UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

HeartView™

This educational publication has been reviewed by the University of Ottawa Heart Institute, Division of Cardiology

A Marked Canadian Presence at the American Heart Meeting

A report from the

81st Scientific Sessions of the American Heart Association

November 9-12, 2008 / New Orleans, Louisiana

Canadian researchers participated in several of the most significant advances reported at this year's American Heart Association Scientific Sessions. This included two late-breaking trials and innovative work that is advancing the potential for progenitor cell engraftment to regenerate myocardium in heart failure. Preliminary data from a registry tracking survivors of sudden cardiac arrest with preserved left ventricular function were also the product of Canadian research. The AHA has increasingly served as a global forum for research into cardiovascular disease, generating an enormous amount of new data with immediate clinical applications as well as providing an update on new directions in research. This report provides a selection of both clinical and basic research among more than 6000 scientific presentations over a four-day period.

TIMACS: Early vs. Late Invasive Therapy in Non-ST-Segment MI

Risk stratification may be important for accelerating invasive treatment of non-ST-segment elevated myocardial infarction (N-STEMI), according to results of the late-breaking TIMACS (Timing of Intervention in Acute Coronary Syndrome) study. It compared early to late angiography and revascularization in 3031 N-STEMI patients treated at 100 medical centres in 17 countries. In those at high risk, an early diagnostic angiogram followed by a percutaneous intervention (PCI) or coronary artery bypass grafting (CABG) reduced the relative risk of all-cause death, MI or stroke by 35% (P=0.005) at six months. In those at low risk, the early diagnostic angiogram with revascularization was associated with a non-significant 14% (P=0.43) increased risk in the same outcome.

"If patients with an acute coronary syndrome are at low risk or intermediate risk for death, it does not matter whether you have your angiogram early or late, but if you are high risk, the early intervention strategy is far better," according to senior author Dr. Shamir R. Mehta, Director of Interventional Cardiology, Hamilton Health Sciences Corporation, and Associate Professor, McMaster University, Hamilton, Ontario.

Patients were eligible for this study with a diagnosis of unstable angina (UA) or N-STEMI and if they were suitable for revascularization. They also had to meet two of an additional three criteria: age >60 years, ischemic changes on electrocardiogram (EKG) and an increase in a biomarker diagnostic for MI. The early intervention was defined as coronary angiography as soon as possible followed within 24 hours by PCI or CABG. The delayed intervention was defined as angiography any time more than 36 hours after admission followed by PCI or CABG.

At 180 days, the 15% relative reduction (hazard ratio [HR] 0.85; 95% CI: 0.68-1.06, P=0.15) in the primary end point favouring early intervention was not significant. However, the 28% reduction in a secondary end point of death, MI or refractory ischemia favouring early intervention did reach statistical significance (P=0.002). The high-risk patients, who had a significant benefit on the primary end point, were defined by a GRACE (Global Registry of Acute Coronary Events) score of ≥140. However, the authors concluded that early intervention might be the best choice even for low-risk patients because of an opportunity for a reduced risk of refractory ischemia. They said this conclusion is supported by the fact that early intervention appears to be as safe as late intervention in low- as well as high-risk patients.

JUPITER: hsCRP Isolates Individuals Without Hyperlipidemia Who Benefit from Statins

Terminated earlier this year because of overwhelming benefit in the active treatment arm, the JUPITER (Justification of the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study demonstrated that older individuals

without hyperlipidemia benefit from intensive reductions of LDL-C if they have elevated high-sensitivity C-reactive protein (hsCRP). The results of JUPITER, presented as a latebreaker, are expected to alter treatment guidelines because it defines a group of patients who benefit from statin treatment that are not necessarily identified by other risk factors.

In JUPITER, a primary prevention trial, 17,802 men over the age of 50 and women over the age of 60 were randomized to rosuvastatin 20 mg once daily or placebo. The study, led by Dr. Paul Ridker, Harvard Medical School, Boston, Massachusetts, included sites in 17 countries, including Canada. For entry patients were required to have hsCRP >2.0 mg/L but an LDL-C <3.4 mmol/L. After only 1.9 years of a planned five-year study, rosuvastatin was associated with a 44% reduction (HR 0.56, 95% CI: 0.46-0.69, $P<0.00001$) in the primary composite end point of MI, stroke, arterial revascularization, hospitalization for UA or death from a CV cause relative to placebo. Rosuvastatin was also associated with a 20% ($P=0.02$) reduction in all-cause mortality despite the early termination of the study.

Both the treatment and the very low levels of LDL-C appeared to be safe. The rate of serious events was comparable in the two study arms and there were no significant differences between study groups in regard to muscle weakness or other side effects observed in early statin trials. One reason may be that the large reductions in LDL-C were achieved with a relatively modest dose of rosuvastatin. Cancer rates did not differ, although cancer death was significantly lower ($P=0.02$) on rosuvastatin.

Evidence that intensive lipid lowering reduces risk in individuals identified solely on the basis of elevated hsCRP is expected to alter treatment guidelines in Canada and elsewhere.

Collagen Matrix Improves Progenitor Cell Engraftment

One of the most exciting emerging areas in CV medicine is the potential application of cell therapy to repair damaged cardiac muscle. A series of increasingly sophisticated studies support the promise of progenitor cell engraftment to restore or improve cardiac function, but durable retention of cells capable of regeneration has been a significant hurdle. In a study from the Ottawa Heart Institute, a collagen-based delivery matrix demonstrated substantial promise for preserving newly recruited cells at the repair site. Although conducted in an experimental setting, the work may be essential for moving to the clinical arena.

When progenitor cells were injected into a collagen matrix in an ischemic hindlimb muscle of rats, "Radioactivity biodistribution confirmed that accumulation was increased by 92.5% [$P=0.024$]," reported Dr. Yan Zhang, Ottawa Heart Institute. When compared to injection of cells without the collagen matrix, anti-human mitochondria staining showed more than a 50% increase ($P=0.048$) in cell retention. Even more encouraging, the retention rate at 14 days after injection was more than twice as great ($P=0.004$) when cells were engrafted onto a collagen matrix.

Dr. Zhang suggested that understanding the mechanism by which the matrix increases cell retention "has potential implications for the optimization of cell therapy," particularly in the early stages after cell delivery when retention is most difficult to achieve. He added that the principle of progenitor cell engraftment is moving forward. Although human studies remain some distance away, there is evidence from numerous fields that progenitor cells can acquire the characteristics of cells in tissue to which they are engrafted. This may provide a more fundamental fix for failing cardiac muscle cells than any of the currently available treatments.

Cardiac Arrest Survivors Without LV Dysfunction: Registry Results

Initial results of an ambitious registry of cardiac arrest survivors without left ventricular (LV) dysfunction or other evidence of cardiac disease has produced some provocative results. In the first 51 cases entered into this registry, a diagnosis of the cause of the arrest was determined in 43%. The two most common diagnoses were long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). Arrhythmogenic right ventricular cardiomyopathy (ARVT), coronary spasm and Brugada syndrome were also observed but much less frequently. A greater understanding of the relative risk for cardiac arrest posed by these conditions is anticipated as the registry, known as CASPER, grows.

"The CASPER study approach helps to diagnose primary electrical diseases as well as latent structural causes of cardiac arrest," reported Dr. Andrew D. Krahn, University of Western Ontario, London Health Sciences Centre. "Systematic testing is proving useful for unmasking the etiology of apparent unexplained events."

One of the hypotheses behind CASPER, which includes participation by major centres across Canada, is that uncommon genetic conditions are producing abnormal electrical events or cardiomyopathy. In the registry, investigators are not only evaluating survivors of cardiac arrest without obvious pathology but first degree relatives of sudden death cardiac victims under the age of 35 who have a negative autopsy. In survivors, a broad battery of tests is being performed to identify potential etiologies for sudden cardiac death. This includes voltage mapping, selective electrophysiological testing, right ventricular angiography and biopsy. In relatives, testing has been non-invasive.

"Enrolment to date has included 58 unexplained cardiac arrest patients, 25 first-degree relatives of these patients and 27 first-degree relatives of sudden cardiac death victims," Dr. Krahn reported. Although a diagnosis has been made in less than half of the patients, the information generated by this registry may eventually yield patterns which will help identify causes and markers of risk in a challenging group of individuals.

Drug-eluting Stents May Be Superior to Bare Metal Stents in Patients with Diabetes

When evaluated after three years of follow-up, mortality rates are lower when patients with diabetes received a drug-eluting coronary stent (DES) compared to a bare metal stent (BMS), according to a large consecutive series of 5051 patients with diabetes who are enrolled in the MASS-DAC Registry. Unadjusted mortality rates at three years were 14.4% in the DES group ($P<0.001$) and 22.2% in the BMS group. When adjusted for risk, the advantage for DES remained significant

for death (17.5% vs. 20.7%; *P*=0.02), MI (13.8% vs. 16.9%; *P*=0.02) and revascularization (18.4% vs. 23.7%; *P*<0.001).

"In real-world reporting, DES appears to provide better outcomes than BMS," stated Dr. Laura Mauri, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. The advantage of DES over BMS appears to be particularly important in patients with diabetes because of the higher rate of adverse events after stenting relative to those without diabetes. Due to rising rates of diabetes and the increased risk of CV events imposed by diabetes, it is estimated that patients with diabetes now represent about one-third of all revascularization procedures.

Perhaps anticipating these results, DES were implanted in 66.1% of patients with diabetes in this registry, or nearly double the 33.9% who received BMS. The investigators controlled for a broad array of confounders including concurrent conditions and medications in the adjusted comparisons. Although the preponderance of previous studies have suggested that DES are superior for preventing early stenosis and BMS are superior for preventing late stenosis, this has been a persistent area of controversy, particularly for specific risk groups such as those with diabetes. Although the authors say longer follow-up is needed to confirm the advantage of DES, this evaluation goes a long way toward providing clinical guidance.

More Evidence Dietary Supplements Provide Little Help in Heart Disease

Two very large latebreaking studies evaluating dietary supplements were both negative. In SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine), 12,064 patients with a previous MI were randomized to vitamin B9 (folic acid) 2 mg and B12 1 mg/day or placebo. In the second Physician's Health Study (PHS II), 14,641 US male physicians ≥50 years were randomized to vitamin E 400 IU every other day and vitamin C 500 mg daily or placebo.

In SEARCH (which also included an arm that compared simvastatin 20 mg to 80 mg and found no significant advantage for the higher dose), the event rates over 6.7 years of follow-up were actually slightly but not statistically higher in the group that received folic acid/B12, producing an HR of 1.04 in favour of placebo for the primary composite end point of major coronary events, stroke and revascularization.

"It is really a very robustly negative result," remarked Dr. Jane M. Armitage, Professor of Clinical Trials and Epidemiology, University of Oxford, UK. "There were no subgroups in whom there was any benefit." Indeed, when the results of this very large study are combined with a series of previous prospective studies that were also unable to find any significant benefit from this strategy, "I think we can now rule out any major cardioprotective effect from folic acid."

Unlike SEARCH, the study of vitamins E and C, which have antioxidant effects, was mostly one of primary prevention. Only 5% of individuals had CV disease at entry. Over a mean of eight years of follow-up, the HR of the primary end point of MI, stroke and CV mortality was 1.01 (*P*=0.86) among those taking the vitamins relative to those taking placebo. When HRs were evaluated for the individual outcomes, there was no signal of benefit from taking antioxidant vitamins.

"Neither vitamin E nor vitamin C supplementation demonstrated any propensity to reduce the risk of major CV events," reported senior author Dr. Howard D. Sesso, Division of Preventive Medicine, Brigham and Women's Hospital. "These data provide no support for the use of these supplements for the prevention of CV disease in middle-aged and older men."

New Data from ATHENA Study Confirm Reduction in Hospitalizations

New data from ATHENA (A Trial with Dronedarone to Prevent Hospitalization of Death in Patients with Atrial Fibrillation) have confirmed steep reductions in CV hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) who are treated with the anti-arrhythmia agent dronedarone. The primary result, reported earlier this year, associated dronedarone with a 24% (*P*<0.001) reduction in the composite outcome of CV hospitalization or all-cause death. The drug was well tolerated.

In the new analysis, a more detailed evaluation of hospitalizations confirmed a 25% reduction (*P*<0.001) relative to placebo for first hospitalization, a 27% reduction (*P*<0.001) in hospitalizations due to AF, a 35% reduction (*P*<0.001) in hospital due to CV causes and a 47% reduction (*P*=0.015) in days spent in the intensive-care unit (ICU) or CV care unit (CCU). According to the senior author of this analysis, Dr. Christian Torp-Pedersen, the 1020 days of hospital stay could be eliminated for every 1000 patients treated with dronedarone for one year.

In ATHENA, 4628 patients with AF who were considered to be at high risk either because of an age >75 years or an age >70 years with an additional risk factor, such as diabetes or prior stroke, were randomized to dronedarone 400 mg b.i.d. or matching placebo. The mean follow-up was 21 months. The reduction in hospitalization is significant because previous studies with such drugs as amiodarone have not demonstrated this benefit and because hospitalization is a common and expensive complication of AF. For this reason, Dr. Torp-Pedersen concluded from ATHENA results that dronedarone substantially reduces total hospital burden.

Canada Unprepared for Projected Rise in Adult Congenital Heart Disease

A survey of the infrastructure and human resources for managing adult congenital heart disease in Canada found that current waiting times for health care services are beyond Canadian recommended targets and are projected to worsen. In a report from the Canadian Adult Congenital Heart Network (CACH) presented by Dr. Luc M. Beauchesne, Ottawa Heart Institute, several potential obstacles to appropriate care were identified. For example, only about 20% of the cardiologists in the 15 centres registered with CACH have formal training in adult congenital heart disease care.

Due to better management in newborns with congenital heart disease, the proportion of individuals surviving into adulthood is increasing. This has increased demand for adult congenital heart disease management. The survey presented by Dr. Beauchesne suggests that more resources in Canada should be directed to this area of cardiac care. ❑

Division of Cardiology
University of Ottawa Heart Institute

Dr. Kathryn J. Ascah
Dr. Rob S. Beanlands
Dr. Luc M. Beauchesne
Dr. David H. Birnie
Dr. Ian G. Burwash
Dr. Kwan L. Chan
Dr. Benjamin J. Chow
Dr. Richard F. Davies
Dr. Ross A. Davies
Dr. Michele de Margerie
Dr. Lloyd J. Duchesne
Dr. Michael P. Froeschl
Dr. Christopher A. Glover
Dr. Michael H. Gollob
Dr. Martin S. Green (Editor of HeartView)
Dr. Haissam A. Haddad
Dr. Renée C. Hessian
Dr. Marino Labinaz
Dr. Frans H. Leenen
Dr. Michel R. Le May
Dr. Robert Lemery
Dr. Jean-Francois Marquis
Dr. P. Ruth McPherson
Dr. Lisa M. Mielniczuk
Dr. Pablo B. Nery
Dr. Edward R. O'Brien
Dr. Andrew L. Pipe
Dr. Emoke T. Posan
Dr. Robert Roberts (President and CEO)
Dr. Terrence D. Ruddy (Head of Cardiology)
Dr. Derek Y. So
Dr. William L. Williams

University of Ottawa Heart Institute
40 Ruskin Street
Ottawa, Ontario K1Y 4W7
www.ottawaheart.ca
Telephone: (613) 761-5000
Fax: (613) 761-5323

Commentary

by Ruth McPherson, MD, PhD, FRCPC

JUPITER: A New Era in Primary Prevention

Although coronary artery disease (CAD) secondary prevention strategies have improved and are economically attractive, a substantial percentage of previously asymptomatic individuals die within minutes to weeks of their initial coronary event or are left with debilitating and life-limiting cardiac damage. Physicians have at their disposal a number of effective strategies to reduce cardiovascular (CV) risk from intensive lifestyle counselling to proven medical therapies such as statins and ASA. Thus the early identification and treatment of asymptomatic individuals at future risk is a major healthcare priority. Over the last decade, a large body of epidemiological evidence has accumulated indicating that high-sensitivity C-reactive protein (hsCRP) is a significant independent CAD risk marker that adds to the predictive value of a Framingham Risk Factor Score (FRS).

The JUPITER study tested the hypothesis that above average hsCRP levels (>2.0 mg/L) in otherwise healthy middle-aged men and women define a population who will clearly benefit from intensive statin therapy (rosuvastatin 20 mg q.d.). JUPITER was important for several reasons. Not only was this the largest primary prevention study to date (over 17,802 subjects), it was the only study to have enrolled a significant number of women (6801). Notably, the subjects randomized in JUPITER would not have been candidates for lipid-lowering therapy based on current guidelines since LDL-C concentrations were <3.4 mmol/L and mean LDL-C at randomization was only 2.7 mmol/L. Importantly, after less than two years of treatment, there was a 54% decrease in major CV events and a 20% decrease in total mortality, making this the first primary prevention trial to clearly demonstrate a mortality benefit. The number needed to treat to prevent one CV event over five years was 25, comparable to many secondary prevention studies. Although the median achieved LDL-C levels in the rosuvastatin-treated group was 1.4 mmol/L and 25% of subjects achieved LDL-C levels below 1.1 mmol/L, there was no difference in side effects, including muscle discomfort, between the treatment and placebo groups. Cancer deaths were slightly but significantly lower in the rosuvastatin arm but as reported in other statin studies, there was a slight increase in new diabetes cases in the active treatment group.

JUPITER provides three clear messages. First of all, measurement of hsCRP can help to identify a subset of middle-aged to elderly patients with a FRS of 5% to 19% who will benefit from statin therapy. Secondly, the decision to treat with a statin should be based on the level of risk, including risk factors such as hsCRP, and not only the level of LDL-C. Finally, for patients who merit statin therapy, treatment to lower LDL-C by at least 40% to 50% is appropriate.

Topics presented in HeartView™ are independently selected and reviewed by physician members of the Division of Cardiology, UOHI, under agreement that ensures educational integrity and independence from industry. For this report and other educational material, please visit us at www.ottawaheart.ca and Medical Education Network at www.mednet.ca.

Published in conjunction with Medical Education Network and the Division of Cardiology, University of Ottawa Heart Institute.