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Management of Stable COPD: Overview of Combination Inhalers LABA/LAMA and LABA/ICS

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Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease of the airways and lungs which leads to parenchymal damage and impaired gas exchange.[1] The manifestation of COPD includes symptoms such as wheezing, shortness of breath, chronic cough, and increased sputum production. The most common etiologic factor of COPD is smoking although other airborne pollutants and occupational exposures could foster the disease.[2] In 2014, COPD was the third ranked cause of mortality in the United States. An estimated 16 million people (6.4%) have reported a diagnosis of COPD in 2013 with the number increasing every year.[3] In 2010, the direct and indirect costs of COPD were approximated to be just under 50 billion USD. With an estimated cost of $4,000 per patient year, providing the best management strategies through optimal therapy may help reduce hospitalizations. These hospitalizations account for 45%-50% of total direct costs.[4] Exacerbations, an acute event that is worse than the patient's typical symptoms, are one of the main reasons patients have to be hospitalized from the disease. In most cases, exacerbations indicate a need for medication changes.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides guidelines for the diagnosis, management, and treatment of COPD. These guidelines are updated on a regular basis to provide the most current and evidence based information to healthcare professionals. In 2011, the ABCD assessment tool was introduced providing major advancements in COPD management over the previous spirometric system. This new tool added exacerbations and patient symptoms into the scheme along with spirometry to help guide diagnosis and treatment. The ABCD algorithm was revised again in 2017 for further simplification by separating patient symptoms and exacerbations from FEV1 values. The revision brought awareness of patient individualization when deciding on a therapeutic plan. FEV1 values do not always provide the best assessment when trying to develop a plan for treatment since patient's symptoms and exacerbations are not consistently correlated to a certain spirometry value. The latest 2018 GOLD guideline report has only minor changes compared to the previous report and includes new research publications from January 2016 to July 2017. The purpose of this article is to provide information on the pharmacological management of stable COPD. The focus will be on comparing the safety and efficacy of long-acting beta agonists (LABAs) in combination with either long-acting muscarinic antagonists (LAMA) or inhaled corticosteroids (ICS).[1]

GOLD Guideline Diagnosis and Treatment Recommedations

According to the GOLD guidelines, a diagnosis of COPD is made from a post-bronchodilator spirometry FEV1/FVC value below 0.70 with exposure to causative toxins and related symptoms.[1] Once diagnosed, the classification of COPD can be placed into an ABCD category based on airflow limitation using FEV1, breathlessness using the Modified Medical Research Council Dyspnea Scale (mMRC), symptoms using the COPD Assessment Test (CAT), and exacerbation history. The mMRC scale ranges from 0 to 4 based off of the amount of exertion it takes a patient to become short of breath with a higher number indicating more dyspnea. A CAT score ranges from 0 to 40 based off of severity of COPD symptoms with higher numbers indicating a greater impact on quality of life. The goals of pharmacotherapy are to reduce exacerbations, subdue symptoms, and improve the overall quality of life in COPD patients. The GOLD score has 4 categories based on patients' symptoms and COPD exacerbation rate:

- **A**: 0-1 yearly exacerbations and mMRC 0-1 or CAT <10
- **B**: 0-1 yearly exacerbations and mMRC ≥2 or CAT ≥10
- **C**: ≥2 exacerbations (or hospitalization) and mMRC 0-1 or CAT <10
- **D**: ≥2 exacerbations (or hospitalization) and mMRC ≥2 or CAT ≥10

Optimal choice of therapy is often driven by a patient's GOLD score (figure 1).

Clinical Pharmacology

Beta Agonists

Beta-2 receptor agonists directly stimulate beta 2 adrenergic receptors and dilate pulmonary smooth muscle. LABAs act locally on pulmonary tissue, but systemic exposure and adverse effect rates increase as dose increases. Formoterol and salmeterol have a duration of action of 12 hours and are dosed twice-daily. In-

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dacaterol, olodaterol and vilanterol have a longer duration of action of 24 hours and can be dosed once daily.[5] (see **TABLE 1**)

Muscarinic Antagonists

Antimuscarinics block acetylcholine from binding to M3 muscarinic receptors on airway smooth muscle preventing bronchoconstriction effects. LAMAs bind to the M3 receptor longer than short-acting beta agonists (SAMAs) resulting in a more prolonged duration of bronchodilation.[1] LAMAs are not systemically absorbed as these drugs are all quaternary amines with a permanent positive charge preventing its passage across hydrophobic pulmonary membranes into the blood. Tiotropium and umeclidinium are dosed once daily while aclidinium and glycopyrronium are both dosed twice daily.[6,7](see **TABLE 1**)

Inhaled Corticosteroids

ICS decrease pulmonary and systemic inflammation in patients with COPD.[8] ICS are absorbed into the systemic circulation through the lungs as well as the gastrointestinal tract when inhalations are improperly administered. The oral bioavailability of budesonide is between 9 and 21%.[9] Mometasone, fluticasone propionate and fluticasone furoate all have an oral bioavailability <1%. Inhalers containing fluticasone furoate are dosed once daily due to its half-life of 24 hours. Fluticasone propionate, budesonide and mometasone all require twice daily dosing due to their shorter half-lives compared to fluticasone furoate.[10,11] (see **TABLE 1**)

Clinical Trials

Multiple clinical trials have been completed comparing the safety and efficacy of LABA/LAMA and LABA/ICS against placebo and their mono-components. Few studies have made the direct comparison of LABA/LAMA to LABA/ICS. An important consideration in the interpretation of these trial results is the significance of the outcomes that were measured, such as FEV1 and exacerbation rates. FEV1 has historically been used as one of the primary variables in the diagnosis of COPD. It has a long-established association with increased mortality in COPD considering many patients who die from the disease have reduced lung function. Although it is used to assess severity of disease, it is not very sensitive to changes in small airway function and correlates poorly with clinical parameters such as dyspnea, quality of life and cost of care.[12,13] The following sections will provide information from key trials comparing the use of combination therapy in COPD patients.

LABA/LAMA and LABA/ICS Studies

GOLD 2-4[14]

This study, published in 2015, compared the efficacy and safety of tiotropium/olodaterol fixed-dose combinations (FDC)

Figure 1 | GOLD Guideline Preferred COPD Treatment

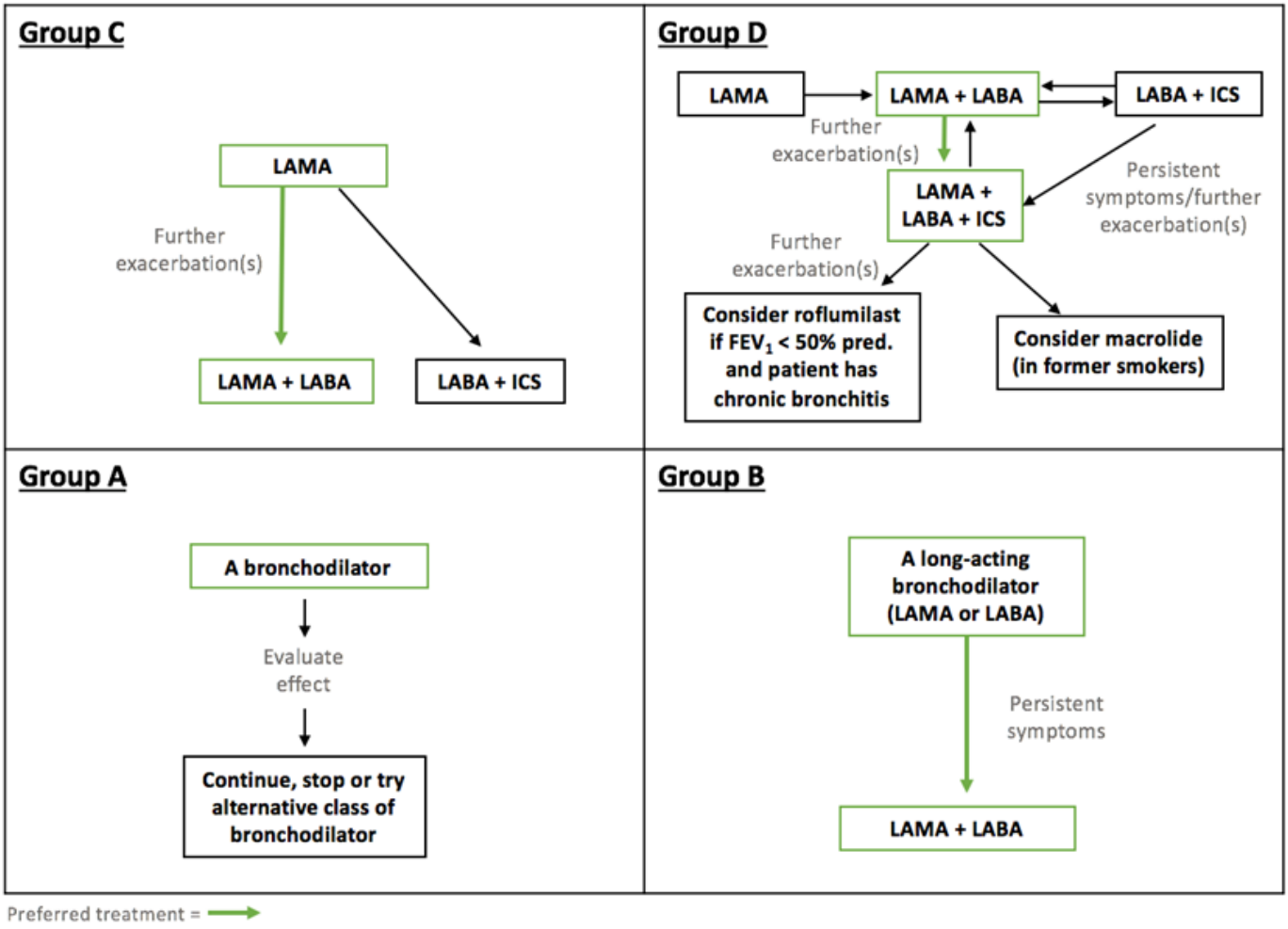

Table 1 | List of Available Inhalers for COPD Treatment

Drug	How Supplied	Dosing	Max Daily Dose
Long-acting Beta 2 Agonists (LABAs)			
Arformoterol (Brovana)	**Neb solution:** 15 mcg/2 mL	15 mcg every 12 hours	30 mcg
Formoterol (Perforomist)	**Neb solution:** 20 mcg/2 mL	20 mcg every 12 hours	40 mcg
Indacterol (Arcapta Neohaler)	**DPI:** 75 mcg capsule	75 mcg once daily	75 mcg
Olodaterol (Striverdi Respimat)	**MDI:** 2.5 mcg/act (4 g)	Two 2.5 mcg inhalations once daily	5 mcg
Salmeterol (Serevent Diskus)	**DPI:** 50 mcg/inh (28 ea, 60 ea)	One inhalation every 12 hours	100 mcg
Long-acting Muscarinic Antagonists (LAMAs)			
Aclidinium bromide (Tudorza Pressair)	**DPI:** 400 mcg/act (60 act)	One 400 mcg inhalation every 12 hours	800 mcg
Glycopyrronium bromide (Seebri Neohaler (DPI)) (Lonhala Magnair Refill/ Starter kit (Neb))	**DPI:** 15.6 mcg cap **Neb:** 25 mcg/mL	**DPI:** One capsule inhaled every 12 hour **Neb:** 1 vial (25 mcg) inhaled every 12 hours	**DPI:** 31.2 mcg **Neb:** 50 mcg
Tiotropium (Spiriva Respimat (MDI)) (Spiriva Handihaler (DPI))	**MDI:** 1.25 mcg/act (4 g), 2.5 mcg/act (4 g) **DPI:** 18 mcg/capsule	**MDI 2.5 mcg/act:** 2 inhalations (5 mcg) once daily **DPI:** 1 cap (18 mcg) inhaled once daily	**MDI:** 5 mcg **DPI:** 18 mcg
Umeclidinium (Incruse Ellipta)	**DPI:** 62.5 mcg/inh (7 ea, 30 ea)	One inhalation (62.5 mcg) once daily	62.5 mcg
LABA and LAMA Combinations			
Formoterol/glycopyrronium (Bevespi Aerosphere)	**MDI:** 4.8 mcg/9 mcg/act (5.9 g, 10.7 g)	Two inhalations every 12 hours	Glycopyrronium: 36 mcg Formoterol: 19.2 mcg
Indacaterol/glycopyrronium (Utibron Neohaler)	**DPI:** 27.5 mcg/15.6 mcg capsule	One capsule inhaled every 12 hours	Indacaterol: 55 mcg Glycopyrronium: 31.2 mcg
Vilanterol/umeclidinium (Anoro Ellipta)	**DPI:** 25 mcg/62.5 mcg	One inhalation once daily	Umeclidinium: 62.5 mcg Vilanterol: 25 mcg
Olodaterol/tiotropium (Stiolto Respimat)	**MDI:** 2.5 mcg/2.5 mcg (4g)	Two inhalations once daily	Tiotropium: 5 mcg Olodaterol: 5 mcg
LABA and ICS Combinations			
Formoterol/budesonide (Symbicort)	**MDI:** 4.5 mcg/80 mcg (6.9 g, 10.2 g), 4.5 mcg/160 mcg (6 g, 10.2 g)	Two inhalations every 12 hours	Budesonide: 640 mcg Formoterol: 18 mcg
Formoterol/mometasone (Dulera)	**MDI:** 5 mcg/100 mcg/act (8.8 g, 13 g), 5 mcg/200 mcg (8.8 g, 13 g)	Two inhalations every 12 hours (both strengths)	Mometasone: 800 mcg Formoterol: 20 mcg
Salmeterol/fluticasone (Advair Diskus)	**DPI:** 50 mcg/100 mcg, 50 mcg/250 mcg, 500 mcg/50 mcg (14s, 60s)	**DPI 50 mcg/250 mcg:** One inhalation every 12 hours	Fluticasone: 500 mcg Salmeterol: 100 mcg
Vilanterol/fluticasone furoate (Breo Ellipta)	**DPI:** 25 mcg/100 mcg, 25 mcg/200 mcg (28s, 60s)	**DPI 25 mcg/100 mcg:** One inhalation once daily	Fluticasone: 100 mcg Vilanterol: 25 mcg

DPI = Dry powder inhaler; **g** = gram; **mcg** = microgram; **mL** = milliliter; **MDI** = metered-dose inhaler; **Neb** = nebulizer

with the mono-components using results from two clinical trials.[14] Patients with moderate to very severe COPD in two multinational, replicate, phase III, multicenter, randomized, double-blind, active-controlled, five-arm, parallel-group studies were evaluated. Patients were randomly allocated to receive once daily dosing of either the combined product tiotropium/olodaterol FDC 2.5/5 mcg (n=522) or 5/5 mcg (n=522), single agent of tiotropium 2.5 mcg (n=525) or 5 mcg (n=527), or single agent olodaterol 5 mcg (n=528) over 52 weeks. The three primary endpoints were FEV1 area under the curve from 0 h to 3 h response (AUC_{0-3}), trough FEV1 response, and St George's Respiratory Questionnaire (SGRQ) total score. A greater statistically significant FEV1 AUC_{0-3} response was seen with tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg as compared to tiotropium 2.5 mcg or 5 mcg and olodaterol 5 mcg with values of 241, 256, 148, 139 and 133 mL respectively in one study and 256, 268, 125, 165 and 136 mL in the other ($p<0.0001$ for tiotropium/olodaterol FDC 2.5/5 mcg or 5/5 mcg compared to the corresponding individual components). A greater statistically significant trough FEV1 response was seen with tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg as compared to tiotropium 2.5 mcg or 5 mcg and olodaterol 5 mcg with values of 111, 136, 83, 65 and 54 mL, respectively, in the first study, and 125, 145, 62, 96 and 57 mL, respectively, in the second study ($p<0.05$ for tiotropium/olodaterol FDC 2.5/5 mcg or 5/5 mcg compared to the corresponding individual components). The SGRQ score uses three components combined in an algorithm to determine the impact COPD has on quality of life. Analysis of the adjusted mean SGRQ total score revealed statistically significant improvements in baseline for tiotropium+olodaterol FDC 5/5 mcg verses olodaterol alone (-1.693 [95% CI, -2.778 to - 0.608]; $p< 0.01$) and tiotropium alone (-1.233 [95% CI, -2.313 to - 0.153]; $p< 0.05$) but not for tiotropium+olodaterol FDC 2.5/5 mcg. The tiotropium+olodaterol FDC 5/5 mcg appears to be optimal, providing significant improvement in all three primary end points (FEV1 AUC_{0-3}, trough FEV1, and health status) compared to tiotropium or olodaterol administered alone.[14]

TORCH Trial[15]

The TORCH trial, published in 2007, was a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol/fluticasone propionate with each of the components alone and with placebo. Patients were randomly stratified in a 1:1:1:1 ratio to salmeterol/fluticasone propionate 50 mcg/500 mcg combination therapy (n=1,546), salmeterol 50 mcg monotherapy (n=1,542), fluticasone propionate 500 mcg monotherapy (n=1,551), or placebo (n=1545) all given as an inhaler for a total duration of 3 years. Primary outcome results did not demonstrate a difference in death rates between any of the groups. The absolute risk reduction for death in the salmeterol/fluticasone propionate group as compared with the placebo group was 2.6%, (HR=0.825 [95% CI, 0.681 to 1.002]). The salmeterol/fluticasone combination therapy group had lower rates of exacerbations per patient year when compared to salmeterol monotherapy (RR=0.88 [95% CI, 0.81 to 0.95]) and fluticasone propionate monotherapy (RR=0.91 [95% CI, 0.84 to 0.99]).[15]

SUMMIT Trial[16]

The SUMMIT trial was published in 2016. It was a double-blind, parallel group, placebo-controlled, event-driven randomly controlled trial where patients received either placebo (n=4111), fluticasone furoate 100 mcg (n=4135), vilanterol 25 mcg (n=4118), or the combination of fluticasone furoate and vilanterol 100/25 mcg (n=4121) given once daily as an inhaler.[16] The study objective was to assess improvement in survival on combination LABA/ICS therapy compared with the individual components or placebo in patients with moderate COPD and heightened cardiovascular risk. Patients included in the trial were current or former smokers with at least a 10-pack-year history, aged 40–80 years, had a FEV1 between 50% and 70% and an FVC of 0.70 or less, achieved a score of 2 or greater on the mMRC dyspnea scale, and have a history, or be at increased risk, of cardiovascular disease. Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery, long-term oxygen, oral corticosteroid therapy, severe heart failure (New York Heart Association Class IV or ejection fraction <30%), life expectancy less than 3 years, and end-stage chronic renal disease. The primary efficacy outcome was the time to death from any cause. Secondary endpoints include the on-treatment composite cardiovascular endpoint of cardiovascular death and exacerbations. Results showed that all-cause mortality was unaffected by the combination therapy of fluticasone furoate/vilanterol compared to placebo (HR=0.88 [95% CI, 0.74 to 1.04]). In contrast to the mortality results, the percent reduction in moderate and severe exacerbations was significantly reduced as compared to placebo by 12% for the fluticasone furoate group, 10% for the vilanterol group, and 29% for the fluticasone furoate/vilanterol. Fluticasone furoate/vilanterol had no effect on the composite cardiovascular endpoint when compared to placebo (HR=0.93 [95% CI, 0.75 to 1.14]).[16]

LAMA/LABA Compared to ICS/LABA

FLAME Study[17]

The FLAME study, published in 2016, was a multicenter, randomized, double-blind, double-dummy parallel group non-inferiority trial comparing indacaterol/glycopyrronium to salmeterol/fluticasone. Inclusion criteria were age 40 years, mMRC score $\geq$2, a post-bronchodilator FEV_1 between 25% to <60%, a post-bronchodilator FVC of <0.70, and a history of at least one COPD exacerbation during the previous year that required treatment with systemic glucocorticoids, antibiotics or both.[17] The study had a one week screening period and four week run in period during which all patients were treated with inhaled tiotropium 18 mcg once daily. After the run-in period, tiotropium was discontinued and the patients were randomly assigned to receive indacaterol/glycopyrronium 110 mcg/50 mcg once daily (n=1680) or salmeterol/fluticasone 50 mcg/500 mcg twice daily (n=1682) for 52 weeks. The primary outcome for the study, annual rate of all COPD exacerbations (mild, moderate or severe), were 3.59% in the indacaterol/glycopyrronium group and 4.03% in the salmeterol/fluticasone group (RR = 0.89 [95% CI, 0.83 to 0.96]), meeting the superiority criteria for the indacaterol/glycopyrronium group. Notably, pneumonia occurrence was significantly less in the indacaterol/glycopyrronium (3.2%) compared to the salmeterol/fluticasone group (4.8%; p=0.02). Incidence of other adverse events was similar in the two treatment groups. Another notable safety finding in a subgroup of patients (n=535) was the median percentage change over the 52 week period in the 24-hour urinary cortisol to creatinine ratio of 5.62% in the indacaterol/glycopyrronium group and -10.39% in the salmeterol/fluticasone group. This decrease in urinary cortisol levels implies that the ICS is being absorbed systemically and inhibiting the adrenal system.[17]

LANTURN Study[18]

LANTERN, published in 2015, was a multicenter, randomized, double-blind, double-dummy, parallel group study comparing indacaterol/glycopyrronium 110 mcg/50 mcg once daily (n=372) to salmeterol/fluticasone propionate 50 mcg /500 mcg twice daily (n=372) in predominantly Chinese patients. Inclusion criteria were age ≥40 years, moderate-to-severe COPD (stage II and III as defined in the GOLD 2010 criteria) and mMRC ≥ 2. Participants could not have more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the year before the screening visit or during the run-in period. The primary objective was to demonstrate non-inferiority of indacaterol/glycopyrronium to salmeterol/fluticasone in post-dose trough FEV1 at week 26. Indacaterol/glycopyrronium was superior to salmeterol/fluticasone for trough FEV1 (treatment difference = 75 mL [95% CI, 44 to 107]). Indacaterol/glycopyrronium was also superior compared to salmeterol/fluticasone in FEV1 AUC $_{0\text{-}4\,h}$ at day 1 and week 26 (treatment difference = 65 mL and 122 mL, respectively, p<0.001). Annualized rate of moderate or severe COPD exacerbations was significantly lower with indacaterol/glycopyrronium compared with salmeterol/fluticasone at 0.3 with indacaterol/glycopyrronium and 0.46 with salmeterol/fluticasone (ratio of rate=0.69 [95% CI, 0.48 to 1.00]). Overall, adverse events including worsening COPD, nasopharyngitis, upper respiratory infection (URI), pneumonia, dyspnea and oropharyngeal pain were lower in the patients treated with indacaterol/glycopyrronium compared with salmeterol/fluticasone. Pneumonia rates were 0.8% in the indacaterol/glycopyrronium and 2.7% in the salmeterol fluticasone group.[18]

AFFIRM COPD Trial[19]

Published in 2016, the AFFIRM COPD trial, another randomized, double-blind, double-dummy, active-controlled, multicenter, phase 3b study compared aclidinium/formoterol to salmeterol/fluticasone propionate in symptomatic patients with stable, moderate-to-severe (COPD GOLD 2013 criteria: post-bronchodilator FEV1/forced vital capacity <70% and FEV1 <80% predicted). Patients were randomly allocated to receive aclidinium/formoterol 400 mcg/12 mcg twice daily (n=468) to salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily (n=463) over 24 weeks. The primary outcome was peak FEV1 at week 24 (defined as maximum FEV1 from 0 to 3 h after the morning dose) to demonstrate the superiority of aclidinium/formoterol to salmeterol/fluticasone propionate. Secondary objectives were dyspnea and symptoms and health status between the two therapies. The mean increase in peak FEV1 at week 24 was 93 mL greater with aclidinium/formoterol than salmeterol/fluticasone propionate, demonstrating superiority (p=0.0001). Improvements in dyspnea, CAT scores and SGRQ were similar between the two treatments. Incidence of significant AEs was also similar between the groups. The incidence of pneumonia was 0.6% in the aclidinium/formoterol group and 1.9% in the salmeterol/fluticasone propionate group.[19]

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The results of two multicenter, randomized, double-blind, double-dummy, parallel-group trials were published in 2015. DB2114930 (T1), was conducted between 26 March 2013 and 26 October 2013 in 63 centers in seven countries (Argentina, Chile, Greece, Peru, Romania, Ukraine, USA). DB2114951 (T2) was conducted in 71 centers in seven countries (Chile, Mexico, Norway, Romania, Russian Federation, South Africa, USA) between 13 June 2013 and 9 January 2014. These studies both investigated once-daily umeclidinium/vilanterol 62.5 mcg/25 mcg (T1: n= 353, T2: n= 349) versus twice-daily salmeterol/fluticasone 50/250 mcg (T1: n=353, T2: n=348) over 12 weeks in patients with symptomatic moderate-to-severe COPD (FEV1 ≥30% and ≤70%) without a documented COPD exacerbation within the previous year. The goal was to identify improvements in lung function, dyspnea, and quality of life (QoL). Umeclidinium/vilanterol demonstrated statistically significant improvements in least squares (LS) mean change from baseline in 0–24 h weighted mean FEV1 (primary endpoint) versus salmeterol/fluticasone on day 84 (T1 treatment difference = 0.074 [95% CI, 0.038 to 0.110], T2 treatment difference = 0.101 [95% CI, 0.063 to 0.139]). There was no significant difference in Transition Dyspnea Index (TDI) scores, mean SGRQ scores or CAT scores between the two treatment groups.[20]

Triple Therapy Trials

IMPACT Trial[21]

The IMPACT trial, published in 2018, was a randomized control trial done to compare 52 weeks of a once-daily combination of fluticasone fuorate, umeclidinium and vilanterol 100 mcg/62.5 mcg/25 mcg (n=4151) to fluticasone fuorate/vilanterol 100 mcg/25 mcg (n=4134) and umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2070). The primary outcome was annual rate of moderate or severe COPD exacerbations. The rate of moderate or severe exacerbations during treatment in patients on triple therapy was 0.91 per year and the rates for fluticasone furoate/vilanterol and umeclidinium/vilanterol were 1.07 and 1.21, respectively, per year. Triple therapy was found to significantly reduce these exacerbations when compared to for fluticasone furoate/vilanterol (0.85; [95% CI, 0.80 to 0.90]) and umeclidinium/vilantero (0.75; [95% CI 0.70 to 0.81]). However, there was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (HR 1.53; [95% CI, 1.22 to 1.92]). There was no significant difference in the risk of pneumonia between triple therapy and fluticasone furoate–vilanterol (HR 1.02; [95% CI, 0.87 to 1.19]). [21]

WISDOM Trial[22]

Published in 2014, the WISDOM trial was a double-blind, parallel-group study done on COPD patients receiving triple therapy consisting of tiotropium 18 mcg daily, salmeterol 50 mcg twice daily, and fluticasone propionate 500 mcg twice daily during a 6-week run-in period (n=2485).[30] Patients were then randomly assigned to continue triple therapy or withdrawal of fluticasone in three steps over a 12 week period. The primary endpoint was the time to the first moderate or severe COPD exacerbation. Results showed a nonsignificant difference between time to first exacerbation in patients stepping down from glucocorticoids compared to patients continuing steroid therapy (HR=1.06 [95% CI, 0.94 to 1.19] P=0.35)). A secondary outcome showed the adjusted event rate for moderate or severe exacerbations was 0.95 per patient-year (95% CI, 0.87 to 1.04) in the glucocorticoid-withdrawal

group and 0.91 per patient-year (95% CI, 0.83 to 0.99) in the glucocorticoid-continuation group.[22]

DISCUSSION

In the trial comparing tiotropium and olodaterol fixed-dose combination to its individual components, both lung function (FEV1) and health status (SGRQ score) were significantly improved in patients taking the combination inhaler, as expected. Since the combination was compared to current treatments in COPD, the relevance of these improvements is high. However, the trial was not designed to assess the use of the medications on exacerbation reduction even though a trend of exacerbation reduction was noted with the combination product that correlate with findings from other studies.[12]

Meta-analysis data has demonstrated LABA/LAMA inhaler combination superiority over the individual components in 23,168 patients. Meta-analysis results are broken down based on each type of LABA/LAMA combination as follows:

- aclidinium/formoterol combination significantly increased FEV1 by 33.39 mL (95% CI, 13.40 to 53.38) compared with mono-components (P < .001)
- glycopyrronium/indacaterol combination increased FEV1 by 89.44 mL (95% CI, 76.04 to 102.85) vs mono-components (P < .001)
- tiotropium/olodaterol combination significantly improved FEV1 by 54.75 mL (95% CI, 45.70 to 63.80) vs mono-components (P < .001)
- umeclidinium/vilanterol combination) increased FEV1 by 83.66 mL (95% CI, 65.65 to 101.67) compared with mono-components (P < .001)
- glycopyrronium/formoterol combination significantly improved FEV1 by 59.15 mL (95% CI, 49.12 to 69.17) compared with mono-components (P < .001)

The secondary outcomes of the SGRQ score and TDI score were significantly reduced in all of the investigated LAMA/LABA combinations compared with mono-components, (P < .05) and (P < .001), respectively. The meta-analysis did not reveal a difference between the different combinations of LABA/LAMA medications for the outcomes assessed, indicating their FEV1 improvements are a class effect. However, a lack of head-to-head studies have been completed between LABA/LAMA combinations and it is unknown definitively if there are any differences between the available products. The use of these drugs in reducing mortality was not analyzed by the review.[23]

Two trials have been reviewed comparing a LABA/ICS combination to either its individual components or placebo for the reduction in mortality of COPD patients. The TORCH trial did not show a significant reduction in mortality when using LABA/ICS over placebo. Similarly, the SUMMIT trial results also showed no reduction in mortality compared to placebo using a LABA/ICS medication. However, both trials did show a reduction in exacerbations compared to the individual components of LABA/ICS therapy and placebo. These trials indicate that the use of LABA/ICS combination therapy is helpful in symptom reduction and exacerbations but may provide little to no benefit in mortality.[13,14]

In December 2017, the FDA removed the black box warning of asthma-related death for the use of LABA/ICS combination products based off safety results from recent clinical trials. The trials reviewed showed that LABA/ICS combinations did not increase the risk of serious asthma outcomes compared to ICS alone and actually decreased the need for oral corticosteroids prescribed for asthma attacks. LABA products alone are still shown to have increased risk of asthma-related death and will retain the boxed warning. Also, the LABA/ICS combination products will retain a warning about the use of LABA medications in asthma without a combination ICS product.[24]

Trials comparing LABA/LAMA combinations to LABA/ICS combinations in patients with COPD directly are limited. The FLAME trial demonstrated superiority of the indacaterol/glycopyrronium combination for exacerbation prevention compared to LABA/ICS. It is unknown definitively whether the FLAME results are a combination class effect or specific to the indacaterol/glycopyrronium combination.[15] However, the meta-analysis reviewed above demonstrated no difference in outcomes between the different LABA/LAMA combinations.[23] In the LANTERN trial, Indacaterol/glycopyrronium was superior to salmeterol/fluticasone in both trough FEV1 and FEV1 AUC $_{0\text{-}4\,h}$ improvement. LANTERN also showed a reduction in exacerbations with LABA/LAMA use over that of LABA/ICS correlating with the findings of the FLAME trial.[16] Both studies showed reductions in pneumonia occurrence when using the LABA/LAMA combination compared to LABA/ICS. These findings strongly conclude that LABA/LAMA combinations are superior to LABA/ICS in exacerbation reduction and pneumonia prevention. Since both of these outcomes are correlated with increased costs, the use of LABA/LAMA will likely be cost beneficial to the overall healthcare system. A summary of the head-to-head, LABA/LAMA vs. LABA/ICS trials that we review in this article can be found in **TABLE 2**.

Aggregate data of LABA/LAMA combinations compared to LABA/ICS combinations from clinical trials has been reported in a recent meta-analysis with a combined study population of 20,185 patients. The results of the meta-analysis suggest a significantly improved FEV1 from baseline to week 12 with LABA/LAMA combination versus LABA/ICS (mean difference 0.08 L, P<0.0001). More patients seem likely to achieve improvements in FEV1 of >100 mL with LABA/LAMA than with LABA/ICS (RR = 1.44, [95% CI, 1.33 to 1.56]) and LABA/LAMA combinations tend to reduce moderate/severe exacerbation rate better than LABA/ICS (RR = 0.82 [95% CI, 0.75 to 0.91]). These findings are of direct relevance to clinical practice since they included all currently available LABA/LAMAs and comparators, only at doses approved for clinical use. The meta-analysis supports the findings found from the above clinical trials. [25]

The current treatment for stable COPD continues to be modified as new trials are conducted and evidence grows. Patient specific factors such as exacerbation risk, past medical history, and medication adherence should always be considered when choosing appropriate therapy. One of the major contributors to selection of therapy is cost for the patient. Some inhalers used to treat COPD can be expensive to certain patients while affordable to others dependent on patient income, insurance, and other contributing factors. In the past, many prescribers used LABA/ICS combination inhalers more frequently only because they were cheaper than prescribing separate LABA and LAMA drug inhalers. However, LABA/LAMA combination inhalers are now available and patients are able to use these medications at prices equal or lower than LABA/ICS inhalers.[26]

ADVERSE EFFECTS AND PRECAUTIONS

In the meta-analysis reviewed, LABA/LAMA-treated patients had significantly lower overall incidence of AE rates com-

Table 2 | LABA/LAMA vs. LABA/ICS Trials: Summary of Findings

Trial	Study Populations	Intervention	Primary Outcome	Results
FLAME[17]	FEV_1 25% to <60% predicted and a post-bronchodilator FEV_1/FVC <0.70	IND/GLY (110 mcg/50 mcg) QD (n=1680) SAL/FLU (50 mcg/500 mcg) BID n=1682)	Annual rate of all COPD exacerbations (mild, moderate, or severe) over 52 weeks	IND/GLY: 3.59% SAL/FLU: 4.03% RR=0.89 (0.83 to 0.96)
LANTERN[18]	Stage II and III COPD	IND/GLY (110 mcg/50 mcg) QD (n=372) SAL/FLU (50 mcg/500 mcg) BID (n=372)	Treatment difference in post-dose trough FEV_1 after 26 weeks	IND/GLY: 1.26 L SAL/FLU: 1.18 L Δ: 75 mL (44 to 107 mL; p<0.001)
AFFIRM COPD[19]	FEV_1 <80% predicted and a post-bronchodilator FE-V_1/FVC <0.70	ACL/FORM (400 mcg/12 mcg) BID (n=423) SAL/FLU (50 mcg/500 mcg) BID (n=414)	Treatment difference in peak FEV_1 after 24 weeks[a]	ΔACL/FORM - SAL/FLU = 93 mL (70 to 131 mL; p<0.0001)
Donohue et al.[20]	FEV_1 ≥30% and ≤70%	**Trial 1:** UMEC/VIL (62.5 mcg/25 mcg) (n=353) SAL/FLU (50 mcg/500 mcg) (n=353) **Trial 2:** UMEC/VIL (62.5 mcg/25 mcg) (n=349) SAL/FLU (50 mcg/500 mcg) (n=348)	Treatment difference in change from baseline in 0-24 hours wmFEV_1 over 12 weeks	**wmFEV_1** **Trial 1:** UMEC/VIL (1.49 L) vs SAL/FLU (1.42 L) Δ: 74 mL v **Trial 1:** UMEC/VIL (1.53 L) vs SAL/FLU (1.43 L) Δ: 101 mL (p<0.0001)

a: Peak FEV_1 was defined as the maximum FEV_1 from 0 to 3 h after the morning dose.

ACL = aclidinium; **FEV_1** = forced exiratory volume in 1 second; **FORM** = formoterol **FLU** = fluticasone; **FVC** = forced vital capacity; **GLY** = glycopyrronium; **IND** = indacaterol; **L** = liter; **mcg** = mi-

pared with LABA/ICS treatment with a RR 0.94 (95% CI, 0.89 to 0.99). Specifically, the meta-analysis showed significantly fewer incidences of pneumonia in the LABA/LAMA treatment arm versus the LABA/ICS treatment arm (RR 0.59 [95% CI, 0.43 to 0.81]).[24] Relevant side effects to consider with LABA use are tachycardia, arrhythmias, somatic tremor, hypokalemia, increased O2 consumption under resting conditions in patients with CHF, and mild falls in PO2 after administration. These side effects are rare and since they are associated with the beta-agonist, they should not influence decision between LABA/LAMA or LABA/ICS considering both combinations contain this component. LAMAs typically have few side effects due to their lack of absorption into systemic circulation. Side effects of LAMAs are typically local and include dry mouth or bitter metallic taste. Occasional urinary symptoms have been reported with LAMAs, but there is no proven causal relationship. As compared with the mild adverse effects of LAMAs, ICS have many negative side effects associated with their use such as increased risk of pneumonia, oral candidiasis, hoarse voice, skin bruising, decreased bone density/increased fractures, increased risk of diabetes/poor control of diabetes, cataracts, and mycobacterial infection.[1] However, not all LABA/ICS combinations are created equal in terms of their side effect profile. Inhalers containing budesonide (such as Symbicort) have a lower risk of pneumonia compared to fluticasone-containing inhalers.[27]

Clinicians need to consider drug-drug interactions with beta agonists when prescribing LABA/LAMA combinations. However, these same drug-drug interactions will need to be considered with LABA/ICS in addition to drug interactions with ICS. Beta agonist effects can increase blood pressure and heart rate and caution is warranted in patients with cardiovascular disease. Drug-drug and drug-disease interactions for LABA/ICS include the interactions mentioned above due to the LABA component.[5] Additionally, ICS can interact with strong CYP3A4 inhibitors (e.g. ritonavir) and may result in increased systemic effects of corticosteroids. Corticosteroids may also lead to increased intraocular pressure, open-angle glaucoma and cataracts with prolonged use. LABA/ICS is contraindicated for use as primary treatment of status asthmaticus, or acute COPD requiring intensive measures.[8] A summary of the adverse effects that were reported in the trials directly comparing LABA/LAMA to LABA/ICS can be found in **TABLE 3**.

CONCLUSION

COPD is a progressive lung disease and patients often report symptoms that include, breathlessness, chronic cough, and increased sputum production. The GOLD guidelines recommend using LABA/LAMA combination therapy over the combination of LABA/ICS. The reviewed clinical trials show exacerbation

Table 2 | LABA/LAMA vs. LABA/ICS Trials: Summary of Common Adverse Effects

Trial	Treatment	COPD Exacerbations	Nasopharyngitis	LRTI/ Bronchitis	URTI	Pneumonia	Dyspnea	Oral candidiasis
FLAME[17]	IND/GLY (n=1678)	77.4%	11.7%	4.9%	4.8%	3.2%	2.9%	1.2%
	SAL/FLU (n=1680)	81.8%	11.6%	5.8%	4.9%	3.0%	4.2%	1.4%
LANTERN[18]	IND/GLY (n=372)	20.2%	8.1%	1.9%	3.5%	0.8%	0.5%	NR
	SAL/FLU (n=369)	26.3%	12.2%	1.1%	7.0%	2.7%	1.6%	NR
AFFIRM COPD[19]	ACL/ FORM (n=467)	17.1%	5.6%	1.5%/1.1%	NR	0.6%	NR	NR
	SAL/FLU (n=466)	17.8%	6.0%	4.5%/1.3%	NR	1.9%	NR	NR
Donohue et al.[20]	UMEC/VIL T1 (n=353) T2 (n=353)	**T1:** 3% **T2:** 3%	**T1:** 5% **T2:** 4%	**T1:** 0% **T2:** <1%	NR	**T1:** <1% **T2:** <1%	NR	NR
	SAL/FLU T1 (n=349) T2 (n=348)	**T1:** 3% **T2:** 3%	**T1:** 3% **T2:** 3%	**T1:** <1% **T2:** <1%	NR	**T1:** 1% **T2:** 1%	NR	NR

ACL = aclidinium; **FEV_1** = forced exiratory volume in 1 second; **FORM** = formoterol **FLU** = fluticasone; **FVC** = forced vital capacity; **GLY** = glycopyrronium; **IND** = indacaterol; **L** = liter; **mcg** = microgram; **SAL** = salmeterol; **VIL** = vilanterol; **wm** = weighted mean; Δ = treatment difference

reduction, improvements in lung function, and decreased adverse effects with the combinations of LABA/LAMA vs LABA/ICS resulting in cost savings and improved quality of life. LABA/LAMA is the best first line dual-therapy treatment for the management of Stable COPD.

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Editor's Corner

2018 Update to the AHA/ACC Guideline on the Management of Blood Cholesterol

In November 2018, the AHA/ACC published an updated cholesterol guideline from their previous release in 2013. Recommendations were updated to include additional cholesterol lowering therapy in addition to statins when lifestyle changes still leave patients at risk. Additionally, the AHA/ACC has reintroduced LDL-C goals for optimal care.

A major recommendations include the consideration to add an additional cholesterol lowering medication for very high-risk patients on a maximally tolerated statin with a LDL-C greater than 70 mg/dL. Very high-risk is described as patients with multiple major atherosclerotic cardiovascular disease (ASCVD) events or a major ASCVD event with multiple high-risk conditions. The preferred therapy in addition to a statin is ezetimibe. Evidence for the initiation of ezetimibe in this patient population is classified as IIa, B-R (benefit outweighs the risk and the evidence is from at least 1 randomized controlled trial) and stems from the IMPROVE-IT trial published in 2015. The guidelines state a PCSK-9 inhibitor is reasonable as third line, but the cost-benefit ratio is very low. Evidence for starting a PCSK-9 inhibitor stem from the FOURIER and ODYSSEY OUTCOMES trials and are given a IIb, B-R level or evidence.

The guidelines have also updated recommendations for cholesterol lowering therapy in adults 40 to 75 years of age without diabetes and a 10-year ASCVD of 7.5% or greater. The recommendations are to start a moderate intensity statin for a 10-year ASCVD risk of 7.5 to 19.9%, and to start a high intensity statin for a 10-year ASCVD risk of 20% or greater. In addition, certain risk enhancing factors have been taken into account on whether to start someone on a statin with an ASCVD risk between 5 and 7.4%. Risk factors that would incline the provider to initiate statin therapy include: family history of premature ASCVD, persistently elevated LDL-C levels greater or equal to 160 mg/dL, metabolic syndrome, chronic kidney disease, history of preeclampsia or premature menopause, chronic inflammatory disorders, high-risk ethnic groups (e.g., South Asian), persistent elevations of triglycerides of 175 mg/dL or greater, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9, and lipoprotein (a) ≥50 mg/dL.

If the patient does not have any of the above indications, and the initiation of a statin is still uncertain, the guidelines recommend obtaining a coronary artery calcium (CAC) score. If the CAC score is zero, statin therapy may be delayed. A CAC score of 1 to 99 favors statin therapy, and a score above 100 gives an indication for a statin.

Other general recommendations remain relatively the same to the previous 2013 edition of the guidelines. No additional recommendations are made for patients 75 years of age or older. Treatment recommendations at large remain focused on statin therapy, with adjunct cholesterol lowering management if the patient is not achieving the expected greater than 50% reduction in LDL-C. Considerations to prescribing additional LDL-C lowering therapy will likely be driven by patient preference. Most notably, the PCSK-9 inhibitors annual cost are currently placed at approximately $5850. Given an absolute risk reduction in ASCVD events of 1.5% in the FOURIER trial (NNT = 67), the cost for the minimal benefit is significant.

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