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Comparison of high-dimensional confounder summary scores in comparative studies of newly marketed medications

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Abstract

Objective: To compare confounding adjustment by high-dimensional propensity scores (hdPSs) and historically developed high-dimensional disease risk scores (hdDRSs) in three comparative study examples of newly marketed medications: (1) dabigatran vs. warfarin on major hemorrhage; (2) on death; and (3) cyclooxygenase-2 inhibitors vs. nonselective nonsteroidal anti-inflammatory drugs on gastrointestinal bleeds.

Study Design and Setting: In each example, we constructed a concurrent cohort of new and old drug initiators using US claims databases. In historical cohorts of old drug initiators, we developed hdDRS models including investigator-specified plus empirically identified variables and using principal component analysis and lasso regression for dimension reduction. We applied the models to the concurrent cohorts to obtain predicted outcome probabilities, which we used for confounding adjustment. We compared the resulting estimates to those from hdPS.

Results: The crude odds ratio (OR) comparing dabigatran to warfarin was 0.52 (95% confidence interval: 0.37−0.72) for hemorrhage and 0.38 (0.26−0.55) for death. Decile stratification yielded an OR of 0.64 (0.46−0.90) for hemorrhage using hdDRS vs. 0.70 (0.49−1.02) for hdPS. ORs for death were 0.69 (0.45−1.06) and 0.73 (0.48−1.10), respectively. The relative performance of hdDRS in the cyclooxygenase-2 inhibitors example was similar.

Conclusion: hdDRS achieved similar or better confounding adjustment compared to conventional regression approach but worked slightly less well than hdPS.

Keywords: Comparative safety study; Propensity score; Disease risk score; Confounding adjustment; Administrative data; Historical cohort

1. Introduction

Nonrandomized comparative studies on the effectiveness and safety of medication can provide important information about the value of newly marketed drugs as experience with these products grow in routine care [1,2]. Administrative and electronic health record databases are well suited for these studies as they offer readily available data on the longitudinal use patterns of medications in

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What is new?

Key findings

- The application of a novel confounding adjustment approach – the historically-developed high dimensional disease risk score (hdDRS) – was feasible and performed similar to or better than conventional regression methods that did not include empirically identified covariates.
- The performance of hdDRS was slightly lower than that of the high dimensional propensity score approach in the three examples that were studied.

What this adds to what was known?

- Confounding adjustment in comparative studies of newly marketed medications is challenged by small numbers of patients exposed to the new drug, and even fewer outcome events. hdDRS developed in a historical cohort can be a useful alternative confounding adjustment approach.

What is the implication and what should change now?

- Historically-developed hdDRS should be considered as an option for confounding adjustment in studies of newly marketed medications where the numbers of exposed patients and/or outcomes are small, such as in the very early marketing period.
- Studies should further determine the conditions under which the hdDRS is preferred over other confounding adjustment approaches, such as in the presence of historical data with large a number of outcomes and rapidly evolving prescription patterns of the new drug shortly after the market entry.

large-scale populations outside of controlled research environments, but confounding control for valid inference remains a challenge in such observational studies [3]. With a large number of potential confounding factors, or proxies thereof, empirical confounder selection has been shown to improve confounding control in database studies [4–6]. An automated variable selection approach using the high-dimensional propensity score (hdPS) algorithm can facilitate the adjustment for a large number of confounders by prioritizing and selecting variables most likely to induce confounding bias based on their associations with the exposure and outcome [7]. However, in studies of newly marketed medications, few exposed patients and even less frequent outcomes can limit the feasibility of the hdPS algorithm [8].

Disease risk scores developed in a historical cohort of comparator drug users have been suggested as an alternative to propensity scores [9] and may be especially well suited for studies of newly marketed drugs [10,11]. A high-dimensional disease risk score (hdDRS) approach which empirically identifies and selects outcome predictors, and models the outcome using principal component analysis and lasso regression in the historical cohort, has been proposed for studies of newly marketed drugs [12]. Historically developed hdDRS and hdPS share the ability to reduce the dimensionality of a large number of potential confounding factors and their proxies, but they differ in several fundamental aspects. Although the hdPS improves the comparability of exposed and unexposed patient groups by modeling the exposure and balancing all measured potential confounders and outcome predictors in the two groups, hdDRS achieves this by modeling the outcome and by balancing the risk of the outcome [9], but not necessarily the individual covariates between the treatment groups. It is also an advantage of hdPS that it directly models the exposure in the concurrent cohort of new and comparator drug initiators, whereas the historically developed hdDRS is modeled in data preceding the actual study population, which may lead to reduced applicability of the scores to the concurrent study cohort. Historically developed hdDRS models require assumptions of consistency in covariate measurement and coding patterns between the historical and concurrent cohorts to achieve consistency in estimated covariate-outcome associations between the historical and concurrent cohorts [9–11].

The purpose of this study was to compare the effect of confounding adjustment with historically developed hdDRS vs. hdPS in three comparative example studies using RCT evidence as a benchmark.

2. Methods

2.1. Data sources, study cohorts, and outcomes

We evaluated the performance of hdDRS and hdPS in three comparative study examples from two study cohorts: (1) dabigatran vs. warfarin on major hemorrhage; (2) on death; and (3) cyclooxygenase-2 inhibitors (coxibs) vs. nonselective nonsteroidal anti-inflammatory drugs on gastrointestinal bleeds.

2.1.1. Dabigatran study cohort

The dabigatran vs. warfarin comparisons were conducted using the UnitedHealth Clinformatics insurance claims database. As the concurrent comparison study cohort, we identified patients aged 18 years or older, who initiated warfarin or dabigatran between October 1, 2010, the month in which dabigatran entered the market, and June 30, 2012. Initiation of the drugs was defined as a new prescription after no use of warfarin, dabigatran, or rivaroxaban for 365 days, and we designated the date of the first prescription as the cohort entry date. We required patients to have a prior diagnosis of atrial fibrillation as defined by ICD-9