Limited Impact of Drug Exposure Misclassification From Non-Benefit Thiazolidinedione Drug Use on Mortality and Hospitalizations From Saskatchewan, Canada: A Cohort Study

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ABSTRACT

Purpose: Our purpose was to measure the effect of non-benefit drug use on observed associations between exposure and outcome, thereby documenting an empirical example of the potential magnitude of biases introduced when exposure status is misclassified from a restrictive drug coverage policy.

Methods: New users of antidiabetic agents were identified with a 1-year washout period between January 1, 1995, and December 31, 2005, in Saskatchewan, Canada, and were followed until December 31, 2008. Within this population-based cohort, persons were classified as users of benefit or non-benefit thiazolidinediones (TZDs) according to their first prescription record between January 1, 2006, and December 31, 2006 (non-benefit prescription records were not captured before 2006). An intention-to-treat approach was used to categorize TZD exposure over time. We evaluated the potential bias introduced by drug exposure misclassification by evaluating bootstrapped differences in hazard ratio (HR) estimates of all-cause hospitalization or death between users and nonusers of TZDs obtained from analyses that contained complete drug use (non-benefit and benefit drug use) versus benefit drug use only (non-benefit drug use was misclassified as unexposed). All analyses were replicated within the same cohort of new users of antidiabetic agents for clopidogrel and β-blocker (bisoprolol or carvedilol) users versus nonusers because these agents were also subject to exposure misclassification from non-benefit drug use during the period of the study.

Findings: Among 27,333 new users of antidiabetic agents, we identified 5759 TZD users (28% non-benefit) and 21,574 nonusers of TZDs. The crude HR for hospitalization or death among TZD users versus nonusers was higher in a database that contained benefit-only prescriptions than in a database that contained all prescriptions (HR = 1.11 [95% CI, 1.05–1.18] vs HR = 0.99 [95% CI, 0.94–1.04]). However, the differences in HRs after adjustment for demographic characteristics, health care utilization, comorbidities, and medications suggested minimal bias was introduced when TZD exposure was misclassified in the benefit-only database (adjusted HR [aHR] = 1.04 [95% CI. 0.98–1.10] vs aHR = 0.99 [95% CI, 0.94–1.04]; bootstrapped aHR difference = +0.05 [95% CI, 0.02–0.08]). Minimal differences in aHRs were also observed within analyses of clopidogrel (1551 users [24% non-benefit]; bootstrapped aHR difference = +0.01 [95% CI, –0.04 to 0.06]) and β-blocker users (351 users [42% non-benefit]; bootstrapped aHR difference = +0.06 [95% CI, –0.09 to 0.20]) versus nonusers.

Implications: Although patient characteristics and outcomes differed between users of non-benefit and benefit drugs, misclassification of drug exposure did not meaningfully bias estimates of all-cause mortality

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and hospitalization after covariate adjustment in our study. (*Clin Ther*. 2015;37:629–642)

Key words: bias, cohort study, health outcomes, mortality, pharmaceutical policy, pharmacoepidemiology.

INTRODUCTION

Drug safety profiles and comparative effectiveness studies often rely on secondary analysis of administrative databases.[1] However, such observational studies require accurate drug exposure data, and this exposure may be misclassified within administrative databases for numerous reasons, including, but not limited to, nonadherence,[2] free samples,[3] immeasurable time,[4] and over-the-counter medication use.[5] Another source of drug exposure misclassification, which has been recognized but not rigorously studied, is the impact of a drug's benefit status within a drug insurance plan's formulary.[6–12]

Administrative databases often only capture drug exposure data for drugs that are a benefit through a government or private insurance drug plan.[13] Policies that limit or restrict drug coverage, by not listing a drug on formulary or by using a policy such as a prior authorization program, may result in drug exposure misclassification. For example, if a drug is not covered or a patient is denied coverage, a patient may pay out of pocket or use an alternative drug insurance plan. Thus, the entire drug exposure period (or portions thereof) may be falsely classified as not exposed. Moreover, drug exposure misclassification may occur if changes occur in a drug's benefit status during the study period, whereby a previously non-benefit drug may become a benefit either because the drug plan itself has changed the drug coverage policy or a patient initially denied coverage is approved later in the course of treatment.

Studies within the United States and Canada have indicated at least 10% to 20% of people may be missing drug dispensation information within certain administrative databases.[6,14] Moreover, newly marketed drugs, such as NSAIDS and cardiovascular and diabetes medications, were more likely to be missing from administrative claims data.[14] For instance, a study that used Canadian administrative data indicated that up to 70% of thiazolidinedione (TZD) users would have been misclassified as not exposed on the basis of benefit records reimbursed by the provincial drug insurance plan only.[15] Another study found that drug data from the French national health insurance database captured 32% to 81% of drugs actually sold.[16] Drug databases used in pharmacoepidemiologic studies from several other countries, including Germany, Belgium, Finland, Ireland, Poland, and Spain, are limited to reimbursed drugs only; therefore, they may be missing non-benefit drug exposure data.[17] Beyond under-ascertainment of drug exposure, other factors such as exposure prevalence, sensitivity and specificity of the exposure ascertainment process, outcome frequency, and whether outcome frequency differ across misclassified exposure categories.

Although these studies suggest substantial misclassification of drugs may exist in databases that capture benefit drugs only, empiric evidence of the impact of this misclassification on results of pharmacoepidemiologic studies is lacking. Thus, we designed this study to assess the potential magnitude of bias introduced within a typical pharmacoepidemiologic cohort study within an administrative database that relies on benefit claims data only.

METHODS

Study Design and Setting

We conducted a population-based cohort study that used the administrative health care databases of the Saskatchewan Ministry of Health.[18] Approximately one million residents of Saskatchewan are eligible for provincial health services coverage, of which 90% are eligible for prescription drug benefits. There is no age restriction for eligibility, unlike other public payer drug plans (eg, Ontario Drug Benefit Program or US Medicare) that are limited to patients aged 65 years and older.

The Saskatchewan Drug Plan operates under a variety of cost-sharing arrangements that range from first-dollar coverage to an income-based program with some beneficiaries receiving no financial benefit from the government.[19] Only drugs included in the Saskatchewan Formulary are eligible for coverage. Details about the drug review process to determine which drugs are included on the formulary are described elsewhere.[19]

Some drugs are covered for specific patients under a prior authorization program (Exception Drug Status [EDS] program), and quantity limits may apply to all drugs. The EDS program restricts coverage for drugs