

# The Role of Bronchodilators in Preventing Exacerbations of Chronic Obstructive Pulmonary Disease

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Bronchodilators are the cornerstone of symptomatic chronic obstructive pulmonary disease (COPD) treatment. They are routinely recommended for symptom reduction, with a preference of long-acting over short-acting drugs. Bronchodilators are classified into two classes based on distinct modes of action, i.e., long-acting antimuscarinics (LAMA, once-daily and twice-daily), and long-acting  $\beta$ 2-agonists (LABA, once-daily and twice-daily). In contrast to asthma management, evidence supports the efficacy of both classes of long-acting bronchodilators as monotherapy in preventing COPD exacerbations, with greater efficacy of LAMA drugs versus LABAs. Several novel LAMA/LABA fixed dose combination inhalers are currently approved for COPD maintenance treatment. These agents show superior symptom control to monotherapies, and some of these combinations have also demonstrated superior efficacy in exacerbation prevention versus monotherapies, or combinations of inhaled corticosteroids plus LABA. This review summarizes the current data on clinical effectiveness of bronchodilators alone or in combination to prevent exacerbations of COPD.

**Keywords:** Pulmonary Disease, Chronic Obstructive; Therapy; Bronchodilators

## Exacerbations and Bronchodilator Therapy

The term chronic obstructive pulmonary disease (COPD) has been established as an umbrella term to label a clinical syndrome characterized by chronic, poorly reversible airflow obstruction, airway inflammation in the presence of chronic bronchitis and/or pulmonary emphysema<sup>1</sup>. It is, however,

increasingly recognized, that distinct COPD phenotypes exist, and these may be prone to a more personalized, “targetted” management approach<sup>2</sup>. In this regard, a “frequent exacerbator” phenotype has been identified, and exacerbation risk is now used to classify COPD patients according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy paper (GOLD groups C and D, subjects with a history of 2 moderate, or one severe hospitalized exacerbation in the past years)<sup>1</sup>.

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Exacerbations are considered key events in the clinical course of COPD, and the prevention of exacerbations is highlighted as a pivotal therapeutic goal and relevant outcome measure by current treatment strategies or guidelines. While these events are somehow associated with the severity of COPD, the distribution of exacerbations in COPD is not uniform, with seasonal or temporal clustering<sup>3,4</sup>, in particular in a subset of COPD patients at high risk for exacerbations, where the individual history of prior exacerbations is the strongest single predictor of future events<sup>5</sup>.

Current strategies recommend long-acting bronchodilators as first line maintenance therapy for symptomatic COPD<sup>1</sup>. Long-acting bronchodilators produce consistent improvements in lung function and patient-centred outcomes,

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including airflow (forced expiratory volume in 1 second), hyperinflation (inspiratory capacity or functional residual capacity), symptomatic control of dyspnea, health-related quality of life, exercise capacity, prevention of exacerbations, and, potentially, mortality in subsets of patients<sup>1,6,7</sup>. To achieve bronchodilation, two classes of drugs are currently available, namely long-acting muscarinic antagonists (LAMA), and long-acting  $\beta$ 2-agonists (LABA). Both classes of agents have been demonstrated to be clinically effective, with acceptable safety profiles<sup>7</sup>. Importantly, the combined use of two bronchodilators with different mechanism of action is considered an effective strategy to optimize bronchodilation in COPD, and there is now ample evidence for the improved clinical efficacy of fixed combinations of long-acting bronchodilators versus monotherapies or inhaled corticosteroid (ICS)/LABA combinations, in particular with regards to functional and symptomatic outcomes<sup>8-11</sup>. Importantly, in COPD, bronchodilators can also effectively prevent exacerbations of the disease, as single agents or in combinations. The potential mechanisms, by which bronchodilators may prevent exacerbations have been under discussion. These may include direct effects on airflow, reduced hyperinflation, thus leading to improved respiratory mechanics and increased thresholds for development of symptoms, but also indirect mechanisms (improved secretion clearance through better airway patency) and anti-inflammatory properties of bronchodilators (reduced sputum production, cytokine release) have been proposed (Figure 1). An in-depth review on this topic was published by Wedzicha et al.<sup>12</sup>.

This review will discuss the available evidence of the clinical effectiveness of long-acting bronchodilators to prevent COPD exacerbations. As ICS have also demonstrated efficacy in decreasing exacerbations<sup>13</sup>, an important question that is now being addressed in many clinical trials is which combinations of these agents have the greatest benefit for decreasing exacerbations.

## LABA: Salmeterol, Formoterol, Indacaterol, and Olodaterol

Available LABAs for the maintenance treatment of COPD include twice-daily drugs with approx. Twelve hours duration of action (formoterol [FOR] and salmeterol [SAL]), and once-daily drugs with 24 hour bronchodilator effect (indacaterol [IND] and olodaterol [OLO]). Recent meta-analyses on the preventive effect of the older drugs SAL and FOR confirm some clinical benefits of these drugs on exacerbations, although results from single studies are conflicting<sup>7,14</sup>. It must be considered that most of the studies with data on exacerbations with twice-daily LABAs were not powered to show an effect on exacerbation prevention as primary study endpoint. The largest body of evidence has been generated with SAL, often in the context of the pivotal trials that led to approval of the ICS/LABA combination fluticasone/salmeterol (FLU/SAL), where SAL monotherapy was used as active comparator. In the Towards a Revolution in COPD Healthcare (TORCH) long-term trial, SAL twice-daily over 3 years in 6,112 COPD patients led to a significant reduction of the overall annualized exacerbation rate, the number of exacerbations requiring systemic corticosteroids and/or hospitalization versus placebo<sup>15</sup>.

In contrast, during a one year trial in 812 patients with budesonide/formoterol with FOR monotherapy as control arm, FOR 12  $\mu$ g twice-daily did not reduce moderate or severe exacerbations versus placebo<sup>16</sup>.

IND, a once-daily LABA approved at doses of 75 (United States), 150 or 300  $\mu$ g (Europe and Asia) was shown to reduce moderate-to-severe exacerbations in studies over at least 6 months duration versus placebo, in a *post-hoc* analysis of randomized trials in 2,716 moderate-to-severe COPD patients. Indacaterol at doses of 150 and 300  $\mu$ g significantly reduced the COPD exacerbation rates compared with placebo by 31% and 29%, respectively (both  $p=0.002$ ), and also significantly prolonged the time to first moderate-to-severe exacerbation

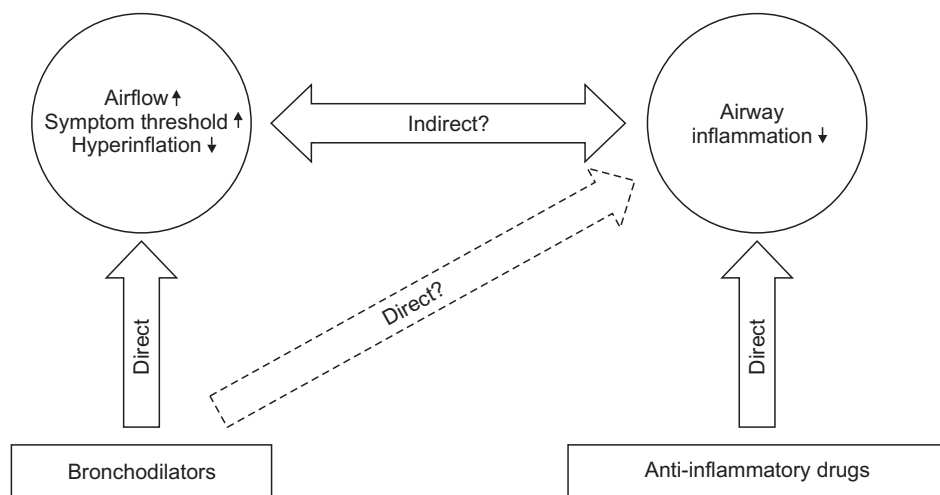


Figure 1. Potential mechanisms of chronic obstructive pulmonary disease exacerbation prevention.

versus placebo<sup>17</sup>.

OLO is another once-daily LABA licensed for the maintenance treatment of COPD (approved dose 5 µg, once-daily). In phase III long-term trials over 48 weeks, clinical benefits in terms of lung function and symptomatic improvements comparable to other available LABAs were observed; however, exacerbation were collected only as safety endpoints, with no conclusive effect of OLO versus placebo or comparators<sup>18,19</sup>.

Finally, the once-daily LABA vilanterol (VI) is used as a partnering agent for the ICS/LABA combination fluticasone furoate/vilanterol (FF/VI) and the LAMA/LABA combination umeclidinium/vilanterol (UMEC/VI). In the large-scale "Study to Understand Mortality and Morbidity" (SUMMIT) randomized trial over a median study period of 1.8 years in 16,590 COPD patients<sup>20</sup>, VI monotherapy reduced the annual rate of moderate/severe exacerbations versus placebo (0.31 vs. 0.35,  $p=0.017$ ). However, VI is not licensed as a monotherapy for the maintenance therapy of COPD.

## LAMA: Tiotropium, Glycopyrronium, Umeclidinium, and Acclidinium

LAMAs are considered a first-line option for the long-term maintenance treatment of COPD. Of these, the richest body of evidence exists for tiotropium (TIO) once-daily (18 µg delivered via HandiHaler or 5 µg via Respimat Soft Mist Inhaler), with experience from clinical trials and everyday practice of >10 years. The preventive effect of TIO on exacerbations has been repeatedly and consistently demonstrated in well-controlled long-term trials. In particular, two studies with >1,000 patients were specifically designed to evaluate the effect of TIO versus placebo on moderate or severe, hospitalized exacerbations over 6 and 12 months treatment duration<sup>21,22</sup>. Both studies showed consistent reductions in the total number of exacerbations, the proportion of subjects experiencing at least one exacerbation, and prolongation of the time-to-first exacerbation. In the study by Niewoehner et al.<sup>22</sup>, there was also a trend towards reduction of hospitalized exacerbations with tiotropium versus placebo. Finally, in the long-term UPLIFT trial, TIO was superior to the control arm in a number of exacerbation outcomes<sup>23</sup>. Exacerbation prevention with tiotropium delivered by the Respimat was also shown to be non-inferior to the HandiHaler device in the large-scale TIOSPIR trial<sup>24</sup>.

In head-to-head comparator trials, TIO once-daily was superior to SAL twice-daily in all exacerbation-related outcomes<sup>25</sup>. The superiority of the LAMA TIO was further confirmed in a head-to-head trial versus the once-daily LABA IND, where TIO significantly prolonged the time to first moderate-to-severe exacerbation versus LABA<sup>26</sup>. Finally, in another head-to-head trial of TIO versus ICS/LABA, there was no difference between treatments in reducing the overall annual rate of

moderate-to-severe exacerbations<sup>27</sup>. Altogether, these results led to the recommendation of using the LAMA TIO as a first-line treatment also in subjects with a high risk for exacerbations (GOLD 2016 groups C and D).

More recently, additional LAMA drugs have been introduced into the COPD management options, including once-daily glycopyrronium (licensed as twice-daily drug in the United States), umeclidinium, and the twice-daily drug aclidinium.

In a 1-year phase III trial<sup>28</sup>, glycopyrronium 50 µg once-daily reduced the risk of a moderate-to-severe exacerbation in moderate-to-severe COPD patients by 34% versus placebo, an effect comparable in magnitude to the effect of tiotropium in the control arm (open label, 39% reduction vs. placebo).

For umeclidinium (62.5 µg once-daily), no data on exacerbation prevention have been reported this far. Effects on other clinical outcomes in studies over 3 to 6 months duration suggest comparable efficacy to other LAMAs, though<sup>29</sup>.

Exacerbations (diary or healthcare resource utilization defined) were evaluated as secondary outcome parameter in the 24-week randomized, placebo-controlled ATTAIN trial with twice-daily aclidinium (400 µg twice-daily)<sup>30</sup>. In this study, a 33% reduction in the overall exacerbation rate versus placebo was observed with aclidinium. Longer trials with exacerbations as primary endpoint, however, have not been performed. A recent systematic review performed by the German Institute for Quality and Efficiency in Healthcare (IQWiG) as part of the mandatory national value assessment procedure for novel drugs, using data from the aclidinium/formoterol fixed combination pivotal phase III trials, suggests there is some incremental benefit of aclidinium over formoterol twice-daily in preventing severe exacerbations<sup>31</sup>.

Altogether, the current evidence suggests, that LAMAs, in particular TIO, represent the most effective monotherapy to prevent exacerbations of COPD. Hence, the first-line recommendation of this class of bronchodilator as preferred option over LABAs for maintenance therapy in patients with high risk of exacerbations appears clearly justified.

## LABA Plus ICSs

Unlike in asthma, there is no recommendation for ICS monotherapy in COPD, based on their limited efficacy on relevant outcomes in COPD. ICS, however, may improve clinical effects observed with bronchodilator monotherapy alone, in particular when combined with LABAs. The primary domain of ICS/LABA in COPD is the prevention of exacerbations in high-risk patients with at least severe airflow limitation. Available ICS/LABA combinations include twice-daily FLU/SAL, budesonide/formoterol (BUD/FOR), beclomethasone/formoterol, and once-daily FF/VI. ICS/LABA combinations consistently reduce exacerbation rates in high-risk patients

versus placebo, although less consistently against monotherapies<sup>32,33</sup>. For example, in the TORCH trial, FLU/SAL reduced the rate of moderate/severe exacerbations versus placebo by 25%, versus SAL by 12%, while the rate of severe hospitalized exacerbations was not different from SAL monotherapy<sup>15</sup>. In the TRISTAN study, moderate/severe exacerbation rates, in contrast, were similar between ICS/LABA and LABA monotherapy<sup>34</sup>. Similar results have been seen with BUD/FOR versus LABA component alone. A more recent meta-analysis estimated the exacerbation reduction of ICS/LABA versus LABA alone by 17%, without demonstrable effect on hospitalized exacerbations<sup>32</sup>. As described earlier, an ICS/LABA combination was not superior to a LAMA alone in preventing exacerbations in the INSPIRE study<sup>27</sup>.

Since the year 2013, a once-daily ICS/LABA combination, FF/VI, has been approved for COPD. In two pivotal phase III studies, the combination of FF/VI reduced exacerbation rates versus VI alone in one study, while the other study did not show any difference<sup>35</sup>. More recently, in the SUMMIT study<sup>20</sup> a numerical reduction of exacerbations with FF/VI versus VI alone was seen (0.25 vs. 0.31, no formal statistical comparison was reported), but this study included COPD patients with a low exacerbation risk (GOLD B). In line with other studies, the occurrence of pneumonia was increased with ICS/LABA combination therapy versus LABA alone<sup>35</sup>.

## Novel Developments: Dual LABA/LAMA Fixed Combinations

It has been known for decades, that in COPD a combination of bronchodilator drugs with different mode of action provides better lung function improvements and clinical outcomes than one drug alone<sup>36</sup>. The first study specifically designed to evaluate the impact of combined bronchodilator therapy on exacerbations was published in 2007<sup>37</sup>. In this study, an accepted definition for an exacerbation was used, the study duration was appropriate (52 weeks), and exacerbations were the primary endpoint. Over the study period of 1 year, no difference in the incidence of exacerbation was observed for tiotropium vs tiotropium plus SAL or SAL/FLU (62.8% of

patients vs. 64.8% and 60.0%, respectively). In addition, the time to first exacerbation was not different between treatment arms. However, the study was limited by a high dropout rate, therefore further studies evaluating the benefits of dual bronchodilator therapy versus single agents in carefully selected patient groups were required.

With the advent of long-acting bronchodilator drugs, several novel LAMA/LABA fixed combinations have been approved for COPD maintenance treatment (Table 1). These include once-daily options glycopyrronium/indacaterol (GP/IND), tiotropium/olodaterol (TIO/OLO), UMEC/VI, and finally, twice-daily aclidinium/formoterol (ACL/FOR). Consistently, these combinations provide superior lung function improvements versus bronchodilator monotherapies and ICS/LABA combinations, while also improving patient-related outcomes like dyspnea or quality of life in most controlled trials<sup>8-11,38</sup>. Given the excellent efficacy of LAMA monotherapy in preventing exacerbations, it was tempting to speculate on whether these novel dual combinations with superior, at times so far unseen, bronchodilator efficacy would also lead to further improvements in exacerbation prevention, in particular as—on average—exacerbation frequency increases with airflow obstruction, and a reasonable correlation of the magnitude of hyperinflation with exacerbation occurrence have been observed. Indeed, this question has now been addressed in a few controlled clinical trials with LAMA/LABA combination therapy versus active controls, using exacerbations as key outcomes.

Firstly, the SPARK Study evaluated the effect of 1-year treatment with once-daily GP/IND (50/110 µg) on the annual rate of moderate/severe exacerbations in 2,224 severe to very severe COPD patients with a history of at least one moderate exacerbation in the years prior to study entry (GOLD groups C and D), using LAMA monotherapy (GP 50 µg once-daily, open-label TIO 18 µg once-daily) as active control<sup>39</sup>. For all exacerbations (mild, moderate, and severe), GP/IND reduced the annual exacerbation rate by 15% and 14% versus GP and TIO, respectively (p=0.001 and p<0.01). Regarding the primary endpoint (moderate/severe exacerbations), GP/IND significantly reduced these events versus GP alone by 12% (p<0.05), while a nonsignificant reduction by 10% was seen versus open

**Table 1.** Overview of dual LAMA/LABA fixed combination currently approved

Drug	Company	Dosage/Regimen
Glycopyrronium/Indacaterol	Novartis	43/85 µg once-daily (EU, Japan) 15.6/27.5 µg twice-daily (USA) via SDDPI
Umeclidinium/Vilanterol	GSK	62.5/25 µg once-daily via MDDPI
Tiotropium/Olodaterol	Boehringer Ingelheim	5/5 µg once-daily via Soft Mist Inhaler
Aclidinium/Formoterol	AstraZeneca	340/12 µg twice-daily via MDDPI

LAMA: long-acting antimuscarinics; LABA: long-acting β<sub>2</sub>-agonists; SDDPI: single dose dry powder inhaler; MDDPI: multi dose dry powder inhaler.

label TIO ( $p=0.09$ ). IND/GP also improved health-related quality of life (St. George's Respiratory Questionnaire) significantly versus both controls.

In the pivotal phase III TONADO replicate 1-year trials comparing TIO/OLO fixed combination (5/5  $\mu\text{g}$  once-daily via Respimat) versus single components, the occurrence of exacerbations was lowest in the TIO/OLO combination group as compared to the monotherapy comparators<sup>8</sup>. However, numerical trends were observed only, and TONADO trials were no dedicated exacerbations trials. Nonetheless, given these encouraging results, the comparative efficacy of TIO/OLO over TIO monotherapy is currently evaluated in a large, long-term study using various exacerbation outcomes as primary endpoints (DYNAGITO; Clinicaltrial.gov identifier: NCT02296138). Hopefully, this study will shed more light on the potential superior efficacy of dual bronchodilation to prevent exacerbations versus the current "gold standard," TIO.

Recently, results from a head-to-head comparator trial of GP/IND once-daily versus a twice-daily ICS/LABA combination (FLU/SAL) were reported (FLAME Study)<sup>10</sup>. The study aimed to demonstrate non-inferiority of the dual LAMA/LABA combination versus ICS/LABA in terms of the total annual exacerbation rate. While non-inferiority was demonstrated, the secondary analyses also proved superiority of the LAMA/LABA combination over ICS in reducing the rate of all (mild, moderate, and severe) and moderate/severe exacerbations. This was supported by superiority of several additional exacerbation endpoints (time-to-first mild, moderate, and severe exacerbation), as well as improvements in lung function and health status. The FLAME study therefore for the first time demonstrated superiority of a "pure" bronchodilator approach versus a regime containing an anti-inflammatory component to prevent exacerbations in high-risk subjects with COPD. Strikingly, the superior effect of the dual bronchodilation approach was independent of the baseline level of blood eosinophils, a biomarker that has recently been suggested to suit as a guidance to identify COPD patients with responsiveness to

the exacerbation prevention effect of ICS<sup>11</sup>.

For both UMEC/VI and ACL/FOR, no dedicated exacerbations studies have been performed. For ACL/FOR, some subgroup analyses suggest a benefit of ACL/FOR versus FOR monotherapy in preventing exacerbations (IQWIG)<sup>12</sup>, however these effects require confirmation in longer-term studies.

## Summary

Bronchodilators are the cornerstone COPD management. They are recommended on a regular basis to prevent or reduce symptoms, improve health status and exercise tolerance. Importantly, long-acting bronchodilators also prevent the occurrence of exacerbations, with superior efficacy of LAMA over LABA in head-to-head trials. With two classes of bronchodilators with distinct, yet complementary mode of action available (LAMA and LABA), either class of drug can be given alone or in combination, the latter is now possible in form of fixed drug combinations. Currently, the role of LAMA/LABA dual bronchodilator drugs is seen as alternative options in more severely symptomatic patients, not necessarily with a background or risk of exacerbations (Table 2). However, given the superior clinical efficacy in improving lung function and symptoms versus monotherapies, this view will likely change in the near future. Importantly, recent large scale trials indicate the superiority of a pure dual bronchodilator approach over LAMA monotherapy and ICS/LABA combinations also in high-risk exacerbators (COPD GOLD groups C and D), challenging our current clinical practice to optimally prevent exacerbations in these patients. In the future, development of "triple therapies" (ICS/LAMA/LABA) will help to clarify a potential role of ICS when added to "optimal" bronchodilator background.

**Table 2. GOLD 2016: pharmacologic therapy for stable COPD**

Patient	Recommended No. 1. choice	Alternative choice	Other possible treatment
A	SAMA or SABA	LAMA or LABA or SABA+SAMA	Theophyllin
B	LAMA or LABA	LAMA+LABA	SABA and/or SAMA, theophyllin
C	Inhaled corticosteroid+LABA or LAMA	LAMA+LABA or LAMA+PDE-4-inhibitor or LABA+PDE-4-inhibitor	SABA and/or SAMA, theophyllin
D	Inhaled corticosteroid+LABA and/or LAMA	Inhaled corticosteroid+LAMA+LABA or inhaled corticosteroid+LABA+PDE-4-inhibitor or LAMA+LABA or LAMA+PDE-4-inhibitor	Carbocysterin, N-acetylcysteine, SABA and/or SAMA, theophyllin

Adopted from Global Initiative for Chronic Obstructive Lung Disease (2016)<sup>1</sup>, <http://www.goldcopd.org>.

GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; SAMA: short-acting antimuscarinic; SABA: short-acting beta-agonist; LAMA: long-acting antimuscarinics; LABA: long-acting  $\beta_2$ -agonists; PDE-4: phosphodiesterase 4.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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