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EDITORIAL COMMENT

Statins in Secondary Prevention

Intensity Matters*

Neil J. Stone, MD

Statins are a mainstay in the secondary prevention of atherosclerotic cardiovascular disease (ASCVD). In survivors of myocardial infarction (MI) and stroke, statins, compared with placebo, reduce rates of recurrent coronary heart disease (CHD) and the need for revascularization procedures. Moreover, mortality is reduced (1). Despite the consistent evidence that high-intensity statin therapy reduces ASCVD risk in those with acute coronary syndrome, a large multinational trial found that only some patients were treated in this manner (2). The importance of statin adherence in high-risk ASCVD patients is highlighted by a recent study of Medicare beneficiaries hospitalized for MI: those with statin intolerance had an increased risk for recurrent MI and CHD events compared with those with high statin adherence (3).

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As reported in this issue of the *Journal*, Rosenson et al. (4) used data derived from commercial and Medicare sources to track high-intensity statin use in the United States. They found a progressive increase in prescriptions for high-intensity statins following hospitalization for MI from 2011 through 2014. High-intensity statin use was associated with males and guideline-directed practices such as prescriptions for beta-blockers and anti-platelet drugs and attending cardiac rehabilitation. The 2013 American College of Cardiology/American Heart Association cholesterol guidelines designated atorvastatin, 40 or 80 mg/day, or rosuvastatin, 20 or 40 mg/day, as high-intensity statins (5). These are doses that, on average, lower low-density lipoprotein-cholesterol (LDL-C) by 50%. The guidelines noted that the percentage of LDL-C reduction may not only confirm adherence but also may reflect biological variability in the response to statin therapy. This variability has been highlighted by a meta-analysis of statin trials that focused on very low levels of atherogenic lipoproteins achieved with statins (6).

Although they were aware that, in high-risk patients, high intensity is preferred for most, developers of the 2013 guidelines did not recommend high-intensity statins for all. This was due to a concern for net benefit. In patients 75 years of age and younger, the 2013 guidelines showed strong evidence to recommend high-intensity statin therapy for those with clinical ASCVD. On the other hand, in secondary prevention patients >75 years of age, the guideline panel endorsed initiation of therapy using moderate intensity statins. These are statins that lower LDL-C by 30% to <50% on average. High-intensity statins could be continued if well tolerated. As noted by others, there is randomized controlled trial (RCT) evidence showing benefit of high-intensity statins in these older individuals (2). And in appropriately selected patients, this may be appropriate. However, the panel felt the RCT data in those >75 years of age was limited, in part due to concerns that elderly clinical trial participants did not necessarily represent the many elderly with significant noncardiac morbidity, the burden of polypharmacy and heightened potential for drug-drug interactions. Thus, the guidelines noted it was "reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug-drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin." Also, in those ≤75 years of age, a moderate intensity statin was recommended if a high-intensity statin therapy

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From the Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Stone has reported that he has no relationships relevant to the contents of this paper to disclose.

was contraindicated or if characteristics predisposing to statin-associated adverse effects were present. Thus, the goal for statin use in secondary prevention was maximally tolerated statin therapy that provided net benefit. High-intensity statins matter, but their use requires a critical benefit-safety appraisal in the individual patient and not reflex prescription to increase the tally of those taking a high-intensity statin.

The Veterans Affairs (VA) administration lipid guidelines placed greater emphasis on moderate intensity statins in secondary prevention (7). These guidelines recommended moderate intensity statins first and then up-titrating to high-intensity statins in the presence of acute coronary syndrome, recurrent ASCVD events, or multiple uncontrolled risk factors.

Unlike the 2013 guidelines, they did not endorse LDL-C monitoring for adherence and adequacy of effect. Bennet et al. (8) critically reviewed this guideline and among their concerns were its recommendation to limit high-intensity statin usage in secondary prevention. They felt it did not give appropriate weight to the morbidity benefits of high-intensity statins. Moreover, a recent retrospective analysis from the VA of 509,766 eligible adults with ASCVD at baseline showed over 1 year a graded association between intensity of statin therapy and mortality (9). High-intensity statins were associated with a small but significant survival advantage compared with moderate intensity statins. Retrospective data for consecutive patients undergoing transcatheter aortic valve replacement also suggest the potential for benefit from high-intensity statins in this high-risk, older subgroup (10).

An encouraging aspect of these new data for use of high-intensity statin from Rosenson et al. (4) suggests that clinicians do understand that not all high-intensity statin regimens have equivalent efficacy and safety. Based on unfavorable RCT data (11), a black box warning by the FDA (12), as well as lack of inclusion in 2013 guidelines (5), use of simvastatin, 80 mg, has appropriately been curtailed. There has been 10-fold reduction in those who filled 80 mg of simvastatin following hospital discharge, resulting in <1% of patients filling this medication in 2013 and 2014 (4). The generic availability of both atorvastatin and rosuvastatin and the RCT data showing that ezetemibe added to moderate intensity simvastatin provides incremental benefit in very high-risk secondary prevention patients (13) make it unclear why 80-mg simvastatin is still available.

Guideline implementation continues to be a challenge (4,14). Intensity matters, but in individual cases, clinical judgment based on specific patient characteristics and patient preference matter greatly. Indeed, a limiting factor to attaining 100% adherence is what the 2013 guidelines emphasized: "These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate." For specific patients, this is the high-intensity matter that may matter most.

ADDRESS FOR CORRESPONDENCE: Dr. Neil J. Stone, Northwestern University Feinberg School of Medicine, 676 North St. Clair, Suite 600 (Cardiology), Chicago, Illinois 60611. E-mail: n-stone@northwestern.edu.

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