Correspondence

Letter by Azoulay and Suissa Regarding Article, “Statins and the Risk of Cancer After Heart Transplantation”

To the Editor:

We read with interest the study published by Fröhlich et al in a recent issue of Circulation. The authors investigated the effects of statins in the prevention of cancer in 255 patients who underwent heart transplantation at the University Hospital Zurich between 1985 and 2007. The use of statins was associated with a 67% (hazard ratio, 0.33; 95% confidence interval, 0.21–0.51) risk reduction of cancer. We believe this important risk reduction may primarily be the result of immortal time bias.2

Immortal time bias is introduced by the method used to classify drug exposure, in this case to statins, during follow-up. As is common with such cohort studies, the majority of the 151 patients who were classified as statin users most likely did not start statins at the time of transplantation, but rather at some point during follow-up. As such, the time period between cohort entry and the first statin prescription is called immortal, because no cancers (the end point) could have occurred during this time period. Moreover, patients were not yet exposed during this immortal period, yet they were classified as statin users. It is then necessary to classify this immortal person-time period as unexposed until the time of statin initiation, and as exposed subsequently, using statistical techniques for time-dependent exposures.3 Doing so will avoid immortal time bias, which increases with the amount of immortal time in a study.2

This study in particular was based in an era during which the use of statins was not yet recommended for this population, and when these drugs were gradually being introduced on the market. As such, it is expected that a sizable proportion of the statin-exposed group was likely composed of individuals who received statins some time after their heart transplantation, thus likely augmenting the amount of immortal time.

Although the necessary data are not provided in the article to assess the magnitude of this potential bias, we can assume for illustration purposes that the 104 unexposed generated 650 person-years of follow-up, whereas the statin-exposed generated 1570 person-years of follow-up (using median follow-up times provided in Table 2). However, the latter included immortal person-time (ie, time between cohort entry and the first statin prescription where no cancer could have occurred). Assuming an average 3-year gap between cohort entry and the first statin prescription, a total of 453 immortal person-years would have been misclassified as exposed. By correctly reclassifying this person-time, the rate of cancer in the unexposed group would become 54/(650+453)=4.9 per 100 person-years, whereas the rate in the statin-exposed group would become 54/(1570-453)=4.8 per 100 person-years instead of 3.4 per 100 person-years, resulting in a corrected crude rate ratio of 0.98.

Although this illustration shows the potential impact of immortal time bias in cohort studies, it would be constructive if the authors redid their analyses by defining statin exposure in a time-dependent fashion, while also considering issues of latency and the impact of reverse causality.

Disclosures

None.

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References

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