Research Methods & Reporting

Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes

BMJ 2010 ; 340 doi: https://doi.org/10.1136/bmj.b5087 (Published 12 March 2010)
Cite this as: *BMJ* 2010;340:b5087

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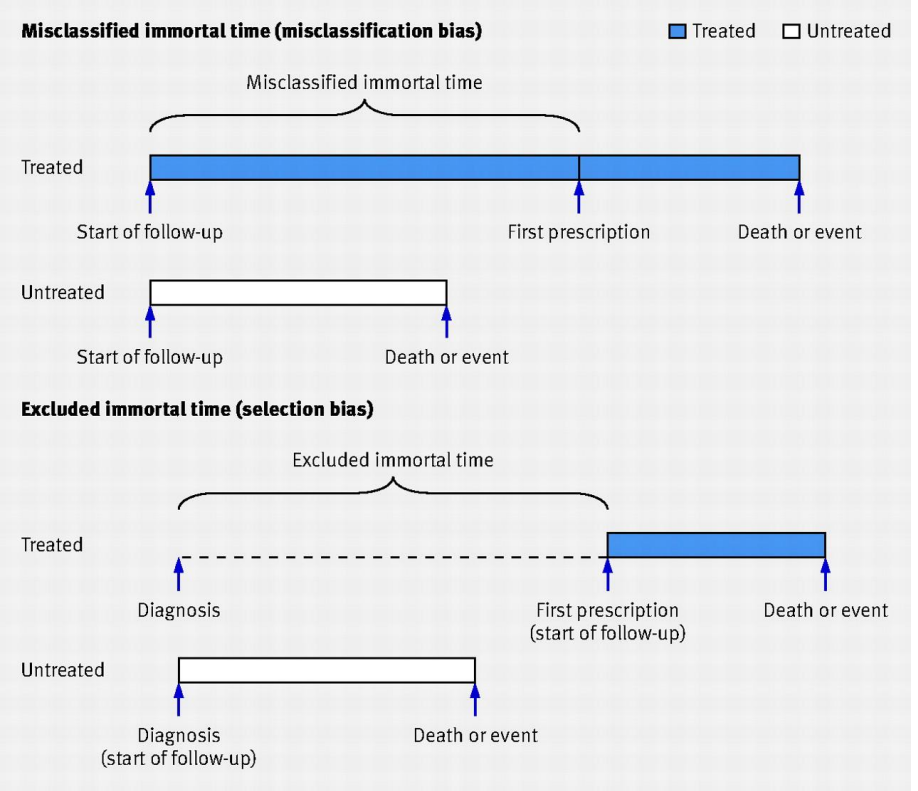
Accepted 25 August 2009

What is immortal time bias (ITB)?

Fig 1 Immortal time bias is introduced in cohort studies when the period of immortal time is either incorrectly attributed to the treated group through a time fixed analysis (top) or excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group (bottom)

ITB is particularly problematic because it necessarily biases the results in favour of the treatment under study by conferring a spurious survival advantage to the treated group.



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An example of ITB

- A study of statins that reported a 26% reduction in the risk of diabetes progression with one year or more of treatment (adjusted hazard ratio 0.74, 95% confidence interval 0.56 to 0.97)
- This association would be expected to yield a hazard ratio >1.0 because people whose diabetes progresses are more likely to develop cardiovascular disease, an indication for statins.

- This is a replication study of the study by Yee et al's statin study using the same Saskatchewan Health databases
  - To show how ITB **can be introduced** in cohort studies
  - **quantify** the relation between **the extent of IT** and **the magnitude of the bias**
  - **determine the extent** to which this **bias accounted for the protective association** previously reported
  - to show how ITB can **be prevented through time dependent analysis**

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Key definitions

Data sources: Saskatchewan Health databases generated by the province's universal health programmes. Information for about 91% of residents (roughly one million people)

P:Individuals aged 30 years and older, newly treated with a sulfonylurea or metformin between 1 January 1991 and 31 December 1996.

I/E: New users of statins.If there was at least one year between the date of their first and last prescription; those with a shorter interval were considered non-users from an aetiological perspective.

C: Non users

O: starting insulin treatment (as a surrogate end point for progression of diabetes). Date of the first insulin prescription dispensed after cohort entry

S: Population based cohort

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Key definitions

Start of follow-up/ cohort entry: date of this first prescription.

Individuals were followed until study outcome, end of health coverage (because of death or emigration), death, or 31 December 1999 (end of study)

Exclusion criteria:

Individuals that did not have at least one year of health coverage before cohort entry or had received oral hypoglycemics or insulin during the year before entry

Individuals who had received a lipid lowering drug from three years before to six months after cohort entry were excluded

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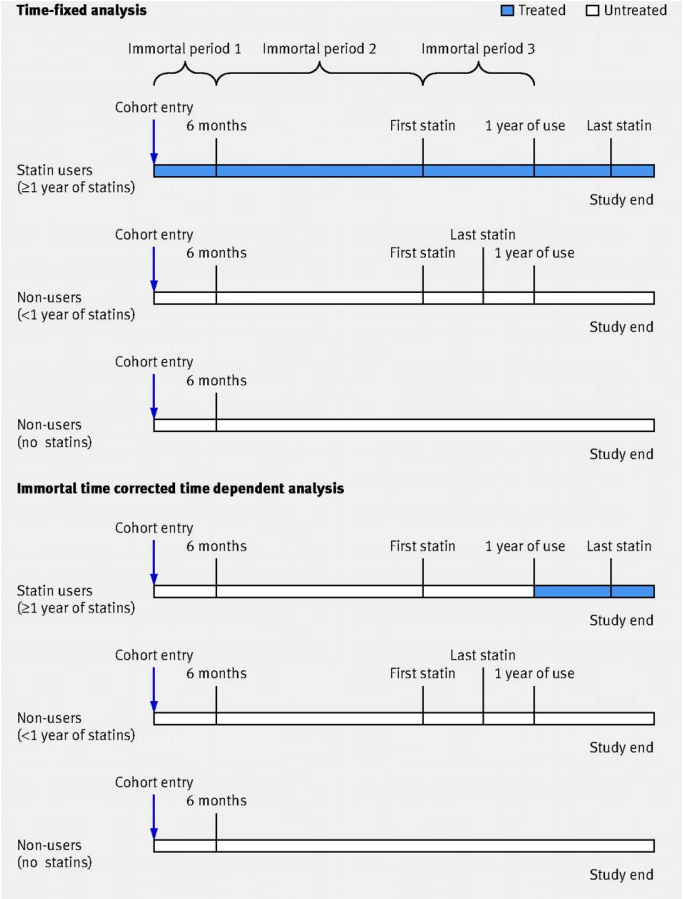
Fig 2 Depiction of typical statin user and non-user and sources of immortal time bias



Demonstration of bias

Replicated the time fixed (time independent) analysis used by Yee et al to estimate the statin-insulin association and compared it with a simple time dependent analysis that corrected the misclassified immortal time.

In the **time fixed analysis**, all person days between cohort entry and end of follow-up were classified as treated for those who met the statin user definition, regardless of the date on which they met this definition and as untreated for non-users

In the **time dependent analysis**, person days of follow-up were correctly classified as untreated until the intended treatment definition of “one year of use” was met, and as treated thereafter.

Poisson regression to quantify the magnitude of the misclassified immortal person time and estimate the statin-insulin association, and then used the Cox proportional hazards model.

In the Cox model, hazard ratios were adjusted for the potentially confounding effects of determinants of diabetes progression, correcting cumulatively for each period of immortal time.

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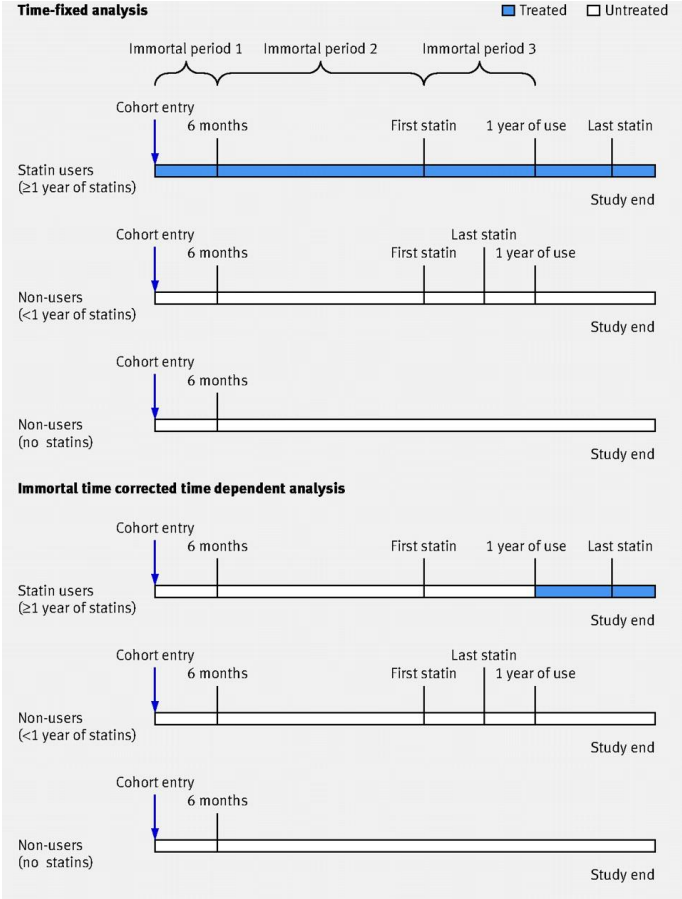

Quantification

- The cohort of adults newly treated with an oral hypoglycaemic was comparable in size and clinical profile to that of the previous study.
- During an average follow up of 4.9 years, 532 (4.6%) met the definition of statin users (at least one year of use), and 522 (4.5%) had received statins for less than one year and were classified as non-users from an aetiological perspective.
- An additional 10 607 were classified as non-users because they did not receive any statin prescriptions during follow-up
- During follow-up, 1418 (12.2%) people started insulin treatment (study outcome), some during periods of immortal time

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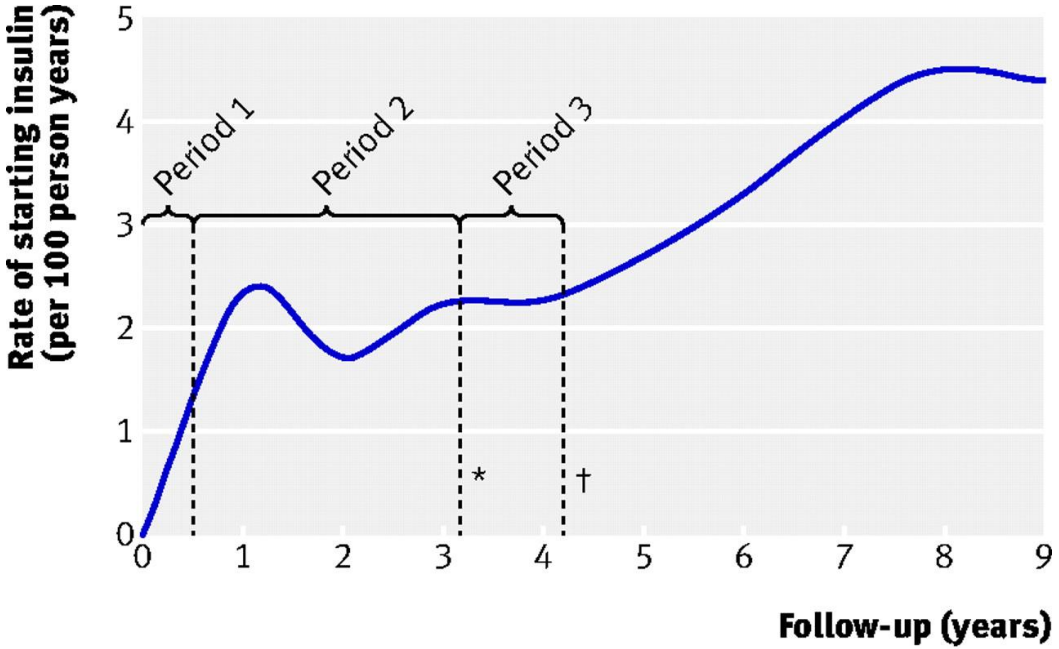
Fig 3 Rate of starting insulin (outcome event) during follow-up



Period 1: 6 month exclusionary period for statin use after cohort entry
Period 2: From the end of the exclusionary period until the date of the first statin prescription. Mean time to first statin prescription for "statin users" was 3.1 years
Period 3: Time needed, after the first statin prescription to fulfil the intended "statin user" definition of at least one year of use

* Mean time to first statin prescription for statin users (3.1 years)
† Mean time to fulfilment of statin user definition (4.1 years)

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Table 2 Distribution of person time and events according to use of statins before and after correcting for immortal time bias using Poisson regression and adjusted hazard ratios for starting insulin treatment

	Statin users*			Non-users†			Crude rate ratio‡	Adjusted hazard ratio§ (95% CI)
	Person years of follow-up	No starting insulin	Rate/ 100 person years	Person years of follow-up	No starting insulin	Rate/ 100 person years		
Biased time fixed analysis								
Immortal person time¶	2174	0		0	0			
At risk person time	1046	68		53 446	1350			
Total	3221	68	2.1	53 446	1350	2.5	0.84	0.74 (0.58 to 0.95)
Corrected time dependent analysis								
Immortal person time¶	0	0		2174	0			
At risk person time	1046	68		53 446	1350			
Total	1046	68	6.5	55 621	1350	2.4	2.68	1.97 (1.53 to 2.52)

* ≥1 year between the first and last statin prescription any time during follow-up.15

†No statin prescriptions or <1 year between the first and last such prescription any time during follow-up.15

‡ Poisson regression (assumes constant rate of event over follow-up).

§ Cox regression. Adjusted for age at cohort entry; sex; history of macrovascular disease, congestive heart failure, and hypertension; concomitant use of aspirin, β blockers, nitrates, angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics; and two validated measures of health status20 21

¶ Time from cohort entry (start of follow-up) until the day the definition of “at least 1 year of statin use” was met.

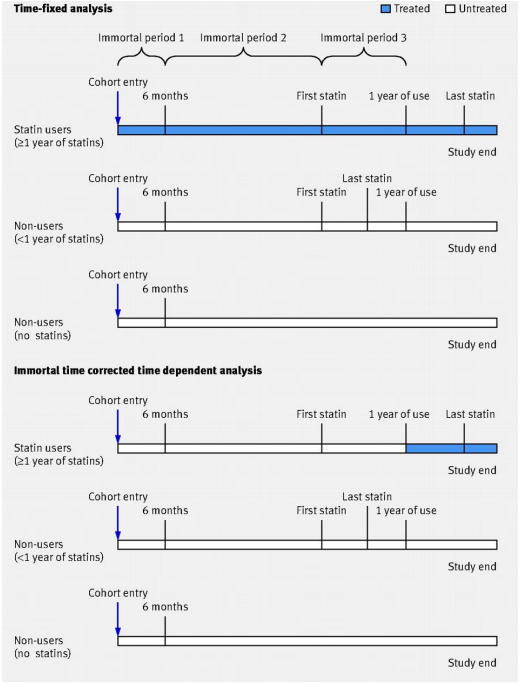
Table 3 Effect of correcting for different sources of immortal time bias from time fixed analysis on association between statin use and starting insulin

Source of immortal time*	Immortal and misclassified person time, years (proportion of total statin user person time (n=3221))†	Immortal period corrected by time dependent analysis	Corrected immortal and misclassified person time (years)	Adjusted hazard ratio‡ (95% CI)
All periods	2174 (67.5)	None	0	0.74 (0.58 to 0.95)
Period 1	266 (8.3)	1	266	0.82 (0.64 to1.05)
Period 2	1376 (42.7)	1 and 2	1642	1.37 (1.07 to 1.76)
Period 3	532 (16.5)	1, 2, and 3	2174	1.97 (1.53 to 2.52)

* Period 1=time from cohort entry until 6 months later (period during which cohort members could not receive a statin); period 2=time from 6 months after cohort entry until the first statin prescription; period 3=time from the date of the first statin prescription to one year later.

†Classified as treated in time dependent analysis (see table 2 for details).

‡Adjusted for age at cohort entry; sex; history of macrovascular disease, congestive heart failure, and hypertension; concomitant use of aspirin, β blockers, nitrates, angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics; and two validated measures of health status.[20 21]



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Validation of bias

To validate the presence of the immortal time bias, we repeated the same study and analyses in the same cohort but with **different treatments of interest: non-steroidal anti-inflammatory drugs and gastric acid suppressive drugs** (histamine-2 (H2) receptor antagonists or proton pump inhibitors). These drugs **were chosen because they are commonly prescribed and have no known beneficial effects on diabetes progression or the need to start insulin**.

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Table 4 Crude and adjusted hazard ratios for starting insulin treatment associated with use of non-steroidal anti-inflammatory drugs and gastric acid suppressive drugs before and after correcting for immortal time bias using Cox regression

	No of events	Person years	Crude hazard ratio	Adjusted hazard ratio* (95% CI)
Non-steroidal anti-inflammatory drugs				
Biased time fixed analysis:				
Non-users (reference)	706	27 390	1.00	1.00
Users	92	4 448	0.75	0.77 (0.62 to 0.96)
Corrected time dependent analysis:				
Non-users (reference)	706	28 935	1.00	1.00
Users	92	2 903	1.42	1.45 (1.16 to 1.83)
Gastric acid suppressive drugs				
Biased time fixed analysis:				
Non-users (reference)	1101	45 231	100	1.00
Users	87	3 967	0.85	0.90 (0.72 to 1.13)
Corrected time dependent analysis				
Non-users (reference)	1101	46 930	1.00	1.00
Users	87	2 268	1.76	1.84 (1.47 to 2.31)

*Adjusted for age at cohort entry; sex; history of macrovascular disease, congestive heart failure, and hypertension; concomitant use of aspirin, β blockers, nitrates, angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics; and two validated measures of health status.[20 21]

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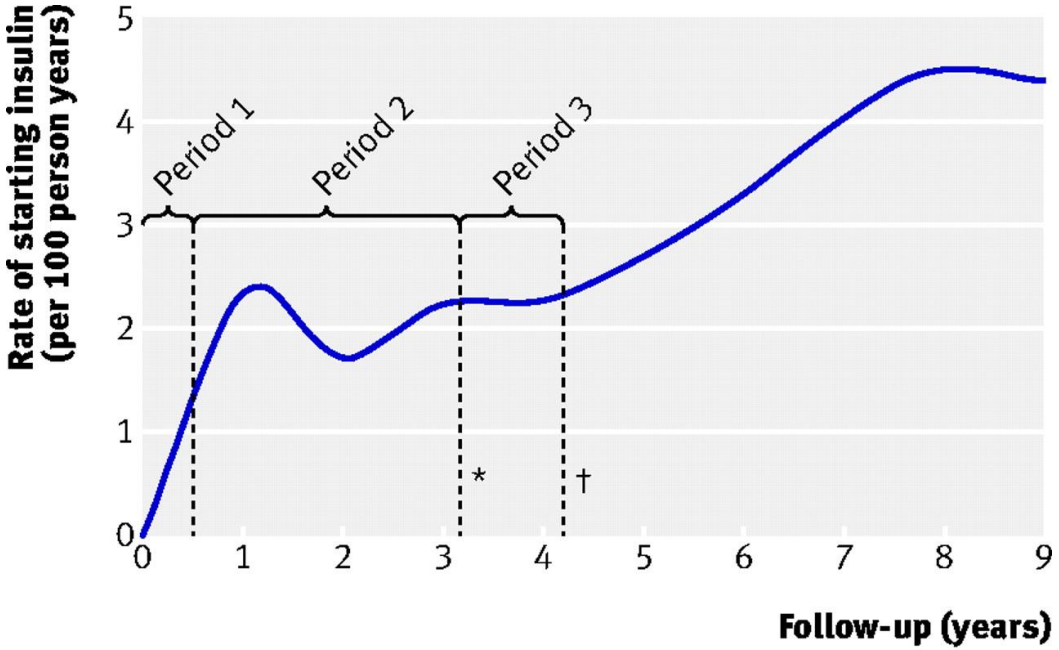
Accounting for immortal time

The immortal and untreated person time that was incorrectly allocated to the treated group in the time fixed analysis represented **two thirds of total follow-up for statin users. This resulted in a spuriously low rate of events for this group compared with that for non-users**.

We have also provided additional evidence of the **direct relation between the duration of the immortal period and the magnitude of the bias**.



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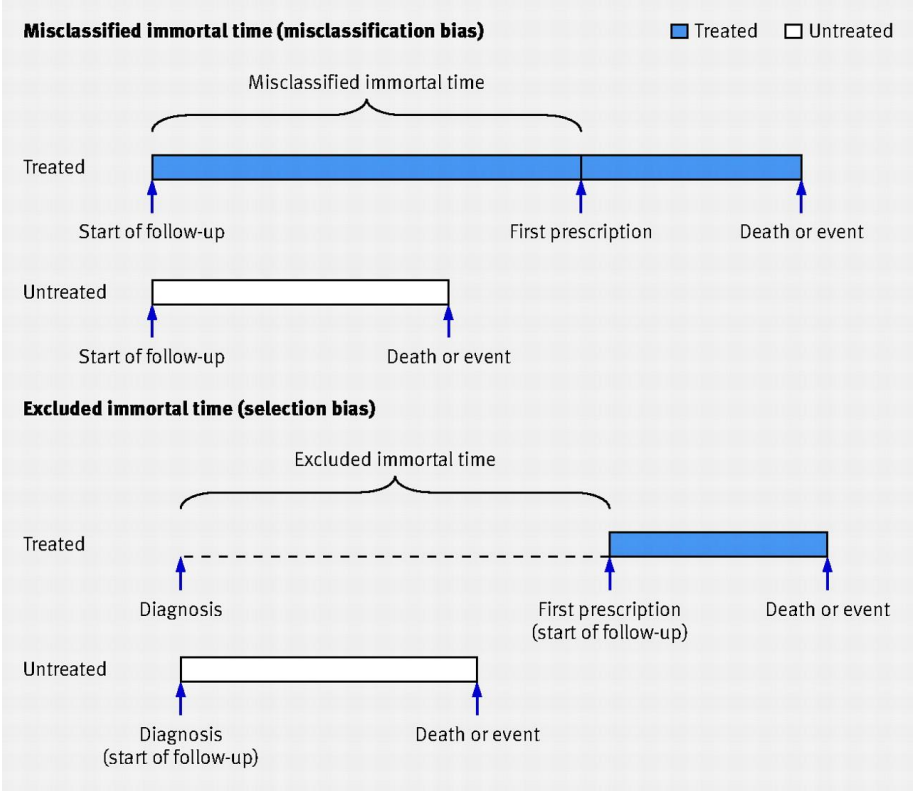
ITB example on treatment misclassification

bias can also be introduced when periods of immortal time are differentially excluded from the analysis (selection bias). This occurs when the start of follow-up is defined as the start of treatment for the treated group and the date of diagnosis for the untreated or comparator group



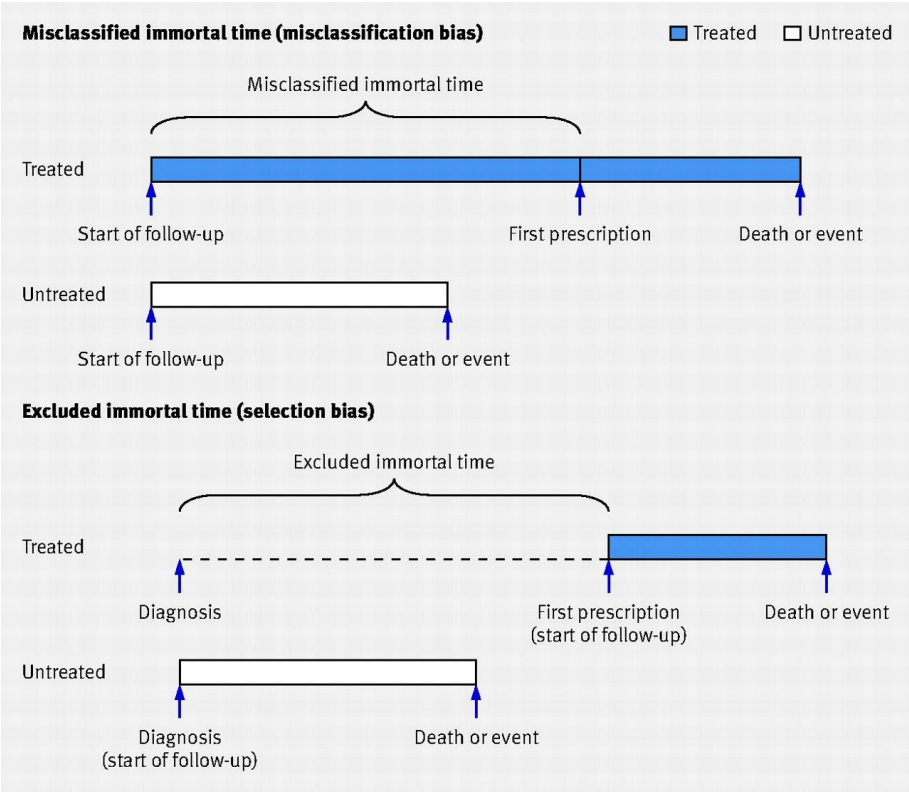
How to prevent immortal time bias?

Using a time dependent analysis
studying only “survivors” of the immortal period

By moving the start of follow-up to the end of the immortal period

By moving the start of follow-up to the date the treatment definition is met for users and a date assigned according to the distribution of users’ immortal time for non-users.

Alternatively, a time matched, nested case-control analysis of the cohort can be used, its inherent time dependent nature means that it is also free of immortal time bias



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Other sources of bias

Confounding by indication. As diabetes progresses, individuals are more likely to develop cardiovascular disease, an indication for statins.

Dichotomous definition of statin users in the time dependent analyses may have resulted in **residual misclassification** of treatment status. **Later events may have been incorrectly attributed to statin users rather than to non-users**. The long duration of follow-up and high rate of late events may have accentuated the effect of this differential misclassification. This may also explain why the associations studied were all >1.0 after we had corrected for immortal time bias.

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Conclusion

This bias is not specific to studies of drug effects. Consequently, all cohort studies should be assessed for the presence of immortal time bias using appropriate validity criteria

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Criteria for identifying immortal time bias in cohort studies

- Was treatment status determined after the start of follow-up or defined using follow-up time?
- Was the start of follow-up different for the treated and untreated (or comparator) group relative to the date of diagnosis?
- Were the treatment groups identified hierarchically (one group before the other)?
- Were subjects excluded on the basis of treatment identified during follow-up?
- Was a time fixed analysis used?

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Common manifestations of immortal time

- **Treatment defined as at least one prescription dispensed after hospital discharge**, when the discharge date represents the start of follow-up (cohort entry)—for example, dispensation of an inhaled corticosteroid after a hospital stay for chronic obstructive pulmonary disease
- **Treatment groups defined in terms of when after hospital discharge (start of follow-up) a prescription is dispensed**—for example, cardiac drugs dispensed within 7 days of discharge for acute myocardial infarction versus later or early versus delayed dispensation of clopidogrel post percutaneous coronary intervention
- **Treatment defined as at least one prescription dispensed after a diagnosis**, when the date of diagnosis represents the start of follow-up—for example, starting interferon beta after diagnosis of multiple sclerosis
- **Treatment status determined over the duration of follow-up**—for example, determining an individual's immunisation status at the end of each influenza season or use of β blockers any time during follow-up

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