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Trial Evidence for Statin-Based Primary Prevention Remains Dubious

Although the primary prevention of atherosclerotic disease events by the use of statins is both widely promoted and commonly prescribed, Mills et al. (1) astutely note that the clinical trial evidence for this clinical practice is inconsistent. There has been a lack of compelling evidence that statins prevent cardiovascular events in initially healthy adults generally, and a near absence of trial evidence for treatment of hypercholesterolemia in women and the elderly.

Unfortunately, the meta-analyses and results presented by Mills et al. (1) can be questioned in several respects. First, although declaring exclusion of trials whose subjects included a large proportion with pre-existing coronary heart disease, the authors do include the entire PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) sample even though 2,565 participants (44%) had pre-existing heart disease and the trial report provides results separately for the primary prevention arm (2). In addition, the meta-analysis includes 5 trials enrolling only patients with known clinical peripheral vascular disease or demonstrable carotid artery atherosclerosis. Finally, persons with diabetes are widely known to have a substantially higher risk for cardiovascular events than nondiabetic persons, yet the meta-analysis includes 2 large trials of diabetic patients. Trials testing the efficacy of statins in diabetic subjects are appropriately summarized elsewhere (3) and cannot be used to justify statin treatment in nondiabetic persons.

Mills et al. (1) could better advance this field by presenting analyses that more completely exclude evidence derived from patients with pre-existing atherosclerosis and diabetes. Furthermore, we still have no assembled evidence to justify prescribing statins to generally healthy women or elderly patients.

***Matthew F. Muldoon, MD, MPH**

*University of Pittsburgh
Center for Clinical Pharmacology
506 Old Engineering Hall
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania 15260
E-mail: mfm10@pitt.edu

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Reply

In our systematic review (1) we decided a priori to include trials in which <50% of the population had a history of coronary heart disease. The complete PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) trial fulfills our eligibility criteria (2). Although the PROSPER trial reported the results of their primary composite outcome for the primary prevention group, they did not report the results for the individual components of their composite. Thus, this information does not meet our specified end point criteria, because we excluded composite outcomes, for good reason (3).

We believe that there is a continuum of risk among diabetic patients, and we do not believe that younger, lower-risk patients should be considered at the same risk as those patients enrolled in secondary prevention trials (4). We excluded trials in high-risk diabetic patients, because we accept that their expected event rates are similar to patients with established vascular disease.

When we exclude the trials with predominantly diabetic patients and the PROSPER trial, the results of our meta-analyses are unchanged for both all-cause mortality (relative risk [RR]: 0.93, 95% confidence interval [CI]: 0.87 to 0.99, $p = 0.039$, $I^2 = 5.6\%$, $p = 0.38$) and cardiovascular disease (CVD) mortality (RR: 0.84, 95% CI: 0.72 to 0.98, $p = 0.025$, $I^2 = 12.3$, $p = 0.31$). Therefore, we stand by our conclusions.

This letter gives us the opportunity to update our analysis in light of the largest primary prevention trial yet, the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial of rosuvastatin for primary cardiovascular prevention (n = 17,802) (5). When we add this trial to our primary analysis, all-cause mortality is RR: 0.92 (95% CI: 0.86 to 0.98, $p = 0.006$, $I^2 = 14\%$, $p = 0.26$) and CVD mortality is RR: 0.85 (95% CI: 0.76 to 0.95, $p = 0.004$, $I^2 = 30\%$, $p = 0.10$).

There is clear evidence for primary and secondary prevention of clinical events across the broad populations involved, including women (6). History has displayed how naïve subgroup concerns can lead to withholding effective treatments from vulnerable populations (7).

***Edward J. Mills, PhD, MSc**
Philip J. Devereaux, MD, PhD

*McMaster University
1200 Main Street West
Hamilton, Ontario L8N 3Z5
Canada
E-mail: millsej@mcmaster.ca

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