

RESEARCH

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS)

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Abstract

Objective To investigate the occurrence of pneumonia and pneumonia related events in patients with chronic obstructive pulmonary disease (COPD) treated with two different fixed combinations of inhaled corticosteroid/long acting β_2 agonist.

Design Observational retrospective pairwise cohort study matched (1:1) for propensity score.

Setting Primary care medical records data linked to Swedish hospital, drug, and cause of death registry data for years 1999-2009.

Participants Patients with COPD diagnosed by a physician and prescriptions of either budesonide/formoterol or fluticasone/salmeterol.

Main outcome measures Yearly pneumonia event rates, admission to hospital related to pneumonia, and mortality.

Results 9893 patients were eligible for matching (2738 in the fluticasone/salmeterol group; 7155 in the budesonide/formoterol group), yielding two matched cohorts of 2734 patients each. In these patients, 2115 (39%) had at least one recorded episode of pneumonia during the study period, with 2746 episodes recorded during 19 170 patient years of follow up. Compared with budesonide/formoterol, rate of pneumonia and admission to hospital were higher in patients treated with fluticasone/salmeterol: rate ratio 1.73 (95% confidence interval 1.57 to 1.90; $P<0.001$) and 1.74 (1.56 to 1.94; $P<0.001$), respectively. The pneumonia event rate per 100 patient years for fluticasone/salmeterol versus budesonide/formoterol was 11.0 (10.4 to 11.8) versus 6.4 (6.0 to 6.9) and the rate of admission to hospital was 7.4 (6.9 to 8.0) versus 4.3 (3.9 to 4.6). The mean duration of admissions related to pneumonia was similar for both groups, but mortality related to pneumonia was

higher in the fluticasone/salmeterol group (97 deaths) than in the budesonide/formoterol group (52 deaths) (hazard ratio 1.76, 1.22 to 2.53; $P=0.003$). All cause mortality did not differ between the treatments (1.08, 0.93 to 1.14; $P=0.59$).

Conclusions There is an intra-class difference between fixed combinations of inhaled corticosteroid/long acting β_2 agonist with regard to the risk of pneumonia and pneumonia related events in the treatment of patients with COPD.

Trial registration Clinical Trials.gov NCT01146392.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation, exacerbations, and accelerated decline in lung function over time.¹ The disease is an important and growing cause of morbidity and mortality worldwide,² with pneumonia as a common complication associated with considerable health costs and mortality.³⁻⁵ Combination treatment with inhaled corticosteroids and long acting β_2 agonists decreases the risk of exacerbation and improves quality of life in patients with severe COPD.⁶⁻⁹ In Sweden, two products combining an inhaled corticosteroid and a long acting β_2 agonist in one dry powder inhaler are available: budesonide/formoterol (Symbicort Turbuhaler, AstraZeneca, Södertälje, Sweden) and fluticasone/salmeterol (Seretide Diskus, Glaxo Smith Kline, Middlesex, UK). These treatments seem to be equally effective in decreasing exacerbations and improving quality of life in patients with COPD.¹⁰

An issue of potential concern with the use of such combination treatments is an associated increased risk of pneumonia. A large observational study identified a dose related association between inhaled corticosteroid and an increased incidence of admissions to hospital related to pneumonia and mortality in 175 906 older patients with COPD.¹¹ In randomised controlled trials, fluticasone alone or in combination with salmeterol has been linked with increases in the incidence of pneumonia compared with alternative bronchodilator regimens.⁷⁻¹² In the TORCH trial, the absolute risk of pneumonia with salmeterol/fluticasone also increased with GOLD stage.⁷⁻¹³ In a large meta-analysis in COPD, budesonide was not associated with an increased risk of pneumonia.¹⁴ With the Buscher method for indirect comparisons between clinical trials with a common placebo comparator, budesonide/formoterol was associated with significantly fewer adverse events related to pneumonia and serious adverse events than fluticasone/salmeterol.¹⁵ While these data suggest intraclass differences in combination treatments with pneumonia as an adverse event, definitive conclusions are limited by the lack of long term head to head trials in patients with COPD.¹⁵

Comparative effectiveness data from observational databases of propensity matched cohorts provide an alternative means to balance study groups to minimise bias when randomisation is not possible.¹⁶ In this long term observational cohort study matched for propensity score we investigated the incidence of pneumonia and events related to pneumonia, including mortality, in a population with COPD treated with fixed combinations of inhaled corticosteroid/long acting β_2 agonist (fluticasone/salmeterol or budesonide/formoterol) using data based on linkage of electronic primary care medical records with national Swedish healthcare registries.

Method

Study design, protocol, and data sources

We carried out an observational retrospective cohort study, matched for propensity score, linking primary care medical records to data from national mandatory Swedish registries. The Swedish National Board of Health and Welfare performed the data linkage. The linked database was held and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden.

Seventy six primary healthcare centres were included, with a catchment area covering 8% of the population. Medical records data (such as date of birth, sex, diagnoses by ICD-10-CM (international classification of diseases, 10th revision, clinical modification) codes, number of healthcare contacts, lung function assessments, and drug dispensations) were extracted with an established software system (Pygargus Customized eXtraction Program, CXP, Stockholm, Sweden).¹⁷ We collected national registry morbidity and mortality data from the National Patient Register, data on inpatient hospital care (admission and discharge dates, main and secondary diagnoses) and outpatient hospital care (number of contacts, diagnoses as specified by ICD-10-CM codes), and data from the cause of death register (date and cause(s) of death). Drug prescription data from hospital care and primary care were collected from the Swedish Prescribed Drug Register. We replaced personal identification numbers used to identify included patients in all healthcare contacts with study identification numbers before further data processing.

Study population

We included all male and female patients of any age with COPD diagnosed by a physician (ICD-10 code J44, according to the 2011 ICD-10-CM). No predefined exclusion criteria were included in the protocol.

Patients eligible for matching were receiving fixed combinations of inhaled corticosteroid/long acting β_2 agonist (budesonide/formoterol Turbuhaler or fluticasone/salmeterol Diskus). Patients were followed from January 1999 until December 2009; the index date was defined as the date of the first prescription of fixed combination treatment after a diagnosis of COPD. The end of the study was 31 December 2009 or the end of treatment with a fixed combination, emigration, or death.

Outcome measures

The yearly pneumonia rate was defined as number of events with diagnosis for ICD-10 code J10-J18 from inpatient and outpatient hospital care records or primary care medical records. Pneumonia events occurring within 14 days were counted as one single event, if not otherwise specified.

Time to first pneumonia event was defined as the time from the index date to the first pneumonia event (ICD-10 codes as above). Mortality related to pneumonia was defined as mortality with ICD-10 code J10-J18 stated as the underlying cause or contributing to the cause of death in the cause of death registry.

Statistical analysis

We used pairwise 1:1 propensity score matching (greedy 5-to-1 digit matching without replacement),¹⁸ including logistic regression, to reduce concerns related to non-random assignment of patients to treatments. The propensity score method has previously been used to reduce potential confounding caused by unbalanced covariates.¹⁹⁻²⁰ The matching starts with the smallest population (2738 patients in the fluticasone/salmeterol group) and matches 1:1 to the larger treatment group. Patients treated with either treatment combination were matched on the following criteria during the two years before index and at index: age; sex; available lung function measurements; number of prescriptions for antibiotics, oral steroids, tiotropium, ipratropium, inhaled corticosteroids, short acting β_2 agonists, long acting β_2 agonists, angiotensin receptor blockers, β blockers, statins, calcium antagonists, and thiazides; diagnosis of diabetes, asthma, cancer, rheumatoid arthritis, heart failure, hypertension, and stroke; and number of previous admissions to hospital. The standardised difference between the two treatment groups was calculated as the percentage of the absolute difference in population means divided by an estimate of the pooled standard deviation.²¹

The yearly pneumonia event rate (diagnoses and admissions to hospital) observed with each inhaled corticosteroid/long acting β_2 agonist regimen and comparisons between groups were analysed with Poisson regression, with events as the dependent variable and time on specific fixed combination treatment as an offset variable. Time to first pneumonia event and death related to pneumonia was compared between treatments with Cox regression after tests for constant hazard ratio versus time, with time calculated as the difference between index date and event date for patients on the same fixed combination treatment as at index date. Patients were censored when they switched to the other fixed combination and when they left the study because of death or immigration. We used the latest time point alive to censor patients without an event.

We performed sensitivity analyses by analysing rates of pneumonia and mortality from pneumonia in the crude (unmatched) populations and by dividing the matched cohorts into quarters based on the baseline propensity score, denoted as low (first quarter), medium (second quarter), high (third quarter), and very high (fourth quarter) disease burden as a proxy for severity. Numbers needed to treat (NNT) with 95% confidence intervals were calculated with the method described by Suissa.²²

In the dose-response analyses of inhaled corticosteroid dose (Cox regression), we stratified the inhaled combination by collected mean daily steroid dose (budesonide dose <640 µg or ≥640 µg for budesonide/formoterol and fluticasone dose <1000 µg or ≥1000 µg for fluticasone/salmeterol), both with and without severity (propensity score) as covariate. The steroid dose was also recalculated to equivalents of beclometasone dipropionate.²³

Data management and statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, US).

Results

In total, 9893 patients had a record of treatment with a fixed combination of inhaled corticosteroid/long acting β₂ agonist after a diagnosis of COPD and were eligible for matching (7155 patients received budesonide/formoterol Turbuhaler and 2738 patients received fluticasone/salmeterol Diskus at index date). Before propensity score matching, the fluticasone/salmeterol population was older, with fewer smokers and patients with diabetes and used lower doses of inhaled corticosteroid; the other variables were similar in the two groups (table 1). Furthermore, 2497 patients (25%) had at least one pneumonia event recorded during the two years before the index date; the difference between the treatment groups at index date was not significant (P=0.6).

Pairwise matching (1:1) of the budesonide/formoterol and fluticasone/salmeterol populations resulted in two similar cohorts of 2734 patients each (table 1). Four patients in the fluticasone/salmeterol treated group could not be matched, and, together with the remaining 4421 patients in the budesonide/formoterol treated group, were excluded from the matched analysis. The mean collected budesonide dose over time in the study was 568 (SD 235) µg/day (matched patients treated with budesonide/formoterol) and the mean fluticasone dose was 783 (SD 338) µg/day (matched patients treated with fluticasone/salmeterol). Smoking status was similar in the two matched populations but did not constitute a matching variable (table 1).

Events related to pneumonia

In the matched groups, 2115 patients (39%) had at least one diagnosis of pneumonia recorded during the study period, resulting in a total event burden of 2746 recorded pneumonia events during 19 170 patient years of follow-up. There were significantly more pneumonia events in patients treated with fluticasone/salmeterol than with budesonide/formoterol (table 2). The pneumonia rate was 73% higher with fluticasone/salmeterol than with budesonide/formoterol (rate ratio 1.73, 95% confidence interval 1.57 to 1.90; P<0.001), with event rates of 11.0 (10.4 to 11.8) and 6.4 (6.0 to 6.9) per 100 patient years, respectively. The difference remained when we included the beclometasone dipropionate equivalent dose as a covariate in the Poisson regression. The corresponding number needed to treat (NNT) to avoid one pneumonia event per year was 23 (95% confidence interval 18 to 37). Similarly, admission

to hospital related to pneumonia was 74% higher in the fluticasone/salmeterol treatment group than the budesonide/formoterol group (rate ratio 1.74, 1.56 to 1.94; P<0.001; NNT=34, 24 to 59), with a corresponding 82% increase in days in hospital (53 v 29 days per 100 patient years, respectively; P<0.001; table 2). The mean duration of admission for pneumonia was similar in both groups (fluticasone/salmeterol 6.5 (SD 6.6) v budesonide/formoterol 7.1 (SD 7.2) days; P=0.12). The difference observed between budesonide/formoterol and fluticasone/salmeterol with regard to pneumonia diagnosis was independent of where the diagnosis was recorded, in primary care or at hospital (67% of all diagnoses; table 2). Yearly data for the pneumonia event rate for the unmatched populations showed a rate ratio of 1.76 (1.63 to 1.89) in patients treated with fluticasone/salmeterol versus budesonide/formoterol. The cumulative number of pneumonia events showed a uniform pattern over time (fig 1) and was independent of time after index date. The number of patients with at least one event was 32% higher with fluticasone/salmeterol than budesonide/formoterol (28% v 21%, respectively), but the number of patients with multiple events during the follow-up period (for example, ≥2 and ≥3 pneumonia events) was 61% (11% v 7%) and 85% (6% v 3%) higher, respectively (fig 2).

The incidence of pneumonia increased in both treatment groups with increasing disease burden, evidenced by the analysis of pneumonia rate by quarter of baseline propensity score (fig 3). The mean age in the respective quarters, from low to very high burden, was 65.4, 66.2, 68.1, and 70.9, and the number of previous pneumonia events/year was 0.06, 0.10, 0.15, and 0.24. The difference in pneumonia rates between the treatment groups was larger in patients with a higher disease burden.

Mortality related to pneumonia

During follow-up, 149 matched patients (52 patients in the budesonide/formoterol cohort and 97 patients in the fluticasone/salmeterol cohort) died with pneumonia listed as one cause of death. This corresponded to a 76% increase in risk of mortality related to pneumonia with fluticasone/salmeterol versus budesonide/formoterol (hazard ratio 1.76, 95% confidence interval 1.22 to 2.53; P=0.003; fig 4). Data for the crude populations showed a hazard ratio of 1.73 (1.30 to 2.29) for fluticasone/salmeterol compared with budesonide/formoterol. Matching for age, sex, and number of exacerbations and pneumonia events in the two years before the index date gave a risk ratio of 1.80 (1.63 to 1.98). Division into quarters based on baseline propensity score showed both an increasing number of deaths with increasing disease burden and a higher mortality related to pneumonia for fluticasone/salmeterol in all groups (fig 5).

All cause mortality did not differ between the two treatments (hazard ratio 1.08, 0.93 to 1.14; P=0.59).

Sensitivity analyses

Table 3 shows sensitivity analyses based on age, sex, duration of treatment, history of exacerbations, history of asthma, history of pneumonia, and previous treatment with bronchodilator for COPD. A diagnosis of pneumonia during the two years before the index date was not associated with an increase in the overall pneumonia rate after the index date with fluticasone/salmeterol versus budesonide/formoterol (risk ratio 1.73, 95% confidence interval 1.47 to 2.04; P<0.001); however, the pneumonia rate was higher in patients treated with fluticasone/salmeterol than with budesonide/formoterol who had no history of pneumonia

in the two years before the index date (1.76, 1.57 to 1.98; $P < 0.001$). Patients with a concomitant diagnosis of asthma had a higher rate of pneumonia, and the rate ratio between fluticasone/salmeterol and budesonide/formoterol was similar to the overall result (tables 2 and 3). $\downarrow\downarrow\downarrow$

We found no indication of a dose related difference in the risk of a first pneumonia diagnosis in either treatment group, stratified by collected mean daily steroid dose and including disease burden in the analysis to exclude confounding by severity (hazard ratio 1.00, 95% confidence interval 0.64 to 1.57; $P = 0.99$).

Discussion

In this observational retrospective matched cohort study patients with chronic obstructive pulmonary disease (COPD) who were treated with fluticasone/salmeterol were significantly more likely to experience pneumonia and had a higher mortality related to pneumonia than patients treated with budesonide/formoterol. The higher risk of pneumonia with fluticasone/salmeterol was independent of whether or not patients had a recorded episode of pneumonia before the index date. Our findings showed no dose-response relation with regard to increased risk of pneumonia with the two treatments—that is, any excess risk was linked with the choice of inhaled corticosteroid/long acting β_2 agonist and not the dose prescribed and collected by the patient.

Strengths and weaknesses of study

Matched cohort studies of this type are not without limitations. These results are based on retrospective observational data and, although the included patients were matched pairwise with respect to several variables, there could still be possible unknown confounding factors. The accuracy and severity of the physician diagnoses of COPD could also not be fully verified by spirometry in all cases. Furthermore, similar to most previous randomised controlled trials, pneumonia was based on clinical diagnosis without access to severity grading, laboratory, or radiography data. The lack of a standardised definition for pneumonia is one limitation of the current analyses. Most diagnoses, however, were recorded at hospitals where radiography is a standard procedure.²⁴ A subanalysis of these patients showed that the increased risk of pneumonia with fluticasone/salmeterol versus budesonide/formoterol was unchanged.

Notwithstanding these limitations, our study also has several important strengths, not least the primary care setting used to initially identify patients with COPD, without restrictions in age, employment status, concomitant drug treatments, comorbidities, and healthcare insurance. This non-biased data extraction from electronic primary healthcare medical records linked with mandatory national healthcare registers with high coverage and quality, together with the opportunity to follow a patient through their treatment by using personal identification numbers, provides solid and unique data. The external validity of our findings to the treatment of COPD in general practice might, therefore, be greater than for controlled clinical trials. Finally, the follow-up time and patient years covered were substantial (over three years on average) for both drugs, without the potential for increased and differential drop-out rates with either treatment, which often confounds results of longer term placebo controlled studies.²⁵ The present dataset adds robustness to the increased association between pneumonia and fluticasone found by others in placebo controlled trials.^{10 15}

Interpretation with reference to other studies

Fluticasone/salmeterol has been associated with a higher incidence of pneumonia than placebo, salmeterol alone,^{7 26} or tiotropium.^{3 12} In the three year TORCH study, a significant 64% increase in the occurrence of non-fatal pneumonia was reported in patients treated with fluticasone/salmeterol versus placebo.²⁶ Likewise, the risk of pneumonia was 94% higher with fluticasone/salmeterol than tiotropium in the two year INSPIRE study.³ These findings support those from a Cochrane systematic review of seven randomised controlled trials that highlighted that fluticasone/salmeterol increased the risk of pneumonia 1.8-fold compared with placebo.¹⁰ No increased risk was found in a meta-analysis of budesonide studies of at least three years' duration, in which treatment with budesonide and budesonide/formoterol was pooled and compared with treatments that did not contain inhaled corticosteroid.¹⁴ Our findings also support those of Halpin and colleagues, who found a twofold increase in the risk of adverse events related to pneumonia and serious adverse events with fluticasone/salmeterol versus budesonide/formoterol in eight fluticasone/salmeterol placebo controlled trials and four budesonide/formoterol placebo controlled trials in COPD with the Bucher adjusted indirect method of comparisons between studies.¹⁵

The risk of pneumonia, particularly admission to hospital and mortality, associated with the use of inhaled corticosteroid has been suggested to be dose related,¹¹ but lower doses of fluticasone/salmeterol (500 $\mu\text{g}/\text{day}$) have been reported to carry a similarly increased risk.²⁷

Furthermore, our analysis shows no association between the length of admissions related to pneumonia or all cause mortality based on inhaled corticosteroid use or type, suggesting that any increased risk of mortality associated with pneumonia was probably related to the initial diagnosis of pneumonia and not the ability to successfully manage these events, which is in keeping with the findings of Ernst and colleagues.^{11 12} Other COPD registry studies, which did not find an association between inhaled corticosteroid use and mortality related to pneumonia, have followed patients only after arrival at hospital.²⁸ In the INSPIRE study, a significant excess of antibiotic driven exacerbations of COPD and a significant increase in pneumonia events was observed in patients treated with fluticasone/salmeterol compared with those treated with tiotropium.¹² These excess pneumonia events observed during fluticasone/salmeterol treatment were not related to de novo events without associated exacerbations but were apparent only after unresolved exacerbations.³ In our study, the incidence of pneumonia was also clustered to a greater degree with previous events in the fluticasone/salmeterol group, so while the risk of a first pneumonia was 25% greater with fluticasone/salmeterol versus budesonide/formoterol, the difference in overall event rate was about 75% higher.

Previous studies indicate that the two inhaled corticosteroid/long acting β_2 agonist treatments investigated in our present study are equally effective at decreasing exacerbations and improving quality of life in patients with COPD,¹⁰ although in a separate analysis of the present study population, budesonide/formoterol was associated with fewer exacerbations than fluticasone/salmeterol.²⁹ This difference was, however, smaller than the difference in the incidence of pneumonia between the two treatment alternatives.

Plausible explanations

Explanations for the difference in risk of pneumonia between COPD patients treated with inhaled corticosteroid/long acting β_2 agonist combinations containing budesonide or fluticasone could be related to differences in the intrinsic properties of the two inhaled corticosteroids. Corticosteroid inhalation yields high local concentrations of the drug in the lungs and could increase the risk pneumonia because of their immunosuppressive effects.³⁰ As the immunosuppressant potency of fluticasone is reported to be up to 10-fold higher than that of budesonide with regard to ex vivo inhibition of human alveolar macrophage innate immune response to bacterial triggers,³¹ this factor alone could explain our findings. Differences in pharmacokinetic and pharmacodynamic properties related to differences in lipophilicity and hydrophilicity profiles of the respective inhaled corticosteroids have also been shown²⁶ and proposed as an explanation for the difference in risk of pneumonia between budesonide and fluticasone.³² In patients with severe COPD, the highly lipophilic fluticasone molecule can remain in the mucosa and epithelial lining fluid of the bronchi longer than budesonide.³³ It might, therefore, be speculated that suppression of local immunity is both more potent and has a longer duration of effect after intake of fluticasone than budesonide, thereby causing an increased risk of local bacterial proliferation and a pneumonia outbreak.

A considerable proportion of patients with stable COPD show a spectrum of pathogens colonising the lower airways.³⁴ This bacterial load increases during exacerbations compared with the stable state³⁵; consequently, COPD exacerbations might be associated with pneumonia in patients treated with inhaled fluticasone to a greater extent than budesonide.

Conclusions and future research

This observational matched cohort study indicated that there is an intraclass difference between inhaled corticosteroid/long acting β_2 agonist regarding the risk of pneumonia and pneumonia related mortality in the treatment of patients with COPD. The higher risk of pneumonia in patients treated with fluticasone/salmeterol might be related to differences in immunosuppressant potency and pharmacokinetic and pharmacodynamic properties between budesonide and fluticasone. Whether other unknown risks of pneumonia that were not adequately controlled for in this matched cohort study contributed to our findings remains uncertain. The magnitude of the intraclass difference in pneumonia needs to be put in context with the benefits of each regimen in preventing exacerbations. Long term randomised controlled trials comparing fixed combinations of inhaled corticosteroid/long acting β_2 agonist in COPD with respect to occurrence of pneumonia and exacerbations are, therefore, warranted.

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Contributors: All authors participated equally in the study conception, design, and statistical analysis planning. LJ was responsible for statistical analyses, CJ for the manuscript draft and finalisation, and GJ for handling of data and the study database. All authors analysed and interpreted the data, revised the manuscript, had access to complete study data, and had authority over manuscript preparation, approval of final version and the decision to submit for publication. KL is guarantor.

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by AstraZeneca. Data collection was performed by Pygargus AB, Uppsala, Sweden, and funded by AstraZeneca. The statistical analysis plan was agreed on by the study steering committee, and data analysis was performed by the study database owner in collaboration with AstraZeneca. As member of the study steering committee AstraZeneca took part in the interpretation of the data and the drafting of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: CJ has received honorariums for educational activities from AstraZeneca, GlaxoSmithKline, and Merck Sharp and Dohme. KL has served in an advisory board and/or served as a speaker and/or participated in education arranged by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, MSD, Nycomed, Novartis, and Pfizer. KL has also received unrestricted research grants from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. KHL has received speaking fees from AstraZeneca, Boehringer Ingelheim, and Merck Sharp and Dohme. BS has received honorariums for educational activities from AstraZeneca, GlaxoSmithKline, and Merck Sharp and Dohme. GJ has served on an advisory board arranged by AstraZeneca and Takeda. GS, HG, and LJ are fulltime employees of AstraZeneca Nordic.

Ethical approval: The study protocol was reviewed and approved by the regional ethics committee in Uppsala, Sweden (Dnr 2010/040) and registered at ClinicalTrials.gov (clinical trial identifier NCT01146392).

Data sharing: The dataset is still subject to further analyses, but will continue to be held and managed by the Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden. Relevant anonymised patient level data are available on reasonable request from the authors.

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What is already known on this topic

Pneumonia is a common complication of COPD, which is associated with considerable morbidity, mortality, and health costs

Treatment with inhaled corticosteroids and long acting β_2 agonists (fixed dose combinations) can increase the risk of pneumonia in these patients, though it is not known if there is a variation in risk between different combinations

What this study adds

This observational matched cohort study indicated that there is an intraclass difference between fixed combinations of inhaled corticosteroid/long acting β_2 agonist with regard to risk of pneumonia and pneumonia related events in patients with COPD

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Tables

Table 1 | Baseline characteristics in two years before first prescription for inhaled corticosteroid/long acting β 2 agonist after diagnosis of COPD according to fixed combination treatment. Unmatched and pairwise (1:1) propensity matched populations are shown. Figures are means (SD) unless specified otherwise

Variable	Unmatched				Matched			
	Fluticasone/salmeterol (n=2738)	Budesonide/formoterol (n=7155)	P value	Standardised difference	Fluticasone/salmeterol (n=2734)	Budesonide/formoterol (n=2734)	P value	Standardised difference
Age (years)	67.6 (10.4)	66.7 (10.8)	<0.001	8.5	67.6 (10.4)	67.6 (10.9)	0.9	2.2
No (%) females	1459 (53)	3815 (53)	0.98	0.06	1456 (53)	1446 (53)	0.8	1.5
Post-bronchodilator FEV ₁ , % predicted normal*	50.5 (13.9)	55.2 (19.2)	<0.001	25.5	50.4 (19.3)	51.3 (20.2)	0.6	4.4
No (%) with any exacerbation	2105 (77)	5584 (78)	0.2	2.8	2101 (77)	2106 (77)	0.9	2.1
No (%) current smokers*	341 (48)	1337 (53)	0.03	9.2	341 (48)	397 (49)	0.7	6.9
Oral steroid prescriptions/year†	0.91 (2.37)	0.90 (2.41)	0.8	0.5	0.90 (2.31)	0.87 (2.27)	0.7	0.36
Respiratory antibiotic prescriptions/year†	0.95 (1.69)	1.02 (1.70)	0.06	4.2	0.95 (1.69)	0.95 (1.53)	0.9	0.02
Inhaled steroid prescriptions/year†	0.93 (2.04)	1.23 (2.55)	<0.001	13.1	0.93 (2.04)	0.96 (1.97)	0.5	1.0
No (%) with pneumonia diagnosis	701 (26)	1796 (25)	0.6	1.2	700 (26)	694 (25)	0.9	1.3
No of pneumonia diagnoses/year	0.15 (1.22)	0.13 (1.21)	0.5	1.7	0.15 (1.22)	0.12 (1.12)	0.4	0.49
Days in hospital because of pneumonia/year	0.14 (1.12)	0.11 (0.99)	0.2	2.7	0.14 (1.12)	0.13 (1.05)	0.8	0.71
No (%) with comorbidities:								
Asthma	1053 (38)	2300 (32)	<0.001	13.2	1052 (38)	1069 (39)	0.6	1.9
Heart failure	472 (17.2)	1169 (16.3)	0.3	2.4	470 (17.2)	483 (17.6)	0.6	0.38
Ischaemic heart disease	299 (10.9)	833 (11.6)	0.3	2.3	298 (10.9)	296 (10.8)	0.9	0.24
Diabetes	288 (11)	967 (14)	<0.001	9.3	288 (11)	283 (10)	0.8	0.95

COPD=chronic obstructive pulmonary disease; FEV₁=forced expiratory volume in 1 second.

*Limited data available.

†Prescriptions for drugs for COPD in Swedish prescription database generally correspond to three months' drug supply (value of 1.0 could equal >1 inhalers/month for up to 3 months).

Table 2| Pneumonia events by type for pairwise (1:1) propensity score matched populations treated with budesonide/formoterol versus fluticasone/salmeterol for COPD. All P<0.001, Poisson regression

Measure	Event rate (95% CI)		
	Fluticasone/salmeterol	Budesonide/formoterol	Treatment contrast
Diagnosis of pneumonia overall†	11.0 (10.4 to 11.8)	6.4 (6.0 to 6.9)	1.73 (1.57 to 1.90)
Admission to hospital because of pneumonia†	7.4 (6.9 to 8.0)	4.3 (3.9 to 4.6)	1.74 (1.56 to 1.94)
Diagnosis of pneumonia in primary care†	4.2 (3.9 to 4.5)	2.7 (2.5 to 2.9)	1.56 (1.39 to 1.75)
Diagnosis of pneumonia in hospital outpatient care†	1.3 (1.2 to 1.4)	0.7 (0.7 to 0.8)	1.75 (1.53 to 2.00)
Days in hospital because of pneumonia‡	52.8 (48.9 to 57.0)	29.0 (26.5 to 31.7)	1.82 (1.62 to 2.05)

*Rate ratio (95% CI) in reference to budesonide/formoterol.

†Expressed as rates per 100 patient years.

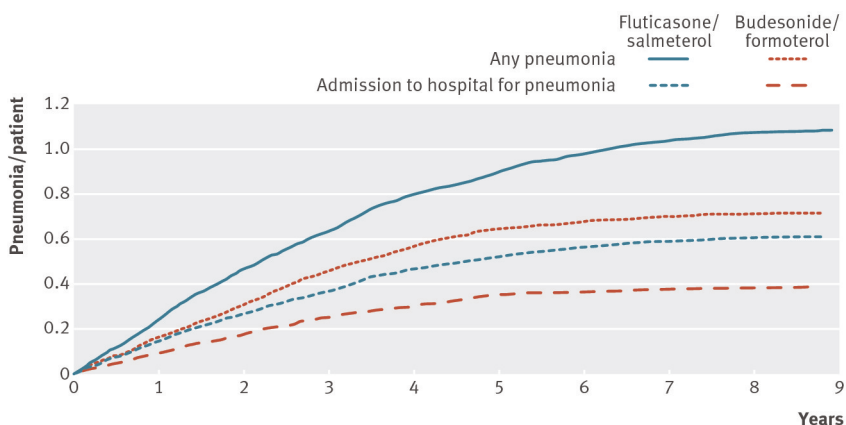
‡Expressed as hospital days per 100 patient years.

Table 3| Pneumonia rates in subpopulations of pairwise (1:1) propensity matched populations* treated with fluticasone/salmeterol versus budesonide/formoterol. All P<0.001, Poisson regression

Subpopulation	Yearly rate		
	Fluticasone/salmeterol	Budesonide/formoterol	Treatment contrast†
Females	11.0	5.9	1.87 (1.64 to 2.13)
Males	11.1	7.0	1.59 (1.38 to 1.83)
Age ≤60	8.5	4.0	2.14 (1.75 to 2.62)
Age >60	12.1	7.5	1.62 (1.45 to 1.80)
Pneumonia diagnosis before index:			
Yes	22.4	12.9	1.73 (1.47 to 2.04)
No	7.6	4.3	1.76 (1.57 to 1.98)
Oral steroids/antibiotics used before index‡:			
Yes	11.7	7.3	1.61 (1.44 to 1.80)
No	9.5	4.3	2.19 (1.82 to 2.64)
Long acting bronchodilators used before index‡:			
Yes	11.4	6.6	1.73 (1.55 to 1.93)
No	9.9	5.7	1.72 (1.43 to 2.08)
Asthma diagnosis before index:			
Yes	12.4	6.6	1.88 (1.63 to 2.17)
No	9.7	6.2	1.56 (1.37 to 1.78)
Events after index:			
<1 year	13.9	8.3	1.68 (1.49 to 1.89)
<2 years	12.3	7.2	1.71 (1.53 to 1.91)
<3 years	11.8	7.3	1.63 (1.46 to 1.80)

*All event rates are expressed per 100 patient treatment years for all subpopulations based on baseline characteristics collected up to 2 years before index.
†Rate ratio (95% CI) in reference to budesonide/formoterol.
‡Drug used to define COPD exacerbation history before index.

Figures



Patients at risk by year after index date

Treatment	0	1	2	3	4	5	6	7	8	9
Fluticasone/salmeterol	2734	2234	1795	1427	1041	671	442	270	148	76
Budesonide/formoterol	2734	2165	1711	1329	947	558	344	187	65	9

Fig 1 Cumulative number of pneumonia events and admissions to hospital because of pneumonia per patient over nine years after index date

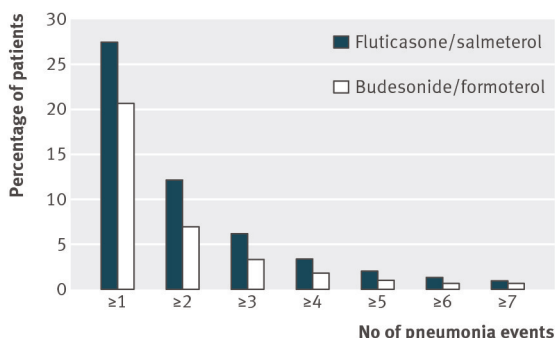
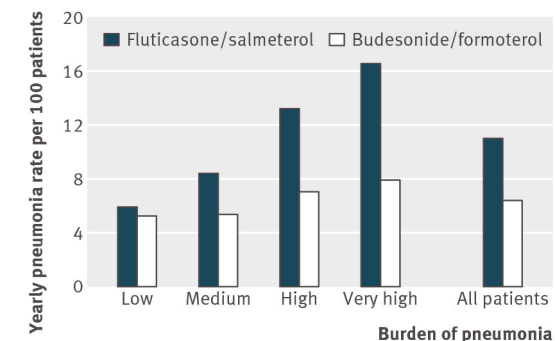
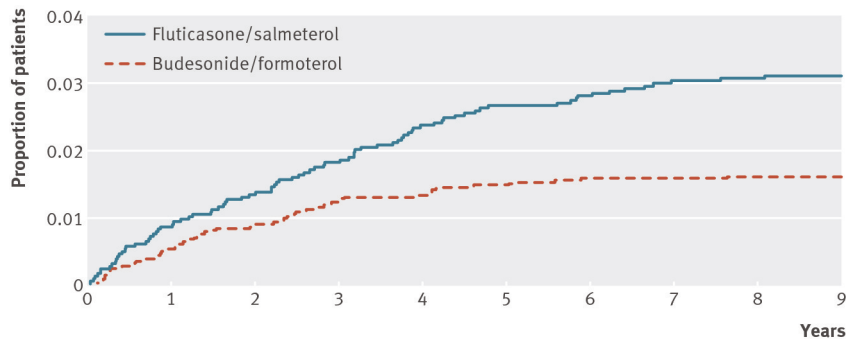


Fig 2 Distribution of number of pneumonia events per patient by treatment (budesonide/formoterol v fluticasone/salmeterol)



	Low	Medium	High	Very high	All patients
Relative risk	1.13	1.57	1.87	2.09	1.73
P value	<0.08	<0.001	<0.001	<0.001	<0.001
NNT	155	35	18	13	23

Fig 3 Pneumonia event rate by treatment and by disease burden (quarters based on baseline propensity scores), with number need to treat (NNT)



Patients at risk by year after index date

Fluticasone/salmeterol	2734	2234	1795	1427	1041	671	442	270	148	76
Budesonide/formoterol	2734	2165	1711	1329	947	558	344	187	65	9

Fig 4 Fraction of patients with mortality related to pneumonia by treatment (budesonide/formoterol v fluticasone/salmeterol)

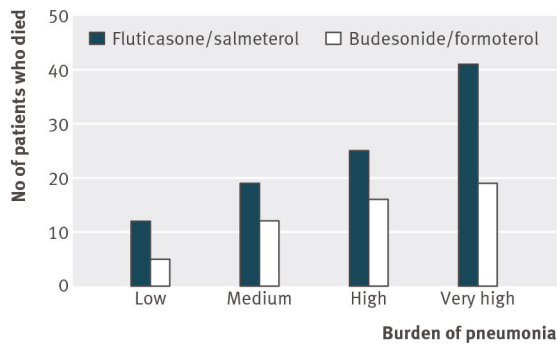


Fig 5 Number of patients with mortality related to pneumonia (52 patients in budesonide/formoterol cohort; 97 patients in fluticasone/salmeterol cohort) by disease burden (quarters based on propensity scores at baseline)