Co-Morbidity in COPD: The Effects of Cardiovascular Drug Therapies

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Key Words

Bias • Cardiovascular disease • Chronic obstructive pulmonary disease • Immortal time • Statins

Abstract

Cardiovascular disease is a major co-morbidity in chronic obstructive pulmonary disease (COPD) patients and is a predictor of all-cause mortality. This paper reviews the study design and data analyses of observational studies of cardiovascular drug effects in patients with COPD and evaluates the potential for bias on the validity of their findings. Three recent observational studies of statin use in the setting of COPD show surprisingly high efficacy results which, by their magnitude, demand closer analysis. Such analysis reveals that immortal time and immeasurable time biases likely accounted for dramatic findings of reduced mortality with aggressive treatment for cardiovascular disease. After removing these sources of bias, the effects are mitigated or may disappear entirely. Investigation of methods and results in the statin studies reviewed in this article reveals significant bias that has skewed the results of these early studies. Correcting these methodological flaws with proper statistical analysis may attenuate or even eliminate these apparent benefits.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the USA and an important cause of hospitalization [1]. Cardiovascular disease (CVD) is a major co-morbidity in COPD patients and is a predictor of all-cause mortality [2]. Both diseases share common risk factors, such as smoking, advanced age, and decreased physical activity [3]. The hallmark features of COPD – chronic bronchitis and impaired lung function – have also been shown to predict ischemic heart disease [4, 5]. Because of the important inter-relation of the two conditions, the cardiovascular status of patients with COPD is starting to receive extensive attention, yet research into this issue is still scant.

An issue that has received much attention has been the role of medications for cardiovascular disease in COPD. Indeed, the strong interrelation between the two diseases suggests the need for aggressive treatment of CVD risks in patients with COPD. Recently, several observational

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studies have explored the efficacy of statins, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers to reduce overall cardiovascular risks, morbidity and mortality in patients with COPD. Increasingly, observational studies are conducted to evaluate long-term disease outcomes of medication use and are often structured in a manner similar to randomized controlled studies, using study cohorts and specific medical outcomes, minus the fact of randomization. While these studies can provide useful data on the effects of drugs used to treat co-morbid conditions, their approach to study design and data analysis can lead to bias.

In this paper, we review some of the epidemiological data on COPD and cardiovascular co-morbidity, and review the observational studies of cardiovascular drug effects that have been conducted to date. We discuss their study design and data analyses and evaluate the potential for bias to influence the validity of their findings.

COPD and Cardiovascular Co-Morbidity

In a recent study [3], Huiart et al. quantified cardiovascular morbidity and mortality in a population-based cohort of COPD patients in comparison with the general population. The study cohort was selected from the entire population of the Canadian province of Saskatchewan (1 million people), and included all 5,648 individuals who were newly-treated COPD patients aged 55 years or greater. At cohort entry, a large number of patients were being treated for some cardiovascular risk factors or had been previously hospitalized for CVD. The COPD cohort was followed for an average of 4.1 years for the outcomes of cardiac hospitalization and death. After controlling for the effects of age, gender and calendar year, subjects with COPD were reported to be hospitalized more frequently for CVD than the general population [standardized rate ratio (SRR) 1.89, 95% CI 1.83–1.94]. The study revealed that COPD patients were three times more likely to be hospitalized for heart failure than individuals in the general population (SRR 3.07, 95% CI 2.91–3.23). Additionally, CVD far exceeded COPD as the underlying cause of death (37.6 vs. 14.3%, respectively). Ischemic heart disease was the most common cause of CVD death, representing nearly half of all cardiovascular deaths. When compared with mortality data for the general Saskatchewan population, COPD patients experienced a nearly twofold increase in CVD deaths [standardized mortality ratio (SMR) 1.95, 95% CI 1.83–2.07], with heart failure accounting for the largest SMR (2.83, 95% CI 2.32–3.33).

Fig. 1. Death rates by type of CVD according to age. Reprinted with permission from [3].

Ischemic heart disease was shown to be the first cause of death across all age groups (fig. 1). Contrary to expectations, the death rates for COPD and CVD remained fairly consistent over time, and the gap between COPD and CVD mortality did not decrease. These findings highlight the importance of CVD in COPD patients. But whether the onset of COPD will eventually increase the incidence of heart disease and hasten heart failure is still unknown.

Another study, based on medical records of members of the Northern California Kaiser Permanente Medical Care Program, also reported on the relationship between COPD and the incidence of CVD hospitalization and mortality [6]. In this large cohort study, 45,966 patients over the age of 40 with COPD identified between 1996 and 1999 were compared with an equal number of plan members matched on age, gender and enrollment history, but without COPD. The cohort was followed for CVD outcomes that involved hospitalization or mortality. Unlike the Saskatchewan study, the Kaiser study excluded COPD patients who had prevalent CVD at baseline. Findings for the two studies, however, were similar. COPD was a predictor of CVD hospitalization [rate ratio (RR) 2.09, 95% CI 1.99–2.20] and mortality (RR 1.68, 95% CI 1.50–1.88) over an average follow-up time of nearly 3 years. Notably, younger patients (<65 years) and female patients had higher risks for these two outcomes than older and male patients.

Statin Studies: Immortal Time Bias

The first study to evaluate the effect of statins in COPD, conducted by Soyseth et al. [7], used a retrospective analysis of a cohort of 854 patients discharged from a Norwegian hospital between 2000 and 2003 following treatment for a COPD exacerbation. Patients were followed for up to 4 years from the date of hospital discharge until death or the end of observation. The median follow-up was 1.9 years, during which 40% of patients died. The study compared 118 patients who received a prescription for statins with 736 patients who did not. The resulting hazard ratio (HR) of death was 0.57 (95% CI 0.38–0.87) with statin treatment relative to no statin treatment. Mortality was also lower with inhaled corticosteroid (ICS) use (HR 0.73, 95% CI 0.57–0.94). Moreover, the combination of statin and ICS was associated with yet lower mortality (HR 0.39, 95% CI 0.57–0.94).

This study yields several surprising findings, the first being that any statin use was shown to prevent mortality for up to 4 years. The authors stated that they did not assess the continuity or quantity of prescriptions but simply reported on whether the patient had received a statin or not. Therefore, even a single prescription for a statin was defined as statin use and could be considered to be protective against mortality. Second, the study outcome was all-cause mortality as opposed to cardiovascular mortality. Given that statin use is associated with reduced cardiovascular mortality, an outcome of all-cause mortality includes causes of death not known to be directly related to statin treatment. Third, ICS were reported to yield a 27% reduction in all-cause mortality, an effect that contradicts the findings of the TORCH randomized controlled trial. Fourth, the study reported that statins given concomitantly with ICS reduced all-cause mortality by over 60%. These findings are so dramatic that they may appear to be too good to be true, warranting a closer examination of the study methodology.

An investigation of the methods revealed a significant source of immortal time bias. This bias was initially identified in studies of drug treatments for COPD and allergic rhinitis which under-estimated RR to falsely report treatment effectiveness for study outcomes [8–11]. Immortal time bias has been documented in a disturbing number of observational studies of commonly prescribed drugs [12]. This form of bias results from the immortal time span during which, because of exposure definition, the study outcome could not occur [13]. The present cohort study identified exposure to statins ‘from the medical record of each patient’ [7]. Since this study was based on a

retrospective search of medical records, statin exposure could have included the use of statins after hospital discharge. Thus, the time between hospital discharge for COPD and the first prescription for a statin in the medical record is clearly ‘immortal’: to have received the treatment implies that the subject ‘survived’ until this first prescription. Consequentially, many of the 118 subjects classified as exposed to statins will have a guaranteed survival advantage over unexposed subjects since the follow-up for the unexposed individuals began immediately after hospitalization and was not potentially delayed by awaiting a prescription for the statin. The potential delay results in this immortal time [10]. Indeed, patients who received a statin prescription after hospital discharge will necessarily have a longer survival from the time of discharge than the patients who did not receive statin prescriptions; however, this is artificial since it includes the immortal time period during which treatment had not yet occurred. The solution is to classify the unexposed time prior to the first prescription as non-user time and, following the first statin prescription, patients should then be classified as statin users. This phenomenon has been described in detail [8] and in an insightful editorial [11] to explain an observational cohort study suggesting an important 29% reduction in all-cause mortality associated with ICS use in COPD [14]. A replication of this study demonstrated the impact of immortal time bias using data from another cohort of COPD patients: the 29% reduction in mortality was replicated using the biased approach and, after removing the source of bias, the effect disappeared entirely [8].

The second study of the effects of statins on mortality from influenza and COPD is also subject to immortal time bias [15]. This study, involving a cohort of over 19,000 users of statins and over 57,000 non-users, reported that the risk of death from COPD was dramatically reduced with moderate doses of statin (≥ 4 mg/day; OR 0.17, 95% CI 0.07–0.42), as was the risk of death from influenza/pneumonia (OR 0.60, 95% CI 0.44–0.81). Here again, a close look at the study design reveals the presence of immortal time bias. Indeed, to be classified as a statin user, a patient needed to have ‘at least 90 days of cumulative statin exposure’ between 1992 and December 2003. In other words, some patients categorized as statin users could have been prescribed 90 days of statins spread over a long period. This immortal time artificially prolongs survival in these patients and guarantees that they live longer as a result of the definition of statin exposure.

Fig. 2. Description of typical case and control subjects with a 30-day exposure time period prior to the index date, with the time in hospital being immeasurable as outpatient prescriptions that define exposure cannot occur. Reprinted with permission from [17].

Statin Studies: Immeasurable Time Bias

An observational study recently evaluated the effects of statins, ACE inhibitors, and angiotensin-receptor blockers (ARB) on COPD patients with and without heart disease [16]. Study outcomes included COPD hospitalization, myocardial infarction, and total mortality over a seven year period. The study included two population-based retrospective cohorts: COPD patients among a cohort of patients who had undergone coronary revascularization (high cardiovascular risk cohort), and COPD patients among a cohort of patients treated with nonsteroidal anti-inflammatory drugs without previous myocardial infarction (the low cardiovascular risk cohort). The study reported cardioprotective effects of statins, ACE inhibitors and ARBs in COPD patients regardless of their cardiovascular risk profile. Risk reductions ranged from 10 to 66%. Combination therapy with statins and either ACE inhibitors or ARBs yielded the greatest benefits. In particular, all cause mortality was reduced with statin/ACE-ARB combination therapy by 58% (RR 0.42, 95% CI 0.33–0.52) in the high cardiovascular risk cohort and by 64% (RR 0.36, 95% CI 0.28–0.45) in the low cardiovascular risk cohort.

These surprising reductions in all-cause mortality are likely the result of immeasurable time bias. This bias is idiosyncratic to observational studies that use computerized databases and is caused by the impossibility of iden-

tifying exposure when it is based on outpatient drug prescriptions [17]. For a case-control study, immeasurable time refers to a period of time during which the drug exposure cannot be measured. For example, as shown in figure 2, the problem can result when the cases of the case-control study refer to deaths (as in the Mancini study) and the cases were hospitalized just prior to death, so that the computerized database would not find outpatient prescriptions before death (as these databases do not typically record inpatient drugs). Exposure as defined during this time period is thus immeasurable. Immeasurable time is particularly important in studies involving chronic illnesses, such as COPD, that are characterized by frequent and lengthy hospitalizations just prior to death. The key concern with this phenomenon is that multiple hospitalizations will lead to an apparently lower probability of drug exposure, while being likely associated with an increased risk of death, thus resulting in an underestimation of the RR or OR. Because this phenomenon is more likely and persists for longer periods of time for cases than for control subjects, the result will be an underestimate of the RR, producing the illusion that the drug is effective at preventing mortality [17].

An illustration of this phenomenon involved a cohort of 2,049 patients hospitalized for COPD between 1990 and 1999, from which a case-control analysis was performed whereby for each of the 1,313 deaths (cases) occurring during cohort follow-up, one control (alive) was selected. Of the cases, 16% received had an outpatient ICS prescription during the 30 days prior to death, compared with 26% for the controls. However, the cases spent 11 days, on average, in the hospital during the 30 days prior to death, compared with 2.3 days for the controls, which is immeasurable time for outpatient ICS prescriptions. The straightforward naïve analysis that does not take this hospitalization information into account finds an OR of death of 0.60 (95% CI 0.50–0.73) associated with ICS use, which gives the appearance of a very beneficial significant effect. On the other hand, using an analysis that accounts for the different measurable times between cases and controls, the OR of death becomes 0.98 (95% CI 0.83–1.17) after adjustment [16].

Conclusions

CVD is clearly important in terms of its magnitude in COPD and frequently precedes the diagnosis of COPD. It is uncertain, however, whether and to what extent CVD onset occurs prior or subsequent to COPD onset or diag-

nosis. Whether COPD contributes to CVD mortality, or vice versa, has not been determined.

What is known is that CVD is common in patients with COPD, and is a frequent cause of mortality. Thus great interest has recently been given to the role of cardiovascular medications such as statins, ACE inhibitors, ARBs and beta-blockers to reduce morbidity and mortality in patients with COPD.

The recent observational studies of statin use in the setting of COPD show surprisingly high efficacy results which, by their magnitude, demanded closer analysis. Our investigation of study methods and results in the statin studies reviewed in this article reveals significant bias that skewed the results of these early studies. The reports of remarkable statin effectiveness in reducing all-cause mortality in COPD are in fact the result of immortal time bias and immeasurable time bias. Correcting these methodological flaws with proper statistical analysis may attenuate or even eliminate these apparent benefits.

These examples highlight the limitations of observational studies in assessing drug effectiveness. Although observational studies are useful for determining drug safety, randomized controlled trials remain the gold standard to evaluate drug efficacy and effectiveness. It is important to highlight, however, that randomized controlled trials are often undertaken based upon the flawed findings of observational studies. Careful analysis of observational study methods and appropriate adjustment of study findings to eliminate bias can help prevent the conduct of frivolous controlled trials.

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