Treatment algorithm and emerging evidence of managing COPD

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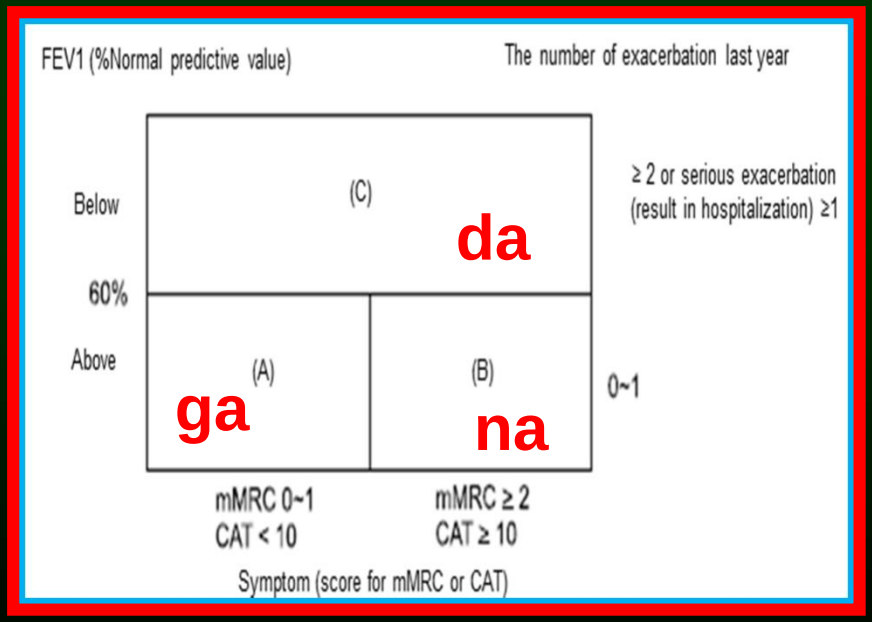
Optimal and practical Treatment Algorithm?

- Lung function-guided ?
- Phenotypes?
- Biomarkers?
- Stepwise treatment policy?
- ABCD group guided treatment?
- GOLD I-IV and Group A-D (A1-D4, 16 subgroup)?
- Functional assessments, 6-min-W T? Image ?
- Treatment traits
- Others…..

COPD classification in Korea

- The Korean COPD guideline categorizes severity into 3 groups, Group ga (GOLD Group A), Group na (GOLD Group B) and Group da (GOLD Group C&D)
- The spirometric cut-points of FEV1 is 60% predicted to distinguish Group ga, na from Group da



ORIGINAL ARTICLE
Respiratory Diseases

JKMS

http://dx.doi.org/10.3346/jkms.2014.29.8.1108 • *J Korean Med Sci 2014; 29: 1108-1112*

Comparison of Korean COPD Guideline and GOLD Initiative Report in Term of Acute Exacerbation: A Validation Study for Korean COPD Guideline

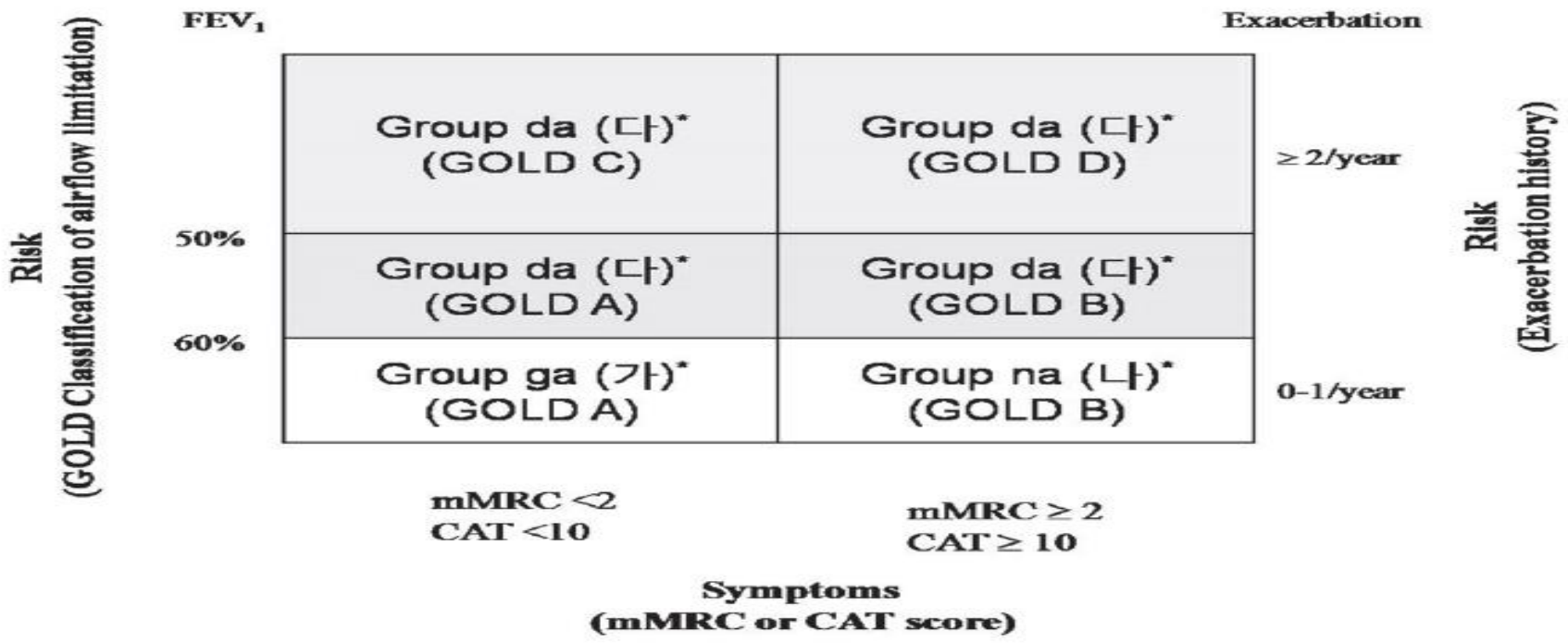


Fig. 1. Korean COPD classification system and GOLD classification system.

J Korean Med Sci. 2014; 29: 1108-1112

COPD Korea guideline

Ga group =A group

Na group = B group

Da group = C ;D group

	$FEV_1 \geq 60\%$ 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

Add on therapy

Exacerbation or mMRC ≥ 2

LAMA + LABA†

Exacerbation or mMRC ≥ 2

LAMA + 24시간 LABA ICS/LABA + LAMA PDE4 inhibitor‡

LAMA or Once daily (24hr duration) LABA or ICS/LABA or LABA + LAMA

Included once daily LABA

*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.

In patient with FEV_1 < 50% of the predicted normal, chronic cough and a history of exacerbation

Stepwise Management of Stable COPD

LUNG FOUNDATION AUSTRALIA
"When you can't breathe... nothing else matters"®

	MILD	MODERATE	SEVERE
Typical Symptoms	• few symptoms • breathless on moderate exertion • recurrent chest infections • little or no effect on daily activities	• increasing dyspnoea • breathless walking on level ground • increasing limitation of daily activities • cough and sputum production • infections requiring steroids	• dyspnoea on minimal exertion • daily activities severely curtailed • experiencing regular sputum production • chronic cough
Lung Function	**FEV_1 ≈ 60-80% predicted**	**FEV_1 ≈ 40 -59% predicted**	**FEV_1 < 40% predicted**

Non-Pharmacological Interventions

Management of stable COPD should centre around supporting smoking patients to quit. Encouraging physical activity and maintenance of a normal weight range are also important. Pulmonary rehabilitation is recommended in symptomatic patients.

- **RISK REDUCTION** Check smoking status, support smoking cessation, recommend annual influenza and pneumococcal vaccine according to immunisation handbook
- **OPTIMISE FUNCTION** Encourage physical activity, review nutrition, provide education, develop GP management plan and initiate regular review
- **CONSIDER CO-MORBIDITIES** especially osteoporosis, coronary disease, lung cancer, anxiety and depression
- **REFER TO PULMONARY REHABILITATION** and consider psychosocial needs, agree written action plan
- Consider oxygen therapy, surgery, palliative care and advanced care directives

Pharmacological Interventions

The aim of pharmacological treatment may be to treat symptoms (e.g. breathlessness) or to prevent deterioration (either by decreasing exacerbations or by reducing decline in quality of life) or both. A stepwise approach is recommended, irrespective of disease severity, until adequate control has been achieved.

- **CHECK DEVICE USAGE TECHNIQUE AND ADHERENCE AT EACH VISIT** - Up to 90% of patients don't use devices correctly
- **SHORT-ACTING RELIEVER MEDICATION:** salbutamol or terbutaline or ipratropium bromide
- **SYMPTOM RELIEF**: Long-acting muscarinic antagonist (LAMA: tiotropium bromide, glycopyrronium bromide or aclidinium bromide) and/or long-acting $beta_2$agonist (LABA: salmeterol, eformoterol or indacaterol). **This may also help to prevent exacerbations. **SEE PRECAUTIONS[1-4]****
- **EXACERBATION PREVENTION:** (When FEV_1 < 50% predicted AND patient has had 2 or more exacerbations in the previous 12 months) commence inhaled corticosteroid (ICS)/LABA combination therapy (fluticasone propionate/salmeterol or budesonide/eformoterol). ****SEE PRECAUTIONS[5]****
- Consider low dose theophylline

Based on COPD-X Plan: Australian and New Zealand Guidelines for the Management of COPD; Australian Therapeutic Guidelines.

SEPTEMBER 2014

[1] Indacaterol (a monotherapy LABA) should not be used in asthma or on its own in Asthma-COPD overlap.
[2] Once a LAMA is commenced, ipratropium bromide (a SAMA) should be discontinued.
[3] Care should be taken to ensure that the addition of LABA/LAMA combination therapies do not result in excess doses. Refer to Table 1 on reverse.
[4] An assessment should be undertaken to exclude asthma or Asthma-COPD Overlap before initiating LABA monotherapy.
[5] LABA monotherapy should be ceased once ICS/LABA combination therapy is initiated.

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Japan COPD Treatment Guideline-3rd

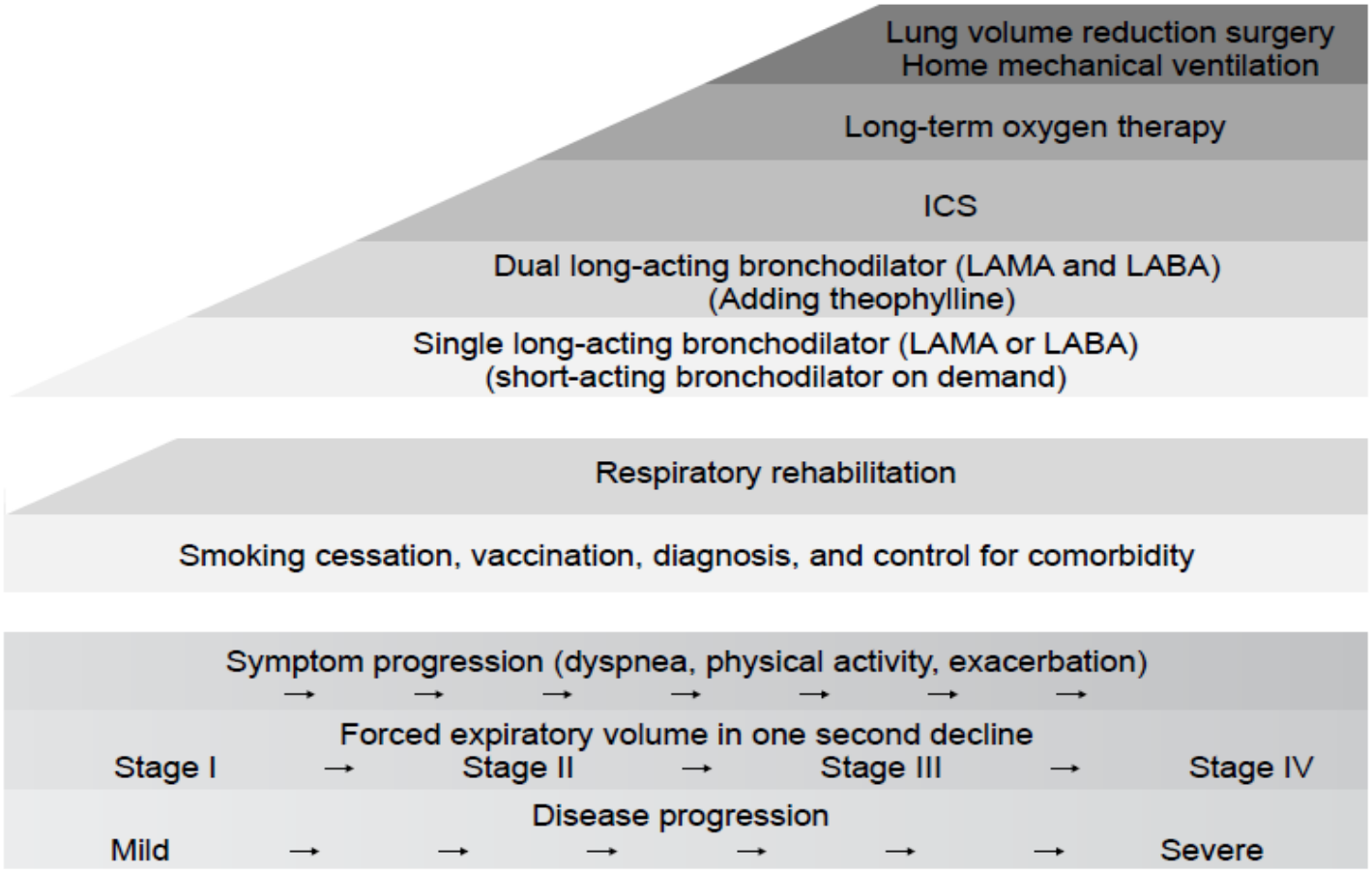
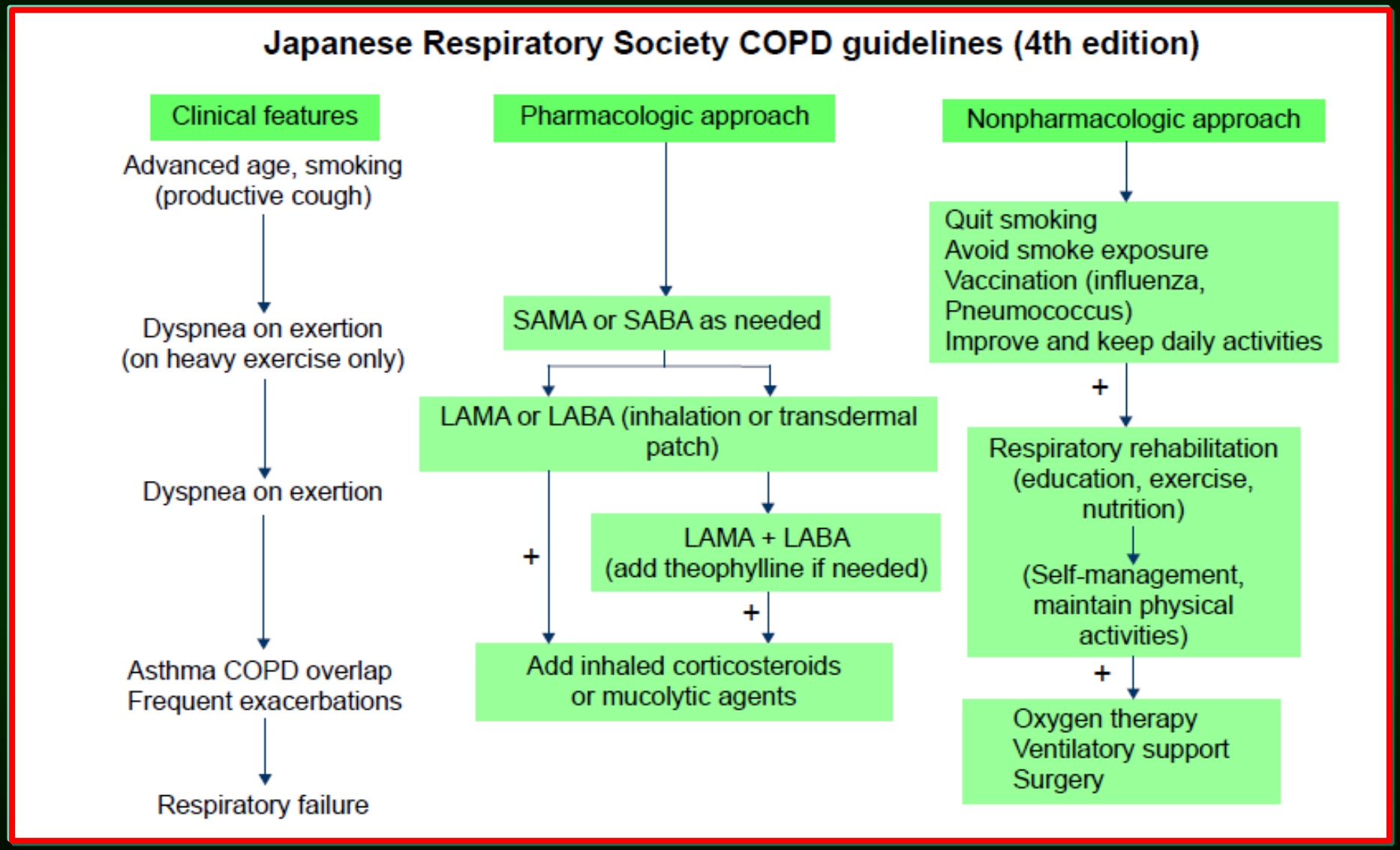


Figure 2 Stepwise approach recommended by the fourth edition of Japanese Respiratory Society COPD guidelines.
Notes: Copyright ©2013 The Japanese Respiratory Society. Adapted from Fourth Edition of the Japanese Respiratory Society COPD Guideline for Diagnosis and Treatment. Tokyo, Japan: The Japanese Respiratory Society; 2013. Japanese.[36] Arrows indicate disease progression.
Abbreviations: LAMA, long-acting muscarinic antagonist; LABA, long-acting beta agonist; ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease.

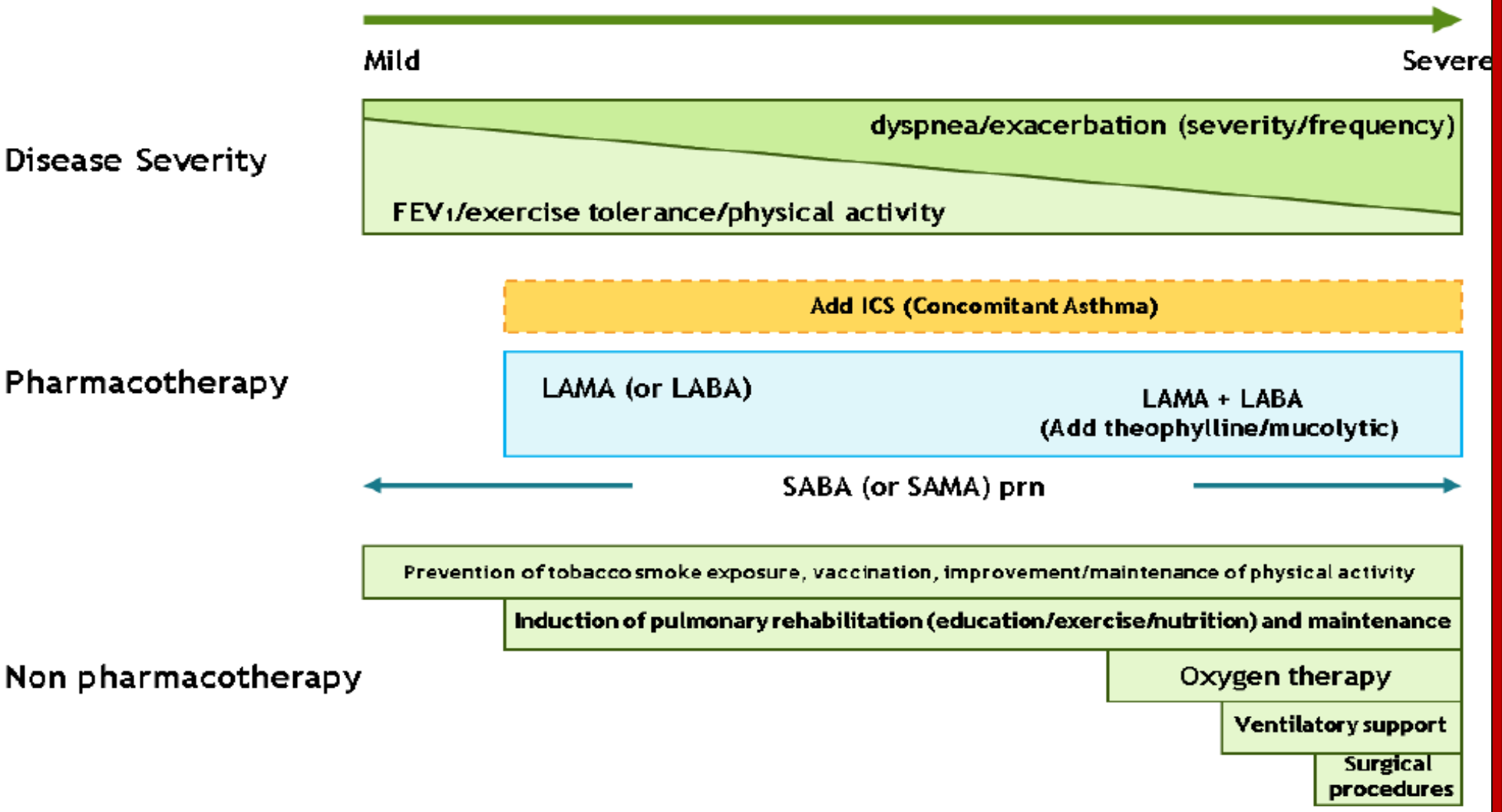
International Journal of COPD. 2015; 10: 813-822

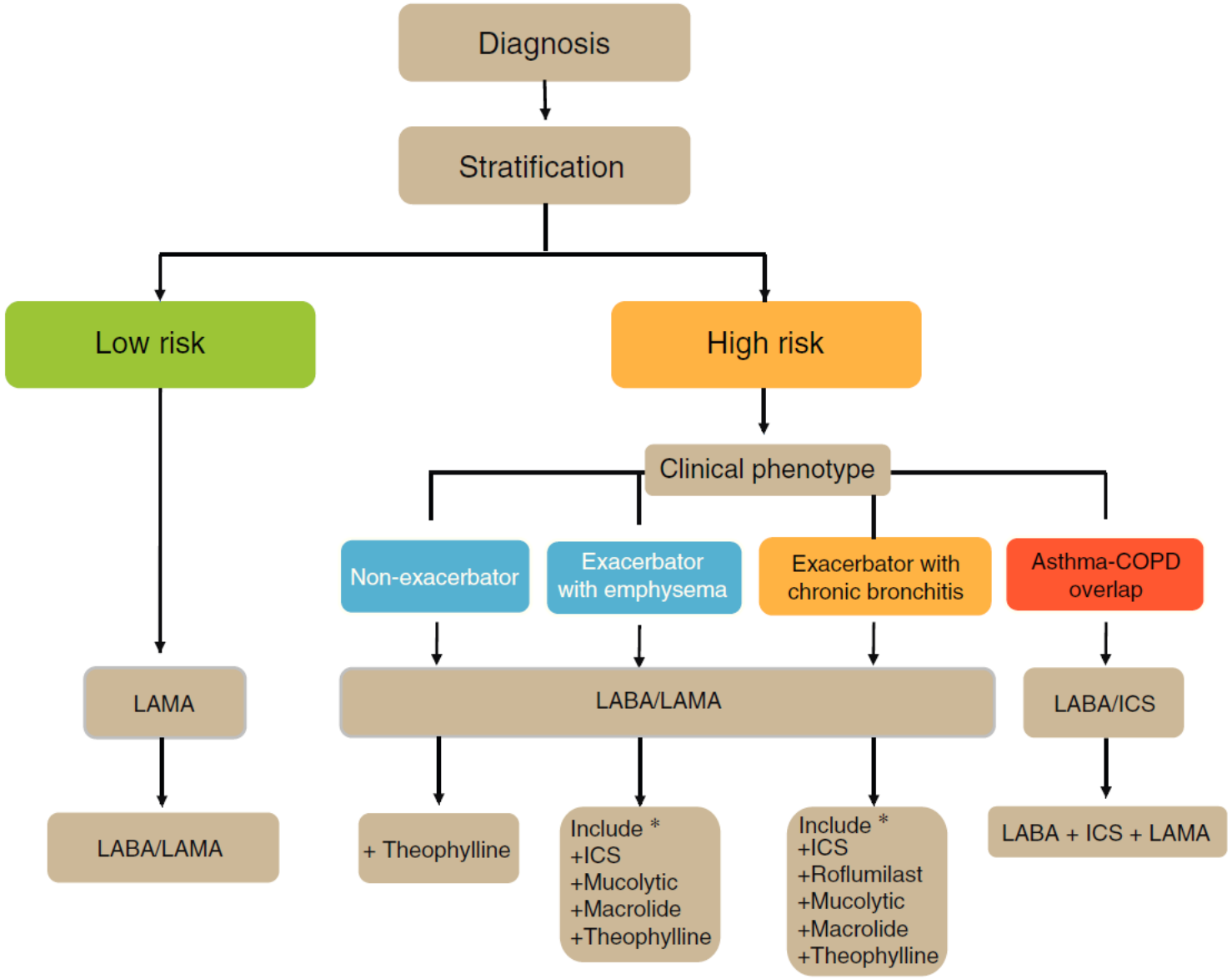
Japan COPD Treatment Guideline-4th



International Journal of COPD. 2015; 10: 1093-1102

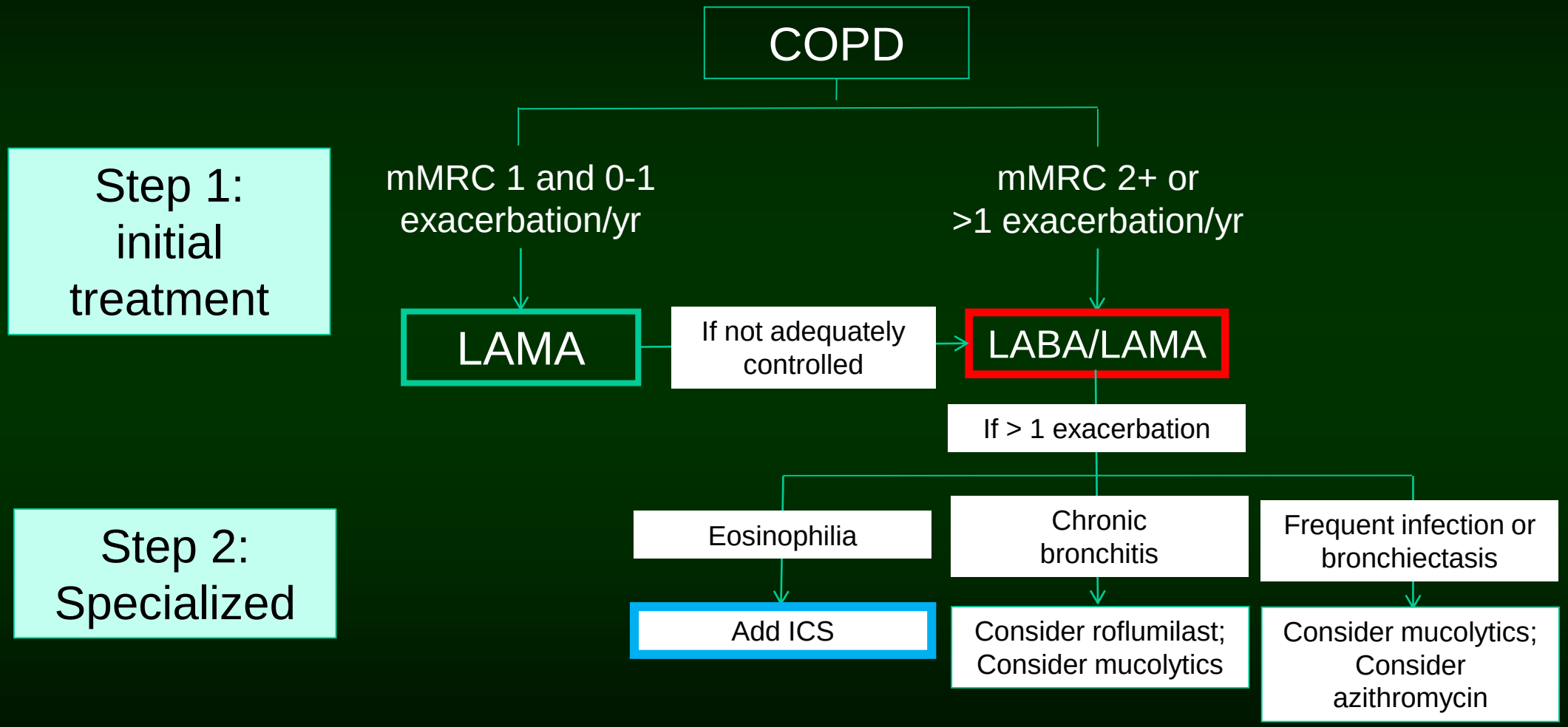
Japan COPD Treatment Guideline-5th (2018)





Arch Bronconeumol 2017 Jun;53(6):324-335.

A simplified two-step algorithm for the treatment of COPD



Miravitlles M, Anzueto A. A new two-step algorithm for the treatment of COPD. Eur Respir J 2017

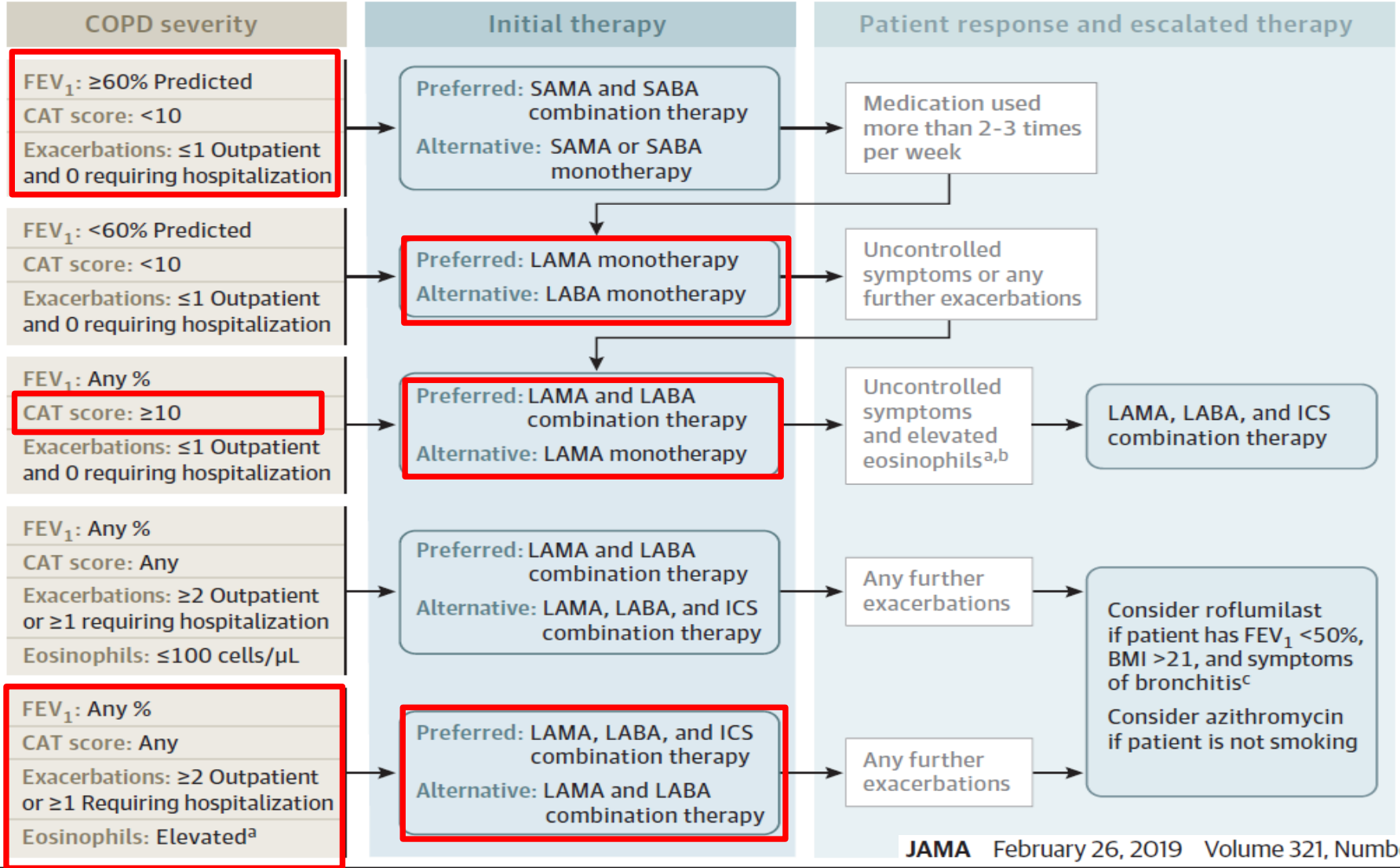
COPD Management Suggestion

JAMA | Review

Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease
A Review

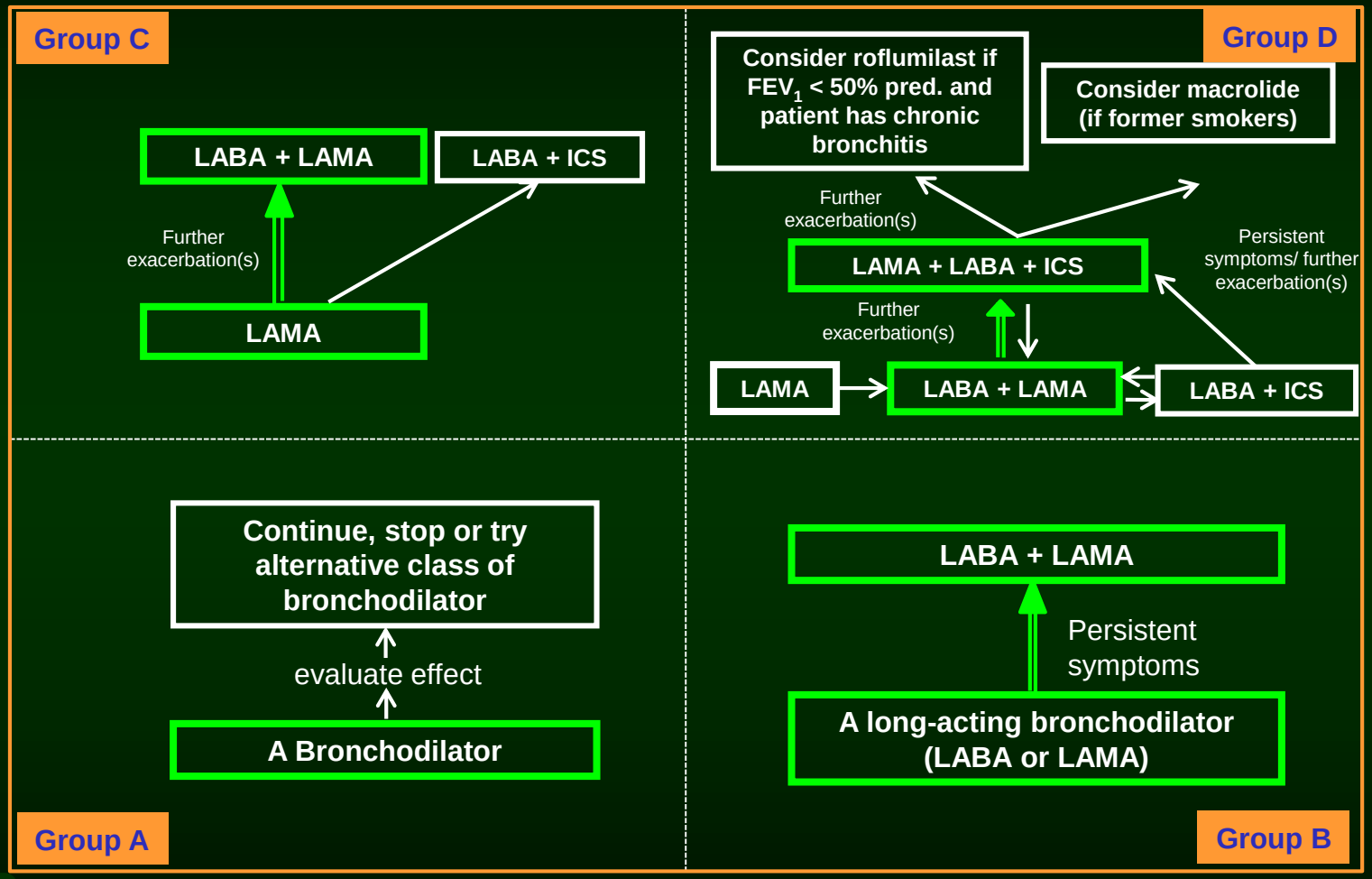
Craig M. Riley, MD; Frank C. Sciurba, MD

Figure 2. Medical Treatment Algorithm for Chronic Obstructive Pulmonary Disease



TW1904994904

Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted

GOLD. 2017

INITIAL PHARMACOLOGICAL TREATMENT

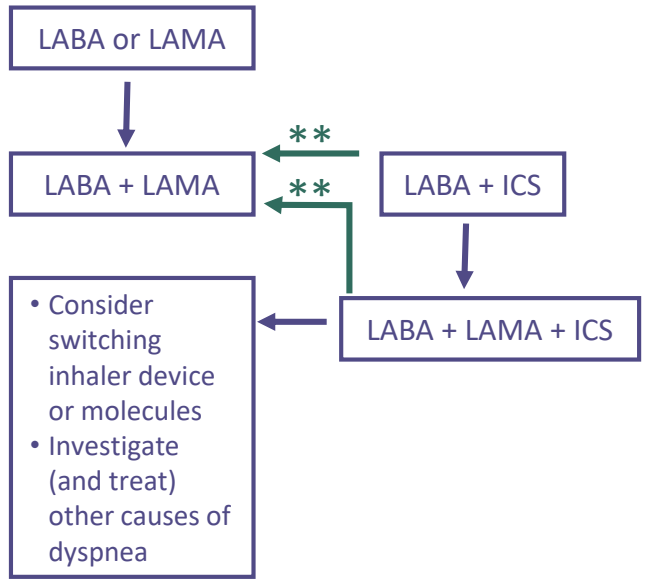
≥2moderate exacerbations or ≥1 leading to hospitalization	Group C **LAMA**	Group D LAMA or LAMA+LABA* or ICS+ LABA** * Consider if highly symptomatic (e.g. CAT >20) ** Consider if eos ≥300
0 or 1 moderate exacerbations (no leading to hospital admission)	Group A **A Bronchodilator**	Group B **A Long Acting Bronchodilator (LABA or LAMA)**
	mMRC 0-1 CAT <10	mMRC ≥2 CAT ≥ 10

GOLD guideline 2019-2020

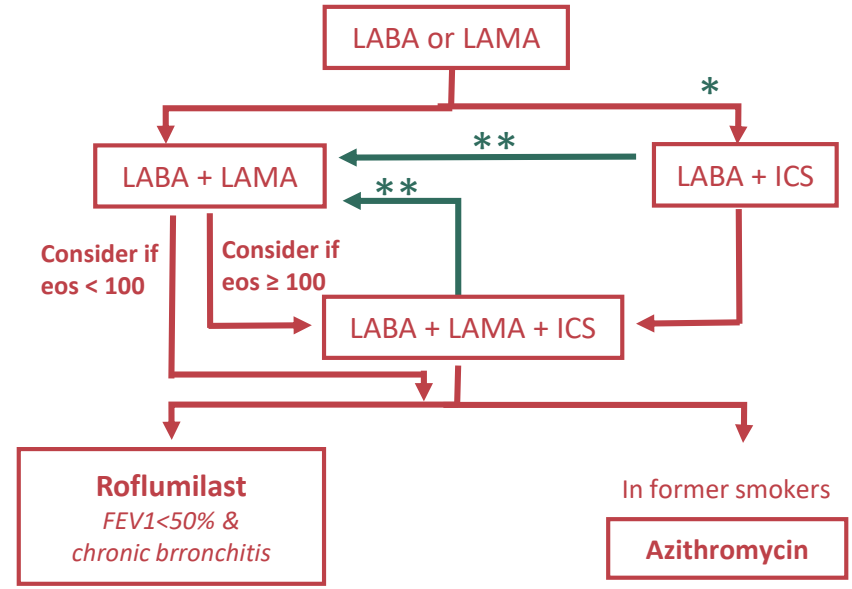
FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target(dyspnea or exacerbations)
     - – Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCE assessment at diagnosis

• DYSPNEA •



• EXACERBATIONS •

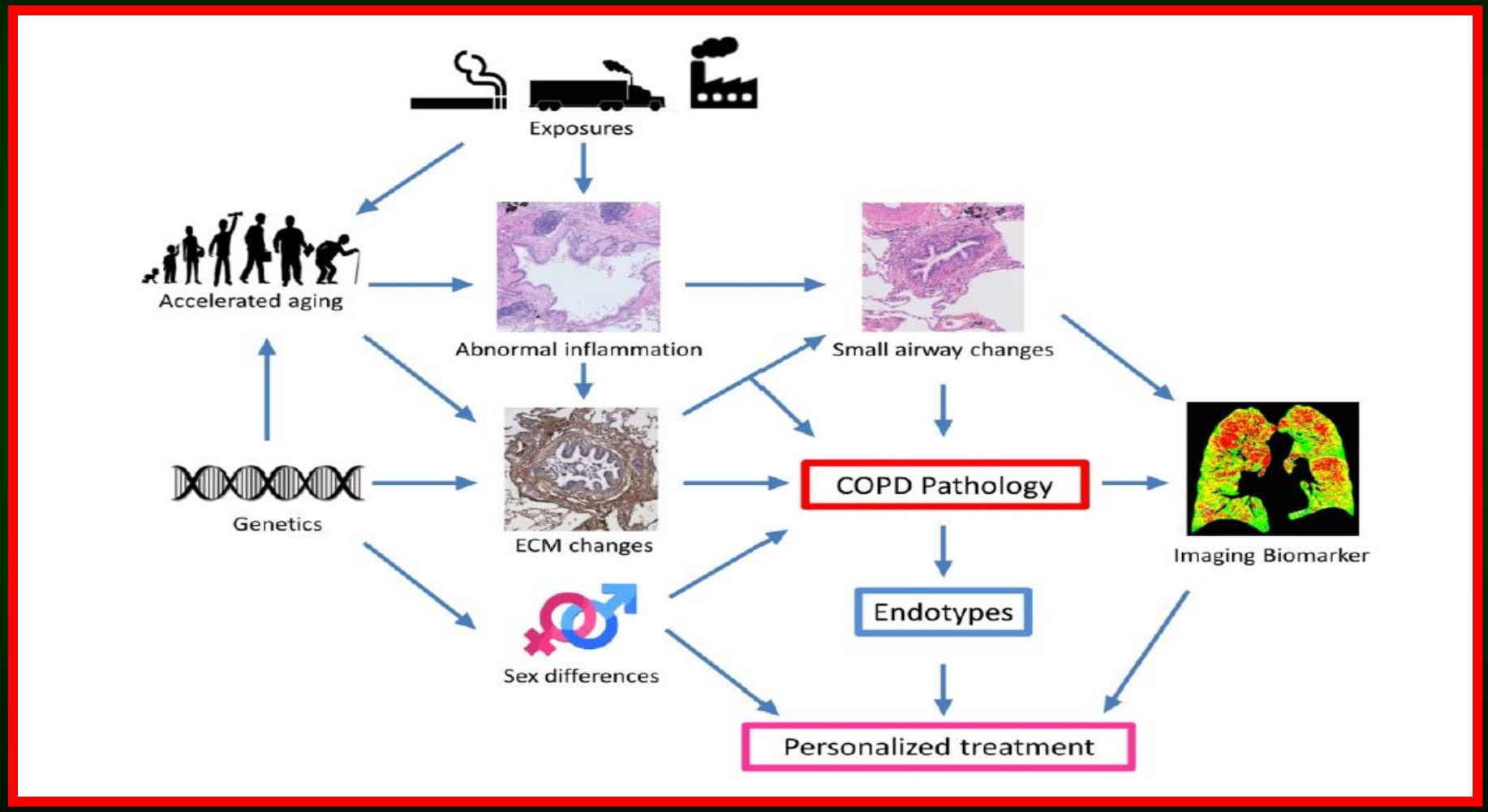


Eos = blood eosinophil count (cells/µL)

****Consider if eos ≥300 or eos ≥100 AND ≥ moderate exacerbations / 1 hospitalization***

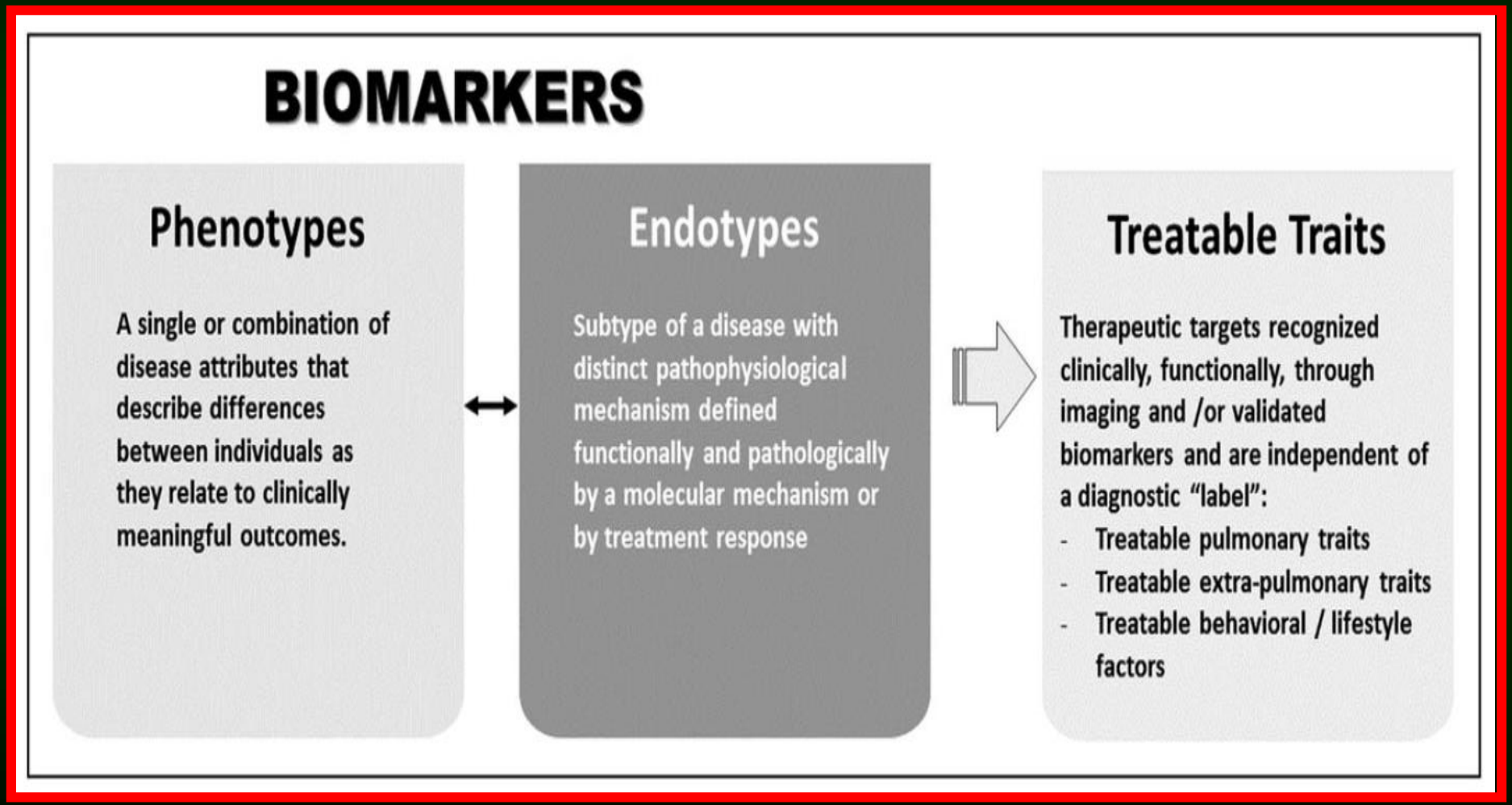
***** Consider de-escalation of ICS or switch if pneumonia, in appropriate original indication or lack of response to ICS***

Recent advances in COPD pathogenesis: from disease mechanisms to precision medicine



J Pathol. 2019 Nov 5. doi: 10.1002

Precision medicine and treatable traits in chronic airway diseases



Curr Opin Pulm Med. 2019 Oct 21. doi: 10.1097

Treatable traits for "heterogenous" COPD

Behavioural

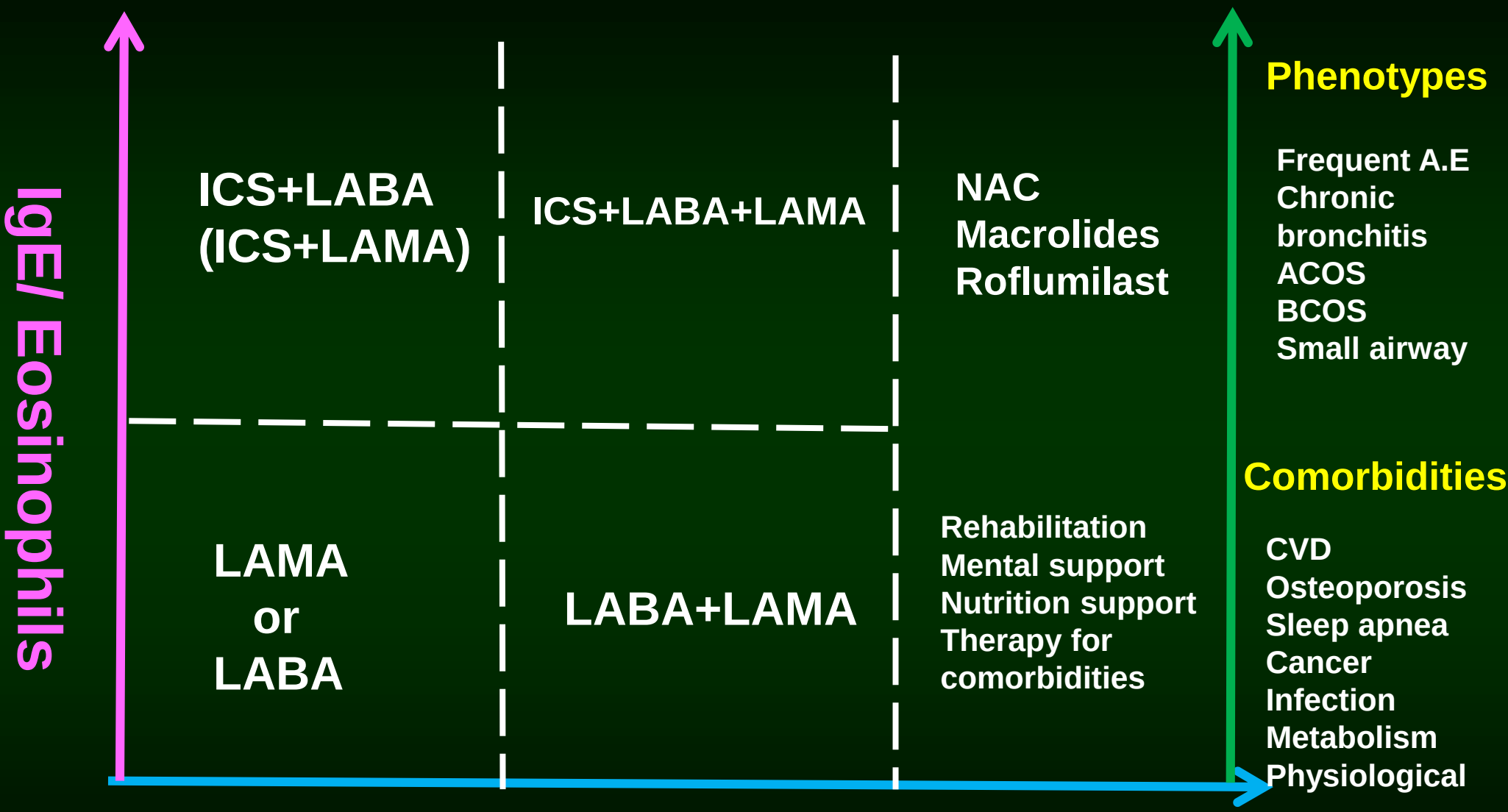
- Symptom perception
- Inhaler device polypharmacy
- Adherence to treatment
- Poor inhaler technique
- Family and social support

Exposure to sensitizing agents

Family and social support

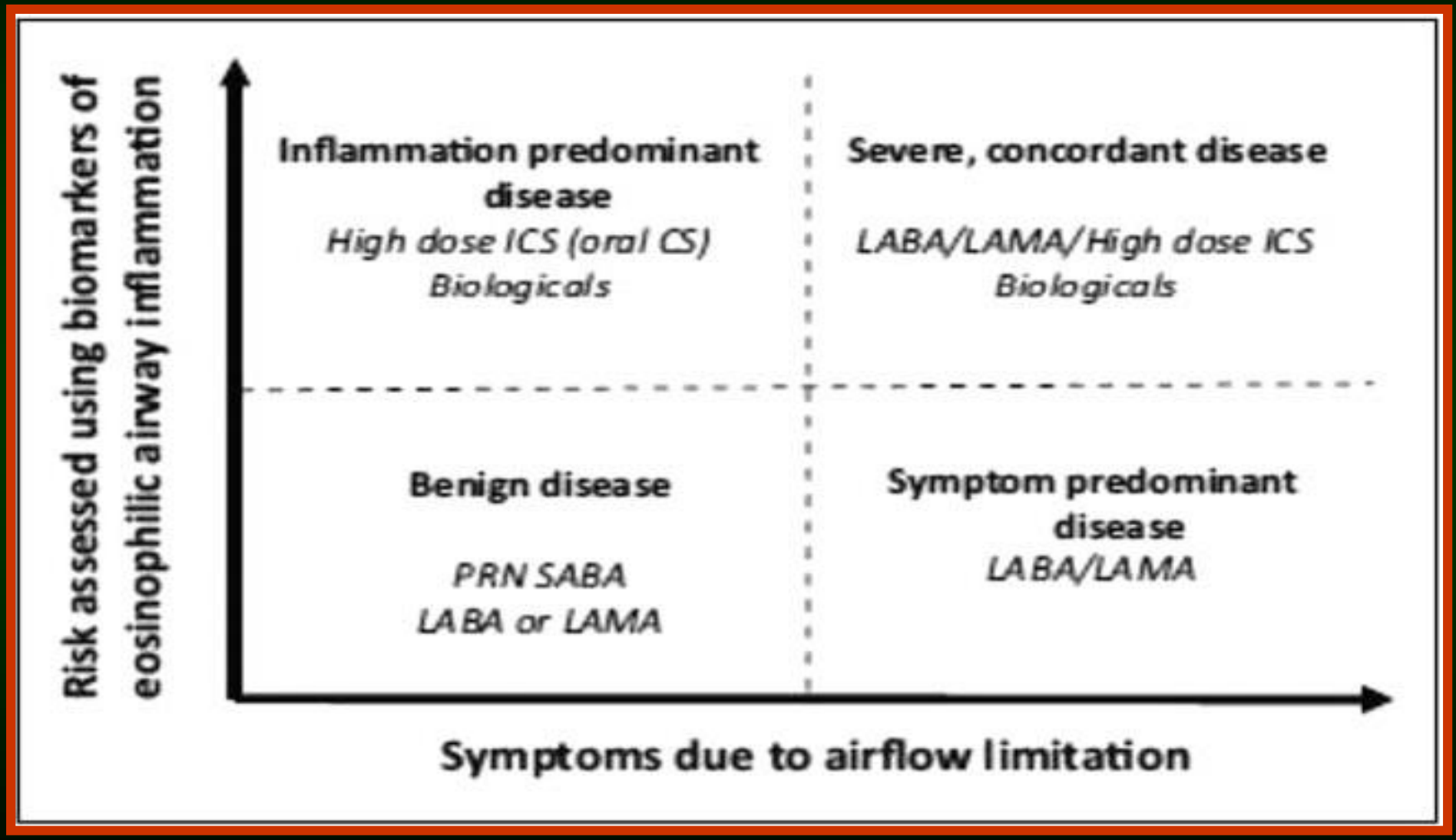
Agusti A, et al. Eur Respir J 2016; 47:410–419.

COPD: Guiding treatment choice in clinical practice



Cheng SL. et al. Int J Chron Obstruct Pulmon Dis. 2017 Jul 31;12: 2231-2238

The two major treatable traits in patients with airways disease, eosinophilic inflammation and airflow limitation



Clin Sci (Lond). 2017 May 1;131(10):1027-1043

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.

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High eosinophil counts in COPD with frequent A.E.

34%

	Eosinophil≥3% (HE, n=85)	Eosinophil<3% (LE, n=163)	p level
Age	68.7±19.2	70.5±21.4	0.46
Sex (M/F)	69/16	143/20	0.75
Smoking (pack-years)	27.4 ± 16.5	29.1 ± 19.3	0.52
A.E. (>1 admission)*	23 (27.1%)	12 (7.4%)	0.01*
Lung Function test			
Bronchodilator test respond (+)	19 (22.2%)	24 (14.5%)	0.08
Mild obstructive (%)	0	12 (7.4%)	0.31
Moderate obstructive (%)	45 (52.9%)	92 (56.4%)	
Severe obstructive (%)	29 (34.1%)	41 (25.2%)	
Very severe obstructive (%)	11 (12.9%)	18 (11.0%)	
FEV1(L) (% of predicted)	1.29 (50.3)	1.32 (52.5)	0.32
FVC (L) (% of predicted)	2.36 (60.4)	2.45 (61.7)	0.41
FEV1/FVC (% of predicted)	48.1 ± 20.3	50.6 ± 22.9	0.14
FEV1 reversibility (%)	8.3 ± 5.1	9.7 ± 7.4	0.44
CAT baseline	18 ± 6	19 ± 7	0.37
Medications			
Higher ICS/LABA (HD)	42 (49.4%)	82 (50.3%)	0.39
Medium ICS/LABA (MD)	43 (50.6%)	81 (49.7%)	
Comorbidity			
HTN	19 (22.4%)	31 (19.0%)	0.26
DM	14 (16.7%)	26 (15.9%)	
CAD	7 (8.2%)	16 (9.8%)	
CHF	9 (10.6%)	28 (17.2%)	

*A.E.: acute exacerbation with hospitalization in a previous one year

Cheng SL, *et al. Int J Chron Obstruct Pulmon Dis. 2016. 11: 2341-2348.*

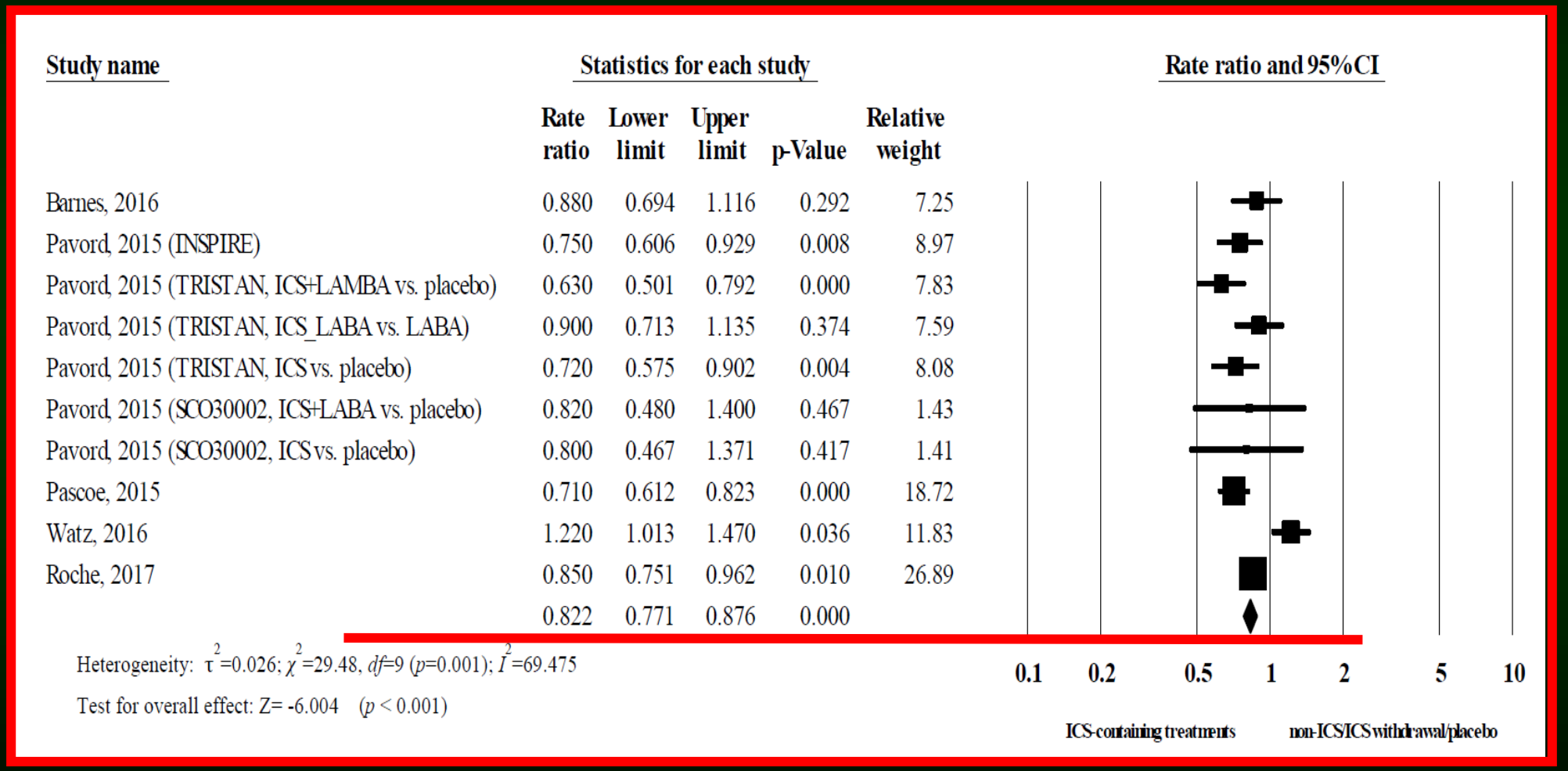
High Eosinophils and ICS response in COPD

Table 2 Treatment effectiveness in COPD patients with allergic phenotypes

	HEE (n=85)	*P*-value	HEO (n=51)	*P*-value	HIE (n=47)	*P*-value
Lung function FEV_1 (mL)		<0.008*		0.072		0.129
ICS-based therapy†	132.4±28.8		115.5±30.9		119.8±31.4	
BD-based therapy†	85.7±24.2		96.1±28.7		97.4±32.7	
Lung function FVC (mL)		<0.007*		0.141		0.352
ICS-based therapy	141.1±39.6		119.9±42.3		123.8±40.7	
BD-based therapy	105.8±41.7		124.6±39.7		126.6±44.1	
COPD Assessment Test		0.042*		0.032*		0.416
ICS-based therapy	8±5		7±6		9±7	
BD-based therapy	12±7		13±9		11±8	
Acute exacerbation (>1 hospitalization)		<0.008*		0.245		0.475
ICS-based therapy	10 (11.7%)		7 (13.6%)		6 (13.4%)	
BD-based therapy	21 (24.1%)		10 (19.8%)		10 (20.3%)	

Cheng SL. et al. Int J Chron Obstruct Pulmon Dis. 2017 Jul 31;12:2231-2238

High eosinophil counts (>2%) COPD patients with ICS therapy: systemic review and Meta-analysis



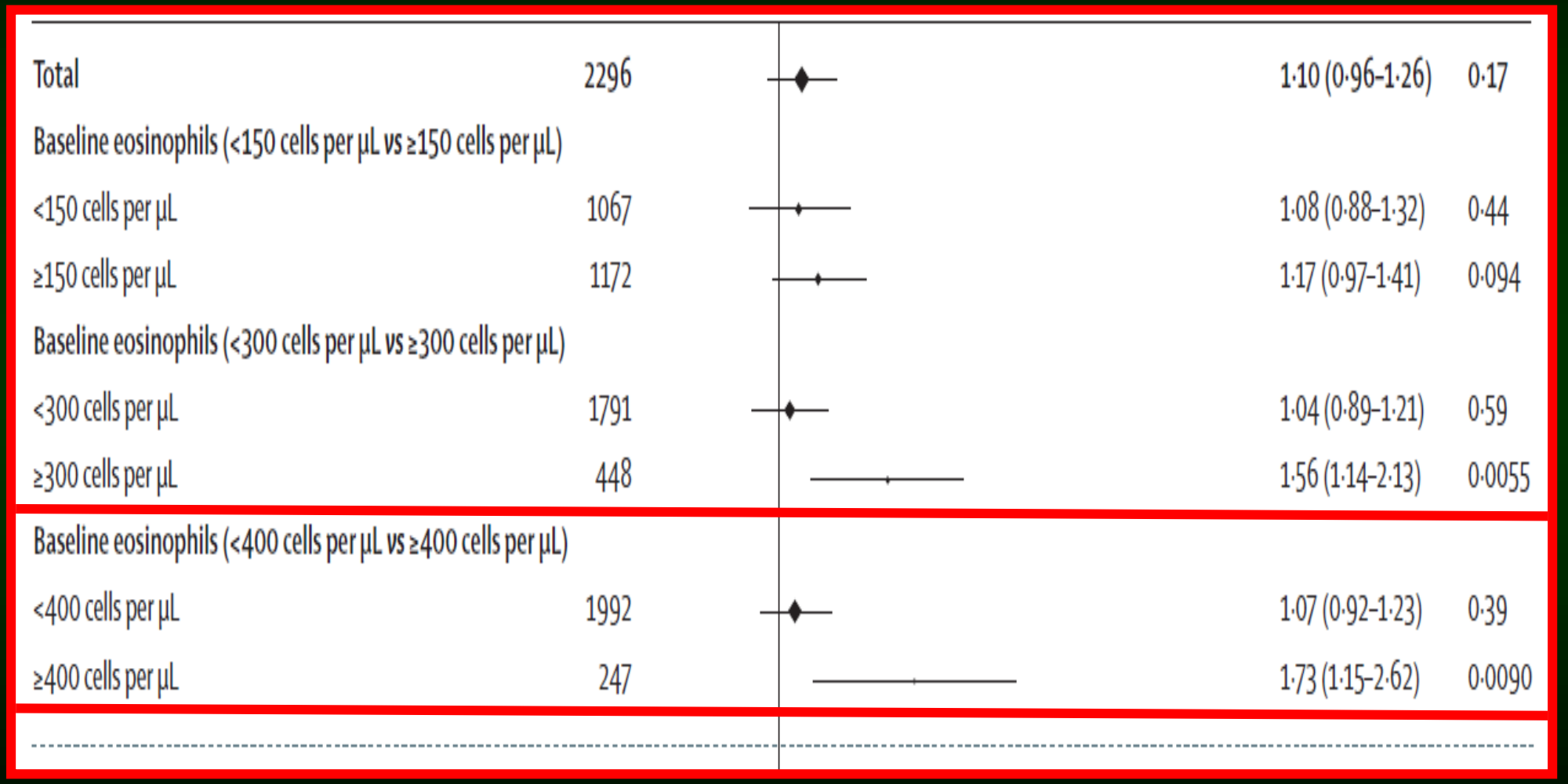
Cheng SL. Int J Chron Obstruct Pulmon Dis. 2018 Sep 6;13:2775-2784

Initial Treatment with LAMA or ICS/LABA in COPD in UK Cohort Study

	Number of patients	Number with events	Person-years	Rate per 100 per year	Crude* HR	Adjusted† HR (95% CI)
Moderate or severe exacerbation						
LABA-ICS	12 366	2307	4354	53·0	1·02	0·95 (0·90–1·01)
LAMA	12 366	2339	4646	50·3	1·00	1·00 (ref)
Stratified by eosinophil concentration						
<2%						
LABA-ICS	4009	808	1404	57·6	1·09	1·03 (0·93–1·13)
LAMA	4231	823	1610	51·1	1·00	1·00 (ref)
2–4%						
LABA-ICS	5156	934	1821	51·3	1·09	1·00 (0·91–1·10)
LAMA	5143	896	1968	45·5	1·00	1·00 (ref)
>4%						
LABA-ICS	3201	565	1129	50·0	0·85	0·79 (0·70–0·88)
LAMA	2992	620	1068	58·1	1·00	1·00 (ref)

Lancet Respir Med. 2018 Oct 17. pii: S2213-2600(18)30368-0

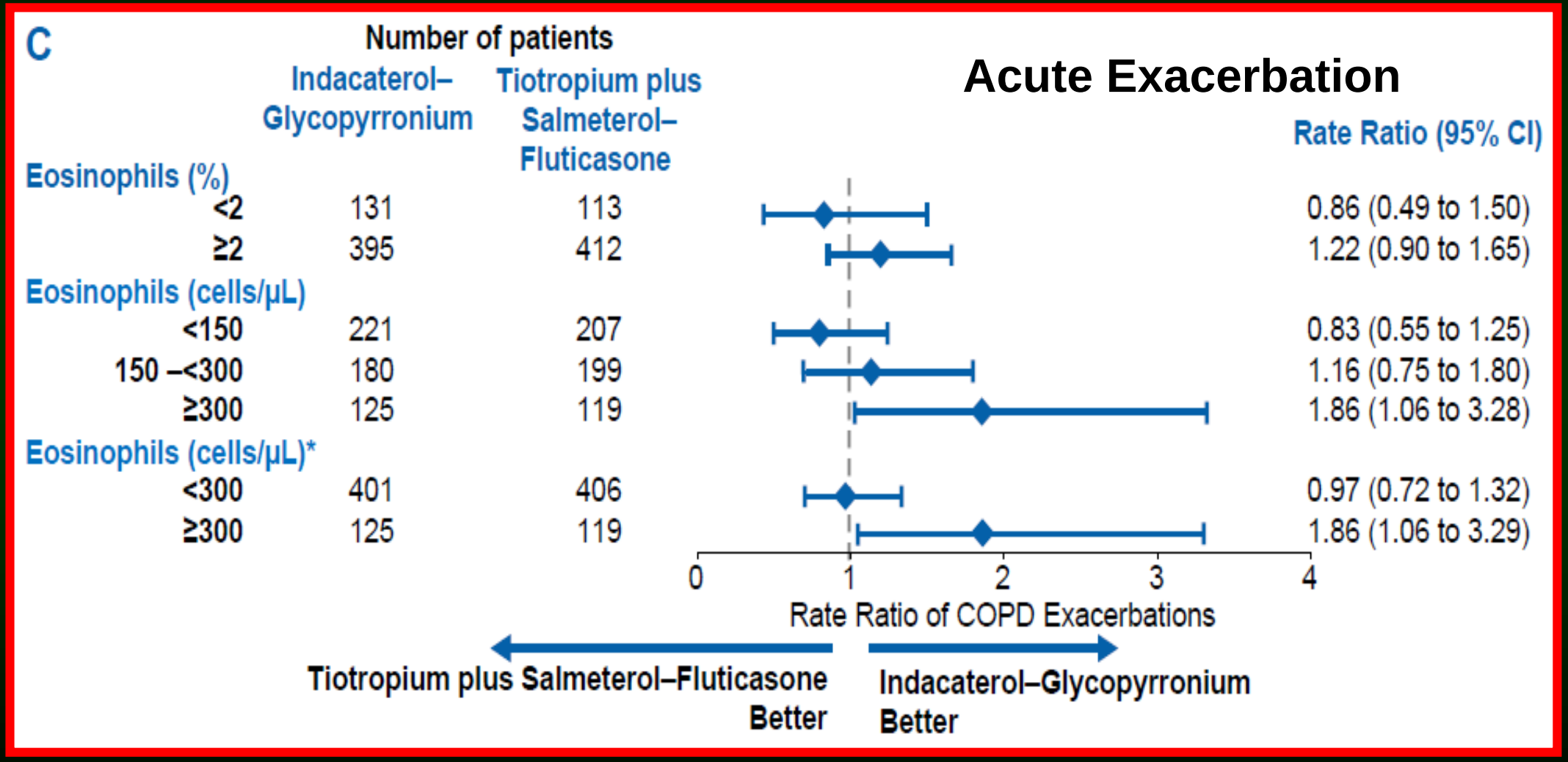
Risk for A.E on ICS withdrawal by eosinophils sub-group-WISDOM study



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

Lancet Respir Med. 2016 May;4(5):390-8

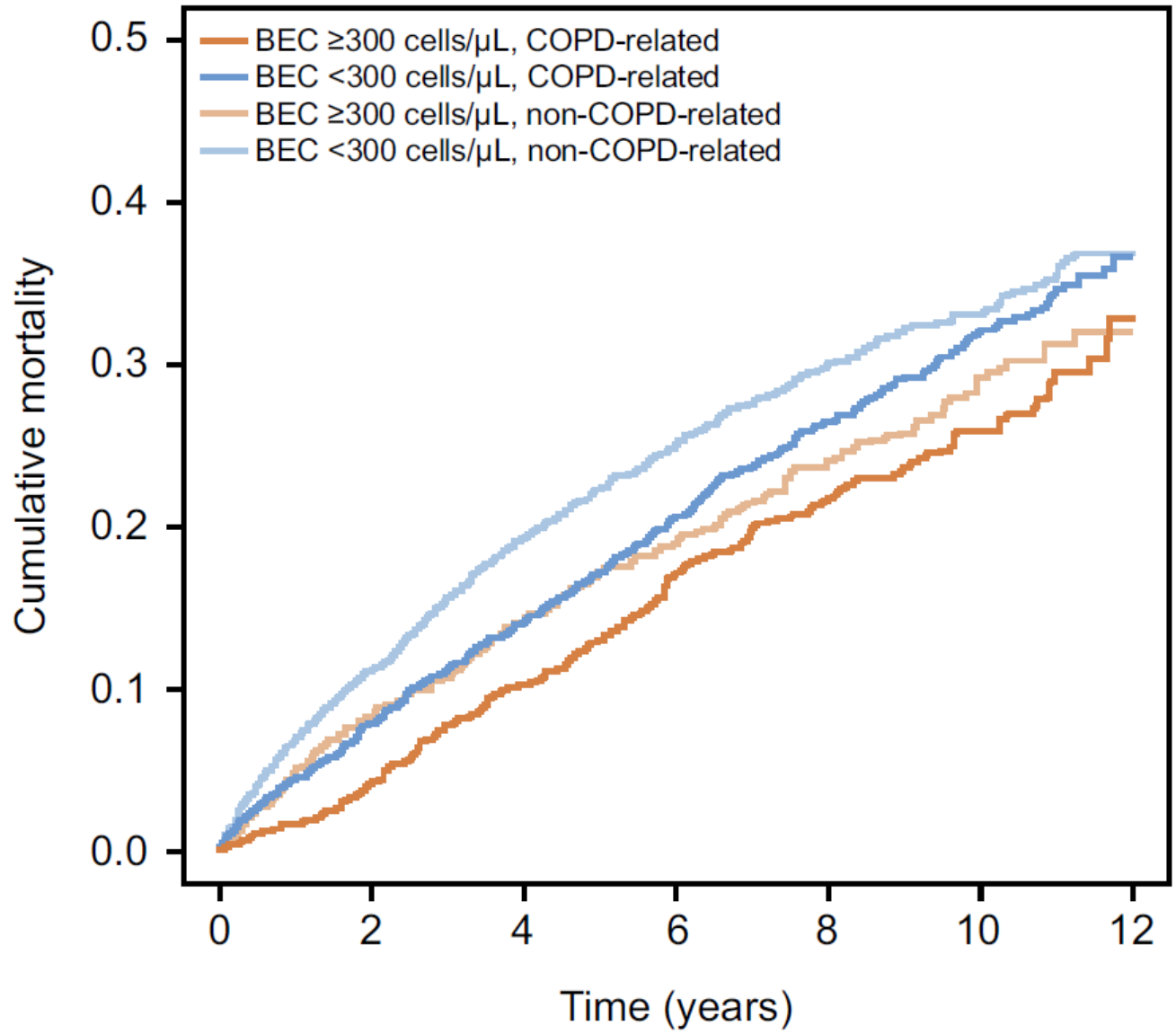
Long-term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in COPD Patients (SUNSET) Trial



Am J Respir Crit Care Med. 2018 May 20.

D

COPD- and non-COPD-related mortality by blood eosinophil count[b]



Model 1

	% CI)	p value
Severe		<0.01
Clinically		<0.01
Age		<0.01
Female		<0.01
BEC ≥3		<0.01
BEC unk		0.92

B

Model 2

	% CI)	p value
Severe		<0.01
Clinically		<0.01
Age		<0.01
Female		<0.01
BMI		<0.01
Charlson		<0.01
BEC ≥3		0.04
BEC unk		0.03
FEV_1/FV		0.04
Current		<0.01

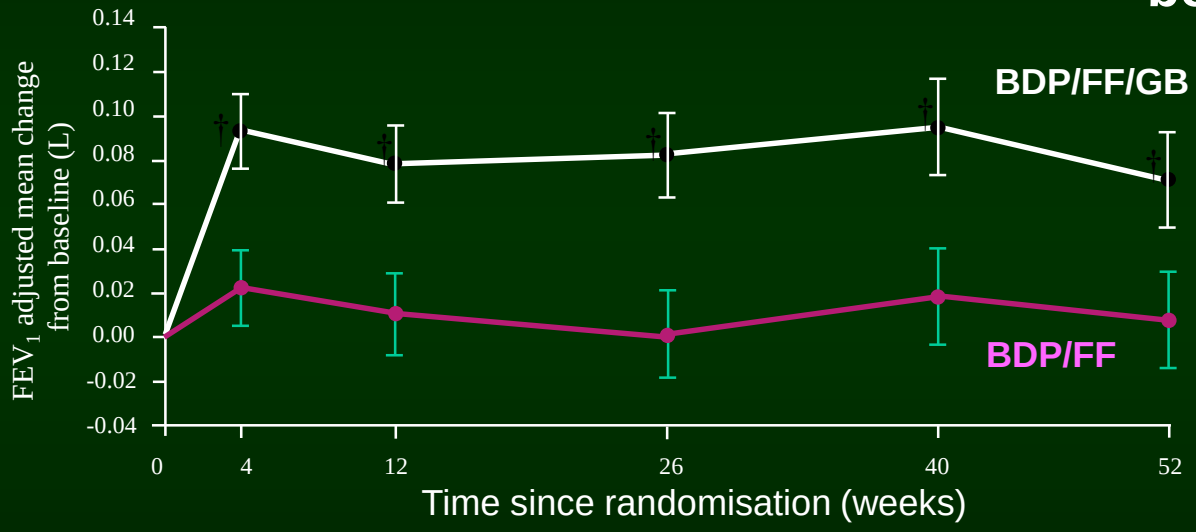
5;14:2409-2421.

Role of Triple therapy

- A double-blind, parallel group, RCT reported that treatment with extrafine fixed triple therapy had clinical benefits compared with tiotropium in patients with symptomatic COPD, FEV1 <50%, and a history of exacerbations. (TRINITY trial)
- Another double-blind RCT reported benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD. (TRILOGY; IMPACT trial)
- Double-blind RCT reported benefits of single inhaler triple therapy compared with LABA/LAMA (TRIBUTE)

GOLD 2020 guideline

Triple therapy resulted in lung function improvement (pre-dose FEV_1): TRILOGY study



Adjusted mean difference between BDP/FF/GB vs BDP/FF

Week 26

81 mL

95% CI 0.052-0.109
$p < 0.001$

Week 52

63 mL

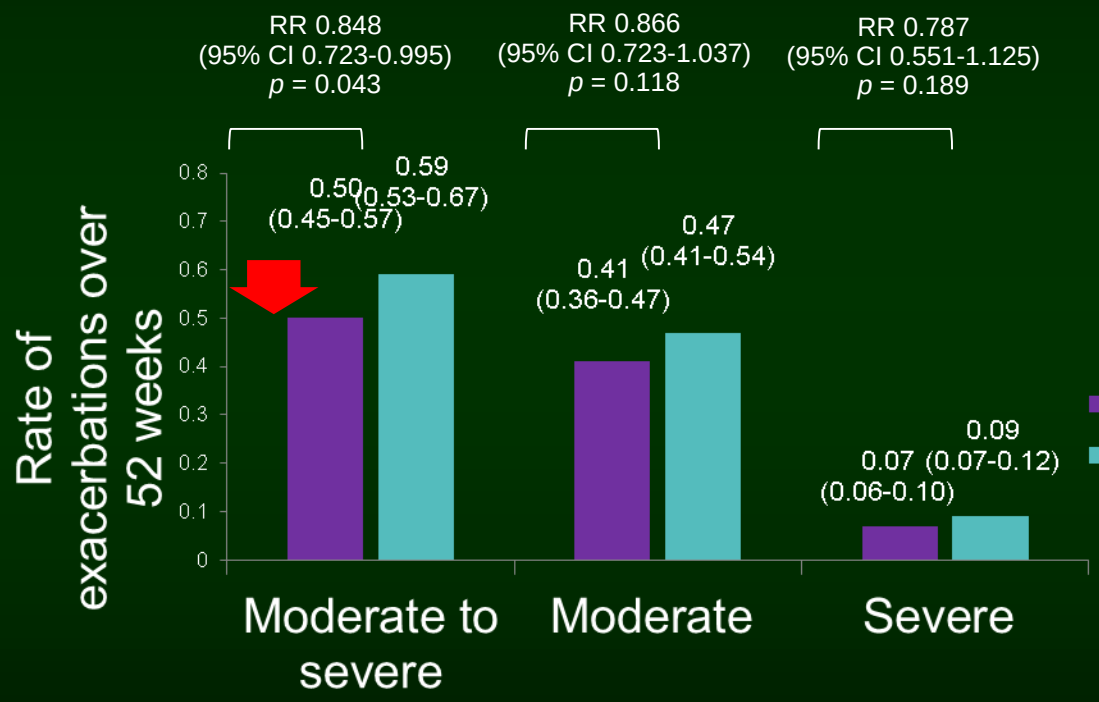
95% CI 0.032-0.94
$p < 0.001$

†p < 0.001 for the difference between BDP/FF/GB and BDP/FF.

FEV_1: forced expiratory volume in 1 second; BDP: beclomethasone dipropionate; FF: formoterol fumarate; GB: glycopyrronium bromide; h: hour; CI: confidence interval.

Singh D, et al. Lancet 2016;388:963-73.

Triple therapy resulted in moderate-to-severe exacerbations reduction: TRIBUTE study



BDP/FF/G vs. IND/GLY
Moderate-to-severe exacerbations

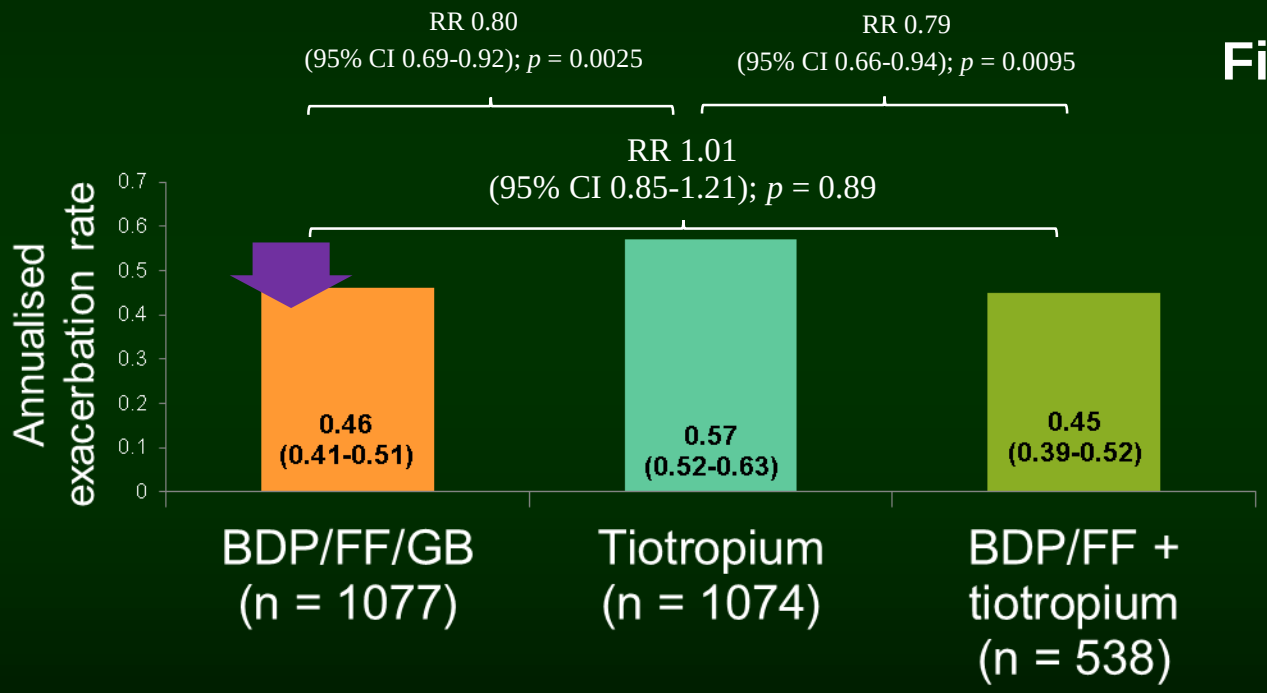
15%

RR 0.848
(95% CI 0.723-0.995)
p = 0.043

BDP: beclometasone dipropionate; FF: formoterol fumarate; G: glycopyrronium; IND: indacaterol; GLY: glycopyrronium; RR: rate ratio; CI: confidence interval.

Papi A, et al. Lancet 2018;391:1076–84.

Triple therapy resulted in moderate-to-severe exacerbations reduction: TRINITY study



Fixed Triple vs tiotropium

Moderate-to-severe exacerbations

20%

RR 0.80
(95% CI 0.69-0.92)
p = 0·0025

RR: rate ratio; CI: confidence interval; BDP: beclometasone dipropionate; FF: formoterol fumarate; GB: glycopyrronium bromide.

Vestbo J, et al. Lancet 2017;389(10082):1919-29.

Triple therapy resulted in a lower rate of moderate or severe COPD exacerbations: IMPACT study

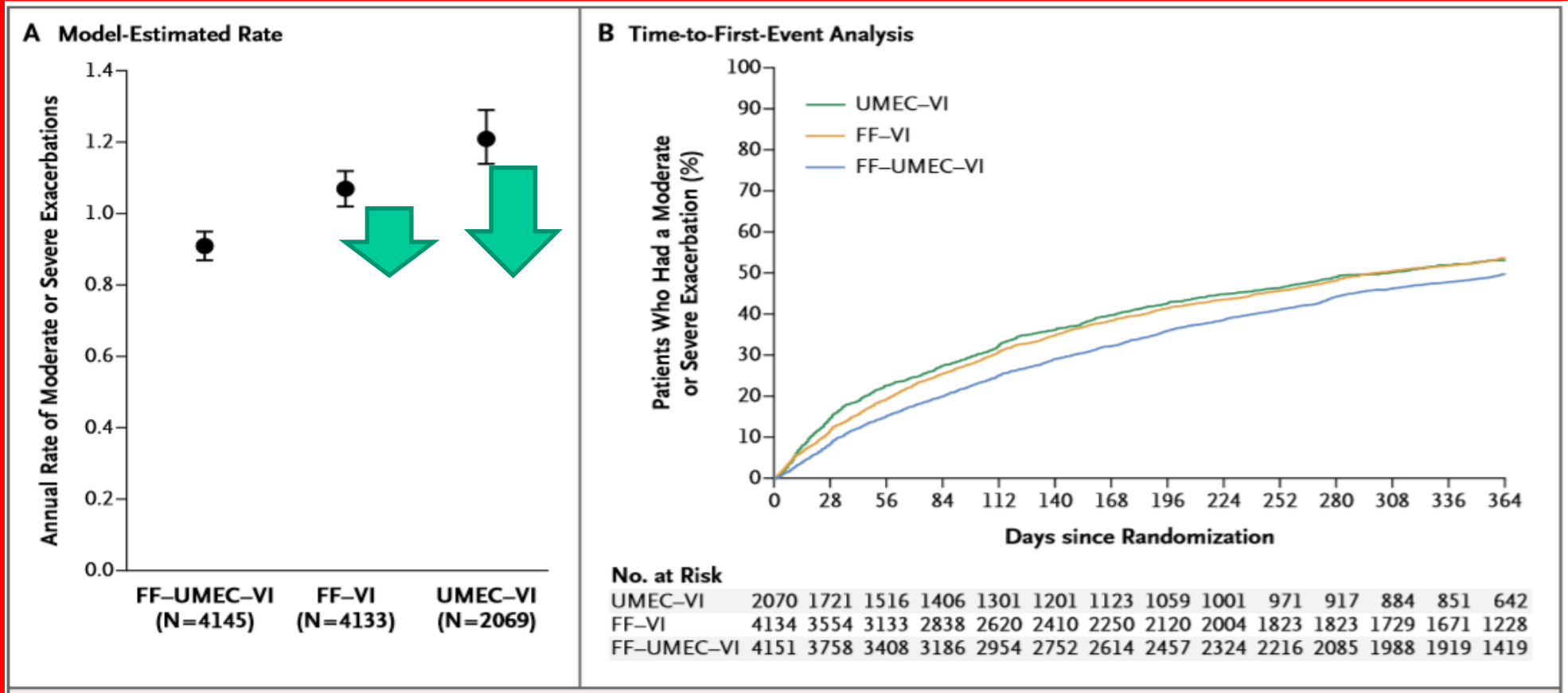


Figure 1. Moderate or Severe COPD Exacerbations (Intention-to-Treat Population).

IMPACT- N Engl J Med 2018;378:1671-80

BDP/FF/GLY (Triple)>IND/GLY(Dual)

Triple better than dual BD Significant benefits in

1. **Chronic bronchitis** (0·752, 0·605–0·935, p=0·010),
2. **Eosinophils > 2% (0·806, 0·664–0·978; p=0·029),**

TRIBUTE trial

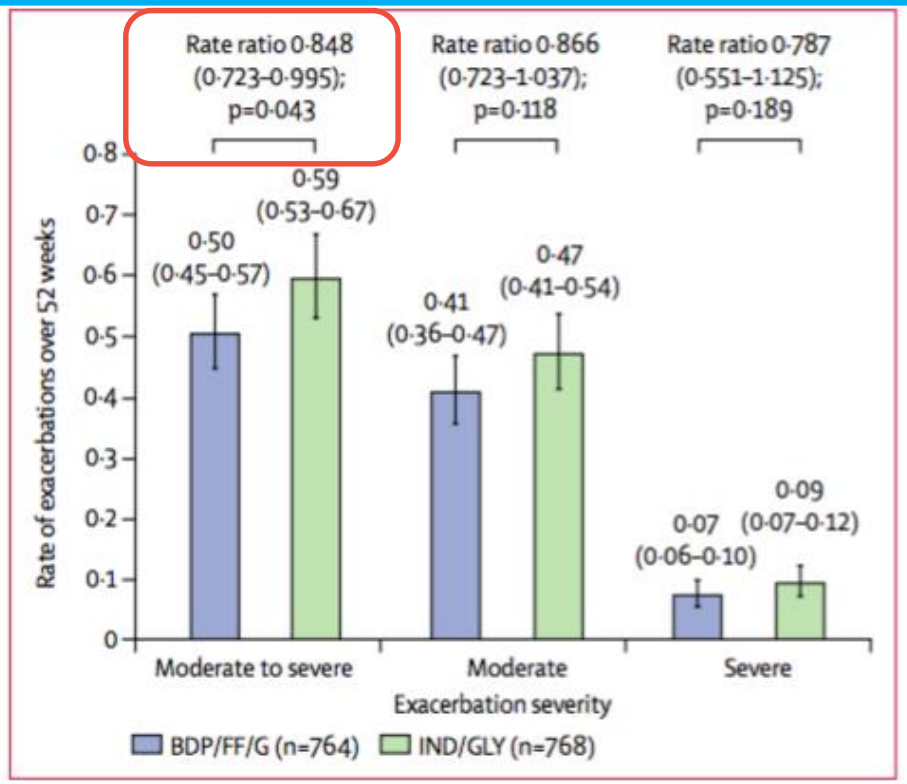
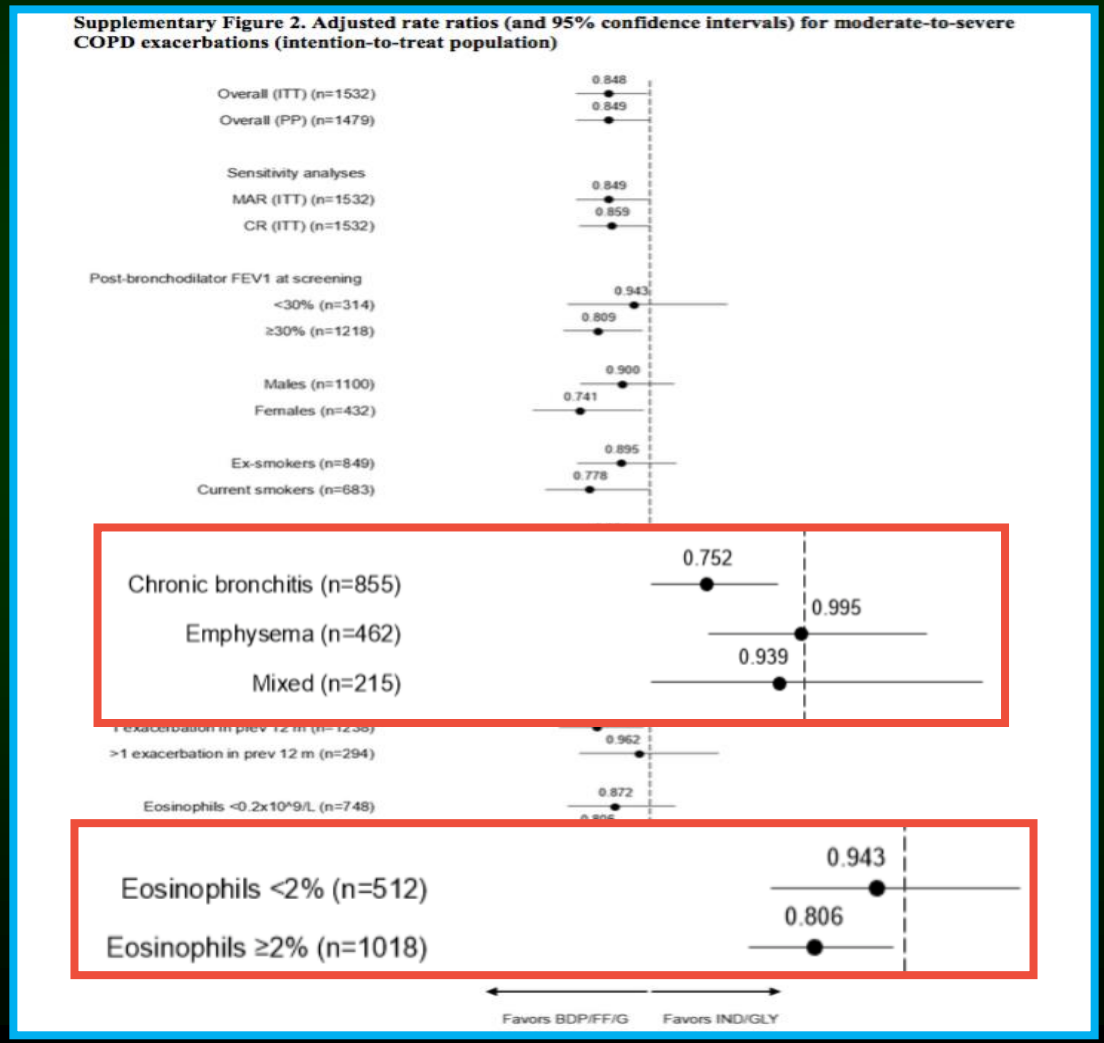


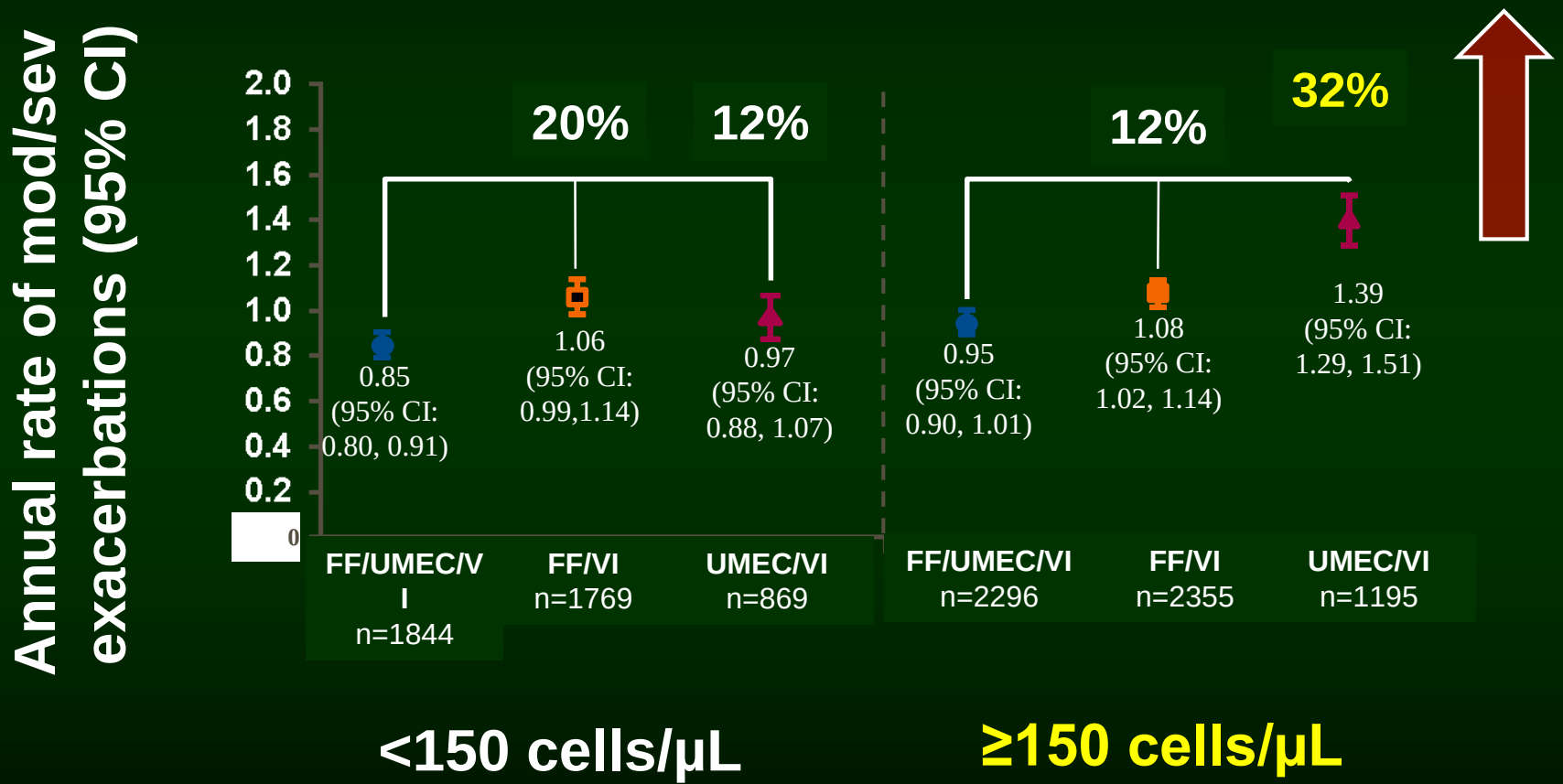
Figure 2: **Adjusted rate of moderate-to-severe, moderate, and severe COPD exacerbations**



The Lancet Vol 391, No. 10125, 17 March 2018

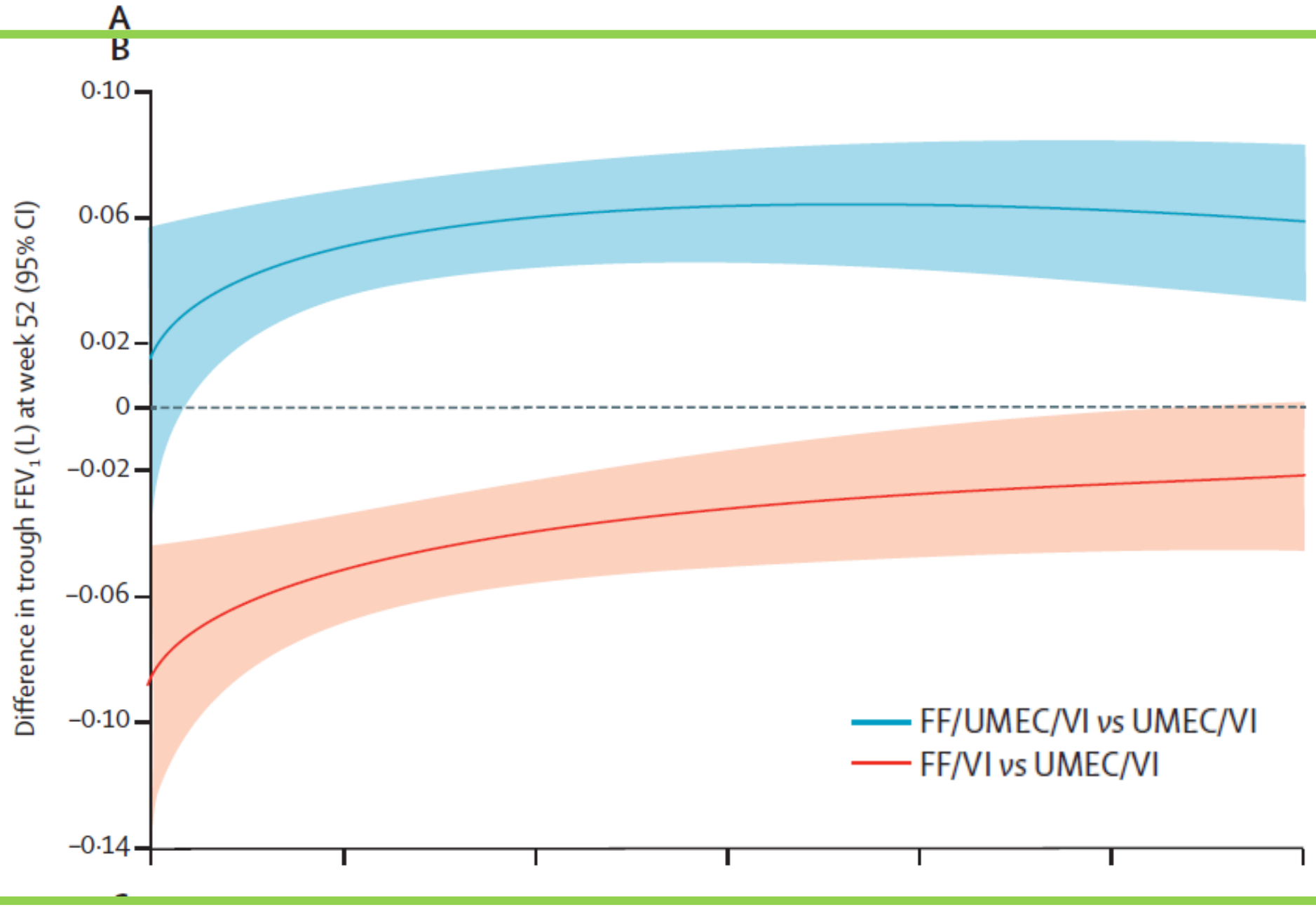
Rate of moderate/severe exacerbations by Blood Eosinophil Count

IMPACT Study



Lipson DA, et. al. N Engl J Med. 2018;378

Lipson DA, et. al. N Engl J Med. 2018;378



Lancet Respir Med. 2019 Sep;7(9):745-756

Triple therapy in COPD: systemic review

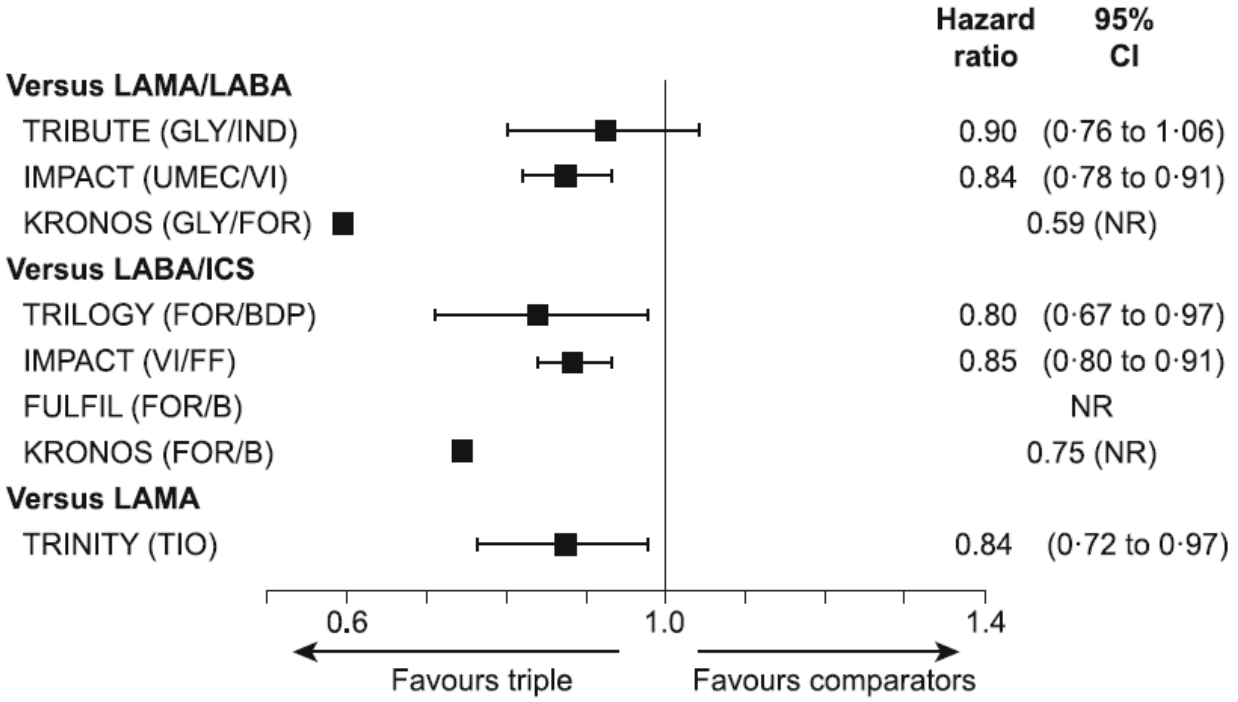


Fig. 4 Time to first moderate or severe exacerbation. *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *FULFIL* Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy, *ICS* inhaled corticosteroids, *IMPACT* InforMing the PAthway of COPD Treatment, *LABA* long-acting β_2 agonist, *LAMA* long-acting muscarinic antagonist, *NR* not reported, *TIO* tiotropium. Hazard ratios for time to first moderate or severe exacerbation with triple therapy compared with comparators

Respir Res. 2019 Nov 4;20(1):242

Mortality benefit with triple therapy in COPD

- Prior randomized tails with mortality as the primary endpoint failed to show a statistically significant survival benefit with ICS/LABA compared to mono-components and placebo.
- Recently, there are statistically significant 42.1% reduction in the risk of on-treatment all-cause mortality comparing triple therapy with LABA/LAMA. (IMPACT study)
- A post-hoc pooled analysis of triple therapy clinical trials conducted in severe COPD patients with a history of exacerbations showed a trend for lower mortality with use of triple inhaled therapy compared to non-ICS based treatments, but the differences was not statistically significant. (Trilogy, Trinity, Tribute)
- These effects are most likely to be seen in patients with COPD who are severely symptomatic, have moderate to very severe airflow obstruction and a history of exacerbations.

Global Initiative For Chronic Obstructive Lung Disease 2020 Report
Eur Respir J. 2018 Dec 13;52(6)

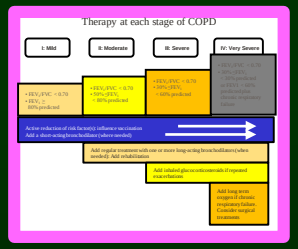
COPD management guidelines are evolving towards a personalised approach to treatment

Guideline evolution reflects an increasing understanding of COPD as a complex & heterogeneous disease

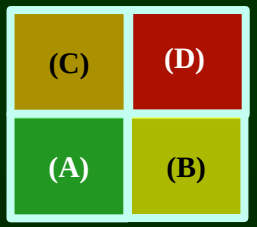
One size fits all → Stratified medicine → Personalized medicine Treatable Traits

2006 → 2011-2020 → Future

GOLD 2006
FEV_1 – centric approach to COPD management



GOLD 2020
COPD patients stratified by airflow limitation, exacerbation history, and symptoms



? GOLD in future ?
A series of disease components provide additional, independent, clinically useful information to inform patient management

Severity/Activity
FEV_1
IC/TLC
PaO_2
Exercise capacity
Comorbidity

Biomarkers
Eosinophil
Fibrinogen
CRP
BNP
IgE

Phenotype
ACOS
BCOS
Frequent A.E
Allergic Phenotypes

CAT, COPD Assessment Test; FEV_1, forced expiratory volume; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NICE, National Institute for Clinical Excellence

Thanks for Your Attention !