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Accurate CV Risk Stratification to Ensure Adequate Statin Treatment

Montreal - Whether in primary or secondary prevention of cardiovascular (CV) events, physicians, including specialists, are not lowering blood lipid levels sufficiently, according to data presented here at the CCC. One obstacle appears to be an inadequate evaluation of risk factors. This appears to be particularly true in managing patients without a previous history of CV disease. Relatively simple tools, including high-sensitivity C-reactive protein, can distinguish intermediate from low-risk patients, but risk stratifications are not being performed accurately even among those who claim to use established methodology such as the Framingham Risk Score. Moreover, even when patients have had a CV event and clearly require maximum lipid-lowering therapy to reach guideline-recommended targets, suboptimal dosing is common. The failure to treat patients aggressively with statins, which are extremely well-tolerated, results in missed opportunities to reduce the morbidity and mortality of coronary artery disease in Canada.

The history of statin trials has been one of very large reductions in major adverse cardiac events achieved in both primary and secondary prevention. Trials that have contributed to progressively lower targets suggest that essentially any LDL-C level is too high in an individual who has a cardiovascular (CV) event. In primary prevention, adequate treatment depends on accurate risk stratification, which is essential to ensure that a statin is on board for those who can benefit.

The Evidence from PARADIGM

The most recent evidence that candidates for statins are routinely missed was generated by the PARADIGM (Primary Care Audit of Global Risk Management) study. Unlike the 2009 Canadian Cardiovascular Society (CCS) guidelines for the diagnosis and treatment of dyslipidemia, which specifically endorse the Framingham Risk Score (FRS) as a tool for screening, only about one-third of physicians in PARADIGM were using this approach. The CCS guidelines also suggest evaluating high-sensitivity C-reactive protein (hsCRP) in intermediate-risk patients, with or without the Reynolds Risk Score (RRS), which includes this measure, but the PARADIGM results suggest that no tool is being used accurately.

“Primary care physicians report that they are calculating risk scores in their patients, but they are not doing an effective job,” reported PARADIGM senior author, Dr. Milan Gupta, a member of the Canadian Cardiovascular Research Network and Associate Professor of Medicine, Division of Cardiology, McMaster University, Hamilton, Ontario. Although self-reports suggested that only 28% of primary care physicians rely on clinical judgment alone in evaluating CV risk, the correlation between physician-estimated risk assessed by a centralized analysis centre was only fair, even among the 34% who reported using the FRS.

In this study, 3015 generally healthy participating patients were evaluated at baseline for a variety of common risk factors. The blood work included analysis of lipoprotein levels as well as hsCRP. At a second visit within 60 days of the baseline assessment, 105 primary care physicians reviewed the physical and laboratory findings and were then asked to determine whether the patient was at low, intermediate or high risk for CV disease. These were defined, respectively, as <10%, 10% to 20%, or >20% risk of a CV event within the next 10 years. The participating physicians were permitted to use any method of risk assessment. In addition to the 28% who reported using clinical judgment and the 34% who reported using the FRS, 16% reported that their predominant method of assessment was hsCRP, 12% reported counting risk factors and the remaining reported some other methodology.

The overall agreement between physicians and central risk calculations was 58%, producing a kappa of 0.27 for correlation (100% agreement would produce a kappa of 1.0). Dr. Gupta characterized this level of correlation as “marginal or fair.” Moreover, when agreement was evaluated among the 34% who said they used the FRS, the correlation was still only 69% for a kappa of 0.43, which Dr. Gupta characterized as just “moderate.”

These results are alarming for several reasons. One is that the vast majority of CV risk assessment in Canada is performed by primary care physicians. Another is that physicians within this study expressed confidence in their risk assessment technique. Again, the disparity was notable in those at intermediate risk, where statins can lower risk substantially even when lipid levels are unremarkable. This was demonstrated in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial that compared rosuvastatin to placebo in apparently healthy men over the age of 50 and women over

the age of 60 (Ridker et al. *N Engl J Med* 2008;359:2195-207). Patients were required to have an LDL-C of no more than 3.4 mmol/L and hsCRP >2.0 mg/L.

JUPITER, which had a planned follow-up of 5 years, was stopped after a median follow-up of 19 months by the Data and Safety Monitoring Committee when rosuvastatin had already achieved a 44% relative reduction (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$) in the primary composite end point of myocardial infarction (MI), stroke and death from CV causes. The change in the 2009 Canadian guidelines to endorse hsCRP as a screening tool in intermediate-risk patients was based primarily on the JUPITER results.

CCC Debate: The Role of hsCRP

In a debate at the CCC about the importance of hsCRP in standard care, Dr. Guy Tremblay, Professor of Medicine, Université Laval, Quebec City, Quebec, assumed an antagonist position. Based on the assertion that such established risk factors as hyperlipidemia, hypertension and smoking explain the majority of CV risk, he suggested that hsCRP might only occasionally influence treatment decisions. For primary care physicians already burdened with time constraints, he questioned the value of this extra tool even while acknowledging that evidence of a pro-inflammatory state might provide prognostic information in CV disease.

The protagonist position was assumed by Dr. Subodh Verma, Canada Research Chair in Atherosclerosis, St. Michael's Hospital, Toronto, Ontario. He cited evidence that hsCRP might provide as much or more information about CV risk as blood pressure and cholesterol after adjusting for variables such as age and gender (Emerging Risk Factor Collaborators. *Lancet* 2010;375:132-40). In addition to the benefits associated with selecting elevated hsCRP as a marker for treatment with rosuvastatin in JUPITER, he cited a meta-analysis of hsCRP studies that associated high hsCRP with a 60% (HR 1.6; 95% CI, 1.37-1.83) increase for CV events relative to a low hsCRP (Buckley et al. *Ann Intern Med* 2009;151:483-95). Although he agreed that hsCRP is valuable only when trying to identify intermediate-risk patients missed by the FRS alone, he believes that this information could and should influence treatment decisions.

Missed Opportunities in STEMI Patients

However, even when risk is high, physicians are not always pursuing evidence-based target LDL-C levels. In a study of patients discharged after an ST-segment elevation MI (STEMI), the efficacy of rosuvastatin and atorvastatin was found to be similar, but this is likely due to the fact that patients on each drug were on suboptimal doses. Although 20 mg rosuvastatin provides LDL-C reductions that are at least equivalent to the maximum dose of atorvastatin, these doses were rarely used even when patients were not at target. The authors of the study, led by Dr. Olivier F. Bertrand, Quebec Heart and Lung Institute, Ste-Foy, concluded that physicians are not being sufficiently aggressive in lipid management of these high-risk patients regardless of which statin they prescribe.

In high-risk patients, as in intermediate-risk patients, an inadequate appreciation of the opportunities of risk reduction appears to be inhibiting opportunities to improve long-term outcomes. In the intermediate-risk population, the obstacle may be failure to employ established methodology for evaluating risk, which can reveal patients who benefit from statins and other risk reduction strategies and who might otherwise be missed. In high-risk patients, the obstacle appears to be treating to target. In both cases, evidence-based guidelines have provided clear strategies to improve care.

Summary

Accurate risk stratification is a critical first step to adequate treatment. In intermediate-risk patients, primary care physicians in Canada are not employing risk assessment strategies appropriately, judging from the PARADIGM study. In intermediate-risk patients, results of the JUPITER study demonstrated that there is a particular opportunity for elevated hsCRP levels to identify patients, particularly those with modest or no dyslipidemia, who will benefit from statins. Statins are one of the most effective tools for reducing risk of both first CV events and recurrent events. Recent evidence that targets are not being met even in patients in very high-risk categories suggests that morbidity and mortality rates can be lowered with greater efforts to match treatment with evidence. □

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