Statins for Primary Prevention in Older Adults: An Unresolved Conundrum

The value of statins for primary prevention of cardiovascular disease (CVD) in older adults is controversial,[1,2] primarily because individuals aged 75 and older, and especially those aged 80 and older, have been markedly underrepresented in statin clinical trials. This controversy is reflected in the 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, which states that "initiation of statins for primary prevention of atherosclerotic CVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care."[3] Similarly, in a recent editorial, Gurwitz and colleagues opined that, "In the absence of clear evidence of net benefit for statins for primary prevention in adults older than 75 years and uncertainty about the risks of therapy, clinicians might reasonably follow a shared decision-making approach in discussing the use of statins for this indication with older patients."[4]

Despite the paucity of data from high-quality clinical trials, the question of whether to prescribe (or de-prescribe) statins in individuals aged 75 and older without known CVD is one that clinicians confront virtually every day. Thus, new evidence to help guide such decisions is needed, and therein lies the importance of the study by Orkaby and colleagues reported in this issue of the *Journal of the American Geriatrics Society*.[5]

The authors conducted a propensity analysis using a one-to-one greedy-matching protocol to examine the association between statin use and mortality and cardiovascular (CV) events in 1,130 matched pairs of male physicians aged 70 and older (median age 77) without preexisting CVD who participated in the Physicians' Health Study and were followed for a median of 7 years. As shown in the authors' Table 1, statin users and nonusers were well matched on relevant baseline characteristics.

The principal findings of the study were that all-cause mortality was 18% lower in the statin group (hazard ratio (HR) = 0.82, 95% confidence interval (CI) = 0.69–0.98), and although not statistically significantly so, there were fewer major CV events and strokes in those receiving statins. In subgroup analysis, the effect of statins on all-cause mortality was more pronounced in participants aged 70 to 76 (HR = 0.83, 95% CI = 0.61–1.11) than in those aged 77 and older (HR = 1.14, 95% CI = 0.89–1.47) at baseline, but the CIs overlapped. Participants with baseline total cholesterol of 200 mg/dL or greater who were taking statins experienced fewer major CV events than those who were not (HR = 0.68, 95% CI = 0.50–0.94), while those with baseline cholesterol of less than 200 mg/dL who were taking statins had more CVD events than those who were not (HR = 1.43, 95% CI = 0.99–2.07), although there was no evidence of a differential effect of statins on mortality as a function of baseline cholesterol. The effects of statins on mortality and CV events were similar in participants with and without functional limitations.

How should these findings be interpreted? The authors concluded that statins were associated with lower mortality and a nonsignificantly lower risk of CV events in this cohort of male physicians aged 70 and older without known CVD. In our opinion, the findings warrant a more-nuanced interpretation. Although CIs for the effect of statins on mortality in participants aged 70 to 76 versus those aged 77 and older at baseline overlapped, the test for interaction was marginally significant ($P = 0.047$), suggesting that any benefit of statins may be limited to the younger subgroup. There was also no evidence that statins reduced major CV events in participants aged 77 and older at baseline (HR = 1.05, 95% CI = 0.77–1.45).

The apparent lack of benefit of statins for primary prevention in participants aged 77 and older at baseline in the Physicians' Health Study is consistent with prior reports. As the authors noted, a metaanalysis of eight primary prevention trials in older adults (mean age 73) found fewer CV events but not lower mortality.[6] Similarly, the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin failed to show a survival benefit in 5,695 individuals aged 70 and older followed for a median of 1.9 years.[7] More recently, an analysis from the lipid arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found that pravastatin 40 mg compared to usual care (no statin) was associated with mortality hazards of 1.08 (95%CI 0.85-1.37; $P = 0.55$) for adults aged 65 to 74 years and 1.34 (95% CI 0.98-1.84; $P = 0.07$) for those 75 years and older.[8] Another analysis found that treatment of all U.S. adults aged 75 to 94 with a statin would increase disability-adjusted life-years and would be cost effective, but even a small adverse effect of statins on health-related quality of life would eliminate these benefits.[9,10]

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Apart from these considerations, the study has some limitations, most of which the authors acknowledge. The study cohort comprised relatively healthy male physicians, and the findings may not be applicable to women or older adults with multimorbidity or frailty. Despite propensity matching, there was potential for residual confounding, including confounding by indication. The lack of information on statin use during follow-up precluded conducting a time-varying analysis that could have provided further insights into the association between statin use and clinical outcomes.

Another limitation relates to the method of conducting the time-to-event analysis. The metric of time that was used was time since enrollment rather than age at event. Age and risk are confounded. Of greatest import is the dichotomization of age at 76. In a study with up to 12 years of follow-up (median 7 years), all surviving participants, including those initially younger than 77, would age into the older subgroup (≥77), and many of the subjects in the younger group at baseline spent the majority of the follow-up period aged 77 and older.

There are two possible solutions to this problem. First, the authors could have used time-varying covariates to define age group as the actual age group at the time of the event (and, similarly, for statin use at the time of the event, had that information been available). Second, the authors could have defined the metric of time as age at event, rather than time to event, with left censoring to address the immortal time. Such an analysis could have easily incorporated age group membership at the time of the event. Thus, the results presented must be interpreted as age cohort effects that fail to consider the effect of increasing age over the course of follow-up.

In the end, the study by Orkaby and colleagues is important because it adds to the ongoing discussion about the role of statins for primary prevention in older adults. The findings support the use of statins for primary prevention in selected individuals up to age 76 at baseline (especially those with high total cholesterol), but their value in individuals aged 77 and older is uncertain. There is a compelling need for prospective randomized trials to provide more definitive data on the utility of statins for primary and secondary prevention of CVD in individuals aged 75 and older. The ongoing Australian Statin Therapy for Reducing Events in the Elderly Trial is randomizing subjects aged 70 and older without CVD, diabetes mellitus, advanced kidney disease, or dementia to atorvastatin 40 mg or placebo.[11] The primary outcome is disability-free survival outside long-term residential care. Target enrollment is 18,000 participants, and the trial is projected to conclude in December 2020. At the time of this writing, the National Institutes of Health is also contemplating a statin trial in older adults; the authors of this editorial strongly support such an initiative.

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