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Editorial

To Risk Stratify or Not for Statin Therapy

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See article by Khunti et al., pages 644–652 of this issue.

The 2016 Canadian Cardiovascular Society (CCS) guidelines for the management of dyslipidemia[1] recommend the use of statin treatment for the primary prevention of cardiovascular (CV) events in: (1) patients with a high risk (10 year incidence of > 20%) of CV disease, calculated using the **F**ramingham **R**isk **S**core (FRS); and (2) patients with an intermediate risk (FRS 10%-20%) with (i) low-density lipoprotein (LDL) cholesterol > 3.5 mmol/L, or (ii) LDL cholesterol < 3.5 mmol/L but non-high-density lipoprotein (HDL) > 4.3 mmol/L or apolipoprotein B > 1.2 g/L, or (iii) men 50 years of age and older and women 60 years of age and older with additional CV risk factors that include low HDL cholesterol, impaired fasting glucose, increased waist circumference, cigarette smoking, and hypertension (with additional risk factors that include left ventricular hypertrophy). Low-risk patients with a FRS calculated risk of < 10% are not recommended to receive statin treatment.

The recommendation to use statin therapy in individuals with intermediate risk and 1 or more additional CV risk factors is on the basis of the results of the **H**eart **O**utcomes **P**revention **E**valuation (HOPE)-3 study.[2] HOPE-3 was a pragmatic trial that used simple selection criteria and treated patients with moderate intensity statin therapy, with no treatment targets and minimal monitoring of treatment. The selection criteria included clinical risk factors (elevated waist to hip ratio, history of a low level of HDL cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction) with no consideration of LDL cholesterol levels. Unlike the CCS guideline recommendation, patients in the HOPE-3 study did not undergo any risk stratification before selection for treatment. However, rosuvastatin, 10 mg daily over 5.6 years, reduced the composite coprimary end point of CV death, nonfatal myocardial infarction, or stroke by 24% (3.7% in the rosuvastatin group vs 4.8% in the placebo group; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.64-0.91; $P = 0.002$; number needed to treat, 91).

The current CCS dyslipidemia guidelines[1] have modified the simplified inclusion criteria of HOPE-3 by requiring patients to have an intermediate FRS score of 10%-19%, excluding lower risk patients with FRS < 10% and modifying the selected risk factors. In the present issue of the *Canadian Journal of Cardiology*, Khunti et al.[3] report on the effect of pretreatment risk assessment on the outcome benefits of statin treatment in subjects in the HOPE-3 trial. Patients were risk-stratified to low (< 10%), intermediate (10%-20%), and high (> 20%) risk categories using the American College of Cardiology/American Heart Association risk table and the FRS. The overall extrapolated 10-year CV death/myocardial infarction/stroke risk in the placebo group of HOPE-3 patients was 8.6%. According to the CCS guidelines, patients with a FRS < 10% 10-year risk would not qualify to receive statin treatment. Using the American College of Cardiology/American Heart Association score, 31.8% of patients classified as low risk at an extrapolated 10-year risk of 2.2% had a nonsignificant treatment benefit (HR, 0.82; 95% CI, 0.53-1.28). With the FRS, 12.2% were in the low risk group with a 10-year event rate of 5.0% (treatment HR, 0.69; 95% CI, 0.36-1.35).

Risk stratification of patients for the primary prevention of CV disease has several important limitations. First, a large proportion of physicians do not use any risk evaluation score and decide on statin treatment on the basis of subjective assessment.[4] Second, different risk evaluation scores yield different proportions of risk as is illustrated in the current HOPE-3 analysis.[3] Guidelines have arbitrarily determined threshold 10-year risk levels to initiate statin therapy, which vary from 7.5% to 20%. Assessed risk is strongly age-dependent, and underestimates risk in the younger population and overestimates risk in older subjects. In young patients with a myocardial infarction, 71% of patients had a low risk score before the event, and would not have been eligible for statin treatment.[5] Unfortunately, most events occur in patients in the "low risk" group, which is the largest group of the at-risk population. However, risk scores can also overestimate risk, as shown in an analysis of the **M**ulti-**E**thnic **S**tudy of **A**therosclerosis (MESA) population, in which 44% of patients classified as statin-eligible had 0 calcium scores[6] and were

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consequently reclassified to the low risk category with no expected benefit from statin treatment. Risk scores are not calibrated to provide accurate CV risk in all ethnic groups, and tend to underestimate risk in South Asian individuals and to overestimate risk in a Chinese population.[7] Using HOPE-3 inclusion criteria, the analysis of Khunti et al.[3] shows similar proportions of Hispanic, Asian, and white populations would have risk scores > 10%, and thus be eligible for statin treatment.

The study of Khunti et al.[3] shows that if the HOPE-3 selection criteria for statin therapy were applied without previous risk stratification, only a small additional number of patients currently classified as low risk using the FRS would receive statins. Yet, even these low-risk patients likely benefit from treatment. The patient selection strategy for statin treatment used in the HOPE-3 study is applicable to a wide range of populations including those in locations where lipid monitoring is not readily accessible. Statins are widely available as generic formulations at low cost and are well tolerated with minimal serious adverse effects, with most adverse effects not attributable to the treatment.[8] Currently many patients at significant risk do not receive vascular protection with statins for a number of reasons, including a perceived low 10-year CV risk. The simplified strategy, that does not include age as a risk factor, might encourage physicians to start treatment in patients at an earlier age, rather than waiting until age pushes CV risk over the treatment threshold; thus, affording a longer period of reduced LDL cholesterol and a greater treatment benefit.

The study of Khunti et al.[3] provides clinical trial evidence to support a transition from a risk score-centric strategy to a simple pragmatic selection of patients for statin treatment for the primary prevention of CV disease. The study indicates that selection using these criteria would unlikely result in "mass statinization." However, it would be of interest to see a cost-effectiveness analysis on the basis of this strategy. Without risk stratification there remain 2 groups of patients who potentially could be overlooked and not receive statin therapy as recommended by the current guidelines. First, patients with FRS of 10%-19% with LDL cholesterol > 3.4 mmol/L, and second, high-risk patients with FRS > 20%. However, it is likely that most high-risk patients would have one or more of the HOPE-3 risk factors. A registry analysis would be useful to answer both of these issues.

Disclosures

The author has no conflicts of interest to disclose.

References

1. Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32:1263-82.

2. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021-31.

3. Khunti K, Jung H, Dans AL, et al. Statin use in primary prevention; a simple trial-based approach compared with guideline recommended risk algorithms for selection of eligible patients. Can J Cardiol 2019;35:644-52.

4. Law TK, Yan AT, Gupta A, et al. Primary prevention of cardiovascular disease: global cardiovascular risk assessment and management in clinical practice. Eur Heart J Qual Care Clin Outcomes 2015;1:31-6.

5. Singh S, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. J Am Coll Cardiol 2018;71:292-302.

6. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66:1657-68.

7. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet 2000;356:279-84.

8. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2017;389:2473-81.