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**Title:** Towards clinical phenotyping of COPD : effects of inhaled corticosteroide in the GLUCOLD study  
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Self-monitoring day-to-day health status and peak-flow: effect of long-term treatment with inhaled corticosteroids and long-acting $\beta_2$-agonists in COPD

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Abstract

Aims: It is unknown to what extent daily patient-monitored outcomes are responsive to long-term therapy in COPD. This study assessed the long-term effects of inhaled corticosteroids with or without long-acting $\beta_2$-agonists on day-to-day symptoms and Peak Expiratory Flow (PEF) in mostly steroid-naive patients with moderate to severe COPD.

Methods: In a double blind, placebo controlled study 114 patients received short-term (6 months) or long-term (30 months) fluticasone propionate 500 $\mu$g twice daily (bid), long-term fluticasone/salmeterol 500 $\mu$g/50 $\mu$g bid (single inhaler), or placebo bid. The clinical COPD questionnaire (CCQ) was used to measure day-to-day health status. 2-Week diary cards with daily CCQ and PEF were collected every three months.

Results: Short-term addition of salmeterol to fluticasone treatment improved mean daily total and functional CCQ score (-0.2, p=0.008; -0.3, p=0.002, respectively) and improved mean morning PEF from baseline (10.6 l/min, p<0.002). Long-term treatment with inhaled corticosteroids improved the mean daily total and functional CCQ score (-0.09/yr, p=0.003; -0.12/yr, p<0.001 respectively) and improved change in morning PEF from baseline (2.46 l/min/yr, p=0.052). Stopping inhaled corticosteroids after 6 months worsened the mean daily total, symptom and functional CCQ score (0.09/yr, p=0.003; 0.14/yr, p=0.001; 0.07/yr, p=0.043). More patients had a relevant worsening of the CCQ total score (OR 10.4, p=0.024) and less patients had a relevant improvement in morning PEF change (OR 15.0, p=0.009). Addition of long-acting $\beta_2$-agonists to inhaled corticosteroids provided short-term benefits.

Conclusions: Long-term therapy with inhaled corticosteroids improves daily reported general and functional health status in a group of patients with mostly steroid-naive, moderate to severe COPD. Stopping inhaled corticosteroids worsens health status and addition of long-acting $\beta_2$-agonists provides initial benefits. Part of self-monitored outcomes were clinically relevant. This study indicates modest benefit of long-term combination therapy on self-monitored outcomes in COPD.
**Introduction**

The current rise in disease prevalence of Chronic Obstructive Pulmonary Disease (COPD) in a greying society will enhance the burden to society enormously (www.goldcopd.org) [1]. Patients with COPD experience themselves day-to-day symptoms and limitations in physical activity, with an adverse impact on health status [2]. Currently the emphasis in healthcare is shifting from physician-based to patient-centred care and self-monitoring of respiratory symptoms provides the opportunity to engage patients in their care [3;4]. Therefore, regular assessments made by the patients themselves are needed, which may better reflect treatment impact from the patient perspective whilst providing direct feedback in a standardized way.

Patient diary cards and brief questionnaires can be used as direct measures for self-monitoring. Diary cards assess daily questions on respiratory symptoms and lung function. The clinical COPD questionnaire (CCQ) is a short practical tool that can be used to evaluate the effect of treatment on symptoms [5;6]. The weekly CCQ has been shown to be able to discriminate between stable state of COPD and exacerbations, and may be used in early detection of exacerbations [7]. Self-monitoring can be used to assess treatment effects. However, the responsiveness of the daily CCQ to long-term treatment in stable COPD is as yet unknown.

Large epidemiological studies did not show long-term effects of inhaled corticosteroids on physiological outcome in COPD, such as the decline of forced expiratory volume in one second (FEV₁) [8;9]. However, COPD is a heterogenous disease and in certain subgroups of patients long-term therapy with inhaled corticosteroids (ICS) can improve dyspnea and FEV₁ decline in patients with moderate to severe COPD[10], whilst discontinuation worsens dyspnea and FEV₁ decline [11]. Hence, self-monitoring may provide relevant additional signals of treatment benefits during long-term treatment of COPD patients. In addition, self-monitoring may strengthen the adherence to chronic medications when immediate and clinically important impact on symptoms and lung function can be demonstrated [12].
We hypothesised that maintenance treatment with inhaled corticosteroids with and without β₂-agonists improves self-monitored day-to-day health status and lung function in patients with moderate to severe COPD. To that end, we examined effects of 2.5 years versus 6-month treatment of fluticasone propionate with and without salmeterol, as well as cessation of fluticasone on day-to-day health status and Peak Expiratory Flow (PEF) in COPD. In addition, the number of patients with a minimally important clinical change in outcome was explored.

**Methods**

We conducted a 2.5 year prospective longitudinal, randomised, double blind, placebo-controlled two-centre trial, called the Groningen Leiden University Obstructive Lung Disease (GLUCOLD) study. The methodology has been described in detail previously [11;13]. Briefly, patients had irreversible lung function loss that was compatible with the Global initiative for chronic Obstructive Lung Disease (GOLD) stages II and III, and had ≥ 10 pack years smoking [1]. Asthma was excluded by doctors diagnosis and self-reported symptoms, treatment or diagnosis of asthma. Participants with inhaled and oral corticosteroids within 6 and 3 months of trial entry were not included in the study. Seven patients ever used a short-term course of corticosteroids and only five patients ever used maintenance therapy with inhaled corticosteroids. The vast majority of patients were recruited from general practices between 2000 and 2003 and all patients had been clinically stable for at least 2 months before entry. The study was approved by local ethics committees and all subjects gave written informed consent.

Patients were randomly assigned to receive either 500 μg fluticasone propionate (FP) twice daily for 2.5 years, 500 μg FP twice daily for 6 months, 50 μg FP/salmeterol (S) twice daily for 2.5 year or placebo (P). Study medication included Diskus® dry powder inhalers (GlaxoSmithKline, The Netherlands), and active treatment and placebo were identical in appearance. Randomisation was performed by an independent randomisation centre using a minimisation procedure balancing treatment groups for a number of variables (centre, gender, current smoker, FEV₁/IVC < or ≥ 60%, PC_{20} methacholine < or ≥ 2 mg/ml). Regular visits with measurements of symptoms and lung function were made every 3 months. Methacholine challenge was performed at 0, 6 and 30 months. Compliance was checked by counting the doses on the Diskus® inhalers.
Patients completed 2-weeks diary cards every three months prior to the visit. Records were reviewed at each visit. Amongst validated disease-specific health status questionnaires such as the clinical COPD Questionnaire (CCQ) and the COPD assessment Test (CAT) [14], we have chosen to use the daily CCQ measure day-to-day health status. The CCQ is a 10-item health status questionnaire from which the following scores were assessed: total, symptom, functional and mental scores (0=best score, 6=worst score). Daily Peak Expiratory Flow (PEF) measurements were performed three times in the morning and three times in the evening. The best of three measurements in the morning was used for analysis. Patients were asked not to use rescue medication 6 hours prior to the measurement. The minimal important difference (MID) of the CCQ that represents a clinically relevant change in health status is 0.4 points [15]. There is no validated MID for PEF measurements in patients with COPD. However, the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial showed that two-third of patients with COPD experienced a clinically meaningful reversibility of 15% PEF at baseline. [16] This is comparable to the MID known in patients with asthma [17]. Therefore, a change of 15% was defined as clinically relevant (i.e. minimal important difference) PEF.

Spirometry was measured after 400 mcg salbutamol, according to standardized guidelines [13].

Statistical analysis
The power of the GLUCOLD study was based on the primary outcome and included the standard deviation (0.77) of the fluticasone-induced short-term change in submucosal CD8$^{+}$ cell counts in COPD patients [11;18]. Because this was an efficacy trial, per-protocol analysis included all available data from randomised patients who were compliant with study medication (using ≥70% of the prescribed dose), including data from patients who did not complete follow-up. A linear mixed effects model was used for analysis of mean CCQ scores and PEF values. The linear mixed models included the main effect of treatment (3 indicators), the main effect of time (2 indicators) and the interaction of treatment and time. Treatment effects were assessed from: a. long-term treatment with inhaled fluticasone vs placebo, b. discontinuation of fluticasone after 6 months vs its continuation, and c. the additional treatment effect of adding salmeterol to fluticasone vs fluticasone alone. Apart from analysis of the outcome parameters as continuous variables, patients were classified in the following 4 categories by health status and PEF for clinical
interpretation: 1) number of patients with a (relevant) improvement that reached the minimal important difference (MID); 2) the number of patients with a (non-relevant) improvement lower than the MID; 3) number of patients with a (non-relevant) worsening lower than the MID; 4) number of patients with a (relevant) worsening that reached the MID. A logistic random effects model was used for analysis. All analyses were performed with STATA 11.

Results
From 114 patients, 101 patients were adherent. Data from 88 patients who performed diary cards at baseline were analysed. 82 Patients had moderate COPD at baseline with GOLD stage II and 6 patients had severe COPD, stage III (Table 1).

**Table 1. Baseline characteristics per treatment group***

<table>
<thead>
<tr>
<th></th>
<th>Placebo, 30 mo</th>
<th>Fluticasone 6 mo, then followed by placebo, 24 mo</th>
<th>Fluticasone 30 mo</th>
<th>Fluticasone plus salmeterol, 30 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean daily CCQ ‡ score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total score</td>
<td>1.42 (1.2)</td>
<td>0.95 (0.5)</td>
<td>1.10 (0.5)</td>
<td>1.21 (0.7)</td>
</tr>
<tr>
<td>- symptom score</td>
<td>1.82 (1.0)</td>
<td>1.49 (0.6)</td>
<td>1.67 (0.6)</td>
<td>1.68 (0.7)</td>
</tr>
<tr>
<td>- functional score</td>
<td>1.38 (1.3)</td>
<td>0.85 (0.7)</td>
<td>1.01 (0.6)</td>
<td>1.18 (0.9)</td>
</tr>
<tr>
<td>- mental score</td>
<td>0.71 (1.3)</td>
<td>0.089 (0.2)</td>
<td>0.13 (0.3)</td>
<td>0.36 (0.6)</td>
</tr>
<tr>
<td><strong>Stable mean PEF †, l/min</strong></td>
<td>271 (66)</td>
<td>337 (88)</td>
<td>333 (112)</td>
<td>305 (83)</td>
</tr>
<tr>
<td><strong>GOLD §</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- stage II, n</td>
<td>19</td>
<td>19</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>- stage III, n</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation (SD); definition of abbreviations: mo=months; ‡Clinical COPD Questionnaire with range 0 (best) to 6 (worst score); †Peak Expiratory Flow (PEF); §the Global initiative for Chronic Obstructive Lung Disease (GOLD).

**Short-term effects of ICS with or without salmeterol on clinical control and lung function**
Short-term addition of salmeterol to fluticasone treatment improved mean daily total and functional CCQ score compared with placebo (-0.2/6months, p=0.008; -0.3, p=0.002, respectively) and improved mean morning PEF from baseline (10.6 l/min per 6 months, p<0.002, Table 2, Figure 1). A lower CCQ score indicates improved health status. Figure 2 shows the number of patients with a (relevant) improvement or worsening of health status and lung function during follow-up. Fewer patients had a relevant worsening of the CCQ total,
functional and mental score by adding salmeterol to short-term fluticasone (OR 11.1, p=0.014; OR 12.6, p=0.007; OR 15.4, p=0.021, respectively, Figure 2). More patients had a relevant worsening of PEF with short-term therapy with fluticasone as compared to placebo (OR 53, p=0.010, Figure 2).

Table 2. Effects of inhaled corticosteroids with or without long-acting β₂-agonists on clinical control and PEF

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Effect of long-term continuation with fluticasone</th>
<th>Effect of cessation with fluticasone at 6 mo</th>
<th>Addition of short-term salmeterol</th>
<th>Addition of long-term continuation with salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coeff, 95% CI, P value</td>
<td>coeff, 95% CI, P value</td>
<td>coeff, 95% CI, P value</td>
<td>coeff, 95% CI, p-value</td>
</tr>
<tr>
<td>Mean daily CCQ ‡ score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total score</td>
<td>-0.09, -0.15 to -0.03, 0.003</td>
<td>0.09, 0.03 to 0.15, 0.003</td>
<td>-0.22, -0.39 to -0.06, 0.008</td>
<td>0.11, 0.05 to 0.17, &lt;0.001</td>
</tr>
<tr>
<td>- symptom score</td>
<td>-0.08, -0.17 to 0.001, 0.053</td>
<td>0.14, 0.06 to 0.22, 0.001</td>
<td>-0.21, -0.45 to 0.03, 0.087</td>
<td>0.11, 0.03 to 0.2, 0.008</td>
</tr>
<tr>
<td>- functional score</td>
<td>-0.12, -0.19 to -0.06, &lt;0.001</td>
<td>0.07, 0.02 to 0.13, 0.043</td>
<td>-0.30, -0.49 to -0.11, 0.002</td>
<td>0.12, 0.05 to 0.18, 0.001</td>
</tr>
<tr>
<td>- mental score</td>
<td>-0.04, -0.09 to 0.01, 0.13</td>
<td>0.02, -0.03 to 0.07, 0.38</td>
<td>-0.12, -0.26 to 0.03, 0.12</td>
<td>0.07, 0.02 to 0.12, 0.007</td>
</tr>
<tr>
<td>Stable mean PEF †, l/min</td>
<td>2.46, to -0.02 to 4.94, 0.052</td>
<td>-2.42, -4.92 to 0.09, 0.058</td>
<td>10.6, 3.9 to 17.3, 0.002</td>
<td>-1.23, -3.7 to 1.25, 0.33</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ‡Clinical COPD Questionnaire; †Peak Expiratory Flow (PEF).

Figure 1. Change in CCQ score and PEF by fluticasone

Adjusted mean change ± 95% CI over time during treatment with fluticasone (500 μg bid) for 30 months (FP 30), fluticasone (500 μg bid) 6 months (FP 6), followed by placebo, the combination of fluticasone/salmeterol (500/50 μg bid) 30 months (FP/S 30) and placebo (bid), in patients with moderate to severe COPD. Data are presented for: A) mean Clinical COPD Questionnaire (CCQ) Total score; and B) mean CCQ Symptom score; C) mean CCQ Functional score and D) Peak Expiratory Flow (PEF, l/min).
Relevant changes over time are presented during treatment with fluticasone (500 μg bid) for 30 months (FP 30), fluticasone (500 μg bid) for 6 months (FP 6), followed by placebo, the combination of fluticasone/salmeterol (500/50 μg bid) for 30 months (FP/S 30) and placebo (bid), in patients with moderate to severe COPD. Data are presented for: A) total Clinical COPD Questionnaire (CCQ) score; and B) Peak Expiratory Flow (PEF). Four categories are shown: 1) relevant improvement depicted in upper part; 2) improvement that is not clinically relevant (upper middle part); 3) worsening that is not clinically relevant (lower middle part); 4) relevant worsening (lower part).
Long-term effects of ICS with or without salmeterol on clinical control and lung function

Long-term continuation with fluticasone improved mean daily total and functional CCQ score after 2.5 years, compared to placebo (-0.09/yr, p=0.003; -0.12, p< 0.001, Figure 1) and improved change (non-significant) in morning PEF from baseline (2.46 l/min/yr, p=0.052, Figure 1). Fewer patients had a relevant (non-significant) worsening of the CCQ functional score by using long-term therapy with fluticasone (OR 5.4, p=0.054, Figure 2). Cessation of fluticasone at 6 months worsened the mean daily total, symptom and functional CCQ score at 2.5 years versus long-term fluticasone (0.09/yr, p=0.003; 0.14/yr, p=0.001; 0.07/yr, p=0.043, Figure 1) and worsened change (non-significant) in morning PEF from baseline (-2.42/yr, p=0.058). More patients had a relevant worsening of the CCQ total score by stopping fluticasone (OR 10.4, p=0.024) and less patients had a relevant improvement in morning PEF change from baseline (OR 15.0, p=0.009, Figure 2). Long-term continuation of salmeterol increased (worsened) the CCQ score on the dimensions total (0.11/yr, p<0.001), symptom (0.11/yr, p=0.008), functional (0.12/yr, p=0.001) and mental (0.07/yr, p=0.007) compared to fluticasone alone (Figure 1).

Discussion

The findings of the present study show that long-term treatment with inhaled corticosteroids improves patient-reported day-to-day health status and functional performance in steroid-naive patients with moderate to severe COPD. Stopping fluticasone treatment at 6 months worsens daily patient-reported health status, symptoms and functional performance. Addition of a long-acting $\beta_2$-agonist to ICS provides short-term benefit on health status, functional performance and PEF, but does not provide an additional long-term benefit. The observed effects on health status and PEF partly reached the minimal important difference (MID) of 0.4 points for the CCQ and 15% change from baseline for PEF. These long-term effects on daily reported health status point to some benefits for patients in daily symptoms and lung function. The novelty of this study is that COPD patients with stable disease benefited from long-term inhaled corticosteroids as reflected in self-monitored daily health status and lung function. In asthma, self-monitoring of asthma control including symptoms and PEF is recommended in combination with an action plan common in clinical trials and it has been shown that this may enhance adherence to monitoring the disease [12;17]. In addition, in clinical trials such
as the Gaining Optimal Asthma control (GOAL) study PEF data were used to measure effects of ICS and combination therapy on asthma control [19]. However, it is likely that the monitoring approach that has been found useful in asthma cannot simply be extrapolated to COPD [20].

Our findings with patient-monitored outcomes in COPD demonstrate that COPD seems to be a treatment responsive disease. Indeed, controlled trials have provided a rationale for treatment in specific subgroups of patients with COPD [1]. The combination of ICS and long-acting β₂-agonist has provided positive effects on 3-monthly measured health status and lung function [10;11]. Inhaled corticosteroids decrease exacerbations in more severe disease and improve quality of life [8]. Three studies reported benefits from long-term combination therapy in specific groups of patients [10;11;21] We extended these findings by showing positive effects on patient centred, daily reported health status and PEF.

Although the present study showed positive effects of inhaled corticosteroids on day-to-day health status and PEF, there are some limitations. A relatively small number of patients was enrolled in the study, since sample size was based on inflammatory cell counts in bronchial biopsies as primary outcome of the study. Although long-term treatment with ICS was effective at the patient level, there was a limited number of patients where effects reached the MID. First, this may be COPD-specific, due to the notion that COPD patients are generally older than asthma patients, having more complex multi- and/or co-morbidity and are more readily adapting to their disease due to the slow disease progression. Second, it may be explained in part by differences in populations. The original MID for the CCQ was established in patients with more advanced disease, and who were admitted to the hospital for an exacerbation of COPD [15]. Third, the MID can be determined by different methods, which may influence the MID [22;23]. In addition, the individual patient is the only one who can judge whether there is an improvement or worsening that is clinically relevant [24;25]. Finally, prior to the study, patients were mostly steroid-naïve. Since many patients in daily practice use combination therapy, this may hamper generalisation of the results. However, because of the present study design, the observed effects of ICS were not biased by carry-over effects from previous treatment.

How can we interpret our findings? Long-term self-monitoring has been shown to positively influence the impact of exacerbations on health status, and decrease respiratory symptoms of exacerbations [26]. Therefore, one might argue that self-monitoring should be part of disease management in COPD.
These programs include many aspects such as education about the disease, optimisation of evidence based medication and self-management. In patients with relatively mild disease monitoring patients with integrated disease management improved health status and exercise capacity [27;28]. Disease management programs include non-medical and medical interventions. Interestingly, we found that long-term ICS improved daily reported health status and functional impairment in moderate to severe stable COPD. This could promote regular physical activity, which is associated with higher CO-diffusion capacity, muscle strength and exercise capacity as well as lower levels of systemic inflammation [29]. This suggests that long-term ICS provide modest benefit at the patient level in certain COPD patients.

In conclusion, long-term ICS improves day-to-day health status, functional impairment and PEF in a patients with mostly steroid-naïve, moderate to severe COPD. Stopping ICS worsens health status and addition of long-acting β₂-agonist provides initial benefits. Part of the observed effects were clinically relevant. This study suggests that the benefits of long-term effects of combination therapy on clinical health status and PEF in moderate to severe COPD is modestly experienced at the patient level.

References


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