Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

Results from Two Observational Designs Free of Immortal Time Bias

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Rationale: **Recent cohort studies in chronic obstructive pulmonary disease (COPD) have questioned the validity of previously reported associations between inhaled corticosteroids (ICS) and reductions in mortality and rehospitalization in observational studies. Using time-dependent versions of statistical survival models, these studies have suggested immortal time bias as responsible for the proposed beneficial association.** *Objectives:* **We explored the extent of this bias in a study of patients with COPD monitored for a year from COPD discharge with two designs free of any immortal time bias in the General Practice Research Database in the United Kingdom.** *Methods:* **In Design 1, we used only patients whose treatment status was defined on the same day of discharge to obtain a matched cohort based on propensity scores, which were derived from the patient-level baseline characteristics. In Design 2, we identified all in the study cohort who experienced death or rehospitalization and then matched each case to up to four noncases by randomly sampling from the cohort risk sets without regard to treatment status.** *Measurements and Main Results:* **The propensity scores matched cohort analysis of 786 patients without a wait time found a significant risk reduction associated with use of ICS: hazard ratio, 0.69 (95% confidence interval, 0.52–0.93). The matched nested case-control analysis of 2,222 patients, designed without regard to exposure status and hence free of immortal time bias, gave a similar association with exposure to ICS in the last 6-month period: hazard ratio, 0.71 (0.56–0.90).** *Conclusions:* **We conclude that immortal time bias cannot account for the risk reduction associated with ICS exposure in observational studies.**

Keywords: chronic obstructive pulmonary disease; epidemiologic methods; immortal time bias; nested case-control design; propensity scores matched cohort; time-dependent model

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death, responsible for more than 2.5 million deaths per year worldwide, and it is estimated to become the third most important cause of death by 2020 (1). COPD is a leading cause of hospitalization in adults in the United States, particularly in older populations. In 1998, almost 662,000 hospitalizations (1.9% of total hospitalizations) were attributed to COPD, and the rate of hospitalizations with COPD as the primary cause of hospitalization was 38.3/10,000 individuals in 1998 (2). An additional 2.5 million hospitalizations (7.0% of total hospitalizations) had COPD listed as a contributing cause.

Inhaled corticosteroids (ICS) reduce exacerbations in patients with moderate to severe COPD (3–5). The Global Initiative for Obstructive Lung Disease guidelines now recommend long-term use of ICS for patients with COPD with post-bronchodilator FEV_1 of less than 50% predicted and repeated exacerbations (6), as do the recent American Thoracic Society/European Respiratory Society COPD treatment guidelines (7).

Several observational studies have suggested that treatment with ICS is associated with risk reduction of rehospitalization or death (8–12). These pharmacoepidemiologic studies have used automated, linked health care and pharmacy data or electronic medical record databases, and, due to the nonrandom allocation of treatment exposure, they are by nature subject to bias. However, other recent COPD observational studies have failed to find favorable effects of ICS (13–15). These studies attributed immortal time bias as responsible for the indicated beneficial association. Immortal time bias results from cohort studies with follow-up time during which a subject cannot, by definition, incur the outcome event under study. That is, when the exposure time overlaps follow-up time, patients who die during the exposure time cannot by definition obtain the medication in question and as such will be classified as nonexposed. This is believed to result in underestimation of person-time without ICS treatment leading to overestimation of any treatment effect (13).

Because the applied and suggested analyses vary among the studies published until now, we explored the extent to which immortal time bias can account for the associations found previously. We used the U.K. General Practice Research Database (GPRD) to examine the effect of ICS on the risk of rehospitalization or death among 4,604 patients with COPD within a year of discharge from a first COPD hospitalization, on the basis of two different designs both free from immortal time bias. Some of the results of the study have been previously reported in the form of an abstract (16).

METHODS

Database Setting and Cohort Definition

The GPRD is an automated database of primary care in the United Kingdom that provides a unique source for investigating the implications of therapy on disease from a "real life" perspective. Detailed descriptions of the GPRD data file contents, validity, and research uses are well documented elsewhere (17–22). We retrospectively identified all patients with newly diagnosed COPD aged 50 years and older from 1990 to 1999. We defined the study cohort as all those hospitalized for a COPD-related condition during this period. Cohort entry was taken as the date of discharge from a first COPD hospitalization, with follow-up restricted to 1 year. The criteria for hospitalization for a COPD-related condition included codes for pneumonia and chest infection, and patients with no record of general practice contact in the 1-year

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follow-up period were excluded. The Scientific and Ethical Advisory Group of the GPRD approved the study protocol.

Drug Exposure and Outcome

Drug exposure was defined in terms of prescription of ICS given during a specified treatment window in the follow-up period. Thus, a patient was considered a user in a given window if he or she received at least one such prescription.

The outcome of interest was rehospitalization for a COPD-related medical condition or death within the 1-year follow-up period, whichever occurred first. In the GPRD, a COPD-related hospitalization would have a COPD medical code alongside the hospitalization outcome entry on the patient's medical records on the same day (22). Censoring was defined as end of record on database, hospitalization, death, or 365 days after cohort entry.

Study Designs and Statistical Analysis

Propensity scores matched-cohort design. In a randomized trial, the randomization of subjects to different treatment groups guarantees that, on average, there should be no systematic differences (i.e., bias) between treatment groups. In observational studies, investigators do not assign the treatment as in a randomized trial. Therefore, differences in observed patient-level characteristics in the two treatment groups may exist, and these differences could lead to biased estimates of treatment effects. The propensity score is the conditional probability of assignment to a particular treatment given a set of observed patient-level characteristics and is increasingly being used to adjust for nonrandom treatment assignment (23–25). Using only patients whose treatment status was defined on the same day of discharge, we fitted a logistic-regression model that predicted whether a patient would be prescribed ICS on the day of discharge as a function of the 27 variables listed in Table 1, including patient-level baseline characteristics on previous diagnostic label of asthma, smoking, age, sex, comorbidities, and respiratory medications before the first COPD-related hospitalization to obtain a matched cohort. Each ICS user was matched with a nonuser with the closest estimated propensity on the logit scale (i.e., within 0.01 caliper) to reduce differences between treatment groups. We used only patients without waiting times because propensity scores by themselves do not account for immortal time bias (Figure 1).

We fitted the proportional hazards model adjusting for age and sex as well as smoking, use of oral steroids and other respiratory medications at baseline, and the comorbidities specified in Table 1.

Nested case-control design. Patients in the study cohort who experienced the outcome (death or rehospitalization) were defined as cases. Each case was then matched to up to four noncases by random sampling from the cohort risk sets without regard to treatment status. Cases and their control subjects were matched on four factors: follow-up duration (time between discharge and index dates), sex, age (within 1 year), and discharge date (within 30 days) (26–28). To reduce exposure misclassification, we excluded patients who were first exposed to ICS beyond the first 90 days after hospital discharge. Index date was the outcome date and comparison was between those with any ICS prescription in the 6 months before the index date (i.e., exposed) versus those without any

TABLE 1. PROPENSITY SCORES SAMPLE: CHARACTERISTICS OF COHORT SUBJECTS FROM FIRST HOSPITALIZATION FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE ACCORDING TO INHALED CORTICOSTEROID PRESCRIPTION ON DAY OF DISCHARGE, BEFORE AND AFTER MATCHING BY PROPENSITY SCORES

	Before Matching			After Matching	
	Non-ICS	ICS	C-stat†	Non-ICS	ICS
Total	538	1,091		393	393
Mean age, yr (SD)	74.3 (9.2)	71.3 (9.3)*	0.592	72.8 (8.7)	74.4 (8.3)*
Male, %	56.7	50.3*	0.532	55.5	50.1
Current smoker, %	50.9	54.8	0.519	52.4	53.2
Asthma recorded previously, %	49.1	68.6*	0.597	49.6	59.0*
Respiratory drug use in the 90 d before first COPD-related hospitalization, %					
ICS	20.3	64.9*	0.723	26.0	33.1*
Inhaled β2-agonist	48.0	62.6*	0.573	48.3	47.8
Oral β2-agonist	7.8	7.2	0.503	7.4	7.9
Xanthines	27.1	14.0*	0.566	19.8	16.5
Anticholinergics	23.6	15.0*	0.543	17.8	17.0
Oral corticosteroids	33.6	38.1	0.522	34.4	33.8
Combined short-acting bronchodilators	8.6	6.0	0.513	10.2	4.6*
Home oxygen therapy	9.3	3.8*	0.528	9.4	2.3*
Home nebulized therapy	7.2	1.7*	0.528	5.9	2.0*
Baseline comorbidity, %					
Myocardial infarction	10.0	9.1	0.505	9.9	8.9
Congestive heart failure	32.7	25.7*	0.535	29.5	28.0
Peripheral vascular disease	3.3	2.8	0.503	3.6	2.0
Cerebrovascular disease	6.1	3.4*	0.514	5.9	3.6
Dementia	1.5	0.6	0.504	1.5	1.0
Rheumatologic disease	1.9	1.3	0.503	2.3	1.3
Peptic ulcer	5.9	7.8	0.509	6.6	7.1
Mild liver disease	0.2	0.0	0.501	0.3	0.0
Moderate/severe liver disease	0.4	0.5	0.500	0.3	0.5
Diabetes	6.1	5.4	0.504	6.6	5.1
Diabetes with complication	0.2	0.1	0.500	0.3	0.0
Hemiplegia or paraplegia	2.2	1.2	0.505	2.3	0.5*
Renal disease	2.2	1.6	0.503	2.3	1.5
Cancer	1.3	0.8	0.502	1.5	1.3

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid.

Control subjects received no ICS prescription during follow-up after hospitalization.

* Significant p value < 0.05 in between-groups comparison.

† A measure of the predictive ability of the logistic model fitted with the corresponding variable (in terms of probability which by definition must lie between 0.5 and 1.00).

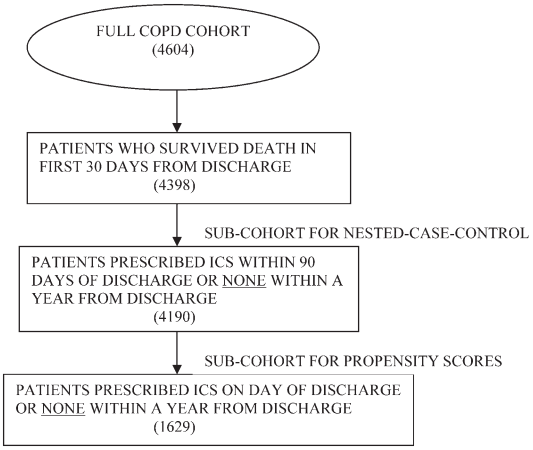

Figure 1. Selection of subcohorts for the propensity scores matched and nested case-control designs.

ICS prescription in the same period (i.e., unexposed). Thus, the design was similar to that of Suissa and coworkers (29) and Huiart and colleagues (30), and there was no bias due to wait time in the assessment of possible association between exposure and outcome. The confounding variables listed in Table 2 were adjusted for using conditional logistic regression.

Confounders. Other respiratory medications used in the baseline period were treated as eight distinct class (binary) variables. Information on tobacco use was categorized as either nonsmoker (to represent never and ex-smoker), current smoker, or unknown, based on the patient's records in both the medical and prevention databases. Comorbidities were identified from patients' medical records and for the nested case-control design; these were categorized into three groups based on the Charlson comorbidity scores (31) as 0, 1, and 2+, in the direction of increasing burden (Tables 1 and 2).

RESULTS

For the propensity scores matched cohort, we identified 1,629 patients with records of a first COPD-related hospitalization and who either received a prescription for ICS on the day of discharge or were never exposed to ICS in their entire follow-up period, having excluded all those who died within 30 days of discharge, in line with the previous studies (8, 10, 12). Of these, 1,091 patients were given ICS prescriptions. The final matched cohort was made up of 393 exposed and 393 unexposed patients; 210 suffered rehospitalization or death during follow-up and the characteristics of the two groups are given in Table 1. For treatment with ICS, we obtained a hazard ratio estimate of 0.69 (95% confidence interval, 0.52–0.93) from this propensity scores matched-cohort analysis, with a C-statistic of 0.82 (a measure of the predictive ability of the model in terms of probability).

The nested case-control design was based on the full cohort of 4,604 patients, including those who waited for at least a day and no more than 90 days before receiving an ICS prescription. We identified 4,190 such patients with records of a first COPD-related hospitalization, having also excluded all patients that died within 30 days of discharge. We were able to match 675 of the cases to noncases at a ratio of up to four control subjects per case. Table 2 gives the characteristics of the cases and their 1,547 control subjects. As shown in Table 3, the matched nested case-control analysis gave rate ratio estimates of 0.71 (0.56–0.90) for those with any prescription of ICS in the last 6 months and decreasing rate ratios with increasing number of prescriptions. This indication of a gradual decrease in the event rate with the number of prescriptions of ICS received could also be expressed using a continuous quantity response analysis estimating that the rate ratio decreased by 6% (rate ratio, 0.94; 0.89–0.99) for each additional prescription in the period.

TABLE 2. NESTED CASE-CONTROL SAMPLE: CHARACTERISTICS OF CASES (THOSE WHO WERE REHOSPITALIZED OR DIED WITHIN 12 MONTHS FROM DISCHARGE FROM HOSPITAL FOR A CHRONIC OBSTRUCTIVE PULMONARY DISEASE–RELATED ILLNESS) AND MATCHED CONTROL SUBJECTS IN THE NESTED CASE-CONTROL ANALYSIS

	Cases	Control
Total	675	1,547
Mean age, yr (SD)	72.7 (8.3)	72.2 (7.6)
Male, %	56.0	54.4
Current smoker, %	51.4	53.0
Asthma recorded previously, %	65.5	67.2
Respiratory drug use during 6 mo before the index date, %		
Inhaled corticosteroid	74.2	80.9 *
Inhaled β2-agonist	76.9	72.8*
Oral β2-agonist	5.2	4.0
Xanthines	28.7	18.4*
Anticholinergics	30.2	25.5*
Oral corticosteroids	51.7	34.8*
Combined short-acting bronchodilators	11.1	5.3*
Home oxygen therapy	18.4	7.6*
Home nebulized therapy	6.4	3.6*
Baseline comorbidity, %		
Myocardial infarction	13.9	11.3
Congestive heart failure	40.1	28.8*
Peripheral vascular disease	4.7	3.0*
Cerebrovascular disease	8.0	4.5*
Dementia	1.2	1.1
Rheumatologic disease	1.2	1.2
Peptic ulcer	9.9	8.5
Mild liver disease	0.1	0.0
Moderate/severe liver disease	0.1	0.4
Diabetes	5.9	6.5
Diabetes with complication	0.0	0.1
Hemiplegia or paraplegia	1.5	1.7
Renal disease	1.9	1.2
Cancer	2.5	1.2*

Control subjects were randomly drawn from the corresponding risk set without regard to treatment status and were matched for the index date when outcome occurred in the case (within 30 days) for interval between discharge and index date, age, and sex.

* Significant p value < 0.05.

DISCUSSION

Our results of the propensity scores matched-cohort and matched nested case-control analyses, both of which by design were free of immortal time bias, indicate a beneficial association of ICS and the risk of death or rehospitalization in COPD, in line with our previous findings using a cohort analysis strategy (11). These findings are strengthened by the observed relationship between increased regularity of ICS prescriptions and reductions in event rates.

The propensity scores approach is a recommendation of a recent editorial on the subject (32), whereas the nested case-control approach has been described as a method that simplifies the cohort analysis when "exposures vary over time and leads to valid estimates of rate ratios with a negligible loss in precision" (33). Our matched nested case-control design did not involve any patient follow-up and exposure status was only determined in the last 6 months before the index date for each case and his or her corresponding control subject. Consequently, it was free of immortal time bias in its estimation of possible association between treatment and the risk of interest. However, the study

TABLE 3. MATCHED ADJUSTED RATE RATIOS FOR DEATH OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE–RELATED REHOSPITALIZATION IN THE U.K. GENERAL PRACTICE RESEARCH DATABASE CHRONIC OBSTRUCTIVE PULMONARY DISEASE COHORT (NESTED CASE-CONTROL ANALYSES)

	Cases, No. (%)	Control, No. (%)	Adjusted Rate Ratio	95% CI
No. subjects	675	1,547		
ICS prescriptions 6 mo before index date				
None	174 (25.8)	296 (19.1)		
Any	501 (74.2)	1,251 (80.9)	0.71	(0.56–0.90)
1–2 prescriptions	307 (45.5)	722 (46.7)	0.76	(0.59–0.97)
3–5 prescriptions	152 (22.5)	403 (26.1)	0.64	(0.47–0.86)
⩾ 6 prescriptions	42 (6.2)	126 (8.1)	0.52	(0.33–0.81)
Per additional prescription			0.94	(0.89–0.99)

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroid.

Cases and control subjects were matched on follow-up duration (time between discharge and index dates), sex, age (within 1 year), and discharge date (within 30 days).

base for both sets of analysis was an observational database, and our findings cannot be interpreted as a proxy for an efficacy study. At best, our study tries to measure effectiveness and, even for that, other sources of bias (e.g., group imbalance from unmeasured factors) may be present and affecting our results.

Our findings are distinctly different from those of Suissa (13), and this difference can be due to both the different methods of analysis and the population studied. The study by Suissa (13) did not assess the extent to which immortal time bias was a factor and relied instead on a methodology of restrictive application and allowing subjects to change from "nonexposed" to "exposed" in the observation period. We know from the assumptions underpinning the time-dependent Cox model that regression to the null is a possible indication of inappropriate application. The model used by Suissa is otherwise known as the "treatment switching" method, for which it is a necessary requirement that the reason for switching is unrelated to the subsequent risk of an event (34). Indeed, the fundamental weakness of this approach has recently been illustrated in a study by Rothman (35) that revealed the problem associated with treatment switching, even in a randomized controlled trial setting that allowed for switching at the start of the open-label phase. It is questionable if the condition for appropriate application can be tenable in general practice data. The problems associated with the use of statistical models to estimate time-dependent variables are seldom simple enough to resolve, and most studies are therefore designed to avoid the use of such models (36–38). That the immortal time bias is a potential source of bias is, however, undoubtedly true and should warrant attention in pharmacoepidemiologic studies. Thus, it is likely that the previous studies by Sin and Tu (8) and Soriano and colleagues (10) were affected by immortal time bias by their inclusion of the 90-day treatment assignment period in patient follow-up, and Suissa was correct to highlight this problem (12).

We are aware that there are likely to be differences in treatment patterns for COPD in the United Kingdom, Canada, and the United States, and that such differences could impact the different risk estimates observed beyond the study design. For instance, the GPRD suggests that 83% of patients with COPD received an ICS within 180 days of discharge. This is considerably higher than in other countries and may explain some of the differences observed; that is, those who do not receive ICS may receive substandard care overall and hence a higher risk of mortality.

As of 2005, there is still an ongoing controversy on whether ICS have significant benefits in COPD. Most likely, a higher level of evidence will be available within a few years (39). Until then, we can only speculate that the epidemiologic signal of the beneficial effects of ICS in COPD in the U.K. GPRD is of such a magnitude that all reanalyses conducted to date with different study designs or criteria, including the propensity scores and nested case-control designs in this study, produce beneficial associations, indicating high internal consistency. It is hoped that research on the effectiveness of ICS in COPD will help those in the emergent discipline of COPD pharmacoepidemiology (40) and ultimately their patients.

In conclusion, our analyses revealed significant influence of study design on the effect of ICS on adverse outcomes after hospitalization. With different study designs reducing potential bias, we consistently found an association between ICS use and reduction of risk of rehospitalization and death.

Conflict of Interest Statement: V.A.K. has been an employee with GlaxoSmithKline (GSK) from 1999 to date. N.B.P. has been a consultant on COPD for GSK and is currently on an advisory committee for a long-term trial of treatment of COPD sponsored by GSK, for which he has received a total of $6,500 since 2002. J.B.S. declares that she has been a GSK employee from 1998 to date. J.V. received $8,000 in 2002 and $10,000 in 2004 for speaking at conferences organized by GSK; $4,000 in 2002, $7,000 in 2003, and $2,000 in 2004 for speaking at conferences organized by AstraZeneca; and $1,000 in 2004 for speaking at a conference organized by Boehringer-Ingelheim. He has served on advisory boards for GSK, receiving $2,000 annually in 2002–2004. His previous department (Department of Respiratory Medicine, Hvidovre University Hospital, Copenhagen, Denmark) received a research grant for approximately $400,000 during 2001–2003 to support research into the genetic basis of COPD. His wife (Inge Vestbo) has been an employee of GSK from 1988 to January 2004. Neither J.V. nor his wife has shares or options in GSK or any other pharmaceutical company.

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