

CAN WE
DO MORE
FOR OUR
COPD PATIENTS?
NEW FRONTIERS
IN CLINICAL CARE

最新的COPD 三合一療法 -給病人更好的未來-

中國醫藥大學附設醫院
胸腔暨重症系
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111-11-19



Global Initiative for
Chronic Obstructive
Lung Disease

**2023
REPORT**



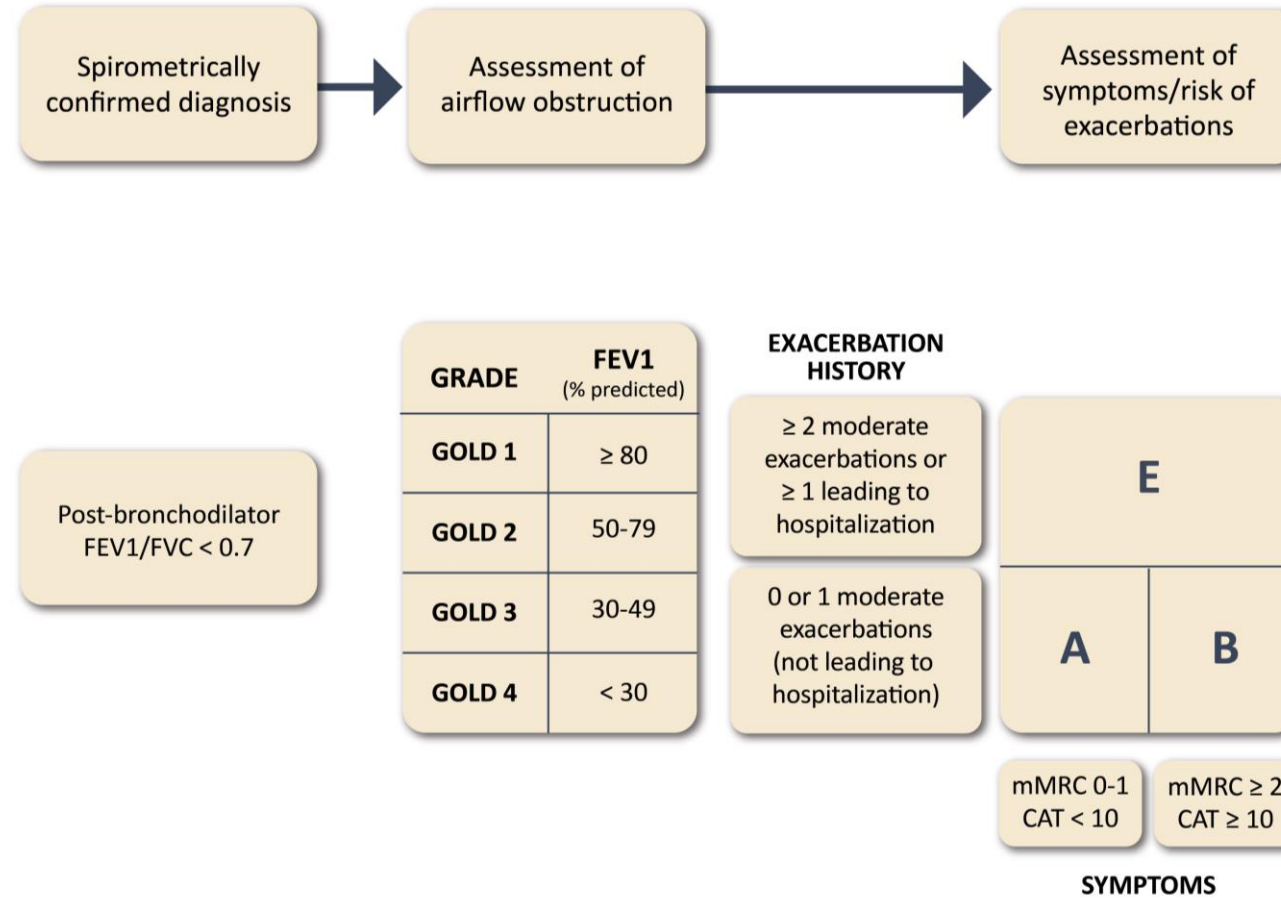
Global Strategy for the Diagnosis, Management, and
Prevention of Chronic Obstructive Pulmonary Disease

GOLD 2023

**Global Strategy for the Diagnosis,
Management, and Prevention of
Chronic Obstructive Pulmonary Disease**

GOLD ABE Assessment Tool

Figure 2.3



Initial Pharmacological Treatment

Figure 4.2

2023
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*single inhaler therapy may be more convenient and effective than multiple inhalers

- 對初始治療的推薦有顯著的調整，主要是在B組把LABA+LAMA作為唯一的推薦(有別於GOLD2022可以有3種選擇)和在E組，推薦LABA+LAMA和有條件($\text{EOS} \geq 300/\mu\text{l}$)推薦LABA+LAMA+ICS。
- 在GOLD2023中，LABA+LAMA成為主流的起始治療推薦，而LABA+LAMA+ICS在起始治療中也有一席之地。
- ICS+LABA在起始治療中不再推薦。然而，在正文中也有說明，對於已使用ICS+LABA的患者，如治療效果好，可以繼續維持治療。



GOLD 2023

KEY CHANGES SUMMARY

Group B

► Treatment should be initiated with a LABA+LAMA combination. It has been shown in a RCT that in patients with ≤ 1 moderate exacerbation in the year before the study and a CAT™ ≥ 10 LABA+LAMA is superior to a LAMA with regard to several endpoints.⁽⁵⁾ Therefore, providing there are no issues regarding availability, cost and side-effects LABA+LAMA is the recommended initial pharmacological choice.

**複方氣管擴張劑：
對沒有用ICS治療過的
symptomatic COPD病人
(CAT ≥ 10 , AE ≤ 1 /yr), 使用
LABA/LAMA比單方LABA或
LAMA好**

GOLD 2023

KEY CHANGES SUMMARY

Group E

- ▶ A Cochrane systematic review and network meta-analysis comparing dual combination therapy versus mono long-acting bronchodilators showed that the LABA+LAMA combination was the highest ranked treatment group to reduce COPD exacerbations.⁽²⁵⁶⁾ Therefore, provided there are no issues regarding availability, cost and side-effects LABA+LAMA is the preferred choice. LABA+LAMA is the preferred choice for initial therapy in group E patients.
- ▶ Use of LABA+ICS in COPD is not encouraged. If there is an indication for an ICS, then LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice.^(133,204)

複方氣管擴張劑：
預防急性惡化, 使用
LABA/LAMA比單方LABA或
LAMA好

三方氣管擴張劑：
預防急性惡化, 若需使用ICS, 使
用ICS/LABA/LAMA比
ICS/LABA好

Factors to Consider when Initiating ICS Treatment

Figure 3.1

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE

History of hospitalization(s) for exacerbations of COPD[#]

≥ 2 moderate exacerbations of COPD per year[#]

Blood eosinophils ≥ 300 cells/μL

History of, or concomitant asthma

FAVORS USE

1 moderate exacerbation of COPD per year[#]

Blood eosinophils 100 to < 300 cells/μL

AGAINST USE

Repeated pneumonia events

Blood eosinophils < 100 cells/μL

History of mycobacterial infection

[#]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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Blood Eosinophils and Chronic Obstructive Pulmonary Disease

A Global Initiative for Chronic Obstructive Lung Disease Science Committee

2022 Review

6 Dave Singh¹, Alvar Agusti², Fernando J. Martinez³, Alberto Papi⁴, Ian D. Pavord⁵, Jadwiga A. Wedzicha⁶, Claus F. Vogelmeier⁷, and David M. G. Halpin⁸

Table 1. Global Initiative for Chronic Obstructive Lung Disease 2022 Report: Key Evidence and Recommendations for Blood Eosinophil Counts in Chronic Obstructive Pulmonary Disease

Prediction of ICS benefits

The use of BEC to predict ICS effects should be combined with exacerbation risk (using exacerbation history).

The relationship between BEC and ICS effects is continuous; no/small effects are observed at lower BEC, with increasing effects at higher BEC.

Less than 100 cells/ μ l and ≥ 300 cells/ μ l are estimates, not precise cutoff values, to identify individuals with the lowest and greatest (respectively) likelihood of ICS benefit.

T2 inflammation

Higher BEC are associated with increased lung eosinophil numbers and higher concentrations of T2 inflammation markers in the airways.

The differences in T2 inflammation can explain the differential ICS response according to BEC.

COPD vs. control subjects

A subset of patients with COPD has BEC above those found in control subjects.

Microbiome

Lower BEC are associated with a greater presence of proteobacteria, notably *Haemophilus*, and increased bacterial infections and pneumonia.

Future risk of exacerbations/disease progression

In younger individuals without COPD, higher BEC are associated with an increased risk of FEV₁ decline and the development of COPD.

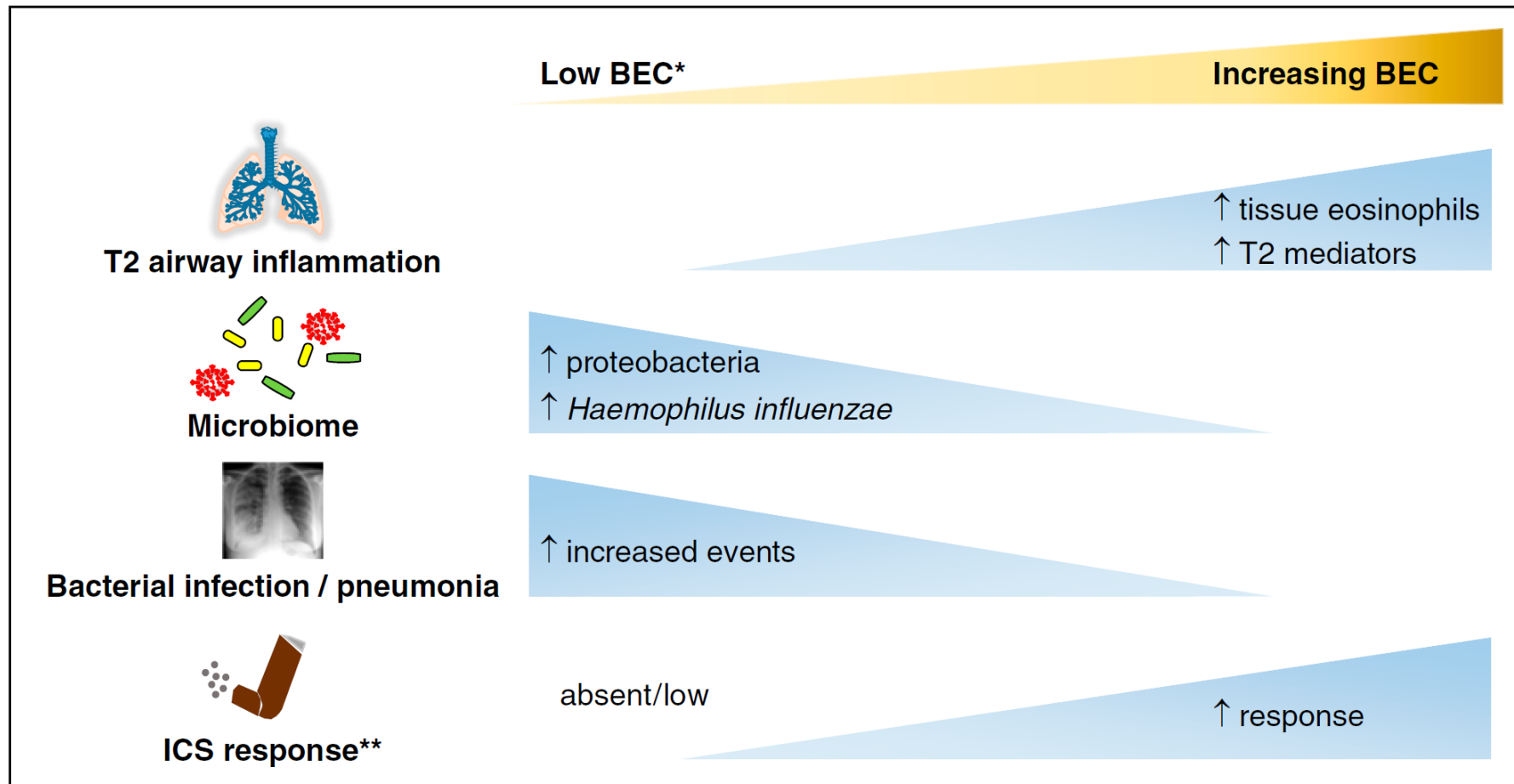
BEC cannot be used as a standalone biomarker of future risk without considering exacerbation risk and ICS use.

Blood Eosinophils and Chronic Obstructive Pulmonary Disease

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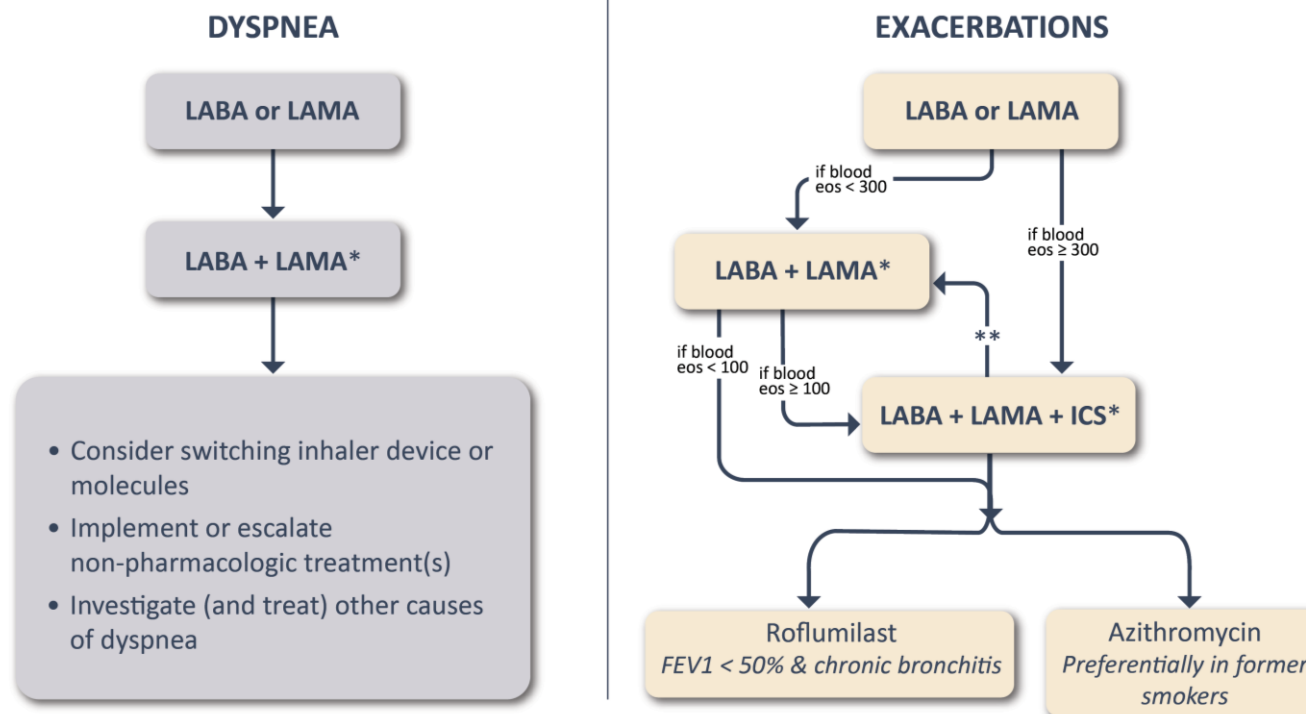
Follow-up Pharmacological Treatment

Figure 4.4

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1 IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.

- 2 IF NOT:
- Check adherence, inhaler technique and possible interfering comorbidities
 - 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 ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/ μ l de-escalation is more likely to be associated with the development of exacerbations

(1)針對呼吸困難為主要表現的患者中，不再推薦LABA+ICS和LABA+LAMA+ICS治療；
(2)針對頻繁急性加重的調整治療中，不再推薦LABA+ICS。



Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Table 3.6

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Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS ¹	Yes	Triple compared to dual LABD relative risk reduction: IMPACT HR 0.72 (95% CI: 0.53, 0.99) ETHOS HR 0.51 (95% CI: 0.33, 0.80)	Symptomatic people with a history of frequent and/or severe exacerbations
Non-Pharmacological Therapy			
Smoking (Sm) Cessation ²	Yes	8.83/1000 person-years (Sm cessation) vs 10.38/1000 person-years (UC) (p = 0.03)	Asymptomatic or mildly symptomatic
Pulmonary Rehabilitation (PR) ³	Yes	After early PR: RR 0.58 (95% CI 0.35, 0.98) and at the longest follow-up RR 0.55 (95% CI 0.12, 2.57)	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks post d/c)
LTOT ⁴	Yes	NOTT, ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction MRC, ≥ 15 hours vs no oxygen: 50% reduction	PaO ₂ ≤ 55 or < 60 mmHg with <i>cor pulmonale</i> or secondary polycythemia
NPPV ⁵	Yes	12% in NPPV (high IPAP level) and 33% in control (HR 0.24; 95% CI 0.11, 0.49)	Stable COPD with marked hypercapnia
LVRs ⁶	Yes	0.07 deaths/person-year (LVRs) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome)

1. IMPACT and ETHOS trials (Lipson et al. 2020; Martinez et al. 2021). 2. Lung Health Study (Anthonisen et al. 2005). 3. Review and meta-analysis (Ryso et al. 2018) 4. NOTT and MRC trials (NOTT 1980; MRC 1981) 5. Kohlein et al., trial (Kohlein et al. 2014) 6. NETT trial (Fishman et al. 2003)

ICS: inhaled corticosteroid; LABA: long-acting B2-agonist; LAMA: long acting anti-muscarinic; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRs: lung volume reduction surgery; UC: usual treatment control group.





WHO

Who needs triple therapy



最新的COPD三合一療法

-給病人更好的未來-

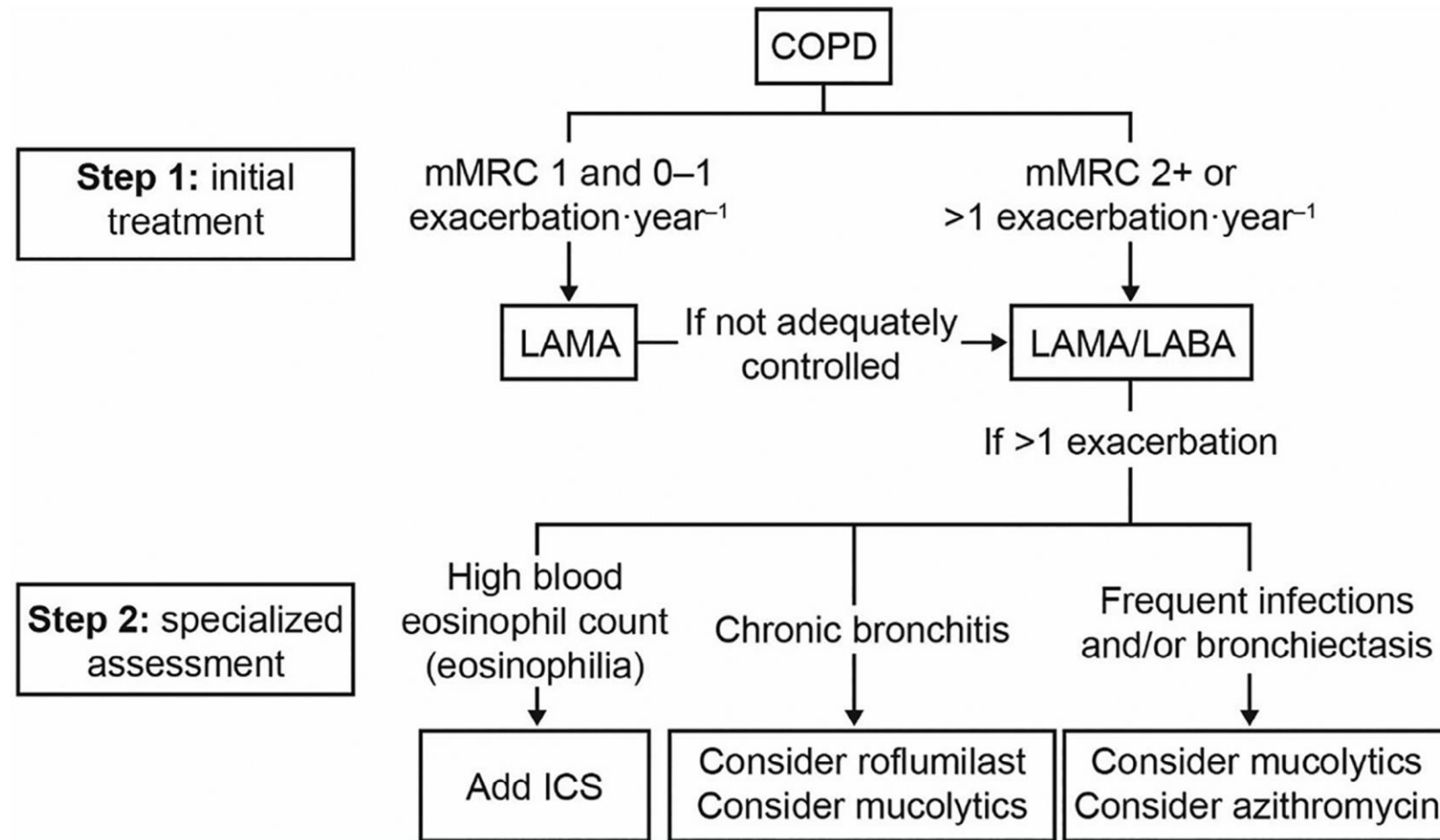
The Role of Fixed-Dose Dual Bronchodilator Therapy in Treating COPD

Antonio Anzueto, MD,^a Marc Miravittles, MD^b

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Spanish COPD guidelines (GesEPOC) 2021: Updated pharmacological treatment of stable COPD☆☆

Marc Miravittles,^{a,b,*} Myriam Calle,^c Jesús Molina,^d Pere Almagro,^e José-Tomás Gómez,^f Juan Antonio Trigueros,^g Borja G. Cosío,^{b,h} Ciro Casanova,ⁱ José Luis López-Campos,^{b,j} Juan Antonio Riesco,^{b,k} Pere Simonet,^l David Rigau,^m Joan B. Soriano,^{b,n} Julio Ancochea,^{b,n} Juan José Soler-Cataluña^{b,o}

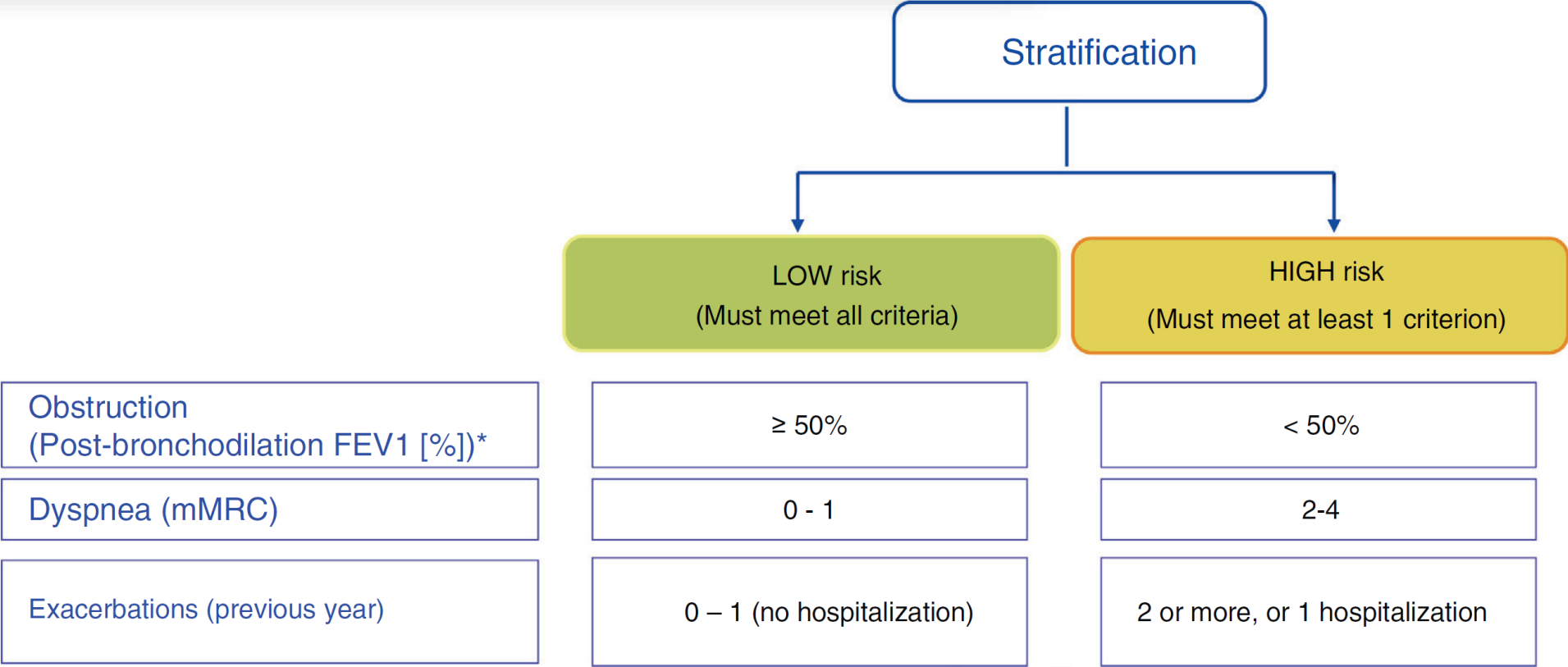
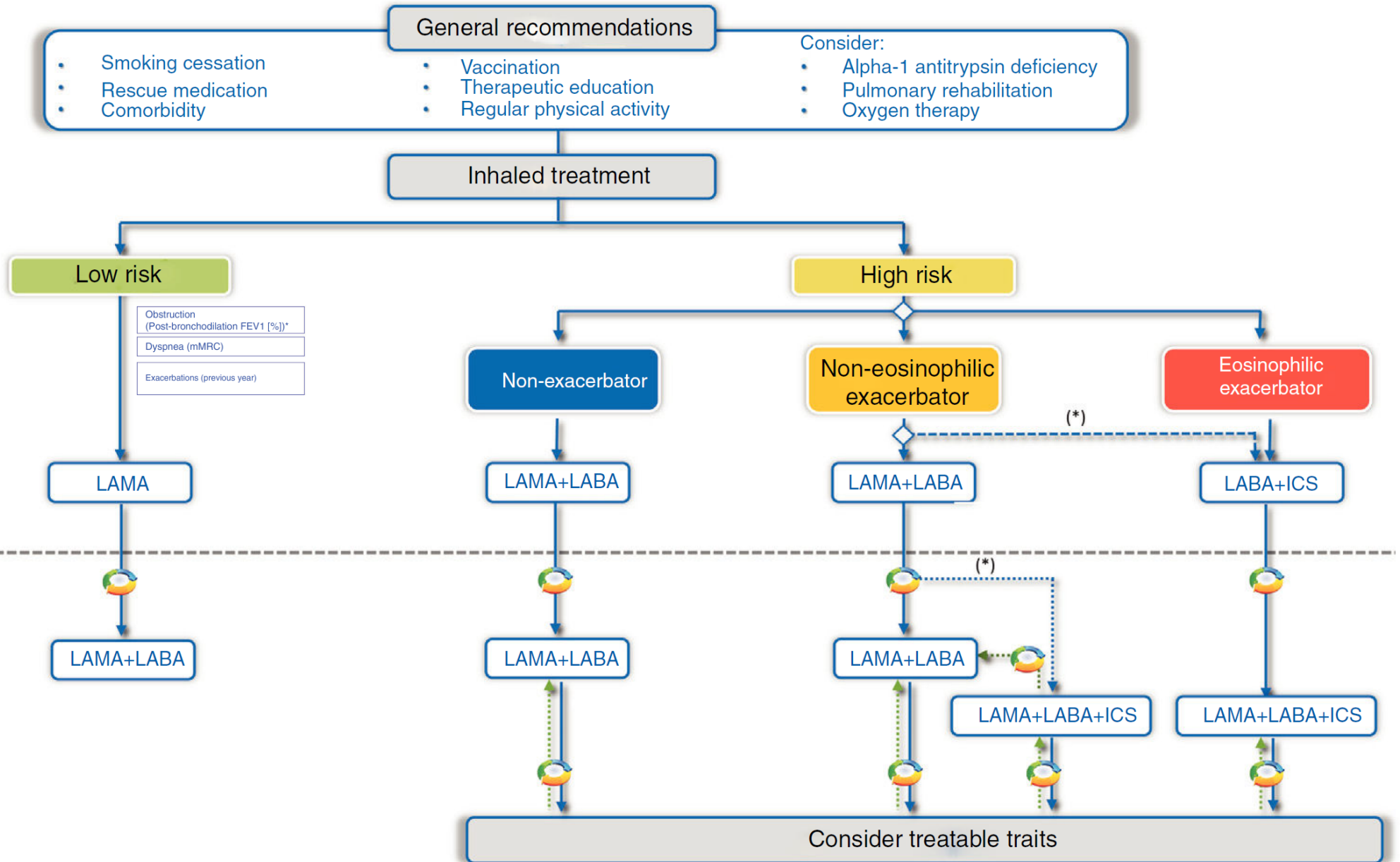


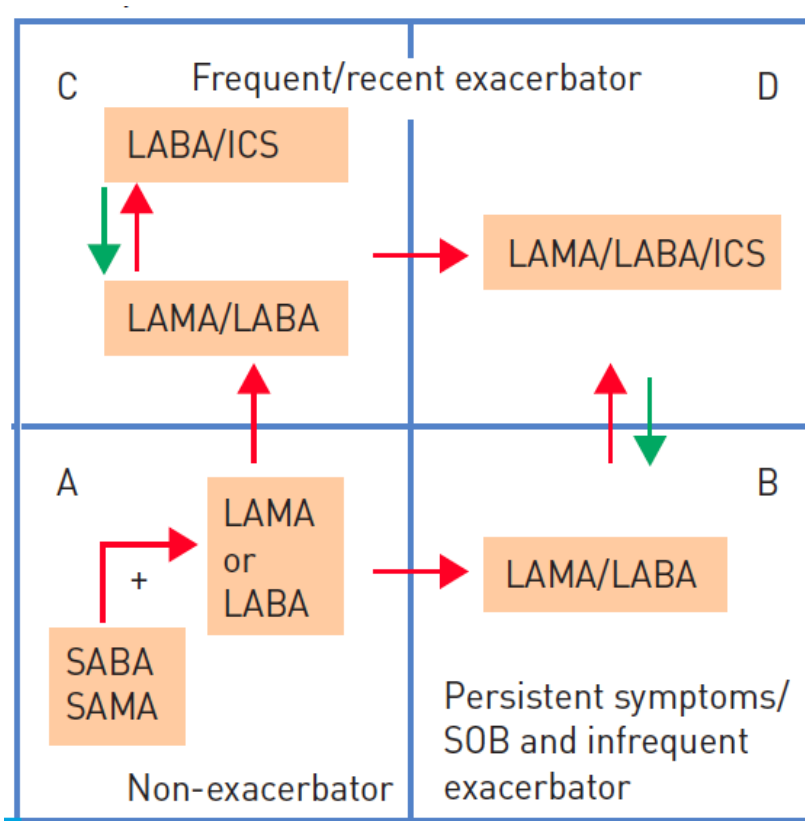
Fig. 1. Risk stratification in COPD patients.

All

Initial treatment

Follow-up





“Step-up” (escalation)

- Recent “**exacerbation**” or **chest infection** history
- **Symptom score** (CAT>10) or persistent **SOB**
- **Low** expiratory flow rates (FEV1< 50%)
- “**High**” blood serum **eosinophil** count (>300 uL or > 4 %)

ICS “Step-down” (de-escalation)

- Not **ACOS**
- No **exacerbations** or **chest infections** in last 1-2 years and stable dyspnea
- Recent **pneumonia** (CxR confirmed) or other ICS related complications
- “**Low**” blood serum **eosinophil** count (<300 uL or < 4 %)

A New Alphabet

- (E) Frequent Exacerbations
 (≥ 2 per year, ≥ 1 hospitalisation)
 High Eosinophils
 ($\geq 3\text{--}4\%$ or $\geq 200\text{--}300$ cells per high power field)
 ACOS
 (Asthma age ≤ 40 years, atopy + IgE tests)

Initial treatment

Alternative treatment
 (move up to next
 severity class)

Low airflow Post-bronchodilator FEV ₁ <50%	(E)	
	(C)	(D)
High airflow Post-bronchodilator FEV ₁ $\geq 50\%$	(A)	(B)
	Low symptoms mMRC <2 CAT <10	High symptoms mMRC ≥ 2 CAT ≥ 10

(E) Exacerbation-ICS therapy ICS/LABA	Exacerbation-triple therapy ICS/LABA+LAMA
(D) Combination-Dual bronchodilator LAMA/LABA	Exacerbation-triple therapy ICS/LABA+LAMA
(C) Combination-Dual bronchodilator LAMA/LABA	Exacerbation-triple therapy ICS/LABA+LAMA
(B) Bronchodilator LAMA or LABA	Combination-Dual bronchodilator LAMA/LABA
(A) As needed SABA, SAMA or SAMA/SABA	Bronchodilator LAMA or LABA

↑
Increase therapy if symptoms or risks

All patients also utilise as needed SABA, SAMA, SAMA/SABA
 rescue therapy



WHEN


When prescribe triple therapy



最新的COPD三合一療法



-給病人更好的未來-

A perspective for chronic obstructive pulmonary disease (COPD) management: six key clinical questions to improve disease treatment

Marco Contoli ^a, Luca Morandi^a, Fabiano Di Marco^b and Mauro Carone^c

ICS Use or Withdrawal	ATS Document [67]	ERS Document [68]	GOLD Document [62]
Use	<ul style="list-style-type: none">• Patients with blood eosinophilia and a history of ≥ 1 exacerbation in the past year requiring antibiotics or oral steroids or hospitalization	<ul style="list-style-type: none">• Eosinophil count ≥ 300 cells/μL: strong recommendation for ICS continuation (irrespective of exacerbations and/or hospitalizations)	<ul style="list-style-type: none">• History of hospitalization(s) for exacerbations• ≥ 2 moderate exacerbations per year• Blood eosinophils > 300 cells/μL• History of, or concomitant asthma
Withdrawal	<ul style="list-style-type: none">• Patients on triple therapy (ICS/LABA/LAMA) and no exacerbations in the past year	<ul style="list-style-type: none">• Eosinophil count < 300 cells/μL and exacerbations < 2 per year and no hospitalization: conditional recommendation for ICS withdrawal	<ul style="list-style-type: none">• Repeated pneumonia events• Blood eosinophils < 100 cells/μL• History of mycobacterial infection
Case consideration	<ul style="list-style-type: none">• No recommendation either for use or withdrawal of ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia	<ul style="list-style-type: none">• Eosinophil count < 300 cells/μL and exacerbations ≥ 2 per year or 1 hospitalization: limited evidence available. Discuss risks and benefits with the individual patient	<ul style="list-style-type: none">• 1 moderate exacerbation per year• Blood eosinophils 100–300 cells/μL

Triple therapy (ICS/LABA/LAMA) in COPD: thinking out of the box

Lowie E.G.W. Vanfleteren , Anders Ullman, Anita Nordenson, Anders Andersson, Kristina Andelid and Leonardo M. Fabbri 



Recommended triple therapy as the initial treatment under the following conditions

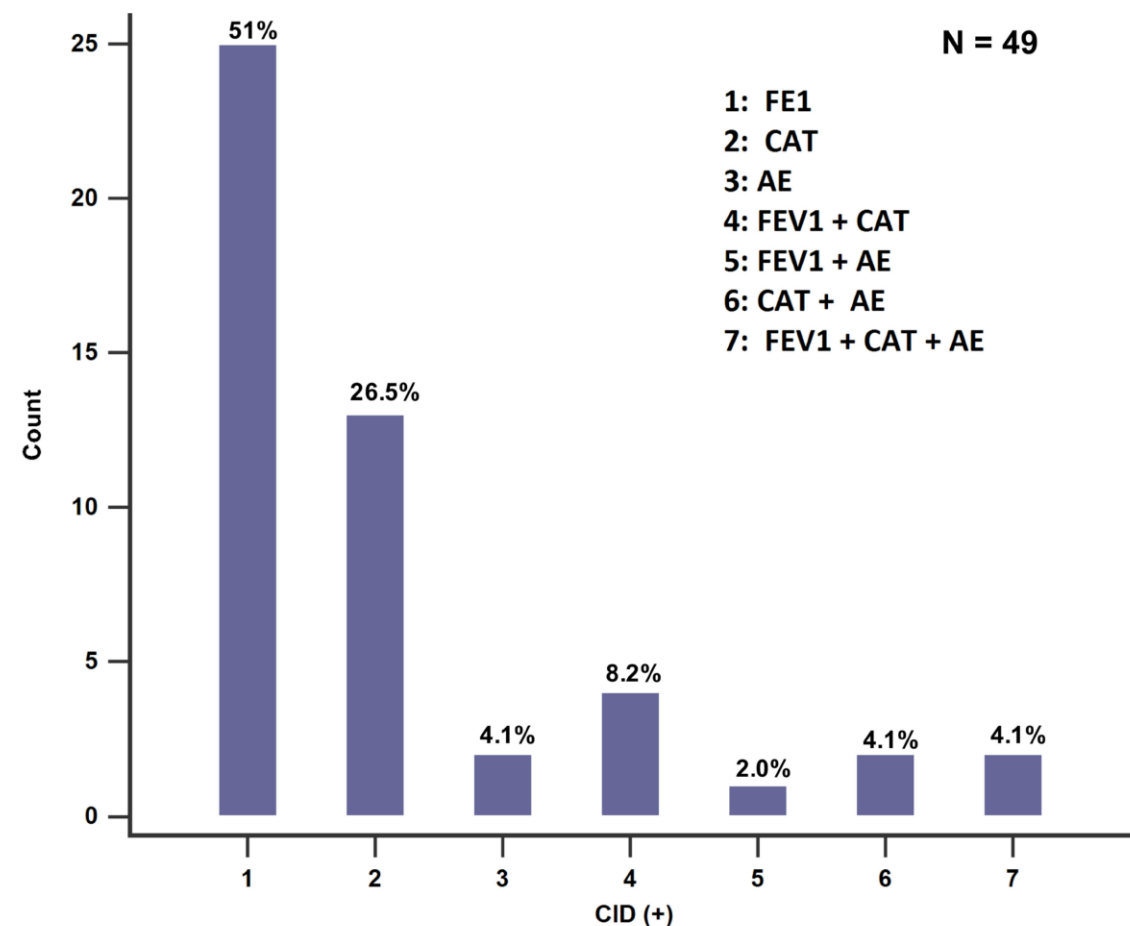
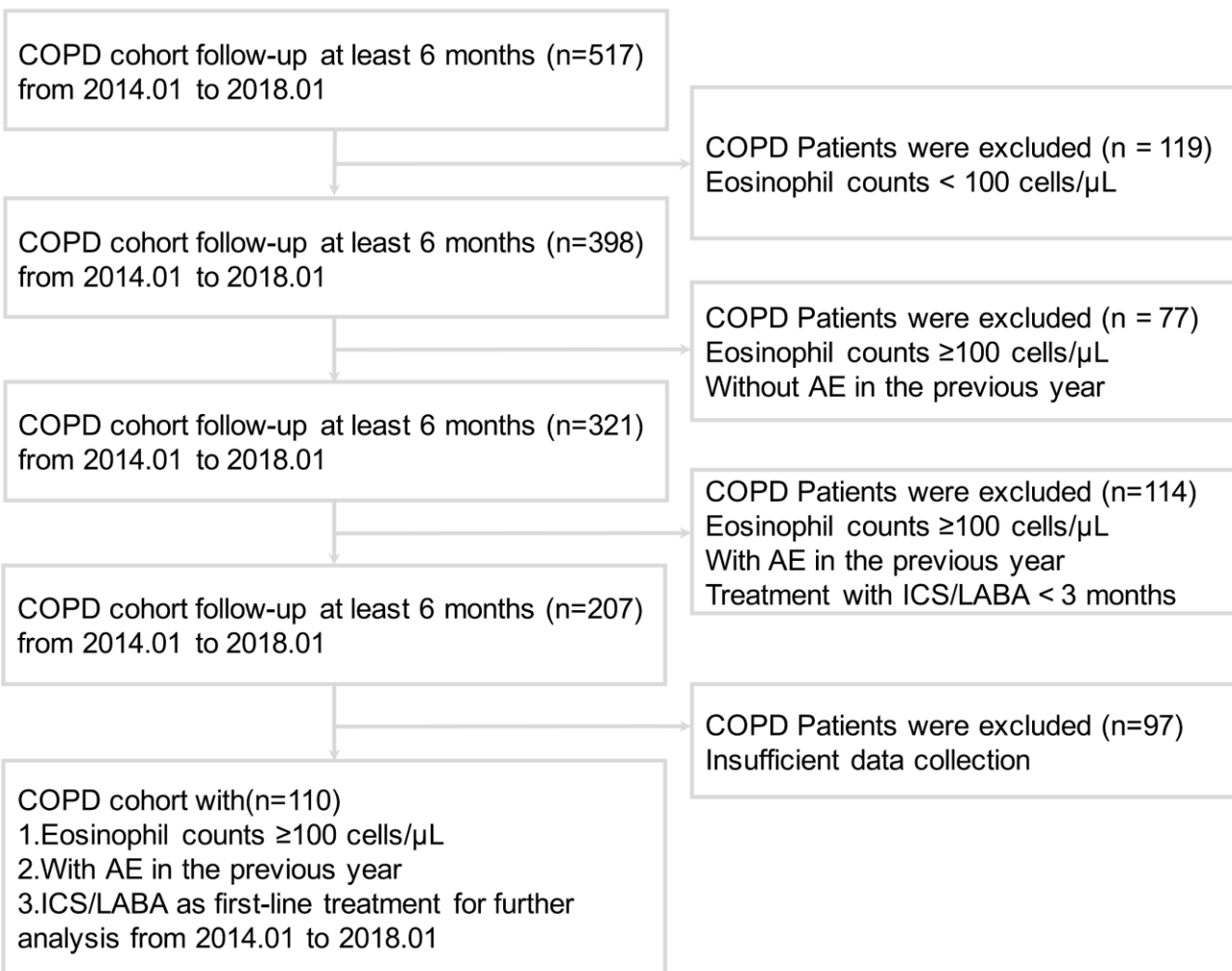
- Patients who are diagnosed with COPD for the first time because of **severe exacerbations**
- Patients who are diagnosed with
 - ✓ **Severe airflow limitation (FEV1 < 50%)**
 - ✓ **Symptomatic**
 - ✓ **Frequent moderate (≥ 2)**
 - ✓ **Severe exacerbations in the previous year**
- Peripheral **eosinophilia** (> 300/μL).

Beyond Dual Bronchodilation – Triple Therapy, When and Why

Immediate choice in

- Patients who present for the first time, and have severe airway obstruction ($FEV_1 < 50\%$) and are symptomatic
- Patients who have had frequent (≥ 2) moderate or severe exacerbations (≥ 1 hospitalisation) in the previous year
- Patients who have peripheral eosinophilia ($> 300 \text{ cells } \mu\text{L}^{-1}$)
- Patients with significant lung function decline
- Patients discharged from hospital after a COPD exacerbation.

When to Use Initial Triple Therapy in COPD: Adding a LAMA to ICS/LABA by Clinically Important Deterioration Assessment



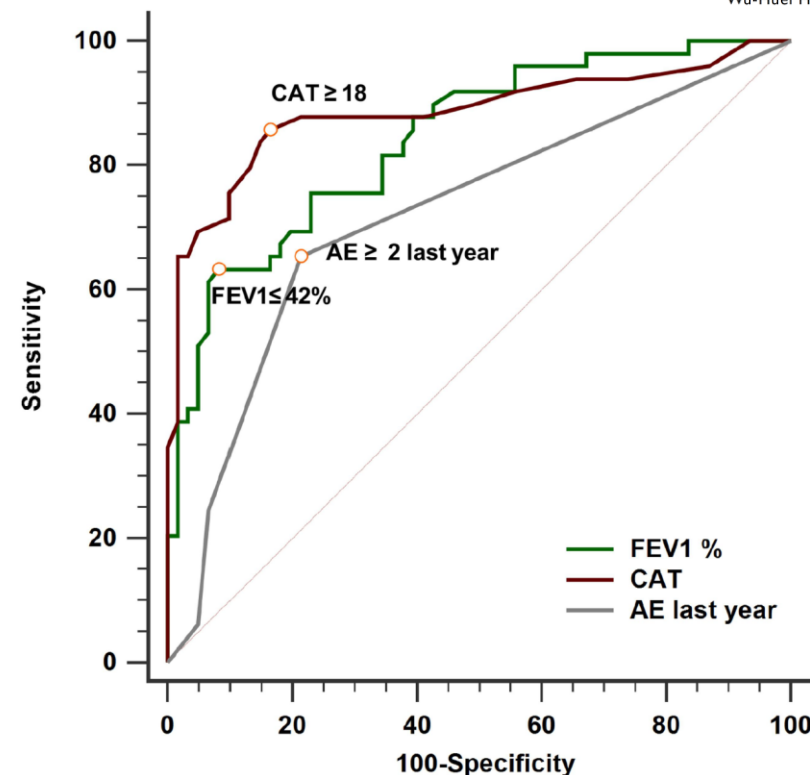
When to Use Initial Triple Therapy in COPD: Adding a LAMA to ICS/LABA by Clinically Important Deterioration Assessment

Clinical Factors	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	0.96(0.93–1.01)	0.141	-	-
Group	1.97(1.32–2.95)	<0.001	3.75(0.86–16.37)	0.077
Eosinophil/mL	0.99(0.99–1.01)	0.745	-	-
FEV1 (%)	0.90(0.87–0.94)	<0.001	0.81(0.70–0.94)	0.004
CAT	1.29(1.18–1.40)	<0.001	1.89(1.22–2.95)	0.004
mMRC	4.69(2.65–8.31)	<0.001	0.11(0.01–1.06)	0.056
RV/TLC	1.08(1.03–1.14)	0.001	1.01(0.91–1.12)	0.829
AE ≥ 2 last year	6.95(2.97–16.25)	<0.001	19.86(1.58–249.5)	0.021

Initial eosinophil >100 with **1** AE

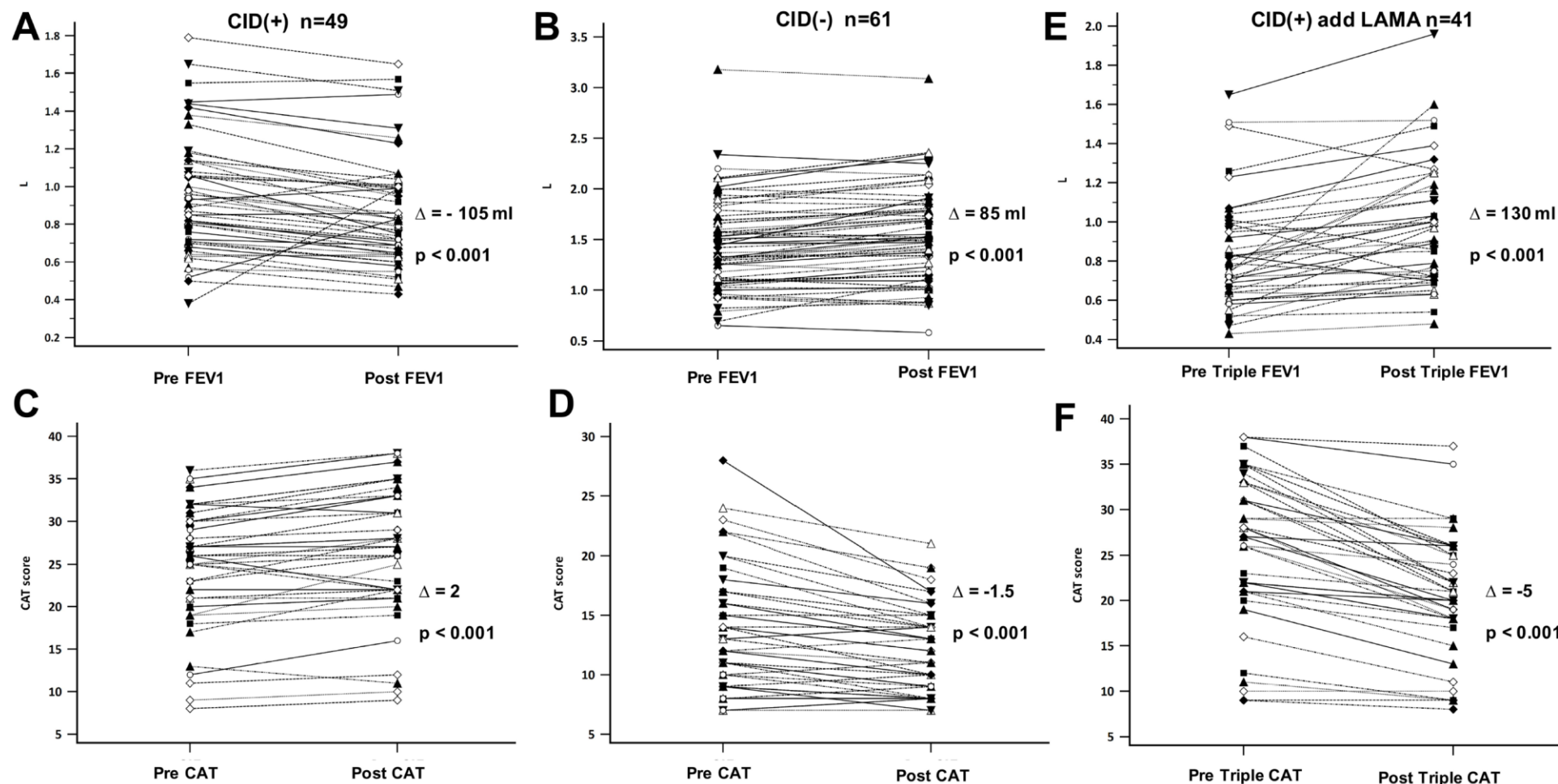
Consider triple therapy in

CAT ≥ 18, FEV1 ≤ 42%, AE ≥ 2

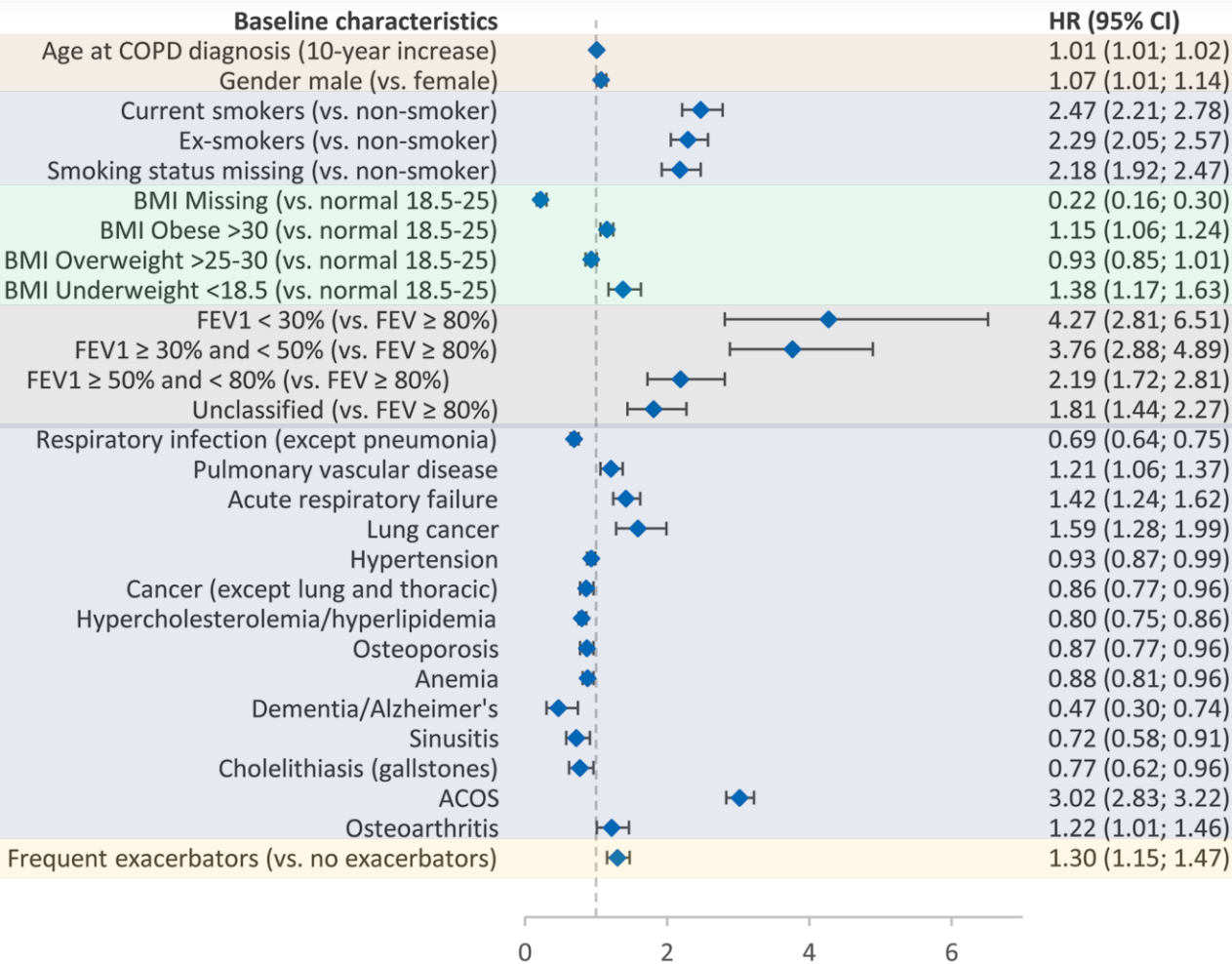
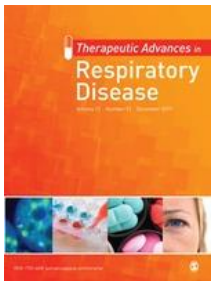


Variable	AUC	95%CI
CAT ≥ 18	0.885	0.810 to 0.938
FEV1 ≤ 42%	0.842	0.761 to 0.905
AE ≥ 2 last year	0.721	0.627 to 0.802

When to Use Initial Triple Therapy in COPD: Adding a LAMA to ICS/LABA by Clinically Important Deterioration Assessment



Prescribing pathways to triple therapy in patients with chronic obstructive pulmonary disease in the United States



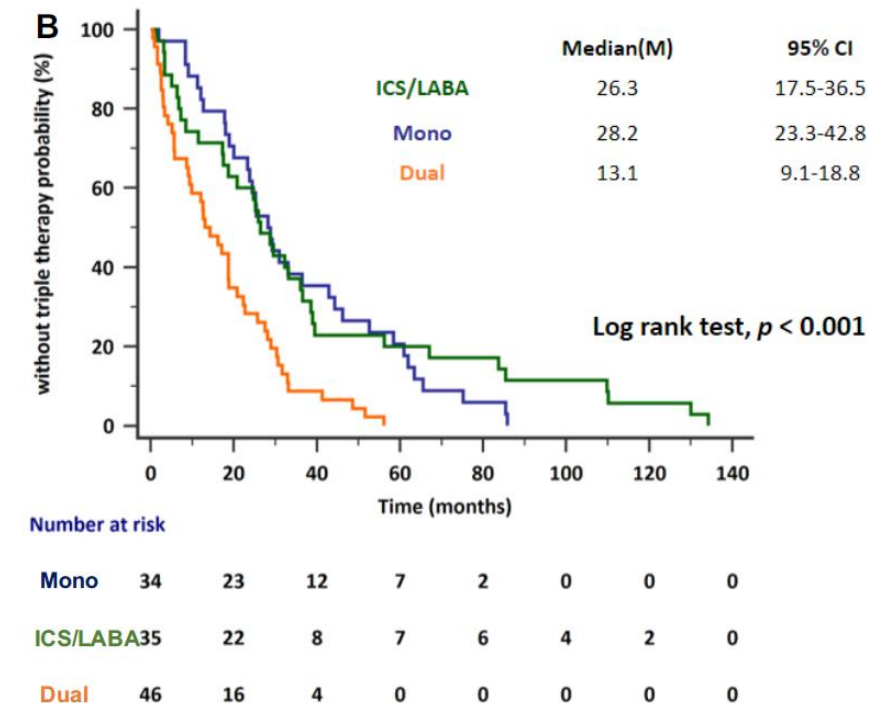
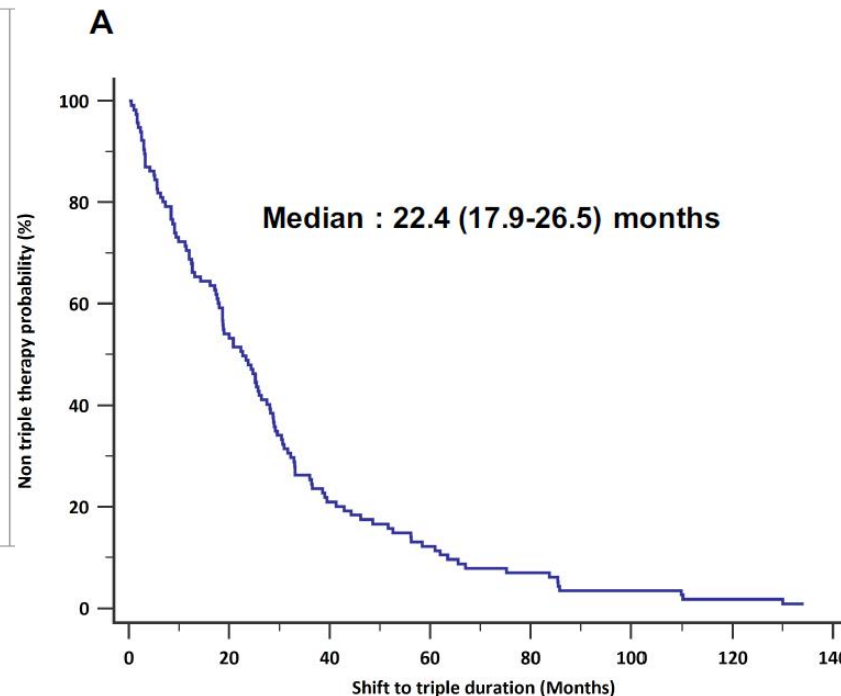
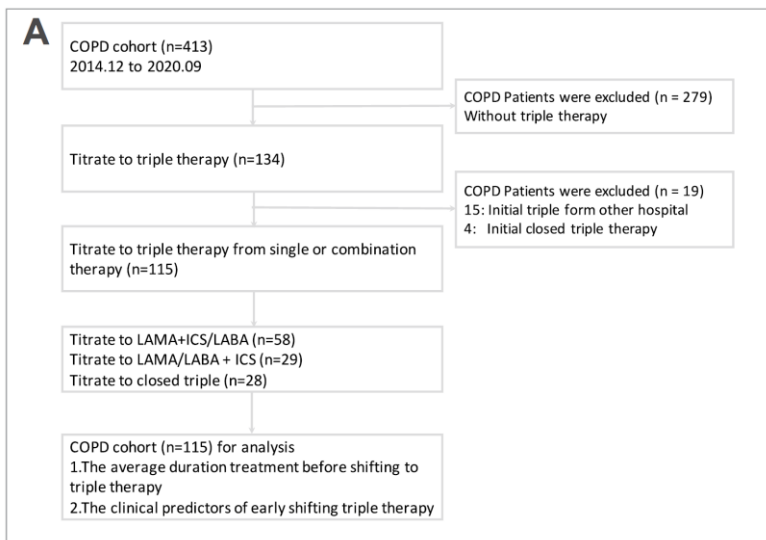
- Old age and male
- Current smoker
- Obesity
- Underweight
- Low FEV1
- Comorbidity
 - Pulmonary vascular disease
 - Lung cancer
 - ACO
 - Osteoarthritis
- Frequent exacerbator

A Real World Study to Assess the Effectiveness of Switching to Once Daily Closed Triple Therapy from Mono/Dual Combination or Open Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

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 Wei-Chih Liao^{1,2}
 Biing-Ru Wu^{1,3,4}
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 China Medical University Hospital



A total 115 patients with COPD were stepped up to triple therapy

The median duration from receiving initial COPD treatment to inhaled triple therapy.

A Real World Study to Assess the Effectiveness of Switching to Once Daily Closed Triple Therapy from Mono/Dual Combination or Open Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

	Shift to Triple ≥ 22 m (n=52) Group 1	Shift to Triple < 22 m (n=63) Group 2	p-value
Age, years (SD)	64.6±10	67.9±9.9	0.075
Sex, male (%)	48(92.3)	62(98.1)	0.217
BMI, Kg/m ²	23.9±4.14	22.8±4.36	0.188
Smoking, pack-years	43.1±31.5	53.6±31.9	0.089
Blood Eosinophil cells/uL	434.5±375.1	489.6±660.8	0.589
AE ≥ 1 last year (%)	16(30.8)	29(46.0)	0.096
AE, last year	0.36±0.62	0.60±0.75	0.071
Initial FEV1, L	1.31±0.39	1.23±0.57	0.402
Initial FEV1 (%)	51.5±16.37	45.8±16.39	0.066
Initial FEV1/FVC (%)	56.6±10.7	55.1±11.2	0.445
Initial RV (%)	217.3±82.0	194.3±72.7	0.244
GLAD (%)			0.063
I	3(5.8)	1(1.6)	
II	23(44.2)	23(36.5)	
III	22(42.3)	28(44.4)	
IV	4(7.7)	11(17.5)	
Group (%)			0.036
B	28(53.8)	32(50.8)	
C	8(15.4)	2(3.2)	
D	16(30.8)	29(46.0)	
Reversible airway (%)	24(46.2)	16(25.4)	0.021
Initial CAT score	9.6±4.3	10.2±5.2	0.531
Initial mMRC ≥ 2 (%)	34(65.4)	44(71.0)	0.524
Comorbidity (%)			
HTN	16(30.8)	19(30.2)	0.943
CHF	3(5.8)	4(6.3)	1.000
Asthma	3(5.8)	10(10.9)	0.137
Bronchiectasis	4(7.7)	3(4.8)	0.699
Cancer	2(3.8)	8(12.7)	0.110
Initial treatment (%)			0.003
LABA or LAMA	19(36.5)	15(23.8)	
ICS/LABA	21(40.4)	14(22.2)	
LABA and LAMA	12(23.1)	34(54.0)	

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	1.034	0.99–1.07	0.073	1.057	1.01–1.11	0.027
Smoking, pack years	1.012	0.99–1.03	0.075	1.011	0.99–1.03	0.186
AE, last year	1.678	0.95–2.96	0.065	2.151	1.04–4.44	0.038
FEV1 (%)	0.978	0.96–1.01	0.063	0.973	0.94–1.01	0.066
Group “ABCD”	1.228	0.83–1.82	0.301	1.024	0.59–1.75	0.932
Reversible airway	0.397	0.18–0.87	0.019	0.235	0.08–0.64	0.004
Asthma	3.082	0.81–11.8	0.079	10.27	1.59–66.1	0.014
Initial Treatment	1.929	1.21–3.07	0.004	1.911	1.08–3.37	0.025

Predict COPD Patient with Stepping Up to Triple Therapy Early

- High blood eosinophilia
- Older age
- More AEs in the previous year
- ACO



WHY

**Why needs
triple therapy**

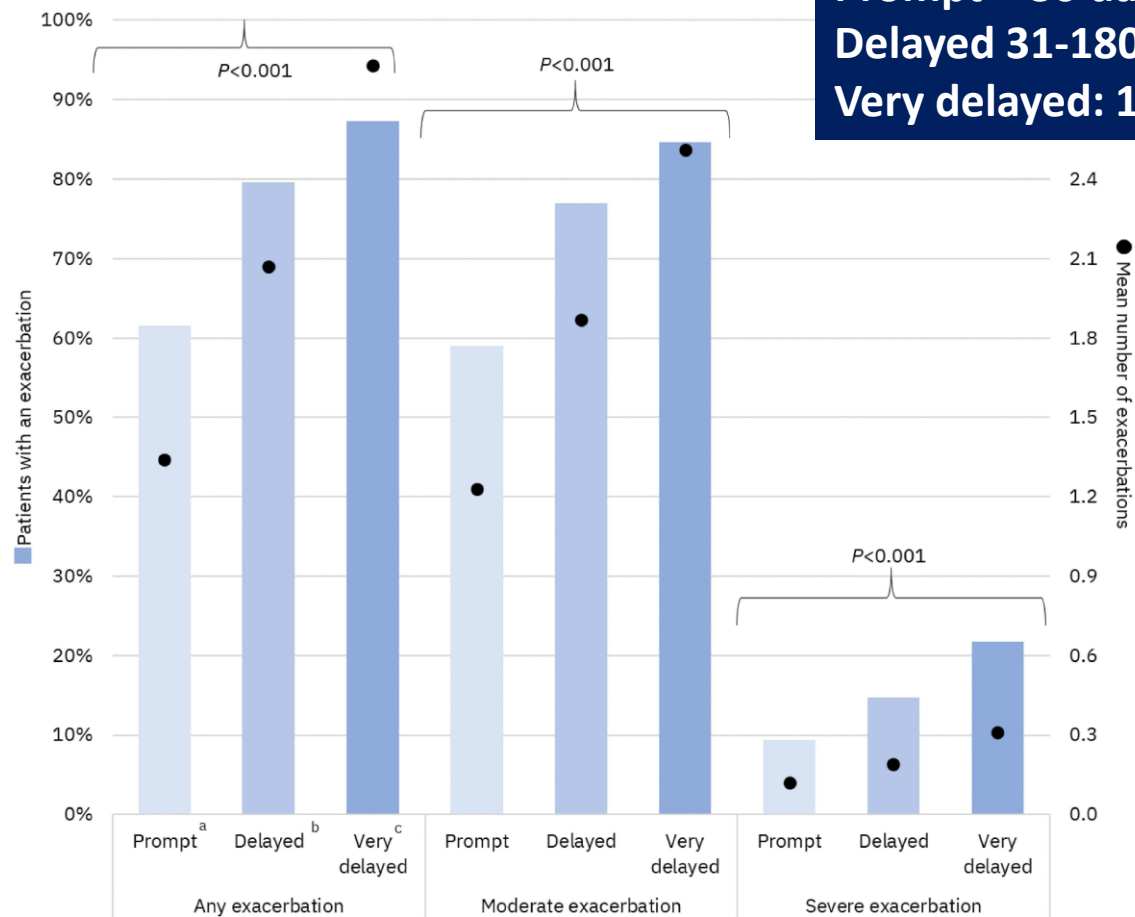


最新的COPD三合一療法

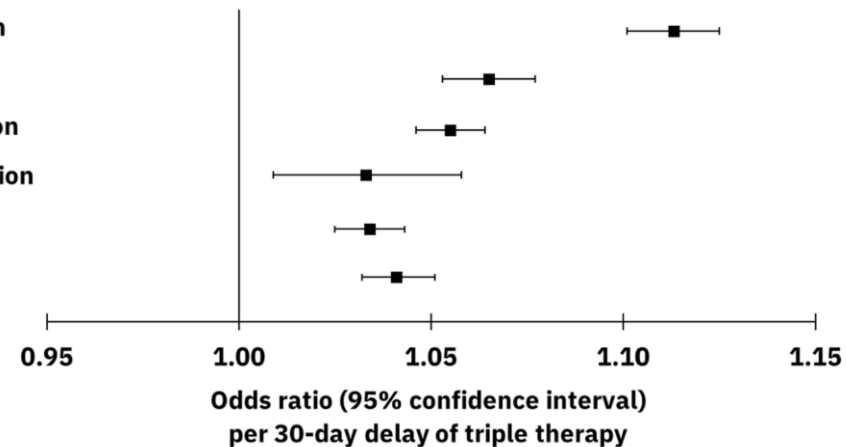
-給病人更好的未來-

PRIMUS – Prompt Initiation of Maintenance Therapy in the US: A Real-World Analysis of Clinical and Economic Outcomes Among Patients Initiating Triple Therapy Following a COPD Exacerbation

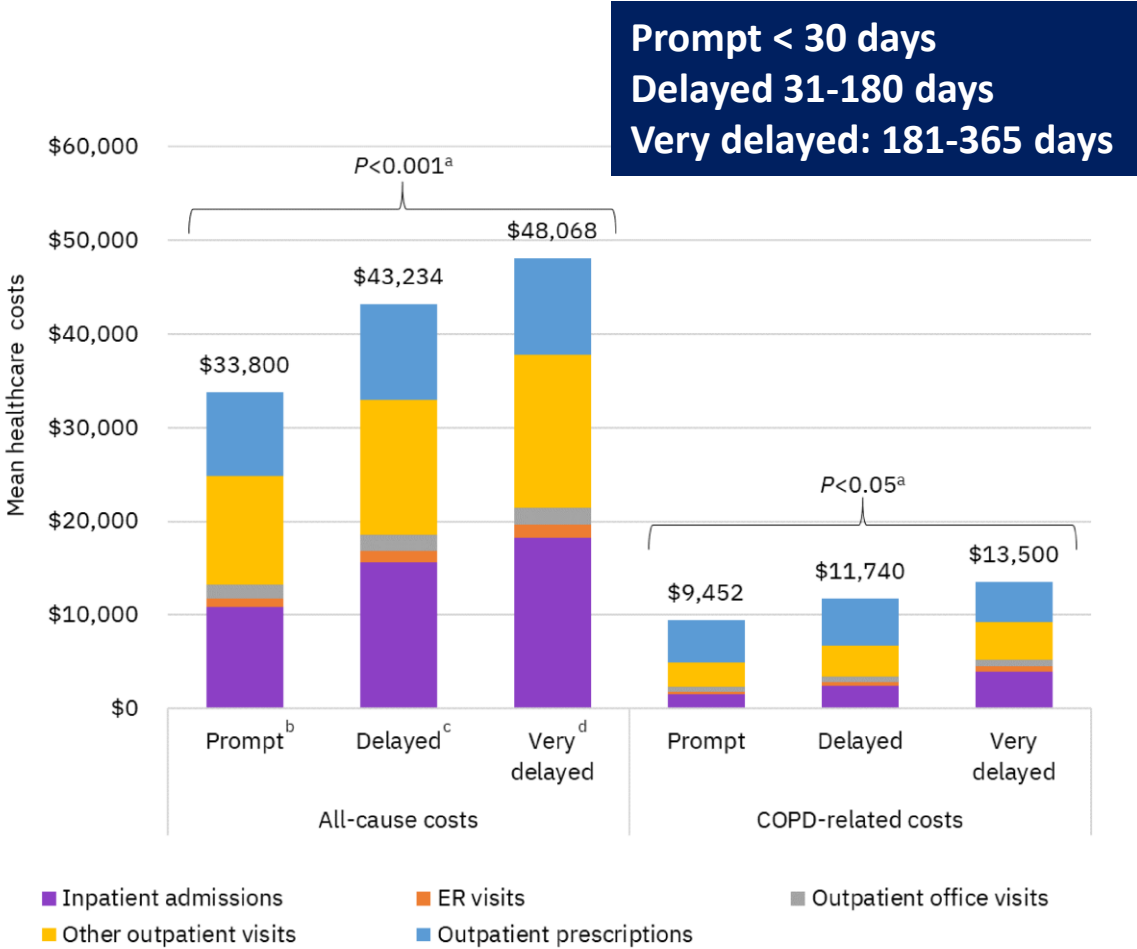
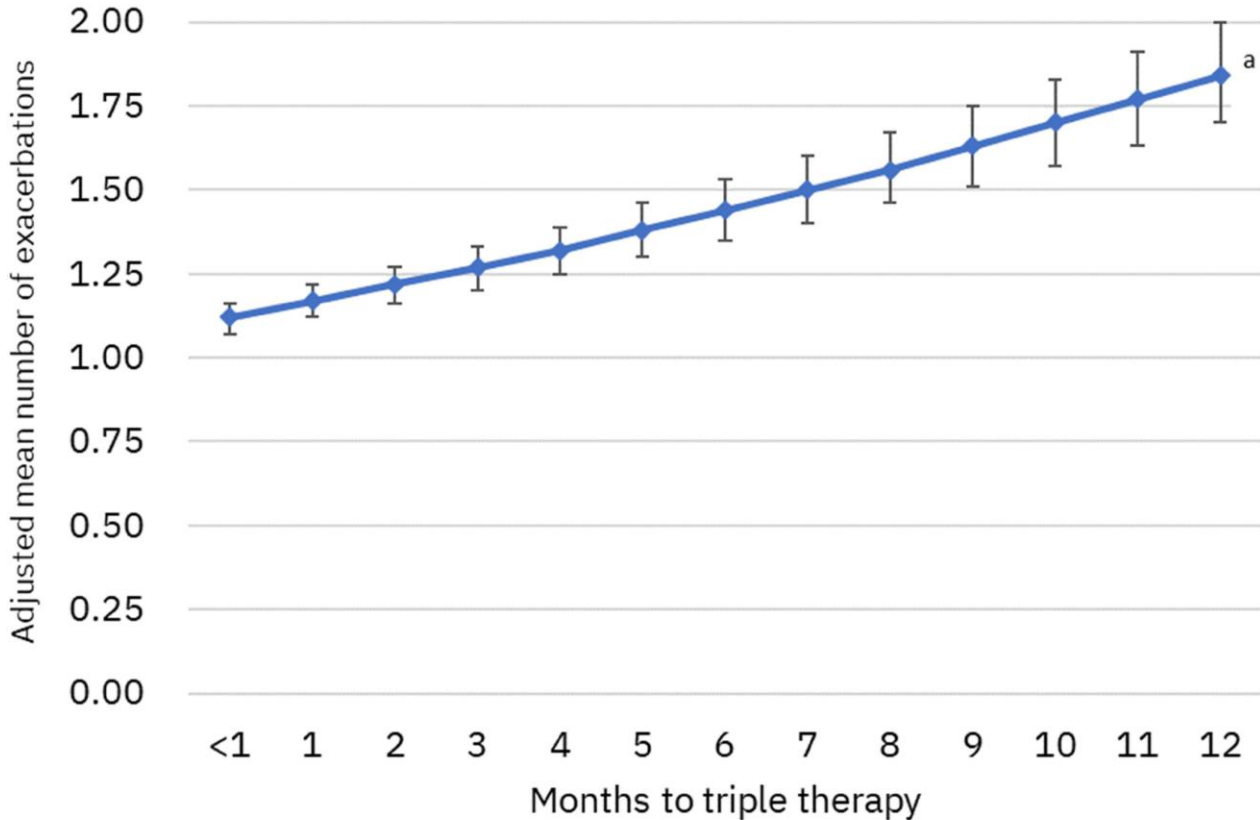
Prompt < 30 days
Delayed 31-180 days
Very delayed: 181-365 days



Any COPD exacerbation
Severe exacerbation
All-cause hospitalization
90-day COPD readmission
All-cause ER visit
COPD-related ER visit



PRIMUS – Prompt Initiation of Maintenance Therapy in the US: A Real-World Analysis of Clinical and Economic Outcomes Among Patients Initiating Triple Therapy Following a COPD Exacerbation





WHICH

Which triple therapy



最新的COPD三合一療法

-給病人更好的未來-

BUD/FORM/GLY is a fixed-dose ICS/LABA/LAMA therapy for the maintenance treatment of COPD

2 inhalations equal one dose and deliver a total dose of:

ICS (BUD)
budesonide 160mg

LAMA (GLY)
glycopyrronium 14.4 µg

LABA (FORM)
formoterol fumarate
dihydrate 10 µg

Dosage

2 inhalations, BID^{1,2}



**Administered via the
AEROSPHERE™ inhaler**

Indication: maintenance bronchodilator treatment in adult COPD patients



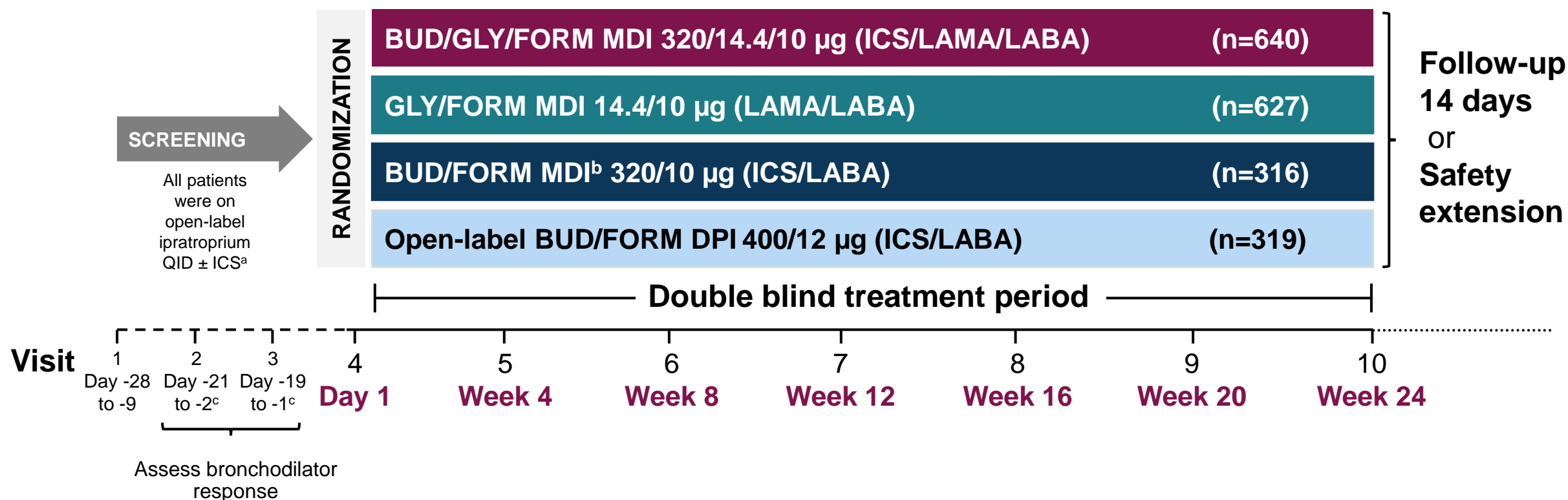
- 1. Ferguson GT et al. *Lancet Respir Med.* 2018;6:747-758; 2. Rabe KF et al. *Respir Med.* 2019;158:59-66.

ATHENA Phase III Clinical Trial Program

	TELOS ¹	SOPHOS ²	KRONOS ³	ETHOS ^{4,5}
Study Length and Description	24-week lung function study in patients with moderate to very severe COPD	12- to 52-week lung function study in patients with moderate to very severe COPD	24-week lung function study in patients with moderate to very severe COPD	52-week exacerbation study in patients with moderate to very severe COPD
Treatment Arms	BUD/FORM MDI 320/10 µg BID BUD/FORM MDI 160/10 µg BID FORM MDI 10 µg BID BUD MDI 320 µg BID BUD/FORM DPI 400/12 µg BID	BUD/FORM MDI 320/10 µg BID BUD/FORM MDI 160/10 µg BID FORM MDI 10 µg BID	BUD/GLY/FORM MDI 320/14.4/10 µg BID GLY/FORM MDI 14.4/10 µg BID BUD/FORM MDI 320/10 µg BID BUD/FORM DPI 400/12 µg BID	BUD/GLY/FORM MDI 320/14.4/10 µg BID BUD/GLY/FORM MDI 160/14.4/10 µg BID GLY/FORM MDI 14.4/10 µg BID BUD/FORM MDI 320/10 µg BID
Background Therapy	Must be using ≥1 inhaled bronchodilator as maintenance therapy	Must be using ≥1 inhaled bronchodilator as maintenance therapy	Use of ≥2 inhaled maintenance therapies for ≥6 weeks prior to screening	Use of ≥ 2 inhaled maintenance therapies for ≥ 6 weeks prior to screening
Exacerbation History	History of exacerbations not required	Documented history of exacerbations	History of exacerbations not required	Documented history of exacerbations
Patients, N	2389	1876	1902	8588
Primary Endpoint	Change from baseline in morning predose trough FEV ₁ and FEV ₁ AUC ₀₋₄	Change from baseline in morning predose trough FEV ₁	Change from baseline in morning predose trough FEV ₁ and FEV ₁ AUC ₀₋₄	Annual rate of moderate or severe exacerbations
Select Secondary Endpoints	<ul style="list-style-type: none"> • SGRQ responders • Peak change from baseline FEV₁ • Rescue medication use • Time to onset of action 	<ul style="list-style-type: none"> • SGRQ responders • Rescue medication use • EXACT total score • TDI focal score • Time to first moderate or severe exacerbation • Time to first CID 	<ul style="list-style-type: none"> • SGRQ total score and responders • Rescue medication use • Peak change from baseline in FEV₁ • Rate of moderate/severe exacerbations • RS-Total score • Time to CID • Time to onset of action 	<ul style="list-style-type: none"> • Time to first moderate or severe exacerbation • Rate of severe exacerbations • Rescue medication use • SGRQ total score • EXACT total score • TDI focal score

Study Design

Phase III, randomized (2:2:1:1), double-blind, parallel-group, 24-week trial conducted in 4 countries
All treatments were administered twice-daily and MDI treatments were administered via a single AEROSPHERE™ inhaler



^aAll patients received salbutamol sulphate for rescue use as needed; ^bBUD/Form MDI administered via the AEROSPHERE™ inhaler is not an available product;

^cReversibility to salbutamol sulphate was assessed at Visit 2 and reversibility to ipratropium bromide was assessed at Visit 3.

Baseline Patient Demographics (mITT Population)

	BUD/GLY/Form 320/14.4/10 µg (n=639)	GLY/Form 14.4/10 µg (n=625)	BUD/Form MDI 320/10 µg (n=314)	Open-label BUD/Form DPI 400/12 µg (n=318)
Age, mean (SD), years	64.9 (7.8)	65.1 (7.7)	65.2 (7.2)	65.9 (7.7)
Male, n (%)	460 (72.0)	430 (68.8)	224 (71.3)	236 (74.2)
Body mass index, mean (SD), kg/m ²	26.1 (6.7)	26.3 (6.4)	26.1 (5.8)	26.2 (6.3)
Current smoker, n (%)	256 (40.1)	257 (41.1)	115 (36.6)	122 (38.4)
Number of pack-years smoked ^a , median (range)	45.0 (10.0-256.0)	45.0 (10.0-171.0)	45.0 (10.0-192.0)	45.0 (10.0-180.0)
Ethnicity, n (%)				
White	329 (51.5)	301 (48.2)	157 (50.0)	163 (51.3)
Black	23 (3.6)	38 (6.1)	15 (4.8)	14 (4.4)
Asian	284 (44.4)	285 (45.6)	142 (45.2)	141 (44.3)
Other	3 (0.5)	1 (0.2)	0	0
Salbutamol reversible, ^b n (%)	286 (44.8)	266 (42.6)	130 (41.4)	140 (44.0)
Use of ICS at screening, n (%)	464 (72.6)	447 (71.5)	225 (71.7)	225 (70.8)
Post-salbutamol FEV ₁ , mean (SD), % predicted	50.2 (14.3)	50.2 (13.8)	50.0 (14.0)	50.7 (13.8)

Note: All treatments were administered BID.

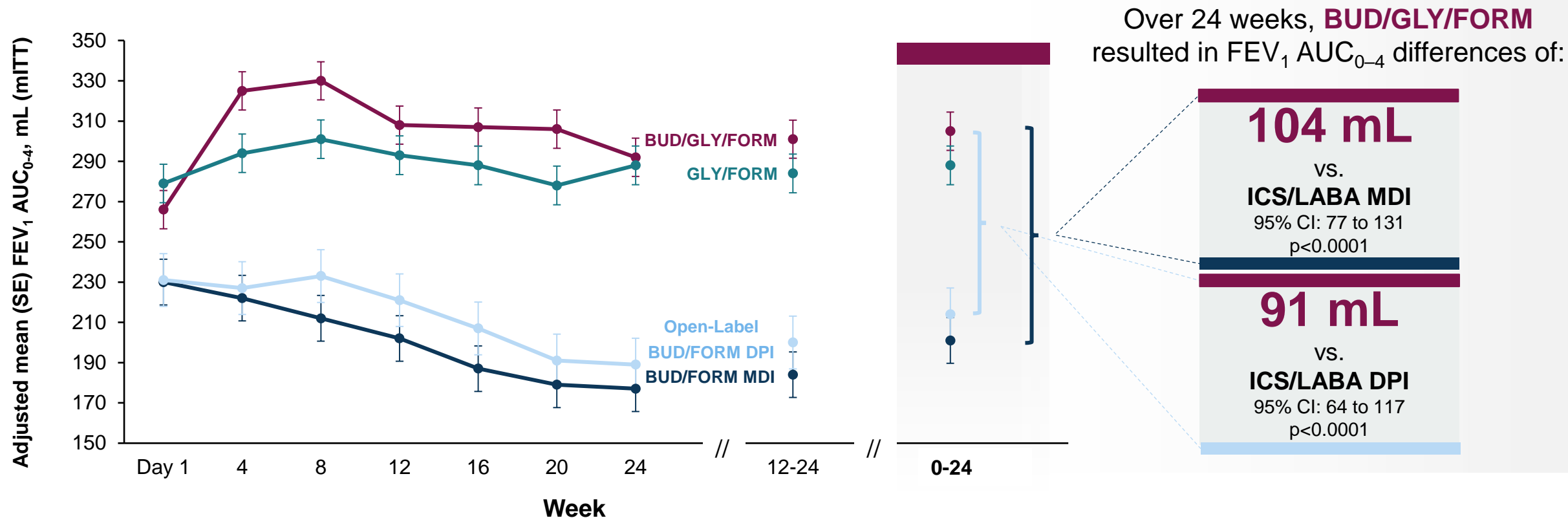
^aNumber of pack-years smoked = (number of cigarettes each day/20) x number of years smoked; ^bBronchodilator reversibility is defined as improvement in FEV₁ after salbutamol administration compared to before salbutamol administration of ≥12% and ≥200 mL.

Baseline Patient Demographics (mITT Population)

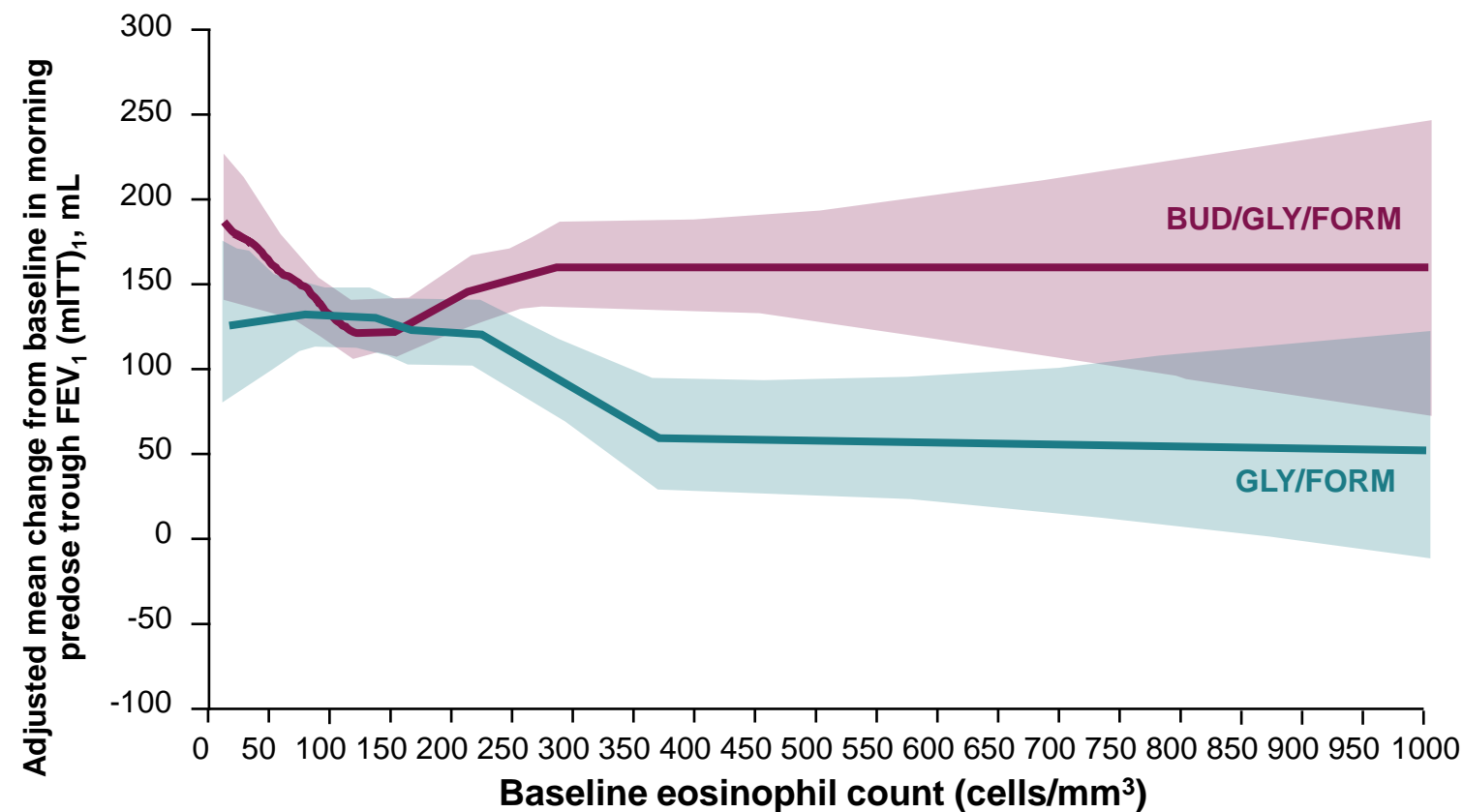
	BUD/GLY/FORM 320/14.4/10 µg (n=639)	GLY/FORM 14.4/10 µg (n=625)	BUD/FORM MDI 320/10 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
CAT total score, mean (SD)	18.7 (6.4)	18.1 (6.1)	18.4 (6.6)	18.0 (6.4)
Moderate or severe COPD exacerbation ^a , n (%)				
0	469 (73.4)	473 (75.7)	235 (74.8)	234 (73.6)
1	125 (19.6)	108 (17.3)	61 (19.4)	59 (18.6)
≥2	45 (7.0)	44 (7.0)	18 (5.7)	25 (7.9)
Moderate or severe exacerbation rate, mean (SD)	0.4 (0.8)	0.3 (0.7)	0.3 (0.6)	0.4 (0.8)
COPD severity, n (%)				
Mild	2 (0.3)	0	1 (0.3)	0
Moderate	310 (48.5)	306 (49.0)	154 (49.0)	160 (50.3)
Severe	275 (43.0)	267 (42.7)	133 (42.4)	138 (43.4)
Very severe	52 (8.1)	52 (8.3)	26 (8.3)	20 (6.3)
COPD duration, mean (SD), years	7.1 (6.0)	6.5 (5.4)	7.3 (6.2)	6.7 (5.5)
Rescue medication use, median (range), puffs/day	3.6 (1.0-13.0)	3.7 (1.0-18.4)	3.9 (1.0-17.7)	3.9 (1.0-20.3)
Eosinophils, n (%)				
<150 cells/mm ³	314 (49.1)	291 (46.6)	151 (48.1)	157 (49.4)
≥150 cells/mm ³	325 (50.9)	334 (53.4)	163 (51.9)	161 (50.6)

Note: All treatments were administered BID; ^aPast 12 months.

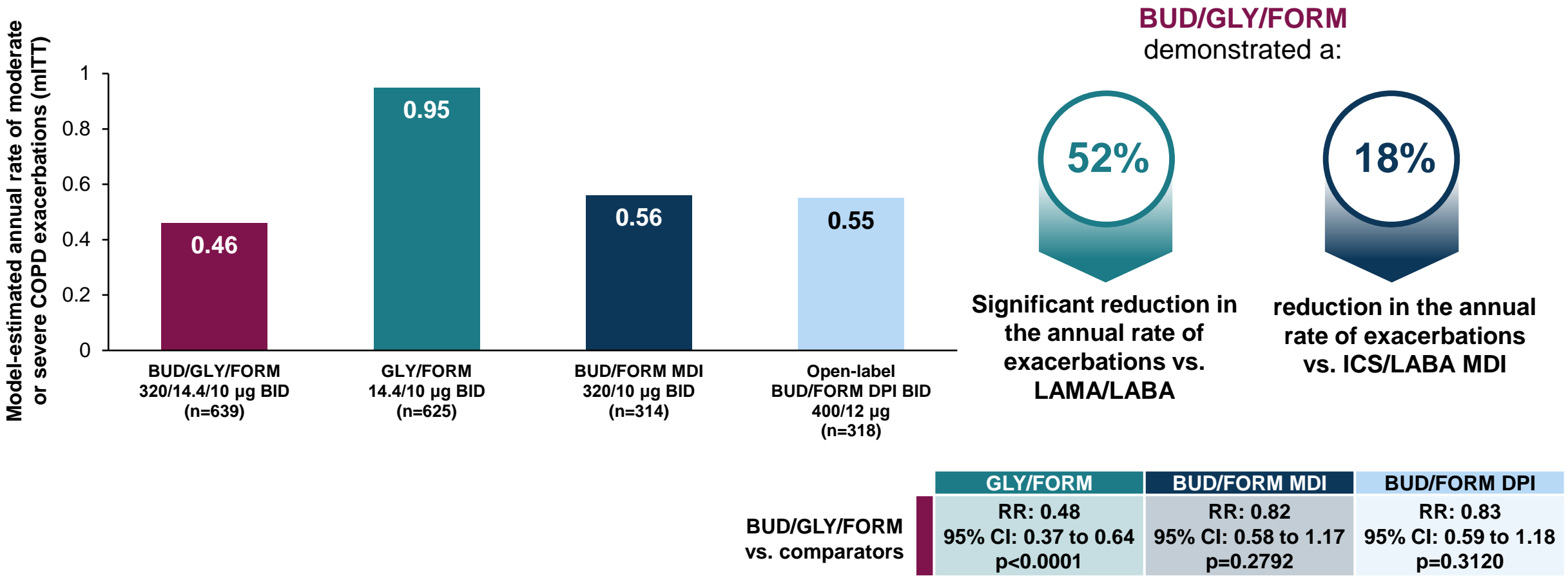
BUD/GLY/FORM significantly improved FEV₁ AUC₀₋₄ vs. ICS/LABA



BUD/GLY/FORM had greater improvements in morning predose trough FEV₁ vs. LAMA/LABA with increased blood eosinophil counts

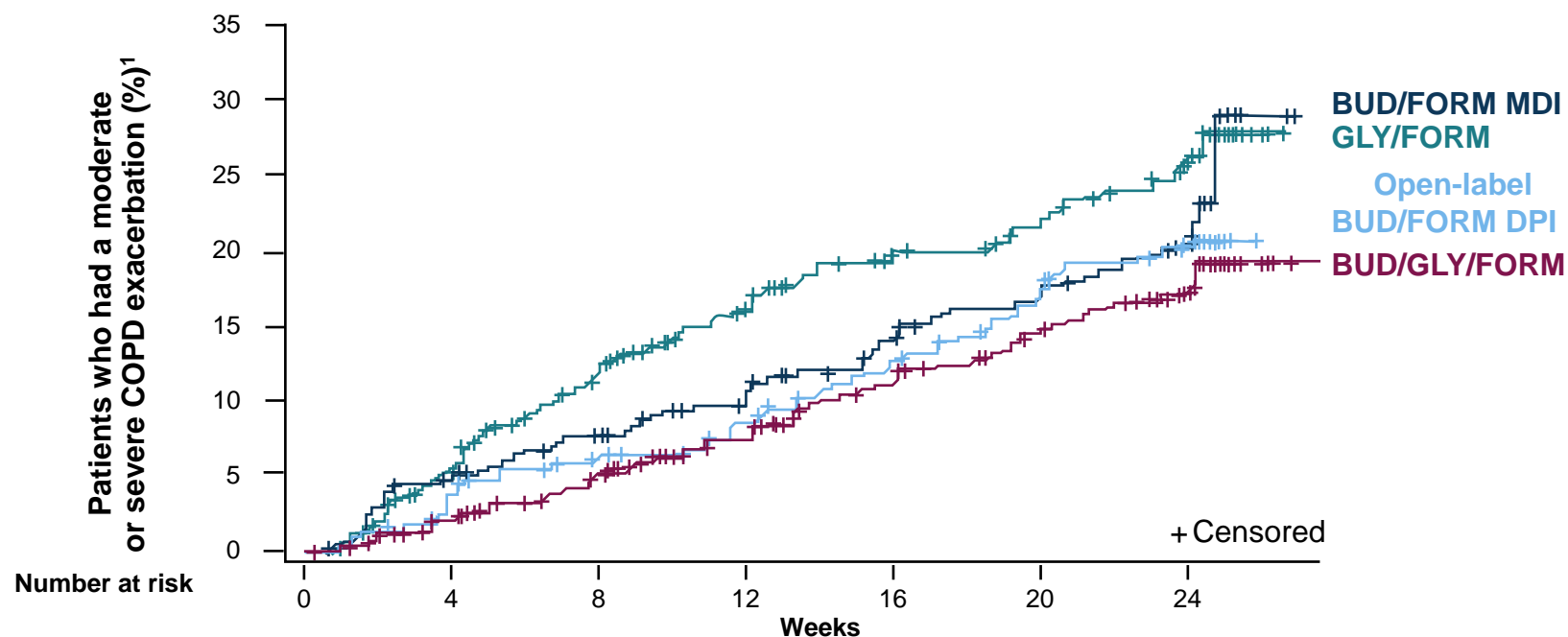


BUD/GLY/FORM significantly reduced the rate of moderate or severe exacerbations vs. LAMA/LABA^{1,2}



For medical reactive use only

BUD/GLY/FORM significantly increased time to first moderate or severe exacerbation vs. LAMA/LABA^a



BUD/GLY/FORM vs. dual therapies²:

HR, 0.59

95% CI, 0.46 to 0.76
unadjusted $p < 0.0001^{a,b}$
unadjusted $p = 0.0001^{a,c}$

vs.

LAMA/LABA

HR, 0.75

95% CI, 0.55 to 1.02
 $p = 0.0635^b$
unadjusted $p = 0.0281^{a,c}$

vs.

ICS/LABA MDI

HR, 0.85

95% CI, 0.62 to 1.17
 $p = 0.3225^b$
 $p = 0.0832^c$

vs.

ICS/LABA DPI

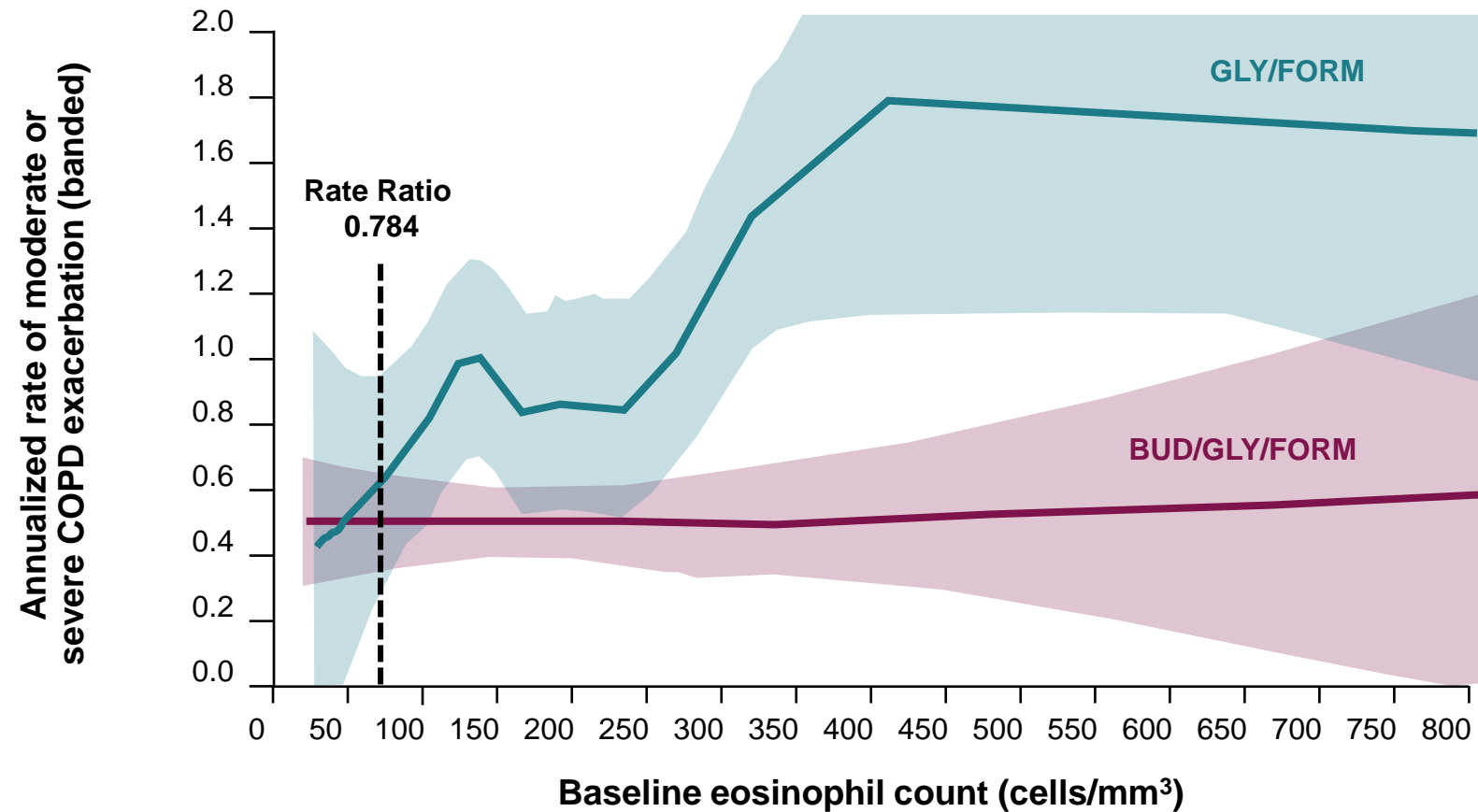
^ap-value is unadjusted - an endpoint earlier in the Type I error control testing hierarchy did not reach significance or it was not included in the Type I error control strategy; ^bCox regression;

^cLog rank.

For medical reactive use only



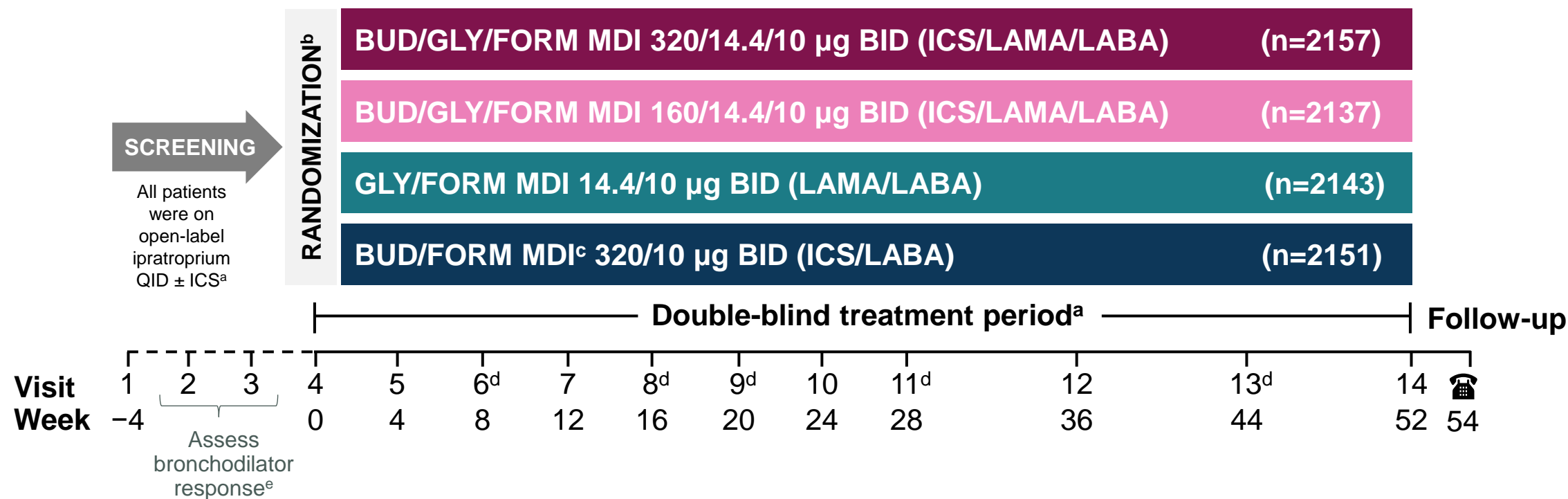
The exacerbation benefit of BUD/GLY/FORM vs. LAMA/LABA increased with blood eosinophil counts



Study Design

Phase III, randomized, double-blind, parallel-group, 52-week trial conducted in 26 countries^{1,2}

All treatments were administered twice daily via a single AEROSPHERE™ inhaler



^aAll patients received albuterol sulfate for rescue use as needed; ^bRandomization was stratified by exacerbation history (1 or ≥2 moderate/severe exacerbations), post-bronchodilator FEV₁ (25% to <50% or 50% to <65% predicted), blood eosinophil count (<150 or ≥150 cells/mm³), and country; ^cBUD/FORM MDI delivered via the AEROSPHERE™ inhaler is not an available product; ^dVisit conducted via telephone contact; all other visits were conducted in the clinic; ^eReversibility to a SABA (for classification) and to a SAMA (for characterization) was tested at Visit 2 and Visit 3, respectively.

Other
Fixed-Dose
Triple Therapy
Studies Design
Differences

Baseline Patient Demographics

Demographics ^a	BUD/GLY/Form 320/14.4/10 µg (n=2137)	BUD/GLY/Form 160/14.4/10 µg (n=2121)	GLY/Form 14.4/10 µg (n=2120)	BUD/Form 320/10 µg (n=2131)
Age, mean (SD), years	64.6 (7.6)	64.6 (7.6)	64.8 (7.6)	64.6 (7.6)
Male, n (%)	1260 (59.0)	1298 (61.2)	1244 (58.7)	1279 (60.0)
Race, white, n (%)	1819 (85.1)	1783 (84.1)	1808 (85.3)	1816 (85.2)
Current smoker, n (%)	910 (42.6)	865 (40.8)	856 (40.4)	864 (40.5)
Number of pack-years smoked, ^b mean±SD	47.0 (25.1)	47.9 (25.8)	48.4 (26.5)	47.1 (26.3)
COPD exacerbation history, ^c mean (SD)	1.7 (0.8)	1.7 (0.9)	1.7 (0.8)	1.7 (0.9)
1 moderate or severe, n (%)	940 (44.0)	932 (43.9)	907 (42.8)	912 (42.8)
≥2 moderate or severe, n (%)	1195 (55.9)	1187 (56.0)	1211 (57.1)	1217 (57.1)
≥1 severe, n (%)	451 (21.1)	463 (21.8)	429 (20.2)	458 (21.5)
Blood eosinophil count, n (%)				
≥150 cells/mm ³	1277 (59.8)	1258 (59.3)	1272 (60.0)	1294 (60.7)
≥300 cells/mm ³	310 (14.5)	318 (15.0)	293 (13.8)	333 (15.6)
Post-albuterol FEV ₁ , % of predicted, mean (SD)	43.6 (10.3)	43.1 (10.4)	43.5 (10.2)	43.4 (10.4)
50% to <80% (moderate COPD), ^d n (%)	613 (28.7)	604 (28.5)	596 (28.1)	614 (28.8)
30% to <50% (severe COPD), n (%)	1305 (61.1)	1270 (59.9)	1293 (61.0)	1283 (60.2)
<30% (very severe COPD), ^d n (%)	217 (10.2)	245 (11.6)	229 (10.8)	233 (10.9)
Bronchodilator reversibility, ^e n (%)	657 (30.7)	631 (29.8)	669 (31.6)	654 (30.7)
Use of ICS at screening, n (%)	1706 (79.8)	1729 (81.5)	1707 (80.5)	1704 (80.0)
CAT score, mean (SD)	19.7 (6.5)	19.6 (6.6)	19.5 (6.6)	19.5 (6.5)

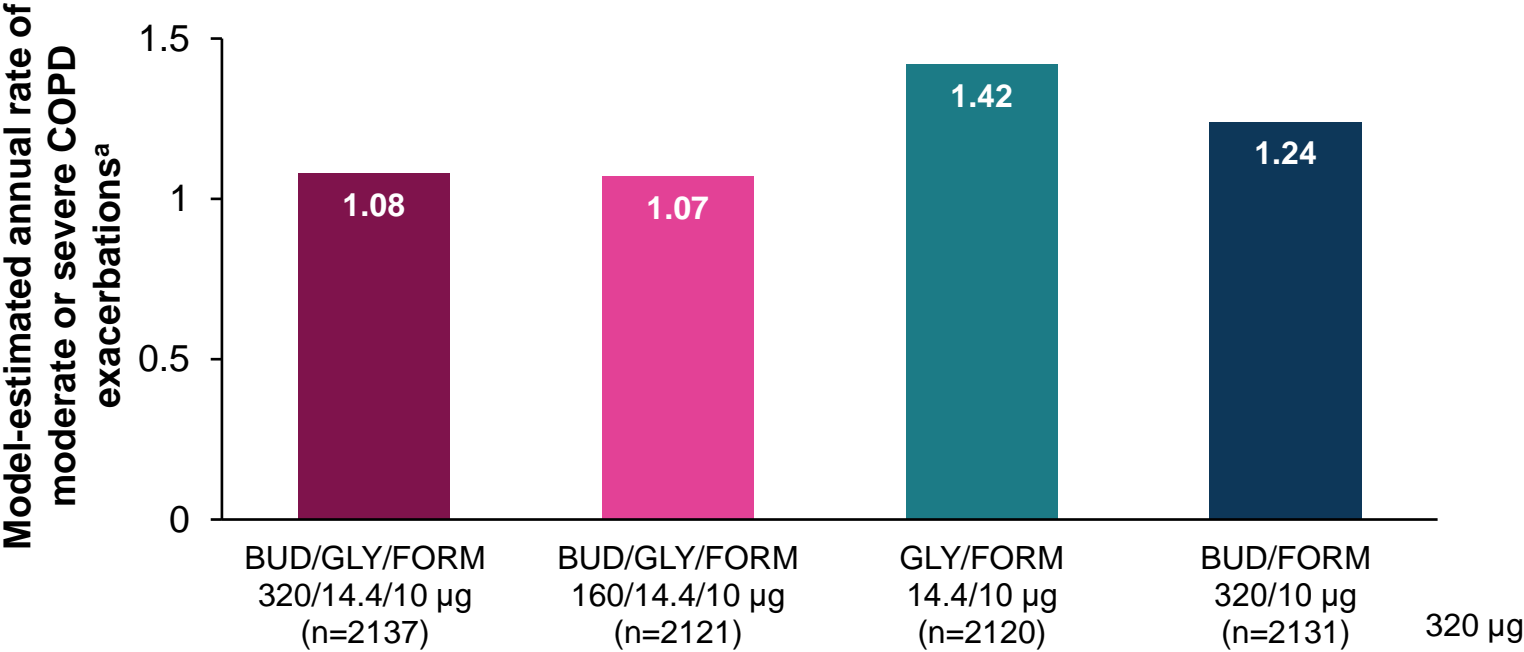
Note: All treatments were administered BID.

^amITT population; ^bNumber of pack-years smoked = (number of cigarettes each day/20) x number of years smoked²; ^cPast 12 months; ^dThe study only enrolled patients with postbronchodilator FEV₁ 25% to 65% predicted normal; ^eBronchodilator reversibility is defined as an increase in FEV₁ of ≥12% and ≥200 mL after administration of albuterol.

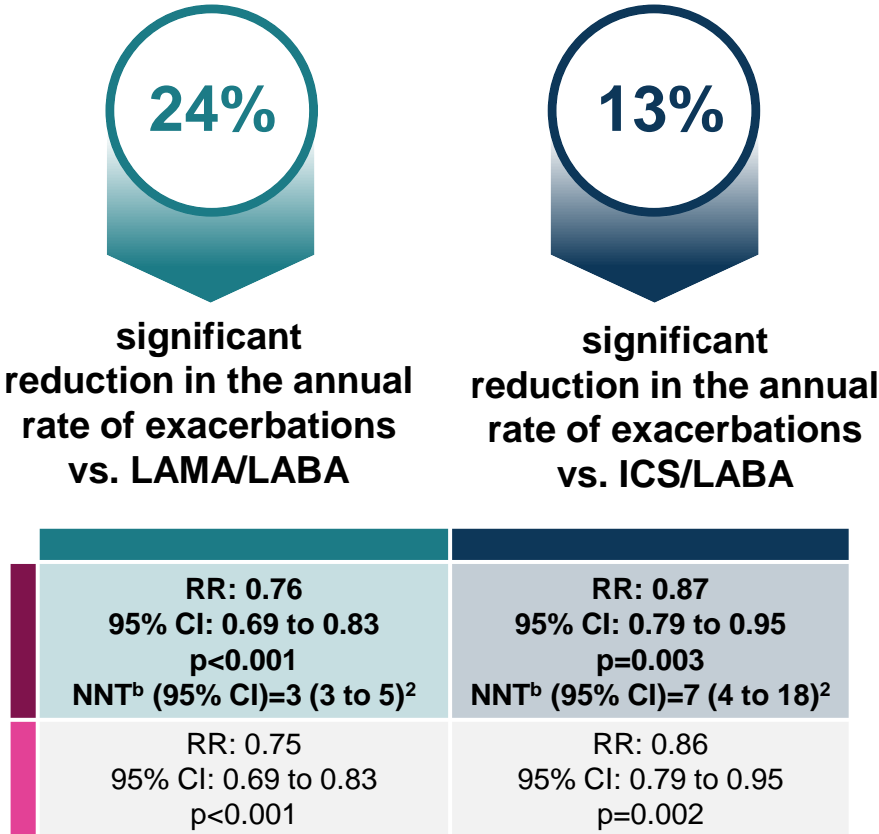
Prior COPD-
Related
Inhaled
Therapies

Baseline
Characteristics
Differences

BUD/GLY/FORM Significantly Reduced the Rate of Moderate or Severe Exacerbations vs. Dual Therapies¹



BUD/GLY/FORM 320/14.4/10 µg demonstrated a:

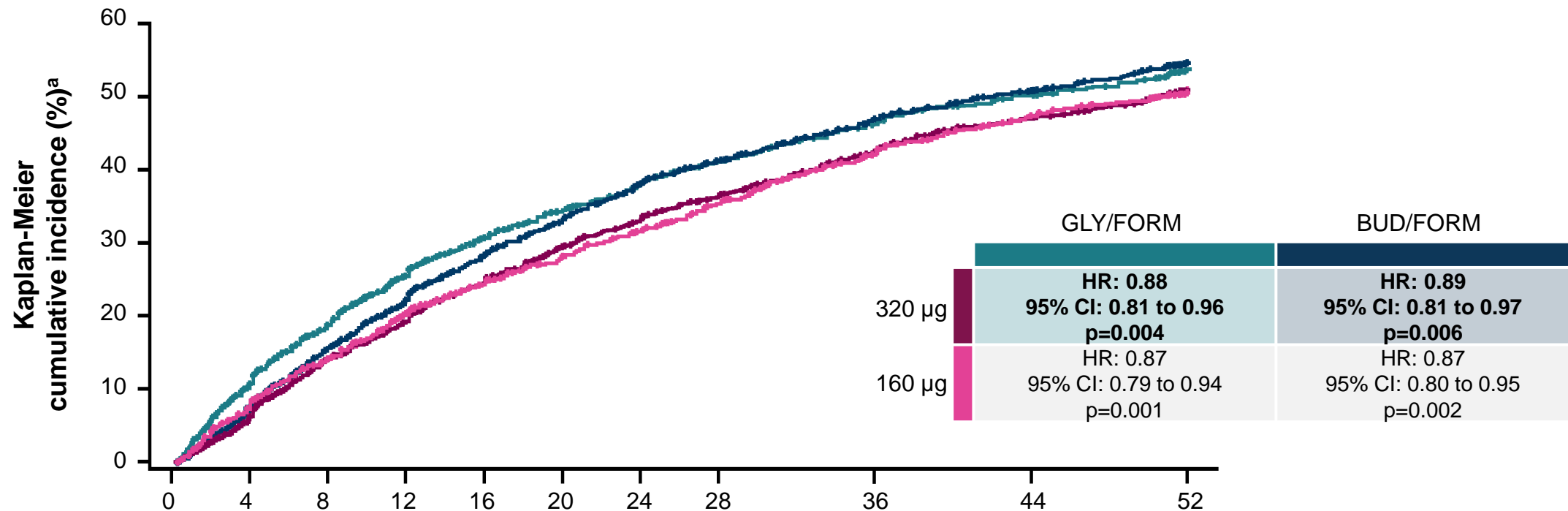


Notes: All treatments were administered BID. In the secondary analysis of the primary endpoint, the rate ratios of moderate or severe exacerbations that were determined with the use of the attributable estimand were similar to the rate ratios in the primary analysis.

^amITT population; ^bNNT calculated using 1/(rate_{BUD/GLY/FORM} - rate_{comparator}).

Exacerbation Rate
Based on
Exacerbation History

BUD/GLY/FORM Significantly Prolonged the Time to First Moderate/Severe COPD Exacerbation vs. Dual Therapies

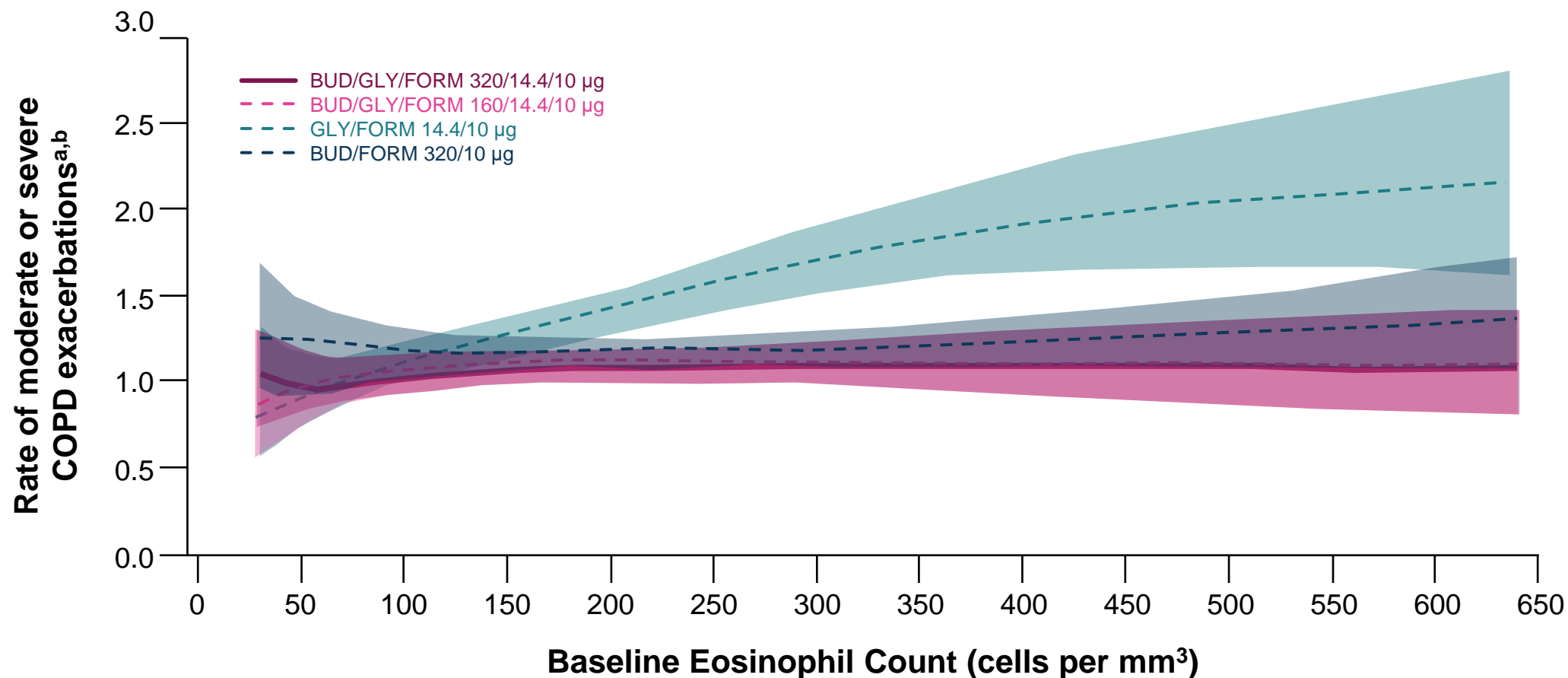


Number of Patients at Risk		Weeks									
BUD/GLY/FORM 320/14.4/10 µg	2137	1989	1776	1651	1523	1402	1318	1241	1106	996	760
BUD/GLY/FORM 160/14.4/10 µg	2121	1936	1767	1623	1510	1426	1347	1259	1108	985	767
GLY/FORM 14.4/10 µg	2120	1849	1633	1466	1338	1251	1166	1096	988	907	692
BUD/FORM 320/10 µg	2131	1935	1721	1564	1410	1300	1196	1119	989	899	678
+ Censored											

Note: All treatments were administered BID.

^amITT population.

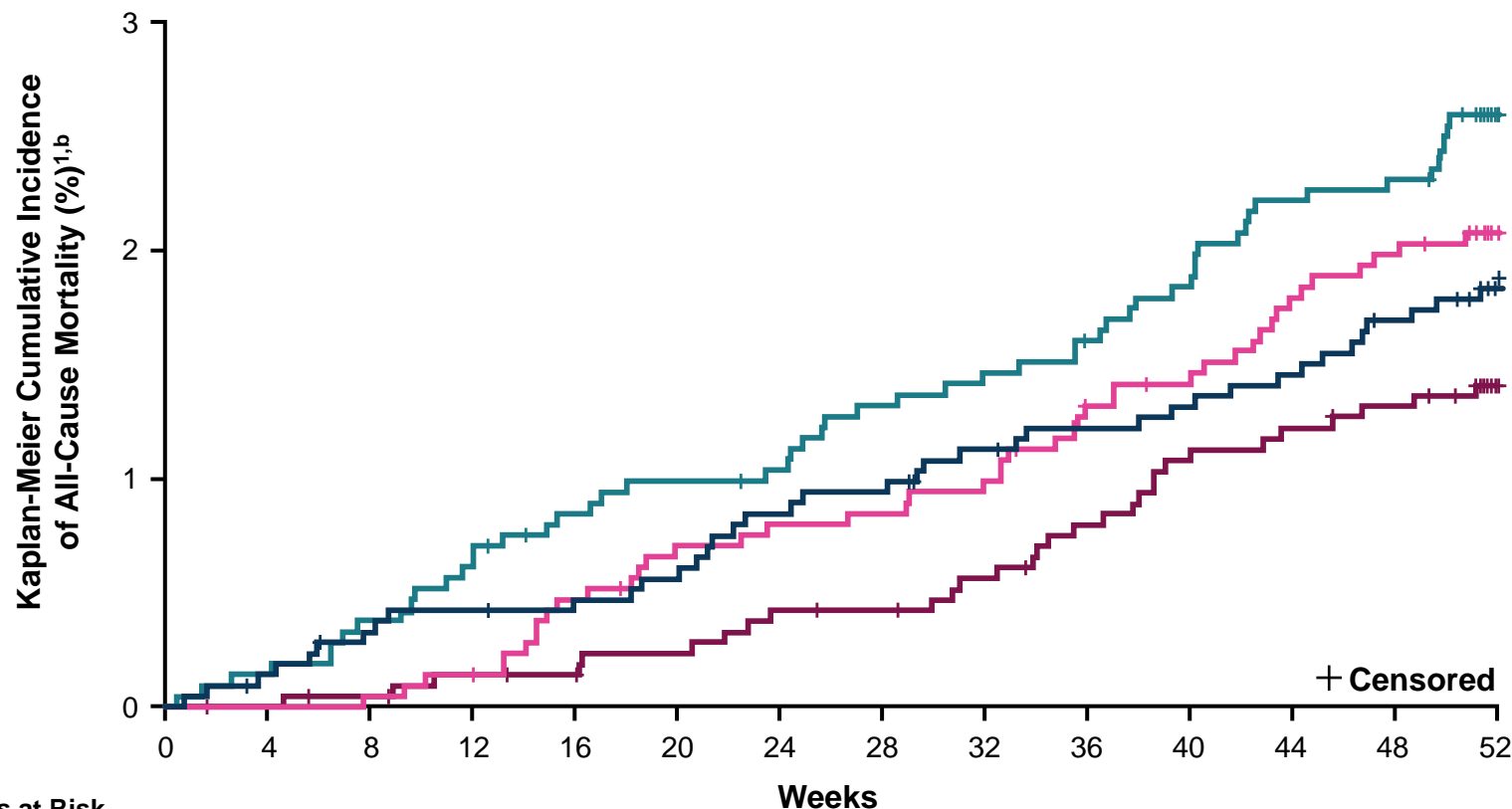
The Exacerbation Benefit of BUD/GLY/FORM vs. LAMA/LABA Increased With Increased Eosinophil Counts



Notes: All treatments were administered BID.

^amITT population; ^bBanded areas indicate 95% confidence intervals.

BUD 320/GLY/FORM Significantly Reduced Risk of All-Cause Mortality vs. LAMA/LABA^a in the Original and Final Retrieved Datasets^{1,2}



Over 52 weeks
BUD/GLY/FORM 320/14.4/10 µg
demonstrated a:

49%

**significant reduction
vs. LAMA/LABA^{1,c,d}**

HR: 0.51; 95% CI: 0.33 to 0.80;
unadjusted p=0.0035^a

NNT = 80 vs. LAMA/LABA
(95% CI: 58 to 198)

28% reduction vs. ICS/LABA
HR: 0.72; 95% CI: 0.44 to 1.16; p=0.1721

Patients at Risk

Weeks

BUD/GLY/FORM 320/14.4/10 µg	2137	2136	2134	2131	2130	2127	2123	2122	2118	2112	2106	2103	2100	2075
BUD/GLY/FORM 160/14.4/10 µg	2121	2121	2120	2118	2110	2104	2102	2101	2098	2087	2084	2076	2072	2062
GLY/FORM 14.4/10 µg	2120	2117	2112	2106	2100	2097	2095	2089	2086	2082	2077	2069	2067	2045
BUD/FORM 320/10 µg	2131	2127	2122	2120	2118	2116	2110	2108	2102	2099	2097	2094	2088	2075

Note: All treatments were administered BID. ^aSignificant p-values in the original dataset are unadjusted due to an endpoint in the Type I error control testing hierarchy not reaching significance; ^bITT population; ^cResults shown include additional data from 354 patients who had incomplete 1-year vital status at the time of trial completion; ^dThe percentage of patient deaths included in the time to death analysis in each arm were as follows: BUD 320/GLY/FORM, 1.4%; BUD 160/GLY/FORM, 2.1%; GLY/FORM, 2.6%; BUD/FORM, 1.9%.

1. Adapted from Martinez FJ et al. Article and supplementary appendix. *Am J Respir Crit Care Med.* 2021;203(5):553-564; 2. Rabe KF et al. Article and supplementary appendix.

**Mortality Results in
Original Dataset**



Device

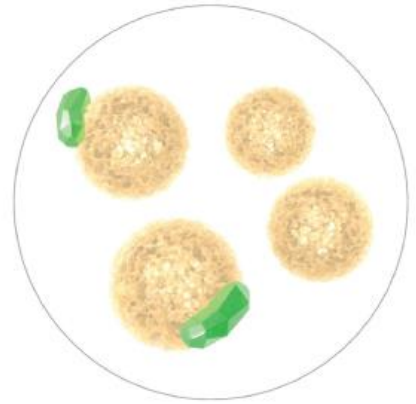


最新的COPD三合一療法

-給病人更好的未來-

Co-suspension delivery technology, as used in the Aerosphere inhaler

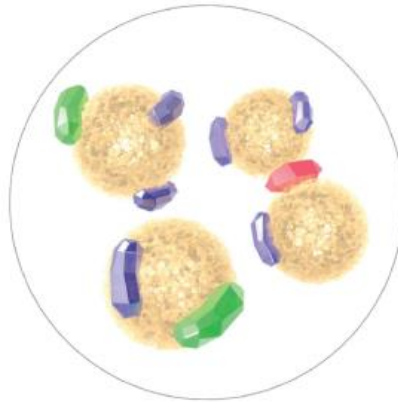
Monocomponent suspension
(eg GP MDI)



Dual FDC suspension
(eg GFF MDI)



Triple FDC suspension
(eg BGF MDI)



Spray-dried phospholipid/ CaCl_2 porous particle



LAMA crystal



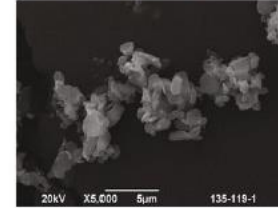
LABA crystal



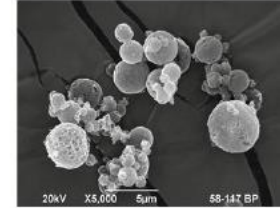
ICS crystal



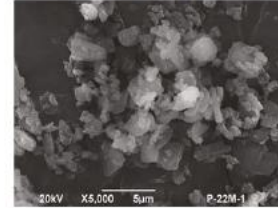
GP Drug Crystals



Porous Particles



FF Drug Crystals

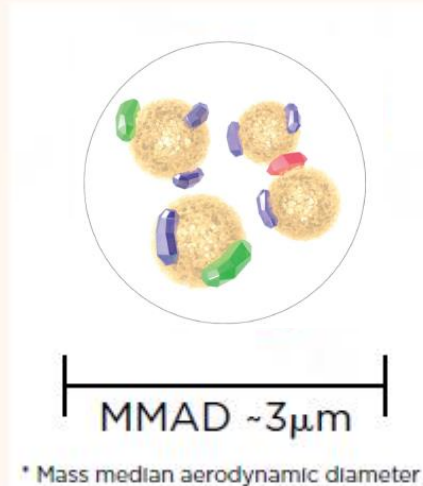


Porous particles made of phospholipids, a natural component of lung surfactant

Similar FPFs, MMADs, and particle size

AEROSPHERE™ Delivery Technology is an innovative technology providing effective, consistent drug delivery to the whole lung

Optimally-sized vehicles for delivering inhaled drugs



Drug crystals attach to light, porous particles made of phospholipids, a natural component of lung surfactant^{2,3}

A stable, homogenous suspension that delivers a consistent dose



The particles form a stable suspension in the device and deliver the right dose, every dose – from first to last inhalation¹

Effective, consistent delivery to the whole lung – both large and small airways



On inhalation, the aerodynamic particles act as vehicles, delivering the drug combination to the large and small airways^{1,2,5}

Consistent deposition of drug combination in the airways



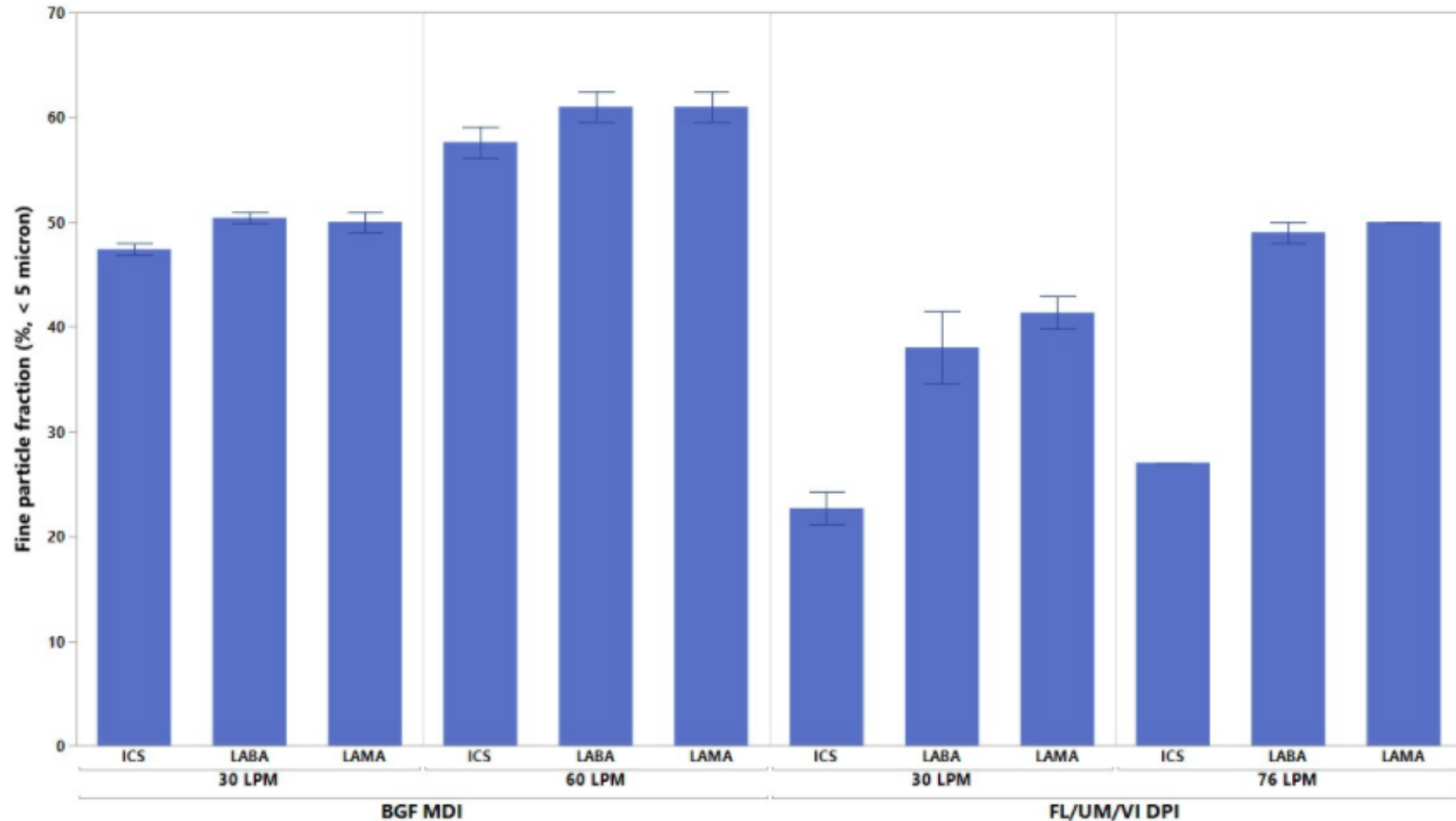
The particles then disperse on the airway surface, effectively depositing the drug combination throughout the lung^{2,4}

Supporting references

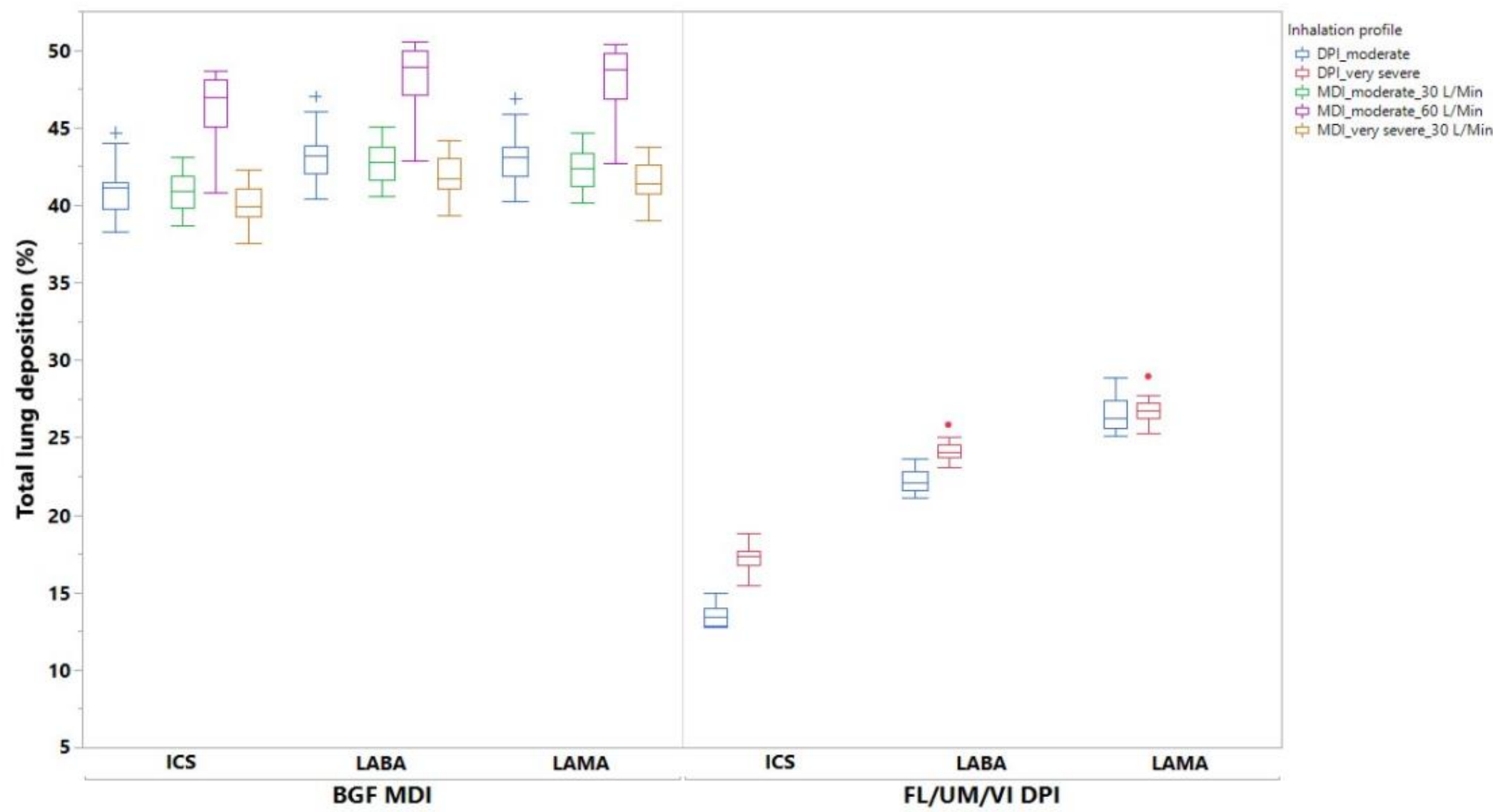
1. Vehring et al. *Langmuir*. 2012;28(42):15015-15023. doi:10.1021/la302281n
2. Taylor et al. *Eur J Pharm Sci*. 2018 Jan 1;111:450-457
3. Wauthoz N et al. *Eur J Lipid Sci Technol*. 2014; 116(9):1114-1128
4. Lechuga-Ballesteros D et al. *Future med Chem* 2011; 3:1703-18
5. Fernandez-Tena A. et al. *Arch Bronconeumol*. 2012 Jul;48(7):240-6



Consistent lung delivery of inhaled triple ICS/LAMA/LABA combination using the co-suspension delivery technology: an in silico modelling study



Consistent lung delivery of inhaled triple ICS/LAMA/LABA combination using the co-suspension delivery technology: an in silico modelling study



Efficacy and safety of ICS/LABA/LAMA FDCs in COPD: a network meta-analysis

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²Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy.



Introduction

Triple FDC therapy is recommended in severe COPD patients experiencing frequent exacerbations and/or symptoms not controlled by dual FDCs. Nevertheless, no RCTs have directly compared the different ICS/LABA/LAMA FDCs.

Aim

To compare the approved ICS/LABA/LAMA FDCs on the main functional, clinical, and safety outcomes in COPD.

Methods

A network meta-analysis was performed by connecting BDP/FOR/GLY, BUD/GLY/FOR, and FF/UMEC/VI via ICS/LABA or LABA/LAMA FDCs arms. The following outcomes were investigated: risk of exacerbation, trough FEV₁, TDI, SGRQ, risk of serious adverse events (SAEs), cardiovascular (CV) SAEs, pneumonia, and all-cause mortality. The Implemented Bidimensional Surface under the cumulative ranking curve analysis (IBIS) was also carried out. The study was consistent with PRISMA-P and registered in PROSPERO (CRD42022301189).

Results

Data from 21,809 COPD patients were extracted from the ETHOS, IMPACT, KRONOS, and TRILOGY studies (Figure 1). No significant ($P > 0.05$) differences were detected across the triple FDCs with respect to the risk of exacerbation, trough FEV₁, TDI, SGRQ, risk of serious adverse events, cardiovascular SAEs, pneumonia, and all-cause mortality (Table 1). According to IBIS score, BDP/FOR/GLY 200/12/25 µg BID was the FDC reporting the best combined efficacy/safety profile (area 41.41%), although FF/UMEC/VI 100/62.5/25 µg QD showed the greatest efficacy profile (50.54%) (Figure 2). The protection against mortality related to the dose of ICS.

Conclusion

All triple FDCs are effective and safe in COPD regardless of the regimen of administration (twice daily vs. once daily), with no relevant difference on the risk of CV SAEs and pneumonia. The effect against the risk of AECOPD was not related to the level of ICS in the FDC, and the FDC including an ICS at lower dose was less effective in improving trough FEV₁.

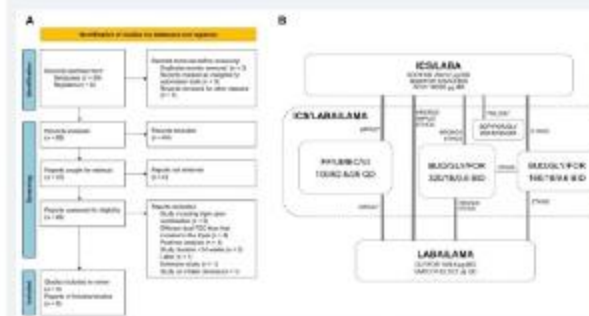


Figure 1. PRISMA 2020 flow diagram (A) and diagram displaying the Bayesian network across the treatments (B).

Comparison	Number of studies included in meta-analysis	Length (95% CrI)	TD (point)	SGRQ (point)	CV SAEs (95% CrI)	Pneumonia (95% CrI)	All-cause mortality (95% CrI)
BDP/FOR/GLY 200/12/25 µg BID vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BUD/GLY/FOR 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
FF/UMEC/VI 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BDP/FOR/GLY 200/12/25 µg BID vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BUD/GLY/FOR 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
FF/UMEC/VI 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BDP/FOR/GLY 200/12/25 µg BID vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BUD/GLY/FOR 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
FF/UMEC/VI 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BDP/FOR/GLY 200/12/25 µg BID vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
BUD/GLY/FOR 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00
FF/UMEC/VI 100/62.5/25 µg QD vs. LABA/LAMA 5/5/25 µg QD	10	10.25 - 10.40	0.00	0.00	0.00	0.00	0.00

Table 1. RCTs included in the meta-analysis. Relative effects with 95% CrI and GRADE score resulting from the overall network meta-analysis.

Quality of evidence according to GRADE: +++++ high, +++ moderate, ++ low, + very low.

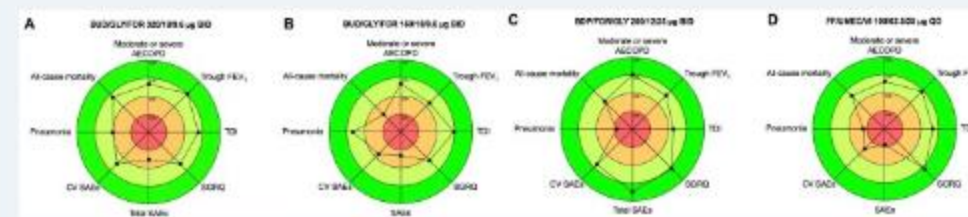


Figure 2. Graphical representation of combined efficacy/safety profile of ICS/LABA/LAMA FDCs in COPD patients according to the IBIS score: the greater the area, the better the efficacy/safety profile.

BUD/GLY/FOR 320/18/9.6 µg BID vs.								
BUD/GLY/FOR 160/18/9.6 µg BID	0.89 (0.31 – 2.63) +++	8.86 (-52.71 – 71.98) +++	-0.02 (-0.43 – 0.33) +++	-0.17 (-1.68 – 1.45) +++	0.93 (0.39 – 2.30) +++	0.82 (0.37 – 1.69) +++	1.14 (0.60 – 2.27) ++++	0.73 (0.37 – 1.61) ++++
FF/UMEC/VI 100/62.5/25 µg QD	0.83 (0.24 – 2.92) ++	-20.11 (-90.78 – 58.07) ++	0.09 (-0.36 – 0.56) ++	0.47 (-1.27 – 2.31) ++	0.87 (0.31 – 2.43) ++	0.65 (0.26 – 1.49) +++	0.85 (0.43 – 1.85) +++	0.95 (0.40 – 2.42) +++
BUD/GLY/FOR 160/18/9.6 µg BID vs.								
FF/UMEC/VI 100/62.5/25 µg QD	0.93 (0.22 – 3.89) ++	-29.36 (-108.70 – 57.26) ++	0.11 (-0.37 – 0.66) ++	0.62 (-1.38 – 2.68) ++	0.94 (0.30 – 3.05) ++	0.80 (0.30 – 1.98) ++	0.75 (0.34 – 1.72) ++++	1.28 (0.55 – 3.30) ++++

Quality of evidence according to GRADE: +++++ high, +++ moderate, ++ low, + very low.

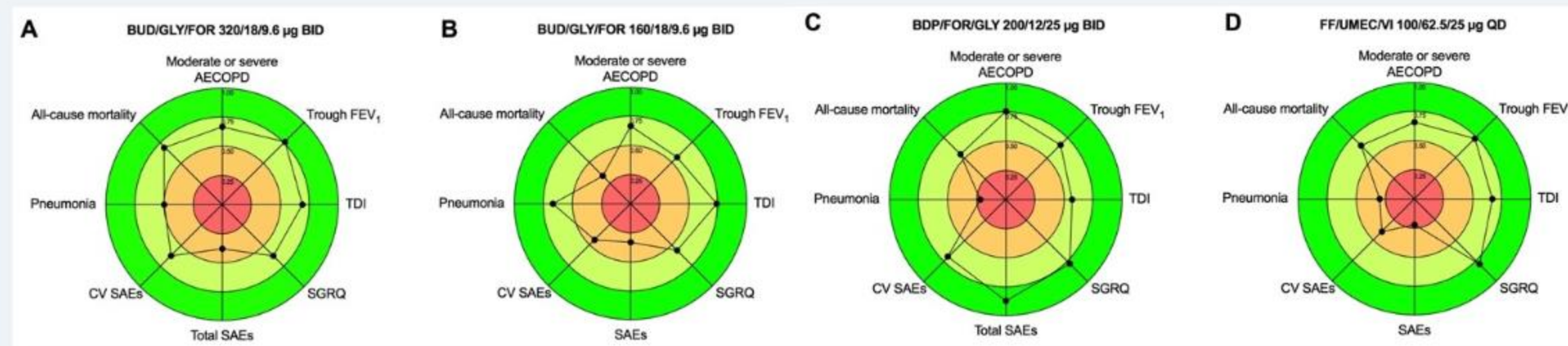


Figure 2. Graphical representation of combined efficacy/safety profile of ICS/LABA/LAMA FDCs in COPD patients according to the IBiS score: the greater the area, the better the efficacy/safety profile.

Maintenance and reliever therapy with budesonide/formoterol versus fixed-dose fluticasone/salmeterol in patients with COPD

Introduction

Maintenance and reliever therapy (MART) with inhaled corticosteroid (ICS)/formoterol effectively reduces exacerbations compared to fixed-dose therapy with ICS/long-acting β_2 -agonist [1]. No studies have investigated MART in patients with chronic obstructive pulmonary disease (COPD).

Aims

We aimed to compare the efficacy and safety of budesonide/formoterol MART versus fixed-dose fluticasone/salmeterol in patients with moderate to severe COPD.

Methods

Patients with COPD and ≥ 1 exacerbation in the previous 2 years were randomly assigned to open-label MART (Spiromax® budesonide/formoterol 160/4.5 μg 2 inhalations twice daily + 1 prn) or fixed-dose therapy (Diskus® fluticasone propionate/salmeterol combination (FSC) 500/50 μg 1 inhalation twice daily + salbutamol 100 μg prn) for one year in a multicenter study. The primary outcome was the rate of moderate/severe exacerbations, defined by treatment with oral prednisolone and/or antibiotics.

Results

Table 2: Exacerbations and (Serious) Adverse Events

Variable	MART n = 103	Fixed-dose n = 92	P-value
Total no. of patient years of study treatment (= patient-yr)	85	66	
Patients with exacerbation, n (%)	59 (57.3)	54 (58.7)	0.842
Exacerbations per patient during study, n (%)			
0	44 (42.7)	38 (41.3)	0.368
1	25 (24.3)	32 (34.8)	
≥ 2	34 (33)	22 (23.9)	
Total no. of exacerbations per patient-yr	1.32	1.32	0.984*
Total no. of moderate exacerbations per patient-yr	1.16	1.18	0.963*
Total no. of severe exacerbations per patient-yr	0.15	0.14	0.936*
Patients with at least one adverse event, n (%)	75 (73)	62 (68)	0.408
Serious adverse events, n (%)	20 (20)	17 (19)	0.857
Hospitalisation due to pneumonia	5 (5)	0 (0)	
Hospitalisation due to exacerbation	8 (8)	9 (10)	
Other	8 (8)	8 (9)	
Patients with confirmed or probable pneumonia, n (%)			
0	96 (93)	91 (99)	0.068*
1	6 (6)	1 (1)	
2	1 (1)	0	
Patients with X-ray confirmed pneumonia, n (%)	5 (4.9)	1 (1.1)	0.216
ICS dosage/day, $\mu\text{g/day}$ in budesonide equivalents (IQR)	928 (798-1168)	1747 (1643-1877)	<0.001*

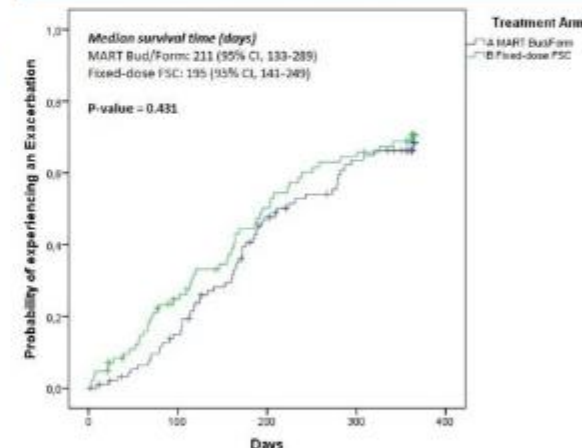
Conclusions

This first study of MART in COPD found that budesonide/formoterol MART is similarly effective as fluticasone/salmeterol fixed-dose therapy in moderate-severe COPD patients, at a lower daily inhaled corticosteroid dosage.

Table 1: Baseline characteristics

Characteristic	MART n = 103	Fixed-dose n = 92
Age, years	65 (7.83)	65 (6.98)
Male ^a , n (%)	63 (61.2)	73 (79.4)
Smoking, packyears (IQR)	45 (31-71)	51 (30-70)
ICS use at entry, n (%)	84/100 (84)	74/91 (81.3)
Exacerbations during last 12 months, n (%)		
0	18 (17.5)	18 (19.6)
1	44 (42.7)	41 (44.6)
2	24 (23.3)	19 (20.7)
>2	17 (16.5)	14 (15.1)
FEV ₁ % predicted, post-BD (IQR)	53 (40-63)	53 (42-66)
Blood eosinophils, 10 ⁹ /L (IQR)	0.18 (0.12-0.26)	0.22 (0.12-0.32)

Figure 1: Time to first exacerbation



Data presented as median (IQR), n (%) or mean \pm SD. Patient-years were based on exposure time to study medication. BD: bronchodilator; FEV₁: forced expiratory volume in 1 s; ICS: inhaled corticosteroids. P-value based on Chi-Square test unless stated otherwise. ^a Difference in male-female ratio arose by accident during randomisation. * P-value based on Mann-Whitney U test. # P-value based on Fisher's exact test.

References

1. Sobieraj DM, et al. JAMA 2018 Apr 10;319(14):1485-1496.



Conclusion



最新的COPD三合一療法

-給病人更好的未來-

WHO

Initial triple therapy

- First diagnosed COPD due to severe AE
- Patients who are diagnosed with
 - ✓ severe airflow limitation ($FEV_1 < 50\%$)
 - ✓ Symptomatic
 - ✓ frequent moderate (≥ 2)
 - ✓ severe exacerbations in the previous year
- Peripheral eosinophilia ($> 300/\mu L$).

ERJ Open Res 2019; 5: 00185-2018

- Initial eosinophil > 100 with 1 AE
 - ✓ Consider triple therapy in $CAT \geq 18$, $FEV_1 \leq 42\%$, $AE \geq 2$

Int J Chron Obstruct Pulmon Dis 2020;15 3375–3384

- Old age and male
- Current smoker
- Obesity / Underweight
- Low FEV_1
- Pulmonary vascular disease / Lung cancer / ACO / Osteoarthritis
- Frequent exacerbator

Ther Adv Respir Dis 2021, Vol. 15: 1–14

- High blood eosinophilia
- Older age
- More AEs in the previous year
- ACO

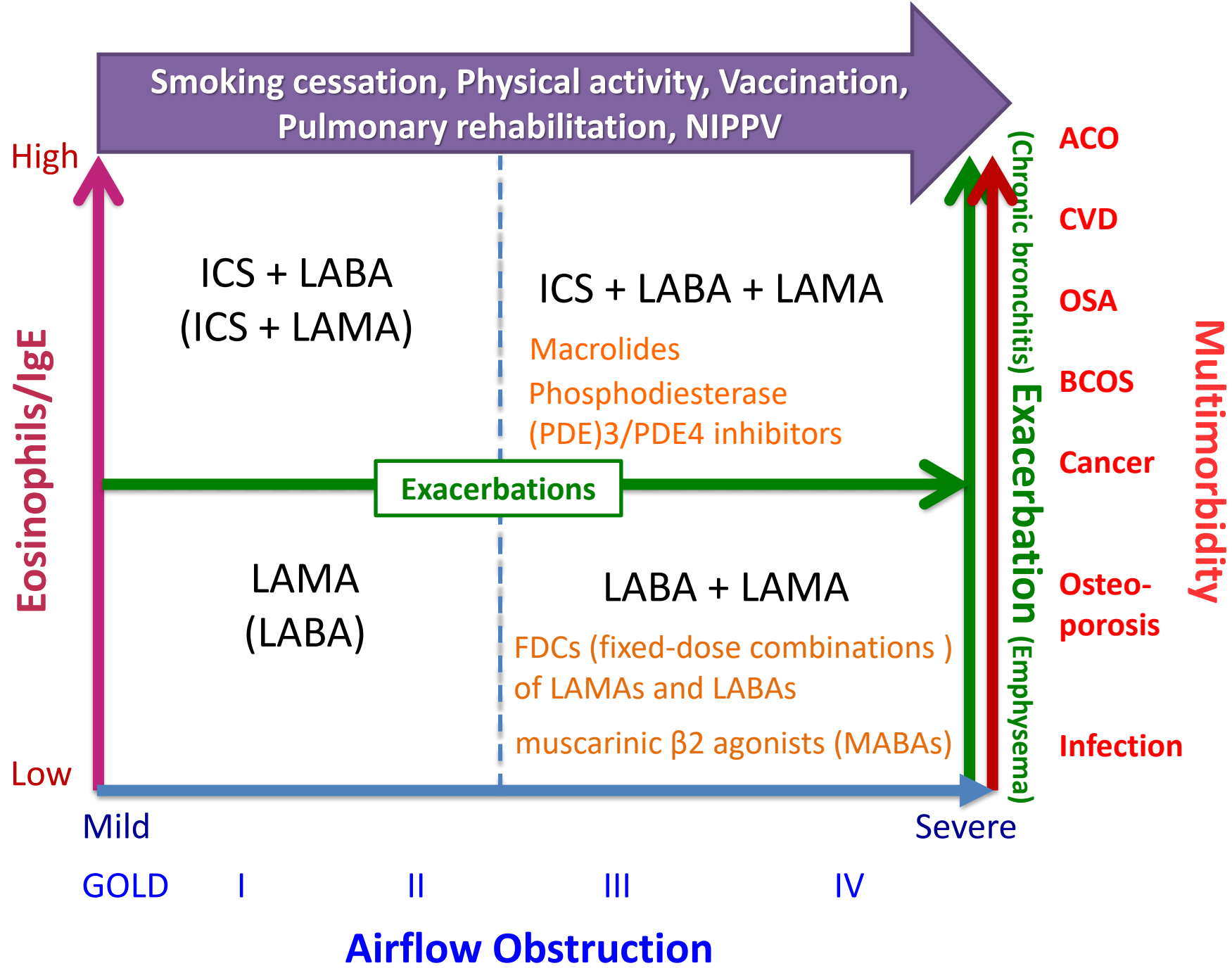
Int J Chron Obstruct Pulmon Dis 2021 Jun 3;16:1555-1568

Initial Pharmacological Treatment

Figure 4.2



*single inhaler therapy may be more convenient and effective than multiple inhalers



CMUH Pulmonary & Critical Care



Thanks for Your Attention!

中國附醫 陳家弘醫師