Mondul et al. (1) concluded that statin therapy is unlikely to be beneficially influencing the development or course of lower urinary tract symptoms (LUTS) in older men. The investigators recognized the importance of controlling confounding. However, there are several limitations that were not addressed by the authors that could have led to a null finding.

First, statins have been hypothesized to lower the risk of LUTS through their cholesterol-lowering and/or anti-inflammatory effects (1). When using a reference exposure, it is crucial that that exposure does not have similar effects as the drug of interest. However, several antihypertensive drugs, which were used as a reference exposure, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and third-generation β blockers have been reported to possess similar anti-inflammatory properties (2–4). Hence, their choice has likely resulted in bias toward a null finding.

Second, even if antihypertensive drugs did not have anti-inflammatory properties, using these drugs as a reference group (1) does not prevent confounding by indication. Patients using statins concomitantly with antihypertensive drugs will likely have higher baseline cholesterol levels than patients using only antihypertensive drugs. In fact, excluding patients with a history of cardiovascular disease (1) may increase bias, because a population remains in which treatment decisions are even more determined by cholesterol levels.

A third sensitivity analysis, which the authors restricted to patients with hypercholesterolemia (1), may indeed have reduced confounding. However, residual confounding likely remains as a result of using a binary indicator for cholesterol levels and the presence of other unmeasured risk factors.

Third, the study population was not restricted to new users, which may result in selection bias (5). Suppose statins would decrease the risk of LUTS, whereas antihypertensive drugs would have no effect, and follow-up is started 2 years after treatment initiation. The group of prevalent statin users will then likely include more susceptible patients than the antihypertensive user group (5). This selection bias is induced because the susceptible patients using antihypertensive drugs are less likely to reach the study start event-free because they are, in contrast to the statin users, not protected during the first 2 years after treatment initiation. Thus, by including prevalent users, the results are likely biased away from a protective association.

Fourth, by including prevalent users, potential confounders are measured after treatment initiation in part of the population. Because some of the potential confounders for which the authors adjusted may consequently be affected by prior treatment, the results may be further biased toward the null (5).

In summary, we agree with the authors that confounding must be addressed in observational studies. However, we want to emphasize that one should also be aware of selection bias and preferably restrict the analysis to incident users. Moreover, it should be carefully considered whether the comparison drug could display a similar effect as the drug of interest and whether the indications of both drugs are really similar.

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