Correspondence

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

To the Editor:

We read with interest the recently published study by Fröhlich et al.,1 which reported a 67% reduction of incident cancers for statin-treated patients after heart transplantation (HTX) and a significant reduction in all-cause mortality, which was not further quantified. The authors cited several observational studies in nontransplant patients where statin use has been associated with a decreased risk of cancer; however, we would additionally like to mention the results of a large randomized trial of >20,000 nontransplant patients with a mean follow-up of 11 years, where no reduction of cancer incidence of all sites or cancer mortality was observed.2

Although there might be a protective effect of statins, we are concerned that their beneficial effects might have been overestimated in this study for the following methodological reasons: In their study, the investigators assigned to the statin group all patients who received a statin during follow-up, stating that “statin therapy was initiated usually three to twelve months after transplantation.” However, follow-up started at the time of HTX ie, the time interval between HTX and the initiation of statin therapy was considered as exposed person-time, whereas it should have been classified as unexposed person-time. Thus, the denominator of the exposed group might have spuriously included unexposed person-time in the analysis. In Switzerland, the first statins were approved in 1990, and therefore the misclassified person-time might have been up to 5 years for patients who underwent HTX in 1985. Because no information on the cumulative time from HTX to initiation of statin use was provided, the magnitude of this potential bias is unclear. In the epidemiological literature, such a misclassification of person time has been referred to as immortal time bias and shown to falsely increase the therapeutic or preventive effect of medications in many studies.3 In the present study, immortal time bias could be prevented by using a time-dependent model that accounts for the unexposed person time from HTX to initiation of statin treatment.4

Secondly, we are concerned that unmeasured confounding might have biased the results. It has been shown that patients who use preventive medications, such as statins, have lower rates of clinical outcomes (eg, falls, fractures, skin infections, asthma/chronic obstructive pulmonary disease) compared with nonusers, indicating a better overall health status of statin users. Therefore, the protective effect of statins can be overestimated, if confounding factors related to health status and lifestyle are not assessed (healthy user bias).5

In their Cox regression analysis for the risk of cancer, the authors adjusted for age, sex, underlying condition for HTX, and treatment with immunosuppressants. For the outcome all-cause mortality, the authors computed unadjusted Kaplan–Meier estimates and log-rank tests. We wonder whether information on important possible confounders (eg, physical activity, smoking, diet, alcohol intake) would have been available and, for all-cause mortality, a multivariate analysis might have yielded more reliable results.

Overall, the authors have addressed an important area of research, although immortal time bias and healthy user bias might have exaggerated the protective effect of statins in their study.

Disclosures

None.

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References


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