Response to Letters Regarding Article, “Statins and the Risk of Cancer After Heart Transplantation”

We thank the authors Garbe, Suissa, and Vorlat for their interest in our study, and we would like to reply to the different issues raised in their letters. Dr Garbe outlined that a previous large randomized trial involving 20,536 patients with coronary artery disease, peripheral artery disease, or diabetes mellitus failed to demonstrate an improved cancer-free survival in patients who received 40 mg simvastatin and had an 11-year follow-up.2,3 However, there remain several methodological issues with this study. The mean follow-up in the original randomized trial was 5.3 years, and only inclusion of a nonrandomized post-trial observational time yielded a follow-up of 11 years. Importantly, 70% of patients were on statin therapy in both groups, the original statin and the original placebo group, 2 years after the original randomized study was finished. The switch of a significant proportion of patients to statin treatment may indeed explain why no reduction of cancer risk could be detected in the statin group in this study.2

In contrast, a recent study involving 295,925 patients demonstrated a clear survival benefit in patients with cancer who were on statin therapy. It is of note that statin trials or meta-analyses on cancer risk so far have mostly included only patients without immunosuppression and might therefore not be applicable to patients after solid organ transplantation, in whom the relative cancer risk may increase up to 100-fold as compared with the normal population.3

Some concerns were raised that potential confounders (healthy user bias, immortal time bias, smoking status, different eras of inclusion) have not been addressed in our original statistical analysis. As already extensively discussed in our article, observational studies are limited by potential unmeasured confounders, especially if the follow-up period is very long, as in the present study. Although a healthy user bias (heart transplant recipients obviously are not healthy users) is unlikely to have influenced the results, we acknowledge that all organ recipients have a close follow-up in a highly-specialized heart transplant clinic. Although data on physical activity or alcohol intake cannot be provided because of the retrospective nature of the study, we now present an updated Cox regression analysis for cancer risk and mortality. In both multivariate analyses we have adjusted for statin use now as a time-dependent covariate (accounting for potential immortal time bias attributable to delayed onset of statin therapy after heart transplantation), the smoking status at baseline, the year of transplantation, age, sex, and ischemic versus nonischemic heart failure.

These multivariate analyses further corroborate the findings that statin use may be associated with a reduced cancer risk (HR 0.51, 95% confidence interval, 0.29–0.93; P=0.026). Apart from age (hazard ratio, 1.05; 95% confidence interval, 1.02–1.08; P<0.0001), all other tested parameters, including the year of transplantation, were not associated with cancer risk. It is of note that only 18% of our patients were switched to new immunosuppressive drugs (mammalian Target Of Rapamycin inhibitors or tacrolimus) in recent years. Interestingly, statin use was also associated with a hazard reduction of 56% for overall mortality (95% confidence interval, 0.24–0.82; P=0.009). Because it is not possible to adjust away all potential confounders in an observational study, only an adequately powered, long-term, prospective, randomized trial will yield data robust enough to finally clarify the role of statins for cancer prevention in immunosuppressed patients.

Disclosures

Prof Lüscher receives research grants and honoraria from Pfizer. Prof Ruschitzka receives research grants and speaker honoraria from Pfizer and MSD.

Georg Marcus Fröhlich, MD
Frank Enseleit, MD
Mathias Wolfrum, MD
Michelle von Babo, MD
Michelle Frank, MD
Reto Berli, MD
Mathias Hermann, MD
Johannes Holzmeister, MD
Georg Noll, MD
Thomas F. Lüscher, MD
Frank Ruschitzka, MD

Cardiovascular Center, Cardiology
University Hospital Zurich
Zurich, Switzerland

Kaspar Rufibach, PhD
Division of Biostatistics, Institute for Social and Preventive Medicine
University of Zurich
Zurich, Switzerland

Markus Wilhelm, MD
Volkmar Falk, MD

Department of Cardiothoracic Surgery
University Hospital Zurich
Zurich, Switzerland

References

Response to Letters Regarding Article, "Statins and the Risk of Cancer After Heart Transplantation"
Georg Marcus Fröhlich, Frank Enseleit, Mathias Wolfrum, Michelle von Babo, Michelle Frank, Reto Berli, Mathias Hermann, Johannes Holzmeister, Georg Noll, Thomas F. Lüscher, Frank Ruschitzka, Kaspar Rufibach, Markus Wilhelm and Volkmar Falk

Circulation. 2013;127:e442
doi: 10.1161/CIRCULATIONAHA.112.147595
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/5/e442

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/