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Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice

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Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. J.B. Soriano, J. Vestbo, N.B. Pride, V. Kiri, C. Maden, W.C. Maier. ©ERS Journals Ltd 2002.

ABSTRACT: Despite substantial evidence regarding the benefits of combined use of inhaled corticosteroids and long-acting β_2-agonists in asthma, such evidence remains limited for chronic obstructive pulmonary disease (COPD). Observational data may provide an insight into the expected survival in clinical trials of fluticasone propionate (FP) and salmeterol in COPD.

Newly physician-diagnosed COPD patients identified in primary care during 1990–1999 aged $\geqslant$50 yrs, of both sexes and with regular prescriptions of respiratory drugs were identified in the UK General Practice Research Database. Three-year survival in 1,045 COPD patients treated with FP and salmeterol was compared with that in 3,620 COPD patients who regularly used other bronchodilators but not inhaled corticosteroids or long-acting β_2-agonists. Standard methods of survival analysis were used, including adjustment for possible confounders.

Survival at year 3 was significantly greater in FP and/or salmeterol users (78.6%) than in the reference group (63.6%). After adjusting for confounders, the survival advantage observed was highest in combined users of FP and salmeterol (hazard ratio (HR) 0.48 (95% confidence interval 0.31–0.73)), followed by users of FP alone (HR 0.62 (0.45–0.85)) and regular users of salmeterol alone (HR 0.79 (0.58–1.07)) *versus* the reference group. Mortality decreased with increasing number of prescriptions of FP and/or salmeterol.

In conclusion, regular use of fluticasone propionate alone or in combination with salmeterol is associated with increased survival of chronic obstructive pulmonary disease patients managed in primary care.
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Chronic obstructive pulmonary disease (COPD) is a respiratory disorder representing a major healthcare burden [1]. Smoking cessation is the only intervention proven to modify the progressive development of airflow limitation, and, to date, only smoking cessation and long-term oxygen therapy have been shown to delay death. The role of pharmacological interventions in modifying the natural history of COPD has not been well established. Inhaled corticosteroids alone [2] or in combination with long-acting β_2-agonists (LABAs) have been shown to be effective in asthma [3], but more research is needed in COPD [4]. The place of inhaled corticosteroids and LABAs in COPD management is the subject of current debate [5–7]. Many general practitioners (GPs) and respiratory physicians in the UK treat both asthma and COPD patients, accumulating experience and empirical treatments in the care and management of both conditions. Current British Thoracic Society (BTS) guidelines for COPD, published in 1997, recommend short-acting bronchodilators for all symptomatic patients, but state that there is insufficient evidence for the use of inhaled corticosteroids or LABAs [8]. Nevertheless, as much as 48% of COPD patients in the UK are currently receiving long-term inhaled corticosteroid therapy [9].

Although the effectiveness of inhaled fluticasone propionate (FP) and salmeterol in mortality reduction in COPD patients is currently being assessed in randomised controlled trials (RCTs), observational data may provide insights regarding the magnitude of the expected outcomes [10]. The UK General Practice Research Database (GPRD), an automated database of primary care covering a total population of >3.4 million inhabitants (~5.7% of the population), represents a unique source of data for investigating this question. The effect of FP and salmeterol on mortality in COPD was explored because both were first licensed in the UK; salmeterol is the predominant LABA drug in the UK and FP is the inhaled corticosteroid that has been studied in longer-term trials in COPD.

The primary objective of the present study was to compare all-cause mortality over a 3-yr period in COPD patients with regular prescriptions of FP

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and/or salmeterol to that in COPD reference patients with regular prescriptions of bronchodilators but not inhaled corticosteroids or LABAs. The secondary objectives were to demonstrate the same effect in users of both drugs combined, users of FP alone and users of salmeterol alone.

Methods

Database

The study protocol and manuscript were approved by the Scientific and Ethical Advisory Group of the GPRD. The GPRD has been described elsewhere [11, 12], and has been utilised previously to obtain information on epidemiological trends in COPD [13, 14].

The study group was a retrospective cohort of newly physician-diagnosed COPD patients identified in the GPRD during 1990–1999, aged $\geqslant 50$ yrs, of both sexes, and with regular prescriptions of one of the following drug groups: inhaled/oral short- and long-acting β-agonists, xanthines, cromones, corticosteroids, and combined bronchodilator products.

Drug exposure

Drug exposure was categorised to simulate an "intention-to-treat" analysis. The drug groups (*i.e.* duration and type of exposure) were defined as follows. Users of FP or salmeterol were physician-diagnosed COPD patients who had received three or more prescriptions of salmeterol or FP over an initial 6-month period. The reference group comprised physician-diagnosed COPD patients who had received three or more prescriptions over an initial 6-month period for one of the following groups of drugs: short-acting β-agonists, xanthines, anticholinergics, and combined bronchodilators, but had not used inhaled corticosteroids or LABAs since diagnosis with COPD.

Users of FP or salmeterol were stratified into three treatment groups: users of salmeterol alone, users of FP alone, and combined users of both FP and salmeterol. Initiation of pharmacotherapy was taken as the first date of regular usage (*i.e.* first prescription). Initiation of pharmacotherapy for the combined FP and salmeterol group was taken as the first date of overlap of both drugs (*i.e.* the start date of the second regular drug). Patients on regular treatment with inhaled corticosteroids or LABAs other than FP and salmeterol after COPD diagnosis were excluded.

Death

Death and date of death were identified by the specific Oxford Medical Information System (OXMIS) code for death in the registration status file of the GPRD plus an extended set of 10 OXMIS and READ codes from the medical file including the terms "death", "died" or "dead".

Covariates

Asthma. In order to demonstrate the ability of database codes to allow good differential diagnosis between COPD and asthma in the GPRD, 300 questionnaires were mailed to a random sample of GPRD surgeries in charge of 225 patients with a diagnosis of COPD and an age/sex-matched group of 75 patients with asthma. The response rate was 85.7%. The sensitivity of a correct COPD diagnosis was 71.2% and 80.3% in moderate and severe COPD patients, respectively. However, because a substantial number of COPD patients in the GPRD have at some time had asthma-compatible mention in their record, this was included as a confounder variable in the analysis.

Smoking. Information on tobacco use resulted in categorisation as nonsmoker (including never and exsmoker), unknown or current smoker based on the database medical and prevention files of the patient. Cumulative cigarette consumption (in pack-years) was estimated for the identified smokers.

Courses of oral steroids. The use of one or more courses of oral steroids, a potential modifier of the association between inhaled corticosteroids and mortality [15], during the follow-up period was estimated as a yes/no categorical variable.

Comorbid conditions. Baseline comorbid conditions were identified from the database medical file prior to the initiation of therapy and categorised into a modified Charlson comorbidity index [16]. COPD was excluded from the list.

Year of entry. The year of entry into the drug exposure category was also included in the multivariate analysis.

Statistical analysis

Crude and adjusted survival analyses were used for comparison of groups according to drug exposure [17]. Patients were only included if they remained alive for 6 months after entry. This 6-month period was used to ensure proper classification into treatment groups based on the assumption that regular prolonged treatment is necessary in order to demonstrate a treatment effect in COPD [18]. As a result, the duration of survival was defined as the time period from 6 months after entry until the time of death or censoring in all treatment groups. Individuals were considered censored if no GP contact was recorded 12 months after their last visit. Kaplan-Meier survival estimates were obtained for samples stratified by sex, age interval (50–59, 60–69, 70–79 and $\geqslant 80$ yrs) and mention of asthma in their record. Cox proportional hazards estimates were adjusted by sex, age, year of entry, smoking status (nonsmoker, unknown and current smoker), comorbid conditions (zero, one, two, or three or more comorbid conditions), asthma mention in their record and use of oral steroids.

A dose/response analysis on the effect on survival of increasing number of prescriptions of salmeterol and

FP was conducted in a nested case/control study within the present cohort. This design was used to improve evaluation of treatment response over time [2]. Cases were defined as dead patients with $\geqslant 1$ yr of follow-up. Each case was then matched with a COPD control patient within the cohort with the same date of diagnosis of COPD and a follow-up at least as long as that of the case. The cumulative amount of exposure to each treatment type was taken as the total number of prescriptions during the entire period of follow-up. The mean annual exposure to FP and salmeterol was then obtained. Estimates of adjusted mortality rate ratios, each as a function of mean annual drug exposure, were obtained using conditional logistic regression for 1:1 matched case/control data. All adjustments involved the same possible confounding risk factors, but were not included in the matching criteria [19].

A sensitivity analysis was performed *a posteriori* to determine whether or not there was an association between survival and regular use of any inhaled corticosteroid (beclomethasone, budesonide or FP), or combined use of inhaled corticosteroids and salmeterol. Regular users of these drugs prior to first diagnosis of COPD were excluded. An association between survival and class of LABA (salmeterol, formoterol and bambuterol) could not be determined because salmeterol is the predominant LABA in the UK and in the GPRD system, accounting for >95% of prescriptions of LABAs in COPD patients.

Results

A total of 1,045 COPD patients who were regular users of salmeterol and/or FP were compared with 3,620 COPD patients. During year 1, the mean number of salmeterol prescriptions was 8.59, 0.13 and 7.03 in the combined salmeterol and FP, FP alone and salmeterol alone groups respectively. Similarly, the mean number of FP prescriptions was 9.19, 8.64 and 0.05 in the combined salmeterol and FP, FP alone and salmeterol alone groups, respectively. These usage patterns were also maintained in the second and third year of follow-up.

The baseline characteristics of all of the drug exposure groups are shown in table 1. Users of FP and/or salmeterol were more often female, diagnosed at an earlier age and categorised as having severe COPD ($p<0.05$). In the 6-month baseline period prior to initiation of pharmacotherapy, users of FP and/or salmeterol received more prescriptions of inhaled corticosteroids, xanthines, anticholinergics, oral corticosteroids and combined bronchodilator products ($p<0.05$). Baseline use of general and COPD-related health services was similar between groups, whereas a history of comorbid conditions was more common in the reference group. There were no significant differences in baseline and demographic characteristics within the subgroups of patients using combined FP and salmeterol, FP alone and salmeterol alone.

Table 1. – Baseline characteristics of chronic obstructive pulmonary disease (COPD) patients taking fluticasone propionate (FP) and/or salmeterol and reference patients

	FP and salmeterol	FP alone	Salmeterol alone	Reference
Patients n	317	431	297	3620
Female %	52.7*	52.7*	49.2*	44.2
Age at diagnosis yrs[#]	64.6±8.5*	66.1±8.8*	68.6±9.2*	72.2±9.8
Smoking status %				
Non or exsmoker	35.0*	32.5*	33.7*	26.9
Unknown	6.9*	7.0*	12.5*	20.7
Current smoker	58.0	60.6*	53.9	52.4
Daily cigarette consumption packs[#]	0.69±0.39	0.73±0.50	0.67±0.41	0.71±0.46
Severe COPD[¶] %	6.6*	5.1	8.4*	3.8
Baseline[+] treatment				
Inhaled corticosteroids %	89.3*	66.4*	39.7*	4.4
Inhaled β_2-agonists %	89.3*	71.0*	65.0*	33.1
SABA	73.8*	67.3*	51.5*	31.3
LABA	65.6*	9.0*	23.9*	0.4
Other adrenergic stimulants %	2.8	1.2	4.4*	2.4
Oral β_2-agonists %	7.6	7.2	6.1	8.6
Xanthines %	16.7*	14.2	13.1	10.8
Anticholinergics %	26.2*	23.0*	24.6*	5.8
Oral corticosteroids %	58.7*	57.8*	37.4*	16.8
Combined bronchodilator products %	7.3*	5.3*	5.4*	1.8
Oxygen therapy %	2.8	2.8	4.0	3.1
Nebulised therapy %	4.1*	2.3*	5.1*	0.9
Baseline[+] use of health services				
COPD-related GP visits %	64.0	67.7	65.3	68.7
COPD-related hospitalisation[§] %	7.9	6.7	5.4	6.2
COPD-related A&E visits %	1.6*	0.0	0.0	0.1
History of comorbid conditions[f]				
Comorbid conditions present %	23.0*	31.1*	31.3*	43.3

SABA: short-acting β_2-agonists; LABA: long-acting β_2-agonists; GP: general practitioner; A&E: accident and emergency. [#]: mean±SD; [¶]: as defined in [14]; [+]: 6 months before start of regular treatment; [§]: in- and outpatient; [f]: as defined in [16]; *: $p<0.05$ *versus* reference group.

Table 2. – Survival of chronic obstructive pulmonary disease patients receiving fluticasone propionate (FP) and/or salmeterol and reference patients[#]

	FP and/or salmeterol	Reference
Total n	1045	3620
Survival %		
Year 1	96.2*	88.4
Year 2	89.4*	75.0
Year 3	78.6*	63.6
Females n	540	1600
Survival %		
Year 1	96.0*	88.6
Year 2	89.3*	76.2
Year 3	80.4*	65.6
Males n	505	2020
Survival %		
Year 1	96.4*	88.3
Year 2	89.5*	74.0
Year 3	76.4*	62.0
Age at diagnosis n (% 3 yr survival)		
50–59 yrs	225 (91.5)	367 (90.7)
60–69 yrs	397 (87.4)*	931 (75.0)
70–79 yrs	328 (68.9)*	1362 (62.2)
⩾80 yrs	95 (46.5)	960 (45.7)
Mention of asthma n (% 3 yr survival)		
Yes	777 (79.5)*	1009 (63.1)
No	268 (75.4)*	2611 (63.8)

[#]: Kaplan-Meier estimates of survival per 100 patients. *: $p<0.05$ *versus* reference group.

COPD patients who were regular users of FP and/or salmeterol showed significantly greater crude 3-yr survival rates (78.6%) than the reference group (63.6%) (Kaplan-Meier $p<0.05$). Similar patterns were observed in both the male and female subgroups, in the subgroups of COPD patients with and without concomitant asthma mention and regardless of age; rates were not significantly different between younger (50–60 yrs) and older (⩾80 yrs) groups (table 2). The adjusted survival curves are presented in figure 1, with significant differences in survival for COPD patients using FP and salmeterol and FP alone compared with the reference group (Cox adjusted p-values of 0.0008 and 0.0028, respectively).

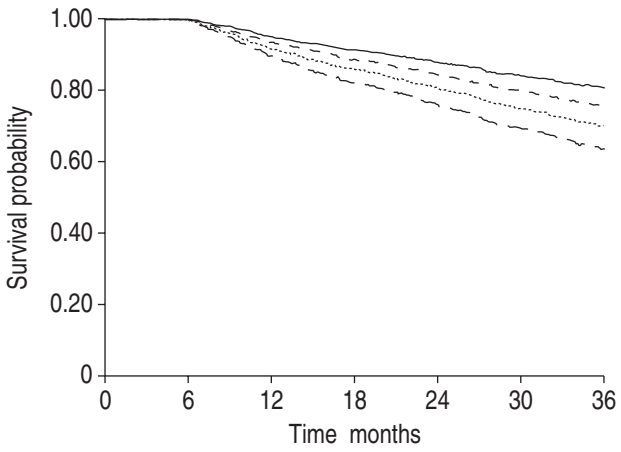

Fig. 1. – Adjusted survival function of chronic obstructive disease patients by therapy with combined fluticasone propionate (FP) and salmeterol (——), FP alone (- - - -) and salmeterol alone (·····) *versus* reference group (– – – –).

Figure 2 shows a multivariate analysis of the effects on mortality of each drug and a number of confounders. Increasing age was the strongest predictor of mortality; male sex, earlier year of entry, increasing number of comorbid conditions and courses of oral steroids were also associated with a significantly increased death risk. After adjustment for sex, age, year of entry, smoking, comorbid conditions, mention of asthma in their record and use of oral steroids, the survival observed in COPD users of salmeterol and/or FP was highest in combined users of FP and salmeterol (hazard ratio (HR) 0.48 (95% confidence interval (CI) 0.31–0.73)), followed by users of FP alone (HR 0.62 (95% CI 0.45–0.85)) *versus* the

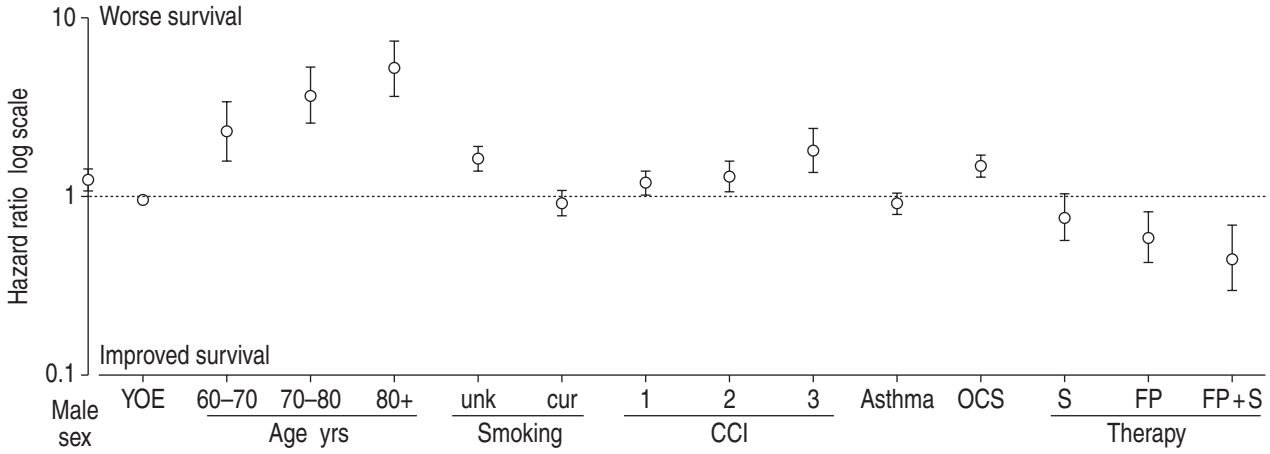

Fig. 2. – Hazard ratio (log scale) for 3-yr survival in chronic obstructive pulmonary disease patients by therapy with combined fluticasone propionate (FP) and salmeterol (S), FP alone and S alone *versus* reference group in a Cox proportional hazards function adjusted by sex, year of entry (YOE), age, smoking, comorbid conditions, oral corticosteroids (OCS) and mention of concomitant asthma (·····: unaltered survival). Data are presented as mean and 95% confidence interval. unk:unknown; cur: current; CCI: Charlson comorbidity index.

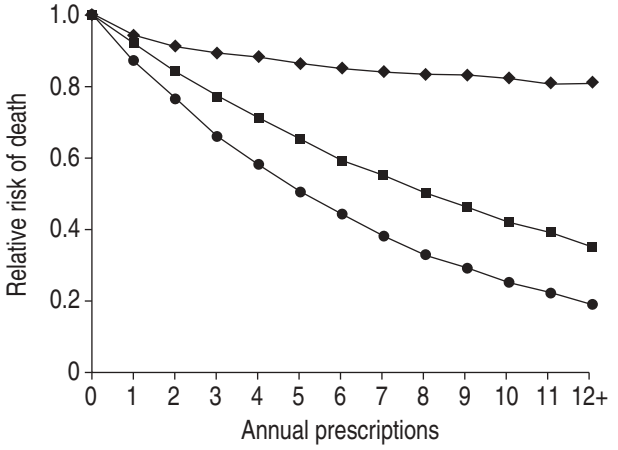

Fig. 3. – Dose/response adjusted relative risk of death as a function of mean annual number of prescriptions of combined fluticasone propionate (FP) and salmeterol (●), FP alone (■) and salmeterol alone (◆).

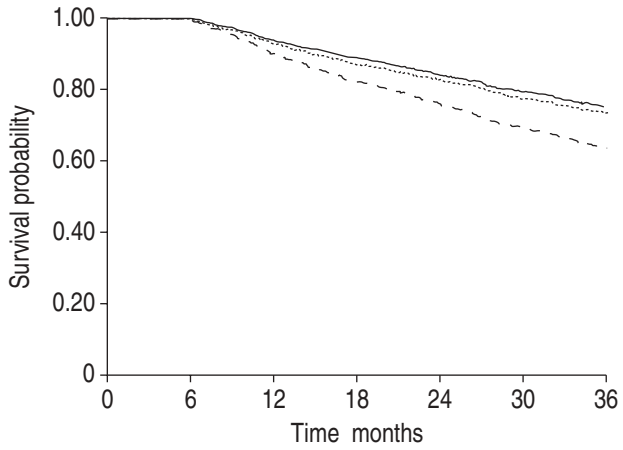

Fig. 4. – Adjusted survival function of chronic obstructive pulmonary disease patients by therapy with any inhaled corticosteroids plus salmeterol (——) and inhaled corticosteroids alone (·····) *versus* reference group (- - - -).

reference group. Salmeterol alone was not significantly associated with increased survival in COPD (p=0.123), but a HR of 0.79 (95% CI 0.58–1.07) indicated a trend towards this association.

A dose/response association was used to investigate the relationship between the adjusted matched mortality rate ratios and the mean annual number of prescriptions of the respective therapy (fig. 3). A nonlinear relationship was observed with increasing number of prescriptions and decrease in mortality, nonsignificant with salmeterol and significant with FP or combined use of FP and salmeterol. Rate ratios declined by 13% as a result of an additional annual combined prescription (relative risk 0.87 (95% CI 0.80–0.95)) and the rate among combined FP and salmeterol users receiving five or more prescriptions of both drugs was reduced by >50% *versus* the reference group. Figure 3 also suggests that the mortality risk among users of FP alone and salmeterol alone declined steadily with each increase in mean annual number of prescriptions.

Finally, a sensitivity analysis was performed *a posteriori* to determine 3-yr survival rates in COPD patients who were regular users of any inhaled corticosteroid (beclomethasone, budesonide or FP) (n=9,842) and of any inhaled corticosteroid plus salmeterol (n=1,291). This analysis found a class effect association, with similar adjusted survival probabilities for any inhaled corticosteroid alone (77.9%) and any inhaled corticosteroid plus salmeterol (82.1%) to those seen in the primary analysis with FP alone and combined FP and salmeterol. The adjusted survival analysis (Cox model) presented in figure 4 and an additional nested case/control analysis gave similar results to those seen in the primary analysis.

Discussion

In the present observational study using a GP-based database in the UK, regular treatment with FP and salmeterol was associated with greater survival in COPD patients. Mortality decreased with increasing intensity of prescription of FP and salmeterol. A similar greater survival was found with treatment with any inhaled corticosteroid and salmeterol. The results are noteworthy as medical treatment of COPD is often characterised by considerable nihilism and is believed to be associated with only very modest symptomatic benefit.

The GPRD is a unique source of information for investigating the pharmacoepidemiology of COPD in general and the present research question in particular. It is one of the largest population-based medical databases in the world. Also, it has advantages over health maintenance organisation databases in the USA, in which elderly people are frequently lost to follow-up, and pharmacoepidemiological databases in Canada, because combined use of inhaled corticosteroids and LABAs is uncommonly seen in COPD patients in Canada. Previous RCTs of each of these drugs in COPD have not focused on mortality [20], or were not sufficiently powered to do so. To date, the four published long-term (3-yr) RCTs of inhaled corticosteroids in COPD, namely the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease [21], the Copenhagen City Lung Study [22], the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial [23] and the Lung Health Study II [24], have used forced expiratory volume in one second (FEV1) decline as the primary effect parameter, a measure which seems well chosen for studying drugs which may affect the natural history of the disease [25]. Although inhaled corticosteroids had no significant effect on FEV1 decline in any of these trials, inhaled corticosteroids significantly reduced the number of exacerbations in the ISOLDE trial [23], the Lung Health Study II [24] and the 6-month study of PAGGIARO *et al.* [26]. Studies of salmeterol in COPD give some support to a mechanism of the long-acting bronchodilator being responsible for nonbronchodilating properties, and for a cytoprotective effect being

responsible for the reduction in infective exacerbations [27].

Strictly statistically speaking, in the present study, salmeterol alone *versus* reference (p=0.127) or in combination with FP *versus* FP alone (p=0.303) was not associated with increased survival. Indeed a key issue is whether or not the addition of a LABA to an inhaled corticosteroid is of significant benefit. The present study was powered to detect differences in survival in users of FP and/or salmeterol *versus* the reference group, but was underpowered for comparisons within the three drug exposure groups of interest. However, to the authors' knowledge, this is the first study showing a beneficial effect on mortality in COPD patients using inhaled corticosteroids and LABAs.

The sensitivity analysis, presented in figure 4, indicates an association between survival in COPD patients and regular use of any inhaled corticosteroid. It consistently identifies the same magnitude of effect, *i.e.* 78% survival after 3 yrs of use in COPD patients of any inhaled corticosteroid, as in the 35% of COPD patients who regularly use FP alone. This class effect of inhaled corticosteroids and survival in COPD patients confirms a recent report from Canada [28]. Whether or not the additional effect of combination therapy, *i.e.* inhaled corticosteroid and LABA, can be associated with further survival benefit in COPD patients remains to be seen in other observational studies and ongoing RCTs.

The present study is observational and thus open to all the usual criticism that can be applied to such studies. However, this study reflects the consequences of treating "real-life" COPD outside rigorous RCTs, for which patients are usually highly selected and their medication under such scrutiny that the generalisability of the results can often be questioned. Some shortcomings of the present study merit discussion. The choice of reference group is critical in observational studies. COPD patients, for whom a GP regularly prescribed other bronchodilators, as recommended in current BTS guidelines [8], were chosen from the same study base, ensuring that all patients in the study were seen and cared for by their GP in a similar manner. Lack of randomisation in observational studies entails a risk of bias resulting from comparing treatment groups imbalanced in the distribution of factors influencing study outcome. In the present study, the two groups were relatively well balanced by COPD severity at baseline. Subanalyses of crude survival stratified by major confounders, including age at diagnosis or mention of asthma, and analysis with a multivariate adjustment, maintained the association between treatment groups. Since age at COPD diagnosis might be a major determinant of the survival differences between groups, 3-yr survival was recalculated in the subgroup of 1,700 referents with the same age distribution (mean 66.3 yrs) as the cases. Survival increased from 63.6 to 68.8% in the reference group, still significantly lower than the 78.6% survival observed in FP and/or salmeterol users.

The ability to differentiate between COPD and asthma is obviously critical. In the present study, the majority of patients had "asthma" mentioned in their medical record; this occurred more frequently in users of FP and/or salmeterol than in the reference patients. Despite this frequent mention of asthma, the patients in the present study exhibited current smoking (>50%), anticholinergic use (24%) and mortality rates that were much higher than those expected among an asthmatic population. The validation study also found that the authors' definition of COPD was able to satisfactorily distinguish COPD from asthma and describe different levels of severity among COPD patients, with a sensitivity of a correct COPD diagnosis of 71.2 and 80.3% in moderate and severe COPD patients, respectively. Examination of cause of death revealed that only nine patients (three in the treated and six in the reference group) had asthma recorded as their cause of death. Moreover, there were only 298 patients with a retrospective asthma diagnosis before the age of 50 yrs, and the mortality rate differences from the present study were similar between the total population and the population restricted to those without any evidence of asthma. For these reasons, the authors believe that the present results are not attributable to misclassification of asthma as COPD, and that their efforts to take asthma into account at least match the efforts of two recent pharmacoepidemiological studies in COPD patients [28, 29], for which no validation study was conducted and asthma exclusion criteria were based only on age.

The present drug exposure information may be inaccurate as the GPRD system maintains records of prescribed rather than dispensed medication. Nevertheless, information on active drugs, other drugs and death is considered to produce nondifferential misclassification by treatment group. The present reported dose/response association of FP and salmeterol, based on standard techniques [2], found a decrease in the risk of death, nonsignificant with salmeterol and significant with FP or combined salmeterol and FP. Interestingly, the use of short-acting β-agonists, xanthines, anticholinergics or combined bronchodilators was maintained in each year in both treatment groups, indicating the main difference between groups continued to be the regular use or not of FP and salmeterol.

The impact of the exclusion strategy used must be considered. All patients who died within 6 months following potential entry into any of the drug exposure groups were excluded from the study, to ensure that a survival difference might represent a treatment effect. However, the impact of including these early deaths was to increase the positive association with survival of regular users of FP and salmeterol *versus* reference COPD patients (data not shown).

The present results are important as they imply a potential pharmacological effect on COPD progression of combination therapy, *i.e.* inhaled corticosteroid with LABA, as described by others with respect to inhaled corticosteroids alone [28]. Replication in other observational studies and ongoing clinical trials will confirm/reject the trend and magnitude of the survival association reported here.

In conclusion, it appears that regular use of fluticasone propionate, alone or in combination with

salmeterol, is associated with improved survival of chronic obstructive pulmonary disease patients managed within the UK primary care system.

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