MARCH 16 - 20, 2008
Lake Louise, Alberta
CONFERENCE OVERVIEW

This year’s Annual Cardiovascular Conference at Lake Louise attracted more than 200 Canadian clinicians with representation from all the provinces across the country. From its inception 25 years ago, the ACC Lake Louise meeting has provided an opportunity to learn from distinguished faculty in a unique, collegial atmosphere. This year was no exception: the topics covered have very current relevance to Canadian clinical practice, covering a wide spectrum of cardiovascular topics from the latest diagnostic and therapeutic approaches, to heart health and disease prevention. Importantly, new guideline updates were a key feature of the plenary sessions, whereby expert opinion leaders shared their interpretations and recommendations for how the guidelines might impact routine clinical practice.

“This conference attracts many repeat attendees and faculty year after year because it provides an opportunity for clinicians to communicate and network with their colleagues from interdisciplinary specialties,” said Dr. Peter Klinke, Program Director. This newsletter will review some of the key points from the diverse presentations; slides can also be accessed through the ACC Lake Louise website. It is hoped that reading this newsletter will provide attendees with another opportunity to reflect on the information and knowledge they gained during the conference in March, and stimulate continued discussions with their colleagues.

The ACC Lake Louise planning committee looks forward to celebrating its 25th anniversary with another stellar scientific program in March 2009.

THE LOCAL AND GLOBAL BURDEN OF CARDIOMETABOLIC DISEASE

MANAGEMENT OF CARDIOMETABOLIC RISK

In Western societies, the obesity epidemic is well established and is associated with significant public health concerns. In 2004, 65% of Canadian men and 53% of women were overweight or obese. More alarmingly, more than 25% of boys and girls are overweight or obese and research has shown that obese children tend to become obese adults with more concomitant diseases. The medical complications of obesity are numerous, complex and affect several systems. In Canada, 1 in 10 adult deaths can be directly related to obesity, a number that has doubled in the last 20 years.

Obesity is characterized by a large amount of adipose tissue, which is now regarded as a distinct and active endocrine organ. Adiponectin, TNF-α, leptin and C-reactive protein are all secreted by adipocytes and are associated with insulin resistance, inflammation, hypertension, diabetes and dyslipidemia. Increased secretion of adipokines has also been linked to endothelial dysfunction and CVD.

Dr. David Lau, a clinician researcher at the Julia McFarlane Diabetes Research Centre at the University of Calgary, presented an overview of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity. Some of the key takeaways for clinicians include the following:

- Measure BMI and waist circumference in all patients to assess obesity-related health risks.
- Most overweight individuals will benefit from lifestyle modifications including diet changes and regular physical activity.
- Obese patients may require pharmacotherapy and even surgery in the most severe cases.
- When designing a treatment plan for overweight patients, the main goal should be weight loss because even a modest decrease has beneficial effects (for example, a 4-5% reduction in body mass loss decreases risk of diabetes by 58%).
- After efficient weight loss, patients should be monitored closely for reinforcement of lifestyle modifications and weight maintenance.
ALCOHOL AND HEART DISEASE

Lifestyle modification generally consists of increased physical activity and healthy dietary changes, which may include recommendations for alcohol consumption. Several studies and meta-analyses have suggested beneficial effects of moderate alcohol consumption on mortality rates. Evidence suggests the relative risk of total mortality is lowest at daily doses of approximately 10 mg ethanol, the equivalent of 80 mL of wine or 200 mL of beer. Mortality risks increase with higher daily consumption, especially in women.

Is wine ‘healthier’ than beer? Dr. Jacques Genest Jr., Professor and Novartis Chair in Medicine at McGill University, explained that some types of alcohol contain purported healthy ingredients, such as resveratrol in red wine. While this compound was shown to extend life, prevent cancer, improve athletic performance, protect the central nervous system and provide antiviral protection in animal models; the concentration of resveratrol in wine is unlikely sufficient to have significant physiological impact in humans. Other mechanisms to explain beneficial health effects of alcohol include increased HDL-cholesterol and fibrinolysis, decreased platelet aggregation, reduced inflammation, and antioxidant effects. However, these benefits are partly offset by alcohol-related morbidity and mortality. Excessive alcohol consumption increases risk of cancer, hypertension, cardiomyopathy, liver disease, cerebrovascular events as well as fatal road-traffic accidents.

MANAGEMENT OF THE CARDIOVASCULAR COMPLICATIONS OF DIABETES

Obesity is a risk factor for type 2 diabetes mellitus, whose increased prevalence in Canada has paralleled rising rates of overweight and obesity. Diabetes increases the risk for cardiovascular disease, coronary heart disease (CHD), stroke and all-cause mortality, in addition to its well-known microvascular complications and risks of end-organ damage. Dr. David Lau presented an update on optimal management of the cardiovascular complications of diabetes. Glycemic control can significantly reduce the risk of cardiovascular complications, but risks remain elevated compared to non-diabetic controls. While glycemic targets are generally 7-7.9% Hb1Ac, the ACCORD study is investigating whether even more aggressive glucose reduction (i.e., <6% Hb1Ac) can delay or prevent CVD.

CVD Risk Reduction in Patients With Diabetes

- Treat to glycemic target
  - BG 4-7 mM
- Regular surveillance for
  - A1C ≤ 7%
- Treat lipid and BP to goal targets:
  - LDL < 2.0 mM
  - TC/HDL-C ratio < 4
  - BP < 120/80 mmHg
- ECASA, ACEI for vascular protection
- ACEI, ARB for renal protection
- Smoking cessation

Other management priorities to reduce cardiovascular outcomes in this high-risk patient population include lipid management, blood pressure reduction, vascular and renal protection and smoking cessation. The STENO-2 study supports a combined intensive approach to diabetes risk management to reduce cardiovascular events and mortality.
THE GLOBAL BURDEN OF CARDIOVASCULAR DISEASE

Cardiovascular disease and obesity are no longer conditions of the developed countries. The rising rates of obesity, diabetes and cardiovascular disease (CVD) are also a concern for developing countries that are incorporating elements of the Westernized lifestyle into their daily lives. In fact, developing nations are at similar risks – if not greater – than industrialized countries. Dr. Bernard Gersh, Professor of Medicine at the Mayo Clinic College of Medicine in Rochester, Minnesota, shared disturbing statistics with the audience at the ACC Lake Louise meeting. The projected increase in CVD-related mortality between 1990 and 2020 is approximately 125% in developing countries compared to 40% in developed countries. Moreover, 80% of the 16.7 million CVD deaths worldwide occur in developing countries. “The high prevalence of chronic diseases coupled with an increasingly older population has considerable implications for the socioeconomic status of developing countries,” said Dr. Gersh. The burden of chronic and degenerative diseases includes high health care costs, thereby diverting already limited resources. Moreover, patients with diabetes and/or CVD have lower productivity, which reduces the available work force. In the long-term, these challenges can create social and political instability that can have global implications.

STATINS AND HDL-RAISING DRUGS: LOOKING TO THE PAST AND THE FUTURE

THE ACC LAKE LOUISE RONNIE CAMPBELL MEMORIAL LECTURE

This year, the Ronnie Campbell Memorial Lecture was delivered by Dr. Jacques Genest Jr., Professor and Novartis Chair in Medicine at McGill University, who presented a talk aptly called “Statins at 21: A Brief Look Back and a Long Look Forward.”

The first statins were introduced in the 1980s and, since then, they have become the preferred cholesterol-lowering agents. Currently, several statins are available and studies have demonstrated their beneficial effects on a number of surrogate endpoints. First, statins’ main effect is to reduce LDL-cholesterol by as much as 30 to 55% after 6 weeks of treatment. Subsequently, multiple studies showed a relationship between LDL-C reduction and protection against CHD. In addition, research suggested that statins have pleiotropic effects including improvement of endothelial function through nitric oxide synthesis, decreased endothelin-1 synthesis and inhibition of LDL-C oxidation, reduced inflammatory responses, stabilization of atherosclerosis plaques and reduced thrombogenic responses. However, these observations have been largely made in vitro, and some researchers have suggested that statins have no beneficial effects beyond LDL-C reduction in humans.

More recently, randomized controlled trials (RCTs) have used arterial imaging procedures as to assess the impact of treatment on disease progression or regression. Treatment with simvastatin for 2 years significantly decreased plasma LDL-C and carotid intima-media thickness (cIMT).

Moreover, studies in acute coronary syndrome (ACS) patients demonstrated that atorvastatin was more effective than pravastatin in reducing death or major cardiovascular events through more potent LDL cholesterol reduction. This benefit was evident as early as 30 days after the start of therapy. The net effect may be substantial, as studies have demonstrated that a 1 mmol/L reduction in LDL-C was associated with a reduction in major coronary and vascular events of 23% and 21%, respectively.

Although clinical trials of statins for secondary prevention of cardiovascular events provide compelling evidence of their benefits, statins may not work for everyone. For instance, statins may not have an appreciable impact on mortality when used as primary prevention. In addition, women, elderly patients and those with end-stage diseases do not respond as well to statin therapies. Indeed, for women with cardiovascular disease, lipid lowering does not appear to significantly affect total or CHD mortality. Likewise, atorvastatin had no significant effect in lowering CHD mortality in diabetes patients undergoing hemodialysis.

WHY HAVE HDL-RAISING DRUGS FAILED TO DEMONSTRATE IMPROVED PATIENT OUTCOMES?

It took almost 40 years to prove that statins effectively reduce cardiovascular events (by approximately 35%), and now they are a preferred treatment for hyperlipidemia. However, this leaves 65% of the potential risk reduction beyond LDL-C reduction...
untapped. Studies suggest that HDL-C levels at the time of presentation with ACS predict the risk of future events. Therefore, increasing HDL-C is a logical strategy to improve patient outcomes. The HATS study demonstrated that the combined effects of decreasing LCL-C with a statin and increasing HDL-C with the addition of niacin resulted in a significant reduction in cardiovascular events. Professor John Kastelein, from the Department of Vascular Medicine at the University of Amsterdam, reviewed the evidence for HDL-raising strategies and their future directions.

HDL-C is involved in reverse cholesterol transport (i.e., from the tissues back to the liver for excretion) and has multiple properties that protect the vessel wall including anti-inflammatory, anti-oxidant, anti-apoptotic and anti-thrombotic effects, endothelial repair, and modulation of endothelial function. HDL-C metabolism is a complex affair, providing multiple potential targets for pharmacotherapeutic agents. There is compelling evidence that apolipoprotein A1 has anti-atherogenic potential and could be a rational target for raising HDL levels. Strategies for upregulation of ApoA1 that are being investigated include PPAR-α and –δ agonists and gene therapy.

Another mechanism for raising HDL-C is cholesterol ester transport protein (CETP) inhibition, since higher levels of CETP are associated with increased risk of future CAD. While clinical trials of torcetrapib with or without a statin demonstrated its efficacy at raising HDL-C, clinical development of this compound was halted when a significantly increased risk of mortality and cardiovascular events was observed. Interestingly, there was an increase in HDL-C particle size and researchers believe these HDL-c particles may have different activity. “HDL particles at the size extremes are not protective, and in fact may be detrimental. We never entertained this possibility, and it underscores the need to measure more parameters than serum levels alone,” suggested Dr. Kastelein.

What now for HDL-raising drugs? “They remain an attractive, but are still a hypothetical, target,” said Dr. Kastelein.

**WHY DO WE NEED TO DO CLINICAL TRIALS?**

The year 2008 marks the 60th anniversary of the RCT, the gold standard that provides the foundation of evidence-based medicine. This relatively recent development allows investigators to systematically answer an important question… and to answer it clearly. Dr. Peter Sleight, Professor Emeritus and Honorary Consultant Cardiologist at the Oxford Radcliffe Hospital in the United Kingdom, was involved in some of the earliest landmark cardiovascular trials, and shared his continuing experience and expertise with the audience. “Good RCTs utilize hard endpoints, are adequately powered, avoid potential sources of bias, and
provide statistically robust results that are widely applicable in clinical practice,” he summarized. Although traditionally focused on efficacy, large RCTs provide valuable information on safety outcomes.

Several large RCTs, including ISIS, GISSI, ISAM, TIMI, and TAMI have guided the practice of cardiovascular medicine and confirm the strong data derived from observational and epidemiological studies such as INTERHEART. More recently, HOPE, CURE, PROGRESS, HPS, EUROPA, SEARCH, and ALLHAT have provided important answers on treatment strategies that optimize patient outcomes. Shortly following this ACC Lake Louise conference, another major RCT called ONTARGET published results that, for the first time, demonstrate equivalent cardioprotection for the ARB, telmisartan, compared to the gold standard ACE inhibitor, ramipril, in a broad population of high-risk patients with prior CVD or diabetes. This trial utilized a design that was informed by the HOPE trial, used the same hard clinical endpoint of death or MI, and had one of the lowest rates of discontinuation ever observed in a cardiovascular clinical trial.

Large RCTs such as ONTARGET form the basis of evidence-based guideline recommendations, and the results of this trial are likely to be included in future guideline updates. Although guideline recommendations arise from RCTs, the sheer volume of different guidelines and the length of each one can be daunting for the clinician. So how should they inform daily practice? Dr. Sleight closed his presentation with the following advice: “Look at RCTs and appraise them carefully. Look at the confidence intervals, not just at p-values, and if the bottom value is close to [the line of unity], don’t change your practice in a hurry; wait for better evidence.”

POST-SCRIPT COMMENTARY ON THE ONTARGET RESULTS

The ONTARGET results were published in the New England Journal of Medicine in April 2008, reporting equivalent efficacy for the ARB, telmisartan, as the current gold standard, the ACE inhibitor ramipril, in reducing the risk of cardiovascular death, myocardial infarction, stroke and hospitalization for congestive heart failure in a population of high-risk cardiovascular patients. Telmisartan is now the only ARB to have demonstrated both cardio and vascular risk reduction benefits beyond blood pressure reduction alone, in this high-risk population.

In a post-ACC conference interview, Dr. Peter Sleight, one of the ONTARGET investigators, suggested that these benefits might be attributed to the specific pharmacological properties and mode of action of the drug. “We are pleased to have a clear result in that telmisartan is non-inferior to ramipril. This will be good news for the sizeable group of patients (around 15-25%) who do not tolerate ACE inhibitors… telmisartan may well be the drug of choice for reasons of compliance and hence speedier control of blood pressure,” said Dr. Sleight. “This trial adds another good choice for the physician treating patients.”

NEW INSIGHTS INTO MANAGEMENT OF ACUTE CORONARY SYNDROMES

RECENT ACS GUIDELINE UPDATES AND IMPLICATIONS FOR PRACTICE

Clinical guidelines provide evidence-based recommendations on how results of clinical trials can be translated into clinical practice. Recently, a focused update to the 2004 guidelines for STEMI was published, and Dr. Paul Armstrong, Director of the Canadian VIGOUR Centre and Professor of Medicine at the University of Alberta, addressed the implications for Canadian clinicians. The update takes into account new evidence from numerous RCTs. While the updated guidelines are extensive, Dr. Armstrong summarized some of the key takeaways:

• Upfront clopidogrel appears beneficial in patients with or without fibrinolytic therapy.
• IV beta-blockers should be used with caution in the first 24 hours after STEMI.

• Enoxaparin and fondaparinux provide new effective anticoagulant strategies, however enoxaparin is preferred if PCI is intended or likely.

• Facilitated PCI with full dose fibrinolysis should not be undertaken.

• Rescue PCI should be undertaken in patients with failed fibrinolysis based on failure of ST resolution and with consideration to the residual territory at risk.

• Effective triage of high-risk patients should be employed to ensure they are identified and receive the earliest possible reperfusion therapy. Secondary prevention and follow-up monitoring deserve emphasis. NSAIDs should be discontinued and avoided at the time of STEMI presentation.

Future directions in the management of ACS involve strategies to combat reperfusion injury, stem cell therapy for cardiac remodeling, pharmacogenomics, and the introduction of “polypill” combination therapies that could enhance adherence rates, and facilitated PCI with novel pharmacologic therapy “will ultimately succeed,” according to Dr. Armstrong. “Stay tuned.”

RESCUE PCI IN STEMI: OUTCOMES AND EVIDENCE REVISITED

Two meta-analyses evaluating rescue or late PCI in STEMI have recently been published, and Dr. Allan Ross, Professor Emeritus of Medicine at George Washington University in Washington, D.C, reviewed how their conclusions might impact clinical practice. The first, by Wijeysundera et al. (JACC 2007) considered rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for STEMI. The primary endpoint, mortality, did not reach statistical significance (p=0.09). “Most rescue interventions are likely performed too late, when there is little benefit to be gained due to reduced effects of plasminogen on old clots and a decreasing quantity of ischemic but salvageable myocardial tissue,” explained Dr. Ross. However, this meta-analysis was widely accepted as an endorsement for rescue PCI in failed fibrinolysis, in the absence of a finding of statistical significance. Indeed, guidelines suggest that rescue PCI might be a reasonable consideration in moderate- to high-risk patients after suspected failure on fibrinolysis, but do not endorse its routine, systematic use.

The second meta-analysis by Abbate et al. (JACC 2008) concluded that late PCI (i.e., 12 hours to 60 days) was associated with significant improvements in cardiac function and survival over medical therapy. Similarly, this conclusion is not supported by statistical significance on the primary endpoint, death or non-fatal recurrent MI or stroke (p=0.22), although survival was significantly better for rescue PCI (p=0.03). On closer examination of the trials included in this meta-analysis, it becomes evident that the results of a single trial “pulled the endpoint to significance,” suggested to Dr. Ross.

Dr. Ross concluded that meta-analyses should be not be unduly persuasive in guiding clinical decisions for individual patients because they usually include small RCTs that suffer from various sources of bias such as dissimilar trial designs and inclusion/exclusion criteria. “Although the available evidence does not support routine rescue PCI or a clear cut benefit for late PCI in stable STEMI patients, there is support for selective use of both approaches in specific clinical circumstances, such as hemodynamic instability, definitive evidence for residual ischemia, and other clinical markers of a poor prognosis.”

SYSTEMS APPROACH TO STEMI

It is well established that optimal treatment of STEMI is achieved through rapid reperfusion, either fibrinolytic therapy or primary PCI. Yet 30% of STEMI patients do not receive any reperfusion therapy even when it is available and in the absence of any contraindications to its use. According to Dr. Robert Welsh, Associate Professor of Medicine at the University of Alberta and Director of Adult Catheterization and Interventional Cardiology, this long-standing care gap provides a compelling reason for a systems approach to STEMI. “The real benefit of a systems approach is the pre-hospital identification of patients with STEMI with direct access to the catheterization lab for timely reperfusion therapy,” said Dr. Welsh. This is especially important in community hospital and rural areas, and Canada is emerging as a leader in this aspect of care.
Contemporary management of STEMI involves a two-step process centered on empowering decision-makers and avoiding “reperfusion paralysis”. The first step involves assessing the time since symptom onset, the patient’s baseline risk, and time until angiography and PCI can be performed. The next step involves choosing whether fibrinolysis or an invasive strategy is preferred for an individual patient.

The Vital Heart Response program is a region-wide systematic approach to STEMI care based on best evidence and regional expertise, which has been implemented in Edmonton. This program takes a patient-centered approach to provide the best reperfusion therapy, delivered at the best time and in the best place. Emergency medical services are intricately engaged in a pre-hospital diagnosis, treatment and triage of STEMI patients with pre-fibrinolysis or direct transport for primary PCI with emergency department bypass. Implementing well-designed systems approach increases collaboration between paramedics, acute care nurses, emergency physicians, internists, family physicians and cardiologists, making it possible to reduce reperfusion delays and improve quality of care. A systems approach, according to Dr. Welsh, “Allows us to move care out to patients, where access to tertiary centres isn’t as easy or timely.”

Dr. Welsh is currently involved in the multinational STRategic Reperfusion Early After Myocardial Infarction (STREAM) trial, which will evaluate pre-hospital lysis (with tenecteplase) followed by catheterization or rescue PCI if required. In a second arm of the study, patients will receive anti-thrombotic/anti-platelet therapy according to local standards in conjunction with primary PCI with expedited care delivered in all patients in the pre-hospital setting.

**TAILORED ANTI-THROMBOTIC AND ANTI-PLATELET THERAPY FOR PATIENTS WITH ACS**

Morbidity and mortality from non-STE ACS have declined significantly over the past 20 years, largely due to advances in anti-thrombotic and anti-platelet therapy. While these treatments have definitive benefits, they are also associated with an increased risk of bleeding, which has important adverse clinical outcomes. The question remains, is bleeding the cause or a marker of a bad outcome? Recent clinical trials have demonstrated improved outcomes with reduced rates of bleeding, making this an important clinical goal.

Dr. David Fitchett, Director of the Cardiac Intensive Care Unit at St Michael’s Hospital and Associate Professor of Medicine at the University of Toronto, presented a new paradigm based on an assessment of benefit of early revascularization and stratification by risk of bleeding. Benefits of early revascularization include a 25% reduction in overall mortality rates compared with more conservative approaches.

Bleeding may be influenced by multiple risk factors, including the presence of anemia, renal impairment, hypertension, early catheterization, femoral access, use of multiple medications, and racial differences in metabolism of anti-thrombotic and anti-platelet agents. Dual anti-platelet therapy with ASA and clopidogrel is recommended for all patients with non-STE ACS, with benefits achieved within hours of administration. The need for and timing of revascularization impacts on the choice and dose of anti-thrombotic therapy. There is still a role for heparin, which has a rapid onset of action and can be reliably measured. Heparin can be particularly useful in patients who will rapidly access the catheterization lab. “Institutions should choose either enoxaparin or fondaparinux and not switch between the two,” recommended Dr. Fitchett.

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<th>LEVEL OF EVIDENCE</th>
<th>2007 ESC GUIDELINES 2007</th>
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<td>Enoxaparin, UFH</td>
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<td>Fondaparinux**</td>
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<td>IIa, B</td>
<td>Enoxaparin*, LMWH, UFH</td>
<td>Enoxaparin, fondaparinux preferred unless CABG &lt;24 hours</td>
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*Enoxaparin only if bleeding risk is low; ** Fondaparinux preferred over enoxaparin if bleeding risk is high.
THE IMPORTANCE OF PREVENTING BLEEDING COMPLICATIONS FOLLOWING PCI

Strategies for minimizing bleeding complications post-PCI were the focus of a presentation by Dr. Eric Cohen, from Sunnybrook Health Sciences Centre in Toronto. Although rates of bleeding in clinical trials have decreased, “Bleeding complications of PCI may be more frequent than we appreciate in routine practice,” warned Dr. Cohen. It is estimated that up to one in five PCI patients experiences a clinically significant bleed. In clinical practice, risk factors for bleeding include advanced age, female sex, and renal insufficiency, as well as improper dosing of anti-thrombotic and anti-platelet therapies, particularly in elderly patients. Importantly, bleeding is not only an adverse event, but may lead to secondary events. Studies suggest that bleeding is an independent predictor of clinical events and late mortality, therefore its prevention is of utmost clinical importance.

Non-pharmacologic strategies, such as using radial access, employing good technique for vascular access and sheath removal, opting for short or possibly staged procedures, gastric protection with proton pump inhibitors, and low-dose ASA, can reduce the risk of bleeding.

Anti-thrombotic and anti-platelet therapies have been associated with different risk profiles for bleeding and secondary events. For example, the OASIS-5 study suggests that fondaparinux is associated with significantly less bleeding than enoxaparin through 9 days post-PCI, as well as a significantly lower mortality rate through 180 days of follow-up. Similarly, the REPLACE-2 study demonstrated that bleeding was significantly less frequent in patients receiving bivalirudin than heparin and a GP IIb/IIIa inhibitor (GPI). Although differences in overall 1-year mortality were not statistically significant, subgroup analyses suggest that bivalirudin may be particularly beneficial in high-risk populations such as the elderly, diabetics, and patients with renal impairment. Similar results have been demonstrated in the ACUITY and HORIZONS AMI trials comparing bivalirudin with heparin/enoxaparin plus a GPI, or heparin plus a GPI, respectively. Taken together, these findings suggest that regimens associated with lower risk of bleeding may positively impact long-term outcomes, and support a tailored approach to anti-platelet and anti-thrombotic therapy in patients undergoing PCI.

MANAGEMENT OF ACS IN DIABETIC PATIENTS

Although traditionally considered an endocrine disease, diabetes is a cardiovascular disease in which a significant care gaps exists. Diabetic patients often present with atypical symptoms, which can further delay their presentation and diagnosis of ACS. An ACS registry supports the observation that patients with diabetes fare worse than non-diabetic patients, and that the increased risk persists beyond release from the hospital. “This is a condition associated with very high risks, and warrants more attention,” said Dr. David Fitchett, Director of the Cardiac Intensive Care Unit at St Michael’s Hospital and Associate Professor of Medicine at the University of Toronto.

Studies suggest that blood glucose levels in the first 24 hours of AMI predict mortality, and that abnormal glucose tolerance is a risk factor for AMI even in the absence of diagnosed diabetes. For diabetics, does control of blood glucose impact on ACS outcomes? Few studies have prospectively addressed this question and the optimal treatment agent(s) and glycemic targets remain controversial, however there is evidence to suggest that glucose management is nonetheless important.

Evidence from subgroup analyses of RCTs suggests that diabetic patients stand to benefit from ACS treatments including GPs and early invasive interventions. Yet diabetic patients are less likely to receive fibrinolysis, anti-platelet agents or anticoagulation in the first 24 hrs after ACS. They are also less likely to undergo invasive management and revascularization. This is also the case after AMI. In fact, diabetic patients have the worst outcomes after AMI but stand to benefit the most from available treatments, such as statins and ACE inhibitors. Nonetheless, they have a compromised opportunity for optimal therapy. Dr. Fitchett concluded, “Diabetes is the strongest predictor of not receiving optimal treatment for ACS… Under-treatment may be contributing to worse prognosis in diabetes patients.”
NEW ADVANCES IN HEART FAILURE

STUDIES THAT IMPACT MEDICAL THERAPY OF CHF FROM NOW TO 2010

Dr. Jean Rouleau, from the Université de Montréal, gave an overview of the history of treatment for heart failure (HF) and a glimpse into what’s in store in the next 2 years. Non-pharmacologic strategies such as mechanical circulatory support, volume overload management, and cell therapies, are likely to provide the most promising results in the coming years. “There has been no good news [in terms of medical therapy] in the last few years, but such is not the case for mechanical devices,” he said.

Mechanical strategies such as ultra-filtration are being developed and evaluated in CHF patients for volume overload management, with some exciting results. Dr. Rouleau suggested that indications for cardiac surgical therapy should be revisited, since data comparing CABG to medical therapy is old, and studies used comparator medical therapies that are no longer in routine use. Optimal patient selection for CABG remains controversial, with a large proportion of patients falling “in the cracks” between clear indications. The STICH trial will be the largest randomized surgical trial in cardiology, and will address how to best manage patients who need bypass surgery. The role of PCI remains to be clarified, but there are indications that this therapy is overused in HF. Surgical ventricular restoration, where scar tissue is removed to restore the heart’s normal form, is a hot topic in cardiology and has provided some encouraging results.

Although treatment of HF will probably be much the same in 2010 as it is today, Dr. Rouleau remains optimistic that therapies are continually improving and highlighted the importance of continually updating the data to inform clinical practice as progress is made.

RESYNCHRONIZATION THERAPY FOR SEVERE HF

Much evidence has been published in the last 10 years supporting the use of cardiac resynchronization therapy (CRT), with three key studies (MIRACLE, COMPANION and CARE-HF) demonstrating a dramatically better impact on patient quality of life compared to beta-blocker therapy. Optimal identification of patients eligible for CRT and who are most likely to benefit, is key to maximizing the benefits of this treatment strategy. Dr. Derek Exner, Associate Professor at the Libin Cardiovascular Institute of Alberta and University of Calgary, reviewed recent and ongoing trials of CRT. Proper lead position improves the likelihood of successful patient outcomes, and new strategies are being investigated that combine pre-operative imaging with CRT. This can help visualize scar tissue, identify important anatomical features, recognize dyssynchrony, and ultimately target leads to areas that will derive the most benefit. Results from ongoing trials are expected to provide important information that could help inform clinical guideline recommendations. “There has been a lot of evidence for CRT since 1999. The future will probably involve

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### General Treatment Strategies in HF

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comprehensive pre-implant assessment to determine if CRT is viable in an individual patient or not,” predicted Dr. Exner.

VENTRICULAR ASSIST DEVICES AND TRANSPLANTATION FOR END STAGE HF

For patients with progressive end-stage HF that is unresponsive to medical, device or standard surgical therapy, options are limited. While transplantation remains the gold standard for such patients, donor waiting lists can be long. Alternative therapies such as cardiac restraining devices or mechanical circulatory support, can function as a bridge until a donor becomes available. As Dr. Renzo Cecere, Associate Professor of Surgery at McGill University, told the ACC Lake Louise Conference attendees, technology for ventricular assist devices has improved to the point where these alternative therapies are now being used serving as much more than just a bridge.

Enlargement is a characteristic feature of HF, and is a predictor of mortality. Therefore, cardiac restraining devices such as CorCap, Acorn and HeartNet can be surgically positioned around the heart to halt progression of HF. For patients who are worsening and showing signs of end organ failure, mechanical circulatory support may be required. Third-generation ventricular assist devices (VADs) such as Levacor use rotary pumps with non-contact bearings, are smaller than earlier models, and are designed for long-term support. Microaxial VADs such as Impella are even smaller, allowing for ease of transplantation, and have the added benefit of requiring minimal anticoagulation. Results have been positive and they are now being investigated for “destination” therapy as a long-term alternative to heart transplantation for patients with end-stage HF and minimal comorbidities. To date, studies suggest that destination therapy offers patients a significantly longer survival than either optimal medical therapy or third-generation VADs, and might provide an outright alternative to heart transplantation. Despite such advances, Dr. Cecere believes that further improvements can still be made. “Can we do better? We think we can. We’re not there yet, but we’re moving in the right direction with destination therapy.”

CLINICAL CONUNDRUMS IN HEART FAILURE

This case study series formed the first workshop of the ACC Lake Louise Conference. Drs. Debra Lynne Isaac, Anique Ducharme and Justin Ezekowitz presented unique case vignettes and facilitated group discussions on topics ranging from myocarditis to amyloid heart disease to the effects of cancer therapies on the heart. Optimal management in these settings is sometimes controversial, and lacks clear-cut direction for clinical practitioners. Some of the key takeaways from this workshop included the following:

- Myocarditis tends to be a diagnosis of exclusion; currently available diagnostic tools lack either sensitivity or specificity.
- Biopsy remains important for patients with suspected myocarditis; clinical criteria for cardiac magnetic resonance (CMR) guided biopsy are currently being developed.
- Conduction problems are common in amyloid heart disease; therefore diuretics and nitrates remain a mainstay of therapy.
- Fat pad biopsy is a relatively simple method for diagnosing amyloidosis and is less invasive than rectal or myocardial biopsy.
- Chemotherapeutic drugs can have significant side effects that affect heart function.
- Patients who have had an episode of chemotherapy-induced HF are at risk of further episodes and permanent heart damage; a step-wise approach to identifying and avoiding the offending agent is necessary.
**UPDATE ON SURGICAL INTERVENTIONS IN CARDIOLOGY**

**MANAGEMENT OF CHRONIC STABLE ANGINA: DO WE HAVE THE COURAGE?**

Coronary revascularization has revolutionized therapy for ischemic heart disease, providing benefits in patients with ACS, post-MI, and patients with chronic stable angina (CSA). Recently, the COURAGE trial comparing optimal medical therapy (OMT) with PCI in patients with CSA were reported, and the study generated a great deal of controversy with its conclusion that PCI, as an initial management strategy, did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT. However, PCI was associated with significantly fewer late revascularization procedures over the following 4.5 years.

Dr. Bernard Gersh, from the Mayo Clinic in Rochester, Minnesota, reviewed the COURAGE study and conclusions in addition to recent controversial findings of other analyses of practice patterns in the USA that demonstrated that there were regional differences in revascularization rates, and the suggestion that PCI is over-utilized in certain regions. Further, like all revascularization trials, COURAGE was probably underpowered due to logistical constraints. This makes drawing clinically relevant conclusions, even in the presence of statistically significant results, a challenge. However, “The COURAGE results largely support clinical practice guidelines, therefore no changes in clinical practice are required at this point,” noted Dr. Gersh. Ongoing trials will explore indications for revascularization in specific sub-populations such as diabetics and those with milder CSA.

**THE EFFICACY & SAFETY OF DRUG-ELUTING STENTS**

“Restenosis can be considered the Achilles Heel of PCI,” according to Dr. Eric Cohen, from Sunnybrook Health Sciences Centre in Toronto. Rates of restenosis range from 15-20% with bare metal stents to 30-40% for angioplasty. Since their introduction in 2003, drug-eluting stents (DES) have come to dominate the field, with proven efficacy at lowering the requirements for repeat interventions. Despite their lower risk for restenosis, current DES are associated with a small incremental risk of stent thrombosis, which is of clinical concern since it frequently results in MI or death. Anti-platelet therapy can significantly reduce the risk of stent thrombosis, however the benefits of very long-term or indefinite dual therapy remain unknown. Bioabsorbable DES have generated much excitement and although the anti-restenotic effect appears durable, there are some concerns that the scaffolding integrity might not persist over the long-term.

When choosing between CABG, bare metal stents or DES, appropriate patient selection is critical. Current Canadian recommendations suggest that DES may be most useful in patients at high risk for repeat intervention such as those with diabetes, whereas there appears to be little difference between bare metal and DES in rates of target vessel revascularization in non-diabetic patients. Extended dual anti-platelet therapy might be beneficial for selected patients, if they are willing and able to adhere to long-term therapy. Regardless of which intervention is selected, patients should be well informed of the potential risks and benefits of all therapeutic options.

**PRACTICAL SOLUTIONS FOR ANTICOAGULATION BRIDGING FOR SURGICAL PROCEDURES**

Balancing a patient’s need for anticoagulation therapy with surgical bleeding risk can be a clinical challenge. Dr. Reginald Smith, a clinical researcher at the Victoria Heart Institute, shared his knowledge on anticoagulation bridging strategies using a case-based presentation. Patients with prosthetic heart valves, atrial fibrillation or venous thromboembolism, are candidates for anticoagulation bridging. Not only can successful anticoagulation bridging improve patient outcomes, it can also save the health care system considerable hospital expenses. A bridging strategy should be planned in advance so that patients can visit the clinic prior to hospital admission for their surgery and learn to self-inject LMWH.
Factors predictive of a high risk for bleeding include neurosurgery, prostatectomy, bladder tumour resection, cardiac surgery, solid organ or cervical cone biopsy, bowel polypectomy, and patients with a pacemaker; low to moderate risk factors include cataract extraction, laparoscopic cholecystectomy, single dental extraction, most cutaneous surgeries, and hernia repair. For epidural anesthesia, close attention should be paid to discontinuing anti-thrombotic and anti-platelet therapy in the days and hours prior to surgery to minimize the risk of bleeding. ASA and NSAIDs do not appear to be associated with hematoma and can be continued. Most agents should be restarted as soon as possible (i.e., within hours following the procedure).

The upcoming Periop 2 trial will evaluate major thromboembolic or hemorrhagic events in high-risk patients undergoing noncardiac elective surgery and compare dalteparin bridging with placebo.

**NOVEL CARDIOVASCULAR TARGETS AND TREATMENT STRATEGIES**

**THE CURRENT AND FUTURE POTENTIAL OF CARDIAC STEM CELL THERAPY FOR REGENERATION**

The promise of cardiac regeneration using stem cell therapy has been the topic of many presentations in past years at the ACC Lake Louise Conference. This year, Dr. Peter Liu, a Senior Scientist at the University of Toronto Health Network, presented new findings that were released early in 2008 and represent considerable advances in stem cell technology. New endothelial cells are involved in neovascularization and angiogenesis, and may thus contribute to cardiac remodeling. One of the challenges with stem cell research has been finding a source of stem cells that can regenerate the myocardium. Bone marrow cells may facilitate nature’s innate repair process but they do not differentiate into myocytes. Embryonic stem cells are a promising source of myocytes, however there remain ethical issues surrounding their harvest and use.

Recently, Takahashi et al. made a “seismic” leap forward in stem cell technology when they demonstrated the ability to reprogram skin cells into pluripotent stem cells in the presence of a cocktail of growth factors. The technique essentially shocks the cells back into being pluripotent cells, with the potential to differentiate into myocytes. The strategy has proven effective in a mouse model of sickle cell anemia, and several companies are now trying to commercialize the technology. “We now know how to take normal cells and turn them into pluripotent stem cells. The next challenge will be to control growth once they turn into myocytes,” commented Dr. Liu.

**THE RENIN-ANGIOTENSIN SYSTEM IN CARDIOVASCULAR DISEASE**

The renin-angiotensin-aldosterone system (RAAS) is a familiar topic and has been the focus of many antihypertensive
strategies. Robust activation of the RAAS is known to result in systemic injury beyond cardiovascular and renal disease; it is also an important factor in end-organ damage and stroke. Landmark clinical trials such as HOPE and ONTARGET have demonstrated that ACE inhibitors and ARBs potently reduce blood pressure and the risk of adverse clinical outcomes. These agents form the foundation of treatment regimens for cardiovascular disease, and have largely contributed to reducing cardiovascular mortality. However, not all patients are able to achieve target blood pressure values even when using combination therapy, and remain at risk of cardiovascular events.

Several new aldosterone modulators that act further upstream in the RAAS than ACE inhibitors and ARBs, have been the focus of recent clinical trials. The first in a new class of antihypertensive agents called direct renin inhibitors was approved in Canada in late 2007. Aliskiren is indicated for the first-line treatment of uncomplicated hypertension in adults, or as add-on therapy to ACE inhibitors, diuretics or dihydropyridine calcium channel blockers (CCBs) in patients with uncontrolled hypertension. Studies have demonstrated the additive blood pressure reduction of aliskiren when combined with gold standard antihypertensive agents such as ACE inhibitors or ARBs. Notably, the combination of aliskiren with an ACE inhibitor reduced the incidence of cough, headache and diarrhea, side effects that can be problematic with ACE inhibitors. In a short-term placebo-controlled study in HF patients, the addition of aliskiren to an ACE inhibitor, ARB or beta-blocker significantly reduced levels of B-type natriuretic peptide (BNP), a biomarker for mortality. “This type of data is encouraging because it’s in line with the drug’s biological activity,” commented Dr. Liu.

Preclinical studies have shown that stimulation of the recently identified ACE 2 or angiotensin 1-7 can reduce blood pressure, increase coronary blood flow, and reduce secondary end-organ damage. Small molecules that upregulate the ACE 2 enzyme are being developed to stimulate this protective pathway. Another molecule generating interest is apelin, an angiotensin II modulator. Preclinical studies suggest that apelin is vasodilatory, maintains cardiac function, reduces hypertrophy, and leads to decreased food intake. “We may in fact be at the beginning of the road when it comes to RAAS modulation,” said Dr. Liu. Stay tuned for new findings regarding the ACE 3 enzyme.

**PFO AND STROKE: CAUSE AND EFFECT OR GUILT BY ASSOCIATION?**

Patent foramen ovale (PFO) describes the incomplete fusion of the primary and secondary septum, and is present in 25-30% of the normal population. According to Dr. Martha Grogan, from the Mayo Clinic in Rochester, Minnesota, retrospective studies suggesting an association between PFO and atrial septal aneurysm (ASA) in patients with cryptogenic stroke, have lead to a “guilty by association” verdict. More recently, prospective population-based studies employing trans-esophageal
echocardiography (TEE) suggest that PFO is not an independent risk factor for future cerebrovascular events in the general population after adjustment for age and comorbidities. However, in an individual patient, PFO may be associated with stroke. Patients with a PFO or ASA who have suffered a stroke do not appear to be at increased risk of recurrent stroke, however those with both conditions are at greater risk.

For patients at risk of recurrent events, anti-platelet therapy is preferred over anticoagulation unless they are at risk of thromboembolic events. There are currently no approved device closures for PFO after cryptogenic stroke, although surgical closure may be an option for patients who have suffered a documented recurrent stroke while on optimal medical therapy. Dr. Grogan concluded her presentation by stating that “Until RCTs provide evidence to suggest otherwise, PFO is innocent until proven guilty.”

13th ANNUAL PFIZER/NOVARTIS RESIDENT’S RESEARCH COMPETITION

Every year, the ACC Lake Louise holds a resident’s research competition sponsored by Pfizer and Novartis. The competition is open to trainees in cardiology and cardiac surgery across the country. Abstracts describing research based upon a clinical question or problem are judged by a blinded panel of experts. The authors of the 4 best submissions are invited to ACC Lake Louise to present their research before an internationally recognized panel of research clinicians. In addition to discussing their work with world experts, the opportunity to present their work to a larger audience, and to discuss this and other questions within the collegial atmosphere of ACC Lake Louise has proven to be an exciting and rewarding experience. Previous winners, such as Dr. Derek Exner, have returned to the ACC Lake Louise Conference as faculty members, highlighting the stellar research potential of the candidates. Many others have gone on to important academic and clinical postings across Canada.

This year’s award was presented to Dr. Jonathon Afilalo from McGill University. His research evaluated age-related changes in lamin A/C expression in cardiomyocytes. Low levels of this nuclear protein have been associated with age-related conditions such as osteoporosis. Dr. Afilalo’s hypothesis was that reduced expression might also be implicated in heart failure. This was stimulated by the observation that familial cardiomyopathy presented a phenotype that was similar to senile cardiomyopathy in elderly patients. Using a mouse model of aging, Dr. Afilalo showed that lamin A/C levels were indeed reduced in older mice. Further, older mice displayed perinuclear distribution of this protein, suggesting that localization of this protein might be more relevant that its quantity. The next step will be to determine whether changes in lamin expression and localization cause myocardial aging or vice versa.
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