Reply to Strandberg and Tienari

To the Editor—We examined whether statins were associated with a heightened risk of herpes zoster in patients aged ≥66 years and found a small but significantly increased risk among statin users relative to a propensity-matched group of nonusers of these drugs. As noted in our study [1], we did not have access to serum cholesterol levels, and could therefore not account for this variable when matching users and nonusers of statins. We did, however, consider an array of clinically important predictors of statin use when deriving the propensity score. Strandberg and Tienari suggest that despite propensity score matching, users and nonusers of statins differed with respect to cardiovascular disease burden [2]. However, standardized differences for all baseline variables were <0.1, indicating that intergroup differences between these covariates were negligible [3,4].

Strandberg and Tienari are correct that unmeasured confounders and confounding by indication are potential threats to the validity of all observational studies, including ours. They cite 2 studies supporting their hypothesis that serum cholesterol and the apolipoprotein E epsilon 4 (APOE4) allele are associated with herpes zoster [5,6]. For these variables to act as confounders, they must be extraneous risk factors for herpes zoster, and the studies cited by Strandberg and Tienari are problematic in supporting this assertion [7]. In the first study, investigators found that cholesterol levels were higher among 12 heart transplant patients who developed herpes zoster in the month prior to the episode than those of the same patients within the first posttransplant year (P = .007) or those of control patients within the first posttransplant year (P = .025) [5]. Although these data suggest that a correlation may exist between serum cholesterol and herpes zoster, the report is limited by a very small sample size, the high-risk nature of the patients, and a lack of control for potential confounders, importantly statin use. The second study compared the distribution of APOE alleles among 104 herpes zoster patients with those of a control group [6]. The authors found that women with herpes zoster were more likely to be homozygous for APOE4 relative to women with no history of herpes zoster, although the absolute numbers were too small to draw firm conclusions [6]. Similar findings were not observed in men, no data on cholesterol levels were provided, and another report found no difference in the distribution of APOE alleles between patients with and without herpes zoster [8].

Although conclusive evidence associating cholesterol levels and/or APOE4 with herpes zoster is lacking, this may simply reflect a deficit in the state of knowledge regarding the pathophysiology of varicella zoster reactivation. As with most diseases, the etiology of herpes zoster is multifactorial, and it is possible that cholesterol and statin use are both components of a specific causal pathway that results in varicella zoster virus reactivation. We agree with the editorialist’s call for replication of our findings in other databases [9].

Notes

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Tony Antoniou,1,2,3 David N. Juurlink,3,4,5 Muhammad M. Mamdani,2,3,4,6,7 and Tara Gomes2,3,4,6

1Department of Family and Community Medicine, and 2Keenan Research Centre of the Li Ka Shing Knowledge Institute, St Michael’s Hospital, 3University of Toronto, 4Institute for Clinical Evaluative Sciences, 5Sunnybrook Research Institute, and 6Applied Health Research Centre, St Michael’s Hospital, Toronto, Ontario, Canada; and 7King Saud University, Riyadh, Saudi Arabia
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