Statins for Primary Prevention in Older Adults: Who Is High Risk, Who Is Old, and What Denotes Primary Prevention?

Whether to treat older adults with statin medications for primary prevention of cardiovascular events remains a clinical conundrum. A number of observations with regard to increasing age stoke this dilemma: The association between elevated cholesterol levels and cardiovascular risk diminishes (1), risk-prediction tools (such as the Framingham risk score) become less accurate (2, 3), supporting clinical trial data become limited, and the decreasing life expectancy versus time to medication benefit constantly shifts. Additional downsides of statins for older adults include medication cost, polypharmacy, and possible side effects. Conversely, age alone makes older adults inherently high risk and statins reduce cardiovascular events and death and may have other beneficial effects. Clinical trial data support secondary prevention of cardiovascular events with statins for persons 80 years or younger, but data are scant thereafter. As the number of persons 65 years or older rapidly increases, and more so the number of persons 85 years or older, this clinical question needs to be addressed.

In this issue, Glynn and colleagues (4) report a retrospective analysis of older patients (aged ≥70 years) in JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) to assess whether 20 mg of rosuvastatin is safe and efficacious in reducing cardiovascular events compared with placebo. By using a posttrial age cut-point of 70 years ($n = 5695$), the investigators report a 39% reduction in a composite end point of first cardiovascular event (myocardial infarction, stroke, unstable angina, revascularization, or cardiovascular death) after a median follow-up of 2 years due to early trial termination by the data safety and monitoring board. Persons 70 years or older had a greater reduction in cardiovascular events (difference of 0.52 event per 100 person-years) compared with those younger than 70 years. Individual secondary outcome events included a 45% reduction in both myocardial infarction and stroke. Rosuvastatin seems safe in these older persons without increase in serious adverse events during this relatively short follow-up, although adherence to study medication was not reported.

Taken in the context of a post hoc analysis, the magnitude of cardiovascular event reduction associated with rosuvastatin was impressive in older persons. This surprising degree of risk reduction during such a short follow-up period has been commented on before (5) and may suggest other pleiotropic statin effects. We commend the investigators for this analysis of JUPITER. It raises awareness and provides data to address the conundrum of statins for primary cardiovascular prevention in older adults. We propose 4 questions about the possible clinical implications: Which older patients are truly at high risk for cardiovascular events? What age defines older adults? What constitutes primary prevention in older adults? Should this change standard clinical practice?

JUPITER was designed to determine the efficacy of rosuvastatin versus placebo for primary prevention of cardiovascular events in healthy older persons. These persons were identified as men 50 years or older and women 60 years or older without diabetes or a history of myocardial infarction, stroke, arterial revascularization, or coronary artery disease equivalent by National Cholesterol Education Program guidelines and with low-density lipoprotein (LDL) cholesterol levels less than 3.37 mmol/L (30 mg/dL), triglyceride levels less than 5.65 mmol/L (500 mg/dL), and high-sensitivity C-reactive protein levels of 2 mg/L or more (6). Despite average to low LDL cholesterol levels, these persons were considered to have high vascular risk because of elevated high-sensitivity C-reactive protein levels (7). Baseline Framingham risk score was not provided for the overall JUPITER cohort. In this substudy, almost 70% of persons had a Framingham risk score greater than 10%, and given their age and prevalence of hypertension (>65%), many probably had a Framingham risk score greater than 20%; by National Cholesterol Education Program guidelines, these persons should receive aggressive treatment. The benefit of rosuvastatin was absent for the subgroup without hypertension. Whether high-sensitivity C-reactive protein levels add additional information to risk prediction in older persons is also controversial because high-sensitivity C-reactive protein levels increase with age (8, 9). This increase may reflect, in part, an upregulation of inflammatory pathways and oxidative stress, increases due to comorbid conditions, or both.

The second issue revolves around the age-old question of "who is old." Clinical guidelines have started considering older adults in 3 age ranges—65 to 74 years, 75 to 84 years, and 85 years or older (as young-old, middle-old, and old-old, respectively) (10)—to acknowledge physiologic differences, relevant clinical data, and life-expectancy issues. Clinical trials of statins for primary cardiovascular risk reduction are conflicting: ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm) (11) reported a 31% stroke risk reduction in persons aged 70 to 79 years and a 26% decrease in composite cardiovascular events in persons aged 60 to 79 years. PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) (12) showed a 15% risk reduction in the combined end point of coronary heart disease death, nonfatal myocardial infarction, and fatal or nonfatal stroke with pravastatin in persons aged 70 to 82 years, but the benefit was not seen among those with no previous vascular disease (that is, persons who received treatment of pri-

mary prevention). To our knowledge, no prospective study has examined this question to date in persons older than 80 years. What can we glean from this subanalysis of JUPITER? The descriptive characteristics reveal a mainly young-old population (median age, 74 years), with 75% of persons younger than 77 years. Thus, these data best apply to the young-old persons but leave uncertainty about the old-old, for which evidence is much needed. An age interaction was not found, which may reflect an age-associated change in cholesterol levels and cardiovascular risk.

The third question is the definition of primary prevention in older adults. Despite the absence of known cardiovascular disease in JUPITER participants, the prevalence of silent or occult ischemia by provocative testing in asymptomatic persons increases with advancing age (13, 14). Subclinical disease is more prevalent in older adults and further complicates risk stratification because subclinical atherosclerosis does not necessarily equate future cardiovascular event risk (15). An autopsy study of persons 70 years or older showed 72% of men and 54% of women had 75% or more stenosis of 1 or more major coronary artery, which is much higher than clinical prevalence (16). As technology to identify subclinical atherosclerosis advances, the line between primary and secondary prevention blurs. As atherosclerosis increases with age in most but not all older persons, we need methods to discern which older adults with atherosclerosis are at the greatest risk for cardiovascular events.

This leads to the important question of whether the substudy provides information that might change standard clinical practice. This older population was inherently at high risk by their age and comorbid conditions, such as hypertension. The target LDL cholesterol level in such a high-risk cohort would be 2.59 mmol/L (100 mg/dL) (65% of the substudy cohort had LDL cholesterol levels from 2.59 to 3.34 mmol/L [100 to 130 mg/dL]). As expected, the forest plot in the article by Glynn and colleagues (4) confirms that rosuvastatin provided clearest benefit in those with a Framingham risk score greater than 10%. Current guidelines use different criteria to define high-sensitivity C-reactive protein levels. The U.S. Preventive Services Task Force reports that most studies have shown that high-sensitivity C-reactive protein levels greater than 3 mg/L can reclassify persons with an intermediate Framingham risk score to high risk (17), whereas the 2009 Canadian cholesterol guidelines (18) states that a high-sensitivity C-reactive protein level greater than 2 mg/L adds risk to those in the moderate Framingham risk score category. Although the investigators do not provide specific baseline high-sensitivity C-reactive protein levels in this subanalysis, persons with levels less than 5 mg/L had a statistically significant reduction in the primary outcome, whereas those with levels of 5 mg/L or greater did not. These data do not support use of high-sensitivity C-reactive protein levels as an additional risk-stratifying tool for older adults.

This is an important subanalysis of the JUPITER trial showing a statistically significant cardiovascular event risk reduction in persons 70 years or older treated with rosuvastatin compared with placebo. Benefit was seen soon after therapy initiation and rosuvastatin was safe over the median 2 years of follow-up. These data help to address the uncertainty of time to benefit in older adults. Future research should focus on more accurate risk-prediction tools for persons older than 80 years, a rapidly growing and resource-consuming segment of the population. The value of high-sensitivity C-reactive protein in older persons also needs clarification before it is used routinely as a screening and risk-prediction tool. Prospective clinical trials for both primary and secondary cardiovascular and stroke risk reduction are also needed in persons older than 80 years, especially those with several comorbid conditions that reflect real-life dilemmas.

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