

How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease?

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At-a-Glance Commentary

Results from multiple clinical trials have demonstrated that fixed combinations of long-acting β -adrenergic agonists (LABA) and long-acting muscarinic antagonists (LAMA) are significantly superior to their monocomponents and to the combination LABA and an inhaled corticosteroid in decreasing the frequency of exacerbations in patients with chronic obstructive pulmonary disease. At present, the mechanism(s) underlying this clinical benefit are not fully understood. This review considers potential mechanisms whereby LABA/LAMA combinations might exert additive or synergistic effects that lead to a decrease in exacerbations. Mechanisms considered include effects on lung hyperinflation and mechanical stress, inflammation, excessive mucus production with impaired mucociliary clearance, and symptom severity and variability.

Abstract

Decreasing the frequency and severity of exacerbations is one of the main goals of treatment for patients with chronic obstructive pulmonary disease (COPD). Several studies have documented that long-acting bronchodilators (LABDs) can reduce exacerbation rate and/or severity, and others have shown that combinations of long-acting β_2 -adrenergic agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) provide greater reductions in exacerbation frequency than either their monocomponents or LABA/inhaled corticosteroids (LABA/ICS) combinations in patients at low and high risk for these events. In this review, small groups of experts critically evaluated mechanisms potentially responsible for the increased benefit of LABA/LAMA combinations over single LABDs or LABA/ICS in decreasing exacerbation. These included effects on lung hyperinflation and mechanical stress, inflammation, excessive mucus production with impaired mucociliary clearance, and symptom severity. The data assembled and analyzed by each group were reviewed by all authors and combined into this manuscript. Available clinical results support the possibility that effects of LABA/LAMA combinations on hyperinflation, mucociliary clearance, and symptom severity may all contribute to decreasing exacerbations. While preclinical studies suggest LABAs and LAMAs have anti-inflammatory effects, such effects have not been demonstrated yet in patients with COPD.

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Introduction

Exacerbations are cardinal events in the lives of patients with COPD(1). Exacerbations accelerate the decline in pulmonary function (2), increase the risk for acute cardiovascular events (3), decrease health status (4, 5), impair activities of daily living (6, 7), and increase the risk for future hospital admissions for COPD exacerbations (8) and mortality (9). Accordingly, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations for the treatment of COPD patients have identified reducing the risk for exacerbations as one of the major goals of management for these individuals (10).

There are various risk factors for exacerbations including older age (11), presence and severity of symptoms (cough, sputum, and dyspnea) (4, 12), poor health status (4, 13), more severe airflow limitation (14), presence of hyperinflation (15), persistent pulmonary and systemic inflammation (16, 17), airway bacterial colonization (18), cardiovascular comorbidities (19, 20), and gastroesophageal reflux disease (21). However, the most important indicator of future exacerbation risk is the past exacerbation history (14).

Long-acting bronchodilators (LABDs) are central to the management of patients with COPD, and clinical trial results have repeatedly demonstrated the efficacy of these agents in decreasing the frequency and severity of exacerbations together with improvement in other clinically relevant endpoints (22-24). Inhaled corticosteroids (ICS) in combination with a LABA have also demonstrated efficacy in decreasing exacerbations and improving COPD symptoms (25).

Recently, the two classes of LABDs, long-acting β_2 -adrenergic agonists (LABAs) and long-acting

muscarinic antagonists (LAMAs), have been combined in single inhalers in an effort to improve lung function, symptoms, and clinical outcomes, including risk for exacerbations, in COPD (26, 27, 28). The combination of indacaterol and glycopyrronium has been shown to provide reductions in exacerbations greater than those achieved with a single long-acting bronchodilator (29) and to have significant superiority over the LABA/ICS combination in decreasing exacerbation risk (24, 30). Results from the 52-week FLAME study comparing indacaterol/glycopyrronium once daily vs the LABA/ICS combination of salmeterol/fluticasone showed that the LABA/LAMA combination was significantly superior to LABA/ICS in increasing the times to and decreasing the rates of all and moderate or severe exacerbations, and increasing the time to severe exacerbations (mild = worsening of symptoms for >2 consecutive days but not leading to treatment with systemic glucocorticoids or antibiotics; moderate = leading to treatment with systemic glucocorticoids, antibiotics, or both; severe = leading to hospital admission or a visit to the emergency department that lasted >24 hours in addition to treatment with systemic glucocorticoids, antibiotics, or both [31]) (29). The importance of accurate exacerbation detection was highlighted in this study that used electronic diaries to detect and flag exacerbations; this resulted to higher rates of reported exacerbations vs most previous studies, but the authors emphasized that this was unlikely to bias treatment comparisons. This view is supported by the fact that results for mild exacerbations (those most likely to be increased with the reporting method used) were matched by those for moderate or severe exacerbations (29). Other results have suggested that the superiority of indacaterol/glycopyrronium over LABA/ICS may not extend to all other LABA/LAMA combinations. Results from a 24-week comparison of aclidinium/formoterol vs

salmeterol/fluticasone in 933 patients with COPD indicated no significant between-treatment difference for exacerbation frequency (32).

The reason(s) for the superiority of LABA/LAMA over single LABDs and LABA/ICS in reducing exacerbation is not clear. Clinical studies have highlighted the additive effect of LABAs and LAMAs when they are administered together (33), and some preclinical studies provide some implications for potential synergistic effects (34, 35). Inhibition of M2 receptors enhances the actions of norepinephrine at β_2 receptors by interacting with adenylyl cyclase to raise intracellular cyclic adenosine monophosphate (cAMP) levels in airway smooth muscle cells and thus relax airway smooth muscle (35). Interestingly, this interaction only lasts for a few hours, which has led to speculation about the potential improvements in efficacy when a LABA and LAMA are administered together (36).

The aim of this narrative review is to summarize the evidence regarding the possible mechanisms underlying the ability of LABDs, and especially dual bronchodilation, to decrease the frequency of COPD exacerbations. The main mechanisms related to the reduction of exacerbations by LABDs explored in this review include the decrease in hyperinflation and mechanical stress, the modulation of mucus production and mucociliary clearance, the improvement of symptoms fluctuation and severity, and some potential direct and indirect anti-inflammatory properties (Figure 1).

Methodology used in the development of this review

The content of the manuscript was developed in the following way: 1) Small working groups comprised of three to four of the authors searched, reviewed, and interpreted the relevant literature for a given section of the manuscript (eg, hyperinflation) and developed the initial draft; 2) Sections were assembled using editorial support; 3) All portions of the manuscript were reviewed by each of the authors; and 4) The manuscript was revised and submitted. All authors agree on the content of the manuscript.

Improvement in static and dynamic hyperinflation

Hyperinflation is characterized by an increased volume of air remaining in the lungs at the end of tidal expiration, leading to increased resting functional residual capacity (FRC) (37).

Hyperinflation can either be static or dynamic. Static hyperinflation is present during tidal breathing and leads to changes in shape of the thorax (barrel-shaped chest wall), while dynamic hyperinflation results from rapid breathing, hyperventilation, and exercise. Most patients with COPD have some degree of hyperinflation (37), and there is a significant relationship between hyperinflation and dyspnea (38). Hyperinflation is also a better predictor of exercise capacity than FEV₁ in patients with COPD (39). Hyperinflation adversely affects cardiovascular and diaphragmatic function in patients with COPD, decreasing ventricular preload and venous return at rest and during exercise and increasing left ventricular afterload (40, 41).

Hyperinflation is also associated with increased mortality in patients with COPD (42).

Exacerbations are characterized by the occurrence or worsening of lung hyperinflation. Airway resistance is abruptly increased during exacerbations as a result of bronchospasm, mucosal edema, and decreased fluidity of sputum. These changes worsen expiratory flow limitation, prolong the time constant for lung emptying, and increase end expiratory lung volume (EELV). Patients also tend to adopt a rapid shallow breathing pattern during exacerbations. This further limits the time available for lung emptying and exacerbates dynamic hyperinflation (Figure 2A) (43, 44, 45). Recovery of dyspnea following acute exacerbations is associated with reduction in lung hyperinflation and increased expiratory flow rates (Figure 2B) (43). A mechanistic relationship between the reduction of hyperinflation and risk for exacerbations is supported by the decreased risk for exacerbations following lung volume reduction surgery (LVRS) (46). However, the changes in static lung volumes after LVRS did not predict reduction in exacerbation frequency (46), suggesting that other factors may contribute to this observation.

Administration of LABA/LAMA decreases hyperinflation (47). LAMAs reduce cholinergic tone resulting in improved airway conductance (48), whereas LABAs relax airway smooth muscle, improve small airway patency, and enhance lung deflation, as reflected by a reduction in end expiratory lung volume (ie, dynamic FRC) (49). Respiration at a lower FRC decreases the work of breathing while placing the respiratory muscles in a more efficient arrangement for pressure generation (50). Decreased work of breathing and better ventilatory pump performance in turn result in improved exercise tolerance and a reduction in dyspnea (15, 49). Results from clinical trials have demonstrated that the combination of a LABA and a LAMA is significantly superior to a single bronchodilator and to a LABA plus ICS in improving spirometry measures related to

hyperinflation. A comparison of indacaterol plus glycopyrronium vs indacaterol alone showed that the combination was significantly superior to monotherapy in increasing inspiratory capacity (IC) (51). A study of 46 patients with COPD showed that the combination of indacaterol and tiotropium was significantly superior to salmeterol and fluticasone in increasing IC (+298.9 vs 92.6 mL, $P=0.043$), but not FRC (-35.0 vs -23.3 mL, $P=0.199$) (52). The combination of formoterol and tiotropium has also been shown to be significantly superior to formoterol alone ($P=0.027$) in reducing EELV in a study of 33 patients with COPD (53). Indacaterol plus tiotropium has also been shown to be significantly superior to tiotropium monotherapy for improving IC ($P<0.05$ at all time points evaluated) in two studies that included a total of 2,276 patients with COPD (54).

Hyperinflation is partly reversible with administration of bronchodilators, resulting in symptom improvement, most notably reduced dyspnea (55, 56). Decreasing the work of breathing in stable COPD via appropriate long-acting bronchodilators (LABD) treatment may thus lead to a greater difference between “steady state” and the threshold work of breathing that results in reporting of an exacerbation. Deflation of hyperinflated lungs with LABDs brings the thoracic cage into a more favorable position with improved diaphragmatic function and prolonged time to respiratory muscle fatigue (57). Hyperinflation may also result in alveolar stress and release of inflammatory cytokines. This potential inflammatory effect might also be reduced by administration of effective long-acting bronchodilation (58). The improvement in lung mechanics, combined with the reduction in dyspnea and the potential reduction of mechanical

stress in the lungs, represents the main plausible mechanisms for the potential reduction of exacerbations through the reduction of lung hyperinflation by dual bronchodilation.

Reduction of mucus hypersecretion and improvement of mucociliary clearance

Chronic cough and sputum production are associated with decline in FEV₁ (59), increased risk for pulmonary infections (60), and elevated frequencies of exacerbations and hospitalizations (12). Overproduction and hypersecretion of mucus by airway epithelial goblet cells and by submucosal gland cells and decreased elimination of mucus are the primary mechanisms responsible for excessive mucus levels in COPD. A decreased number of ciliated cells lead to prolonged clearance times and airway mucus accumulation, and decreased mucociliary clearance is correlated with increased frequency of exacerbations in patients with COPD (61). Mucus accumulation in COPD patients has adverse effects on several important outcomes, such as lung function, health-related quality of life, exacerbations, hospitalizations, and mortality. Mucus plugging of small airways increases with COPD severity and is associated with decreased survival (62).

Impact of anticholinergic therapy on mucus secretion

Acetylcholine (ACh) induces mucus secretion predominantly via M3 receptors expressed on submucosal glands; and electrolytes and water secretion are regulated by muscarinic M1 and M3 receptors. It has also been shown that airway epithelial cells differentiate into goblet cells that produce mucus in response to ACh (63).

Results from experimental models have demonstrated that LAMAs decrease mucus production (64) and COPD patients treated with tiotropium have reported a subjective decrease in sputum production (65). MUC5AC is the predominant mucin gene expressed in human airway epithelial cells (66). The muscarinic agonist carbachol upregulates MUC5AC expression in these cells by activation of muscarinic receptors and transactivation of epidermal growth factor receptors (EGFR). Acclidinium has been shown to decrease this effect *in vitro* (67). Treatment with tiotropium has also been demonstrated to improve mucociliary clearance, as reflected by reduced nasal clearance time, in patients with COPD (68).

Impact of β_2 adrenoceptor agonist on mucociliary clearance

There is evidence of impaired mucociliary clearance in patients with COPD and this may be associated with depressed ciliary beating (69). Mucociliary clearance efficiency depends on the capacity of apical plasma membrane ion channels to maintain airway hydration, ciliary beating, and appropriate rates of mucin secretion (70). LABD treatment has been shown to improve mucociliary clearance in patients with COPD. In one study, 24 patients with mild-to-moderate COPD receiving formoterol were assessed with a radioaerosol technique to determine effects of treatment on mucus clearance. Results indicated that a single dose of formoterol significantly enhanced radioaerosol clearance (71). Treatment with salmeterol also has been shown to increase mucociliary clearance in patients with COPD (72).

Cough and sputum production (mucus in large airways) are related to exacerbations and the frequent exacerbator phenotype. There is good evidence from experimental models that

LAMAs decrease mucus production via blockade of ACh-induced EGFR activation. LABA exposure has been shown to increase ciliary beating *in vitro*, and there is some evidence that LABAs (but not LAMAs) increase mucociliary clearance in peripheral airways of COPD patients. However, there are no clinical data showing a relationship between decreased mucus hypersecretion and effects of LABDs on exacerbations and this represents a potential target for future studies.

Symptom severity

Symptoms per se are relevant in the natural history of COPD as demonstrated by results from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, which suggested that the presence of symptoms is associated with increased future risk, as GOLD groups B and C carry equally poor clinical outcomes though for different reasons (73). GOLD subgroup B, characterized by more severe dyspnea, had significantly poorer survival than group C, in spite of higher FEV₁ in a study of the general population in Copenhagen (74). This subgroup of patients warrants special attention, as the poor prognosis could be caused by cardiovascular disease or cancer, requiring additional assessment and treatment. Analysis of patients included in the Lung Health Study showed that the combination of cough and phlegm, but not either symptom alone, was associated with increased mortality risk over 12.5 years of follow-up (75). Higher overall symptom severity as measured by Chronic Obstructive Pulmonary Disease Assessment Test (CAT) scores is associated with increased risk for exacerbations (76). Dyspnea grade is also closely linked to risk for exacerbations (20), and severity of dyspnea is a significant predictor of mortality in patients with COPD (77). LABA/LAMA combinations have

been repeatedly shown to decrease symptom severity in patients with COPD; in the majority of studies, these reductions have been demonstrated to be significantly greater than those achieved with individual agents (78-80). However, it is not clear how improvement in symptoms with LABDs decreases the risk for exacerbations.

Symptom variability and exacerbations

Several studies have described fluctuations of COPD symptoms over the day, with morning considered the time when symptoms are more severe, whereas symptom severity has also been reported to vary over the course of weeks and months in patients with COPD (81). The COPD and Seretide: a Multi-Center Intervention and Characterization (COSMIC) Study evaluated the symptom diary cards of COPD patients and assessed symptom progression during the days prior to and after exacerbations (82). The perception of cough, sputum, dyspnea, and nocturnal awakenings steadily increased beginning 2 weeks prior to an exacerbation. Symptom variability did not change prior to the first and second moderate exacerbations; however, variability was substantial in the days before a hospital admission. Results from a second study suggested that patients who had 2 or more exacerbations in the previous year were more likely to experience variability in breathlessness over the course of a week (81). Donaldson et al. evaluated daily peak expiratory flow (PEF) variability using detrended fluctuation analysis (DFA) and showed that it is associated with exacerbation frequency in patients with COPD (83). In an additional analysis of PEF data from a double-blind study of tiotropium, the authors were able to show that PEF variability measured by DFA was responsive to treatment, ie it was lower in patients

receiving tiotropium compared to placebo, and may therefore serve as a surrogate marker of exacerbation frequency (83).

LABD, symptom severity, and exacerbations

In a pooled analysis of 23 studies of LABDs, the improvement in lung function, as expressed by improvement in trough FEV₁, was associated with significant improvements in patient-reported outcomes, including quality of life and dyspnea, and in exacerbations (84). Results from additional studies have demonstrated strong correlations between severity of dyspnea and hyperinflation in patients with COPD (Figure 3A) (85-87); and decreased dyspnea following LABD treatment is correlated with improvement in measures associated with hyperinflation, such as inspiratory capacity (IC) and tidal volume (Figure 3B) (88, 89).

The stabilization of the airway by effective long-acting bronchodilation may lead to a reduction of day-to-day variability of symptoms and this may lead to a reduction in the increased bursts of symptoms that may be reported as exacerbations. In Figure 4, we provide a schematic representation of potential mechanisms of symptom improvement at stable state and during the course of an exacerbation by treatment interventions. Dual bronchodilation may effectively lower both the baseline symptoms and the magnitude of symptoms during the exacerbation (Figure 4C).

In summary, symptoms contribute to the risk for exacerbations. The more effective improvement in symptoms by LABA/LAMA combinations compared to monocomponents and LABA/ICS may contribute to the decrease of exacerbations at the patient level.

Anti-inflammatory properties of long-acting bronchodilators

Results from multiple *in vitro* studies as well as those from experimental models of pulmonary disease have demonstrated anti-inflammatory effects of LABAs and LAMAs as well as additive effects of agents from these two classes. In contrast, limited data available from patients with COPD have not indicated significant anti-inflammatory effects of LABDs and it should be emphasized that the relationships between such findings and effects of LABD treatment on exacerbations in patients with COPD have not been established.

Modulation of inflammation by β_2 adrenoceptors and muscarinic receptors

Both β_2 adrenoceptors and muscarinic receptors may modulate inflammation. β_2 adrenoceptors are located not only on bronchial smooth muscle cells, epithelial cells, and pneumocytes, but also on multiple types of inflammatory cells (90). Stimulation of β_2 -adrenergic receptors is believed to exert largely inhibitory effects on cells of the immune system by increasing levels of cAMP and protein kinase A (91). Activation of β_2 adrenoceptors may also contribute to regulation of fluid transport (92) and may be important in the pathogenesis and/or resolution of acute lung injury.

M3 receptors are predominantly expressed in peripheral airways. Epithelial cells may release acetylcholine (ACh) in response to inflammatory stimuli, such as tumor necrosis factor (TNF)- α , contributing to locally regulated inflammation. In addition, inflammatory cells express muscarinic receptors, and anti-inflammatory effects of tiotropium may result from blockade of M3 receptors located on inflammatory cells (93). All five muscarinic cholinergic receptor subtypes (M1-M5) are expressed by dendritic cells, macrophages, T-cells, and B-cells (90, 94), and activation of M1 and M3 receptors may play an important role in the immune-responsivity of lymphocytes (95).

Direct anti-inflammatory effects of LABDs

Results from *in vitro* and *in vivo* experimental studies have demonstrated anti-inflammatory effects of LABDs (93, 94, 96, 97). Tiotropium reduces lipopolysaccharide-induced increases in neutrophils in a guinea pig model of COPD (96) and decreases TNF- α -mediated chemotaxis and reactive oxygen species release by alveolar macrophages isolated from patients with COPD (98). Tiotropium also attenuates the transforming growth factor (TGF)- β 1-mediated neutrophilic inflammation in induced sputum of patients with COPD and combined administration with olodaterol augments this effect (Figure 5) (99).

The combination of tiotropium and formoterol decreases human leukocyte antigen-antigen D-related (HLA-DR) expression on lymphocytes as well activated CD4+ CD25+ cells in sputum from patients with COPD (100). LABD treatment may also decrease oxidative stress (101). Tiotropium has also been shown to decrease the replication of respiratory syncytial virus (RSV) in epithelial

cells and may reduce production of inflammatory cytokines, suggesting a potential anti-inflammatory role on viral infections (102). It has also been shown that exposure to the combination of indacaterol and glycopyrronium resulted in greater decreases of interleukin (IL)-1 β -stimulated IL-8 production by fibroblasts and IL-1 β -stimulated IL-6 production from airway smooth muscle cells isolated from patients with COPD than either drug alone (103).

Activation of β_2 adrenoceptors inhibits inflammatory responses by neutrophils and mononuclear cells *in vitro* and in mouse models of lung inflammation *in vivo* (104).

Pretreatment with inhaled salmeterol inhibits lipopolysaccharide-induced neutrophil influx, neutrophil degranulation, TNF- α release, and HLA-DR expression in healthy subjects (105).

Potential indirect anti-inflammatory effect of LABD

The bronchial epithelium stretches and relaxes during the normal respiratory cycle, and both *in vitro* and *ex vivo* studies have demonstrated a marked effect of stretch on bronchial epithelial cell function, including production and release of inflammatory molecules (eg, IL-8 and TGF- β) (106). Mechanical stretch is also associated with increased mucus production by the airway epithelium (107). While data are not available for patients with COPD, the relation between mechanical factors and inflammation is supported by results from studies of patients with asthma, where compressive mechanical forces that arise during bronchoconstriction can induce airway remodeling without additional inflammation (108).

Clinical studies

In contrast to the above-mentioned pleiotropic anti-inflammatory effects of LABD *in vitro*, most clinical study results have not provided strong support for anti-inflammatory effects of LAMAs or LABAs. Results from one study of patients treated with tiotropium indicated no significant effects of this intervention on airway and systemic inflammation, including sputum IL-8 and serum C-reactive protein (CRP) and IL-6 (109). Similarly, administration of salmeterol had no significant effects on numbers of inflammatory cells in sputum samples or bronchial biopsies in patients with COPD (110). Future trials will need to explore whether anti-inflammatory effects of LABDs observed *in vitro* can be demonstrated in patients with COPD.

Potential differences in mechanisms underlying effects of LABD according to different types of exacerbations

At present, there is limited information about the benefits of LABDs in preventing different types of exacerbations or the influence of specific comorbidities on the efficacy of LABD treatment. Blood eosinophil counts have been proposed as a marker to define exacerbations that might typically need corticosteroid treatment. Bafadhel et al. evaluated subjects at presentation to hospital with an exacerbation of COPD and stratified them into eosinophilic exacerbations if the peripheral blood eosinophil count on admission was ≥ 200 cells/ μL and/or $\geq 2\%$ of the total leukocyte count; the observed detrimental effects of steroids in the group with low eosinophils suggested that eosinophils can be used for stratification of exacerbations (111).

The hypothesis that currently arises is whether the blood eosinophil count could be a marker that identifies patients in whom a certain treatment has greater efficiency in preventing exacerbations. Results from Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) study showed differences in treatment requirements for residual exacerbations in patients randomized to LABA/ICS vs LAMA alone (112). Over 2 years, the estimated overall rates of exacerbations did not differ between an ICS/LABA and a LAMA. However, exacerbations requiring antibiotics occurred more frequently in patients treated with LABA/ICS vs LAMA, while those requiring oral corticosteroids were significantly more common in patients treated with a LAMA vs those who received LABA/ICS (112).

This suggests potential differentiation in the mechanisms underlying exacerbation prevention between these two treatments. Post hoc analyses of studies comparing LABA/ICS and LABA have suggested that the presence of increased eosinophil counts is associated with better response to LABA/ICS (113, 114). In a prospective analysis of blood eosinophils the FLAME study, the superiority of LABA/LAMA combination of indacaterol/glycopyrronium vs ICS/LABA in the reduction of the rate of COPD exacerbations was independent of the baseline blood eosinophil count (24). Therefore, we still need to clearly define the role of biomarkers before establishing a therapeutic strategy that properly identifies patients who may benefit from this diagnostic approach.

LABA/LAMA vs triple combination therapy

While clinical trial results have demonstrated greater efficacy of LABA/LAMA combinations in decreasing the frequency of exacerbations, improving pulmonary function, and reducing symptom severity vs monocomponents and LABA/ICS, there is much less information about the efficacy of LABA/LAMA vs triple therapy (LABA/LAMA/ICS). Triple therapy has been shown to be significantly superior to LABA/ICS and LAMA monotherapy for improving pulmonary function and symptoms (115, 116). Results from the OPTIMAL study indicated no significant difference between tiotropium plus salmeterol and fluticasone vs tiotropium and salmeterol for the proportion of COPD patients experiencing exacerbations over 1 year of treatment (117). Triple therapy has been compared with LABA/ICS in TRILOGY, a randomized, parallel group, double-blind, active-controlled study in which 1,368 patients received either beclomethasone, formoterol, and glycopyrronium or beclomethasone and formoterol. Adjusted annual moderate-to-severe exacerbation frequencies were 0.41 for triple therapy and 0.53 for beclomethasone and formoterol, corresponding to a 23% reduction in exacerbations with triple therapy vs LABA/ICS (118). Other recent results have shown that the combination of umeclidinium, vilanterol, and fluticasone showed a reduction in the annual rate of moderate/severe exacerbations over 52 weeks of treatment compared to budesonide/formoterol (119). The ongoing IMPACT study, which began in 2014 and is expected to report out in 2017, compares the effects of umeclidinium, vilanterol, and fluticasone vs fluticasone plus vilanterol and umeclidinium plus vilanterol in reducing the rate of exacerbations (120). The ongoing TRIBUTE trial also compares LABA/LAMA (indacaterol/glycopyrronium) vs triple therapy (beclomethasone/formoterol/glycopyrronium) and is also expected to report out in 2017 (121).

These two studies should provide information on the clinically relevant question of the potential benefit of triple therapy vs LABA/LAMA in the reduction of exacerbations in COPD.

Conclusions

The rationale for LABA/LAMA treatment in patients with COPD is well established and includes complementary additive effects on airflow obstruction. LABA/LAMA combinations have been shown to be more effective than single bronchodilators or the combination of LABA/ICS in decreasing COPD exacerbations, and here we have discussed several mechanisms by which this could occur. LABDs decrease hyperinflation and symptom severity, improve sputum clearance by reducing mucus hypersecretion and increasing mucociliary clearance, and improve symptoms and reduce symptom variability by “stabilizing” the airways in patients with COPD. The potential anti-inflammatory actions of LABDs demonstrated *in vitro* and in experimental models have not been confirmed in patients with COPD. Future studies focus on the correlation of patient-level results for each of these actions, and effects of LABD treatment on risk for exacerbations may provide insights regarding which actions of single agents play significant roles in reduction of exacerbations. This may explain the overall improvement in exacerbation reduction by dual bronchodilation.

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Figure Legends

Figure 1. Mechanisms by which LABA/LAMA may decrease the frequency of exacerbations

*Anti-inflammatory mechanisms have been demonstrated *in vitro* and in animal models, but have not been demonstrated yet in patients with COPD

Figure 2. A. Schematic of mechanical effects of COPD exacerbation. Representative pressure-volume plots during stable COPD and during an exacerbation. During exacerbation, worsening expiratory flow limitation results in dynamic hyperinflation with increased end expiratory lung volume (EELV) and residual volume (RV). Corresponding reductions occur in inspiratory capacity (IC) and inspiratory reserve volume (IRV). Total lung capacity (TLC) is unchanged. As a result, tidal breathing becomes shifted rightward on the pressure-volume curve, closer to TLC. Mechanically, increased pressures must be generated to maintain tidal volume (VT). At EELV during exacerbation, intrapulmonary pressures do not return to zero, representing the development of intrinsic positive end expiratory pressure (PEEPi) which imposes increased inspiratory threshold loading (ITL) on the inspiratory muscles (inset); during the subsequent respiratory cycle, PEEPi must first be overcome in order to generate inspiratory flow.

B. Representative flow-volume loops from a patient before and after onset of symptoms compatible with exacerbation. During exacerbation, there is evidence of worsening EFL (arrow) resulting in hyperinflation with an increased EELV and reduced IC (15).

Figure 3. A. Relationship between severity of exertional dyspnea and IC at the end of 6-minute walk distance ($r = -0.49$, $P < 0.00001$). (88).

B. Relationship of changes in visual analogue scale (VAS) measurement of dyspnea with placebo correction (%) with changes in IC 30 minutes after bronchodilation in patients with baseline IC $< 80\%$ predicted (●: salbutamol; △: formoterol; ■: salmeterol; ◇: oxitropium ($r = 0.70$, $P < 0.001$)) (89).

Figure 4. Schematic representation of symptom improvement in an individual patient by treatment interventions during the course of a single exacerbation: (A) a small reduction in the baseline threshold of symptoms accompanied by a similar magnitude of reduction of exacerbation symptoms; (B) reduction of exacerbation symptoms only; (C) a significant reduction of the threshold of baseline symptoms accompanied by a significant reduction of exacerbation symptoms. Solid lines represent the course of symptoms without intervention; dotted lines represent the course of symptoms after intervention.

Figure 5. A. Effects of the LAMA tiotropium, the LABA olodaterol, and their combination on neutrophil adhesion stimulated by sputum supernatants from patients with COPD.

B. Expression of MAC-1 adhesion protein by neutrophils in induced sputum supernatants (99).

* $p < 0.001$ vs COPD; ** $p < 0.0001$ vs COPD; # $p < 0.01$ vs COPD; ### $p < 0.001$ vs COPD

Figures

Figure 1

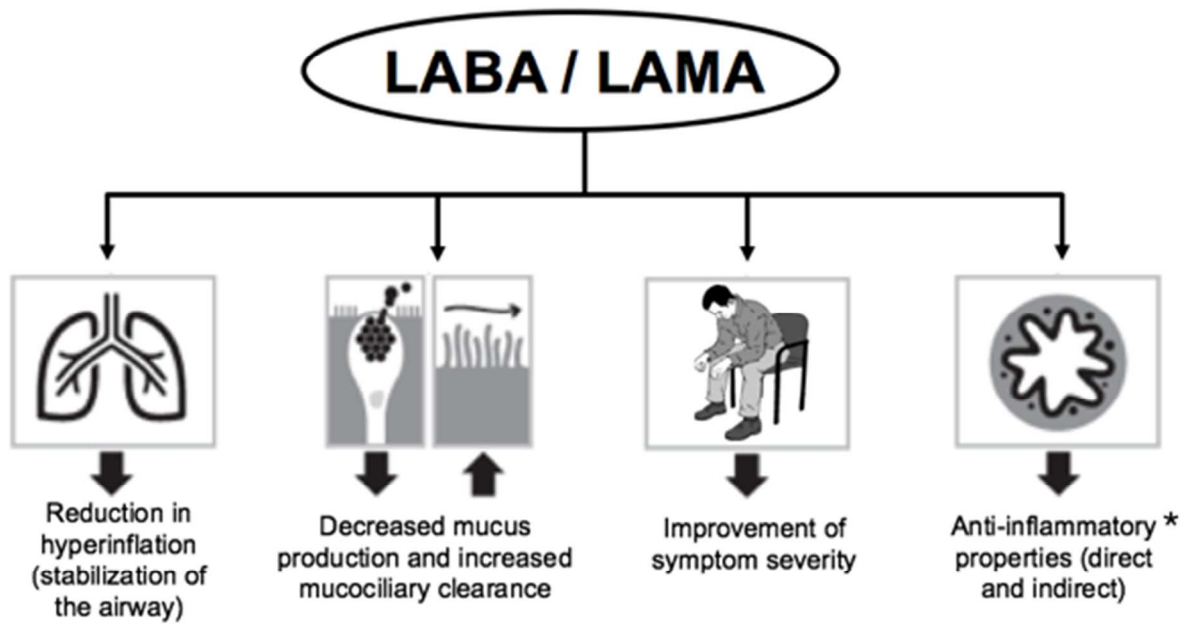


Figure 2.

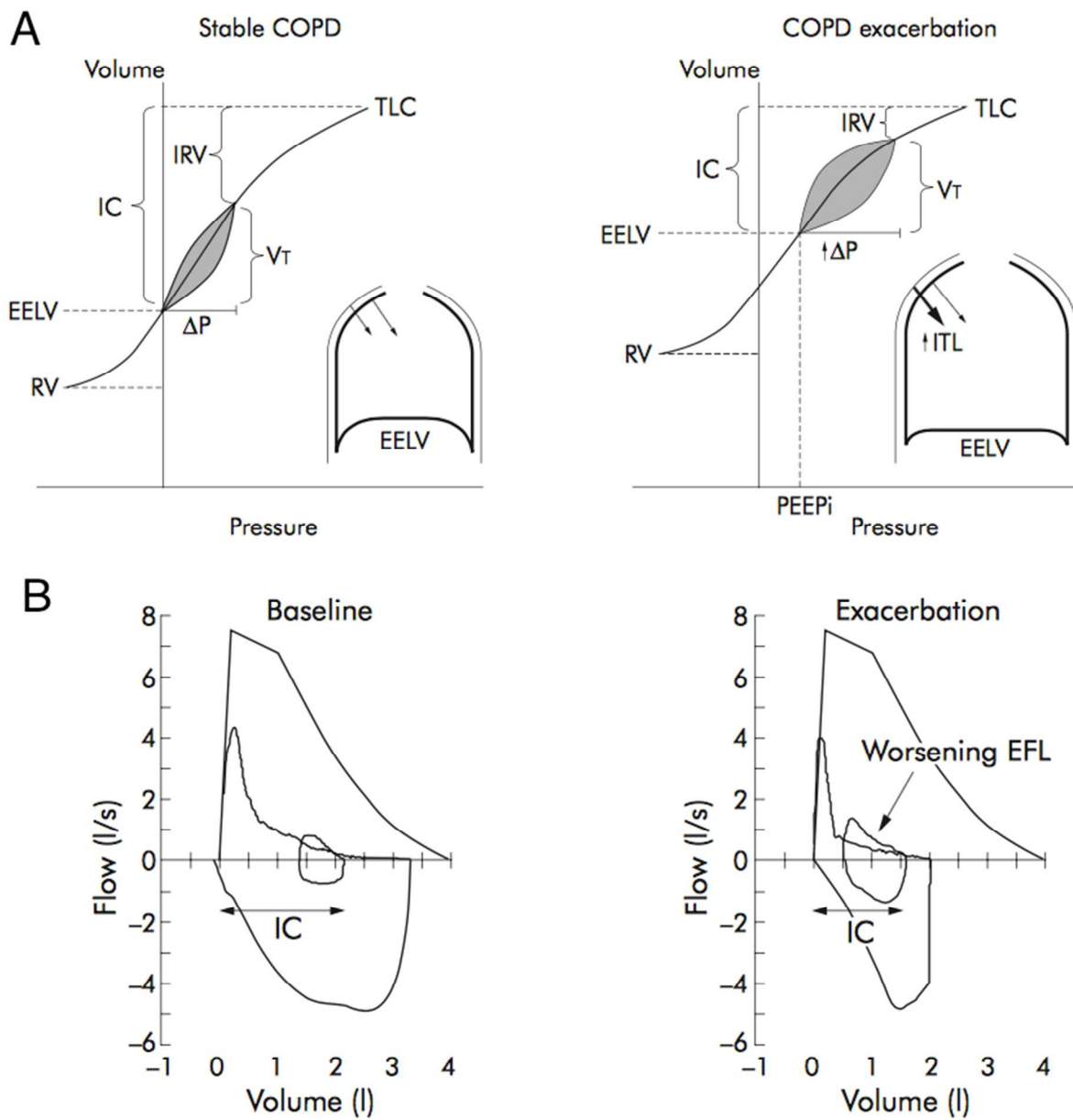


Figure 3.

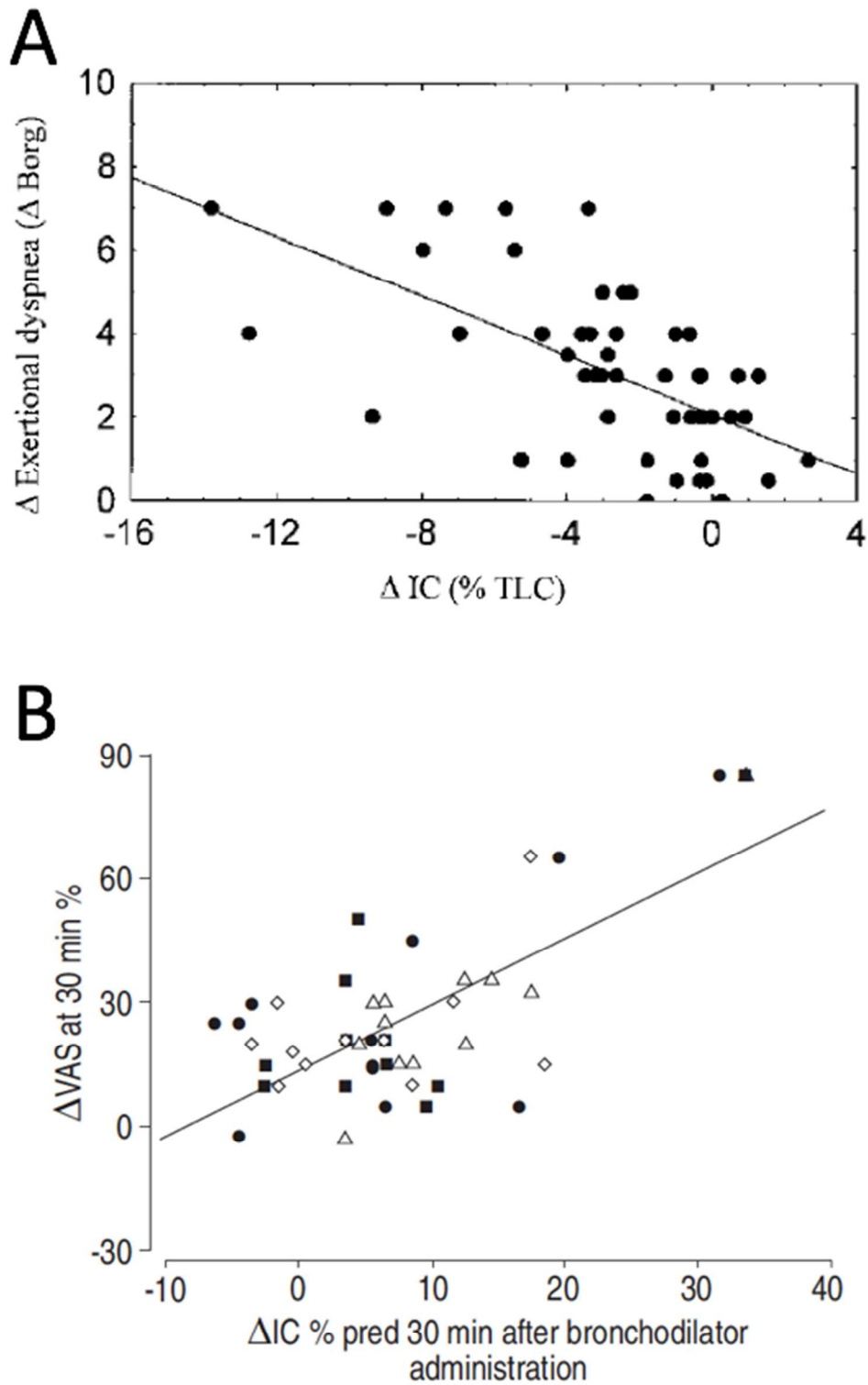


Figure 4.

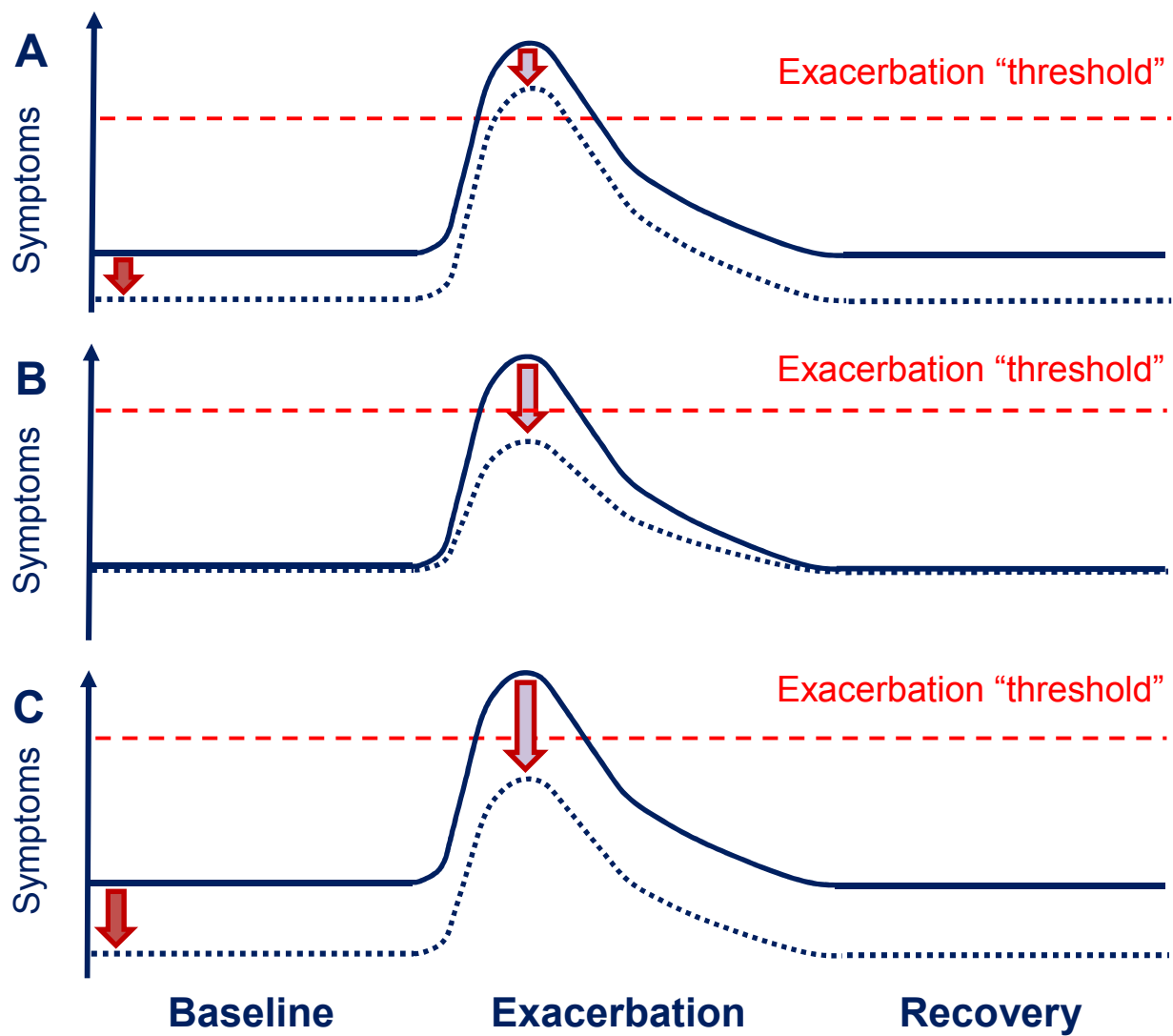


Figure 5.

