



## Canadian Cardiovascular Congress

Toronto, Ontario / October 25-29, 2008

### Cardiovascular Risk Prediction and Protection: Singling out High-risk Groups

**Toronto** - Gaps between lipid targets set by guidelines and levels achieved in clinical practice continue to be reported, at least in part because targets for high-risk patients are difficult to achieve with well-tolerated doses of statin monotherapy. Alternatively, physicians may choose to combine optimal statin therapy with a cholesterol absorption inhibitor to achieve further reductions in LDL-C without incurring additional side effects. Although cardiovascular (CV) risk assessment tools are helpful in identifying patients at elevated risk for CV disease, the use of surrogate markers is being explored as a means of improving risk prediction models. Chronic kidney disease and diabetes represent two of the highest risk states for CV events and prevention in these key patient groups is paramount.

**Toronto** – On continue de rapporter des écarts entre les taux lipidiques recommandés et les taux observés dans la pratique clinique, l'une des raisons étant que les taux ciblés chez les patients à risque élevé sont difficiles à atteindre avec des doses bien tolérées de statines en monothérapie. Cela dit, le médecin a aussi la possibilité d'associer une statine à dose optimale et un inhibiteur de l'absorption du cholestérol pour obtenir une réduction plus marquée du taux de C-LDL sans pour autant causer d'autres effets indésirables. Bien que les outils d'évaluation du risque cardiovasculaire (CV) nous soient déjà utiles pour repérer les patients exposés à un risque élevé de maladie CV, on étudie la possibilité d'utiliser des marqueurs de substitution pour améliorer les modèles de prédiction du risque. L'insuffisance rénale chronique et le diabète étant au nombre des grands facteurs de risque d'événements CV, la prévention revêt une importance capitale chez ces patients.

By Pam Harrison

Cardiovascular disease (CVD) risk prediction, chronic kidney disease (CKD) and its association with CVD, and prevention of CVD in high-risk patients are all on the agenda during the 4th Annual Medical Debate on Lipid Management scheduled for Sunday.

Lipid expert and symposium chair Dr. Lawrence Leiter, Professor of Medicine, University of Toronto, Ontario, will guide discussion and debate between faculty and delegates as they tackle issues such as care gaps in dyslipidemia management in Canada; assessment of patients with elevated CV risk; the role of carotid intima media thickness (IMT) studies and biomarkers as adjunctive measures of that risk; and CV risk in special populations. With guidelines indicating that high-risk patients need to achieve LDL-C targets of <2 mmol/L and a total cholesterol:HDL-C <4, physicians may well find it difficult to reduce lipids to such low levels with well tolerated doses of statin monotherapy. Thus, combination therapy using optimal doses of any statin, combined with the cholesterol absorption inhibitor ezetimibe, is increasingly favoured as a well-tolerated strategy to reduce LDL-C to recommended targets in high-risk patients.

As will be discussed by Dr. Eva Lonn, Professor of Medicine, McMaster University, Hamilton, Ontario, a range of CV risk assessment tools are available to help assess risk for CVD, the most familiar being the Framingham risk score (FRS). This score was designed to assess 10-year risk of CVD and helps predict which patients are at greater lifetime risk for CVD. Based on 7926 participants in the Framingham Heart Study—all free of CVD on study entry—for example, participants who did not smoke and who did not have diabetes, and who had optimal levels of cholesterol and blood pressure on study entry, had a

significantly lower lifetime risk of developing CVD at 5.2% in men and 8.2% in women, compared with men and women who had two or more major risk factors at study entry, among whom CVD rates were 68.9% and 50.2%, respectively. However, as Dr. Lonn observes, the FRS does not stratify lifetime risk well in younger patients, especially in women. Research into what drives the atherosclerotic disease process has identified certain markers of inflammation that may serve as adjunctive tools to assess CVD risk, most notably C-reactive protein (CRP). In the PROVE-IT trial, researchers reported that patients in whom statin therapy reduced LDL-C levels to <1.8 mmol/L had lower event rates than those with higher levels (Ridker et al. *N Engl J Med* 2005;352(1):20-8). Conversely, a difference was seen between patients who had CRP levels of <2 mg/L after therapy and those with higher levels and this effect was observed at all levels of LDL-C.

In a number of primary prevention cohorts, lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) activity was associated with an elevated risk of coronary artery disease (CAD) as well as ischemic stroke, suggesting that in the general population, those with the highest levels of Lp-PLA<sub>2</sub> activity have a greater risk of coronary and cerebrovascular events compared to those with the lowest levels.

A meta-analysis of studies in which carotid IMT—increasingly used as a surrogate marker for atherosclerosis—was measured found that carotid IMT is indeed a strong predictor of future vascular events (Lorenz et al. *Circulation* 2007;115(4):459-67). Taken together, results from the Cardiovascular Health Study indicate that at 12 years' follow-up, those with a baseline CRP level >3 mg/L and who had

detectable atherosclerosis on baseline ultrasound were at 72% increased risk for CVD death and a 52% increased risk for all-cause mortality (Cao et al. *Circulation* 2007;116(1):32-8). In contrast, an elevated CRP in those who had no baseline evidence of atherosclerosis did not increase the risk for either CVD or all-cause mortality. These observations suggest that the addition of CRP or carotid IMT to conventional risk factors modestly increases the ability to predict CVD.

### CKD and Lipid-lowering Strategies

As will be discussed by Dr. Sheldon Tobe, Associate Professor of Medicine, University of Toronto, CKD is a marker of CVD. Different studies indicate that CVD is present in between 23% and 46% of patients with impaired renal function and that prognosis in patients with vascular disease is worse if kidney function is impaired. In the HOPE study, for example, CVD death occurred in 11% of patients who had a baseline creatinine >124 mmol/L compared with 6.6% of those with normal renal function, while total mortality rates were higher at 17.8% vs. 10.6% for the same two groups, respectively. HOPE also showed that the presence of microalbuminuria at baseline more than doubled mortality risk in placebo patients and almost doubled the risk in patients receiving ramipril (Gerstein et al. *JAMA* 2001;286(4):421-6).

RENAAL showed that the presence of baseline albuminuria predicted not only progression to end-stage renal disease (ESRD) in the setting of diabetic nephropathy but also CV end points as well as heart failure. The large-scale PREVENT trial also indicated that albuminuria predicted CV mortality in the general population (Hillege et al. *Circulation* 2002;106(14):1777-82). Thus, it is certainly fair to speculate that CKD may be a CVD risk equivalent, as is generally believed to be true for type 2 diabetes. As Dr. Tobe indicates, there are as yet no hard outcome data supporting statin use in CKD. Yet physicians should keep in mind that for every 1 mmol/L reduction in LDL-C, investigators recently reported a 9% reduction in all-cause mortality, a 22% reduction in myocardial

infarction (MI) or coronary death, a 25% reduction in coronary revascularization and a 21% reduction in stroke in the setting of type 1 and type 2 diabetes (Cholesterol Treatment Trialists' Collaborators. *Lancet* 2008;371(9607):117-25). Dr. Tobe emphasizes that all patients with diabetes should be on a statin.

Researchers recently reported that more patients with type 2 diabetes and microalbuminuria who received intensified multifactorial interventions were far more likely to achieve risk factor targets than those who received conventional therapy, and there were many more CV events in the conventional group compared with the intensive intervention group (Gaede et al. *N Engl J Med* 2008;358(6):580-91). In the 4D German study involving hemodialysis patients, there was an 8% relative risk reduction in cardiac death, non-fatal MI and stroke in patients who received atorvastatin compared with placebo at a median follow-up of four years, the difference in LDL-C between the two arms being 1 mmol/L.

The SHARP study will seek to determine if effective lipid-lowering with the ezetimibe/simvastatin combination in CKD patients alters the time to the first major vascular event, and whether it also affects progression to ESRD in predialysis patients. Until results are in, Dr. Tobe reminds us that if there are good reasons to treat, treatment should not be modified because of CKD, including the need to intensify a regimen to achieve target levels.

In the absence of established CAD, he will indicate that CKD should be treated as a CVD risk factor and physicians should use a primary prevention strategy such as optimal statin therapy, possibly accompanied by ezetimibe, to more readily achieve target LDL-C levels. Lower achieved LDL-C levels are also associated with better outcomes and targets should be achieved with whatever strategy optimally allows for effective LDL-C-lowering. Lastly, key opinion leader Dr. Sergio Fazio, Professor of Medicine and Pathology, Vanderbilt University, Nashville, Tennessee, will discuss how to prevent CVD events in patients with type 2 diabetes, a well-defined high-risk group among whom the great majority will die of CVD. □

### Please plan to attend:

“Meeting the Challenge of Evolving Evidence.” Sunday, October 26, 2008, 10:00-12:00, Room 718 A.

*This symposium is accredited and co-developed as an Accredited Group Learning Activity under Section 1 of the framework of Continuing Professional Development options as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada (RCPSC).*

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