

Canadian Cardiovascular Congress



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



PLEASE PLAN TO ATTEND

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

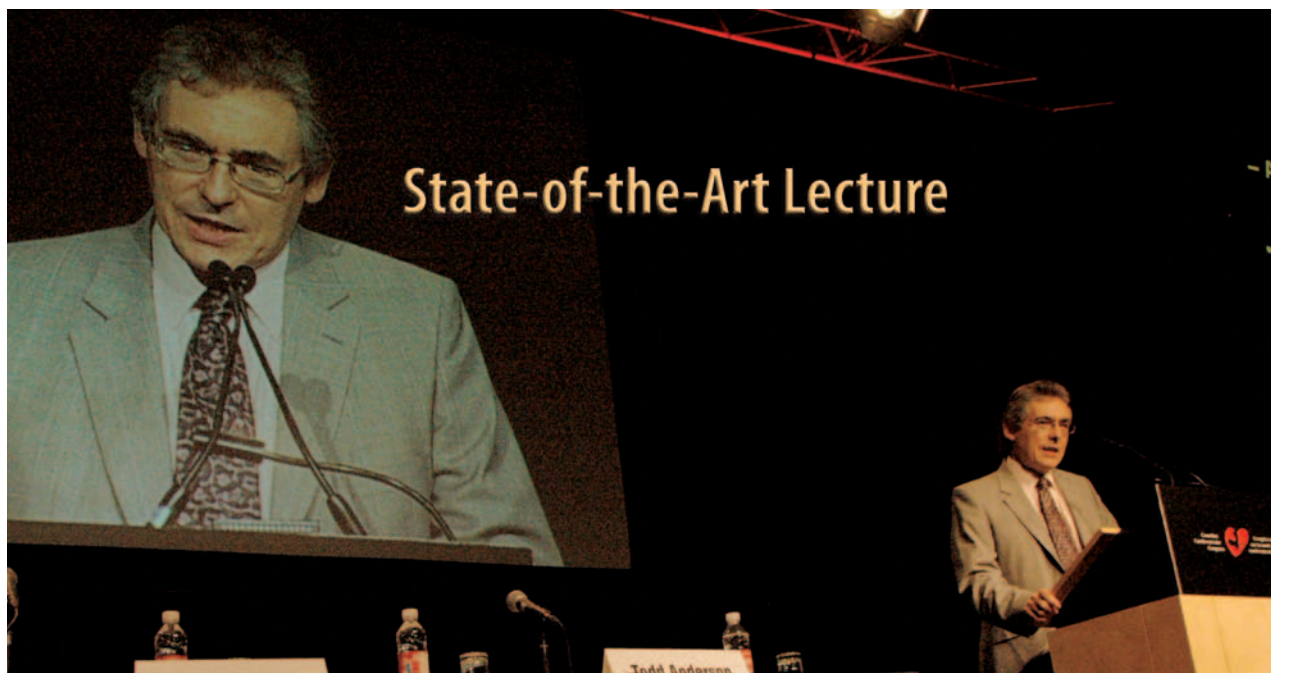
WEDNESDAY, October 24

"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

Tuesday/Wednesday Edition
12th Anniversary of the Official Newspaper of the
Annual Canadian Cardiovascular Congress
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INFO CARDIO

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State-of-the-Art Lecture: Prof. John Cleland's "Trials and Tribulations"

Researchers must tread carefully in the execution of randomized clinical trials, as attested by Prof. John Cleland, this year's State-of-the-Art lecturer and trialist *par excellence* and Foundation Chair of Cardiology, University of Hull, UK.

"Randomized clinical trials are the worst form of evidence—apart from everything else that has been tried," he noted. For example, patient selection alone is just one element in a long list of confounders that can end up skewing clinical trial results and their interpretation. Take trials involving patients with heart failure (HF) but with preserved systolic function (so-called "diastolic dysfunction"). As Prof. Cleland showed, patients with diastolic dysfunction frequently do not have HF at all but symptoms caused by some other underlying medical condition.

Indeed, until fairly recently, patients enrolled in HF trials were entered on the basis of clinical symptoms alone. Now that trialists are required to confirm the diagnosis of HF by measuring ejection fraction, "this led to a law of unintended consequences," explained Prof. Cleland, as at any arbitrary cut point based on ejection fraction will exclude disproportionate numbers of women and the elderly, the latter because there are more women than men who live to a very old age.

"We're also missing a lot of HF," Prof. Cleland remarked. In the SPORTIF trial, for example,

Conférence sur l'état actuel des connaissances : les tribulations du P^r John Cleland

Les chercheurs doivent avancer à pas feutrés dans l'exécution des essais cliniques randomisés, souligne le P^r John Cleland, auteur de la Conférence sur l'état actuel des connaissances de cette année, chercheur clinicien par excellence et directeur de la cardiologie, *University of Hull*, Royaume-Uni.

« Les essais cliniques randomisés constituent la pire preuve imaginable, sans compter tout le reste qui a été essayé », lance-t-il. Par exemple, la sélection des patients n'est que l'un des nombreux facteurs de confusion qui peuvent fausser les résultats d'un essai clinique et leur interprétation. Prenons l'exemple des essais portant sur des patients souffrant d'insuffisance cardiaque (IC) à fonction systolique conservée (la prétendue « dysfonction diastolique »). Comme l'a démontré le P^r Cleland, il est fréquent que les patients présentant une dysfonction diastolique ne souffrent pas du tout d'IC et que leurs symptômes soient plutôt imputables à une autre maladie sous-jacente quelconque.

En effet, il n'y a pas si longtemps, la sélection des sujets d'une étude clinique sur l'IC reposait uniquement sur les symptômes cliniques. L'obligation actuelle pour les chercheurs de confirmer le diagnostic de l'IC en mesurant la fraction d'éjection s'est soldée par « la loi des conséquences involontaires », explique le P^r Cleland, car tout seuil arbitraire fondé sur la fraction d'éjection exclut un nombre disproportionné de femmes et de personnes âgées, les femmes étant plus nombreuses que les hommes à vivre jusqu'à un âge très avancé.

« Nous ratons aussi beaucoup de cas d'IC », fait remarquer le P^r Cleland. Lors de l'essai SPORTIF, par

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which involved approximately 7000 participants, patients who were taking a loop diuretic even though they had not been diagnosed with left ventricular dysfunction (LVD) ended up having a worse outcome than those with LVD—a sure sign that they did have HF, but it was simply missed, he told listeners.

In CHARM-Preserved, HF patients with preserved LV systolic function did benefit to a certain extent from angiotensin II receptor blockade but because their enrolment was again made on a clinical basis, the benefit seen in this arm of CHARM was considerably lower than that seen in the other two arms—“and I would strongly suspect that as much as one-third of patients in CHARM-Preserved didn’t have HF, which is perhaps why the benefits were less in that population,” he commented.

Prof. Cleland also questioned the wisdom of using hospitalization as an outcome measure in HF trials, given that most patients involved in these trials die a short while later. “If mortality is going to happen down the road, why soften your end point?” Prof. Cleland mused. “Hospitalization is not a hard outcome.”

Stratifying HF patients with diastolic dysfunction into different risk categories has often proved unsuccessful using traditional measures such as those provided by ECG. On the other hand, in the PEP-CHF trial carried out in patients over the age of 70, what did help was measurement of NT-proBNP levels, where those in the highest quartile had a significantly higher annual incidence of death or HF-related hospitalization than those in the lower quintiles of NT-proBNP. This observation was corroborated by COMET study data in which HF patients with the lowest levels of NT-proBNP had less than a 1% per year risk of dying of progressive HF—“so if you are designing a treatment for worsening HF, this is the tool for you,” Prof. Cleland confirmed.

Patients whose HF is very stable are also unlikely to show much change in their symptoms with any intervention, while those who are too sick may well be beyond the help of any intervention as well. The wrong dose, the wrong dosage schedule or an inappropriate comparator can also falsify results of a clinical trial, as Prof. Cleland pointed out. Trials can also be too short to show an advantage for a given intervention that may have appeared had the trial been of longer duration. But they can also go on for too long, at which point results will be confounded by patients who eventually cross over to the experimental arm, wiping out any real differences if they once existed between the interventions being compared.

Clinical trial enrolment can also be too high. According to Prof. Cleland, “If you need 10,000 patients to show a difference [between interventions], your treatment is ineffective by definition because you needed 10,000 patients to show a difference. Large trials should not be considered positive just because they observed a statistical difference.” □

exemple, qui regroupait environ 7000 participants, les résultats ont finalement été pires chez les patients qui prenaient un diurétique de l'anse sans avoir reçu de diagnostic de dysfonction ventriculaire gauche (DVG) que chez les patients présentant une DVG – ce qui démontre sans l'ombre d'un doute qu'ils souffraient d'IC, mais c'est passé inaperçu, explique-t-il.

Lors de l'essai CHARM-Preserved, les insuffisants cardiaques dont la fonction systolique du VG était intacte ont bénéficié du blocage des récepteurs de l'angiotensine II dans une certaine mesure mais, comme le recrutement était là encore fondé sur des critères cliniques, le bénéfice observé dans ce groupe de CHARM a été considérablement moins marqué que le bénéfice observé dans les deux autres groupes – « et je soupçonne fortement que jusqu'au tiers des sujets de CHARM-Preserved ne souffraient pas d'IC, ce qui pourrait expliquer que les bienfaits aient été moindres dans cette population », enchaîne-t-il.

Le P^r Cleland se demande aussi s'il est sage d'utiliser l'hospitalisation comme paramètre d'évaluation dans les essais sur l'IC, compte tenu du fait que la plupart des sujets de ces essais meurent peu de temps après. « Si la mort est sur le point de survenir, pourquoi relâcher les critères?, s'interroge le P^r Cleland d'un air perplexe. L'hospitalisation n'est pas un paramètre majeur. »

Il a souvent été démontré que la stratification des insuffisants cardiaques présentant une dysfonction diastolique en différentes catégories de risque est inefficace si l'on a recours à des critères traditionnels comme l'ECG. Par contre, lors de l'essai PEP-CHF réalisé chez des patients de plus de 70 ans, le dosage du NT-proBNP s'est révélé fort utile, la mortalité ou la fréquence des hospitalisations pour cause d'IC ayant été, par année, beaucoup plus élevées chez les patients dont le taux de NT-proBNP se situait dans le quartile le plus élevé que chez les patients dont le taux se situait dans les autres quintiles. Cette observation a été corroborée par les données de l'essai COMET lors duquel les insuffisants cardiaques dont le taux de NT-proBNP était parmi les plus faibles étaient exposés à un risque annuel inférieur à 1 % de mortalité par progression de l'IC – « de sorte que si vous concevez un traitement pour faire échec à l'aggravation de l'IC, c'est l'outil idéal pour vous », confirme le P^r Cleland.

Chez les patients dont l'IC est très stable, il est aussi improbable que les symptômes évoluent, peu importe l'intervention évaluée, alors que ceux qui sont trop malades ne bénéficieront probablement d'aucune intervention. La mauvaise dose, le mauvais calendrier posologique ou un agent de comparaison inapproprié sont autant de facteurs qui peuvent fausser les résultats d'un essai clinique, précise le P^r Cleland. Un essai est parfois trop bref pour montrer qu'une intervention est bénéfique, et peut-être ce bénéfice se serait-il manifesté si l'essai avait duré plus longtemps. À l'inverse, si l'essai est trop long, le passage des patients dans le groupe expérimental après un certain temps finira par confondre les résultats, neutralisant ainsi toute différence réelle, si différence il y avait entre les interventions comparées.

Le nombre de sujets est parfois trop élevé, poursuit le P^r Cleland. « Si vous avez besoin de 10 000 patients pour objectiver une différence [entre deux interventions], votre traitement est inefficace par définition puisqu'il vous a fallu 10 000 patients pour faire ressortir une différence! Un essai de grande envergure ne doit pas être considéré comme positif uniquement parce qu'il met une différence statistique en évidence », conclut-il. □

Heart failure recommendations: managing new challenges

Uncertainties in the management of heart failure will be singled out during the consensus conference symposium this year to make sure last year's recommendations are implemented into everyday practice.

“We’ll be highlighting key recommendations from 2007 based on feedback from the target audience who identified troublesome areas in the management of heart failure,” confirms CCS vice-chair and consensus conference co-chair Dr. Malcolm Arnold, Professor of Medicine and Director of Research Affairs (Cardiology), University of Western Ontario, London. The first troublesome area is what to do with heart failure medications when a patient has an intercurrent illness such as diabetes. “We’ll be strongly emphasizing the importance of treating diabetes aggressively because diabetes creates adverse outcomes in heart failure,” Dr. Arnold reveals.

Indeed, the choice of medications for diabetic patients with heart failure is the same as it is for diabetic patients without heart failure, he adds. The “only caveat” is with the thiazolidinedione insulin-sensitizing drug class which in some patients may increase the risk of heart failure. Nevertheless, provided patients are monitored closely, “we recommend all standard medications generally be used to aggressively treat diabetes in heart failure as that will help the heart failure in the long run,” Dr. Arnold states.

In addition, patients with diabetes and heart failure often have some renal dysfunction, the presence of which may prompt some physicians to decrease the dose of either the ACE inhibitor or the angiotensin II receptor blocker (ARB) the patient is on. These two classes of medications are, however, extremely important in the management of heart failure, as Dr. Arnold stresses, and should be used even if a patient's serum creatinine is 200 µmol/L or less. He also emphasizes that an initial increase in the serum creatinine of up to 30%, which is to be expected on introduction of these agents, is “no reason to stop the medication prematurely.”

Both he and fellow co-chairs Dr. Jonathan Howlett, Medical Director, Cardiac Transplant and Heart Function Clinic, Queen Elizabeth II Health Sciences Centre, and Associate Professor of Medicine, Dalhousie University, Halifax; and Dr. Robert McKelvie, Medical Director, Heart Function Clinic, Hamilton Health Sciences Corporation and Professor of Medicine, McMaster University, will also make strong



Dr. Malcolm Arnold

recommendations about the use of beta blockers, especially in patients with acute heart failure. “Once they’ve stabilized, we want them on a low dose of a beta blocker as soon as possible and we recommend a beta blocker be started prior to hospital discharge,” Dr. Arnold explains. For patients with an intercurrent illness such as pneumonia that may aggravate the heart failure, “again, the beta blocker should generally be continued at its previous dose but if physicians want to decrease the dose, they need to re-uptitrate it to the previous dose as soon as the patient is stable.”

Patients who are in acute heart failure and who are very ill also need aggressive treatment early on with close monitoring, and early referral to a centre with more resources and specialized staff should be considered “sooner rather than later in the sickest patients,” he adds.

The use of biomarkers—notably B-type natriuretic peptide (BNP), a protein produced by the ventricles of the heart, has proved challenging for some physicians as well, Dr. Arnold notes. However, there is “clear evidence that BNP does help make an accurate diagnosis of heart failure whenever physicians are in doubt as to whether or not symptoms are heart failure, or due to COPD, or pneumonia or a pulmonary embolism, for example.” According to Dr. Arnold, BNP should be used in cases of uncertainty, although unfortunately, BNP determinations are still not available in many Canadian centres. However, if they are, “it will be helpful both to shorten the time to the diagnosis and to direct optimal therapy in hospital.”

Recommendations on the management of heart failure issued last year built upon those made in the 2006 paper which were more broad-based and general. The 2007 recommendations targeted more specific areas of interest for practicing physicians but in addition, they placed considerable emphasis on the importance of preventing heart failure with early use of ACE inhibitors and beta blockers in asymptomatic patients with left ventricular dysfunction. Currently, consensus panel members are finishing the 2008 recommendation paper which will go further to address when to suspect, how to diagnosis and how to treat specific cardiomyopathies.

The consensus conference on heart failure recommendations takes place Tuesday, October 23, at 14:00-15:00, in Room 2000A-B, Level 2. □



Late-Breakers: Canadian presence on the international scene

Canadian participation in international trials of significant stature, along with those which are uniquely Canadian, will be featured during the final late-breaking clinical trials session.

- *Congestive heart failure assessment and management in primary care (CHAMP-C)*: CHAMP-C was a regional effort involving 53 family practitioners (FPs) who collectively managed 176 community-based heart failure patients. Practitioners were randomized to an intervention in which a nurse specializing in heart failure care would review each patient's current management strategies prior to each office visit and, if necessary, recommend changes to their medical regimen or to usual care. Standardized care maps that charted recommendations on how to optimize medical therapy were developed and used for each heart failure patient in each of the FPs' practices but the FPs were the ones who made the recommended changes. They also attended three CME programs on heart failure management during the intervention. Investigators found there was a significant improvement from baseline to month 6 in the intervention group in terms of achieving optimal use and doses of heart failure medication, a change that was maintained at month 12 vs. no change in medical care in the usual-care group. "Heart failure clinics are great but they aren't accessible for all patients," remarks principal investigator Dr. Catherine Demers, McMaster University, Hamilton, "and we believe the same approach is widely applicable to other regions as well."
- *Effect of homocysteine-lowering B vitamins on carotid atherosclerosis. The Homocysteine and Atherosclerosis Reduction Trial (HART)*: Last year, Hamilton-based investigators presented the parent HOPE-2 study in which the effect of B vitamins on clinical CVD events was evaluated. As they reported last year, combined daily use of 2.5 mg of folic acid, 50 mg of vitamin B₆ and 1 mg of vitamin B₁₂ over a treatment interval of five years had no beneficial influence on major vascular events in a high-risk vascular disease population. It was postulated that the use of this vitamin cocktail, which reduces plasma homocysteine levels by 25% to 30%, would significantly reduce major vascular events attributable to high homocysteine levels compared with placebo. This year, investigators under Dr. Eva Lonn, Professor of Medicine (Cardiology), McMaster University, will present HART results in which the effect of the same vitamin cocktail on change in the mean maximal intima thickness across 12 carotid artery segments will be compared against the same end point in placebo controls. HART was a substudy of the HOPE-2 trial in which 900 participants underwent yearly carotid B-mode ultrasound examinations over five years of follow-up to arrive at the primary end point.
- *The impact of a multidisciplinary, information technology-supported program on blood pressure control in primary care (the LOYAL study)*: Researchers at Université Laval developed a computerized, telephone-based voice-activated response system to enhance a multidisciplinary support program that helps patients monitor their own blood pressure (BP) and compliance with their medication and keeps nurses, physicians and pharmacists all informed about patient compliance and BP control while respecting patient confidentiality. Some 500 patients were recruited for the study, half of whom will be involved in the information technology program plus usual care and the other to usual care alone. "We hypothesize that the program will improve BP control by helping patients take their medication properly and by helping doctors ensure that the best strength and kinds of medication are used to control high BP," lead investigators write, "and we believe the program will achieve this by helping to improve communication between patients and healthcare providers."
- *Catheter ablation vs. antiarrhythmic drugs for paroxysmal atrial fibrillation (A4): A multicentre randomized trial*: A4 randomized patients with symptomatic, paroxysmal atrial fibrillation (AF) lasting at least six months with at least two episodes per month to receive either antiarrhythmic drug therapy

or ablation. Patients also had to be resistant to at least one class I or III antiarrhythmic drug, and the majority were on anticoagulation therapy. The primary end point was AF recurrence lasting more than three minutes. After a mean of 1.8 ablations per patient in the ablation group, 75% were free of arrhythmia recurrence at one year's follow-up vs. 7% of the antiarrhythmic drug group. Importantly as well, anticoagulation therapy was discontinued in 60% of the ablation group vs. 25% in the antiarrhythmic drug group and most quality-of-life indices were significantly better in the ablation group as well. These findings suggest that ablation produces better outcomes in patients with symptomatic paroxysmal AF who have failed at least one antiarrhythmic treatment strategy.

- *The Simplified Treatment Intervention to Control Hypertension (STITCH) Trial: A cluster randomized controlled trial of a step-care algorithm using initial fixed-dose combination therapy for the management of hypertension*: One strategy to improve BP control is to simplify the treatment regimen and enhance adherence. STITCH was designed to determine whether implementation of a simplified treatment algorithm consistent with the Canadian Hypertension Education Program (CHEP) guidelines but using a step-care approach might improve the management of hypertension. The simplified treatment algorithm incorporated early use of a fixed-dose combination strategy. The primary outcome of the trial was the proportion of patients who achieved target BP goals of <140/90 mm Hg at six months. The principal investigator of STITCH was Dr. Ross Feldman, Robarts Research Institute, London.
- *Effectiveness of optimal medical therapy in the COURAGE trial: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)*: COURAGE compared a strategy of PCI plus optimal medical therapy (OMT) vs. OMT alone in patients with stable coronary artery disease (CAD). Patients with one-, two-, or three-vessel disease (>70% visual stenosis of proximal segment), with anatomy suitable for PCI, and CCS class I-III angina were enrolled in the study. At a mean follow-up of 4.6 years, there was no difference in the rate of freedom from death from any cause or nonfatal MI between the PCI and OMT-alone groups (19.0% vs. 18.5%, respectively). Nor were there any differences in the individual rates of all-cause mortality, MI, stroke, or hospitalization for ACS. Yet differences were seen in revascularization procedures needed in the PCI group, which were significantly lower than rates in the OMT group; the PCI group was also more likely to remain free from angina than the OMT group. Findings from COURAGE reinforce existing clinical practice guidelines, which state that PCI can be safely deferred in patients with stable CAD, even in those with extensive multivessel involvement, and provided patients receive OMT.
- *The effect of the novel antioxidant AGI-1067 (succinobucol) on glycaemic control, new-onset diabetes and clinical events in patients with a recent acute coronary syndrome: The Aggressive Reduction of Inflammation Stops Events Study (ARISE)*: ARISE evaluated a new antioxidant agent, succinobucol, vs. placebo in recent ACS patients. With over 3,000 patients in each arm, there was no difference in the primary composite end point of CV death, cardiac arrest, MI, stroke, unstable angina or coronary revascularization vs. placebo at two years. However, the incidence of CV death, cardiac arrest, MI, or stroke was lower with active treatment than placebo, as was the incidence of new-onset diabetes. In contrast, heart failure occurred more frequently in the succinobucol arm, although the incidence of serious adverse events occurred with similar frequency between the two arms. Investigators suggested that further research on the novel compound is called for.

The late-breaking and featured clinical trials session will take place Wednesday, October 23, 9:00-11:00 in Room 2000A-B on Level 2. □

Canadian Heart Health Survey: focus on hypertension

Results from a new hypertension survey carried out in Ontario indicate that physicians are doing a far better job at detecting and treating hypertensive patients than they did 15 years ago.

When the Canadian Heart Health Survey was carried out in the early 1990s, the overall prevalence of hypertension in Canada was about 20% and rates in older adults were much higher. "With increasing obesity in Canada, we thought the prevalence of hypertension today might be higher," admits Dr. Frans Leenen, Director, Hypertension Unit, University of Ottawa Heart Institute, and one of the principal investigators of the survey. His co-investigator is university colleague Dr. George Fodor. The survey itself was sponsored by the Heart and Stroke Foundation of Ontario and was undertaken in collaboration with Statistics Canada.

Findings from the survey indicate that the prevalence of hypertension hasn't changed all that much from earlier days, he notes. What is different, however, is how aware both physicians and the public are of hypertension. Today, patients are aware of the risk of hypertension and physicians are diagnosing it at far higher rates than those recorded in the Canada Heart Health Survey.

More importantly, dramatically more patients are receiving treatment for elevated blood pressure and many more are at goal than the often-cited 16% of Canadians who were treated and at goal based on the earlier survey. "The whole

playing field has changed dramatically; there's much more awareness of the importance of hypertension as a risk factor for cardiovascular disease (CVD) and both the public and the medical community are more in tune with prevention," Dr. Leenen tells *INFO-Cardio*.

Perhaps as importantly, there are far more antihypertensive strategies to choose from now, and they are better tolerated than the older classes of diuretics and beta blockers, which was more or less the extent of options available to most patients in the early 1990s.

"Physicians generally think they are doing a good job but if you don't measure your efforts, you don't know for sure," Dr. Leenen remarks. "What this survey tells us is that management of hypertension has dramatically improved to the point where the majority of patients with diagnosed hypertension are at treatment goals and the number of people who are unaware they are hypertensive has dramatically decreased as well. So I would say that at the moment, the medical community in Ontario are doing a very good job at managing hypertension—in fact, probably about the best in the world."

Whether the rest of the country measures up to Ontario's performance will be the subject of another Canada-wide hypertension survey, now in the early stages of implementation. □

CAIC/CCS Consensus Conference: recommendations on DES, antiplatelet therapy

Important recommendations on the use of drug-eluting stents (DES) developed by the Canadian Association of Interventional Cardiology and the CCS will be featured during the Consensus Conference discussion, held this year on Tuesday, October 23, at 14:00-15:00, in Room 2000A-B on Level 2.

As Dr. Michael Love, interventional cardiologist and Assistant Professor of Medicine, Dalhousie University, Halifax, and colleagues write, reports documenting late stent thrombotic events have raised concerns about the safety of DES and their role in the management of coronary artery disease (CAD). These concerns prompted members of both organizations to review available evidence relating to DES thrombosis and to develop recommendations about their use, as well as the appropriate use of antiplatelet therapy in the context of DES.

As published in the *Canadian Journal of Cardiology* (February 2007), here are the key recommendations from that joint statement.

Recommendations for DES use

Physicians should always carefully consider the benefits and risks on an individual patient basis when choosing between DES and BMS (bare metal stents).

Physicians should weigh the benefits and risks especially carefully when considering DES use for unapproved (off-label) indications. While many of these

patients may benefit from the significant reduction in restenosis and the need for repeat revascularization through DES implantation, it may be at the expense of a higher risk of very late stent thrombosis.

Interventional cardiologists should be meticulous in their stent deployment techniques. High-pressure balloon inflation should be considered to optimize DES deployment, and intravascular ultrasound should be considered when the adequacy of deployment is uncertain.

DES should not be deployed in patients who are unable to comply with or tolerate prolonged dual antiplatelet therapy. Reasons may include bleeding risk, side effects, cost issues or a history of noncompliance with other medical interventions. In some situations, the obstacle(s) to prolonged therapy may be overcome with additional education and financial support. However, it is the responsibility of the referring physician, the interventional cardiologist and other members of the health care team to assess the issue carefully via direct questioning and to communicate any concerns actively before a decision is taken to implant a DES.

DES should not be deployed in patients who have known upcoming surgical procedures for which dual antiplatelet therapy will need to be discontinued.

Recommendations for antiplatelet therapy

It is recommended that all patients treated with DES

should remain on dual antiplatelet therapy with ASA 81 mg to 325 mg daily and clopidogrel 75 mg daily for at least 12 months.

Even longer-term dual antiplatelet therapy should be considered in patients treated with DES who are thought to be at higher risk for very late stent thrombosis or in whom stent thrombosis is likely to have fatal consequences (e.g. multiple stents, bifurcation stenting or left main stem intervention). Many patients will likely require long-term dual antiplatelet therapy; however, the exact duration of treatment should be determined on an individual patient basis after careful consideration of the competing risks of stent thrombosis and bleeding.

Physicians must counsel their patients in clear terms against premature discontinuation of dual antiplatelet therapy. If temporary or permanent premature discontinuation becomes necessary, it must be done in consultation with an interventional cardiologist. If discontinuation of both antiplatelet agents is required in a patient who is thought to be at high risk of stent thrombosis or in whom stent thrombosis would be catastrophic, consideration should be given to temporary anticoagulation with heparin.

There is no evidence to support restarting clopidogrel in patients who have completed their course of dual antiplatelet therapy and remained event-free on ASA monotherapy. □

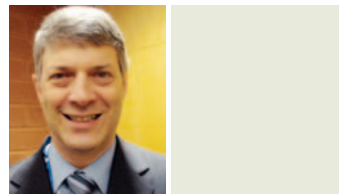
DELEGATES' CORNER

Question: What makes the Canadian Cardiovascular Congress special for you?



Dr. Malcolm Arnold: The CCC is special in that it brings together so many different people from across Canada. It's a wonderful opportunity to learn about things that I don't practice everyday; it's a wonderful opportunity to hear outstanding speakers from Canada and internationally; and it's a wonderful opportunity just to network with friends and colleagues and to learn things that I can take back into my regular practice. So the CCC combines wonderful new science with up-to-date education and that combination is a really winning one.

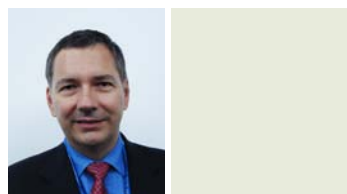
Dr. Lawrence Leiter: I think the CCC meeting is a great meeting because it involves not just cardiology but also associated specialties. I also think they've done a really great job over the past few years to get into all areas of cardiovascular medicine and include other specialties beyond cardiology and CV surgery, such as endocrinologists, nephrologists and other people who are all interested in reducing risk for our patients.



Dr. Jacques Genest, Jr.: It's such a multi-disciplinary meeting. We are grouping 13 organizations in the cardiovascular field here at the CCC, so all the stakeholders are here. It's a great place of learning, a great place for networking and it's also fun. So I enjoy it thoroughly.



Dr. George Honos: The CCC is the largest yearly occasion where all specialists and individuals dealing with cardiovascular health issues in Canada get a chance to meet under the same roof, exchange ideas and collegiality, getting to know what each and everyone is involved with in terms of research, and essentially doing what we can to promote the health of Canadians in the field of cardiovascular diseases.



Dr. Gilles Dagenais: First, that it's here in Quebec City this year, which is lovely, but it's always a wonderful opportunity to meet and network with others in the field of cardiovascular medicine and learn from everyone's experience. The meeting is also very well organized and everything is going extremely well and as planned.



Dr. Michael Baird: I especially like the venue, but whether it's here or Vancouver or Montreal or Toronto, the venue is always lovely. The science is good, as is meeting old friends and colleagues, of course.



SCORE Canada



Dr. Guy Tremblay

After four years of development, the Canadian Cardiovascular Coalition will launch SCORE Canada during a symposium Tuesday, October 23, 11:00 (Room 202, Level 2). SCORE Canada is a relatively simple system for scoring cardiovascular (CV) risk in asymptomatic individuals. It is based on Canadian data and provides a major new tool for primary care physicians to identify patients who need risk reduction and what the targets should be. It collates recommendations from a broad array of Canadian medical organizations, including the CCS, to provide a unified message.

"The problem SCORE Canada addresses is identifying those at high risk but do not yet have CV disease or diabetes. SCORE Canada should not be used in patients over the age of 70 or in patients who already have very high levels of a single risk factor, such as a total cholesterol (TC) of 8 mmol/L or greater. It is designed to identify the patients we are missing now," emphasizes Dr. Guy Tremblay, Chair, SCORE Canada, and a cardiologist at *Université Laval*, Quebec City.

There are a number of risk scoring systems available, but many, including Framingham, address only risks. SCORE Canada, based on a widely used risk engine in Europe called SCORE, is designed to address risk of any fatal CV event, including stroke. SCORE Canada was based completely on Canadian statistics. The model quickly produces a 10-year percentage risk of a fatal CV disease by plugging in age, gender, smoking status, systolic blood pressure, and TC:HDL-C ratio.

Dr. Tremblay states, "In the past, different medical groups had produced different goals. The Canadian Vascular Coalition, which includes representatives from a broad array of groups, such as the Canadian Hypertension Society and the Canadian Diabetes Society, has worked together to provide one message: the principle is that if you know your risk and know your target, you can act to make a change." □

TSUNAMI, CHAOS AND GLOBAL HEART



Dr. Vivian Rambihar, recipient of the Segall Award of Merit, and Dr. Sherryn Rambihar are co-authors of the book "Tsunami, Chaos and Global Heart: Using Complexity Science to Rethink and Make a Better World."

The book is available at no cost at femmefractal.com or by simply Googling key words like tsunami, chaos, global or heart.





Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Closing the Care Gap Between Guidelines and Practice

Quebec City – Aggressive LDL-C lowering has been widely accepted by Canadian lipid experts as the most effective strategy by far to lower cardiovascular (CV) risk in high-risk patients. Yet studies such as CALIPSO and GUIDE showed that many patients, especially high-risk patients such as those with diabetes, are not at LDL-C goals and more effective strategies are clearly needed to close the care gap. Guidelines indicate that physicians should try to achieve LDL-C targets using statin monotherapy first but real obstacles often mitigate against achieving these goals. An alternative strategy, recommended by lipid experts as well, is to use the combination of a cholesterol absorption inhibitor plus a statin, which lowers LDL-C effectively and is often better tolerated than high-dose statin therapy.

Québec – Il est largement admis par les experts en lipides du Canada que la baisse vigoureuse du taux de C-LDL est de loin la stratégie la plus efficace pour réduire le risque cardiovasculaire (CV) chez les patients à risque élevé. Pourtant, des études comme CALIPSO et GUIDE ont révélé que de nombreux patients, surtout les patients à risque élevé comme les diabétiques, n'atteignent pas les taux cibles de C-LDL. Il est donc clair que nous avons besoin de stratégies plus efficaces pour combler cette lacune clinique. Selon les lignes directrices, le médecin doit d'abord tenter de parvenir au taux cible de C-LDL à l'aide d'une statine en monothérapie, mais il est fréquent que divers obstacles réels l'en empêchent. L'une des solutions de rechange – également recommandée par les experts – consiste à combiner un inhibiteur de l'absorption du cholestérol et une statine; cette association permet de réduire le taux de C-LDL efficacement et est souvent mieux tolérée qu'une statine à forte dose.

By: Pam Harrison

As Dr. Jacques Genest, Jr., Director of Cardiology, MUHC-Royal Victoria Hospital, Montreal, notes, Canadian Lipid Guidelines now indicate high-risk patients, including most patients with diabetes, need to achieve a LDL-C target of <2.0 mmol/L. This new target was chosen as the primary lipid-lowering goal as it has been consistently shown that intensive lipid-lowering provides additional cardiovascular (CV) risk reduction in high-risk patients. Once this new, low LDL-C target is met, attempts should be made to reduce the total cholesterol:HDL-C ratio to <4.0, again in high-risk patients, Dr. Genest states.

CALIPSO

However, as evidence continues to show, there is often a large gap between recommended LDL-C target levels and what is achieved in clinical practice. One such study showing a significant care gap was the Canadian Lipid Study—Observational (CALIPSO) (*Can J Cardiol* 2005;21:1187-93).

CALIPSO was a cross-sectional study involving a number of physicians in Canada. Each physician enrolled 15 patients who had been diagnosed with hypercholesterolemia and who had been taking a statin for at least eight weeks. Out of the 3721 patients enrolled in CALIPSO, 46.4% had established CV disease, 33.9% had diabetes and 59.5% had hypertension. Patients had also been treated with statin therapy for an average of 4.3 years and 24.2% were on high-dose statin therapy.

Despite this, 27.2% of patients overall, and 36.4% of those judged to be high-risk patients, were not at the then-LDL-C target of <2.5 mmol/L. Had that LDL-C target been at the currently recommended target of <2.0 mmol/L, “then approximately 70% of patients would not be at target,” Dr. Genest observes. A national chart audit of 2473 Canadian patients with type 2 diabetes showed that fewer than half of them were receiving any lipid-lowering therapy at all.

GUIDE

More recently, the GUIDE experience (Guidelines Based Undertaking for Improvement in Dyslipidemia), of which Dr. Anatoly Langer, University of Toronto, is co-investigator, again showed that a “significant care gap” continues to exist in the management of high-risk patients both with and without diabetes. As part of a quality enhancement research initiative, 224 primary care physicians and specialists from Canada were asked to enrol 2567 high-risk patients with a LDL-C above the recommended target despite being on statin therapy.

Physicians then followed an algorithm of increasing tolerated statin therapy or adding the cholesterol absorption inhibitor ezetimibe to achieve an LDL-C target of <2.5 mmol/L in those enrolled prior to September 2006 or <2.0 mmol/L in patients enrolled thereafter. Patients were then evaluated three times over a period of 26 weeks. At baseline, no patients with or without diabetes were at LDL target.

By the fourth visit, 64% of patients with diabetes were at target (median LDL-C 2.1 mmol/L) but for those without diabetes, only 2% were at target (median LDL-C 2.3 mmol/L) at the same assessment point. From these findings, the authors concluded that treatment of hypercholesterolemia in high-risk patients, including those with diabetes, needs to be “more intensive” and in accordance with 2006 CCS guidelines.

ACTFAST

One strategy that may help get more patients to goal is that adopted by ACTFAST investigators in which a flexible starting dose of atorvastatin, plus one uptitration if needed, helped 81% of statin-naïve patients reach their target. However, only 61% of ACTFAST patients who had previously received statin therapy achieved the same LDL-C goal. These observations clearly demonstrate that a more effective strategy to lower LDL-C to target is often needed and combination therapy may well be the final solution.

Overcoming Barriers

As observes Dr. Milan Gupta, Assistant Clinical Professor of Medicine, McMaster University, Hamilton, there are a number of reasons why patients fail to achieve LDL-C targets, not the least of which are concerns about statin safety. Even though data from clinical trials and meta-analyses have consistently affirmed the safety of currently available statins, “some physicians are reluctant to go to the higher doses,” Dr. Gupta notes, largely out of concern that patients will not tolerate higher doses well. (It is known, for example, that muscle symptoms are more likely to occur at higher doses of statin therapy).

Then there are “system” barriers that make uptitration of a statin difficult, he added. For example, an estimated 5 million Canadians do not even have a family physician, according to a new poll by the College of Family Physicians of Canada, so accessing a family practitioner is not possible for many patients, let alone the need to make repeat visits. It is also difficult to bring patients back to the office solely to check their cholesterol levels and, if not at target, increase the dose of the statin, as family practitioners are all busy and may be inundated by more urgent medical needs.

For these reasons, Dr. Gupta favours a “combination” strategy from the outset, one in which ezetimibe, which inhibits cholesterol absorption, is used together with any statin. “The combination approach where we use ezetimibe together with low-dose statin therapy provides the same degree of LDL-C reduction as using high-dose statin therapy,” states Dr. Gupta, providing on average an additional 20% reduction in LDL-C.

Based on results from a number of phase III trials, ezetimibe 10 mg and simvastatin 10 mg, for example, achieved the same degree of LDL-C reduction as maximal-dose simvastatin. Likewise, ezetimibe 10 mg and atorvastatin 10 mg achieved very similar reductions in LDL-C as would be expected if using atorvastatin 80 mg. For high-risk patients such as the South Asians who are at increased risk for CV events compared with other ethnic groups, experts suggest that the combination of ezetimibe and rosuvastatin, both given at a dose of 10 mg, appears to work particularly well.

“For physicians who are uncomfortable with high doses of statins, I would propose that combination therapy is the right approach,” Dr. Gupta concludes. □

Based on:

“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.

Please plan to attend:

“Pharmacological Approaches to Reaching LDL Targets – Statin Monotherapy Achieves Canadian Lipid Targets in Most Patients”/ “Combination Therapy Achieves Lipid Targets with Greater Ease.” Wednesday, October 24, 7:20, during the symposium “Expert Opinions: Current Issues in Cardiology,” 7:00-9:00, Room 200B, Level 2. *Presenter:* Dr. Milan Gupta

AND

CCC #641. Langer A, Bissonnette S, Goodman SG, Tan M, Casanova A, Leiter L. Dyslipidemia management in patients with diabetes: the Guidelines-based Undertaking for Improvement in Dyslipidemia-related Events (GUIDE) experience. Tuesday, October 23, 10:00-12:30, Community Forum.

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 (RCPC).

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Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

The Need for Novel Therapies in Acute Heart Failure

Quebec City - There is a dearth of agents offering meaningful symptomatic relief and improvements in clinical outcomes in acute heart failure (HF). An area of ongoing investigation is the clinical value of administering exogenous brain or B-type natriuretic peptide (BNP), which has vasodilatory as well as natriuretic properties. At a session on October 24, an expert panel will examine HF pathophysiology and the evidence for using a recombinant BNP, nesiritide; and will explain the rationale behind the ASCEND trial. Several Canadian substudies will augment this large global research effort, which is aimed at confirming whether the agent reduces hospitalization rates and mortality as well as dyspnea.

Québec – Dans l'insuffisance cardiaque (IC) aiguë, les agents qui soulagent les symptômes et qui améliorent les résultats cliniques de façon notable font cruellement défaut. L'utilité clinique d'un traitement par le peptide natriurétique de type B (BNP) exogène – qui est doté de propriétés vasodilatatrices et natriurétiques – est actuellement à l'étude. Dans le cadre d'une séance qui aura lieu le 24 octobre, un groupe d'experts se penchera sur la physiopathologie de l'IC et sur les données militent en faveur de l'utilisation d'un BNP recombinant, le nesiritide; on y expliquera aussi le bien-fondé de l'étude ASCEND. Plusieurs études satellites réalisées au Canada viendront étoffer ce projet de recherche d'envergure mondiale, dont l'objectif est de confirmer si cet agent diminue le taux d'hospitalisation, la mortalité et la dyspnée.

By: Carol Duthie

The burden of heart failure (HF) is huge and increasing owing to longer natural lifespans and enhanced survival after acute coronary events, according to Dr. Paul Armstrong, Professor of Medicine and Director, Virtual Coordinating Center for Global Collaborative Cardiovascular Research, University of Alberta.

Acute HF is an area of enormous unmet medical need. "While extensive research has led to tremendous benefits and advances in the treatment of chronic HF, with improvements in outcomes, that's not true in acute HF. The mortality rates, complications and burden of acutely decompensated HF have either not changed or have worsened in the last 25 years," affirms Dr. Jonathan Howlett, Associate Professor of Medicine, Dalhousie University, and Medical Director, Cardiac Transplant and Heart Function Clinic, Queen Elizabeth II Health Sciences Centre, Halifax. According to recent research, some 16% of Canadian patients die during their first acute episode of HF; and those who survive frequently require readmission to hospital when they experience an exacerbation of their condition. Readmission for HF is one of the most common and costly health problems in Canada and other western nations. Repeated hospitalization is associated with poor outcome.

Initial treatment in acute HF is aimed at achieving hemodynamic stability, oxygen delivery to the tissues, and symptomatic improvement. According to current HF treatment guidelines, intravenous diuretics are standard first-line agents for patients with congestion; vasodilators may be employed for patients with dyspnea at rest or in the initial management of those with systolic blood pressure higher than 100 mm Hg. "There are some other drugs—for example, the

so-called positive inotropic agents—that we have used but many [have been abandoned] because while they initially appeared promising, they ultimately led to harm. For example, agents that strengthen the force of the heart but also create disturbances of rhythm...So there is room for new therapies," observes Dr. Armstrong.

Natriuretic Peptides in Heart Failure

Release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) is a physiologic response to atrial and ventricular strain in HF. "[The circulatory system] has been characterized as a battlefield...where there are some substances emitted by organ systems that are protective and some that end up being harmful. The battlefield is very much populated by the natriuretic peptides, which have two important characteristics: they play a vasodilating and facilitating role in terms of heart function, and they may well enhance the way the kidneys work and the body clears fluid," Dr. Armstrong explains. Studies suggest that their benefit relates in part to reduction in circulating angiotensin II and aldosterone.

Measurement of BNP or its precursor NT-proBNP is now recommended as a complement to clinical evaluation in HF diagnosis. An area of ongoing investigation is the clinical value of administering exogenous BNP in HF management. A recombinant form of BNP, nesiritide, has been shown to have positive neurohormonal and vasodilatory properties. To date, it has been studied in 10 clinical trials in chronic and acute HF. From this research, it is possible to suggest that "the anticipated benefits of using vasodilator therapy such as

nesiritide, especially if it has positive neurohormonal effects, will depend on the population that you treat. For [patients] in a chronic stable condition, while it's well tolerated, there's not a lot of further clinical benefit. However, in higher-risk populations, such as those who undergo cardiac surgery or in those who have decompensated HF, there's a clear improvement in morbidity and probably an improvement in mortality. We're awaiting definitive studies to determine that," Dr. Howlett reveals.

Main Trial Evidence to Date

The evidence on the benefits of nesiritide in acutely decompensated HF emanates largely from the VMAC (Vasodilator in the Management of Acute Heart Failure) study (*JAMA* 2002;287:1531-40). In this trial, nesiritide proved more effective than placebo and nitroglycerin in reducing pulmonary capillary wedge pressure and was more effective than placebo at reducing dyspnea. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natreacor Therapy) study, nesiritide was shown to be as effective as dobutamine at producing symptomatic improvement in acute HF, but unlike dobutamine had no proarrhythmic effects (*Am Heart J* 2002;144:1102-8). While these data were encouraging, two meta-analyses (Sackner-Bernstein et al. *JAMA* 2005;293:1900-5, *Circulation* 2005;111:14987-91) engendered some debate about the agent's safety, determining that nesiritide treatment increased 30-day mortality (adjusted hazard ratio 1.8, $P=0.057$) and raised the relative risk of renal dysfunction by about 50% ($P=0.003$). An expert review panel later concluded that while the compound is associated with a dose-dependent increase in serum creatinine, the implication of this alteration is unclear. It also found that early differences in mortality might be explained by baseline patient characteristics and that nesiritide was not associated with increased mortality at six months. According to the panel's recommendations, "The drug should be restricted to patients meeting the VMAC criteria and that a further large clinical trial should be undertaken to test whether the drug improves mortality or rehospitalization rates," indicates Dr. Justin Ezekowitz, Assistant Professor of Medicine and Director, Heart Function Clinic, University of Alberta Hospital.

ASCEND to Extend the Evidence

The ASCEND study, now enrolling subjects at 600 centres worldwide, will provide additional evidence on the role of this novel agent in patients with acutely decompensated HF. Approximately 7000 patients will be randomly allocated to treatment with nesiritide or placebo in addition to usual care. Nesiritide will be given as a bolus of 2 µg/kg followed by continuous infusion at 0.01 µg/kg/min for 24 hours to seven days depending on individual clinical improvement. The study's primary objectives are to assess patient outcomes, including the composite of HF rehospitalization and all-cause mortality up to 30 days after the index hospital admission; and to evaluate improvement in symptoms such as dyspnea at six and 24 hours after treatment initiation. Additional clinical end points include improvement in the patients' sense of well-being at six and 24 hours and number of days spent outside the hospital at 30 days. The ASCEND trial is scheduled to be completed by 2010.

The Canadian contribution to ASCEND is substantial, remarks Dr. Armstrong, who points out that early findings on the heart as an endocrine organ and the discovery of natriuretic peptides were also products of work in this country. To date, 40 HF centres—urban and rural, academic and community—are taking part. A number of substudies to be performed here will complement the main research protocol, Dr. Ezekowitz adds. "In fact, there's a unique Canadian perspective built into the trial to make sure we understand [the evidence] in Canadian terms and in much greater detail than other countries are doing... Other substudies are testing clinical ideas such as: does nesiritide in fact make people breathe better because it changes their bronchoconstriction? In addition, a large registry will follow patients who are not in the trial for a comparative analysis of who gets in a trial and who doesn't, and what patients we actually see in the emergency room. We are also following renal function and biomarkers and there's a pharmacogenomics component," he reports.

"We have a lot of people on board who are interested in pushing the science forward and understanding if we do have a new treatment for HF patients. Currently, we have no drugs in acute HF that reduce rehospitalization rates or reduce the odds of death. This would be the first drug in the field [to do so]," Dr. Ezekowitz states. □

Please plan to attend:

"The Clinical Roadmap to Acute Heart Failure: ASCENDING to New Heights." Wednesday, October 24, 2007, 7:00-9:00, 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 (RCPC).

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Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Novel Strategies for the Treatment of Obesity and its Cardiometabolic Complications: The Endocannabinoid System and CB₁ Receptor Blockade

Quebec City - Abdominal obesity—or so-called visceral fat—is now recognized as an important endocrine organ, responsible for the production of largely toxic adipocytokines that increase cardiometabolic risk. Abdominal obesity is also frequently accompanied by a highly atherogenic lipid profile and insulin resistance, all of which increase the risk of both cardiovascular disease and type 2 diabetes. A novel CB₁ receptor blocker that inhibits CB₁ receptors throughout the endocannabinoid system has been shown to target not only abdominal obesity as expressed by significant reductions in waist circumference but also surrogate markers for cardiometabolic risk, including the metabolic syndrome. Whether these favourable changes translate into reduced cardiometabolic risk has yet to be proven, but the link between abdominal obesity and cardiometabolic risk is well forged and expectations are that reductions in markers for that risk will lead to improved cardiometabolic outcomes.

Québec – L'obésité abdominale, aussi appelée graisse viscérale, est maintenant reconnue comme étant un important organe endocrine. Cette graisse génère des adipocytokines, toxiques pour la plupart, qui augmentent le risque cardiométabolique. De plus, l'obésité abdominale s'accompagne souvent d'un bilan lipidique hautement athérogène et d'une résistance à l'insuline, lesquels augmentent le risque de maladie cardiovasculaire et de diabète de type 2. Il a été démontré qu'un nouvel antagoniste des récepteurs CB₁, qui bloque tous les récepteurs CB₁ du système endocannabinoïde, cible non seulement l'obésité abdominale en réduisant sensiblement le tour de taille, mais aussi les marqueurs de substitution du risque cardiométabolique, entre autres le syndrome métabolique. S'il n'a pas encore été prouvé que ces changements favorables se traduisent par une diminution du risque cardiométabolique, le lien entre l'obésité abdominale et le risque cardiométabolique est bien établi, et l'on s'attend à ce qu'une baisse des marqueurs de ce risque améliore les résultats.

By: Pam Harrison

Abdominal obesity—alternatively referred to as visceral adiposity or visceral fat—has increasingly been recognized as a major cardiometabolic risk factor, equal to traditional cardiovascular (CV) risk factors including hypertension and smoking. This recognition has come about largely as a result of work carried out by Dr. Jean-Pierre Després, Director of Cardiology Research, Centre de recherche de l'Hôpital Laval, and Professor of Medicine, Université Laval, Quebec City, and colleagues. As Dr. Després has established, abdominal obesity is associated with a cluster of metabolic abnormalities, increasing the risk of both coronary artery disease (CAD) and type 2 diabetes.

This is because abdominal obesity is frequently accompanied by hyperinsulinemia and insulin resistance which in turn may evolve into impaired glucose homeostasis—and why many obese patients eventually develop diabetes. Abdominal obesity is also frequently accompanied by a highly atherogenic lipid profile including low HDL-C, elevated triglycerides and an increased concentration of the most atherogenic form of LDL-C, even though LDL-C levels may be in the normal range.

Abdominal obesity is also a “powerful predictor” of the presence of inflammatory cytokines including elevated levels of C-reactive protein and free fatty acids, which increase the risk of both CAD and type 2 diabetes as well. “Adipose tissue is a remarkable endocrine organ and it releases compounds

that increase the risk of both heart disease and diabetes,” Dr. Després confirms.

Thus, any approach that will lead to the loss of visceral adipose tissue—a healthy diet, more physical activity or pharmacotherapy aimed at the endocannabinoid system—should contribute to substantial improvements in the cardiometabolic risk profile of patients with abdominal obesity.

Endocannabinoid System

The endocannabinoid system represents a novel target that has many implications in the treatment of disease including cardiometabolic risk. Early experimental work demonstrated that a selective cannabinoid type-1 (CB₁) receptor antagonist, now known as rimonabant, reliably suppressed food intake in laboratory animals. This was the first evidence that the endocannabinoid system was involved in regulation of appetite and it heralded the beginning of new ways of thinking about treating obesity. A wide range of metabolic effects are modulated by the endocannabinoids, including hepatic fat metabolism, plasma lipoproteins and insulin sensitivity.

Cardiometabolic risk is defined by the presence of abnormalities in plasma lipoproteins and insulin resistance among other key features. Thus, inhibition of

endocannabinoid activity at each of these interfaces with CB₁ receptor blockade clearly has important therapeutic implications for reduction of cardiometabolic risk.

Many cell types express these CB₁ receptors, key among them adipocytes and hepatocytes, and the endocannabinoids directly target these receptors to mediate their toxic effects. Research in animal models indicates that CB₁ blockade either with rimonabant or with genetic ablation of CB₁ receptors has direct peripheral and central effects on fat metabolism and appetite.

Other research has also shown a high-fat diet induces insulin resistance in wild-type mice but not in CB₁ knockout mice on the same high-fat diet. Extrapolating from animal studies to the clinic, CB₁ receptor blockade offers a promising strategy not only for reducing weight and abdominal adiposity but also for preventing and reversing its metabolic consequences (*Am J Med* 2007;120:S18-S24).

RIO-Europe

Results from phase III clinical trials support the beneficial effect of rimonabant on fat metabolism, insulin resistance and related metabolic parameters.

As presents Dr. Luc Van Gaal, University Hospital Antwerp, Belgium, RIO-Europe, one of four phase III clinical trials in the Rimonabant in Obesity/Overweight (RIO) program, involved 1507 overweight or obese patients who were assigned to rimonabant 20 mg/day, 5 mg/day or placebo. Mean body mass index at baseline was 36.6 kg/m² and the mean waist circumference was 110 cm. Patients were asked to reduce their daily caloric intake by 600 kcal/day but otherwise no other intervention was required.

After one year of treatment, mean weight loss was 6.6 kg in the 20-mg group, 3.4 kg in the 5-mg group, and 1.8 kg in the placebo group, a significant difference between high-dose active treatment and placebo ($P<0.001$). Patients in the 20-mg group also lost a mean of 6.5 cm in waist circumference at one year vs. a mean loss of 3.9 cm in the 5-mg group and 2.4 cm in placebo controls.

Data from two years showed that results seen at one year were largely maintained. At two years, mean weight loss was 7.2 kg for rimonabant 20 mg, 1.6 kg for 5 mg and 2.5 kg for

placebo, indicating a significant difference between 20 mg and placebo ($P<0.001$). Mean changes in waist circumference at two years were 7.5 cm for 20 mg, 5.3 cm for 5 mg, and 3.4 cm for placebo controls ($P<0.001$ for 20 mg vs. placebo).

The per cent of patients who lost at least 10% or more of their body weight at one year was 39% in the 20-mg arm, while at two years, it was 32.1%, both of which were statistically significant vs. placebo ($P<0.001$). The more dramatic reduction in weight loss and waist circumference in actively treated patients suggests that the weight loss was predominantly due to loss of visceral fat, a key feature in the metabolic syndrome, as researchers have suggested.

RIO-Europe investigators also observed significant improvements in several metabolic parameters including HDL-C and triglycerides. As anticipated from animal studies, insulin sensitivity also improved in the rimonabant 20-mg group compared with those on placebo ($P<0.001$).

The number of patients who had the metabolic syndrome at study entry based on National Cholesterol Education Program criteria was reduced by roughly half in the higher-dose group, and this influence was maintained throughout the study.

Side effects were mainly seen during the first year, the most common being nausea (13.7%), dizziness (9.3%), diarrhea (8.2%) and vomiting (5.2%) (20-mg group). Approximately 13% of this patient cohort discontinued treatment over the two-year study due to an adverse event vs. 18.9% of placebo patients, but no significant changes in ECG, blood pressure or heart rate were seen in any of the actively treated patients.

It is also noteworthy that investigators involved in the RIO clinical program believe that at least part of the improvement seen in metabolic abnormalities with rimonabant are not related to weight loss *per se* but rather that they are most likely mediated through peripheral sites of action.

It is equally clear from RIO-Europe and similar findings in their sister programs, RIO-Lipids and RIO-North America, that increased endocannabinoid activity has a pathogenic role in obesity and associated metabolic abnormalities and that CB₁ blockade thus represents a novel strategy by which to block this pathogenicity. □

Please plan to attend:

“Harnessing the Endocannabinoid System to Reduce Cardiometabolic Risk.” Tuesday, October 23, 2007, 7:00-9:00, Room 200B, 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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Canadian Cardiovascular Congress 2007

Quebec City, Quebec / October 20-24, 2007

Credit to All Who Make the CCC Possible / Hommage à tous ceux qui font du CCSC une réalité

Quebec City – The science as represented by over 1000 abstracts presented during the Canadian Cardiovascular Congress this year was again wide-ranging and mirrored the diverse interests of attending delegates. Out of many worthy studies, a few stood out as having important clinical implications for practicing cardiologists. We have excerpted findings from a few of these studies, knowing full well that we could have chosen from any number of excellent presentations that are likely to have similar important and potentially far-reaching implications for specialists in the field. It is a credit to all of those who make this meeting possible that the quality of the research presented here is consistently excellent, and the cardiovascular community as a whole should be proud that they have yet again created a professional experience that is uniquely Canadian.

Québec – Les résumés présentés dans le cadre du Congrès canadien sur la santé cardiovasculaire – dont le nombre totalise plus d'un millier – témoignent cette année encore de la vaste portée scientifique de la médecine cardiovasculaire et de la grande diversité des champs d'intérêt des congressistes. Parmi le grand nombre d'études méritoires, quelques-unes se démarquent en raison du retentissement clinique qu'elles auront sur l'exercice de la cardiologie. Nous présentons ici les grandes lignes de quelques-unes de ces études, sachant fort bien que plusieurs autres présentations d'excellente qualité pourraient avoir des retombées importantes, voire une grande portée, pour les spécialistes du domaine. Année après année, la qualité indiscutable de la recherche présentée au CCSC est à l'honneur de ceux qui y contribuent, et tous les professionnels de la santé cardiovasculaire ont de quoi être fiers de cet événement purement canadien.

By: Pam Harrison

Experience from the first 100 high-risk patients to undergo either transarterial or transapical balloon expandable aortic valve implantation has demonstrated that the new technology leads to sustained clinical benefits for up to two years in patients with aortic stenosis.

Dr. Sanjeevan Pasupati, St. Paul's Hospital, Vancouver, and colleagues treated 75 patients with severe vascular disease using the femoral arterial approach and another 25 patients using the apical approach. Clinical and ECG follow-up were carried out every six months for one year, and again at 24 months. Unsuccessful patients were censored at 30 days.

At a mean age of 82 years, overall procedural success was 92%, although it was lower in the first 25 patients (76%) using the femoral approach; in the remainder of this cohort, the procedural success rate was 96%, as it was for the 25 patients who underwent the procedure using the apical approach. Peri-procedural cerebrovascular accidents occurred in four patients, while malposition occurred in three patients.

Intra-procedural mortality rate was 2%, which was far less than the predicted mortality rate of 32% had patients undergone the repair surgically. Operative mortality at 30 days was 15%. As the authors note, mild para-valvular aortic regurgitation was common but no severe instances were observed following implantation of the valve, nor did regurgitation become more severe throughout the first post-procedural year. No structural valve deterioration was observed either.

At 24 months, 76% of implant recipients were still alive, and procedural outcome continues to improve with experience and device development, as investigators observe.

Post-PCI Complications

Capital Health Region (CHR) investigators under Stephanie Wold, MsN, in turn reported that 40% of patients undergoing non-emergent percutaneous coronary intervention (PCI) are either admitted to hospital or visit the emergency room (ER)

within six months of their index PCI. For the analysis, investigators used the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry to identify patients who underwent PCI in the CHR between January 2002 and December 2004. Data were then linked to ICD-10 codes to identify the frequency of and reasons for ER visits and hospital readmissions.

Analyses revealed that in-patient readmissions accounted for 8% of the visits, while 32% of patients visited the ER. "The mean time to readmission was 1.9 months and the mean number of visits was 2.5, with 23% [of patients] having greater than one readmission," the authors note. Of the diagnostic categories deemed to be directly related to the PCI ER visits or readmissions, the main reasons patients visited the ER were chest pain, atherosclerotic heart disease, myocardial infarction, bleeding or complications with anticoagulation and procedural complications.

The same reasons were also linked to the need for readmission, with additional heart failure and phlebitis being listed as reasons for readmission as well. "Rehospitalization post-PCI can have an enormous impact on both the health care system as well as patients' lives," investigators state. "It is therefore imperative that current procedures and practices for the care and treatment of patients post-PCI be re-evaluated to better assist patient recovery and substantially decrease the need for already constrained ER and hospital resources."

Meanwhile, Montreal-based investigators under lead author Dr. Alexis Matteau, *Université de Montréal*, reported that immediate re-transfer back to the referring hospital after primary PCI in selected stable STEMI patients is feasible and is associated with a low risk of major clinical adverse events once they are transferred back to the referring hospital. This strategy would increase primary PCI availability to patients presenting with STEMI in community hospitals, as they suggest. Patients, however, had to be hemodynamically stable and have no immediate post-PCI complications to be eligible for immediate post-PCI transfer.



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