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Suspected survivor bias in case−control studies: stratify on survival time and use a negative control

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Abstract

Objectives: Selection bias in case−control studies occurs when control selection is inappropriate. However, selection bias due to improper case sampling is less well recognized. We describe how to recognize survivor bias (i.e., selection on exposed cases) and illustrate this with an example study.

Study Design and Setting: A case−control study was used to analyze the effect of statins on major bleedings during treatment with vitamin K antagonists. A total of 110 patients who experienced such bleedings were included 18−1,018 days after the bleeding complication and matched to 220 controls.

Results: A protective association of major bleeding for exposure to statins (odds ratio [OR]: 0.56; 95% confidence interval: 0.29−1.08) was found, which did not become stronger after adjustment for confounding factors. These observations lead us to suspect survivor bias. To identify this bias, results were stratified on time between bleeding event and inclusion, and repeated for a negative control (an exposure not related to survival): blood group non-O. The ORs for exposure to statins increased gradually to 1.37 with shorter time between outcome and inclusion, whereas ORs for the negative control remained constant, confirming our hypothesis.

Conclusion: We recommend the presented method to check for overoptimistic results, that is, survivor bias in case−control studies.

Keywords: Anticoagulants; Case−control studies; Epidemiology; Hemorrhage; Hydroxymethylglutaryl-CoA reductase inhibitors; Selection bias

1. Introduction

Case−control studies are commonly used because it is an efficient way to study rare outcomes. They can be as credible as randomized studies, when correctly designed and performed [1]. Cases are those who experience the event of interest, and controls are a random sample from the source population from which the cases arose [2]. Selection bias in case−control studies is well known to occur when control selection is inappropriate [2]. However, selection of cases can result in bias as well, which is less well recognized. This selection bias can occur when cases are selected a long period after the event, and exposed cases have an increased risk of severe illness or death compared with nonexposed cases [3]. In this article, we provide procedures to check for possible selection bias of cases and illustrate this with an example of a case−control study on the association of statin use and bleeding risk during treatment with vitamin K antagonists.

2. Methods

The study used to illustrate this bias is the ‘‘factors in oral anticoagulation safety (FACTORS)’’ case−control study, which has been described before [4]. Briefly, cases reported a nontraumatic (nonfatal) major bleeding complication, during treatment with vitamin K antagonists (oral anticoagulants). Major bleeding was defined as a bleeding leading to hospitalization, a sudden hemoglobin decrease of higher than 1.25 mmol/L, or an intracranial, intra-abdominal, muscle, joint, or intraocular bleeding. These bleedings occurred between 1999 and 2001, and because vitamin K antagonists are characterized by a narrow therapeutic index, careful

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What is new?

- Selective survival in cases can occur in retrospective case−control studies. To detect selective survival, we propose to stratify on time between the event and inclusion in the study of the cases and, if available, also to use a negative control.
- Our case-control study showed a protective assocation of statin use towards major bleeding during treatment with vitamin K antagonists. However, this protective association could be explained by the sampling method.
- These results reinforce that caution is warranted when interpreting an observational study that reports protective effects of statins on disease outcomes when patients had to survive until inclusion.

monitoring is necessary. In the Netherlands, this is performed by anticoagulation clinics [5].

For every case, one to four controls without major bleeding event were matched on anticoagulation clinic, age, indication of anticoagulation, sex, vitamin K antagonist type (acenocoumarol or phenprocoumon), and whether treatment with vitamin K antagonists stopped before blood collection. Cases and controls were interviewed, and blood was drawn for testing on genetic variants [4]. Inclusion of cases took place 18−1,018 days after the major bleeding event (on average 425 days).

Cases and controls were considered statin users when they reported using this medication at time of the bleeding event (for cases) and during the interview (for controls). Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated by means of conditional logistic regression, and were adjusted for comorbidity (diabetes and hypertension) and use of antiplatelet drugs. Written informed consent was obtained from all subjects, and the study was approved by the institutional review boards of the Leiden University Medical Center and the Academic Medical Center in Amsterdam. All statistical analyses were performed in SPSS 17.0 for windows (SPSS, Inc., Chicago, IL).

3. Results

Complete data of the 110 cases and 220 controls were available, except for data on blood group (unavailable in 10 subjects). Clinical characteristics are shown in Table 1. Among both cases and controls, statin users suffered more frequently from comorbid conditions and used antiplatelet drugs more frequently.

The OR of developing a major bleeding event in statin vs. nonstatin users was 0.56 (95% CI: 0.29−1.08; Table 2). We expected that adjustment for comorbidity and use of antiplatelet drugs would lead to an even stronger protective risk estimate, as these confounding factors increase the risk for bleeding complications [6] and are related to statin treatment. However, after adjustment for comorbidity and use of antiplatelet drugs, no stronger protective risk estimate was observed (OR: 0.53, 95% CI: 0.27−1.03).

These findings were somewhat counterintuitive: first of all, statins gave a nearly 50% risk reduction of major bleeding, even if the indications for which statins are prescribed give an increased risk of major bleeding events. Second, adjustment for these confounders did not lead to a stronger protective risk estimate. We could have concluded that statins are powerful drugs, but instead hypothesized that this result might be biased.

Survivor bias occurs when exposed cases are less likely to take part in a study (e.g., because they died or became severely ill) than unexposed cases. This could mean that exposed cases in this study (i.e., patients who experienced a bleeding event and used statins) were less likely to participate (because of death or severe illness) when time between the event and inclusion in the study increased. Therefore, time between bleeding event and inclusion was taken into account because with more time between a bleeding event and inclusion the higher the possibility that a potential (exposed) case was not able to participate in our study. Therefore, selected cases (with their matched controls) were stratified on time between the bleeding event and inclusion (less than 2.00, 1.75, 1.50, 1.25, and less than 1.00 year). We saw that ORs increased gradually from 0.56 (95% CI: 0.29−1.08) to 1.34 (95% CI: 0.52−3.42) when cases were included within 3 and 1 year(s) after the bleeding event, respectively. After adjustment for comorbidity, this pattern remained the same (Table 2).

Although this stratified analysis suggests that our results were due to survivor bias, numbers were small, which may have led to this finding by chance. We therefore decided to explore this potential bias further, and repeated the analysis, only this time using exposure to blood group non-O as a "negative control," meaning an exposure that, although related to the outcome, is not related to increased risk of death or severe illness [7]. Risk estimates should remain stable with increasing time between the event and inclusion in the study to confirm our hypothesis of survivor bias. Indeed, the OR for major bleeding complications in patients with blood group non-O as compared with blood group O was 0.70 (95% CI: 0.43−1.14), and remained stable after stratifying on time between the major bleeding event and inclusion (Table 2).

4. Discussion

We showed that an association found in a straightforward analysis of a case−control study can be biased due to selective survival of the cases. In our example, cases with major