



Canadian Cardiovascular Congress

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Examining Cardiovascular and Metabolic Disease Management

Toronto - The combination of metabolic and cardiovascular disease is a common and sometimes complex problem to address. Speakers here employed a long-term sequential case scenario to illustrate and discuss contemporary and real-world issues in risk assessment and management. They touched on improved stratification in patients with moderate risk according to Framingham assessment, updated guidelines on diabetes management, novel approaches for glycemic control, and strategies for blood pressure control that are beneficial in diabetes and associated conditions.

Toronto – *Si courante soit-elle, la coexistence d'une maladie métabolique et d'une maladie cardiovasculaire est parfois complexe et difficile à prendre en charge. À l'aide d'un scénario commun qui simulait le suivi d'une patiente dans le temps, plusieurs conférenciers ont discuté des difficultés contemporaines auxquelles les médecins font face au quotidien sur les plans de l'évaluation et de la prise en charge du risque. Au nombre des questions qu'ils ont abordées : amélioration de la stratification des patients exposés à un risque modéré selon l'équation de Framingham; mise à jour des recommandations sur le traitement du diabète; nouvelles stratégies de contrôle glycémique; et stratégies antihypertensives bénéfiques en présence de diabète et de maladies connexes.*

By Carol Duthie

Lipid lowering with a statin has well documented clinical advantages, including a consistent reduction in risk for cardiovascular (CV) events of 25% to 35%. To address the residual risk for events, clinicians may wish to consider targeting a broader lipid profile or stratifying patients more precisely, stated Dr. Robert Hegele, Distinguished Professor of Medicine and Biochemistry, University of Western Ontario, London. An aggressive approach to risk assessment, using traditional and novel markers, can help clarify patients' long-term prognosis and ensure beneficial modifications such as lifestyle changes and lipid-lowering treatment are initiated in a timely fashion.

Case Study

A 35-year-old woman who smokes, is modestly overweight and borderline hypertensive, and has dyslipidemia on a Framingham risk factor assessment (10-year risk=17%). A strong family history of premature CV mortality and risk factors suggesting the metabolic syndrome double her baseline risk. Positive results on optional tests, such as measurement of ApoB, Apo(a), hsCRP, or carotid intima-media thickness may tip the scale toward early and aggressive primary preventive action. While these tests are not recommended for routine use, "if you put together all these 'not ready for prime time' factors, the risk is actually very high," observed Dr. Hegele. In this case example, recommended steps include lifestyle intervention for global risk management and lipid-lowering therapy aimed at achieving a 55% LDL-C reduction or LDL-C <2.0 mmol/L, Dr. Hegele indicated. A reduction of this magnitude may be possible with a maximal dose of a potent statin, but probably will require a second agent, such as a cholesterol absorption inhibitor or niacin. Studies aimed at reducing triglycerides with fibrates have been inadequately conclusive to date, and the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study of statin vs. statin/fenofibrate treatment in patients with diabetes are highly anticipated, Dr. Hegele suggested. Other new agents for lipid modification currently under investigation include niacin with a PG2 inhibitor that will diminish the side effect of flushing, and agents aimed at raising HDL-C, he added.

New Information on Diabetes and CV Risk

The patient mentioned above has a high lifetime risk for developing diabetes, which is the most important risk factor for heart disease and advances the timing of high-risk status by several years, noted Dr. Lawrence Leiter, Professor of Medicine and Nutritional Sciences, University of Toronto, Ontario. Prevention and control of diabetes is clearly a crucial element of risk reduction. "Although there is still some controversy about whether glucose lowering reduces macrovascular risk, there is no doubt it reduces microvascular risk [so] even if glucose lowering is neutral, when it comes to CV disease, the fact that it reduces eye and kidney disease is reason enough to optimize glucose levels. Furthermore, we know that renal disease is associated significantly with CV risk, so in reducing risk through that pathway, we're also ultimately reducing the risk for macrovascular disease."

An important concept to keep in mind is "metabolic memory," which indicates that CV risk is dictated not by current glucose levels but by those experienced approximately a decade earlier. "The blood vessels remember what happened 10 or 15 years ago and that determines one's atherosclerotic risk," Dr. Leiter explained. First noted in type 1 diabetes, metabolic memory in type 2 disease was suggested by the 20-year follow-up of patients in the UKPDS (UK Prospective Diabetes Study). According to this report, a 15% reduction in MI incidence associated with intensive glucose intervention became significant only after two decades of follow-up. Similarly, all-cause mortality was not reduced significantly in the original study but the 13% difference between the treatment and usual care groups was significant 10 years on (Holman et al. *N Engl J Med* 2008;359:1577-89). This hypothesis may be further supported by the results of the Steno-2 trial of multifactorial risk reduction strategy in type 2 diabetes, he added. According to the recent publication of 13-year data including passive follow-up for five years, total mortality was reduced in the intervention group by 50% (Gaede et al. *N Engl J Med* 2008;358:580-91). Although these findings were not replicated in other more recent studies of type 2 diabetes interventions, it may be that macrovascular disease

risk can be reduced only over treatment periods spanning at least two decades and/or begun early on in the disease process. “UKPDS patients had their glucose lowering starting at the time of diagnosis of diabetes, whereas in the more recent studies, patients had diabetes at least 10 years before entering the trial. So it may have been too late [and] it may take a long time to see the effect of glucose lowering when it comes to atherosclerosis,” Dr. Leiter remarked.

Emerging evidence suggests two-hour postprandial glucose (PPG) levels constitute a better risk predictor than fasting blood glucose or hemoglobin A_{1c} (HbA_{1c}), particularly at lower HbA_{1c} levels. When patients have HbA_{1c} <7.3%, for example, 70% of the hyperglycemia experienced is accounted for by postprandial hyperglycemia. This information supports the notion that treatment must be individualized, Dr. Leiter indicated. While PPG should be 5 to 10 mmol/L, “if HbA_{1c} targets are not being met, we should then try to get the postprandial sugars under 8 mmol/L... only then will we be able to get the HbA_{1c} down to target.” Lifestyle measures including a diet of low-glycemic-index foods can be an element in this strategy. Several of the oral antidiabetic agents available are effective at reducing PPG, Dr. Leiter added, including alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and short-acting insulin secretagogues.

The newest agent in the Canadian diabetes armamentarium, sitagliptin, is one of several medications (DPP-4 inhibitors and analogues of glucagon-like peptide 1) that promote the incretin effect in the gut, in a manner akin to that induced by food consumption. “The way that incretins work is that they increase insulin in a glucose-dependent fashion,” Dr. Leiter explained. Because of this mechanism of action, sitagliptin has additional clinical advantages including a negligible risk of weight gain and hypoglycemia relative to other medications. “One of the advantages of a DPP-4 inhibitor is that it’s one of the few pharmacologic strategies we have that will reduce postprandial hyperglycemia without an increased risk for hypoglycemia,” he noted. Although long-term safety data on this agent are still sparse, studies to date show it is well tolerated and no serious adverse effects have been reported.

Addressing Hypertension and Diabetes

As is well known, patients with diabetes are at risk of renal complications and hypertension, and addressing these factors is a crucial element of CV risk reduction. “Blood pressure (BP) control in people with diabetes is so cost-effective, it’s cost-saving,” remarked Dr. Sheldon Tobe, Associate Professor of

Medicine, University of Toronto, and Chair, Canadian Hypertension Education Program recommendations task force. While multiple medications are generally necessary to achieve the recommended BP goal of <130/80 mm Hg, the use of an ACE inhibitor or angiotensin receptor blocker (ARB) is recommended, given their positive effects on microalbuminuria or proteinuria. Recent data suggest intensive and long-term renin-angiotensin system inhibition and urinary protein reduction is beneficial, Dr. Tobe indicated. “While BP lowering with these agents plateaus, target organ protection with ACE inhibitors or ARBs does not.” In the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study, for example, patients treated with losartan continued to have lower rates of death and dialysis than those receiving placebo, even in the presence of doubled creatinine.

Additional data presented here confirm the efficacy and safety of ARB treatment in patients with hypertension that is difficult to control (as may be the case in patients with diabetes) or associated with microalbuminuria. In a phase IV study, Racine et al. (Abstract 0748) determined that one year of titration-based treatment with losartan or losartan/hydrochlorothiazide (HCTZ) effectively reduced BP in 1575 middle-aged patients with metabolic syndrome, and worked equally well in individuals at high, intermediate or low CV risk (SBP/DBP changes 18.0/9.4, 16.1/9.1, 16.9/10.2 mm Hg). Moreover, the treatment did not lead to elevations in serum glucose. Similarly, Lacourcière et al. (Abstract 0499) confirmed in a study of 105 patients that individuals with hypertension refractory to standard fixed-dose combination therapy with losartan/HCTZ (50 mg/12.5 mg), a high-dose regimen of losartan 150 mg/HCTZ 37.5 mg produced an additional antihypertensive effect with good tolerability and no significant adverse metabolic effects. In this study, BP decreased from baseline by 21.3/9.8 mm Hg in patients treated with the high-dose therapy. A second higher-dose regimen, losartan 150 mg/HCTZ 25 mg, lowered BP by 17.7/8.5 mm Hg from baseline (all values *P*<0.0001).

Summary

The case discussion here followed current Canadian Hypertension Education Program guidelines and the Canadian Diabetes Association’s stated priorities for CV risk reduction, which include – in order – protection for the vasculature, BP control and prevention of kidney disease. Current evidence encourages early control of metabolic risk factors to ensure length and quality of life in patients at high CV risk. □

Based on:

“Managing Cardiovascular and Metabolic Challenges—Treatment Strategies for Cardiovascular Risk Reduction.” Sunday, October 26, 2008, 18:00-21:00, Room 701 AB.

Abstract #049-092. Comparative antihypertensive effects of 2 fixed-dose combinations of losartan plus hydrochlorothiazide (150/25 mg vs. 150/37.5 mg) in patients with inadequately controlled ambulatory systolic hypertension.” CHS Poster Session III, Monday, October 27, 2008, 11:00-13:00, Community Forum (Level 800).

Please plan to attend:

Oral #0748. “Efficacy of titration as needed regimen with losartan 50 mg, losartan 100 mg/HCTZ 12.5 mg and losartan 100 mg/HCTZ 2.5 mg in hypertensive patients with the metabolic syndrome.” CHS Oral Session VI, Tuesday, October 28, 2008, 9:45-10:00, Room 705.

These sessions are 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 (RCPCSC).

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