Association Between Statins and Mortality

To the Editor—Vandermeer et al [1] reported the results of a retrospective cohort study evaluating the association between statin use and risk of mortality among older adults hospitalized within 14 days of a positive influenza test. In unadjusted analyses, the association was nonsignificant (odds ratio, 0.71; 95% confidence interval, .49–1.03), but in adjusted models use of statins was associated with a significant 41% reduction in risk of death within 30 days of the positive influenza test.

The influence of a healthy-user bias in this association is not only possible but, in the absence of other information, is the most likely explanation for the observed apparent benefit of statin therapy. Study subjects who were taking a statin at the time of admission had at some time in the past been prescribed that medication, suggesting that they had an estimated life expectancy that would reasonably be considered to allow the long-term benefits of statin therapy to outweigh the risks, and they were adherent in that they had continued their prescribed medication. There may thus be very influential differences between subjects who were taking statins and those who were not. This bias is suggested by studies that have found that older adults who are more adherent to statin therapy are at substantially lower risk of burns, falls, and motor vehicle crashes than their less adherent peers [2]; that, among elderly adults, receipt of preventive medications such as antiglaucoma drugs are paradoxically associated with a significantly lower risk of all cause mortality [3]; and that, in numerous analyses of subjects randomized to receive placebo in prospective clinical trials, subjects who were more adherent to placebo were at significantly lower risk of all-cause mortality than those who were less adherent [4–6]. The associations can only be due to bias and, in all cases, persisted despite attempts to control for confounding by adjustment for indicators of comorbidity.

The importance of the use of negative controls to detect bias in observational studies is increasingly recognized [7], and the use of negative exposure and outcome controls in the study by Vandermeer and colleagues would have potentially aided interpretation of their findings. To determine the specificity of their reported association, they could have evaluated the association of mortality with other exposures, such as medications unlikely to prevent influenza-related mortality (negative exposure control), and with other outcomes, such as risk of mortality beyond the 30-day window (negative outcome control). Future studies should incorporate these methods in order to allow better estimation of the likelihood that the observed association in the hypothesized exposure-outcome relationship is in fact causal.

Notes

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