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Statin therapy in the frail elderly: A nuanced decision

THE GROWING ELDERLY POPULATION varies widely in functional capacity and mental agility. Age by itself is not a reliable indicator of physiologic performance in patients with cardiovascular disease.¹

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The concept of frailty helps to identify elderly patients most susceptible to adverse outcomes. Frailty is a powerful indicator of disability, loss of independence, hospitalization, and death. In a patient whose health is declining, frailty is an appropriate impetus for the clinician and patient to reevaluate the goals of care.

In this issue of the *Journal*, Mallery et al² address an important topic: the use of preventive lipid-lowering therapies in frail patients with limited life expectancy. For these patients, they recommend against lipid-lowering therapy for primary prevention, and only in extenuating circumstances for secondary prevention.

No trials have evaluated lipid-lowering therapy specifically in frail older adults, and therefore, these recommendations are based on an evidence-informed appraisal of the literature. Mallery et al² suggest that in the frail elderly, improvement in function and quality of life are more relevant end points than traditional cardiovascular outcomes. They conclude that available evidence does not support lipid-lowering therapy for most patients with advanced frailty.

POINTS TO CONSIDER

Mallery et al² effectively articulate the need for frailty-specific care. Multimorbidity, polypharmacy, and increased adverse drug effects

require special attention in the frail elderly. The authors make a sound argument against lipid-lowering therapy for primary prevention in the severely frail elderly, in whom the evidence for short-term benefit is not compelling. They also recommend against nonstatin lipid-lowering medications, and against statin therapy for heart failure, which is consistent with major guidelines. In the modern era of reflexive testing and prescribing, the authors' "less is more" approach provides needed encouragement for thoughtful care in these vulnerable patients.

However, certain points of contention deserve additional consideration, including the imprecise definition of frailty, potential benefits and harms of statin therapy in high-risk patients, and the importance of shared decision-making.

How should frailty be defined?

Frailty biology is a field of ongoing research, and there is a lack of consensus on how best to define the condition.³ Estimates of the prevalence of frailty among older adults with cardiovascular disease range from 10% to 60%, owing to considerable variability in the tools used for frailty assessment.⁴

Mallery et al² consider an individual to be severely frail if he or she requires assistance with basic activities of daily living as the result of any physical or cognitive deficit (derived from the Clinical Frailty Scale or Frailty Assessment for Care Planning Tool). While functional dependence may be a consequence of frailty, this generalized definition does not characterize the clinical phenotype, which includes slowness, weakness, low physical activity, exhaustion, and unintentional weight loss.

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Furthermore, this definition offers no insight into the unique characteristics, causes, and clinical course related to frailty. Significant heterogeneity among “frail” patients precludes a uniform treatment approach in this population.

Do statins benefit frail patients at high risk?

Regarding secondary prevention, the authors highlight a meta-analysis by Afilalo et al,⁵ the most comprehensive assessment to date of statin therapy in elderly patients with documented coronary heart disease. This study included nearly 20,000 elderly patients in nine secondary prevention trials, including the secondary prevention subgroup of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial.⁶

Afilalo et al⁵ calculated that statin therapy reduced the rates of all-cause mortality by 22% and coronary death by 30%, with even greater reductions in the rates of nonfatal myocardial infarction, stroke, and revascularization. Furthermore, the absolute risk reduction was higher and the number needed to treat was lower in those over age 80. Overall, these data convincingly showed that high-risk patients ages 65 to 82 enrolled in clinical trials derive substantial benefit from statin therapy.

Mallery et al² contend that many of the secondary prevention statin trials evaluated composite outcomes over many years of follow-up and therefore are not generalizable to the frail elderly. However, the Afilalo meta-analysis⁵ does not provide patient-level data, and therefore the benefit for different clinical and demographic subgroups is unknown. It is only speculative to infer that those with frailty are unlikely to benefit. In fact, the improved outcomes observed with increasing age would argue against this notion.

Given the compelling data supporting statin therapy in the high-risk elderly population, some patients and clinicians may reasonably feel there is value in statin therapy—even in those with advanced frailty.

What about symptoms, disability, quality of life, and short-term benefits? Asymptomatic or “silent” myocardial infarction is associated with angina, congestive heart failure, and subsequent symptomatic myocardial infarction.^{7,8}

Dismissing the importance of these end points in clinical trials fails to recognize potential downstream effects that are directly relevant to a patient’s overall health status.

The Study Assessing Goals in the Elderly (SAGE) trial⁹ assessed the effect of statin therapy on ischemia burden in patients ages 65 to 85 with stable coronary disease. The results showed that both moderate and intensive statin dosing significantly reduced myocardial ischemia at 3 and 12 months, as detected by continuous electrocardiographic monitoring.

More research is needed to determine the effect of statin therapy on functional capacity and quality of life. Currently, it is premature to conclude that statins have no relevance to these important patient-centered outcomes.

What are the potential harms?

Mallery et al² cite numerous articles that emphasize the potential adverse effects of statin therapy in the elderly. Unfortunately, data supporting the safety of statin therapy in the elderly were not included. This should be stressed, given that older statin-eligible patients are often undertreated in contemporary practice.¹⁰

A 2015 systematic review and meta-analysis indicated that statin-related events are relatively rare in the elderly.¹¹ Another study showed elderly patients who started statin therapy after a myocardial infarction had no change in short-term cognitive or physical function.¹²

Older age and low body mass index are risk factors for statin myopathy, underscoring the need for close monitoring in frail patients. However, it is important to maintain an objective and balanced approach when considering potential harms.

Need for shared decision-making

Mallery et al² make no mention of shared decision-making. Best practice guidelines for the management of frailty support a holistic medical review to establish an individualized care plan for each patient.¹³ Firm recommendations based on indeterminate evidence undermine the patient-physician relationship and do not allow for personal preferences of care. In an environment of uncertain benefit and harm, the patient’s priorities and values should serve as the cornerstone for clinical decisions. ■

More research is needed to determine the effect of statin therapy on functional capacity and quality of life

REFERENCES

1. Barakat K, Wilkinson P, Deaner A, Fluck D, Ranjadayalan K, Timmis A. How should age affect management of acute myocardial infarction? A prospective cohort study. *Lancet* 1999; 353:955–959.
2. Mallery L, Moorhouse P, McLea Veysey P, Allen M, Fleming I. Frail elderly patients do not need lipid-lowering drugs. *Cleve Clin J Med* 2016; 83:131–142.
3. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm—issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007; 62:731–737.
4. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014; 63:747–762.
5. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 2008; 51:37–45.
6. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360:1623–1630.
7. Nadelmann J, Frishman WH, Ooi WL, et al. Prevalence, incidence and prognosis of recognized and unrecognized myocardial infarction in persons aged 75 years or older: The Bronx Aging Study. *Am J Cardiol* 1990; 66:533–537.
8. Sheifer SE, Gersh BJ, Yanez ND 3rd, Ades PA, Burke GL, Manolio TA. Prevalence, predisposing factors, and prognosis of clinically unrecognized myocardial infarction in the elderly. *J Am Coll Cardiol* 2000; 35:119–126.
9. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 2007; 115:700–707.
10. Maddox TM, Borden WB, Tang F, et al. Implications of the 2013 ACC/AHA cholesterol guidelines for adults in contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. *J Am Coll Cardiol* 2014; 64:2183–2192.
11. Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2015; 80:363–371.
12. Swiger KJ, Martin SS, Tang F, et al. Cognitive and physical function by statin exposure in elderly individuals following acute myocardial infarction. *Clin Cardiol* 2015; 38:455–461.
13. Turner G, Clegg A; British Geriatrics Society; Age UK; Royal College of General Practitioners. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. *Age Ageing* 2014; 43:744–747.

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