

ALTERNATIVE VIEWPOINTS

Immortal Time Bias in Effects of Lipid Lowering Agents on Pneumonia

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The evaluation of HMG CoA reductase inhibitors in reduction of non-cardiovascular events is becoming an area of increasingly popular epidemiologic research. The recent article by Schlienger and his colleagues in *Pharmacotherapy* is both an interesting and timely analysis examining the association of lipid lowering agents and pneumonia related outcomes.¹ The authors conclude that the current use of statins is associated with a reduced risk of pneumonia, particularly in those with fatal pneumonias. However, one major bias was unaccounted for in their statistical analysis, namely, that of immortal time.

Immortal time bias can be described as a period of follow-up during which an event cannot occur.² This type of bias most commonly affects classic cohort studies and has been well described in the COPD literature evaluating the use of inhaled corticosteroids.³⁻⁶ However, this bias may also occur in cohort studies with a case-control analysis as in the study by Schleinger and his colleagues. This case control study uses the General Practice Research Database (GPRD) in the UK to define a cohort and subsequently conduct a case-control analysis to determine

odds ratios. The bias arises in the manner by which the cohort is defined. The authors defined the cohort as those aged 30 years or older who enrolled in the GPRD between January 1, 1995 and April 30, 2002. The cohort included (1) all those who had received at least one prescription for a lipid lowering agent, (2) all patients with a diagnosis of hyperlipidemia without any prescriptions for a lipid lowering agent and (3) a random sample of patients with neither hyperlipidemia nor any prescriptions for a cholesterol lowering agent.¹ Cohort entry time, although not explicitly defined, was presumably the date of entry into the GPRD database for both exposed and unexposed individuals. Cases were identified as those in whom the outcome of interest (pneumonia) occurred, which was defined as the index date. The outcome of interest, although not explicitly defined, was presumably the incident case during the individuals' cohort duration. Matched controls were then selected at random in a 4:1 fashion from the original cohort (presumably after removal of the cases). Subsequently, an odds ratio was calculated using the formula AD/BC (Table 1). However, this computation can result in a spuriously low odds ratio. The reason is that for exposed cases, the index date could only occur after exposure to a lipid lowering agent, which may have occurred some time after entry into the GPRD database. This means the time from cohort entry to the first statin prescription is by definition immortal (an exposed person cannot incur the outcome during this period). This may result in a smaller number of exposed cases (the A cell). The controls, on the other

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Table 1. Odds ratio is expressed as AD/BC

	Exposed	Unexposed
Cases	A	B
Controls	C	D

hand, could have received a statin prescription any time during the follow up period giving rise to a relatively larger denominator for the OR (AD/BC).

This bias is easily avoided by the use of a time-dependent analysis such as the Cox proportional hazards model in the case of a cohort study or a time-matched case-control study.⁷

We are concerned that such biases in pharmacoepidemiology may give rise to inappropriate prescribing of medications and may give false hope to those who may be looking for a “magic pill” for disease prevention. Given this potential bias these data ought to be reassessed for immortal time bias using a time dependent analysis.

References

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Authors' Reply

We read with interest the commentary by Wiens and his colleagues on our recently published study on statin use and the risk of pneumonia using the UK-based General Practice Research Database.¹ We reported a decreased risk of fatal pneumonia for current statin users, but not for past statin users and not for fibrate users, and we found no statistically significant association between statin use and uncomplicated pneumonia. The authors of the commentary propose that our findings are the result of a so-called ‘immortal time bias’, a bias which has recently been discussed in detail² and

which seems to become increasingly ‘en vogue’ as an alternative explanation for findings in observational studies.

We do not share their view that ‘immortal time bias’ could have explained the findings of our study on statins and pneumonia. The authors describe ‘immortal time bias’ as a period of follow-up during which an event cannot occur. Thus, this bias may be present if an exposed population can by definition develop an outcome of interest only after exposure, while the unexposed population can develop an outcome at any time. This may increase the amount of person-time in the unexposed and reduce the number of exposed cases (the ‘A cell’ in a two-by-two table), leading to a spuriously low odds ratio in a nested case-control analysis. However, in our study there was no such time period in which an outcome could not occur. Our study population consisted of users of lipid-lowering drugs (LLDs), of patients with diagnosed hyperlipidemia without LLD use, and of a random sample of the GPRD-population without diagnosed hyperlipidemia and without LLD use. Subjects in the study population could have developed pneumonia at any time, before or after receiving a first prescription for a LLD. Thus, at the time of the pneumonia diagnosis they could have been unexposed and were treated accordingly in the analysis. This technique is valid and does not lead to ‘immortal time bias.’ Our approach can be seen as a more efficient alternative to a ‘simple’ case-control analysis including all pneumonia cases identified in the database. In addition, it is difficult to understand how such a bias would affect preferentially cases with fatal pneumonia, while the findings related to uncomplicated pneumonia were unaffected, and how such a bias would only affect the findings related to current statin, but not to current fibrate use. Thus, we do not agree that our findings are likely to be the result of a distortion called ‘immortal time bias’, or whatever new label we may give to an old bias.

We fully agree with Wiens and his colleagues that inappropriate prescribing based on findings from observational studies must be avoided, so that one not give false hope to those who look for a ‘magic pill’. However, this does not mean that one should disregard findings from well-conducted observational studies such as ours. Our findings, together with similar results from many other studies, provide further support for the proposition that further research on pleiotropic effects of statins may be worthwhile.³

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