Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
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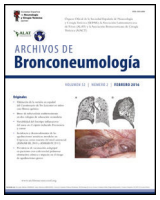

Review Article

Rethinking GOLD E: The Significance of a Single Moderate Exacerbation in COPD

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ARTICLE INFO

Article history:
Received 11 January 2026
Accepted 27 January 2026
Available online xxx

Keywords:
GOLD
GesEPOC
Exacerbations
Guidelines
Treatment

ABSTRACT

The new GOLD 2026 classification includes, for the first time, patients who experience one moderate exacerbation in a year in the E category. This change may have substantial implications, as patients with one moderate exacerbation are more frequent than those with two or more moderate exacerbations or at least one severe exacerbation considered together, according to population-based studies. This reclassification implies that patients with one moderate exacerbation and elevated blood eosinophil counts may initiate triple therapy, and, by being classified as GOLD E, may become candidates for second-line preventive treatments, despite GOLD recommendations for escalation only after two or more moderate exacerbations or one severe exacerbation. The rationale for classifying patients with one moderate exacerbation as GOLD E should rely on evidence of the clinical impact of a single moderate exacerbation and the associated increased risk of poor outcomes. This review summarises evidence from large trials and epidemiological studies regarding these aspects and proposes a pragmatic approach to management for patients with one moderate exacerbation. In conclusion, the impact of a single moderate exacerbation is limited at a population level and although the risk of future exacerbations is higher than in patients with none, it remains low, usually below 50%. Decisions regarding escalation or initiation of preventive therapy in COPD should be individualised, considering additional risk factors such as age, symptom burden, lung function impairment, and comorbidities, as well as patient preferences and values.

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Introduction

Chronic obstructive pulmonary disease (COPD) is highly heterogeneous, with marked individual differences in exacerbation risk. The strongest predictor of future exacerbations is a history of previous exacerbations [1], and therefore, there is broad consensus that preventive therapy is indicated for frequent exacerbators, defined as patients who experienced two or more moderate or at least one severe exacerbation in the previous year [2]. However, the optimal management of patients with only one moderate exacerbation in the previous year remains unclear.

For the first time, GOLD 2026 classifies patients with one moderate exacerbation in the previous year as GOLD E [3], a change affecting a substantial number of patients. In large randomised clinical trials, such as POET with over 7000 patients, up to 23% experienced one moderate exacerbation in the previous year, compared with only 13% with two or more or at least one hospitalisation [4]. In the UPLIFT trial, 34% had a mean of one moderate exacerbation per year, versus 33% with two or more [5]. Similar patterns are observed in large database analyses, such as a US retrospective cohort of 1.5 million patients, in which 21.3% had one moderate exacerbation, compared with 16.9% with two or more or at least one severe exacerbation [6].

Intensifying pharmacological and non-pharmacological therapy for patients with one moderate exacerbation in the previous year could lead to substantial overtreatment and increased healthcare costs. Therefore, the inclusion of these patients in GOLD E should ideally be justified by evidence of significant impact on outcomes or increased risk of future events. This article is a narrative review with an expert perspective on this new approach of management of COPD.

Impact of one moderate exacerbation on lung function decline, cardiovascular risk and mortality in COPD

Exacerbations are associated with accelerated lung function decline, impaired quality of life, reduced activity, and higher mor-

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https://doi.org/10.1016/j.arbres.2026.01.011
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Please cite this article as: M. Miravitlles, Rethinking GOLD E: The Significance of a Single Moderate Exacerbation in COPD, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2026.01.011

tality [7]. This impact depends on the number and severity of exacerbations; however, the specific impact of one moderate exacerbation has been infrequently analysed, and it is unclear whether a single moderate exacerbation in a year warrants classification as an exacerbator and escalation of therapy.

Data from UPLIFT demonstrated some increase in the rate of decline of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) associated with exacerbations, but these analyses included all exacerbation types, with severe events more likely to influence lung function [8]. More studies have focused on cardiovascular outcomes. Exacerbations, particularly severe ones, are associated with increased cardiovascular (CV) risk, but moderate exacerbations may also contribute. In the international EXACOS-CV study, a single moderate exacerbation in the previous year was associated with a significant CV risk [9]. However, evaluation is limited due to missing key information such as lung function and comorbidities; in some countries participating in the study, up to 91% of patients were on cardiac medication and 62% on metabolic medications [9].

In a UK population-based study, the risk of a CV event one year after any moderate exacerbation was elevated (hazard ratio (HR) 1.84; 95% confidence interval (CI) 1.78–1.91) [10], but the analysis did not differentiate between one moderate exacerbation and multiple episodes. A subsequent study from the same group demonstrated that CVD risk increased progressively with the number and severity of exacerbations and became significant only after two moderate exacerbations per year [11]. Indeed, in patients with one moderate exacerbation, CVD risk was not significantly increased compared with those without exacerbations (adjusted HR 1.06; 95% CI 0.97–1.17). Similarly, in a large cohort of over 66,000 patients, one moderate exacerbation in the previous year was not associated with increased risk of myocardial infarction (HR 1.10; 95% CI 0.97–1.24), whereas two or more exacerbations were (HR 1.57; 95% CI 1.38–1.78) [12].

Evidence regarding the impact of a single moderate exacerbation a year on mortality is inconsistent. In a Danish cohort of 8453 COPD patients followed for three years, one moderate exacerbation was associated with increased risk of further moderate/severe exacerbations or death compared with patients without exacerbations in the previous year. Notably, all patients were highly symptomatic (modified Medical Research Council (mMRC) dyspnoea $\geq$2), 60% had FEV_1 <50% predicted, and there was considerable undertreatment (only 4.9% using dual bronchodilation, up to 40% on monotherapy or no treatment) [13]. By contrast, in a UK study with over 99,000 patients followed for ten years, one moderate exacerbation was not associated with increased mortality, whereas five or more moderate exacerbations doubled the risk of death, and one severe exacerbation increased mortality 14-fold [14]. Similar results were reported in a Swedish cohort of over 45,000 patients [15].

Large clinical trials confirm this pattern. In POET, only severe exacerbations were associated with increased mortality; but any number of moderate exacerbations did not increase death risk [4]. In UPLIFT, patients with a mean of one moderate exacerbation per year had mortality rates similar to those with none, while patients with two or more exacerbations had significantly higher mortality [5].

In contrast, the ETHOS trial reported a modest but significant increase in risk of death associated with one moderate exacerbation (HR 1.8; 95% CI 1.1–2.9), though substantially lower than the risk associated with a severe exacerbation (HR 11.4; 95% CI 7.7–17.0) [16]. This likely reflects participant selection: unlike POET and UPLIFT, all ETHOS participants had severe COPD and were frequent exacerbators before randomisation, representing the extreme end of the spectrum among patients with one moderate exacerbation.

In conclusion, there is clear evidence that severe or frequent moderate exacerbations adversely affect lung function, cardiovascular outcomes, and mortality. However, the impact of a single moderate exacerbation in a year is very limited, except perhaps in the most severe COPD patients.

Future risk of exacerbations in patients with one moderate COPD exacerbation in the previous year

Having one moderate exacerbation in a year is a poor predictor of future risk. In the ARCTIC study conducted in Sweden, only 23.5% of patients with one exacerbation in the previous year experienced another, and 16% progressed to two or more exacerbations, whereas up to 60.5% had no exacerbations in the following year [17]. Similarly, in a large US study, the most frequent trajectory among patients with one moderate exacerbation was no exacerbations in the subsequent year (65%), followed by persistence of one exacerbation (20%), while only 15% escalated to more frequent or severe exacerbations [6].

Despite the low risk of future exacerbations associated with a single moderate episode, some studies have reported a significantly higher risk compared with that observed in patients with no exacerbations. In the study by Vanfleteren et al. [15], the probability of a first exacerbation during follow-up was higher in patients with one prior moderate exacerbation than in those without. However, only 32–39% of patients with one moderate exacerbation at baseline experienced an exacerbation during the first year of follow-up, indicating that they were almost twice as likely to have no exacerbations as to have one in the following year. Müllerova et al. [18] also identified an increased risk of moderate-to-severe exacerbations in patients with one moderate exacerbation in the previous year compared with those without (odds ratio (OR) 1.89; 95% CI 1.79–1.99); nevertheless, the absolute risk remained low, with fewer than 50% experiencing another exacerbation during follow-up.

When comparing future risk according to baseline exacerbation frequency, all studies consistently show that one moderate exacerbation in a year is associated with an intermediate level of risk. This support considering this group as distinct from patients with no exacerbations and those with two or more. In the aforementioned study by Rothnie et al. [14], there was a graded increase in the rate of moderate exacerbations during follow-up with increasing baseline exacerbation frequency. The relative risk of further moderate exacerbations increased from an HR of 1.71 (95% CI 1.66–1.77) in those with one baseline moderate exacerbation to 5.50 (95% CI 5.32–5.68) in those with five or more, compared with patients with none at baseline. Nevertheless, the risk of exacerbation in the following year among those with one moderate exacerbation was approximately 50%.

Vogelmeier et al. [19] reported that the risk of exacerbation in patients with one moderate episode in the previous year was double that of patients with no exacerbations (38% versus 19%), but still below 50% and substantially lower than the 69% risk observed in patients with two or more previous exacerbations. In a large UK study, Halpin et al. [20] found a 59% risk of exacerbation in the following year among patients with one moderate exacerbation, compared with 34% in those with none, but this was still approximately half the risk observed in patients with two or more prior exacerbations (118%). The higher risk observed in this study may be explained by the greater disease severity of the population, as 80% had an FEV_1 <50% predicted. In another UK study, a similar 60% increase in risk was reported for patients with one moderate exacerbation (risk ratio (RR) 1.60; 95% CI 1.53–1.67), compared with a 361% increase in those with two or more exacerbations (RR 3.61; 95% CI 3.48–3.74) [21].

Table 1
Characteristics of studies reporting risk of an exacerbation over a year follow-up of patients with one moderate exacerbation in the previous year.

Authors, year (ref.)	*N* and country	Mean age	Mean FEV1 (%)	PROs	CVD
Larsson, 2021 [17]	18,586 Sweden	68.2–69.5	61.4%–65.1%	NR	35.6%–41.6%
Sethi, 2022 [6]	1,492,108 US	70.9	NR	NR	38%
Vanfleteren, 2023 [15]	45,350 Sweden	71.5	60.4%	CAT: 13.2	18.4%
Müllerova, 2014 [18]	58,589 UK	69.5	60%	NR	10%
Rothnie, 2018 [14]	99,574 UK	66.9	62.1%	NR	14.5%
Vogelmeier, 2021 [19]	250,723 Germany	63	NR	NR	38%
Halpin, 2024 [20]	15,717 UK	66.1	NR	CAT: >10 61%	5.8%
Hurst, 2010 [1]	International 2,138	63	48%	SGRQ: 50	NR

US: United States; UK: United Kingdom; FEV1: forced expiratory volume in one second; PROs: patient reported outcomes; CVD: cardiovascular disease: NR: not reported; CAT: COPD Assessment Test; SGRQ: St. George's Respiratory Questionnaire.

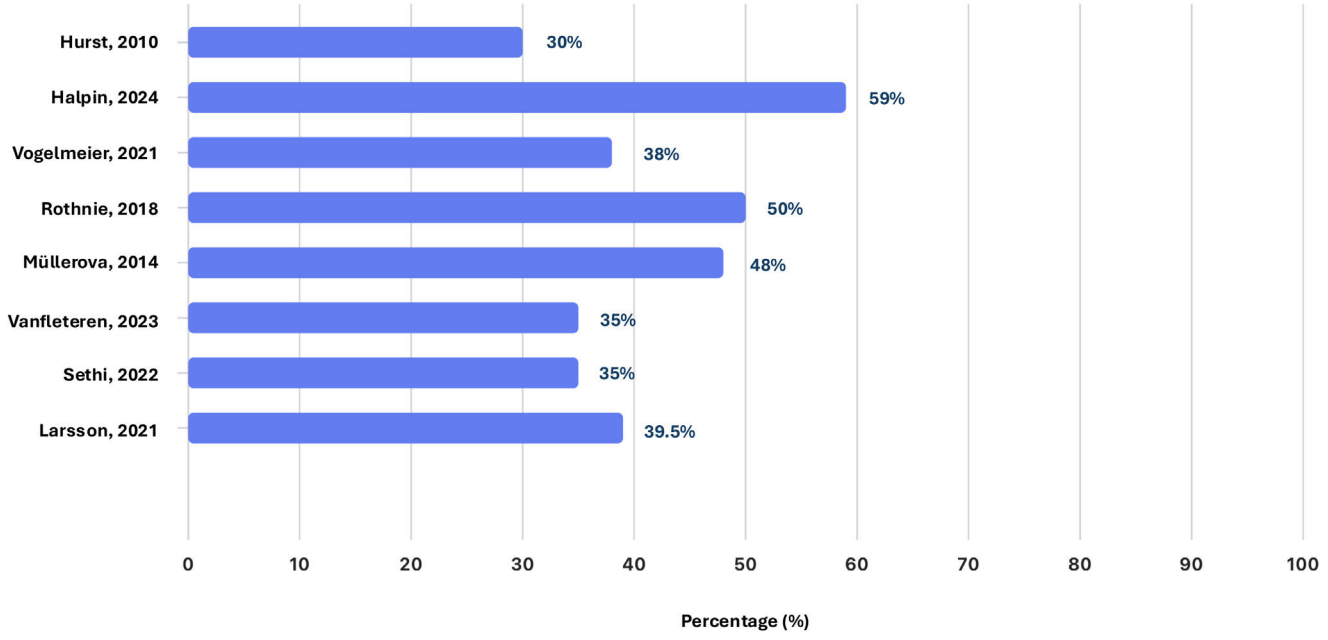

Fig. 1. Risk of an exacerbation over a year follow-up of patients with one moderate exacerbation in the previous year.

Evidence from clinical trials is limited but confirms a significantly higher risk associated with frequent moderate exacerbations compared with a single moderate episode. In the POET study, patients with two or more exacerbations in the previous year had a significantly shorter time to first exacerbation than those with only one moderate exacerbation (HR 1.33; $p < 0.001$) [16]. Table 1 summarises the characteristics of studies assessing exacerbation risk in patients with one moderate episode, and Fig. 1 presents the main results.

Overall, these studies indicate that future exacerbation risk increases with the number of prior exacerbations, although considerable variability remains. Sadatsafavi et al. [22] demonstrated that observed exacerbation rates over a 12-month period may vary widely from year to year due to the inherent randomness of events. For individuals with an underlying exacerbation rate of 0.8–3.1 events per year, the frequent exacerbator phenotype may change from one year to the next in 30% or more of cases, and in those with rates between 1.2 and 2.2 events per year this probability exceeds 45%, which is close to the chance finding related to flipping a coin. Given this instability, treatment recommendations based solely on exacerbations in the previous year may be problematic, particularly for therapies with modest effects. For example, triple therapy (TT) reduces exacerbation risk by only around 18% compared with dual bronchodilation in severe COPD patients with one moderate exacerbation [23]. In such cases, the biological effect of treatment may be obscured by year-to-year variability in exacerbation occurrence [22].

Extending observation beyond a single year could improve predictive accuracy, although this may be difficult in newly diagnosed patients. Alternatively, incorporating additional predictors of exacerbation risk may improve risk stratification [22]. Several studies have identified associations with more severe airflow limitation, worse dyspnoea, asthma, and comorbidities such as cardiovascular disease and depression [14,18]. Rothnie et al. [24] showed that among GOLD A and B patients, lower FEV_1 and higher symptom burden were stronger predictors of severe exacerbations than a history of one moderate event. These factors should be considered when assessing future risk in patients with COPD, particularly those with a previous single moderate exacerbation. Prediction models incorporating multiple variables rather than exacerbation history alone may be more informative [22], as illustrated by recently developed models predicting first severe exacerbations in newly diagnosed COPD patients [25].

Treatment of patients with one moderate COPD exacerbation: the evidence

Two distinct clinical scenarios should be considered: initiation of treatment and continuation or escalation of existing therapy. In the first scenario, GOLD 2026 suggests considering TT for patients with one moderate exacerbation and blood eosinophil counts (BEC) >300 cells/μL [3]. Given the high prevalence of patients with one moderate exacerbation and the fact that 20–30% have BEC >300 cells/μL [26,27], this recommendation would have substan-

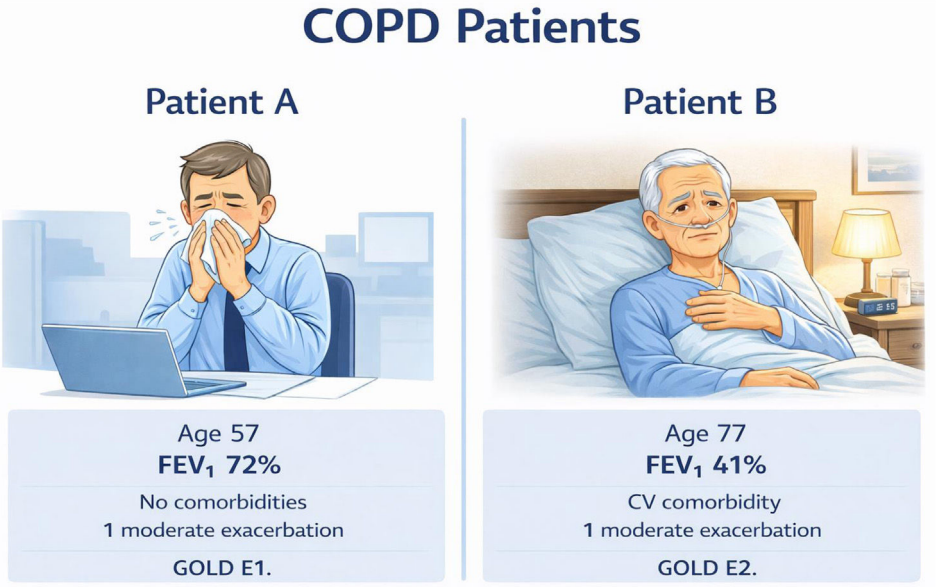

Fig. 2. Two different types of GOLD E patients with one moderate exacerbation in the previous year. GOLD E1 (Patient A) represents a patient with low impact and risk of future exacerbations and GOLD E2 (Patient B) represents a patient at higher risk. Generated using ChatGPT 4.1 (OpenAI).

tial clinical impact. However, no studies have evaluated the efficacy of TT as initial therapy in COPD, at any BEC level, compared with LABA/LAMA or LAMA monotherapy; furthermore, there is not even evidence comparing LABA/LAMA versus LAMA as initial therapy in patients with one moderate exacerbation in the previous year.

In the second scenario, evidence supporting the superiority of TT over LABA/LAMA in patients already receiving treatment and experiencing one moderate exacerbation is very limited. In a post hoc analysis of patients with a single moderate exacerbation enrolled in the IMPACT trial, no differences were observed between dual therapy and TT in time to first exacerbation – whether moderate or severe combined, or severe alone– nor in the annual rate of severe exacerbations. Only the annual rate of moderate exacerbations showed a small but statistically significant benefit in favour of TT compared with LABA/LAMA (18% reduction; RR 0.82; 95% CI 0.71–0.95) [23,28].

A subgroup analysis from the ETHOS trial found no significant differences in time to death between dual therapy and TT in patients with one moderate exacerbation [29]. Similarly, a pooled analysis of six trials including patients with mild to very severe COPD, most of whom had a low exacerbation risk, found no mortality difference between LAMA/LABA and TT [30]. By contrast, some studies have reported reductions in exacerbations with TT compared with LABA/LAMA in patients with no exacerbations or only one prior moderate event; however, these represent mean effects in previously treated populations and are subject to substantial inter-individual variability, particularly according to BEC levels [31,32]. Moreover, an important limitation common to most clinical trials is inhaled corticosteroid (ICS) withdrawal [33], which substantially limits their applicability when informing decisions on initial therapy in patients with a single moderate exacerbation.

Beyond clinical trials, some large observational studies have provided opposite results. A study including +4500 COPD patients across a wide range of disease severity found a higher, although not statistically significant, number of exacerbations with TT compared with LABA/LAMA [34]. In another real-world study from Germany including patients at low exacerbation risk, again significantly more exacerbations were observed in those treated with TT compared with LABA/LAMA (26.6% versus 15.5%; $p < 0.001$) [35].

In summary, the new Spanish COPD Guidelines (GesEPOC 2025) evaluated the available evidence in a systematic review and metanalysis on the treatment of patients with one moderate exacerbation and recommended classifying these patients as low risk and initiating treatment with long-acting bronchodilators (strength of recommendation: weak; level of evidence: low) [2].

Risk of overtreatment in COPD and a treatment proposal for patients with one moderate exacerbation per year

Recognising that preventive and safety-oriented rationale must guide the guideline development, classifying all patients with one moderate exacerbation the previous year as GOLD E may carry a substantial risk of overtreatment. There is already clear evidence of frequent overuse of TT as initial therapy. In a large primary care study in Spain including nearly 70,000 newly diagnosed COPD patients, 12.5% initiated TT at or immediately after diagnosis, despite 72% of these patients being classified as GOLD A or B [36]. Furthermore, a recent clinical trial comparing TT with LABA/LAMA in GOLD B patients with one moderate exacerbation was discontinued partly because of slow recruitment, as most screened patients were already receiving TT despite not being recommended in guidelines [37,38].

When prescribing treatment, the balance between expected benefit and potential harm must always be considered. In the case of initial TT recommended by GOLD for patients with one moderate exacerbation and BEC >300 cells/μL [3], the expected benefit is minimal: future exacerbation risk is low, the impact of an additional moderate exacerbation is limited, and the addition of ICS to LABA/LAMA reduces exacerbation risk by only around 18% [23]. This modest benefit must be weighed against the short- and long-term adverse effects associated with ICS use [39].

In an ideal setting, ICS use would be reassessed at every visit, with treatment de-escalation considered when patients meet withdrawal criteria and are well controlled [2,40,41]. In routine practice, however, this reassessment rarely occurs, and ICS withdrawal is uncommon [42,43]. Consequently, the most effective strategy to minimise harm may be to avoid initiating ICS unless there is a clear indication [44]. Importantly, the new GOLD 2026 classification

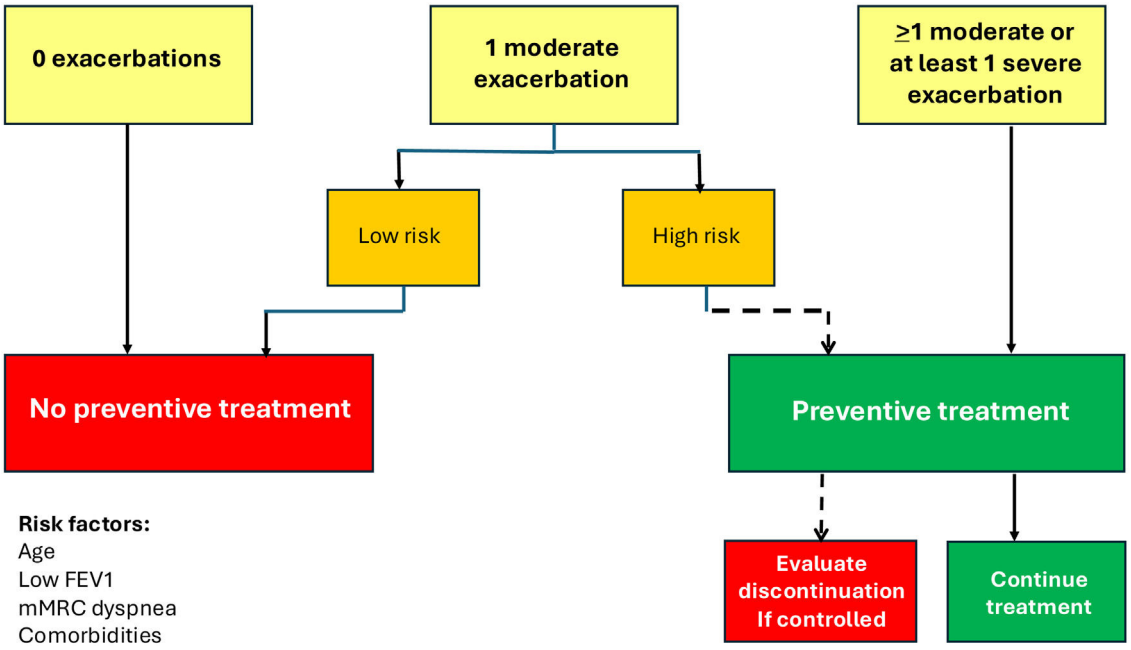

Fig. 3. Algorithm for preventive treatment for future exacerbations in patients with COPD according to previous frequency and severity of exacerbations. Dotted line indicates the suggestion to review and consider withdrawal of preventive therapy.

affects not only ICS use; although the GOLD treatment continuation algorithm recommends treatment escalation when patients experience two or more exacerbations [3], patients classified as GOLD E at diagnosis solely on the basis of one moderate exacerbation the previous year are likely to be labelled as high risk and therefore considered candidates for preventive therapies, such as azithromycin, roflumilast, or emerging biologic agents, many of which are associated with adverse effects.

If it is accepted that patients without prior exacerbations do not require preventive therapy, and that those with frequent or severe exacerbations do, the key question concerns patients with a previous single moderate exacerbation. There is unlikely to be a single, simple recommendation. A clinical example may help illustrate this point. Consider a 57-year-old patient who presents after an exacerbation treated with three days of azithromycin, without work absence, with spirometry showing an FEV_1 of 72% predicted and no significant cardiovascular comorbidity. Contrast this with a 77-year-old patient with severe cardiovascular disease who reports an episode of "bronchitis" requiring five days of bed rest at home and treatment with oral corticosteroids and antibiotics, and whose FEV_1 is 41% predicted. Both patients are classified as GOLD E due to one moderate exacerbation and, if BEC were >300 cells/μL, would be candidates for TT. Nevertheless, their future risks are clearly not comparable (Fig. 2).

Therefore, in patients with one moderate exacerbation in the previous year, other established risk factors for future events should be systematically considered [14,18,28,45,46]. Based on this approach, a treatment strategy can be proposed in which preventive therapy is reserved for patients with additional risk factors. In such cases, preventive treatment should be reassessed after one year, and discontinuation should be considered in patients with good control and/or a high risk of adverse effects (Fig. 3). Direct evidence supporting this strategy is lacking, but the same limitation applies to the recommendation of TT as initial therapy in patients with one moderate exacerbation and BEC >300 cells/μL. This approach may increase the complexity of COPD management, but COPD has never been a simple disease to manage.

Conclusion

Although previous exacerbation frequency is the strongest predictor of future events, the occurrence of a single moderate exacerbation does not reliably identify patients at high risk. While the risk associated with one moderate exacerbation in the previous year is higher than in patients with none, it remains low – most often below 50%, and frequently close to chance – and is far lower than the risk observed in patients with two or more moderate exacerbations or at least one severe event. Moreover, the clinical impact of a single moderate exacerbation per year is limited and, in many population-based studies, almost negligible. Consequently, classifying all patients with one moderate exacerbation as GOLD E carries a substantial risk of overtreatment.

The risk of future exacerbations should be assessed at the individual patient level before preventive treatment strategies are initiated. Exacerbation rates vary widely from year to year due to the inherent randomness of events. Consequently, many patients with one moderate exacerbation in the previous year may not require long-term preventive or anti-inflammatory treatment, associated with potential adverse effects. Final treatment decisions in this group of COPD patients should integrate additional factors, including age, disease severity, comorbidities, and patient preferences and values [47].

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT 4.1 in order to develop Fig. 2. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Bial, Chiesi, Cipla, GlaxoSmithKline, Glenmark Pharmaceuticals, Menarini, Kamada, Takeda, Zambon, Tabuk Pharmaceuticals, CSL Behring, Specialty Therapeutics, Sanofi/Regeneron, Grifols and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, BEAM Therapeutics, GondolaBio, Chiesi, GlaxoSmithKline, CSL Behring, Ferrer, Korrobio, Menarini, Mereo Biopharma, Specialty Therapeutics, Takeda, Novartis, Novo Nordisk, Roche, Sanofi/Regeneron, Zambon, Zentiva and Grifols and research grants from Grifols.

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