



## Canadian Cardiovascular Congress

Toronto, Ontario / October 25-29, 2008

### Attenuating Cardiometabolic Risk: Expert Opinion Debate on Lifestyle Changes vs. Pharmacotherapy

**Toronto** - Even for patients who receive optimal prevention strategies, residual cardiovascular (CV) disease risk remains at least partly due to intra-abdominal obesity and accompanying metabolic abnormalities. Reducing cardiometabolic risk first and foremost should be addressed with lifestyle changes, as will be debated by expert Dr. David Lau, as even modest weight loss can lead to significant health benefits. Pharmacotherapy can, however, be helpful, as expert Dr. Peter Liu will counter, as CB<sub>1</sub> receptor inhibition results in positive changes in lipids, weight, waist circumference and other abnormalities that contribute to cardiometabolic risk. The same treatment strategy may also attenuate progression of atherosclerosis. It is likely that both treatment strategies will be needed to optimally attenuate cardiometabolic risk and offer centrally obese patients the best protection against future CV events.

**Toronto** – Même chez les patients qui bénéficient d'un traitement préventif optimal, la présence d'une obésité abdominale et des anomalies métaboliques qui en découlent peut contribuer à un risque résiduel de maladie cardiovasculaire (CV). Pour réduire le risque cardiométabolique, estime le Dr. David Lau, un expert en la matière, on doit d'abord et avant tout amener le patient à modifier ses habitudes de vie, car une perte de poids même légère peut se traduire par des bienfaits considérables pour la santé. Toutefois, réplique le Dr. Peter Liu, un autre expert, la pharmacothérapie peut être utile, car l'inhibition du récepteur CB<sub>1</sub> modifie favorablement les taux lipidiques, le poids, le tour de taille et d'autres anomalies qui contribuent au risque cardiométabolique. Cette même stratégie de traitement pourrait aussi atténuer la progression de l'athérosclérose. Cela dit, les deux stratégies sont probablement nécessaires si l'on aspire à réduire le risque cardiométabolique de façon optimale chez les patients présentant une obésité abdominale et à offrir à ces derniers la meilleure protection qui soit contre les événements CV futurs.

By Pam Harrison

Data from the REACH (Reduction of Atherothrombosis for Continued Health) global registry indicate that many patients at high risk for cardiovascular (CV) disease or who already have vascular disease in at least one arterial bed are under-treated. In North America, for example, approximately 40% of REACH registry participants are not at blood pressure targets while 28% still have total cholesterol values >200 mg/dL (>5.2 mmol/L).

The consequences of undertreatment are not trivial. In one-year CV disease event rates (CV death, myocardial infarction or stroke), the overall rate among registry participants was 4.24%–4.69% for those with established vascular disease vs. 2.15% for those with multiple risk factors only (Steg et al. *JAMA* 2007;297(11):1197-206). When hospitalizations for a thrombotic event were included in the same end point, one-year event rates were 15.2% for those with coronary artery disease, 14.53% for those with cerebrovascular disease and 21.14% for those with peripheral vascular disease.

Furthermore, even when optimally initiated, preventive strategies, whether in a primary or secondary prevention setting, do not fully reduce risk for future or recurrent events. Substantial clinical trial evidence indicates that at best, full doses of statins used over a treatment interval of five years reduce morbidity and mortality in all patient groups by about one-third. Consequently, physicians are left to deal with what many now refer to as “residual risk” for CV disease events—at least part of which is conferred by excess accumulation of intra-abdominal obesity or visceral fat.

As will be debated by Dr. David Lau, Professor of Medicine, Biochemistry and Molecular Biology, University of Calgary, Alberta, the concept of cardiometabolic risk seen in association with intra-abdominal obesity is characterized by changes in lipid metabolism, mostly notably high triglycerides

and low HDL-C levels, a particularly atherogenic form of dyslipidemia.

Many of these patients are also hypertensive, as he will point out, so cardiometabolic risk in this constellation of abnormalities is often seen in men and women with intra-abdominal or central obesity. As Dr. Lau observes, no single treatment exists that addresses all of these metabolic abnormalities and ameliorates cardiometabolic risk but lifestyle modification, when successful, comes close. Patients who reduce their caloric intake and increase levels of physical activity may not lose substantial amounts of weight, as Dr. Lau notes, but it is important to keep in mind that even modest weight loss—even a 1% loss of weight over a year—can result in substantial benefits for patients, and modest weight loss in and of itself is a highly laudable goal to reduce cardiometabolic risk.

#### CB<sub>1</sub> Receptor Inhibition

Dr. Peter Liu, Heart & Stroke/Polo Chair Professor of Medicine, University of Toronto, Ontario, will in turn suggest that inhibition of the cannabinoid receptor type 1 (CB<sub>1</sub>) is an important addition to the cardiologist's armamentarium. Many investigators believe that dysregulation of the endocannabinoid system, a complex endogenous signalling system that influences multiple metabolic pathways, contributes to the development of intra-abdominal obesity and dyslipidemia, thereby escalating cardiometabolic risk in centrally obese patients.

As suggested by Dr. Vincenzo Di Marzo, Research Director, Italian National Research Council, Naples, the CB<sub>1</sub> receptor is activated in visceral fat and it has now been shown that chronic CB<sub>1</sub> receptor antagonism in obese individuals reduces body weight independent of anorectic effects, and

significantly improves dysregulated metabolism and dyslipidemia that accompanies intra-abdominal obesity (Di Marzo V. *Nat Clin Pract Cardiovasc Med* 2008;5(10):610-2).

The recent ADAGIO-LIPIDS trial suggests that cardiometabolic risk may indeed be attenuated as reflected by positive changes in dyslipidemia, weight and intra-abdominal obesity in patients with elevated cardiometabolic risk. As presented by principal investigator Dr. Jean-Pierre Després, Université Laval, Quebec City, Quebec, at the European Atherosclerosis Society earlier this year, investigators randomized 799 abdominally obese patients with characteristic hypertriglyceridemia and low HDL-C to a reduced calorie diet (600 kcal/day less than usual) and then to either the CB<sub>1</sub> receptor antagonist rimonabant 20 mg/day or placebo. Patients with a history of depression were excluded. For the first time, investigators also carried out a CT substudy to determine whether treatment induced a preferential loss of visceral fat along with fat in the liver.

At the end of 12 months, results showed that rimonabant increased HDL-C by 7.4% relative to placebo ( $P<0.0001$ ) and reduced triglycerides by 18% again relative to placebo ( $P<0.0001$ ). LDL-C did not change significantly over the course of the study but investigators did observe a shift in the size of LDL particles, active therapy significantly reducing the proportion of small, atherogenic LDL particles by 6.5% ( $P<0.0001$ ) and increasing the concentration of large LDL particles by 4.8% both relative to placebo.

There was also a 17% reduction in C-reactive protein compared with placebo ( $P<0.01$ ) accompanied by a significant increase in adiponectin at approximately 19% vs. placebo ( $P<0.0001$ ). Adiponectin is derived from adipocytes and plays a key role in insulin sensitization of skeletal muscle. Levels of adiponectin are often abnormally low in abdominally obese patients. Importantly, as CT analysis revealed, active treatment did reduce visceral adipose tissue by approximately 10% compared with placebo ( $P<0.0005$ ), about twice as much as was seen in reductions in subcutaneous fat. It also mobilized fat in the liver as reflected by a significant decrease in the fatty liver index vs. placebo ( $P<0.05$ ) and a significant improvement in ALT levels ( $P<0.001$ ).

The incidence of side effects leading to discontinuation was essentially similar to previously published incidence rates from phase II studies, suggesting that rimonabant has an acceptable safety profile when used as recommended, namely

only in those individuals without a history of depression or who are not on antidepressant therapy, as it would appear that CB<sub>1</sub> receptor blockade exacerbates pre-existing psychiatric disorders.

#### STRADIVARIUS Trial

Whether CB<sub>1</sub> receptor antagonism could also counteract the atherosclerotic disease process brought about by dyslipidemia among other central obesity factors was addressed by the STRADIVARIUS trial. Since no obesity management strategy has been shown to achieve this end, Nissen et al. randomized 839 patients to receive rimonabant 20 mg/day or placebo. Patients underwent coronary intravascular ultrasonography at baseline and at study completion (n=676). The primary efficacy end point was change in per cent atheroma volume, while the secondary efficacy parameter was change in normalized total atheroma volume.

At the end of 18 months of treatment, the CB<sub>1</sub> receptor antagonist did not affect disease progression as reflected by non-significant changes in the per cent atheroma volume. However, active therapy did have a favourable effect on normalized total atheroma volume, decreasing by 2.2 mm<sup>2</sup> in the active treatment arm vs. an increase of 0.88 mm<sup>2</sup> in the placebo arm. As expected, treated patients lost more weight at 4.3 kg and had a greater reduction in waist circumference at 4.5 cm than placebo counterparts, among whom there was a 0.5 kg decrease in weight and a 1 cm reduction in waist circumference ( $P<0.001$  for both comparisons). HDL-C levels also increased by 22.4% over baseline in the active treatment cohort vs. 6.9% for placebo patients, while median triglyceride levels decreased by 20.5% from baseline in the active therapy arm vs. 6.2% in placebo controls ( $P<0.0001$ ).

Unlike the ADAGIO-LIPIDS trial, patients receiving treatment for depression were not excluded in the STRADIVARIUS trial. Psychiatric adverse effects that led to discontinuation of therapy were more frequent than have been reported in previous studies and more common in the active treatment arm than placebo controls at 9.5% vs. 3.1%, respectively.

Both studies indicate that patients with intra-abdominal obesity—accompanied by high triglycerides, low HDL-C and inadequate insulin sensitivity—are more likely to achieve the greater reduction in cardiometabolic risk with active therapy. □

#### Please plan to attend:

“Expert Opinion: Current Issues in Cardiology.” Wednesday, October 29, 2008, 7:00-9:00, Room 701 AB.

*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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