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Selecting the Optimal Design for Drug Discontinuation Trials in a Setting of Advanced, Life-Limiting Illness

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To the Editor

We read with great interest the recent study on discontinuing statin therapy in individuals with advanced illness by Kutner and colleagues.¹ Though we appreciate the spirit of the study and the difficulty of conducting a randomized clinical trial in this challenging population, we disagree with the authors' interpretation that the results suggest that stopping statin medication therapy is safe according to the prespecified criteria for noninferiority. As is stated in the results, the noninferiority end point for the primary outcome of death within 60 days was not met. The statin discontinuation group had 23.5% mortality at 60 days vs 20.5% in the continuation group, an absolute risk difference of 3.5% (90% CI, -3.5% to 10.5%). The possible excess mortality of up to 10.5%, indicated by the upper limit of the 90% CI, is over twice the value of the noninferiority margin of 5% selected by the authors. Consequently, claiming that stopping statin therapy is safe appears to overstate the findings for the primary outcome of the study.

Furthermore, the authors failed to consider this result in the context of the findings for their secondary outcomes. They report that the discontinuation group had a median survival of 229 days vs 190 days for the continuation group, a meaningful absolute increase of 39 days (though fewer than a third of individuals overall survived past 180 days). The 90% CI for this difference is not given, making it difficult to interpret whether the estimate for this increase was within the noninferiority margin. Regardless, the point estimate appears to suggest a potential benefit in survival for the statin discontinuation group. Taken together, we suggest an alternate interpretation of the study findings: discontinuation of statin therapy may be associated with a small increase in 60-day mortality but may also be associated with modestly increased survival in those surviving past 60 days. Additional data on the proportion of deaths within 60 days attributable to cardiovascular causes would be helpful to better interpret these findings.

Despite the limitations of the study by Kutner and colleagues,¹ we wholeheartedly agree with the authors' assertion that patient-centered decision making regarding statin therapy

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discontinuation is warranted given the uncertain benefit of statin therapy with life-limiting illness and functional decline. We appreciate this important contribution to the evidence base for caring for individuals with advanced illness and look forward to seeing longer-term outcomes with additional follow up of this study population.

References

1. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med.* 2015; 175(5):691–700. [PubMed: 25798575]