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Consistent Use of Risk Stratification Protocols to Guide CV Treatment Decision-Making

Chicago - Cardiovascular (CV) event rates could be reduced dramatically if clinicians simply employed effective screening methods consistently to identify at risk patients. The importance of expanding the focus on individual modifiable risk factors to global risk is based on evidence that lipid lowering may be appropriate even in the absence of traditional definitions of hyperlipidemia. The ability of statins to reduce the likelihood of events even when cholesterol levels are unremarkable was first demonstrated in patients with established CV disease. In these patients, incremental reductions in LDL-C produced incremental reductions in CV risk essentially independent of baseline levels. On a modified basis, the same basic principle is relevant to primary prevention. The large event reductions achieved with lipid lowering in patients with unremarkable lipid levels and at moderate CV risk when identified with such markers as elevated high-sensitivity C-reactive protein levels emphasizes that formal risk stratification protocols are essential for guiding treatment decisions.

As clinicians are doing better in identifying and treating patients at high risk of cardiovascular (CV) disease, protecting patients at moderate risk may now be the greatest challenge for reducing CV events in Canada. Intermediate-risk patients, (defined as at least a 10% but less than a 20% likelihood of having an event in the next 10 years) are not readily identified by clinical judgment, but do benefit from lipid-lowering therapies. In the current Canadian guidelines for prevention of CV disease, the LDL-C target for intermediate risk patients is <2.0 mmol/L or a 50% reduction from baseline (Genest et al. *Can J Cardiol* 2009;25:567-79). However, clinicians do not appear to be performing appropriate risk assessment, often missing even those at high risk, according to results of a recently completed Canadian study.

In this study of CV risk stratification by primary care physicians in Canada, "Two-thirds of high-risk patients were classified at lower risk levels," reported Dr. Milan Gupta, Canadian Cardiovascular Research Network (CCRN), Brampton, Ontario. Presenting updated data at the AHA from a study originally presented earlier at the Canadian Cardiovascular Congress (CCC), Dr. Gupta, Associate Professor of Medicine, McMaster University, Hamilton, Ontario, reported that the accuracy of both intermediate and high-risk patients was poor even though nearly 35% of the physicians reported using the Framingham Risk Score (FRS). Most of the others reported some other form of systematic risk assessment.

Formal Risk Assessment Mandated in Guidelines

Use of formal methods of assessing risk is recommended in the most recent Canadian guidelines. The FRS, which has been validated in Canada, and the Reynolds Risk Score (RRS), which takes into account family history

and high-sensitivity C-reactive protein (hsCRP) levels, were both identified as acceptable. However, Dr. Gupta suggested that the exact method of risk assessment might be less important than using any systematic and validated approach consistently and accurately. He noted that 35% reported using FRS in this study, which evaluated agreement between centralized FRS analysis and risk assessment by 105 primary care physicians evaluating 3015 middle-aged healthy adults. However, a large percentage appear to be misinterpreting the results based on poor agreement with an independent assessment.

Specifically, agreement between primary care physicians and a centralized risk assessment using FRS was only 65.7% for those at low risk, falling to 50.4% for intermediate-risk patients and to 34.2% for high-risk patients. When just those physicians who claimed to be using FRS were isolated in this study, called PARADIGM (Primary Care Audit of Global Risk Management), agreement improved but only modestly.

Although these results highlight poor risk assessment of primary care physicians in both high- and intermediate-risk patients, there is concern that even specialists are not accurately identifying those at intermediate risk if they rely on clinical judgment alone. The presence of hypertension, diabetes and hyperlipidemia provide clear signals of patients at elevated risk, but the substantial proportion of patients who have a CV event without classical risk factors has generated a number of important initiatives to identify additional risk markers. One of the new markers, now incorporated into the Canadian guidelines, is hsCRP. The evidence that it can and should be used to identify intermediate-risk candidates for lipid lowering is the large risk reductions observed in the landmark JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial (Ridker et al. *N Engl J Med* 2008;359:2195-207).

Lipid-lowering Benefit even Without Elevated Lipids

Indeed, the premise of JUPITER was that a group of intermediate-risk patients can be identified who will benefit from lipid lowering even when they do not have remarkably elevated LDL-C. Like secondary prevention studies that demonstrated that essentially any LDL-C is too high in patients who have had a CV event, JUPITER demonstrates that even relatively average LDL-C levels are too high in those who have an elevated hsCRP. In JUPITER, 17,802 apparently healthy men and women were entered if they had an elevated hsCRP (≥ 2.0 mmol/L). Although there were numerous criteria to exclude high-risk patients, including any history of CV disease, a LDL-C >3.4 mmol/L and triglyceride level >5.6 mmol/L, the only other significant risk inclusion other than elevated hsCRP was an age of at least 60 years in men and at least 50 years in women. The patients were randomized to rosuvastatin 20 mg or placebo.

The study, which had a planned follow-up of 5 years, was stopped after a median follow-up of 19 months. At that time, there was 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. Large event reductions, including a 20% relative reduction in all-cause mortality ($P = 0.02$), were observed across a number of important end points, including a 54% relative reduction ($P = 0.0002$) in myocardial infarction, a 48% reduction ($P = 0.002$) in stroke, and a 47% relative reduction ($P < 0.00001$) in revascularization and hospitalisation due to unstable angina.

Bayesian Calculations Reinforce VTE Protection

The JUPITER results continue to be explored in a variety of analyses, including one presented at the AHA, which employed a Bayesian analysis to evaluate a number needed to treat (NNT) for the statin in this study to prevent venous thromboembolism (VTE). Bayesian analysis is a statistical methodology for estimating an underlying distribution based on observed values. In this case, experiential probabilities for preventing VTE were obtained from the JUPITER trial. Led by Dr. Christopher D.

Lang, University of Rochester Medical Center, New York, the analysis found that the five-year NNT of 25 reported by JUPITER investigators is likely to be an underestimate.

“The Bayesian calculations support a clinically important benefit from rosuvastatin in the prevention of total VTE events with risk reduction correlated with increasing values of hsCRP,” Dr. Lang told delegates. Although this study was not designed to evaluate mechanism of action, the results are consistent with the premise that upregulation of the inflammatory system, which is suggestive of elevated hsCRP, is an important pathophysiologic factor in VTE similar to the way it is suspected to be a driver of CV events.

Although risk stratification by hsCRP has been incorporated into treatment guidelines, this is not an independent risk assessment tool. According to many experts, including Dr. Gupta, hsCRP is meaningful and helpful only in middle-aged patients whose risk status remains uncertain after considering conventional characteristics such as body mass index (BMI), blood pressure, hyperlipidemia, family history of CV and smoking status. In otherwise healthy patients younger than those evaluated in JUPITER, the significance of an elevated hsCRP is unclear, and in high-risk patients, hsCRP does not add information because such individuals should already be receiving aggressive lipid lowering. While additional methods of identifying at-risk patients are being sought, lowering lipids in intermediate-risk patients represents an important opportunity to reduce CV event rates in Canada.

Summary

In patients who have had a previous CV event, lipid lowering reduces risk almost regardless of the baseline level. In primary prevention of CV events, current guidelines recommend that attention to global risk, identified by risk scoring systems such as the FRS, is essential for understanding treatment goals. In patients identified as being at intermediate risk using current risk evaluation tools, including hsCRP, lipid lowering is also beneficial even when baseline levels are unremarkable. Although treatment targets should be pursued for all modifiable risk factors, formal risk assessment expands guidance for therapeutic decisions. □

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