

# Fixed combination therapies in COPD – effect on quality of life

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**Abstract:** Chronic obstructive pulmonary disease (COPD) represents a major global cause of disability and death. COPD is currently the fourth most common global cause of death and also exerts an enormous toll on patients quality of life. The present database analysis aimed to identify clinical trials using fixed combination therapies that have assessed the impact on the patients quality of life. Within the different studies, questionnaires including the George's Respiratory Questionnaire (SGRQ) the Chronic Respiratory Disease Questionnaire (CRDQ) and the Clinical COPD Questionnaire (CCQ) were used and differing results in quality of life were obtained when combination therapies such as fluticasone/salmeterol or fluticasone/salmeterol were compared with monotherapies. While there were some differences in favor of combination therapies reported when the combination therapy was compared to inhaled steroid monotherapy there were no consistent differences when combination therapies were compared to bronchodilator monotherapies. Future trials will lead to a proof-of-principle stage concerning the use of combination therapies.

**Keywords:** COPD, combination therapy, corticoid, steroid, corticosteroid

## Introduction

Chronic obstructive pulmonary disease (COPD) has evolved as one of the major global causes of death and disability over the past decades (Hansen-Flaschen 2003). The global burden of disease studies reported in alarming increase in COPD prevalence (Murray and Lopez 1997a, b, c). As with other respiratory diseases, COPD is related to exposure against air pollutants (Boschetto et al 2006; Groneberg-Kloft et al 2006). In 1990, the disease was classified as the sixth most common global cause of death. For the year 2020, it was predicted that COPD would become the third commonest cause of death irrespective of public-health intervention. Also, COPD was reported to become the fourth most important disease leading to disability by the year 2020 (Murray and Lopez 1997a, b, c). WHO studies lead to the assumption that these predictions are likely to be correct since COPD had become the fourth commonest global cause of mortality (Murray et al 2001). The National Heart, Lung, and Blood Institute reported for the US that COPD has increased in importance during the past two decades in contrast to all other causes of chronic disability (National Heart 2002). Concomitant with these increases, COPD is more often diagnosed by general practitioners as reported for the UK: Here, an increase in COPD diagnosis was reported for the period 1990–1997 (Soriano et al 2000) which was paralleled by an increase in COPD-related hospital admissions (Calverley and Walker 2003). In the context of disease management, acute exacerbations are important clinical events in COPD and largely contribute to a decline of quality of life. The life quality in patients with COPD as assessed, ie, by activities of daily living, emotional functioning, social-role functioning, and recreational pastimes was found to be impaired relative to healthy subjects on all dimensions (McSweeney et al 1982;

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Jones et al 1992; Ketelaars et al 1996; Hajiro et al 1998). Depression was the preponderant emotional disturbance reported, difficulties with home management and reduction in social interaction were the primary social-role deficits while sleep and rest, mobility, and a variety of recreational pastimes were also severely affected (McSweeney et al 1982). Patients with COPD also only have low expectations of medical care, and many of them do not complain despite substantial disease-associated disabilities (Rennard et al 2002). This reluctance to ask for an increased attention may be related to increased emotional disturbances such as depression (McSweeney et al 1982).

As COPD is characterized by a variable pathology among patients (Welte and Groneberg 2006) and there are no specific "COPD-drugs" available, an international standardization of disease management has been difficult to establish over the past years. However, with an increasing significance of COPD concerning the global burden of disease, important guidelines to optimize disease management were proposed by several thoracic societies and international organizations in the past years (Society 1987; Siafakas et al 1995; Fabbri et al 1998; Balter et al 2003). The most prominent guidelines are the Global initiative for chronic Obstructive Lung Disease (GOLD) which was initiated by the WHO and the US National Heart, Lung, and Blood Institute (Pauwels et al 2001) and the international guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (Celli and MacNee 2004).

Prior to assessing the impact of drug therapies it is crucial to define the disease entity since there have been various approaches towards the definition in the past decades. The clinical diagnosis of COPD largely relies on the patient's history and abnormal lung function tests. As COPD is characterized by a variable pathology and the molecular mechanisms are not completely understood, it has been difficult to agree on a simply disease definition. First approaches based on epidemiological features of chronic cough and sputum production such as lasting of symptoms for 3 months over a period of at least 2 years (chronic bronchitis) or on pathological features such as the identification of emphysema in COPD airway tissues. However, these approaches did not prove to be efficient in the clinical management of the disease.

A keystone in the approach towards a rational disease definition is represented by the first reports that related disability and death in COPD to a progressive decrease in the forced expiratory volume in 1 second ( $FEV_1$ ) (Fletcher and Peto 1977; Peto et al 1983).

**Table 1** Stage-specific therapy of stable COPD. Potential use of combination therapy with inhaled corticosteroid and bronchodilator instead of bronchodilator monotherapy

<b>Stage 0: At Risk</b>	<ul style="list-style-type: none"> <li>Avoidance of risk factors, influenza vaccination</li> </ul>
<b>Stage I: Mild</b>	<ul style="list-style-type: none"> <li>Add: short-acting bronchodilator when needed</li> </ul>
<b>Stage II: Moderate</b>	<ul style="list-style-type: none"> <li>Add: regular treatment with one or more long-acting bronchodilators</li> <li>Question: Is fixed combination therapy superior?</li> <li>Add: rehabilitation</li> </ul>
<b>Stage III: Severe</b>	<ul style="list-style-type: none"> <li>Add: inhaled corticosteroids if repeated exacerbations</li> </ul>
<b>Stage IV: Very severe</b>	<ul style="list-style-type: none"> <li>Add: long-term oxygen if chronic respiratory failure</li> <li>Consider: Surgical options</li> </ul>

It is now generally accepted that COPD diagnosis crucially relies on the presence of airflow obstruction defined as decreased  $FEV_1$  to FVC (forced vital capacity) or vital capacity ratio. However, it should also be critically remarked that lung function only partly correlates to other prognosis parameters. Therefore, the BODE (body-mass index, airflow obstruction, dyspnea, and exercise capacity index) score was developed (Celli et al 2004).

Extending the basic functional features, the GOLD guidelines introduced persistent inflammation and the potential presence of noxious stimuli to the disease definition. With the persistent inflammation being an accepted feature of the disease, the question arises whether combination therapies with inhaled bronchodilators and steroids are superior to monotherapies with inhaled bronchodilators (Table 1). Therefore the present analysis aims to assess the effects of the fixed combination therapies budesonide/formoterol and fluticasone/salmeterol on the quality of life.

## Methods

### Sources

Clinical trials were identified by the use of the PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL. Also, hand-searching of pulmonary journals and meeting abstract booklets was performed. The terms "COPD" and "chronic obstructive pulmonary disease" were searched in combination with the terms (quality of life), (\*steroid or steroid\* OR corticosteroid\*) and ((beta\* and agonist\*) and long\*) or ((beta\* and adrenergic\*) and long\*) and (formoterol and

budesonide) or Symbicort and (fluticasone and salmeterol) or Seretide or Advair. The most recent search was run in July 2007.

## Analysis

The analysis was performed by independently identifying abstracts of trials which appeared relevant. Then the full text of each study was used and trials were selected for inclusion in the analysis. After a preliminary assessment of all studies was performed to confirm the basic requirements, the methodological quality of the included studies was assessed using accepted Cochrane criteria with grade A: adequate concealment, grade B: uncertain, grade C: clearly inadequate concealment.

## Results

### Data selection

Using database searches a large number of entries related to COPD (Figure 1) and quality of life (Figure 2) was found that was further classified and analysed for publication dates (Figure 3) and the following study parameters.

### Trial quality

All included trials had a randomized, double-blind, placebo controlled parallel group design. Methods of randomization were described only in one study (Mahler 2002). Method of blinding was not fully described in all trials. All included participants suffered from COPD, with variable definition of COPD and reversibility.

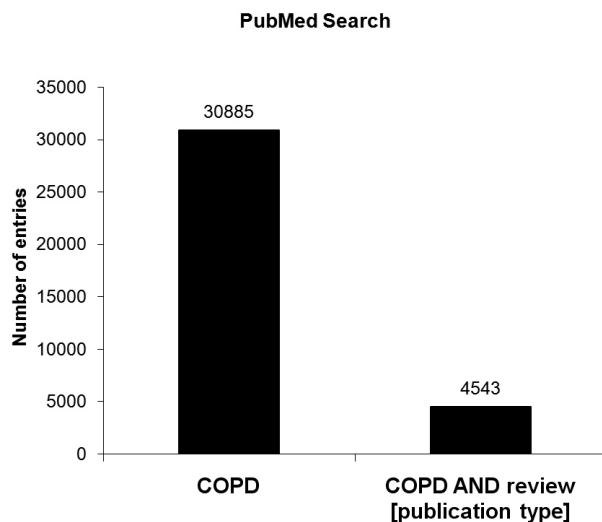


Figure 1 Database analysis for COPD. Search date: 2007-7-24.

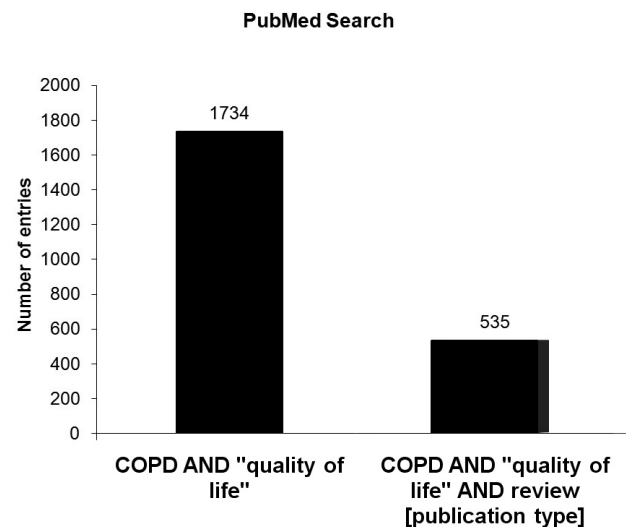


Figure 2 Database analysis for COPD and quality of life. Search date: 2007-7-24.

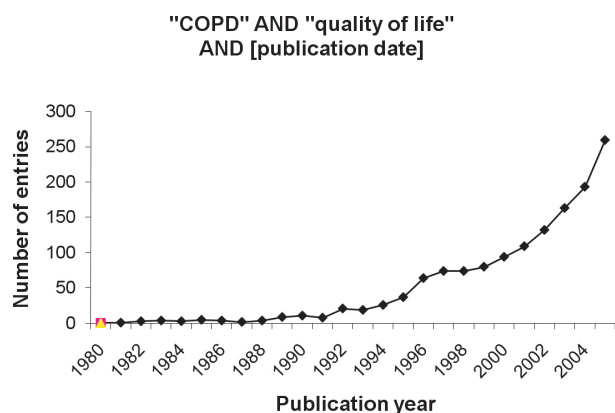
### Health-related quality of life

Most studies assessed the quality of life either using the St. George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRDQ), partly only reporting single domains. Concerning the analysis if the SGRQ it needs to be criticized that most of the studies only reported the mean values of the SGRQ scores. In this respect, it should have been important to know if there is a difference between the numbers of patients with an increase in the score of 4 units (cut-off point for significant improvement). Also, a separate analysis of single domains should not be performed.

### Fluticasone/salmeterol

To assess the health-related quality of life the St. George's Respiratory Questionnaire (SGRQ) (Calverley et al 2003a; Wouters et al 2005), the Chronic Respiratory Disease Questionnaire (CRDQ) (Mahler et al 2002; Hanania et al 2003) and the Clinical COPD Questionnaire (CCQ) (Wouters et al 2005) were used. For the global SGRQ score one study (Calverley et al 2003a) reported a significant difference favorable for a combination therapy in comparison to fluticasone monotherapy (score was 1.4 units lower) after 1 year of therapy. Also a significant difference favorable for a combination therapy in comparison to salmeterol monotherapy was found after 44 weeks in this study (score was 2.24 units lower) (Calverley et al 2003a).

A further study reported a significant difference after 24 weeks of combination therapy (500 µg fluticasone) in the CDRQ total score and in the dyspnea score in comparison to fluticasone monotherapy (the total score was 4.8 units higher



**Figure 3** Database analysis for COPD and quality of life and publication dates. Search date: 2007-7-24.

than the monotherapy score) (Mahler et al 2002). However, there were no differences in comparison to salmeterol monotherapy (Mahler et al 2002). The study using a lower dosage (250 µg fluticasone) (Hanania et al 2003) did not find any significant differences in comparison to monotherapy. The CRDQ total score increased after 24 weeks of therapy with combination therapy (250 and 500 µg fluticasone) with 10 units in comparison to baseline values. The dyspnea score increased with 3.9 (250 µg fluticasone) and 4.2 (500 µg fluticasone) units. For the CDSQ one study found a significant difference in favor of the combination therapy (Mahler et al 2002) in comparison to the fluticasone monotherapy. However, there were no differences in comparison to the salmeterol monotherapy. The same results were reported for the study with the lower dosage (Hanania et al 2003). Absolute differences in these scores in comparison to the baseline values were similar in both studies (Hanania et al 2003).

An important contribution towards the understanding of effects of combined therapies on quality of life is the TORCH study (Calverley et al 2007). This randomized, double-blind trial compared salmeterol at a dose of 50 microg plus fluticasone propionate at a dose of 500 microg twice daily (combination regimen) with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was mortality from any cause for the comparison between the combination regimen and placebo. While the reduction in death from all causes among patients with COPD in the combination-therapy group did not reach the predetermined level of statistical significance, significant benefits were present in all other outcomes measured (Calverley et al 2007). Concerning the quality of life, the St. George's Respiratory Questionnaire (SGRQ) was used. Total scores on the St. George's

Respiratory Questionnaire initially improved from baseline in all groups, with the greatest changes occurring in the combination-therapy group (mean score at baseline, 48.7, with a mean reduction of 3.0 units averaged over 3 years), as compared with the placebo group (a mean score of 48.4 at baseline, with an increase of 0.2 unit in the placebo group) (Figure 4). Averaged over 3 years, the health status in the combination-therapy group was significantly better than in the groups receiving placebo, salmeterol alone, or fluticasone propionate alone (Calverley et al 2007).

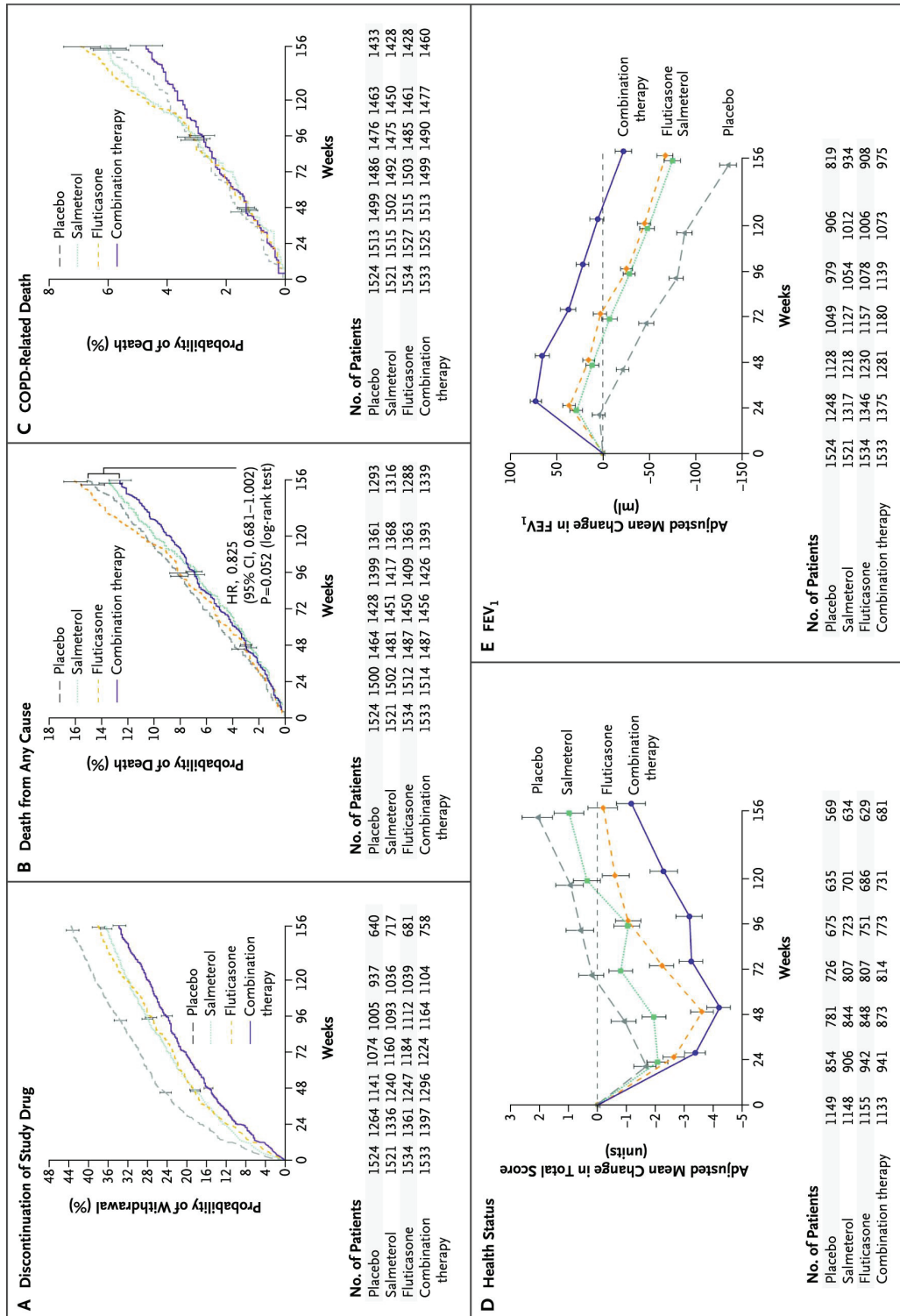
## Budesonide/formoterol

When the combination budesonide/formoterol was assessed for effects on quality of life data from two studies demonstrated a significant effect in favor of budesonide/formoterol compared with placebo of  $-6.06$  units on the SGRQ; 95%CI  $-7.90$  to  $-4.22$  (Szafranski et al 2003; Calverley et al 2003b; Nannini et al 2004). However, there appeared to be a high level of heterogeneity when these data were pooled ( $I^2$  71.8%) as indicated by a Cochrane analysis. Random effects modelling also generated a significant effect (weighted mean difference WMD  $-5.8$  units; 95% CI  $-9.32$  to  $-2.28$ ). The improvement from baseline in the budesonide/formoterol group was 3.9 units (Szafranski et al 2003). This was not dissimilar to change scores from post run-in treatment in the other study (Calverley et al 2003b). Comparisons with monotherapies were not fully reported in the studies but Szafranski et al reported similar effects observed in patients treated with formoterol monotherapy (3.6 units) (Szafranski et al 2003).

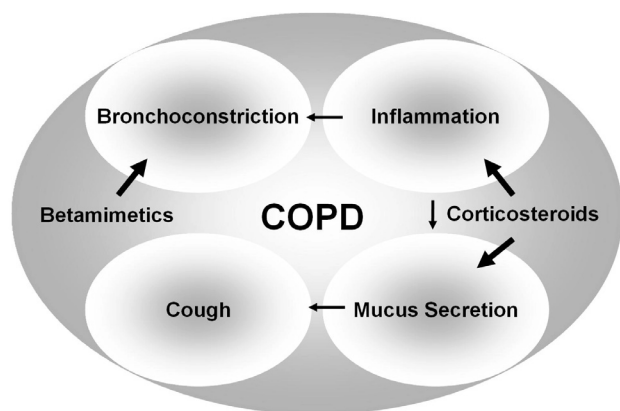
## Discussion

COPD is characterized by slowly progressive development of a poorly reversible airflow limitation and inflammatory airway changes. Since it is estimated to be currently the fourth most common global cause of death and success of pharmacotherapy is still limited, new therapeutic regimen need to be evaluated. One of the most promising approaches should be the use of combined inhaled betamimetics and corticosteroids with the corticosteroids targeting the features of inflammation and mucus secretion and thus inhibiting further symptoms including airflow limitation and cough (Figure 5). The present analysis assessed the effects of combination therapies on the quality of life. There were differing results concerning quality of life when fluticasone/salmeterol was compared with inhaled steroids alone while there were no significant differences present between fluticasone/salmeterol and long-acting





**Figure 4** Outcomes in the TORCH study. In the combination regimen, salmeterol was administered at a dose of 500 µg twice daily. Salmeterol alone was administered at a dose of 50 µg twice daily, and fluticasone propionate alone was administered at a dose of 500 µg twice daily. The effect of each study medication on health status (assessed according to changes in patients' total scores on the St. George's Respiratory Questionnaire). Vertical bars represent standard errors. Reproduced with permission from Calverley PM, Anderson JA, Celli B, et al. 2007. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 356:775-89. Copyright © 2007 Massachusetts Medical Society. All rights reserved.



**Figure 5** Concept of the use of combined inhaled corticosteroids and betamimetics. While betamimetics target the symptom of bronchoconstriction corticosteroids should be beneficial in targeting inflammation and mucus secretion and thus abolishing further symptoms such as mucus-induced cough and airflow limitation.

beta-agonist in quality of life scores. The combination budesonide/formoterol was also shown to improve symptoms when compared with the budesonide monotherapy but not with formoterol. There were differing results in quality of life scores when budesonide/formoterol was compared with monotherapies.

It can be assumed that the combination of inhaled corticosteroids and salmeterol led to benefits over monotherapies on certain clinical outcomes but not in others. Differences in the treatment protocols in the budesonide/formoterol combination studies may explain the differences between health status scores. Although differences between combination therapies and placebo were statistically significant, the difference from the study of Calverley et al suggested that the combination of inhaled steroids and betamimetics led to a clinically relevant advantage compared with placebo treatment (Calverley et al 2003b). This difference may be interpreted with caution due to a pre-treatment with high dose prednisolone and formoterol, leading to an increase of 4.5 units in the SGRQ.

Future trials will lead to a proof-of-principle stage concerning the use of combination therapies. In these studies, combinations should be compared with separate administrations of long acting beta-agonists and inhaled corticosteroids. Of course, the design should be in a double-dummy design fashion in large scale multi-centre studies. These studies should also include an assessment of the patient compliance and the patient preference which has not been accomplished in the presently available studies. Also, pharmacoeconomic studies could be helpful to assist health agencies.

In summary, it can be stated that while there were some differences in favor of combination therapies reported when

the combination therapy was compared with inhaled steroid monotherapy there were no consistent differences when combination therapies were compared to bronchodilator monotherapies. Future trials are needed to lead to a proof-of-principle stage.

## Disclosures

AF and TW have received research funding from several pharmaceutical companies with an interest in COPD. They have spoken at meetings sponsored by companies including GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Altanta Pharma, Schering Plough, and Novartis.

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