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Introduction

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Chronic obstructive pulmonary disease (COPD) threatens an emerging public health crisis. The two major drivers for this are the ageing of the world's population and the impressive, if deplorable, success of the multinational tobacco companies at forcing open world markets. Although the World Health Organization estimates that COPD is the sixth most common cause of death worldwide and that by 2020 it will be the third most common, COPD is also an orphan condition that overwhelmingly affects the poor and has been broadly ignored by scientists and by governments. Although the cost-effectiveness of smoking cessation, pulmonary rehabilitation, and long-term oxygen therapy in the later stages of the disease are all high, there is little active treatment that can currently be offered.

Recently, randomised controlled trials, specifically of inhaled corticosteroids (ICS) in patients with COPD have failed to show any modification of the decline in lung function associated with the disease. Analyses have, however, suggested that these drugs may reduce the number of exacerbations, which are related to quality of life. These findings remain controversial, since in some cases they are based on secondary analyses, have inevitably been carried out in selected populations, the results appear to be sensitive to the design of the trials and confidence intervals are often wide. More recently still, evidence has begun to emerge that the use of ICS and possibly long-acting β_2-agonists may also reduce mortality as well as exacerbations in these patients. Exacerbations of COPD, particularly those leading to hospitalisation, are an important cost driver in the healthcare system and may account for three-quarters of the additional costs of a patient with COPD. With the lack of good alternative remedies, such an effect would clearly be important not only to patients but also to the health services.

Much of the new evidence comes, however, not from experimental studies, but from observational studies based on a variety of administrative databases. Although these databases have had an important part in the development of information about drug effects since the 1960s, interpretation of the data contained in them is less straightforward. Most recently, S. Suissa proposed a particular problem with some of the estimates of the effects of ICS on COPD from these sources, the so-called problem of "immortal time". This bias arises when time is allocated to the control (or treatment) group as "incident-free" even though no incident could have occurred during the period because of the definitions used in the study. It was suggested that some of the reports that ICS are effective in reducing mortality in patients with COPD can be accounted for by this bias. Combined with the surprisingly large effects that have been estimated using these methods, this bias has cast doubt on the robustness of these reports' findings.

The issues raised are not only relevant to the current debate on the effectiveness of ICS in COPD but affect a wide range of common problems in health policy. Use of databases is important, not simply as a substitute for randomised clinical trials that would be too large or expensive to undertake. They are also important for a broader understanding of the effectiveness of drug treatments. Very often, trials that are undertaken raise unrealistic hopes for effectiveness in the broader population, either because they are carried out in a highly restricted patient group or because use of the medication in practice is restricted by availability or by patient compliance. These issues need to be explored and one method of doing this is through the use of administrative databases. Robust interpretation of these data is therefore key to adequate policy-making.

The symposium reported here brought together a group of scientists who had experience in this field and many who had used different databases to explore the issue of the effectiveness of ICS and, in most instances, long-acting β_2-agonists to improve the outcomes of patients with COPD. The result was not only an excellent review of what is known of the effectiveness of these drugs, but also an important review of the methods, problems, and potential pitfalls of the uses of administrative databases for pharmacoepidemiological research.

The idea for the symposium arose from a discussion between S. Suissa of McGill University, Montreal, Canada, and J.B. Soriano of GlaxoSmithKline, Greenford, UK, and was financially supported by GlaxoSmithKline. The proceedings will be of interest to those interested in the treatment of COPD and also to any interested in the appropriate use of administrative databases in pharmacoepidemiology.

Epidemiology of COPD: overview and the US perspective

W.M. Vollmer

Summary

The burden of chronic obstructive pulmonary disease (COPD) is increasing in the USA. The prevalence of COPD is now almost equal in males and females. Although objectively measured, airflow limitation is now generally believed to provide the most accurate estimates of disease; international guidelines on the diagnosis and treatment of COPD do not agree on standards for objectively defined measures. Cigarette smoking continues to be the primary risk factor for COPD, however, work-related exposures may be an important contributor to the overall burden of COPD. Approximately 7% of the adult population in the USA has low lung function; 70% of these adults with low lung function have never had a diagnosis of any obstructive lung disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and results in a substantial economic and social burden to society. In the USA, it is currently the fourth leading cause of death [1], and the World Health Organization (WHO) estimated that there were 2.74 million deaths worldwide from COPD in the year 2000 [2]. In 1993, the cost of COPD to the US economy was an estimated $23.9 billion, including $14.7 billion in direct medical costs and an additional $9.2 billion in indirect costs [1].

The global burden of COPD has also been increasing and is expected to continue to increase in the coming decades. According to the Global Burden of Disease Study, COPD, ranked twelfth worldwide in 1990 in terms of its impact on disability-adjusted life-yrs, is projected to rank fifth by the year 2020 [3, 4]. In the USA, death rates for COPD have climbed steadily over the past 40 yrs. While rates have begun to stabilise for males in recent years, they are, if anything, increasing for females [1]. A similar pattern of increase is seen if trends in COPD-related healthcare utilisation, rather than mortality, are examined [5]. What is even more striking is that these trends, at least in the USA, fly in the face of declining mortality from cardiovascular disease [2].

The two main reasons for these patterns are the increased consumption of cigarettes, especially in developing countries, and among females and the elderly. It has long been known that cigarette smoking is the primary risk factor for COPD [6]. According to the third National Health and Nutrition Examination Survey (NHANES III) carried out in the USA between 1988–1994, current cigarette smokers are 3–5-times more likely than never-smokers to have airflow limitation and to report chronic respiratory symptoms [7, 8] (table 1). The WHO estimates that there are now 1.1 billion smokers worldwide [9] and this figure is expected to increase to 1.6 billion by 2025 [10].

The deleterious effects of cigarette smoking take some time to manifest symptoms. Pronounced airflow limitation does not really begin to show up until the mid-to-late 40s and increases thereafter. As the world′s population ages, therefore, it is inevitable that the burden of COPD will only increase. A recent United Nations report predicts that the percentage of the world′s population >60 yrs of age will double in the next 50 yrs, and that the number reaching 100 yrs will be 15-times higher in 2050 than it is today. Looked at another way, in 2002 only one in 10 of the world′s population (some 6.29 billion individuals), are 60 yrs of age or older. By 2050, approximately one in three will be 60 yrs of age or older [11].

Table 1. – Prevalence of low lung function and chronic cough

	Males# %	Females# %
Chronic cough		
Smokers	34.9	28.6
Exsmokers	9.1	9.3
Never-smokers	8.1	9.5
Low lung function		
Smokers	25.8	22.2
Exsmokers	15.3	11.1
Never-smokers	8.1	5.7

Age adjusted to all study participants; Low lung function is described as a forced expiratory volume in one second (FEV1)/forced vital capacity ratio of <0.70 and an FEV1 of <80% of the predicted value. #: includes Black and White subjects. Data from the third National Health and Nutrition Examination Survey 1988–1994 [8].

Prevalence of chronic obstructive pulmonary disease

The WHO Global Burden of Disease Study used data from a variety of published and unpublished sources to estimate the prevalence of COPD in various countries and regions throughout the world [3, 4]. While the methodologies varied and some of the estimates are admittedly imprecise, a few general patterns emerged. First, the prevalence tended to be highest in countries where cigarette smoking is common, and the prevalence generally tends to be higher in males than in females. Recently, a different pattern has emerged in the USA with prevalence of COPD being almost equal in males and females [1, 5, 7]. This likely reflects the increase in smoking among females that has occurred in the USA since World War II.

Estimates of the prevalence of COPD will depend on the definition and criteria used to define it [12]. Estimates based on self-report of respiratory symptoms are very nonspecific and likely result in overestimates of disease, while estimates based on physician diagnosis will tend to lack sensitivity since mild disease is often undiagnosed. Objectively measured airflow limitation is now generally believed to provide the most accurate estimates of disease, but, even here there is a lack of consensus, since the American Thoracic Society, European Respiratory Society, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definitions all differ. CELLI *et al.* [13] recently compared a number of objectively defined measures and reported that prevalence estimates sometimes varied by as much as 100%. They recommended the GOLD clinical definition of a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio <0.70 on the basis of its simplicity and accuracy [12]. While it may be simple, its accuracy is still in question. HARDIE *et al.* [14] recently reported on 71 asymptomatic, nonsmoking adults, selected as a random sample of adults of >70 yrs of age. Thirty-five per cent had a prebronchodilator ratio <0.70 and this increased to 50% among those of >80 yrs. One-third of those >80 yrs actually met GOLD stage II criteria despite having no history of smoking or any apparent symptoms.

Some of the best prevalence data for COPD come from the USA NHANES III study. This large probability sample of the US population included a subsample of >16,000 adults for whom pulmonary function tests, a complete medical history, and self-reported diagnostic data were available. COPD (defined as the presence of airflow limitation) was estimated to be present in ~24% of current smokers, 13% of exsmokers, and 7% of never-smokers (table 1). These estimates were very similar for males and females [7, 8]. The prevalence of physician-diagnosed COPD, defined as chronic bronchitis or emphysema, increases steadily in both males and females through the mid-to-late adult years and, in this latter age range, tends to be greater for males than for females (table 2).

Table 2. – Prevalence of physician-diagnosed chronic obstructive pulmonary disease

	Age yrs					
	17–24	25–44	45–64	65–74	75–84	⩾85
Males %						
White	0.8	1.2	5.0	10.2	7.9	8.0
Black	0.2	1.1	2.8	4.1	4.9	0
Females %						
White	3.1	2.1	6.0	7.8	7.2	9.7
Black	0.8	2.1	2.9	2.8	1.9	0

Data from the third National Health and Nutrition Examination Survey 1988–1994 [8].

Objectively measured airflow limitation also increases with increasing age, at least until age 84 yrs, with a likely survivor effect thereafter, and is again higher in males than in females in the older age categories (table 3).

If the overlap between objectively measured COPD and physician diagnosis of asthma, chronic bronchitis, and emphysema is examined, every possible combination of outcomes is seen. In particular, it is seen that physician-diagnosed disease captures only a small portion of the COPD pie. Among individuals with an FEV1/FVC ratio <0.70, only approximately one-third report a previous diagnosis of emphysema, chronic bronchitis, or asthma, and <20% report a current diagnosis of one of these three conditions [5, 15].

The NHANES III data can also be used to estimate the contribution of occupation to COPD [16]. Using the GOLD stage II criterion of an FEV1/FVC ratio <0.70 and an FEV1 <80% of predicted, the fraction of COPD that may be attributable to work among individuals aged 30–75 yrs has been estimated as 19.2% overall and 31.2% among never-smokers.

Table 3. – Prevalence of forced expiratory volume in one second (FEV_1)/forced vital capacity ratio of <0.70 and FEV_1 <80% predicted

	Age yrs					
	17–24	25–44	45–64	65–74	75–84	⩾85
Males %						
White	0.9	2.6	11.4	23.7	24.2	18.3
Black	2.6	2.0	12.9	23.9	35.0	6.5
Females %						
White	0.9	2.3	10.9	16.3	16.3	9.9
Black	1.3	1.6	8.3	8.7	10.7	6.0

Data from the third National Health and Nutrition Examination Survey 1988–1994 [8].

Conclusion

Overall, the NHANES data suggest that 7% of the adult population in the USA have low lung function and that this is closely related to cigarette consumption and increasing age. These data also suggest that ~70% of adults with low lung function have never had a diagnosis of any obstructive lung disease and that work-related exposures may be an important contributor to the overall burden of COPD.

Epidemiology of COPD: a European perspective

G. Viegi

Summary

Mortality rates from chronic obstructive pulmonary disease (COPD) vary across Europe. However, the continuing elevated prevalence rates of current smoking among males and the increasing trend observed in females in the last decades predicts an increase of COPD mortality in many countries in the coming years. The real prevalence of COPD within a given population may vary widely depending upon the tools used for its identification: reported respiratory symptoms, medical diagnosis and abnormal lung function. Even when the diagnosis is based on an objective tool like spirometry, largely variable prevalence rates are found within the same population. In view of the different criteria endorsed by different scientific societies, it is clear that further research is needed to reach a standardised criterion for airways obstruction. Patients underestimate their own morbidity and may therefore be undertreated. The cost of COPD, largely driven by exacerbations, is expected to increase considerably in the future, reflecting the previous smoking habits of an ageing population. The impressive prevalence in current smokers <45 yrs of age in most countries highlights the need to improve the quality of prevention; early detection and screening programmes may be useful in this population of smokers.

Introduction

Chronic obstructive pulmonary disease (COPD) is a very important cause of mortality and morbidity in Europe [17]. Although COPD and asthma are considered different entities with respect to pathophysiological and cellular conditions [18], it is well recognised that chronic persistent asthma may have the feature of irreversible airflow obstruction, thus being encompassed within the term COPD, as clearly shown in the nonproportional Venn diagram published in the 1995 American Thoracic Society (ATS) guidelines [19]. Further, many available statistics on COPD mortality and morbidity data are based upon the combination of chronic bronchitis, emphysema and asthma; codes 490–493 of the International Classification of Diseases, ninth revision (ICD-9) [20], or codes J40–47 of ICD-10 [21]. Sometimes, code 496 ICD-9 is also used to include within COPD the airflow obstruction not classified elsewhere.

Mortality

On a worldwide scale, according to the estimates by MURRAY and LOPEZ [22], if tobacco epidemics will not change their trends, in the interval 1990–2020, COPD will jump from the sixth to the third rank among the leading causes of death. At the European level, huge differences in the mortality rates have already been depicted in the Appendix "Epidemiology" of the European Respiratory Society (ERS) Consensus Statement on COPD [17]. It has been reported that mortality rates for COPD vary more than five-fold among the European countries and that they increase greatly with age and are considerably lower in females [23]. More recent data encompassing the period 1993–1997, provided by the World Health Organization [24], show a wide range in the mortality rates from >70 in Hungary to <10 in Greece (per 100,000 population of 35–74 yrs of age). Analogous figures for females range between ~40 in Scotland to <5 in Greece.

The comparison of mortality rates among different countries depends upon the relative weight of relevant risk factors in the different populations, but it is also linked to technical factors such as the use of different reference

populations for standardising the rates, and the use of different codes for reporting the same disease (*e.g.* code 491 ICD-9 is used more in south Europe, code 496 ICD-9 in the north).

Current trends in COPD in the UK [25] differ from those in many other countries, because in the past COPD was much more common than in other countries undergoing a smoking epidemic at the same time, and peak cigarette consumption in males and females occurred >25 yrs ago. Male mortality from COPD has been falling for 30 yrs, while female mortality has risen steadily during the same period. A strong socioeconomic gradient in morbidity and mortality persists.

In Italy, of 36,834 deaths that occurred in 1998 for respiratory diseases [26], approximately one-half have been caused by COPD (codes 490-493 ICD-9). The number of deaths stratified by sex, standardised mortality rates per 100,000 people (with the world population as reference), and male/female ratios for all respiratory diseases and COPD are reported in table 4.

When comparing COPD mortality data in 1980 and in 1998, a decreasing trend emerged in Italy from 21.1 to 11.9 per 100,000 inhabitants, which applied to both sexes [26]. This indicates a different tendency in Italy with regard to other developed countries. However, recent data from the USA indicate that, for the first time, a decrease of 1.7% deaths for COPD occurred in the year 2000 with respect to the year 1999 [5]. Further, it is possible that in Italy there is a larger misclassification of respiratory diseases, with respect to cardiovascular diseases, in the compilation of death certificates. Such misclassification is a common experience [27]. Indeed, the continued elevated prevalence rates of current smoking among males and the increasing trend observed in females in the last decades, have led to the hypothesis that an increase of COPD mortality will be seen in Italy in the coming years, as it has been anticipated for other countries, such as Japan where the mortality rate in 1999 was 10.4 per 100,000 people [28].

Among the factors that have been related to an increased risk of mortality (or of lower survival) for COPD in the general population, epidemiological data from Denmark have stressed the role of forced expiratory volume in one second (FEV1) and chronic mucus hypersecretion. For subjects with an FEV1 $\leqslant$40% at baseline, 5-yr survival after subsequent hospitalisation was only 28% [29]. Within the framework of a 10–12-yr follow-up, chronic mucus hypersecretion was found to be a significant predictor (relative risk (RR) 3.5) of COPD-related death with pulmonary infection implicated [30].

Morbidity

Although COPD represents one of the main health issues of the present and the near future worldwide, some of its features are still undefined from a social and economic point of view. The real prevalence of COPD within a given population may vary widely depending upon the tools used for its identification: reported respiratory symptoms, medical diagnosis and abnormal lung function. Community surveys in countries of both northern and southern Europe [23] indicate that 4–6% of the adult population suffer from clinically relevant COPD. The prevalence increases greatly with age, however, two-thirds have only a mild reduction in lung function.

According to the Italian National Statistics Agency multipurpose survey on households, performed in 1999–2000, 4.4% of the Italian population (4.8% males, 3.9% females) suffered from chronic bronchitis and/or emphysema and/or respiratory failure. The highest rates have been found in the elderly >64 yrs of age (total 14.1%, males 18.3%, females 11.2%) [31].

Another source of routinely collected statistics is the hospital discharge standard form. Data pertaining to the year 2000 in Italy show that 20.6% of discharges for respiratory diseases are caused by Diagnosed Related Group 88 - COPD (126,927 cases). Total hospital days were 1,159,995 with an average length of stay of 9.4 days [32].

A dynamic multistate life table model was used to compute projections for the Netherlands [33]. Changes in the size and composition of the population caused COPD prevalence to increase from 21 per 1,000 in 1994 to 33 per 1,000 in 2015 for males, and from 10 per 1,000 to 23 per 1,000 for females. Changes in smoking behaviour reduce the projected prevalence to 29 per 1,000 for males, but increase it to 25 per 1,000 for females. Total years of life lost increase by >60%, and disability-adjusted life-yrs lost increase by 75%. Costs rise 90%; smokers cause ~90% of these costs. The model demonstrates the unavoidable increase in the burden of COPD, an increase that is larger for females than for males. The major causes of this increase are past smoking behaviour and the ageing of the population. According to the authors, changes in smoking behaviour will have only a small effect in the near future.

It is interesting to point out that among industrialised countries, Japan shows extremely low prevalence rates of COPD; in 1999, it was estimated that 212,000 people (139,000 males) were affected by COPD with a prevalence of 0.17% in the general population [28]. One of the reasons that account for these values is the long delay in the uptake of tobacco smoking in Japan for cultural and socioeconomic reasons after the second World War.

The importance of sex, ageing and tobacco smoking in the development of COPD has been examined, in Italy, by VIEGI *et al.* [34], using data collected, through questionnaire, in two longitudinal surveys carried out in the rural area of Po Delta (northern Italy) and in the urban area of Pisa-Cascina between 1980–1993. Data on prevalence rates of chronic bronchitis and emphysema (medical diagnosis) and of some respiratory symptoms, stratified by sex and smoking habit were obtained. The prevalence rate of chronic bronchitis was lower than that of chronic cough and phlegm, symptoms on which the diagnosis of chronic bronchitis is based [35]. It confirms an underestimate of the frequency of such disease, when only medical diagnoses are considered [36].

The underestimate of COPD prevalence, possibly 25–50% and higher, has been found by several investigators [17, 37, 38]. Two cross-sectional studies of respiratory symptoms and

Table 4. – Deaths for respiratory diseases in Italy in 1998 (total and chronic obstructive pulmonary disease)

	Code	M		F		Total		Ratio M/F
		Deaths n	Rate	Deaths n	Rate	Deaths n	Rate	
Total respiratory diseases	460–519	21,591	34.28	15,243	13.22	36,834	23.75	1.42
Bronchitis, emphysema, asthma	490–493	11,847	18.36	6,339	5.37	18,186	11.86	1.87

M: males; F: females. The National Institute of Health specifies that the provided data are being updated and may, therefore, be slightly modified. Code refers to International Classification of Diseases, ninth revision. Mortality rates adjusted by age, per 100,000 persons, utilising the world population as reference.

diseases in two population samples (~5,700 subjects aged 35–36, 50–51 and 65–66 yrs) living in the same areas in northern Sweden were performed 6 yrs apart through a postal questionnaire [39]. Lung function measurements were performed in stratified samples. Of the subjects diagnosed with chronic bronchitis, only 25% in 1986 and 23% in 1992 had been diagnosed prior to the study as having chronic bronchitis, emphysema or COPD. Chronic airflow limitation, defined as FEV1/forced vital capacity (FVC) <70% and FEV1 <80% of predicted value, was found in 171 subjects in 1986–1987 (12% of the examined subjects), and 166 subjects in 1993–1994 (11%). In 1986–1987, 26% of the subjects with chronic airflow limitation had been diagnosed as having chronic bronchitis or emphysema prior to the survey, while a diagnosis of asthma, chronic bronchitis or emphysema, or use of asthma medicines, was found in 58%. The corresponding figures in 1993–1994 were 31% and 63%, respectively.

Large differences in the prevalence of physician-diagnosed chronic bronchitis have been found in a postal survey conducted in 1996 in three countries [40]: 10.6% in Tallinn, Estonia, 3.4% in Helsinki, Finland and 3.0% in Stockholm, Sweden. A representative sample of 14,076 French individuals of $\geqslant$25 yrs completed a self-administered questionnaire [41]. Prevalence rates of chronic bronchitis and of chronic cough and/or expectoration were 4.1% and 11.7%, respectively; in individuals with comorbidity, these figures were 10.4% and 24.4%, respectively. Smoking was associated with an increased frequency of chronic bronchitis. In subjects with chronic bronchitis, 44.6% had spirometry or peak expiratory flow measurements, 24% were diagnosed as having chronic bronchitis and 7.2% received care.

Even when the diagnosis is based on an objective tool like spirometry, largely variable prevalence rates are found within the same population in view of the different criteria endorsed by different scientific societies. For instance, VIEGI *et al.* [42] have shown in adults of $\geqslant$25 yrs of age (n=1,727 in 1988–1991) that the prevalence rates of airflow obstruction range from 11% with the ERS criteria [17] to 18% with the "clinical" criteria (later labelled as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria Stage I) [43] to 40.4% with the 1986 ATS criterion [44]. Corresponding figures for subjects aged 25–45 yrs and subjects of $\geqslant$46 yrs of age were as follows: ERS 10.8 and 12.2%, clinical 9.9 and 28.8%, and ATS 27 and 57%, respectively. When considering only moderate/severe obstruction, the rates were as follows: ERS 0.4 and 3.6%, clinical 0.3 and 4.4%, and ATS 0.5 and 5.2%, respectively. The trend was confirmed after stratifying for smoking habit and the presence/absence of respiratory symptoms/diseases. The highest specificity and predictive value for any respiratory symptom/disease was shown by the ERS, and the lowest was shown by the ATS criterion, while the reverse was true for sensitivity; overall accuracy was slightly lower for the ATS criterion. Multiple logistic regression models indicated a higher number of significant associations with known risk factors for airways obstruction according to clinical and ATS criteria than ERS criterion. The authors concluded that further research was needed to reach a standardised and epidemiologically consistent criterion for airways obstruction.

Probably, such a goal has not yet been achieved, even after the introduction of the GOLD criteria. Its ability to provide information of prognostic value in COPD patients has been questioned by VESTBO and LANGE [45]. Its applicability to the whole population regardless of age, has been criticised by HARDIE *et al.* [14].

An interesting experience on early detection of COPD or asthma in a random sample from the general population aged 25–70 yrs has been carried out in 10 general practices located in the eastern part of the Netherlands within the framework of the Detection, Intervention, and Monitoring Programme of COPD and Asthma (DIMCA) [46]. There was a two-stage protocol involving screening and a subsequent 2-yr monitoring of all subjects with positive results of screening. All known COPD and asthma patients were excluded. Of those eligible, 1,155 subjects (66%) participated in the screening stage, and 384 subjects (64% of those with positive screening results) participated in the monitoring stage. During the second stage, 252 subjects were detected with objective signs of COPD or asthma at an early stage. Smoking status as a screening criterion was neither sensitive nor specific. By extrapolation, 7.7% of the general population showed persistently reduced lung function or increased bronchial hyperresponsiveness (BHR). Another 12.5% of the general population showed a rapid decline in lung function (>80 $mL \cdot yr^{-1}$) in combination with signs of BHR, and a further 19.4% of the general population showed mild objective signs of COPD or asthma.

A promising approach in early detection of COPD in high-risk populations using spirometric screening also comes from a Polish experience [47] on 11,027 smokers of >39 yrs with a smoking history of >10 pack-yrs. Spirometric signs of airway obstruction were found in 24.3% of the screened subjects: mild 9.5%, moderate 9.6%, and severe obstruction 5.2%. In addition, the same research group [48] was able to demonstrate in a subgroup of screened smokers that, after a minimal antismoking intervention, those with abnormal lung function had a nearly doubled quitting rate at 1 yr compared with those with normal spirometry.

An assessment of the international variation in the prevalence of chronic bronchitis and its main risk factor, smoking, has been performed in 35 centres from 16 countries on 17,966 subjects (20–44 yrs of age), randomly selected from the general population, in the frame of the European Community Respiratory Health Survey [49]. The median prevalence of chronic bronchitis was 2.6%, with wide variations across countries (0.7–9.7%). The prevalence of current smokers ranged 20.1–56.9%, with a median value of 40%. Current smoking was the major risk factor for chronic bronchitis, especially in males. Only 30% of the geographical variability in prevalence could be explained by differences in smoking habits, suggesting that other environmental and/or genetic factors may play an important role.

Recently, the first international survey estimating the burden of COPD in the general population was published [50]. The Confronting COPD International Survey aimed to quantify morbidity and burden in COPD subjects in 2000. From a total of 201,921 households screened by random-digit dialling in the USA, Canada, France, Italy, Germany, the Netherlands, Spain and the UK, 3,265 subjects with a diagnosis of COPD, chronic bronchitis or emphysema, or with symptoms of chronic bronchitis, were identified. The mean age of the subjects was 63.3 yrs and 44.2% were female. Subjects with COPD in North America and Europe appeared to underestimate their morbidity, as shown by the high proportion of subjects with limitations to their basic daily life activities, frequent work loss (45.3% of COPD subjects <65 yrs of age reported work loss in the past year) and frequent use of health services (13.8% of subjects required emergency care in the last year), and thus may be undertreated. There was a significant disparity between subjects' perception of disease severity and the degree of severity indicated by an objective breathlessness scale. Of those with the most severe breathlessness (too breathless to leave the house), 35.8% described their condition as mild or moderate, as did 60.3% of those with the next most severe degree of breathlessness (breathless after walking a few minutes on level ground).

Some relevant issues in the natural history

The Danish research group of the Copenhagen City Heart Study has elucidated the relationship of mucus hypersecretion and COPD morbidity. Among males, chronic mucus hypersecretion was associated with an excess FEV1 decline of 22.8 $mL \cdot yr^{-1}$ (95% confidence interval (CI) 8.2–37.4) and with subsequent hospitalisation due to COPD after adjusting for age and smoking (RR 2.4, 95% CI 1.3–4.5) [51]. Socioeconomic factors operating from early in life affect the adult risk of developing COPD independently of smoking in both females and males [52].

In a follow-up of 8,955 adults, elevated plasma fibrinogen was associated with reduced FEV1 and an increased risk of COPD hospitalisation rates [53]. In a 21-yr follow-up on 9,187 adults, α_1-antitrypsin MZ heterozygotes had a slightly greater rate of decrease in FEV1 and were modestly overrepresented among persons with airway obstruction and COPD. In the population at large, MZ heterozygosity may account for a fraction of COPD cases (~2%), similar to the percentage of persons with COPD who have the severe but rare ZZ genotype [54]. Among subjects with severe disease (FEV1/FVC <0.7) in a 14-yr follow-up of COPD patients, there was a significant risk ratio modification between effect of baseline body mass index (BMI) and weight change [55]. In the normal-to-underweight (BMI <25), best survival was seen in those who gained weight, whereas for the overweight and obese (BMI $\geqslant$25), best survival was seen in stable weight. A high proportion of subjects with COPD experienced a significant weight loss, which was associated with increased mortality.

The Norwegian research group from Bergen tested the comparability of telephone and postal survey questionnaires for respiratory symptoms and risk factors [56]. Furthermore, it demonstrated the use of biomarkers, like α_1-antitrypsin and calprotectin, and lung function tests different from FEV1, like diffusing capacity [57]. This group has provided a major contribution in understanding the role of occupational exposure on the development of COPD [58]. In a 25-yr follow-up on 951 subjects from a random sample of 1,933 males aged 22–54 yrs, the decline in FEV1 was associated with age, body height and smoking. Accelerated decline in FEV1 was observed in subjects exposed to sulphur dioxide gas and metal fumes at work. The adjusted decline in FEV1 increased progressively in subjects exposed to increasing numbers of occupational agents.

Among the environmental risk factors, an increasing body of evidence is accumulating on air pollution, especially urban air pollution [59] whose acute increases (mainly the particulate matter) have been related to short-term health effects (*i.e.* mortality and hospital admissions) in patients suffering from COPD. Beyond the acute effect, chronic exposure to air pollution seems related to lung function impairment and development of COPD. The few cross-sectional studies performed have shown an increase of self-reported diagnosis of chronic bronchitis and emphysema, breathlessness, and mucus hypersecretion and lower levels of lung function in the more polluted areas. The only cohort study in adults showed a faster decline of lung function. The great importance for public health knowledge of air pollution is due to its ubiquitous nature that renders the whole general population at risk.

Costs

In the above-mentioned DIMCA study [46], the costs involved in detection (lung function assessments, organisation, transportation, and patient time) were calculated for three different scenarios, as follows: 1) the detection of subjects with persistently decreased lung function or an increased level of BHR during 6 months of monitoring; 2) scenario 1 plus the detection of subjects with a rapid decline in lung function with signs of BHR during 12 months of monitoring; and 3) scenario 2 plus the detection of subjects with a moderate increase in the decline in lung function or signs of BHR during 24 months of monitoring. The average costs per detected case varied from US $953 (scenario 1) to US $469 (scenario 3). Thus, detection of COPD or asthma at an early stage by means of a two-stage protocol seems feasible at relatively little expense in comparison with other mass screening programmes.

Further, in a prospective, randomised consent trial [60], the utilisation of healthcare resources and cost were ascertained in two groups: a screened group (n=416) and a control group (n=462). During an average follow-up of 3.6 yrs, there were no significant differences in healthcare resource utilisation and cost between the screened subjects and the controls. Resource utilisation before screening was not significantly different from resource utilisation after screening. Within the screened group, positive subjects with signs or symptoms of obstructive airway disease consulted their general practitioners 3.7-times more frequently for respiratory reasons than negative subjects. As expected, the total healthcare cost due to respiratory disease in screen-positive subjects was 6.4-times higher. Overall, there were no indications that screening for obstructive airway disease led to increased cost, above that of average care.

The burden of asthma and COPD on the general population is considerable in the Netherlands [61]. The main cost element of asthma is medication, whereas hospitalisation accounts for the largest proportion of costs for COPD. Consequently, the annual cost per patient of managing COPD is almost three-times as high as that for asthma. Together, the two respiratory conditions cost the Dutch healthcare system US $346 million for direct medical costs in 1993, amounting to 1.3% of the total healthcare budget. The burden of COPD is expected to increase considerably in the future, reflecting the previous smoking habits of an ageing population.

Within the framework of the Italian National Healthcare System, a cost-of-illness analysis of three pathologies affecting the lower respiratory tract (community-acquired pneumonia (CAP), COPD and asthma) was conducted in a large region of north-east Italy, Triveneto, between 1999–2000 [62]. Patients of both sexes $\geqslant$14 yrs of age were randomly selected from 28 centres of pneumology. Consumption of medical resources used during the follow-up period was valued according to market prices and published official tariffs. A total number of 1,068 patients (596 males and 458 females) were selected: 42.5% were affected by asthma, 46.3% by COPD and 11.2% by CAP. Mean cost per patient per year for patients affected by asthma and COPD ranged €608–2,457 and from €1,500–3,912, respectively, depending on illness severity. The mean cost per episode of CAP was €1,586.

Exacerbations are the key drivers in the costs of COPD in Sweden [63]. Among 202 subjects with COPD (defined according to the British Thoracic Society and ERS criteria), at least one exacerbation was reported by 61 subjects, who were then interviewed regarding resource use for these events. The average healthcare costs per exacerbation were Swedish krona (SEK) 120 (95% CI 39–246), SEK 354 (252–475), SEK 2,111 (1,673–2,612) and SEK 21,852 (14,436–29,825) for mild, mild/moderate, moderate and severe exacerbations, respectively. Exacerbations account for 35–45% of the total per capita healthcare costs for COPD.

Conclusion

Two comprehensive reviews summarising the European perspective on COPD epidemiology were published in 2001 [64, 65]. Chronic bronchitis is too infrequently diagnosed, investigated, and cared for. It is a substantial health problem even in young adults. The impressive prevalence in current smokers of <45 yrs of age in most countries highlights the need to improve the quality of prevention. Even if the current decline in the prevalence of smoking continues in Europe, in the near future there will be an increase in the prevalence of COPD (with the increase probably higher among females than males), largely due to the ageing of the population. Keeping these statistics in mind, decision-makers allocating funds to healthcare services need to consider that the prevention of moderate-to-severe exacerbations could be very cost-effective and improve quality of life. There is also a need for intervention studies that aim to avoid weight loss in normal-to-underweight COPD patients.

The burden of illness and economic evaluation for COPD

S.D. Sullivan

Summary

This article reviews the important factors to consider in the design of economic evaluations or cost-effectiveness analyses (CEAs) of chronic obstructive pulmonary disease (COPD) treatments. The relevant costs associated with COPD can be divided into direct (direct medical and direct nonmedical) and indirect (programme and productivity) costs. The differences between the human-capital and friction-cost approaches to evaluate the impact of productivity loss are discussed. Since the primary cost-driver for COPD is hospital care for exacerbations, this may be the major outcome measure of interest in COPD economic evaluation studies. Robust CEA evaluations that take into account all of these factors will aid decision-makers in evaluating COPD therapies.

Introduction

Given the rising prevalence of chronic obstructive pulmonary disease (COPD) worldwide, it is urgent that its economic burden is understood and that more robust evaluations of healthcare interventions are designed to reduce its incidence and impact. Studies designed for making decisions and policy must apply robust methods and report results in a standardised fashion.

Economic evaluations are often known less precisely as cost-effectiveness analyses (CEAs). Although these terms have subtle differences, for purposes of this article, and to avoid confusion, "CEA" will refer to studies designed to evaluate the incremental impact of a particular COPD therapy or programme (usually new) *versus* the conventional approach. In recent years, standardised methods for conducting and reporting these studies have been embraced [66–70].

Capturing relevant costs related to chronic obstructive pulmonary disease and its treatment

Economic studies of COPD must include all relevant costs associated with the illness. Such costs should include not only the intervention of interest (*e.g.* inhaled bronchodilator therapy), but also all components associated with therapy, such as nebuliser equipment. Such costs can be divided into direct (direct medical and direct nonmedical) and indirect (programme and productivity) costs.

Programme costs refer to costs associated with building the infrastructure needed to deliver the technology. Many studies fail to take into account programme costs when evaluating interventions. For example, an evaluation of a new intensive smoking cessation clinic should include clinic costs (such as rent for office space and staff costs) amortised across the patient group as well as the cost of associated therapies such as nicotine patches or buspirone. Direct medical costs include all medical goods and services used to treat the illness. Usually, these costs are the easiest ones to identify and are thus part of most economic studies.

Direct nonmedical costs include items related to care not directly linked to the healthcare system. Comprehensive evaluations of nonmedical costs are needed for COPD. Such costs can include hired caregiver expenses, costs to the family, lost wages of family caregivers, expenses associated with modifications to living facilities, and transportation and parking costs for patients visiting their physicians. As these costs usually are not reimbursed by health insurance and are difficult to track, they are often excluded from economic studies. As a result, almost no information exists on the value of direct nonmedical costs in COPD. This may be an important oversight, particularly for developing countries. For example, transportation costs may be one of the largest expenses for those who have to travel from remote areas to receive care.

Productivity costs refer to the value of lost wages resulting from illness and from seeking treatment. They are particularly difficult to estimate and are usually excluded from economic evaluations. Nevertheless, productivity is reduced by sporadic absences, visits to healthcare providers and premature mortality. Even more so than direct nonmedical costs, this may be a particularly important omission where COPD is concerned, especially for burden-of-illness studies in developing countries. The value of permanent work loss is particularly important for diseases with high rates of premature mortality such as COPD. As productivity in COPD is potentially important, the two major approaches to valuing productivity, human-capital and friction-cost, are reviewed here in some detail.

Capital and friction-cost approaches to valuing productivity costs

The traditional approach to evaluating the impact of productivity loss caused by illness is the human-capital approach. This term derives from the observation that a person′s earnings over a lifetime reflect an investment in that individual through education, on-the-job training, and work experience [71, 72]. As these investments influence that individual′s value to the economy, productivity loss usually is valued using market wage rates. For those not working for a wage (*e.g.* homemakers), wages are valued at those that replacement workers would earn for their specific services.

The friction-cost method differs from the human-capital approach in that it allows for the replacement of an absent worker by other workers or by those in the unemployed pool. The friction-cost method values productivity as the loss incurred during the time between a person's absence from work or termination of employment and the time at which another worker fills that position [73–75]. The time required for worker replacement is called the "friction period."

Unfortunately for researchers, there is no general agreement on whether the human-capital or friction-cost method is more valid for measuring the productivity costs of illness [76–79]. Further complicating the matter is that the estimate will vary greatly depending on which method is applied. For example, in a study of schizophrenia's impact on productivity, the human-capital and friction-cost methods resulted in an 85-fold difference in the estimate of productivity cost [80].

Time horizon

All downstream effects related to treatment for COPD should be included in cost studies. These costs should be tracked or modelled during the time that the intervention is expected to affect the individual or group. Often in the case of COPD, this time horizon equals a person's lifetime.

Key factors influencing cost

The call to "capture all costs" must be tempered by the reality of the study design's limitations and the budget available for conducting economic analyses. As there is no comparison group in burden-of-illness evaluations, comprehensiveness is more important for these studies than for CEAs of healthcare programmes. For CEAs, the intervention of interest is likely to have a large effect on some aspects of healthcare utilisation (*e.g.* hospital days), but little on other aspects. Since CEAs are an incremental form of analysis, it is only necessary to measure healthcare items that are expected to vary between the intervention and control groups. Of course, it is difficult to predict beforehand what will vary as a result of the intervention. Studies have shown that the primary "cost-driver" for COPD is hospital care for exacerbations, accounting for ~70% of all direct medical costs in developed countries for this disease [81–86]. Thus, if the intervention is expected to influence hospital care significantly, this may be the only item necessary to measure accurately. Other items with more subtle effects (*e.g.* office visits, medications) will probably require a more comprehensive analysis.

Methodological issues for cost-effectiveness studies

Cost-effectiveness studies are now common in medicine and have been applied to several therapies for COPD. Nevertheless, outside of smoking cessation programmes [87–93], few high quality CEAs exist for widely used COPD therapies [94]. In fairness to researchers, few therapeutic breakthroughs for this disease have occurred, and many traditional therapies are perceived as only modestly effective (it could be argued that minimally effective therapies are not cost-effective and should not be applied). More recently, however, several therapies have begun development for persons with COPD [95]. Ever tightening health budgets will force payers to scrutinise the value for expenditures of these new therapies more closely. In this context, it is an opportune time to review the important issues involved for conducting robust CEA evaluations of treatments.

Pharmacotherapy of COPD

L.M. Fabbri

Summary

There are multiple goals to manage in chronic obstructive pulmonary disease (COPD) patients. The benefits of current pharmacological treatments for COPD are discussed here. The use of theophyllines remains somewhat controversial in the management of stable COPD, while the use of long-acting bronchodilators (such as salmeterol, formoterol, or tiotropium) alone or in combination with short-acting bronchodilators or theophylline are effective maintenance treatments for COPD. Treatment with inhaled corticosteroids (ICS) reduces symptoms and the frequency of exacerbations and improves the quality of life, but does not influence the long-term decline of forced expiratory volume in one second. However, combination therapy with ICS and long-acting β_2-agonists improves lung function and symptoms and reduces rescue medication use and the frequency of moderate and/or severe COPD exacerbations. The Global Initiative for Chronic Obstrutive Lung Disease guidelines have recently been revised to recommend maintenance therapy with inhaled long-acting bronchodilators starting from moderate (stage II) COPD, and combination therapy with ICS starting from severe (stage III) COPD to prevent exacerbations.

Introduction

The main objectives of chronic obstructive pulmonary disease (COPD) management are the prevention of disease progression, the relief of symptoms, the improvement of exercise tolerance and health status, the prevention and treatment of exacerbations and/or complications, and the reduction of mortality and of side-effects from treatment [12].

The long-term therapy of moderate and severe COPD consists of pharmacological treatment, such as the regular use of bronchodilators, and of nonpharmacological treatment, such as rehabilitation and/or long-term oxygen in the presence of respiratory failure. The most recent COPD guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognise, as part of the definition of the condition, that there is "an abnormal inflammatory response" in the lung to noxious gases or particles [12]. This suggests the need for effective anti-inflammatory treatment in COPD. However, inhaled corticosteroids (ICS) have not been shown to have a consistent anti-inflammatory effect in patients with COPD, and thus, based on the results of clinical trials, treatment with ICS is recommended in some, but not all COPD patients, and, in particular, in patients with severe and very severe (stages III and IV, respectively) COPD and repeated exacerbations.

Bronchodilator medications, such as short-acting and long-acting β_2-agonists, anticholinergics, and theophylline, are central to the symptomatic management of COPD. Long-acting inhaled β_2-agonists, such as salmeterol and formoterol, have a duration of action of up to 12 h and significantly improve symptoms, exercise capacity, and health status in patients with COPD. The use of salmeterol (a long-acting β_2-agonist) in COPD patients has been shown to significantly reduce dyspnoea and to improve forced expiratory volume in one second (FEV1) values after long-term treatment [96, 97], and to reduce dynamic hyperinflation [97]. Formoterol, both a short- and long-acting β_2-agonist, demonstrates better spirometric efficacy than either ipratropium [98] or theophylline alone [99], and its efficacy improves when administered in combination with ipratropium [100]. A new long-acting once-daily anticholinergic agent, tiotropium, produces benefits of equivalent or greater size than salmeterol or formoterol [101], and is likely to be a useful addition to treatment for COPD. Thus, tiotropium has been shown to provide significant bronchodilation in terms of FEV1 response, and reduces dyspnoea and frequency of COPD exacerbations [102]. Theophyllines remain somewhat controversial in the management of stable COPD. They have a slow onset of action and are used as a maintenance treatment rather than for rapid relief of symptoms.

Combination treatment with formoterol plus ipratropium provides better improvement of pulmonary function and a greater reduction in symptoms [103]; similarly, combination treatment with salmeterol plus theophylline provides significantly greater improvements in pulmonary function, significantly greater reductions in symptoms, dyspnoea, and albuterol use, and significantly fewer COPD exacerbations [104]. Taken together, these two studies suggest that combination therapy with long-acting bronchodilators with different mechanisms of action may, in fact, produce additive effects.

Whether ICS have an anti-inflammatory effect in patients with COPD remains controversial [105, 106]. It is clear that these drugs do not modify the natural history of COPD, as measured by the rate of decline in FEV1 [107–110]. Data from studies on long-term effects of ICS provide evidence that regular treatment with ICS is only appropriate for symptomatic patients with severe to very severe COPD with an FEV1 <50% predicted (stage III: severe COPD, and stage IV: very severe COPD), and for repeated exacerbations requiring treatment with antibiotics or oral corticosteroids [111, 112]. These studies have shown that long-term treatment with ICS reduces symptoms and the frequency of exacerbations and improves the quality of life [107–110, 112].

The recent randomised controlled trials examining the benefits of combining ICS and inhaled long-acting β_2-agonists in the treatment of COPD have shown interesting results. The combination of fluticasone propionate and salmeterol improves lung function and symptoms, reduces the severity of dyspnoea and rescue bronchodilator use [111, 113], and reduces the frequency of moderate and/or severe COPD exacerbations [111]. The combination of budesonide and formoterol reduces the mean number of severe exacerbations, improves FEV1 and peak expiratory flow values, and reduces all symptom scores and the use of rescue β_2-agonists [114].

While ICS should be used only in patients with severe to very severe COPD, they are considered to be first choice maintenance treatment in mild, moderate and severe persistent asthma [115]. Asthma may cause fixed airflow limitation and, thus, elderly asthmatics, in particular, may be misdiagnosed with COPD. The characteristics of asthmatics who develop fixed airflow limitation still fit the definition of asthma in terms of pathology [18], natural history [116], and response to treatment [117]. These patients should be diagnosed and treated as asthmatics and not COPD patients. In this respect, it is recommended that asthma be excluded from the Venn diagram that is frequently used to illustrate the different components of COPD.

Conclusion

To conclude, on the basis of this evidence, the update of the GOLD guidelines on the management of COPD suggests regular treatment with inhaled long-acting bronchodilators (including tiotropium) and rehabilitation, starting from moderate (stage II) COPD. The evidence also suggests treatment with combined therapy with ICS starting from severe (stage III) COPD to prevent exacerbations.

Possible sources of bias in observational studies of the effectiveness of inhaled corticosteroids in COPD

S. Suissa

Summary

The possible sources of bias that can arise from observational studies using computerised claims databases are discussed. The four classes of bias are selection (asthma *versus* chronic obstructive pulmonary disease) and confounding (indication, age, duration and severity of disease), choice of outcome (morbidity or mortality), timing of the drug exposure (*i.e.* cohort or case-control design), or time-related issues (incident or prevalent cohort and immortal time concerns).

Introduction

The observational studies conducted on the effectiveness of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) have all used computerised claims databases that have several limitations. The possible sources of bias that can arise from the use of these databases can be classified into four types.

Sources of bias

The first class of bias is selection and confounding. One challenge is to deal with the differential diagnosis of COPD and asthma, which is particularly crucial because the effectiveness of ICS has been very well established in asthma. Thus, as the inclusion of asthma patients may exaggerate the effectiveness of ICS, the study population must have clear criteria to identify COPD patients and exclude asthma patients. In particular, definitions and criteria based on a physician′s reported diagnosis, drug treatment and age must be carefully combined to optimise the diagnosis of COPD. The study

design used, namely, cohort or case-control approach may also engender some form of selection bias. Thus, the design must be carefully selected as must the source population and the base cohort. An important source of bias is confounding by indication. The disease severity and its markers must be identified and quantified to control for any imbalance between the users of ICS and the nonusers. In particular, the use of health services and the profile of use of other drugs for COPD must be examined and analysed to provide the proper statistical adjustment and elimination of confounding. Two additional confounding factors that must be taken into account are age and duration of COPD. Finally, the approach to account for these factors can either be by matching cases and controls on these factors, by restricting the study to subjects who have or do not have some of these factors, and of course, by statistical analysis using a multivariate regression model that will control for these differences simultaneously. An important point of discussion should be the timing of these markers of disease severity with respect to the outcome and the ICS exposure. For instance, should disease severity be evaluated at the start of disease or at the time of the outcome under study?

The second source of bias is related to the choice of the outcome, morbidity or mortality. Morbidity can be evaluated from exacerbations, outpatient or emergency room visits, as well as hospitalisation. An exacerbation can be identified in some databases by the use of drugs, such as the simultaneous treatment with oral corticosteroids and antibiotics, or indicated by a diagnostic code posed by a physician or during a hospitalisation. With respect to mortality, an issue raised by the studies conducted, to date, is the use of all-cause mortality as an outcome, as opposed to death due to COPD. Since medications would be expected to be more specific to the outcome of COPD death, studies that would focus on all-cause mortality may provide an underestimate of the effect since other causes may not be affected by the medication under study. Nevertheless, studies focusing on COPD mortality should address the validity of the cause of death in death certificates, as well as the issue of other causes and underlying cause, since these patients may have several conditions at the time of death.

The third source of bias is related to the exposure. An important point is the timing of the drug exposure, in particular, whether exposure is selected at cohort entry or at the time of the outcome under study. This question relates to the choice of design, cohort or case-control. In addition, whether the effects are acute or whether regular treatment is required to attain the effectiveness under study needs to be considered with respect to drug exposure. Drug exposure also affects the choice of the reference group and whether this group can include patients who do not currently use ICS but who used them previously, or patients who are restricted to other drugs or classes of drugs, such as bronchodilators. With these classifications and the question of timing of use, concern must then be placed upon issues of exposure misclassification. For instance, patients who are not using ICS should not be classified as users and *vice versa*. Finally, the exposure and its timing will also relate to the analysis of the data, and, particularly, whether exposure is fixed, such as for the intention-to-treat approach, or time-dependent, such as that used in nested case-control analysis.

The last source of bias is that arising from time-related sources. The cohorts under study may be incident (based on newly diagnosed patients) or prevalent (patients well into their disease) cohorts. It is determined by whether patients at time zero already have had COPD for some time or have already been exposed to the drug under study for some time. It may be preferable to use incident cohorts where new treatment or new disease defines time zero for the cohorts. If this is not possible, the duration of prior COPD or prior drug use should be examined and accounted for in the analysis. The choice of time zero is important and may be taken as the date of first COPD diagnosis, the date of the first hospitalisation for COPD, the date of any hospitalisation for COPD, or the first time an ICS or a referent drug was used. Finally, in all cohort studies that involve time-dependent exposure, immortal time should be identified and accounted for [118–120]. Immortal time periods, defined by follow-up times during which patients cannot, by definition, incur the outcome, have to be identified and accounted for with a proper analysis. In addition, studies that improperly exclude immortal time or do not account for it in the proper exposure group should be identified and assessed with respect to bias.

Discussion

SORIANO: There is evidence that COPD patients who have an asthma component die more frequently than COPD patients without an atopy or hyperresponsiveness component. COPD patients with an asthmatic component are a subgroup of patients with more severe COPD. This subpopulation is easily 30–50% of individuals with COPD.

FABBRI: According to BURROWS *et al.* [116], this is not true, *i.e.* smokers with COPD and asthma have a 10-yr survival (~65%) that is in between smokers with COPD without asthma and asthmatics. In fact, nonsmoking asthmatics with fixed airflow limitation have a life expectancy similar to normal subjects.

VIEGI: In contrast to L. Fabbri's suggestion that the Venn diagram be removed, I believe that, rather than removing, we should understand these complex relationships better. Also, should we consider COPD just as a smoking-related disease? Fifteen per cent of COPD is work-related. What about the contribution of air pollution? We cannot anticipate the prevalence of COPD as only related to smoking.

ERNST: There are certainly patients with "pure" asthma or COPD. There are a number of patients, however, that fall somewhere in the middle. It is not appropriate to pretend that everyone falls in that middle group, since this would not allow us to aim the correct treatment at the correct patients. While there will always be people with components of both asthma and COPD, I do not think that these are the majority of COPD patients.

BOURBEAU: We have to ask ourselves, what exactly is our question or intent in these studies. If we are trying to understand COPD as a complex disease in an epidemiological study, we may be interested in looking at different populations including the nonsmoker. But if you want to test an intervention, it is best to define a population of patients who most likely have COPD, so then it should be related to smoking.

HAGAN: Another factor to consider is the perspective of pharmaceutical industry. When we are designing randomised clinical trials (RCTs), we have to abide by the criteria requested by Regulatory Agencies. For example, forced expiratory volume in one second reversibility criteria are getting more and more stringent because we have to prove that these are pure COPD patients. But, in the real world, most COPD patients do not have pure COPD.

MAPEL: When wrestling with this issue of how to define COPD, there are three areas in our end-points that are problematic. First, in spirometry itself, we tend to fixate solely on airway obstruction and ignore dynamic hyperinflation. In a population of female smokers that we brought in for testing with no diagnosis, we performed complete lung volumes and we found that a large population of female smokers had

normal spirometry but remarkably elevated residual volumes. The first change in objective measures with smokers is increased residual volumes. However, we missed that completely when we used spirometry as an end-point. Spirometry is really an illogical end-point. Most of the people in a study are still smoking. If you do not get away from exposure, then disease will progress. So we need to expand the end-points. Exacerbations and hospitalisation rates, for example, are important and exciting end-points that are starting to be used. Pathological end-points are also important. The Hattatua study focused on chronic bronchitis patients without an asthma component (pure COPD) and found significant reductions in subepithelial mast cells. There are probably some inflammatory mechanisms in COPD that will be affected by corticosteroids. However, even in the pathological studies, we are seeing null results because they are looking at the wrong end-points. The truth is that we know remarkably little about the pathology of the disease.

HAGAN: It is interesting to note that the Hattatua study in patients with pure COPD used exactly the same entry criteria as the Inhaled Steroids in Obstructive Lung Disease in Europe trial. That does provide some pathological basis for selection criteria that we use in industry when selecting patients for COPD studies.

ERNST: But, I hope that we are not sending a message that we should use poorly reproducible surrogate end-points, such as mast cells or residual volumes. I would hope that we would be going towards outcomes such as hospitalisations and exacerbations that actually have an impact.

VIEGI: I think we need to go back to the basic issues. We cannot still use reference equations that were collected 40 yrs ago. Although there are attempts to standardise, there is still high technical and population variability. We cannot just use one reference equation. We need to recognise that when we start to measure lung function, we should check which is the best reference equation for our clinic setting and population.

FABBRI: The Global Initiative for Obstructive Lung Disease (GOLD) guidelines are becoming increasingly evidence-based. If you want to issue recommendations for treatment based on evidence, you should specify the entry criteria of the study you cite. And the entry criteria of most of the studies I presented excluded atopy, history of asthma, *etc.* However, you still may have the problem of the mixed population. But, we need studies of that mixed population, too.

BOURBEAU: In trying to make a diagnosis of COPD as epidemiologists, we will not be able to do better than what our current understanding is of the disease. We have a poor understanding of the phenotyping of COPD. There are many phenotypes of the disease, but it is too early to distinguish what they are. We should try to distinguish what is an asthma population, a COPD population and the in-between questionable population. When we are doing a pharmacoepidemiological study, we should probably look at these populations of patients differently and try to validate (what we have done very little of in pharmacoepidemology studies so far) from the different administrative databases what is asthma and what is COPD and then, in our conclusions, we should be able to speak the same language. This will evolve over the next 10 yrs as our understanding of the disease increases and we hope that pharmacoepidemiology studies will also evolve with that understanding.

PRICE: L. Fabbri said that the guidelines are becoming increasingly evidence-based and that recommendations will have to be made based on RCTs. Yet, the challenge from the industry perspective is that to meet regulatory requirement they will have to study patients from narrower and narrower groups. The industry is trying to produce more generalisable data and more pragmatic trials with different populations in spite of having to produce more regimented trials for registration purposes. We just had a new evidence-based asthma guideline produced in the UK. One of the challenges of the evidence-based hierarchy as it has been implemented in our asthma guidelines is that if you have a discrepancy between an observational database and an RCT, the RCT wins, rather than viewing the evidence as complementary and trying to look at understanding why the discrepancies may occur. In COPD, it will be particularly important that we look for generalisability, and we need to have a way of handling within the guidelines that breadth of data rather than a straight evidence-based hierarchy. Are there plans to encompass these kinds of data as complementary within the hierarchy or will they stay as inferior?

FABBRI: When we discussed the criteria for grading evidence within the GOLD Scientific Committee, there was a strong suggestion to downregulate Cochrane reviews, *post hoc* analyses, and meta-analyses, with the understanding that these studies may help to generate hypotheses but do not provide evidence and that the evidence is provided only by RCTs. The hypotheses generated by *post hoc* analyses or meta-analyses and Cochrane reviews should then be properly tested in RCTs.

SORIANO: The reality is that we do not know the general epidemiology of COPD within the community. We still do not have a Framingham study in COPD. The majority of COPD patients are managed by general practitioners (GPs) and we know that GPs have been treating COPD patients with asthma drugs for a number of years. Probably, pharmacoepidemiological studies will help define what the outcomes are in COPD patients from the general population.

VOLLMER: We are all aware that individuals who enroll in RCTs are not representative of the general population. Entry criteria are often highly restrictive and participants highly motivated. While I have enormous respect for the value of RCTs, I also have respect for what can be learned from the large databases that we are beginning to collect from real-life experience. The trick with looking at these databases is to figure out the proper analytical methods to use. I am convinced that we need to find a way to marry these two sources of evidence.

WEISS: As chairman of the guidelines development committee for the American College of Physicians, I find myself asking the question, "How do we step away from the RCT, so that we can incorporate these other pieces of data?" We do not want to end up saying that, because of lack of data, it is best left up to the physician′s best judgment. What kinds of questions should be addressed in non-RCT databases that won′t be addressed in RCTs? Question-asking may be one of the most important ways to begin these discussions.

Methodological issues

PRICE: There may be issues of bias in terms of what analyses are being done and what actually gets published. We can get around that by registering clinical trials and data analysis plans. This is important to capture what was done *versus* what was reported. Another issue is that of clustering and the effect of centres in RCTs. In the General Practice Research Database, some GPs are much better at using their systems than others.

DAVIS: We can use this as a matching factor.

SUISSA: Matching does not resolve this issue. In certain studies, the drug may not be used appropriately or measurements themselves may be appropriate in some centres but not in others. If you then match on centres, your result will be attenuated towards a null effect, because you will have created all kinds of measurement errors, whereas in the

centres where data are well collected, you may be closer to the truth. Therefore, rather than matching on the centre, a stratified analysis by these centres will provide more accurate estimates.

VOLLMER: It is not just measurement error, but variation in practice patterns.

WEISS: This relates to the clustering of effects above the individual level that have to be accounted for and most of those that we perceive right now are in the health system design whether it be in the actual practice of providers, the way they practice as a group, or how this system is financed. So we have to ask, is it important to account for these?

SULLIVAN: What about major health systems changes, like payments to hospitals that can affect the rate of hospitalisations or exacerbations, independent of anything going on with the disease or treatment?

SUISSA: That also speaks to time-related bias. It would be important that a patient in January 2001 gets compared with all patients in the database in January 2001, so that they are all subject to the same rate at that point in time. If the drug will increase or decrease this rate, it will be assessed at the same time point.

BURNEY: But, it is not just time. What about from institution to institution and the way they manipulate the data?

SULLIVAN: You may have local variations in these factors.

SUISSA: Definitely, stratification on the region would then be important.

VOLLMER: You also need to account for in-migration. These individuals have no prior history in the database and could be incorrectly classified as incident cases when they first present for care. This can be partially addressed by treating those who seek care during an initial enrolment period, say 6 months, as having prevalent disease.

STURKENBOOM: Confounding by indication or by contraindication is also a consideration. It is not so much about the severity of COPD but about the severity of all types of comorbidities.

MAPEL: A difficult confounder that we have spent time wrestling with is comorbid illnesses, particularly heart disease. The single most common death in COPD patients has been cardiac arrest. How you deal with that will greatly affect the results. If you use it as an exclusion criterion, you end up wiping out half of your population. But if you use Charlson index or a similar technique to adjust for that, it changes your results.

ERNST: The comorbidity problem is a big problem especially in COPD. We have looked at cause of death in patients in our COPD cohort and the most common cause of death is cardiovascular. Even among those who are hospitalised with a primary diagnosis of COPD, the primary cause of death is cardiovascular. A lot of this represents misclassification.

VOLLMER: Adjusting for severity is also difficult, since we will typically have very imprecise tools for assessing it. Furthermore, the measures that are generally available to us for defining severity are inevitably closely related to the same measures we would use to assess current level of control, which is an outcome. This creates the potential for over-adjusting in our analyses.

VIEGI: Besides the time dimension we should also use the space dimension. There is overwhelming evidence coming from recent air pollution epidemiology data. Differential exposures to air pollution can represent an important source of variability when we compare studies on drug efficacy coming from different populations. Another issue comes from the problem of compliance. We know from P. Burney's study that there can be an inverse relationship between the rate of compliance and hospitalisation. Those who do not take medications are more at risk of being hospitalised.

DAVIS: The issue of patient care in observational studies is a potential source of bias. Some may argue that patients on ICS are getting better because they are getting better care overall.

TAYLOR: The checklist of potential biases that S. Suissa has presented really provides us with ways to try to minimise bias, but, they focus mostly on internal validity. However, it is also important to look at external validity, which is particularly important for observational databases.

FABBRI: We often have problems with the definitions of exacerbation, particularly for hospitalisation, when you may see a diagnosis for exacerbation or respiratory failure linked to COPD, but, in fact, we may face a complex that goes from heart failure, thromboembolism, or pneumonia. In other words, worsening of symptoms of COPD (particularly dyspnoea, but also cough and occasionally sputum) may be due to complications rather then exacerbations of the underlying disease.

ERNST: I am more concerned about all the hospitalisations for heart failure, which are actually COPD, right heart failure, or cor pulmonale. In my clinical experience, the diagnosis of heart failure is often made when it is actually COPD.

The Ontario and Alberta experience with administrative databases in COPD research

D.D. Sin

Summary

Administrative databases were used from two different provinces in Canada to evaluate the relationship between inhaled corticosteroid (ICS) therapy and clinical health outcomes in patients with chronic obstructive pulmonary disease (COPD), who were previously hospitalised for their disease. In the first study, health databases from Ontario, Canada, (n=22,620) were used and it was found that elderly patients ($\geqslant$65 yrs), who received at least one dispensation of ICS within 90 days of hospital discharge, had a combined 26% lower adjusted relative risk (RR) for respiratory hospitalisation and all-cause mortality than those who did not receive these medications (RR 0.74, 95% confidence interval (CI) 0.71–0.78).

In the second study, administrative databases in Alberta, Canada, (n=6,740) were used to evaluate the long-term "effects" of ICS among elderly COPD patients and to determine whether the survival benefits were dose-dependent. It was found overall that patients who received at least one dispensation of ICS during follow-up (average follow-up 32 months) had a 25% relative reduction in the risk for all-cause mortality (RR 0.75, 95% CI 0.68–0.82) compared with those who did not receive any ICS during follow-up. Patients on medium (501–1,000 $\mu g \cdot day^{-1}$ of beclomethasone equivalent) or high-dose

therapy (>1 mg·day^{-1} of beclomethasone) had lower risks for mortality than those on low doses (RR 0.77, 95% CI 0.69–0.86 for low dose; RR 0.48, 95% CI 0.37–0.63 for medium dose; and RR 0.55, 95% CI 0.44–0.69 for high dose).

Methods

Study design

In the first study, health databases from Ontario, Canada (total population ~11 million) were used to identify all elderly patients (≥65 yrs), who had a primary hospitalisation for chronic obstructive pulmonary disease (COPD) exacerbation (International Classification of Diseases, ninth revision (ICD-9) codes 490.x, 491.x, 492.x and 496.x) between 1992–1997 [121]. Patients who died within 30 days of discharge or during the initial hospitalisation, or were transferred to another acute care facility for active treatment were excluded. The remaining cohort was then divided into two mutually exclusive groups based on whether or not they received at least one dispensation of an inhaled corticosteroid (ICS; beclomethasone, budesonide, triamcinolone, and flunisolide) within 90 days of hospital discharge. These patients were followed from the date of hospital discharge until the date of their death, a repeat respiratory hospitalisation, or 1 yr of completed follow-up, whichever was earliest. A Cox proportional hazards model was used to compare the risk of all-cause mortality or repeat respiratory hospitalisation during the follow-up period between those who did and did not receive ICS within 90 days of discharge. In this model, the factors adjusted for were age (as a continuous variable), sex, modified Charlson comorbidity score [122], use of other anti-COPD medications (short-acting β_2-adrenergics, ipratropium bromide, antibiotics and oral corticosteroids), and history of emergency or office visit for asthma within the year previous to the initial hospitalisation.

In the second study, which used administrative health databases from Alberta, Canada, the COPD cohort was identified by searching through the hospital discharge abstracts from Alberta′s version of the Canadian Institute for Health Information (CIHI) [123]. Similarly to the Ontario study, residents of ≥65 yrs of age, who had at least one hospitalisation for COPD as the most responsible diagnosis between 1994–1998 using ICD-9 codes 490.x, 491.x, 492.x, and 496.x were included. Patients who died during the index hospitalisation were excluded. All hospital visits occurring after the first hospital visit were censored for each study patient in order to avoid double counting. The cohort was then divided into five mutually exclusive categories based on the use of ICS: 1) those who did not receive any ICS; and 2) those who received low dose (≤500 μg·day^{-1} of beclomethasone or equivalent); 3) medium dose (501–1,000 μg·day^{-1}); 4) high dose (>1,000 μg·day^{1}); or 5) an indeterminate dose of ICS. The last category contained patients who received only one dispensation of ICS during the follow-up period. Although the average daily dose for these individuals could not be calculated, they most likely received an average daily dose that was lower than that in the low-dose category. Since Alberta Blue Cross provides data on the quantity of medications dispensed rather than the daily dose, the average daily dose of ICS was imputed by determining the total dose of these medications dispensed for each patient for the first two prescriptions and dividing the total dose of the first dispensation by follow-up time (in days) between these two doses. The calculated average dose was rounded to a clinically plausible dose [124]. To allow cross-comparisons between different ICS preparations, all formulations were converted into beclomethasone dipropionate equivalents based on equivalency calculations suggested by the Canadian Asthma Consensus Report [125]. The study patients were then followed for 3 yrs following discharge from the initial hospitalisation for COPD, or until the date of their death, whichever was the earliest. A Cox proportional hazards model was used to compare the survival rate between those who did and did not receive ICS during follow-up and across the various dose categories, adjusted for age, sex, Charlson comorbidity scores [122], admittance to an intensive care unit (ICU) during the initial hospital stay (yes or no variable), and the filling prescriptions of various pulmonary medications including short-acting β_2-agonists, ipratropium bromide, oral corticosteroids and oral theophyllines. A series of sensitivity analyses were conducted to determine the robustness of the main findings to a different set of conditions and assumptions.

Databases used

Cohort identification

For the first project [121], study patients were identified using discharge abstracts from Ontario′s version of the CIHI database [126]; for the second project, Alberta′s version of the CIHI database was used to identify the study patients. The CIHI Discharge Abstract Database contains data on hospital discharges from all Canadian provinces except for Quebec and parts of Manitoba. Each abstract has information on patient demographics, contents of the hospital stay (including date of admission, date of discharge, the most responsible diagnosis and up to 15 secondary diagnoses) and disposition [126]. In the CIHI Discharge Abstract Database, the most responsible diagnosis is defined as "the one diagnosis, which describes the most significant condition of the patient which causes his stay in hospital" [127].

The CIHI employs a continuous quality assurance programme to ensure that the information contained within the Discharge Abstract Database is of excellent quality [128]. In >85% of the cases, the most responsible diagnosis in the CIHI Discharge Abstract Database matches the (most responsible) diagnosis obtained through independent chart audits performed by trained medical analysts [128]. For most common conditions in the CIHI databases, the false-positive rate ranges 0–11% and the false-negative rate ranges 0–13% [128]. False-positives are most commonly observed among ambulatory sensitive conditions such as depression and diabetes. COPD is not an ambulatory sensitive condition, and, as such, would be expected to have a very low false-positive rate (between 5–7%) but a slightly higher false-negative rate between 10–12%. These internal CIHI estimates are similar to those reported independently by RAWSON and MALCOLM [129]. This group showed that a CIHI coding of COPD in the most responsible diagnosis field had a sensitivity of 94% in identifying COPD cases compared with primary data abstracted from patient charts [129]. The sensitivity and specificity may be improved by increasing the minimum inclusion age of the study population, as COPD-related hospitalisation does not occur in appreciable numbers until >55 yrs of age with a majority of patients being >65 yrs [81, 130]. In general, studies that probe the principal diagnostic field for COPD patients in the CIHI database may miss 10–12% of the total pool of available COPD patients. However, among those identified with COPD, the diagnosis is likely to be correct.

Identification of medications

Alberta Blue Cross and Ontario Drug Benefit plan for seniors

In Alberta, Canada, seniors (those $\geqslant$65 yrs of age) receive direct government subsidies for purchase of prescription medications, which are listed on the government's formulary of approved drugs. In most circumstances, the individual is asked to pay for 30% of the total cost of the drug, up to a maximum of $25 per drug. This fee is waived if a senior has a very low income [131]. This database should be accurate and reliable since this information serves as a basis for financial reimbursement to pharmacies to cover 70% of total cost of the medications. The Ontario Drug Benefit (ODB) Programme extends similar coverage for senior residents living in Ontario [132]. Although the provincial government of Ontario recently instituted a small co-payment system for prescription medications, during the period of the first study (1992–1997), prescriptions were dispensed free of charge to patients, aged $\geqslant$65 yrs. As with the Alberta Blue Cross database, the ODB should be accurate and reliable as the provincial government has a rigorous set of quality controls in place to ensure that the information within this database could be used for surveillance and reimbursement purposes. In both provinces, all commonly used formulations of ICS are covered under provincial drug plans.

Vital statistics

In Ontario, two sources of data were used to confirm inhospital deaths: CIHI Discharge Abstract Database and Registered Persons Database of Ontario. In Alberta, the Alberta Health Insurance Plan Registry as well as the CIHI Discharge Abstract Database were used. Using these sources, >95% of deaths occurring in hospitalised patients were able to be cross-validated. For deaths occurring outside the hospital setting, the Registered Persons Database was used for Ontario patients and the Alberta Health Insurance Plan Registry for Alberta patients. Both of these databases are likely to be comprehensive and accurate because the annual emigration rate from Ontario and Alberta is generally <0.5% and <2.0%, respectively [133].

Results

In Ontario's study, there were 22,620 study patients who met the inclusion and exclusion criteria. The mean age of the study patients was 75 yrs; approximately one-half were female. When adjusted for various factors, it was found that those patients who had received ICS within 90 days of discharge had a relative risk (RR) of 0.74 (95% confidence interval (CI) 0.71–0.78) for combined hospitalisation and all-cause mortality. The RR was 0.71 (0.65–0.78) for all-cause mortality and 0.76 (0.71–0.80) for repeat respiratory hospitalisation. There was a significant relationship between the use of ICS and survival (fig. 1).

Importantly, use of other common anti-COPD medications was associated with either no or slightly increased mortality risk. For instance, dispensation of a β_2-adrenergic or ipratropium within 90 days of discharge was not associated with survival. When the cohort based on the number of physician visits, which occurred within 1 yr prior to the index hospitalisation (as a marker of disease severity; 0, 1, 2, $\geqslant$3 visits·yr^{-1}) was stratified, it was found that the largest risk reduction for the combined end-point associated with ICS was in the group that had three or more visits; the smallest benefit was in the group that did not have any physician visits (p=0.001). A

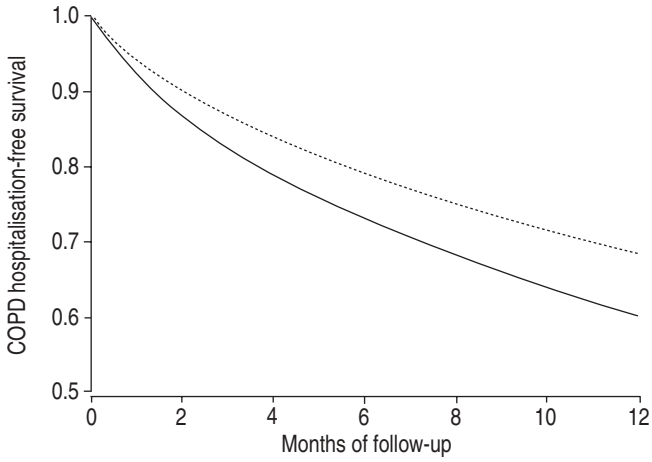

Fig. 1. – The relationship between inhaled corticosteroids (ICS) and survival. Cox proportional hazard model. COPD: chronic obstructive pulmonary disease. - - -: ICS; ——: no ICS.

series of sensitivity analyses was conducted to test the robustness of the main findings to various conditions. Even among the youngest of the cohort (65–74 yrs of age) and those without any comorbidities, where the effects of confounding should be minimal, ICS therapy was significantly associated with both improved survival and repeat hospitalisation rate.

In Alberta's study, data from 6,740 patients were used. The mean age of the study population was 76 yrs. Of these patients, 3,661 (54.3%) were males; 3,744 (55.6%) had no comorbidities. Overall, 3,343 (49.6% of total) patients received an ICS during the study period. Of these patients, 2,011 (61.2%) used low-dose therapy, 318 (9.7%) used medium-dose therapy, 413 (12.6%) used high-dose therapy, and 601 (18.0%) received an indeterminate dose. After adjustments for age, sex, comorbidities, ICU stay, and use of other pulmonary medications, a 25% reduction in the overall mortality rate was observed in those who received ICS compared with those who did not (RR 0.75, 95% CI 0.68–0.82). Patients dispensed low-dose therapy had a 23% (RR 0.77, 95% CI 0.69–0.86) reduction in the mortality rate compared with those who did not receive any ICS. Those on medium-dose therapy experienced a 52% reduction (RR 0.48, 95% CI 0.37–0.63), while those on high-dose therapy experienced a 45% relative reduction in the mortality rate compared with those who did not receive any ICS (RR 0.55, 95% CI 0.44–0.69). Patients on indeterminate doses did not experience any significant decline in their all-cause mortality rate (RR 0.88, 95% CI 0.76–1.03; p=0.108). A significant relationship was also found between survival and the number of canisters of ICS received by patients during a given year (fig. 2). Interestingly, no such relationship was found between ipratropium bromide and survival (fig. 3). With short-acting β_2-adrenergics, there was a slight increase in mortality risk along the dispensation gradient, which may reflect confounding by indication or severity (fig. 4).

To determine the robustness of the ICS therapy and mortality relationship, a series of subgroup analyses were conducted. Survival benefits of ICS were observed across different age groups, sex, comorbidity and medication status. Even among the healthiest members of the cohort, ICS were associated with a significant survival advantage. In those between 65–74 yrs of age without any comorbidities, it was found that ICS were associated with a 37% relative reduction in the all-cause mortality rate compared with no therapy (RR 0.63, 95% CI 0.50–0.79). Low-dose therapy was associated with a 37% reduction (RR 0.63, 95% CI 0.49–0.82), medium-dose was associated with a 50% reduction (RR 0.50, 95% CI 0.30–0.83) and high-dose therapy was associated with a 57%

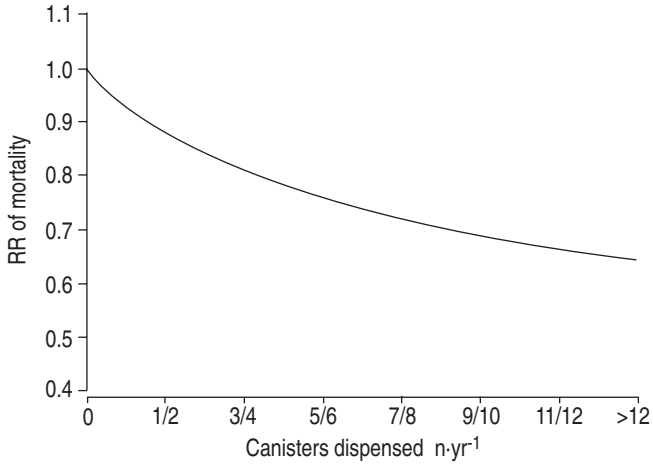

Fig. 2. – The relationship between inhaled corticosteroids and survival according to the average number of canisters received during a given year. RR: relative risk.

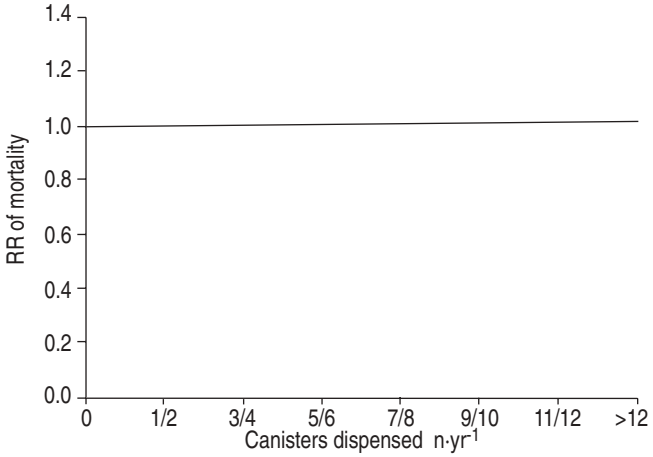

Fig. 3. – The relationship between inhaled (short-acting) anticholinergic and survival according to the average number of canisters received during a given year. RR: relative risk.

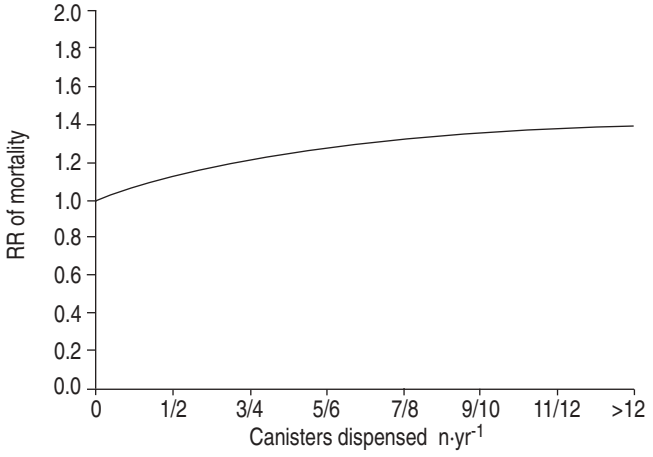

Fig. 4. – The relationship between inhaled short acting β_2-agonists and survival according to the average number of canisters received during a given year. RR: relative risk.

reduction (RR 0.43, 95% CI 0.27–0.70) in the all-cause mortality rate.

Since survivor treatment selection bias was a potential concern for the analysis, sensitivity analyses were performed including only certain subgroups [134]. For instance, a subgroup analysis was performed excluding all patients who had a follow-up time of 90 days or less and, thus, had a lower probability of receiving ICS than the rest of the cohort. In this analysis, ICS were associated with a 43% lower risk of mortality (RR 0.57, 95% CI 0.51–0.63). Using cut-offs of 6, 9 or 12 months made little difference to the overall findings (RR 0.57 for 6 months, RR 0.58 for 9 months, RR 0.58 for 12 months) suggesting that survivor treatment selection bias was not a significant concern for the analysis.

Interpretation

There are several important advantages of using administrative databases for research. Research studies based on administrative databases: 1) contain large sample sizes; 2) are population-based (unlikely to suffer from selection bias); 3) are relatively inexpensive to conduct; 4) can generate data quickly; 5) have very good follow-up of cohort (outmigration is usually $<2\%\cdot yr^{-1}$ from most provinces in Canada); 6) reflect "real-life" experiences (and do not suffer from "volunteer" bias or "Hawethorne" effects); 7) are able to determine whether effectiveness applies to subpopulations, which are generally excluded in randomised controlled trials (RCTs; *e.g.* elderly, females, certain racial groups, patients with multiple comorbidities); and 8) have the power to evaluate the effects of an intervention on hard clinical outcomes (such as mortality and hospitalisation), rather than relying on intermediate measurements, which may not adequately predict hard clinical outcomes and may suffer from ascertainment bias.

There are several important limitations: 1) diagnostic misclassification is possible as investigators have to rely on self or physician diagnosis of COPD; 2) administrative databases may not contain physiological and/or biochemical measurements, thus, adjustments for severity are problematic; 3) confounding by indication or severity can be problematic; 4) while administrative databases allow investigators to determine which study patients did and did not receive certain medications, patients′ compliance with these medications are rarely found in these databases; 5) exposure misclassification may also be problematic. For example, if some patients who initially used ICS decide not to use them later on, while some initial nonusers become users, then exposure misclassification may occur. However, this type of "bias" is usually nondifferential in nature and pulls the RR towards the null value; 6) studies that use a longitudinal analytical design (*e.g.* Cox proportional hazards model) are susceptible to survivor treatment selection bias. For example, patients living longer are more likely to be exposed to ICS than those who die earlier. This bias will make ICS more efficacious than they really are. The longer the follow-up period, the more likely this bias is to be present. It is important, therefore, to perform sensitivity analyses. One method is to perform a similar type of analysis using other anti-COPD medications. If this bias is operative, then other drugs should also demonstrate a similar survival benefit. Another method of checking for this bias is to shorten the follow-up period. A third method is to exclude patients who died early on in the follow-up period to ensure that in the remaining cohort, all study patients had a reasonable chance of receiving ICS. In the Alberta study, all of these sensitivity analyses were conducted and it was found that the results were materially unaffected by changes in the follow-up period or in the exposure period; and 7) data from

research studies based on administrative records are best used to complement findings from RCTs or to generate novel hypotheses that should be tested in large RCTs.

Discussion

ERNST: I am curious about the magnitude of effect on the reduction of all-cause mortality in this study (29%) *versus* what you may see in cardiovascular trials (33–36%) with simvastatin *versus* placebo, for example. How could ICS have an effect similar to antiplatelet therapy for myocardial infarction?

SIN: That is an excellent point. Do ICS reduce mortality? What is the magnitude of that reduction? I think observational studies are much stronger to answer the former rather than the latter. Our observational study suggests that they reduce mortality. Is there a plausible mechanism by which mortality can be reduced? Your point that the single most frequent cause of COPD mortality is cardiovascular is a germane one. So, if ICS have this powerful effect on mortality reduction, they have to have some effect on the cardiovascular system, but I do not know what that mechanism is.

ERNST: Did you try to look at the number of patients who may have been labelled as asthmatic?

SIN: No we did not do that. But, I think we are getting back to that whole business of what is COPD and what is asthma in the elderly? I do not think anybody has an answer to that.

BOURBEAU: First, the magnitude of effect of ICS, assuming that there is a true effect, could very well be magnified. It is known that observational studies may show a higher magnitude of effect than an RCT, which we usually refer to as the gold standard. Second, I also have some concerns in these studies with the diagnosis of COPD based only on the primary discharge diagnosis. With regard to COPD, we could exclude patients with associated asthma as a secondary diagnosis to obtain a strict definition of COPD. As it is, part of the effect observed could be influenced by patients with asthma. We do not know about this for sure. It would be of great value to validate the diagnosis of COPD *versus* asthma used from databases and see how it corresponds to the definition that we use in clinic.

ERNST: I think there is a problem with what we are doing with nonexposed time. In the Alberta cohort, a patient could get a prescription anytime in the last 3 yrs. Let us talk, for example, about a patient who is exposed in the last 6 months and dies on the last day of follow-up. The first 2.5 yrs, when the patient had no ICS, is counted as exposed time in the intention-to-treat analysis. I do not see how this can be correct.

SIN: I think that is the survivor treatment selection bias. Greater than 80% receive their first dispensation within the first 100 days. If they did not receive it within that time-frame, then it was highly unlikely that they would receive it. That is why you need to do secondary analyses to make sure your data are robust. That is why we looked at ipratropium and short-acting β-agonists. If survivor treatment selection bias was the main culprit here, it should also be evident in those drugs.

ERNST: I disagree. I think these drugs are prescribed very differently. They are the standard after being discharged from the hospital with COPD. There is less confounding by indication with those drugs. Perhaps we should call this immortal time when they are not exposed and they are not at risk for the outcome, because if they had the outcome before exposure they would be in the nonexposed group. So I think the follow-up time is going in the wrong group.

WEISS: Is this a direct treatment effect? What were the care pattern differences that may also be highly associated with the treatment pattern? You controlled for primary *versus* specialty. How did you do that? That assignment may have created some ambiguity and added noise to the model. That may have explained why you saw such a big effect size in your hazard ratios because you are picking up a care difference.

SIN: We looked at the principle care provider at the time of discharge of these patients.

WEISS: That may not be appropriate, because it really asks the question of who your system is assigning as the care provider. Whoever did the abstract discharge for that day and signed as the care provider was the doctor on record. So it is that care process that may be so closely associated with that dispensing moment that is really important.

FABBRI: What do you think is the strength of your own data? Based on your mortality data, would you be ready to issue a recommendation to tell your government to put this drug on the formulary to prevent COPD death?

SIN: I do not think you can make firm recommendations from observational studies. You have to look at the totality of evidence and formulate a rational recommendation. Our study has to be put into the pool of other studies published in this area. Right now, for moderate-to-severe patients, ICS appear to have a positive protective effect on reducing exacerbations and hospitalisation. More work needs to be done on mortality rates. If indeed, ICS produce an effect on mortality, there has to be some biological mechanism to explain that. So we cannot make any definitive statement about mortality. But, we should not dismiss the data because we do not understand how it works.

FABBRI: Do you think an observational study would be sufficient in this case?

SIN: No, I would also do an RCT.

WEISS: But, as soon you say let us do an RCT, then you are saying let us wait 7 yrs to get the results on this! Can we further investigate the biases in this study, explore how generalisable this is in other observational studies and see if one can converge the observational study environment on a similar set of findings. This will take just a few years, rather than 7 yrs for an RCT. The convergence of the observational realm would be a near approximation to the experimental realm.

STURKENBOOM: The results suggest that the way to look at responsiveness is to look at the number of canisters dispensed per year. I do not quite agree with that. Patients who take 10 canisters·yr^{-1} are those who are surviving up to 10 canisters·yr^{-1}. By doing so, patients with 10 canisters·yr^{-1} are forced to have a lower mortality rate. This is again the issue of immortal time. Using data during follow-up to define exposure is not the right way, and you should probably use a time-dependent approach.

HAGAN: There may be selection bias in the opposite direction. I would expect that salbutamol-ipratropium patients would have milder COPD while those getting ICS would be sicker. Therefore, I would have expected the death rate to go the other way around.

McLAUGHLIN: The same thing goes for treatment *versus* no treatment. In an observational database, if you are not receiving treatment, physicians believe you do not require treatment and you are probably less severe.

HAGAN: And if you do get a better effect from the ones that you thought were sicker patients, then something must be happening.

SORIANO: This is called negative confounding by indication. They will be more severe. In our studies, the individuals

who are treated *versus* those who are not treated eventually get a better outcome.

STURKENBOOM: That suggests you are more severe, but if you are more severe, then you are not being treated. If you find an effect, the real effect should be even bigger, but here it can be the other way around.

SORIANO: The solution is that it is better to compare not taking the drug with taking another drug. You partly overcome this problem when you use a reference group that includes treatment with another drug.

PRICE: Some patients will have had asthma. Are there any data on accuracy of hospital diagnosis of COPD upon admission?

SIN: Regardless of diagnostic issues, if the data are indeed true and ICS reduce all-cause mortality, that in itself is a powerful observation, even if it is driven by asthmatics.

VOLLMER: The issue of is it asthma or is it COPD has been a recurrent theme in this discussion. I am not sure I would worry too much about what diagnosis these patients really have. The fact is that they have been diagnosed as having COPD and are being treated accordingly. Thus, we can fairly clearly ask what happens when doctors treat their "COPD" patients with ICS. It is an interesting question, though not quite the same perhaps as studying the effect of ICS therapy in those who truly have COPD.

DAVIS: Did your crude values for adjustment of comorbidities change much? Are these really confounders? Are they associated both with the outcome we are interested in and the probability of getting an ICS?

SIN: With the separate analyses that we did, we were fairly confident that heart disease was not a major confounder.

The UK General Practice Research Database Experience in COPD pharmacoepidemiology

J.B. Soriano

Summary

The UK General Practice Research Database (GPRD), an automated database of primary care covering a total population in excess of 3.4 million inhabitants (~5.7% of the population) in the UK, provides a unique source of data to investigate the epidemiology of chronic obstructive pulmonary disease (COPD) from a population perspective and the effects of drugs on COPD-related outcomes. After formal validation of COPD and asthma definitions in this database and the description of the clinical epidemiology and trends in incidence and prevalence of disease, the results of two recent pharmacoepidemiology studies of COPD in the GPRD are comprehensively discussed.

Introduction

The UK General Practice Research Database (GPRD) database has been described in detail elsewhere [135–137], and has been utilised previously to obtain epidemiological trends of chronic obstructive pulmonary disease (COPD) incidence and prevalence in the UK during the 1990s [138, 139] (fig. 5). The GPRD is the world's largest computerised database of anonymised longitudinal patient records from general practice, containing >35 million patient-yrs of data. It is a significant resource for the following areas of study: clinical epidemiology, drug safety, pharmacoepidemiology, health outcomes, health service planning and pharmacoeconomics. It is used regularly by academics, the UK Department of Health, the Office for National Statistics (ONS), medicines regulatory authorities and the pharmaceutical industry. All research conducted within the database requires a protocol submitted and approved by the Scientific and Ethical Advisory Group of the GPRD. The GPRD bibliography now contains over 200 scientific papers and editorials published in top biomedical journals, demonstrating the quality and wide applicability of the GPRD data.

As a brief historical note, the GPRD was established in June 1987 as the VAMP Research Databank. At this time, participating general practitioners (GPs) received practice computers and the VAMP Medical, text-based practice management system in return for undertaking data quality training and submitting anonymised patient data for research purposes. The number of practices participating in this arrangement grew rapidly and the first research studies using GPRD were published during the early 1990s.

In November 1993, Reuters Health Information acquired VAMP Ltd. In 1994, Reuters decided to donate the database to the Department of Health, while it continued its interest in the provision of practice management software. The database was renamed GPRD at this time. In 1995, Reuters launched Vision, a major new Windows-based practice management software application, which has subsequently become the dominant practice software used by GPs in the GPRD scheme.

Since 1994, the Secretary of State for Health has owned the database. Between 1994–1999, the database was managed by the Department's Statistics Division and operated by the ONS. In 1999, the Medicines Control Agency (MCA) took over management of the GPRD, relocated GPRD's operations from ONS to the MCA, and initiated a major redevelopment programme to enable broader research usage of the data both within the UK and overseas.

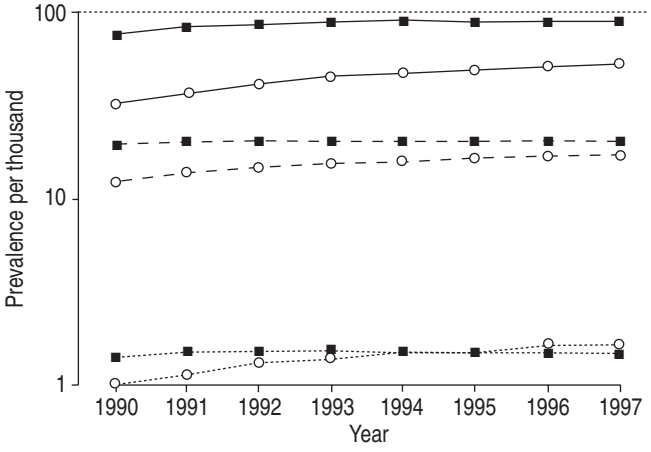

Fig. 5. – Prevalence trends of physician-diagnosed chronic obstructive pulmonary disease during the 1990s, by sex and age. ○: females; ■: males. ——: >65 yrs; - - -: 45–65 yrs; ·····: 20–44 yrs. Adapted from [139].

Methods

The chronic obstructive pulmonary disease General Practice Research Database definition

The identification of incident COPD patients in primary care and chest clinics is a medical challenge in the UK. Furthermore, there is no single COPD diagnosis code in the GPRD, therefore, specific searches had to be conducted to identify both the Oxford Medical Information System codes based upon the International Classification of Disease (ICD)-8 coding system and Read codes that determine COPD diagnoses within the database.

To demonstrate the ability of the GPRD database codes to provide a good differential diagnosis of COPD *versus* asthma in the GPRD, a validation study was conducted. Briefly, 300 questionnaires were mailed to a random sample of GPRD surgeries in charge of 225 patients with a diagnosis of COPD and an age- and sex-matched group of 75 patients with asthma. The response rate was 85.7%. The validation study found that the 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 [140]. The specificity of the definitions of moderate and severe COPD was 75.0 and 81.4%, respectively.

However, a key question in any COPD clinical or epidemiological study is the reliability of the differential diagnosis of COPD *versus* asthma. Therefore, as a further safeguard, only patients >50 yrs of age have been included in the GPRD COPD analyses. Other demographic features, such as smoking history are supportive; indeed, the high mortality rate observed would itself make frequent misdiagnosis of asthma unlikely.

Finally, examination of cause of death revealed that only nine patients (three in the treated and six in the comparison group) had asthma recorded as their cause of death. Moreover, there were only 298 (6.4%) patients with an historical asthma diagnosis before the age of 50 yrs and the mortality rate differences from the study were similar between the total population and the population restricted to those without any evidence of asthma. For these reasons, it is believed that misclassification of asthma as COPD did not occur frequently in these GPRD studies. The efforts to take asthma into account at least match the efforts of other recent pharmacoepidemiological studies in COPD patients, where no validation study was conducted and asthma exclusion criteria were only based on restricting the population to older ages. Hence, from the double diagnosis by GP and hospital doctors at discharge, after several days of hospital admission to consider that patients were not asthmatic, there is considerable confidence in the validity of the GPRD diagnosis of COPD.

When studying COPD, the choice for study design in the GPRD has been the cohort rather than cross-sectional or case-control designs. The GPRD allows researchers to identify individuals from birth or registration within the database up to death or censoring. The advantages of identifying incident COPD, severity and duration of the condition have been presented elsewhere. In the two GPRD pharmacoepidemiology studies, individuals followed up for 3 yrs after COPD diagnosis [141], and those individuals followed up for 1 yr after a COPD hospital admission discharge [142] were examined.

Drug exposure

In studies regarding the beneficial effects of drugs in pharmacoepidemiology, it is recommended to compare a given drug *versus* a reference group exposed to another drug, rather than to a group of nonusers, to avoid or reduce confounding by indication *i.e.* treatment may be chosen for an individual patient because of the presence or absence of specific features of disease, and patients who have a diagnosis in their record but remain untreated are likely to be less severe [143].

The GPRD approach has been to compare potential drug exposure groups with current recommendations in clinical practice. Current British Thoracic Society guidelines for COPD, published in 1997, recommend short-acting bronchodilators for all symptomatic patients, but state that there is insufficient evidence for use of inhaled corticosteroids (ICS) or long-acting β-agonists [144]. Therefore, all drug comparisons are categorised to simulate an "intention-to-treat" analysis, and compared with a reference group of physician-diagnosed COPD patients who received three or more prescriptions over an initial 6-month period of one of the following groups of drugs: short-acting β-agonists, xanthines, anticholinergics or combined bronchodilators, but no use of ICS or long-acting β-agonists since diagnosis with COPD.

In contrast with research that evaluated the effect of ICS alone, this study focused on the effect of the combination of long-acting β-agonists and ICS due to physiological, clinical and statistical evidence. There seems to be at least an additive effect of combined long-acting β-agonists and ICS use in respiratory disease [111, 145], and their molecular mechanisms of action are different [145]. Combined use of ICS and long-acting β-agonists for COPD is currently being assessed in ongoing randomised controlled trials (RCTs) (Trial of Inhaled Steroids and Long-Acting β_2-Agonists [111] and Towards a Revolution in COPD Health trials). Finally, from the statistics perspective, comparison with other drug classes (*i.e.* short-acting bronchodilators, xanthines, anticholinergics, oxygen and other) would have required adjustment for multiple comparisons beyond the initial primary analysis.

Outcomes

The outcome of interest for the two studies was the occurrence of death [141], or of a first severe COPD exacerbation, defined either as rehospitalisation for a COPD-related medical condition or death [142]. Due to the competing risks of these two outcomes, the main outcomes are presented separately for COPD rehospitalisations and all-cause mortality within a year.

Covariates

Asthma. Since a substantial number of COPD patients in the GPRD have at some time had asthma mentioned in their record, this is included as a potential confounder variable in the analysis.

Smoking. Information on tobacco use was categorised as nonsmoker (including never- and exsmoker), unknown or current smoker based on the database medical and prevention files of the patient. Pack-yrs of smoking were estimated in the identified smokers.

Oral steroids. Courses of oral steroids during the follow-up period, a potential confounder of the association between ICS and mortality [146], were included as a yes/no categorical variable.

Comorbidities. Baseline comorbidities were identified from the database medical file 12 months prior to the initiation of

therapy and categorised into a modified Charlson comorbidity index [122]. 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 in an effort to control for prescribing trends.

Statistical analysis

Standard survival analysis was used for comparison of groups according to drug exposure [147]. Duration of follow-up was defined as the time period between COPD diagnosis and death or censoring; or from discharge from a first COPD hospitalisation and the next COPD hospitalisation, death or censoring. An immortal person-time period of 180 or 30 days was used to ensure that classification into treatment groups was based on a reasonable period of observation [119, 144]. Therefore, in all treatment groups, patients who failed to complete a postdiagnosis of 180 days or a postdischarge 30-day period of observation for drug use were excluded from analyses.

Crude Kaplan-Meier and adjusted Cox survival estimates were then obtained for each drug exposure group. Relative risks were obtained using Cox′s proportional hazards model, with adjustments for sex, year of entry, age, smoking status (non-, unknown and current smoker), comorbidities (absence, 1, 2 or 3+ comorbidities), oral corticosteroids and concomitant asthma mention in the patient′s record.

Results

A total of 1,045 COPD patients who were regular users of salmeterol or fluticasone propionate (FP; alone or combined) 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-only and salmeterol-only groups, respectively. Similarly, the mean number of FP prescriptions was 9.19, 8.64 and 0.05 in the combined salmeterol and FP, FP-only and salmeterol-only groups, respectively. These usage patterns were also maintained in the second and third year of follow-up.

Baseline characteristics of all drug exposure groups are shown in table 5. Users of FP and/or salmeterol were more often female, diagnosed at an earlier age, and were more often categorised as having severe COPD ($p<0.05$). In the baseline period of 6 months prior to initiation of pharmacotherapy, users of FP and/or salmeterol received more prescriptions of ICS, xanthines, anticholinergics, oral corticosteroids and combined bronchodilator products ($p<0.05$). Baseline use of general and COPD-related health services were similar between the groups, whereas a history of comorbidities was more common in the comparison group. There were no significant differences in baseline and demographic characteristics within the subgroups of patients using combined FP and salmeterol, FP only and salmeterol only (table 5).

After a GP diagnosis of COPD, survival at year 3 was significantly greater in FP and/or salmeterol users (78.6%) than in the comparison group (63.6%, Kaplan-Meier $p<0.05$). After adjustment for confounders, the survival advantage observed was highest in the combined users of FP and

Table 5. – Descriptive characteristics of chronic obstructive pulmonary disease (COPD) patients after general practitioner (GP) diagnosis who are regular users of fluticasone propionate (FP) and salmeterol or comparison

COPD groups	FP and salmeterol	FP only	Salmeterol only	Comparison
Total n	317	431	297	3620
Female	52.7*	52.7*	49.2*	44.2
Age at diagnosis of COPD yrs	64.6±8.5*	66.1±8.8*	68.6±9.2*	72.2±9.8*
Smoking				
Non/ex	35.0*	32.5*	33.7*	26.9
Unknown	6.9*	7.0*	12.5*	20.7
Current	58.0	60.6*	53.9	52.4
Daily 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[¶]				
ICS	89.3*	66.4*	39.7*	4.4
Inhaled β_2-agonists	89.3*	71.0*	65.0*	33.1
Short-acting β-agonists	73.8*	67.3*	51.5*	31.3
Long-acting β-agonists	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 hospitalisations	7.9	6.7	5.4	6.2
COPD-related A&E room visits	1.6*	0.0	0.0	0.1
History of comorbidities[+]				
Presence of comorbidities	23.0*	31.1*	31.3*	43.3

Data are presented as mean±SD or % unless otherwise stated. ICS: inhaled corticosteroids; A&E: accident and emergency. *: $p<0.05$ *versus* comparison group; [#]: as in [122]; [¶]: baseline refers to prior 6 months before start of regular treatment, hospitalisations refer to in- and outpatient hospitalisations; [+]: as in [119]. Adapted from [141].

salmeterol (hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.31–0.73), followed by users of FP only (HR 0.62, 95% CI 0.45–0.85), and regular users of salmeterol only (HR 0.79, 95% CI 0.58–1.07), *versus* the comparison group (fig. 6). Mortality decreased with increasing number of prescriptions of FP and combined salmeterol/FP (data not shown).

In the second GPRD study, a total of 4,263 patients with COPD were identified after a first hospitalisation due to COPD; 3,636 of these patients received at least one prescription for ICS and/or long-acting β-agonists from their GP in the first 90 days following the hospitalisation discharge date. The reference group comprised 627 COPD patients who received prescriptions for short-acting bronchodilators but not ICS or long-acting β-agonists. The four drug exposure groups of COPD patients were relatively well balanced regarding sex, age and smoking (table 6). The reference COPD patients had received, by definition, no prescriptions of ICS or long-acting β-agonists in the first 90 days after discharge. However, they had more nebulised or oxygen treatment, and received more prescriptions of xanthines, anticholinergics and combination bronchodilators in the first 90 days after discharge ($p<0.05$). Use of oral corticosteroids was highest in ICS and long-acting β-agonists users. Finally, use of nasal corticosteroids and antihistamines were very low in all groups.

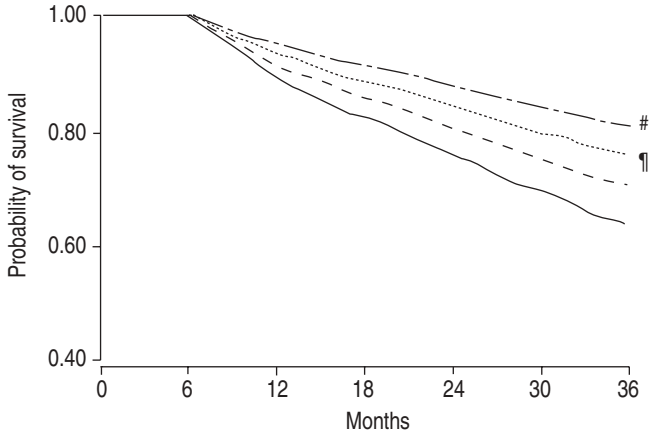

Fig. 6. – Three-year Cox-adjusted survival function of chronic obstructive pulmonary disease patients by therapy with combined fluticasone propionate (FP) and salmeterol (— - —), FP only (·····), salmeterol only (– – –) *versus* comparison (———). #: $p<0.0008$ *versus* comparison; ¶: $p<0.028$ *versus* comparison. Adapted from [141].

During the 1-yr follow-up, the number of prescriptions of ICS or long-acting β-agonists per quarter were maintained well in each of the drug exposure groups, by quarter during the year, after hospitalisation and were minimal in the reference group (table 7). The use of oral corticosteroids was similar and followed a pattern of decrease of mean number of prescriptions in each of the drug exposure groups.

Rehospitalisation within a year occurred in 13.2% of the reference COPD patients, 14.0% of users of long-acting β-agonists only, 12.3% of users of ICS only, and in 10.4% of users of ICS and long-acting β-agonists. Death within a year occurred in 24.3% of the reference COPD patients, 17.3% of users of long-acting β-agonists only, 17.1% of users of ICS only, and in 10.5% of users of ICS and long-acting β-agonists.

Table 6. – Descriptive characteristics of chronic obstructive pulmonary disease (COPD) patients with inhaled corticosteroids (ICS)/long-acting β-agonists *versus* reference COPD patients within the first 90 days of discharge from a first COPD-related hospitalisation

Groups	ICS and long-acting β-agonist	ICS only	Long-acting β-agonist only	Comparison
Total n	496	3049	91	627
Female	50.2	48.9	45.1	45.9
Age at hospitalisation yrs	68.7±8.5*	71.8±9.0*	70.2±9.1*	73.4±9.4
Smoking				
Never/ex	33.9	32.1	35.2	29.8
Unknown	11.1*	15.0*	13.2*	19.9
Current	55.0	52.9	51.6	50.2
With asthma labels	83.9*	66.9*	64.8	54.1
Treatment				
ICS	100.0*	100.0*	0.0	0.0
Fluticasone	23.8*	4.8*	0.0	0.0
Beclomethasone	67.7*	78.5*	0.0	0.0
Budesonide	15.3*	18.9*	0.0	0.0
Inhaled β_2-agonists	100.0*	77.2*	100.0*	62.0
Short-acting β-agonists	75.6*	76.9*	63.7	61.9
Long-acting β-agonists	100.0*	0.0	100.0*	0.0
Salmeterol	96.4*	0.0	84.6*	0.0
Formoterol	0.6	0.0	2.2*	0.0
Bambuterol	3.4*	0.0	14.3*	0.0
Other adrenergic stimulants	1.4	1.1	0.0	1.0
Oral β_2-agonists	5.2	4.5	3.3	5.1
Xanthines	23.8*	17.5*	27.5*	45.6
Anticholinergics	31.5*	22.4*	34.1*	51.8
Oral steroids	52.8*	37.0	50.5	38.3
Combined short-acting bronchodilators	5.4*	5.9*	4.4*	14.0
Oxygen therapy	8.7*	8.3*	14.3	14.5
Nebulised therapy	5.2	2.5*	14.3	8.3
Nasal corticosteroids	2.8*	3.7*	4.4*	1.1
Antihistamines	2.6	2.2	2.2	2.4

Data are presented as mean±SD or % unless otherwise stated. *: $p<0.05$ *versus* the comparison group. Adapted from [142].

Table 7. – Mean±SD prescriptions of inhaled corticosteroids (ICS), long-acting β-agonists and oral corticosteroids by drug exposure group per quarter

	First quarter	Second quarter	Third quarter	Fourth quarter
ICS				
ICS and long-acting β-agonists	2.49±1.46	1.88±1.57	1.61±1.58	1.37±1.50
ICS only	2.18±1.27	1.58±1.47	1.39±1.43	1.23±1.45
Long-acting β-agonists only	0.00±0.00	0.58±1.05	0.51±0.90	0.39±0.82
Reference	0.00±0.00	0.29±0.73	0.34±0.85	0.34±0.87
Long-acting β-agonists				
ICS and long-acting β-agonists	2.29±1.23	1.82±1.58	1.48±1.48	1.24±1.49
ICS only	0.00±0.00	0.04±0.31	0.07±0.41	0.07±0.44
Long-acting β-agonists only	1.73±0.97	1.44±1.41	0.97±1.23	0.82±1.21
Reference	0.00±0.00	0.04±0.29	0.02±0.20	0.04±0.31
Oral corticosteroids				
ICS and long-acting β-agonists	1.71±2.15	1.29±2.18	1.26±2.19	1.06±2.48
ICS only	1.37±1.43	0.98±1.32	0.94±1.31	0.83±1.29
Long-acting β-agonists only	1.83±1.63	1.45±1.47	0.95±1.18	0.88±1.49
Reference	1.44±1.50	1.21±1.51	1.10±1.52	0.93±1.46

Adapted from [142].

In multivariate analyses, the risk of rehospitalisation or death was reduced by 10% in users of long-acting β-agonists only (NS), by 16% in users of ICS only ($p<0.05$), and by 41% in users of the combination of ICS and long-acting β-agonists ($p<0.05$; fig. 7).

Overall, the use of ICS with or without long-acting β-agonists was associated with a reduction in total mortality, 3 yrs after COPD diagnosis by a GP, and with a reduction of rehospitalisation or death in COPD patients 1 yr after being discharged from hospital with a first COPD hospitalisation.

Interpretation

The GPRD has stringent mechanisms of quality control but relies on the good practice of participating GPs who are invited to enter all significant morbidity events on each individual patient in the computer record, irrespective of whether the event occurred in the surgery, at a visit, or over the phone. All diagnoses and procedures communicated to the GP as a result of a hospital or other specialist visit (inpatient, outpatient, or in an accident and emergency unit) must be recorded when the GP is informed. Compared with data from an RCT and similar to other administrative and research databases, the GPRD lacks valid, complete information on respiratory function, weight, alcohol and tobacco consumption. Differential diagnosis or drug dosages are often difficult to assess, but major diagnoses, use of health services, and medication are registered with an acceptable degree of validity [148]. Offsetting these drawbacks are the very large sample size and the extensive information of medical events and treatments that are available from practices in all parts of the UK. More extensive information on the advantages and limitations of the GPRD can be found elsewhere [149].

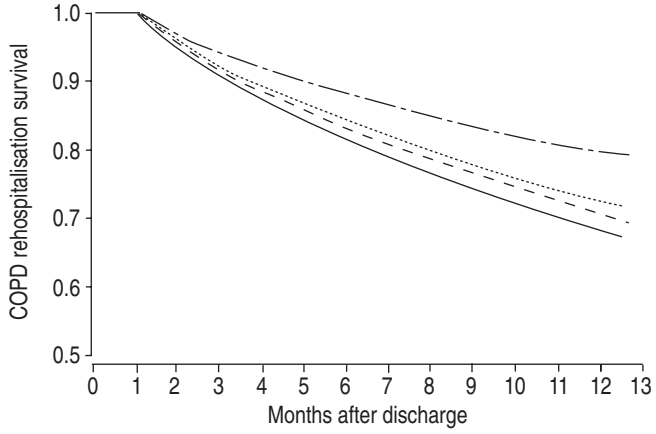

Fig. 7. – One-year Cox-adjusted survival function of time to rehospitalisation or death in chronic obstructive pulmonary disease (COPD) users of inhaled corticosteroids (ICS) and long-acting β-agonists (— - —), ICS only (·····), long-acting β-agonists only (– – –) *versus* comparison (———). Adapted from [142].

The GPRD framework is currently in transition to a full-featured online version that should reduce the current time gap between individual data entry and availability of cleared data for research from 12–15 months to weeks only. Additionally, there are renewed efforts to standardise drug dosing and to reinforce regular entry of tobacco and alcohol consumption information. Due to competition with other new systems, trends of attrition in participating practices and the final number of surgeries enrolled should determine the representativity of GPRD of the current UK population.

By reducing the gap time of GPRD data availability from 12–15 months to weeks, the GPRD has the potential to become a powerful tool for postmarketing drug safety studies. Its use for the early detection of safety signals in the general population of recently released respiratory drugs seems feasible. The opportunity for selection of population controls is most attractive.

Other current ongoing or planned COPD efforts in the GPRD include the automatic determination of cause of death in COPD individuals, the assessment of patterns of comorbidities and its changes, the determination of risk of fractures in COPD patients according to use of respiratory drugs, and the development of the clinical epidemiology and natural history of lung/bronchial cancer in COPD patients to enable future pharmacoepidemiology studies.

Discussion

COULTAS: I would like to mention the possibility of diagnostic misclassification, confounding by indication, and the effect of socioeconomic status in this study. You tried to validate by GP self-report of diagnosis, but with no objective information. As part of a randomised trial I am conducting, I took administrative data from our primary care network to

identify patients aged ⩾45 yrs with COPD-related ICD-9 code (GP diagnosed). We randomly selected persons and sent them postcard questionnaires about symptoms and smoking, and conducted spirometry in the home. We excluded those diagnosed with asthma. We excluded 43% based on lack of symptoms or smoking and 15% based on spirometry. Of the 426 persons with a clinical diagnosis of COPD, moderate-to-severe COPD was confirmed in only 42%. These results suggest that COPD may be overdiagnosed when using administrative data that rely on GP diagnosis.

I also attempted to look at confounding by indication by comparing the GPRD reference group with our validated COPD data. The use of short-acting β-agonists and anticholinergics in the reference group in the GPRD population is quite low. Is there something about that population that the GPs were treating differently? Is it possible that these patients had severe underlying concomitant disease? I believe this is indirect evidence of confounding by indication.

SORIANO: With regard to socioeconomic data, to ensure confidentiality, the pharmaceutical industry does not have access to geographic area or other proxies of socioeconomic information.

ERNST: How do you account for immortal time?

SORIANO: We start assessing the window of exposure within 90 days. For example, an individual is discharged from the hospital, goes to the GP next week and is prescribed an ICS, then dies within 1 week. That individual is excluded because the death occurred within the 90-day immortal time period from hospital discharge. In a sensitivity analysis, by changing the window of exposure (30 or 90 days), excluding or including deaths or COPD hospitalisation 30 or 90 days after discharge, the results were maintained or even more beneficial for combination treatment.

ERNST: Which of these analyses showed more benefits?

SORIANO: The combination became more beneficial when we included deaths that occurred within the first 90 days, but I have no explanation for this.

PRICE: Was the index date the same in all four groups? It is likely that you have reduced your power rather than increased it.

SORIANO: This could be a secondary effect of the use of ICS, long-acting β-agonists, or both. Although we included the year of entry, it was a factor that was irrelevant. It did not explain any change within the 3 yrs of follow-up. We did many analyses by practice, matching one individual in the FP, salmeterol or combination group with an individual in the same practice in the reference group and the results remained the same. That is why we think the analyses and results are robust.

BOURBEAU: In this database, the drug is collected from what the physician reported that (s)he is prescribing and not the actual filled prescription, unlike D.D. Sin′s database. So you cannot extrapolate and say that this is representative of what the patient is taking over the year. In D.D. Sin′s database, you still do not know if the patient is taking the drug, but it is one step closer to patient drug compliance.

PRICE: In our practice, we found that >95% of patients were filling their prescriptions for ICS across the board. This system works in the UK because they can get the prescriptions when they ask for them. They do not come to see us each time to get a prescription, so they have already chosen to get that prescription issued to them, which is different than what is seen in the USA. There are some data on refill rates for computer prescriptions, which suggest that >90% of prescriptions are filled [150].

SIN: There is likely to be a gap between prescription dispensation and medication consumption. However, in practical terms, that gap is likely to bias the result toward the null value. I think I am less bothered by the gap issue than by some other issues.

The Saskatchewan Experience

J. Bourbeau

Summary

The present study used the Saskatchewan administrative database to assess the effect of inhaled corticosteroid (ICS) therapy on hospitalisation related to chronic obstructive pulmonary disease (COPD) exacerbation. A nested case-control strategy within this cohort of patients (n=843) was used to allow assessment of exposure to ICS in relation to the timing of a rehospitalisation, and tight matching of subjects to compare patients of similar severity. Unlike the results from previous studies, no benefit of ICS on reducing severe exacerbations requiring hospitalisation among patients with COPD could be shown.

Introduction

The Saskatchewan administrative database has been the source of numerous pharmacoepidemiological studies in the past. Studies that are very well known are those in patients with asthma [151, 152]. These studies have been conclusive in showing a reduction of the risk of hospitalisation for patients prescribed inhaled corticosteroids (ICS) compared with those not on ICS. More recently, the Saskatchewan database has been used for the construction of a cohort of chronic obstructive pulmonary disease (COPD) patients after first hospitalisation, using a similar research design as in the asthma studies, to assess the effect of ICS in preventing hospital readmission [153]. In this COPD study, the use of ICS, even in patients that were prescribed high doses ($\geqslant$800 $\mu g \cdot day^{-1}$ of beclomethasone equivalent), could not be demonstrated to reduce the risk of severe acute exacerbations requiring hospital admission.

The Saskatchewan database

The computerised administrative databases of the Saskatchewan universal healthcare insurance system were the source of information for this COPD study. The administrative database of the Saskatchewan is unique in Canada as it includes all patients in the general population receiving medications commonly prescribed for the treatment of COPD and hospitalised for this condition. Since 1975, with the exception of registered First Nations Canadians, members of the Royal Canadian Mounted Police and Armed Forces, Saskatchewan residents have been issued a unique health services number, which is used to obtain healthcare, including reimbursement of prescription drugs, in the universal health programmes offered by the provincial government. One of the

advantages of this database is that it has been used extensively in the past and has been shown to be both comprehensive and valid [129]. In this database, the assessment of the use of any drugs is considered complete because the provincial drug plan is the primary insurer of Saskatchewan formulary benefits (therefore, claims must be processed through the drug plan's online system) and the drugs of interest are listed on the formulary. Furthermore, the information related to the drugs represent dispensed prescription by the patient, which is likely to be more accurate than patient- or physician-reporting drug prescription. Finally, the prescription drug database is submitted to several validation checks.

The diagnostic and treatment classification system used in the Saskatchewan COPD study was the World Health Organization International Classification of Diseases, ninth revision codes 490, 491, 496. A previous validation study of the Saskatchewan databases has shown the hospitalisation diagnosis of COPD to be quite accurate [129]. However, it has been recognised that this is true so long as no attempt is made to differentiate asthma from COPD and that both disorders are considered together. This confusion in the diagnosis with a risk of misclassification bias is common to all administrative databases although it is rarely recognised by the reader. Everyone will understand that including an asthmatic in a cohort of COPD patients may favourably influence the response, especially with pharmacological treatment such as ICS. The consequence will be that a clinician may generalise the results in their practice to a population of COPD patients that is completely different than the population originally under study. In the Saskatchewan COPD study, the importance of this problem has been recognised and the confusion limited. The cohort has been limited to the subjects with onset of treatment after the age of 55 yrs and excluded patients with prior asthma therapy, specifically those prescribed cromolyn, nedocromil, or ketotifen, nasal or oral ICS in the prior 5 yrs. Patients in the final cohort were those who were discharged from a first hospitalisation for COPD.

Methods

In the Saskatchewan COPD study, one main difference with other pharmacoepidemiological studies was the use of a nested case-control strategy within the original cohort of COPD patients (after their first hospitalisation for exacerbation). This is an important point of this study. It has allowed the assessment of exposure within specific windows of time in relation to the outcomes of interest. For example, the window of time of exposure could be examined just a few months before hospitalisation for acute exacerbation. These patients would be expected to benefit more from a drug treatment such as ICS than those who have stopped taking their medication long before the study outcome. Using a cohort analysis, as in most pharmacoepidemiology studies in COPD, would be restrictive in this matter. Patients defined in the exposed group will still be considered to be exposed without knowing if they have stopped their medication during follow-up. In addition, patients defined in the nonexposed group could very well start to take ICS during the follow-up. These potential biases related to inappropriate allocation of exposure, possibly present in cohort study design, were brought to attention in a recent publication by SUISSA [120]. In the same paper, another potential bias called "immortal time bias" was explicitly developed; although, this bias was not recognised until recently.

In the Saskatchewan study, a conditional logistic regression with matched case-control sets was used, and adjustments for age, sex, number of hospitalisations for health problems other than COPD (to account for comorbidities), calendar year oral and inhaled bronchodilators, oral corticosteroids, and antibiotics in the year prior to rehospitalisation were made. Confounding by indication remains a common bias in this study as it is present in all observational studies.

Results/interpretation

Using the Saskatchewan database with a nested case-control strategy within a cohort of COPD patients, hospitalised for exacerbation, did not show ICS to reduce the risk of rehospitalisation. These results are, therefore, not consistent with previous reports of a significant benefit of ICS in reducing rehospitalisation for COPD [121, 141]. Recently, many potential biases that could be seen in certain observational studies have been brought to attention [120]. There are still uncertainties regarding the effects of ICS and results from other pharmacoepidemiology studies should be interpreted very cautiously.

Large ongoing randomised controlled trials will help to clarify this and other issues. It is also vital that understanding of the mechanisms responsible for inflammatory response in COPD and what treatments are effective in suppressing inflammation are improved.

Discussion

VOLLMER: My first comment regards the definition of the study population and whether or not these patients are truly COPD patients. Because there was no screening for asthma in this study, we cannot be sure that these patients do not have an asthma component.

BOURBEAU: I am not so worried about there being asthmatics in the group. This would have been more of a concern if we had demonstrated a protective effect of ICS on hospitalisation. But, what kind of COPD patient have we selected for here? If these results are true, then we do not want to generalise this information to the entire population of COPD. The message here is that you cannot show a protective effect in preventing a second hospitalisation in this particular population of COPD, when patients are treated with ICS after a first hospitalisation.

VOLLMER: Is overmatching a concern? Matching was done to control for severity (based on medications). Why not match on severity at time of first hospitalisation rather than just prior to the index event?

SUISSA: The matching issue would be relevant if the exposure was defined at the time of first hospitalisation. If you adjust for the very recent covariates, then, yes, there would be overmatching because these would be in the causal pathway. But in this study, we have the reverse. The exposure is very close to the time of the event, in fact, "current use" and the covariates come in the year before. What is the strength of the association between the exposure and all of these covariates on the outcome? We have to look at the crude effect. If the crude effect was protective with respect to the exposure and this adjustment made it go away, then one explanation could be that it is overmatching but, in fact, the crude effect was above one and the adjustment effect made it equal to one.

BOURBEAU: With regard to the suggestion of adjusting for the severity of the disease at the time of hospitalisation, I would not expect that it would be particularly helpful here. If you look at the way a COPD exacerbation is treated in the hospital across provinces, treatment is very similar so I would not expect to see much variation.

SUISSA: In matched studies, the population is defined by the cases, and the cases are more severe than the ones who are

not readmitted to the hospital. In this way, when you match the cases with the controls from the cohort, you are actually selecting only the more severe ones. Therefore, the final sample will represent a more severe group than the entire cohort.

SORIANO: The mean age of this population was 76 yrs. Is this an age that is too old to show effectiveness?

ERNST: The average age of patients in D.D. Sin's study was the same.

SORIANO: The average age in our General Practice Research Database (GPRD) study was 69 yrs. Is it possible that your null hypothesis was negative and that your results should be inconclusive rather than negative?

BOURBEAU: I think we are not comparing the same populations here. The GPRD looked at a population of general practitioners. We are looking at a population of COPD patients that have been hospitalised. They will be older, for sure. I would expect a younger average age in the GPRD study. The average age of a COPD patient in most of the clinical trials is <65 yrs.

ERNST: I do not think that the conclusion of this study is that ICS do not work in COPD. The conclusion was that we were unable to show an effect in that population. It is important to understand why other investigators are showing an effect and what we can attribute these differences in results to.

WEISS: One of the interesting aspects of this study is the attempt to control severity in a way that is much more specific to COPD. That is a defining characteristic of this study *versus* using a number of comorbidities or the use of oxygen. We should not overlook that when discussing overmatching issues. What would it look like if we had those same kind of covariates in your cohort studies?

Immortal time bias in cohort studies of inhaled corticosteroid effectiveness

S. Suissa

Summary

Immortal time bias, which can arise in observational studies using computerised databases, refers to a period of follow-up time in a cohort study during which no outcome events can occur. Data from the Saskatchewan chronic obstructive pulmonary disease (COPD) cohort using rehospitalisation for COPD as the outcome, and the design of the Sin and Tu study [121] were used to illustrate immortal time bias. The misclassified analysis based on a 90-day exposure period definition produced a rate ratio of 0.69. When the immortal person time (30.2 person-yrs) was correctly allocated to the nonuse group, the crude rate ratio increased to 0.82. Using the Cox proportional hazards regression model analysis with the misclassified exposure produced an adjusted rate ratio of 0.71 (95% confidence interval (CI) 0.55–0.91), while with the properly classified exposure, the adjusted rate ratio was 1.13 (95% CI 0.87–1.47). This bias increased with increasing length of the exposure period. This bias acts by artificially increasing the rate of the outcome among "unexposed" patients and, once corrected, resulted in no association between inhaled corticosteroid (ICS) use and COPD readmission. These data illustrate that immortal time bias is present in observational studies that evaluate the effectiveness of ICS in COPD and suggest that their reanalysis is warranted to account for this bias.

Introduction

There has been a recent surge in observational studies of drug effectiveness in asthma and chronic obstructive pulmonary disease (COPD). A large number of these studies employed a cohort approach and were conducted using computerised databases. The cohort design offers several options to define exposure and to analyse the resulting data. The preferred approach of these recent studies has been to use an intention-to-treat definition of exposure with an analysis where the exposure remains time-fixed. Most studies presented in this publication use this approach. A bias that is little known in pharmacoepidemiology and that has only been briefly documented is that of "immortal person time" [118, 119]. It refers to a period of follow-up time in a cohort study during which no outcome events can occur. The improper account of such immortal person time will produce a biased estimate of the rate ratio.

To describe the role of immortal time bias in these recent studies, the approach taken by Sin and Tu [121] and replicated in several studies presented in this report was used. Briefly, the study by Sin and Tu [121] employed a retrospective cohort design to verify whether the use of inhaled corticosteroids (ICS) after discharge from hospital for COPD was effective at reducing the risk of COPD readmission or all-cause death. All 22,620 patients of >65 yrs of age admitted to hospital for COPD in Ontario, Canada, between April 1992 and March 1997 were identified from Ontario's health insurance database. The patients were followed from the date of discharge for up to 1 yr, or earlier if they were readmitted or died, in which case follow-up ceased at those points. The 11,481 patients who filled at least one prescription for an ICS during the first 90 days after discharge, or less if they had an event and were followed for <90 days, were classified as users. The remaining 11,139 who did not were considered as nonusers. An intent-to-treat analysis was performed on the basis of this classification using the proportional hazards regression model, accounting for several covariates, including comedication. The adjusted rate ratio of COPD readmission or all-cause death was 0.74 (95% confidence interval (CI) 0.71–0.78) for ICS use relative to nonuse. The adjusted rate ratio of COPD readmission was 0.76 (95% CI 0.71–0.80), while for all-cause death it was 0.71 (95% CI 0.65–0.78).

Immortal time bias is introduced in this design by the definition of exposure. A subject is considered exposed when an ICS is dispensed at any time during the 90-day period after discharge. Hence, to be exposed, a patient must survive until they receive that first prescription in that 90-day period. Thus, the span between the date of discharge and the date of the first prescription of ICS is immortal. Since no outcome events can occur during this immortal period, the survival function will necessarily be distorted. Moreover, this immortal period is considered "exposed" although the patient could not, in fact, become exposed until the first prescription in that 90-day period was dispensed. The question is then but to what extent this immortal time biases the results.

Data from the Saskatchewan COPD cohort was used to replicate the Sin and Tu [121] design and illustrate the

immortal time bias. The impact of this bias on the rate ratio of COPD outcomes was quantified for ICS use. Since the exact replication of the SIN and TU study [121] has already been published [120], for this illustration the study was replicated using another outcome, namely, hospitalisation for COPD.

Methods

The source cohort was described previously [120] and in J. Bourbeau's presentation (see above). Briefly, COPD patients were identified using the computerised databases from the universal health insurance programme of Saskatchewan, Canada [154]. Focus was placed upon the cohort of patients who were hospitalised for COPD between January 1, 1990 and December 31, 1997. Cohort entry was taken as the date of discharge of the first hospitalisation with a primary diagnosis of COPD. All subjects were followed for up to 1 yr, their first readmission with a primary diagnosis of COPD, or death from any cause during the 1-yr follow-up, whichever occurred first. As done by SIN and TU [121], all subjects who died within 30 days of cohort entry were excluded.

A subject was considered "exposed" if they received an ICS during the first 90 days of follow-up and "unexposed" otherwise. To illustrate the bias, the length of the 90-day time period selected to determine exposure was varied. Cox's proportional hazards models were used to estimate the rate ratio for the time-fixed exposure definition of SIN and TU [121]. The time-dependent definition of exposure that classified a subject as unexposed prior to filling the first ICS prescription was also considered.

Results

The cohort included 979 subjects, of whom 299 were rehospitalised for COPD during the 1-yr follow-up. During the first 90 days of follow-up, 39% were dispensed an ICS. As in the SIN and TU [121] study, the users of ICS were much more likely to have received inhaled β-agonists, ipratropium bromide, oral corticosteroids, antibiotics, and xanthines during this same 90-day period.

Table 8 compares, using the person-time analysis, the rate of readmission between users and nonusers of ICS. The misclassified analysis based on the 90-day definition of exposure produces a rate ratio of 0.69. When the immortal (and unexposed) person time preceding exposure, which amounts to 30.2 person-yrs, is correctly allocated to the nonuse group, the crude rate ratio increases to 0.82.

In table 9, when the size of the exposure time window varies from 15–365 days, the rate ratio from the time-fixed analysis decreases gradually from 1.05 for a 15-day exposure period to 0.57 for the full 365-day period. Conversely, the rate ratio from the time-dependent analysis ranges 1.06–1.18, with none statistically different from one. For the 90-day exposure definition used by SIN and TU [121], the rate ratio of 0.72 (95% CI 0.57–0.91) underestimates the corrected time-dependent estimate of 1.09 (95% CI 0.85–1.40). The crude and adjusted rate ratios for the 90-day exposure definition are given in table 10.

Interpretation

It has been shown that the bias from misclassified immortal time can have a very large impact on the observational studies of the effectiveness of ICS in preventing COPD outcomes. The bias artificially increases the rate of the outcome among unexposed patients. After correcting this bias, the proper analysis found no association between ICS use and COPD readmission.

The bias arises from misclassifying unexposed immortal time as exposed. To be considered exposed, a subject must be dispensed an ICS at anytime during a 90-day period after

Table 8. – Distribution of person time and readmissions according to use and nonuse of inhaled corticosteroids (ICS) for the chronic obstructive pulmonary disease (COPD) cohort study before and after correction for the exposure bias

	Exposed to ICS			Not exposed to ICS			Rate ratio
	Person-yrs	Events n[#]	Rate[¶]	Person-yrs	Events n[#]	Rate[¶]	
Biased analysis							
Immortal period	30.2	0		0	0		
At-risk period	279.0	101		417.4	198		
Total	309.2	101	32.7	417.4	198	47.4	0.69
Corrected analysis							
Immortal period	0	0		30.2	0		
At-risk period	279.0	101		417.4	198		
Total	279.0	101	36.2	447.6	198	44.2	0.82

[#]: outcome is the first occurrence of readmission to hospital for COPD within the first 12 months of follow-up; [¶]: rate per 100 per year.

Table 9. – Crude rate ratio of readmission for chronic obstructive pulmonary disease (COPD) with the use of inhaled corticosteroids from the Saskatchewan COPD cohort, using different time windows of exposure, estimated by the time-fixed and time-dependent analyses

Length of exposure period	Exposed %	Time-fixed analysis[#]		Time-dependent analysis	
		Rate ratio	95% CI	Rate ratio	95% CI
15 days	13.9	1.05	0.76–1.45	1.17	0.85–1.61
30 days	24.0	0.88	0.67–1.15	1.06	0.81–1.40
90 days	39.1	0.72	0.57–0.91	1.09	0.85–1.40
180 days	45.8	0.64	0.51–0.81	1.16	0.91–1.49
Entire follow-up 1 yr	49.0	0.57	0.45–0.72	1.18	0.92–1.51

CI: confidence interval. [#]: used in [121].

Table 10. – Crude and adjusted rate ratios of readmission for chronic obstructive pulmonary disease (COPD) for 90-day use of inhaled corticosteroids from the Saskatchewan COPD cohort, estimated by the time-fixed and time-dependent analyses

	Crude		Adjusted[#]	
	Rate ratio	95% CI	Rate ratio	95% CI
Inhaled corticosteroids				
Time-fixed analysis[¶]	0.72	0.57–0.91	0.71	0.55–0.91
Time-dependent analysis	1.09	0.85–1.40	1.13	0.87–1.47

CI: confidence interval. [#]: adjusted for age, sex and other COPD medications during same time period; [¶]: used in [121].

discharge. Thus, the exposed subject must necessarily survive until they receive their first prescription in the 90-day period. The span between the date of discharge and the date of the first prescription of ICS is thus immortal. Moreover, this immortal period is considered exposed by the intention-to-treat approach employed by SIN and TU [121], although the patient could not in fact become exposed until the first prescription in that 90-day period was dispensed. As a result, the rate is underestimated in the exposed group and overestimated in the unexposed group. This will produce an underestimate of the rate ratio comparing the exposed to the unexposed.

The bias increases with increasing length of the exposure period. It was taken to be 90 days in the study of SIN and TU [121], although no justification was offered for this choice. Clearly, the opportunity for longer immortal time increases as the exposure window increases. As a result, the biased rate ratios decreased from 1.05 to 0.57 as the length of the exposure window increased from 15 to 365 days. With the correct time-dependent analysis, the rate ratios were stable.

These analyses indicate that immortal time bias is present in observational studies of the effectiveness of ICS in COPD and may explain the apparent benefit found in those studies [121, 123, 142]. These studies should present a reanalysis of their data using the proper time-dependent approach before they can be considered as part of the evidence concerning the effectiveness of ICS in COPD. In addition, other cohort studies using a similar design should also be assessed for the possibility of immortal time bias [141].

Discussion

SIN: If a drug (ICS) is effective in producing beneficial outcomes, you would think that they would be most beneficial during a time period when a patient is at the greatest risk of developing these outcomes. For most drugs, if you look at the survival curves, they diverge relatively quickly, then the effect is not as pronounced later on. So, one way to address this concern is to eliminate that period and increase immortal time, but the risk in doing that is that you may miss subtle but powerful effects during the period when the patient is most susceptible in developing those outcomes. We have to be careful about the assumptions that we make. There are pros and cons to every approach.

SUISSA: I had the same concern. Should it take a certain amount of time before the effect is seen? That is why I replicated these analyses using different time windows and examined the effect of the definition of exposure on the estimate of the rate ratio. If we used a 365-day time window, the equivalent rate ratio for exposed *versus* unexposed would be 0.57. If we used a 15-day time window, the rate ratio is 1.05. We looked at 30 days and 90 days and we noted that there was a gradient. When the time window was very short, the rate ratio was high and as the time window increases, rate ratio decreases.

SIN: Or perhaps using the 15-day window results in more exposure misclassification because you are not giving them sufficient time to fill their prescription.

SUISSA: It is hard to know. But, the results remain the same when you vary this time window, with time-dependent approach that is not subject to this immortal time bias.

SORIANO: Such a short window of exposure may create drug misclassification. This problem happens when you compare one drug exposure *versus* no drug exposure. I think that this would not happen if you used another drug as a reference group.

SUISSA: There is also disagreement about whether patients are exposed or unexposed during this immortal time.

VOLLMER: Yes, but, if you look at dispensing data for the 2–3 months prior to the first admission, you should be able to make some reasonable hypothesis about who is likely to be exposed during the immortal time.

SUISSA: So you would define exposure prior to the initial hospitalisation? That is interesting. If subjects were actually using ICS before hospitalisation, the inclusion of this information may help attenuate the bias from immortal time and exposure misclassification. This would need to be investigated in these studies.

Acknowledgement. Some of the data in this article of immortal time bias in COPD studies have already been published in the *Americal Journal of Respiratory and Critical Care Medicine* [120]. This is a transcription of an oral presentation given at the workshop. Data presented in this study are based on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

The USA Lovelace Experience: examining systematic biases that affect the relationship between inhaled corticosteroids and survival in COPD

D.W. Mapel

Summary

To examine the relationship between the use of inhaled corticosteroids (ICS; with or without the use of salmeterol) and survival in patients with chronic obstructive pulmonary disease (COPD), information from the administrative databases of two regional health maintenance organisations, the Lovelace Health Plan and Kaiser-Permanente, were used in a retrospective cohort analysis (n=1,685). After adjustment for age, medication use, sex, COPD severity, and comorbidities,

COPD patients with mild asthma had significantly better survival than those without asthma (hazard ratio 0.672, p=0.0138). Hazard ratio estimates remain remarkably similar regardless of the time required to achieve the exposure criteria or changes in the duration of the exposure period, suggesting that the measurement errors are minor and that the positive association between ICS with or without salmeterol is robust. The survival benefit observed for ICS and salmeterol use did not appear to be significantly confounded by differences in smoking behaviour or comorbid conditions.

Introduction

The New Mexico Chronic Obstructive Pulmonary Disease (COPD) Outcomes Project was started to examine a variety of clinical issues, including how the diagnosis of COPD is usually made, the primary factors affecting utilisation among persons with this disease, and the relationships between airflow obstruction, quality of life and healthcare costs. The project has been conducted in three healthcare centres that represent the major types of delivery systems in the area: 1) Lovelace Health Systems, a regional for-profit system that provides care largely through the Lovelace Health Plan (LHP), its staff-and-network model health maintenance organisation (HMO); 2) the Albuquerque Veterans Administration Medical Center; and 3) the University of New Mexico Hospital, which serves as a tertiary referral centre and the primary care provider for the area.

Last year, the resources and experience that had been developed in examining COPD outcomes were used to conduct a project designed to examine the relationship between use of inhaled corticosteroids (ICS), with or without use of salmeterol, and survival. One of the goals of the project was to see if the results of the General Practice Research Database study could be reproduced [141]. To improve the power of the study and the generalisability of the results, the LHP database was merged with that of the Kaiser-Permanente, Georgia (KP-GA), which is an HMO of a similar size based in Atlanta, GA.

One of the major challenges of any clinical or epidemiological study is to identify the biases affecting the relationship between the exposure and the outcome of interest and to control for these biases in the analysis when possible, or describe their potential influence when not possible. Systematic biases can usually be classified as either selection biases, measurement errors or confounding. One of the goals of the New Mexico COPD Outcomes Projects was to describe the biases that are likely to affect COPD clinical studies, especially those that are prone to affect cross-sectional or retrospective analyses. In this discussion, the major systematic biases considered in the COPD Survival Project are presented, and how they are likely to have affected the results and the results of similar projects from other databases.

Methods

Selection biases

The most problematic issue in working with COPD is that it is not a disease. It is a clinical syndrome encompassing several diseases that share a common physiological phenomenon, forced expiratory airflow obstruction. Emphysema and chronic bronchitis are traditionally accepted as the two major disease entities included in COPD because they are both caused by cigarette smoking and because most COPD patients have both to varying degrees. The heterogeneity caused by just these two diseases would be enough to make this syndrome a challenge, but practicing clinicians treating COPD also tend to include asthma, particularly asthma that has a large fixed airflow obstruction component, or asthma patients who smoke. Therefore, even if the situation is simplified by saying that each COPD patient either has or does not have each of these three lung diseases, eight possible categories are still available to stratify patients into ($n^x=2^3=8$). Based on the current understanding of the pathophysiology and clinical presentation of these three diseases, it may be expected that persons with emphysema are likely to have a different response to ICS than those who have asthma, and that chronic bronchitis may or may not have a response depending on what inflammatory marker or clinical outcome is chosen. Thus, even in randomised, prospective, clinical trials for COPD, the categorisation of these patients is highly problematic, the results are still susceptible to selection biases and misclassification errors, and positive treatment effects can be overlooked if appropriate end-points are not selected.

To help understand the COPD population at Lovelace and how clinicians use these diagnostic terms associated with COPD, a detailed abstraction of the medical records of 200 randomly selected COPD patients who were treated by the LHP in 1998 was conducted, followed by an abstraction of every available medical record of the 2,600 COPD patients treated by the LHP in 1999. In these abstractions, the diagnostic term most commonly used by their primary caregiver or pulmonologist to describe each patient′s lung disease (the primary diagnosis) has been captured, along with any other terms that have been used to characterise the disease (the secondary diagnosis). The majority of patients (62%) were simply labelled "COPD" without further elaboration. Emphysema is a term that was uncommonly recorded by clinicians (4%), which is interesting because it is the term most commonly listed by LHP COPD patients when asked about their lung disease. Chronic bronchitis, or chronic bronchitis with COPD, was the most commonly used term used for 20% of the LHP cohort, and asthma or asthma with COPD was used as the primary diagnosis for 9%. Almost all of these asthma patients were either never-smokers who had severe asthma with a fixed airflow obstruction component, or asthma patients who were current or former smokers. The remainder of this population (5%) was comprised of persons with lung diseases that may be associated with airflow obstruction but are not usually thought of as COPD, such as cystic fibrosis, bronchiectasis, pulmonary fibrosis, and obstructive sleep apnoea.

Clearly, there are misclassification errors that could affect how LHP COPD patients respond to ICS, but can the direction in which these errors will go be predicted? For example, ICS are well established as first-line therapy for asthma because they have been shown to improve a number of outcomes including survival. However, in previous longitudinal studies of COPD, persons with increased airway reactivity and responsiveness to bronchodilators (*i.e.* asthma features) have had significantly accelerated decline in lung function and poorer clinical outcomes. It is impossible therefore to predict *a priori* whether the benefits imparted by use of ICS in this "COPD with asthma" subpopulation will overcome their predisposition towards worse survival. Another factor that makes prediction of misclassification errors difficult is the problem of continued cigarette use. It is known from the chart abstraction that up to one-half of the LHP COPD patients were documented as using cigarettes at least occasionally at some point during the study year. Smoking status is highly correlated with age and stage of lung disease, so that younger COPD patients with mild disease are more likely to still be smoking than older COPD patients with severe disease. As previously noted, the COPD patients with

asthma in this cohort tended to be either younger patients who were still smoking, or older persons with a fixed baseline airflow obstruction considered "mild" in COPD but severe in asthma, so an asthma patient's mortality risk could potentially be worse than that of an older generic "COPD" patient with moderate disease who managed to quit smoking more than a decade ago.

To adjust for having concomitant COPD and asthma in the analysis of ICS and survival, two different approaches were used. The first was to adjust for the presence and severity of asthma in the Cox proportional hazards model. Patients who had a primary discharge diagnosis of asthma were labelled as "severe" asthma, patients who had one or more emergency department encounters (not admitted) for asthma were labelled as "moderate" asthma, and those who had two or more clinic visits coded as asthma were labelled as "mild" disease.

Results

After adjustment for age, medication use (ICS and salmeterol), sex, COPD severity, and comorbidities, COPD patients with mild asthma had significantly better survival than those without asthma (hazard ratio (HR) 0.672, p=0.0138). Patients with moderate asthma (HR 0.997, p=0.99) and severe asthma (HR 0.97, p=0.91) had the same survival rate as those with no asthma. Thus, it appears that a concomitant diagnosis of asthma made by a clinic physician is likely to identify a patient who has a significant likelihood of better survival even after adjustment for confounding factors. Furthermore, because asthma is also a heterogeneous condition, some attention needs to be made to adjusting for the severity of the asthma component of the disease to avoid problems with residual confounding.

Another way of dealing with the asthma problem is to simply eliminate all patients who have any mention of asthma in their clinical record to see how this affects the HR estimates. In the database, this reduced the number of available patients by one-half (n=840), and most of the eliminated patients were from the ICS- and salmeterol-treated groups. However, the HR estimates for ICS, salmeterol, and combined ICS/salmeterol use changed very little, and the combination of ICS and salmeterol continued to be significantly associated with improved survival despite the substantial reduction in power (table 11).

Although the potential for systematic bias due to misclassification of COPD and asthma still exists, the robustness of the ICS/salmeterol survival association suggests that this is a true treatment effect and not simply a problem with asthma.

Another concern is that patients with more severe COPD may be more or less likely prescribed ICS or salmeterol; therefore, disease severity could be a selection bias. Disease severity in COPD is usually described as per cent of predicted forced expiratory volume in one second (FEV1), or stage of disease per the American Thoracic Society, European Respiratory Society, or Global Initiative for Chronic Obstructive Lung Disease staging systems. That poses a problem for most administrative databases, because, typically, very few clinical data outside of International Classification of Diseases, ninth revision (ICD-9) or ICD-10 codes are included. Furthermore, in cross-sectional or retrospective studies, it is unlikely that many COPD patients will have spirometry tests available that were obtained during the time interval of interest. An earlier project that was conducted using the LHP database suggests, however, that healthcare utilisation and the presence of comorbid conditions such as heart disease or cancer are better predictors of outcome than the degree of airflow obstruction. Using the clinical data abstracted from the chart review of 2,600 COPD patients (1,100 of whom had spirometry data), multivariate models were developed that identified the clinical characteristics present in calendar year 2000 that best predicted a poor outcome, such as high healthcare costs or death, in calendar year 2001. In bivariate analysis, per cent of predicted FEV1 was only weakly associated with high future healthcare costs (p=0.05). Actual healthcare utilisation, such as the number of inpatient, outpatient, and urgent care visits for COPD during the year 2000, the use of supplemental oxygen, or the presence of a serious comorbid condition such as heart disease, were much stronger independent predictors of a poor outcome in the following year (p<0.001). In multivariate models that included age, healthcare utilisation,

Table 11. – Hazard ratio (HR) estimates for all chronic obstructive pulmonary disease (COPD) patients (n=1685) and for those without any clinical mention of asthma (n=840)

Variable	Original study		Original study without asthma	
	HR	p-value#	HR	p-value#
HMO 1 member	1.412	0.0315	1.422	0.1429
ICS	0.594	0.0001	0.739	0.0941
Long-acting β-agonists	0.546	0.0154	0.566	0.1021
ICS plus long-acting β-agonists	0.344	<0.0001	0.112	0.0312
57–65 yrs	1.903	0.0610	0.905	0.8320
66–72 yrs	2.145	0.0223	1.149	0.7609
>72 yrs	4.336	<0.0001	2.259	0.0643
Male	1.092	0.4594	1.231	0.2325
3–19 COPD outpatient encounters in year prior to exposure	2.072	<0.0001	1.973	0.0136
⩾20 COPD outpatient encounters in year prior to exposure	3.380	<0.0001	3.108	0.0003
⩾1 COPD emergency dept encounter in year prior to exposure	1.282	0.2516	1.107	0.7766
⩾2 COPD hospitalisations in year prior to exposure	1.348	0.1667	2.329	0.0099
⩾1 Respiratory hospitalisation in year prior to exposure	1.106	0.5725	0.608	0.1230
⩾2 Asthma outpatient encounters in year prior to exposure.	0.672	0.0138		
⩾1 Asthma emergency dept encounter in year prior to exposure	0.997	0.9949		
⩾1 Asthma hospitalisation in year prior to exposure	0.970	0.9153		
Charlson score ⩾1 based on hospitalisations in year prior to exposure	1.264	0.2115	1.015	0.9584
Charlson score ⩾1 based on outpatient encounters in year prior to exposure	1.122	0.3881	1.151	0.4748

HMO: health maintenance organisation; ICS: inhaled corticosteroids. #: p-value derived from a Chi-squared test.

and the presence of serious comorbid conditions, per cent of predicted FEV1 was no longer a significant predictive factor ($p>0.10$). Therefore, when trying to adjust for disease severity in longitudinal or prospective analyses of COPD, the best predictor of future behaviour is previous behaviour, and FEV1 data are not essential.

To adjust for disease severity in this mortality study, the natural distribution of utilisation for inpatient, emergency department, and outpatient service encounters for COPD were examined in this cohort; then the group was stratified in each of these areas. It was found that after adjustment for age, health plan, medication use, comorbidities, and asthma, patients with $\geqslant 20$ outpatient services for COPD in the year prior to exposure had significantly poorer survival (HR 3.5, $p<0.0001$), than those with 3–19 encounters (HR 2.33, $p<0.0001$).

Measurement errors

Although electronic pharmacy databases have the advantage of being able to describe when a specific drug was dispensed during a specific time interval, they still have limitations, and there are still potential systematic errors in their analysis that may affect the exposure/outcome relationship. Therefore, there are several potential measurement errors that must be considered when using pharmacy data.

Previous studies have set an arbitrary minimum exposure period of 90 days′ worth of respiratory drug fills to help establish that their use is causally associated with survival [19, 141]. This criterion implies several assumptions that are probably not accurate. First, it may be inferred that all patients have been fully compliant with their ICS or salmeterol treatment for 90 consecutive days and that they continue to be compliant with their treatment throughout the follow-up period. Neither is likely. Patients may take >1 yr to accumulate 90 days′ worth of exposure, and if they stop their inhalers at day 91, they are still considered to be in the treated group. Secondly, it is known when a prescription fill is made, but in the Lovelace database, the number of inhalers dispensed or how the patient was instructed to take the medication is not known. Pharmacists generally dispense a 1-month supply at the initial fill and a 90-day supply on refills, but it is left to their discretion to interpret the prescription and decide how many inhalers will be needed for this time interval. Finally, the 90-day criterion is arbitrary, and it is not known how a shorter or longer exposure interval may affect the outcome.

Without further examination, it could be assumed that most of these factors are biases towards a null effect. Noncompliant patients who were dispensed just enough ICS or long-acting β-agonist to fulfill the minimum exposure criterion but who never really used the treatment regularly should have an outcome more similar to the never-treated group. Any observed difference between the observed and treated group is therefore likely to be a true effect because of the heterogeneity of the exposure among the treated.

The exposure measurement problem was examined in several ways. First, the mean and median number of days required to accumulate the 90 days of exposure by drug group were calculated, assuming that all prescription fills were for 30 days initially and 90 days at follow-up. The mean$\pm$SD and median cumulative time to reach 90 days of exposure in the exposed groups (mean 353$\pm$345, median 213; $p<0.0001$) are highly variable and overlap that of the comparison (*i.e.* short-acting bronchodilator) group (mean 276$\pm$274, median 169; $p<0.0001$). The combined ICS and long-acting β-agonist group is the only one that is statistically different from the comparison group (mean 576$\pm$450, median 421; $p<0.0001$ for both), and it is not surprising that it took substantially longer to fulfill the criteria in the combined group because there had to be at least 90 days of overlapping fills to be included. What effect the longer time to full exposure may have had in the ICS and long-acting β-agonist group is unclear, but it does not appear likely that the longer exposure time could solely explain the enhanced survival benefit for the combination of the two. Also, note that the mean and median time to achieve 90 days exposure in the ICS (mean 281$\pm$267, median 182) and comparison groups (mean 276$\pm$274, median 169) were very similar, and therefore unlikely to explain the survival benefit seen with ICS alone.

A similar comparison was conducted after eliminating all COPD patients with asthma (table 12). Again, the HRs have not substantially changed, and statistically significant categories continued in spite of a rather small study population.

Finally, to examine the issue concerning minimum length of time needed to count as an exposure, the HRs for cohorts that required 60, 90 and 180 days of drug exposure were recalculated (table 13). Note that the HR estimates for the treatment groups actually become stronger with increasing exposure time, suggesting a positive dose/response with treatment. Also note that the small survival advantage found in the Georgia group with the 90-day criteria is no longer seen when the criteria is set at 180 days.

In summary, measurement errors introduced by imprecise drug exposure information do not appear to explain the survival benefit observed in the treatment groups. In fact, exposure definitions should tend to bias the results towards a null effect, so the true survival benefit may actually be stronger than the estimates. Furthermore, HR estimates remain remarkably similar regardless of the time required to achieve the exposure criteria, or changes in the duration of the exposure period. This suggests that the measurement errors are minor, and that the positive association between ICS with or without salmeterol is robust.

Confounding

Cigarette smoking can be both a confounding factor (there is a direct relationship between the number of cigarettes smoked and death) and an effect modifier (ICS may have a survival benefit only for those who have quit smoking). Measuring smoking exposure is problematic in any study due to the problems with self-reported behaviours, inconsistent medical record documentation, variability in inhalation patterns, and differences in the smoke contents among different brands of cigarettes. Current smoking is associated with a higher risk of most adverse events than former smoking, but as previously noted, there is a strong relationship between smoking status and age. In many longitudinal studies, current smoking status is associated with a survival advantage, which is usually due to the effects of residual confounding and measurement errors, and not some inherent health benefit from cigarettes.

For the survival analysis, all available medical records were abstracted and pack-yr smoking estimates were obtained whenever they were recorded or were estimated from the provided information. The pack-yr smoking histories of 73% of the cohort were able to be estimated. When examined in a survival model that included age, sex, drug treatment, and comorbid illnesses, smoking pack-yrs were not independently associated with survival, and they did not have a significant effect on the ICS/salmeterol survival relationship (data not shown). The lack of a relationship between smoking and survival in this model most likely indicates that smoking effects on survival are accounted for by other factors in the

Table 12. – Comparison of hazard ratios (HRs) of original study cohort (n=840) to a subgroup who accumulated 90 days of drug exposure within 1 yr (n=594)

Variable	Original cohort ⩾90 days drug exposure accumulated within study window		⩾90 days drug exposure accumulated within 1 yr	
	HR	p-value[#]	HR	p-value[#]
HMO 1 member	1.352	0.1656	1.422	0.1429
ICS	0.744	0.0672	0.739	0.0941
Long-acting β-agonists	0.600	0.0958	0.566	0.1021
ICS plus long-acting β-agonists	0.349	0.0037	0.112	0.0312
57–65 yrs	1.120	0.7939	0.905	0.8320
66–72 yrs	1.425	0.3986	1.149	0.7609
>72 yrs	3.000	0.0061	2.259	0.0643
Male	1.156	0.3378	1.231	0.2325
3–19 COPD outpatient encounters in year prior to exposure	1.716	0.0170	1.973	0.0136
⩾20 COPD outpatient encounters in year prior to exposure	2.786	<0.0001	3.108	0.0003
⩾1 COPD emergency dept encounter in year prior to exposure	1.112	0.7297	1.107	0.7766
⩾2 COPD hospitalisations in year prior to exposure	1.989	0.0143	2.329	0.0099
⩾1 Respiratory hospitalisation in year prior to exposure	0.749	0.2793	0.608	0.1230
Charlson score ⩾1 based on hospitalisations in year prior to exposure	0.964	0.8844	1.015	0.9584
Charlson score ⩾1 based on outpatient encounters in year prior to exposure	1.064	0.7123	1.151	0.4748

HMO: health maintenance organisation; ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease. Data are taken from patients without asthma. [#]: p-value derived from a Chi-squared test.

Table 13. – Comparison of hazard ratios (HRs) for patients with ⩾60 days (n=1405), ⩾90 days (n=1685), or ⩾180 days (n=1162) of drug exposure

Variable	⩾60 days drug exposure[#]		⩾90 days drug exposure		⩾180 days drug exposure	
	HR	p-value[¶]	HR	p-value[¶]	HR	p-value[¶]
HMO 1 member			1.412	0.0315	1.039	0.8371
ICS	0.680	0.0074	0.594	0.0001	0.562	0.0003
Long-acting β-agonists	0.598	0.0516	0.546	0.0154	0.432	0.0084
ICS plus long-acting β-agonists	0.408	0.0003	0.344	<0.0001	0.253	0.0002
57–65 yrs	3.635	0.0343	1.903	0.0610	1.624	0.2095
66-72 yrs	3.891	0.0229	2.145	0.0223	1.870	0.0981
>72 yrs	8.040	0.0004	4.336	<0.0001	4.112	<0.0001
Male	1.000	0.9980	1.092	0.4594	1.338	0.0490
3–19 COPD outpatient encounters in year prior to exposure	1.742	0.0015	2.072	<0.0001	2.031	0.0033
⩾20 COPD outpatient encounters in year prior to exposure	2.988	<0.0001	3.380	<0.0001	2.918	<0.0001
⩾1 COPD emergency dept encounter in year prior to exposure	2.386	0.0011	1.282	0.2516	1.210	0.4482
⩾2 COPD hospitalisations in year prior to exposure	1.448	0.1349	1.348	0.1667	1.321	0.2356
⩾1 Respiratory hospitalisation in year prior to exposure	1.327	0.1397	1.106	0.5725	1.302	0.1932
⩾2 Asthma outpatient encounters in year prior to exposure.	0.649	0.0227	0.672	0.0138	0.900	0.5876
⩾1 Asthma emergency dept encounter in year prior to exposure	0.803	0.7659	0.997	0.9949	0.927	0.8762
⩾1 Asthma hospitalisation in year prior to exposure	0.850	0.6185	0.970	0.9153	1.060	0.8664
Charlson score ⩾1 based on hospitalisations in year prior to exposure	1.173	0.4180	1.264	0.2115	1.999	0.9983
Charlson score ⩾1 based on outpatient encounters in year prior to exposure	1.258	0.0948	1.122	0.3881	1.038	0.8235

HMO: health maintenance organisation; ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease. [#]: Lovelace HMO only, includes patients not in original study. [¶]: p-value derived from a Chi-squared test.

model. In any case, the survival benefit observed for ICS and salmeterol use does not appear to be significantly confounded by differences in smoking behaviour.

The other major confounding issue of interest is that of the presence of comorbid conditions. Comorbid illnesses could affect a physician's decision about whether or not to prescribe an ICS or salmeterol. For example, a physician may be reluctant to prescribe an ICS to a COPD patient who also has diabetes, or prescribe salmeterol to a COPD patient who also has arrhythmias. The SIN and TU [121] study described a significantly higher prevalence of comorbid conditions in the non-ICS-treated group, although the difference was small and probably not clinically relevant.

Comorbid illnesses were adjusted for using the Deyo modification of the Charlson Index. One limitation of this method is that the Charlson Index was validated on a hospitalised

population, thus its validity when used on an outpatient population is uncertain. This problem was addressed by calculating Charlson Index scores based on inpatient and outpatient codes separately, then including both in the model.

The Charlson Index was not a significant independent factor in the models unless the exposure criterion was cut to 60 days, and that is only seen in the outpatient score. This suggests that comorbidities are more likely to be responsible for the early deaths and that it is very reasonable to have a 90-day exposure requirement to eliminate any bias that may be introduced by other serious illnesses.

Interpretation

In many retrospective or cross-sectional surveys, the epidemiologist′s challenge is to eliminate or adjust for systematic biases so that an exposure/disease relationship can be seen. Even with comprehensive population-based longitudinal data, such as that found in the LHP and KP-GA databases, the problems are often overwhelming, and large numbers of cases are needed to overcome signal variability. In examining the relationship between ICS and salmeterol use and survival in COPD, the starting point was a very strong unadjusted association, and the major potential sources of bias that could explain this relationship were examined. After adjusting for all of these factors, the relationship remains, and in some ways is even stronger. Owing to the limitations of this database and the analysis methods, the study cannot "prove" a causal relationship between ICS use, with or without salmeterol, and survival in COPD. Nevertheless, the strength of the relationship, the robustness of the findings, the similarities between the results and those of studies from other countries, and the similarities in these findings and those of randomised clinical trials suggest that this is a true relationship. Hopefully, the data from current randomised clinical trials, coupled with a better understanding of the inflammatory mechanisms in COPD, will resolve this question in the near future.

Discussion

WEISS: To bring up the patient care issue, I would like to present data from the US Veterans Administration dataset, which is a very stable cohort of patients with a high prevalence of COPD. We looked at patients with COPD as a primary outpatient visit and ended up with a dataset of 100,000 patients. We found that the mean number of days that patients went from hospitalisation to hospitalisation without any intervention by a physician visit was 71 days. That is terrible care. Is the health system watching over them during that time period? Are we looking too narrowly at outcomes? It is important to think about not just one drug stopping those events, but instead, a whole cascade of care activities happening or not happening to that patient that may, in fact, be more likely driving what that outcome is.

DAVIS: This analysis looked at mortality. Confounding by indication is a problem, but in this case we are seeing the reverse pattern in that you would assume that those taking ICS would be the sicker patients.

WEISS: We do not know that. We have not delved into the care patterns enough to know who these people are and why they are not getting the drugs. Maybe they are healthy or maybe they are terminal, that is the piece we do not understand. The problem remains about confounding by indication or by severity. What are the best measures of controlling for severity? I think that spirometry data will make the difference in the analysis. Although this study used some spirometry data, we do not really have a good way to work with spirometry in these databases, yet. These data can be very messy and it is not what you would see in a randomised controlled trial. For those of us who do not have spirometry data to work with, does the Charlson index help, especially if applied to outpatient data?

SIN: I think your spirometry data, particularly FEV_1, would help a lot, despite all the noise that could easily be put aside by the sheer power of the sample size. Secondly, Charlson is never used to control for severity, more for morbidities. Finally, in J. Bourbeau′s study [155], all indicators seem to show that patients diagnosed with COPD and who are receiving ICS have greater severity of disease, not less. I think that empiric evidence suggests that confounding by indication, while we cannot fully explain that away, is unlikely to whittle away the differences.

WEISS: It is just one study and in just one population. We need more studies.

ERNST: With regard to the confounding by severity issue, I think there are differences between patients in the reference groups in this study. There are those who are getting short-acting bronchodilators and who are being treated according to the usual care of 5 or 10 yrs ago *versus* those patients who are now getting combination therapy, which may be usual care for 2005. I think there are differences in the practice patterns of physicians prescribing these different medications and I think there are differences in their patient populations.

VIEGI: It is surprising to see that smoking does not affect survival.

MAPEL: Smoking activity between the treatment groups was the same. So, in this study it does not explain the difference in survival. Also, how do you include a term for current or exsmoking? That is problematic because even in a chart abstraction, it is poorly reported, so how will you classify it? Perhaps, if we had a larger population it would have made a difference. But for this analysis, the differences in smoking behaviour do not explain survival benefit.

SORIANO: G. Viegi′s point is very important. Others have explained the paradoxical effect of smoking in COPD patients in clinical trials. When COPD patients quit smoking, they die more frequently. The reason is that if you are a long-term smoker, you will only quit your addiction when you have a life-threatening event.

SUISSA: In this study, the group with the combined medications has a shorter follow-up, ~1,000 days. The reference group has 1,800 days. I suspect this is because to enter the group with two drugs, you have to have first survived that period. Is it possible that this period of immortal time that was excluded outright should be considered and perhaps classified in either the ICS only, long-acting β-agonist only, or the unexposed group? The short follow-up is a clear indicator that there could have been substantial immortal time before then.

To understand this, let us say that someone starts 90 days of short-acting bronchodilator and then 2 yrs later they actually start long-acting β-agonist and ICS at the same time. There is a 2-yr period where nothing happened until they received their dual medications. At that point, they get classified in the double-drug group. Let us assume that they had died before they received this dual therapy. Where would they have been classified? In the reference short-acting bronchodilator group. But, because they did not die and they made it to the point where they could receive two medications, immortal time has been created, and this patient will now be classified into the combined treatment groups. Therefore, by excluding such immortal time from the reference exposure group, we overestimate the rate of death in the reference short-acting bronchodilator group and that creates a drop in its survival curve.

SIN: I would be a bit concerned about that patient who

suddenly got 90 days of the combination towards the end. There is probably a reason why it was prescribed. It may suggest a worsening of the condition.

ERNST: I think the effect is independent of a confounding by indication. I think all that time before the combination therapy is dispensed is counted in the wrong group.

SORIANO: Yes, but the patient is older.

SUISSA: As a matter of fact, because of these confounding issues, *i.e.* the patients are older and they are getting worse, we would have expected the graph to be reversed. The ones getting both drugs are presented as having a worse prognosis than the ones getting one. We are not seeing this either crudely or after adjustments for age and severity. Therefore, I believe that the unaccounted immortal time issue is causing the bias we discussed.

MAPEL: What gets confusing is when you look at the combination group. They are different patients. They are ~4–5 yrs younger. There is additional time that is required to get that dual exposure. If we started from the very first day they got a prescription and we did not throw anybody out who died early, it would end up looking the same.

ERNST: But you would still have the time before they got there to worry about. You are making the problem smaller but it is still there in this type of analysis.

WEISS: It is the cohort analysis that is limiting. The case control may allow you more flexibility.

The USA PharMetrics Experience in COPD: hospitalisation risk and COPD medication

T. McLaughlin

Summary

The hospitalisation risk of various initial treatment regimens for chronic obstructive pulmonary disease was compared using the PharMetrics Integrated Outcomes Database® in a retrospective observational cohort study (n=4,038). Patients treated with inhaled corticosteroids (ICS) and salmeterol had the greatest hospitalisation risk reduction (74%, hazard ratio (HR) 0.26, 95% confidence interval (CI) 0.14–0.46) followed by patients treated with ICS and ipratropium (IPR) (45%, HR 0.55, 95% CI 0.41–0.74) and those treated with ICS (29%, HR 0.71, 95% CI 0.61–0.82). This benefit remained after excluding patients with concomitant asthma in all the cohorts except the ICS plus IPR cohort (HR 0.72, 95% CI 0.49–1.05).

Introduction

The objective of this study was to compare the hospitalisation risk of various initial treatment regimens for chronic obstructive pulmonary disease (COPD) in a retrospective observational cohort study. The PharMetrics Integrated Outcomes Database® was used for this analysis. This database consists of administrative claims data from enrollees of >20 large, managed, care plans across the USA and is representative of a commercially insured population. All covered medical claims (inpatient, outpatient, pharmacy) are captured for enrollees during the study period. Data were available for January 1997 to December 2000. The results of this analysis were presented at the American College of Chest Physicians' 2002 Annual Meeting in San Diego, CA, USA.

Methods

Inclusion/exclusion criteria

Patients of ⩾45 yrs of age enrolled in one of 24 different managed care plans across the USA during 1998–1999 with a primary diagnosis of COPD (International Classification of Diseases, ninth revision clinical modification 491, 492, 496 were identified). Study patients were required to have ⩾24 months of continuous enrolment centred on the index prescription claim for one of the following: ipratropium (IPR) or IPR plus albuterol fixed combination, salmeterol, or inhaled corticosteroid (ICS).

Study design

Five therapy cohorts were identified: IPR, salmeterol, ICS, ICS plus IPR, and ICS plus salmeterol based on medication utilisation within the first 60 days following the index date. Patients were excluded from the analysis if they received other treatments for COPD including cromolyn, theophylline and leukotriene-modifying agents, 12 months prior to their initial prescription.

Statistical analysis

Cox proportional hazard analysis comparing all the cohorts to the IPR cohort was performed, investigating the time to first COPD hospitalisation adjusting for age, sex, concomitant asthma and other respiratory disorders, previous hospitalisation, managed care plan, baseline oral steroid use and physician specialty.

Results

Of 4,038 patients identified, 1,975 (48%) were on IPR, 1,122 (27%) were on ICS, 416 (10%) were on ICS plus IPR, 291 (7%) were on salmeterol and 234 (6%) were on ICS plus salmeterol. Compared with IPR, all other treatment cohorts had a lower risk of COPD hospitalisation during the study period, except for salmeterol (hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.59–1.13). Patients treated with ICS had a 29% lower risk of hospitalisation (HR 0.71, 95% CI 0.61–0.82), ICS plus IPR patients had a 45% lower risk (HR 0.55, 95% CI 0.41–0.74), while ICS plus salmeterol was better with a 74% risk reduction (HR 0.26, 95% CI 0.14–0.46). This benefit remained after excluding patients with concomitant asthma in all the cohorts except the ICS plus IPR cohort (HR 0.72, 95% CI 0.49–1.05).

Interpretation

The results of this analysis suggest that initial treatment with ICS, alone or in combination with salmeterol, compared with IPR, was associated with a significant decrease in the risk of COPD hospitalisation during the first 12 months of initial therapy independent of concomitant asthma diagnosis. The combination of ICS plus salmeterol, as an initial treatment for

COPD, was associated with the greatest decrease in risk, suggesting that further work should focus on this combination to confirm these findings.

Discussion

PRICE: I think the outcomes we have been using, hospitalisations and deaths, may not be the best way forward if we are going to try to answer some of these questions of potential confounders. I would like to put to rest the issue of misdiagnosis and underdiagnosis of COPD. We are conducting a study in the UK in one general practice centre (12,000 patients), in patients of >50 yrs who are on respiratory medications. We compared diagnoses before and after formal spirometric assessment. The pre-diagnosis of asthma dropped substantially and the pre-diagnosis of COPD increased dramatically.

In another large database (43,000 patients), patients diagnosed with respiratory disease underwent spirometry and reversibility and were subsequently relabelled based on this information. We found that a substantial number of patients got relabelled as COPD patients, but very few patients got relabelled with asthma.

Also, we are getting a consistent theme that patients are clear about when they need to see a physician about their COPD. The decision for hospitalisation is really about seeing a doctor they do not know. That worries me about using hospitalisation as an outcome because we have lots of variables inputting into that, including the patient, the doctor, and the system. The decision to see the physician is more about the patient and less about the physician and the system. I would argue that healthcare consultations for COPD may be actually a stronger outcome to use. There is also a lot more of them, which will increase power and you can compare them before exposure.

Another potential confounding issue is age. In the Glenfield database, there were few individuals <60 yrs who fit into the Global Initiative for Chronic Obstructive Lung Disease 2 or 3 severity category. I think it is important that patients of <60 yrs be examined separately in these administrative databases. No one has given me a plausible reason why we are preventing hospitalisation and deaths using ICS and long-acting β-agonists in those younger patients if their COPD is unlikely to be severe.

HAGAN: I would like to challenge D. Price′s paradigm on age. Of COPD patients who have a hospitalisation, 25% are dead in the next year and 2–3 die in the next 3 yrs. The benefit of using ICS is to reduce exacerbations, which drive deterioration of lung function and health status leading to hospitalisation. So if there is a benefit with ICS, they must be introduced early. So the opposite of what you are saying may be true. Younger patients would benefit most from ICS.

PRICE: In terms of exacerbation, if you are arguing for using these drugs in an earlier stage of the disease, then we need to be using outcomes that are actually going to show a difference.

SORIANO: I would also like to challenge the statement that "We cannot diagnose or use any individual with COPD before the age of 60." From a public health point of view, we are seeing younger patients with COPD. If you screen for COPD in younger patients and get a smoker to quit smoking early in life, you will change the natural history of COPD in that patient.

PRICE: But, when we are trying to understand the databases, I think we actually have a lot more asthma in the databases. We just have to do stratified analyses and we should be suspicious about the data we see in the younger age groups.

One of the major struggles that we are having as a group is that we are not sure whether our datasets are truly comparable. I would like to find an outcome that we could compare with pre-exposure. By looking at hospitalisation and deaths, we are making it almost impossible to compare.

WEISS: I agree that it would be nice to walk forward from mortality and hospitalisation and into a more detailed look at care. That could be exacerbations, at least by some definition that we would create. We were saying earlier that all-cause mortality made sense because half of COPD-related deaths are cardiovascular events. D.D. Sin was also hinting that he is looking into how well ICS may prevent cardiovascular deaths. What are we proposing that the ICS are doing for the other half of deaths? What is going on with these ICS that may be life-saving? Are they preventing respiratory failure or pneumonias? I think we need to look at those questions because if we are thinking that these are the outcomes, we better have some mechanistic way of linking exposure to outcome.

SULLIVAN: What is it about combination therapy from a mechanistic standpoint that makes it better than salmeterol or ICS alone?

SORIANO: Looking at the survival curves for these data, I am not convinced that the combination treatment with IPR and ICS is significant. However, I am pretty convinced that the addition of salmeterol is very significant. As we have heard, it is possible that this could be due to a design issue, that the use of two drugs could be expanding and biasing the effect. However, it should be noted that there is molecular research that shows complementary mechanisms of action between long-acting β-agonists and ICS.

ERNST: Part of why the combination of IPR is very different from that of salmeterol is that the IPR group is likely a very different population that marks a group of older people with COPD. It is a much more COPD-specific drug.

FABBRI: If you are thinking about mechanism and start speculating about the interactions between COPD and cardiovascular pathophysiology, you have to be careful before translating a molecular interaction into a clinically relevant effect. I have shown you the results of several clinical trials demonstrating an almost identical effect on moderate and/or severe exacerbations of drugs with completely different mechanisms of action, for example, long-acting β_2-agonists, anticholinergics, and ICS.

VIEGI: In the last 10 yrs, there has been a lot of information about air pollution studies and fine particles. They have prompted a series of studies on the mechanisms involved. Those who die from air pollution are the sick and the elderly. These particles are proinflammatory agents that give rise to a cascade of inflammatory cytokines that have an important effect on cardiac arrhythmias. This type of research may be useful in understanding the results of the study on the beneficial effect of ICS and long-acting β-agonists from a mechanistic point of view.

SULLIVAN: I would like to discuss this issue of treatment concomitance and exposure. There is a window defined within, which needs to have the presence of two of the combination products to define combination exposure. But, there is never any evaluation downstream about whether the patient continues on both medications. Is it truly concomitant consumption or just an overlap of two prescriptions?

McLAUGHLIN: That is a limitation of this study design. The solution is that we would have to follow all patients for a longer period of time and ensure that they are adherent to medications.

ERNST: Another solution is to change the study design. If you can use a nested case-control approach, you can see the

pattern of exposure in relationship to the events of interest. We did this for asthma years ago showing that it was not the number of prescriptions of β-agonists that was associated with adverse outcomes, but rather the pattern of use. There are all sorts of ways of doing this if you are willing to give up the classic design.

McLAUGHLIN: Would the nested case-control answer S. Sullivan′s question about true concomitant use?

ERNST: You can look over the last year and define regularity of use in both products and then you can compare with another group of compliant patients, if you want. Starting from the event and going back to the exposure allows you to do all those things without creating immortal time. When you try to do those things in the proportional hazard model, you are adding immortal time as you are waiting for these things to happen.

SUISSA: It is important to note that to be able to receive these two medications, the patient needs to survive at most 60 days. That 60-day period is crucial and appears to impact on the analysis, if you look at the early part of the survival curves. The subjects with the full 60-day period had zero events during that time. That is what defined them into coming into the study, whereas the others are allowed to have events during that time period. That may explain the large discrepancy at the beginning of follow-up and would be important to report.

McLAUGHLIN: We actually did exclude all patients who had an event within the first 60 days and the results were similar.

SIN: L. Goldman recommends the use of propensity scores for large datasets with lots of variables to adjust for residual compounding. None of these studies used propensity adjustment. What does the group think about using propensity scores to further adjust for various confounding factors and should epidemiologists mandate propensity scores for future studies that use observational data?

SUISSA: It would not help at all in our context. There is little difference between adjusting for the many variables that were adjusted for in all of these studies and adjustment by propensity score measures. Propensity scores were designed specifically for studies that have small numbers of subjects (*e.g.* 150 subjects) and where there are many potential confounding variables. With studies using these large databases, propensity scores would not be helpful.

The Integrated Primary Care Information Experience in COPD in the Netherlands

M.C.J.M. Sturkenboom

Summary

Using an intent-to-treat analysis approach, a retrospective study (n=1,096) compared the survival rates of treatment with salmeterol, fluticasone, fluticasone plus salmeterol, and a reference group utilising data from the Integrated Primary Care Information database in the Netherlands, a longitudinal observational database consisting of computer-based patient records of >150 general practitioners in the Netherlands. Treatment with salmeterol plus fluticasone (adjusted risk ratio (RRadj) 0.37, 95% confidence interval (CI) 0.21–0.67) or fluticasone alone (RRadj 0.34, 95% CI 0.18–0.66) resulted in significant survival advantage compared with the reference group alone. This result did not change in a series of sensitivity analyses that aimed to study the effect of quality care, disease misclassification, or exposure misclassification.

Introduction

The Dutch system of healthcare is based on general practitioners (GPs) who practice in the community but not in the hospital, referring ambulatory patients to specialists for outpatient or inpatient care. Specialists report their findings to the GP, who acts as a gatekeeper. Approximately 90% of the patients′ presenting problems are addressed by the GP. Full-time staff physicians who are specialists of various kinds provide hospital care. Medical care, including prescription drugs, is essentially paid for by a combination of public and private insurers. The public insurers are regional agencies collectively called the Sickfunds. They provide insurance coverage for 60% of the population, *i.e.* generally those who fall below an annual income level (€25,000). A flat fee per year reimburses the GP for Sickfund patients; for privately insured patients the GP is reimbursed on a fee for service basis. Patients should be registered with one GP but are free to change, which happens infrequently and nearly always because the patient moves out of the area. When a patient transfers, so does the record. More than 75% of the patients will visit their GP at least once a year [156].

The Dutch hypothesis has claimed for several years that asthma and chronic obstructive pulmonary disease (COPD) were obstructive lung diseases with a similar origin and recommended that these diseases be called chronic nonspecific lung disease (CARA) [157]. Therefore, many GPs have diagnosed patients with CARA without specifying asthma or COPD in the past. Starting from the second half of the 1990s, GPs began distinguishing COPD and asthma but the change in habit has been slow. The Dutch hypothesis is problematic for the retrospective identification of COPD patients and requires specific identification and validation algorithms.

The Dutch GPs′ treatment guidelines for COPD recommend smoking cessation as a first intervention [158]. Pharmacological treatment should start with short-acting bronchodilators (such as an anticholinergic or short-acting β_2-agonists such as salbutamol, terbutaline, or fenoterol). If effectiveness is not satisfactory after 2 weeks, a change of bronchodilator should be considered. If the second is not effective, both bronchodilators should be given together. If use of short-acting bronchodilators is not effective in ameliorating nightly dyspnoea, a long-acting β-agonist should be prescribed. In case of insufficient effect, the addition of xanthine derivatives should be considered, which is usually limited to severe cases. Initiation of xanthines should be performed by a pulmonary physician. The use of inhaled corticosteroids (ICS) or acetylcysteine is not generally recommended and inhalational steroids should be reserved for patients with an atopic constitution or patients with >3 exacerbations per year.

The type of care and the referral of patients to specialists are based on the severity (classified by European Respiratory Society criteria) of COPD, level of dyspnoea, diagnostic problems, and the effectiveness in controlling the disease. Patients should be referred to a specialist in the following

circumstances: 1) COPD is suspected in subjects <50 yrs of age; 2) doubt about COPD or heart failure as the origin of worsening dyspnoea; 3) forced expiratory volume in one second <50%; 4) progressive worsening under maximum treatment; 5) unintended loss of weight; 6) >2 exacerbations per year; and 7) an indication for oxygen therapy (long-term oxygen therapy).

The GP receives letters from the specialist that report on the findings and undertaken actions. Specialists often issue prescriptions that are not registered by the GP but which will be repeated by the GP. These (first) specialist prescriptions may go unnoticed in a database that is based on GP records.

In the Netherlands, the "healthy" elderly may transfer to homes for the elderly, in which they remain rather independent and keep their own GP. If they become ill, care-dependent patients are transferred to nursing homes where they receive care from an internal physician. This feature of Dutch healthcare may lead to the loss of patients in the end stage of life, particularly those who are chronically ill. If a patients' registration with the GP is (erroneously) not terminated upon transfer to a nursing home, the occurrence of death may be missed or the date of death may be reported with a delay.

Methods

Database

A retrospective study was conducted that utilised data from the Integrated Primary Care Information (IPCI) database in the Netherlands, a longitudinal observational database, with data from computer-based patient records of >150 GPs in the Netherlands.

In 1992, the IPCI was started by the Department of Medical Informatics of the Erasmus University Medical School (MIEUR), Rotterdam, initially in collaboration with IMS but independently from 1999 onwards. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs throughout the Netherlands that voluntarily chose to supply data to the database [159]. Practitioners control usage of their data and only receive a minimal reimbursement. The collaborating GPs are comparable with other Dutch GPs regarding age and sex.

As of December 2002, there are 93 active practices belonging to 118 GPs that are providing ongoing data to the database. The first practice was recruited into the IPCI project in 1994. Practices have therefore been supplying data for varying periods of time. The database now contains information on 485,000 patients. This is the cumulative number of patients who have been part of the dynamic cohort of registered patients. Turnover occurs as patients move and transfer to new practices. The records of "transferred out" patients remain on the database and are available for retrospective study with the appropriate time periods. As of December 2002 there were >370,000 active patients registered with the collaborating GPs, 49.1% were male, 57% were insured through the Sickfund, and the mean±SD age was 37.7±21.9 yrs. On average, patients were only 1 yr younger than the average of the Dutch population in 2001. In addition, the percentage of persons insured through private insurance was higher than the Dutch average.

The database contains identification information (date of birth, sex, patient identification, insurance, date of registration and transferring out, date of death), notes (subjective and assessment text), prescriptions, and indications for therapy, physical findings, referrals, hospitalisations, and laboratory values, which have been stored directly onto computer. MIEUR has implemented a research-specific module in the software that requires linkage of an indication to each prescription. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text that is available as raw data [160]. Prescription data such as product name, quantity dispensed, dosage regimens, strength, and indication are entered into the computer to produce printed prescriptions [159]. The National Database of drugs, maintained by the Z-index, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the World Health Organization [161].

Data are downloaded on a monthly basis and the information is sent to the gatekeeper who ensures all information is anonymous before further access is provided. Access to original medical records (discharge letters of hospitals) and administration of questionnaires to GPs is possible through the gatekeeper after approval of the Steering Committee.

Data accumulated in the IPCI database have proven to be of high quality and suitable for epidemiological and pharmacoepidemiological research [159].

Study population and follow-up

For comparison of mortality between patients treated with fluticasone, salmeterol, or other bronchodilators, the population comprised all persons >50 yrs of age newly diagnosed with COPD who had received at least two prescriptions of salmeterol, or at least two prescriptions of a short-acting β-agonist, xanthines, anticholinergics, or combined bronchodilators, but had not used ICS or long-acting β-agonists since diagnosis with COPD. Patients were excluded if they had <6 months of follow-up. In a sensitivity analysis, patients with <6 months of follow-up were included.

Identification and definition of chronic obstructive pulmonary disease

All subjects who had a potential diagnosis of COPD were identified by an automated database search on ICPC-coded diagnoses (ICPC codes R91 and R95), markers (CARA, COPD) and string searches that included the words: "CARA", "bronchitis", "COPD", "obstructive" "lung disease" and "emphysema", "R91", and "R95".

In a second step, all records with denials of COPD (such as no COPD, COPD-) and records that indicated acute bronchitis or bronchiectasis were excluded. In a third step, a manual review of the records that included words such as family, father, mother, brother, *etc.* was conducted. All records that suggested COPD in a family member rather than the patient, and all records that did not clearly indicate the existence of COPD, chronic bronchitis, emphysema, or obstructive lung disease were excluded. Subsequently, patients were classified as having a diagnosis of COPD or not. Patients without any record of COPD but instead one indicating CARA, were classified as COPD if they were >45 yrs of age, if they were <45 yrs of age they were considered asthmatics. The first record consistent with COPD was used as the index date (onset of COPD).

To conduct sensitivity analyses, COPD patients were further divided into probable or possible categories. Since all COPD patients should be treated with bronchodilators (according to the recommendations), all possible COPD patients who had not been diagnosed by a lung physician and

had no prescription for any type of bronchodilator were excluded.

Cases were classified as "probable" COPD if the medical record comprised a coded diagnosis of COPD or chronic bronchitis (R91, R95), or a specialist-based diagnosis of COPD (COPD diagnosis mentioned in specialist letter) and if they received at least one prescription for a bronchodilating drug (β-agonists, anticholinergics) or xanthine derivative (ATC: R03AC, R03AH, R03AK, R03BB, R03C, R03DA).

Subjects were classified as "possible" COPD if a specialist letter mentioned COPD, emphysema, or chronic obstructive lung disease but they had no GP prescription of a bronchodilator or xanthine derivative (these could be patients treated only by the lung physician). If patients had a mention of COPD but no specialist diagnosis and no use of bronchodilators, the patient was not considered a COPD patient.

Deaths

Death and the date of death were identified by looking at the population file that included the date of death, and by a search in the patient medical record on the terms "dead", "death", "died". A manual review was conducted to validate the occurrence of death in the person at stake and the date of death.

Exposure to drugs

In line with an earlier study conducted in the General Practice Research Database, similar criteria to classify drug exposure were applied [141]. Basically an intention-to-treat approach was used, which had an additional advantage in this setting since it reduces the problem of exposure misclassification due to prescriptions written by a specialist. In the exposure groups all persons needed to be newly diagnosed with COPD and $\geqslant$50 yrs of age and treated with at least two bronchodilators (short-acting β-agonists, anticholinergics, xanthines or combined bronchodilators). Within this group of COPD persons regularly treated with bronchodilators, the following groups of patients were distinguished. 1) Reference: patients who never had a long-acting β-agonist (salmeterol/formoterol:R03AC12/R03AC13/R03AK06/R03AK07) and never had an ICS (R03BA). Start of follow-up was identified as the first prescription of bronchodilators after COPD diagnosis and the end of follow-up was death, transferring out or last data draw down, whichever date was earliest. 2) Salmeterol-only group: patients with at least two prescriptions for salmeterol and one or less than one prescription for fluticasone. 3) Salmeterol plus fluticasone: all patients with at least two prescriptions for salmeterol and at least one overlapping prescription for fluticasone. 4) Fluticasone-only group: all patients without use of long-acting β-agonists and at least two prescriptions for fluticasone.

Start of follow-up was defined as the first prescription of salmeterol after COPD diagnosis among persons who used salmeterol alone, the latest of salmeterol or fluticasone among persons with the combination treatment (although 75% of salmeterol and fluticasone combined prescriptions were single dose units), and as the first fluticasone prescriptions in those persons who were part of the fluticasone group.

Covariates

For the overall mortality study in COPD patients *versus* non-COPD patients, the (modified) chronic comorbidity score was assessed over 1 yr prior to the index date. For the treatment mortality study, the chronic disease score in the 1 yr prior to the index date, respiratory treatment in the 6 months prior to the index date, year of diagnosis, duration of COPD prior to entry, presence of asthma in the patients' history, the severity of COPD, and the number of GP visits in the 6 months prior to the index date, referrals to a lung physician, and the use of oral corticosteroids during follow-up were all assessed.

Severity of chronic obstructive pulmonary disease

All patients were considered to have at least moderate-to-severe COPD in the treatment mortality study, since criteria for entry required at least regular treatment with bronchodilators. Patients were considered to suffer from severe COPD at baseline if they used oxygen therapy or nebulised therapy prior to baseline, if they were judged by the physician to have severe COPD (obtained from clinical notes), or if they had more than two prescriptions for antibiotics indicated for respiratory tract infections in the 6 months prior to baseline.

Statistical analysis

Standard survival analyses (Kaplan Meier) and Cox proportional hazards were conducted to compare survival between treatment groups assuming an intention-to-treat analysis and considering the persons without long-acting β-agonists and ICS as the reference group. Patients were only included if they had a follow-up of at least 6 months after entry, since treatment effects may not be expected directly after start of treatment. The survival was defined as the time period from 6 months after entry until the time of death. Follow-up time was censored at 3 yrs. Cox proportional hazard estimates were calculated by adjusting for all covariates that were univariately associated with mortality ($p<0.10$)

Results

A total of 1,096 newly diagnosed COPD patients were eligible for entry in the study as they met the inclusion criteria and had >6 months of follow-up after entry. The reference cohort comprised 371 persons, the salmeterol-only group (n=109), the salmeterol/fluticasone group (n=433) and the fluticasone-only group (n=179). Most of the persons in the combination group used the single unit combination (seretide). The reference group comprised fewer females and was older, but less frequently suffered from severe COPD compared with the index cohorts. In addition, the reference cohort suffered slightly less from other chronic comorbidities (NS) and had a diagnosis of asthma less often in their history. Regarding respiratory treatment in the 6 months prior to baseline, the reference group had significantly lower use of ICS, short-acting β_2-agonist, oral steroids, mucolytics and combined products. The GP contact rate was equal between the groups but the reference group had been referred to a specialist less frequently (statistically significant), which is an indicator of lower severity.

Treatment with salmeterol and fluticasone (adjusted risk ratio (RRadj) 0.37, 95% confidence interval (CI) 0.21–0.67) or fluticasone alone (RRadj 0.34, 95% CI 0.18–0.66) resulted in significant survival advantage compared with the reference group alone. This result did not change in a series of sensitivity analyses that aimed to study the effect of quality care, disease misclassification or exposure misclassification.

Interpretation

Advantages

The advantages are the availability of indication (antibiotics and oral corticosteroids were considered only if they had a respiratory indication), the GP is gatekeeper and the IPCI database contains information on specialist diagnoses.

Disadvantages

The disadvantages are that there are no complete data on spirometry, smoking, and alcohol use; CARA diagnosis in the past complicates distinction between asthma and COPD; confounding by severity and inability to measure severity completely (however, the inability to adjust for severity would lead to results in the other direction and cannot explain the observed result); missing data on prescriptions from specialists; few patients on salmeterol alone; short follow-up; loss to follow-up for patients transferring to nursing homes.

Discussion

MAPEL: One of the challenges of trying to present this information is that you are presenting it to different audiences. Clinicians do not like hazard ratios. They like to see Kaplan Meier curves. "Gamblers understand risks, physicians understand ratios, but only epidemiologists and statisticians think they understand risk ratios." So in a pulmonary journal, how do I communicate this back to the practicing pulmonologist? That is one of the advantages of working with intention-to-treat analyses, because intuitively you can deal with that. It is a little more confusing to present time-dependent analyses. I agree that it should be done to double-check our validity, but the difficulty is in communicating this information to clinicians. You need to be able to show that graphically in a figure because looking at risk ratios are meaningless.

ERNST: Being a clinician, I think it is very easy to communicate the concept that patients who took drug A in the past year did well while patients who took drug B did not. To me that is more relevant. I want to know what caused my patient to die or end up in the hospital. I do that by taking a history and that is what the nested case-control analysis does. That is more intuitive to the clinician instead of these forced curves that look pretty but are all the same and no one quite understands them.

MAPEL: What if you adjusted for what happened before exposure?

ERNST: I want to know what has happened before the event. What is relevant is the time before that event. The randomised controlled trial paradigm that we are married to (the intention-to-treat analyses) does not allow you to do that.

WEISS: Perhaps the two greatest effect modifications in your model were the comorbidity scores and whether or not they had a pulmonary physician. There are primary care physicians who do not treat COPD well because they do not think there is a good way to treat it. When patients exacerbate, they send them to the hospital. Lung specialists are used to treating these patients and that probably has some effect on mortality. One simple way to look at this in your database would be to look at shared care *versus* exclusive primary care *versus* exclusive pulmonary care.

STURKENBOOM: The problem of not being able to identify prescriptions by lung physicians is one of the major reasons why I did not start out with a case-control study or a time-dependent analysis. If you do want to do an as-treated analysis, you need accurate data on treatment episodes. Regarding different care of persons who are treated by a lung physician, we are exploring that further.

Use of routine databases in health technology assessment: a policy maker′s perspective

R. Taylor

Summary

The role of observational studies *versus* that of randomised clinical trials (RCTs) in the assessment of a drug′s potential effectiveness is discussed. There are special circumstances in which the design of an observational database, rather than an RCT, would be desired. Decision analytical models and checklists for RCTs/observational studies can be used to assist policy makers in determining a drug′s efficacy and to assess the quality of database studies.

Introduction

The traditional skepticism held by policy makers towards observational evidence is neatly summed up by the following quotation from the late A. Cochrane, "Observational evidence is clearly better than opinion, but it is thoroughly unsatisfactory. All research on the effectiveness of therapy was in this unfortunate state until the early 1950s. The only exceptions were drugs whose effects on immediate mortality were so obvious that no trials were necessary, such as insulin, sulphonamide, and penicillin" [162].

It has long been recognised that observational designs may lead to the overestimation of a drug′s treatment effect. For example, SACKS *et al.* [163] examined the effect of anticoagulants on the mortality in myocardial infarction patients by comparing meta-analyses of observational (historical control) studies compared with randomised controlled trials (RCTs). Despite correcting for potential biases, the observational studies overestimated drug benefit more than three-fold, compared with the magnitude of drug benefit estimated by the RCTs. Therefore, when it comes to addressing the policy question of a drug′s potential effectiveness, the gold standard form of evidence is, and will continue to be, the RCT.

Nevertheless, there is growing recognition of the role of observational studies, and routine databases specifically, in assisting policy decisions about drug therapies. There will always be situations where undertaking an RCT is not possible, either for ethical or practical reasons. A nonexperimental or observational design will therefore, instead, need to be employed as an alternative. However, to conclude that the role of databases stops here would be to substantially underplay their potential value.

Policy makers, particularly at a local level (*e.g.* a hospital or

primary care trust), often want to know the potential service implications of the introduction of a new drug. For example, "What will be the uptake of the drug in practice? How adherent will patients be in taking the drug? What will be the impact on a healthcare budget?" Although addressed to some extent by RCTs, such questions can be better answered by routine databases.

There are a number of situations where efficacy and effectiveness cannot be fully addressed by the RCT. These include the assessment of treatments for rare outcomes (requiring prohibitively long follow-up), subgroup effects in specific patient groups (which an RCT is usually underpowered to assess), inability to consider all possible comparators, and the practical difficulty in assessing long-term outcomes [164]. Only by using information from routine databases can the findings of RCTs be effectively extended to address these additional important issues. Increasingly, decision analytical models are being used to provide a framework whereby the results of an RCT(s) and an observational study (or studies) can be combined to address the policy maker's question regarding a drug [165].

The focus of this workshop has been to discuss appropriate methodological approaches to ensure that routine databases provide reliable and robust conclusions. An important extension to this is the development of checklists that policy makers can easily apply to routine database studies to assess their quality. Although there are published checklists for RCTs and for a number of observational designs [166, 167], there is a lack of such instruments for routine databases. It is important that such checklists address not only the internal validity (*i.e.* the identification of biases) in routine databases, but also their external validity (*e.g.* how representative are the patients and clinicians covered by the database), and the quality of reporting (*e.g.* prestatement of study hypotheses).

To conclude, with the drive towards policy makers assessing the "real world" impact of drugs, there is likely to be an increased use of routine databases alongside RCTs. The future utility and success of such database evidence depends on a number of factors: 1) harmonisation of methods and reporting of database analyses; 2) the improved compatibility and linking of current information systems; and 3) the adequate resourcing and funding of database initiatives.

The TORCH study: towards a revolution in COPD health

G.W. Hagan

Summary

Some of the methodological concerns identified in the previously mentioned research on the efficiency of respiratory drugs in chronic obstructive pulmonary disease (COPD) are intrinsic by the observational nature of epidemiological research. A large randomised controlled trial is currently being conducted. This trial has been powered to demonstrate an effect of respiratory drugs on COPD survival if any. The design and methods of this trial are summarised below.

Methods

Post hoc analysis of data from the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study suggests a reduced mortality rate in chronic obstructive pulmonary disease (COPD) subjects randomised to fluticasone propionate (FP) compared with placebo during the 3 yrs postrandomisation [110, 168]. Although ISOLDE was not designed to investigate mortality, and therefore the study should be regarded as a pilot, the data provide a rationale on which to base a definitive mortality study. No prospective mortality data are available for subjects treated with salmeterol either. However, it can be hypothesised that the properties of salmeterol, particularly its cytoprotective effects, and hence its potential to reduce infective exacerbations, could have a significant impact on subject survival. If this is the case, there could be, at least, an additive effect of salmeterol and FP in reducing mortality in subjects with COPD. Therefore, the objectives of the Towards a Revolution in COPD Health (TORCH) study are to investigate the long-term effects of the salmeterol/FP combination product at a strength of 50/500 μg twice daily compared with salmeterol 50 μg twice daily alone and FP 500 μg twice daily alone, on survival of COPD subjects over 3 yrs of treatment. The primary efficacy of endpoint is all-cause mortality. Secondary efficacy end-points include rate of severe or moderate COPD exacerbations and quality of life assessed by the St George's Respiratory Questionnaire.

TORCH is a multicentre, randomised, double-blind, parallel-group, placebo-controlled study conducted wordwide. Inclusion criteria are as follows: male or female outpatients aged 40–80 yrs with a baseline forced expiratory volume in one second (FEV_1) of <60% of predicted normal, an established clinical history of COPD (per European Respiratory Society consensus statement), current or exsmokers with a smoking history of ⩾10 pack-yrs, poor reversibility of airflow obstruction defined as <10% increase in FEV_1 as a percentage of normal predicted, 30 min after inhalation of 400 μg salbutamol *via* metered dose inhaler and spacer, and baseline FEV_1/forced vital capacity ratio ⩽70%. With ~6,000 patients randomised, TORCH should have sufficient sample size to determine whether FP, alone or in combination with salmeterol, has an effect in survival in COPD patients treated during 3 yrs. The first results are expected around 2006.

Future perspectives

Discussion

SUISSA: The issue of immortal time bias is fundamental to all the studies presented. We have seen in these studies three different types of designs. In the SIN and TU approach [121], there is clearly a problem of misclassified exposure before the subject actually starts to be exposed, which is compounded by it being a period of immortal time. To better quantify the

proper rate ratio estimate, we should reclassify the patients into the correct exposure categories so that we can minimise the amount of bias from misclassification of exposure. With the approach that J.B. Soriano took with the General Practice Research Database, immortal time was dealt with by removing it rather than misclassifying it. This is an improvement, but I believe that immortal time must still be accounted for in the denominator of the reference group. In essence, we should be evaluating people at the beginning of the first of their treatments and not at the beginning of the treatment of interest because during that early excluded time, they had to have survived to get there. Somehow, that time has to be accounted for using time-dependent exposures either with Cox models or with the nested case-control approach.

The second issue is the relationship between exposure and outcome. In the cohort approach that emulates a randomised controlled trial, we have an exposure at baseline and we associate it with an outcome that occurs later. Somehow, we have to be able to make a solid link between the outcome that occurs 3 yrs later and a baseline exposure to the treatment that we are studying. For example, J.B. Soriano has presented data showing that patients who were exposed to long-acting β-agonists and inhaled corticosteroid (ICS) combination therapy continue to use this therapy throughout the follow-up. Another approach, the nested case-control approach that J. Bourbeau presented, associates the outcome with current exposure within a certain period of time close to the outcome under study.

I believe these two issues must be addressed before we can say that these studies have no bias in their estimates. I challenge those who have the data available, to return to the databases, reclassify the patients accordingly, and properly account for immortal time. When these new results can be presented to us, we may have more confidence in concluding that ICS are effective in preventing mortality and hospital readmission.

PRICE: Some combination of treatment and care is associated with different outcomes. We need to try and disentangle these two. One way is to think about our outcome variables so we can compare our outcomes in our different populations before and after. Where we may go with the observational work is to end up with two different grades of exacerbations, moderate (general practitioner consults) and severe (hospitalisation/deaths). We could use the moderate exacerbation as our way to compare our two groups before and after. Correcting for centres may be difficult because of the size of the numbers involved. We may look at the possibility of prospective rather than retrospective studies possibly using higher quality routinely recorded data.

WEISS: The issue may not be between centres, but, it may be more about the type of provider and the shared relationship between provider and patient. How much of that is correlated with the concept of severity? I have seen four different versions of severity presented here. How much should we push to get spirometry data entered into this discussion?

VOLLMER: When thinking about the intention-to-treat *versus* nested design, we need to remember that we have an exposure variable (medication status) that changes over time. We also need to think about how we control for severity, which gets back to the issue of overmatching.

WEISS: M.C.J.M. Sturkenboom raised the issue of coincident disease. In her analysis, heart disease and diabetes were discussed. We are beginning to ask questions about mental health and depression, since depression is a predictor of mortality and highly coincident with COPD. Perhaps we should be allowing ourselves to look at not just one disease, but, a cluster of diseases and how those clusters actually work over time.

BOURBEAU: We have been talking about pharmacological treatment, but we have not considered nonpharmacological treatment. There are issues such as education, self-management, and pulmonary rehabilitation that are recognised to be effective treatments. Our database does not collect everything we need. We need to join our database with a more clinical database and find a way to integrate the pharmacological and nonpharmacological treatments.

VIEGI: Since we already have data on younger patients (*i.e.* age >45 yrs, people who are still working), one of the potential outcomes could be reduction of absenteeism after proper management of disease. The other suggestion is to have an integration of industry and public health resources to manage this very important research.

BURNEY: It has always been true that experimental studies are good at saying what is true and observational studies are better at saying what is more important. Both of these have their relevance and interpreting one without the other is difficult.

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