Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence

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Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence

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ABSTRACT

In this guideline update, we highlight important and new findings related to pharmacological therapy of chronic obstructive pulmonary disease (COPD) that should change clinical practice and improve disease management. We present updated evidence, recommendations and expert clinical remarks on maintenance pharmacotherapy in patients with stable COPD. The diagnosis and nonpharmacological therapy of COPD are out-of-scope for this update.

In patients with COPD who have persistent shortness of breath, exercise intolerance and/or poor health status despite using inhaled LAMA or LABA monotherapy, we recommend augmenting treatment to LAMA/LABA dual therapy. In patients with high-risk exacerbations, LAMA/LABA is the preferred choice to ICS/LABA except in patients with previous exacerbations who have higher peripheral eosinophilia. There is no role for ICS monotherapy; when indicated, ICS should only be used in combination with bronchodilators. Treatment "step up" in COPD is proposed as a practical construct supported by evidence that inhaled combined therapy is superior to monotherapy and triple therapy to dual therapy in certain patient populations. Because the superiority of inhaled triple or dual bronchodilator therapy may not be achieved in every patient, "step down" may be considered for some patients (not at high risk for future exacerbations), but should be done with close medical supervision, as the risk of clinical deterioration is real and continues to exist. The decision of changing a therapy should always occur after a complete evaluation of the patient and the potential benefit to a change in therapy; as well as an assessment of any adverse effects of the therapy, and with a review of patient adherence, inhaler technique and patient preferences. Pharmacological therapy plays a foundational role in therapy, but it should never be the sole treatment in managing COPD patients. Clinicians should always combine and optimize pharmacological and nonpharmacological therapies with the dual goals of reducing symptoms and preventing acute exacerbations of COPD (AECOPD).

RÉSUMÉ

La présente mise à jour des lignes directrices met de l'avant de nouveaux résultats importants sur le traitement pharmacologique de la maladie pulmonaire obstructive chronique (MPOC) qui devraient modifier la pratique clinique et améliorer la prise en charge de la maladie. Nous présentons une mise à jour des données probantes et des recommandations, et des observations cliniques d'experts sur la pharmacothérapie d'entretien pour les patients dont la MPOC est stable. La présente mise à jour ne porte pas sur le diagnostic et le traitement non pharmacologique de la MPOC.

Chez les patients ayant une MPOC et dont l'essoufflement, l'intolérance à l'effort et la détérioration de l'état de santé persistent malgré une monothérapie d'antimuscarinique à longue durée d'action (AMLA) ou de bêta$_2$-agoniste à longue durée d'action (BALA), nous recommandons une progression du traitement vers une bithérapie AMLA/BALA. Chez les patients présentant un risque élevé d'exacerbations, il faut privilégier une bithérapie AMLA/BALA plutôt qu'une association de corticostéroïde en inhalation (CSI)/BALA, sauf chez les patients ayant déjà subi des exacerbations et dont le nombre d'éosinophiles de sang périphérique est élevé. Il n'y a pas lieu de recourir à la monothérapie de CSI; lorsqu'ils sont indiqués, les CSI doivent être utilisés uniquement

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en association avec des bronchodilatateurs. Pour la mise en place du traitement dans les cas de MPOC, il est proposé d'adopter une approche pratique et fondée sur les données probantes selon laquelle une inhalothérapie combinée est supérieure à la monothérapie et une trithérapie est supérieure à une bithérapie chez certaines populations de patients. Étant donné que la supériorité de la trithérapie ou de la bithérapie à l'aide d'un bronchodilatateur pourrait ne pas être observée chez tous les patients, il faudra envisager une dégression de traitement pour certains patients (qui ne présentent pas de risque élevé d'exacerbations futures), mais sous une étroite supervision médicale, car le risque de détérioration clinique est réel et persiste. La décision de modifier un traitement doit toujours être prise après une évaluation complète du patient et des avantages possibles d'une modification du traitement; ainsi qu'une évaluation de tous les effets indésirables du traitement et une vérification de l'observance du patient, de sa technique d'inhalation et de ses préférences.

La pharmacothérapie joue un rôle fondamental, mais elle ne doit jamais être utilisée comme seul traitement pour la prise en charge des patients ayant une MPOC. Les cliniciens doivent toujours associer et optimizer les traitements pharmacologiques et non pharmacologiques en ayant le double objectif de soulager les symptômes et de prévenir les exacerbations aiguës de la MPOC (EAMPOC).

Introduction

Since the last published Canadian Thoracic Society (CTS) position statement on the pharmacotherapy in patients with chronic obstructive pulmonary disease (COPD) in 2017,[1] several important publications have necessitated an update to the current approach. This document is intended to guide best practice in light of recent research.

In clinical practice, an integrated, comprehensive approach to care should include:

- a diagnosis of COPD confirmed with spirometry;
- clinical evaluation of the patient; and
- comprehensive management, which includes non-pharmacological and pharmacological interventions (Figure 1).

The *diagnosis of COPD* should be considered in patients at risk of developing this disease. Patients' smoking history should be the main focus as it remains the most important risk factor. However, clinicians should be aware of an increased risk of COPD in individuals reporting a past medical history of asthma and/or severe childhood respiratory disease. Additionally, patients who have been exposed to passive smoke and/or to indoor biomass fuel are also at increased risk for the development of COPD.[2] This includes individuals from developing countries where indoor biomass exposure is the leading cause of COPD. Physicians should also be attentive to patients presenting with "exacerbation-like respiratory events" in the office or emergency setting, which may be an initial presentation of previously undiagnosed COPD. These events are common in undiagnosed COPD (22% in undiagnosed compared to 40% in diagnosed COPD) and have substantial impact on health service utilization, such as emergency department (ED) visits and hospital admissions.[3] An exacerbation-like respiratory event can be a trigger (opportunity) for patients to come to the attention of the healthcare system and for clinicians to consider the diagnosis of COPD and/or to optimize disease management.

Recent robust population data have confirmed that many individuals with COPD remain undiagnosed, but symptomatic, with an increased risk of exacerbations, pneumonia and death.[4] However, undiagnosed COPD, but asymptomatic, can also have exacerbations and pneumonia.[4] These patients who are "asymptomatic" may have adapted their lives to the limitations associated with their disease and may not want to reflect upon changes that occur to them as being a problem, that is, denial. If the physician uses probing questions, then symptoms may be better determined. This reality calls into question the validity of current recommendations for diagnosis of COPD that suggest targeted testing with spirometry only for symptomatic individuals.

It is important to remind physicians that *spirometry* is essential for the diagnosis of COPD, that is, a fixed post-bronchodilator ratio of the FEV_1/FVC of <0.70 or $<$ the lower limit of normal (LLN) ratio (i.e., less than the lower fifth percentile of the reference value from a healthy population). Recent results support the use of fixed ratio less than 0.70 as appropriate to identify individuals at risk of clinically significant COPD.[5,6] However, more than a single post-bronchodilator spirometric assessment may be necessary for diagnosing COPD for patients with mild airway obstruction at baseline.[7] We suggest post-bronchodilator FEV_1/FVC ratio should be confirmed by a repeat spirometry on a separate occasion if the value is between 0.6 and 0.8, because the ratio may change as a result of biological variation. Findings, however, indicate that if the initial post-bronchodilator FEV_1/FVC ratio is less than 0.6 it is very unlikely to rise above 0.7 spontaneously. While the diagnosis of COPD is confirmed by a reduced FEV_1/FVC ratio < 0.7, the severity of airflow obstruction in COPD should be assessed by the degree of reduction in the post-bronchodilator FEV_1 (% predicted).

Non-pharmacological therapy is complementary to inhaled or oral medication and should be a foundational aspect of the comprehensive management of COPD. Physicians must ensure patients have the proper support to live in a smoke free environment, receive appropriate vaccinations, adhere to prescribed medication (including using proper inhaler technique), receive self-management education and coaching, remain physically active and be referred to and complete pulmonary rehabilitation.[1,8,9] In a recent survey by the COPD Foundation,[10] patients reported gaps such as not receiving information after diagnosis of COPD, and receiving almost no education on self-management skills. Patients wished they had mastered these skills sooner to recognize early signs of an exacerbation and what to do about it, to stay active, and to cope with episodes of anxiety and dyspnea.

In this guideline update, we highlight important and new findings related to pharmacological therapy that should change clinical practice and improve disease management. We present updated evidence and recommendations, and expert clinical remarks on maintenance pharmacotherapy in patients with stable COPD. The diagnosis and non-pharmacological therapy of COPD are out-of-scope for this update.

Objectives

The overall objective of this CTS clinical practice guideline is to help clinicians to match their therapeutic decisions to the clinical status of each patient. This is a step toward personalizing therapy based on increasing individual characterization.

The specific objective is to provide clinical guidance with evidence-based recommendations and expert-informed clinical remarks to optimize maintenance pharmacological therapy for patients with COPD.

Target patient population

The update applies to all individuals with stable COPD.

Target users

Healthcare	Nonhealthcare
Certified respiratory educators	Healthcare decision-makers
Internists	Patient advocates
Nurse practitioners	Patients
Pharmacists	
Primary care physicians	
Respirologists	
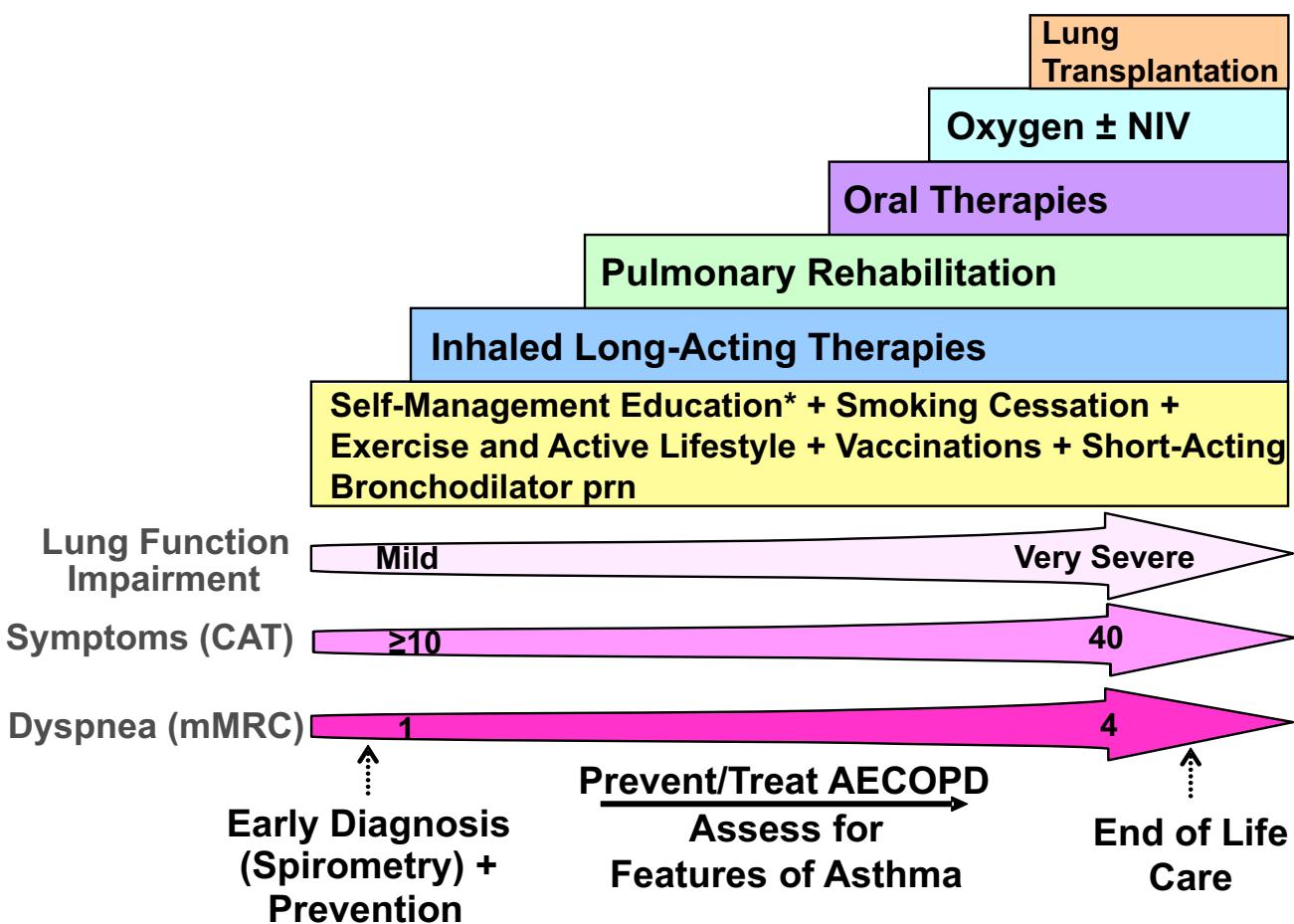
Figure 1. Comprehensive management of COPD.
Integrated approach to care that includes confirming COPD diagnosis with spirometry, evaluation of symptom burden and risk of exacerbations with on-going monitoring, assessment for features of asthma, and comprehensive management, both non-pharmacologic and pharmacologic.
* = **Self-Management Education** includes appropriate inhaler device technique and review, breathing techniques and review, early recognition of AECOPD, written action plan development and implementation (if appropriate).
mMRC is a modified (0-4 scale) version of the MRC breathlessness scale which was used in previous CTS guidelines. The mMRC aligns with the Global Initiative for Chronic Obstructive Airways Disease (GOLD) 2019 report.
Abbreviations: CAT = COPD assessment test; mMRC = Modified Medical Research Council; prn = as-needed; AECOPD = acute exacerbation of COPD; Inhaled Long-Acting Therapies = long-acting muscarinic antagonist and/or long-acting ß2-agonist and/or inhaled corticosteroid; NIV = non-invasive ventilation.

Key definitions

Bronchodilators open up the airways in the lungs by relaxing airway smooth muscle. They also reduce lung hyperinflation. Bronchodilator medications can be short- or long-acting. Different types of short- or long-acting bronchodilators work in different ways.

- Short-acting bronchodilators can be either *SABAs* (short-acting beta agonists) or *SAMAs* (short-acting muscarinic antagonists).
- Long-acting bronchodilators can be either *LABAs* (long-acting beta2 agonists) or *LAMAs* (long-acting muscarinic antagonists).

Acute Exacerbations of COPD (AECOPD): Exacerbations are "event-based" occurrences; that is, respiratory symptom(s) that worsen beyond the normal day-to-day variability and may require the use of antibiotics and/or systemic corticosteroids and/or healthcare services. The varying levels of exacerbation severity are:

- mild (worsening or new respiratory symptoms without a change in prescribed medications);
- moderate (prescribed antibiotic and/or oral corticosteroids); and
- severe (requiring a hospital admission or ED visit).

We have chosen to reconsider the classification of exacerbations into low- and high-risk of future exacerbations to align with patients enrolled in recently published randomized clinical trials. This was a necessary decision considering that the recommendations made in the guideline are evidence based.

Low- and high-risk of future exacerbations: Patients are considered to be at:

- **low-risk of exacerbations** if they had ≤ 1 moderate exacerbation in the last year and did not require an ED visit or hospitalization
- **high-risk of exacerbations** if they had ≥ 2 moderate or ≥ 1 severe exacerbation in the last year requiring a hospital admission/ED visit.

Stable COPD: Patients are considered to have "stable COPD" in all clinical states other than during the period of an AECOPD. However, patients with "stable COPD" may have progressive symptoms and/or have experienced an exacerbation.

Symbol "/" for combination therapy: The symbol "/" refers to: combination products (in the same device) and combination regimens (in separate devices). Single or multiple inhalers for combination therapy represent the clinical reality of different approaches to manage patients for a variety of considerations, such as access to medication, response to treatment, medical conditions other than COPD and patient preference.

Methodology

This guideline was developed in accordance with the CTS guideline development process.[11] The panel used the AGREE II checklist to guide the development of the guideline.[12]

Guideline panel composition

The COPD guideline panel comprised 12 experts: six respirologists with experience in COPD management, research and research methodology including three clinicians/epidemiologists; two primary care physicians appointed by the College of Family Physicians of Canada; and one pharmacist. All author conflicts of interests are available at https://cts-sct.ca/guideline-library/.

Key clinical questions

The key clinical questions were developed using the **P**atient/population; **I**ntervention or interventions; **C**omparison groups; **O**utcome or outcomes of interest (PICO) method. The PICO questions were based on the last published CTS position statement on the pharmacotherapy in patients with COPD in 2017.[1] We identified new evidence for PICO questions 1 and 2 but no new evidence to support an update of PICO 3 on Asthma COPD overlap (ACO). We did not include new interventions or *de novo* clinical questions in this review.

Literature search and screening of abstracts

This update includes all new research publications from the end-date of the literature search for the 2017 CTS position statement on pharmacotherapy in patients with chronic obstructive pulmonary disease.[1] An initial search was conducted through the CTS/McMaster Plus database with selected relevant manuscripts included with publication dates through October 31, 2018. A dedicated literature search and additional articles were found by reviewing the references in included articles and based on authors' knowledge of other relevant publications. See Appendix 1 for details of the search strategy and a flow chart of search results and articles reviewed. We indexed the studies according to the PICO questions and made them available to the guideline panel on a dedicated software platform for manual assignment to individual reviewers.

For each PICO question, two panel members scrutinized titles and abstracts to decide whether the article was relevant (JB/PH-PICO 1; MB/DM-PICO 2). Where opinions differed, the two panel members resolved the conflict by discussion. Upon reaching consensus on the list of relevant abstracts, we obtained and reviewed copies of the full articles of all relevant and possibly relevant articles. The chosen inclusion and exclusion criteria (Appendix 1) were documented at both the abstract and full-text review stages.

Study selection criteria

We excluded studies if they were not related to maintenance pharmacotherapy in patients with stable, moderate to very-severe COPD. We included only randomized clinical trials and systematic reviews for further review and inclusion. The same pairs of reviewers who scrutinized titles and abstracts also assessed inclusion/exclusion criteria (Appendix 1) for full-text articles. The Cochrane Risk of Bias Tool for randomized clinical trials was used to assess the risk of bias in individual studies. The Documentation and Appraisal Review (DART) tool was used to assess the quality of systematic reviews addressing a variety of research designs.

Critical appraisal of identified studies

We compiled data from all articles relevant to each PICO question into evidence tables (available at: https://cts-sct.ca/guideline-library/). The entire panel discussed each PICO question via webinars in June 2019, at which time, all evidence tables were reviewed. Accordingly, we established group consensus on the quality and strength of the evidence addressing each clinical question according to the GRADE criteria (Appendix 1).[13] In instances where there was insufficient evidence but a recommendation was still warranted, a suggestion was developed and "consensus-based (CB)" replaced the grade.

Synthesis of evidence-base and clinical judgment of risk-versus-benefit

For each clinical question, we considered the strength and directness of the evidence supporting an intervention or treatment approach. For each therapeutic approach, we also considered: the potential health benefit to the patient; the morbidity and mortality impact on the overall COPD population; risks/harms; the burden placed on the patient; and the cost-effectiveness (these are the factors categorized under the "Contextualization and Deliberations" domain of the guidelines).[14]

We also included *informed clinical remarks* with PICO clinical questions and recommendations, in an effort to compliment recommendations with practical clinical advice. Some of these remarks are not based on strong evidence, but represent the consensus opinions of panel members based on expertise.

Update of recommendations and classification

We used recommendations in the 2015 Prevention of Acute Exacerbations of COPD – American College of Chest Physicians, the Canadian Thoracic Society Guideline document[15] for PICO 2, and from the 2017 CTS Position Statement: Pharmacotherapy in patients with COPD — An Update[1] for PICOs 1 and 2.

Following open and extensive discussions and evidence review for each PICO question, the entire panel proposed wording updates to each prior recommendation pertaining to that PICO question, and where applicable, a change to the strength of the recommendation to reflect newly published literature. We based strength of the recommendation on the GRADE quality of evidence[13] (Appendix 1), and our synthesis of clinical judgment. The CTS Canadian Respiratory Guidelines Committee (CRGC) Chair then vetted the recommendations to optimize language with a view to improving likelihood of uptake.[16,17] Recommendations were then voted upon by electronic survey using a six-point voting scale, whereby it was defined *a priori* that a recommendation would only be accepted if each panel member voted for option 1, 2 or 3 (wholeheartedly agree, agree or can support). For a recommendation to be accepted, it had to be voted on by 75% of the eligible panel members and achieve ratings 1, 2 or 3 by 80% of the voting panelists. In the event of a failure to reach 80% of votes with ratings 1, 2 or 3, another period of discussion ensued, whereby dissenting opinions were heard and considered. The recommendation was revised and followed by a second round of voting by electronic survey using a three-point scale, for which acceptance of a recommendation required a majority (80%) of panelists to choose option 1 or 2 (Appendix 1). Throughout this process all recommendations achieved acceptance, with no recommendation requiring a second round of voting.

Review and approval process

The CTS independently invited formal review of the update by an external (non-CTS) content expert. The lead author responded to the comments and made corresponding changes. Two members of the CRGC then completed their own review and provided further feedback for consideration. Upon acceptance, the Committee recommended approval of the guideline to the CTS Executive Committee.

Living guideline/future updates

The guideline will be formally reviewed every three years or sooner to determine the need for and nature of any updates, in accordance with the CTS Living Guideline Model (details available at https://cts-sct.ca/guideline-library/methodology/). Authors and/or the CTS COPD Assembly Steering Committee members will also use the continuously updated McMaster Plus database, whereby they will receive alerts when new articles pertaining to these PICO questions are published (starting from the last date of the literature search conducted for this guideline). This will serve to prompt members to consider timely guideline updates with evolving evidence and will facilitate formal literature reviews.

Summary PICO 1: Improving symptoms, exercise tolerance, physical activity and health status in stable COPD patients

Among respiratory symptoms, shortness of breath (dyspnea) on exertion is the most debilitating symptom COPD patients experience.[18] Since disease progression reduces patients' capacity to exercise and, therefore, affects the ability to perform the activities of daily life,[19,20] they consider relief of this symptom to be one of the most important outcomes in the management of their disease.[21] Shortness of breath also contributes to the established extra-pulmonary manifestations of COPD, including anxiety, depression,[22] cardiovascular disease[23] and peripheral locomotor muscle deconditioning.[24] Importantly, it is strongly associated with increased morbidity and mortality in adults with COPD.[25,26] Persistent shortness of breath is associated with increased exacerbation risk.[26,27] Dyspnea and exacerbation are not independent or dichotomous outcomes and they are often present in the same patient. Alleviating shortness of breath is a key goal of COPD management.

Inhaled bronchodilators are the mainstay medications in the pharmacologic management of COPD. There are two main classes of bronchodilators: B_2-adrenoreceptor agonists and muscarinic antagonists, both in long- and short-acting forms. They can be used as monotherapy, combined as dual bronchodilators or combined with ICS for maintenance treatment. Bronchodilators enhance the neuromechanical coupling of the respiratory system and delay the onset of mechanical constraints, providing relief from exertional shortness of breath with concomitant improvement in exercise tolerance in patients with COPD.[28]

This section discusses the optimal use of inhaled and oral pharmacologic maintenance therapies shown to improve shortness of breath, exercise tolerance, physical activity and health status in stable COPD patients.

Key evidence

Based on this review for PICO 1, recommendations 1, 3, 7 and 8 remain unchanged, while recommendations 2, 4 and 5 have a change in GRADE assessment due to new research findings, and 2, 5 and 6 are revised based on evidence from published literature. See Appendix 2 detailing the upgrades and revisions from 2017.

As stated in the previous position statement, use of LAMA or LABA monotherapy is endorsed to reduce shortness of breath, improve exercise tolerance and improve health status in patients with stable COPD. Although LAMA is often preferred to LABA in monotherapy, the evidence of its superiority comes primarily from studies in which the main outcome was to prevent COPD exacerbations. In patients with COPD who have persistent shortness of breath, exercise intolerance and/or poor health status despite using inhaled LAMA or LABA monotherapy, we recommend augmenting treatment to LAMA/LABA dual therapy. Patients should be routinely monitored and evaluated for their response after any change in their therapy, as many have persisting symptoms with an impact on their well-being.[29]

In terms of improving physical activity, the evidence suggests that combining a self-management behavioral intervention with exercise and pharmacologic interventions has the largest effect on physical activity and symptom improvement. A self-management behavioral intervention is more likely to help patients change their behavior and can lead to long-term adoption of a more physically active lifestyle.[30,31] For patients who remain symptomatic and have poor exercise tolerance or health status despite being on LAMA/LABA combination therapy, the evidence supports patients enrolling in a pulmonary rehabilitation program.[32] For patients who remain symptomatic and have poor health status despite these interventions, a clinician should consider "step up" to triple therapy (LAMA/LABA/ICS), although each individual should be evaluated for risk/benefit of adding ICS in these circumstances. Evidence for its benefit has been demonstrated primarily in patients who have a high risk of exacerbations.[33,34]

For PICO 1, data is lacking with respect to withdrawal or "step down" from LAMA/LABA/ICS to LAMA/LABA dual therapy or from dual therapy to monotherapy. We continue to support guidance from the previous position statement.[1] The consensus was that, in patients with COPD with no improvement in shortness of breath, exercise tolerance or health status despite the use of triple inhaled therapy or inhaled LAMA/LABA dual therapy, clinicians may *cautiously* consider "step down" treatment for some patients. These patients need to be monitored carefully with close clinical follow-ups to detect any signs of clinical deterioration after medication "step down."

As per previous guidelines, oral therapies such as theophylline, phosphodiesterase-4-inhibitor, mucolytics, statins, anabolic steroids, oral Chinese herbal medicines or phosphodiesterase-5-inhibitor demonstrate no evidence of conferring additional benefit in patients already on combination long-acting bronchodilators. We reiterate that ICS monotherapy, as a lone intervention, has no place in treating COPD patients. If there is an indication for ICS therapy or the patient has asthma in addition to COPD, then ICS should be prescribed in a combination inhaler with long-acting bronchodilator(s).

Table 1. 2019 Recommendations on improving symptoms, exercise tolerance, physical activity and health status in stable COPD patients.

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce symptom burden (notably dyspnea and exercise intolerance), increase physical activity, and improve health status?

#	Grade	Guidance	Clinical Remarks	References
1.1	1A	We *recommend* an inhaled long-acting bronchodilator, either LAMA or LABA monotherapy, to reduce dyspnea, improve exercise tolerance, and improve health status.	LAMA is preferred over LABA therapy to prevent AECOPD (see PICO 2).	35–71
1.2	1A	We *recommend* an inhaled LAMA/LABA dual therapy in patients who experience persistent dyspnea, exercise intolerance, and/or poor health status despite the use of LAMA or LABA monotherapy.	Shortness of breath and exercise tolerance improve with LAMA/LABA dual therapy over monotherapy; health status has not been addressed as a primary outcome.	30,40,72–90
1.3	2A	We *suggest* an inhaled long-acting bronchodilator, i.e., LAMA, LABA, or LAMA/LABA dual therapy, to increase physical activity.	A long-acting bronchodilator may improve exercise capacity but not improve physical activity unless a behavioral intervention is offered as well.	30,38,51,91–94
1.4	2A	We *suggest* LAMA/LABA dual therapy rather than ICS/LABA dual therapy in COPD patients who have persistently poor health status despite the use of maintenance LABA.	ICS/LABA should be preferred to LAMA/LABA only in COPD patients with concomitant asthma.	95,96
1.5	2A	We *suggest* LAMA/LABA/ICS triple therapy in COPD patients with persistent dyspnea and poor health status in the last year despite the use of inhaled LAMA/LABA dual therapy.	Dyspnea and exacerbation are often present in the same patient.	33,34,97,98
1.6	Consensus	In stable COPD patients with no improvement in dyspnea, exercise tolerance or health status, despite the use of LAMA/LABA/ICS triple therapy or LAMA/LABA dual therapy, treatment "step down" may be considered. There is *insufficient evidence* to determine whether "step down" (LAMA/LABA/ICS triple therapy to LAMA/LABA dual therapy, or LAMA/LABA dual therapy to LAMA or LABA monotherapy) is safe and/or reduces patient benefit.	Withdrawing ICS may lower health status and lung function in some patients. Do not undertake "step down" in patients at high risk of AECOPD (see PICO 2).	99
1.7	2C	There is *insufficient or equivocal evidence* to determine whether the addition of an oral therapy, such as theophyllines, phosphodiesterase-4-inhibitors, mucolytics, statins, anabolic steroids, oral Chinese herbal medicines, or phosphodiesterase-5-inhibitors confers additional benefit to LAMA or LABA monotherapy, or LAMA/LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels, and/or improving health status.		76,100–119
1.8	Consensus	We *recommend* against treatment with ICS monotherapy in stable COPD patients.	When indicated, ICS should ideally be administered in a combination therapy in COPD patients.	

Stable COPD: Patients are considered to have "stable COPD" in all clinical states other than during the period of an acute exacerbation of COPD (AECOPD). However, patients with "stable COPD" may have progressive symptoms and/or have experienced an exacerbation. Bronchodilators open up the airways in the lungs by relaxing airway smooth muscle. They also reduce lung hyperinflation. Bronchodilator medications can be short- or long-acting. Different types of short- or long-acting bronchodilators work in different ways.

- Short-acting bronchodilators can be either *SABAs* (short-acting beta agonists) or *SAMAs* (short-acting muscarinic antagonists).
- Long-acting bronchodilators can be either *LABAs* (long-acting beta2 agonists) or *LAMAs* (long-acting muscarinic antagonists).

Symbol "/" for combination therapy: The symbol "/" refers to: combination products (in the same device) and combination regimens (in separate devices). Single or multiple inhalers for combination therapy represent the clinical reality of different approaches to manage patients for a variety of considerations, such as access to medication, response to treatment, medical conditions other than COPD and patient preference.

Exacerbations: Exacerbations are "event-based" occurrences; that is, respiratory symptom(s) that worsen beyond the normal day-to-day variability and may require the use of antibiotics and/or systemic corticosteroids and/or healthcare services. The varying levels of exacerbation severity are:

- mild (worsening or new respiratory symptoms without a change in prescribed medications);
- moderate (prescribed antibiotic and/or oral corticosteroids); and
- severe (requiring a hospital admission or ED visit).

Low- and high-risk of future exacerbations: Patients are considered to be at:

- Low-risk of exacerbations if they had ≤1 moderate exacerbation in the last year and did not require an ED visit or hospitalization.
- High-risk of exacerbations if they had ≥ 2 moderate or ≥ 1 severe exacerbation in the last year requiring a hospital admission/ED visit.

Abbreviations: PICO, Patient/population - Intervention or interventions - Comparison groups - Outcome or outcomes of interest; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; ED, emergency department.

Summary PICO 2: Preventing acute exacerbations in stable COPD patients

In Canada, AECOPD continues to be the most frequent cause of acute hospitalization in adults,[120] and is associated with the highest total hospital cost of care (2016–2017). The cost of hospitalizations related to COPD is more than 30% higher than that of the next most expensive health condition (heart failure).[121] AECOPDs are a gateway to poor outcomes and adverse consequences.[122–124] They accelerate lung function decline, dramatically reduce quality of life, and are strong predictors of future AECOPDs. They are acute, trajectory-changing manifestations of a chronic disease associated with increased mortality. COPD is the third leading cause of death worldwide.[125,126]

A fundamental and achievable goal of therapy in managing stable COPD is to reduce the occurrence and severity of AECOPDs. Furthermore, providing appropriate preventive therapy for patients at increased risk of exacerbation increases the likelihood of reducing and preventing ED visits and hospital admissions. In patients with severe COPD, reducing AECOPD may also reduce mortality.[33]

This section discusses the optimal use of inhaled and oral pharmacologic maintenance therapies shown to prevent AECOPD in patients with stable COPD, not the treatment of acute exacerbations.

Key evidence

Based on this review for PICO 2, recommendations 3 and 10 remain unchanged, while recommendations 1, 2, 4, 5, 6, 7, 8 and 9 have a change in GRADE assessment due to new research findings. Recommendations 5, 6, 7, 9 and 11 are revised based on evidence from published literature. See Appendix 2 detailing the upgrades and revisions from 2017.

A significant change is the use of either an ICS/LABA or LAMA/LABA as a first step in patients with high risk of AECOPD. Although ICS/LABA or LAMA/LABA is a viable inhaled therapeutic option in this setting, LAMA/LABA is the preferred choice except in patients with previous exacerbations who have higher peripheral eosinophilia (Figure 2). In this case, ICS/LABA could be the favored therapy as stated by the evidence described in the Discussion section of this guideline. Monotherapy with either LAMA or LABA is not the optimal initial maintenance treatment for patients who experience or are at high risk of AECOPD. Acknowledging the significant adverse consequences of AECOPD, consider inhaled therapy with either ICS/LABA or LAMA/LABA as the acceptable minimum maintenance therapy for this high risk population. It is important to remember that in real life practice, it is the exception to treat a patient only to prevent exacerbations; the vast majority of time we optimize bronchodilator therapy to improve a patient's dyspnea.

Similar to our analysis in PICO 1, we conclude that there is no role for ICS monotherapy and ICS should only be used in combination with bronchodilators. ICS/LABA and LAMA/LABA/ICS are the only current single inhaler options. Health Canada has not approved an inhaled ICS for monotherapy use in COPD. Furthermore, in prior studies, the monotherapy ICS arm underperformed compared to combination ICS/

LABA, and *post-hoc* analysis suggested increased mortality in the ICS monotherapy participants.[127] Administering ICS with LAMA/LABA in separate inhalers has not been studied in COPD.[120,122,123] When combination ICS/LABA or LAMA/LABA/ICS is used, high doses of ICS[122] are not typically necessary to achieve optimum benefit in COPD, as shown by a relatively flat dose-response curve[128] and greater incidence of adverse effect with higher inhaled ICS doses.[129]

There remains clinical uncertainty regarding potential "step down" of therapy[90,123] in patients with a history of a high risk of future AECOPD. Evidence from a randomized clinical trial involving participants with COPD receiving combination ICS/LABA with LAMA in separate inhalers who underwent stepwise ICS withdrawal suggests the intervention is not associated with a significantly increased risk of exacerbation over a short term of follow up.[130] However, in this study the initial baseline exacerbation rate was low, about one-third of participants had not previously required inhaled triple therapy before recruitment, there was a statistically significant reduction in FEV_1 (43 mL, p = 0.001) after ICS withdrawal, and the number of deaths was numerically small but higher in the ICS withdrawal group (n = 40) compared to the ICS continuation group (n = 34). More recently, another randomized clinical trial of patients with COPD with low risk of AECOPD on long-term triple inhaled therapy with direct de-escalation to LAMA/LABA led to a small decrease in lung function as a primary endpoint, with no difference in exacerbation rate. However, the primary study endpoint was not met, with confidence limits for trough FEV_1 exceeding the non-inferiority margin of −50 mL. Further analysis of these studies revealed a higher rate of exacerbation in patients with ≥300 blood eosinophils/μL, suggesting that, as a biomarker, blood eosinophil at ≥300/μL in patients with previous AECOPD could be useful to predict a favorable response to ICS when combined with long-acting bronchodilator(s). However, no RCT has compared ICS/LABA versus LABA/LAMA in patients with high risk of and blood eosinophil at ≥300/μL, with exacerbation as a primary endpoint.

Given these findings and acknowledging the negative impact of AECOPD, reductions in lung function and the potential adverse consequences of therapy, we continue to support guidance from the previous CTS guidance document[123] that the clinical phenotype should drive pharmacotherapy for patients with COPD. If therapy was started without a clear indication (such as the use of an ICS in a patient with no history of exacerbations), you may consider initiating a "step down." However, if therapy was started according to recommendations (such as the use of LAMA/LABA/ICS in a patient with moderate-severe COPD with poor quality of life and history of frequent and/or severe AECOPD) and treatment has been effective, a "step down" is NOT recommended. Given the potential for serious negative consequences of AECOPD, including hospitalization and death, we believe that de-escalation should only be considered in patients at low risk of morbidity and mortality, and this after a period of considerable stability. Moreover, while awaiting objective documentation supporting the safety of this approach, if you decide to "step down," we highly recommend monitoring your patients

carefully with regular clinical assessments that includes the monitoring of lung function and re-occurrence of AECOPD.

As noted, the incidence of pneumonia is higher with maintenance therapy of ICS-containing inhaled medicines, especially in COPD patients with severe and very severe disease. However, these are also the patients who benefit most from an ICS-containing regimen. Debate still ensues as to an intra-class difference between fixed combinations of inhaled corticosteroid/long acting β_2 agonist regarding the risk of pneumonia and pneumonia-related events in treating patients with COPD.[131] However, the clinical significance of increased pneumonia in COPD patients who use ICS remains unclear, since there is no concurrent documented increase risk of mortality in this group.[131] Results from a large clinical trial[33] confirmed a higher incidence of pneumonia with ICS-combination therapy, but this was accompanied by significant improvements in lung function and quality of life and significant reductions in exacerbations and mortality, which are endpoints of significant importance.

As stated in the previous position statement, if patients with COPD continue to experience exacerbations despite being on optimal long-acting inhaled therapy, consider adding a daily macrolide (e.g. Azithromycin) as maintenance therapy in appropriate patients who have normal QT interval on ECG and no evidence of either colonization or acute infection with atypical mycobacterium. Also consider oral Roflumilast or oral N-acetylcysteine (600 mg po BID) in those having a clinical phenotype by history in keeping with chronic bronchitis. In recommendation 2.11 in this update, recent evidence supports not using theophylline in patients who are on long-acting inhaled therapy. We reiterate that systemic corticosteroids should not be used for maintenance pharmacotherapy in stable COPD.
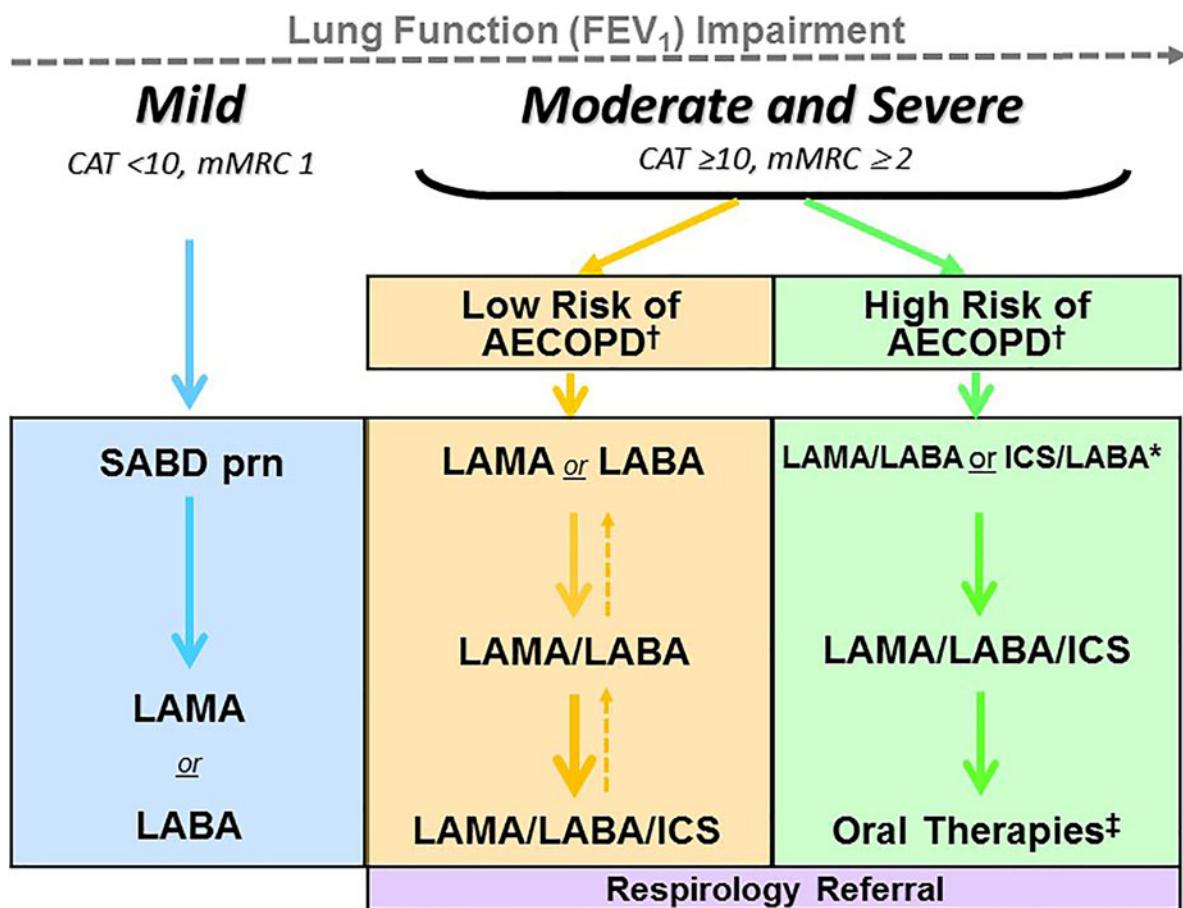

Figure 2. COPD Pharmacotherapy.
COPD pharmacotherapy promoting an approach that aligns treatment decisions with symptom burden and risk of future exacerbations. To learn more about the Asthma-COPD Overlap (ACO) treatment algorithm, refer to the CTS position statement on the pharmacotherapy in patients with COPD in 2017.[1]
mMRC is a modified (0-4 scale) version of the MRC breathlessness scale which was used in previous CTS guidelines. The mMRC aligns with the Global Initiative for Chronic Obstructive Airways Disease (GOLD) 2019 report.
SABD prn (as needed) should accompany all recommended therapies. Solid arrows indicate step up therapy to optimally manage symptoms of dyspnea and/or activity limitation, as well as prevention of AECOPD where appropriate. Dashed arrows indicate potential step down of therapy, with caution and with close monitoring of patient symptoms, exacerbations and lung function. Symbol "/" refers to combination products (in the same device) and combination regimens (in separate devices). ICS should ideally be administered in a combination inhaler.
†Patients are considered at Low Risk of AECOPD with ≤1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids), and did not require hospital admission/ED visit; or at High Risk of AECOPD with ≥2 moderate AECOPD or ≥1 severe exacerbation in the last year (severe AECOPD is an event requiring hospitalization or ED visit).
*Blood eosinophil ≥300/μL in patients with previous AECOPD may be useful to predict a favorable response to ICS combination inhaler.
‡Oral Therapies = Roflumilast, N-acetylcysteine, daily dose Azithromycin could be considered with patients with high risk AECOPD despite on optimal long-acting inhaled therapy. Oral corticosteroids as maintenance therapy are not indicated in COPD.
Abbreviations: CAT = COPD assessment test; mMRC = Modified Medical Research Council; SABD prn = short-acting bronchodilator as needed; AECOPD = acute exacerbation of COPD; LAMA = long-acting muscarinic antagonist; LABA = long-acting ß2-agonist; ICS = inhaled corticosteroid.

Table 2. 2019 Recommendations on preventing acute exacerbation in stable COPD.

PICO 2. How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of AECOPD?

#	Grade	Guidance	Clinical Remarks	References
2.1	1A	We *recommend* either LAMA or LABA monotherapy over a SABD prn.	This is applicable to a patient at low risk of AECOPD.	67,69,71,123,132–139
2.2	1A	We *recommend* LAMA monotherapy over LABA monotherapy.	This is applicable to a patient at low risk of AECOPD.	69,123,124,138
2.3	1A	We *recommend* LAMA monotherapy over a SAMA. AND	This is applicable to a patient at low risk of AECOPD.	59,123,136,138
	2C	We *suggest* LABA monotherapy over a SAMA.		123,138
2.4	1B	We *recommend* LAMA/LABA dual therapy for patients experiencing AECOPD despite use of LAMA or LABA monotherapy.		85,123,140–148
2.5	1A	We *recommend* ICS/LABA dual therapy over SABD prn to prevent AECOPD in patients at high risk of AECOPD. AND		123,139,149–155
	1A	We *recommend* ICS/LABA dual therapy over LABA monotherapy to prevent AECOPD in patients at high risk of AECOPD.		123,139,149–157
2.6	1B	We *recommend* either LAMA/LABA or ICS/LABA dual therapy for patients at high risk of AECOPD.		33,123,130,145,146,158–162
2.7	1A	We *recommend* LAMA/LABA/ICS triple therapy for patients at high risk of AECOPD despite the use of LAMA monotherapy or dual therapy (ICS/LABA or LAMA/LABA).		33,123,134,163–168
2.8	1A	We *recommend* oral Roflumilast for patients with chronic bronchitis and a high risk of AECOPD despite optimal long-acting inhaled therapy.		118,123,169–176
2.9	1B	We *recommend* oral N-acetylcysteine (600 mg po BID) for patients with chronic bronchitis and a high risk of AECOPD despite optimal long-acting inhaled therapy.		123,177–185
2.10	2A	We *suggest* macrolide maintenance therapy for patients with a high risk of AECOPD despite optimal long-acting inhaled therapy.	Weigh the benefits against the risks of potential microbial resistance, hearing impairment and QT-prolonging drug interactions.	123,158,186–189
2.11	2B	We *suggest* that oral slow-release theophylline **should not be used**, as it does not prevent AECOPD in patients on optimal long-acting inhaled therapy.		123,190

Stable COPD: Patients are considered to have "stable COPD" in all clinical states other than during the period of an acute exacerbation of COPD (AECOPD). However, patients with "stable COPD" may have progressive symptoms and/or have experienced an exacerbation. SABD prn (as needed) should accompany all recommended therapies. Bronchodilators open up the airways in the lungs by relaxing airway smooth muscle. They also reduce lung hyperinflation. Bronchodilator medications can be short- or long-acting. Different types of short- or long-acting bronchodilators work in different ways.

- Short-acting bronchodilators can be either *SABAs* (short-acting beta agonists) or *SAMAs* (short-acting muscarinic antagonists).
- Long-acting bronchodilators can be either *LABAs* (long-acting beta2 agonists) or *LAMAs* (long-acting muscarinic antagonists).

Symbol "/" for combination therapy: The symbol "/" refers to: combination products (in the same device) and combination regimens (in separate devices). Single or multiple inhalers for combination therapy represent the clinical reality of different approaches to manage patients for a variety of considerations, such as access to medication, response to treatment, medical conditions other than COPD and patient preference.

Exacerbations: Exacerbations are "event-based" occurrences; that is, respiratory symptom(s) that worsen beyond the normal day-to-day variability and may require the use of antibiotics and/or systemic corticosteroids and/or healthcare services. The varying levels of exacerbation severity are:

- mild (worsening or new respiratory symptoms without a change in prescribed medications);
- moderate (prescribed antibiotic and/or oral corticosteroids); and
- severe (requiring a hospital admission or ED visit).

Low- and high-risk of future exacerbations: Patients are considered to be at:

- Low-risk of exacerbations if they had ≤1 moderate exacerbation in the last year and did not require an ED visit or hospitalization.
- High-risk of exacerbations if they had ≥2 moderate or ≥1 severe exacerbation in the last year requiring a hospital admission/ED visit.

Oral Therapies are Roflumilast, N-acetylcysteine or daily dose Azithromycin. Oral corticosteroids as maintenance therapy are not indicated in COPD. Optimal long-acting inhaled therapy is therapy that has been tailored to the patient's exacerbation history, in accordance with Figure 2.

Abbreviations: PICO, Patient/population - Intervention or interventions - Comparison groups - Outcome or outcomes of interest; COPD, chronic obstructive pulmonary disease; BID, bis in die (twice a day); ICS, inhaled corticosteroid; ED, emergency department; SABD prn, short-acting bronchodilator as needed.

Discussion

Since the 2017 CTS pharmacotherapy position statement, there have been several important clinical trials that have necessitated an update. In this guideline we have incorporated new evidence from published large multicenter clinical trials and systematic reviews that have an impact on clinicians' approach to the medical management of patients living with COPD. We have summarized our updated recommendations in Tables 1 and 2 and included a comparison of 2017 and 2019 recommendations in Appendix 2. An updated COPD pharmacologic algorithm (Figure 2) that reflects these updates was also derived.

The treatment propositions presented in this updated Guideline, in particular the approach of a treatment "step up" and "step down" are pragmatic and intended to provide meaningful guidance for clinicians. Most research trials were not strictly designed to assess such a therapeutic approach. However, treatment "step up" in COPD is a practical construct with wide appeal that is supported by evidence that inhaled combined therapy is superior to monotherapy and triple therapy to dual therapy in certain patient populations. Because the superiority of inhaled triple or dual bronchodilator therapy may not be achieved in every patient, "step down" may be considered for some patients, but should only be done with close medical supervision, as the risk of clinical deterioration is real and continues to exist.

There are several important considerations in the management of COPD that are not addressed by the PICO questions in this guideline document. We have therefore provided a commentary of selected topics in this discussion. A full review of these clinical issues may be undertaken in subsequent guideline development.

Choice of inhaler device

The choice of the inhaler device and/or the decision to use single or multiple devices for combination therapy remains a subject of clinical interest and controversy. Very few studies have compared combination products in the same device compared to separate devices. In the only randomized clinical trial examining this issue, a single-inhaler LAMA/LABA/ICS was compared to an ICS/LABA and LAMA in separate devices; this study demonstrated non-inferiority between the two treatment strategies.[191] There is no study that has been performed in COPD comparing LABA or combined LAMA/LABA with ICS in single and separate devices. Although the use of single or multiple devices for combination therapy is a clinical reality, properly designed trials or real-life data are lacking in COPD.

Choice of bronchodilator combination

Another topic is the question clinicians may have with respect to the equivalence or superiority of the various combined long-acting bronchodilators (LAMA/LABA). Few comparative efficacy trials compared combination long-acting bronchodilator therapy; those that did showed between-treatment differences in FEV_1 that were small and of uncertain clinical significance.[192,193]

Interval for changing inhaler therapy

The decision to change a therapy should always occur after a complete evaluation of the patient and the potential benefit of a change in therapy; as well as an assessment of any adverse effects of the therapy, and with a review of patient adherence, inhaler technique and preferences. Although there is no absolute interval time at which the evaluation should be performed following a change in therapy, 6 months after initiating a long acting bronchodilator and 12 months after initiating a combination regimen with an ICS are suggested timeframes.

Peripheral blood eosinophils in COPD

While peripheral blood eosinophil counts have demonstrated reasonable repeatability over a year in a population-based cohort of COPD patients in primary care,[194] practical uncertainty remains regarding the exact cut-off level of sputum or blood eosinophils for predicting therapeutic response in COPD. Despite this uncertainty, peripheral blood eosinophil counts may play a role in certain clinical settings. New information is incorporated into this update with respect to blood eosinophils as a potential biomarker for use in COPD patients known to have exacerbations to prevent future exacerbations. A consistent pattern of results from randomized clinical trials conducted in COPD patients at risk of exacerbations has emerged. Lower eosinophil counts (<100 eosinophils/µL) predict a lower or no response to ICS containing regimens in terms of preventing exacerbation. ICS containing regimens will benefit in reducing the likelihood of exacerbations in the magnitude of effect being greater at higher eosinophil counts, particularly ≥300 eosinophils/µL.[156] This provides a measure of probability of response to ICS containing regimen in patients who had previous exacerbations, aligning with a more personalized approach.

Mortality

Reducing mortality has been a long-standing goal of therapy in COPD. Older studies have revealed mortality-reducing trends with inhaled therapy[127,195] but statistical significance was not achieved. Although there is still no definitive answer, more recent evidence from a large randomized controlled trial study demonstrated significant relative reduction in all-cause mortality during treatment with regimens that included inhaled ICS/LABA or triple therapy (LAMA/LABA/ICS) compared to LAMA/LABA for COPD patients with high risk of exacerbations. Despite a higher incidence of study-reported pneumonia in the ICS-containing treatment regimens, mortality was reduced by 42% in favor of LAMA/LABA/ICS vs. LAMA/LABA (unadjusted $p = 0.01$), and 39% in favor of ICS/LABA vs LAMA/LABA (unadjusted $p = 0.02$). An analysis of adjudicated cause-specific death during treatment demonstrated fewer deaths from both

respiratory and cardiovascular etiologies in the ICS-containing regimens. This topic requires further attention, but mortality is an important outcome that should have our consideration in clinical decision.

Dissemination and implementation

Our guideline will be disseminated through traditional channels including this publication, through the CTS website and social media channels, and through an accompanying slide deck that will be used to present this content to various target groups across the country. It is also anticipated that we will produce a separate implementation document that will include key indicators of appropriate care and practical guidance for healthcare system change. Our goal is to monitor the impact of these actionable recommendations through their ability to correct knowledge gaps and improve actual behaviors within the target user groups. On a population level, we also believe that monitoring the frequency of COPD ED visits, hospital admissions and re-admissions would be relevant metrics to assess the success of this guideline. For messages targeting nonexperts, we will seek to tailor messages and produce corresponding educational content, in collaboration with key stakeholders such as provincial lung associations, RESPIPLUS and RESPTREC.

Conclusion

This update is an important step toward optimizing the pharmacologic management of COPD. Recommendations enable better-personalized therapy based on more specific individual characteristics. The update further highlights the intent and benefit of therapy in both improving symptoms and activity limitations, and reducing the risk of AECOPD. Areas of debate still require further study, including approach to treatment "step down" targeting specific group of patients, blood eosinophil use and its cut off, and use of single or multiple inhalers for combination therapy, but recent evidence has strengthened many recommendations to optimize management of COPD. In summary, pharmacological therapy plays a foundational role in therapy, but it should never be the sole treatment in managing COPD patients. Clinicians should always combine and optimize pharmacological and non-pharmacological therapies with the dual goals of reducing symptoms and preventing AECOPD.

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Editorial independence

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Disclosures

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Appendix 1

A) Search strategy

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce symptom burden (notably dyspnea and exercise intolerance), increase physical activity and improve health status?

PICO elements

Population	Intervention (s)	Comparator	Outcomes
Adults with stable COPD*, chronic bronchitis, emphysema	Maintenance inhaled therapy, alone or in combination: short-acting anticholinergic, short-acting beta-agonists, long-acting bronchodilators, long-acting beta-agonists, long-acting anticholinergic, long-acting muscarinic antagonists, inhaled corticosteroids, dual long-acting bronchodilators, combination ICS/LABA, triple therapy; oral therapy, alone or in combination(s): methylxanthines, theophylline, antibiotics, n-acetylcysteine, PDE-4 inhibitors, Roflumilast.	Placebo, combination therapies compared to single modality, head-to-head comparison	Dyspnea, exercise, exercise tolerance, exercise capacity, health-related quality of life

Search Terms

acute exacerbations, COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive), chronic disease management, prevention, nonpharmacologic therapies, education, self-management, case management, action plans, in-home monitoring, tele-intervention, telehealth, tele-health, E-health, e-health, tele-healthcare, telecare, telemedicine, tele-monitoring, E-medicine, telecommunications and medicine, tele-consult, respiratory rehabilitation pulmonary rehabilitation, (exercise, exercise training, activity, physical activity, exercise movement techniques, muscle training, kinesiotherapy, strength, training, walking, ambulation, mobilization, mobility, fitness exercise)—only if exercise is included, immunizations, vaccination, influenza prevention, pneumococcal prevention, smoking cessation

PICO 2: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of AECOPD?

PICO Elements

Population	Intervention (s)	Comparator	Outcome
Adults with stable COPD,* chronic bronchitis, emphysema	Maintenance inhaled therapy, alone or in combination: short-acting anticholinergic, short-acting beta-agonists, long-acting bronchodilators, long-acting beta-agonists, long-acting anticholinergic, long-acting muscarinic antagonists, inhaled corticosteroids, dual long-acting bronchodilators, combination ICS/LABA, triple therapy; oral therapy, alone or in combination(s): methylxanthines, theophylline, antibiotics, n-acetylcysteine, PDE-4 inhibitors, Roflumilast.	Placebo, combination therapies compared to single modality, head-to-head comparison	Exacerbations requiring change in medication (antibiotic and/or prednisone), ER and hospital admissions/readmissions, time to first exacerbation, exacerbation rate

Search Terms

acute exacerbations, COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive), chronic disease management, prevention, inhaled therapy, long acting beta agonists, long acting anticholinergics, short-acting anticholinergics, inhaled corticosteroids

Inclusion/Exclusion Criteria (PICO 1)

English language studies, studies will be included based on population, intervention, comparison and outcome defined above. Include studies with follow-up duration of 3 months or greater and studies with follow-up duration of 6 months or greater. Primary and secondary outcomes will be included. If studies are included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes will be carefully examined and the body of evidence will be downgraded for risk of bias, if deemed necessary.

Inclusion/Exclusion Criteria (PICO 2)

English language studies, studies will be included based on population, intervention, comparison and outcome defined above. Include studies with follow-up duration of 3 months or greater and studies with follow-up duration of 6 months or greater. Primary and secondary outcomes will be included. If studies are included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes will be carefully examined and the body of evidence will be downgraded for risk of bias, if deemed necessary.

Abbreviations: PICO, Patient/population - Intervention or interventions - Comparison groups - Outcome or outcomes of interest; COPD, chronic obstructive pulmonary disease; ICS/LABA, inhaled corticosteroid/long-acting beta agonists; AECOPD, acute exacerbation of COPD; ER, emergency room. Databases searched for both PICOs: MEDLINE (OVID), Embase (OVID), Cochrane Library, PubMed and National Guideline Clearinghouse.
*Patients are considered to have "stable COPD" in all clinical states other than during the period of an AECOPD.

B) Flow chart of search results: PRISMA diagram
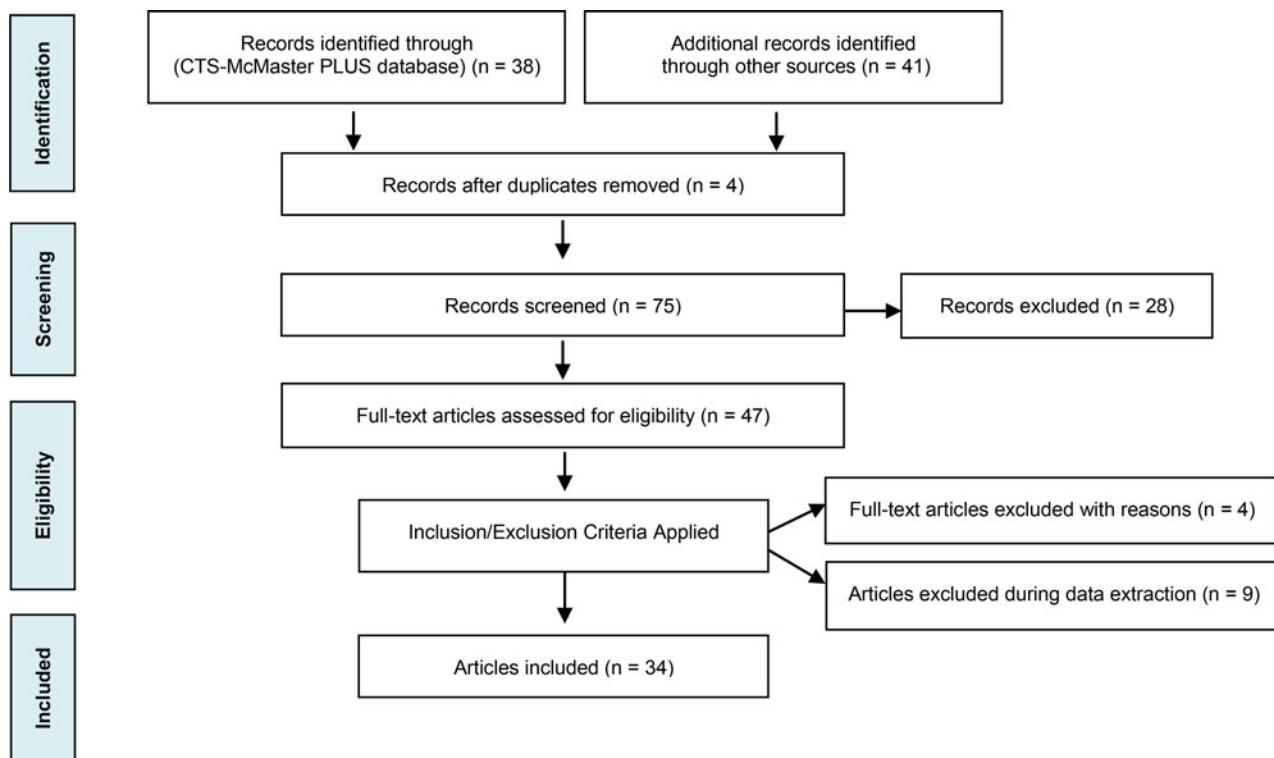
Literature search — March 1, 2017 to August 31, 2018 (CTS/McMaster Plus database under each topic area) with selected relevant manuscripts included with publication dates up to October 31, 2018

Reference: Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement; 2009. PLoS Med. 6(7): e1000097. www.prisma-statement.org.

C) Strength of the recommendations grading system

Grade of Recommendation		Benefit vs. Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	1A	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations, or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	1B	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence	1C	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect, and may well change the estimate.
Weak recommendation, high-quality evidence	2A	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations, or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	2B	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect, and may change the estimate.
Weak recommendation, low- or very-low-quality evidence	2C	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect, and may well change the estimate.

Reference: Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines report from an American College of Chest Physicians task force. *Chest.* 2006;129(1):174–181.

D) Voting scales for assessing consensus on draft recommendations

First round of voting	1. Wholeheartedly agree 2. Agree 3. Can support 4. Reservations: would like more discussion 5. Serious concerns: needs more discussion 6. Cannot participate: block it
Second round of voting	1. Agree 2. Can support 3. Cannot support: block it

Appendix 2: Summary of updates by section/recommendation

RECOMMENDATIONS — Improving Symptom, Exercise Tolerance and Health Status in Stable COPD

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce symptom burden (notably dyspnea and exercise intolerance), increase physical activity, and improve health status?

2017	2019		
Rec 1 – We *recommend* the use of an inhaled long-acting bronchodilator, either LAMA or LABA monotherapy, to reduce dyspnea, improve exercise tolerance and improve health status in stable COPD patients. (Grade 1A)	We **recommend** an inhaled long-acting bronchodilator, either LAMA or LABA monotherapy, to reduce dyspnea, improve exercise tolerance, and improve health status. *Clinical remark: LAMA is preferred over LABA therapy to prevent AECOPD (see PICO 2).*	**GRADE 1A** unchanged	• Recommendation not updated • New clinical remark
Rec 2 – We *suggest* that in stable COPD patients who experience persistent dyspnea, exercise intolerance, and/or poor health status despite use of inhaled LAMA or LABA monotherapy that they are considered for treatment "*step up*" with LAMA plus LABA dual therapy. (Grade 2A)	We **recommend** an inhaled LAMA/LABA dual therapy in patients who experience persistent dyspnea, exercise intolerance, and/or poor health status despite the use of LAMA or LABA monotherapy. *Clinical remark: Shortness of breath and exercise tolerance improve with LAMA/LABA dual therapy over monotherapy; health status has not been addressed as a primary outcome.*	**GRADE 1A** From 2A	• **Recommendation updated** • New clinical remark
Rec 3 – We *suggest* the use of a treatment with an inhaled long-acting bronchodilator, i.e., LAMA, LABA or LAMA plus LABA dual therapy, to improve physical activity levels in stable COPD patients. (Grade 2A)	We **suggest** an inhaled long-acting bronchodilator, i.e., LAMA, LABA, or LAMA/LABA dual therapy, to increase physical activity. *Clinical remark: A long-acting bronchodilator may improve exercise capacity but not improve physical activity unless a behavioral intervention is offered as well.*	**GRADE 2A** unchanged	• Recommendation not updated • New clinical remark
Rec 4 – We *suggest* in stable COPD patients without ACO who have persistently poor health status despite the regular use of a LABA, to "*step up*" therapy to an inhaled LAMA plus LABA dual therapy rather than to inhaled ICS/LABA combination. (Grade 2B)	We **suggest** LAMA/LABA dual therapy rather than ICS/LABA dual therapy in COPD patients who have persistently poor health status despite the use of maintenance LABA. *Clinical remark: ICS/LABA should be preferred to LAMA/LABA only in COPD patients with concomitant asthma.*	**GRADE 2A** From 2B	• Recommendation not updated
Rec 5 – There is *insufficient evidence* in stable COPD patients to determine whether inhaled LAMA plus ICS/LABA triple therapy confers additional benefit to inhaled LAMA plus LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels, or improving health status. However, in stable COPD patients with high symptom burden and poor health status despite the use of inhaled LAMA plus LABA dual therapy, "*step up*" of treatment to LAMA plus ICS/LABA triple therapy may be considered. (Consensus-based).	We **suggest** LAMA/LABA/ICS triple therapy in COPD patients with persistent dyspnea and poor health status in the last year despite the use of inhaled LAMA/LABA dual therapy. Clinical remark: Dyspnea and exacerbation are often present in the same patient.	**GRADE 2A** From consensus-based	• **Recommendation updated**
Rec 6 – There is *insufficient evidence* in stable COPD patients to determine whether treatment "*step down*," i.e., inhaled triple therapy to inhaled LAMA plus LABA dual therapy or inhaled LAMA plus LABA dual therapy to LAMA or LABA monotherapy can be safe and/or without reducing patient benefits (i.e., dyspnea, exercise tolerance and health status). However, in stable COPD patients with no improvement of dyspnea, exercise tolerance or health status despite the use of triple inhaled therapy or inhaled LAMA plus LABA dual therapy, treatment "*step down*" may be considered (Consensus-based).	In stable COPD patients with no improvement in dyspnea, exercise tolerance or health status, despite the use of LAMA/LABA/ICS triple therapy or LAMA/LABA dual therapy, treatment "step down" may be considered. There is *insufficient evidence* to determine whether "step down" (LAMA/LABA/ICS triple therapy to LAMA/LABA dual therapy, or LAMA/LABA dual therapy to LAMA or LABA monotherapy) is safe and/or reduces patient benefit. *Clinical remark: Withdrawing ICS may lower health status and lung function in some patients. Do not undertake "step down" in patients at high risk of AECOPD (see PICO 2).*	**Consensus-based** unchanged	• **Recommendation revised** • New clinical remark
Rec 7 – There is *insufficient or equivocal evidence* in stable COPD patients to determine whether the addition of an oral therapy, such as theophyllines, phosphodiesterase-4-inhibitors, mucolytics, statins, anabolic steroids, oral Chinese herbal medicines or phosphodiesterase-5-inhibitors, confers additional benefit to inhaled LAMA or LABA monotherapy, or LAMA plus LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels or improving health status. (Grade 2C).	There is *insufficient or equivocal evidence* to determine whether the addition of an oral therapy, such as theophyllines, phosphodiesterase-4-inhibitors, mucolytics, statins, anabolic steroids, oral Chinese herbal medicines or phosphodiesterase-5-inhibitors confers additional benefit to LAMA or LABA monotherapy, or LAMA/LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels and/or improving health status.	**GRADE 2C** unchanged	• Recommendation not updated

(continued)

2017	2019	Consensus-based	
Rec 8 - We *recommend* against treatment with ICS monotherapy in stable COPD patients. (Consensus-based)	We *recommend* against treatment with ICS monotherapy in stable COPD patients. **Clinical remark:** *When indicated, ICS should ideally be administered in a combination therapy in COPD patients.*	Consensus-based unchanged	• Recommendation not updated • New clinical remark

RECOMMENDATIONS – Preventing acute exacerbation in stable COPD

PICO 2. How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of AECOPD?

2017	2019	Consensus-based	
Rec 1 - We *recommend* the use of an inhaled LAMA (Grade 1A) or an inhaled LABA (Grade 1B) compared with placebo (i.e., SABD prn) to prevent AECOPD.	We *recommend* either LAMA or LABA monotherapy over a SABD prn. **Clinical remark:** *This is applicable to a patient at low risk of AECOPD.*	GRADE 1A From 1B (for LABA only)	• Recommendation not updated
Rec 2 - We *recommend* the use of an inhaled LAMA as a preferred choice compared with an inhaled LABA to prevent AECOPD (Grade 1B).	We *recommend* LAMA monotherapy over LABA monotherapy. **Clinical remark:** *This is applicable to a patient at low risk of AECOPD.*	GRADE 1A From 1B	• Recommendation not updated
Rec 3 - We *recommend* an inhaled LAMA (Grade 1A) or *suggest* an inhaled LABA (Grade 2C) compared with an inhaled short-acting muscarinic antagonist to prevent AECOPD.	We *recommend* LAMA monotherapy over SAMA. AND We *suggest* LABA monotherapy over a SAMA. **Clinical remark:** *This is applicable to a patient at low risk of AECOPD.*	GRADE 1A unchanged GRADE 2C unchanged	• Recommendation not updated
Rec 4 - We *recommend* inhaled LAMA plus LABA dual therapy for patients experiencing AECOPD despite the use of inhaled LAMA or LABA monotherapy (Grade 1C).	We *recommend* LAMA/LABA dual therapy for patients experiencing AECOPD despite use of LAMA or LABA monotherapy.	GRADE 1B From 1C	• Recommendation not updated
Rec 5 - We *recommend* combination ICS/LABA compared to placebo (Grade 1B) or an inhaled LABA (Grade 1C) to prevent AECOPD.	We *recommend* ICS/LABA dual therapy over SABD prn to prevent AECOPD in patients at high risk of AECOPD. AND We *recommend* ICS/LABA dual therapy over LABA monotherapy to prevent AECOPD in patients at high risk of AECOPD.	GRADE 1A From 1B GRADE 1A From 1C	• Recommendation updated
Rec 6 - We *recommend* inhaled LAMA plus LABA dual therapy as a preferred choice compared with ICS/LABA combination therapy to prevent AECOPD (Grade 1C).	We *recommend* either LAMA/LABA or ICS/LABA dual therapy for patients at high risk of AECOPD.	GRADE 1B From 1C	• Recommendation updated
Rec 7 - We *recommend* LAMA plus LABA/ICS triple therapy to prevent AECOPD for patients experiencing AECOPD despite the use of inhaled LAMA (Grade 1B) or ICS/LABA (Grade 1C).	We *recommend* LAMA/LABA/ICS triple therapy for patients at high risk of AECOPD despite the use of LAMA monotherapy or dual therapy (ICS/LABA or LAMA/LABA).	GRADE 1A From 1C	• Recommendation updated
Rec 8 - We *recommend* the use of oral Roflumilast to prevent AECOPD for patients with chronic bronchitis and a history of at least one exacerbation in the previous year despite long-acting inhaled therapy (Grade 1B).	We *recommend* oral Roflumilast for patients with chronic bronchitis and a high risk of AECOPD despite optimal long-acting inhaled therapy.	GRADE 1A From 1B	• Recommendation not updated
Rec 9 - We *suggest* treatment with oral N-acetylcysteine (600 mg po BID) to prevent AECOPD for patients with chronic bronchitis, a history of at least one exacerbation in the previous year, and on long-acting inhaled therapy (Grade 2B).	We *recommend* oral N-acetylcysteine (600 mg po BID) for patients with chronic bronchitis and a high risk of AECOPD despite optimal long-acting inhaled therapy.	GRADE 1B From 2B	• Recommendation updated
Rec 10 - We *suggest* a macrolide as maintenance therapy to prevent AECOPD for patients with a history of recurrent moderate or severe COPD exacerbations in the previous year despite long-acting inhaled therapy (Grade 2A).	We *suggest* macrolide maintenance therapy for patients with a high risk of AECOPD despite optimal long-acting inhaled therapy. **Clinical remark:** *Weigh the benefits against the risks of potential microbial resistance, hearing impairment and QT-prolonging drug interactions.*	GRADE 2A unchanged	• Recommendation not updated • New clinical remark
Rec 11 - We *suggest* treatment with oral slow-release theophylline to prevent AECOPD for patients on long-acting inhaled therapy (Grade 2B).	We *suggest* that oral slow-release theophylline **should not be used**, as it does not prevent AECOPD in patients on optimal long-acting inhaled therapy.	GRADE 2B unchanged	• Recommendation updated

Abbreviations: PICO, Patient/population - Intervention or interventions - Comparison groups - Outcome or outcomes of interest; COPD, chronic obstructive pulmonary disease; ICS/LABA, inhaled corticosteroid/long-acting beta agonists; AECOPD, acute exacerbation of COPD; LAMA, long-acting muscarinic antagonists; SABD, SABD prn, short-acting bronchodilator as needed; SAMA, short-acting muscarinic antagonists; BID, bis in die (twice a day).