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REVIEW

The role of combination inhaled corticosteroid/long-acting β-agonist therapy in COPD management

***Douglas W Mapel[a], Judith S Hurley[b], Anand A Dalal[c], Christopher M Blanchette[d]**

[a] Lovelace Clinic Foundation, Albuquerque, New Mexico, USA
[b] Hurley Health and Medical Communications, Placitas, New Mexico, USA
[c] GlaxoSmithKline, U.S. Health Outcomes, North Carolina, USA
[d] Lovelace Respiratory, Research Institute, Kannapolis, North Carolina, USA

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Abstract

Chronic obstructive pulmonary disease (COPD) is now the fourth leading cause of death, affects an estimated 24 million Americans, and accounts for over ten million physician and emergency department (ED) visits and hospitalisations each year. The diagnosis and management of COPD falls largely to primary care practitioners. Previously, COPD management options were limited, but newer treatments have been shown to slow lung deterioration, reduce symptoms and preserve quality of life. Combination therapy with an inhaled corticosteroid and a long-acting β_2-agonist (ICS/LABA) is an effective therapy for COPD that, compared to other therapies, has been shown to reduce exacerbations, hospitalisations, ED visits and health care costs. This review focuses on the role of combination ICS/LABA therapy in managing COPD, including indications, potential benefits and considerations that affect therapy decisions.

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Keywords COPD, treatment, ICS, LABA, combination therapy, outcomes

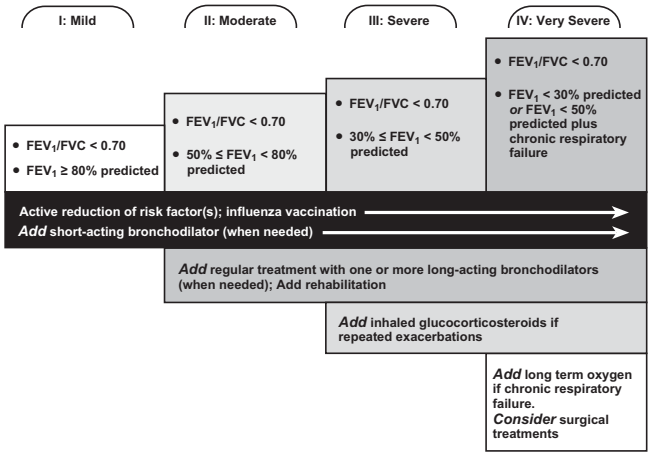
Contents

Introduction

The burden of chronic obstructive pulmonary disease (COPD) in the United States of America (USA) is enormous and growing. In 2000, COPD accounted for at least 8 million physician visits, 1.5 million emergency department (ED) visits and 726 000 hospitalisations.[1] While mortality from heart disease and stroke has decreased in recent decades, mortality from COPD has more than doubled since 1970.[2] Now the fourth leading cause of death in the USA, COPD is expected to become the third leading cause by 2020.[3] The early detection and management of COPD falls largely to primary care practitioners.[4] In a recent survey, private- and hospital-based primary care physicians reported that, on average, 12% of their adult patients have COPD.[4] That figure represents just part of the picture, as only half of the estimated 24 million individuals with COPD in the USA have been diagnosed.[1]

* Corresponding author: Dr Douglas W Mapel, Lovelace Clinic Foundation, 2309 Renard Pl SE, Suite 103, Albuquerque, New Mexico, 87106, USA.
Tel: 505-938-9900 Fax: 505-938-9940 E-mail: dmapel@comcast.net

Figure 1. Therapy at each stage of COPD.



*Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD

Source: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD. Updated December 2007.

International guidelines recommend a long-acting bronchodilator (anticholinergic or long-acting β_2-agonist [LABA]) for symptomatic patients with moderate to severe COPD, and the addition of inhaled corticosteroid (ICS) for patients with severe disease and repeated exacerbations (see Figure 1).[5,6] These guidelines are based on data from randomised controlled trials (RCTs) and other studies which have shown that long-acting 'controller'-type therapies can help prevent exacerbations and other serious complications of this disease.

Combination therapy has become more feasible with the availability of single inhaler devices containing both LABA and ICS. A number of recent clinical trials and retrospective cohort studies suggest potential benefits from combining ICS and LABA therapy that are greater than the benefits seen with either drug type alone. This review focuses on the role of combination ICS/LABA therapy in managing COPD, including demonstrated clinical benefits and side-effect considerations that affect therapy decisions.

Clinical benefits

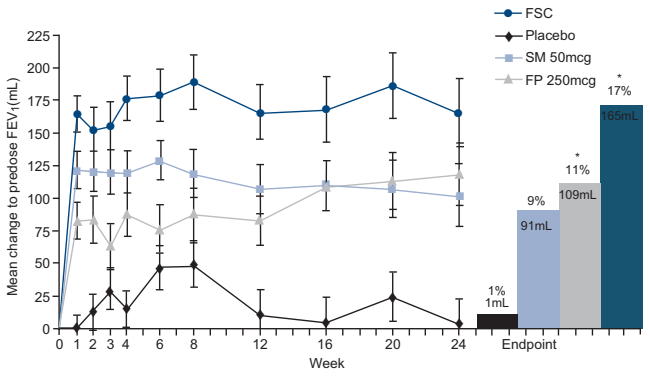
COPD comprises several components including bronchoconstriction, airway inflammation, airway remodeling, mucociliary dysfunction and systemic inflammation. Therapy for COPD has traditionally focused on symptom control, but more recent approaches also target the inflammation that underlies all stages of the disease.[7] LABAs have bronchodilator effects and ICS have strong anti-inflammatory effects. Together, however, the two agents demonstrate anti-inflammatory effects that are greater than the effects of ICS alone, suggesting complementary and synergistic interactions at the molecular level.[7-9]

Lung function

Clinical trials have demonstrated improvements in lung function, including airflow (usually described as the forced expiratory volume in one second, FEV_1), chronic bronchitis symptoms, symptom-free nights and night awakenings, frequency of rescue medication use, and quality of life in patients receiving ICS plus LABA compared to monotherapy with either agent (see Table 1 and Figure 2).[10-15] The ICS/LABA combination increases FEV_1 and has been shown to improve peak expiratory flow and breathlessness by the second day of treatment.[12,16] Combination ICS/LABA therapy has also demonstrated advantages compared to combination therapy with a short-acting anticholinergic and short-acting β_2-agonist, with greater improvements in dyspnoea, lung function and nocturnal symptom measures.[17,18]

There are also data suggesting that combination ICS/LABA therapy may help to preserve lung function in COPD. The TORCH study, a recently completed large RCT of 6112 patients with moderate to severe COPD, compared inhaled fluticasone propionate and salmeterol alone or in combination as a salmeterol/fluticasone propionate (FSC) inhaler, with placebo.[19] In this three-year study, FSC was associated with a slower rate of lung deterioration (FEV_1) compared to placebo.[20] An analysis of pooled results from seven placebo-controlled RCTs found a significantly reduced decline in FEV_1 among FSC users during the first six months of therapy.[21] Withdrawal of fluticasone propionate in patients using FSC has been shown to result in deterioration in lung function and dyspnoea and an increase in mild exacerbations, providing further evidence of the additive benefits of FSC combination therapy.[22]

Figure 2. Improvement in FEV_1 with fluticasone propionate/salmeterol combination therapy compared with fluticasone propionate alone, salmeterol alone and placebo.



*p<0.001, FSC vs placebo; p=0.012, FSC vs SM; p<0.001, FP vs placebo

Source: Hanania NA, Darken P, Horstman D, *et al.* The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus Inhaler for the treatment of COPD. *Chest*. 2003;**124**:834-43.

Table 1. Lung function in COPD: Results from randomised controlled trials of inhaled corticosteroid/long-acting β-agonist (ICS/LABA) combination therapy versus ICS or LABA monotherapy.

Study	No. of patients (duration)	Treatment comparisons	Primary outcome measure	Major findings
Calverley *et al*, 2003 [10]	1465 (52 weeks)	Twice daily FSC 500/50µg vs. FP 500µg, salmeterol 50 µg, or placebo	Lung function	At 52 weeks, pretreatment FEV_1 increased 10% (133cc) with FSC, 2% (95cc) with FP, and 2% (73cc) with salmeterol, and decreased 3% in the placebo group (p<0.0001 for all diff.)
Celli *et al*, 2008 [20]	5343 (3 years)	Twice daily FSC 500/50µg vs. FP 500µg, salmeterol 50µg, or placebo	Decline in lung function	FSC reduced rate of decline in FEV_1 by 16cc per year (p<0.001), compared to 13cc per year for either FP or salmeterol alone (p = 0.003), versus placebo.
Hanania *et al*, 2003 [13]	723 (24 weeks)	Twice daily FSC 250/50µg vs. FP 250µg, salmeterol 50µg, or placebo	Lung function	Morning pre-dose FEV_1 improved 17% (165cc) with FSC, 11% (109cc) with FP, 9% (91cc) with salmeterol, and 1% (1cc) with placebo.
Mahler *et al*, 2002 [14]	691 (24 weeks)	Twice daily FSC 500/50µg vs. FP 500µg, salmeterol 50µg, or placebo	Lung function	Morning pre-dose FEV_1 improved 15% (159cc) with FSC, 11% (105cc) with FP, and 10% (92cc) with salmeterol, vs. placebo (p<0.001 for all diff.)
Rennard *et al*, 2009 [55]	1964 (1 year)	BFC 320/9µg, BFC 160/9µg, formoterol 9µg or placebo	Lung function	Pre-dose FEV_1 at 12 months improved 12% (120cc) for 320/9µg dose, 9% (90cc) for 160/9µg dose, 3% (30cc) for formoterol alone, and decreased 2% (20cc) for placebo (p<0.05 for diff. between both BFC doses, formoterol, and placebo)
Tashkin *et al*, 2008 [56]	1704 (6 months)	BFC 320/9µg, BFC 160/9µg, budesonide 320µg, formoterol 9µg or placebo	Lung function	Pre-dose FEV_1 at 6 months improved 9% (90cc) for 320/9µg dose, 7% (70cc) for 160/9µg dose, 1% (10cc) for budesonide alone, 5% (50cc) for formoterol alone, and 1% (10cc) for placebo (p<0.05 for diff. between 320/9µg BFC and formoterol, budesonide, or placebo)

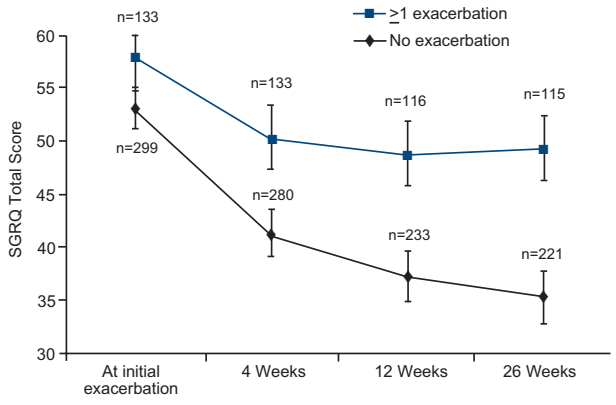
BFC, budesonide/formoterol combination therapy; FP, fluticasone propionate; FSC, fluticasone propionate/salmeterol combination therapy; NS, difference not statistically significant.

Additional benefits in lung function may be gained with the addition of an inhaled long-acting anticholinergic agent to ICS/LABA therapy.[9,23-25] Randomised controlled studies have found greater improvements in spirometric measures, as well as improved quality of life and reduced exacerbations, when ICS/LABA was added to tiotropium compared to either ICS/LABA or tiotropium alone.[9,23-25] With increased interest in combination therapy, it can be anticipated that more trials will be conducted to clarify the relative effects of various drug regimens on lung function and other markers of COPD.

Exacerbation reduction

A COPD exacerbation may be defined as a sustained worsening of respiratory symptoms, including cough, sputum production, shortness of breath, and wheezing.[8] Mild or moderate exacerbations are usually defined as those that require temporary increases in use of respiratory medications or short courses of outpatient antibiotics or systemic corticosteroid treatment, while severe exacerbations require hospitalisation.[8] Preventing exacerbations is an important goal

Figure 3. Impact of COPD exacerbations on health status.



SGRQ, St. George's Respiratory Questionnaire (a higher score indicates a worse respiratory health status; a change in score of at least 4 is needed to be considered a clinically significant change).

Source: Spencer S, Jones PW, for the GLOBE Study Group. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax*. 2003;**58**:589–93.

Table 2. Exacerbations in COPD: Results from randomised controlled trials of inhaled corticosteroid/long-acting β-agonist (ICS/LABA) combination therapy versus ICS or LABA monotherapy.

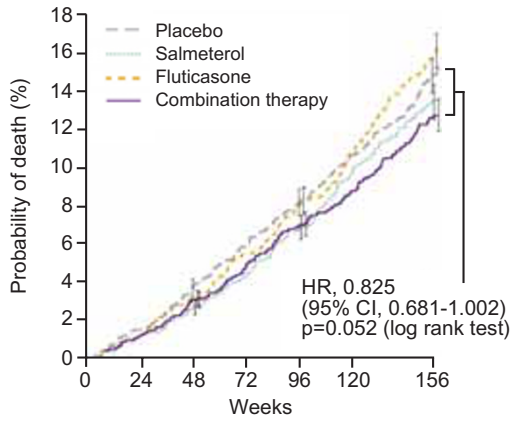
Study	No. of patients (duration)	Treatment comparisons	Exacerbation Reduction	Number needed to treat*
Anzueto *et al*, 2009 [31]	797 (52 weeks)	Twice daily FSC 250/50µg vs. salmeterol 50µg	FSC reduced moderate/ severe exacerbations by 30.4% vs. salmeterol alone	2.0 patients treated with FSC instead of salmeterol for one year to avoid one moderate/severe exacerbation*
			FSC reduced hospitalisations due to exacerbations by 36% vs. salmeterol alone	
Calverley *et al*, 2003 [11]	1022 (52 weeks)	Twice daily BFC 320/9µg vs. budesonide 400µg, formoterol 9µg, or placebo	22.7% lower rate of exacerbations with BFC vs. budesonide; 29.5% lower rate with BFC vs. formoterol	2.4 patients treated with BFC instead of formoterol for one year to avoid one moderate/severe exacerbation*
Ferguson *et al*, 2008 [32]	782 (52 weeks)	Twice daily FSC 250/50µg vs. salmeterol 50µg	30.5% lower rate of moderate/severe exacerbations with FSC vs. salmeterol	2.1 patients treated with FSC instead of salmeterol for one year to avoid one moderate/severe exacerbation*
Kardos *et al*, 2007 [33]	994 (44 weeks)	Twice daily FSC 500/50µg vs. s almeterol 50µg	35% lower rate of moderate/severe exacerbations with FSC vs. salmeterol	2.1 patients treated with FSC instead of salmeterol to avoid one moderate/severe exacerbation
Szafranski *et al*, 2003 [15]	812 (52 weeks)	Twice daily BFC 160/4.5µg vs. budesonide 200µg, formoterol 4.5µg or placebo	BFC reduced severe exacerbations by 24% versus placebo and 23% versus formoterol (p<0.05)	2.2 patients treated with BFC instead of placebo for one year to avoid one mild or severe exacerbation
			BFC reduced mild exacerbations by 62% versus placebo and 35% versus budesonide (p<0.05)	2.4 patients treated with BFC instead of formoterol for one year to avoid one mild or severe exacerbation
Calverley *et al*, 2007 [19]	6112 (3 years)	Twice daily FSC 500/50µg vs. FP 500µg, salmeterol 50µg, or placebo	12% lower rate of moderate/ severe exacerbations with FSC vs. salmeterol; 9% lower rate with FSC vs. FP	6.3 patients treated with FSC instead of salmeterol to avoid one moderate/severe exacerbation
			13% lower rate of exacerbations requiring oral corticosteroids with FSC vs. FP; 29% lower rate with FSC vs. salmeterol	3.6 patients treated with FSC instead of placebo to avoid one moderate/severe exacerbation

BFC, budesonide/formoterol combination therapy; FP, fluticasone propionate; FSC, fluticasone propionate/salmeterol combination therapy; NS, difference not statistically significant. * Calculated by the authors using available data.

of COPD management, since they accelerate deterioration in lung function, reduce quality of life and are associated with poorer prognosis (see Figure 3).[7,8,26,27]

A number of clinical trials have shown that ICS reduce COPD exacerbations by about 10-20%,[28,29] although the statistical methods used in some have been the subject of debate.[30] There is less evidence that LABA alone is effective in reducing exacerbations. A 12-month RCT found that salmeterol reduced exacerbations by 20% compared to placebo (P=.0027).[10] However, several trials have shown that combination ICS/LABA therapy is superior to LABA or ICS alone in reducing exacerbations.[11,15,19,31-33] In the TORCH study (n=6112), FSC therapy for three years reduced moderate/severe exacerbations by 25% compared to placebo (P<.001), by 12% compared to salmeterol (P=.002), and by 9% compared to fluticasone (P=.02),[19] and a recent analysis of TORCH data found that FSC was associated with a 31% reduction in exacerbations in patients with GOLD stage 2 disease.[34] In a 44-week RCT of 994 COPD patients randomised to either FSC or salmeterol, the FSC group had 35% fewer exacerbations than the salmeterol group (P<.0001).[33] A 12-month trial of 812 COPD patients observed a 35% lower rate of mild exacerbations with budesonide/formoterol combination (BFC) compared to budesonide alone (P=.022).[15] The same study found a 23% lower rate of severe exacerbations with BFC versus formoterol

Figure 4. Survival of patients receiving fluticasone propionate combination therapy, fluticasone propionate, salmeterol or placebo in the TORCH study.



Source: Calverley PM, Anderson JA, Celli B, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Eng J Med*. 2007;**356**:775-89.

(P=.043), but no difference versus budesonide (P=.385). More recently, two one-year RCTs observed a reduction in moderate/severe exacerbations of 30.4% (P<.001) and 30.5% (P<.001) with FSC compared to salmeterol.[31,32] In contrast, the 12-month TRISTAN trial observed no significant difference in the decrease in exacerbation rates between FSC and either salmeterol or fluticasone propionate alone.[10]

The effectiveness of combination ICS/LABA therapy in reducing exacerbations has also been compared to that of tiotropium. The INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study, a two-year trial with 1323 patients, reported that FSC was equivalent to tiotropium in reducing exacerbations but superior in terms of improved health status and significantly lowered mortality.[35] The INSPIRE study was a direct comparison of FSC to tiotropium without a placebo group, so it is difficult to know what the baseline untreated lung function, symptoms, and exacerbation rates were in the study population. However, long-acting bronchodilators are the accepted standard of care for moderate COPD or worse, so placebo controls are now considered unethical. Triple therapy with ICS/LABA and tiotropium is also clinically beneficial. In a six-month study, the rate of severe exacerbations was decreased by 62% when BFC was added to tiotropium therapy (7.6% vs. 18.5% in patients taking only tiotropium, P<.001).[25]

The different patient populations, definitions of exacerbations, trial duration, and power to detect exacerbations as an endpoint may have contributed to the disparities in findings across studies.[8,26] Overall, there is strong clinical trial evidence that combination therapy prevents exacerbations in patients with severe disease and more limited evidence for patients with milder disease.[8,34,36]

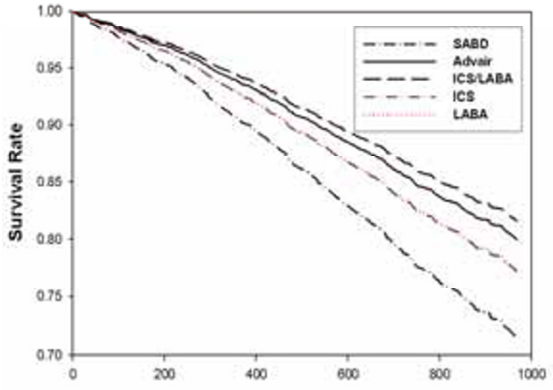
Survival

Data from RCTs and large historical cohort studies suggest that ICS plus LABA may confer a substantial survival benefit in COPD patients. The TORCH study demonstrated a 17.5% lower risk for death (absolute risk reduction of 2.6%) in the combination therapy group, although this finding did not reach statistical significance (95% confidence interval [CI], 0.681 to 1.002; P=.052) (see Figure 4).[19] A pooled analysis of seven RCTs showed a decrease in all-cause mortality of about 25% with ICS plus LABA relative to placebo (hazard ratio [HR] 0.73, 95% CI, 0.55 to 0.96).[37] A meta-analysis comparing combined ICS plus LABA to LABA alone did not find a survival benefit.[38] However, the TORCH study is the only ICS/LABA study designed with survival as its primary end point, so the disparity in these combined analyses says more about the limitations of combining dissimilar clinical trials than it does about the significance and reliability of their results. In several retrospective studies, FSC or ICS has been associated with significantly reduced mortality risk (Figure 5).[39-43] Other retrospective analyses have failed to find a survival benefit.[44-46] The exact mechanism by which FSC might impart a survival benefit is uncertain. However, the epidemiological and clinical trial evidence of improved survival is consistent with clinical data showing reduced risk for exacerbations, which are known to be associated with accelerated deterioration in lung function and increased risk of death.

Utilisation and healthcare costs

Direct medical costs for COPD patients are roughly twice those of non-COPD patients of the same age, and

Figure 5. Survival among COPD patients using fluticasone propionate/salmeterol in combination versus other inhaled steroids and bronchodilators.



Adjusted survival curves for Cox proportional hazards analysis. The differences between the four treatment groups (FSI, ICS/LABA, ICS, and LABA) and the reference group (SABD) are statistically significant ($p < 0.05$), while the differences among the four treatment groups do not reach significance.

Source: Mapel DW, Nelson LS, Lydick E *et al*. Survival among COPD patients using fluticasone/salmeterol in combination versus other inhaled steroids and bronchodilators alone. *COPD*. 2007;**4**:127-34.

exacerbation-related and emergency department (ED) visits account for a large fraction of COPD costs.[47] Treatments that reduce serious events can be expected to lower significantly the overall disease burden.[48] Combination ICS/LABA therapy has been associated with a decreased risk of hospitalisation in several studies. A retrospective study in managed care enrollees found that compared with ipratropium alone, ICS plus LABA was associated with a 47% lower risk for COPD hospitalisation (HR 0.533, 95% CI, 0.328 to 0.865) and 36% lower risk for any respiratory hospitalisation (HR 0.643; 95% CI, 0.512 to 0.808).[49] A study using the UK General Practice Database observed that patients with prescriptions for both ICS and LABA had a 38% lower risk for rehospitalisation or death than patients receiving ICS and SABA (HR 0.62; 95% CI, 0.43 to 0.87; P<.007).[50] Another study found a 41% reduced risk for rehospitalisation or death in the subsequent year following a COPD hospitalisation in patients discharged with ICS plus LABA compared to patients discharged with SABA (P<0.05).[43]

A lower risk for hospitalisation occurs even in newly diagnosed COPD patients treated with ICS and LABA. Using managed care claims data, Akazawa and colleagues found initial maintenance therapy with FSC was associated with a 32% lower risk of any hospitalisation or ED visit during the first six months of therapy compared with ipratropium alone (HR 0.685, 95% CI, 0.620 to 0.757), a greater risk reduction than was seen with fluticasone propionate or salmeterol alone or ipratropium plus albuterol.[51] In a study of newly diagnosed COPD patients in a Texas Medicaid population, FSC, but not fluticasone propionate or salmeterol alone, was associated with a 27% reduced risk for any COPD-related hospitalisation or ED visit compared to IPR (HR 0.733, 95% CI, 0.650 to 0.826).[48] A retrospective study of initial maintenance therapy in a cohort of 1051 Medicare-eligible health plan members with COPD found a 45% lower risk for COPD-related hospitalisations and ED visits in those receiving FSC compared to ipratropium (HR 0.547, 95% CI, 0.301 to 0.995).[52]

Combination therapy may result in decreased total health

Table 3. Risk for hospitalisation and emergency department visits in COPD: Observational studies of inhaled corticosteroid /long-actingβ-agonist (ICS/LABA) combination therapy versus other COPD therapy.

Study	No. of patients	Treatment comparisons	Primary outcome measure	Major findings
Akazawa *et al*, 2008 [51]	8551	FSC 250/50µg, salmeterol, ICS, ipratropium	Hospitalisations/ ED visits	32% lower risk of all-cause hospitalisation/ED with ICS/LABA vs. IPR; 21% lower risk with salmeterol vs. IPR; 23% lower risk with ICS vs. IPR 56% lower risk of COPD-related hospitalisation/ED with ICS/LABA vs. IPR; 34% lower risk with salmeterol vs. IPR; 37% lower risk with ICS vs. IPR
Anzueto *et al*, 2004 [49]	3616	IPR (with or without albuterol), LABA, ICS, ICS + IPR, ICS + LABA	Hospitalisations	36% lower risk of COPD-related hospitalisation with ICS vs. IPR; 47% lower risk with ICS + LABA vs. IPR
Blanchette *et al*, 2008 [52]	1051	FSC 500/50µg vs. IPR	Hospitalisations/ ED visits	Risk of all-cause hospitalisation/ED with FSC vs. IPR NS 45% lower risk of COPD-related hospitalisation with FSC vs. IPR
Delea *et al*, 2009 [54]	9217	FSC, ICS, salmeterol, IPR, and IPR + albuterol	Hospitalisations/ ED visits	16% lower risk of all-cause hospitalisation/ED with FSC vs. IPR 41% lower risk of COPD-related hospitalisation with FSC vs. IPR
Rascati *et al*, 2007 [48]	6793	FSC, ICS, salmeterol, IPR	Hospitalisations/ ED visits	9% lower risk of all-cause hospitalisation/ED with FSC vs. IPR 27% lower risk of COPD-related hospitalisation/ ED with FSC vs. IPR
Kiri *et al*, 2005 [50]	437	ICS + LABA (with or without SABA) and ICS + SABA	Rehospitalisations/ death	38% lower risk of COPD-related rehospitalisation/death with ICS + LABA vs. ICS + SABA
Soriano *et al*, 2003 [43]	3636	ICS, LABA or SABA	Rehospitalisations/ death	15% lower risk of hospitalisation/death with ICS vs. SABA; 41% lower risk with ICS/LABA vs. SABA

ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; SABA, short-acting β agonist; NS, difference not statistically significant.

care costs. Cost analyses have reported lower overall medical costs for FSC therapy compared to ipratropium therapy, even though pharmacy costs for FSC are higher.[48,51] The higher pharmacy costs are more than offset by reductions in outpatient and inpatient costs. Two studies found that annual pharmacy costs for patients receiving FSC were $415 and $570 higher, respectively, than for patients receiving ipratropium (both P<.05); however, annual non-pharmacy medical costs were $1,735 and $6,913 lower (both P<.05).[48,52] A third study observed no significant differences in annual total costs between FSC and ipratropium.[51] Relevant cost and utilisation studies are summarised in Table 3.

Adherence

Patient adherence to treatment regimens in COPD is not optimal and treatment persistence is generally low for inhaled medications.[53] Because LABAs provide symptom relief, however, patients are more likely to comply with scheduled dosing regimens when ICS and LABAs are combined in the same inhaler device.[8] An observational study of pharmacy claims found that medication compliance was 12% greater with FSC than with IPR (P<.05).[54] A second observational study noted that patients receiving FSC refilled their prescription more often in a 12-month period than patients receiving either salmeterol or ICS alone.[51] Thus, single inhaler ICS/LABA is an appropriate choice when both agents are needed and may result in better treatment adherence.[8,52]

Safety

Treatment with ICS/LABA is generally well tolerated. In several RCTs, rates of serious adverse events were no different for FSC than for other active or placebo treatments. Adverse event rates for TORCH, the trial with the longest duration to date, are provided in Table 4.[19] The most frequent adverse event associated with ICS use is oral candidiasis; patients should be educated about flushing their mouths with warm water after ICS use to eliminate any drug particles. In a safety substudy of the TORCH trial, there were no significant differences in bone density or incidence of cataracts between patients receiving active study drugs and the placebo group.[19] Therapy with BFC is also generally well tolerated and no difference in adverse event rates were seen between active drug and placebo groups in a 12-month trial.[11] In a second 12-month trial, no treatment-related differences in clinical chemistry, haematology or ECGs were observed.[15] The most frequent adverse event reported for BFC is respiratory tract infections,[7] including bronchitis.[55,56]

An unexpected result of the TORCH study was a higher incidence of pneumonia in the FSC and fluticasone propionate groups (19.6% and 18.3% respectively, compared to 13.3% in the salmeterol group and 12.3% in the placebo group, all P<.001).[19] There was no corresponding increase in pneumonia-related hospitalisations or deaths in the FSC group and the decrease in exacerbation events (0.28 events/100 patients/year) was greater than the increase in pneumonia events (0.03 events/100 patients/year). The INSPIRE study also found a higher incidence of pneumonia adverse events with FSC than tiotropium (8% vs. 4%; P<.01).[35] Similarly, an RCT that compared FSC to inhaled salmeterol over 44 weeks reported a higher incidence of pneumonia in the FSC group (4.5% vs. 1.8%; P-value not given).[33] However, because reported pneumonia events in these trials were not an anticipated adverse event, no specific measures were taken to capture information about how the diagnosis was made, nor were pneumonia events necessarily confirmed by chest X-ray, leading to uncertainty about the diagnosis. In contrast, no differences between groups in pneumonia events were seen in three recent trials of BFC, although as mentioned above, slightly higher rates of bronchitis were associated with BFC treatment in two trials.[25,55,56] Pneumonia was not reported as an adverse outcome in 13 previous RCTs of ICS.[57] Although the data are inconsistent, on balance the findings to date suggest the effect of increased pneumonia risk is real, albeit rather small, and additional research is warranted.

Therapy considerations

The decision about when to initiate combined ICS/LABA therapy is based on clinical judgments about when the benefits of therapy outweigh the potential risks. Current guidelines recommend ICS as add-on therapy in patients with stage III (severe, FEV_1= 30%-50% predicted) and stage IV (very severe, FEV_1 < 30%) COPD with chronic symptoms or repeated exacerbations (e.g., three in three years).[6] However, based on recent findings of the TORCH study that FSC is associated with a reduced rate of exacerbations, improved lung function and health-related quality of life, and possible survival benefits, European regulators recently approved its use in patients with milder COPD (FEV_1 ≤60% of predicted pre-bronchodilator value and history of exacerbations).[7]

The FSC combination is available as 100mcg, 250mcg or 500mcg of fluticasone propionate combined with the standard 50mcg of salmeterol per dose. The 250/50 strength is the only product approved in the USA for twice daily maintenance therapy to improve lung function and reduce exacerbations; the FDA has concluded that an efficacy advantage of the 500/50 over the 250/50 strength has not been demonstrated. The approved dose in Europe is 500/50 mcg and other regulatory authorities have approved both the 250/50 and 500/50 doses. The BFC combination is available as 40mcg, 80mcg or 160 mcg budesonide combined with 4.5mcg formoterol in a single inhaler. The 40/4.5 and 80/4.5 products are indicated for treatment of asthma and the 160/4.5 product for treatment of COPD. Guidelines suggest that when ICS is used in COPD, physicians should choose a

Table 4. Adverse events in the TORCH study. Adverse events among 6184 patients in the safety population and 658 patients in the substudy of bone mineral density.

	Placebo group (n=1544)	Salmeterol group (n=1542)	Fluticasone propionate group (n=1552)	Combination therapy (FSC) group (n=1546)
Reported during treatment--% of patients				
Any event	90	90	90	89
Serious event	41	40	42	43
Drug-related event	13	12	19	18
Event resulting in withdrawal or discontinuation of study medication	24	20	23	18
Total exposure to study medication--year	3278	3531	3555	3700
Most commonly reported event during treatment—rate per patient per year				
COPD exacerbation	0.92	0.76	0.78	0.67
Upper respiratory tract infection	0.10	0.08	0.09	0.11
Nasopharyngitis	0.09	0.09	0.10	0.10
Pneumonia	0.04	0.04	0.07	0.07
Bronchitis	0.05	0.05	0.05	0.05
Headache	0.08	0.06	0.06	0.05
Back pain	0.04	0.04	0.04	0.04
Sinusitis	0.03	0.03	0.04	0.04
Cough	0.03	0.03	0.04	0.03
Hypertension	0.03	0.03	0.03	0.02
Additional events associated with the use of corticosteroids—rate per year				
Candidiasis	0.02	0.02	0.09	0.07
Dysphonia	0.004	0.005	0.017	0.028
Of specific interest during treatment--% of patients				
Pneumonia	12.3	13.3	18.3*	19.6†
Fractures				
Total	5.1	5.1	5.4	6.3
Nontraumatic	1.8	2.5	1.7	1.7
Eye Disorders	3.6	4.3	4.1	5.2
Safety substudy				
Cataracts				
None at baseline—no. of patients/total no.	47/164	41/166	47/163	52/165
Developed during treatment – no. of patients/total no. (%)	10/47 (21)	6/41 (15)	8/47 (17)	14/52 (27)
Bone mineral density				
Hip—no of patients/total no.	52/164	78/166	65/163	82/165
Change from baseline --%	-3.1	-1.7	-2.9	-3.2
Lumbar spine—no of patients/total no.	50/164	76/166	63/163	81/165
Change from baseline--%	0	1.5	-0.3	-0.3

* P<0.001 for the comparison between the fluticasone propionate group and the placebo group.

† P<0.001 for the comparison between the combination therapy group and the placebo group and between the combination therapy group and the salmeterol group.

Source: Calverley PM, Anderson JA, Celli B *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Eng J Med*. 2007;**356**(8):775-89.

strength sufficient to establish control and then consider reducing the dose to a level that maintains control while minimising risk of side effects.

It should be noted that the FDA has placed a "black box" warning on all products containing LABAs due to studies in asthma patients suggesting an increased risk of serious asthma exacerbations and death in patients prescribed LABAs in addition to their regular asthma therapy.[58] However, there is no evidence of an increased risk of severe asthma exacerbations in adult asthma patients treated with ICS/LABA combinations. Furthermore, RCTs such as the TORCH study and retrospective studies that have followed COPD patients taking LABAs without ICS have consistently shown a trend towards improved survival. Therefore, in contrast to asthma guidelines, which recommend ICS as first-line treatment and the addition of LABAs for those not adequately controlled, COPD guidelines recommend a LABA or long-acting inhaled anticholinergic as initial therapy for COPD.[5,6]

Discussion

In our review, we have focused on the clinical outcomes and considerations of most interest to clinicians, and we have

emphasised data from RCTs. Although the available studies of ICS/LABA therapy are very encouraging, they are still few in number, and even RCTs are subject to methodological problems. For example, the comparison groups in the TORCH study had substantially higher drop-out rates due to exacerbations of COPD and other complications than the FSC group. Because clinical trials are designed *a priori* to report results using an intent-to-treat analysis approach, drop-outs contribute to the effect estimates and complication rates even though they did not stick with their allocated treatment group. The drop-out rates among ICS/LABA clinical trials have consistently been greater in the placebo groups. This results in a bias that usually reduces the power to detect a significant difference.[59] Others have cast doubts on studies that have used exacerbations as an outcome measure, suggesting that there is a difference in the response to therapy between steroid-naïve and -experienced patients.[60] However, this theory is based on a *post-hoc* analysis of one small study in which all patients were given a baseline treatment with tiotropium. These assertions have been tested and proven false in subsequent studies.[61]

To compensate for the limited amount of survival data, others have tried to combine the available ICS/LABA studies using meta-analyses.[38] However, a fundamental assumption for valid meta-analysis is that the studies that are included have similar study design, populations, and outcomes measures. The TORCH study is the only study specifically designed and powered with survival as the primary endpoint, and all TORCH subjects were followed for at least three years.[19] The 17 other clinical trials included in this meta-analysis[38] had enrolment criteria that specifically excluded unstable patients who were at risk of death, and these other studies followed patients for as little as eight weeks, and none more than 12 months. Furthermore, mortality among the 1,533 FSC users in TORCH was 12.6%, while mortality among the 3759 FSC users in these other studies was only 1.2%. The heterogeneity in these study designs and clinical populations creates a strong bias toward the null, making the conclusions from these analyses[38] highly suspect.

Proof of efficacy is best established using RCTs, but treatment effectiveness should also be proven in the general population where drugs are applied to a broader range of patients who do not meet narrow RCT inclusion/exclusion criteria, and where treatment compliance is usually much poorer.[37,39-46] Safety concerns also need to be examined in the general population. In a recent examination of 5245 COPD patients enrolled in three large managed care organisations in the USA, we found a small but non-significantly increased risk for pneumonia among ICS users (OR=1.29; 95%CI: 0.96-1.73), but no increase among those using ICS/LABA combinations (OR=1.03; 95%CI: 0.74-1.42) or LABA alone (OR=0.92; 95%CI: 0.69-1.22).[62] This risk increase among ICS users was minor in comparison with the increased pneumonia risk associated with advanced age or more severe disease.[63]

Conclusions

Not long ago, the poor prognosis and lack of treatment options for COPD caused most physicians to have a rather nihilistic attitude towards this disease. The availability of new treatments, including combination ICS/LABA inhalers, and growing evidence of their substantial clinical benefits, has caused a revolutionary change in our perspective.[64] In pharmacotherapy, the old palliative approach that focused on episodic symptom relief and improved FEV_1 is being replaced by an aggressive approach emphasising prevention of exacerbations, improvement in baseline function and quality of life, and improved survival.[6] Although a substantial minority of COPD patients who start ICS/LABA combination therapy will not experience an immediate change in their day-to-day symptoms, they may still benefit from reduction in frequency and severity of exacerbations, and preservation of long-term lung function. Patients need to be educated that their COPD maintenance medications need to be taken every day in order to avoid complications, much as patients have to take their blood pressure and cholesterol medications everyday in order to avoid strokes or heart attacks. Although data from clinical trials are still limited, combination ICS/LABA therapy has earned a place in the current management of a large proportion of the COPD patients who are managed by primary care physicians. All physicians who manage COPD patients need to be able to identify those patients who stand to benefit from ICS/LABA therapy and communicate the potential benefits and risks of therapy to those patients.

Conflict of interest declarations

Dr. Mapel has received research support from and served as a consultant to GlaxoSmithKline (GSK), Pfizer Pharmaceuticals and Boehringer-Ingelheim. Ms. Hurley has served as a consultant to GSK. Dr. Dalal is an employee of GSK and owns GSK company stock. Dr. Blanchette has received research support from and served as a consultant to GSK, AstraZeneca and Sepracor.

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