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HOPE for Rational Statin Allocation for Primary Prevention: A Coronary Artery Calcium Picture Is Worth 1000 Words

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Abstract

Allocation of statin therapy for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) in borderline- and intermediate-risk patients has traditionally been based on population-based global risk assessment and other clinical and laboratory characteristics. Patient-specific treatment decisions are needed to provide maximal benefit and avoid unnecessary treatment. Guideline-based lipid management proposes that coronary artery calcium scoring is reasonable to implement in patients with a 10-year risk of 5.0% to 19.9% (borderline to intermediate risk) by using the pooled cohort equations when the decision about whether to initiate statin therapy is uncertain. We report data from both observational studies and a large primary prevention randomized controlled trial that support the position that this decision is, in fact, uncertain in about half of such patients because of risk misclassification. Such misclassification can be largely avoided by more widespread implementation of coronary calcium scoring, which helps to identify those with coronary artery calcium scores of 0, a finding associated with a less than 5.0% 10-year probability of an ASCVD event. Deferral of statin therapy in such patients, in the absence of smoking, diabetes, or a family history of premature ASCVD, provides more individualized and appropriate care and avoids the expense and potential adverse effects of statin therapy in those with low potential for absolute risk reduction. A rationale is also provided for the importance of coronary artery calcium scoring in women 50 years and older, possibly in place of 1 screening mammogram in women at least 55 years of age to avoid incremental radiation exposure, on the basis of the substantially higher lifetime risk of morbidity and mortality from ASCVD than from breast cancer. In patients with borderline or intermediate ASCVD risk, coronary artery calcium scoring should be used, whenever possible, as an aid to rational statin allocation for the primary prevention of ASCVD.

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The decision about whether to recommend a statin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) is generally straightforward in adults aged 40 to 75 years with a low or high estimated 10-year ASCVD risk. Although the relative risk reduction for ASCVD events is similar regardless of baseline risk, the absolute risk reduction is small in those at low risk[1] and considerably greater in those at high risk, especially in individuals with higher baseline low-density lipoprotein (LDL) cholesterol levels.[2] However, as most primary prevention patients have an estimated risk that falls between those 2 extremes, the decision about whether to prescribe a statin is often considerably more nuanced. This decision has far-reaching implications that may either substantially benefit the patient by lowering the risk of an ASCVD event or result in decades of unnecessary drug therapy, with its attendant costs and potential for treatment-related adverse effects.

GUIDELINE-BASED CLINICAL DECISION MAKING

The 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood

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TABLE 1. Atherosclerotic Cardiovascular Disease Risk–Enhancing Factors[a]

Genetic and acquired factors associated with increased ASCVD risk

- Family history of premature ASCVD (men, age <55 y; women, age <65 y)
- Primary hypercholesterolemia (LDL-C level, 160-189 mg/dL [4.1-4.8 mmol/L]); (non–HDL-C level, 190-219 mg/dL [4.9-5.6 mmol/L])[b]
- Metabolic syndrome (increased waist circumference, elevated triglyceride level [>175 mg/dL (1.98 mmol/L)], elevated blood pressure, elevated glucose level, and low HDL-C level [<40 mg/dL (1.04 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women] are factors; tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR, 15-59 mL/min per 1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplant)
- Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
- History of premature menopause (before the age of 40) and history of pregnancy-associated conditions that later increases ASCVD risk, such as preeclampsia
- High-risk race/ethnicities (eg, South Asian ancestry)

Laboratory markers associated with increased ASCVD risk

- Persistently[b] elevated triglyceride level (≥175 mg/dL [1.98 mmol/L]) in the absence of secondary causes
- If measured:
  - Elevated high-sensitivity C-reactive protein level (≥2.0 mg/L)
  - Elevated Lp(a) level: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) level of ≥50 mg/dL (≥125 nmol/L) constitutes a risk-enhancing factor, especially at higher levels of Lp(a)
  - Elevated apoB level ≥130 mg/dL (1.30 g/L): A relative indication for its measurement would be triglyceride level ≥200 mg/dL (2.26 mmol/L). A level of ≥130 mg/dL corresponds to an LDL-C level of >160 mg/dL (4.14 mmol/L) and constitutes a risk-enhancing factor
  - ABI <0.9

[a]ABI = ankle-brachial index; AIDS = acquired immunodeficiency syndrome; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein a; non–HDL-C = non–high-density lipoprotein cholesterol; RA = rheumatoid arthritis.

[b]Optimally 3 determinations.

Adapted from the *Journal of the American College of Cardiology*,[3] with permission.

Cholesterol (2018 Guideline) recommends the use of the pooled cohort equations to assess 10-year ASCVD risk as the initial step in cholesterol treatment decision making for adults aged 40 to 75 years without clinical ASCVD or diabetes mellitus and with an LDL cholesterol level of 70 to 189 mg/dL (1.81 to 4.90 mmol/L).[3] For those patients found to be at intermediate 10-year risk (7.5% to 19.9%), the 2018 Guideline indicates that there is strong evidence supporting the net ASCVD risk reduction benefit of moderate-intensity statin therapy. For those at borderline 10-year risk (5.0% to 7.4%), there is moderate evidence for benefit from statins.

For borderline- and intermediate-risk primary prevention patients, a clinician-patient discussion about benefits, risks, costs, and goals of therapy is advocated, and if the decision is made to initiate drug therapy as an adjunct to lifestyle, a moderate-intensity statin is recommended. If uncertainty about treatment persists, the presence of one or more group of risk-enhancing factors (Table 1) may be useful for additional support regarding statin initiation.[3] The risk-enhancing factors include various additional genetic and acquired characteristics that, if present, may be associated with increased risk in the general population. However, it is difficult to quantify how much a risk-enhancing factor affects risk in a given patient.[3,4]

When the decision about the initiation of statin therapy remains uncertain after consideration of estimated 10-year risk and risk-enhancing factors, coronary artery calcium (CAC) scoring is identified by the 2018 Guideline as a reasonable next step in the decision-making process, because of its superiority over any serum biomarker to discriminate the likelihood of future ASCVD events as compared with the pooled cohort

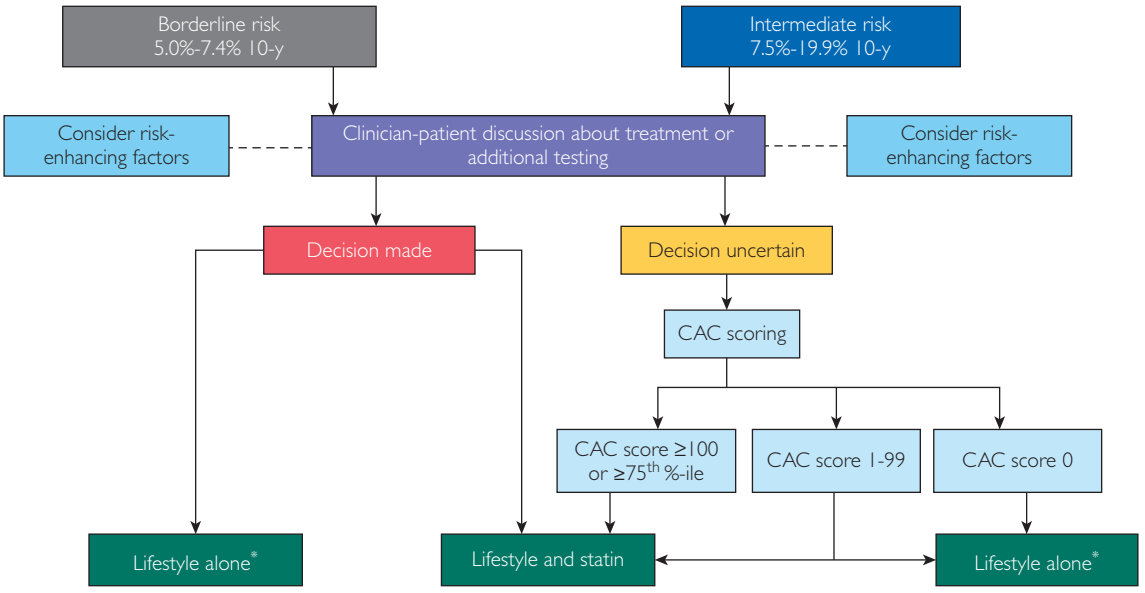

FIGURE 1. 2018 cholesterol guideline–based approach to the risk assessment and management of borderline- and intermediate-risk patients. CAC = coronary artery calcium. *Except if active smoker, had type 2 diabetes mellitus, or had a family history of premature atherosclerotic cardiovascular disease, consider statin.

equations[5,6] as well as its ability to reclassify ASCVD risk.[5-11] The finding of a CAC score of 0 Agatston units in such patients, in the absence of diabetes, current cigarette smoking, or a family history of premature ASCVD, is associated with a low absolute 10-year ASCVD risk. A score of 100 or more (or at the 75th percentile or higher) is considered a finding that strongly supports the initiation of statin therapy. When the score is 1 to 99, a clinician-patient discussion about the pros and cons of statin therapy is advised. The algorithm that illustrates the 2018 Guideline–based approach to the risk assessment and management of borderline- and intermediate-risk patients is illustrated in Figure 1.

Data from the Multi-Ethnic Study of Atherosclerosis (MESA),[7] BioImage, and other cohorts[8-11] have suggested that 10-year ASCVD event risk in patients with borderline to intermediate calculated 10-year risk, but with CAC scores of 0, is consistently less than 5.0%, allowing reclassification into a low-risk category. Such patients would be expected to experience a small absolute risk reduction with statin therapy. These findings have led to the perspective that a CAC score of 0 may be used as a "de-risking" strategy in patients aged 40 to 75 years with borderline or intermediate risk. In such individuals, withholding or postponing the initiation of statin therapy for at least 5 years is reasonable.[3,4] Even in older patients with nearly universal statin eligibility based on the pooled cohort equation calculation, coronary calcium scoring may be a valuable adjunct when considering statin allocation. In an analysis of 5805 BioImage participants with a mean age of 69±6 years (86% [4966 subjects] of whom were statin eligible on the basis of the pooled cohort equation calculations) followed for a median period of 2.7 years, a CAC score of 0 or 10 or less was found to be associated with an approximately 80% lower risk of coronary heart disease events than expected on the basis of traditional risk factor assessment.[12]

The uncertainty inherent in the traditional decision-making process about statin therapy for borderline- and intermediate-risk primary prevention patients is supported by an analysis of 4203 primary

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prevention participants free of diabetes mellitus and with a mean age of 59±9 years from the MESA cohort. In this group, 589 were identified as being at borderline risk and 1381 at intermediate risk. Among borderline-risk individuals, 57% had CAC scores of 0, and among intermediate-risk individuals, 45.0% had CAC scores of 0. Overall, CAC scores of 0 reclassified ASCVD risk in 49% (956 of 1970) of those with calculated ASCVD risk between 5.0% and 19.9%.[7] Thus, in the absence of information on CAC scoring, the odds of misclassifying a borderline- or intermediate-risk patient's 10-year risk were similar to that of a coin flip. These results reinforce the central role that CAC scoring can play as a guide to decisions about whether absolute ASCVD risk is high enough to consider the initiation of statin therapy.

ILLUSTRATING THE POTENTIAL FOR MORE INFORMED STATIN ALLOCATION IN PRIMARY PREVENTION—THE THIRD HEART OUTCOMES PREVENTION EVALUATION EXPERIENCE

Although CAC scoring was not used as an entry criterion in the large primary prevention trials using statin therapy, it is important to appreciate that a substantial percentage of patients enrolled in these studies were likely to have had CAC scores of 0. Application of the above CAC scoring reclassification data from the 2 cohorts (MESA and BioImage) to a contemporary large ASCVD outcomes primary prevention study, the Third Heart Outcomes Prevention Evaluation (HOPE-3) trial, illustrates the potential use of CAC scoring to inform the clinician-patient discussion in patients with borderline or intermediate calculated 10-year risk.

The HOPE-3 trial enrolled 12,705 multiethnic men and women from 6 continents without clinical ASCVD at baseline and with an intermediate estimated risk of ASCVD events and a mean age of 66±6 years. Participants were randomly assigned to receive moderate-intensity (10 mg/d) rosuvastatin or placebo and followed for a median period of 5.6 years.[13] The results for the coprimary outcome of fatal and nonfatal ASCVD events (myocardial infarction or stroke) suggested a highly significant benefit of rosuvastatin therapy compared with placebo (hazard ratio, 0.76; 95% CI, 0.64-0.91; P=.002).

The cumulative incidence of ASCVD events in the placebo arm was 4.8%. The projected 10-year risk in the placebo arm was 8.74%, confirming that the study sample was at intermediate risk on average, consistent with the study design. It is therefore likely that nearly all HOPE-3 participants would have fallen within the 5.0% to 19.9% 10-year ASCVD risk range, in whom CAC testing is most helpful in guiding statin allocation. Table 2 summarizes the results of HOPE-3 overall and in projected CAC score categories based on prevalence values and event rates in the MESA and BioImage cohorts.[7,9]

This analysis illustrates that the projected absolute risk reduction with moderate-intensity statin therapy in patients with CAC scores of 0 is low (<0.5%). Conversely, CAC testing also identifies a subset with increased risk with CAC scores of 100 or more, in whom the estimate of absolute risk reduction is more than 4-fold higher (>2%). The projected number needed to treat (NNT) with rosuvastatin for 5.6 years to prevent 1 event is thus more than 200 for those with CAC scores of 0, as compared with 50 for those with CAC scores of 100 or more.

AVAILABILITY AND COST OF CAC SCORING EXAMINATIONS

The CAC scoring test is widely available. The greatest impediment to more widespread implementation in appropriate patients is that the test has limited coverage by most insurance carriers and is therefore most often a cash-pay test. Although the cost of a CAC scoring examination is variable, it is available in many locations for less than $100.[7] Given that roughly half of patients at borderline or intermediate calculated risk of an ASCVD event have CAC scores of 0 and would be candidates to have statin therapy withheld or postponed

TABLE 2. Estimated Event Rates and NNTs to Prevent 1 Event in HOPE-3 by Estimated CAC Score Categories at Baseline[a]

Variable	Placebo	Rosuvastatin 10 mg/d
Total, n	6344	6361
CAC score 0 (44%),[b] n	2791	2799
CAC score 1-99 (28%),[b] n	1776	1781
CAC score ≥100 (28%),[b] n	1776	1781
ASCVD events, n (%)[c]	304 (4.80)	235 (3.70)
ASCVD events, CAC score 0, n (%)[c]	59 (2.11)	46 (1.62)
ASCVD events, CAC score 1-99, n (%)[c]	89 (5.13)	69 (3.98)
ASCVD events, CAC score ≥100, n (%)[c]	156 (8.77)	120 (6.75)
% Risk difference,[d] total	—	−1.10
% Risk difference,[d] CAC score 0	—	−0.49
% Risk difference,[d] CAC score 1-99	—	−1.12
% Risk difference,[d] CAC score ≥100	—	−2.02
NNT, total	—	91
NNT, CAC score 0	—	206
NNT, CAC score 1-99	—	89
NNT, CAC score ≥100	—	50

[a]ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; HOPE-3 = Third Heart Outcomes Prevention Evaluation; NNT = number needed to treat.

[b]Prevalence of CAC scores of 0, 1-99, and ≥100 Agatston units estimated from values observed in the MESA and BioImage cohorts.[7,9] Group for the CAC score 0 and ≥100 Agatston unit subgroups were estimated from event rates in those categories in the MESA and BioImage cohorts, and the incidence in the CAC score 1-99 subgroup was calculated from the total events minus those estimated for the other 2 groups. The cumulative incidence in the rosuvastatin group and subgroups was calculated using a relative risk of 0.77 on the basis of the overall results of HOPE-3 (note that the relative risk of 0.77 based on cumulative incidence was slightly different from the reported hazard ratio of 0.76 based on incidence rates).

[c]Cumulative incidence in the placebo.

[d]Percent absolute risk difference for the rosuvastatin group/subgroup compared with that for the placebo group on the basis of cumulative incidence or estimated cumulative incidence as described above.

(in the absence of cigarette smoking, diabetes, or a family history of premature ASCVD), it is reasonable to assume that patient and insurer cost savings related to less need for medication, follow-up testing, and office visits would easily exceed the cost of a CAC scoring examination, even if it was repeated for those with scores of 0 every 5 to 10 years between ages 40 and 75 years.

There has also been concern about added costs to the patient and insurers related to incidental findings noted during CAC testing. A prospective study of procedural costs and resource consumption in a group of 1381 nonpaid volunteers recruited from major medical centers and teaching hospitals, who were followed for a median of 4 years, found that more than 90% of the screened individuals with CAC scores 0 to 10 did not have procedures during 1 year of follow-up. Additional testing and invasive procedures were limited largely to a low number of individuals with CAC scores greater than 400.[14]

As is common with other radiographic screening examinations, incidental findings may sometimes prompt the need for additional testing. With CAC scoring, incidental findings of uncertain clinical significance (particularly pulmonary nodules) may be encountered in 10% or more of patients. A systematic approach to these findings aids the clinician in management decisions.[15,16]

AN INFORMED CLINICIAN-PATIENT DISCUSSION FOR SHARED DECISION MAKING

On the basis of the above information, the clinician, without knowledge of the risk discrimination and reclassification data

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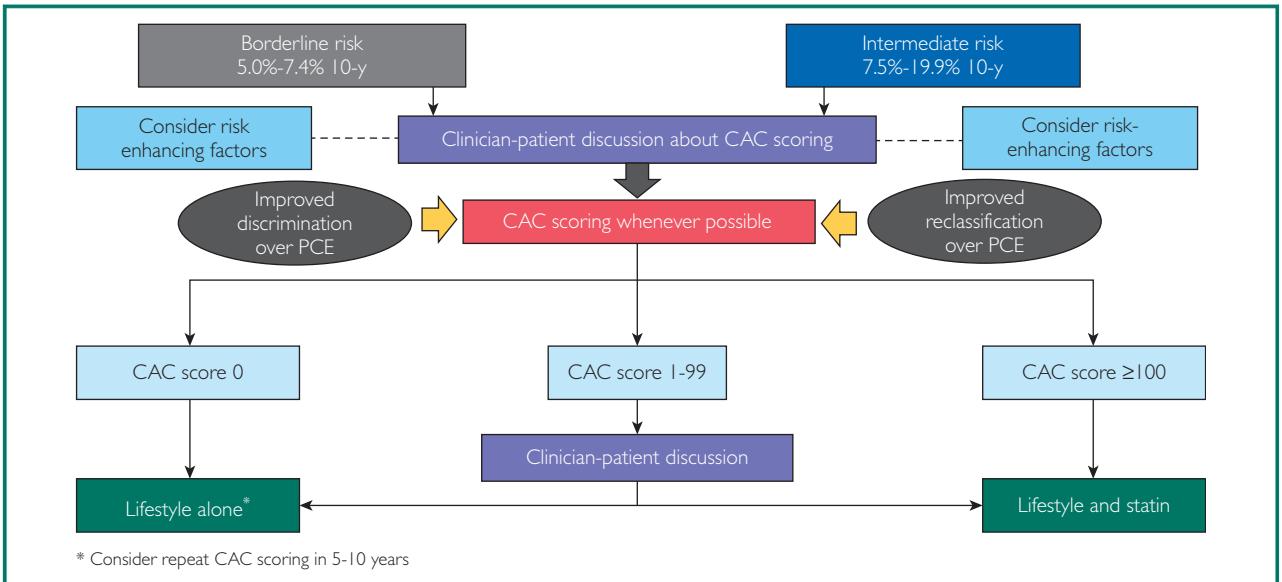

FIGURE 2. Proposed approach to the risk assessment and management of borderline- and intermediate-risk patients. CAC = coronary artery calcium; PCE = pooled cohort equation. *Except if active smoker, had type 2 diabetes mellitus, or had a family history of premature atherosclerotic cardiovascular disease, consider statin.

provided by a CAC examination, can only provide his or her "best guess" about which borderline- and intermediate-risk patients should be recommended long-term statin therapy, because 40% to 50% have CAC scores of 0. Therefore, a truly informed clinician-patient discussion in these individuals might include the following information:

1. Although risk calculations for populations can give a rough estimate of heart attack and stroke risk, your risk score is in the middle range in which the true risk is less certain. If your risk is high enough, a statin to lower your cholesterol level would be expected to substantially reduce your chance of experiencing a heart attack or stroke. However, there is a 40% to 50% chance that your risk is really in the low category, in which case a statin would provide limited risk reduction and would subject you to added costs, inconvenience, and the potential for medicine-related adverse effects.
2. Coronary artery calcium testing helps to more precisely estimate risk, thus allowing a more accurate assessment of the potential net benefit of statin therapy.
3. A CAC examination is often a cash-pay test (ie, not covered by health insurance) but is often available for less than $100 and associated with minimal radiation exposure.
4. Incidental findings may be noted, but most are benign, and there are established protocols for dealing with such findings.
5. If the CAC score is 0 on the initial examination, follow-up CAC testing may be reasonable every 5 to 10 years in those with scores of 0 or with scores less than 100 but not taking statins. For those found to have scores of 100 or more, repeat CAC scoring will not be necessary.

The information reviewed above provides support for the perspective that most patients aged 40 to 75 years with a 5.0% to 19.9% calculated 10-year risk and not treated with a statin should undergo at least 1 CAC scoring examination to facilitate allocation of statin therapy to those most likely to benefit and to avoid treatment in those for whom absolute benefit and cost-effectiveness are likely to be low. Such testing would most appropriately be performed in men at an earlier age (40 years or older) than women

(50 years or older). Our proposal for modification of the recommended use of CAC scoring for borderline- or intermediate-risk patients is summarized in Figure 2.

CONCERNS ABOUT RADIATION EXPOSURE

Implementation of the more widespread use of CAC scoring reasonably requires consideration of radiation exposure. The median radiation exposure for this procedure with modern testing equipment is approximately 1 mSv, the dose produced by exposure to 1 mGy of radiation.[17] By comparison, the Digital Mammographic Imaging Screening Trial from the American College of Radiology Imaging Network identified the mean radiation dose of 1.86 mGy to the breast from a single digital mammography view, with considerable variability per view (21% of screening examinations used >4 views).[18] Radiation exposure is greater for those with dense breast tissue. Mammography for breast cancer detection clearly reduces breast cancer deaths but entails risk due to radiation exposure, as women undergo repetitive mammographic studies over the course of a lifetime.[19]

The current pattern of providing insurance coverage for multiple routine screening mammograms vs no coverage for CAC scoring is not consistent with the morbidity and mortality risk associated with breast cancer compared with ASCVD. In US women, the lifetime risk of breast cancer is approximately 12% to 13% and the risk of death from breast cancer is 2% to 3%.[20] In contrast, the lifetime risk of ASCVD (including coronary heart disease, stroke, and heart failure) in women is approximately 56% and the risk of cardiovascular mortality is 15% to 20%.[21] The American Cancer Society Guidelines for the Early Detection of Cancer recommends annual screening mammography from ages 45 to 54 years and then either annual or biennial screening beginning at the age of 55 years for as long as a woman is in good health and is expected to live for 10 years or longer.[22] As the lifetime risk of morbidity or mortality from cardiovascular disease is approximately 5- to 10-fold higher than that from breast cancer and as radiation exposure attendant to a single CAC scoring test is low, an informed clinician-patient discussion about the importance of CAC scoring could reasonably include, in the absence of a strong family history or genetic sequence variations associated with a high risk of breast cancer, a recommendation to forego 1 annual screening mammogram for those women 55 years and older at borderline or intermediate 10-year ASCVD risk and substitute a CAC scoring examination.

LIMITATIONS

This approach to statin allocation as part of shared decision making has certain limitations. Coronary artery calcium scoring is not currently performed in most borderline- or intermediate-risk patients. Its accuracy for risk stratification is well established for general population samples, but additional information is needed for some subgroups, particularly those with other conditions that may enhance risk, including patients with chronic inflammatory conditions such as rheumatoid arthritis or human immunodeficiency virus infection.

Because insurance coverage for the procedure is limited at this time, in most cases, the patient assumes the cost of the test. The test is widely, but not universally, available. Thus, the implementation of this strategy has the potential to increase health care disparities and to disfavor those of lower socioeconomic status or with less access to preventive health care services.

The authors recognize that there have been no prospective randomized studies in borderline- or intermediate-risk individuals comparing ASCVD outcomes and cost-effectiveness of treating all such patients with moderate-intensity statins vs treating only those with any detectable CAC or with CAC scores of 100 or more. A potential limitation of the proposed model is that there is a wide range of anticipated ASCVD risk in individuals in the 7.5% to 19.9% 10-year risk category, even with CAC scores of 0. As those with 10-year risk values above

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15.0%, and especially those with 10-year risk near 20%, might still sustain substantial absolute benefit from statin therapy,[4] this issue may be reasonably addressed by rechecking the CAC score in 5 years in those with a risk level of 15.0% to 19.9%, in 10 years in those with 10-year risk less than 10%, and using clinical judgment for the time of retesting for those whose 10-year risk is 10.0% to 14.9%.

It should be noted that the estimates herein from the HOPE-3 trial suggest a higher NNT value than do those in a recent publication from the Copenhagen General Population Study. Data from this cohort with a mean follow-up of 10.9 years were analyzed to assess the NNT to prevent 1 ASCVD event in 10 years according to primary prevention statin eligibility criteria from the 5 guidelines, including the 2018 Guideline. The investigators assumed a 25.0% relative risk reduction per 38.7 mg/dL (1 mmol/L) reduction in LDL cholesterol level and that moderate- and high-intensity statin therapy reduced the LDL cholesterol level by approximately 50% and 30%, respectively. At baseline, 42% were eligible for statin therapy according to the 2018 Guideline. The estimated NNTs to prevent 1 hard ASCVD event using moderate- and high-intensity statins were 30 and 20, respectively. These are lower than those observed in the HOPE-3 trial, in which the projected 10-year NNT with 10 mg/d of rosuvastatin (moderate-intensity therapy) to prevent 1 event was 50.[23]

The results from a microsimulation model for a hypothetical, but representative, sample of individuals from the US population, 40 to 75 years of age, suggested that statin treatment of those with a 7.5% or more 10-year risk calculated using the pooled cohort equations was cost-effective, with an incremental cost of $37,000 per quality-adjusted life-year gained (QALY) compared with a 10% or higher threshold. The use of a 5.0% or more risk also projected to an acceptable to good incremental cost of $57,000 per QALY.[24] Another microsimulation model suggested that treating all individuals with pooled cohort equations estimated risk of at least 5.0% would be highly cost-effective ($33,558 per QALY) and would prevent the most ASCVD events.[25] However, the authors of an overview of systematic reviews of randomized controlled trials examining statin therapy vs placebo, or no treatment, on cardiovascular and mortality end points concluded that additional supportive data are needed to aid in shared decision making, particularly for patients at lower cardiovascular risk where the boundaries between appropriate use, overuse, and low value care are difficult to ascertain.[26,27] The expanded use of CAC scoring would help to more clearly define these boundaries, because a CAC score of 0 reliably identifies individuals with a 10-year risk of less than 5.0%, a group in which the cost exceeds $150,000 per QALY. Moreover, patients with CAC scores of 100 or more are in a group for whom the ratio of benefits to costs and risks is more clearly favorable. Thus, our proposed algorithm, especially when CAC scoring test is available at less than $100, has favorable cost implications, provides the opportunity to treat those patients most likely to benefit, and has the potential to reduce medication requirements and adverse effects in a large segment of the population.

CONCLUSION

Statin allocation for the primary prevention of ASCVD in patients 40 to 75 years of age with intermediate or borderline estimated ASCVD event risk requires an informed clinician-patient discussion in which the clinician identifies the major risk factors and the importance of control of these using lifestyle approaches as the basis for prevention. When statin therapy is being considered, the first step is consideration of calculated 10-year risk, followed by consideration of additional information on family history, certain coexisting medical conditions, and, if available, laboratory studies to aid in shared decision making. Because CAC scoring is the most evidence-based, practical, and clinically available noninvasive test to improve discrimination and reclassification of ASCVD risk as compared with the

pooled cohort equations and because this test can effectively identify those most likely to exhibit larger absolute risk reduction from statin therapy, this test should be offered, whenever possible, to provide optimal preventive care for these patients.

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Abbreviations and Acronyms: **2018 Guideline** = 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol; **ASCVD** = atherosclerotic cardiovascular disease; **CAC** = coronary artery calcium; **HOPE-3** = Third Heart Outcomes Prevention Evaluation; **LDL** = low-density lipoprotein; **MESA** = Multi-Ethnic Study of Atherosclerosis; **NNT** = number needed to treat; **QALY** = quality-adjusted life-year gained

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