Statins and Incidence of Perioperative Mortality in Patients Undergoing Major Noncardiac Vascular Surgery

To the Editor:

Poldermans et al published a retrospective study in which they found evidence that statin use reduces perioperative mortality in patients undergoing major vascular surgery. We have, however, some methodological concerns pertaining to selection, information, and confounding bias that were not discussed but that may have harmed validity.

First, the authors do not provide data on length of hospital stay. Assuming a protective effect of statins, the identification of cases determined as patients who died in-hospital may have led to nonrandom misclassification because healthier patients who die after leaving the hospital can never become cases. It would have been better had the authors taken a fixed time window.

In the design, the type of surgery and calendar year were the basis of stratification. This may have introduced confounding bias, because it is conceivable that type of surgery is related to statin use as well as perioperative mortality. Analyses stratified by type of surgery probably would have been of additional benefit.

Although the description of the ascertainment of drug use does not allow any conclusion, we assume that these are interview data. These data are unreliable with respect to aspects of dose and duration. Moreover, because actual chronic exposure of statins varies over the calendar year (a 6-fold increase in the study period) and age, interview data have varying sensitivity and specificity with regard to this long-term use. This may have led to (non-) random misclassification of exposure, which could bias the risk estimate in any direction.

In retrospective studies, subjects with missing values often represent a selective category. In case of missing values, the choice is to limit the analysis to the complete cases or to analyze all available data. Both methods may suffer from substantial bias and may only be applied in a valid way if the strong assumption of “missing completely at random” holds for the missing values, i.e., the missing value is not related to the other measured data or to unmeasured data. To judge validity, it is, therefore, important to at least describe the characteristics of this population and/or to perform a sensitivity analysis.

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Response

We thank Drs in ’t Veld and Arbous for their positive response and constructive comments regarding our manuscript.

We demonstrated that patients undergoing noncardiac major vascular surgery who died during their hospital stay, excluding those who died after >30 days of continuous hospital stay, had significantly lower statin use than controls, who were selected from among vascular surgical patients who survived the hospital stay or 30 days, whichever came first. We agree with Drs in ’t Veld and Arbous that patients who survived surgery and were dismissed from the hospital alive could never become a case, and nonrandom misclassification could have occurred. However, the majority of fatal events after vascular surgery occur within 72 hours, and the incidence of such complications is extremely low in the period from hospital discharge to 30 days (≤0.5%). Therefore, for practical reasons, we did not attempt in retrospect to complete a follow-up of all 2816 patients up to 30 days.

Drs in ’t Veld and Arbous further suggested that analyses stratified by type of surgery would have been of additional benefit. We agree with this comment, and actually we have performed our analysis accordingly. In the Results section (p 1849), we indicated that there was no evidence of a heterogeneity in the difference of statin use between cases and controls according to type of surgery.

A third comment relates to the quality of the presented data. We would like to emphasize that drug use was not based on interview data only. Actually, data were retrieved from all medical records, including referral notes of the general practitioners, as well as patient discharge letters. Therefore, we consider these data to be reliable.

The final comment about the importance of missing data in a retrospective study is well taken. However, we do not report any missing data in this study.

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Circulation. 2003;108:e151
doi: 10.1161/01.CIR.0000100887.99439.83
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 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:
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