

## Canadian Cardiovascular Congress



Co-hosted by the  
Canadian Cardiovascular Society and the  
Heart and Stroke Foundation of Canada



Look for the  
**PRIORITY PRESS™**  
Clinical Supplements from  
Medical Education Network  
in this issue of **INFO-CARDIO**

*Veuillez prendre note que la version française des suppléments cliniques d'Info-Cardio est accessible sur le site [www.cardiocongress.org](http://www.cardiocongress.org).*

### Meeting at a Glance

**TUESDAY, October 24**

**9:00-9:45** John Keith Lecture: "Kawasaki Disease 2006"  
*Presenter: Dr. Jane Newburger*  
Location: Exhibit Hall C, Convention Centre

**9:45-10:30** Wilfred G. Bigelow Lecture: "Challenge, change and choice: The life and hard times of a coronary surgeon"  
*Presenter: Dr. Bernard Goldman*  
Location: Exhibit Hall C, Convention Centre

**11:00-12:30** CIHR/ICRH Distinguished Lecture. "NHLBI's Framingham Heart Study: Past achievements, current directions and future ambitions"  
*Presenter: Dr. Daniel Levy*  
Location: Exhibit Hall C, Convention Centre

**12:45-13:30** CCCN Closing Plenary: "Toward 2020: New Directions for Canadian Nursing"  
*Presenter: Michael J. Villeneuve*  
Location: Regency Ballroom D, 3rd Floor, Hyatt Regency

**14:00-15:00** CCS Consensus Conference: "Recommendations for heart failure 2006: Diagnosis and management"  
Location: Exhibit Hall C, Convention Centre

**15:30-17:00** CCS Position Paper Workshop: "Guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease"  
Location: Crystal Ballroom, Pan Pacific Hotel

**WEDNESDAY, October 25**

**9:00-10:45** Late-breaking Clinical Trials Session  
Location: Ballroom A-B, Convention Centre

All CCC Satellite Symposia have been accredited as a Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

**Info-Cardio**, the official newspaper of the CCC, is made possible through unrestricted grants from industry.

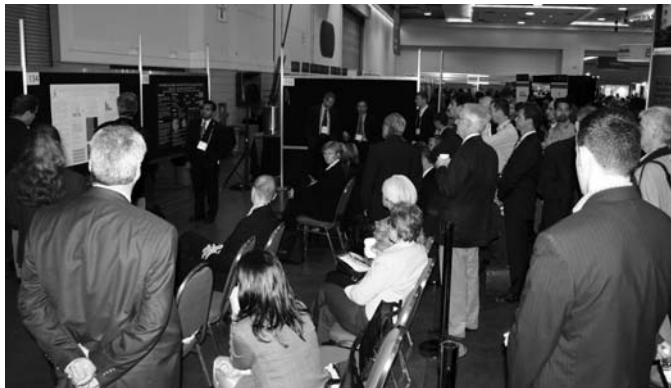
**Thank you to this year's supporters!**

**AstraZeneca Canada Inc.**  
**Merck Frosst Canada Ltd.**  
**Merck Frosst/Schering Pharmaceuticals**  
**Novartis Pharmaceuticals Canada Inc.**  
**Pfizer Canada Inc.**  
**sanofi-aventis**

# INFO-CARDIO

**TUESDAY/WEDNESDAY EDITION**

**11th Anniversary of the Official Newspaper of the  
Annual Canadian Cardiovascular Congress  
October 21-25, 2006 / Vancouver, British Columbia**



**New Moderated Poster Theatre Sessions  
a success this year!**



**The Honourable Senator Wilbert Keon presenting  
at the Public Policy "Access to Care" Session**

Photo: Duncan

## Framingham Heart Study: still transforming the nature of CVD prevention

The contributions made by the renowned Framingham Heart Study have transformed the nature of cardiovascular disease (CVD) prevention around the world, and they will continue to do so as investigators begin to explore genetic variants giving rise to CVD risk factors and disease expression.

As will be detailed by Canadian Institutes of Health Research lecturer Dr. Daniel Levy, Director, National Heart, Lung and Blood Institute, the Framingham Heart Study was launched in 1948 at a time when little was known about the general causes of CVD and nothing about its prevention. "At the time, the principles of epidemiology had been previously used for tackling problems about acute infection but never for chronic disease, and there were many people who were very much opposed to applying epidemiology to CVD, as it would take such a long-term commitment," Dr. Levy relates.

It did take a while: the first paper on risk factors in CVD first started to appear about 13 years after the study had begun. But investment in time and effort "paid off in spades," as Dr. Levy reports, "because it led to an understanding of major modifiable risk factors, and that taught us about the benefits of lowering blood pressure and cholesterol and of stopping smoking." Indeed, as he notes, if these three risk factors were eradicated, most of the CVD in the population would be vanquished. First and foremost, then, identification of CVD risk factors and, in turn, the impact that various interventions targeting these risk factors had on hard clinical outcome were pivotal contributions the study has made to the world.

Yet study investigators also demonstrated that epidemiology is a "highly suitable and relevant discipline" to gain insight into CVD and its prevention. Now, in what will be the largest genomic project ever conducted in human populations, the genetic



**Dr. Daniel Levy**

information that will be gathered, combined with clinical data collected on thousands of participants over a long period of time, will allow investigators to identify genetic variants that are associated with alterations in risk factors and in predisposition to disease in adults.

"That in turn will allow us, we hope, to identify new pathways in the development of disease and we also hope this will stimulate research into, for example, designer drugs that target those pathways and allow us to intervene even sooner and prevent CVD," Dr. Levy confirms.

Under the direction of the then National Heart Institute (now the National Heart, Lung and Blood Institute), the original objective of the Framingham Heart Study was to identify common factors or characteristics that contribute to CVD. The original cohort consisted of over 5200 participants who had no signs of overt CVD at study enrolment. In 1971, a second group of over 5100 adult children from the original cohort began to participate in a second-generation study, while in 2002, the grandchildren of the original cohort were enrolled in the third-generation phase of the study.

The most recent phase, the Framingham Heart Study Genome-Wide Association Study, will collect DNA from approximately 8000 participants across all three generations currently enrolled in Framingham and their DNA will be analyzed for the presence of single nucleotide polymorphisms. With the help of sophisticated software, researchers will try to relate a large catalogue of genetic results to clinical and laboratory measurements gathered from participants over the years.

Within the next five to 20 years, these two avenues of data should provide even more detail on the root causes of CVD as well as new targets for its eradication. □



## John Keith Lecture: exploring the enigmatic and challenging Kawasaki Disease



Dr. Jane Newburger

Raising awareness of the still baffling childhood condition known as Kawasaki disease will be explored in this year's John Keith Lecture, to be given by Dr. Jane Newburger, Professor of Pediatrics, Harvard University, Boston. Dr. Newburger is considered one of North America's foremost authorities on the disease.

Kawasaki disease is an acute illness associated with vasculitis that usually affects children under the age of five. At an annual incidence of between six and 11 cases per 100,000 in North America, it is very rare, and many of its symptoms, including fever, conjunctivitis, rash and cervical lymphadenopathy, mimic those of more common childhood illnesses. With no known cause and no definitive diagnostic test, the diagnosis of Kawasaki disease is all the more

challenging. As Dr. Newburger notes, these often lead to delays in the recognition and treatment of the disease, thereby increasing the risk of cardiac complications, coronary artery dilation and coronary aneurysms in particular.

As Dr. Newburger explains, "In the early 1980s, it became apparent that more children were being diagnosed with Kawasaki disease but because it was rare, it would serve their care best if a small group of cardiologists became especially acquainted with the issues surrounding their care.... and I soon became fascinated by the disease."

Dr. Newburger is also Associate Cardiologist-in-Chief at Children's Hospital, Boston. The task of diagnosing Kawasaki disease usually falls to the pediatrician, she notes, but cardiologists can be helpful once a referral is made, as they have an

important role in delineating the extent of coronary artery involvement. Sometimes, the presence of coronary artery dilation helps to make the diagnosis in a child with fever and fewer than four clinical criteria, but imaging with echocardiography is a critical part of the evaluation in patients suspected to have the disease, Dr. Newburger emphasizes, as long-term management is directed by the degree of coronary involvement. Meanwhile, the etiology of Kawasaki disease remains a mystery. As she acknowledges, "We can only speculate about the cause at present. There continues to be disagreement among experts about whether Kawasaki disease is caused by a single [pathogen] or by multiple agents with a final common inflammatory pathway."

One unproven possibility is an abnormal immune response to a known or undiscovered infectious agent, she reveals. Genetic studies carried out in children with Kawasaki disease and their parents have shown associations with a variety of polymorphisms in genes that regulate inflammation, vascular health and thrombosis, raising the possibility of genetic susceptibility.

Current clinical approaches to Kawasaki disease, from evaluation to follow-up, are guided by the American Heart Association/American Academy of Pediatrics statement (*Circulation* 2004;110:2747-71), of which Dr. Newburger was the lead author. She was also instrumental in the study of effective treatments for the disease, including intravenous gamma globulin (IVIG). "I am proud that a dedicated group of physicians in the US and Canada have performed clinical trials that have brought new treatments to children with Kawasaki disease that have significantly decreased the likelihood that a child, promptly diagnosed, will develop coronary aneurysms," she states. Several recent studies, including a multicentre, randomized trial carried out by Dr. Newburger's team, have investigated the role of steroids as an add-on strategy to IVIG; she will address their findings and their clinical implications in her lecture. □

## Wilfred G. Bigelow Lecture: open-heart surgery endangered in face of PCI

After 38 years of performing open-heart surgery, this year's Wilfred G. Bigelow lecturer Dr. Bernard Goldman, Director, Pacemaker Clinic, Sunnybrook Health Science Centre, and Professor of Surgery, Division of Cardiovascular Surgery, University of Toronto, is concerned that the burgeoning field of percutaneous coronary intervention (PCI) is threatening his own field of cardiac surgery.

"I began practice in 1968, just at the very beginning of surgical coronary bypass, and I'm finishing my career as an open-heart surgeon at probably the most challenging time we've ever faced," he admits. Part of that challenge comes from public perception that a less invasive procedure—as is PCI relative to coronary artery bypass surgery (CABG)—may be far preferable to open-heart surgery, even though in experienced hands, the complication rate from CABG is in the 1% range.

The incidence of "upfront" complications in the catheter laboratory is admittedly small, Dr. Goldman observes, but there is confusion in the public's mind—and possibly in the minds of cardiologists—between early success of PCI and the long-term durability of each procedure. At least 98% of patients have no recurrent angina one year after CABG and half are still free of angina 10 to 12 years' post-operatively. Open-heart surgery also allows for more complete revascularization than PCI.

There are also highly promising innovations now emerging in cardiac surgery. With the help of robots, surgeons under Dr. Bob Kiaii, leader of the Canadian Surgical Technologies and Advanced Robotics (CSTAR) Robotic Coronary Artery Bypass research project, London Health Sciences Centre, are combining minimally invasive, robotic-assisted CABG with angioplasty plus stenting in one episode of care, thereby shortening hospital stay by approximately two days compared to traditional approaches and reducing hospital-based costs.

PCI in turn has not completely eluded the problem of restenosis, which still occurs in a sizable proportion of patients, and now there is concern that drug-eluting stents, initially welcomed as a means to restenosis-free PCI, are associated with a higher incidence of late thrombotic complications, as well as a costly strategy.

Yet amidst the current climate of "stent euphoria," Dr. Goldman asks, "Where does the patient come in?"

It turns out that patients are often denied access to an informed consent process during which they would make a decision about undergoing PCI or CABG, but



Dr. Bernard Goldman

only after being told the advantages and disadvantages of each procedure. Dr. Goldman explains, "Almost 60% of percutaneous interventions are being done at the same time of day as the diagnostic angiogram and no surgeon is involved in this process, so the patient is not getting the benefit of having a discussion with a surgeon."

This may not be as great a concern for patients with single- and double-vessel disease, where PCI may well remain the procedure of choice. But when a patient has multi-vessel disease, diabetes and other complicating risk factors, "one wonders if we have gone beyond the bounds of rational judgment," Dr. Goldman muses, by offering these high-risk candidates only PCI. Indeed, he believes that cardiac surgeons have almost assumed a "back-up role to catch the debris" when PCI fails rather than serve in an "upfront" role as a consultant for individual patients.

Furthermore, in Dr. Goldman's view, the inappropriate use of PCI causes more than just personal loss to cardiac surgeons. As he recalls, CABG used to be the most common operation carried out by cardiac surgeons and it allowed them to teach heart surgery to trainees and to carry out proper research. Now that PCI has eroded CABG rates by 30 to 40%, who, a tenured cardiac surgeon as himself may reasonably ask, is going to teach future cardiac surgeons how to handle complex cardiac procedures, or even standard bypass grafting?

Dr. Goldman also worries that PCI enthusiasts are painting a false picture about how successful and safe PCI really is. Patients enrolled in most randomized trials evaluating PCI tend to be "ideal" patients, in that they are typically at low risk for complications, as Dr. Goldman observes. Consequently, procedural results will be highly promising. According to Dr. Goldman, "Cardiology has extrapolated results from these 'ideal' patients to the more complex, real-world patients and uses randomized trials to justify everyday decision making." Thus, real-world results from routine PCI carried out in catheter labs around the country may well be less optimal than those published by large academic centres.

"I have no argument with properly applied PCI and constantly improving technology," stresses Dr. Goldman. "My argument is with the unbridled and indiscriminate application of stents. We have to make significant changes; we have to be more involved in the selection of treatments offered to each patient and force our hospitals to develop revascularization strategies and properly informed consent in order to provide safeguards for our patients." □

## The Mazankowski Alberta Heart Institute: Countdown to 2007 begins

Excitement is building as the countdown to the completion of the Mazankowski Alberta Heart Institute begins. In fact, a 10-foot-tall digital clock on the construction site is physically counting down the days until the \$196 million facility opens its doors to Canada and beyond in the fall of 2007.

A collaborative effort between Capital Health and the University of Alberta, the Alberta Heart Institute is right on schedule. "We are very pleased with how the Heart Institute is progressing," remarks Dr. Arvind Koshal, Mazankowski Alberta Heart Institute Director of Development and External Affairs. "It will be a superb clinical and academic environment and a beautiful place for patients and staff."

Named after Edmonton native the Right Honourable Don Mazankowski, former deputy prime minister and federal finance minister, the Institute includes a two-storey healing garden that will be flooded with light from a giant high-tech curtain wall of glass that controls temperature and humidity inside. On its multilevel rooftops, lush gardens will reflect heat and give patients a pleasant view. Attached to the University of Alberta Hospital and the Stollery Children's Hospital in Edmonton, the Alberta Heart Institute will bring both pediatric and adult heart patients under one roof.

The Institute will also be fully equipped with state-of-the-art technology including diagnostic equipment, cardiac catheterization laboratories and operating rooms, all

Continued on page 4

## Late-breaking clinical trials session: changing day-to-day practice

The late-breaking clinical trials session will give Canadian investigators an opportunity to inform delegates about research that may well change day-to-day practice. “Clinical guidelines are based primarily on clinical trial results and many of these trials do change the way we practice medicine,” says late-breaker co-chair Dr. Eva Lonn, “so it’s important to highlight these results and make sure people really are up to date on the latest in evidence-based medicine.”

Each study will also have a discussant and will place the new findings in the context of other related studies, a feature of the session that Dr. Lonn is certain will be very helpful, “as most delegates put weight into what key opinion leaders say about the trial and how they interpret the results.” Here are the studies to be discussed in detail on Wednesday morning:



Dr. Eva Lonn

- *MC-1 to eliminate necrosis and damage in CABG (MEND-CABG-1)*. A new approach to decrease inflammation in patients following bypass surgery, the study was designed to evaluate the cardioprotective effects of MC-1 in high-risk patients undergoing CABG.
- *Effects of fondaparinux on mortality and reinfarction in patients with acute ST segment elevation myocardial infarction (OASIS 6)*. OASIS-6 compared fondaparinux with unfractionated heparin or no antithrombotic therapy in a broad spectrum of STEMI patients. As published results indicate, fondaparinux reduced mortality and reinfarction without increasing bleeding and it appeared to be of benefit in all groups, apart from those patients undergoing primary PCI, in whom it was associated with a higher risk of catheter thrombosis. It is expected that investigators will present a combined analysis of the two OASIS trials—OASIS 5 and 6—which together involved more than 32,000 patients with acute coronary syndromes.
- *PET and recovery following revascularization trial (PARR-2): FDG PET-guided therapy versus standard care in severe LV dysfunction*. A Canadian-led, multicentre, randomized trial in which patients with poor ventricular function and CAD were randomized to either FDG PET-guided imaging or standard care. The study was designed to establish whether the use of this new modality improves patient outcome, the primary outcome being a composite end point of cardiac death, MI, transplantation, or re-hospitalization for cardiac cause. Participating patients had EF  $\leq 35\%$  due to CAD, and were being considered for revascularization or heart failure work-up.
- *Homocysteine lowering in chronic stable vascular disease: The Heart Outcomes Prevention Evaluation-2 trial*. HOPE-2 was the world’s largest trial in which investigators evaluated the effect of lowering homocysteine levels with B vitamins on major CV events. Vitamins used included folic acid (2.5 mg), vitamin B6 (50 mg) and vitamin B12 (1 mg) or placebo. There were approximately 2700 patients in each arm, over 80% of whom had CAD. Patients were followed for an average of five years.
- *The ACCLAIM trial: A multi-centre, randomized double-blind, placebo-controlled study of immune modulation therapy in patients with heart failure due to systolic left ventricular dysfunction*. In the ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy) study, investigators randomized 2400 heart failure patients on optimal heart failure therapy to either active treatment with immunotherapy using the Celacade System or placebo (sham treatment) on days 1, 2, and 14, and then every 28 days thereafter until study end. Celacade immunotherapy has been shown to down-regulate pro-inflammatory cytokines and in patients with atherosclerosis, the same immunotherapy resulted in a marked reduction in hs-C-reactive protein (hsCRP). The hypothesis tested in ACCLAIM was that autologous red blood cells treated with oxidative stress would interact with antigen-presenting cells upon re-administration and elicit a systemic anti-inflammatory response.
- *Warfarin antiplatelet vascular evaluation (WAVE)*. WAVE is the largest randomized controlled trial yet carried out to determine if moderate levels of oral anticoagulation (INR ratio of 2 to 3) improves outcomes compared with antiplatelet therapy alone in patients with peripheral arterial disease. □

## Consensus Conference 2006: focus on patients with heart failure

Consensus conference committee members have focused on the complex management of the heart failure patient for this year’s consensus conference presentation during the CCC core curriculum. “These consensus recommendations should provide an evidence-based road map to translate knowledge into practice and allow health care practitioners to make the best clinical judgments and decisions for their individual patient,” committee members state. Delegates should note that the recommendations also contain a series of practical tips that add further insight into the diagnosis and management of heart failure. Here are highlights from this year’s recommendations.

### Diagnosis and investigation

- In suspected heart failure, a clinical history, physical exam and a series of investigations must be systematically carried out to establish a diagnosis of heart failure.
- Initial investigations should include a chest X-ray, a transthoracic echocardiogram, and evaluation of B-type natriuretic peptides where available.
- Coronary angiography should be considered in patients with suspected or known CAD leading to heart failure.
- Upon diagnosis, the patient’s functional capacity should be assessed using the NYHA functional classification.
- A six-minute walk test may help assess exercise limitations and prognosis.

### Nonpharmacological management

- All patients should undergo a graded exercise stress test to assess functional capacity before initiating an exercise program.
- Regular physical activity is recommended for all patients with stable symptoms and impaired LVSE, at three to five times a week, 30 to 45 minutes a session, for those with stable NYHA class II and III disease and an EF  $< 40\%$ .
- Both aerobic and resistance training done at moderate intensity are recommended.

### Salt and fluid restriction

- Patients with symptomatic heart failure should limit dietary salt intake to 2 to 3 grams a day, while those with more advanced heart failure and fluid retention should restrict salt intake to 1 to 2 grams a day.

- Patients with fluid retention or congestion not easily controlled with diuretics, as well as those with significant renal dysfunction, should monitor morning weight daily.
- Patients with fluid retention or congestion not easily controlled with diuretics, as well as those with significant renal dysfunction or hyponatremia, should restrict fluid intake to between 1.5 and 2 litres a day.

### Drug therapy

- Low-dose diuretics should be used in most patients with a history of pulmonary or systemic congestion but a second diuretic may be added in severe symptomatic heart failure.
- All patients with an EF  $< 40\%$  should receive an ACE inhibitor plus a beta blocker, unless contraindicated.
- Patients with NYHA class IV heart failure should be stabilized before initiating a beta blocker.
- Both the ACE inhibitor and the beta blocker should be titrated to target doses used in large-scale clinical trials or the maximum tolerated lower dose.
- If the patient is ACE inhibitor-intolerant, prescribe an angiotensin II receptor blocker (ARB).
- If symptoms persist or if patients have NYHA class III heart failure, add an ARB, digoxin plus or minus nitrates and hydralazine.
- If patients have NYHA class IIIb to IV heart failure, add diuretics plus spironolactone.
- ACE inhibitors and beta blockers should also be considered for most patients with heart failure with preserved systolic function.
- ARBs may be considered in the same patient group to reduce hospitalizations for heart failure.

Continued on page 4

### Atrial fibrillation

- Electrical cardioversion may be considered in patients with persistent AF.
- The use of antiarrhythmic therapy to achieve and maintain sinus rhythm in patients with AF and clinical heart failure or reduced EF should be restricted to amiodarone.
- A beta blocker, digoxin or a combination of the two may be considered for ventricular rate control in asymptomatic patients with an EF < 40%.
- Digoxin is the first choice in symptomatic patients with systolic dysfunction, but a beta blocker may be added once the patient has stabilized.
- Rate-limiting calcium channel blockers may be considered in heart failure patients with preserved systolic function.
- Anticoagulation should always be used unless contraindicated in patients with chronic AF.

### Implantable cardioverter defibrillator and cardiac resynchronization therapy

- An ICD should be considered in patients with ischemic heart disease with or without mild to moderate heart failure and an EF  $\leq$  30% at least one month post-MI and at least three months after undergoing a revascularization procedure.
- An ICD may be considered in patients with non-ischemic cardiomyopathy that is present for at least nine months, who have NYHA class II-III heart failure, and an EF  $\leq$  30% or an EF of between 31 and 35%.
- An ICD may be considered in patients with ischemic heart disease, prior MI, three months post-revascularization, EF 31 to 35%, and with inducible VF/sustained VT at EP study or with either no inducible VF/sustained VT at EP study, or without an EP study.
- An ICD should *not* be implanted in patients with NYHA class IV heart failure who are not expected to improve with further therapy and who are not candidates for transplantation.
- Antiarrhythmic therapy is discouraged in heart failure patients unless symptomatic arrhythmias persist despite optimal medical therapy with an ACE inhibitor and a beta blocker and correction of ischemia or electrolyte and metabolic abnormalities.
- Patients with symptomatic NYHA class II-IV heart failure despite optimal medical therapy, who are in normal sinus rhythm with a QRS duration of 120 ms or longer and have an EF  $\leq$  35% should be considered for CRT.
- The addition of an ICD should be considered for patients being referred for CRT who meet ICD requirements.

### Surgical considerations

- Patients with severe refractory symptoms despite optimal medical therapy and an otherwise good life expectancy should be considered for transplantation.
- Patients with persistent symptomatic ischemia or large areas of viability should be evaluated for revascularization, either percutaneous or surgical.
- CABG should be offered to patients with appropriate coronary anatomy and mild to moderate LVD if their predominant symptom is angina.
- Surgical revascularization may be considered in patients with appropriate anatomy and demonstrable areas of reversible ischemia or viability.
- CABG should be considered in patients with severe LVD only by surgical teams with extensive experience.
- Concomitant ventricular reconstruction can be considered by experienced surgical teams in favourable surgical candidates who meet the criteria for revascularization.
- Patients requiring surgical revascularization who have evidence of at least moderate mitral insufficiency may be considered for concomitant mitral valve repair or replacement.
- Mechanical circulatory support may be offered to selected patients with end-stage heart failure who are inotrope-dependent and who are not candidates for transplantation.

### Ethical and end-of-life issues

- Patients with heart failure should be approached early on in the disease process regarding their prognosis, advanced medical directives and wishes for resuscitative care, and their decision should be regularly reviewed.
- A substitute decision-maker (proxy) should be identified
- A living will should be discussed with patients to clarify wishes for end-of-life care where possible.
- Physicians should readdress therapeutic goals as a patient nears end-of-life with a shift of focus to quality of life.
- Psychosocial issues including depression, fear, isolation and need for respite care should be routinely re-evaluated.
- Caregivers of patients with advanced heart failure should be evaluated for their ability to cope and the degree of caregiver burden. □

specifically designed for both children and adults. Research will be a major component of the Alberta Heart Institute as well, with its multiple facilities and research groups, including a Cardiovascular Translational Research Centre to improve cardiac surgery outcomes.

In the Alberta Heart Institute's lower level is the newly-opened Alberta Cardiovascular and Stroke Research Centre—also known as ABACUS—where researchers and clinicians carry out research duties spanning a wide spectrum of fields of interest from molecular sciences to population health outcomes. "It's fitting that ABACUS literally forms the foundation for the Mazankowski Alberta Heart Institute," comments Dr. Gary Lopaschuk, the Institute's Scientific Director. "Our patients will be a 30-second elevator ride away from ABACUS, where investigators will be working to find a cure for their disease. We can rapidly translate research advances into enhancements in clinical care. So researchers benefit, the medical staff benefit and most importantly, patients benefit."

Dr. Stephen Archer, ABACUS Scientific Director, adds that the centre will give research a place of its own but within the supportive systems of a hospital. It will also bring together neurologists, radiologists, cardiologists and other specialists, working alongside scientists in laboratories—"creating important synergies and endless research potential," as he suggests.

### Excellent training ground

The Heart Institute will be an excellent training ground for the next generation of cardiac professionals, too. Capital Health's strategic partnership with the University of Alberta already helps recruit and retain the best students and staff and provides physicians in training with access to the best medical technology. And as the building grows, so does anticipation about what this new facility will mean to Alberta and to Canada.

"The Mazankowski Alberta Heart Institute will be a tremendous asset," confirms Dr. David Johnstone, Clinical Director of the Institute. "It will provide many opportunities for research collaboration and shared training opportunities. As we move forward, we'll be tackling heart disease with the amassed power of major efforts in research, clinical care and education. That's very exciting." □

For more information on the Mazankowski Alberta Heart Institute, visit [www.albertaheartinstitute.ca](http://www.albertaheartinstitute.ca).

## INFO-CARDIO

President, CCS: **Denis Roy**

Vice-President, CCS: **Lyall Higginson**

CCS Scientific Program Committee Chair: **Todd Anderson**

CCS Annual Meeting Chair: **Charles Kerr**

Local Arrangements Committee Chair: **Ken Gin**

Executive Director, CCS: **Anne Ferguson**

Joint Organizing Committee: **Carolyn Brooks (HSFC), Charles Kerr (CCS), George Wyse (CCS), Sally Brown (HSFC), Anne Ferguson (CCS), Mary Elizabeth Harriman (HSFC), Denis Roy (CCS), John Parker (CCS)**

Publisher: **Robert McKinnon**  
Medical Education Network Canada Inc.

Medical Writers: **Carol Duthie, Pam Harrison**



**Dr. Denis Roy keeping up on Congress highlights with Info-Cardio**



**Thanks to all the delegates for attending—see you next year in Quebec City for the CCS's 60th anniversary celebration!**





## Canadian Cardiovascular Congress 2006

Vancouver, British Columbia / October 21-25, 2006

### Seeking Further Stroke Reduction: Benefits of RAS Inhibition

**Vancouver** - Stroke is an important cause of morbidity and mortality, and given its relationship to age, hypertension and other cardiovascular risk factors, is expected to increase in incidence over the next two decades. The control of hypertension has a well-established beneficial impact on the risk of stroke. Here at this session on the opening night of the congress, speakers scrutinized recent research suggesting agents that inhibit the renin-angiotensin system may have additional clinical effects that contribute to their documented reduction of stroke and coronary events. The meeting also included a lively debate on the clinical merits and scientific rationale for using ACE inhibitors or angiotensin receptor blockers for the primary prevention of stroke.

Stroke is currently the fourth leading cause of death and a central cause of severe and costly disability. It is one of several manifestations of cardiovascular disease projected to occur more frequently with the changing demographics of the Canadian population. According to Statistics Canada and Health Canada estimates, stroke incidence, hospitalizations and mortality will increase steadily in both men and women between now and 2025.

Hypertension is the primary modifiable risk factor for stroke, accounting for more than 60% of events worldwide, commented Dr. Jacques de Champlain, Professor of Physiology and Medicine, *Université de Montréal*. Stroke risk extends to blood pressure (BP) levels considered controlled according to current treatment targets, i.e. in the area of 130/80 mm Hg, added Dr. Ross Feldman, Chair, Clinical Pharmacology, Department of Medicine, University of Western Ontario, London. Still, the control of hypertension has a long-established beneficial impact on the risk of stroke and associated mortality. The decrease in stroke incidence is proportional to the decrease in BP achieved. It is generally accepted that a treatment-related drop in systolic BP of 10 mm Hg reduces the relative risk of stroke by 35% to 40%.

#### Risk Reduction with RAS Inhibition

It remains unclear whether any specific antihypertensive class or classes have a more distinct cerebroprotective effect than others, via effects other than BP lowering. In his keynote address, Dr. Salim Yusuf, Professor of Medicine, and Director, Population Health Research Institute, McMaster University, Hamilton, noted that in numerous large clinical trials, patients treated with medications that inhibit the renin-angiotensin system (RAS) have experienced important reductions in their risk of

stroke as well as coronary events. Various studies have indicated that the benefits of RAS blockade include anti-atherosclerotic effects, antiproliferative effects at the level of the vessel and the myocardium, nephroprotection, anti-arrhythmic effects, glucose reduction and, in some studies, prevention of diabetes. "This is one of the most important treatments that we have in cardiovascular disease... surely BP plays a role but there are effects beyond it." He added that the protective impact of RAS inhibition is exemplified by the results of the LIFE study, which compared antihypertensive regimens based on a beta blocker and an angiotensin receptor blocker (ARB). "In a head-on comparison of atenolol plus other agents to losartan plus other agents, the blood pressure difference was 1 mm Hg. [There was] a 30% reduction in events in favour of losartan and most of this was a difference in stroke," Dr. Yusuf indicated.

#### Evidence on Stroke Prevention

Drs. Feldman and de Champlain were asked to debate the benefits of ACE inhibitors and ARBs, respectively, for the reduction of primary stroke.

While all antihypertensive agents are effective, "allow me that fine differences between classes support the use of ACE inhibitors," Dr. Feldman submitted. To support this argument he cited the results of the HOPE study, in which "even within a relatively normotensive population, the ACE inhibitor was clearly effective." The weight of evidence for ACE inhibition is likely stronger in secondary than in primary prevention of stroke, he acknowledged, stressing that current guidelines for risk reduction post-stroke recommend the combination of ACE inhibitor and diuretic.

In primary prevention, any form of angiotensin blockade is good but ARBs have achieved better

results than ACE inhibitors, Dr. de Champlain countered in his presentation. "When you compare one active treatment with another, then you start to see a difference," he commented. One meta-analysis of clinical trials comparing ACE inhibition with diuretics and beta blockers has determined that patients treated with the former experienced 9% more strokes. Similarly, when compared with calcium channel blockers, which have been shown to achieve better results than diuretics or beta blockers, ACE inhibition was associated with a 12% higher incidence of stroke end points.

### **Stroke Prevention with ARBs: Consistent Evidence**

"On the other hand, if you look at the meta-analysis of the ARB trials so far, there was a definite trend toward the prevention of stroke using ARBs and this was consistent in most of the trials," Dr. de Champlain remarked. Over the five years of the LIFE study, for example, "the BP [in both treatment arms] was identical, but... the losartan-treated group had a 25% lower incidence of stroke than the atenolol-treated group." In LIFE patients with isolated systolic hypertension, the reduction in stroke was 40%. The results of LIFE were primarily achieved through a decrease in atherothrombotic ischemic stroke, which accounts for the largest proportion of cerebrovascular events, he added.

A recent report by the Jikei Heart Study Group further supports the beneficial impact of ARBs in high-risk individuals, Dr. de Champlain indicated. This analysis of 3000 Japanese patients with hypertension, ischemic heart disease and/or heart failure compared the cardiovascular event reduction achieved with valsartan and other antihypertensive therapies (chiefly calcium channel blockade). "The BP was absolutely identical in the two treatment groups and... there was a 40% [greater] prevention of stroke in those receiving the valsartan vs. the conventional therapy," he observed. "After three years, the study was stopped because of the results showing a better protection with the ARB."

### **Proposed Mechanisms for Benefit**

Several mechanisms may explain an advantage of ARBs over other agents for achieving a reduction in stroke risk, Dr. de Champlain suggested. Given the likelihood that the RAS is involved in the development of stroke, he noted, "Why would ARBs be better? Because they block more specifically the mechanisms whereby stroke will happen. Probably they are better blockers of the angiotensin molecule which, by acting on the AT<sub>1</sub> receptor, will cause a vasoconstriction in the vessel but in addition, will be pro-oxidant or pro-inflammatory [and lead to] cerebrovascular insufficiency."

A second possibility is that the reduction in stroke with ARB treatment is mediated by prevention of atrial fibrillation, which is the most important cause of stroke in elderly individuals. In five studies, the most recent of which was VALUE, the approximate reduction in atrial fibrillation was 29%, Dr. de Champlain reported. The decrease in atrial fibrillation may be related to a reduction in left ventricular and left atrial size, he stated, although the exact mechanism is unknown.

The link between angiotensin blockade and atrial fibrillation reduction is of interest, Dr. Yusuf agreed. In his presentation, he mentioned a study (Madrid et al.) in which patients who had undergone cardioversion were randomly assigned to receive amiodarone alone or amiodarone plus irbesartan. "Recurrence of atrial fibrillation occurred to a significant degree less in the group who received an ARB. And, as you know, there is a fair amount of data on people with heart failure and left ventricular dysfunction indicating that ACE inhibitors and ARBs prevent atrial fibrillation, including a paper from the CHARM study."

RAS blockade for cardiovascular and cerebrovascular protection constitutes an active field of study, Dr. Yusuf concluded, and within the next few years, such trials as ONTARGET should yield additional important insights into the relative benefits of ACE inhibition and ARBs for stroke prevention, among other effects. □

### **Based on the following session:**

**"Advances in Cardiology,"** Saturday, October 21, 19:00-21:00, Ballroom A-B, Vancouver Convention and Exhibition Centre.

Note: Unless specifically stated otherwise, the opinions and information presented in these reports are those of individuals and do not represent the opinions of the Canadian Cardiovascular Society.

© 2006 Medical Education Network Canada Inc. All rights reserved. Priority Press™ is an independent medical news reporting service providing educational updates reflecting peer opinion from scientific and clinical meetings worldwide. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Support for distribution of this report was provided by industry through an unrestricted grant and under written agreement that ensures independence. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses or doses presently under investigation. No part of this newsletter may be reproduced in any form or distributed without written consent of the publisher. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians' and allied health care providers' understanding of current trends in medicine. Your comments are encouraged.

Medical Education Network Canada Inc. 132, chemin de l'Anse, Vaudreuil, Quebec J7V 8P3  
E-mail: mednet@mednet.ca / Web site: www.mednet.ca **Please e-mail us at our address to receive reports on-line.**



## Canadian Cardiovascular Congress 2006

Vancouver, British Columbia / October 21-25, 2006

### Reducing Cardiometabolic Risk in Patients with Intra-abdominal Obesity

**Vancouver** - Central or intra-abdominal obesity is now linked to a cluster of cardiometabolic risk factors including dyslipidemia, elevations in blood pressure and insulin resistance. This risk is fuelled by release of adipocytokines from adipose tissue, suggesting that intra-abdominal obesity represents an important therapeutic target to reduce cardiometabolic risk in patients with central adiposity. As the first of a new class of CB<sub>1</sub> receptor inhibitors, rimonabant has consistently been shown to promote weight loss and reduce waist circumference in overweight and obese patients with and without diabetes. At the same time, rimonabant was associated with improvements in the overall cardiometabolic risk profile including increases in HDL-C, enhanced insulin resistance and reductions in both hemoglobin A<sub>1c</sub> and triglycerides. Thus, targeting CB<sub>1</sub> receptors in the newly identified endocannabinoid system represents a novel strategy for the treatment of elevated cardiometabolic risk in overweight and obese patients. Treatment with insulin-sensitizing thiazolidinediones is another strategy that has been shown to reduce progression from impaired glucose tolerance or impaired fasting glucose to type 2 diabetes in high-risk patients as well.

The present epidemic in obesity and diabetes is being fuelled by our genetic legacy to store energy in the form of central obesity. Research has demonstrated that intra-abdominal obesity is the link that ties together a cluster of cardiometabolic risk factors including changes in LDL-C particle size, insulin sensitivity and blood pressure (BP) and that these changes can have important cardiovascular consequences. In the landmark INTERHEART study, for example, results demonstrated that the waist:hip ratio—an index of intra-abdominal obesity—was the most important predictor of first myocardial infarction (MI) across many ethnic groups around the world.

As Dr. Subodh Verma, Department of Cardiac Surgery, University of Toronto, suggested, the ratio identified “the importance of visceral adiposity as a target of cardiometabolic risk reduction.” Much of this risk is generated by adipocytokines released by adipose tissue, especially intra-abdominal adipose tissue. Long perceived to be biologically inert, it is now known that adipose tissue is metabolically active, releasing a variety of bioactive molecules including C-reactive protein, an important inflammatory marker, free-fatty acids and adiponectin. As Dr. Verma noted, adiponectin is one of the few protective adipocytokines produced by adipose tissue, as it helps modify the heightened cardiometabolic risk associated with intra-abdominal obesity. Levels of adiponectin are frequently low in individuals with intra-abdominal obesity.

Recently, the endocannabinoid system has been discovered as a key pathway controlling a wide range of biological functions, including satiety. “This system is very similar to the system that is activated when people smoke marijuana,” Dr. Verma observed. As the first of a new class of agents, rimonabant works by inhibiting the signalling of CB<sub>1</sub> receptors in the endocannabinoid system. CB<sub>1</sub> receptors are largely concentrated in the brain but they are also found

peripherally, especially in visceral adipose tissue. By turning off these receptors, the compound has the potential to control appetite, promote weight loss and help reverse cardiometabolic risk associated with central obesity.

#### The RIO Program

There are now four randomized clinical trials in which rimonabant has been tested against placebo: RIO-North America, RIO-Europe, RIO-Lipids, and RIO-Diabetes. In all four trials, patients were instructed to follow a mildly hypocaloric diet (a 600-calorie deficit a day), then randomized to either rimonabant 5 mg or 20 mg, or placebo, for a treatment interval of one year. Patients involved in the four trials were patients that “you and I routinely see,” as Dr. Verma observed, with a mean body weight of 94 to 104 kg, and a mean body mass index of 33 to 38 kg/m<sup>2</sup>.

The “striking observation” from the overall RIO program was the “very consistent change in waist circumference over a short follow-up of one year, with those on 20 mg losing an average of 8.2 cm from their baseline waist circumference at the end of one year compared with 3.9 cm for placebo controls. At the same end point, patients on 20 mg lost 8.6 kg compared with 2.8 kg for placebo controls. Approximately 40% of patients on active therapy also experienced a greater than 10% reduction in their body weight at study end. “This is really a striking observation, since even modest changes in weight of 4 to 6% can change cardiometabolic risk,” Dr. Verma observed. Weight loss changes were accompanied by changes in hemoglobin A<sub>1c</sub> of 0.7 mmol/L—“consistent with many trials done with anti-hyperglycemic agents,” he indicated, “again suggesting a result that was consistent with an overall targeting of visceral adiposity and improvement in insulin sensitivity.”

Indeed, active therapy significantly improved insulin sensitivity (as based on HOMA indices) compared with placebo controls. As part of the overall cardiometabolic risk profile, intra-abdominal obesity is frequently accompanied by elevated triglyceride levels and low levels of HDL-C. Across the RIO program, HDL-C improved by approximately 7 to 9% and triglycerides were reduced by approximately 15%. Changes in lipids were more pronounced in patients who completed one year of therapy, among whom there was a 27% increase in HDL-C and a 10% reduction in triglycerides. In RIO-Lipids, there was also a 27% reduction in the CRP, also known to increase cardiometabolic risk. As assessed by the National Cholesterol Education Program definition of the metabolic syndrome, rimonabant reduced the proportion of patients with the metabolic syndrome by some 45% at one year.

New data also showed that adiponectin was increased by 46% in patients receiving CB<sub>1</sub> blockade compared with placebo, and this increase could not be ascribed solely to an improvement in insulin resistance, as Dr. Verma observed. Importantly, there was no change in measures of anxiety or depression in patients who received active therapy compared with placebo.

“CB<sub>1</sub> blockade with rimonabant in the RIO program demonstrated a significant decrease in weight and waist circumference with an absolute change of 10 to 12 lb. [4.5 to 5.5 kg] over and above a 600-kilocalorie restricted diet and was associated with favourable changes in all risk factors [indicative of] cardiometabolic risk reduction,” Dr. Verma concluded. “CB<sub>1</sub> blockade has the therapeutic potential as a novel approach to the treatment of cardiometabolic risk in patients who are overweight or obese.”

#### Modulation of PPAR-gamma

An alternative strategy for reducing cardiometabolic risk may be through modulation of the PPAR-gamma system with insulin-sensitizing thiazolidinediones (TZDs) such as

rosiglitazone and pioglitazone. As discussed by Dr. Gregory Bondy, Clinical Professor of Medicine and Pathology, University of British Columbia, considerable evidence exists showing the TZDs have a favourable influence on vascular disease. “Essentially, the TZDs are profound anti-inflammatory agents,” Dr. Bondy explained, “and vascular inflammation plays a very important role in the development of atherosclerotic lesions.”

For example, studies have shown the use of TZDs reduced CRP levels by approximately 30%, comparable to that produced by statin therapy. In patients with type 2 diabetes, researchers have also shown that both metformin and rosiglitazone improve glycemic control but only the TZD significantly improved endothelial dysfunction. Researchers also demonstrated that treatment of patients with a TZD prevented the inevitable progression of intima media thickness, a recognized surrogate marker of vascular disease.

Study findings have not uniformly demonstrated treatment with a TZD affects hard clinical end points. In the PROspective PioglitAzone Clinical Trial in Macrovascular Events Study (PROactive) in diabetic patients, the primary end point was the time from randomization to the first occurrence of all-cause mortality, nonfatal MI, acute coronary syndromes, revascularization procedures, stroke and major leg amputation (above the ankle). At the end of 2.4 years, the incidence of the primary composite end point was not significantly lower in patients receiving active treatment compared with placebo.

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial showed that at the end of three years, rosiglitazone 8 mg reduced the incidence of type 2 diabetes by approximately 60% compared with placebo in adults with impaired fasting glucose levels, impaired glucose tolerance, or both at baseline. As Dr. Bondy noted, the TZD also improved liver enzymes, a marker of vascular risk as well as fatty liver, and consistently lowered both systolic and diastolic BP.

“DREAM was strongly positive for diabetes prevention,” he concluded. □

#### Please plan to attend:

**CCS Position Paper Workshop: “Guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease,”** Tuesday, October 24, 15:30-17:00, Crystal Ballroom, Pan Pacific Hotel.

**Symposium: “Current Issues in Cardiology,”** Wednesday, October 25, 7:00-9:00, Ballroom, The Fairmont Waterfront Hotel.

Note: Unless specifically stated otherwise, the opinions and information presented in these reports are those of individuals and do not represent the opinions of the Canadian Cardiovascular Society.

© 2006 Medical Education Network Canada Inc. All rights reserved. Priority Press™ is an independent medical news reporting service providing educational updates reflecting peer opinion from scientific and clinical meetings worldwide. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Support for distribution of this report was provided by industry through an unrestricted grant and under written agreement that ensures independence. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses or doses presently under investigation. No part of this newsletter may be reproduced in any form or distributed without written consent of the publisher. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians' and allied health care providers' understanding of current trends in medicine. Your comments are encouraged.

Medical Education Network Canada Inc. 132, chemin de l'Anse, Vaudreuil, Quebec J7V 8P3  
E-mail: mednet@mednet.ca / Web site: www.mednet.ca **Please e-mail us at our address to receive reports on-line.**