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CLINICAL REVIEW

# Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes

***Thys van der Molen[a], Mario Cazzola[b]**

[a] Department of General Practice, University Medical Center Groningen, Groningen, The Netherlands
[b] Medicina Interna, Università di Roma Tor Vergata, Rome, Italy

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## Abstract

Bronchodilators are central to the management of chronic obstructive pulmonary disease (COPD). Clinical studies combining different classes of bronchodilators, in particular a long-acting muscarinic antagonist (LAMA) and a long-acting $\beta_2$-agonist (LABA), have demonstrated greater improvements in lung function (forced expiratory volume in 1 second, $FEV_1$) in patients with COPD than monotherapy. $FEV_1$ has served as an important diagnostic measurement of COPD, and the majority of clinical studies of currently available pharmacotherapies grade effectiveness of treatment regimens based on improvements in $FEV_1$. However, $FEV_1$ alone may not adequately reflect the overall health status of the patient. Published evidence suggests that LABA/LAMA combination therapies demonstrate greater improvements in patient-centred outcomes such as dyspnoea, symptoms, rescue medication use, and quality of life than individual drugs used alone. Evaluating patient-centred outcomes associated with COPD is likely to play an important role in future research as a measure of overall treatment effectiveness. Raising awareness of the importance of outcomes beyond lung function alone, particularly in primary care where most patients initially present themselves for medical evaluation, should form a fundamental part of a more holistic approach to COPD management.


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## Introduction

Bronchodilators are the cornerstone of pharmacological management of chronic obstructive pulmonary disease (COPD), and current guidelines recommend their use as first-line therapy in symptomatic patients with airflow limitation.[1,2]

Short-acting bronchodilators are typically used for immediate relief of symptoms, with long-acting agents being preferred as maintenance therapy to prevent or reduce symptoms.[3,4]

For patients whose symptoms are not sufficiently controlled by maintenance monotherapy, the combined use of bronchodilators of different classes – in particular an inhaled muscarinic antagonist and a $\beta_2$-agonist – is a favoured strategy for maximising bronchodilation in COPD.[1] Using this combined approach, bronchodilation is obtained both directly, through stimulation of $\beta_2$-adrenergic receptors using $\beta_2$-agonists, and indirectly, by inhibiting the action of acetylcholine at muscarinic receptors using muscarinic antagonists. This proposed pharmacological interaction is supported by clinical evidence which suggests that combinations of long-acting $\beta_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) result in significantly greater improvements in lung function (forced expiratory volume in 1 second, $FEV_1$) than with individual components,[5,6] and that such improvements are maintained in the long term.[7,8]

Although improving lung function is a key goal of COPD pharmacotherapy, $FEV_1$ measurements alone may not adequately reflect the impact of a treatment on a patient, and improvements in patient-centred outcomes such as symptoms, dyspnoea, and health status may better reflect the effectiveness of a particular pharmacotherapy.[9,10] Furthermore, alternative outcome measures may better reflect the overall clinical status of the patient, and may be more significant to patients day-to-day.[11]

* Corresponding author: Professor Thys van der Molen, Department of General Practice, University Medical Center Groningen, PO Box 196, Groningen 9700AD, The Netherlands. Tel: +31 503 637 478 E-mail: t.van.der.molen@med.umcg.nl

Clinical investigations of LABA/LAMA combinations have included patient-centred outcomes as study endpoints; however, available study data have not been systematically evaluated by outcome. This review examines the clinical evidence published to date for the use of LABA/LAMA combinations in COPD, with a focus on outcomes beyond $FEV_1$ alone (see trial overview in Table 1). All trials administered tiotropium and indacaterol once daily and formoterol, arformoterol and salmeterol twice daily, unless otherwise stated.

**Table 1. Clinical trial characteristics: randomised studies of long-acting $\beta_2$-agonists combined with long-acting muscarinic antagonists**

| Authors | Design/duration | Patient characteristics ($FEV_1$ % predicted*) mean $FEV_1$# GOLD stage II† patient number | Treatment groups | Outcomes measured |
|---|---|---|---|---|
| **Formoterol plus tiotropium** | | | | |
| van Noord *et al.* 2006[2] | Randomised, open-label, crossover/2-week treatment periods | COPD (≤60)<br>mean $FEV_1$: 38<br>GOLD stage II: 41 n=95 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + formoterol 12µg qd<br>3. Tiotropium 18µg qd + formoterol 12µg bid | Serial 24-hr spirometry ($FEV_1$, FVC) and resting IC on day 1 and at 2 weeks; diary card PEF; use of salbutamol as rescue; safety |
| Berton *et al.* 2010[16] | Randomised, double-blind, crossover/2-week treatment periods | COPD (<70)<br>mean $FEV_1$: 47.4<br>GOLD stage II: NS n=33 | 1. Formoterol 12µg bid<br>2. Tiotropium 18µg qd + formoterol 12µg bid | Spirometry ($FEV_1$, FVC, IC, residual volume, TLC); dyspnoea (TDI); cardiopulmonary exercise tests (CPX) |
| van Noord *et al.* 2005[23] | Randomised, double-blind, crossover/6-week treatment periods | COPD (≤60)<br>mean $FEV_1$: 37.2<br>GOLD stage II: 28 n=71 | 1. Tiotropium 18µg qd<br>2. Formoterol 12µg bid<br>3. Tiotropium 18µg qd + formoterol 12µg bid | Spirometry ($FEV_1$, FVC), use of salbutamol as rescue |
| Tashkin *et al.* 2009[19] | Randomised, double-blind, parallel-group/12 weeks | Moderate and severe COPD (>30-<70)<br>mean $FEV_1$: NS<br>GOLD stage II: 23.9 n=255 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + formoterol 12µg bid | Spirometry ($FEV_1$, FVC); diary card recorded PEF; symptoms and use of salbutamol as rescue; dyspnoea (TDI); health status (SQRQ); safety |
| Vogelmeier *et al.* 2008[8] | Randomised, partially-blinded, placebo-controlled, parallel-group/24 weeks | Moderate and severe COPD (<70)<br>mean $FEV_1$: 51.6<br>GOLD stage II: NS n=847 | 1. Tiotropium 18µg qd<br>2. Formoterol 12µg bid<br>3. Tiotropium 18µg qd + formoterol 10µg bid<br>4. Placebo | Spirometry ($FEV_1$, FVC); health status (SGRQ); COPD exacerbations; symptom scores; use of salbutamol as rescue; PEF; 6-min walking distance |
| Wang *et al.* 2010[6] | Meta-analysis | n=1868 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + formoterol/arformoterol (10-20µg bid; 12µg qd) | Spirometry ($FEV_1$, FVC); dyspnoea (TDI); exacerbations |
| **Nebulised arformoterol or formoterol plus tiotropium** | | | | |
| Tashkin *et al.* 2009[15] | Randomised, modified-blind, parallel-group/2 weeks | COPD (≤65)<br>mean $FEV_1$: 45.4<br>GOLD stage II: NS n=235 | 1. Tiotropium 18µg qd<br>2. Nebulised arformoterol 15µg bid<br>3. Tiotropium 18µg qd + nebulised arformoterol 15µg bid | Spirometry ($FEV_1$, FVC, IC); dyspnoea (TDI); use of levalbuterol as rescue; safety |
| Tashkin *et al.* 2008[20] | Randomised, double-blind, parallel-group/6 weeks | COPD (≥25-<65)<br>mean $FEV_1$: 38.4<br>GOLD stage II: NS n=130 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + nebulised formoterol 20µg bid | Spirometry ($FEV_1$, FVC); dyspnoea (TDI); health status (SGRQ); diary card recorded symptoms and use of salbutamol as rescue; safety |
| Hanania *et al.* 2009[17] | Randomised, double-blind, parallel-group/6 weeks | COPD (≥25-<65)<br>mean $FEV_1$: 46.1<br>GOLD stage II: NS n=155 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + nebulised formoterol 20µg bid | Spirometry ($FEV_1$, FVC, IC); dyspnoea (TDI); daily symptom scores; health status (SGRQ); use of salbutamol as rescue; safety |
| **Salmeterol plus tiotropium** | | | | |
| van Noord *et al.* 2010[22] | Randomised, double-blind, crossover/6-week treatment periods | COPD (≤60)<br>mean $FEV_1$: 45<br>GOLD stage II: 33 n=95 | 1. Tiotropium 18µg qd<br>2. Salmeterol 50µg bid<br>3. Tiotropium 18µg qd + salmeterol 50µg bid<br>4. Tiotropium 18µg qd + salmeterol 50µg qd | Spirometry ($FEV_1$, FVC); dyspnoea (TDI), diary card recorded PEF; use of salbutamol as rescue |
| van Noord *et al.* 2005[21] | Randomised, double-blind, crossover/6-week treatment periods | COPD (NS)<br>mean $FEV_1$: 39<br>GOLD stage II: NS n=97 | 1. Tiotropium 18µg qd<br>2. Salmeterol 50µg bid<br>3. Tiotropium 18µg qd + salmeterol 50µg qd<br>4. Tiotropium 18µg qd + salmeterol 50µg bid | Dyspnoea (TDI); use of salbutamol as rescue |

**Table 1. Clinical trial characteristics: randomised studies of long-acting $\beta_2$-agonists combined with long-acting muscarinic antagonists (continued)**

| Authors | Design/duration | Patient characteristics ($FEV_1$ % predicted*) mean $FEV_1$# GOLD stage II† patient number | Treatment groups | Outcomes measured |
|---|---|---|---|---|
| Aaron *et al*. 2007[7] | Randomised, double-blind/ 1 year | Moderate or severe COPD (<65) mean $FEV_1$: 42 GOLD stage II: NS n=449 | 1. Tiotropium 18µg qd<br>2. Tiotropium 18µg qd + salmeterol 50µg bid<br>3. Tiotropium 18µg qd + salmeterol/fluticasone propionate 50/500µg bid | Proportion of patients experiencing an exacerbation; lung function; health status (SGRQ); hospitalisations; dyspnoea (TDI); safety |
| Indacaterol plus tiotropium | | | | |
| Mahler *et al*. 2011[18] | Randomised, double-blind (two studies of identical design)/12 weeks | Moderate and severe COPD (NS) Mean $FEV_1$: 49 (Study 1 and Study 2) GOLD stage II: NS n=1134 (study 1), n=1142 (study 2) | 1. Open-label tiotropium 18µg qd + placebo<br>2. Open-label tiotropium 18µg qd + indacaterol 150µg qd | Spirometry ($FEV_1$, IC); use of albuterol as rescue |

bid=twice daily, COPD=chronic obstructive pulmonary disease, $FEV_1$=forced expiratory volume in 1 second, FVC=forced vital capacity, IC=inspiratory capacity, NS=not stated, PEF=peak expiratory flow rate, qd=once daily, SGRQ=St George's Respiratory Questionnaire, TDI=transitional dyspnoea index.

*$FEV_1$ % predicted as inclusion criteria.

#Mean $FEV_1$ % predicted of recruited patients.

†Proportion of patients with moderate COPD, classified as GOLD stage II ($FEV_1$/FVC <0.70; 50%≤ $FEV_1$<80% predicted).

## Beyond spirometry: the effects of LABA/LAMA combination therapy

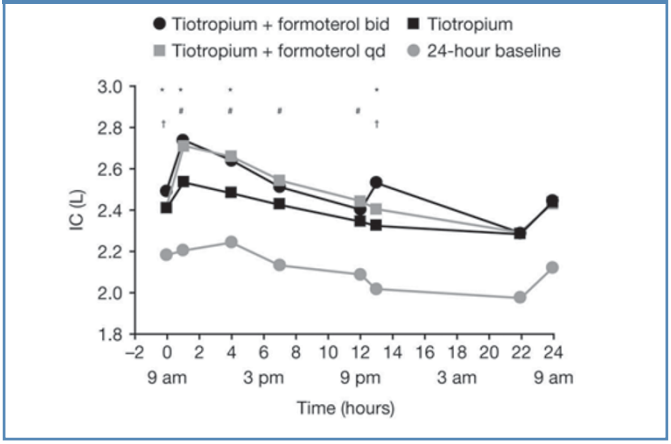
### Inspiratory capacity and reduction of hyperinflation

In patients with COPD, delayed lung emptying can lead to an increase in end-expiratory lung volume (EELV) and consequently lung overinflation or 'hyperinflation'. Increases in EELV correlate with decreases in inspiratory capacity (IC) in COPD, and patients can experience respiratory discomfort.[12-14] Therapies that improve IC (and reduce hyperinflation) may therefore help to lessen the respiratory discomfort experienced by patients with COPD.

There is limited clinical evidence for the effect of LABA/LAMA therapy on EELV/IC outcomes; however, treatment with tiotropium and formoterol/arformoterol combination has demonstrated efficacy over LABA monotherapy in three 2-week studies and one 6-week study.[2,15-17] In the first 2-week study, tiotropium with add-on formoterol once daily in the morning was shown to improve IC for >12 hrs compared with tiotropium alone, with further improvements in patients who received add-on formoterol twice daily; however, the duration of improvement of IC was <10 hrs following the evening formoterol dose (Figure 1).[2] There was no significant difference in trough IC response among the three treatment groups.

In the second 2-week study, nebulised arformoterol and tiotropium combination therapy provided a mean improvement from baseline in IC of 0.29±0.39L compared with 0.20±0.32L (arformoterol) and 0.19±0.32L (tiotropium).[15] The third 2-week study assessed the impact of tiotropium/formoterol combination therapy versus formoterol monotherapy on dynamic hyperinflation and exercise endurance in COPD patients.[16] IC was measured using constant-speed treadmill tests to the limit of tolerance (Tlim), or a maximum of 20 mins. Percentage improvement from baseline in Tlim was significantly greater after

**Figure 1. Mean IC before (24-hr baseline) and at the end of 2-week treatment periods (means adjusted for period, centre, and patient within centre).[2] *p<0.05 tiotropium + formoterol twice daily (bid) vs. tiotropium; #p<0.05 tiotropium + formoterol once daily (qd) vs. tiotropium; †p<0.05 tiotropium + formoterol twice daily vs. tiotropium + formoterol once daily. IC=inspiratory capacity**




combination therapy than with formoterol alone (124±27% vs. 68±14%, p<0.05). EELV was further reduced with the combination versus monotherapy (p<0.05). In addition, a 6-week study demonstrated a significant improvement in post-dose IC with nebulised formoterol plus tiotropium compared with tiotropium alone (p<0.005; peak IC improvement 230mL with combination therapy at week 6 vs. monotherapy).[17]

Furthermore, two 12-week studies demonstrated the superior efficacy of tiotropium and indacaterol combination therapy over LAMA monotherapy.[18] At week 12, addition of indacaterol to tiotropium provided significantly greater increases in trough IC (130mL and 100mL for studies 1 and 2, respectively)

compared with tiotropium alone (both p<0.01). Clinical evidence thus indicates that LABA/LAMA combination therapy improves IC (and, used as a surrogate marker, can therefore be considered to reduce hyperinflation) in patients with COPD.

## Dyspnoea

Dyspnoea is a common and troublesome manifestation of COPD and relief from dyspnoea is an important goal of pharmacotherapy.[1] Studies of LABA/LAMA combination therapy that included dyspnoea as an endpoint are detailed in Table 2. All studies of tiotropium and formoterol/arformoterol combination therapy improved dyspnoea (assessed by the Transitional Dyspnoea Index (TDI)) to a greater extent than either monotherapy.[6,15-17,19,20] Two further studies of tiotropium plus salmeterol (once or twice a day) also showed a marked improvement in dyspnoea with combination therapy over either monotherapy.[21,22] In a study by Aaron *et al.*,[7] no significant difference in mean TDI total score was demonstrated between tiotropium plus salmeterol, tiotropium plus salmeterol/fluticasone and tiotropium alone; however, it should be noted that a large number of patients discontinued during this study (61.0% completed), making it difficult to draw firm conclusions on efficacy between treatment groups.

A greater proportion of patients achieved the minimum clinically important difference (MCID) in TDI total score of ≥1 unit with combination therapies than with LABA or LAMA monotherapy. The proportion of patients achieving the MCID in TDI total score was 31.1–57.1% for tiotropium monotherapy, 48.0–66.7% for LABA monotherapy, and 57.7–77.9% for LABA/LAMA combination therapy.[17,19,20,22]

Overall, LABA/LAMA combination therapy demonstrated clinically relevant improvements in dyspnoea, greater than those seen with LABA or tiotropium alone.

**Table 2. Dyspnoea reported in long-acting $\beta_2$-agonist/long-acting muscarinic antagonist (LABA/LAMA) combination therapy clinical trials**

| Authors | Duration | Mean BDI score | Mean TDI total score | Patients achieving MCID (change ≥1 unit) in TDI total score, n (%) |
|---|---|---|---|---|
| Berton *et al.* 2010[16] | 2 weeks | <9* | Formoterol: 2.9<br>Tiotropium + formoterol: 3.8 (p=0.054 vs. formoterol) | – |
| Tashkin *et al.* 2009[15] | 2 weeks | Nebulised arformoterol: 5.8<br>Tiotropium: 5.8<br>Tiotropium + nebulised arformoterol: 5.5 | Nebulised arformoterol: 2.3<br>Tiotropium: 1.8<br>Tiotropium + nebulised arformoterol: 3.1 | Nebulised arformoterol: 50 (66.7%)<br>Tiotropium: 44 (57.1%)<br>Tiotropium + nebulised arformoterol: 60 (77.9%) (statistically significant vs. tiotropium; 95% CI 0.06, 0.35) |
| Tashkin *et al.* 2008[20] | 6 weeks | Tiotropium: 6.4<br>Tiotropium + nebulised arformoterol: 6.3 | Tiotropium: 0.16<br>Tiotropium + nebulised arformoterol: 2.3 (LS mean difference vs. tiotropium=1.80; 95% CI, 0.859 to 2.740, p=0.0002) | Tiotropium: 63 (31.1%)<br>Tiotropium + nebulised arformoterol: 66 (57.7%) |
| Hanania *et al.* 2009[17] | 6 weeks | Tiotropium: 5.80<br>Tiotropium + formoterol: 5.92 | Tiotropium: 0.87<br>Tiotropium + formoterol: 1.59<br>(LS mean difference vs. tiotropium= 0.72; –0.16 to 1.60, p=0.11) | Tiotropium: 34 (47.2%)<br>Tiotropium + formoterol: 45 (58.4%) |
| van Noord *et al.* 2010[22] | 6 weeks | 7.0 | Tiotropium: 1.18<br>Salmeterol bid: 0.97<br>Tiotropium + salmeterol qd: 2.56<br>Tiotropium + salmeterol bid: 2.71<br>(p<0.005 for tiotropium + salmeterol (qd or bid) vs. either monotherapy) | Salmeterol bid: 95 (48%)<br>Tiotropium: 95 (57%)<br>Tiotropium + salmeterol qd: 95 (67%)<br>Tiotropium + salmeterol bid: 95 (72%) |
| van Noord *et al.* 2005[21] | 6 weeks | 6.9 | –<br>(tiotropium + salmeterol (bid or qd) superior to either monotherapy in perceived dyspnoea) | – |
| Tashkin *et al.* 2009[19] | 12 weeks | Tiotropium: 5.67<br>Tiotropium + formoterol: 5.34 | Tiotropium: 1.53<br>Tiotropium + formoterol: 1.60<br>(difference between treatments significant only at week 8 (1.86 tiotropium + formoterol vs. 1.01 tiotropium; 95% CI 0.18 to 1.51; p=0.013) | – |
| Aaron *et al.* 2007[7] | 1 year | Tiotropium: 6.3<br>Tiotropium + salmeterol: 6.5<br>Tiotropium + salmeterol/fluticasone: 6.5 | Tiotropium: 1.78<br>Tiotropium + salmeterol: 1.40<br>Tiotropium + salmeterol/fluticasone: 1.84<br>(no significant difference between treatment groups) | – |
| Wang *et al.* 2010[6] | Meta-analysis | – | –<br>Mean change in TDI greater with tiotropium + formoterol vs. tiotropium (p<0.0001) | –<br>Larger proportion of patients receiving tiotropium + formoterol achieved clinically significant change in TDI vs. tiotropium (p<0.0001) |

BDI=baseline dyspnoea index, bid=twice daily, MCID=minimum clinically important difference, qd=once daily, TDI=transitional dyspnoea index.

*Specified as inclusion criteria, value not stated.

### Symptoms, symptom scores, and rescue medication use

Several studies have assessed the impact of LABA/LAMA combination therapy on patient-reported respiratory symptoms, and on the use of rescue medication to relieve symptoms.

In a 6-week study, shortness of breath, chest tightness, night-time awakenings, and total respiratory symptom scores all significantly improved with nebulised formoterol plus tiotropium compared with tiotropium alone. Cough scores also improved, but did not significantly differ between treatment groups.[20] Another 6-week study found no difference in overall symptom scores following treatment with nebulised formoterol plus tiotropium or tiotropium monotherapy.[17] In a 12-week study, a combination of formoterol and tiotropium significantly improved symptom scores from baseline to last study visit compared with tiotropium alone, although there was no difference between groups in the number of nocturnal awakenings.[19] A longer-term study (6 months) showed no difference in average daily symptom scores for patients receiving combination therapy (formoterol plus tiotropium) compared with those receiving bronchodilator monotherapy.[8]

Short-acting $\beta_2$-agonists (e.g. salbutamol/albuterol) are often used by COPD patients as rescue medication to help alleviate symptoms. Short-term (≤6 weeks) and longer-term (≥12 weeks) studies demonstrated a decrease in rescue medication use with tiotropium and LABA (formoterol/arformoterol/salmeterol) combination therapy compared with either monotherapy, which may be associated with the improvements in symptoms observed with LABA/LAMA combination therapies in these studies.[2,8,15,17,19-23] The reduction in rescue medication use in a 2-week and 6-week study of tiotropium plus formoterol compared with tiotropium is shown in Figure 2.[2,17] Two 12-week studies also demonstrated a numerically greater reduction in rescue medication use with tiotropium/indacaterol combination therapy compared with tiotropium alone.[18]

Overall, there was a trend for improvement in symptom scores and rescue medication use in favour of combination therapy compared with monotherapy.

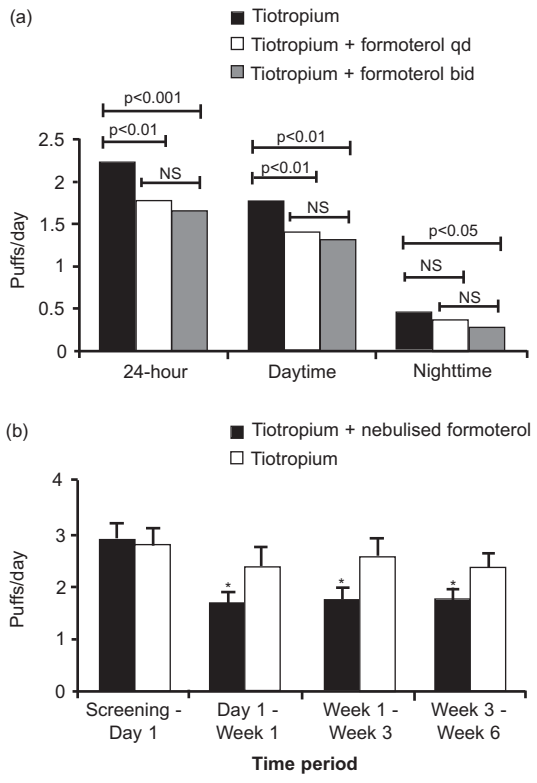
### Exacerbations

Prevention of exacerbations is one of the most important goals of COPD management. However, only a small number of LABA/LAMA combination studies have included exacerbations as an endpoint, and across these studies the definition of an exacerbation differs (or is not detailed), making it difficult to draw conclusions on efficacy (Table 3). Overall, no significant difference was demonstrated in the incidence of exacerbations or the time to first exacerbation between LABA/LAMA combination treatments and monotherapy.[6-8,19] Further studies assessing the impact of combination bronchodilator therapy on COPD exacerbations are required.

### Health status

As COPD progresses, the ability to function and perform activities on a daily basis reduces and, consequently, health status deteriorates.[1,24] The St George's Respiratory Questionnaire (SGRQ) is a validated measure of health status that is frequently used in clinical trials.[24] The MCID is defined as a decrease from baseline or placebo of ≥4 points in the SGRQ total score.

**Figure 2. Mean number of puffs of rescue medication (salbutamol) per day over (a) 2-week[2] and (b) 6-week[17] treatment periods. NS=not significant, SEM=standard error of mean. *p<0.05 vs. tiotropium**




A total of five studies have examined the effect of LABA/LAMA treatment on health status, and all used the SGRQ as the assessment tool.[7,8,17,19,20] In longer-term studies (≥12 weeks), both LAMA (tiotropium) and LABA/LAMA combination therapies improved total SGRQ from baseline (Table 4).[7,8,19] In two studies the improvement in SGRQ with tiotropium plus formoterol or tiotropium plus salmeterol was greater than with tiotropium alone, with the difference attaining statistical significance in one study.[7,19] These two studies also reported the values for change in total SGRQ, indicating that the total scores were around the MCID for tiotropium (improvement of 3.8 and 4.5) and well above the MCID for tiotropium plus formoterol or salmeterol (4.81 and 6.3).[7,19] These results indicate that the improvement in SGRQ total score was clinically significant with LABA/LAMA treatment. In a third long-term study, the improvements in SGRQ total score with tiotropium, formoterol, and tiotropium plus formoterol were significantly greater than with placebo, but did not show any significant difference between treatment groups.[8] The lack of a consistent statistically significant difference in improvement in the SGRQ score between LAMA and LABA/LAMA treatment may be

**Table 3. Exacerbations reported in long-acting $\beta_2$-agonist/long-acting muscarinic antagonist (LABA/LAMA) combination therapy clinical trials**

| Authors | Duration | Exacerbation definition | Incidence of exacerbations, n (%) | Mean duration of exacerbation | Time to first exacerbation (days) |
|---|---|---|---|---|---|
| Tashkin *et al.* 2009[19] | 12 weeks | – | Tiotropium: 14 (11%)<br>Tiotropium + formoterol: 21 (17%)<br>(no significant difference between treatment groups; p=0.149) | Tiotropium: 19.4 days<br>Tiotropium + formoterol: 16.2 days | – |
| Vogelmeier *et al.* 2008[8] | 24 weeks | 'COPD exacerbation days' = days with at least two symptoms (0-3 scale of breathlessness, cough, wheeze, amount of sputum, colour of sputum) recorded as being worse than usual | Tiotropium: 23 (10.4%)<br>Formoterol: 17 (8.1%)<br>Tiotropium + formoterol: 13 (6.3%)<br>Placebo: 30 (14.4%) | Formoterol: 2.4†<br>Tiotropium: 3.3†<br>Tiotropium + formoterol: 3.3† | – |
| Aaron *et al.* 2007[7] | 1 year | At least one exacerbation of COPD requiring treatment with systemic steroids or antibiotics within the 12 months before randomisation | Tiotropium: 98 (62.8%)<br>Tiotropium + salmeterol: 96 (64.8%)<br>Tiotropium + salmeterol/fluticasone: 87 (60.0%)<br>(no significant difference in absolute risk reduction between either combination therapy and tiotropium) | – | Tiotropium: 130<br>Tiotropium + salmeterol: 128<br>Tiotropium + salmeterol/fluticasone: 217 (compared with tiotropium, tiotropium + fluticasone/salmeterol did not statistically prolong time to first exacerbation; adjusted HR=0.80 (95% CI0.60 to 1.08, p=0.15) |
| Wang *et al.* 2010[6] | Meta-analysis | – | Tiotropium: 8.9%*<br>Tiotropium + formoterol: 8.3%*<br>(no difference between treatment groups: OR=0.93, 95% CI 0.45 to 1.93, p=0.85) | – | – |

HR=hazard ratio, OR=odds ratio. *Overall cumulative incidence. †COPD exacerbation days (% of treatment days).

because of the substantial improvement attained in both treatment groups, making differentiation between treatments difficult. Moreover, as assessment of health status was not the primary endpoint in these studies, it is unlikely the studies were sufficiently powered to show a difference in SGRQ total score between active treatments.

Two short-term studies (6 weeks) of tiotropium plus nebulised formoterol versus tiotropium monotherapy found no difference in SGRQ scores from baseline to week 6 or between treatments.[17,20] This is perhaps not surprising given the short duration of the studies; the effect of treatment on health status may not be apparent after only 6 weeks of treatment.

The improvement in SGRQ total score with LABA/LAMA treatment appears to be driven by the effect on the symptom domain of the SGRQ rather than the domains of activity or impact. Indeed, several studies have shown an improvement in the symptom domain with LABA/LAMA treatment compared with LAMA monotherapy, which was statistically significant in two studies.[8,19,20]

The studies identified here all used the SGRQ to assess health status. This is a comprehensive questionnaire that takes time to complete and score, limiting its use in routine clinical practice.[10]

**Table 4. Health status reported in long-acting $\beta_2$-agonist/long-acting muscarinic antagonist (LABA/LAMA) combination therapy clinical trials**

| Authors | Duration | Total SGRQ score | SGRQ domain score |
|---|---|---|---|
| Tashkin *et al.* 2008[20] | 6 weeks | –<br>No significant difference between treatment groups (tiotropium; tiotropium + nebulised formoterol) | Symptom score: tiotropium: +0.5; tiotropium + nebulised formoterol: –5.8 (p=0.04, 95% CI, –12.2 to –0.35)<br>No significant difference between treatment groups for activity or impact scores |
| Hanania *et al.* 2009[17] | 6 weeks | –<br>No significant difference between treatment groups | –<br>No significant difference between treatment groups (tiotropium; tiotropium + nebulised formoterol) |
| Tashkin *et al.* 2009[19] | 12 weeks | Tiotropium: –3.80<br>Tiotropium + formoterol: –4.81<br>No significant difference between treatment groups | Symptom score: tiotropium: –3.97; tiotropium + formoterol: –8.33 (p<0.05 vs. tiotropium alone)<br>No significant difference between treatment groups for activity or impact scores |
| Vogelmeier *et al.* 2008[8] | 24 weeks | –<br>No significant difference between treatment groups (tiotropium; formoterol; tiotropium + formoterol) | –<br>Symptom score: significantly different from placebo for all treatment groups (tiotropium; formoterol; tiotropium + formoterol)<br>No significant difference between treatment groups for activity or impact scores |
| Aaron *et al.* 2007[7] | 1 year | Tiotropium: –4.5<br>Tiotropium + salmeterol: –6.3 (p=0.02 vs. tiotropium)<br>Tiotropium + salmeterol/fluticasone: –8.6 (p=0.01 vs. tiotropium) | – |

SGRQ=St George's Respiratory Questionnaire.

The effect of LABA/LAMA combination on health status measured with shorter questionnaires designed for use in clinical practice such as the Clinical COPD Questionnaire (CCQ)[25] and the COPD Assessment Test (CAT)[26] are currently being investigated.

### Safety

Any new LABA/LAMA combination must also take safety into consideration as additional efficacy or health status benefits must not be at the expense of safety. Several studies have shown no increase in frequency or severity of adverse events with tiotropium plus formoterol compared with tiotropium alone.[2,6,8,15,17,19,20,23] The most common adverse event with both treatments was COPD exacerbation, and the combination was not associated with any clinically relevant changes in laboratory variables.[2,6,8,15,17,19,20,23] Similar findings were recently reported in two large 12-week studies in which concurrent treatment with indacaterol and tiotropium did not increase the incidence of adverse events, serious adverse events, notable laboratory variables (plasma potassium and blood glucose), and ECG findings (QTc interval) compared with tiotropium alone.[18] In another recent study, QVA149, a fixed-dose combination of indacaterol and a LAMA (NVA237), was well tolerated in patients with COPD, with a cardiovascular safety profile and overall adverse event rate similar to placebo.[27]

## LABA/LAMA combination therapy and the future of COPD management

Current guidelines recommend the addition of a second bronchodilator to initial monotherapy in moderate COPD in order to maximise bronchodilation,[1] and the impact of LABA/LAMA combinations on $FEV_1$ has been established.[5] The studies detailed in this review indicate that LABA/LAMA combinations are also effective at improving patient-centred outcomes; however, additional studies assessing these outcomes are needed.

The trials considered here have reported on the free combination of a LABA (salmeterol or arformoterol/formoterol (once or twice a day) or indacaterol (once a day)) with tiotropium. Fixed-dose LABA/LAMA combinations are not currently available; however, the convenience of both agents in a single device may increase compliance and help to simplify COPD management further. It is likely that treatment options for COPD patients will expand further in the future to include free and fixed combinations of new LABAs or LAMAs (including once-daily fixed-dose combinations), which may lead to even greater improvements in patient-centred outcomes.

There are currently a number of LABA/LAMA fixed-dose combinations in development for COPD.[28] QVA149 (an inhaled fixed-dose combination comprising two 24-hr agents, the LABA indacaterol and the LAMA NVA237) has demonstrated rapid and sustained bronchodilation with significant improvements compared with indacaterol monotherapy.[29] Phase III trials in COPD to assess the long-term efficacy and safety of once-daily QVA149 are in progress. Initial studies with a once-daily fixed-dose combination of the LABA olodaterol and tiotropium have also demonstrated superior bronchodilation in COPD compared with tiotropium alone.[30] Other COPD treatment options in development include formoterol plus the LAMA aclidinium, and the LABA vilanterol plus the LAMA GSK-573719.[31] Furthermore, novel compounds are being developed which act as dual antimuscarinic/$\beta_2$-adrenergic receptor agonists (e.g. GSK-961081 and PF-3429281).[31,32]

Despite the promising improvements in lung function demonstrated with current treatments, the question remains whether interventions that significantly improve $FEV_1$ are also associated with improvements in other outcome measures. Several studies have demonstrated a significant relationship between poor lung function and a decline in health status in patients with COPD;[33-38] however, there is limited evidence that changes in lung function associated with a therapeutic intervention correlate with changes in patient-centred outcomes. In a recent analysis, pooled data from three indacaterol studies (12, 26, and 52 weeks in duration) were used to examine relationships between change from baseline of $FEV_1$ and clinical outcomes (dyspnoea (TDI score), health status (SGRQ score) and exacerbations).[39] The results of this analysis suggest that treatment interventions that significantly improve $FEV_1$ are likely to be associated with greater improvements in patient-centred outcomes.

## Conclusions

Studies of LABA/LAMA combinations to date indicate that combining different classes of bronchodilator results in significantly greater improvements in lung function and other meaningful outcomes such as IC, dyspnoea, symptom scores, rescue medication use, and health status compared with individual drugs. Additional studies assessing the impact of LABA/LAMA combination therapies on COPD exacerbations, using a standardised definition of an exacerbation, are clearly needed. Other elements of importance to patients such as exercise capacity, hospitalisations, depression, and pain are likely to be explored.

Bronchodilators remain central to the symptomatic management of COPD and as such, LABA/LAMA combination therapy could play an important role in maximising bronchodilation and improving IC, symptoms, health status and dyspnoea in patients with COPD. The last item is particularly important in those patients with moderate-to-severe disease, whose dyspnoea during daily activities is not relieved by short-acting bronchodilators and who require more effective LABA, LAMA, and combination treatments. The value of $FEV_1$ alone as a surrogate marker of COPD is limited, and patient-centred outcomes are important for both adequate recognition of the disease and effective treatment of patients. Importantly, guidelines also now recognise the significance of such patient-centred outcomes in clinical trials of COPD therapies, with a view that they will better reflect the overall well-being of the patient, beyond lung function measurements alone.

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