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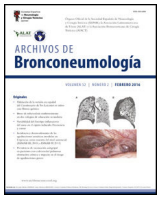

SEPAR/ALAT Voice

Update 2025 of the Spanish COPD Guidelines (GesEPOC): Pharmacological Treatment of Stable COPD☆

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ABSTRACT

The Spanish COPD Guidelines (GesEPOC) were first published in 2012, and since then, several updates have incorporated new evidence regarding the diagnosis and treatment of COPD. GesEPOC is a clinical practice guideline developed with the collaboration of the scientific societies involved in COPD management and the Spanish Patients' Forum. Its recommendations are based on an evaluation of the evidence using the GRADE methodology and on a narrative description of the evidence in those areas where application of this methodology is not feasible.

This article summarizes the updated recommendations on the pharmacological treatment of stable COPD, derived from the development of 12 PICO questions. The COPD treatment process comprises five stages: (1) diagnosis; (2) risk stratification; (3) characterization; (4) initiation and continuation of treatment; and (5) follow-up. For inhaled treatment selection, high-risk patients are classified into three phenotypes: non-exacerbator, eosinophilic exacerbator, and non-eosinophilic exacerbator. Treatable traits include general aspects, applicable to all patients—such as smoking cessation and inhaler technique—and more specific conditions, mainly affecting severe patients, such as chronic hypoxemia or chronic bronchial infection.

☆ More information about the members of the GesEPOC 2025 Working Group is available at Appendix 1.

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The cornerstone of COPD treatment is long-acting bronchodilators, either as monotherapy or in combination, depending on the patient's risk level. Eosinophilic exacerbators should receive inhaled corticosteroids, whereas non-eosinophilic exacerbators require a detailed evaluation to identify the most appropriate therapeutic option. GesEPOC 2025 also includes recommendations on inhaled corticosteroid withdrawal, the introduction of biologics, and the indication for alpha-1 antitrypsin therapy. GesEPOC 2025 represents a more individualized approach to COPD treatment, tailored to the clinical characteristics of patients and their level of risk or complexity.

Introduction

The 2025 Spanish Guidelines for Chronic Obstructive Pulmonary Disease (GesEPOC) represent the fifth update since the first version was published in 2012 [1]. The development of the guideline involved representatives from the scientific societies engaged in the care of patients with chronic obstructive pulmonary disease (COPD) and the Spanish Patients' Forum.

GesEPOC was the first COPD clinical guideline to propose a phenotype-driven therapeutic approach, achieving significant implementation. In the audit of outpatient pulmonology clinics in Spain (EPOCONSUL study), conducted between May 2014 and May 2015, 46.3% of COPD patient medical records already included the GesEPOC 2012 phenotype classification [2], a figure that increased to 63.1% in 2021 [3].

Ongoing research activity in COPD and the continuous generation of new evidence make it necessary to regularly update diagnostic and therapeutic recommendations. This article presents the section on the pharmacological treatment of stable COPD in the new GesEPOC 2025.

Objective and scope of the guideline

The objective of the guideline is to provide support in selecting the most appropriate pharmacological treatment for patients with stable COPD, based on the available evidence. Through a systematic review of the literature and an evaluation of the evidence, the guideline offers personalized treatment recommendations according to the characteristics of COPD patients, with the aim of relieving symptoms, improving quality of life, preventing exacerbations, and enhancing survival.

The scope of the guideline is limited to pharmacological management in the stable phase of COPD. Other important aspects, such as non-pharmacological interventions and the management of COPD exacerbations, are not addressed in this document.

Target users of the guideline

GesEPOC 2025 is intended for healthcare professionals involved in the management of patients with COPD, including pulmonologists, internists, family physicians, nurses, geriatricians, physiotherapists, and pharmacists. It is also aimed at patients, patient associations, healthcare professionals outside the clinical care setting such as health researchers, and healthcare decision-makers at the local, regional, and national levels, with applicability also extending to Latin American countries.

Methodology

GesEPOC 2025 was developed in accordance with the clinical practice guideline development process of SEPAR, following the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation) [4]. The writing group used the AGREE II checklist for its development, as in previous editions of the guideline [1,5]. In this edition, three new PICO (Patient, Intervention, Comparator, Outcome) questions were formulated (questions 3, 5, and 7), while the recommendations from nine PICO questions included in the 2021 GesEPOC edition [6] were retained, as no significant new evidence has emerged in these areas of treatment. The details of the protocol, including the new PICO questions, the literature search, and the evidence tables, can be found in Supplement 1.

The GesEPOC 2025 writing group is composed of 18 experts: 10 pulmonologists, one of them representing the Latin American Thoracic Society (ALAT); 3 family medicine specialists; 1 internist; 1 hospital pharmacist; 2 methodologists; and 1 expert patient. All of them represented their respective scientific societies or patient associations.

All members of the guideline development group declared potential conflicts of interest. Most of the authors had previous collaborations with the pharmaceutical industry in the form of consultancies, lectures, or participation in research projects. However, specific procedures were followed to minimize the influence of these conflicts on the content of the guideline. The methodological committee independently carried out the evaluation of the evidence and proposed the drafting of the recommendations. The final wording was developed by consensus after a detailed and independent review of the recommendations' formulation by the methodological committee to ensure transparency and avoid interpretative bias.

Target patients of the guideline: concept and definition of COPD

GesEPOC 2025 is intended to provide guidance on the pharmacological treatment of stable COPD, as well as to support the diagnosis and follow-up of patients with COPD. COPD is a respiratory disease caused by exposure to inhaled toxins, primarily tobacco smoke, which leads to structural alterations of the airways and/or pulmonary parenchyma, resulting in chronic airflow obstruction. It is commonly associated with respiratory symptoms such as dyspnea, cough, and sputum production, which worsen during exacerbation episodes. Stable COPD refers to the disease outside exacerbation periods. The definition, evaluation, and treatment of the COPD exacerbation syndrome have been addressed in a separate publication [7].

The COPD patient care process

GesEPOC 2025 proposes a five-step evaluation of the patient: (1) diagnosis of COPD and general measures; (2) risk stratification; (3) characterization; (4) treatment selection according to symptoms, clinical phenotype, and treatable traits; and (5) follow-up.

I. Diagnosis

The process begins with diagnostic suspicion in an adult smoker or former smoker with more than 10 pack-years, or with chronic exposure to inhaled toxins, who presents respiratory symptoms

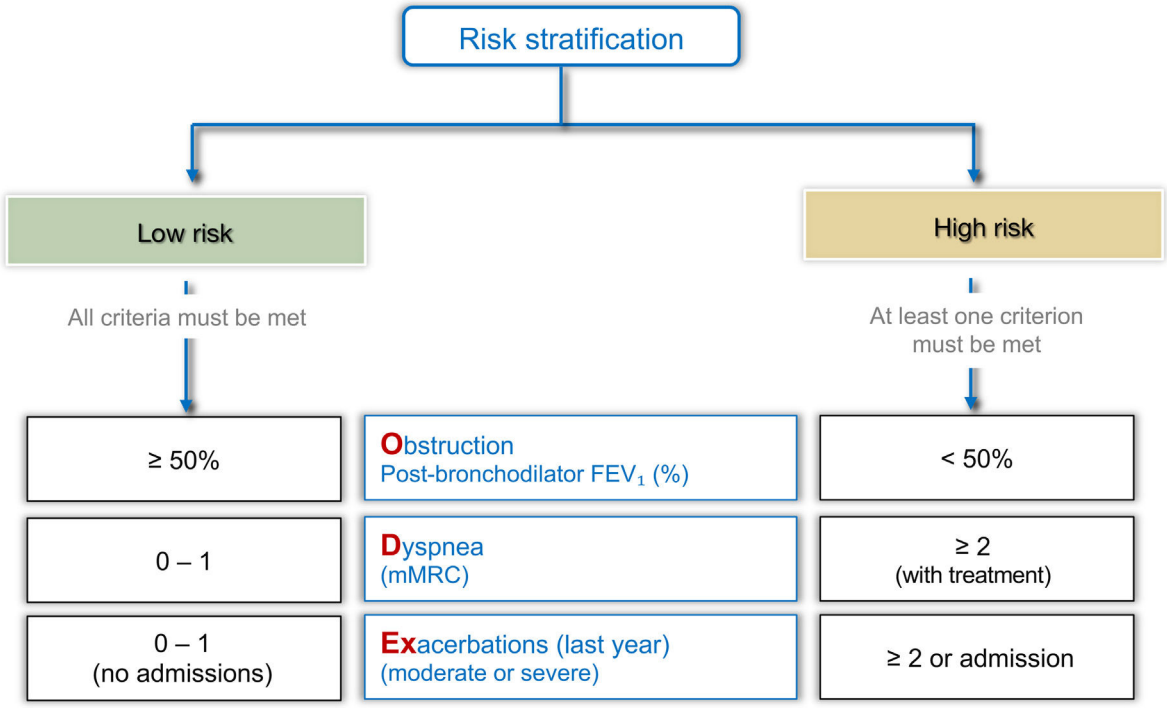

Fig. 1. Risk stratification in patients with COPD.

(dyspnea or chronic cough with or without associated sputum production). Performing spirometry in a clinically stable situation confirms the diagnosis by demonstrating a post-bronchodilator ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) of less than 0.7. However, this threshold may underestimate obstruction in younger individuals and overdiagnose it in older adults, since this ratio physiologically decreases with age [8,9]. Therefore, establishing a diagnosis of COPD requires consideration of three key aspects: prior exposure to risk factors, respiratory symptoms, and post-bronchodilator airflow obstruction on spirometry.

Although spirometry is the diagnostic test for COPD, underdiagnosis remains a well-recognized issue, making opportunistic case finding in at-risk individuals necessary. Multiple data indicate that patients often seek medical care for years before receiving a diagnosis, resulting in many missed opportunities for early detection [10]. To address this, screening questionnaires may be useful for the early identification of COPD patients, such as the COPD-PS (Chronic Obstructive Pulmonary Disease–Population Screener) and the PUMA questionnaire (Prevalence Study and Regular Practice, Diagnosis and Treatment, Among General Practitioners in Populations at Risk of COPD in Latin America). These consist of simple questions related to risk factors and respiratory symptoms. Both questionnaires have been validated for use in primary care and may serve as complementary tools to identify individuals who require diagnostic spirometry [11,12].

Portable spirometers (COPD-6, PIKO-6) may also be useful for early diagnosis, as they allow the identification of individuals with airflow obstruction before the onset of significant symptoms, particularly dyspnea, in at-risk populations such as smokers, former smokers of conventional tobacco, users of new tobacco products, and individuals exposed to pollutants. As a screening tool in primary care, they are accessible and easy to use in clinical practice to select those patients who require full spirometry. These devices provide a rapid measurement of FEV_1/FEV_6, offering an alternative to the traditional FEV_1/FVC ratio, with good correlation for obstruction detection. By preselecting patients with suspected COPD, they optimize the use of conventional spirometry, reducing costs and waiting times, and, importantly, preventing the loss of patients who might otherwise delay returning to clinic. Despite these advantages, portable spirometers do not replace complete spirometry for a definitive diagnosis [13,14].

Once the diagnosis is established, a series of general measures should be applied in all COPD patients. These include smoking cessation, proper nutrition, vaccination, regular physical activity adapted to the patient's age and physical condition [15], and evaluation and treatment of comorbidities [16]. These general measures are not addressed in this publication. Alpha-1 antitrypsin (AAT) determination should be performed in all patients, and its specific management is covered in the treatable traits section of this guideline.

II. Risk stratification

Once the diagnosis has been established by spirometry, the patient's risk level should be assessed. Risk is defined as the probability that the patient may experience exacerbations, disease progression, future complications, increased healthcare resource utilization, or higher mortality. GesEPOC 2025 proposes a two-level risk classification: low and high.

The factors considered for risk assessment include the degree of obstruction measured by post-bronchodilator FEV_1 (%), the degree of dyspnea assessed using the modified Medical Research Council (mMRC) scale, and the history of exacerbations during the previous year (Fig. 1). The components of this risk classification have demonstrated predictive power for mortality [17]. The inclusion of FEV_1 has been shown to significantly increase the predictive value of risk classification [18]. Other studies have demonstrated the applicability of this risk stratification to real-world clinical practice and its usefulness in guiding the selection of pharmacological treatment [19]. The higher the risk level, the greater the need for therapeutic interventions (Table 1).

III. Characterization

Table 1
Alignment of the level of healthcare intervention with risk levels.

Risk level	Therapeutic interventions	
Low risk	Smoking cessation	Counseling Specific treatment
	Therapeutic education	Structured therapeutic education program aimed at: • Promoting self-care • Improving treatment adherence • Correct inhalation technique
	Physical activity	Regular exercise
	Vaccination	• Influenza • Pneumococcal (20-valent conjugate) • COVID-19 • Consider RSV, Tdap, and herpes zoster vaccines
	Alpha-1 antitrypsin deficiency	Augmentation therapy according to clinical guidelines
	Pharmacological treatment	Bronchodilators
	Comorbidities	Management of comorbid conditions
High risk	Add to the previous treatment: Pharmacological treatment	Guided by clinical phenotype/endotype Identification of treatable traits
	Non-pharmacological treatment	• Pulmonary rehabilitation • Consider long-term home oxygen therapy • Consider noninvasive ventilation • Consider lung volume reduction in patients with extensive emphysema • Consider lung transplantation

Footnote: COVID-19: coronavirus disease 2019; RSV: respiratory syncytial virus; Tdap: diphtheria, tetanus, acellular pertussis.

COPD is a highly heterogeneous disease, and appropriate treatment requires characterization that enables the most personalized approach possible. Beyond risk level, characterization also involves evaluating predominant symptoms, clinical phenotype, and inflammatory endotype—predominantly T1/T3 or T2. The T2 endotype can be identified in routine clinical practice through peripheral blood eosinophilia.

Other tools that allow for more precise characterization and have prognostic value include measurement of the diffusing capacity for carbon monoxide (DLco) and chest computed tomography (CT). Patients with COPD present structural changes and physiological abnormalities that sometimes show poor correlation with spirometry, particularly at the alveolar level or within the pulmonary vascular domain [20,21].

DLco measurement is well standardized. Low DLco values have been associated with reduced exercise capacity, poorer health status, pulmonary complications following lung resection, accelerated decline in lung function, and increased risk of hospitalization and mortality, independently of the severity of airflow obstruction. Patients with COPD exhibit a more rapid decline in DLco compared with smokers without the disease; however, this decline is slow and requires 3–4 years to become clinically significant. DLco has proven to be an independent risk factor that adds prognostic value to FEV_1 (%), particularly in more severe cases of COPD [22]. Women with COPD present lower DLco values than men, regardless of the degree of obstruction, and appear to show greater deterioration over time [23].

Beyond its utility as a screening tool for pulmonary nodules and the early detection of lung cancer, CT provides valuable information on the structural and pathophysiological alterations present in COPD, such as emphysema, pulmonary artery enlargement, interstitial lung diseases, and airway abnormalities including bronchiectasis or mucus plugging. Most of these findings have been associated with greater lung function decline, increased exacerbations, and higher mortality, independently of FEV_1 (%). CT can also detect emphysematous lesions in smokers with normal spirometry, who may later develop airflow obstruction during follow-up [24,25]. In patients with severe airway obstruction (FEV_1% between 15–45%) and significant hyperinflation, CT is also used to support decision-making regarding lung volume reduction. Finally, CT allows for the detection of relevant extrapulmonary comorbidities that are often underdiagnosed in the clinical management of COPD patients, such as osteoporosis, hiatal hernia, hepatic steatosis, coronary calcification, and low psoas muscle density. The latter two have been identified as independent risk factors for mortality [26].

IV. Treatment

The general objectives of COPD treatment are summarized as follows: to reduce disease symptoms, decrease the frequency and severity of exacerbations, improve quality of life, and increase survival. Both short-term benefits (disease control) and medium- to long-term goals (risk reduction) must be achieved.

Vaccination is a highly important pharmacological strategy in all COPD patients, regardless of their risk level or phenotype. In addition to routine influenza and pneumococcal vaccines, other immunizations should be considered in these patients, including those against SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), pertussis, respiratory syncytial virus, and herpes zoster. Specific indications, as well as the mode and interval of administration in COPD patients, can be found in recent reviews [27,28].

With regard to initial pharmacological treatment, the GesEPOC guideline proposes an inhaled therapy strategy guided by symptoms in low-risk patients, and by clinical phenotype and endotype in high-risk patients [29]. The key aspects of pharmacological treatment in COPD are summarized in Table 2.

Inhaled treatment in low-risk patients

In low-risk patients, oral or anti-inflammatory therapies are not indicated. Pharmacological treatment will consist of prescribing long-acting bronchodilators (LABDs). In the less frequent situation of mild obstruction with few or intermittent symptoms, short-acting bronchodilators (SABDs) on demand may be indicated.

SABDs can be of two types: anticholinergics (SAMA, short-acting muscarinic antagonists) such as ipratropium bromide, and short-acting β_2-agonists (SABA, short-acting beta-agonists) such as salbutamol or terbutaline. In patients with occasional symptoms, treatment with SABDs reduces symptoms and improves exercise tolerance [30]. Due to their rapid mechanism of action, these drugs, when added to baseline therapy, are the treatment of choice for

Table 2
Key points in the pharmacological treatment of COPD.

The cornerstone of stable COPD treatment is inhaled pharmacotherapy.
Long-acting bronchodilators (LABDs) are the first-line drugs for most patients, and additional treatments to be combined with LABDs at initiation will depend on the patient's risk group, phenotype, and endotype.
Treatment of the non-exacerbator phenotype is based on dual bronchodilation.
Treatment of the eosinophilic exacerbator phenotype is based on the use of LABDs combined with inhaled corticosteroids (ICS).
Treatment of the non-eosinophilic exacerbator phenotype is based on LABDs. ICS may be useful in some cases, although their efficacy is lower.
The identification of treatable traits enables targeted therapy tailored to each patient's specific needs.
COPD control assessment is a useful tool for follow-up and treatment adjustment.

Footnote: COPD: chronic obstructive pulmonary disease; LABD: long-acting bronchodilator; ICS: inhaled corticosteroid.

symptom relief on demand at any severity level. Patients with persistent symptoms or activity limitation due to their respiratory condition require regular baseline treatment with LABDs.

LABDs can be β_2-agonists (LABAs, long-acting beta-agonists) or anticholinergics (LAMAs, long-acting muscarinic antagonists). The LABAs available in Spain are salmeterol, formoterol, indacaterol, olodaterol, and vilanterol, while the LAMAs include tiotropium, aclidinium, glycopyrronium, and umeclidinium (Table 3). LABDs should be used as the first-line option in all patients with persistent symptoms requiring regular treatment, since they provide greater symptom control than SABDs and improve lung function, exercise capacity, and quality of life [31,32]. In addition, both LABAs and LAMAs have been shown to reduce the number of exacerbations [33].

There are differences among the various LABDs: some have a 12-h duration of action (aclidinium, salmeterol, and formoterol), while others last 24 h (tiotropium, umeclidinium, glycopyrronium, indacaterol, olodaterol, and vilanterol). Regarding exacerbation prevention, tiotropium has proven more effective than salmeterol or indacaterol [34,35]. For this reason, when choosing LABD monotherapy, initiation with a LAMA is recommended (Table 4).

PICO 1. In patients with COPD requiring long-acting bronchodilator monotherapy, which treatment is preferred: a LABA or a LAMA?

In patients with COPD who require a long-acting bronchodilator as monotherapy, treatment with a LAMA is suggested.
Strength of recommendation: Weak. **Level of evidence:** Moderate.

In general, long-acting bronchodilators (LABDs) are well tolerated and associated with few adverse effects. Nevertheless, the following should be considered. LABAs: fine tremor of the extremities, muscle cramps, tachycardia, arterial hypertension, peripheral vasodilation, headache, hyperglycemia, hypokalemia, cough, bronchospasm, oropharyngeal irritation, and dyspepsia. LAMAs: treatment may be associated with dry mouth, urinary retention, increased intraocular pressure, and pharyngeal irritation. It should be noted that clinical trials typically exclude patients with significant heart disease; therefore, caution is warranted when prescribing bronchodilators in these patients [31,32].

Table 3
Characteristics of inhaled medications for the treatment of COPD.

	Active ingredient	Device/Presentation	Recommended dose
β_2-Adrenergic agonists	Salbutamol	pMDI: 100 mcg/inh	200 mcg/4–6 h
	Terbutaline	Turbuhaler®: 500 mcg/inh	500 mcg/6 h
	Salmeterol	pMDI: 25 mcg/inh Accuhaler®: 50 mcg/inh	50 mcg/12 h
	Formoterol	pMDI: 12 mcg/inh Turbuhaler®: 9 mcg/inh Aerolizer®: 12 mcg/inh	12 mcg/12 h
	Indacaterol	Breezhaler®: 150 mcg/inh Breezhaler®: 300 mcg/inh	150 mcg/24 h
	Olodaterol	Respimat®: 2.5 mcg/inh	5 mcg/24 h
Anticholinergics	Ipratropium bromide	pMDI: 20 mcg/inh	20–40 mcg/6–8 h
	Tiotropium bromide	Handihaler®: 18 mcg/inh	18 mcg/24 h
		Respimat®: 2.5 mcg/inh	5 mcg/24 h
	Aclidinium	Genuair®: 322 mcg/inh	322 mcg/12 h
	Glycopyrronium	Breezhaler®: 44 mcg/inh	44 mcg/24 h
	Umeclidinium	Ellipta®: 62.5 mcg/inh	62.5 mcg/24 h
LABA/LAMA	Indacaterol/Glycopyrronium	Breezhaler®: 85/43 mcg/inh	85/43 mcg/24 h
	Aclidinium/Formoterol	Genuair®: 322/12 mcg/inh	322/12 mcg/12 h
	Umeclidinium/Vilanterol l	Ellipta®: 55/22 mcg/inh	55/22 mcg/24 h
	Tiotropium/Olodaterol	Respimat®: 2.5/2.5 mcg/inh	5/5 mcg/24 h
LABA/ICS	Beclomethasone/Formoterol	Nexthaler®: 100/6 mcg/inh pMDI Modulite® 100/6 mcg/inh	200/12 mcg/12 h
	Formoterol/Budesonide	Turbuhaler®: 4.5/160 y 9/320 mcg/inh Spiromax®: 4.5/160 y 9/320 mcg/inh Easyhaler®: 4.5/160 y 9/320 mcg/inh	9/320 mcg/12 h
	Salmeterol/Fluticasone propionate	Accuhaler®: 50/500 mcg/inh Forspiro®: 50/500 mcg/inh	50/500 mcg/12 h
	Fluticasone furoate/Vilanterol	Ellipta®: 92/22 mcg/inh	92/22 mcg/24 h
LABA/LAMA/CI	Beclomethasone/Formoterol/Glycopyrronium	pMDI Modulite®: 87/5/9 mcg/inh	174/10/18 mcg/12 h
		Nexthaler®: 88/5/9 mcg/inh	176/10/18 mcg/12 h
	Fluticasone furoate/Umeclidinium/ Vilanterol	Ellipta®: 92/55/22 mcg/inh	92/55/22 mcg/24 h
	Budesonide/Formoterol/Glycopyrronium	pMDI Aerosphere®: 160/5/7.2 mcg/inh	320/10/14.4 mcg/12 h

Footnote: LABA/LAMA: long-acting β_2-agonist/long-acting muscarinic antagonist; LABA/ICS: long-acting β_2-agonist/inhaled corticosteroid; pMDI: pressurized metered-dose inhaler.

Table 4
Recommendations on the pharmacological treatment of stable COPD (GesEPOC 2025).

PICO question	Recommendation	Specifications	Strength of recommendation	Level of evidence
PICO 1. In patients with COPD requiring long-acting bronchodilator monotherapy, which treatment is preferred: LABA or LAMA?	In patients with COPD who require long-acting bronchodilator monotherapy, treatment with a LAMA is suggested.	The analyzed evidence is based on a greater prevention of exacerbations in studies conducted with the LAMA tiotropium. In patients without exacerbations, there are no differences in clinical efficacy between LAMA and LABA.	Weak	Moderate
PICO 2. For initial treatment in a low-risk, non-exacerbator patient, is dual bronchodilation superior to monotherapy?	In low-risk patients who remain symptomatic with a long-acting bronchodilator, dual bronchodilation therapy is recommended. In high-risk symptomatic patients (mMRC > 2), dual bronchodilation therapy is recommended over treatment with a single bronchodilator.	In patients with severe or very severe spirometric impairment, initial dual bronchodilation therapy is superior to monotherapy due to its greater effect on lung function and symptoms.	Strong	Moderate
PICO 3. In patients with a moderate exacerbation in the previous year, is triple therapy (LABA/LAMA/ICS) superior to dual bronchodilation (LABA/LAMA)?[a]	In patients with one moderate exacerbation in the previous year, initial treatment with dual bronchodilation is suggested.		Weak	Low
PICO 4. In patients with exacerbations despite treatment with LABA/LAMA, is triple therapy (LABA/LAMA/ICS) effective?	In patients with exacerbations despite treatment with LABA/LAMA, triple therapy with LABA/LAMA/ICS is suggested.	Triple therapy with LABA/LAMA/ICS provides a greater reduction in the risk of exacerbations and a greater improvement in symptoms compared with dual bronchodilation (LABA/LAMA). It cannot be ruled out that the reduction in exacerbations with triple therapy versus LABA/LAMA in non-eosinophilic exacerbator patients may be clinically irrelevant.	Weak	Moderate
PICO 5. Is treatment with dupilumab effective in COPD?[a]	Treatment with dupilumab is recommended in patients with COPD with predominant type 2 inflammation and mucus hypersecretion who continue to experience exacerbations despite optimal inhaled therapy, usually triple therapy.		Moderate	Moderate
PICO 6. For initial treatment in a non-eosinophilic exacerbator, which treatment is preferred: LABA/LAMA or LABA/ICS?[a]	Initial treatment with LABA/LAMA is suggested in non-eosinophilic exacerbator patients.	The comparison of the efficacy of both alternatives in preventing exacerbations is not conclusive, although the benefit–risk ratio appears to favor LABA/LAMA treatment in the patient profile requiring initial therapy. LABA/ICS therapy is an alternative in patients with very frequent exacerbations and blood eosinophil counts close to 300 cells/mm^3.	Weak	Low
PICO 7. In exacerbator patients with fewer than 100 eosinophils/mm^3, is triple therapy (LABA/LAMA/ICS) effective?[a]	In exacerbator patients with fewer than 100 eosinophils/mm^3, initial treatment with dual bronchodilation (LABA/LAMA) is suggested.		Weak	Low
PICO 8. Is augmentation therapy with AAT effective in slowing emphysema progression in AATD patients?	In patients with AATD-related emphysema, augmentation therapy is suggested with the aim of reducing the loss of lung density as measured by CT.	Augmentation therapy, however, has not demonstrated efficacy in improving symptoms or reducing exacerbations.	Weak	Moderate
PICO 9. When should mucolytics be used to prevent exacerbations?	In COPD patients with the exacerbator phenotype who continue to exacerbate despite adequate treatment, the addition of a high-dose mucolytic is suggested.	The costs associated with treatment using mucolytic agents should be discussed with the patient.	Weak	Moderate
PICO 10. When should roflumilast be used to prevent exacerbations?	The use of roflumilast is suggested as a second-line agent to prevent exacerbations in patients with the exacerbator phenotype, chronic bronchitis, and severe airflow limitation.	Its safety profile may limit drug tolerability. Attention should be paid to the possible occurrence of adverse effects.	Weak	Moderate
PICO 11. When should long-term macrolide therapy be used to prevent exacerbations?	In COPD patients with the exacerbator phenotype and at least three exacerbations in the previous year despite adequate treatment, long-term macrolide therapy is suggested.	This treatment should be restricted to severe patients with frequent exacerbations. Strict monitoring is required for potential adverse effects such as QT interval prolongation, hearing loss, or the development of antibiotic resistance.	Weak	Moderate

Table 4
(*Continued*)

PICO question	Recommendation	Specifications	Strength of recommendation	Level of evidence
PICO 12. Can inhaled corticosteroids be withdrawn in COPD patients?	a) Consider ICS withdrawal in patients with infrequent exacerbations (0-1 moderate previous year) and < 300 eosinophils/mm^3. b) It is recommended not to withdraw ICS in eosinophilic exacerbator patients.	After withdrawal, treatment with long-acting bronchodilators should be continued.	a) Weak b) Strong	Moderate Moderate

[a] PICO questions from the GesEPOC 2025 guideline. The evidence tables can be consulted in Supplement 1.

In symptomatic patients or those with limitations in daily activities despite bronchodilator monotherapy, adherence to treatment and proper inhalation technique should be verified. Switching to a different LABD may also be considered [36].

PICO 2. For initial treatment in a low-risk, non-exacerbator patient, is dual bronchodilation superior to monotherapy?

There is no evidence directly comparing one versus two long-acting bronchodilators as initial treatment.
However, in low-risk patients who remain symptomatic with a single long-acting bronchodilator, dual bronchodilation is recommended.
In symptomatic high-risk patients (mMRC > 2), dual bronchodilation is recommended over treatment with a single long-acting bronchodilator.
Strength of recommendation: Strong. **Level of evidence:** Moderate.

The next therapeutic step is dual bronchodilation. The combination of LABA and LAMA provides additional functional benefits, including reduced need for rescue medication, improvement in symptoms, exercise capacity, and quality of life compared with monotherapy [31,32,37–39] (Fig. 2, Table 3).

Although any exacerbation can impact the natural history of the disease, patients with only one moderate exacerbation are classified as low risk, since these episodes may occur randomly and do not always justify treatment escalation [40]. The limited evidence available, derived from a sub-analysis of a single clinical trial, suggests that triple therapy (LAMA/LABA/inhaled corticosteroids [ICS]) may be associated with an 18% reduction in exacerbation risk in COPD patients with a history of only one moderate exacerbation in the previous year compared with LABA/LAMA (RR: 0.82; 95% CI: 0.71–0.95). This result, however, was considered of limited clinical relevance, with no differences in the risk of severe exacerbations or in time to first exacerbation [41]. Moreover, this trial did not evaluate initial therapy but included moderate-to-severe patients already receiving treatment who continued to exacerbate, and it cannot be excluded that the modest benefit observed was primarily in those with higher eosinophil counts. In this regard, an observational study of patients across a broad spectrum of severity found a higher number of exacerbations with triple therapy compared to LABA/LAMA, although the results were not statistically significant [42]. For this reason, initial treatment with dual bronchodilation remains recommended for low-risk patients with a history of only one moderate exacerbation in the previous year (Fig. 2).

PICO 3. In patients with a moderate exacerbation in the previous year, is triple therapy (LABA/LAMA/ICS) superior to dual bronchodilation (LABA/LAMA)?

In patients with a history of one moderate exacerbation in the previous year, initial treatment with dual bronchodilation is suggested.
Strength of recommendation: Weak. **Level of evidence:** Low.

Inhaled treatment for high-risk patients

In high-risk patients, GesEPOC 2025 recognizes three phenotypes within the pharmacological treatment scheme: (1) non-exacerbator; (2) eosinophilic exacerbator; and (3) non-eosinophilic exacerbator. For the treatment of high-risk exacerbator patients, the first step is to rule out concomitant asthma, known as asthma–COPD overlap (ACO) [43]. The coexistence of an asthma diagnosis as a comorbidity in a COPD patient requires that both diseases be treated.

In COPD patients, it is important to identify their inflammatory endotype. The majority of patients with COPD present predominant T1/T3 inflammation, characterized by increased neutrophils and macrophages in sputum, higher numbers of T helper (Th)1 lymphocytes and innate lymphoid cells (ILC)1, and mediated by cytokines such as interleukin (IL)-1β, IL-17, and tumor necrosis factor (TNF)-α [44]. T3 inflammation is also characterized by neutrophilic infiltration, driven by cytokines such as IL-17 and IL-22, with infiltration of Th17 lymphocytes and ILC3 [44]. By contrast, approximately 20–30% of patients may present predominant T2 inflammation, characterized by increased eosinophils in sputum, higher numbers of Th2 lymphocytes and ILC2, and mediated by IL-4, IL-5, and IL-13. This endotype can be identified by peripheral blood eosinophilia [45,46] and elevated fractional exhaled nitric oxide (FeNO) [47]. This distinction carries important therapeutic implications, since in recent years accumulating evidence has highlighted the predictive role of peripheral eosinophilia in the clinical response to ICS and to new biologic therapies in COPD [46,48]. In GesEPOC 2025, the presence of peripheral eosinophilia (>300 cells/μL) in an exacerbator patient (defined as ≥2 moderate exacerbations in the previous year or ≥1 severe exacerbation) identifies the COPD exacerbator with an eosinophilic endotype.

Accordingly, the GesEPOC 2025 phenotypes/endotypes are defined as follows.

Non-exacerbator phenotype

The non-exacerbator phenotype is characterized by having at most one moderate exacerbation in the previous year without requiring hospitalization. The initial treatment for a high-risk COPD patient with a non-exacerbator phenotype is dual bronchodilation (LABA/LAMA). This recommendation is based on the demonstrated greater bronchodilator efficacy compared with monotherapy, accompanied by significant improvements in dyspnea, quality of life, exercise capacity, and a reduction in the use of rescue medication [35–39] (Table 4, Fig. 2). No superior efficacy of triple therapy over LABA/LAMA has been demonstrated in patients with only one moderate exacerbation (PICO 3, Table 4). The available LABA/LAMA combinations are listed in Table 3.

Eosinophilic exacerbator phenotype

The exacerbator phenotype is defined as any patient with COPD who, in the previous year, has experienced two or more moderate exacerbations requiring treatment with systemic corticosteroids and/or antibiotics, or at least one severe exacerbation requiring hospital care [7]. These exacerbations must be separated

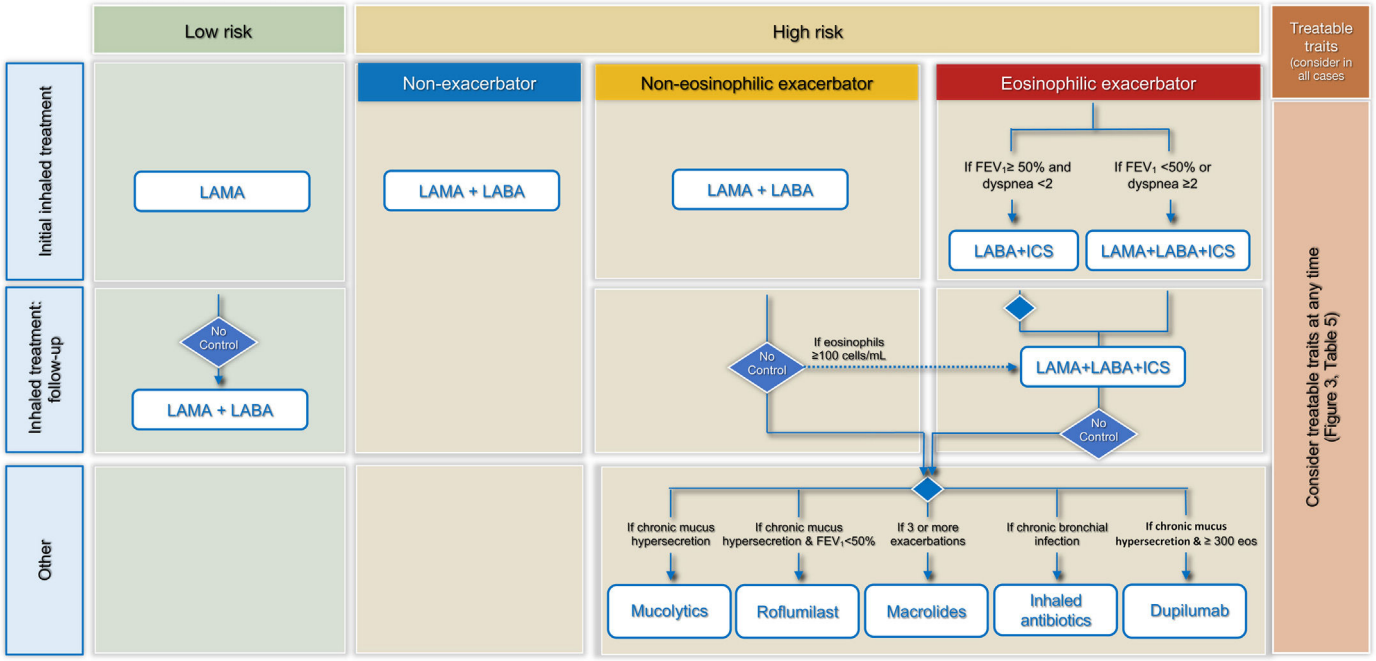

Fig. 2. COPD treatment guided by risk level and clinical phenotype. Footnote: (*) Second-line option in patients with blood eosinophil counts > 100 cells/mm^3, depending on the frequency, severity, and etiology of exacerbations, and considering the risk of pneumonia.

by at least 4 weeks from resolution of the previous exacerbation or 6 weeks from symptom onset, to differentiate a new event from a relapse or treatment failure [7]. Given the different responses to pharmacological treatments, it is important to distinguish those with a T1/T3 (non-eosinophilic) endotype from those with a T2 (eosinophilic) endotype. Patients who, in the stable phase, have > 300 eosinophils/mm^3 in peripheral blood will be classified as eosinophilic exacerbators. Blood eosinophil concentration may vary [49,50]; therefore, in some cases, it may be useful to obtain several measurements, always during the stable phase and within the same period used to assess exacerbation frequency, in order to make a more reliable therapeutic decision. Large studies conducted in Spain show that approximately 15–25% of COPD patients have >300 eosinophils/mm^3 in the stable phase [50,51].

Exacerbator patients with elevated blood eosinophil counts (>300 cells/mm^3) are more likely to have a clinical response to ICS [46,48,52]; this response is graded according to eosinophil concentration, so ICS may also be useful at eosinophil levels < 300 cells/mm^3, although efficacy will be progressively lower as peripheral eosinophilia decreases [46,53] (Table 3).

ICS cannot be used as monotherapy in COPD, and trials of combination therapy have only been conducted with LABA/ICS. This combination has been shown to be superior to LABA/LAMA in eosinophilic exacerbator patients and could be considered an alternative initial therapy in minimally symptomatic patients (mMRC dyspnea < 2) and without severe obstruction.

Given the high efficacy and favorable safety profile of LAMAs, it is reasonable to initiate triple therapy (LABA/LAMA/ICS) when the patient presents a high symptom burden, defined by an mMRC dyspnea score of 2 or more or an FEV_1 (%) below 50% of predicted. In all other cases, treatment can be initiated with LABA/ICS, and triple therapy will be the second therapeutic step in eosinophilic exacerbator patients (Table 3 and Fig. 2). Recent studies of single-inhaler fixed triple therapy have demonstrated greater efficacy in improving lung function and respiratory symptoms and a greater reduction in exacerbation risk than the LABA/ICS combination [54–56]. Triple therapy has also shown a greater reduction in exacerbation risk than the LABA/LAMA combination, especially in patients with higher blood eosinophil concentrations [54,55,57]. These studies included symptomatic patients with frequent and severe exacerbations despite regular COPD treatment; therefore, in most cases, triple therapy is considered continuation treatment rather than initial treatment for COPD [58].

PICO 4. In patients with exacerbations despite treatment with LABA/LAMA, is triple therapy (LABA/LAMA/ICS) effective?

In patients with exacerbations despite treatment with LABA/LAMA, triple therapy with LABA/LAMA/ICS is suggested, especially in those with eosinophilia.
Strength of recommendation: Weak. **Level of evidence:** Moderate.

Despite maximum inhaled treatment with triple therapy, a significant number of patients with severe COPD may continue to experience exacerbations [59,60]. In patients with a T2 endotype, biologic drugs initially developed for asthma have been tested [61]. Among them, dupilumab, a fully human monoclonal antibody that blocks the shared receptor for IL-4 and IL-13, has been shown to reduce the risk of moderate-to-severe exacerbations by 31% in COPD patients with mucus hypersecretion and >300 eosinophils/mm^3 who continued to experience exacerbations despite triple therapy [62]. For this reason, the European Medicines Agency (EMA) has authorized its use, and its commercialization in Spain for the COPD indication is forthcoming. Dupilumab represents the next step in the treatment of high-risk eosinophilic exacerbator patients who continue to exacerbate despite triple therapy, once good adherence and correct inhaler use have been verified (Table 4). Other biologic drugs for COPD are also in develop-

ment, and new products are expected to be launched in the coming years [61].

PICO 5. Is dupilumab effective in COPD?

Treatment with dupilumab is recommended in patients with COPD with predominant type 2 inflammation and chronic bronchitis who continue to experience exacerbations despite optimal inhaled therapy, usually with triple therapy.
Strength of recommendation: Moderate. **Level of evidence:** Moderate.

Non-eosinophilic exacerbator phenotype

This refers to a patient who meets the criteria for the exacerbator phenotype but presents with a predominantly T1 endotype, with <300 eosinophils/mm^3 in peripheral blood. In these patients, the efficacy of ICS is lower, although this does not exclude them from treatment, particularly if the eosinophil count is >100 cells/mm^3 [53].

In this group, the LABA/LAMA combination has shown a modest improvement in preventing exacerbations compared with LAMA alone [63,64], while also providing the added benefit of improving symptoms, exercise capacity, and quality of life compared with monotherapy [31–34,39]. A systematic review and meta-analysis of the results of LABA/LAMA versus LABA/ICS combinations in exacerbation prevention revealed wide differences in effectiveness, mainly due to the varying inclusion criteria of clinical trials. Moreover, none of these studies compared LABA/LAMA with LABA/ICS as initial treatment [54,55,65]. Overall, the LABA/ICS combination shows better results when eosinophil counts are higher (closer to 300 eosinophils/mm^3), when exacerbation frequency is greater, and when previous exacerbations responded well to systemic corticosteroids [55,66], whereas LABA/LAMA shows better results than LABA/ICS when eosinophil counts are lower, exacerbations are less frequent or require antibiotic treatment, while also providing greater bronchodilator effect and a lower risk of pneumonia [65,66].

PICO 6. For initial treatment in a non-eosinophilic exacerbator patient, which therapy is preferred: LABA/LAMA or LABA/ICS?

Initial treatment with LABA/LAMA is suggested in a non-eosinophilic exacerbator patient.
Strength of recommendation: Weak. **Level of evidence:** Low.

Because GesEPOC 2025 considers concomitant asthma as a comorbidity that should be treated, patients with >300 eosinophils/mm^3 are classified within the eosinophilic phenotype, and because most exacerbators patients have only two moderate exacerbations or one hospitalization in the previous year, first-line treatment with LABA/LAMA is recommended for the majority of non-eosinophilic exacerbator patients (Table 4). The LABA/ICS combination (or triple therapy in more symptomatic patients) may be considered when exacerbation frequency is higher, exacerbations respond to systemic corticosteroids, there is no history of pneumonia, and eosinophil counts are closer to 300 eosinophils/mm^3.

The non-eosinophilic exacerbator patient who continues to experience frequent or severe exacerbations despite treatment with LABA/LAMA requires specialized care, and the presence of treatable traits should be investigated [67,68], as will be detailed in the corresponding section. Regarding inhaled therapy, ICS in the form of triple therapy may be useful in patients with eosinophil counts between 100 and 300 cells/mm^3 [54,55,66]. In this situation, the indication for ICS should again consider factors associated with greater efficacy and safety of ICS, namely: (1) more frequent or severe exacerbations, (2) prior exacerbations responsive to oral corticosteroids, (3) non-active smokers, and (4) no history of pneumonia [69].

In contrast, there is no evidence supporting the efficacy of ICS in patients with eosinophil counts < 100 cells/mm^3. In the meta-analysis conducted to evaluate the evidence for this PICO question, no differences were observed in the overall rate of exacerbations, moderate or severe exacerbations, or in the time to first exacerbation between patients receiving triple therapy versus LABA/LAMA, despite the fact that these were already moderate-to-severe patients who had been previously treated. However, there was a small but significant 16% increase in adverse event rates, most of them non-serious, in patients on triple therapy. For this reason, triple therapy is not recommended in patients with <100 eosinophils/mm^3 [54,55,66,70,71] (Table 4). When initial treatment was started with LABA/ICS, escalation should be to triple therapy.

PICO 7. In patients with fewer than 100 eosinophils/mm^3, is triple therapy (LABA/LAMA/ICS) effective?

In exacerbator patients with fewer than 100 eosinophils/mm^3, initial treatment with dual bronchodilation (LABA/LAMA) is suggested.
Strength of recommendation: Weak. **Level of evidence:** Low.

V. Identification and management of treatable traits

The term "treatable trait" is used to refer to a clinical, physiological, radiological, or biological characteristic that can be identified through diagnostic tests or biomarkers and that has a specific treatment with clinical benefit for patients [67,68]. It is important to bear in mind that in a given patient, multiple treatable traits are likely to coexist, and all of them should be considered. In its definition, the essential objective is to improve clinical outcomes for individual patients while minimizing unnecessary side effects in those less likely to benefit from a specific treatment.

Based on their relevance and applicability, GesEPOC 2025 identifies the most important and frequent treatable traits that should be investigated in high-risk patients, with the exception of alpha-1 antitrypsin deficiency, which must be investigated in all COPD patients regardless of their risk level [72] (Table 5, Fig. 3). The details on non-pharmacological treatments for treatable traits have been addressed in other documents [15]; therefore, they will only be briefly mentioned here.

Refractory dyspnea

Dyspnea should be considered a symptom; however, for organizational reasons it is included in this section on treatable traits. Patients who continue to experience significant dyspnea despite dual bronchodilation require an evaluation that includes the possibility of identifying treatable traits and ruling out comorbidities that may worsen dyspnea, such as heart failure. These high-risk patients should be assessed in specialized units and require comprehensive pulmonary function studies, as well as imaging, to determine the potential for non-pharmacological therapeutic alternatives such as pulmonary rehabilitation and/or lung volume reduction.

From a pharmacological perspective, the addition of theophylline may be considered. These are weak bronchodilators with a positive effect on diaphragmatic strength, improved respiratory muscle performance, reduced air trapping, and enhanced mucociliary clearance [73,74]. Although the usual dose is 200–300 mg every

Table 5
Some of the most relevant treatable traits in COPD, particularly important in high-risk patients.

Treatable traits	Indicators	Relevance and therapeutic implications
Alpha-1 antitrypsin deficiency[a]	Serum alpha-1 antitrypsin levels	Associated with an increased risk of COPD and accelerated disease progression. Augmentation therapy prevents emphysema progression [72,82].
Refractory dyspnea	Dyspnea scales	Theophylline may improve dyspnea [73–76]. Pulmonary rehabilitation is effective in controlling dyspnea [15]. In selected patients, lung volume reduction techniques can improve severe dyspnea [84]. Opioids: start with low doses (2.5–5 mg/4 h) and individualize according to response [16].
Chronic bronchitis	Cough and sputum production for at least 3 consecutive months over 2 years	Chronic bronchitis predisposes to exacerbations in COPD. In the exacerbator phenotype with chronic bronchitis, roflumilast is effective in preventing exacerbations [99,100]. Mucolytics/antioxidants are also effective in reducing exacerbations [94–98].
Severe emphysema and pulmonary hyperinflation	Computed tomography, lung volumes, and diffusion capacity measurements	Lung volume reduction techniques in selected patients have been shown to improve exercise tolerance, health status, and lung function [84].
Chronic bronchial infection	Presence of potentially pathogenic microorganisms in respiratory simples	Associated with infective exacerbations of greater frequency and severity, as well as higher mortality and functional decline. Long-term antibiotic therapy added to maintenance medication may reduce exacerbations and improve quality of life [107–109]. Mucolytics/antioxidants are also effective in reducing exacerbations [94–98].
Bronchiectasis	Computed tomography	Associated with worse prognosis and increased frequency and severity of exacerbations. Management should follow the bronchiectasis treatment guidelines [104].
Precapillary pulmonary hypertension	Echocardiography, natriuretic peptide levels, cardiac catheterization	A poor prognostic factor. Its treatment improves symptoms and prevents associated complications [85,86].
Chronic respiratory failure	$PaO_2 < 60$ mmHg and/or $PaCO_2 > 45$ mmHg	Chronic respiratory failure is associated with reduced survival. Long-term oxygen therapy at home has been shown to increase survival and reduce exacerbations and hospitalizations [89]. In patients with persistent hypercapnia and recurrent episodes of respiratory acidosis, noninvasive ventilation has proven beneficial [91].
Cachexia	Body mass index (BMI ≤ 20 kg/m^2)	Malnutrition is associated with increased risk of hospitalization, longer hospital stays, and higher risk of readmission. Nutritional supplements, diet, and physical activity are recommended treatment strategies [92,122].

[a] Alpha-1 antitrypsin deficiency should be investigated in all COPD patients, regardless of their level of risk or disease severity.

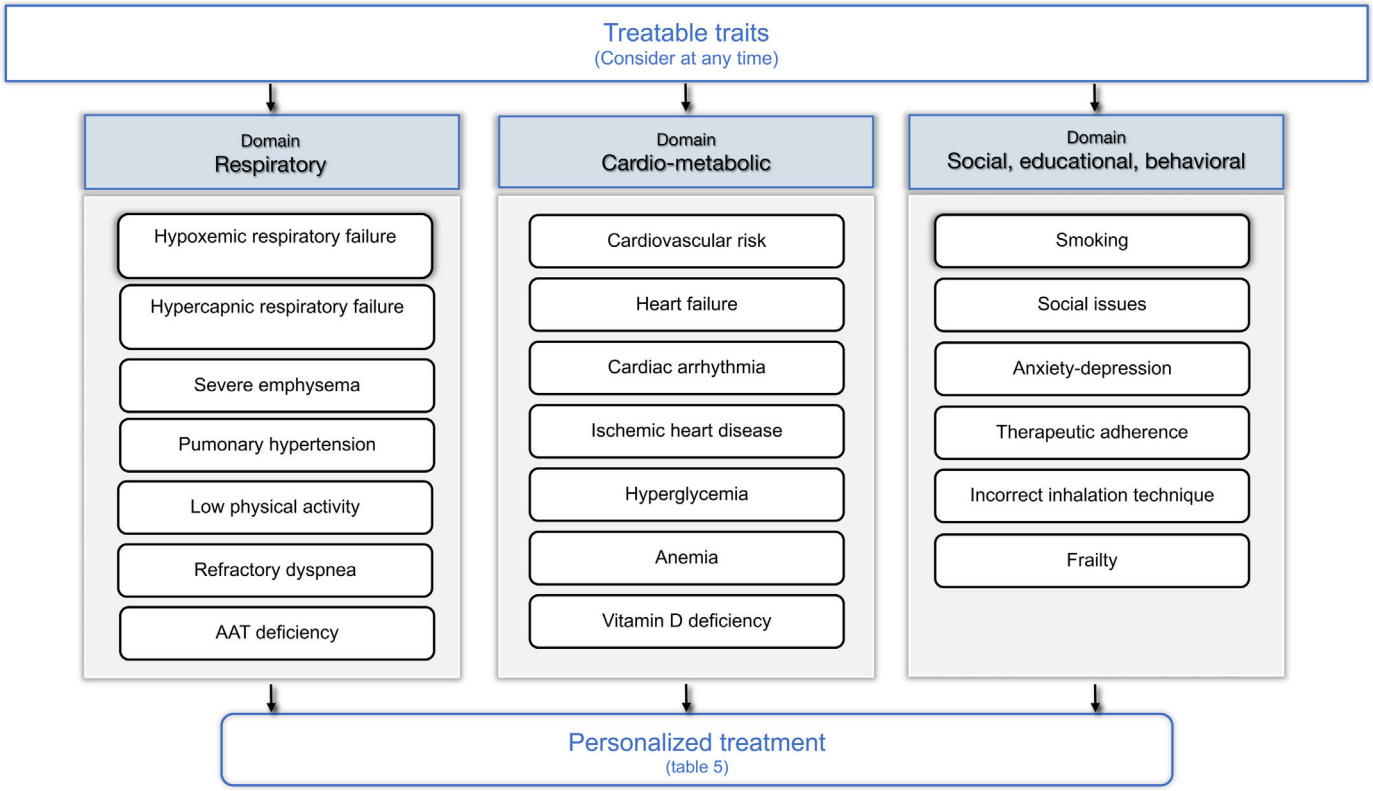

Fig. 3. Main treatable traits in COPD.

12 h orally in sustained-release tablets [74], lower doses (100 mg every 12 h) have been shown to improve pre-bronchodilator FEV_1 [75], although no effect has been demonstrated on exacerbation prevention [76,77].

The toxicity of theophylline is dose-dependent. When administered long-term, plasma concentrations must be monitored, and the risk of interactions with other drugs such as allopurinol, ciprofloxacin, erythromycin, benzodiazepines, or cimetidine, among others, must be taken into account. In any case, its limited clinical efficacy, narrow therapeutic margin, and high potential for drug interactions relegate theophylline to a third-line option, mainly in high-risk patients who remain dyspneic after dual bronchodilator therapy [73].

Low-dose opioids are suggested in patients with refractory dyspnea despite optimized treatment, anticipating potential side effects (e.g., constipation). At low doses, opioids do not increase the risk of hospitalization or mortality, even in patients with advanced respiratory failure. Continuation of treatment should be individualized according to variability in patient response [16].

Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency (AATD) is a congenital cause of emphysema in adulthood [72]. Severe AATD affects approximately 1 in 4500 individuals of Caucasian descent and accounts for about 1 in every 700 COPD cases in southern Europe [78]. For accurate identification, every patient with COPD should undergo at least one measurement of serum AAT concentrations or a genotype determination using noninvasive techniques such as DNA analysis obtained from buccal mucosa cell swabs [79]. Once a patient with AATD has been identified, a family study should be conducted to detect possible undiagnosed cases [72]. Identified cases should be reported to the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency, which is integrated into the European Alpha-1 Antitrypsin Deficiency Research Collaboration (EARCO) registry [80], and they should be referred to a reference center for comprehensive diagnosis, evaluation of potential replacement therapy, and family studies [81].

PICO 8. Is augmentation therapy with AAT effective in slowing the progression of emphysema in patients with AATD?

In patients with emphysema due to AATD, augmentation therapy is suggested with the aim of reducing the loss of lung density as measured by CT.
Strength of recommendation: Weak. **Level of evidence:** Moderate.

Augmentation therapy with purified AAT is indicated in patients with pulmonary emphysema associated with severe AATD because of its effect in slowing the loss of lung density [82] (Table 4). Early diagnosis is essential to avoid risk exposures—particularly smoking—and to initiate replacement therapy as soon as possible in order to preserve lung tissue [72]. However, due to the considerable variability in the progression of emphysema in AATD [83], treatment should be prescribed by experienced specialists in reference centers [81].

Severe emphysema and hyperinflation

The presence of severe emphysema with hyperinflation leads to severe dyspnea and exercise intolerance. Its evaluation requires a detailed assessment with chest CT, lung volumes, DLco, and a 6-min walk test. Depending on the severity and distribution of emphysema, the patient may be a candidate for endoscopic or surgical lung volume reduction techniques, which are not addressed in this document [84].

Pulmonary hypertension

This condition often presents with severe dyspnea that is disproportionate to the degree of bronchial obstruction, and with exercise intolerance accompanied by severe and early desaturation during the 6-min walk test [85]. Evaluation requires arterial blood gas analysis, walk test, echocardiography, natriuretic peptide measurement, and right heart catheterization. Treatment usually involves oxygen therapy in addition to management of the underlying disease [86]. A vascular phenotype of COPD has been described, characterized by hypoxemia with normocapnia or hypocapnia, very low diffusion capacity, and dyspnea with minimal exertion showing a cardiovascular exercise limitation pattern in the presence of only mild to moderate airflow obstruction [87,88].

Respiratory failure

In patients with COPD and severe hypoxemia ($PaO_2 \leq 55$ mmHg) at rest, continuous oxygen therapy has been shown to provide survival and quality-of-life benefits. Continuous oxygen therapy (at least 15 h per day, including sleeping hours) is indicated when PaO_2 at rest is $\leq$55 mmHg, and also when PaO_2 at rest is between 56 and 59 mmHg with evidence of hypoxia-induced organ damage (including right heart failure, pulmonary hypertension, or polycythemia). The oxygen flow rate must be sufficient to maintain a $PaO_2 > 60$ mmHg or a $SpO_2 > 90\%$ [89,90].

Chronic hypercapnia

Long-term home noninvasive mechanical ventilation is recommended in patients with stable hypercapnic COPD ($PaCO_2 > 52$ mmHg) due to its survival benefits, or in those who remain hypercapnic 2–4 weeks after an episode of hypercapnic respiratory failure requiring hospital ventilatory support, given its benefits in prolonging the time to hospital readmission or death [91,92]. Overlap syndrome with obstructive sleep apnea and obesity hypoventilation syndrome should be differentiated from chronic hypercapnia attributable solely to advanced COPD.

Chronic bronchitis

Chronic bronchitis is classically defined as the production of sputum for at least three consecutive months in two successive years, although in practical terms it may be considered as the habitual production of sputum during the stable phase of COPD. It is a risk factor for frequent exacerbations and has a significant impact on patients' quality of life [93].

PICO 9. When should mucolytics be used for the prevention of exacerbations?

In patients with COPD with the exacerbator phenotype who continue to experience exacerbations despite appropriate treatment, the addition of a high-dose mucolytic is suggested.
Strength of recommendation: Weak. **Level of evidence:** Moderate.

Patients who continue to experience exacerbations and have chronic bronchitis despite optimal inhaled therapy may benefit from treatment with mucolytics/antioxidants. Carbocisteine at a dose of 500 mg every 8 or 12 h [94] and high-dose N-acetylcysteine (NAC), considered to have antioxidant effects (600 mg every 12 h), have demonstrated a significant reduction in exacerbations, particularly in high-risk patients (those with $FEV_1 < 50\%$ or with $\geq$2 exacerbations in the previous year, or both) [95–98] (Table 4).

A specific alternative for exacerbator patients with chronic bronchitis is roflumilast. Roflumilast is an oral anti-inflammatory drug and phosphodiesterase-4 inhibitor that has been shown to prevent exacerbations in patients with severe COPD who present with chronic cough and sputum production and also suffer frequent exacerbations [99]. The effect of roflumilast in preventing exacerba-

tions has been observed when added to maintenance therapy with long-acting bronchodilators and even when added to triple therapy, particularly in more severe patients requiring hospital admission [100] (Table 4). The usual dose is 500 μg orally once daily.

PICO 10. When should roflumilast be used for the prevention of exacerbations?

The use of roflumilast is suggested as a second-line therapy to prevent exacerbations in exacerbator phenotype patients with chronic bronchitis and severe airflow limitation. **Strength of recommendation:** Weak. **Level of evidence:** Moderate.

Adverse effects with roflumilast usually appear at the beginning of treatment, are quickly noticed by the patient, and generally resolve within the first four weeks, although in some cases they lead to discontinuation of the drug. The most frequent adverse effects are weight loss, gastrointestinal disturbances, nausea, headache, and loss of appetite. The safety profile of roflumilast is not modified by concomitant COPD treatments the patient may be receiving. The use of roflumilast should be avoided in combination with theophylline. GesEPOC suggests treatment with roflumilast in patients with COPD, severe obstruction, chronic bronchitis, and exacerbations despite adequate inhaled therapy [97].

Bronchiectasis

The exacerbator phenotype may present with bronchiectasis in up to 70% of cases [101], which can contribute to perpetuating a vicious cycle by amplifying underlying inflammation and inducing frequent exacerbations and are even associated with increased mortality [102,103]. In patients with COPD and bronchiectasis, the infectious component and mucus hypersecretion should be managed in accordance with established bronchiectasis treatment guidelines [104].

Chronic bronchial infection

Chronic bronchial infection (CBI) is defined as the isolation of the same potentially pathogenic microorganism in at least three sputum cultures within one year, separated by at least one month between samples [105]. The presence of CBI is associated with increased frequency and severity of exacerbations and poorer prognosis [106]. Treatment is indicated when CBI is associated with frequent exacerbations. There is no evidence supporting the effectiveness of treating CBI in the uncommon case of non-exacerbator patients.

PICO 11. When should long-term macrolides be used for the prevention of exacerbations?

In patients with COPD with the exacerbator phenotype, with at least three exacerbations in the previous year despite appropriate treatment, long-term macrolide therapy is suggested. **Strength of recommendation:** Weak. **Level of evidence:** Moderate.

In exacerbator patients, long-term macrolide therapy is indicated if they present with at least three exacerbations in the previous year despite adequate inhaled treatment [107]. Long-term administration of macrolides has been shown to significantly reduce the number of exacerbations [107,108]. The effectiveness of macrolides in COPD has been observed in patients both with and without associated bronchiectasis [107]. The recommended dosage is azithromycin 500 mg/day, three days per week, or 250 mg/day daily. This treatment should be restricted to reference centers with appropriate monitoring, including clinical assessment, hearing tests, ECG, liver function tests, and microbiological studies to rule out mycobacterial infection. There is limited evidence regarding the efficacy of this treatment beyond one year of follow-up; therefore, an annual evaluation of the potential risk–benefit ratio is recommended [109]. In line with other international guidelines, GesEPOC suggests long-term macrolide therapy in high-risk COPD patients with exacerbations despite adequate inhaled treatment [97] (Table 4).

There is very limited evidence regarding the efficacy and safety of inhaled antibiotic therapy, but it may be considered as an alternative in high-risk patients with frequent exacerbations and CBI, based on existing experience with CBI treatment in bronchiectasis [105,110,111]. It is important to note that tolerance to inhaled antibiotic therapy in COPD may be lower than that observed in bronchiectasis, particularly due to the reduced ventilatory reserve of COPD patients [112].

VI. Treatment adjustment during follow-up

Establishing the level of control

Treatment adjustment should be performed at each medical visit, during which possible changes in risk level, phenotype, or the appearance of new treatable traits should be assessed. GesEPOC proposes evaluating clinical control of COPD through the use of a scale specifically designed and validated to facilitate therapeutic decisions, based on a set of variables that are easy to obtain at each visit [113]. The combination of these variables indicates that the patient is well controlled when they present stability (no exacerbations in the previous 3 months) and a low-impact profile, defined as low levels of dyspnea, absence of sputum or presence of mucoid sputum, infrequent use of rescue medication, and an adequate level of physical activity [114]. The detailed criteria for assessing COPD control are presented in Fig. 4. Patients classified as uncontrolled have a higher risk of exacerbations in both the short term (within the next 6 months) and the long term, as well as a greater risk of deterioration in health-related quality of life [113,115]. Therefore, a detailed analysis of the possible causes of this lack of control is required, and it may be necessary to intensify treatment.

A quantitative control scale, the RADAR scale, has recently been developed to classify three levels of control: uncontrolled, partially controlled, and controlled. This classification is based on the assessment of dyspnea, physical activity performed, exacerbations in the previous three months, and the use of rescue medication [116]. This scale is currently undergoing validation [117]. Fig. 5 provides a series of recommendations to follow when uncontrolled patients are identified during follow-up visits.

Treatment reduction

In controlled patients, treatment de-escalation may be considered. With respect to bronchodilator therapy, it is well known that its effect lasts only during administration; therefore, the withdrawal of a bronchodilator, or its substitution with another of lower bronchodilator potency or shorter duration of action, is expected to result in functional or symptomatic worsening [118,119].

PICO 12. Can inhaled corticosteroids be withdrawn in patients with COPD?

a) ICS withdrawal may be considered in patients with infrequent exacerbations (0–1 moderate exacerbation in the previous year) and <300 eosinophils/mm^3. **Strength of recommendation:** Weak. **Level of evidence:** Moderate.
b) ICS withdrawal is not recommended in eosinophilic exacerbator patients. **Strength of recommendation:** Strong. **Level of evidence:** Moderate.

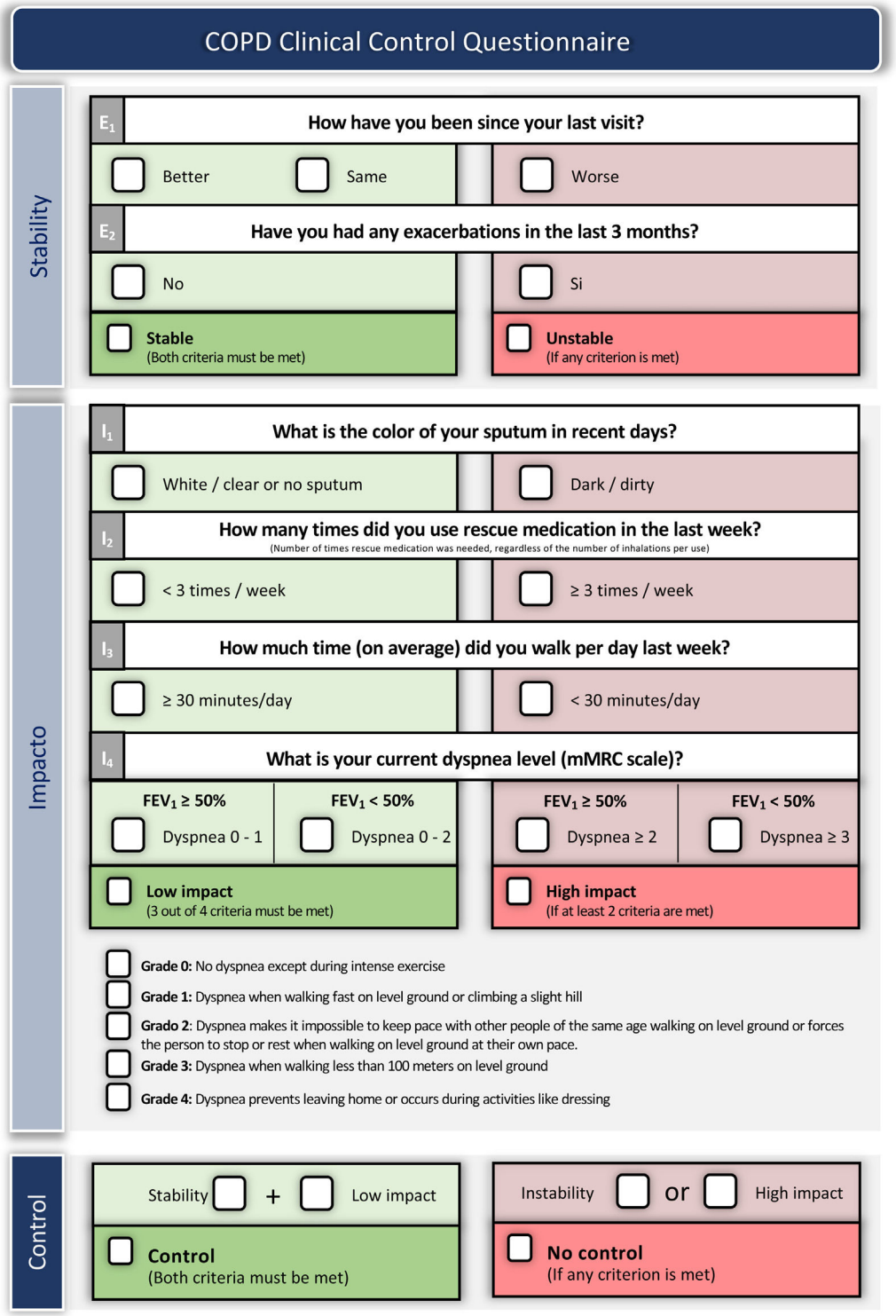

Fig. 4. Criteria for COPD control.

Conversely, GesEPOC suggests the withdrawal of ICS in patients without frequent exacerbations (no more than one moderate episode in the previous year) and <300 eosinophils/mm^3. However, in patients with frequent exacerbations, there is insufficient evidence to establish a recommendation for ICS withdrawal. ICS withdrawal studies have shown a significant increase in the risk of exacerbations when ICS are discontinued in patients with >300 eosinophils/mm^3, which supports a strong recommendation not to withdraw ICS in eosinophilic exacerbator patients [120] (Table 4). The purpose of ICS withdrawal is to avoid the potential occurrence of adverse effects [121] in patients for whom their efficacy has not been demonstrated.

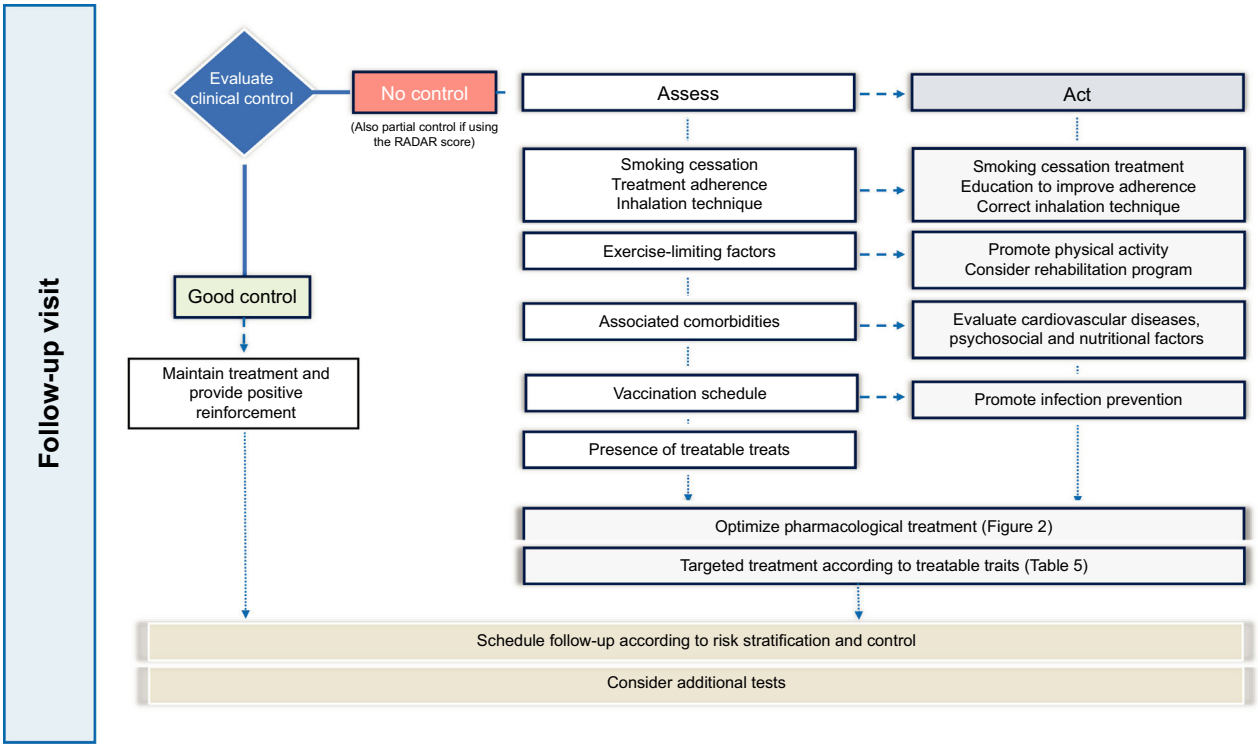

Fig. 5. Follow-up of COPD patients according to their level of disease control.

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Conflict of interests

Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Bial, Glenmark Pharmaceuticals, Menarini, Kamada, Takeda, Zambon, Tabuk Pharmaceuticals, CSL Behring, Zambon, Specialty Therapeutics, Janssen, Sanofi/Regeneron, Grifols, and Novartis; advisory board fees from AstraZeneca, Atriva Therapeutics, AIRNA, Boehringer Ingelheim, BEAM Therapeutics, BridgeBio, Chiesi, GlaxoSmithKline, CSL Behring, Ferrer, Inhbrix, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi/Regeneron, Zambon, Zentiva, and Grifols; and research funding from Grifols.

Myriam Calle has received honoraria for scientific advisory activities and/or lectures from Novartis, Chiesi, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline.

Jesús Molina has received honoraria in the past three years for scientific advisory activities and/or lectures from AstraZeneca, Chiesi, GlaxoSmithKline, Menarini, Novartis, and Pfizer.

Pere Almagro has received honoraria for scientific advisory activities and/or lectures from Chiesi, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Laboratorios Esteve, Menarini, and Novartis.

José-Tomás Gómez has received honoraria for scientific advisory activities and/or lectures from AstraZeneca, BIAL, Chiesi, Laboratorios Esteve, Grifols, GlaxoSmithKline, Mylan, Reig-Jofré, ROVI, TEVA, and Zambon.

Juan Antonio Trigueros has received honoraria for educational activities and participation in clinical studies from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, GlaxoSmithKline, Mundipharma, Menarini, Pfizer, and Teva.

Borja G. Cosío has received honoraria for scientific advisory activities and/or lectures from Chiesi, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Laboratorios Esteve, Faes Farma, Teva, Menarini, Sanofi, and Novartis.

Juan Antonio Riesco has received honoraria for scientific advisory activities and/or lectures from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Mundipharma, Novartis, Pfizer, Rovi, and Teva.

Ciro Casanova has, in the last three years, received honoraria for lectures and/or scientific advisory activities and/or research project funding from AstraZeneca, GlaxoSmithKline, and Menarini.

Pere Simonet has received honoraria for continuing medical education activities from Menarini, GlaxoSmithKline, Chiesi, and AstraZeneca.

David Rigau has no conflicts of interest to declare.

José Luis López-Campos has received honoraria in the past three years for providing lectures, scientific advisory services, participation in clinical studies, or publication writing for (in alphabetical order): AstraZeneca, Bial, Chiesi, CSL Behring, Faes, Gebro, Grifols, GSK, Menarini, Sanofi, and Zambon.

Juan José Soler-Cataluña has received honoraria for scientific advisory activities and/or lectures from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Sanofi/Regeneron, and Zambon.

Bernardino Alcázar-Navarrete has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Takeda, Zambon, CSL Behring, Sanofi/Regeneron, and Novartis; advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, and Sanofi/Regeneron; and research funding from AstraZeneca and GSK.

Efraín Sánchez-Angarita has received speaker fees from AstraZeneca, Boehringer Ingelheim, and Elea.

The remaining authors have no conflicts of interest to declare.

Appendix 1. GesEPOC 2025 Working Group. Pharmacological treatment in the stable phase:

Coordinator: Marc Miravitlles, *Sociedad Española de Neumología y Cirugía Torácica (SEPAR)*. **Executive Committee:** Pere Almagro, *Sociedad Española de Medicina Interna (SEMI)*; Julio Ancochea, Myriam Calle, Ciro Casanova, Borja G. Cosío, José Luis López-Campos, Juan Antonio Riesco, Patricia Sobradillo, Bernardino Alcázar-Navarrete, Juan José Soler-Cataluña *(SEPAR)*; Jesús Molina, *Sociedad Española de Medicina Familiar y Comunitaria (semFYC)*; Efraín Sánchez-Angarita, *Asociación Latinoamericana del Tórax (ALAT)*; Noé Garin, *Sociedad Española de Farmacia Hospitalaria (SEFH);* Mariano Pastor; *Asociación de Pacientes y Familiares de EPOC y Apneas del Sueño (APEAS), Federación Nacional de Asociaciones de Pacientes Respiratorios (FENAER), Foro Español de Pacientes (FEP)*; Pere Simonet, *Grupo de Respiratorio en Atención Primaria (GRAP)*; José-Tomás Gómez, *Sociedad Española de Médicos de Atención Primaria (SEMERGEN)*; Juan Antonio Trigueros, *Sociedad Española de Médicos Generales y de Familia (SEMG)*. **Methodology**: David Rigau, Ainel Iskakova, *Centro Cochrane Iberoamericano, Barcelona, España.*

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2025.10.008.

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