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REVIEW TOPIC OF THE WEEK

Refining Statin Prescribing in Lower-Risk Individuals

Informing Risk/Benefit Decisions

Ashley Pender, MD,[a] Donald M. Lloyd-Jones, MD, ScM,[a,b,c] Neil J. Stone, MD,[a,b] Philip Greenland, MD[a,b,c]

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CME Objective for This Article: After reading this article, the reader should be able to: 1) evaluate cardiovascular risk in primary prevention patients; 2) formulate an approach to the clinician-patient discussion when statin decisions are initially uncertain; 3) select the most appropriate additional tests, beyond the use of traditional risk factors, to assist with the decision about long-term statin therapy; and 4) communicate the risks and benefits of statin therapy, taking into account likelihood of statin side effects and the possibility of conducting individual trials of statin treatment.

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From the [a]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; [b]Division of Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and the [c]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Refining Statin Prescribing in Lower-Risk Individuals

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Ashley Pender, MD,[a] Donald M. Lloyd-Jones, MD, ScM,[a,b,c] Neil J. Stone, MD,[a,b] Philip Greenland, MD[a,b,c]

ABSTRACT

Guidelines from the American College of Cardiology/American Heart Association, as well as those from the Veterans Affairs/Department of Defense and the Joint British Societies all recommended treating more people with statins than previous guidelines. In each guideline, the decision-making process began with an assessment of overall cardiovascular risk. Each group proposed updated treatment thresholds, and all of them lowered the threshold compared with earlier guidelines. Since release of these new guidelines in 2013 and 2014, additional evidence has emerged to suggest a rationale for extending statin consideration to an even larger proportion of asymptomatic adults—even those with a 10-year atherosclerotic cardiovascular disease risk below 7.5%. This review discusses new findings since 2013 and proposes strategies emanating from the current guidelines to help clinicians and patients make more informed decisions about long-term statin use, especially pertinent to lower-risk patients. (J Am Coll Cardiol 2016;68:1690–7)

Using statin drugs for prevention of atherosclerotic cardiovascular disease (ASCVD) events in asymptomatic adults is an established, evidence-based approach (1–3). Four large-scale randomized controlled trials (RCTs) focused exclusively on primary prevention participants have shown highly consistent net benefit of statins for ASCVD prevention (4–7). Although clinicians no longer debate whether to use statins in asymptomatic people, there are lingering questions about which patients are optimal candidates for lipid-lowering drug therapy (2,3,8–10) and which risk assessment tools can help guide the determination to prescribe lipid-lowering medications.

Recent guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) (2), from the Veterans Affairs (VA)/Department of Defense (DoD), and the Joint British Societies (JBS) (1,3) recommended treating more people with statins than previous guidelines. All 3 guidelines begin the decision-making process with an assessment of overall cardiovascular risk. Each group proposed similar treatment thresholds, and all of them lowered the threshold compared with the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (11). Since the release of these new guidelines, additional evidence has emerged that may suggest a rationale for extending statin consideration to an even larger proportion of asymptomatic adults. Some new evidence would support that a treatment threshold even below 7.5% risk of ASCVD in 10 years could be justified. In this review, we discuss new findings since 2013, and propose strategies emanating from the current guidelines to help clinicians and patients make more informed decisions about long-term statin use. This is especially pertinent to lower-risk patients.

MANY EVENTS OCCUR IN "LOW-RISK" PEOPLE

Many ASCVD events occur among people with predicted 10-year risk below 7.5%, raising the potential for additional clinical benefits of a broader application of statins. This issue has been addressed by a number of analyses of population data, and it is clear that large numbers of ASCVD events occur in so-called low-risk people. This is due to the fact that "low-risk" is not the same as "no risk," and very large numbers of low-risk people exist within the general population. For example, Cooney et al. (12) used data from the EuroSCORE (European Systematic Coronary Risk Evaluation) risk assessment method to describe risk in the general European population. More than one-half of the cardiovascular disease (CVD) deaths occurred in the portion of the population traditionally estimated to be "low risk," or <10% CVD death risk. More recently, application of the ACC/AHA 2013 guideline approach to the Copenhagen General Population Study demonstrated that 23% of ASCVD events would occur in people not presently identified for statin consideration (13) due to an ASCVD risk estimate <7.5%.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CHD = coronary heart disease

CVD = cardiovascular disease

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

QALY = quality-adjusted life-year

ACCURACY OF RISK ASSESSMENT TOOLS

Since the release of the ACC/AHA guideline, some debate has focused on the accuracy of the risk estimator, the Pooled Cohort Equation (PCE). Several analyses from cohorts derived from populations with high socioeconomic status, or very healthy or clinical trial populations, reported that the PCE overestimated risk (14,15). Other analyses utilizing populations likely to be more representative of the broad U.S. population suggested that the PCE predicted risk accurately (16,17). At the same time, some observers commented that all risk models are imperfect, a perspective that is important to consider (18). The ACC/AHA Risk Assessment Guidelines (19), and the JBS guideline (20) discussed this topic directly. They both noted that clinical risk equations can accurately assign a group risk (i.e., observed group event rates are close to event rates predicted by the risk model), but have limitations when applying that group risk to an individual patient. A high proportion of events occurring among the low- and intermediate-risk majority explains the apparent paradox of accurate risk stratification (higher vs. lower), but poorer disease prediction for patients.

Recognizing the inaccuracy of all risk estimation approaches, the ACC/AHA Risk Assessment Guideline advised that risk assessment using the PCE should be only the initial step in making an informed decision about statin treatment. The next step for virtually all patients, following either the ACC/AHA guideline (2), the JBS guideline (20), or the VA/DoD guideline (1), is the clinician-patient discussion. Two reasons for the discussion are apparent: 1) patients differ in their preferences and comfort levels with regard to preventive strategies and long-term medication use; and 2) risk assessment is inherently better for populations than it is for specific people. This is also true for benefit assessment. Explicit risk and benefit assessment are an improvement over clinical intuition alone, but they remain essentially educated guesses as to who precisely will benefit (21). As the ACC/AHA cholesterol guideline noted, RCT evidence supports a net absolute benefit of using moderate-to-intensive statin therapy at a baseline 10-year ASCVD risk ≥7.5%; consequently, statins can be strongly recommended in this population group. Available RCT evidence also indicates that when baseline ASCVD risk is 5.0% to <7.5%, at the population level, there is still net absolute benefit with moderate-intensity statin therapy, on average. However, the tradeoffs between the ASCVD risk-reduction benefit and adverse effects are marginal in this lower-risk group. In all risk groups, mindful of the limitations of risk estimation, a clinician-patient discussion is critically important (22). In preventive cardiology, one never knows for certain if the patient is the 1 in 5 (or 1 in 25 or 1 in 50) who will eventually develop a CVD event. The decision, therefore, always represents a tradeoff of benefit and risk, which relies on the best estimates of both of these factors, and a respectful inclusion of patient preferences. This is the essential idea of personalized medicine, a concept that has informed medical practice for decades, if not centuries. What is new is the importance of recognizing that all risk models are somewhat flawed in terms of accuracy of prediction. Their purpose is to provide a general estimate of risk that appropriately begins the decision-making process or risk discussion with the patient (21).

NEW EVIDENCE ON THE ROLE OF ADDITIONAL MARKERS OF RISK IN LOWER- AND INTERMEDIATE-RISK PATIENTS

The 3 recent guidelines all discussed ways of improving risk assessment in selected patients where additional evidence on risk was considered necessary for decision making. The ACC/AHA report stated that additional factors might inform the clinician-patient ASCVD risk discussion, such as primary low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dl or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l; coronary artery calcium (CAC) score ≥300 Agatston units or ≥75th percentile for age, sex, and race/ethnicity; ankle-brachial index (ABI) <0.9; or elevated lifetime risk of ASCVD. The VA/DoD guideline mentioned only 2 tests as having any meaningful utility in improving risk assessment (hsCRP or CAC), but explicitly recommended neither on a routine basis. The JBS guideline also mentioned a variety of additional tests for consideration, but recommended none on the basis of lack of efficacy or lack of sufficient evidence.

New analyses have been reported since 2013 that demonstrated the limits of additional testing for risk assessment. New studies have suggested that some of the tests mentioned by the ACC/AHA in 2013 are not helpful in modifying risk assessment, especially in lower- and intermediate-risk patients where additional testing could be most needed. Blaha et al. (23)

compared 13 risk markers to assess change in estimated risk for a patient after the result of an additional normal or negative test result. The goal of such testing would be to establish a sufficiently low risk, beyond that estimated by the PCE, to justify advice against statin treatment. This study used data from 6,814 participants from the MESA (Multi-Ethnic Study of Atherosclerosis) study. A CAC score of 0, carotid intima-media thickness <25th percentile, absence of carotid plaque, brachial flow-mediated dilation >5% change, ABI >0.9 and <1.3, hsCRP <2 mg/l, homocysteine <10 μmol/l, N-terminal pro-B-type natriuretic peptide <100 pg/ml, no microalbuminuria, no family history of coronary heart disease (CHD) (any or premature), absence of metabolic syndrome, and healthy lifestyle were compared for the endpoints of CHD and all CVD events over 10 years' follow-up. They described these normal or low test results as "negative risk markers." The strongest negative risk marker was a CAC score of 0 for both all CHD and total CVD outcomes, followed by carotid intima-media thickness <25th percentile, perhaps not surprisingly, as they are both markers of atherosclerosis burden. An hsCRP <2 mg/l and normal ABI were not useful for modifying assessment of low risk. Absence of any family history of CHD was also not useful in lowering assessment of risk in lower-risk people. The authors suggested that their results might help guide discussions on the identification of patients less likely to receive net benefit from lifelong preventive statin therapy.

A second analysis by Yeboah et al. (24), also using data from the MESA study, assessed the predictive accuracy and improvement in risk reclassification gained by the addition of CAC score, ABI, hsCRP, or family history of ASCVD to the PCE across all ranges of risk. CAC score, ABI, and family history were independent predictors of ASCVD events in the multivariable Cox models, but not hsCRP. CAC score modestly improved the Harrell's C statistic (0.74 vs. 0.76; $p = 0.04$), whereas the ABI, hsCRP, and family history produced no improvement in the C-statistic when added to the PCE. A third analysis of the MESA study data by Nasir et al. (25) confirmed the findings. These 3 analyses from the MESA study provided previously unavailable evidence that several commonly suggested secondary tests do not add sufficient risk information beyond the PCE to justify use in low-risk patients. The evidence, however, does suggest that CAC score improves reclassification of very low-risk patients. This information could inform meaningfully the clinician-patient discussion when additional information is required.

NEW EVIDENCE ON COST EFFECTIVENESS OF STATINS

Several reports published since 2013 indicate that statins may be considered cost effective, even among relatively low-risk patients, below the 10-year risk threshold of 7.5% from the ACC/AHA guideline (2). Pandya et al. (26) estimated the cost effectiveness of various 10-year ASCVD risk thresholds that might inform guidelines for use of statins in healthy low-risk people. Using a microsimulation model, including a lifetime time horizon, the investigators evaluated hypothetical subjects from a representative U.S. population, 40 to 75 years of age, on the basis of data from the NHANES (National Health and Nutrition Examination Surveys) surveys, large clinical trials, and meta-analyses for statin benefits and treatment. They estimated ASCVD events prevented and incremental costs per quality-adjusted life-year (QALY) gained. The current ACC/AHA risk threshold of 10-year 7.5% or higher ASCVD risk had an incremental cost-effectiveness ratio of $37,000/QALY compared with a 10% or higher threshold. A lower threshold of 4% ASCVD 10-year risk was estimated to recommend statins to 61% of all adults in the United States, with an incremental cost-effectiveness ratio of $81,000, which is considered by some policy analysts as cost effective (27). Galper et al. (28) performed a second cost-effectiveness analysis. Their approach was very similar to that of Pandya et al. (26) and the results were quite similar. Specifically, a strategy of treating all middle-aged adults with high-dose statins dominated all other strategies for both men and women, was cost-saving compared with the 2013 ACC/AHA guidelines, and considerably more cost effective than the ATP III guidelines. Statin benefit with a treat-all approach far outweighed associated adverse events, including liver or muscle toxicities and new-onset diabetes.

Pletcher et al. (29) estimated the cost effectiveness of measuring CAC and prescribing statin therapy on the basis of the resulting score under a range of assumptions, using an established model enhanced with CAC distribution and risk estimates from the MESA study. Ten years of statin treatment for 10,000 women, 55 years of age with high cholesterol (10-year CHD risk, 7.5%), was projected to prevent 32 myocardial infarctions, cause 70 cases of statin-induced myopathy, and add 1,108 years to total life expectancy. Measuring CAC and targeting statin treatment to the 2,500 women with CAC >0 would provide 45% of the benefit (+501 life-years), but CAC measurement would cost $2.25 million and cause an estimated 9 radiation-induced cancers. As with the

finding of the Galper et al. (28) study, "treat all" with a statin was preferable to CAC screening in this scenario and across a broad range of other scenarios (2.5% to 15% CHD risk, 2.5% to 15% risk) when statin assumptions were favorable ($0.13/pill and no quality of life penalty). When statin assumptions were less favorable ($1.00/pill and disutility = 0.00384), CAC screening with statin treatment for persons with CAC >0 was cost effective (<$50,000/QALY) in this scenario, in 55-year-old men with 7.5% CHD risk 7.5%, and in other intermediate-risk scenarios (5% to 10% CHD risk, 5% to 10% risk).

On the basis of these recent cost-effectiveness analyses, which all produced very similar conclusions using differing assumptions and models, statins for primary prevention have emerged as potentially cost effective at levels of estimated ASCVD risk below the current threshold of 7.5% recommended by the ACC/AHA guideline. However, uncertainty in all of these projections, especially on the issue of side effects and risks, gives further justification for seeking patient input when considering statins in lower-risk people.

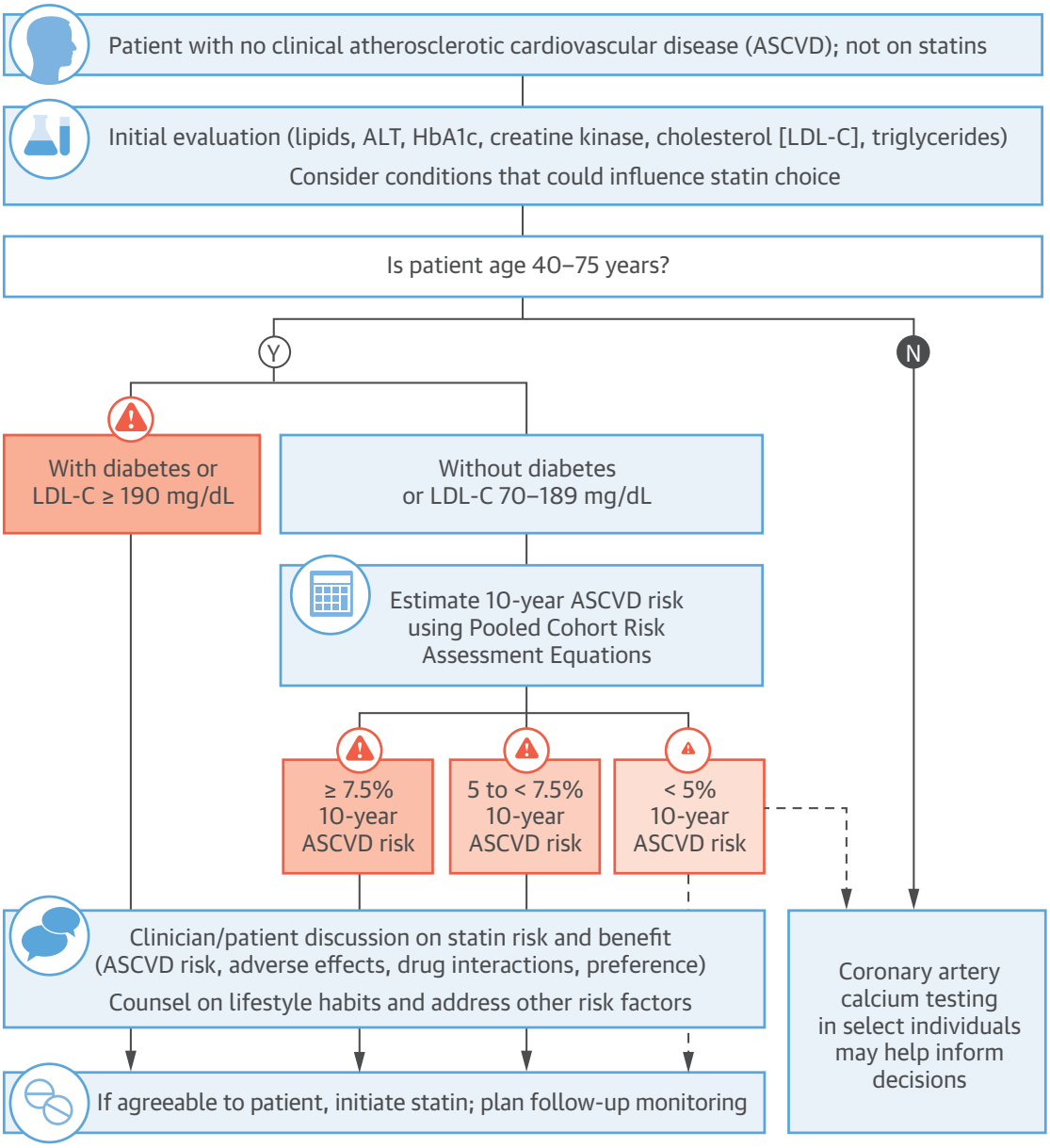
NEW EVIDENCE ON EFFECTIVENESS OF STATINS ON THE BASIS OF RISK ALONE

In considering whether to lower the risk threshold for statin use from a 10-year risk threshold of 7.5%, an important consideration is whether statins are effective in lower-risk people and by how much. Additionally, it is important to assess whether statin effectiveness requires high LDL-C or some other measure of risk, such as hsCRP greater than the population median of 2 mg/l. Both of these critical issues were addressed in the HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial (7). On the basis of previous trials, it was uncertain whether the benefits of statins could be extended to diverse populations without CVD, chosen primarily on overall cardiovascular risk. The HOPE-3 trial randomly assigned 12,705 participants who did not have CVD and had at least 1 cardiovascular risk factor (referred to as "intermediate risk" in the publication) to receive rosuvastatin 10 mg/day or placebo. Median follow-up was 5.6 years. As expected, overall mean LDL-C concentration was 26% (34 mg/dl) lower during follow-up in the group randomized to rosuvastatin compared with the placebo group. Both the primary ASCVD endpoint and secondary CVD event rates were significantly reduced by approximately 25% in the rosuvastatin group compared with the placebo group, with similar relative risk reductions across baseline LDL-C levels, as seen in other statin trials (30). Results were consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, hsCRP level, blood pressure, and race or ethnic group. In addition, during the course of the trial, in the rosuvastatin group, there was no increased risk of diabetes or cancers, but there was a slight increase in rates of cataract surgery and muscle symptoms (in 5.8% of the rosuvastatin participants vs. 4.7% in the placebo group).

As understanding the risk of new onset of diabetes mellitus (NODM) is an important topic in a risk discussion, it is worth noting the difference between the primary prevention JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) and HOPE-3 trials. In the former trial, participants were randomly assigned a high-intensity statin, rosuvastatin 20 mg/day, and the comparator group received placebo (5). A significant relative, but small, absolute increase in NODM was noted in the statin-treated group. A secondary analysis showed that all of those who progressed to diabetes on high-intensity rosuvastatin had from 1 to 4 major diabetes risk factors (31). Even if there was progression to NODM, the reduction in ASCVD events remained substantial, yielding net benefit to those assigned a statin. Indeed, rosuvastatin therapy hastened the diagnosis of NODM by only 5.4 weeks. In contrast, HOPE-3 showed efficacy for those assigned a moderate-intensity statin, rosuvastatin 10 mg/day, as contrasted with placebo, and was not accompanied by an increase in NODM over the trial duration (7).

The HOPE-3 trial data add to the information from previous trials that suggested a statin benefit in lower-risk people. In the Cholesterol Treatment Trialists meta-analysis of 27 randomized statin trials (30) including more than 170,000 research participants, 24,790 of these had estimated risk for a major vascular event <5% in 5 years (roughly equivalent to 10% in 10 years). In the higher-risk patients (5-year risk of ≥10%) described in the meta-analysis, for a 40 mg/dl reduction in LDL-C, relative risk reduction for all high-risk patients was approximately 21% (relative risk: 0.79). This risk reduction was relatively independent of age, sex, baseline LDL-C, or previous vascular disease. In the 24,790 patients studied in the statin trials whose estimated baseline 5-year risk was <5%, the relative risk for major vascular events was 0.62 and for those with baseline risk ≥5% to <10%, the relative risk was 0.69. On the basis of these results, the investigators of the meta-analysis predicted in 2012 that generic statin interventions are "likely to be cost-effective in individuals at annual vascular disease risk down to about 1%" 5-year risk (30). Recent evidence suggests that their prediction is accurate.

CENTRAL ILLUSTRATION **Proposed Updated Approach to Statin Consideration in Lower-Risk Patients: 2016**



Pender, A. et al. J Am Coll Cardiol. 2016;68(15):1690–7.

This approach is a modification of the 2013 American College of Cardiology/American Heart Association Lipid Treatment Guideline. It proposes statin consideration in lower-risk patients and also suggests use of coronary artery calcium testing in selected patients. ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; HbA1c = glycosylated hemoglobin; LDL-C = low-density lipoprotein cholesterol; N = no; Y = yes.

NET BENEFIT AS A TREATMENT CONSIDERATION

With the widespread efficacy of statin drugs, emphasis for primary of prevention of ASCVD has shifted from risk assessment alone to an integrated assessment of net benefit. This paradigm is encapsulated in the current guidelines in the clinician-patient discussion, the 5% optional treatment threshold, and recommendations for considering

additional supporting tests. Some of the recent dialogue on the identification of lower-risk patients most likely to benefit from statin therapy uses absolute risk reduction as a surrogate for net benefit. In an analysis by Thanassoulis et al. (32) of the NHANES cohort, an absolute risk reduction ≥2.3% is used to identify individuals for statin therapy. This approach would identify 9.6 million additional individuals for statin therapy, including many younger patients with higher LDL-C and 10-year risks below the current 7.5% threshold for therapy. It departs from guidelines, given the increased emphasis on LDL-C as a determinant of statin benefit and decreased emphasis on short-term risk, as calculated by the PCE, allowing for statin treatment of 10-year risks as low as 3.75%.

NEW EVIDENCE ON THE FREQUENCY—AND LIKELY OVER-REPORTING—OF STATIN SIDE EFFECTS

An important consideration for any patient receiving a statin is the frequency of side effects. Cost effectiveness tips against statins when drug cost is higher, when overall ASCVD risk is lower, and when harms of treatment are greater. Estimates of the frequency of statin myalgias or weakness, the most common statin treatment side effects, range widely, from 5% to 29% of treated patients, varying by specific drug and dosage (33). The wide range of reported statin-related muscle effects deters many doctors from prescribing statins, perhaps even more so when absolute risks are lower. However, both the recent GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial (34) and an earlier RCT of coenzyme Q10 (35) demonstrated that many patients who report statin-related side effects do not have statin-related symptoms on blinded, crossover rechallenge. Both trials used a placebo versus statin run-in to select only those with complaints on statin therapy. In the GAUSS-3 trial, a total of 492 participants entered the statin rechallenge procedure, with 491 receiving 1 or more doses of study drug. Of these 491 patients, 245 received atorvastatin before placebo and 246 received placebo before atorvastatin. For those receiving atorvastatin first, 51% developed a muscle-related adverse event with atorvastatin, but not placebo. For those receiving placebo first, 34% developed a muscle-related adverse event with atorvastatin, but not placebo. Overall, only 43% of patients screened and enrolled in the GAUSS-3 trial who had a history of muscle-related adverse effects with a statin reported intolerable symptoms when given a double-blind, placebo-controlled atorvastatin rechallenge. These data demonstrate 2 important points about statin muscle symptoms: 1) more than one-half of patients who report muscle-related symptoms on statins may not have true drug intolerance; 2) a placebo-controlled N-of-1 single-patient trial, as suggested by Joy et al. (36), may be useful to evaluate statin-associated symptoms and to assist some patients to resume recommended statin therapy.

CONCLUSIONS

New evidence since 2013 provides a rationale for broader use of statins among lower-risk asymptomatic patients. Nonetheless, a 1-size-fits-all approach is not appropriate because there are still a number of uncertainties. Although absolute risk estimation is inherently limited, it provides a first approximation of risk. Absolute risk estimation is valuable in initiating a risk discussion about which patients to consider for statins. New evidence suggests that statins might be considered, even when risk is as low as 4% to 5% in 10 years. Some have suggested that an additional consideration for shifting the focus of treatment to younger patients is the concept of net benefit. This has been estimated at ±2.3% expected absolute risk reduction. New evidence also suggests that additional testing, other than with coronary calcium score, is not likely to be useful. However, CAC scores may help identify the lowest-risk patients within the low-risk range, who could be safely excluded from therapy, and can also help identify those at higher risk. CAC testing should be selectively used for those patients requiring more precise evidence to reclassify assessment of potential net benefit (or lack thereof) from statin use. Additionally, clinicians should share with their patients that a large proportion of those (at least 50%) who report statin intolerance have similar symptoms on placebo. To resolve the difficult problem of potential statin intolerance, N-of-1 trials may be useful, and may result in more patients who can successfully tolerate and benefit from statin therapy. The **Central Illustration** summarizes new evidence and comparison with previous guidelines.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Philip Greenland, Department of Preventive Medicine, Northwestern University, 680 North Lake Shore Drive, 14th Floor, Suite 600, Chicago, Illinois 60611. E-mail: p-greenland@northwestern.edu.

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