



## Canadian Cardiovascular Congress

Toronto, Ontario / October 25-29, 2008

### The Pre-emptive Attack: Screening Cardiovascular Patients for Vulnerable Plaque

**Toronto** - Rapid advances in understanding the cascade of molecular and cellular events that culminate in myocardial infarction, stroke, and other thrombotic events suggest it will be increasingly possible to screen atherosclerotic lesions for characteristics that predict when an event is imminent. Rather than risk factor scoring now used to predict the likelihood of an event over the coming five, 10 or 20 years, imaging to detect vulnerable plaques may be performed in much the same way as mammography. The identification of a vulnerable lesion may prompt immediate and life-saving interventions. Sunday morning, experts from Canada and the US will assess where this technology stands. Due to the prevalence of cardiovascular disease, the public health implications of effective screening for cardiovascular events could overshadow those of any type of cancer screening.

**Toronto** – Au vu de la rapidité des progrès réalisés dans la compréhension de la cascade des événements moléculaires et cellulaires qui aboutissent à l'infarctus du myocarde, à l'AVC et à d'autres événements thrombotiques, il y a fort à parier que l'on pourra prévoir de plus en plus la survenue imminente de ces événements en dépistant certaines caractéristiques des lésions d'athérosclérose. Les modalités d'imagerie ayant pour objectif de repérer les plaques vulnérables auraient un peu le même rôle que la mammographie : à l'inverse des scores actuellement établis à partir des facteurs de risque et utilisés pour prédire la probabilité qu'un événement survienne dans les cinq, 10 ou 20 prochaines années, la mise en évidence des lésions vulnérables pourrait conduire à des mesures immédiates et susceptibles de sauver des vies. Dimanche matin, des experts du Canada et des États-Unis expliqueront où en est cette technologie. En raison de la prévalence des maladies cardiovasculaires, les retombées d'un dépistage efficace sur la santé publique pourraient éclipser celles de toutes les méthodes de dépistage de cancer.

By Ted Bosworth

The concept that the relative vulnerability of plaques to rupture is far more important for predicting thrombotic events than the size or even the extent of atherosclerosis is increasingly well accepted. There are now abundant data that the least stable plaques are often relatively small and more recently formed. Such vulnerable plaques typically have a large lipid core relative to the thickness of the fibrous plaque and are therefore more susceptible to the fissuring or complete ruptures which incite platelets, blood coagulation factors, and tissue factor to produce acute thrombotic occlusions. The specific features of the vulnerable plaque are becoming sufficiently well defined that the concept of specifically screening for these lesions is becoming a reasonable goal.

“What we have learned is that the vast majority of myocardial infarctions (MIs) occur in people who don't have hemodynamically significant stenosis,” according to Dr. Subodh Verma, Associate Professor of Surgery and Pharmacology, University of Toronto, Ontario. One of the five panellists speaking at the Sunday symposium, Dr. Verma will be assessing what is understood about the biological basis of atherosclerotic plaque vulnerability, which involves the physical characteristics of the plaque but also circulating factors, including blood lipid levels and pro-inflammatory factors such as highly sensitive C-reactive protein (hsCRP).

#### Towards Plaque Stabilization and Regression

Screening for vulnerable plaques is attractive because controlled trials demonstrate that plaque stabilization and even plaque regression is now an achievable goal. A topic to be addressed by another Sunday speaker, Dr. Eva Lonn, Professor of Medicine, Division of Cardiology, McMaster University,

Hamilton, Ontario, several types of imaging studies have suggested that intensive lipid lowering can halt atherosclerotic progression. According to Dr. Lonn, who addressed the same topic during a symposium at the most recent annual meeting of the American College of Cardiology (ACC), these studies have “clearly demonstrated that people who tend to progress in terms of their rates of quantitative coronary angiography (QCA) atherosclerosis progression do worse clinically, and people who progress less or even regress, do better.”

In QCA studies with early-generation statins, such as pravastatin, effective lipid lowering was associated with a reduction in the rate of progression. However, ASTEROID (A Study to Evaluate the effect of Rosuvastatin On Intravascular ultrasound) was the first to associate a statin with regression. ASTEROID demonstrated regression with rosuvastatin using intravascular ultrasound (IVUS), which provides a very precise measure of atheroma burden. However, Dr. Lonn suggests that it is likely that the biological risk of plaque rupture will be increasingly measured in two ways.

“One is just atheroma burden, an anatomic extent of atherosclerosis, and that's what we measure with QCA, intima media thickness (IMT) and classical IVUS without virtual histology,” Dr. Lonn observes. However, with some “novel technologies that look at plaque vulnerability,” there is an opportunity to provide an additional measure of clinical risk. Although Dr. Lonn cautions that there are “no correlations to date to any outcomes to my knowledge,” measures of plaque vulnerability could greatly improve prediction of cardiovascular risk.

Importantly, the effort to correlate change in plaque vulnerability to clinical risk, like the correlation of atheroma

burden to clinical risk, is expected to be conducted primarily with effective lipid lowering, particularly with potent statins.

“From a biological standpoint, there are tons of animal data that suggest that statins not only change the core, the lipid core, but also alter the matrix and alter the support architecture of the entire plaque, and in that fashion make plaques not only smaller by taking away the components of the egg, but also stabilize the egg shell,” Dr. Verma explains. Of strategies to evaluate this change, he suggests, “I think some of the newer modalities are much better able to capture that phenotype such as IVUS and even some of the recent MRI techniques.”

#### hsCRP and Other Markers

Plaque vulnerability may not only be determined by plaque structure. There are a variety of markers of systemic inflammation, including hsCRP, soluble adhesion molecules, and circulating bacterial endotoxin, that have also been proposed as determinants of plaque vulnerability. Another speaker on Sunday, Dr. Paul Ridker, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, will focus on hsCRP, which not only appears to be a risk factor for plaque vulnerability but a treatable risk factor of cardiovascular disease. He may refer to JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), a multinational, double-blind, placebo-controlled trial that randomized individuals with low LDL-C levels but elevated hsCRP to rosuvastatin 20 mg or placebo. The study was stopped early due to the large relative benefit in the active treatment arm.

“There is abundant evidence that hsCRP is an important marker of risk that adds prognostic information at all levels of LDL-C, at all levels of the metabolic syndrome, and at all levels of the Framingham Risk Score,” states Dr. Ridker. “The evidence that CRP is treatable may allow us to build on the benefits we have already observed with statins.”

The ability to screen patients for a vulnerable plaque may be particularly important for altering therapies in patients determined to be at high risk. For example, one approach may be to intensify lipid lowering even among those who are

already at current treatment goals based on the evidence of persistent risk. Another might be to select a statin or a regimen specifically aimed at reducing hsCRP. These types of concepts will be addressed by Dr. Marc Pfeffer, who is also affiliated with Brigham and Women's Hospital. His task is to define the concept of preventative cardiology based on current knowledge and on where the science is heading.

One of the directions appears to be a far more individualized approach to risk management. While treatment guidelines are currently based on population-based studies, there is increasing potential for very precise risk assessment in the individual, a concept that might be characterized as the vulnerable patient. In addition to risk factors, including potential growth in the number of genetic anomalies that predict events, patient risk may be increasingly based on the interrelated concept of vulnerable plaque and vulnerable blood. The vulnerable plaque on imaging will be defined by structural and biological features that predict risk of rupture. The vulnerable blood will be defined by assays of risk markers, including LDL, hsCRP, and other markers, such as increased coagulability. According to Dr. Ridker, the time has already come for hsCRP.

“I would now argue that we also need to measure CRP along with LDL-C in secondary prevention, if we are going to do a better job managing our patients. If we have a simple and inexpensive blood test that can tell us how to get the right dose of the right drug to the right patient, I think that we should use it. That is exactly what is going on here for hsCRP,” Dr. Ridker observes.

#### Summary

The progress in understanding plaque vulnerability makes the Sunday morning symposium one of the most interesting of this year's CCC. Progress in defining plaque vulnerability may permit far more detailed risk analysis and more precise methodology for defining which patients are at risk and what steps should be taken to prevent clinical events. Although plaque vulnerability may help define new therapeutic targets, it may also permit clinicians to employ current therapies, including statins, with more precise goals. □

#### Please plan to attend:

“The CV Show: Expert Insights into Atherosclerotic Vulnerability in the Vulnerable Patient.” Sunday, October 26, 2008, 7:00-9:00, Room 718 B.

*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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