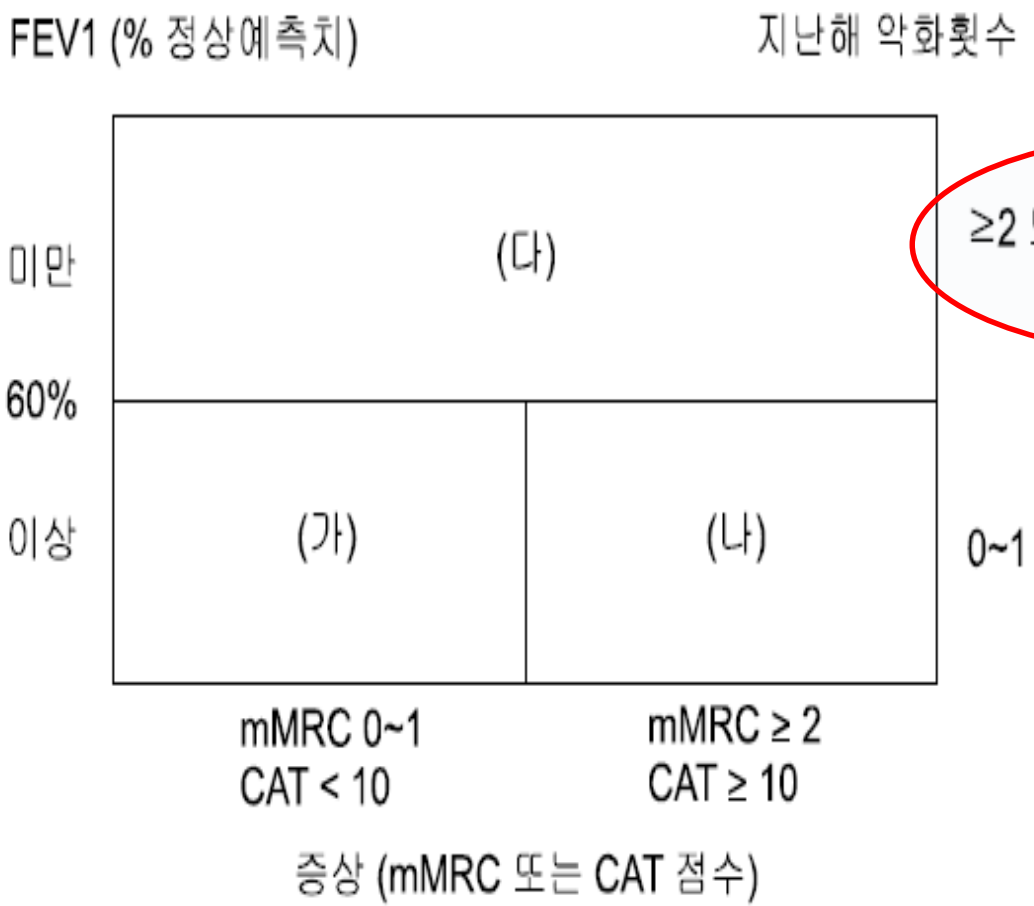


Singh D, et al. AJRCCM. 2016

Contents

- Phenotypes/Endotypes for clinical practice
  - Present
    - Frequent exacerbator, ACOS
    - Blood eosinophil
    - FENO
    - PDE4I
  - Future
    - Monoclonal Ab etc.

COPD 분류 (Korean 2014)



mMRC 2란 호흡곤란 정도가 "평지를 걸을 때 숨이 차서 동년배보다 천천히 걷거나, 자신의 속도로 걸어도 숨이 차서 멈추어 쉬어야 한다"이다. mMRC 본문 21쪽 표 2-4, CAT 본문 22쪽 그림 2-2참조.

GOLD 2017: Symptoms and exacerbation risk should be assessed to determine appropriate treatment

1. Diagnose COPD and determine the severity of airflow limitation (GOLD Grade 1–4) using spirometry
2. Determine GOLD Group (A–D) and subsequent appropriate pharmacological treatment by assessing symptoms and exacerbation history (including prior hospitalizations)

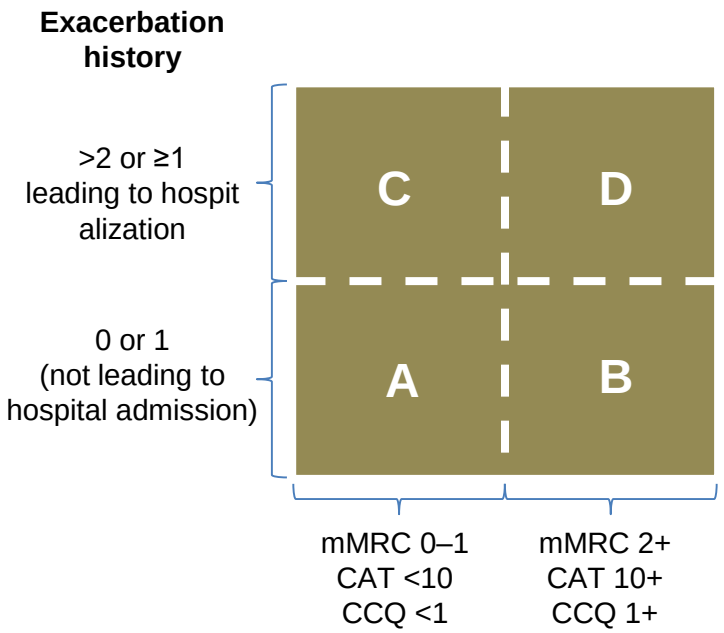
Spirometrically confirmed diagnosis

Post-bronchodilator $FEV_1/FVC < 0.7$

Assessment of airflow limitation

Grade	FEV_1 (% pred.)
1	≥80
2	50–79
3	30–49
4	<30

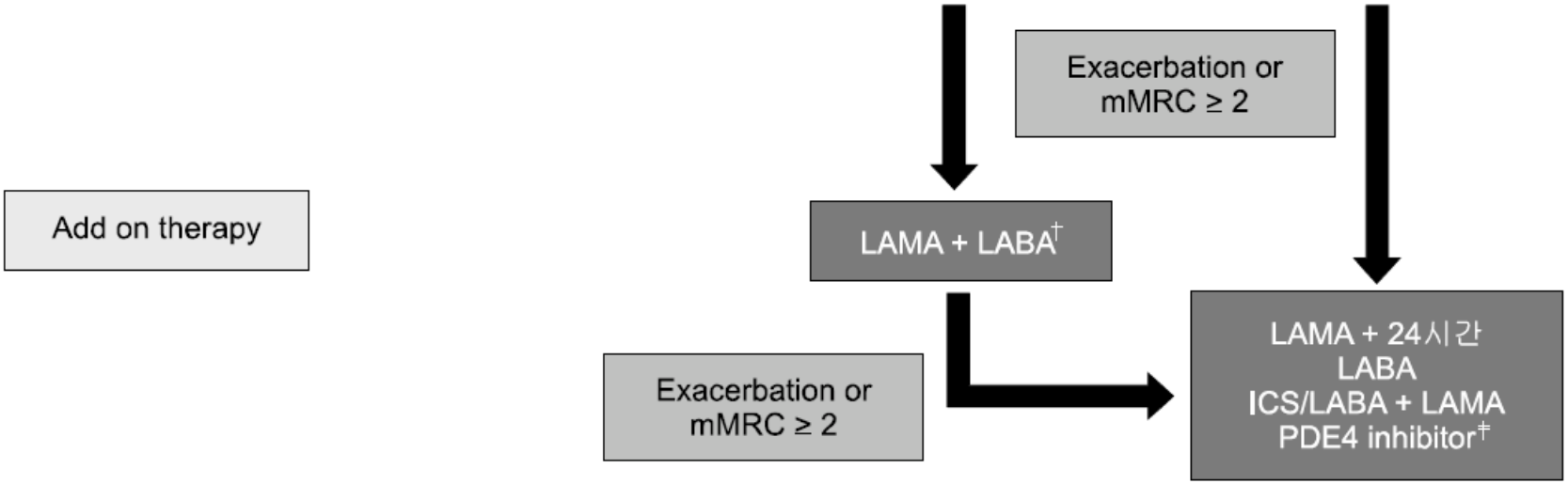
Assessment of symptoms/ risk of exacerbations



CAT = COPD Assessment Test; CCQ = Clinical COPD Questionnaire; COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease
mMRC = modified Medical Research Council

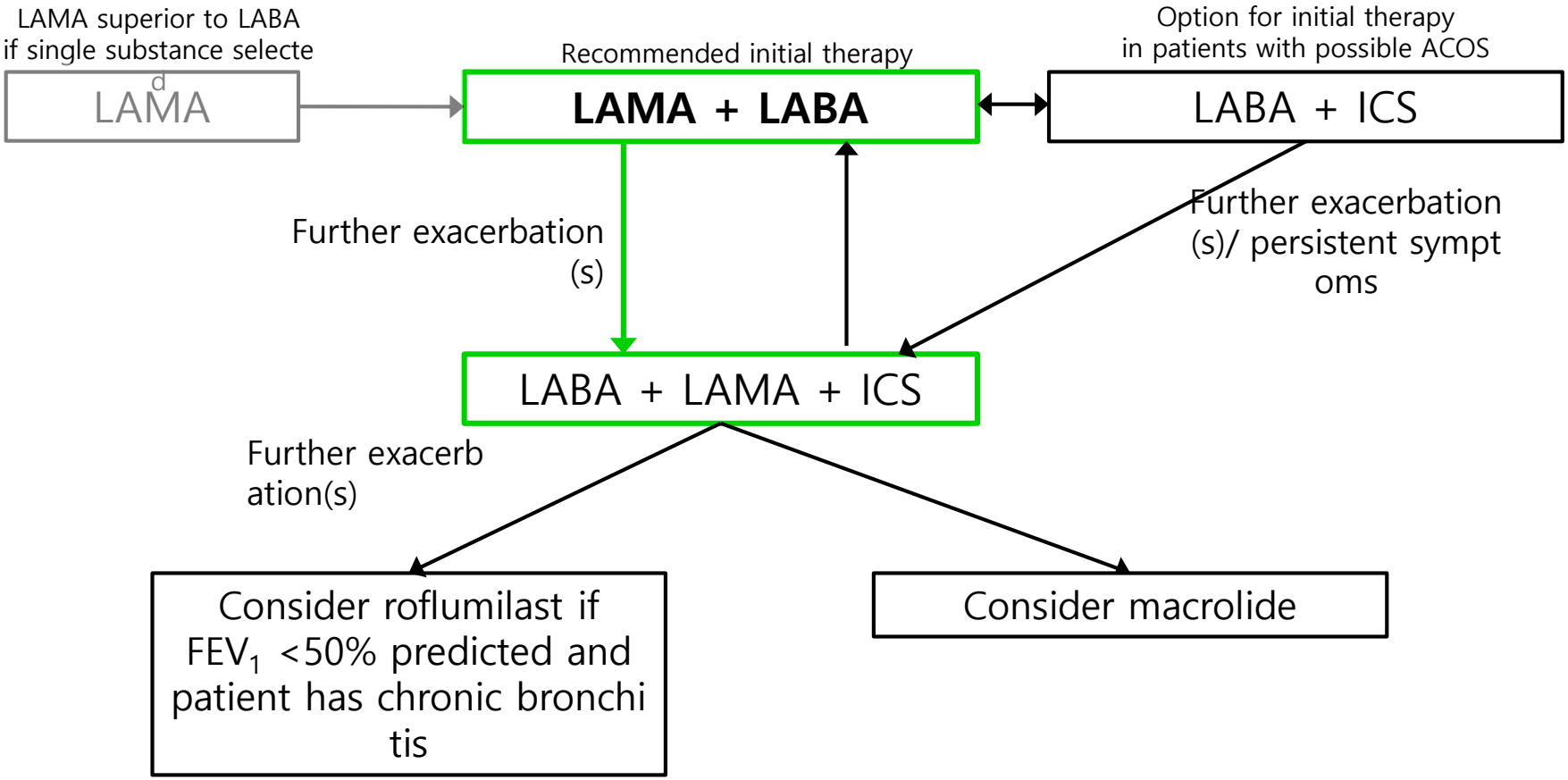
국내 COPD 치료 개정안 (2014)

	FEV_1 ≥ 60% pred. and 0~1 exacerbation/year		FEV_1 < 60% pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA



*AE COPD: Acute exacerbation of COPD.
†24시간 LABA 포함.
‡FEV_1<50% 정상예측치, 만성기침, 악화병력이 있는 환자군.
LABA: Long Acting Bronchodilator, LAMA: Long Acting Muscarinic antagonist.

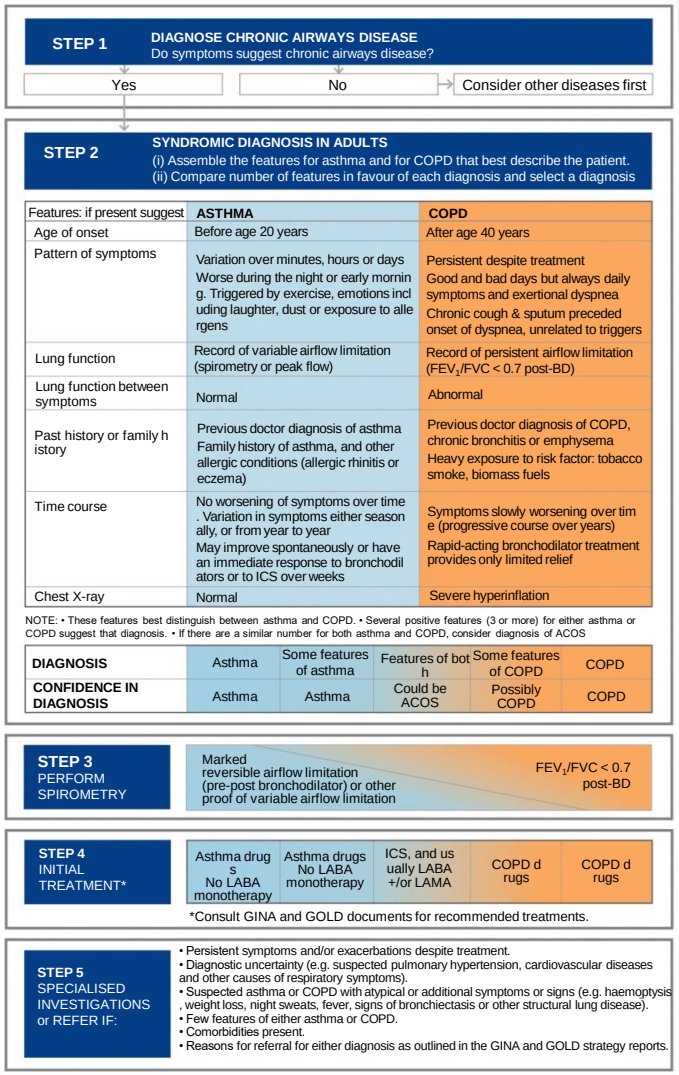
GOLD 2017: Dual bronchodilation is the preferred initial therapy for patients in Group D



ACOS = asthma-COPD overlap syndrome; FEV_1 = forced expiratory volume in 1 second
GOLD = Global initiative for chronic Obstructive Lung Disease ICS = inhaled corticosteroid
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

GOLD 2017

Stepwise approach to diagnosis and initia l treatment



STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

Yes | No → Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Features: if present suggest	ASTHMA	COPD
Age of onset	Before age 20 years	After age 40 years
Pattern of symptoms	Variation over minutes, hours or days Worse during the night or early morning. Triggered by exercise, emotions including laughter, dust or exposure to allergens	Persistent despite treatment Good and bad days but always daily symptoms and exertional dyspnea Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	Record of variable airflow limitation (spirometry or peak flow)	Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
Lung function between symptoms	Normal	Abnormal
Past history or family history	Previous doctor diagnosis of asthma Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	Previous doctor diagnosis of COPD, chronic bronchitis or emphysema Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	Symptoms slowly worsening over time (progressive course over years) Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	Normal	Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

STEP 3 PERFORM SPIROMETRY

Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation → $FEV_1/FVC < 0.7$ post-BD

STEP 4 INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS, and usually LABA +/or LAMA	COPD drugs	COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5 SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

For an adult who presents with respiratory symptoms:

1. Does the patient have chronic airways disease?
2. Syndromic diagnosis of asthma, COPD and ACOS
3. Spirometry
4. Commence initial therapy
5. Referral for specialized investigations (if necessary)

GOLD 2017: Therapy for patients in Group D

- GOLD recommends LABA/LAMA as primary-choice treatment for Group D patients[1]
  - LABA/LAMA has demonstrated superiority versus bronchodilator monotherapy a nd LABA/ICS in exacerbation prevention[2,3]

- **LABA/ICS** may be first choice in patients with a history of and/or features suggestiv e of **asthma-COPD overlap**[1]

- **High eosinophil counts** may also be considered as a parameter t o support the use of ICS, although this is still under debate.

FEV_1 = forced expiratory volume in 1 second
GOLD = Global initiative for chronic Obstructive Lung Disease; ICS = inhaled corticosteroid
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

1. GOLD 2017
2. Wedzicha JA, et al. Lancet Respir Med 2013
3. Wedzicha JA, et al. N Engl J Med 2016

Table 4.6. Key points for the use of anti-inflammatory agents

- Long-term monotherapy with ICS is not recommended **(Evidence A)**.
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators **(Evidence A)**.
- Long-term therapy with oral corticosteroids is not recommended **(Evidence A)**.
- In patients with exacerbations despite LABA/ICS or LABA/LAMA/ICS, chronic bronchitis and severe to very severe airflow obstruction, the addition of a PDE4 inhibitor can be considered **(Evidence B)**.
- In former smokers with exacerbations despite appropriate therapy, macrolides can be considered **(Evidence B)**.
- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**.
- Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**.

- 2017 GOLD

THE LANCET
Respiratory Medicine

Articles

Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial

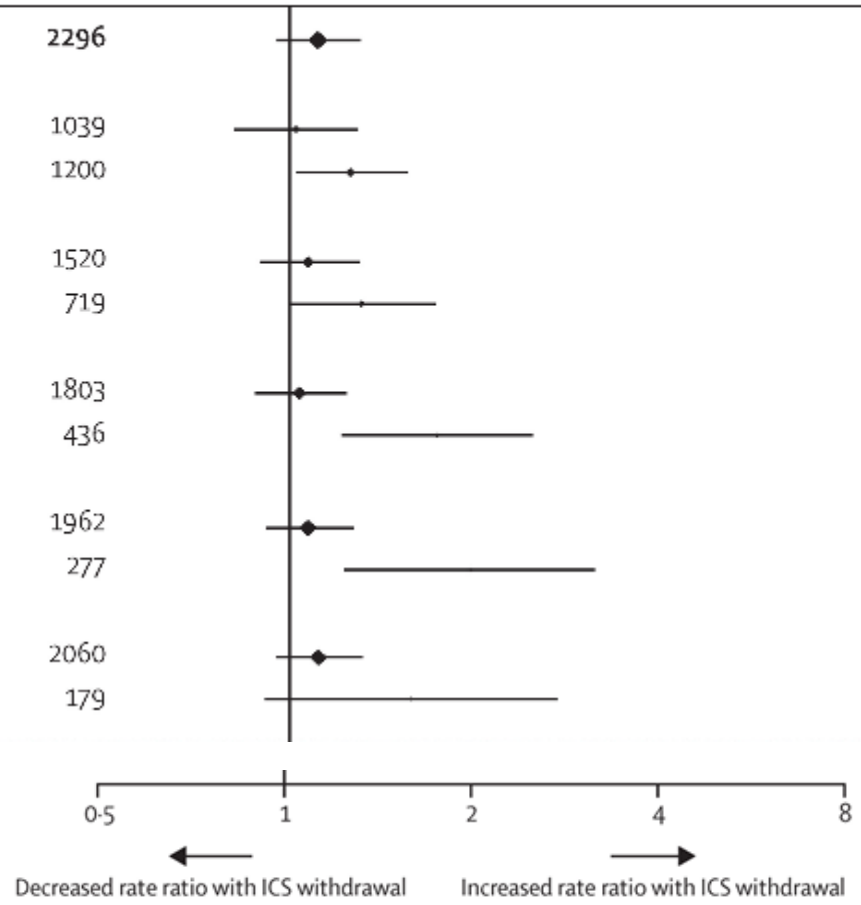
Dr Henrik Watz, MD, Prof Kay Tetzlaff, MD, Prof Emiel F M Wouters, MD, Anne Kirsten, MD, Prof Helgo Magnussen, MD, Prof Roberto Rodriguez-Roisin, MD, Prof Claus Vogelmeier, MD, Prof Leonardo M Fabbri, MD, Prof Pascal Chanez, MD, Prof Ronald Dahl, MD, Bernd Disse, MD, Helen Finnigan, MSc, Prof Peter M A Calverley, DSc

Published: 07 April 2016

Interpretation

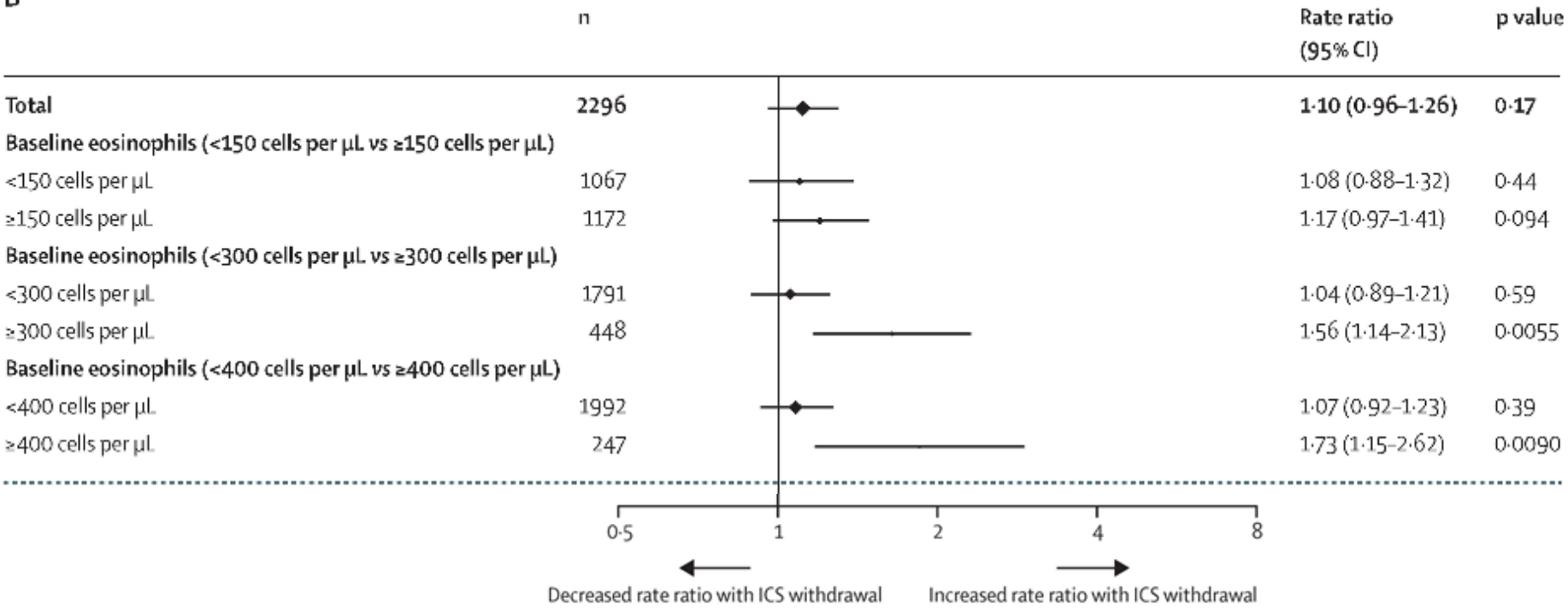
Blood eosinophil counts at screening were related to the exacerbation rate after complete ICS withdrawal in patients with severe to very severe COPD and a history of exacerbations. Our data suggest that counts of **4% or greater or 300 cells** per µL or more might identify a deleterious effect of ICS withdrawal, an effect not seen in most patients with eosinophil counts below these thresholds.

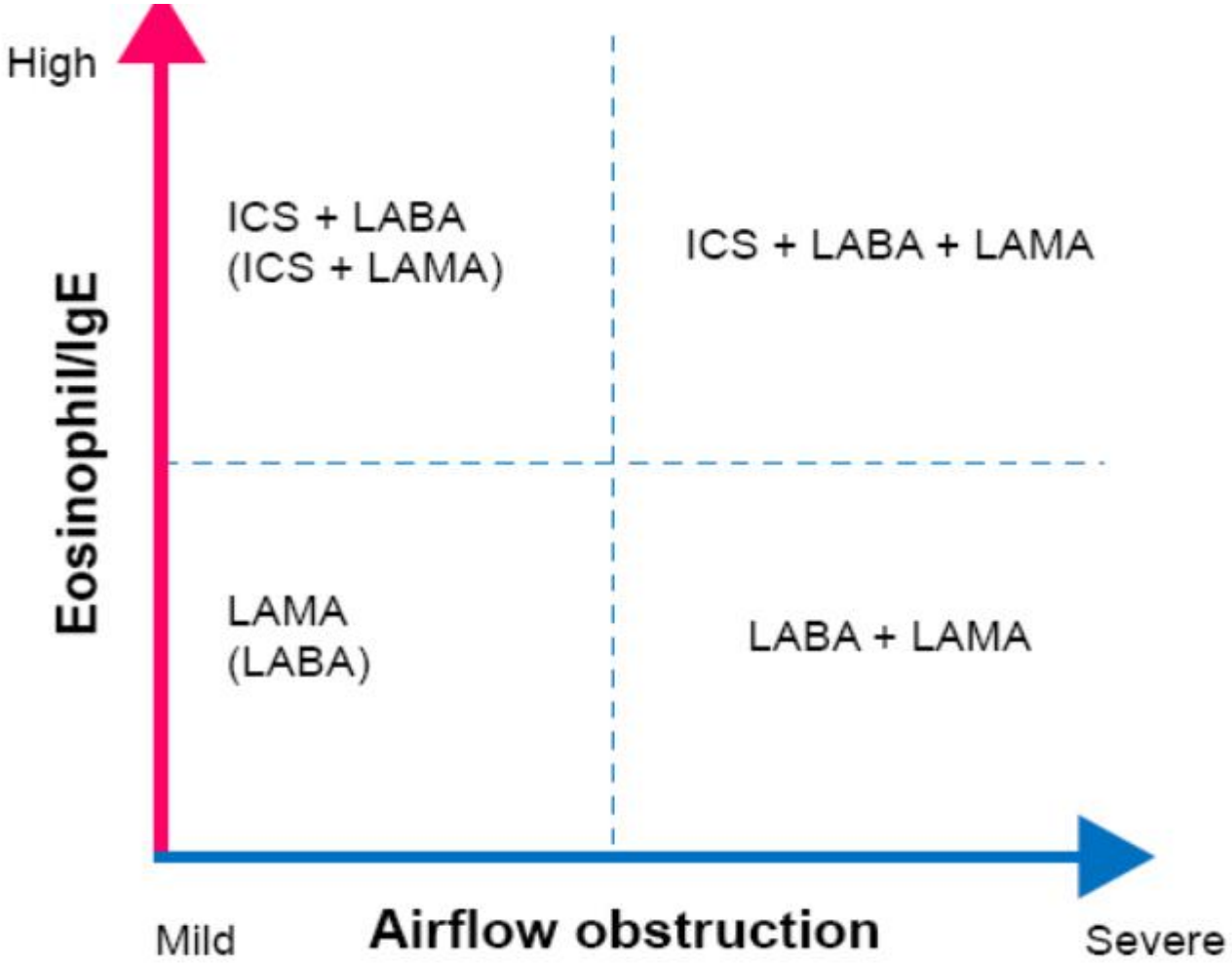
A



	n	Rate ratio (95% CI)	p value
Total	2296	**1·10 (0·96–1·26)**	0·17
Baseline eosinophils (<2% vs ≥2%)			
<2%	1039	1·02 (0·83–1·25)	0·84
≥2%	1200	1·22 (1·02–1·48)	0·033
Baseline eosinophils (<3% vs ≥3%)			
<3%	1520	1·07 (0·90–1·26)	0·46
≥3%	719	1·27 (1·00–1·62)	0·053
Baseline eosinophils (<4% vs ≥4%)			
<4%	1803	1·03 (0·89–1·20)	0·66
≥4%	436	1·63 (1·19–2·24)	0·0025
Baseline eosinophils (<5% vs ≥5%)			
<5%	1962	1·07 (0·92–1·23)	0·39
≥5%	277	1·82 (1·20–2·76)	0·0049
Baseline eosinophils (<6% vs ≥6%)			
<6%	2060	1·10 (0·95–1·27)	0·20
≥6%	179	1·50 (0·92–2·44)	0·11

B


n
Rate ratio (95% CI)
p value
Total
2296
1·10 (0·96–1·26)
0·17
Baseline eosinophils (<150 cells per µL vs ≥150 cells per µL)
<150 cells per µL
1067
1·08 (0·88–1·32)
0·44
≥150 cells per µL
1172
1·17 (0·97–1·41)
0·094
Baseline eosinophils (<300 cells per µL vs ≥300 cells per µL)
<300 cells per µL
1791
1·04 (0·89–1·21)
0·59
≥300 cells per µL
448
1·56 (1·14–2·13)
0·0055
Baseline eosinophils (<400 cells per µL vs ≥400 cells per µL)
<400 cells per µL
1992
1·07 (0·92–1·23)
0·39
≥400 cells per µL
247
1·73 (1·15–2·62)
0·0090
0·5
1
2
4
8
Decreased rate ratio with ICS withdrawal
Increased rate ratio with ICS withdrawal



-Hizawa N. Int J Chron Obstruct Pulmon Dis. 2015 Jun

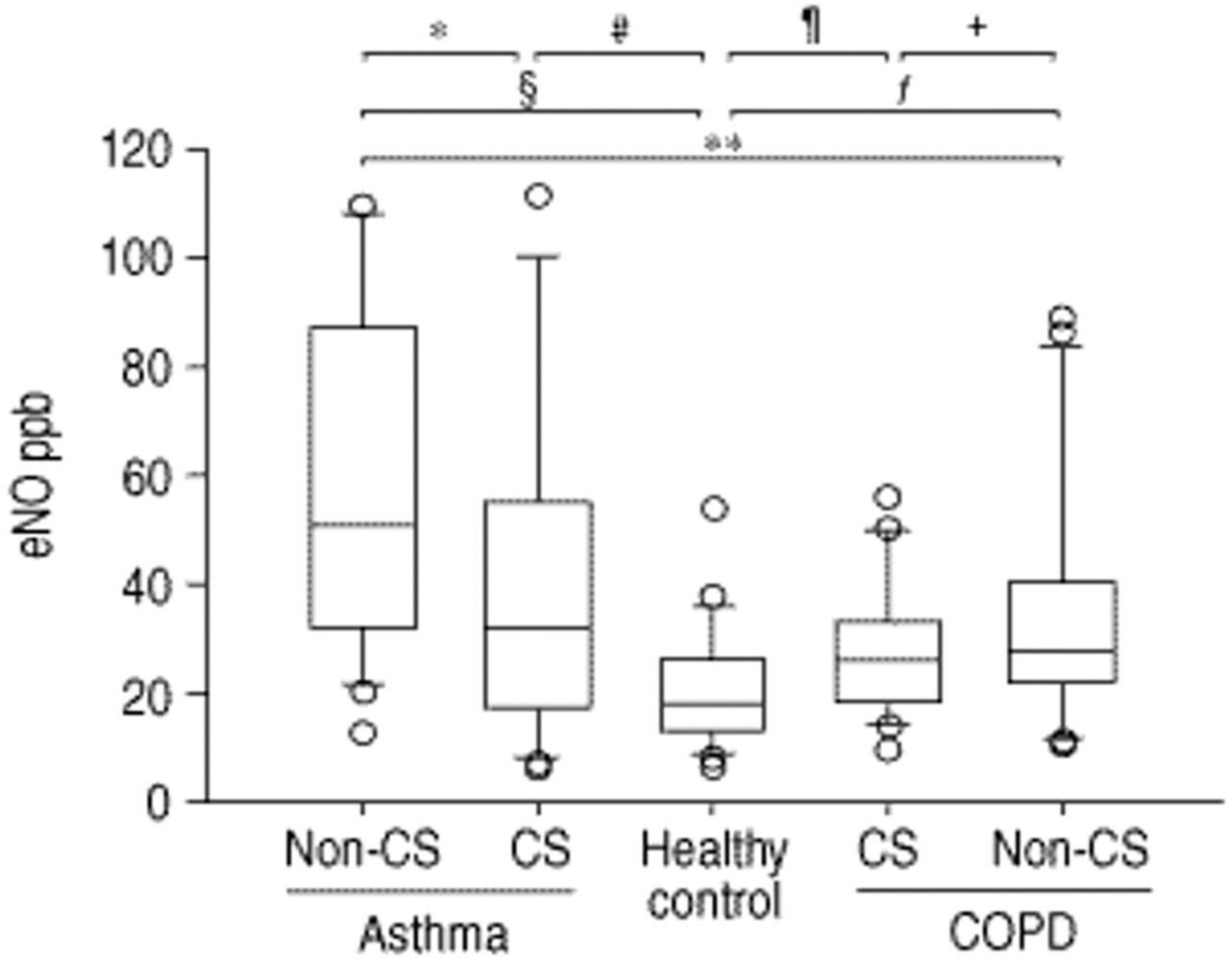
Clin Respir J. 2016 Jun 22. doi: 10.1111/crj.12518. [Epub ahead of print]

Response of exhaled nitric oxide to inhaled corticosteroids in patients with stable COPD: A systematic review and meta-analysis.

Lim CS[1], Rani FA[1,2], Tan LE[1].

CONCLUSION:
Our findings indicate that FeNO levels significantly decreased with corticosteroid treatment in ex-smokers (n=125)with COPD. Additional studies are required to evaluate whether concurrent smoking has significant effect on FeNO response to ICS.

Box plots of exhaled nitric oxide (eNO) values in patients with asthma, chronic obstructive pulmonary disease (COPD, n=32) and in healthy volunteers. ppb: parts per billion; CS: using corticosteroids; Non-CS: not using corticosteroids.



K. Ansarin et al. Eur Respir J 2001;17:934-938

FENO in COPD

- COPD환자 174명

- FENO = 28.05±19.97(ppb)
- FENO <25미만은 95명(55%), 25이상 50미만 39명(22%), >50이상 40명(23%)

- FENO 증가군
  - 혈중 호산구비율(%) 높았음(2.58±02.67 vs 3.68±3.90, p=0.003).
  - 천식 진단력 빈도가 높았음(p=0.003, 교차비 5.508),

- Kim et al. 2016추계호흡기

Am J Respir Crit Care Med. 2016 Sep 1;194(5):559-67. doi: 10.1164/rccm.201607-1349OC.

Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial.

Martinez FJ[1], Rabe KF[2,3,4], Sethi S[5], Pizzichini E[6], McIvor A[7], Anzueto A[8,9], Alagappan VK[10], Siddiqui S[10], Rekeda L[11], Miller CJ[10], Zetterstrand S[12], Reisner C[13], Rennard SI[14,15].

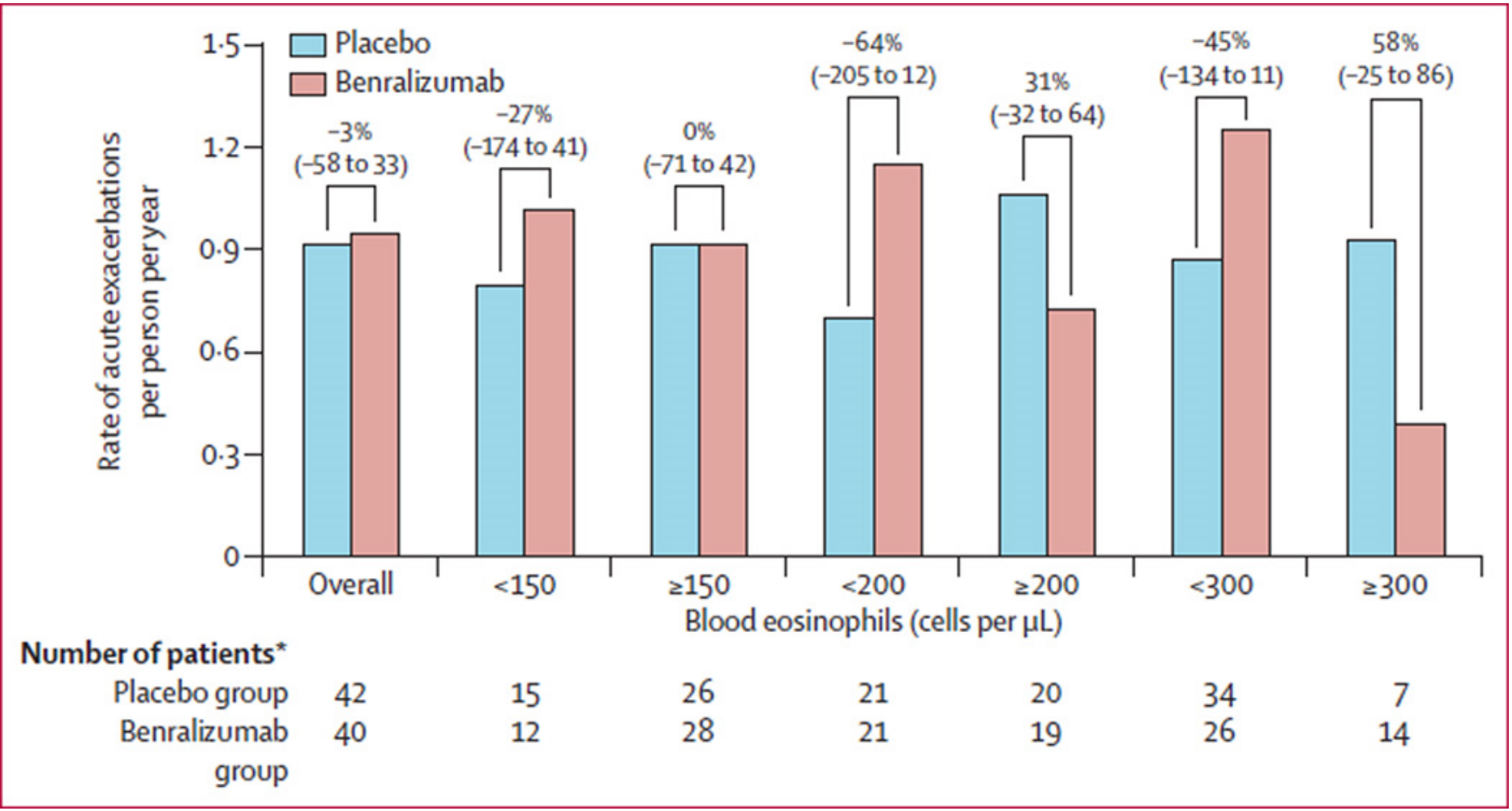
CONCLUSIONS:
Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population. **Roflumilast improved lung function and reduced exacerbations in participants with frequent exacerbations and/or hospitalization history**. The safety profile of roflumilast was consistent with that of previous studies.

Lancet Respir Med. 2014 Nov;2(11):891-901. doi: 10.1016/S2213-2600(14)70187-0. Epub 2014 Sep 7.

Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study.

Brightling CE[1], Bleecker ER[2], Panettieri RA Jr[3], Bafadhel M[4], She D[5], Ward CK[5], Xu X[6], Birrell C[7], van der Merwe R[7].

INTERPRETATION:
Compared with placebo, benralizumab did not reduce the rate of acute exacerbations of COPD. However, the results of prespecified subgroup analysis support further investigation of benralizumab in patients with COPD and eosinophilia.



Number of patients*

Placebo group	42	15	26	21	20	34	7
Benralizumab group	40	12	28	21	19	26	14

Int J Chron Obstruct Pulmon Dis. 2017; 12: 395–402.
Published online 2017 Jan 21. doi: 10.2147/COPD.S120445
PMCID: PMC5268328

Factors associated with plasma IL-33 levels in patients with chronic obstructive pulmonary disease

Sei Won Kim,[1,*] Chin Kook Rhee,[2,*] Ki Uk Kim,[3] Sang Haak Lee,[4] Hun Gyu Hwang,[5] Yu Il Kim,[6] Deog Kyeom Kim,[7] Sang Do Lee,[8] Yeon-Mok Oh,[8] and Hyoung Kyu Yoon[1], On behalf of the KOLD Study Group

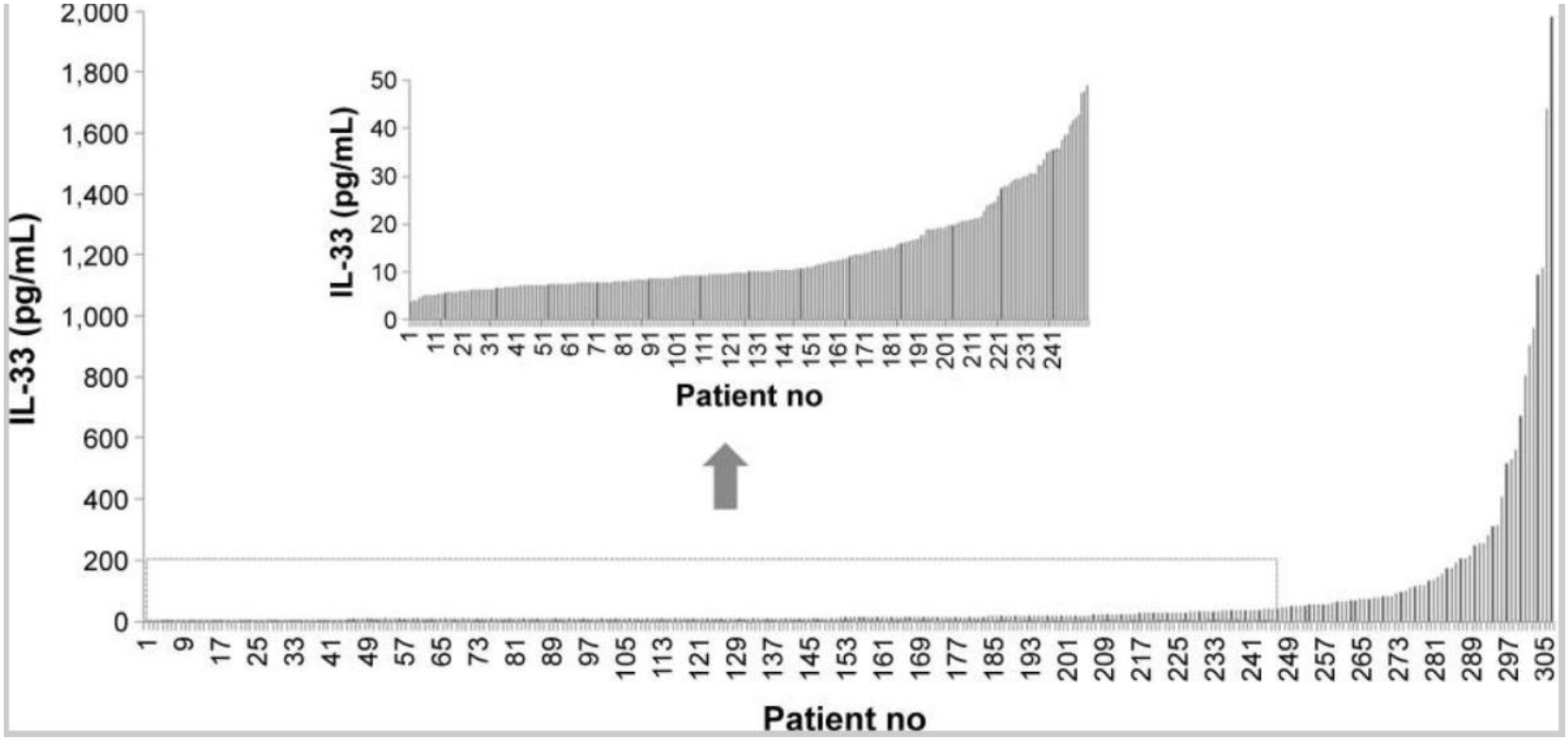
Conclusion

- Plasma IL-33 level in patients with stable COPD was related to eosinophil count and chronic bronchitis phenotype.
- Further studies are needed to identify the precise mechanisms of IL-33/ST2 pathway in patients with COPD.

Associations between IL-33 level and clinical parameters of patients with COPD

Variables	Simple regression		Multiple regression*	
	β ± SE	*P*-value	β ± SE	*P*-value
Age	−2.81±1.57	0.076	−4.41±1.67	**0.009**
Smoking, current	−54.09±24.70	**0.029**	−80.54±26.21	**0.002**
Emphysema index	1.14±0.78	0.144	1.20±0.89	0.178
D_{LCO} (% predicted)	−0.66±0.49	0.181	−0.70±0.58	0.231
Eosinophil, count (/μL)	0.20±0.04	**<0.001**	0.23±0.05	**<0.001**

- Kim et al. Int J Chron Obstruct Pulmon Dis. 2017; 12: 395–402.



- Kim et al. Int J Chron Obstruct Pulmon Dis. 2017; 12: 395–402.

Case 1

- FEV1 40%, FEV1/FVC 30%
- 최근 1년 악화력 > 2회/연
- MRC 4 Dyspnea

- 약물치료는?
  - 1) LABA/LAMA
  - 2) LABA/ICS
  - 3) LABA/LAMA/ ICS

Case 2

- FEV1 40%, FEV1/FVC 30%
- 최근 1년 악화력 > 2회/연
- Chronic cough/sputum (+)
- Tx : ICS/LABA + LAMA

- 추가 치료약물은 ?

Treatable traits : toward precision medicine

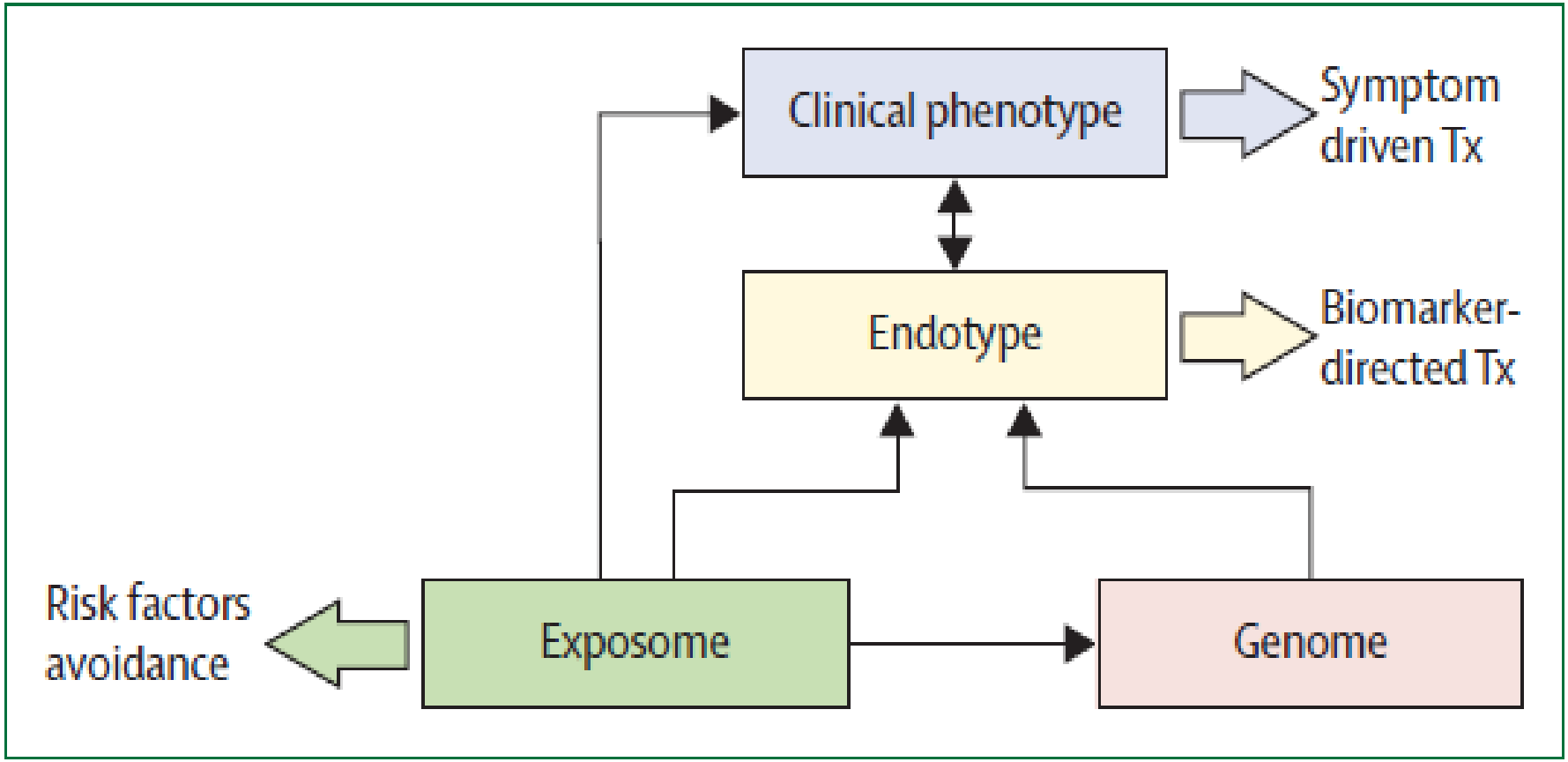
Treatable traits (can coexist)	Imp.	Rec.	Diagnostic criteria	Treatment			e
				First choice	Efficacy	Second choice	
Airflow limitation [9]	+++	+++	FEV_1/FVC <0.7 (or lower limit of normal)				
Airway smooth muscle contraction	++	+++	Bronchodilator reversibility, peak expiratory flow variability, positive PC_{20}	Maintenance: long-acting β_2-adrenergic agonists/muscarinic antagonists; rescue: short-acting β_2-adrenergic agonists/muscarinic antagonists	+++	Inhaled corticosteroids, *bronchial thermoplasty*[¶]	
Loss of elastic recoil (emphysema)	+++	++	Chest computed tomography, D_{LCO}, compliance	Smoking cessation	+	Lung volume reduction surgery, lung transplantation, α_1-anti-trypsin replacement if deficient, *valves, coils*	
Airway mucosal oedema	++	+	*Chest computed tomography, spirometry-induced bronchoconstriction*	Inhaled corticosteroids	++	Oral corticosteroids, *anti-interleukin-5, -13, -4*	
Eosinophilic airway inflammation [55, 56]	+++	+++	Sputum eosinophils, blood eosinophils, F_{ENO}, (*periostin*)	Inhaled corticosteroids	+++	Oral corticosteroids, leukotriene receptor antagonists, anti-IgE, *anti-interleukin-5, -13, -4*	
Chronic bronchitis	++	+++	Cough and sputum 3 months×2 years (no eosinophilic airway inflammation)	Smoking cessation	+	Carbocysteine, macrolides, roflumilast	

Treatable traits: toward precision medicine of chronic airway diseases. Agusti A. et al. Eur Respir J. 2016

TABLE 2 Extrapulmonary treatable traits of airway diseases

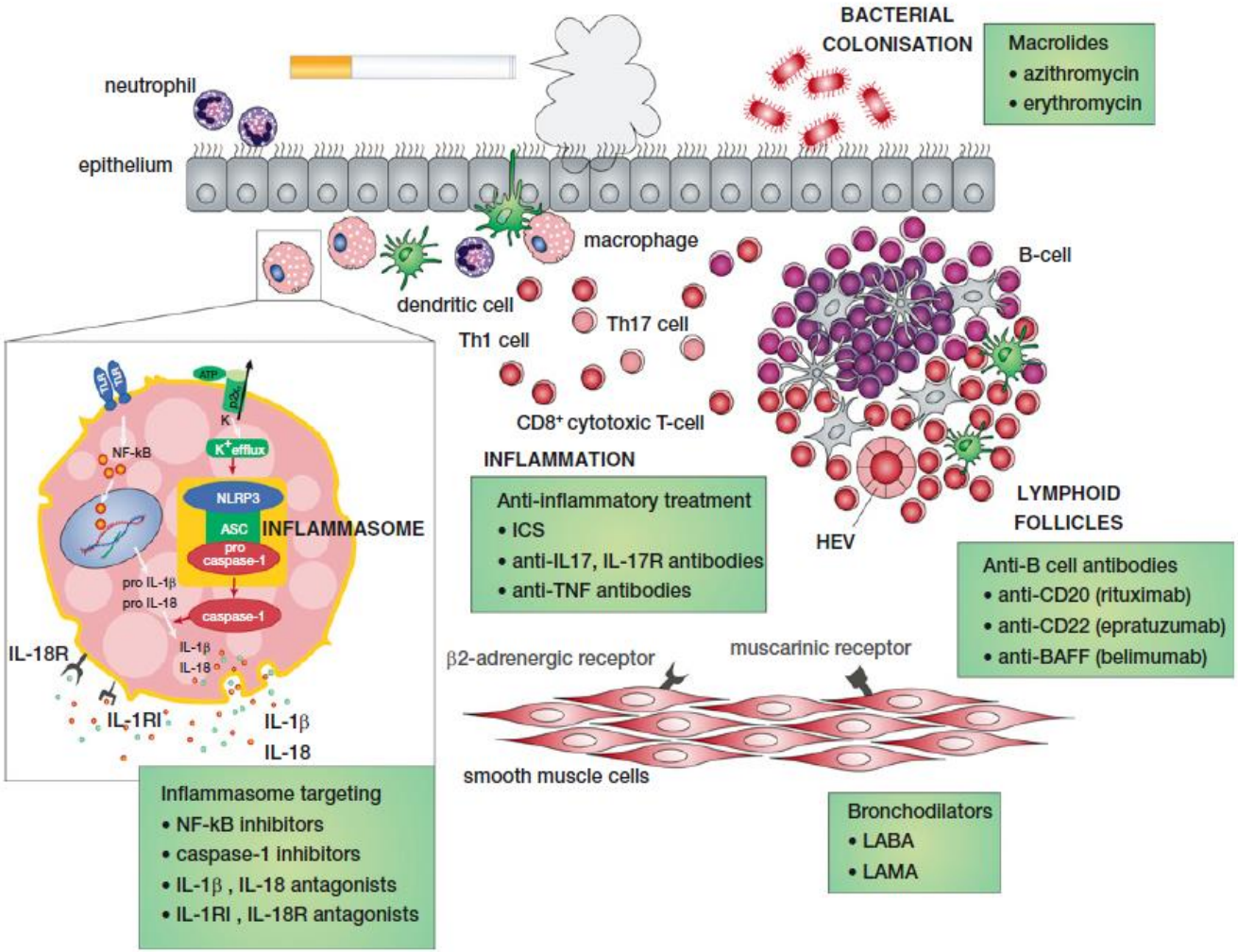
Treatable traits (can coexist)	Imp.	Rec.	Diagnostic criteria	Treatment		
				First choice	Efficacy	Second choice
Deconditioning	+	+	Cardio-pulmonary exercise testing, 6-min walking distance	Exercise, rehabilitation	+	
Obesity	+	+++	Body mass index	Diet, physical activity	+	Medication, bariatric surgery
Cachexia	+	+++	Body mass index	Diet, physical activity	+	
Obstructive sleep apnoea syndrome	+	++	Questionnaires, polysomnography	Continuous positive airway pressure	+	Weight loss, mandibular advancement splint
Cardiovascular disease	++	+++	Electrocardiogram, Doppler echocardiography, brain natriuretic peptide	Angiotensin-converting enzyme inhibitors, diuretics, β-blockers	++	Surgery

Interrelations between exposome, genome, endotype, and clinical phenotype of COPD



Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy. *Prescott G Woodruff et al* . **The Lancet 2015.**

Pathogenic pathways & possible therapeutic targets in COPD

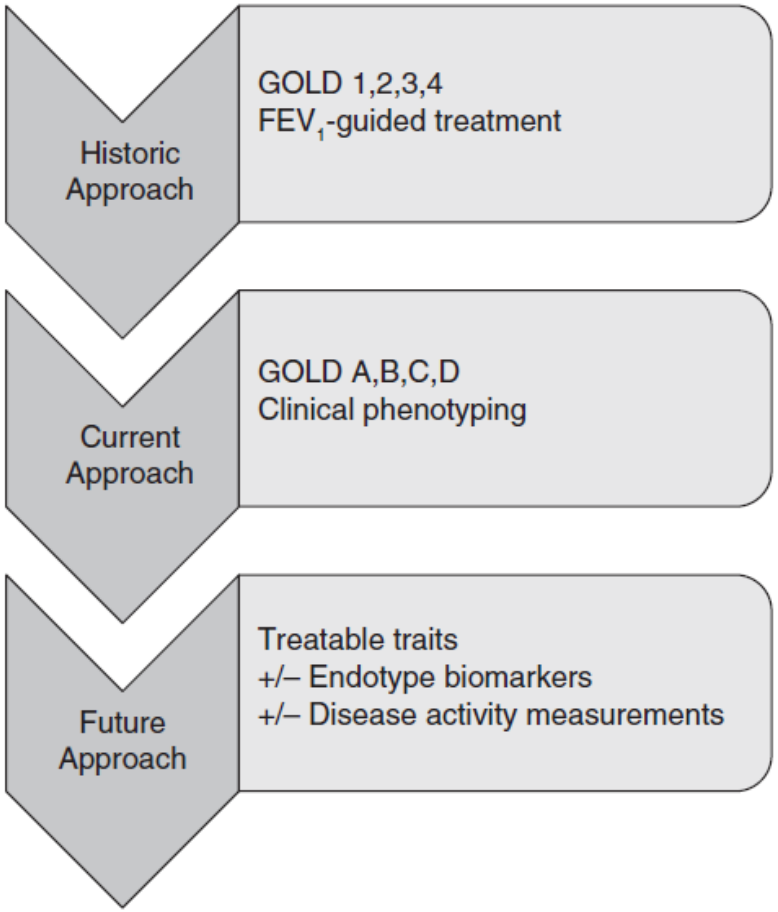


Targeting immune pathways for therapy in asthma and chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2014 Dec

Summary

- Phenotypes/Endotypes for clinical practice
  - Present
    - Frequent exacerbator, ACOS
    - Blood eosinophil
    - FENO
    - PDE4I
  - Future
    - Monoclonal Ab etc.

Changing approaches



- *Singh D, et al. AJRCCM. 2016*