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The proportion of all previous patients was a potential instrument for patients' actual prescriptions of nonsteroidal anti-inflammatory drugs

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Abstract

Objectives: To investigate whether physician's prescribing preference is a valid instrumental variable (IV) for patients' actual prescription of selective cyclooxygenase-2 (COX-2) inhibitors in the German Pharmacoepidemiological Research Database (GePaRD).

Study Design and Setting: We compared the effect of COX-2 inhibitors vs. traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) on the risk of gastrointestinal complications using physician's preference as IV. We used different definitions of physician's preference for COX-2 inhibitors. A retrospective cohort of new users was built which was further restricted to subcohorts. We compared IV-based risk difference estimates, using a two-stage approach, to estimates from conventional multivariate models.

Results: We observed only a small proportion of COX-inhibitor users (3.2%) in our study. All instruments, in the full cohort and in the subcohorts, reduced the imbalance in most of the covariates. However, the IV treatment effect estimates had a highly inflated variance. Compared to the most recent prescription, the proportion of previous patients was a stronger instrument and reduced the variance of the estimates.

Conclusion: The proportion of all previous patients is a potential IV for comparing COX-2 inhibitors vs. tNSAIDs in GePaRD. Our study demonstrates that valid instruments in one health care system may not be directly applicable to others. © 2016 Elsevier Inc. All rights reserved.

Keywords: Confounding by indication; COX-2 inhibitors; German Pharmacoepidemiological Research Database; Instrumental variables; Physician's preference; Two-stage least squares

1. Introduction

Observational studies are necessary to assess the effectiveness and safety of drugs after marketing. Claims databases are frequently used for this purpose. However, because claims data are mainly collected for reimbursement of patients' costs, they lack important confounder information, which in turn leads to biased effect estimates [1]. Instrumental variable (IV) analysis is a "generic" approach to deal with unmeasured confounding [2]. Applications of this method in observational studies of the effectiveness and safety of drugs exploit random variation in treatment assignment to define the IV that influences treatment but does not have an independent effect on the outcome [3]. Using an IV instead of the actual treatment is equivalent to pseudorandomizing the patients to alternative treatments [3]. However, IV analysis can reduce bias in effect estimates due to unmeasured confounding, only if a valid instrument can be identified [4,5]. An observable variable is a valid instrument provided that all three following assumptions are met. First, the IV is associated with the treatment. Second, the IV is independent of unobserved confounders and third, conditionally on unmeasured confounders and treatment, the IV and the outcome are independent, implying that the IV association with the outcome is fully mediated by the observed treatment (exclusion restriction) [6].

Conflict of interest: B.K. is working and I.P. is head of an institute that occasionally performs studies for pharmaceutical industries. The companies include Mundipharma, Bayer-Schering, Stada, Sanofi-Aventis, Sanofi-Pasteur, Novartis, Purdue, Celgene, and GSK, but none of them were involved in this study.

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What is new?

- Previous research has not evaluated the feasibility and validity of using prescribing preference-based instrumental variables (IVs) in German administrative health databases. We demonstrated that the proportion of all previous patients, in an individual physician practice, who were prescribed a given drug, meets the criteria for an IV for the patients' actual prescriptions of cyclooxygenase-2 inhibitors or traditional nonsteroidal anti-inflammatory drugs in Germany.
- Although sample size was large and the instruments met the standard criteria for "strong" instruments, the IV-based estimates of treatment effect suffered from a highly inflated variance and varied substantially depending on the definition of the instrument.
- Our study has shown that valid instruments in one health care system may not be directly applicable to other settings. IV assumptions should be carefully checked for each particular research question and for the relevant study population.

In 2006, Brookhart et al. [7] proposed that the physician's prescribing preferences, which can be quantified based on the physician's prior prescriptions, might be used to define a valid IV. They applied this approach to compare the risk of gastrointestinal (GI) complications associated with nonsteroidal anti-inflammatory drugs (NSAIDs) selective for cyclooxygenase-2 (COX-2) vs. traditional NSAIDs (tNSAIDs). Because then several other studies evaluated different definitions of provider prescribing preference-based IVs and gave ambiguous results regarding the "optimal" IV definition. For example, Henessey et al. [8] reported that physician's preference based on the most recent NSAID prescription was a stronger IV than the IV based on several recent prescriptions. In contrast, Ionescu-Ittu et al. [9] found that IVs depending on the proportion of all previous patients, in a given physician's practice, who were prescribed a specific drug were stronger and had smaller variance than estimates based on the most recent prescription. Abrahamowicz et al. [10] adapted this approach to settings where physician's preferences may change over time and demonstrated through simulations that the change-time method reduced the variance of the IV estimates relative to the IV based on physician's prior prescriptions. However, Davies et al. [11] concluded that the physician's preference based on the most recent prescription had weaker associations with observed confounders and, hence, might be expected to be less related to unobserved confounders than IVs based on multiple prescriptions, but the latter led to treatment effect estimates with smaller standard errors. Finally, Rassen et al. [12] increased the strength of their instruments by restricting the cohort to physicians who treated many patients.

It is plausible that these divergent findings are partly because the validity and the relative strengths of alternative definitions of prescribing preference-based IVs depend on both the assessed drug and the characteristics of the health system, especially those related to prescribing habits. In the present study, we aim to identify a valid IV in the German Pharmacoepidemiological Research Database (GePaRD) [13], to compare the risk of GI complications between users of COX-2 inhibitors and tNSAIDs. Thus, we assess the alternative IVs for the same association as the one studied in the original IV article by Brookhart et al. [7] but applied in a different health system context. We consider three definitions of the physician's preference by using, first, the most recent prescription, second, the proportion of previous patients, and third, a set of indicator variables for the physician's seven prior prescriptions. To increase the strength of the IVs and to create subcohorts with lower variation in unmeasured confounders, we restrict the cohort to subgroups that are more homogenous with respect to either patients or physicians characteristics. We then compare the instruments in terms of strength and ability to balance the distributions of observed covariates both in the full cohort and in the subcohorts and explore a possible violation of the exclusion restriction. Furthermore, we compare IV effect estimates, obtained using a two-stage approach [5], with (1) estimates obtained from the conventional analysis that adjusts only for observed covariates and (2) results of randomized controlled trials and previously published database studies.

2. Methods

2.1. Data source

The study was based on claims data (2004–2009), extracted from GePaRD, from four German statutory health insurances (SHIs). The source population consisted of more than 14 million insurance members and is nationally representative with respect to sex, age, and region of residence. Membership in an SHI is compulsory in Germany for employees below an annual income threshold (approximately 49,000€ in 2009). Although individuals with higher incomes may switch to private health insurances, around 75% of them remain voluntary members of SHIs. About 70 million people (85% of the German population) are SHI members, including about five million voluntary members, children, and patients who are retired or unemployed. For each insurance member, the database contains information on demographics as well as on hospital admissions, outpatient physician visits, and prescriptions [13]. The hospital data comprise the dates of hospitalization, diagnoses,

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