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Evidence-Based Deprescribing of Statins in Patients With Advanced Illness

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Along with acknowledgment of the many advantages of statins, increasing focus has been placed on diminishing benefits and, in some cases, harms of this drug class when used in patients-with limited life expectancy. Statins are prescribed for only preventive purposes, without symptomatic benefit to patients. As such, in some circumstances these agents, which have an estimated time until benefit of more than 2 years, depending on the indication and outcome, are not considered useful in patients with limited life expectancy and are even considered futile at the end of life.[1]

Several observational studies have demonstrated that statins continue to be prescribed for patients with limited life expectancy. In one study,[2] up to 62% of patients with cancer and a poor prognosis continued to receive statins, often for primary prevention of cardiovascular disease. In another trial,[3] the time to stopping treatment with a statin was similar in patients with cancer and in those without cancer, and more than 31%of patients with cancer filled a statin prescription within 30 days of death. Patients with other life-limiting illness, such as advanced dementia, also continued to receive statins even at the end of life.[4]

Why are statins continued until the end of life? This is a complex multifaceted issue. Stopping statin therapy in the case of limited life expectancy has been advocated as a relatively straightforward decision; a recommendation of the Choosing Wisely campaign advises not to start lipid-lowering medications in patients with limited life expectancy.[5] However, at present, little is known about the barriers faced by clinicians when stopping statin treatment in patients with limited life expectancy. There may be continued uncertainty on the part of clinicians about the benefits afforded by continuing the treatment, particularly if a patient has been receiving the medication for a long time without adverse effects. Furthermore, clinicians and patients may be uncertain about the benefits and harms of discontinuing the therapy.

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In this issue of *JAMA Internal Medicine*, Kutner and colleagues[1] present the results of its first multicenter study: a pragmatic randomized trial of statin therapy discontinuation in patients with advanced disease and limited prognosis. This study suggests that stopping statin treatment at the end of life may be safe and is potentially associated with improved quality of life and reduced cost. The importance of these results cannot be overstated; clinicians wishing to recommend discontinuing the treatment in patients with advanced disease and limited life expectancy now have an evidence base to inform their decision making. Indeed, patients and their caregivers can now be advised that both withdrawing and continuing statin therapy are reasonable alternatives in advanced illness and in the absence of recent cardiovascular events.

Will this study provide the evidence needed to help clinicians deprescribe statin treatment? Kutner et al[1] suggest that if this were a trial of a new therapy rather than discontinuation of a proven therapy, it would be considered a success and the drug would be expedited to the market. A significant strength of this study is the inclusion of patients for whom clinicians would not be surprised if they died within the next year. A barrier to deprescribing in advanced illness is determining the patients who are eligible for such interventions—in other words, deciding when is the most appropriate time to start discontinuing medication. The “surprise” question used by Kutner and colleagues is a useful measure that should be easy for clinicians to understand and replicate in their practice. Those who still favor the use of statins in advanced illness may point to the fact that the noninferiority end point was not reached for the difference in survival or in cardiovascular events between patients in the statin treatment discontinuation and continuation groups. There were significant, but small, differences between the groups in the results of quality-of-life subscales, and there were no significant differences in physical symptoms or performance status, indicating that the clinical benefits of discontinuing the treatment were small.

The findings of this study[1] may provide reassurance to patients or caregivers and their clinicians who are considering stopping statin therapy that doing so may not incur harm in the setting of advanced illness and limited life expectancy. Discussions about discontinuing the therapy should occur in the context of shared decision making with a focus on patient and caregiver preference, particularly given that one course of action is not clearly superior to another, as shown in this study.[1] Patients’ preferences are particularly important, further high-lighted by the fact that among the patients eligible for the study who did not enroll, 56.1% were unwilling to participate. Perhaps one of the first steps to deprescribing a statin should be to determine whether a patient has any interest in stopping the medication.

To incorporate the results of this trial into practice, several issues have to be overcome. Two of these issues—the timing of communicating about medication discontinuation with patients and their caregivers and the time required to engage in shared decision making on deprescribing preventive medication therapy—are practical challenges. To support this process, Scott and colleagues[6] propose a protocol that lays out 5 essential steps required in decision making about deprescribing: (1) ascertain all drugs the patient is currently taking and the reasons for each one, (2) consider the overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention; (3) assess each drug regimen for its eligibility to be discontinued, (4) prioritize drug treatments

for discontinuation, and (5) implement and monitor the drug discontinuation regimen. Such a frame-work may be useful to practicing clinicians who struggle with prioritizing and stopping medications. Furthermore, the authors present multiple strategies by which deprescribing could be facilitated in clinical practice, incorporated into research protocols, developed into guidelines, integrated into educational interventions, and included in policy initiatives. This review provides a broad base of recommendations to further the quality and practice of deprescribing and rationalizing medication use.

Moving forward, the statin trial[1] serves as a model for similar trials in advanced illness for other therapeutic drug classes, including treatments for type 2 diabetes mellitus, hypertension, and other chronic illnesses for which patients receive many preventive therapies. The study also provokes the issue of what level of evidence will support the deprescribing of medications for patients with advanced illness. High-quality evidence is required to inform guidelines and change policy. Guidelines that incorporate deprescribing are greatly needed, particularly when counterbalancing clinical practice guidelines that recommend the initiation of preventive medication therapy without consideration of multimorbidity, advanced illness, or limited life expectancy. Indeed, in the case of statins, following the new cholesterol guidelines[7] will double the number of people eligible for statin therapy and will increase the number of people aged 60 to 75 years who are receiving statins from 48% to 78%. As suggested by Scott and colleagues,[6] the results from the statin treatment discontinuation trial could be incorporated into clinical practice guidelines. Such guidelines explain how to initiate therapy but seldom explain how to deprescribe: this situation cannot continue. Guidelines should, in the very least, acknowledge that deprescribing might be warranted in patients with advanced illness. Future deprescribing trials should be designed with a careful consideration between achieving the high-quality level of evidence required for inclusion into clinical practice guidelines while balancing the practical application of the results by including frail patients with advanced illness into pragmatic trials that simulate real-world conditions.

We commend Kutner and colleagues[1] for their work on statin discontinuation. The trial provides a great starting point, and we must continue this trajectory if we are to recognize the development and implementation of evidence-based deprescribing approaches into clinical practice.

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