

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

Nienke van Rein<sup>a,b,\*</sup>, Suzanne C. Cannegieter<sup>c</sup>, Frits R. Rosendaal<sup>a,b,c</sup>, Pieter H. Reitsma<sup>a,b</sup>, Willem M. Lijfering<sup>a,b,c</sup>

<sup>a</sup>Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

<sup>b</sup>Eindhoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands

<sup>c</sup>Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

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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. © 2014 Elsevier Inc. All rights reserved.

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

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## 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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\* Corresponding author. Eindhoven Laboratory for Experimental Vascular Medicine, C2-R, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31-71-526-1648; fax: +31-71-526-6755.

E-mail address: [n.van\\_rein@lumc.nl](mailto:n.van_rein@lumc.nl) (N. van Rein).

### 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 association 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

**Table 1.** Clinical characteristics by cases or controls and statin use

Parameters	Cases ( <i>n</i> = 110)				Controls ( <i>n</i> = 220)			
	Statin users ( <i>n</i> = 18)		Nonstatin users ( <i>n</i> = 92)		Statin users ( <i>n</i> = 56)		Nonstatin users ( <i>n</i> = 164)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age, yr		69 (10)		67 (12)		67 (10)		70 (11)
Men	94		53		71		55	
Body mass index, kg/m <sup>2</sup>		26.6 (3.4)		25.2 (4.0)		27.2 (4.2)		25.8 (3.8)
Positive smoking history	83		78		88		66	
Hypertension	28		30		34		35	
Diabetes	33		9		21		14	
Antiplatelet drugs	6		4		4		1	
Cancer	28		14		13		10	
Years of treatment		6.6 (5.9)		5.1 (6.2)		2.9 (4.3)		2.9 (4.4)

Abbreviation: SD, standard deviation.

bleeding who were statin users were less likely to participate in our study in the period after the event than cases who did not use statins, resulting in finding a 43% risk reduction of major bleeding during treatment with vitamin K antagonists. This could be an important phenomenon that could occur more frequently in case–control studies. We confirmed this phenomenon by performing our analysis for two exposures, but a caveat remains that our study is small numbered. We therefore tried to compare this finding with other studies; but to our knowledge, this is the first time of reporting on the association of statin use and major bleeding during treatment with vitamin K antagonists. However, there are many claims that statins have protective effects for several (non)vascular diseases, including multiple sclerosis, depression, Alzheimer's dementia, atherosclerosis, osteoporosis, AIDS, cancer, and venous thrombosis [8]. For venous thrombosis, a recent meta-analysis of observational studies compares statin users with nonstatin users, and shows a relative risk for venous thrombosis of 0.62 (95% CI: 0.45–0.86) [9]. The lowest relative risks (0.20–0.60) were found in studies that had enrolled patients who had survived their event until inclusion. All other studies reported relative risk estimates that were closer to unity (0.74–1.02) [9]. The studies with the lowest relative risks may therefore have suffered from the same problem, supporting the hypothesis that survivor bias may be more common and not always recognized as such. This is a problem, as causality is often inferred from these

studies, which may lead to advice to prevent venous thrombosis with statins [10].

Although we showed how to detect survivor bias, a possible limitation of our method (stratification on time between outcome and inclusion in the study, preferably repeated for a negative control) remains that it cannot distinguish survivor bias from a possible temporal biological effect of the exposure. To distinguish bias and a temporal effect, one should first look into the biology of the exposure toward the outcome. For this study, it seems that stratification on time is a good method to study survivor bias, as it is biologically implausible that statins do increase the risk for bleedings in the first year of use and then become protective. A limitation of our example study is that numbers became small, especially after stratification on time between bleeding event and inclusion of cases. Therefore, the risk estimate (that was not more protective after adjustment for confounding factors in the stratified analyses) should be interpreted with caution.

A way to overcome issues of survivor bias includes restriction of the analysis to cases who were included within a certain period in the study (dependent on the exposure and outcome). This analysis would be preferable when survivor bias is deemed as present. A negative control (when available) could be used to verify the presence of the bias if these are likely to occur due to chance, as was the case in our study. Another solution could be a study design where the exposure (statin use) and the outcome (major

**Table 2.** Association of major bleeding complications by statin use or blood group non-O, stratified on time between bleeding complication and enrollment

Time between bleeding event and enrollment (yr)	Statin use				Blood group non-O	
	Experienced/not experienced				Experienced/not experienced	
	cases and controls	Odds ratio <sup>a</sup> (95% CI)	Odds ratio <sup>b</sup> (95% CI)		cases and controls	Odds ratio <sup>a</sup> (95% CI)
Any time	18/92, 56/164	0.56 (0.29–1.08)	0.53 (0.27–1.03)		59/50, 133/78	0.70 (0.43–1.14)
<2.00	18/89, 56/158	0.56 (0.29–1.08)	0.55 (0.28–1.08)		56/50, 129/76	0.68 (0.42–1.11)
<1.75	18/79, 53/140	0.60 (0.31–1.17)	0.59 (0.30–1.20)		51/45, 115/69	0.71 (0.43–1.17)
<1.50	17/69, 45/130	0.74 (0.37–1.51)	0.71 (0.34–1.48)		44/41, 106/63	0.68 (0.40–1.17)
<1.25	13/46, 30/89	1.01 (0.46–2.23)	1.00 (0.42–2.36)		29/29, 73/41	0.58 (0.30–1.12)
<1.00	10/25, 18/54	1.34 (0.52–3.42)	1.37 (0.50–3.81)		17/18, 44/25	0.48 (0.19–1.24)

Abbreviation: CI, confidence interval.

<sup>a</sup> Based on conditional logistic regression.

<sup>b</sup> Based on conditional logistic regression and adjusted for diabetes, hypertension, and antiplatelet drugs.

bleeding) are not related to inclusion in a study, for example, a cohort study.

In summary, when both the exposure and outcome are related to death or severe illness, overoptimistic associations could be found in case–control studies. Therefore, we recommend using the method presented in this study (i.e., stratification on time between the event and inclusion in the study, preferably for both the exposure of interest and, in case of low numbers, also repeated in a negative control) to check for selective survival in cases.

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