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REVIEW

Overuse of long-acting β_2-agonist/inhaled corticosteroids in patients with chronic obstructive pulmonary disease: time to rethink prescribing patterns

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality globally. In the major revision of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 report, the scientific committee concluded that the use of long-acting β_2-agonist/inhaled corticosteroids (LABA/ICS) is not encouraged in patients with COPD. However, current prescribing patterns reveal significant use of LABA/ICS. In this paper, the evidence behind the current practice and the latest treatment recommendations is reviewed. We compare the efficacy and safety of combination therapy with long-acting muscarinic antagonist (LAMA) and LABA vs LABA/ICS and note that LAMA/LABA combinations have reduced the annual rate of moderate/severe exacerbations, delayed the time to first exacerbation, and increased post-dose FEV_1 vs ICS-based regimens. The GOLD 2023 report recommends treatment with LABA and LAMA combination (preferably as a single inhaler) in patients with persistent dyspnea, with initiation of ICS in patients based on the symptoms (dyspnea and exercise intolerance as indicated by modified Medical Research Council [mMRC] score ≥ 2 and COPD Assessment Test [CAT™] > 20), blood eosinophil count (≥ 300 cells/μL), and exacerbation history (history of hospitalizations for exacerbations of COPD and ≥ 2 moderate exacerbations per year despite appropriate long-acting bronchodilator maintenance therapy). We describe practical recommendations for primary care physicians to optimize therapy for their patients and prevent overuse of ICS-based regimens. We advocate adherence to current recommendations and a greater focus on effective treatments to successfully control symptoms, minimize exacerbation risk, preserve lung function, maximize patient outcomes, and reduce the burden of drug-related adverse events.

PLAIN LANGUAGE SUMMARY

Chronic obstructive pulmonary disease (COPD) is a common disease of the lungs associated with continued respiratory symptoms and airflow limitation. COPD causes symptoms such as breathlessness, cough, and production of phlegm, and, if not properly managed, these symptoms may get worse and result in flare-ups, also termed exacerbations. COPD management includes controlling symptoms while reducing the risk of exacerbations. COPD treatments include bronchodilators and inhaled corticosteroids (ICS). Bronchodilators help by widening the airways, making it easier to breathe. The two types of bronchodilators are long-acting muscarinic antagonists (LAMAs; these drugs prevent closing of the airways) and long-acting β_2-agonists (LABAs; these drugs relax the muscles around the airways to help keep the airways open for a longer time). ICS may reduce swelling in the airways in some patients with COPD. However, the use of ICS-based regimens as the first treatment choice has been linked to health risks and is not in keeping with the recent national and international recommendations. In this narrative review, we examine why the use of ICS-based regimens is still growing and explore, based on available evidence, and why this treatment course may not be optimal for most patients with COPD. We discuss how the treatment for COPD has changed over time, and our findings support the use of LAMA and LABA as the first course of therapy in many patients with COPD. We conclude that greater adherence to the treatment guidelines can help to improve treatment outcomes for many patients with COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms, such as dyspnea, cough, and sputum production, due to airway (bronchitis and bronchiolitis) and/or alveolar (emphysema) abnormalities resulting in persistent and often progressive airflow obstruction [1,2]. COPD is generally caused by significant exposure to noxious particles or gases and can be influenced by host factors, including genetic abnormalities, abnormal lung development, and accelerated aging [1]. COPD is caused by mechanistically distinct pathophysiological processes that result in diverse clinical presentations, responses to treatment, and patterns of progression [3]. Worldwide, COPD is the third leading cause of mortality, accounting for > 3 million deaths in 2019 [4]. According to the Centers for Disease Control and Prevention, 16 million people suffer from COPD and millions more may remain

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undiagnosed and untreated in the United States (US) [5]. Furthermore, costs linked to COPD in the US increased by 52.6% ($32.1 to $49.0 billion) between 2010 and 2020 [6]. A study conducted in 2018 estimated that the individual direct cost (per year) of COPD in affected patients was significantly higher ($6,246 [95% confidence interval (CI)]: $4,620–$8,623; $p < 0.001$) than in patients without COPD [7].

To reduce the disease burden, long-acting β_2-adrenoreceptor agonists (LABAs), long-acting muscarinic receptor antagonists (LAMAs), and inhaled corticosteroids (ICS) are the three primary classes of inhaled medications used in individual patients along the progressive course of COPD [1]. Single inhaler dual (LABA/ICS and LAMA/LABA) and single inhaler triple (LAMA/LABA/ICS) therapy fixed-dose combinations are available for the treatment of patients with COPD [8,9]. Prior to the publication of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 report, ICS-based regimens were considered a panacea for all patients with COPD. The GOLD 2017 report was a defining point in COPD management that restricted the use of ICS-based regimens to a subset of patients with increased symptom burden and exacerbation history who may show benefit from ICS-containing treatment [10]. The GOLD 2023 report further advocated that the majority of patients with COPD should be recommended LAMA/LABA at initiation of maintenance (GOLD groups B and E, the latter with eosinophils < 300 cells/μL) [1]. However, the availability of different fixed-dose combinations of LAMA/LABA/ICS in single inhaler form (closed triple therapy) has resulted in an increase in the proportion of patients with COPD receiving triple therapy, irrespective of the disease severity [11–13].

In this review, we will question the rationale behind the continued widespread use of ICS-based regimens in patients with COPD and highlight evidence suggesting that extensive prescription of ICS may come at a price in terms of risks vs benefits.

2. Asthma-COPD conundrum and the use of ICS-based regimens in patients with COPD

In the clinical context, spirometry is required for COPD diagnosis [1]. A ratio of post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.70 confirms the presence of persistent airflow limitation and, thus, COPD in patients with related symptoms and significant exposure to noxious stimuli [1]. In some patients, features of asthma and COPD may coexist (asthma-COPD overlap [ACO]) [10]. The similarities between COPD and asthma can confound diagnosis; however, there are many differences, including etiology, symptoms, type of airway inflammation, inflammatory cells and mediators, consequences of inflammation, response to therapy, and the disease course (Figure 1) [14,15]. Despite the lack of recognition of the ACO in the GOLD 2023 report, many clinicians still rely on this definition, and it is recognized that asthma and COPD may coexist [15,16]. Some evidence suggests that asthma is over-diagnosed in patients with COPD, leading to inappropriate prescription of ICS-based regimens [17]. Slowly progressive symptoms and history of tobacco smoking (although approximately 50% of adult patients with asthma are current or former cigarette smokers) or other risk factors are suggestive features of COPD, whereas variable airflow obstruction; wide variation in daily symptoms; worsening of symptoms at night/early morning; presence of allergy, rhinitis, and/or eczema; occurrence in children; and family history are suggestive features of asthma that may help clinicians to distinguish between asthma and COPD [1,18]. Chen et al reported that fractional exhaled nitric oxide (FENO) was significantly higher in patients with ACO compared with those who had COPD (median [interquartile range]: 27 [21.5] parts per billion [ppb] vs 18 ppb [11]), suggesting that FENO measurement was a sensitive, easy-to-implement, and noninvasive method to distinguish between ACO and COPD [19]. Early differentiation between asthma and COPD is essential to manage these conditions appropriately, as COPD has a less favorable prognosis, higher economic burden, and greater morbidity and mortality [20]. The GOLD 2023 report no longer refers to ACO and recommends that if a concurrent diagnosis of asthma is suspected in any patient with COPD, the pharmacotherapy should primarily follow the asthma guidelines that support the use of ICS-based fixed-dose combinations irrespective of the severity of COPD [1,21]. The symptoms, risk factors, spirometric characteristics, diagnostic indicators, comorbidities, role of blood eosinophils, and other disease markers of COPD are summarized in Figure 1 [15].

As chronic airway inflammation is a prominent feature of COPD, it was postulated that ICS may improve the health outcomes of patients with COPD [22]. Historically, the use of ICS-based regimens in COPD management was based on their effectiveness in patients with asthma rather than scientific evidence [23], possibly due to the challenge in differentiation at first diagnosis by primary care physicians who often lack spirometry facilities [24]. Over the years, research has shown that inflammation in COPD is very different from that in asthma; T helper 2 lymphocytes (Th2)-mediated eosinophilic airway inflammation commonly associated with asthma is present in 10%–40% of patients with COPD, and the remaining patients have predominantly neutrophilic inflammation typically associated with Th1-mediated immunity [25]. Generally, ICS is ineffective in suppressing inflammation in patients with COPD, and only approximately 10% of patients who usually have evidence of eosinophils in the airways will respond to an ICS [26].

The TRial of Inhaled STeroids ANd long-acting β_2-agonists (TRISTAN) and TOwards a Revolution in COPD Health (TORCH) studies shed light on the beneficial use of ICS alone or in combination with LABA over placebo in reducing exacerbation frequency in patients with COPD [27,28]. Combination treatment with LABA and ICS resulted in clinically significant improvement in health status and a reduction in daily symptoms [27]. In the TORCH study, a reduction of 17.5% in the mortality risk at any time during the 3-year period was observed with LABA/ICS, although this did not reach statistical significance ($p = 0.052$) [28]. A subsequent post hoc factorial analysis of the TORCH trial showed that the survival benefit was in fact associated with the LABA component and not the ICS component [29]. Although the primary outcome of

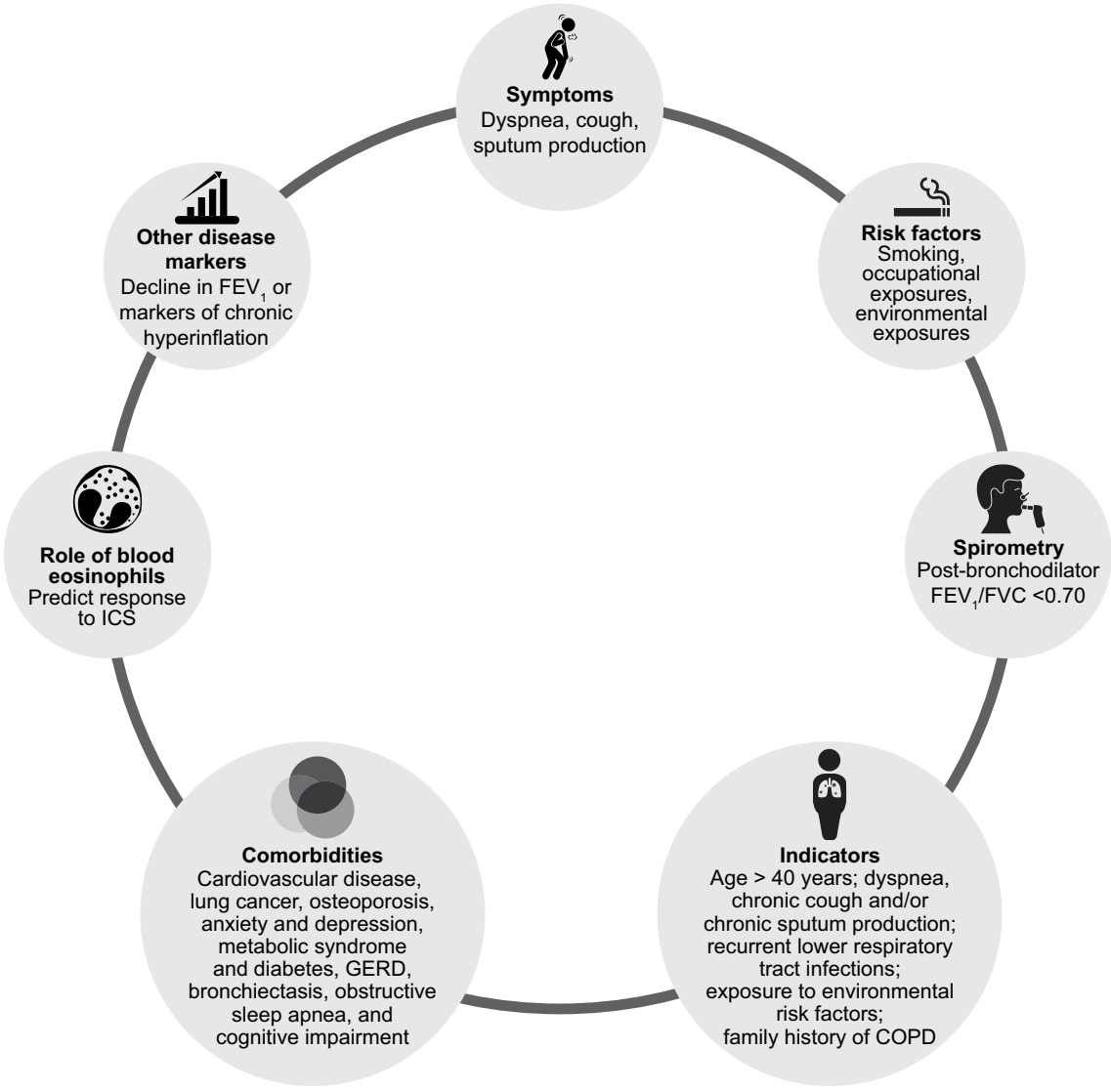

Figure 1. A summary of the characteristics of COPD (adapted from [15]).

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids.

mortality was not significantly different in patients with COPD using LABA/ICS compared with placebo or LABA or ICS monotherapy, other outcomes, including health status and lung function, showed improvement with fewer exacerbations reported in the TORCH study. This finding was also observed in the Study to Understand Mortality and MorbidITy (SUMMIT) study [28,30,31]. In summary, only two randomized controlled trials (RCTs; TORCH and SUMMIT) aimed to assess the effect of maintenance therapy with LABA/ICS fixed-dose combination on survival in patients with COPD, and both studies failed to show a significant effect [28,31]. In an observational study, the combination of ICS (fluticasone propionate) and LABA (salmeterol) demonstrated improved 3-year survival in newly diagnosed patients with COPD managed in the primary care setting compared with patients who used other bronchodilators but not ICS or LABA (78.6% vs 63.6%) [32].

Five studies have reported conflicting results on the efficacy of ICS for COPD, with a small subset of patients showing a slight increase in FEV_1 and none of the studies reporting slowing of FEV_1 decline after ICS administration [33–37]. This may be attributed to the difference in Th2-mediated signaling in patients with COPD as a high Th2 signature score has been shown to be correlated with an improvement in hyperinflation after ICS treatment [38]. The Investigating New Standards for Prophylaxis In Reducing Exacerbations (INSPIRE) study showed no significant differences in exacerbation rates with salmeterol/fluticasone combination (LABA/ICS) vs tiotropium (LAMA) monotherapy in patients with severe-to-very severe COPD and a history of exacerbations [39]. Subsequently, in the Effect of Indacaterol/Glycopyrronium Versus Fluticasone/Salmeterol on COPD Exacerbations (FLAME) study, patients with ≥ 1 exacerbation in the previous year receiving a once-daily dose of indacaterol/glycopyrronium presented a reduced annual rate of moderate or severe exacerbations compared with those receiving LABA/ICS (rate ratio: 0.83; 95% CI: 0.75–0.91) [40]. Two meta-analyses reported fewer exacerbations in patients receiving LAMA/LABA than in those receiving LABA/ICS

[41,42]; however, it must be noted that both meta-analyses included a combination of patients with high and low risks of exacerbations [43].

The InforMing the PAthway of COPD Treatment (IMPACT) study evaluated the effects of 52 weeks of triple therapy (ICS/LAMA/LABA [fluticasone furoate/umeclidinium/vilanterol]) vs LABA/ICS (vilanterol/fluticasone furoate) or LAMA/LABA (umeclidinium/vilanterol) on the rate of moderate or severe COPD exacerbations [44]. The annual rate of moderate or severe exacerbations was greater among patients receiving LAMA/LABA and LABA/ICS than among those receiving triple therapy [44]. Similar results were observed among a subgroup of patients with ≥ 2 moderate or 1 exacerbation resulting in hospitalization in the previous year but not among patients with a history of only one moderate exacerbation in the previous year [44]. It is important to note that the majority (54%) of patients in the IMPACT study [45] had experienced ≥ 2 moderate/severe exacerbations in the previous year compared with ~ 19% in the FLAME study [40]. In the IMPACT study, patients treated with LABA/ICS (vilanterol/fluticasone furoate) and with blood eosinophil counts ≥ 310 cells/μL had lower annual exacerbation rates than those treated with LAMA/LABA (umeclidinium/vilanterol) [46]. The magnitude of the benefit of ICS in reducing the rates of moderate or severe exacerbations and severe exacerbations increased in those patients with higher blood eosinophil counts in both current and former smokers; however, the treatment effect was lower in current smokers compared with that in former smokers [46]. The findings from the IMPACT study suggest that assessment of blood eosinophil count and smoking status could help optimize ICS use in patients with COPD and a history of exacerbations and may advocate identification and development of personalized pharmacotherapies in patients with COPD [46,47].

3. Adverse events associated with ICS-based regimens and selecting the right patient population for treatment with ICS-based regimens

The benefits of any therapy, including ICS, should always be weighed against their potential for adverse outcomes. TORCH was the first study to report the potential risk of pneumonia in patients receiving ICS therapy, with a higher probability of pneumonia in the group that received ICS monotherapy vs the other groups (placebo: 12.3%, LABA: 13.3%; ICS; 18.3%, and ICS/LABA: 19.6%; $p < 0.001$) [28]. Thus, unlike in persistent mild asthma, maintenance ICS monotherapy should not be used in patients with COPD. The reports of a higher incidence of pneumonia among different patient subgroups in the TORCH study prompted future clinical trials to focus on this adverse event (AE) [28], representing an important point in COPD management and providing new perspectives on the benefits and risks of prescribing ICS. Indeed, later studies challenged the relevance of ICS in COPD and indicated that ICS use may be associated with AEs [24,39,40]. In the FLAME study, the incidence of pneumonia was significantly higher in the LABA/ICS group vs the LAMA/LABA group (4.8% vs 3.2%, $p = 0.02$) [40]. A meta-analysis of RCTs of ICS therapy showed that exposure to ICS was also associated with an increased risk of tuberculosis [48]. A systematic review evaluating the risk of adverse effects associated with the long-term use of ICS in patients with COPD revealed an increased risk for local disorders such as oral candidiasis and dysphonia [49]. A meta-analysis of 29 RCTs and nine observational studies assessed the risk of pneumonia in patients receiving ICS-based therapies and concluded that a substantial and significant increase in the unadjusted risk of pneumonia was associated with ICS use [50].

Real-world data from the United Kingdom (UK) primary care revealed that ICS treatment reduced the time to first exacerbation only in patients with baseline eosinophil counts of ≥ 450 cells/μL, suggesting that ICS should be avoided in those with lower eosinophil counts (< 150 cells/μL), which is considered the blood eosinophil cutoff value for regulatory purposes [51]. ICS use in patients with a neutrophilic endotype could alter the composition of the lung microbiome, predisposing patients with neutrophilia to an increased risk of pneumonia and other AEs [52]. Considering that ICS-based regimens may be beneficial to a subset of patients with COPD, there is a need to identify such patients and thereby aim to optimize the risk-benefit and improve treatment outcomes (Figure 2).

4. Evolution of treatment recommendations for patients with COPD

As clinical trial evidence evolved to show the benefits and risks of ICS-based regimens, the guidelines and recommendations for COPD management have evolved to reflect new knowledge and thinking. Recommendations during the 1990s, suggesting that LABA/ICS use decreases COPD exacerbations, were based on evidence that had inherent limitations. Most trials were not intention-to-treat analyses, were biased, used variable definitions of exacerbations, incorrectly calculated the number needed to treat, and incorrectly adjusted for heterogeneity of the number of exacerbations between patients [53]. Moreover, the differences between groups were probably exaggerated by withdrawal of ICS in the placebo and LABA groups [53]. In 1997, the British Thoracic Society advocated ICS use for moderate-to-severe COPD [54]. Later, and in reflection of evolving clinical evidence, both the GOLD 2001 and 2006 reports recommended long-acting bronchodilators (LAMA and LABA) as treatments for improving lung function and reducing symptoms in all patients [55]. ICS use was recommended to be limited to patients with repeated exacerbations and with severe-to-very severe airflow limitation [55]. In the GOLD 2017 report, LAMA/LABA combination therapy was recommended for patients with persistent symptoms despite bronchodilator monotherapy (group B) and as an alternative therapy for patients with exacerbations despite the use of a LAMA (group C) [10]. These recommendations were based on clinical trial data showing consistent clinically significant improvements with LAMA/LABA fixed-dose combination therapies in terms of airway obstruction, dyspnea, and quality of life (QoL) compared with placebo [56]. Modest improvements were also seen with LAMA/LABA fixed-dose combination therapies compared with bronchodilator LAMA and LABA

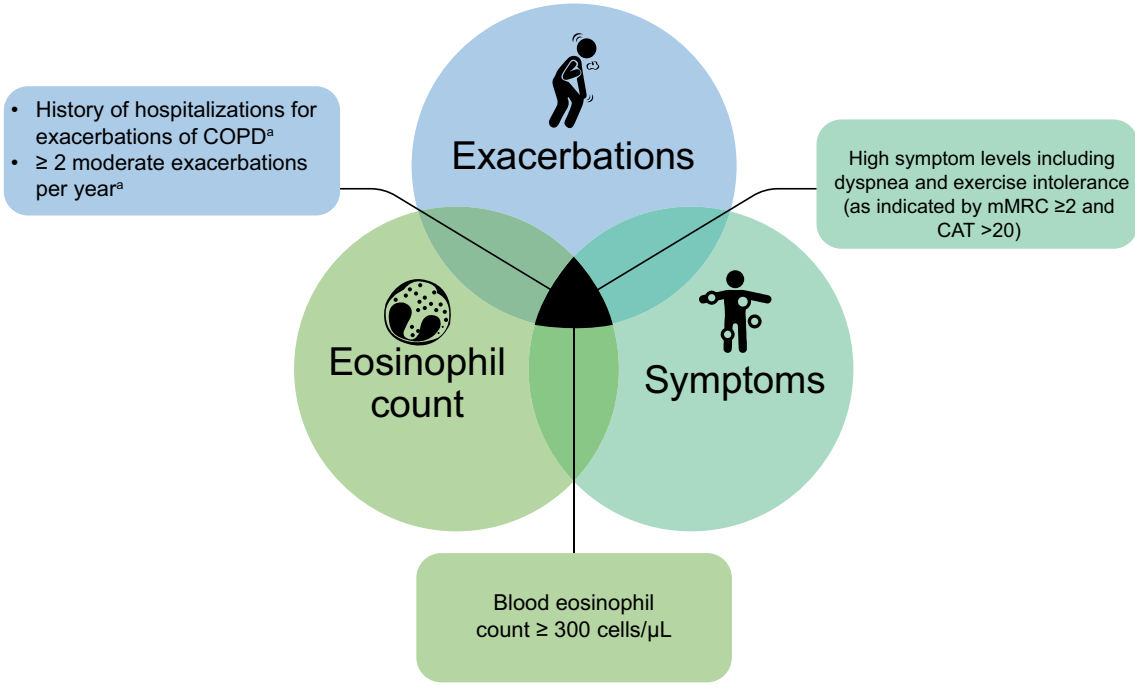

Figure 2. ICS initiation in COPD [1].

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; mMRC, modified Medical Research Council.

[a]Despite appropriate long-acting bronchodilator maintenance therapy.

For patients with asthma, pharmacotherapy should primarily follow asthma guidelines.

monotherapies and combined bronchodilator/ICS therapy [56].

The 'ABE' assessment tool from GOLD 2023 ('ABCD' in GOLD 2022) recognizes the clinical relevance of exacerbations, independent of the level of symptoms, merging groups C and D into a new group E [1]. According to GOLD 2023, patients with COPD should undergo spirometry to determine the severity of airflow limitation (i.e. spirometric grade), followed by assessment of dyspnea using the modified Medical Research Council (mMRC) questionnaire or symptoms using the COPD Assessment Test (CAT™) [1]. Lastly, their history of moderate and severe exacerbations, including prior hospitalizations, should be recorded (Figure 3 and Appendix 1) [1]. The GOLD 2023 report recommends treatment with a combination

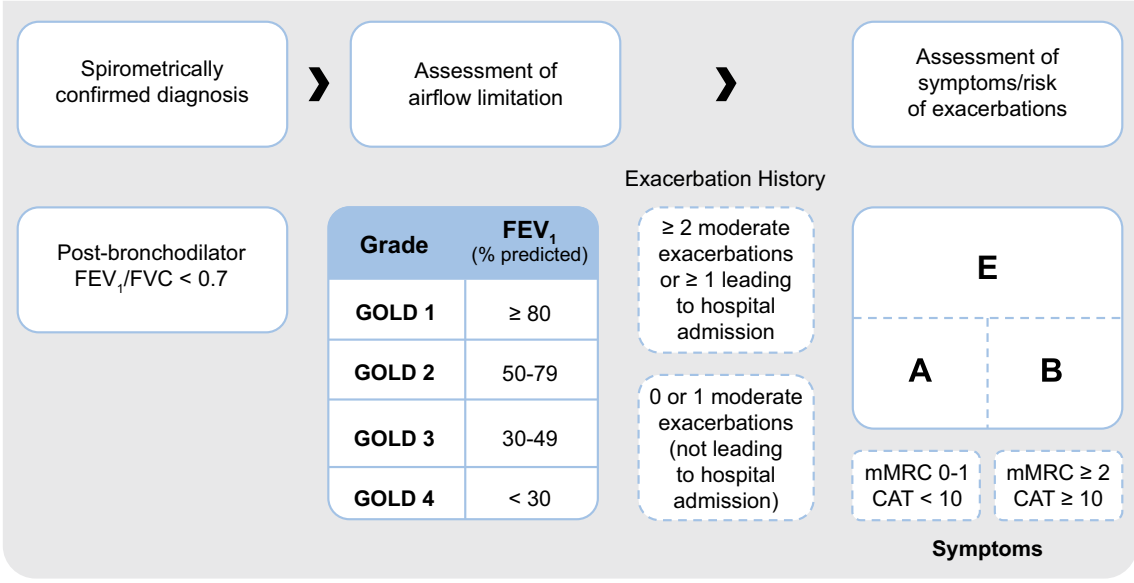

Figure 3. Assessments to guide treatment choice for patients with COPD [1].

COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

of LABA and LAMA (either as single or multiple inhaler treatment) in patients with persistent dyspnea (Evidence A: evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations or requires high-quality evidence from ≥ 2 clinical trials involving a substantial number of subjects or a single high-quality RCT involving substantial number of patients without any bias) [1]. Long-term monotherapy with ICS is not recommended (Evidence A) and recommendations also no longer favor LABA/ICS use for COPD management. In those patients for whom ICS may be indicated, the GOLD 2023 report now advocates the use of LABA plus LAMA plus ICS (either as single or multiple inhalers as an initial treatment). If there is an indication for ICS, the combination of LABA plus LAMA plus ICS (triple therapy) has been shown to be superior to LABA plus ICS and is the preferred therapeutic option [1]. Triple therapy with a LABA plus LAMA and including ICS should be considered as initial pharmacological treatment for patients in group E (those with ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization and poor lung function), with an eosinophil count of ≥ 300 cells/μL and as follow-up pharmacological treatment for patients with an eosinophil count ≥ 100 cells/μL, if a patient's exacerbations remain uncontrolled with LAMA/LABA [1]. Escalation to triple therapy is not recommended for dyspnea alone [1].

The 2020 American Thoracic Society (ATS) clinical practice guidelines provided a conditional recommendation for the use of triple therapy (ICS/LAMA/LABA) over LABA/LAMA in patients with COPD and dyspnea or exercise intolerance who had experienced ≥ 1 exacerbation in the previous year [57]. Further, the use of LABA/LAMA combination therapy over LABA or LAMA monotherapy is strongly recommended in patients with COPD and dyspnea or exercise intolerance [57]. ICS can be withdrawn in patients with COPD receiving triple therapy if the patients have not experienced any exacerbations in the previous year (conditional recommendation, moderate certainty evidence) [57]. There are no recommendations for or against ICS use as an additive therapy to long-acting bronchodilators (LAMA and LABA) in patients with COPD and blood eosinophilia, except for patients with a history of ≥ 1 exacerbation in the previous year requiring antibiotics, oral corticosteroids, or hospitalization. In these patients, ICS is conditionally recommended as additive therapy (moderate certainty evidence) [57] (Table 1).

Clinical practice guidelines developed by the Department of Veterans Affairs and Department of Defense Evidence-Based Practice Work Group in 2021 are an evidence-based framework for evaluating and managing care for patients with COPD toward improving clinical outcomes [58]. These clinical practice guidelines strongly recommend the use of inhaled LAMA as first-line therapy for COPD [58]. The working group also strongly recommends against the use of LABA in patients with symptomatic COPD, unless a LAMA is not tolerated or is contraindicated, and recommends against ICS use as first-line therapy for patients with symptomatic COPD [58]. There is a weak recommendation for the use of combination therapy with LAMA/LABA in patients with moderate-to-severe airflow obstruction who continue to report significant dyspnea or decreased QoL despite using a LAMA [58]. The working group strongly recommends against the use of LABA/ICS as dual therapy [58]. Further, withdrawal of ICS should be considered if patients have not reported moderate-to-severe exacerbations in the previous 2 years [58] (Table 1).

The American Academy of Family Physicians 2021 clinical practice guideline provides primary care–relevant recommendations to family physicians and primary care clinicians for treating adult patients with acute exacerbations of COPD [59]. It recommends that clinicians prescribe corticosteroids (although no preference in the route of administration is specified due to insufficient evidence to guide decisions) for adults with acute exacerbations of COPD to reduce clinical failure, which is a weak recommendation with a low quality of evidence [59]. There is insufficient evidence to guide the dose, route of administration, or duration of treatment [59]. Therefore, physicians should prescribe treatments according to the GOLD 2023 report based on the history of exacerbations and blood eosinophil count [1].

The 2011 joint guideline update of the American College of Physicians, American College of Chest Physicians, ATS, and European Respiratory Society recommend that clinicians prescribe monotherapy using either LAMA or LABA for symptomatic patients with COPD and FEV_1 < 60% predicted (strong recommendation, moderate-quality evidence) [60].

The National Institute for Health and Care Excellence (NICE) from the UK states that compared with other dual-therapy combinations and monotherapy, LAMA/LABA provides the greatest benefit to overall QoL for patients with COPD, reducing the risk of moderate-to-severe exacerbations vs other inhaled treatments, and is the most cost-effective option [61]. Furthermore, the NICE committee recognized that not all patients with COPD would benefit from triple therapy and recommends a clinical review (through a conversation with the patient inquiring about their symptoms rather than relying on tools such as the CAT score or MRC breathlessness score in isolation) to ensure that only those patients who would benefit from triple therapy are prescribed this therapeutic approach [61] (Table 1).

5. Distribution of patients with COPD based on the disease severity, current prescribing patterns, and clinical outcomes

Treatment patterns for patients with COPD often do not follow current recommendations and many patients are prescribed ICS-based regimens without consideration of disease severity [17,62–64]. In 2020, in the US, based on the severity of airflow limitation, there were roughly 3 million, 9 million, 4.5 million, and 1.2 million cases of GOLD grades 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe), respectively [65]. In a retrospective study conducted in the UK to quantify the cross-sectional point prevalence of COPD at the end of 2013 and the 5-year incidence (2009–2012), 66.4% of patients were classified as grade A/B (low symptoms, low exacerbation risk/high symptoms, low risk) and 33.6% as C/D (low symptoms, high risk/high symptoms, high risk) based on the GOLD 2013 criteria [66,67].

Table 1. Current guidelines for initiating and maintaining therapy for COPD.

Recommendation	American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society Joint Guideline Update (2011) [60]	American Thoracic Society (2020) [57]	Department of Veterans Affairs and Department of Defense Evidence-Based Practice Work Group (2021) [58]	Global Initiative for Chronic Obstructive Lung Disease (2023) [1]	National Institute for Health and Care Excellence [61]
Monotherapy (LAMA or LABA)	LAMA or LABA for symptomatic patients with COPD and predicted FEV_1 <60% (strong recommendation, moderate-quality evidence)	-	LAMA as first-line therapy and against the use of LABA among patients with symptomatic COPD (strong recommendation, existing evidence updated)	Short- or long-acting Bronchodilator: • Patients with 0 or 1 moderate exacerbations not leading to hospitalization • mMRC 0–1 and CAT < 10	-
Combination therapy (LAMA/LABA)	-	LABA/LAMA combination therapy over LABA or LAMA monotherapy in patients with COPD and dyspnea or exercise intolerance (strong recommendation, moderate-quality evidence)	Patients with moderate-to-severe airflow obstruction who continue to report significant dyspnea or decreased QoL despite using a LAMA (weak recommendation, existing evidence updated)	• Patients with 0 or 1 moderate exacerbations not leading to hospital admission • mMRC ≥2 and CAT ≥ 10 • Patients with ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization and blood eosinophil < 300 cells/µL	Compared with other dual therapy combinations and monotherapy, LAMA/LABA • provides the greatest benefit to overall QoL for patients with COPD • is better than other inhaled treatments for reducing the risk of moderate-to-severe exacerbations • is the most cost-effective option
Triple therapy (ICS/LAMA/LABA)	-	ICS/LAMA/LABA over dual therapy with LABA/LAMA is advocated for patients with COPD and dyspnea or exercise intolerance who have experienced ≥ 1 exacerbation in the previous year (conditional recommendation, moderate-quality evidence)	Addition of ICS is suggested to patients on LAMA/LABA who continue to experience exacerbations (weak recommendation, existing evidence updated)	• Initial: Patients with ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization • mMRC ≥2 and CAT ≥ 10 and blood eosinophil count ≥ 300 cells/µL Follow-up: Escalate to ICS/LAMA/LABA in patients on LABA/LAMA if exacerbations not controlled on LAMA/LABA and eosinophils > 100 cells/µL.	Not all patients with COPD benefit from triple therapy and NICE recommends a clinical review (through a conversation with the patient inquiring about their symptoms rather than relying on tools such as the CAT score or MRC breathlessness score in isolation) to ensure that only those patients who would benefit from triple therapy receive it
ICS withdrawal	-	Recommended for patients with COPD receiving triple therapy (ICS/LAMA/LABA) if the patient has had no exacerbations in the previous year (conditional recommendation, moderate-quality evidence)	Withdrawal of ICS is only recommended if patients have not reported moderate-to-severe exacerbations in the previous 2 years (weak recommendation, existing evidence updated)	Can be considered if there are adverse effects such as pneumonia or a reported lack of efficacy. However, a blood eosinophil count ≥ 300 cells/µL identifies patients with the greatest likelihood of experiencing more exacerbations after ICS withdrawal and who subsequently should be followed closely for relapse of exacerbations.	-

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MRC, Medical Research Council; mMRC, modified Medical Research Council; NICE, National Institute for Health and Care Excellence; QoL, quality of life.

ICS-based regimens are not recommended as the preferred initial treatment for most patients with COPD [1,57–61]. However, current prescription practices for COPD do not adhere to the recommendations; consequently, a considerable proportion of patients may have poorly controlled disease or be exposed to avoidable risks [68]. In a study conducted in 2019 to understand the use of COPD maintenance medication in the US, <30% of all patients with COPD

had severe or very severe COPD (GOLD D) [69]. Further, only 39.5% and 46.7% of patients classified as GOLD D consulted a primary care physician and a pulmonologist, respectively [69]. Both pulmonologists (31.4%) and primary care physicians (21.7%) most commonly prescribed LABA/ICS as maintenance treatment [69]. LAMA/LABA combination therapy was prescribed only to 15.8% of patients consulting a pulmonologist and 11.5% consulting a primary care physician [69]. A cross-sectional study of patients with COPD in the US Veterans Affairs system found that nearly 25% of patients without an identifiable indication for ICS filled ≥ 2 ICS prescriptions in the year prior to the index date [17]. ICS prescriptions were common among patients without a history of frequent or severe exacerbations, indicating potential overuse and misuse [17]. Older age, white race, and more primary care visits were associated with an increased likelihood of inappropriate ICS use [17]. Many clinicians may escalate to prescribing ICS/LAMA/LABA triple therapy in patients with COPD rather than considering LABA/LAMA treatment as the next step, further compounding the problem of overprescribing ICS with limited evidence of the benefits of this approach [11,70,71]. A retrospective cohort study analyzing the Geisinger Health System electronic medical records in the US from January 2004 to November 2016 revealed that 82.1%, 14.2%, and 3.8% of patients received triple therapy after the initial diagnosis of COPD, before the diagnosis of COPD, and at COPD diagnosis, respectively [64].

Results from a Canadian study also corroborate evidence that the utilization of inhaled therapies for COPD is not aligned with the current guidelines, with ICS, LABA, and LAMA being prescribed to 49.9%, 31.8%, and 10.4% of patients, respectively, during the first year of diagnosis [63]. Interestingly, compared with the treatment recommendations by specialists, those made by general practitioners were potentially more reflective of patients' exacerbation history; however, these findings must be interpreted with caution considering the complexity of clinical scenarios managed by specialists [63].

A retrospective analysis of databases from the US (IBM® MarketScan® claims databases) and the UK (Clinical Practice Research Datalink [CPRD] GOLD electronic health records) conducted during 2015–2018 reported that 66% of patients with COPD in the US and 27% in the UK were prescribed ICS-based regimens as first-line maintenance therapy, suggesting overprescribing of ICS-based regimens without consideration of exacerbation history [11]. Furthermore, 62.2% of patients in the US and 47.5% of patients in the UK were prescribed treatment regimens containing ICS when they transitioned to a second maintenance therapy [12]. A total of 13.1% of patients in the US switched from their first maintenance therapy (LABA/ICS) to a combination of ICS/LAMA/LABA (triple therapy) as a second maintenance therapy, whereas the most common transition from first to second maintenance therapy in the UK was LAMA to LAMA/LABA (32%) followed by LAMA to ICS/LAMA/LABA (14%) [12].

In a cohort of primary care patients with COPD identified from the CPRD in the UK, 46% had moderate-to-severe dyspnea (MRC dyspnea scale ≥ 3) [72]. The presence of dyspnea of any severity was associated with high disease severity (based on the level of airflow obstruction) and an increased risk of exacerbations during follow-up [72]. LABA/ICS was prescribed to 51.8% of all patients in the cohort, including 13.3% of patients with MRC grade 1 and 34.5% of patients with MRC grade 2 [72]. Another study conducted in the primary care setting in the UK using CPRD data revealed that 5104/9475 (54%) patients were prescribed ICS-based regimens (LABA/ICS: 62%, ICS: 36%, LAMA/ICS: 3%) and 4371/9475 (46%) were prescribed non-ICS–containing regimens (LAMA: 77%, LABA: 19%, LAMA/LABA: 4%) [51]. Younger age, female sex, history of asthma, more severe airflow limitation, higher baseline exacerbation frequency, oral steroid use, or hospital admissions were the factors associated with prescription of ICS-based regimens [51]. Exacerbation risk was higher in patients who were prescribed ICS than in those who were prescribed non-ICS treatment [51]. Use of ICS-based regimens in patients with eosinophil counts of < 150 cells/μL was associated with a significantly increased risk of pneumonia (hazard ratio [HR] 95% CI: 1.10 [0.99–1.24]; $p = 0.09$) and pneumonia-related hospitalization (HR [95% CI]: 1.26 [1.05–1.50]; $p = 0.01$) [51]. Evidence from another study conducted in the UK suggested that prescription of a fixed-dose combination of LABA/ICS subsequently triggered the use of triple therapy [73]. In a retrospective cohort study that included newly diagnosed patients with COPD from the CPRD in the UK, LABA/ICS (43%) was the most frequently prescribed maintenance therapy at diagnosis (0–3 months), followed by LAMA (24%) and LAMA/LABA/ICS (23%) [74]. Another study conducted in the UK revealed that prescriptions for triple therapy as the first-line therapy increased rapidly from 2002 to 2014 after which the percentage of prescriptions started to decrease (2002: <1%; 2014: 28%; 2016: 22%), and there was a corresponding increase in prescriptions for LAMA/LABA (2014: 2%; 2016: 8%) [75].

DACCORD was a non-interventional, observational clinical study conducted in Germany that recruited patients following COPD maintenance therapy initiation or change in maintenance therapy between or within therapeutic class [76]. Of the 8,201 patients who completed the 1-year visit, 2,885 were receiving LAMA/LABA and 1,311 were receiving triple therapy [76]. A higher proportion of patients in the triple therapy group had a disease duration of > 1 year and a higher proportion had mMRC score of ≥ 2 [76]. The DACCORD study provided real-world evidence that triple therapy did not improve outcomes, such as health status and exacerbations, compared with LABA/LAMA combination therapy in patients with COPD, most of whom did not experience any exacerbations in the 6 months prior to entry [76].

6. What data support moving away from ICS-based regimens in patients with a lower risk of exacerbation/non-asthma-COPD?

6.1. Recommendations from professional societies

The GOLD 2023 report recommends the use of single inhaler LAMA/LABA as initial pharmacological treatment in group

B patients (mMRC ≥ 2, CAT ≥ 10, and 0 or 1 moderate exacerbations [not leading to hospital admission]) and group E patients (≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization and blood eosinophil count < 300 cells/μL) [1]. The follow-up pharmacological management should be guided by the principles of Review-Assess-Adjust [1]. These refer to the review of symptoms (dyspnea) and exacerbation risk (previous history, blood eosinophils), assessment of inhaler technique and adherence and the role of nonpharmacological approaches, and adjustment of pharmacological treatment, including escalation or de-escalation [1]. Furthermore, a subsequent review of the clinical response (including side effects) is needed whenever there is any change in treatment [1]. If a patient experiences dyspnea or exacerbations despite LABA or LAMA monotherapy as initial pharmacological treatment, then GOLD recommends LAMA/LABA single inhaler therapy if eosinophils are < 300 cells/μL [1]. Triple therapy is recommended as follow-up pharmacological treatment for patients who experience moderate-to-severe exacerbations not controlled on LAMA/LABA and who have a blood eosinophil count of ≥ 100 cells/μL [1]. De-escalation of ICS should be considered if the patient experiences pneumonia or any other considerable side effects; however, it should be noted that de-escalation is more likely to be associated with the development of exacerbations in patients with blood eosinophil count of ≥ 300 cells/μL [1]. These recommendations reinforce the findings of the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study that early exacerbation may be prevented if sudden withdrawal of ICS is avoided in stable COPD [77].

6.2. Evidence from clinical studies

Several studies, a majority of which were RCTs that enrolled mostly patients with moderate-to-severe COPD, have reported improved lung function and a lower or similar risk of exacerbations in patients with COPD treated with LAMA/LABA vs LABA/ICS (Table 2) [40,46,78–84]; however, the mechanism(s) by which ICS, LABA, or LAMA reduce COPD exacerbation rates is still largely unknown.

LAMA/LABA combinations have reduced the annual rate of moderate or severe exacerbations, delayed the time to first exacerbation, and increased standardized area under the curve from 0 to 12 h post-dose for FEV_1 (FEV_1 $AUC_{0\text{-}12\,h}$) compared with ICS-based regimens in patients with COPD [39,85]. The Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD (WISDOM) study evaluated whether patients with COPD who were receiving LAMA/LABA (tiotropium/salmeterol) with ICS would have similar outcomes regardless of whether the ICS was withdrawn or continued [86]. No statistically significant differences were observed in the time to first moderate or severe exacerbation (HR, 1.06; 95% CI, 0.94–1.19) or time to first severe exacerbation (HR, 1.20; 95% CI, 0.98–1.48) between patients who continued with ICS and those withdrawn from ICS [86]. The WISDOM study concluded that in patients with severe COPD receiving tiotropium/salmeterol, the risk of moderate or severe exacerbations was similar among those who discontinued ICS and those who continued ICS [86]. LABA/ICS was more effective than LABA/LAMA only in patients with higher baseline eosinophil counts and > 2 moderate or 1 severe exacerbation; however, in these patients, triple therapy had a greater efficacy compared with LABA/ICS [87]. In contrast, in a real-world setting of COPD treatment (cohorts comprised 117,729 and 26,666 new users of LAMA/LABA/ICS and LAMA/LABA, respectively), there was an increased risk of all-cause mortality (adjusted HR [95% CI]: 1.17 [1.04–1.31]), severe exacerbations, and pneumonia in the triple therapy group compared with the LAMA/LABA group, reinforcing the fact that triple therapy may not be appropriate for the following groups of patients: those without prior exacerbations, those in whom ICS is contraindicated, those without a diagnosis of asthma, and those with very severe airflow obstruction [88]. The EVELUT® real-world study showed that it was possible to switch from LABA/ICS to LAMA/LABA or ICS/LAMA/LABA in patients with dyspnea and symptom burden. Switching to LAMA/LABA was possible in patients without an indication to continue ICS, and switching to triple therapy (ICS/LAMA/LABA) was not associated with additional benefits compared with switching to LAMA/LABA [89]. A meta-analysis of 59 RCTs that enrolled 103,477 patients concluded that ICS treatment significantly increased the risk of pneumonia in patients with COPD [90]. The 2-year data from the DACCORD study indicated that although exacerbations are rare in patients receiving pharmacological intervention, symptom management remains an important part of the treatment [91]. Furthermore, the overall rate of exacerbations during the 2-year follow-up was lower in the subset of patients with no exacerbations at baseline (6 months prior to the observation period) than in those with ≥ 1 or ≥ 2 exacerbations in the past 6 months [91]. These findings were consistent with those of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study in which a history of exacerbations was reported as the single best predictor of exacerbations across all GOLD stages [92].

The DACCORD study also evaluated the effect of ICS withdrawal in patients with COPD who were receiving triple therapy for ≥ 6 months (irrespective of disease severity) [93]. During the 12 months prior to baseline, 48.9% of patients in the triple therapy group and 43.5% of patients in the LAMA/LABA fixed-dose combination group had ≥ 1 COPD exacerbation [93]. A lower proportion of patients in the LAMA/LABA group had COPD worsening at 12 months compared with those in the triple therapy group (32.5% vs 55.7%) [93]. The primary endpoint of time to worsening of COPD was significantly longer in the LAMA/LABA group than in the triple therapy group [93]. The exacerbation rate was significantly lower in the LAMA/LABA group compared with that in the triple therapy group (18.5% vs 28.7%; $p < 0.001$), accompanied by a greater improvement from baseline in the CAT™ total score [93]. The frequency of AEs in the LAMA/LABA group was also lower than that in the triple therapy group (12.9% vs 15.1%). The findings from the DACCORD study revealed that patients with COPD can be successfully 'stepped down' from triple therapy to LABA/LAMA without any overall decline in COPD; indeed, some patients had better outcomes [93].

In patients with COPD at a low risk of exacerbations (< 2 per year or none in the last year in patients with FEV_1 ≥ 50% predicted), withdrawal of ICS can be achieved

successfully, provided that patients continue with maintenance treatment with long-acting bronchodilators [94,95]. A post hoc analysis of the IMPACT trial evaluated whether the efficacy of triple therapy vs LAMA/LABA was related to withdrawal of ICS [96]. The analysis found that triple therapy resulted in a 35% reduction in severe exacerbation rates compared with LAMA/LABA in both non-prior ICS users ($p = 0.018$) and prior ICS users ($p < 0.001$) and overall when excluding data from the first 30 days (29%; $p < 0.001$), suggesting that the benefits of triple therapy were unrelated to abrupt ICS withdrawal [96]. However, when comparing triple therapy vs LAMA/LABA in both ETHOS and IMPACT studies, the number deaths were lower in the triple therapy group than in the dual bronchodilator group during the first 90 days but not during days 91–365, suggesting inconsistent effects of triple therapy in reducing COPD-associated mortality over the 1-year follow-up period [97]. Similarly, in patients not receiving ICS at screening, there was no mortality benefit from triple therapy vs LAMA/LABA [98]. In the WISDOM study, patients withdrawn from ICS experienced a statistically significant mean reduction from baseline in trough FEV_1 compared with those who continued triple therapy ($p = 0.001$) at 52 weeks [86]. In contrast, in the multicenter, prospective, real-life study On the aPpropriaTeness of treatment In Moderate COPD patients (OPTIMO), patients with a low risk of exacerbation receiving ICS and bronchodilator maintenance therapy experienced no deterioration in lung function [94]. Moreover, the exacerbation rate was similar 6 months after ICS withdrawal with appropriate maintenance therapy with bronchodilators compared with that in patients who continued ICS treatment (26% vs 29%, respectively), which may be attributed to the fact that 37% of patients had no exacerbation during the 1 year before recruitment into the study [94]. In the Indacaterol: Switching Non-exacerbating Patients with Moderate COPD from Salmeterol/Fluticasone to Indacaterol (INSTEAD) study, patients who were at a low risk of exacerbations who were switched from LABA/ICS to LABA monotherapy ($n = 293$) had no evidence of an increased rate of exacerbations compared with those who continued receiving LABA/ICS ($n = 288$) over the 26-week study period (exacerbation rate of 0.57 and 0.67 per year, respectively), which may be attributable to the fact that over 99% of patients included in this study had moderate exacerbations according to GOLD 2010 criteria [95].

Skolnik et al have assessed exacerbation risk with LAMA/LABA compared with LABA/ICS, and the available data do not consistently favor either class [43]; however, for exacerbation control and control of symptoms, GOLD 2023 discourages the use of LABA/ICS [1]. In a post hoc analysis of patients from the WISDOM trial who were receiving triple therapy before enrolling in the study, no significant difference was noted in the time to first COPD exacerbation and the number of COPD exacerbations between the subgroup of patients taking triple therapy before enrolling in the study and the overall trial population, suggesting that ICS withdrawal did not increase the exacerbation risk in patients taking triple therapy at screening [99]. These findings were consistent with findings reported in the overall trial population [86].

6.3. Safety and pharmacoeconomic concerns

Inappropriate prescriptions may lead to inadequate symptom control and an increased need for treatments, such as oral corticosteroids and antibiotics, as well as increased hospitalizations, healthcare utilization, and costs [71,100]. The risk of pneumonia associated with ICS use is a serious and costly AE [101]. Despite having potential benefits for a subset of patients with COPD, ICS-based regimens are usually overprescribed and can increase the risk of pneumonia and related healthcare costs [102,103]. A budget impact model implementing Portuguese and Greek national health systems indicated that a switch from ICS-based treatment to LAMA/LABA resulted in cost savings while reducing the number of COPD exacerbations, pneumonia, and diabetes-related events [102]. A retrospective observational study that examined administrative claims data reported lower annualized costs in patients with COPD initiating LAMA/LABA (tiotropium/olodaterol) than in those initiating triple therapy (fluticasone furoate/umeclidinium/vilanterol) in the overall and maintenance-naïve study populations [100]. In contrast, analysis of healthcare resource utilization data from the ETHOS study showed that the average 5-year per patient costs of managing exacerbations were $20,864 for triple therapy (budesonide/glycopyrrolate/formoterol fumarate), $24,792 for LAMA/LABA, and $29,241 for LABA/ICS, an outcome that would be anticipated considering that the ETHOS study enrolled patients with moderate-to-very-severe COPD and ≥ 1 exacerbation in the past year [104,105].

7. Gaps/unmet needs

The practical nature of the recommendations combined with a lack of scientific information and spirometry facilities, referral to specialist facilities for spirometry, cost of implementation, and not including primary care specialists in the development of existing guidelines could explain the gap between the guidelines and current clinical practice [106]. Furthermore, therapeutic inertia (failure to escalate or initiate adequate therapy when treatment goals are not met) has been identified as an important cause of poor management of exacerbations in patients with COPD [107].

8. Recommendations for what a clinician should do to optimize therapy and potentially prevent overuse of ICS-based regimens in COPD

Given the emergence of new clinical data and updates in existing guidelines and recommendations to reflect these data, there are some practical recommendations for primary care physicians that may optimize therapy for their patients and prevent overuse of ICS-based regimens. These include increasing awareness among healthcare professionals regarding guidelines on the diagnosis and treatment of COPD, specifically with a focus on the patient profile who might continue to benefit from ICS treatment (Figure 2). Increasing the interaction and partnership between pulmonologists and allied healthcare providers may also help in the holistic management of patients with COPD [106]. Guideline dissemination

Table 2. Summary of some key studies comparing LABA/ICS vs LAMA/LABA therapy.

Authors, publication year (study design)	Patient characteristics	Intervention, number of patients (treatment duration)	Key efficacy endpoints: Lung function	Key efficacy endpoints: Exacerbations	Key efficacy endpoints: Symptoms	Safety	Key findings
Donohue et al [78] (2015) (multicenter, randomized, double-blind, parallel-group, double-dummy trials) (DB2114930/ NCT01817764; DB2114951/ NCT01879410)	Patients with symptomatic (dyspnea score ≥ 2, mMRC Dyspnea Scale), moderate-to-severe COPD (FEV1 ≥ 30% and ≤ 70%) without a documented history of an exacerbation (COPD symptoms requiring treatment with either oral corticosteroids, antibiotics, and/or hospitalization) in the year before screening.	Once-daily UMEC/VI 62.5/25 µg (delivered doses 55/ 22 µg, morning) via the ELLIPTA® DPI and twice-daily placebo (DISKUS®) ($n = 702$) Twice-daily FP/SAL 250/50 µg via the DISKUS® and once-daily placebo (ELLIPTA® DPI) ($n = 701$) (12 weeks)	UMEC/VI demonstrated statistically significant, clinically meaningful improvements in lung function measures vs FP/SAL. For 0–24 h, wmFEV$_1$ (Day 84), improvements with UMEC/VI vs FP/SAL were 74 mL (95% CI: 38–110; DB2114930) and 101 mL (63–139; DB2114951) (both $p < 0.001$). Trough FEV$_1$ improvements were 82 mL (45–119) and 98 mL (59–137) (both $p < 0.001$) for UMEC/VI vs FP/SAL, respectively.	UMEC/VI vs FP/SAL: 3% vs 3%	UMEC/VI and FP/SAL demonstrated similar clinically meaningful improvements from baseline in dyspnea (TDI focal score > 1 unit) and QoL (SGRQ total score > 4-unit decrease) in both studies with no statistical differences between treatments.	Adverse event rates UMEC/VI vs FP/SAL: 26%–30% vs 27%–31%; the most frequent adverse events were headache and nasopharyngitis.	Once-daily UMEC/VI 62.5/ 25 µg over 12 weeks resulted in statistically significant, clinically meaningful improvements in lung function vs twice-daily FP/SAL 250/50 µg in patients with moderate-to-severe COPD with infrequent exacerbations. Both treatments improved dyspnea and QoL.
Singh et al [79] (2015) (phase IIIb, multicenter, double-blind, parallel-group, double-dummy study) (NCT01822899)	Current/former smokers (≥ 10 pack-years), ≥ 40 years old, post-bronchodilator FEV$_1$/FVC < 0.70, 30% ≤ post-bronchodilator FEV$_1$ ≤ 70% of predicted, and an mMRC score ≥ 2	Treatment with UMEC/ VI OD ($n = 358$) Treatment with FP/SAL BID ($n = 358$) (12 weeks)	UMEC/VI OD significantly improved all lung function endpoints compared with FP/SAL BID	A statistical imbalance in the number of COPD exacerbations was observed between treatment groups (UMEC/VI: 8 [2%] patients vs FP/SAL: 3 [<1%] patients).	There was a clinically significant improvement in symptoms with both treatments (TDI score ≥ 1-unit focal score) and QoL (SGRQ Total score ≥ 4 unit decrease from baseline).	The incidence of adverse events was comparable between both treatment groups (UMEC/VI: 28% vs FP/SAL: 29%); the most frequent adverse events were headache and nasopharyngitis.	Patients with moderate-to-severe COPD and no exacerbations in the year prior to enrollment experienced significant and persistent improvements in lung function with UMEC/VI OD over the course of 12 weeks compared with FP/SAL BID.
Zhong et al [80] (2015) (multicenter, randomized, double-blind, double-dummy, parallel-group study) (NCT01709903)	Male and female patients aged ≥ 40 years with moderate-to-severe COPD (stage II and III, as defined in the GOLD 2010 criteria). All patients had a mMRC grade ≥ 2 at screening.	IND/GLY (110/50 µg) OD ($n = 372$) SFC (50/500 µg) BID ($n = 372$) (26 weeks)	IND/GLY demonstrated statistically significant superiority to SFC for trough FEV$_1$ (treatment difference [Δ] = 75 mL; $p < 0.001$). IND/GLY demonstrated a statistically significant improvement in standardized AUC from 0 to 4 h for FEV1 (FEV1 AUC$_{0–4\,h}$) at week 26 vs SFC (Δ = 122 mL; $P < 0.001$).	IND/GLY significantly reduced the rate of moderate or severe exacerbations by 31% ($p = 0.048$) over SFC.	IND/GLY and SFC had similar improvements in TDI focal score, SGRQ total score, and rescue medication use.	The incidence of adverse events was comparable between IND/GLY (40.1%) and SFC (47.4%). The incidence of pneumonia was three-fold lower with IND/GLY (0.8%) vs SFC (2.7%).	The findings from this study support the use of LABA/LAMA as an alternative treatment, over LABA/ICS in the management of patients with moderate-to-severe COPD (GOLD B and GOLD D) with a history of ≤ 1 exacerbation in the previous year.

(*Continued*)

Table 2. (Continued).

Authors, publication year (study design)	Patient characteristics	Intervention, number of patients (treatment duration)	Key efficacy endpoints: Lung function	Key efficacy endpoints: Exacerbations	Key efficacy endpoints: Symptoms	Safety	Key findings
Beeh et al [81] 2016 (phase IIIb, multicenter, multinational, randomized, double-blind, double-dummy, active-controlled, four-treatment, complete crossover study) (NCT01969721)	A diagnosis of COPD; moderate-to-severe pulmonary impairment (post-bronchodilator FEV1 ≥ 30% and < 80% of predicted normal); post-bronchodilator FEV1/FVC < 70% at screening visit; age ≥ 40 years; current or ex-smoker with a smoking history of > 10 pack-years; able to perform technically acceptable PFT and maintain paper diaries as required; and able to competently inhale medication from the Respimat® inhaler (a metered-dose inhaler) and the Accuhaler®.	Tiotropium/olodaterol (5/5 µg and 2.5/5 µg) OD Salmeterol/fluticasone propionate (50/500 µg and 50/250 µg) BID (6 weeks)	Tiotropium/olodaterol 5/5 µg and 2.5/5 µg demonstrated statistically significant improvements in FEV1 AUC_{0-12} compared with salmeterol/fluticasone propionate (improvements from baseline were 317 mL and 295 mL with tiotropium/olodaterol 5/5 µg and 2.5/5 µg, and 188 mL and 192 mL with salmeterol/fluticasone propionate 50/500 µg and 50/250 µg, respectively). Tiotropium/olodaterol was superior to SAL/fluticasone propionate in lung function secondary endpoints, including FEV1 AUC_{0-24}.	Not available	Not available	The frequency of adverse events was similar between all treatment groups: tiotropium/olodaterol (33.9%–34.4%) vs SAL/fluticasone propionate (29.7%–37.0%); the most frequent adverse events were COPD worsening and nasopharyngitis.	Once-daily tiotropium/olodaterol in patients with moderate-to-severe COPD provided superior lung function improvements to twice-daily SAL/fluticasone propionate.
Vogelmeier et al [82] (2016) (double-blind, double-dummy, active-controlled, randomized, multicenter, phase 3b study) **AFFIRM COPD** (NCT01908140)	Age ≥ 40 years, with a smoking history of ≥ 10 pack-years and diagnosed with moderate-to-severe COPD; CAT score ≥ 10 at the screening and baseline visits; post-bronchodilator FEV_1/FVC < 70% and FEV_1 < 80% predicted.	ITT population: Treatment with aclidinium/formoterol 400/12 µg BID ($n = 468$) Treatment with SFC 50/500 µg BID ($n = 463$) (24 weeks)	Aclidinium/formoterol was superior to SFC in peak FEV_1.	The incidence of exacerbations did not differ significantly between the aclidinium/formoterol and SFC groups.	Similar clinically relevant improvements in the mean TDI focal score at week 24 and at all prior visits were seen with aclidinium/formoterol and SFC. At week 24, clinically significant differences from baseline in CAT total scores of ≥ 2 units were seen with both aclidinium/formoterol and SFC.	Pneumonia occurred less frequently with aclidinium/formoterol than with SFC, and both therapies were well tolerated.	Aclidinium/formoterol treatment was superior to SFC in peak FEV_1. The therapy groups showed equivalent reduction in dyspnea and symptom control. Adverse ICS-related events were less frequent with aclidinium/formoterol. Exacerbation rates were comparable in both groups, although the study was not powered for exacerbations.

(*Continued*)

Table 2. (Continued).

Authors, publication year (study design)	Patient characteristics	Intervention, number of patients (treatment duration)	Key efficacy endpoints				
			Lung function	Exacerbations	Symptoms	Safety	Key findings
Wedzicha et al [40] (2016) (multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority study) **FLAME** (NCT01782326)	Adults aged ≥ 40 years, post-bronchodilator FEV_1 /FVC < 0.70, 25% ≤ post-bronchodilator FEV_1 < 60% of predicted, a mMRC score ≥ 2, and a documented history of at least one exacerbation in the previous year.	Treatment with IND/GLY OD $N = 1,680$ Treatment with SFC BID $N = 1,682$ (52 weeks)	In comparison to the SFC group, the IND/GLY group had improved lung function	Compared with the SFC group, the IND/GLY group demonstrated an 11% ($p < 0.003$) lower annual rate of exacerbations and a longer duration to the first exacerbation (16% lower risk; $p < 0.001$).	Use of rescue medication was significantly reduced and health condition was improved in the IND/GLY group (decrease in SGRQ-C score).	The incidence of adverse events and deaths was similar in the two groups. Pneumonia occurred in 3.2% of the IND/GLY group and 4.8% of the SFC group ($p = 0.02$).	In patients with a history of an exacerbation during the past year, IND/GLY was more effective than SFC at preventing COPD exacerbations. In both the subgroup of patients with blood eosinophil counts < 2% and the subgroup of patients with counts of ≥ 2%, the rates of moderate or severe exacerbations and of all exacerbations were significantly lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group, a finding that suggests that the LABA/LAMA regimen was more effective in reducing the rate of exacerbations than the LABA/ICS regimen in both eosinophil subgroups.
Kaplan et al [83] (2019) (single-cohort, prospective, multicenter, open-label, interventional study) **POWER** (NCT02202616)	Patients aged > 40 years, with physician-diagnosed COPD per the GOLD 2011 criteria, a moderate-to-severe airflow limitation indicated by a pre-dose trough FEV_1 ≥ 30% and < 80% of predicted, a smoking history of > 10 pack-years, CAT score of > 10, and symptomatic despite tiotropium 18 µg OD or SFC BID (any dose)	Treatment with IND/GLY 110/50 µg OD Tiotropium, $n = 248$; SFC, $n = 87$; IND/GLY All patients $N = 338$ (16 weeks)	At week 16, patients who switched to IND/GLY demonstrated a 175-mL mean increase in trough FEV1. When switching from tiotropium, the change from baseline was 176 mL (95% CI: 135–217), and when switching from SFC FDC, it was 172 mL (95% CI: 85–258)	In SFC initiators, exacerbations occurred more frequently.	At week 16, after switching to IND/GLY medication, a significant improvement was seen in the mean TDI total scores ($\Delta = 2.5$) and CAT scores ($\Delta = -6.5$) (both $p < 0.0001$).	In patients with moderate-to-severe COPD, IND/GLY was well tolerated. The prevalence of pneumonia was higher among SFC beginners. There were no patient deaths during the study.	A real-life switch from tiotropium monotherapy or SFC FDC to IND/GLY resulted in clinically significant improvements in lung function, dyspnea, and health-related QoL after 16 weeks of treatment in symptomatic individuals with moderate-to-severe COPD. The IND/GLY transition was well tolerated, and the research has not identified any additional safety signals.

(*Continued*)

Table 2. (Continued).

Authors, publication year (study design)	Patient characteristics	Intervention, number of patients (treatment duration)	Key efficacy endpoints			Safety	Key findings
			Lung function	Exacerbations	Symptoms		
Pascoe et al (2019) [46] (phase 3, randomized, double-blind, parallel-group, multicenter study) **IMPACT** (NCT02164513)	Adults aged ≥ 40 years, CAT score ≥ 10, FEV_1 < 50% of predicted and history of at least one moderate or severe exacerbation in the previous year, or FEV_1 50%–80% of predicted and at least two moderate or one severe exacerbation in the previous year	Treatment with FF/VI OD $N = 4,125$ Treatment with UMEC/VI OD $N = 2,065$ (52 weeks)	At all baseline blood eosinophil counts, the improvement in FEV_1 was greater with UMEC/VI than with FF/VI.	In the overall population, exacerbation rates were lower with FF/VI than with UMEC/VI. Only eosinophil counts of approximately > 200 cells/μL in the overall population with FF/VI were associated with treatment benefit.	At lower eosinophil counts, benefits on SGRQ and TDI were numerically greater with UMEC/VI than with FF/VI. UMEC/VI numerically underperformed FF/VI at higher eosinophil counts.	High pneumonia incidence rates were seen in the FF/VI group. Compared with the UMEC/VI group, the FF/VI group displayed higher rates of events when treated with antibiotics alone.	Compared with a dual long-acting non-ICS bronchodilator (UMEC/VI), the extent of the benefit of ICS-based regimens (FF/VI) in reducing rates of moderate and severe exacerbations increased proportionally with the blood eosinophil count.
Suissa et al (2019) [84] (Real-world study using Clinical Practice Research Datalink from the United Kingdom)	The study cohort was formed by first identifying all members of the base cohort (age ≥ 55 years) with the first occurrence of prescriptions for LABA and LAMA (tiotropium) on the same date, but no ICS. For each subject initiating LABA-LAMA treatment, a matched comparator subject initiating LABA-ICS was identified using a time-conditional propensity score-matched approach.	LABA-LAMA initiators ($n = 1,977$) LABA-ICS initiators ($n = 1,977$)	Not available	The HR of moderate or severe COPD exacerbation associated with LABA-LAMA initiation, relative to LABA-ICS initiation, was 1.04 (95% CI: 0.90–1.20), whereas for a severe exacerbation, it was 0.94 (95% CI: 0.65–1.36).	Not available	The incidence of severe pneumonia requiring hospitalization was lower with LABA-LAMA initiation (HR, 0.66; 95% CI: 0.41–1.05), particularly in the on-treatment analysis (HR, 0.66; 95% CI: 0.50–0.87).	In a real-world clinical practice setting of COPD treatment, combined LABA-LAMA inhalers appear to be as effective as combined LABA-ICS inhalers in preventing COPD exacerbations. However, a LABA-LAMA combination may be preferred because it is associated with fewer severe pneumonias.

AFFIRM COPD, Aclidinium and Formoterol Findings in Respiratory Medicine COPD; AUC, area under the curve; BID, twice a day; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDC, fixed-dose combination; FEV1, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; FVC, forced vital capacity; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroids; IMPACT, InforMing the PAthway of COPD Treatment; IND, indacaterol; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; OD, once a day; PFT, pulmonary function test; POWER, Prospective cohort study for the real-life effectiveness evaluation of glycOpyrronium With indacatERol combination in the management of COPD in Canada; QoL, quality of life; SAL, salmeterol; SFC, salmeterol/fluticasone; SGRQ-C, St. George's Respiratory Questionnaire for COPD; TDI, transition dyspnea index; UMEC, umeclidinium; VI, vilanterol; wm, weighted mean.

must not be unidirectional [106]; general practitioners must be invited to contribute to the development of guidelines from the beginning, and postgraduate education must be cooperatively planned by general practitioners and pulmonologists [106]. Specialty facilities for chest radiography or laboratory for community-acquired pneumonia and spirometry for COPD must be more accessible to clinicians treating COPD [106].

According to the GOLD 2023 report, the use of LABA/ICS is no longer recommended in the treatment of COPD; where ICS use is indicated, a combination of LABA plus LAMA plus ICS (triple therapy) is recommended after assessment of the exacerbation history and blood eosinophil count [1]. In patients with COPD who have concomitant asthma, low risk of COPD exacerbations, and mild symptoms, closed triple therapy may not be the most appropriate choice owing to the cost, and clinicians may consider prescribing other more cost-effective inhalers. Patients who present with features of COPD should be treated in accordance with the GOLD 2023 report: group A to be treated with a bronchodilator), group B with LABA and LAMA, and group E with LABA plus LAMA; inclusion of ICS in group E patients is to be determined based on eosinophil counts (initial pharmacologic treatment: ≥ 300 cells/μL and follow-up pharmacologic treatment: ≥ 100 cells/μL), mMRC grade ≥ 2 or CAT™ score ≥ 10, and patients who have a history of ≥ 2 moderate exacerbations per year or ≥ 1 exacerbation leading to hospitalization [1]. However, the potential instability of eosinophil counts over time should be considered, as evidence shows that the stability of blood eosinophil counts is significantly lower in patients with COPD than those without COPD [108]. Treatment with LABA/LAMA has been shown to produce greater improvement in lung function and reduction in rescue medication use compared with LABA/ICS treatment; however, it remains unclear whether LAMA/LABA provides any additional benefit over LABA/ICS in terms of patient-reported symptoms and QoL measurements [43].

9. Conclusions

Clinicians should consider treatment with LAMA/LABA therapy for the majority of patients with COPD and should reserve ICS-based regimens as triple therapy (ICS/LAMA/LABA) for the small proportion of patients who have ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization and elevated blood eosinophil count. ICS can be withdrawn in patients with COPD receiving triple therapy if the patients have not experienced any exacerbations in the previous year or if patients have not reported moderate-to-severe exacerbations in the previous 2 years and the blood eosinophil count is < 300 cells/μL. Furthermore, this review highlights the need for primary care physicians to adjust management according to the current guidelines to ensure proper treatment to effectively control symptoms, minimize exacerbation risk, preserve lung function, and maximize patient outcomes (Infographic).

Abbreviations

AE	adverse event
ATS	American Thoracic Society
CAT™	COPD Assessment Test
COPD	chronic obstructive pulmonary disease
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
FENO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FLAME	Effect of Indacaterol Glycopyrronium Vs Fluticasone Salmeterol on COPD Exacerbations
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroids
IMPACT	InforMing the PAthway of COPD Treatment
INSPIRE	Investigating New Standards for Prophylaxis In Reducing Exacerbations
ISOLDE	Inhaled Steroids in Obstructive Lung Disease
LABA	long-acting β_2-adrenoreceptor agonist
LAMA	long-acting β_2-adrenoreceptor agonist
mMRC	Modified Medical Research Council
NICE	The National Institute for Health and Care Excellence
OPTIMO	Real-Life study On the aPpropriaTeness of treatment in MOderate COPD patients
QoL	quality of life
PPB	parts per billion
RCTs	randomized controlled trials
SUMMIT	Study to Understand Mortality and Morbidity in COPD\
Th2	T helper 2 lymphocytes
TORCH	TOwards a Revolution in COPD Health
TRISTAN	TRial of Inhaled STeroids ANd long-acting β_2 agonists
UK	United Kingdom
US	United States
WISDOM	Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management

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References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [Internet]. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2023 2023. [cited 2023 Feb 1]. Available from: https://goldcopd.org/2023-gold-report-2/
2. Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. Am J Respir Crit Care Med. 2022;206(11):1317–1325. doi: 10.1164/rccm.202204-0671PP
3. Riley CM, Sciurba FC. Diagnosis and outpatient management of chronic obstructive pulmonary disease: a review. JAMA. 2019;321(8):786–797. doi: 10.1001/jama.2019.0131
4. World Health Organization. Chronic obstructive pulmonary disease (COPD). [cited Nov 14, 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
5. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). [cited 2022 Nov 14]. Available from: https://www.cdc.gov/copd/index.html
6. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). [cited 2022 Nov 14]. Available from: https://www.cdc.gov/copd/infographics/copd-costs.html
7. Patel JG, Coutinho AD, Lunacsek OE, et al. COPD affects worker productivity and health care costs. Int J Chron Obstruct Pulmon Dis. 2018;13:2301–2311. doi: 10.2147/COPD.S163795
8. Cazzola M, Page C, Rogliani P, et al. Dual bronchodilation for the treatment of COPD: from bench to bedside. Br J Clin Pharmacol. 2022;88(8):3657–3673. doi: 10.1111/bcp.15390
9. Dhar R, Talwar D, Salvi S, et al. Use of single-inhaler triple therapy in the management of obstructive airway disease: Indian medical experts' review. ERJ Open Res. 2022;8(1):00556–2021. doi: 10.1183/23120541.00556-2021
10. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–582. doi: 10.1164/rccm.201701-0218PP
11. Bloom CI, Montonen J, Jöns O, et al. First maintenance therapy for chronic obstructive pulmonary disease: retrospective analyses of US and UK healthcare databases. Pulm Ther. 2022;8(1):57–74. doi: 10.1007/s41030-021-00179-0
12. Bloom CI, Montonen J, Jöns O, et al. Treatment transitions in chronic obstructive pulmonary disease: retrospective analyses of US and UK healthcare databases. Pulm Ther. 2022;8(1):75–93. doi: 10.1007/s41030-021-00180-7
13. Bhatt SP, Blauer-Peterson C, Buysman EK, et al. Trends and characteristics of Global Initiative for Chronic Obstructive Lung Disease guidelines-discordant prescribing of triple therapy among patients with COPD. Chronic Obstr Pulm Dis. 2022;9(2):135–153. doi: 10.15326/jcopdf.2021.0256
14. Cukic V, Lovre V, Dragisic D, et al. Asthma and chronic obstructive pulmonary disease (COPD)—differences and similarities. Mater Sociomed. 2012;24(2):100–105. doi: 10.5455/msm.2012.24.100-105
15. Roman-Rodriguez M, Kaplan A. GOLD 2021 strategy report: implications for asthma-COPD overlap. Int J Chron Obstruct Pulmon Dis. 2021;16:1709–1715. doi: 10.2147/COPD.S300902
16. Mekov E, Nuñez A, Sin DD, et al. Update on asthma-COPD overlap (ACO): a narrative review. Int J Chron Obstruct Pulmon Dis. 2021;16:1783–1799. doi: 10.2147/COPD.S312560
17. Griffith MF, Feemster LC, Zeliadt SB, et al. Overuse and misuse of inhaled corticosteroids among veterans with COPD: a cross-sectional study evaluating targets for de-implementation. J Gen Intern Med. 2020;35(3):679–686. doi: 10.1007/s11606-019-05461-1
18. Thomson NC, Polosa R, Sin DD. Cigarette smoking and asthma. J Allergy Clin Immunol Pract. 2022;10(11):2783–2797. doi: 10.1016/j.jaip.2022.04.034
19. Chen FJ, Huang XY, Liu YL, et al. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2385–2390. doi: 10.2147/COPD.S115378
20. Yayan J, Rasche K. Asthma and COPD: similarities and differences in the pathophysiology, diagnosis and therapy. Adv Exp Med Biol. 2016;910:31–38.
21. Global Initiative for Asthma [Internet]. Global strategy for asthma management and prevention: updated 2023 2023. [cited 2023 Oct 13]. Available from: https://ginasthma.org/2023-gina-main-report/
22. Sin DD, Man SFP. Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: does the dose matter? Eur Respir J. 2003;21(2):260–266. doi: 10.1183/09031936.03.00040803
23. Kaplan AG. Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice. Int J Chron Obstruct Pulmon Dis. 2015;10:2535–2548. doi: 10.2147/COPD.S93321
24. Cataldo D, Derom E, Liistro G, et al. Overuse of inhaled corticosteroids in COPD: five questions for withdrawal in daily practice. Int J Chron Obstruct Pulmon Dis. 2018;13:2089–2099. doi: 10.2147/COPD.S164259
25. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis. 2016;7(1):34–51. doi: 10.1177/2040622315609251
26. Adcock IM, Bhatt SP, Balkissoon R, et al. The use of inhaled corticosteroids for patients with COPD who continue to smoke cigarettes: an evaluation of current practice. Am J Med. 2022;135(3):302–312. doi: 10.1016/j.amjmed.2021.09.006
27. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361(9356):449–456. doi: 10.1016/S0140-6736(03)12459-2
28. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–789. doi: 10.1056/NEJMoa063070
29. Suissa S, Ernst P, Vandemheen KL, et al. Methodological issues in therapeutic trials of COPD. Eur Respir J. 2008;31(5):927–933. doi: 10.1183/09031936.00098307
30. Jenkins CR, Jones PW, Calverley PM, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10(1):59. doi: 10.1186/1465-9921-10-59
31. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387(10030):1817–1826. doi: 10.1016/S0140-6736(16)30069-1
32. Soriano JB, Vestbo J, Pride NB, et al. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J. 2002;20(4):819–825. doi: 10.1183/09031936.02.00301302
33. Paggiaro PL, Dahle R, Bakran I, et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet. 1998;351(9105):773–780. doi: 10.1016/S0140-6736(97)03471-5
34. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society study on chronic obstructive pulmonary disease. N Engl J Med. 1999;340(25):1948–1953. doi: 10.1056/NEJM199906243402503
35. Vestbo J, Sørensen T, Lange P, et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353(9167):1819–1823. doi: 10.1016/S0140-6736(98)10019-3

36. Burge PS, Calverley PM, Jones PW, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297–1303. doi: 10.1136/bmj.320.7245.1297
37. Lung Health Study Research Group, Wise R, Connett J, et al. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000;343(26):1902–1909.
38. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7):758–766. doi: 10.1164/rccm.201408-1458OC
39. Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19–26. doi: 10.1164/rccm.200707-973OC
40. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium *versus* salmeterol–fluticasone for COPD. N Engl J Med. 2016;374(23):2222–2234. doi: 10.1056/NEJMoa1516385
41. Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2017;12:907–922. doi: 10.2147/COPD.S130482
42. Horita N, Goto A, Shibata Y, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017;2:CD012066.
43. Skolnik NS, Nguyen TS, Shrestha A, et al. Current evidence for COPD management with dual long-acting muscarinic antagonist/long-acting β2-agonist bronchodilators. Postgrad Med. 2020;132(2):198–205. doi: 10.1080/00325481.2019.1702834
44. Lipson DA, Barnhart F, Boucot I, et al. Exacerbation outcomes with LAMA/LABA and ICS/LABA in high risk COPD patients in the IMPACT trial. Eur Respir J. 2018;52(Suppl 62):A4384.
45. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378(18):1671–1680. doi: 10.1056/NEJMoa1713901
46. Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med. 2019;7(9):745–756. doi: 10.1016/S2213-2600(19)30190-0
47. Franssen FM, Alter P, Bar N, et al. Personalized medicine for patients with COPD: where are we? Int J Chron Obstruct Pulmon Dis. 2019;14:1465–1484. doi: 10.2147/COPD.S175706
48. Ni S, Fu Z, Zhao J, et al. Inhaled corticosteroids (ICS) and risk of mycobacterium in patients with chronic respiratory diseases: a meta-analysis. J Thorac Dis. 2014;6(7):971–978. doi: 10.3978/j.issn.2072-1439.2014.07.03
49. Miravitlles M, Auladell-Rispau A, Monteagudo M, et al. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. Eur Respir Rev. 2021;30(160):210075. doi: 10.1183/16000617.0075-2021
50. Festic E, Bansal V, Gupta E, et al. Association of inhaled corticosteroids with incident pneumonia and mortality in COPD patients; systematic review and meta-analysis. COPD: J Chronic Obstructive Pulmonary Dis. 2016;13(3):312–326. doi: 10.3109/15412555.2015.1081162
51. Ashdown HF, Smith M, McFadden E, et al. Blood eosinophils to guide inhaled maintenance therapy in a primary care COPD population. ERJ Open Res. 2021;8(1):00606–2021. doi: 10.1183/23120541.00606-2021
52. Keir HR, Contoli M, Chalmers JD. Inhaled corticosteroids and the lung microbiome in COPD. Biomedicines. 2021;9(10):1312. doi: 10.3390/biomedicines9101312
53. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. Eur Respir J. 2015;45(2):525–537. doi: 10.1183/09031936.00128914
54. BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD guidelines group of the standards of care committee of the BTS. Thorax. 1997;52(Suppl 5):S1–S28. doi: 10.1136/thx.52.2008.S1.5
55. Woodruff PG, Agusti A, Roche N, et al. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. Lancet. 2015;385(9979):1789–1798. doi: 10.1016/S0140-6736(15)60693-6
56. Deas SD, Huprikar N. Dual bronchodilator therapy for chronic obstructive pulmonary disease: evidence for the efficacy and safety of fixed dose combination treatments in the setting of recent guideline updates. Curr Opin Pulm Med. 2018;24(2):130–137. doi: 10.1097/MCP.0000000000000450
57. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;201(9):e56–e69. doi: 10.1164/rccm.202003-0625ST
58. Va/dod clinical practice guideline for the management of chronic obstructive pulmonary disease. [cited 2022 Nov 14]. Available from: https://www.healthquality.va.gov/guidelines/cd/copd/
59. Stevermer JJ, Fisher L, Lin KW, et al. Pharmacologic management of COPD exacerbations: a clinical practice guideline from the AAFP. Am Fam Physician. 2021;104(1). Online. https://www.aafp.org/pubs/afp/issues/2021/0700/od1.html
60. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of physicians, American College of chest physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155(3):179–191. doi: 10.7326/0003-4819-155-3-201108020-00008
61. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management: updated 2019. [cited 2023 Oct 14]. Available from: https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245
62. Rinne ST, Wiener RS, Chen Y, et al. Impact of guideline changes on indications for inhaled corticosteroids among veterans with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2018;198(9):1226–1228. doi: 10.1164/rccm.201803-0554LE
63. Bahremand T, Etminan M, Roshan-Moniri N, et al. Are COPD prescription patterns aligned with guidelines? Evidence from a Canadian population-based study. Int J Chron Obstruct Pulmon Dis. 2021;16:751–759. doi: 10.2147/COPD.S290805
64. Schabert V, Shah S, Holmgren U, et al. Prescribing pathways to triple therapy in patients with chronic obstructive pulmonary disease in the United States. Ther Adv Respir Dis. 2021;15(17534666211001018):17534666211001018. doi: 10.1177/17534666211001018
65. Chronic Obstructive Pulmonary Disease (COPD). Market insight, epidemiology and market forecast. Available from. 2032:https://www.delveinsight.com/report-store/chronic-obstructive-pulmonary-disease-copd-market
66. Raluy-Callado M, Lambrelli D, MacLachlan S, et al. Epidemiology, severity, and treatment of chronic obstructive pulmonary disease in the United Kingdom by GOLD 2013. Int J Chron Obstruct Pulmon Dis. 2015;10:925–937. doi: 10.2147/COPD.S82064
67. Goossens LMA, Leimer I, Metzdorf N, et al. Does the 2013 GOLD classification improve the ability to predict lung function decline, exacerbations and mortality: a post-hoc analysis of the 4-year UPLIFT trial. BMC Pulm Med. 2014;14(1):163. doi: 10.1186/1471-2466-14-163
68. Moretz C, Hahn B, White J, et al. Symptom burden and GOLD classification in Medicare Advantage patients with COPD initiating umeclidinium/vilanterol or fluticasone propionate/salmeterol therapy. Int J Chron Obstruct Pulmon Dis. 2020;15:2715–2725. doi: 10.2147/COPD.S265037
69. Mannino D, Siddall J, Small M, et al. Treatment patterns for chronic obstructive pulmonary disease (COPD) in the United States: results from an observational cross-sectional physician and patient survey. Int J Chron Obstruct Pulmon Dis. 2022;17:749–761. doi: 10.2147/COPD.S340794

70. Simeone JC, Luthra R, Kaila S, et al. Initiation of triple therapy maintenance treatment among patients with COPD in the US. Int J Chron Obstruct Pulmon Dis. 2017;12:73–83. doi: 10.2147/COPD.S122013
71. Li Y, Lim J, Stemkowski S, et al. Initiation of triple therapy maintenance treatment among patients with COPD. Am J Manag Care. 2020;26(4):e106–e112.
72. Müllerová H, Lu C, Li H, et al. Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. PLoS One. 2014;9(1):e85540. doi: 10.1371/journal.pone.0085540
73. Brusselle G, Price D, Gruffydd-Jones K. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015;10:2207–2217. doi: 10.2147/COPD.S91694
74. Wurst KE, Punekar YS, Shukla A, et al. Treatment evolution after COPD diagnosis in the UK primary care setting. PLoS One. 2014;9(9):e105296. doi: 10.1371/journal.pone.0105296
75. Bloom CI, Elkin SL, Quint JK. Changes in COPD inhaler prescriptions in the United Kingdom, 2000 to 2016. Int J Chron Obstruct Pulmon Dis. 2019;14:279–287. doi: 10.2147/COPD.S190086
76. Buhl R, Criée CP, Kardos P, et al. Dual bronchodilation *vs* triple therapy in the "real-life'" COPD DACCORD study. Int J Chron Obstruct Pulmon Dis. 2018;13:2557–2568. doi: 10.2147/COPD.S169958
77. Jarad NA, Wedzicha JA, Burge PS, et al. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. Respir Med. 1999;93(3):161–166. doi: 10.1016/S0954-6111(99)90001-X
78. Donohue JF, Worsley S, Zhu CQ, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med. 2015;109(7):870–881. doi: 10.1016/j.rmed.2015.04.018
79. Singh D, Worsley S, Zhu CQ, et al. Umeclidinium/Vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. BMC Pulm Med. 2015;15(1):91. doi: 10.1186/s12890-015-0092-1
80. Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:1015–1026. doi: 10.2147/COPD.S84436
81. Beeh KM, Derom E, Echave-Sustaeta J, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat(®) is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler(®) (ENERGITO(®) study). Int J Chron Obstruct Pulmon Dis. 2016;11:193–205. doi: 10.2147/COPD.S95055
82. Vogelmeier C, Paggiaro PL, Dorca J, et al. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study. Eur Respir J. 2016;48(4):1030–1039. doi: 10.1183/13993003.00216-2016
83. Kaplan A, Chapman KR, Anees SM, et al. Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study. Int J Chron Obstruct Pulmon Dis. 2019;14:249–260. doi: 10.2147/COPD.S185485
84. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. Chest. 2019;155(6):1158–1165. doi: 10.1016/j.chest.2019.03.005
85. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1(1):51–60. doi: 10.1016/S2213-2600(12)70052-8
86. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371(14):1285–1294. doi: 10.1056/NEJMoa1407154
87. Stolz D, Miravitlles M. The right treatment for the right patient with COPD: lessons from the IMPACT trial. Eur Respir J. 2020;55(5):2000881. doi: 10.1183/13993003.00881-2020
88. Suissa S, Dell'aniello S, Ernst P. Triple inhaler versus dual bronchodilator therapy in COPD: real-world effectiveness on mortality. COPD J Chronic Obstruct Pulm Dis. 2022;19(1):1–9. doi: 10.1080/15412555.2021.1977789
89. Buhl R, Mattiucci-Gühlke M, Eckhardt S, et al. EVELUT®: dyspnea and symptom burden in COPD patients switching from LABA/ICS to LAMA/LABA or LAMA/LABA/ICS. In: Eastern pulmonary conferences; Palm Beach, FL: 2022.
90. Chen H, Sun J, Huang Q, et al. Inhaled corticosteroids and the pneumonia risk in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. Front Pharmacol. 2021;12:691621. doi: 10.3389/fphar.2021.691621
91. Kardos P, Vogelmeier C, Worth H, et al. A two-year evaluation of the 'real life' impact of COPD on patients in Germany: the DACCORD observational study. Respir med. 2017;124:57–64. doi: 10.1016/j.rmed.2017.02.007
92. Hurst JR, Vestbo J, Anzueto A, et al., Evaluation of COPD Longitudinally to Identify Predictive Surrogate endpoints (ECLIPSE) investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–1138. doi: 10.1056/NEJMoa0909883
93. Vogelmeier CF, Worth H, Buhl R, et al. Impact of switching from triple therapy to dual bronchodilation in COPD: the DACCORD 'real world' study. Respir Res. 2022;23(1):109. doi: 10.1186/s12931-022-02037-2
94. Rossi A, Guerriero M, Corrado A. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). Respir Res. 2014;15(1):77. doi: 10.1186/1465-9921-15-77
95. Rossi A, van der Molen T, del Olmo R, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. Eur Respir J. 2014;44(6):1548–1556. doi: 10.1183/09031936.00126814
96. Han MK, Criner GJ, Dransfield MT, et al. The effect of inhaled corticosteroid withdrawal and baseline inhaled treatment on exacerbations in the IMPACT study. A randomized, double-blind, multicenter clinical trial. Am J Respir Crit Care Med. 2020;202(9):1237–1243. doi: 10.1164/rccm.201912-2478OC
97. Suissa S. Perplexing mortality data from triple therapy trials in COPD. Lancet Respir Med. 2021;9(7):684–685. doi: 10.1016/S2213-2600(21)00238-1
98. Lipson DA, Crim C, Criner GJ, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2020;201(12):1508–1516. doi: 10.1164/rccm.201911-2207OC
99. Ferguson GT, Shaikh A, Tetzlaff K, et al. Effect of inhaled corticosteroid withdrawal on chronic obstructive pulmonary disease exacerbations in patients taking triple therapy at baseline. Int J Chron Obstruct Pulmon Dis. 2020;15: 2879–2888. 10.2147/COPD.S237408.
100. Sethi S, Palli SR, Bengtson LGS, et al. Clinical and economic outcomes in patients with chronic obstructive pulmonary disease initiating maintenance therapy with tiotropium bromide/olodaterol or fluticasone furoate/umeclidinium/vilanterol. J Manag Care Spec Pharm. 2023;29(7):791–806. doi: 10.18553/jmcp.2023.22373
101. Iannella H, Luna C, Waterer G. Inhaled corticosteroids and the increased risk of pneumonia: what's new? A 2015 updated review. Ther Adv Respir Dis. 2016;10(3):235–255. doi: 10.1177/1753465816630208
102. Souliotis K, Silva Miguel L, Hillas G, et al. The cost-saving switch from inhaled corticosteroid-containing treatments to dual bronchodilation: a two-country projection of epidemiological and economic burden in chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2020;14:1753466620926802. doi: 10.1177/1753466620926802
103. Quint JK, Montonen J, Esposito DB, et al. Effectiveness and safety of COPD maintenance therapy with tiotropium/olodaterol versus

LABA/ICS in a US claims database. Adv Ther. 2021;38(5):2249–2270. doi: 10.1007/s12325-021-01646-5
104. Treharne C, Brighton N, Strange C, et al. 5-year US COPD exacerbation costs extrapolated from rhe ETHOS study. Chest. 2021;160(4):A1838–A1839. doi: 10.1016/j.chest.2021.07.1651
105. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med. 2020;383(1):35–48. doi: 10.1056/NEJMoa1916046
106. Lusuardi M. Respiratory medicine in general practice: what is the role of the pulmonary specialist? Monaldi Arch Chest Dis. 2005;63(1):3–5. doi: 10.4081/monaldi.2005.650
107. Singh D, Holmes S, Adams C, et al. Overcoming therapeutic inertia to reduce the risk of COPD exacerbations: four action points for healthcare professionals. Int J Chron Obstruct Pulmon Dis. 2021;16:3009–3016. doi: 10.2147/COPD.S329316
108. Oshagbemi OA, Burden AM, Braeken DCW, et al. Stability of blood eosinophils in patients with chronic obstructive pulmonary disease and in control Subjects, and the Impact of Sex, age, smoking, and baseline counts. Am J Respir Crit Care Med. 2017;195(10):1402–1404. doi: 10.1164/rccm.201701-0009LE