

Canadian Cardiovascular Congress



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



PLEASE PLAN TO ATTEND

MONDAY, October 22

"The 3rd Annual Medical Debate in Lipid Management: Meeting the Challenge of Evolving Evidence"
Monday, October 22, 7:00-9:00, Room 200A, Level 2

"Straight from the Heart: Managing the Cardiovascular Risk Continuum"
Monday, October 22, 7:00-9:00, Room 200C, Level 2

"Expert Opinions: Advances in Cardiology"
Monday, October 22, 12:00-14:00, Room 200B, Level 2

Workshop: "Managing Heart Failure in Complex Clinical Scenarios—A Case-Based Application of the 2007 CCS Heart Failure Guidelines"
Monday, October 22, 14:00-15:30, Room 2000A-B, Level 2

TUESDAY, October 23

"Harnessing the Endocannabinoid System to Reduce Cardiometabolic Risk"
Tuesday, October 23, 7:00-9:00, Room 200B, Level 2

Oral Session: "Heart Failure and BNP"
Tuesday, October 23, 9:00-10:30, Room 302A-B, Level 3

WEDNESDAY, October 24

"Expert Opinions: Current Issues in Cardiology"
Wednesday, October 24, 7:00-9:00, Room 200B, Level 2

"The Clinical Roadmap to Acute Heart Failure: ASCENDING to New Heights"
Wednesday, October 24, 7:00-9:00, Room 200A, Level 2

INFO CARDIO

Monday Edition 12th Anniversary of the Official Newspaper of the Annual Canadian Cardiovascular Congress October 20-24, 2007 / Quebec City, Quebec



CCC OPENING CEREMONIES AND HSFC LECTURE
From left to right: Lyall Higginson (CCS President), Carol Jillings (HSFC Chair), George Wyse (CCS Co-Chair), Fran Gregor (HSFC Co-Chair).

Have-a-Heart Bursary Program: opportunities for promising individuals

Bright young medical students, post-graduate trainees and basic scientists-in-training can thank the Have-a-Heart bursary program for their attendance at the CCC this year.

Sponsored by the Canadian Cardiovascular Society Academy, the 15 recipients of the CCSA bursaries this year include Craig Ainsworth (Mount Hope); Anita Chan (Edmonton); Myra Cocker (Calgary); Rani Cruz (Vancouver); Geoffrey de Couto (Toronto); Vanessa DeClercq (Winnipeg); Genevieve Digby (Kingston); Meghan Elliott (Kingston); Gary Galante (Edmonton); Shereen Hamza (Edmonton); Victoria Lam (Edmonton); Patricia Longmuir (Toronto); Daniel Niven (Calgary); Roxanne Pelletier (Montreal); and Stacey Pollock-BarZiv (Toronto). □

CCS Diamond Anniversary Lecture: The future of cardiovascular medicine

The disease being treated by cardiovascular (CV) specialists right now may not exist in the not-too-distant future, or so predicts Dr. Randall Wolf, the CCS Diamond Anniversary lecturer speaking today at 11:00.

"I will make a compelling argument that CV medicine is going to change dramatically in the next 10 years," Dr. Wolf, Professor of Surgery, Capital University, Beijing, China, and Director of Asian Affairs, DataQuest Healthcare, reveals to *INFO-Cardio*. This "monumental change" will be propelled by the somewhat fearsome constellation of GRIN technologies—genetics, robotics, information technology and nanotechnology—the impact of which is already palpable in aspects of medicine today.

Take, for example, "pharmacogenetics," the science of predicting a patient's hereditary response to drugs. First coined as a term almost 50 years ago, researchers have now shown that, for example, genetic variations influence both baseline cholesterol levels as well as individual response to statin therapy. Further discoveries in the science of pharmacogenetics may soon allow physicians to tailor their medical interventions where, at the



Dr. Randall Wolf

Conférence du 60^e anniversaire de la SCC : L'avenir de la médecine cardiovasculaire

La maladie cardiovasculaire (CV) telle qu'on la connaît aujourd'hui pourrait être chose du passé dans un avenir assez rapproché, estime le Dr. Randall Wolf, qui donnera aujourd'hui à 11 h la conférence du 60^e anniversaire de la SCC.

« Je suis persuadé que la médecine CV se métamorphosera profondément au cours de la prochaine décennie »,

affirme le Dr. Wolf, professeur titulaire de chirurgie, Université de la capitale, Beijing, Chine, et directeur des affaires asiatiques, DataQuest Healthcare. Cette « métamorphose profonde » sera propulsée par la constellation plutôt redoutable des technologies dites GRIN – la génétique, la robotique, les technologies de l'information et la nanotechnologie – dont les retombées sont déjà palpables dans certains aspects de la médecine actuelle.

Prenons la « pharmacogénétique ». Cette science – dont la désignation remonte à près de 50 ans déjà – permet de prédire la réponse héréditaire d'un patient aux médicaments. Les chercheurs ont montré, par exemple, que les variations génétiques influent à la fois sur la cholestérolémie initiale et sur la réponse individuelle à un traitement par statine. D'autres découvertes de la pharmacogénétique pourraient

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smallest possible dose, they can achieve the greatest benefit for individual patients with few if any side effects.

“We also already have a tremendous amount of information about the genome,” Dr. Wolf confirms. This information will allow scientists to eventually predict who will develop CV disease and with that knowledge, “there will be a tremendous emphasis on preventative medicine,” Dr. Wolf anticipates. Indeed, he feels it is entirely possible that physicians will be able to either reverse or even prevent atherosclerosis and wipe out heart disease as we know it, much the way certain infectious diseases, though not yet completely eradicated, are no longer endemic around the world.

Robotics, in turn, will also evolve from their current status of being essentially “remote telemanipulators” to one where they are real robots with true artificial intelligence that can duplicate the actions of humans with no human interference.

Naturally, information technology will also continue to evolve, Dr. Wolf notes. But the real revolution in medicine will be brought about by developments in nanotechnology. “Nanotechnology is the science of miniaturization,” he remarks. And small is an understatement—think five carbon atoms in a row or the length that our fingernails grow in a second to appreciate how small this miniaturization really is. Right now, researchers are already working on “nanobots” that could replace red blood cells in humans. These “nanobots” would be so much more efficient than our own red blood cells that we could sprint for 15 minutes on a single breath, as Dr. Wolf describes it.

Nanotechnology therapies could also be developed that would delve into the roots of disease at a cellular level, he adds. He also anticipates a proliferation of sophisticated biosensors that, like today’s current pacemakers, will activate and deactivate underlying processes that lead to pathological events and prevent them from happening.

Of course, once medicine is irrevocably intertwined with technology, it will evolve the way of technology—and technology is evolving exponentially, Dr. Wolf reminds us. “What you think will happen in the next 100 years will happen in 25 years in CV medicine,” Dr. Wolf foresees. This rapid evolution will demand a new way of training future specialists—one where physicians don’t train to become a surgeon or a cardiologist but where their expertise is based upon specific technologies, such as their ability to grow new organs or even wield sophisticated devices through a labyrinthine vasculature to repair damaged arteries and valves, as many interventionalists now do.

Dr. Wolf emphasizes, “We the educators need to see this coming and be proactive and institute change in the training process that will incorporate this exponential evolution in technology, but I predict that we will conquer atherosclerosis as we know it today, and I will argue that these changes can occur more quickly than we are prepared to accept and incorporate them in the practice of CV medicine.” □

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bientôt permettre au médecin d’administrer la plus faible dose possible d’un médicament donné tout en maximisant son bénéfice thérapeutique et en atténuant, voire en éliminant, ses effets indésirables.

« Nous avons déjà des tonnes de données sur le génome », confirme le Dr Wolf. Ces données permettront un jour aux scientifiques de reconnaître les terrains propices aux maladies CV, de sorte que « la médecine préventive jouera un rôle d’avant-plan », prétend-il. Il estime en effet qu’il est parfaitement envisageable de faire régresser, voire de prévenir l’athérosclérose et ainsi de faire disparaître la maladie cardiaque telle qu’on la connaît actuellement, à la manière de certaines maladies infectieuses qui, sans être enravées, ne sont plus endémiques à l’échelle mondiale.

La robotique – dont le rôle actuel se limite essentiellement aux « télémanipulations » – évoluera à son tour vers la mise au point de robots dotés d’une réelle intelligence artificielle qui pourront reproduire le geste humain sans intervention humaine.

Il va de soi que les technologies de l’information continueront d’évoluer, précise le Dr Wolf, mais la vraie révolution en médecine découlera des développements de la nanotechnologie. « La nanotechnologie est la science de la miniaturisation », explique-t-il. Et quand on dit « nano », on pense par exemple à cinq atomes de carbone successifs ou à la croissance de l’ongle par seconde. Les chercheurs travaillent déjà à la mise au point de « nanobots » qui pourraient remplacer les érythrocytes chez l’humain. Ces « nanobots » seraient tellement plus efficaces que nos propres érythrocytes qu’il suffirait d’une inspiration pour sprinter pendant 15 minutes.

La nanotechnologie pourra aussi servir à la mise au point de traitements qui s’attaqueraient à la source même de la maladie, à l’échelle cellulaire. Il prévoit une prolifération de biodétecteurs complexes qui, à l’instar des stimulateurs cardiaques actuels, activeront et inactiveront les processus sous-jacents menant aux événements pathologiques et en préviendront la survenue.

Évidemment, une fois que la médecine et la technologie seront imbriquées irrévocablement, la médecine évoluera au rythme de la technologie, c’est-à-dire de manière exponentielle, rappelle le Dr Wolf. « Ce que l’on imagine dans un siècle se produira dans 25 ans en médecine CV. » Cette évolution rapide nous forcera à adapter la formation des futurs spécialistes. Un médecin ne sera pas formé pour devenir chirurgien ou cardiologue, mais pour maîtriser certaines technologies bien précises, comme la fabrication d’organes ou le guidage de dispositifs hautement perfectionnés dans le labyrinthe vasculaire pour réparer artères et valvules, comme le font déjà de nombreux spécialistes interventionnistes.

« Nous, les formateurs, devons être proactifs et adapter la formation de façon à intégrer l’évolution exponentielle de la technologie. À mon avis, c’est une question de temps avant que nous puissions conquérir l’athérosclérose telle que nous la connaissons aujourd’hui. Et je dirais même que ces changements se produiront plus rapidement que nous sommes disposés à les accepter et à les intégrer en médecine CV. » □



Nicki Sims-Jones, RN, MScN

Reducing the impact of environmental hazards: Nurses play pivotal role

Nurses have been on the front line of promoting environmental health since Florence Nightingale and that role will only expand now that the impact of environmental degradation on health is attracting so much global attention.

As Nicki Sims-Jones, RN, MScN, will discuss in her keynote address to the Canadian Council of Cardiovascular Nurses (CCCN), Florence Nightingale was the first nurse to recognize the importance of environmental factors such as

cleanliness, light and fresh air in fostering the recovery of wounded military men in the Crimean War. For her modern counterparts, Sims-Jones feels nurses who work with cardiovascular (CV) patients need to continue to focus on environmental health to promote the health of their patients. Nurses are already using strategies such as turning down the lights and minimizing noise to promote critical bedrest, and eliminating obstacles to early ambulation. They can also counsel their patients and their families on strategies to reduce their exposure to smog on bad air days after discharge from hospital.

In a larger context, nurses can also help reduce the environmental footprint of hospitals by working to reduce energy use and toxic waste production. More energy-efficient windows and light bulbs are “all small things but when added together, can have a big impact,” she notes. Many hospitals are reducing the use of products

containing toxic substances such as mercury which can potentially leach into the environment when their useful life is over. “Even cleaning products can be the least toxic available,” adds Sims-Jones, “and we need to make sure that only what needs to be incinerated is incinerated and not garbage that could go into the general waste.”

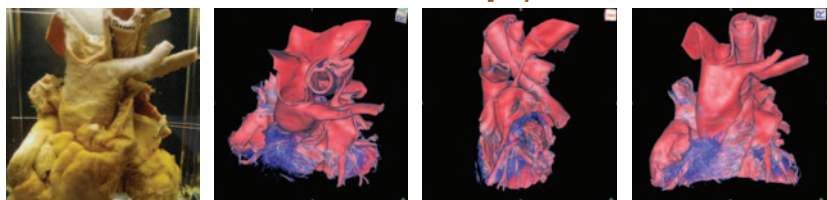
As manager of environmental health at the Canadian Nurses Association (CNA), Sims-Jones also feels that nurses need to be aware of larger governmental initiatives such as the Canadian Environmental Protection Act which focuses on assessing threats posed by chemicals and other substances and putting in place risk reduction measures where necessary. This is important, Sims-Jones stresses, for it is nurses who are most likely to counsel CV patients about the importance of heeding smog alerts and staying indoors when the air quality is poor, or to exercise early in the morning and avoid exercising during the afternoon rush hour to avoid inhaling heavy pollution.

Nurses also need to take into account the environment to which their patients may have been exposed prior to being admitted to the hospital as well as the environment to which they are likely to return, as that environment may well have exacerbated their CVD to begin with and could create difficulties for them on their return. “We are looking at an understanding of environmental health as central to the role of all nurses,” states Sims-Jones.

As part of its centenary activities in 2008, the CNA is launching an initiative in environmental health so that individually and collectively, nurses will be able to respond to issues arising from environmental degradation, climate change and extreme weather events here and elsewhere. The main goal of the initiative is to increase nurses’ awareness of environmental health issues and to provide them with the tools they need to address them. These tools, including background papers and educational modules, will be posted on the CNA Web site.

CCCN opening ceremonies take place today at 8:00 in Room 200D, on the second level of the convention centre. □

Virtual Autopsy



Fragile pathological specimens, such as this vascular ring now resting in the Osler Library’s Maude Abbott Collection at McGill University have been captured for future generations with the help of magnetic resonance imaging by Dr. Luc-Charles Jutras, Assistant Professor of Pediatrics, McGill University. Specimens were successfully

scanned in minutes using MRI and resulted in “virtual autopsy,” high-resolution 3D datasets that can be processed using readily available software. The MRI scans show the anterior view of the original specimen, the left superior oblique view, and the left lateral view. [Poster 668, Poster Board 043, Tuesday, October 23, 10:00-12:30, Community Forum] □

John Keith Lecture: Translating adult surgical procedures to infants and children requiring CABG

Surgical techniques developed to bypass diseased coronary arteries in adults are being successfully deployed in infants and children as indications for coronary artery bypass graft (CABG) surgery expand.

As will be discussed during the lecture on Tuesday morning, CABG has primarily been carried out for ischemic complications of Kawasaki disease in infants and children. However, indications for its application are expanding, notes John Keith lecturer Dr. Constantine Mavroudis, Surgeon-in-Chief, Children's Memorial Hospital, and Willis J. Potts Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and outcomes are generally very promising.

As Dr. Mavroudis and colleagues have discussed in several publications on pediatric CABG, the development of coronary artery aneurysms is the most serious complication of Kawasaki disease, occurring in up to 25% of untreated patients.

Although many aneurysms resolve over time, patients who develop aneurysms of at least 8 mm in internal diameter may go on to develop obstructive coronary artery disease (CAD), myocardial infarction (MI) and sudden death. CABG can reduce the risk of progression, as Dr. Mavroudis and his co-authors have demonstrated. For example, in one of their own series of children with Kawasaki disease, all five who underwent coronary revascularization using internal thoracic arteries—including one eight-month-old infant—did very well, with no post-operative deaths occurring between one month and 11 years of follow-up. Early experience using reversed saphenous vein graft proved unsatisfactory in children; internal thoracic artery bypass grafts are the grafts of choice in infants and children because of their superior patency rates and their ability to grow along with the developing child.



Dr. Constantine Mavroudis

In addition to proving highly beneficial in infants and children with coronary artery stenosis or occlusion due to Kawasaki disease, CABG is also indicated in infants and children who have an anomalous course of the LAD coronary artery between the aorta and the pulmonary artery. Dr. Mavroudis and colleagues have observed that it is similarly indicated in patients with an anomalous origin of the left coronary artery from the pulmonary artery.

CABG has also proven to be helpful among patients who sustain an intraoperative injury of a coronary artery (for example, after arterial switch for transposition of the great arteries), as it has for patients with coronary ostial stenosis. They add that accelerated atherosclerosis is becoming recognized as a major cause of late death as an increasing number of infants and children undergo heart transplantation, another setting in which CABG is indicated.

As Dr. Mavroudis and his colleagues point out, the major impediment to undertaking an internal thoracic artery-CABG procedure in infants and children is probably the small calibre of corresponding vessels as well as the lack of long-term results documenting patency and anastomotic growth. Nevertheless, in a series of angiographic measurements taken in control children a number of years ago, the researchers observed that most coronary arteries are 1 mm or larger, even in the neonatal population, with few exceptions ranging downward to 0.7 mm. Together with their extensive clinical experience, the researchers state that observations would suggest that internal thoracic artery-CABG is feasible in most infants with vessels 1 mm or larger, and possible in vessels as small as 0.7 mm, provided the surgery is accompanied by proper magnification and microvascular suture techniques. □

CIHR/ICRH Distinguished Lecture: discovery of a master cardiac stem cell setting the stage for cardiac cell regeneration

How a master cardiac stem cell, identified by a Boston-based team under Dr. Kenneth Chien, Director, Massachusetts General Hospital Cardiovascular Research Center late last year, may eventually lead to the ability to regenerate cardiac muscle, coronary arterial and pacemaker cells will be the focus of the CIHR/ICRH distinguished lecture this year.

In an earlier discovery, Dr. Chien and colleagues identified a group of cardiac muscle progenitors called *isl1+* cells in heart tissue taken from newborn rodents as well as humans. As pointed out in a description of the earlier discovery in literature from the Massachusetts General Hospital, the *islet-1* protein, for which *isl1+* is named, is expressed in cells from the second cardiac field, which generate structures on the right side of the heart.

More recently, as reported in the December 15 2006 issue of the journal *Cell*, the researchers sought to determine whether these *islet-1*-expressing cells give rise to more than just cardiac muscle cells. In experiments carried out in mice, Dr. Chien and colleagues further identified a population of embryonic *islet-1*-expressing cells that they found could

differentiate into functional cardiac muscle, smooth muscle, pacemaker and endothelial cells lining the major vessels of the heart. Indeed, from these embryonic stem cells, researchers were able to both generate these multipotent embryonic *isl1+* progenitors cells (MIPCs) and to clone and expand populations of each of these cell types *in vitro*.

The Boston researchers have concurrently identified two other important genes, *Nkx2.5* and *flk1*, that appear to govern part of the process by which cells “decide” their developmental fate. “We think these are authentic cardiac stem cells that are responsible for forming the diverse cell types of the heart, although other cells also contribute to some structures,” Dr. Chien was quoted as saying in the MGH release, “and these MIPCs may be excellent candidates for cardiac muscle regeneration studies without risk of tumour formation posed by embryonic stem cells or the limited effectiveness seen in studies using other cell types.”

An independent study published at the same time by researchers at the Children's Hospital Boston, under lead author Dr. Sean Wu, also described the study of

the first cardiac field of progenitor cells expressing the *Nkx2.5* protein that was also found to generate both cardiac and smooth muscle cells. Researchers from both labs are now collaborating to see how the two cell lines may work together.

Commenting on his own research in an on-line interview posted by Essential Science Indicators (www.esi-topics.com/nhp/2006/may-06-KennethRChien.html), Dr. Chien states that studies have explored the potential use of stem cells culled from a variety of organ systems. He cautions, however, “The most recent clinical and experimental data suggest that these may not be the optimal cell types to achieve cardiac muscle regeneration.”

Dr. Chien and his colleagues were able to show how a new cardiac stem cell can be both renewed and expanded, together with its “robust conversion” to a fully differentiated cardiac phenotype. In Dr. Chien's words, this development “makes a case for their utility as a model system for studying cardiogenic signalling pathways which in turn might uncover ways to capitalize on their knowledge to guide new strategies for cardiac regeneration over the long term.” □

CHEP recommendations: reviewing and renewing best hypertension practices

This year's CHEP recommendations will again bring members of the Canadian Hypertension Society up to date on best practices in the management of hypertension based on the latest findings in the field.

“There are new studies coming out every year that help us understand how to manage hypertension better and better reduce target organ damage,” explains Dr. Sheldon Tobe, CHEP Recommendation Task Force chair. In an effort to disseminate recent knowledge, CHEP members carefully extract key findings from recent studies and where warranted, advise physicians on changes they should incorporate into clinical practice based on these new findings.

For example, the recent ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) showed that routine administration of fixed-dose perindopril and indapamide in patients with type 2 diabetes reduced risks of major vascular events, including death, as reported by Medscape from the European Society of Cardiology Congress in Vienna this year.

Critics of the study, however, have suggested that any other antihypertensive combination would be equally protective, provided the drugs also lowered blood pressure and did not have any metabolic side effects. Other key studies reported at meetings and published in the literature will be similarly critically reviewed. “We try to reflect what's best for patients in our recommendations,” Dr. Tobe notes, “and since most of our members are at the CCC, this is a good way to disseminate the information.”



Dr. Sheldon Tobe

The recommendations presented by CHEP at the CCC are not ratified by membership at the time of presentation, so members are required to vote on each recommendation during the presentation itself. Usually, there's not much debate over the content, Dr. Tobe acknowledges. Nevertheless, one recommendation regarding screening for urinary albumin in non-diabetic hypertensives made last year was withdrawn, as members felt it was premature to make any statement regarding the screening test at that point in time. This year, the issue has been reassessed, and results will materialize in a recommendation on the need—or lack thereof—for urinary albumin screening in non-diabetic hypertensive patients. “We'll also be looking at measuring blood pressure at home, and whether or not there is any gender signal in terms of differences in the management of hypertension between men and women,” Dr. Tobe tells *INFO-Cardio*.

Once members ratify the recommendations, CHEP experts will develop implementation tools to bring the new recommendations to the level of individual patients. Members will also post slides on the Canadian Hypertension Society Web site, prepare the scientific paper for publication in the *Canadian Journal of Cardiology* and disseminate summaries to non-peer-reviewed journals to broaden the message.

Affirms Dr. Tobe, “We put as much if not more energy into implementing and disseminating these recommendations as we do coming up with them.”

CHEP recommendations will be presented today at 16:00-17:30, in the Port du Palais on the first floor of the Hilton Hotel. □



Climbing every mountain: Transplant specialist tackles Antarctica for her patients



Dr. Heather Ross

It takes a lot of empathy to want to climb a mountain to see how well your patient does with a transplanted heart. Dr. Heather Ross has it in spades.

As medical director of the cardiac transplant program, Toronto General Hospital, Dr. Ross has climbed not one but two mountains with transplant recipients as part of an effort to

study the physiological effects of mountain climbing on a denervated heart and to raise awareness—and funds—for the treatment of heart failure. “It’s not a hike, it’s a climb with technical challenges and you have to train for it”—a “tall” order, she adds, given that the only real way to train for altitude is to climb mountains.

Nevertheless, together with heart transplant recipient Dale Shippam, hospital colleague Dr. Patricia Murphy, clinical director of the cardiac anesthesia program, and other team members, Dr. Ross trained between 20 and 25 hours a week to get into shape for Mount Vinson, Antarctica’s highest peak, which they climbed last December. Prior to the climb itself, the team had to “get comfortable” carrying a 40- to 50-lb backpack, as they would have to do on their anticipated

climb. “We did a lot of stairs, too,” Dr. Ross adds: Toronto’s Casa Loma, with approximately 200 stairs in total from bottom to top, only has to be done about five or six times to get into the 1000- to 1500-stair range she considers a good workout!

They also did several “practice climbs” in Alberta’s Columbia Ice Fields on Mount Athabasca and Banff National Park. Then last year on December 3, they flew to the continent of Antarctica, where their goal was to scale Mount Vinson, all 4,892 metres, to raise awareness about heart failure and the need to find new ways to treat it. “The first thing we came up against was ensuring Dale’s medications would work despite the cold,” relates Dr. Ross. That meant ensuring the medications wouldn’t freeze when the temperatures dropped to -40°C as it did when the sun fell behind the mountain range (in December, there is 24-hour sunlight in Antarctica, so when the sun slid out from behind the shadows, it would warm up—relatively speaking—to as high as -15° or -20°C). Dale did succeed in keeping his medications from freezing by carrying them on his body at all times.

The second major concern was to make sure there was adequate medical support. Of course, she and Dr. Murphy could cover many of the medical issues that arose, but Mount Vinson is still a good hour’s flight away from a medical mid-station which had no real facilities, and a 4.5-hour flight from there to Chile, weather permitting.

“The other side of the issue was whether Dale, being a heart transplant patient, would have any physiologic issues related to his denervated heart,” Dr. Ross explains. At the time of transplantation, the

vagus nerve is severed. Since the vagus nerve regulates the heart rate, a denervated heart needs a long, slow warm-up until the adrenal glands kick in and give it a boost, which mountain climbing does not necessarily permit. Dale, a firefighter from Thunder Bay, took his training so seriously that by the time the team hit the mountain, he was more than capable of withstanding the rigours of the climb. So did the others, until about 200 vertical metres below the summit...

Within clear view of the summit, both Dr. Ross and Dr. Murphy developed acute pulmonary edema (the irony of developing the very illness she treats was not lost on Dr. Ross). With their health in jeopardy, the team was forced to turn back at that point and make their descent.

In all, they endured two weeks on the Antarctic continent, “two weeks of camping on the snow, no running water, no facilities, no shower—all that good stuff,” Dr. Ross jokes.

On a more serious note, she adds soberly, her illness allowed her to experience what her patients do as their heart deteriorates and they decline into increasingly severe heart failure. “Because I was in acute pulmonary edema at the top of the mountain, I’d like to think it has given me more insight into what my patients go through. And more compassion—at least I hope that’s true,” she reflects.

It’s a pretty safe bet that it has.

Dr. Ross will be speaking at the Women in Cardiac Sciences luncheon presentation entitled “Magic and Mayhem on the Mountain: Climbing Mt. Vinson, Antarctica, 2006,” today at 12:30-14:00, in Room 2000C at the convention centre (invitation only). □

Joint HSFC/CCS awards go to outstanding achievers in their field

Recipients of the Heart and Stroke Foundation of Canada awards as well as recipients of CCS awards were singled out last night for their outstanding achievements in their respective fields during the Joint Awards Ceremony. Here are the winners:

HSFC McDonald Scholarship Award: Dr. John Seubert, Assistant Professor of Pharmacy and Pharmaceutical Sciences, University of Alberta, has devoted his research efforts to defining biochemical pathways affected by cytochrome P450 mono-oxygenases (CYP) that are found in the heart but whose function remains largely unknown.

Henry J.M. Barnett Scholarship Award: Dr. Ken Butcher, Assistant Professor of Medicine, University of Alberta, has been employing the use of CT perfusion imaging to determine whether it is more beneficial to leave blood pressure in the brain very high, as it is following a bleed into the brain, or to lower it quickly. So far, his findings suggest that it is both feasible and preferable to lower blood pressure quickly without reducing blood flow to the brain, which potentially may reduce death and disability among stroke patients.

HSFC/AstraZeneca Research Fellowship: Dr. Mitra Esfandiari, a postdoctoral fellow at the University of British Columbia’s Child and Family Research Institute, is exploring the role of integrin-linked kinases which transmit signals between smooth muscle cells. Because smooth muscle cells have receptors for this molecule, they control the migration and accumulation of these cells and as such could become an excellent target to prevent the accumulation of smooth muscle cells in blood vessel walls, a pivotal step in the development of atherosclerosis.

HSFC/AstraZeneca Research Fellowship: Dr. Hao-Dong Li, a postdoctoral fellow at the University of Alberta, is delving into the workings of a protein “chaperone” called calreticulin which guides other proteins through the important folding process involved in lipid metabolism. The molecule is particularly critical to a process during which protein molecules in the endoplasmic reticulum are folded into the appropriate shapes to carry out particular functions, among them regulation of lipids and how they are stored as energy.

AstraZeneca Research Fellowship: Dr. Noel Ghanem, a postdoctoral fellow with the University of Ottawa’s Neuroscience Research Group, is exploring novel ways to

introduce stem cells into the brain where they may be able to replace dead or damaged neurons following a stroke. One promising approach is to manipulate the function of two retinoblastoma genes so that more neurons derived from stem cells are available for recovery following brain injury.

HSFC/Pfizer Research Fellowship: Dr. Subhadeep Chakrabarti, a postdoctoral fellow at the University of Alberta, is exploring how interference with biochemical signals from estrogen helps promote atherosclerosis in patients with diabetes. He is hoping that hypoglycemic agents might be identified that could overcome resistance to the beneficial effects of estrogen on blood vessel walls and retard the development of this ubiquitous disease.

HSFC/Pfizer Research Fellowship: Dr. Maziar Rahmani, a postdoctoral fellow at the Michael Smith Genome Sciences Centre in Vancouver, is investigating genetic differences between elderly individuals who have developed aortic valve stenosis and others who have remained exceptionally disease-free to identify factors that influence our resistance or susceptibility to develop a disease such as aortic valve stenosis.

CCS Annual Achievement Award: Dr. William Kostuk, cardiologist at London Health Sciences Centre and Professor of Medicine, University of Western Ontario. Since he entered the university in 1972, Dr. Kostuk has led investigations exploring diagnostic and therapeutic interventions for ischemic heart disease, heart failure and transplantation. As importantly, he has placed the needs of his patients first.

CCS Distinguished Teacher Award: Dr. Gary Burggraf, Professor Emeritus (Echocardiography), Queen’s University, inaugurated echocardiography labs at both the Hôtel-Dieu and Kingston General Hospitals from 1974 to 1989, and has contributed to the training of many cardiology residents now practicing and teaching echocardiography in Canada and the US.

CCS Dr. Harold N. Segall Award of Merit: Dr. Vivian Rambihar, cardiologist at the Scarborough Hospital, has studied and taught international audiences about chaos and complexity sciences as a way of better understanding complex interactions between ethnic heritage, culture, customs, family history, gender, genes, the environment and social dynamics that promote either health or disease. His

book, *Tsunami, Chaos and Global Heart*, explores these interactions.

CCS Trainee Excellence in Education Award: Dr. Carolyn Taylor, a cardiology fellow at the University of British Columbia, is using non-invasive imaging to determine how modification of CVD risk factors might correct the earliest signs of disease. She is currently at Harvard University where she is enrolled in a public health program and will continue to focus on CVD prevention.

CCS Young Investigator Award: Dr. Hung Ly, an interventional cardiologist at the Montreal Heart Institute, is studying gene- and cell-based therapeutic interventions that may promote healing of the injured heart. The enhanced expression of the SERCA2a protein that regulates cardiac function, for example, may help the heart remodel scarred cardiac tissues and attenuate the development of heart failure.

CCS Young Investigator Award—First Runner-Up: Dr. Erik Suuronen, Assistant Professor (Scientist), Division of Cardiac Surgery, University of Ottawa Heart Institute, is attempting to use a patient’s own stem cells to grow new tissue that could repair or replace damaged parts of the heart. His aim is to produce material that could be implanted in arteries or other parts of the cardiac system to help regenerate damaged components.

CCS Young Investigator Award—Second Runner-Up: Dr. Simon Bacon, Assistant Professor of Exercise Science, Concordia University, Montreal, is documenting changes in endothelial performance during episodes of stress. As the effects of stress on the endothelium are better characterized, it may be possible to offset them through various stress management techniques.

Anemia Institute for Research and Education Award: Dr. Richard Novick, Chief of Cardiac Surgery, London Health Sciences Centre, is characterizing the advantages and disadvantages of the various heparins. Such differences may well influence patient recovery, suggesting that selection of specific heparins may be important to improve outcomes.

Dr. Robert E. Beamish Award: Named in honour of founding editor-in-chief of the *Canadian Journal of Cardiology*, the recipient of this year’s award is announced during the Joint Awards Ceremony. □



Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

New Targets and Strategies for Improved Cardiovascular Protection

Quebec City - Awareness is growing that physicians need to target a triad of glucose parameters, including post-prandial hyperglycemia, in order to reduce overall glycemic burden and cardiovascular risk. Lowering blood pressure is associated with important end-organ protection but certain antihypertensive agents, notably the angiotensin II receptor blockers, have a clear advantage over conventional antihypertensive regimens for the kidney, brain and heart. Initial combination strategies help get more patients to goal with fewer compounds than the usual stepped-care approach. New lipid-lowering strategies include a combination of extended-release niacin coupled with a flushing inhibitor that promises to reduce residual risk not addressed by the statins by significantly raising HDL-C and lowering LDL-C and triglycerides with manageable side effects.

Québec – *De plus en plus, il est de notoriété commune que le médecin doit cibler une triade de paramètres glycémiques, dont l'hyperglycémie post-prandiale, pour alléger le fardeau glycémique total et réduire le risque cardiovasculaire. Si la baisse des chiffres tensionnels procure une importante protection des organes cibles, certains antihypertenseurs, notamment les antagonistes des récepteurs de l'angiotensine II, sont nettement plus avantageux que les agents traditionnels pour le rein, le cerveau et le cœur. Par comparaison aux soins progressifs usuels, l'administration d'un traitement d'association dès le départ permet à plus de patients d'atteindre leurs cibles tensionnelles à l'aide d'un nombre moindre d'agents. On compte parmi les nouvelles stratégies hypolipidémiantes l'association d'une préparation de niacine à libération prolongée et d'un inhibiteur des bouffées vasomotrices, qui devrait permettre d'augmenter notablement le taux de C-HDL et ainsi d'amenuiser le risque résiduel qui échappe aux statines tout en occasionnant peu d'effets indésirables.*

By: Pam Harrison

Awareness is growing that a triad of glucose parameters need to be targeted in patients with diabetes and not just fasting blood sugar or glycosylated hemoglobin (HbA_{1c}). The day-to-day target for diabetes management has long been fasting plasma glucose (FPG). However, as Leiter et al. argued in a review article, post-prandial hyperglycemia (PPG) may well represent the “first strike” against the body, “setting the stage for the deadly onset of atherosclerosis, long before HbA_{1c} levels rise high enough to trigger microvascular complications” (*Clin Ther* 2005;27(Suppl 2):S42-S56).

PPG also contributes substantially to overall glycemic load. According to other research, PPG only contributed about 30% of the 24-hour AUC in poorly controlled patients, but when HbA_{1c} was better controlled (<7.3%), the PPG contribution increased to at least 70% (Monnier et al. *Diabetes Care* 2003;26(3):881-5).

Evidence also suggests that PPG is a cardiovascular (CV) risk factor in its own right and that FPG levels do not reliably identify patients at CV risk. For example, results from the DECODE/DECODA study showed that approximately one-third of participants diagnosed as having type 2 diabetes based on PPG levels, and at least one-quarter of those with impaired glucose tolerance (IGT), actually had normal FPG levels. “Thus, FPG measurements alone are an unreliable guide to identifying individuals at CV risk due to IGT or diabetes,” according to Dr. Lawrence Leiter, Professor of Medicine and Nutritional Sciences, University of Toronto.

He notes that PPG can be ameliorated by paying attention to its regulation, most notably with short-acting insulins. Acarbose has also been shown to reduce the relative risk of IGT patients developing any CV event by 49% over a mean follow-up of 3.3 years. Other work now indicates that the cardioprotective benefit of PPG regulation likely extends to type 2 diabetes as well.

Conversely, results from the UKPDS study, during which relatively good control of FPG was achieved with intensive therapy, did not control the rise in HbA_{1c} levels over the course of the study. Comments Dr. Leiter, “The most logical explanation for this finding

is the lack of focus on postprandial hyperglycemia, which was neither monitored nor treated in UKPDS.” Indeed, evidence supporting the benefit of managing PPG was deemed compelling enough for the International Diabetes Federation (IDF) to issue recent guidelines on its management. “Postmeal hyperglycaemia is harmful and should be addressed,” the IDF stated, using both pharmacologic and non-pharmacologic strategies to do so.

As the IDF pointed out, new classes of drugs, including the dipeptidyl peptidase-4 (DPP-4) inhibitors, have been shown to significantly reduce both PPG and HbA_{1c}. For example, the addition of the DPP-4 inhibitor sitagliptin to metformin or pioglitazone for 24 weeks allowed almost half of one group of patients with inadequately controlled HbA_{1c} to achieve levels of <7%. The IDF currently recommends that two-hour PPG not exceed 7.8 mmol/L. They also recommend that patients monitor blood glucose levels themselves, as it is the most practical method for measuring PPG.

Beyond Blood Pressure-Lowering

Dr. Pierre Nantel, Co-director, Kidney Foundation of Canada (Quebec Branch) and staff nephrologist, *Centre hospitalier Sorel-Tracy*, offers evidence supporting the benefit of lowering blood pressure (BP) on end-organ protection beyond that provided by BP lowering itself. Limiting his analysis to only those trials where both arms achieved identical BPs, Dr. Nantel singles out the RENAAL trial, in which patients with type 2 diabetes and proteinuria were randomized to a losartan-containing arm or to conventional antihypertensive therapy (no angiotensin receptor blockers [ARBs] or ACE inhibitors allowed). At an average follow-up of 3.4 years—and with almost identical BP reductions in both treatment groups—there was a 16% reduction in the primary composite end point consisting of a doubling of serum creatinine, end-stage renal disease (ESRD) or death in the losartan-containing arm; a 28% reduction in the risk of ESRD; and a 20% reduction in ESRD or death over the conventional therapy arm.

The IDNT study had essentially the same end point as RENAAL. At an average follow-up of 2.6 years, patients in the irbesartan arm were 20% less likely to reach the primary composite end point compared with placebo and 23% less likely than patients in the amlodipine arm.

Albuminuria was the main end point in IRMA-2 and, similarly, hypertensive patients with type 2 diabetes but normal kidney function at baseline were less likely to develop nephropathy when randomized to the higher-dose, ARB-containing arm vs. placebo—again, for almost identical BP reductions. More effective slowing of progressive albuminuria was also demonstrated in MARVEL when patients with type 2 diabetes and microalbuminuria received an ARB compared with an amlodipine-based regimen.

In the brain, the best study supporting additional protective benefits for the same magnitude of BP lowering was seen in LIFE, where the risk of stroke was reduced by 25% among patients who received losartan vs. those who received atenolol. Again, BP control was almost identical in both treatment arms. LIFE also demonstrated that in hypertensive patients with left ventricular hypertrophy (LVH), an ARB-based regimen leads to more effective regression of LVH than an atenolol-based regimen as well as a lower incidence of atrial fibrillation. “The weight of the evidence [for end-organ protection] is for the ARB,” Dr. Nantel confirms.

If end-organ protection is indeed the primary purpose of treating hypertension, physicians should keep in mind that elevated serum uric acid levels are not uncommon in hypertensive individuals either, and they are an important CV disease risk factor in and of themselves, increasing the risk of CAD or cerebrovascular disease by three- to fivefold over normal uric acid levels (*Lancet* 1966;1:15-18). The only antihypertensive agent that has been shown to reduce serum uric acid levels is losartan. In LIFE, it is estimated that up to one-third of the CV benefit of the ARB-based regimen over that seen with atenolol could be ascribed to differences in the effect that these two antihypertensive agents had on serum uric acid levels.

Although the fixed-dose combination was not used in LIFE, the majority of patients in the losartan arm received it plus a thiazide. It is a clinically relevant finding that more patients who receive a fixed-dose combination as initial therapy are more likely to get to goal on fewer drugs and with fewer side effects. In other research, 63.5% of patients assigned to fixed-dose losartan/HCTZ achieved a systolic BP of <130 mm Hg compared with 37.5% in the stepped-care group while twice as many patients in the combination group achieved BP goals with no more than two drugs (30%) vs. approximately 15% in the stepped-care group (Lacourcière et al. *Can J Cardiol* 2007;23(5):377-82). The ARB/HCTZ combination was also better tolerated than the stepped-care approach.

These findings support initiation of an antihypertensive regimen using a fixed-dose combination, especially in patients in

whom larger reductions in BP are needed and who will almost always require more than one agent to bring them to goal.

Improved Lipid Management: The HDL-C Story

The statins may have revolutionized lipid management but they still do not prevent the majority of CV events and there is a clear need to identify new targets to lower residual CV risk. As the first of a new class of cholesterol ester transferase protein (CETP) inhibitors, torcetrapib was felt to hold promise as it targeted HDL-C levels, something the statins do not affect. But according to Dr. Robert Hegele, Professor of Medicine and Biochemistry, University of Western Ontario, London, development was halted when clinical trial results indicated that the compound increased the risk of death and CV events, despite producing favourable biochemical changes.

As his own work with HDL-C reflects, the role of HDL-C is a “very complex story” and is not as simple as lowering LDL-C. There are, he explains, different members of the HDL-C family and the suggestion is that the HDL-C raised by torcetrapib was not very functional. In fact, ultrasound studies demonstrated that the molecule had no beneficial effect on either the coronary or carotid arteries, “and this was very consistent evidence,” Dr. Hegele indicates.

While many hold out hope that raising HDL-C through CETP inhibition will eventually prove successful, Dr. Hegele argues that niacin may be a better option. As a natural form of vitamin B therapy, niacin has long been known to raise HDL-C and lower LDL-C and triglycerides and it has an established safety record. However, niacin does cause flushing, which patients find difficult to tolerate.

A new formulation of extended-release (ER) niacin combined in a single tablet with a specific blocker of a receptor for prostaglandin D₂ (laropiprant), thought to play a key role in niacin-induced vasodilation, is currently in clinical trials. Results from a phase III trial presented recently showed the ER niacin/laropiprant combination reduced LDL-C levels by approximately 19%, increased HDL-C levels by approximately 19% and reduced triglycerides by some 22% between weeks 12 and 24 of the study. Patients in the ER niacin/laropiprant arm also reported significantly less flushing, both when treatment was initiated and during maintenance therapy, than those in the ER niacin monotherapy cohort. Results were similar when the new combination was given with a statin. “With a very simple intervention, we can more or less eliminate flushing, so now the issue is, how will patients react to this combination and what is the added benefit of treating patients to reduce residual risk,” Dr. Hegele concludes. □

Based on:

“Managing Cardiometabolic Complexities: Will New Treatment Strategies Improve Health Outcomes?” Sunday, October 21, 10:00-12:00, Room 200A, Level 2.

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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E-mail: mednet@mednet.ca / Web site: www.mednet.ca **Please e-mail us at our address to receive reports on-line.**

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Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Current Opinion on Drug-Eluting Stents: CAIC/CCS Position Paper Revisited

Quebec City - In February, the Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society published their position paper on the use of drug-eluting stents (DES) and concomitant antiplatelet therapy out of concern of an apparent greater incidence of late stent thrombosis with DES than bare-metal stents. Recent analysis and long-term follow-up of a Canadian cohort receiving sirolimus-eluting stents (SES) are likely to reshape current opinion about DES vs. bare-metal stents, as findings have been consistently reassuring in terms of both the safety of DES in general and of SES in particular. Long-term follow-up of the C-SIRIUS cohort has demonstrated that the excellent clinical outcomes seen in SES-treated patients at one year are sustained at three years, with no evidence of very late stent thrombosis. These new data support the judicious use of DES in the management of CAD along with appropriate antiplatelet therapy. Their use allows patients to benefit from the significant reduction in the need for target lesion revascularization, a well-documented advantage of DES over their bare-metal counterparts.

Québec – En février dernier, l'Association canadienne de cardiologie d'intervention et la Société canadienne de cardiologie publiaient une déclaration de principe sur l'utilisation d'un tuteur médicamenteux (TM) et d'un traitement antiplaquettaire concomitant en réaction à une incidence apparemment plus élevée de thromboses tardives sous TM que sous tuteur métallique non médicamenteux. Or, une analyse récente et le suivi à long terme d'une cohorte canadienne de patients chez qui on avait implanté un tuteur à élution de sirolimus (TES) viendront probablement moduler cette perception des TM, par comparaison aux tuteurs métalliques. En effet, les résultats ont été systématiquement rassurants sur les plans de l'innocuité des TM en général et du TES en particulier. Le suivi à long terme de la cohorte de l'étude C-SIRIUS a montré que les résultats cliniques à un an chez les porteurs d'un TES – qui étaient excellents – se maintenaient à trois ans et que ces patients ne montraient aucun signe de thrombose très tardive attribuable aux tuteurs. Ces nouvelles données militent en faveur de l'utilisation judicieuse d'un TM et d'un traitement antiplaquettaire approprié dans la prise en charge de la maladie coronarienne. Leur utilisation se traduit par une réduction notable des interventions de revascularisation des lésions cibles, avantage bien documenté par rapport aux tuteurs métalliques.

By: Pam Harrison

Recommendations on the use of drug-eluting stents (DES) developed by the Canadian Association of Interventional Cardiology (CAIC) and the Canadian Cardiovascular Society (CCS) and featured this year during the Consensus Conference discussion may have to be reassessed in light of reassuring reports that DES in general, and sirolimus-eluting stents (SES) in particular, are not associated with increased mortality risk or late stent thrombosis compared with bare-metal stents.

Furthermore, significant reductions in the need for target revascularization continue to be observed with DES vs. bare-metal stents, SES having a more pronounced effect on the need for target lesion revascularization than paclitaxel-eluting stents (PES). SES have also been associated with a lower risk of myocardial infarction (MI) than either bare-metal stents or PES. As will be discussed by Dr. Érick Schampaert, Clinical Associate Professor of Medicine, *Université de Montréal*, concerns about late stent thrombosis prompted the CAIC/CCS to review the safety of DES.

The position paper, published in the *Canadian Journal of Cardiology* in February 2007, recommended physicians carefully weigh the benefits and risks of choosing a DES over a bare-metal stent for each patient, especially when considering a DES for off-label use. They also cautioned against DES use in patients who are unable to stay on antiplatelet therapy for at least 12 months or longer in patients at higher risk for very late stent thrombosis. The use of DES should also be avoided in patients scheduled to undergo surgery if their antiplatelet regimen has to be stopped.

However, results from two recent meta-analyses, as well as a study by Dr. Schampaert and colleagues, provide reassuring evidence that the safety issues surrounding DES use appear to have been overstated. As reported by Schomig et al. (*J Am Coll Cardiol* 2007;50(14):1373-80), 16 randomized trials involving 8695 patients were included in the analysis. "The primary efficacy end point...was the need for reintervention (target lesion revascularization)," the authors wrote, "while the primary safety end point...was stent thrombosis." Secondary end points included death and recurrent MI.

The hazard ratio (HR) for reintervention was 0.74 for patients allocated to a SES or a 26% reduction in the relative risk for reintervention in favour of SES ($P < 0.001$). The HR for stent thrombosis for SES vs. PES was 0.66 in favour of SES, investigators added, which corresponds to a 34% risk reduction in stent thrombosis in favour of SES. Looking at mortality outcomes, allocation to the SES group was associated with a non-significant HR of 0.92. Although the difference in MI rates between the two groups was not significant (HR 0.84; $P = 0.10$), as the authors noted, there was a trend towards a higher risk of MI with PES, especially in the first year from the procedure.

While it is important to remember that as with all meta-analyses, there may be some limitations to this particular one, the authors concluded: "The SES are superior to PES in terms of a significant reduction of the risk of reintervention and stent thrombosis."

Collaborative Network Meta-Analysis

In a recent meta-analysis (*Lancet* 2007;370:937-48), investigators identified 38 trials involving 18,023 patients with a follow-up of up to four years. Trialists and manufacturers provided additional data on clinical outcomes from 29 trials. "Safety outcomes included mortality, MI and definite stent thrombosis," investigators write. The need for target lesion revascularization was again chosen as the primary efficacy end point.

Overall, the incidence of death was similar in all three groups—SES patients, PES patients and those with bare-metal stents. Similarly, "the incidence of cardiac death was much the same in all three groups," investigators added. For their analysis of MI rates, results from 37 trials showed that SES were associated with the lowest incidence of MI, whereas the incidence of MI was "much the same" between PES and bare-metal stents.

Data on definite stent thrombosis according to Academic Research Consortium (ARC) criteria were taken from 24 trials involving almost 13,000 patients. Based on this extensive data set, "there was no significant difference in the cumulative incidence of definite stent thrombosis between the three types of stents," the authors stated, nor was there any difference in the incidence of early stent thromboses (up to 30 days' post-procedure) between the three stent types. In contrast, the risk of late stent thrombosis occurring after 30 days' post-implantation "seemed to be roughly doubled" with PES compared with bare-metal stents and SES, they added. There was also no difference in the incidence of late stent thrombosis between SES patients and those who received a bare-metal stent.

Results also confirmed that both types of DES significantly reduced the need for target lesion revascularization compared with bare-metal stents, although the reduction in the need for revascularization was more pronounced with SES than with PES. Indeed, approximately six patients would have to receive a SES rather than a bare-metal stent to prevent one target lesion revascularization over four years, as the authors pointed out. In the Canadian multicentre study to be presented here at the CCC,

Dr. Schampaert and colleagues looked at long-term outcomes in the C-SIRIUS (Canadian Study of the Sirolimus-eluting Stent in the Treatment of Patients with Long *de novo* Lesions in Small Native Coronary Arteries), in which the safety and efficacy of SES was compared with bare-metal stents.

Earlier results had demonstrated a dramatic reduction in both angiographic and clinical restenosis in patients with lesions of 15 and 32 mm in short vessels (2.5 to 3 mm in diameter) at eight and nine months, respectively. Out of 100 patients in the original C-SIRIUS trial, investigators had follow-up results in 88% of patients who had undergone angiography at eight months and clinical follow-up was obtained for 98 patients at three years. Clinical end points included major adverse cardiac events (MACE), including a composite of cardiac and non-cardiac death, MI, clinically-driven target lesion revascularization and stent thromboses.

At one year, the incidence of MACE was 22% in the bare-metal stent group vs. 6% in the SES group ($P=0.041$). Target lesion revascularization rates were identical at 22% in the bare-metal stent group vs. 4% in the SES group ($P=0.015$). "From one year to three years, there was one additional target lesion revascularization at 976 days in the bare-metal stent group," investigators reported, "while in the SES group, there was one non-target vessel cardiac death, one non-cardiac death and one target lesion revascularization at 369 days."

In other words, the incidence of MACE at three years was exactly double at 24% in the bare-metal stent group vs. 12% in the SES group, while the need for target lesion revascularization in the bare-metal stent group was three times greater at 24% vs. 6% in the SES group ($P=0.041$). Importantly, no very late stent thrombosis was observed in either group.

"C-SIRIUS previously demonstrated that SES provided excellent clinical outcomes for patients with long lesions in small vessels at one year, and these benefits were sustained at three years, with no evidence of very late stent thrombosis," investigators concluded. Results at five years will be detailed during the presentation this year. And while not available for this report, "five-year results are in keeping with results from both meta-analyses and are very reassuring," states Dr. Schampaert. □

Based on:

Oral Session: "Interventional Cardiology: Drug-Eluting Stents and ST Elevation Myocardial Infarction." Sunday, October 21, 2007, 16:30-18:00, Room 202, Level 2.

17:15 – #232. Schampaert E, Cohen EA, Reeves F et al. Efficacy and Safety at 3 and 5 Years in the Canadian Multi-centre, Randomized, Double-blind Trial of the Sirolimus-eluting Stent in the Treatment of Patients with *de novo* Coronary Artery Lesions (C-SIRIUS).

Please plan to attend:

"Highlights of Heart Failure Recommendations and the Joint CCS/CAIC Position Statement on Drug-Eluting Stents and Antiplatelet Therapy." Tuesday, October 23, 2007, 14:00-15:00, Room 2000A-B, Level 2.

These symposia 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 (RCPSC).

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Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Preparing for the Next Set of Trials in Cardiovascular Risk Reduction

Quebec City - Several avenues of clinical study have enormous potential to improve control of major cardiovascular (CV) risks, according to a series of presentations made at a symposium on Saturday night. Called "Maximizing the Benefits of Preventative Strategies in Cardiovascular Disease," the symposium provided a preview of where the road in CV risk management is leading. Judging from it, the most imminent and important source of new data will be the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study, which is scheduled for completion in time for the next (2008) meeting of the American College of Cardiology. This study of the optimal approach to reducing CV events in high-risk patients without hypertension (or in whom hypertension has been controlled) is being joined by progress in treatment of stroke, dyslipidemia, and resistant hypertension.

Québec – Selon une série de communications présentées au symposium de samedi soir, plusieurs voies de la recherche clinique offrent d'énormes possibilités d'amélioration de la maîtrise des risques cardiovasculaires (CV) majeurs. Intitulé «Maximiser les bienfaits des stratégies préventives des maladies cardiovasculaires», le symposium a donné un aperçu de l'orientation de la prise en charge du risque CV. Il en est ressorti que la source la plus imminente et la plus importante de nouvelles données sera l'étude ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), qui devrait se terminer à temps pour le prochain congrès de l'American College of Cardiology (2008). Cette étude sur la prise en charge optimale pour réduire le risque d'événement CV chez les patients à risque élevé ne souffrant pas d'hypertension (ou chez qui l'hypertension est maîtrisée) viendra s'ajouter aux progrès accomplis en matière de traitement des ACV, des dyslipidémies et de l'hypertension rebelle.

By: *Ted Bosworth*

The ONTARGET trial programme involving more than 31,000 patients at high risk of cardiovascular (CV) events encompasses ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and the parallel TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease). ONTARGET randomized some 25,620 patients to the angiotensin receptor blocker (ARB) telmisartan, the ACE inhibitor ramipril or both. TRANSCEND recruited 5926 patients who were given telmisartan or placebo. The long-awaited results will be presented in less than five months at the 2008 American College of Cardiology meeting. The studies are not comparing these agents for blood pressure (BP) control. Rather, randomized patients are either without hypertension or with well-controlled BP at entry.

Renin-angiotensin Target Tissue Inhibition

Although telmisartan and ramipril might prove to have additive benefits for CV risk reduction, a large body of data predicts they will not be equivalent. "The ARBs and the ACE inhibitors both block the effects of an upregulated renin-angiotensin system (RAS), but there are some potentially significant differences in their mechanism of action," reports Dr. Marc Pfeffer, Professor of Cardiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

He notes that although both are effective in reducing BP, each has demonstrated BP-independent benefits likely mediated by different pathways. For example, while ACE inhibitors block one of several enzymes responsible for angiotensin II production, they also inhibit degradation of bradykinin, a potent vasodilator. ARBs do not have this direct effect on

bradykinin or any other endogenous vasodilator but block angiotensin II at its receptor sites, likely providing a more complete angiotensin inhibition, particularly at target tissue receptors. In addition, by blocking the AT₁ receptor, more angiotensin II is available to stimulate AT₂ receptors, which have been associated with antiproliferative activity. With new data suggesting that inhibitors of the RAS may also generate meaningful interactions with the inflammatory and fibrinolytic systems, the potential for differences between ACE inhibitors and ARBs has grown increasingly intriguing.

Protecting the Brain, Heart and Kidney: Upcoming Trial Data

The primary end point of the ONTARGET trial, for which Dr. Salim Yusuf, Director, Population Health Research Institute and Professor of Medicine, Division of Cardiology, McMaster University, Hamilton, is a principal investigator, is a composite of CV death, acute myocardial infarction, stroke and hospitalization for congestive heart failure. The size of the study will permit meaningful evaluations for many secondary outcomes, including new-onset diabetes, renal impairment, and some emerging areas of interest such as relative cognitive decline after a CV event. For example, it has been hypothesized that stimulation of AT₂ receptors in the cerebrovascular circulation might be neuroprotective. An advantage for telmisartan for stroke would provide substantial support for this hypothesis.

Although widely regarded as an ARB-vs.-ACE inhibitor comparison, telmisartan has numerous features that distinguish it from other ARBs. For example, of currently available ARBs, it has the longest half-life at 24 hours, while valsartan and candesartan have nine-hour half-lives. This difference could be

important for reducing risk of events strongly associated with circadian morning surges in BP, including stroke. In addition, it has unique mechanisms of action on pathways linked to improvement in glucose and lipid metabolism. Although no large direct comparisons of ARBs have been conducted, several single-centre studies have indicated greater relative benefits with telmisartan than comparator ARBs on these parameters. The applicability of results of ONTARGET to other agents in the ARB class is therefore likely to be controversial.

In stroke, another major study nearing completion also involves telmisartan. However, in the PROfESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, the ARB is being compared to placebo for secondary stroke prevention and is also randomizing patients to extended-release dipyridamole plus ASA or clopidogrel in a 2x2 factorial design.

In reviewing the PROfESS design, Dr. Philip Teal, Clinical Associate Professor of Neurology, University of British Columbia, noted that results will provide important information about optimal secondary stroke prevention while evaluating two different mechanisms of action. The previous MOSES (Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine in Secondary Stroke) study compared eprosartan to nitrendipine for secondary prevention. The ARB showed a significantly greater protective effect against CV events and fatal or non-fatal strokes at the same BP control relative to the calcium channel blocker. PROfESS should build on these data to better define optimal secondary stroke prevention strategies.

According to Dr. George Bakris, Professor of Medicine, University of Chicago, Illinois, there is an intense interest in preserving renal function by aggressive RAS inhibition, including combination regimens, as there is a strong correlation between measures of renal impairment such as glomerular filtration rate and CV risk. Therefore, the use of both ARBs and ACE inhibitors to control microalbuminuria is attractive not only to halt progressive renal disease but also to diminish CV risk.

While ONTARGET will provide insight on dual pathways of RAS inhibition, Dr. Bakris indicated that the favourable effects might spur additional investigation, including efforts to test maximal doses of RAS inhibitors alone or in combination in high-risk patients.

In defining dyslipidemia, there has been no change in the admonition that lower is better in regard to LDL-C despite studies in which the mean level has been reduced to nearly 1.5 mmol/L, according to Dr. Lawrence Leiter, Professor of Medicine and Nutrition, University of Toronto. While such

trials as PROVE-IT and TNT have provided compelling evidence that the LDL-C goal in high-risk patients should be <1.8 mmol/L, studies with intravascular ultrasound (IVUS) have suggested that even lower LDL-C may not just stop progression of atherosclerosis but induce regression. However, due to the residual risk observed even in the most aggressively treated patients, the emerging question is whether other lipid subfractions, particularly HDL-C, might be an additional target for risk reduction.

Recently, disappointing results with torcetrapib, a CETP inhibitor capable of very large increases in HDL-C, has introduced some concern about HDL-C as a target. Although the failure of torcetrapib to yield clinical event reductions may be at least partially due to its association with an increase in systolic BP, IVUS studies were unable to show a significant reduction in atherosclerotic burden. A variety of new strategies for raising HDL-C are being pursued, but Dr. Leiter cautioned that this story remains incomplete.

Lastly, an analysis of approaches to resistant hypertension was discussed by Dr. Richard Lewanczuk, University of Alberta. Where resistance is defined as inability to reach goals with three or more BP-lowering agents, it is a relatively common condition affecting 15% of all hypertensive patients.

Dr. Lewanczuk reported, "True resistant hypertension is associated with a high risk of CV events. Factors involved in resistant hypertension include the use of interfering medications such as NSAIDs, secondary causes of hypertension, patient factors such as poor medication or lifestyle compliance, and using suboptimal drug doses or suboptimal drug combinations," indicating why treatment solutions are needed.

Although resistant hypertension is a challenge, he maintained that "following a systematic algorithm can usually bring the majority of these patients under control."

Summary

Several important trials nearing completion have the potential to alter CV risk management. In high-risk hypertensive patients, the ONTARGET study will generate a massive array of new data about the relative benefits of telmisartan, ramipril, and the combination of an ARB and an ACE inhibitor, not only in regard to the primary end point of major CV end points but also in associated risks such as new-onset diabetes. In secondary stroke prevention, the PROfESS study will provide important insight about the relative effects of RAS inhibition vs. antiplatelet strategies. Along with emerging strategies for raising HDL-C, there may be several new opportunities defined for better CV risk management over the short term. □

Based on:

"Maximizing the Benefits of Prevention Strategies in Cardiovascular Disease." Saturday, October 20, 18:00-21:00, Room 200C, Level 2.

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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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.**

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Clinical Supplement



Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Essential Strategies for Global Cardiovascular Risk Reduction

Quebec City - More than 90% of adult Canadians who have one major modifiable cardiovascular risk factor, such as hypertension, have at least one other. Risk management has been largely based on studies that focus on only one risk factor at a time, but global risk reduction is the new mandate. In a symposium here during the Canadian Cardiovascular Congress, experts explain how clinicians can become more aggressive in addressing multiple risk factors simultaneously. The session emphasizes that a global approach to risk management requires clinicians to adjust strategies. This includes more use of combination therapy and greater focus on treating even the difficult-to-control risks such as smoking.

Québec – Plus de 90 % des Canadiens d'âge adulte qui présentent un important facteur de risque cardiovasculaire modifiable, comme l'hypertension, en présentent au moins un autre. La prise en charge du risque découle en grande partie d'études axées sur un seul facteur de risque, mais le nouveau mot d'ordre est une réduction globale du risque. Au dire des experts réunis dans un symposium du Congrès canadien sur la santé cardiovasculaire, le clinicien peut opter pour une démarche plus vigoureuse en corrigeant simultanément de multiples facteurs de risque. Cette séance met l'accent sur le fait que le clinicien doit ajuster ses stratégies s'il aspire à une prise en charge globale du risque. C'est donc dire qu'il doit avoir davantage recours aux traitements d'association et porter une plus grande attention aux risques plus difficiles à maîtriser comme le tabagisme.

By: Ted Bosworth

In Canada, there are well delineated treatment goals for essentially all of the modifiable cardiovascular (CV) risk factors. Moreover, the published guidelines typically identify first- and second-line therapies to reach these goals based on large clinical trials testing different strategies. However, there is relatively little information about how to integrate risk management in the large majority of patients with multiple risk factors. This is the primary focus of Monday's symposium and an emerging area in clinical medicine. Several studies have now demonstrated that this is feasible, and tools, such as combination pills, are becoming available to facilitate efforts.

"A global risk-reduction strategy can be remarkably effective as shown in a series of recent trials," reports Dr. George Honos, Director of Non-Invasive Cardiology, SMBD-Jewish General Hospital, Montreal. According to Dr. Honos, one of the most significant barriers to global risk management has been inadequate use of "long-acting drugs in combination whenever possible to encourage long-term patient adherence."

Study Findings

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial is cited by Dr. Honos as a recent example of the effectiveness of global risk management (Boden et al. *N Engl J Med* 2007;356(15):1503-16). In this trial, 2287 patients with coronary artery disease, including myocardial ischemia, were randomized to undergo a percutaneous coronary

intervention (PCI) plus intensive medical therapy or intensive medical therapy alone. The intensive medical regimen included antiplatelet therapy, antihypertensive therapy with the calcium channel blocker amlodipine, the beta blocker metoprolol, and isosorbide mononitrate alone or in combination, aggressive LDL-lowering with a target of <2.2 mmol/L, and a renin-angiotensin system (RAS) inhibitor (either an angiotensin receptor blocker or an ACE inhibitor).

After a median of 4.6 years of follow-up, PCI was unable to show a significant advantage over intensive medical therapy alone, which was the primary objective of the comparison. The event rates were <20% in both groups, which was far below the estimated event rates based on baseline risks. While the authors concluded that PCI could be safely deferred, the results also support the use of rigorous treatment of multiple risks to substantially reduce the risk of events.

An earlier, smaller, but perhaps more dramatic demonstration of the same principle was provided by the STENO-2 trial, the second trial by the Steno Diabetes Center, also cited by Dr. Honos. In STENO-2, 80 patients with type 2 diabetes mellitus (DM2) were randomized to receive conventional risk management according to 1988 Danish national guidelines or intensive therapy targeted at multiple risk factors. In addition to being placed on an exercise regimen, the intensive therapy group received an antiplatelet agent, a RAS inhibitor, a combination of glucose-lowering agents to bring HgA_{1c} levels to <6.5%, antihypertensive therapies and atorvastatin at doses up to

80 mg as needed to achieve established goals. After a mean follow-up of 7.8 years, the rate of CV events was reduced by half (hazard ratio 0.47; 95% CI 0.24-0.73) and the rate of nephropathy was reduced by 61% (95% CI 13%-83%).

Intensive therapy to reach treatment goals is a recurring theme in global risk management studies, but it is important to recognize that the optimal regimen for treatment of such risk factors as dyslipidemia has not yet been defined. Currently, the Canadian guidelines for high-risk patients list the target for LDL levels as <2.0 mmol/L, a target supported by the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and TNT (Treating to New Targets) trials. However, both PROVE-IT and TNT suggested further relative protection from CV events at LDL levels lower than mean values achieved with the most intensive therapy. Such levels cannot be achieved routinely even with the highest available doses of many current statins, including lovastatin, simvastatin and pravastatin. In patients with multiple risks, such as hypertension and dyslipidemia, one approach to reduce pill burden and increase patient adherence may be to employ combination pills, such as atorvastatin with amlodipine, that address more than one treatment goal.

More strategies are emerging to address multiple risks. One pressing question is whether elevating HDL levels can build on the benefits achieved by lowering LDL. The epidemiologic data suggest that low HDL is a modifiable risk factor and may account for some of the residual risk observed in patients on maximum LDL-lowering treatments. However, Dr. Lawrence Leiter, Director, Lipid Clinic, St. Michael's Hospital, University of Toronto, cautions that there have been some disappointments with treatments targeted at HDL. In particular, torcetrapib, a CETP inhibitor capable of substantially elevating HDL, failed to achieve anticipated risk reductions in a study completed earlier this year. HDL has not been abandoned as an important potential target, because the negative results in the torcetrapib study may have been due to its association with increased systolic hypertension.

Smoking is perhaps reasonably characterized as the most difficult modifiable risk factor to bring under control, but Dr. Andrew Pipe, Order of Canada recipient and

Medical Director, Prevention and Rehabilitation Centre, University of Ottawa Heart Institute, suggests that it is no longer acceptable to assume a nihilistic attitude. The data suggest that smoking has a "fundamental importance" to CV risk and cannot be ignored. New pharmacologic treatments, such as varenicline, have been shown to increase rates of long-term success, justifying an investment of time by clinicians seeking to provide adequate risk management.

"The reason to include a program of integrated risk management is that smoking is too often overlooked by clinicians who are very aggressive at controlling other risk factors. Yet, smoking is a very important health threat," notes Dr. Pipe, who has long had an interest in improving management of an often neglected problem.

All of the modifiable risk factors, including smoking, dyslipidemia and hypertension, impair endothelial function, a tissue critical to vascular homeostasis. While control of any one risk factor will inhibit progressive atherosclerosis, the greatest opportunities for risk management come from simultaneously addressing all of the risk factors that mediate vascular disease. According to Dr. Honos, there are three important components to integrating effective global risk reduction strategies. These are early identification of high-risk patients; bringing patients to treatment goals for each of their risk factors; and implementation of safe and effective therapies.

Summary

In treatment trials, it has been necessary to study each CV risk factor separately in order to demonstrate change when other variables are controlled. However, modifiable risk factors rarely develop in isolation. Now that there are clear guidelines for most modifiable risks, global risk treatment strategies are a logical approach to reducing the absolute risk of CV events that are driven by interrelated pathologic pathways converging in impairment of vascular health. Such global risk treatment strategies require new approaches to integrating therapies in order to maximize the likelihood of adherence. It also involves considering all of the CV risks, including those most difficult to treat, such as smoking. □

Based on:

"Straight from the Heart: Managing the Cardiovascular Risk Continuum." Monday, October 22, 2007, 7:00-9:00, Room 200C, Level 2.

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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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.**

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