Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD

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**Background.** Previous studies on inhaled steroid and long-acting beta2-agonist combination products may not be representative for the asthma and chronic obstructive pulmonary disease (COPD) patients in family practice.

**Objectives.** To compare in a group of doctor-diagnosed patients with asthma or COPD, the effects of a lower dose of fluticasone in a combination product with salmeterol with conventional treatment (i.e. a higher dose of fluticasone), both supplemented with as-needed use of a short-acting bronchodilator.

**Methods.** The study was a 12-week multicentre, randomized controlled, double-blind trial. In all, 41 family practices recruited 137 patients diagnosed with asthma and 40 patients diagnosed with COPD. Primary outcome was the forced expiratory volume in 1 second (FEV1) as percentage of predicted. Morning peak expiratory flow (PEF), symptom-free days, health status [Asthma Quality of Life Questionnaire (AQLQ) and St. George’s Respiratory Questionnaire (SGRQ)], exacerbations, use of short-acting bronchodilators and adverse events were secondary outcomes.

**Results.** FEV1% predicted increased 2.6% (SD 8.3) in fluticasone/salmeterol- and 0.01% (SD 6.6) in fluticasone-treated patients (overall: *P* = 0.036, asthma: *P* = 0.025 and COPD: *P* = 0.700). PEF increased in favour of fluticasone/salmeterol in asthma patients only (*P* = 0.016). Fluticasone/salmeterol-treated asthma patients had 1.1 more symptom-free days per week (*P* = 0.044); no such effect was observed for COPD (*P* = 0.769). There were no differences in total AQLQ and SGRQ scores, exacerbations, use of reliever puffs or adverse effects.

**Conclusions.** In family practice patients diagnosed with asthma, several treatment goals were better achieved with a lower dose of fluticasone and salmeterol in a combination product than with a higher dose of fluticasone. We found no differences between the two approaches for patients with COPD.

**Keywords.** Asthma, family practice, fluticasone propionate, multicenter studies, pulmonary disease (chronic obstructive), randomized controlled trials, salmeterol xinofoate.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) both have a high and increasing prevalence in family practice.1,2 In spite of that, family practitioners (FPs) do not always seem to differentiate between both disease entities while diagnosing their patients.3 On the other hand, this is actually an impossible pursuit in some patients, as there is a considerable and undeniable overlap between asthma and COPD.4,5 Effective treatments that may be used in both conditions—particularly inhaled corticosteroids—can

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181
minimize the effects of misdiagnosis and maximize the impact of treatment without the associated complexity when both conditions occur together. Although inhaled steroids have a central role in the management of patients with asthma and (severe) COPD, guidelines have not yet firmly established the position of products that combine anti-inflammatory inhaled steroid treatment with a long-acting bronchodilator. At present, two combination products are commercially available: fluticasone plus salmeterol and budesonide plus formoterol. Meta-analyses and several recent large clinical trials indicate that combining an inhaled steroid with a long-acting beta2-agonist in one inhaler is superior in reaching treatment targets in asthma as well as in severe COPD. However, previous studies in asthma have invariably excluded patients with characteristics of COPD, and studies in COPD have done the same for patients with asthma. Moreover, although the recently published trials included large numbers of patients, they were mainly performed in secondary care settings and included patients from the more severe disease stages, where room for improvement often is considerable. It is questionable whether such data can be extrapolated to the larger ‘real-life’ population of patients with obstructive airways disease who are treated in family practice, who may well exhibit features of asthma and COPD simultaneously.

Thus, it is important to establish the value of combination treatment for the patient population that is managed in family practice. In the study reported in this paper, we investigated whether in the heterogeneous patient population with mild to moderate asthma or COPD that is typically treated in family practice, treatment goals are equally or better achieved with a lower dose of fluticasone when this anti-inflammatory drug is combined with salmeterol in the same inhaler. This contemporary approach was compared with a conventional approach, i.e. treatment with a higher dose of fluticasone.

Methods

Design
The study was a 12-week multicentre, randomized controlled, double-blind, parallel group clinical trial comparing an inhaled steroid step-down approach with a fluticasone/salmeterol combination product and continuation of conventional fluticasone treatment without a long-acting bronchodilator. In both treatment groups, patients could use the short-acting beta2-agonist salbutamol as needed.

Study population and sample size
Patients with ‘doctor-diagnosed’ asthma or COPD were recruited by 41 FPs throughout The Netherlands from June 2003 to March 2004. Sample size calculation showed that 170 patients were required to detect a 5% point difference in the primary study outcome, the forced expiratory volume in 1 second (FEV1) expressed as percentage of predicted value (FEV1% predicted based on the European Community for Steel and Coal reference equations). Other assumptions were as follows: 1 - β = 0.90, one-sided α = 0.05 and SD FEV1% predicted = 11% point. Because of an anticipated 8% dropout rate during a 2-week run-in period, 200 patients were included. The run-in period was used to (i) assess the eligibility of study candidates and (ii) establish the required dose of fluticasone for the subsequent blinded treatment phase. Figure 1 shows the run-in entry criteria and trial exclusion criteria. The medical ethics review board of the Foundation for Therapeutic Evaluation of Drugs (STEG, Duivendrecht, The Netherlands) approved the study. All patients gave written informed consent. For patients below the age of 18, parental informed consent was also obtained.

Measurements and outcomes
In the run-in period, patients rated the severity of their daytime symptoms (score range: 0 = ‘No symptoms’, to 5 = ‘Symptoms so severe that I could not go to work or perform normal daily activities’) and nocturnal symptoms (score range: 0 = ‘No symptoms’, to 4 = ‘Symptoms so severe that I did not sleep at all’) on a diary card. A total sum score of daytime and nocturnal symptoms was calculated for the final run-in week (range 0–63). Visits to the family practice took place at the beginning and the end of the run-in phase (the latter being the randomization visit), and then after 4 and 12 weeks. During all visits, spirometry was performed with an electronic turbine spirometer.
Fluticasone/salmeterol combination in asthma and COPD in family practice

Specific quality of life measured with the Asthma Bronchodilator Reversibility Testing was performed.

Secondary study outcomes were as follows: disease-specific quality of life measured with the Asthma Quality of Life Questionnaire (AQLQ) in patients diagnosed with asthma and with the St. George’s Respiratory Questionnaire (SGRQ) in patients diagnosed with COPD, adverse respiratory events, morning peak expiratory flow (PEF) rate, respiratory symptoms, use of salbutamol relief medication and occurrence of drug-related adverse events. The AQLQ is a 32-item instrument that assesses the following four domains: limitation of activity, asthma symptoms, emotional dysfunction and responses to environmental stimuli. An overall score as well as separate domain scores are calculated, a decreased score indicates worsening. For the 50-item SGRQ, the responses are aggregated into an overall score and three domain scores (symptoms, activity and impact). Scores are presented on a 1–100 scale, an increased score indicates worsening.

Diary cards were completed throughout the run-in and trial periods. Apart from daytime and nocturnal symptoms and use of salbutamol puffs, patients also recorded the highest of three morning PEF (l/min) measurements and occurrence of all adverse events. Adverse respiratory events were post hoc defined as an acute exacerbation, a respiratory tract infection or an episode with increased cough or phlegm. Known drug-related side effects of inhaled corticosteroid treatment considered were oral candidiasis, hoarseness, tremor, palpitations and dizziness.

Randomization
A computer-generated balanced block randomization list with a block size of four was drawn up by an independent statistician. Patients who successfully completed the run-in period and met the trial inclusion criteria were randomly assigned to the treatment groups. Randomization was stratified on the level of the run-in symptom score (0 versus 1–14) and level of the FEV1% predicted (60%–90% versus >90%).

Treatment and blinding
After the initial screening visit in the family practice, current inhaled steroids were replaced with open-label fluticasone propionate via Diskus™ inhaler for the run-in phase. Patients stopped using their usual short-acting and/or long-acting beta2-agonist and switched to commercial packs of salbutamol 200 µg as needed via Diskus™ inhaler for symptom relief during the run-in and trial phases. Use of anticholinergic bronchodilators could be continued. Based on the level of respiratory symptoms and FEV1% predicted in the run-in, patients received either the same dose of fluticasone via Diskus™ inhaler (Flixotide™, GlaxoSmithKline, Evreux, France) as in the run-in phase (250 or 500 µg) or a fluticasone/salmeterol combination product via Diskus™ inhaler (Seretide™, GlaxoSmithKline) with about half the dose of fluticasone (100/50 or 250/50 µg) as used during run-in. Patients were instructed to take one inhalation of the trial medication every morning and every evening and to avoid using the salbutamol relief inhaler within 4 hours prior to scheduled practice visits. Patients as well as FPs were blinded towards group allocation. Trial medication was packaged and labelled by the study sponsor and supplied to FPs as numbered and sealed cardboard treatment packs. All analyses were performed with the investigators blinded, as was the writing of the results section of this paper.

Statistical analysis
Analyses were on the basis of intention-to-treat using SPSS version 12.0 for Windows®. The analyses on the total study population are considered as the studies’ primary result. Except for the health status outcomes (AQLQ and SGRQ scores), the analyses were also performed for the subgroups of asthma and COPD patients separately. Analysis of covariance (ANCOVA) with repeated measurements was used to compare changes in FEV1% predicted, absolute FEV1 values, morning PEF rates, AQLQ and SGRQ scores, symptom days and use of salbutamol relief medication between the treatment groups. Covariates included in the ANCOVA models were as follows: starting dose of fluticasone (500 or 250 µg), baseline symptom score (0 or 1–14) and level of the FEV1% predicted (60%–90% or >90%). Average weekly PEF rates were calculated for each successive week in the diary cards. Daytime and nocturnal respiratory symptoms were analysed by calculating the average weekly number of symptom-free days—i.e. days with the sum of daytime and nocturnal symptom scores = 0. Differences in the onset of a first adverse respiratory event were analysed using multivariable Cox proportional hazards regression analysis. Patients without any adverse respiratory event were treated as right-censored cases. All analyses were pre-specified, and P < 0.05 was considered statistically significant.

Results
Study population and treatment
A total of 244 patients were screened for their study eligibility. Finally, 177 patients were randomized in the trial, 137 (77%) with a diagnosis of asthma and 40 (23%) with a diagnosis of COPD. Table 1 shows the characteristics of the study population. There were more current smokers and females among the patients in the fluticasone group (especially in the asthma subgroup) and fluticasone-treated patients had more pack years of cigarette smoking.
During the run-in phase, 59 fluticasone-treated patients (69%) used the lower dose (250 l g) of fluticasone and 27 patients (31%) the higher dose (500 l g). Corresponding numbers for the fluticasone/salmeterol group were 62 (68%) and 29 (32%). Only three patients used an anticholinergic bronchodilator in addition to their trial medication. Figure 2 shows the progress of participants through the trial.

**Effects on lung function**

The intention-to-treat analysis of the change in FEV1% predicted from baseline to 12 weeks follow-up included 86 fluticasone/salmeterol- and 82 fluticasone-treated patients. The mean FEV1 change was 75.8 ml (SD 308) for the fluticasone/salmeterol and –4.5 ml (SD 211) for the fluticasone group. FEV1% predicted values increased 2.6% (SD 8.3) in the fluticasone/salmeterol- and 0.01% (SD 6.6) in the fluticasone-treated group. The course of the FEV1% predicted throughout the trial is depicted in Figure 3. Repeated measurements analysis showed that the difference for the FEV1% predicted in favour of fluticasone/salmeterol treatment was statistically significant (P = 0.036). For the asthma subpopulation, the effect in favour of fluticasone/salmeterol was statistically significant (P = 0.025) and for the COPD subpopulation it was not (P = 0.700). Although not statistically significant for the total group, an average treatment effect of 34 l/min in favour of fluticasone/salmeterol treatment was observed for PEF rates (P = 0.094). Figure 4 shows the course of PEF rates in the asthma and COPD subpopulations. For asthma, the effect on PEF of fluticasone/salmeterol relative to fluticasone treatment was statistically significant (51 l/min, P = 0.016) and for COPD it was not (–20 l/min, P = 0.679).

**Effects on respiratory symptoms and quality of life**

The average proportions of days per week on which fluticasone-treated patients reported daytime and nocturnal symptoms during the trial phase were 4.5 (SD 5.3) and 1.4 (SD 2.9), respectively, against 3.6 (SD 5.0) and 0.8 (SD 1.9), respectively, for fluticasone/salmeterol treatment. For the asthma and COPD subpopulations combined, there was no difference in the proportion of symptom-free days during the trial (P = 0.121). Figure 5 shows that the rate of symptom-free days consistently improved in time in the asthma patients in both groups, which was not the case in the COPD patients. On average, fluticasone/salmeterol-treated asthma patients had 1.1 more symptom-free days per week compared with fluticasone-treated patients (P = 0.044); no difference was observed for COPD (P = 0.769). The average daily use of salbutamol relief puffs was 0.47 (SD 0.85) in the fluticasone/salmeterol and 0.58 (SD 0.91) in the fluticasone group, but no statistically significant differences between the treatment groups were observed for this outcome.

Figure 6 shows the course of the AQLQ and SGRQ scores during the trial phase. Apart from a difference on the symptoms domain of 0.24 points in favour of

| TABLE 1 Baseline characteristics for the total study population and for the asthma and COPD subpopulations |
|---------------------------------------------------------------|----------------|------------------|----------------|----------------|----------------|
|                                                               | Fluticasone | Fluticasone/salmeterol |
|                                                               | Total | Asthma | COPD | Total | Asthma | COPD |
| General                                                       |       |       |      |       |       |      |
| n                                                            | 86    | 68    | 18   | 91    | 69    | 22   |
| Gender, male/female                                          | 32/54 | 22/46  | 10/8 | 40/51 | 31/38 | 9/13 |
| Age, years                                                   | 47.6 (17.2) | 43.5 (15.9) | 63.1 (12.3) | 47.5 (16.1) | 42.8 (14.7) | 62.1 (10.7) |
| Smoking status, current (%)                                  | 31 (36) | 25 (37) | 6 (33) | 21 (23) | 12 (17) | 9 (41) |
| Cigarettes per day                                           | 12.6 (8.3) | 13.1 (9.0) | 11.7 (6.2) | 11.8 (9.9) | 10.7 (7.7) | 13.3 (12.4) |
| Smoking history, pack years                                  | 25.2 (14.5) | 22.1 (13.3) | 34.8 (14.4) | 22.2 (14.5) | 17.4 (11.7) | 29.9 (15.5) |
| Lung function                                                |       |       |      |       |       |      |
| FEV1, l                                                      | 2.68 (0.81) | 2.82 (0.81) | 2.18 (0.63) | 2.83 (0.87) | 3.03 (0.81) | 2.11 (0.67) |
| As % predicted                                               | 85.2 (15.1) | 87.6 (15.0) | 75.8 (11.6) | 87.1 (16.7) | 90.0 (15.5) | 77.7 (17.4) |
| FVC, l                                                      | 3.55 (1.10) | 3.68 (1.08) | 3.09 (1.08) | 3.62 (1.08) | 3.84 (1.05) | 2.84 (0.82) |
| FEV1/FVC                                                     | 0.77 (0.12) | 0.78 (0.11) | 0.73 (0.14) | 0.78 (0.11) | 0.80 (0.11) | 0.74 (0.10) |
| PEFb, l/min                                                  | 400 (103) | 414 (98) | 347 (107) | 422 (116) | 449 (106) | 338 (104) |
| Respiratory symptoms and quality of life                     |       |       |      |       |       |      |
| Daytime symptoms, days/week                                  | 4.6 (3.8) | 4.6 (3.9) | 4.4 (3.6) | 4.8 (5.6) | 4.6 (5.2) | 5.9 (7.0) |
| Nocturnal symptoms, days/week                                 | 1.5 (2.1) | 1.4 (1.9) | 2.2 (3.1) | 1.7 (3.0) | 1.5 (2.8) | 2.3 (3.5) |
| Salbutamol use, puffs per day                                 | 0.9 (1.2) | 0.8 (1.1) | 1.4 (1.5) | 0.7 (1.0) | 0.6 (0.8) | 1.0 (1.5) |
| AQLQ total score,d points                                    | –     | 5.7 (6.8) | –     | –     | 5.7 (6.0) | –     |
| SGRQ total score,d points                                    | –     | –     | 66.0 (16.3) | –     | –     | 68.0 (14.0) |

Figures are means (SD) unless stated otherwise.

a For current smokers.

b Morning PEF rate.

c During the last week of the run-in phase—i.e. the week before randomization.

d The AQLQ was only administered in patients diagnosed with asthma and the SGRQ only in patients diagnosed with COPD.
fluticasone/salmeterol-treated asthma patients [0.38 (SD 0.58) points for fluticasone/salmeterol and 0.14 (SD 0.62) points for fluticasone, respectively; \( P = 0.039 \)], the repeated measurements analysis of the AQLQ total and domain scores showed no statistically significant differences. In the COPD subpopulation, neither the SGRQ total score nor the symptoms, activities or impact domain scores differed between fluticasone and fluticasone/salmeterol treatment.

Adverse events and side effects of study medication
In the fluticasone group, 24 adverse respiratory events were reported, 20 in asthma and 4 in COPD patients. In the fluticasone/salmeterol group, there were 28 adverse respiratory events, 19 in asthma and 9 in COPD patients. COPD patients had a higher rate of adverse respiratory events compared to asthma [odds ratio = 2.7, 95% confidence interval 1.12, 6.35], but no statistically significant effect in favour of either treatment group existed for the total study population or the asthma or COPD subpopulations. Two serious adverse events were reported (atrial flutter with complete recovery and coma with remaining impairment), both in the fluticasone/salmeterol group; both events were considered unrelated to the trial treatment. Drug-related side effects of inhaled corticosteroid treatment were infrequent and their rate was similar in both treatment groups (Table 2).

Discussion

Summary of main findings
In this randomized controlled multicentre study, we investigated whether treatment goals in patients with asthma or COPD in family practice are better achieved with a lower dose of fluticasone in a combination product with salmeterol, compared with higher dosed fluticasone plus a short-acting bronchodilator in separate inhalers. The latter approach can be regarded as the conventional way of pharmacotherapeutic management in obstructive airways disease, the first as a contemporary approach that is now also emerging in...
family practice. With regard to the FEV\(_1\) % predicted, the primary study outcome, we found a statistically significant effect in favour of fluticasone/salmeterol treatment. This effect was mainly due to the patients diagnosed with asthma. Several secondary outcomes—i.e. morning PEF, symptom-free days and symptoms domain of the health status instrument—were also significantly better in asthma patients who had used the fluticasone/salmeterol combination. For the COPD patients in our study population, no clear benefit in favour of either treatment approach appeared in any of the study outcomes.

**Strengths and the limitations of this study**

To our knowledge, this study is the first to compare fluticasone/salmeterol combination treatment in a mixed population of patients with doctor-diagnosed asthma and/or COPD. Because evidence-based treatment decisions are mostly based on studies which include highly selected fractions of the whole asthma or COPD patient population, we agree with other authors\(^{16}\) that it is important to have results from studies like this one available to be able to assess whether reported treatment effects in selected populations can actually be extrapolated to the larger, real-life population of patients with obstructive airways disease in family practice. Generally, FPs will not strive for

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**Figure 3** Course of FEV\(_1\) % predicted during the trial for (a) all patients, (b) patients diagnosed with asthma and (c) patients diagnosed with COPD. Bars are standard errors.

**Figure 4** PEF rates during the trial in the treatment groups for the asthma and COPD subpopulations. Circles indicate fluticasone/salmeterol and triangles indicate fluticasone.
perfection in their diagnostic labelling of patients with chronic respiratory disease, which was the reason to include patients with doctor-diagnosed asthma or COPD in our study, without further a priori confirmation of the actual correctness of the FPs’ diagnosis. FPs will often prescribe inhaled medication on the basis of the patients’ current symptoms and will generally not await the outcome of further diagnostic tests before doing so. Limitations of this study were the relatively short duration of follow-up (12 weeks) and the fact that less COPD-diagnosed patients were included than we anticipated. A flaw in the study design was that separate health status questionnaires were used in the asthma and COPD subpopulations, where, on reflection, a single questionnaire suitable for all patients would have been more appropriate.

Comparison with existing literature
Our findings in patients diagnosed with asthma (i.e. increased lung function and improved symptom control for fluticasone/salmeterol combination treatment) are in line with previous studies on the effect of combination treatment with an inhaled steroid and a long-acting beta2-agonist.9,11–13 Interestingly and in contrast
with previous studies,9,14,15 no prophylactic effect on exacerbations in favour of combination treatment was observed in either the asthma or the COPD subpopulation. This may be caused by the short follow-up period, the limited room for improvement in this mild to moderate patient population (only 52 exacerbations were reported overall), an actual lack of effect or other reasons.

Conclusion and implications for clinical practice
In family practice patients diagnosed with asthma some—but not all—treatment goals were better achieved with a contemporary approach using a lower dose of fluticasone and salmeterol in a combination product than with the conventional approach using a higher dose of fluticasone and a separate short-acting bronchodilator. We found no differences between these two approaches in patients with COPD.

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Declaration

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