CONFERENCE OVERVIEW

Once again, the Annual Cardiology Conference (ACC) at Lake Louise attracted cardiologists from across Canada to learn from recognized national and international clinical researchers and opinion leaders and to engage in collegial discussions during interactive case presentations and question and answer periods. The scientific agenda offered participants a variety of topics that are relevant to current Canadian clinical practice, including recent advances in the state-of-the-art management of acute coronary syndromes, arrhythmias, heart failure, aortic stenosis, and diabetes mellitus. The event continues to offer valuable opportunities for knowledge translation and sharing best practices among clinicians practicing in cardiovascular medicine, drawing together collective knowledge, efforts and innovative strategies to improve patient outcomes and care.

As a value-added component and in an effort to enhance the educational opportunities at the meeting, this report will provide a brief summary of the presentations at the conference.

TAKE HOME MESSAGES FOR CLINICIANS FROM THE 27TH ACC LAKE LOUISE

Dr. Robert Welsh, Co-Chair of the ACC Lake Louise meeting, summarized some of the key messages from this year's conference, with the goal of identifying some practical take-away learnings from the many excellent presentations and high quality scientific content.

Western Canada Atrial Fibrillation Best Practices Meeting

Prior to the start of the ACC Lake Louise meeting, a Best Practices meeting chaired by Drs. Robert Welsh and Russell Quinn and sponsored through an unrestricted grant from Boehringer Ingelheim brought together 16 Western Canadian health professionals with multi-disciplinary expertise in managing atrial fibrillation (AF) to examine care delivery, seek efficiencies, and explore opportunities for supporting optimal patient outcomes. Given the rising burden of AF and associated healthcare utilization, publication of new evidence-based Canadian guidelines for the management of AF, introduction of new therapies for patients with AF, and continuing financial pressures, the timing for this initiative was ideal.

A key opportunity to optimize patient outcomes noted during this Best Practices meeting was the seeking of efficiencies in delivering patient care. Based on the Calgary model, more AF clinics are being established to serve as resources for their surrounding regions. Utilizing the expertise of these clinics represents a unique opportunity to deliver education to all stakeholders in the management of AF, including physicians, nurses, pharmacists, and patients themselves. Likewise, telehealth programs can play an important role in delivering education to both healthcare professionals and patients who live outside larger urban centres.

Dr. Welsh noted that a systematic approach to adopting the CCS guidelines will be required, particularly in implementing changes towards anticoagulation management. As discussed during the Canadian Cardiovascular Society (CCS) workshop on AF management and also noted by Dr. Mario Talajic during his presentation, the new CCS guidelines endorse the use of dabigatran as a preferred agent for many AF patients, and this recommendation should now be adopted into clinical practice. The role of existing anticoagulation clinics “will change substantially in an era where we do not titrate our anticoagulant therapies by testing.”

Because the large majority of AF patients are managed in the primary care setting, connecting AF clinics with primary care providers represents a key opportunity to successfully adopt the CCS recommendations and provide efficient, high-quality patient care. Governments are funding Primary Care Networks (PCNs) to improve patient care through amalgamating care and developing expertise and mechanisms of delivering care. Therefore, “an emphasis in developing a systems approach that
connects AF clinics and anticoagulation clinics with PCNs” will be important. As Dr. Welsh emphasized, “linking into those networks is a key opportunity.”

Sharing Best Practices in ACS

During a second pre-conference meeting sponsored by sanofi-aventis and BMS, the Western Canadian ACS and Interventional Cardiology Working Group met with the objective of sharing best practices and learning from each other’s collective experience. This discussion spanned the entire spectrum of ACS care, from the front end where patients enter into the healthcare system, through the treatment of ACS or elective stable CAD and in-hospital care, to optimal discharge planning, including compliance and communication with other healthcare professionals involved in patient care. Dr. Welsh urged groups that were not involved in this pre-meeting to either link in with the Working Group and to become involved in the sharing best practices concept, or to host their own similar regional meeting. “We have the evidence – we’re really talking now about implementation… we need to now look at collaborating and bringing data together… and really working towards unifying and improving outcomes across the country.”

Disease State Discussion on ACS

There is much excitement around novel antiplatelet agents and the results of recent clinical trials demonstrating that these therapies improve clinical outcomes, including reduced mortality, decreased stent thrombosis, and decreased rates of re-infarction. The increased risk of bleeding associated with these new agents and regimens were well elucidated during the conference. The discussions surrounding the realities of changing patterns of care, which have been developed over a decade or more, is a strong reflection that these new agents are very important. A thoughtful approach to incorporating new agents into clinical practice will be required to prevent the ‘Acute Confusional State’, whereby patients are sent home on new agents that family physicians may not have learned about yet. Changes to current processes of care will need to be carefully and thoughtfully addressed as these agents are introduced into practice.

The complexity around the optimal ASA dose to use in ACS – a drug that has been used for this indication for many decades – provided an interesting discussion. The take home message is that low-dose ASA is effective and safe.

The discussion on “walking the tightrope” – balancing risk and benefit in the management of ACS – underscored the importance of thinking about an individual patient. This entails not only appropriate risk stratification, but also applying the correct dosing of antithrombotic medications so that the risk of ischemic events can be maximized without exposing patients to excessive risk of bleeding.

Clinicians agree that mortality is the final common denominator in clinical trials of ACS. However, in an era of contracting research budgets, powering trials on mortality endpoints alone is unrealistic. Efforts to define multiple endpoints in ACS clinical trials that are both understandable to clinicians and scientifically valid must continue so that new agents can be developed to improve patient care. Clinicians must be prepared to consider new mechanisms and new ways of testing novel drugs to successfully advance them into clinical practice.

ACC Lake Louise Heart Failure Activities

Presentations and workshops related to heart failure management were extensive again this year at the ACC Lake Louise meeting, reflecting the importance of this clinical condition. Drs. Peter Liu and Anique Ducharme were challenged with the task of summarizing the latest evidence in heart failure and how it is impacting current approaches in clinical practice. Drs. Bernard Gersh and Gary Lopaschuk gave conference participants a peek into the future, with an update on stem cell approaches to the management of heart failure and basic science breakthroughs that may impact clinicians in the coming years. The CCS Heart Failure workshop was an integral part of the knowledge translation process and helped to bring all the latest data and guidelines into practical relevance.

Diabetes Mellitus

Clinicians are well aware of the importance of this common condition, which was extensively discussed through several plenary presentations. It will become
Increasingly important for clinicians to understand the role of diabetes in optimizing the care of patients, since it so commonly overlaps with CAD. Despite the recognized importance of diabetes, clinical trials typically fail to show improvements in outcomes despite the extensive effort that goes into the management of this disease. Dr. Welsh opined that “The ACCORD results have left us in an era of disappointment… the enthusiasm of the new group of agents was clearly followed by disappointment.” Improvements have been demonstrated in ACS research using the more potent antiplatelet agents in diabetic patients that in some cases appear to be larger than in non-diabetic populations, but much work remains to be done.

**New Opportunities for Management of Aortic Stenosis**

Transcatheter aortic valve implantation (TAVI) demonstrated positive results in the management of aortic stenosis on a level never before reported, with a significant 20% absolute risk reduction in mortality in the PARTNER trial, representing a number-needed-to-treat of only five. Dr. Welsh pointed out that this benefit would be in the range of using antibiotics for the treatment of pneumonia. “There are very few things we’ve done that make this type of difference,” he stated. However, clinicians will need to take a step back and look at the reality of the numbers from this trial: patients in the PARTNER trial standard of care arm had a 50% mortality rate despite current optimal care, and although an impressive 20% reduction in mortality was shown, 30% of patients still died at 1 year with the TAVI procedure. This is a very complex group of patients, and it will be a challenge to appropriately manage healthcare resources given that the procedure costs approximately $25,000, slightly more than open aortic valve surgery when all the additional costs are included.

**Thoughtful Reflections**

Discussions surrounding the care of elderly patients were prominent at this year’s ACC Lake Louise. Dr. Paul Armstrong gave a very eloquent discussion about the “elderly tsunami” and how it may impact the care of patients today and in the future. Today’s elderly patients are healthier than elderly patients of the past; however, they present with an increasing disease burden due to longer exposure that accompanies increased longevity. Dr. Jean Rouleau delivered the inaugural ACC Lake Louise Annual Lecture and presented some of the ethics of invasive procedures in the frail elderly. This is a complex topic which promises to figure more and more prominently in the practice of all clinicians as the elderly population continues to increase. Some of the difficult considerations include the reality of costs in a healthcare system with limited resources. Physicians will continue to be the gatekeepers of costs, testing, procedures and associated outcomes, with increasing administrative involvement as these challenging decisions are made.
Despite the recognized value of combination antiplatelet and anticoagulant therapy in reducing ischemic events in patients with acute coronary syndromes (ACS), these treatments are also associated with increased bleeding risk, particularly in those who undergo coronary procedures. Dr. Shaun Goodman, a researcher at the Canadian Heart Research Centre and Institute at St. Michael’s Hospital, University of Toronto, addressed the importance of risk stratification to maximize the benefits of antithrombotic therapy while minimizing its associated risks. “Even if we have a good drug, if we don’t apply it in the right way we’ll see an increased risk of bleeding and other adverse outcomes.”

Dr. Goodman cited a recently published editorial by Armstrong & Welsh (J Am Coll Cardiol Intv 2010) highlighting some of the “rear-view mirror observations on bleeding risk in ACS.” Importantly, both the magnitude of benefit and the risk of bleeding shift differentially based on several factors: individual patient characteristics, the evolution of risk during hospital stay, the antithrombotic strategy, and timing of invasive assessment. This presents a clinical dilemma, since patients who are at the highest ischemic risk stand to gain the most benefit from intensive pharmacologic therapy and an early invasive strategy, but they are also at the highest risk of bleeding. Currently, there is no single integrated risk score that combines both efficacy and safety features that would enhance clinical decision-making.

St. Michael’s Hospital has incorporated automated prompts for calculating risk scores into their computerized order entry forms for ACS patients. Other strategies to maximize efficacy and minimize bleeding risk include appropriate antithrombotic dosing based on patient characteristics and concomitant therapies; following evidence-based guidelines for the selection of antithrombotic therapy; using antithrombotic therapy for the minimum duration of time; and selection of the ideal invasive procedural timing, technique (e.g., radial approach) and device (e.g., bare metal stent).
There has been much debate in recent years regarding how to dose ASA appropriately in patients with ACS. Dr. Matthew Roe, from the Duke Clinical Research Institute, discussed current guideline recommendations for ASA dosing, the trials on which current recommendations were based, and how the latest trials using direct P2Y\textsubscript{12} platelet inhibitors might influence future ASA dosing recommendations. The most recent American (ACC/AHA 2007) guidelines recommend the use of high dose ASA initially (up to 325 mg/d) followed by lower dose (75-162 mg/d) as maintenance therapy, depending on type of ACS, presence and type of stent implanted, and the management approach.

Since the guidelines were released, the CURRENT OASIS-7 study was published. Patients were randomized to receive standard or double-dose clopidogrel with high- or low-dose ASA. In the comparison of high- vs. low-dose ASA, there was no difference in the rate of stent thrombosis, suggesting that ACS patients who receive a stent do not require higher doses of ASA. Furthermore, there were no differences in ischemic or bleeding events in patients maintained on high- vs. low-dose ASA. The impact of ASA dose on subgroups of STEMI vs. NSTEMI patients is not yet reported.

The influence of ASA dose on P2Y\textsubscript{12} inhibitors is currently a ‘hot topic’ with recently published results of the TRITON TIMI-38 and PLATO studies. The dose of ASA was not randomized in either study. In the TRITON trial, there was no difference in stent thrombosis across three tertiles of acute ASA dose (<162 mg, 162-300 mg, and >300 mg) irrespective of concomitant treatment with prasugrel or clopidogrel.

The PLATO trial has raised several questions with respect to ASA dosing and P2Y\textsubscript{12} inhibitors. Pre-specified subgroup analyses showed that patients receiving higher doses of ASA (≥300 mg/d) had a higher risk of CV death/MI/stroke, and the risk was highest in patients receiving high-dose ASA plus ticagrelor. These findings suggest that ticagrelor efficacy is dependent on ASA dose.

Dr. Roe predicted that the next updates to clinical practice guidelines will probably recommend low doses of ASA in the maintenance setting for all ACS patients, since data generally do not indicate any clear benefits of doses >100 mg, with potential increased risks of bleeding. Moreover, future ACS trials will likely evaluate the ASA dose effect. Until the next guideline recommendations become available, Dr. Roe advised clinicians to “Evaluate each patient’s ischemic and bleeding risks… and consider the ASA dose and the choice of a P2Y\textsubscript{12} inhibitor within that context.”
Dr. Shaun Goodman summarized the latest evidence for dual antiplatelet therapies in the management of ACS, and offered his perspective on the clinical implications of having a wider variety of available treatment options. Dual antiplatelet therapy with clopidogrel and ASA has become the standard of care in Canada for STEMI, NSTEMI and unstable angina, based on the positive results of randomized controlled trials (RCTs) including CURE, CLARITY-TIMI 28, COMMIT, and more recently, CURRENT-OASIS 7.

Prasugrel overcomes some of the known limitations of clopidogrel by providing the same active compound with one fewer metabolic step and offers more rapid and more potent antiplatelet effects. The TRITON TIMI-38 trial showed a significantly lower risk of the composite primary endpoint of CV death/MI/stroke with prasugrel compared to standard dose clopidogrel in ACS patients undergoing a percutaneous coronary intervention (PCI). Balanced against this greater efficacy was a higher risk of bleeding, including intracranial hemorrhage in patients with a prior history of stroke or transient ischemic attack.

Ticagrelor (which was just approved for use in Canada as of June, 2011), works differently from clopidogrel and prasugrel: it does not require in vivo biotransformation and offers reversible platelet inhibition. The PLATO study demonstrated the benefits of ticagrelor over clopidogrel in a broad range of ACS patients. This novel antiplatelet agent demonstrated a unique effect of reducing cardiovascular mortality and all-cause mortality compared with clopidogrel. Ticagrelor was associated with a higher risk of non-CABG related bleeding, with no significant differences in other types of bleeding.

Dr. Goodman offered the following “bottom line” perspectives on antiplatelet therapies for ACS:

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
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<tbody>
<tr>
<td>Standard dosing (300 mg load → 75 mg/d in ACS patients)</td>
<td>60 mg load → 10 mg/d in ACS patients undergoing PCI</td>
<td>180 mg → 90 mg b.i.d. in ACS patients (antiplatelet effect 24 hours after last dose is at least comparable to clopidogrel)</td>
</tr>
<tr>
<td>Double dosing (600 mg load → 150 mg/d x 6 days) in patients undergoing PCI</td>
<td>Better efficacy (MI reduction) but bleeding concerns especially in prior stroke/TIA; caution in elderly, low body weight</td>
<td>Better efficacy (including mortality reduction) with modest increase in bleeding</td>
</tr>
<tr>
<td>Regular dosing (75 mg/d) for 1 year post-ACS (potentially &gt;1 year for patients with DES)</td>
<td>Which patients? • Primary PCI • NSTEMI and unstable angina (UA) patients who need PCI but have not received antecedent clopidogrel</td>
<td>Which patients? Entire spectrum of ACS (except fibrinolytic-treated STEMI patients)</td>
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Dr. Goodman reminded the audience of some of the practical issues with respect to incorporating new antiplatelet agents into clinical practice. For example, current guidelines and protocols for clopidogrel are well-established; the complexity of picking and choosing between multiple options and incorporating these into care pathways; and post-discharge issues such as drug coverage and the unknown safety issues of switching between antiplatelet agents.
Early studies of thrombolytic therapy suggested that there were hazards with early reperfusion, and that restoring blood flow might liberate damaging cytokines and inflammatory mediators. Several approaches to minimizing reperfusion injury have been developed, but their impact on clinical outcomes remains uncertain. Dr. Matthew Roe reviewed some of the many trials that have evaluated different agents for minimizing reperfusion injury, as well as new strategies currently under investigation to reduce infarct size, improve myocardial healing, prevent apoptosis, and enhance regeneration.

Many exciting compounds have shown positive results in animal models, but proved disappointing in phase I/II human trials. One of the key challenges to reperfusion in humans is the narrow window to prevent irreversible myocardial damage, since the opportunity for salvage typically peaks around 3 hours. Despite public awareness campaigns, it remains a challenge for STEMI patients to present earlier than 90 minutes from symptom onset. More recently, cardioprotective strategies for reducing reperfusion injury have been the focus of research efforts, including ischemic post-conditioning strategies, pharmacologic activation of the reperfusion injury salvage kinase (RISK) pathway, pharmacologic inhibition of mitochondrial permeability transition pore (PTP) opening, and combined pharmacologic approaches. This “new paradigm” to limiting reperfusion injury offers hope for improving survival and salvage, however, further investigation is still needed.

While not all newer strategies are proving successful, they are providing important insights on the complex pathways involved in reperfusion injury and are informing the design of future studies in this area (e.g., anterior MIs and older patients appear to have larger infarcts). Moreover, potential new biomarkers for assessing reperfusion injury are being identified and evaluated for their ability to show early changes in myocardial viability and perfusion measures. Dr. Roe concluded that there are multiple targets currently being studied as reperfusion injury treatments, but he advocated for developing a more standard approach to early phase trials. “We need to be much clearer on what clinical endpoints to use if we have an agent that looks beneficial in phase 2 testing, for how we could take it to phase 3 in a very logical but also accurate manner.”
Dr. Paul Armstrong, from the University of Alberta, presented an overview of outcome measures utilized in recent ACS clinical trials and their limitations. Among the many strategies to improve research on secondary prevention after ACS, he focused on improving the definition of pre-specified composite outcomes.

Dr. Armstrong used two examples to illustrate the problems of using composites as a primary endpoint. First, the CLARITY study reported an impressive 20% reduction in the incidence of CV death/MI/re-ischemia requiring urgent revascularization in STEMI patients receiving clopidogrel versus placebo. While TIMI flow grades and recurrent MI lined up with the composite endpoint, mortality “went the other way.” Likewise, the TRANSFER study reported a significant benefit of early transfer of STEMI patients for PCI after fibrinolysis using a composite endpoint of death/re-MI/recurrent ischemia/CHF/shock, yet mortality and cardiogenic shock were lower in the standard treatment group.

A further limitation to the use of composite primary endpoints is that not all component events are created equal. Moreover, traditional composites capture only a patient’s first event, which may not be their only event or their most important event. Dr. Armstrong suggested that weighted analysis was one approach that future trials should consider when using a composite primary endpoint. Other novel approaches include randomized withdrawal trial designs to assist in defining time over which treatment is beneficial; use of novel endpoints such as aborted MI or number of days symptom-free and other quality of life measures; and use of surrogate endpoints (e.g., biomarkers, imaging, functional assessments).

Dr. Armstrong concluded his presentation by suggesting that “We need to take a second look at composite endpoints and be more critical and more creative as we design more efficient and more cost-effective trials.”

**MONDAY AM**

**INNOVATION IN HEALTH CARE: SHARING BEST PRACTICES FROM WESTERN CANADA**

Last February, a group of experts from major cardiac care centres in British Columbia and Alberta met with the goal of sharing best practices to improve systems of care. Dr. Blair O’Neill, Division Director of Cardiology at the University of Alberta, presented an overview of some of the innovative programs that are helping to improve the patient journey in patients presenting with ACS, including the following:

- Early Cardiac Access Clinic at the Calgary Foothills Hospital
- RADAR (Risk Assessment in ACS patients with early Discharge and Access to cardiac Rehabilitation) at the Mazankowski Alberta Heart Institute
- Radial approach to PCI at the Royal Jubilee Hospital
- Fraser Health Authority’s Rapid access to care in STEMI patients
- Return to Sender same-day repatriation program at the Royal Alexandra Hospital
- LEAN process improvement to reduce patient time in the catheterization lab at the Vancouver General Hospital
- Smoking cessation program at St. Paul’s Hospital

Dr. O’Neill shared the enthusiasm of all of the delegates who were representing their respective centres at the sharing best practices meeting. Knowledge translation was a key component, and strategies to use this concept as a process to implement and spread best practices were discussed. Dr. O’Neill commented that “Knowledge translation, doing things better and closing care gaps can be accomplished locally but you need local champions and advocates… These sharing best practices [meetings] need to be continued.”
UPDATE IN INTERVENTIONAL CARDIOLOGY – IMPACT OF PHYSIOLOGICAL CORONARY ASSESSMENT AND INTRAVASCULAR IMAGING ON PERCUTANEOUS REvascularization

The most recent European guidelines on myocardial revascularization recommend that patients with multivessel disease should be offered revascularization to improve their prognosis, and that revascularization should be targeted to alleviate documented ischemia. Moreover, in the most severe patterns of CAD, CABG appears to offer a survival benefit over PCI, as well as marked reduction in the need for repeat revascularization. This recommendation reflects the 1-, 2-, and 3-year results of the SYNTAX study, which compared CABG to multivessel PCI using Taxus™ drug-eluting stents. More recently, two meta-analyses have supported the use of the other first generation DES, namely Cypher®, and the second generation DES Xience V™, which may reduce the need for repeat revascularization by as much as 50% over the Taxus stent. Another limitation of the SYNTAX study is that angiography was used to identify which lesions to dilate (i.e., those with >50% stenosis). Dr. Erick Schampaert, Head of the Division of Cardiology at the Hôpital du Sacré-Coeur de Montréal, described how new technologies are providing additional guidance on targeted revascularization.

Fractional flow reserve (FFR) is a physiological assessment that describes the extent (%) to which myocardial flow is limited by epicardial stenosis. The FAME study compared angiography-guided vs. FFR-guided PCI in patients with multivessel CAD, and results suggest that FFR simplifies the diagnosis and the procedure allowing for an “all-in-one approach” in the catheterization lab as well as improved patient outcomes. This simple procedure identified that two thirds of lesions with up to 70% stenosis had no ischemia (FFR ≥0.8) and therefore did not require dilatation. Indeed, FFR-guided PCI significantly reduced the number of stents implanted compared to the angiography-guided arm and more importantly, resulted in a 28% reduction in major adverse cardiac events (MACE) at 1 year and a significant reduction in the composite of death/MI at 2 years. During a 2-year follow-up, only 0.2% of deferred lesions based on FFR resulted in a late MI, supporting the safety of this approach.

Intravascular ultrasound (IVUS) offers “virtual histology” that can differentiate tissue that is fibrous, fibro-fatty, densely calcified, or necrotic, and identify plaques that are prone to rupture. In the PROSPECT study, patients with ACS who underwent 1- or 2-vessel PCI also underwent IVUS imaging of the entire coronary tree to obtain grey-scale imaging and virtual histology. Over 3 years of follow-up, the MACE event rate was similar in culprit and nonculprit lesions. Non-culprit lesion events occurred only at sites with at least 40% plaque burden by baseline IVUS, the majority of which were angiographically silent. The results validate the “vulnerable plaque” hypothesis and establish a link between coronary anatomy and pathology. Dr. Schampaert noted that the complication rate related to imaging was 1.6%, therefore, in the absence of documented therapy to improve outcomes beyond aggressive medical therapy, routine imaging of the vessel is not justified at this point in time.

THE ROLE AND APPROPRIATE UTILIZATION OF FUNCTIONAL IMAGING IN MANAGEMENT OF CHRONIC CAD

Dr. Bernard Gersh, from the Mayo Clinic, reviewed the role of functional imaging in the management of patients with chronic CAD. Singe Photon Emission Computed Tomography (SPECT) stress testing can be a useful diagnostic procedure in patients who cannot perform an exercise ECG test, those with a nondiagnostic ECG, or with an intermediate Duke treadmill score. In many cases, functional imaging is important in localizing the extent and severity of ischemia, and it may be helpful in patients where the severity of stenosis is uncertain. However, it is not required in all patients with CAD, and should only be undertaken when the results of the test are
expected to influence clinical management.

Functional imaging can also play a role in determining the prognosis and indications for coronary revascularization. The AHA/ACC guidelines recommend revascularization for patients with severe symptoms of angina despite medical therapy. In patients with mild-to-moderate stable symptoms, noninvasive testing is recommended to inform decisions on revascularization or angiography. Yet studies show that less than half of patients in the USA undergo stress testing prior to elective PCI. Dr. Gersh questioned who these patients are, and suggested that “either they don’t have class III or IV angina, or we’re not following the guidelines… and this is despite a 4-fold increase in the use of medical imaging [from 1995-2005].”

Finally, Dr. Gersh addressed the role of functional imaging in the preoperative evaluation of patients with CAD undergoing noncardiac vascular surgery (e.g., carotid endarterectomy). His key message is that the decision to revascularize should be made independently of the decision for vascular surgery, and that functional imaging can provide guidance on the decision to revascularize.

Dr. Gersh concluded by highlighting some of the potential drawbacks to noninvasive testing. These include the “cascade effect” where patients undergoing noncardiac surgery have incidental findings that shift the focus away from their primary problem towards stable CAD; the non-negligible burden of radiation exposure and its association with cancer; and the limited evidence base showing the impact of imaging on health outcomes such as reduced mortality or CV events.

Demographics in developed countries are undergoing a significant shift, whereby a growing proportion of the population is 65 years of age or older. This “elderly tsunami” is poised to become a powerful multifaceted health challenge, for which, according to Dr. Paul Armstrong, “we are ill prepared.”

The prevalence of many cardiovascular illnesses increases in parallel with aging. While the majority of acute MI events occur in seniors, survival in this group is markedly reduced, partly due to the growing burden of heart failure in the 5 years post-MI. Several important differences have been identified between younger and older patients with cardiovascular conditions, including reduced cardiovascular reserve, reduced creatinine clearance, and altered pharmacodynamics and pharmacokinetics (e.g., reduced lean mass and total body water, relatively increased body fat, changes in gut motility and absorption, and changes in hepatic function that can increase the risk of drug-drug interactions). Moreover, counter-regulatory mechanisms are compromised with advancing age, resulting in the potential exaggeration of drug responses. Dr. Armstrong commented that the Canadian Cardiovascular Society’s guidelines to “start low and go slow… but keep going,” make good clinical sense.

Results of recent trials that included older patients underscore the impact of age on treatment outcomes. For example, a benefit of prasugrel over clopidogrel was not demonstrated in patients aged ≥75 years in the TRITON study, despite a significant benefit in the overall population. This led the FDA to require a black box warning on the product label. The TRILOGY study is expected to provide more information on the safety of prasugrel in older patients, as it evaluates a lower dose (5 mg) in patients aged ≥75 years or those with low body weight (<60 kg). “Before we discard very effective therapies especially in the elderly, we need to be sensitive to issues of dose response,” Dr. Armstrong noted. Tailoring therapy to elderly patients to explore the optimal balance between efficacy and safety should become integrated into future trials, since the number of events is far disproportionate to their representation in trials. The STREAM study will be the first to systematically evaluate lower dosing strategies in older patients receiving reperfusion therapy early after MI.
ARRHYTHMIA

ANTI-THROMBOTIC THERAPY OF ATRIAL FIBRILLATION

Dr. Mario Talajic, a cardiac electrophysiologist at the Montreal Heart Institute and Chair of the Department of Medicine at the University of Montreal, reviewed clinical data for new oral anticoagulants for prevention of stroke in patients with atrial fibrillation (AF). Dabigatran is now available for this indication in Canada based on the results of the large, prospective RE-LY trial, which randomized >18,000 patients with AF and at least one risk factor for stroke to either adjusted-dose warfarin or to dabigatran 110 mg bid or 150 mg bid. RE-LY demonstrated a statistically significant 35% reduction in the primary outcome of stroke or systemic embolism with the 150 mg dose of dabigatran compared to warfarin. Both doses of dabigatran significantly reduced the incidence of hemorrhagic stroke by 69% and 74% compared to warfarin, respectively. In a subgroup analysis, the effects of the 150 mg dose were consistent across patients classified by CHADS2 score, showing benefit even in patients deemed at low risk of stroke. The incidence of major bleeding was lower with the 110 mg dose of dabigatran while the 150 mg dose of dabigatran was similar to warfarin; gastrointestinal bleeding was increased with the 150 mg dose compared to warfarin.

Other subgroup analyses support the benefits of dabigatran even in elderly patients (≥75 years of age). Although the reduced risk of major bleeding associated with the 110 mg dose is attenuated in elderly patients, both doses of dabigatran reduce the risk of intracranial hemorrhage in all age groups. An updated analysis of the RE-LY data evaluating MI rates was recently published. Further screening for asymptomatic MI identified additional cases; when these were considered together with clinical MIs, there was a 0.2% absolute difference in annualized rates between dabigatran and warfarin which was not statistically significant. A net clinical benefit with the 150 mg dose of dabigatran was observed in this analysis, even in patients with previous MI or CAD.

Although dabigatran is not yet listed on provincial formularies, a cost-effectiveness analysis submitted to Quebec’s Conseil des médicaments showed that dabigatran 150 mg bid is more cost-effective than warfarin when the costs of medication, hospitalization, stroke and monitoring are considered. Dr. Talajic noted that “this kind of analysis is useful in convincing our payers that this medication should be provided.”

The Canadian Cardiovascular Society’s most recent AF guidelines recommend that most patients should receive an oral anticoagulant; further, when oral anticoagulation therapy is indicated, dabigatran is preferred over warfarin in most patients. In general, the 150 mg bid dose of dabigatran is preferable to a dose of 110 mg bid. In AF patients at high risk of coronary events, warfarin is preferred over dabigatran. Dr. Talajic remarked that in his opinion, patients at high risk of coronary events are those who have had a recent ACS event, but he would not hesitate to use dabigatran in patients with stable CAD. The situation is more complex in patients with a recent ACS or PCI, where combination oral anticoagulation therapy and antiplatelet therapy is usually required. For these patients, the CCS guidelines recommend ASA plus clopidogrel in patients with a CHADS2 score ≤1, since the risk of stroke is modest, whereas triple oral antithrombotic therapy is recommended in patients with CHADS2 score ≥2.

Dr. Talajic also reviewed clinical trial data for other novel anticoagulants that are in development. The ROCKET-AF study, expected to be published later in 2011, showed that rivaroxaban was non-inferior to warfarin at preventing the primary endpoint of stroke and non-CNS embolism in AF patients with two or more risk factors for stroke and significantly reduced the risk of intracranial hemorrhage. There were no differences between rivaroxaban and warfarin in the rate of major bleeding. Apixaban has been evaluated in two major trials in patients with AF and at least one other stroke risk factor. One trial compared apixaban against warfarin (ARISTOTLE) and the other against ASA (AVERROES). In AVERROES, apixaban was significantly more effective than ASA at preventing stroke, with similar rates of major bleeding. Results from ARISTOTLE are expected later in 2011.
Dr. Talajic pointed out that the clinical trials of new anticoagulants were conducted in markedly different patient populations according to age, CHADS2 score, prior stroke history, comorbidities, and time in therapeutic range for patients treated with warfarin, making their results difficult to compare. Nevertheless, all the new anticoagulant agents appear to markedly reduce the incidence of intracranial hemorrhage, and Dr. Talajic predicted that this will probably drive a lot of the use of these medications in the coming years.

The ACCORD study was a landmark trial that aimed to clarify the optimal goals of therapy for patients with diabetes with respect to glucose, blood pressure and lipids. Dr. Todd Anderson, Director of the Libin Cardiovascular Institute in Calgary, reviewed the results of the ACCORD and similar trials, to provide an update on treatment goals for patients with diabetes.

The glucose control arm of the ACCORD study, where patients randomized to an intensive strategy achieved an average HbA1c level of 6.4% and those treated with standard therapy reached 7.5%, was stopped early due to an excess rate of death in the intensive therapy group at 5 years. At that time, patients in the intensive therapy arm were re-assigned to a more lenient glucose target (HbA1c 7.0-7.9%). Results of the 5-year follow-up were recently published, and show that death from cardiovascular causes and death from any cause continued to be worse in patients originally randomized to intensive therapy. Although the mechanism remains unclear, there was a higher incidence of hypoglycemia and weight gain in the intensive therapy group. Two other glucose control studies were published around the same time as ACCORD: the ADVANCE study and the VADT. Neither study reported an increased risk of death with intensive glucose control, nor did they demonstrate benefits in terms of macrovascular complications when HbA1c targets were <7.0%.

Similarly, the blood pressure arm of the ACCORD study failed to demonstrate a macrovascular benefit of achieving a blood pressure target of <120 mmHg SBP compared with <140 mmHg, although there was a significant advantage in terms of nonfatal stroke. Likewise, the ACCORD study failed to demonstrate a benefit of adding a fenofibrate to statin therapy in terms of the triple endpoint of MI/CV death/CVA. In a post-hoc analysis, there was a hint that patients with higher triglyceride levels and lower HDL did better with dual therapy, however this did not reach statistical significance.

Current guideline recommendations for target goals in diabetes patients are likely to remain unchanged: HbA1c <7%; blood pressure <130/80 mmHg; LDL cholesterol <2.0 mmol/L.
Dr. Anderson concluded his presentation by reflecting on the use of ASA in patients with diabetes. In a recently published review, ASA conferred a non-significant 9% risk reduction in CHD events in patients with diabetes and a 15% risk reduction in stroke that was also not significant. He commented that “we felt it was a given that ASA should be used in patients with diabetes but now it looks like the data is not as clear as we thought it would be... I think we can be selective in our use of ASA in diabetes patients, since not all will gain benefit.”

**RATE, RHYTHM AND REFLECTION IN 2011**

Expanding on Dr. Armstrong’s presentation on the “elderly tsunami,” Dr. Derek Exner, from the Libin Cardiovascular Institute, addressed the looming challenge of managing the growing number of patients with atrial fibrillation. For the majority of patients, decisions surrounding rate or rhythm control remain central, and should be individualized based on a patient’s underlying heart disease characteristics (see figure on the right) as well as their expectations and preferences.

Results of a recent Canadian study suggest that in the real world, more than half of patients presenting to the emergency department with acute atrial fibrillation receive a rate control agent, often in combination with a rhythm control agent. The AFFIRM study suggests that rate control is successful in 81% of patients and can typically be achieved using monotherapy. The RACE II study assessed two different definitions of rate control in patients with permanent atrial fibrillation: strict (heart rate <80 by ECG and <110 at 25% duration of maximal exercise time) versus lenient (HR <110 by ECG). There was no difference in a primary composite outcome that included mortality, stroke and intolerance of drugs, but when the components were evaluated separately, there was a 1% absolute difference in mortality favouring the lenient control group. Although the finding may be due to chance, Dr. Exner suggested that it might also reflect potential complications associated with the higher use of combination therapy in the strict control group (69% vs. 30% in the lenient group). Furthermore, the definition for strict rate control used by the RACE II investigators may not be the most useful in clinical practice.

The most recent CCS guidelines on the management of atrial fibrillation recommend dronedarone as a second-line agent for rate control and as a first-line rhythm control agent, whereas amiodarone has been relegated to second line. These two strategies were compared in the DIONYSOS study, and the results showed that amiodarone was significantly more effective than dronedarone at reducing the recurrence of atrial fibrillation, with a similar incidence of premature study drug discontinuations due to intolerance. However, Dr. Exner cautioned that the short duration of follow-
up of this study (1 year) makes the interpretation of the tolerability findings difficult, since side effects of amiodarone are cumulative and typically do not emerge until more than a year after drug initiation.

There are several ongoing studies that will help guide decisions on the optimal management of atrial fibrillation, including the APHRODITE study comparing the addition of dronedarone to standard rate control therapy; the CABANA study comparing catheter ablation to either rate or rhythm control; and the RAFT AF study comparing ablation-based rhythm control versus drug therapy in patients with heart failure and a high burden of atrial fibrillation. Stay tuned for the results of these trials, which are expected over the next 1-5 years.

**RISKS AND BENEFITS OF CARDIAC RESYNCHRONIZATION THERAPY: EXPANDING INDICATIONS**

Abnormal activation sequences are highly predictive of mortality in patients with symptomatic heart failure (HF), and in this setting, cardiac resynchronization therapy can improve survival and promote cardiac remodeling. Indeed, a meta-analysis of 14 RCTs evaluating cardiac resynchronization therapy demonstrated a highly statistically significant 22% reduction in all-cause mortality in patients with advanced HF (NYHA Class III/IV), with a relatively low risk of system-related adverse effects. While this has become standard recommended therapy for this group of patients, less was known about the benefits and risks of chronic resynchronization therapy in patients with mildly symptomatic HF (NYHA Class I/II). Dr. Brent Mitchell, from the Libin Cardiovascular Institute of Alberta, reviewed the most recent data to shed some light on expanding indications for cardiac resynchronization therapy.

A meta-analysis of four trials suggests that cardiac resynchronization therapy is effective in mildly symptomatic patients with HF and reduces all-cause mortality by 25% over 5 years, with a number-needed-to-treat of 17. The incidence of morbidity (~10%) and mortality (0.1%) were low, and there were subjective improvements in quality of life measures and 6-minute walk test, although these did not reach statistical significance. In a subgroup analysis of the Canadian-led RAFT trial, wider QRS intervals, left bundle branch block (LBBB), and more depressed left ventricular ejection fraction (LVEF) predicted greater benefit of resynchronization therapy with reversal of adverse ventricular structural remodeling, reduction in hospital admissions for HF, and reduction in all-cause mortality. An economic analysis from the RAFT study should provide important information on the cost-effectiveness of this strategy in mildly symptomatic HF patients.
In the last 20 years, improvements in the management of CHF have been characterized predominantly by improvements in hemodynamics and neurohormonal inhibition, as well as by the use of non-pharmacologic devices. New and innovative approaches in development are centered on four main areas (see figure), which were reviewed by Dr. Gersh, a clinical researcher from the Mayo Clinic. Among the new potential therapeutic targets for LV remodeling, natriuretic peptides have received much attention in recent years (and were the topic of a presentation by Dr. Peter Liu at the 2010 ACC Lake Louise). Dr. Gersh predicted that clinicians will see more remote hemodynamic monitoring in CHF in coming years, since studies suggest this approach can reduce death and HF hospitalization. Likewise, pharmacogenomic profiling “is an approach we’ll see much more of in the future.”

The signaling pathways involved in LV hypertrophy and CHF are complex and while the elucidation of these pathways offers a plethora of potential new targets and drugs, the potential problem of cross-talk between protective and pathophysiological pathways will be a challenge to overcome. Nevertheless, “untangling the molecular web” is likely to be another key approach for the future.

Surgical approaches such as revascularization for ischemic cardiomyopathy as well as destination and bridge therapies are currently an area of intense investigation. Cardiac transplantation continues to be limited by donor supply, and although xenotransplantation is a continuing area of research, it presents a formidable immunologic challenge. A subset of patients with dilated cardiomyopathy appear to recover from CHF with LV assist devices, and understanding the molecular mechanisms involved in recovery will help identify new therapeutic targets. A fascinating new approach currently being evaluated in animal models involves a “total biological heart” where a heart is decellularized, and then the scaffold is repopulated with neonatal cardiac and aortic endothelial cells.

Trials evaluating cell repair therapies have shown only modest results, however, Dr. Gersh predicted that as stem cell viability is improved and as more appropriate types of stem cells are selected, the results of clinical trials may prove more promising. Understanding the cellular environment around the infarct will be a key to overcoming the barriers to myocardial regeneration and will guide the development of approaches to make this environment less hostile for stem cell retention. Other evolving stem cell approaches involve cardiopoietic “cardiac cocktails” that guide the differentiation of mesenchymal stem cells into cardiomyocytes and augmenting resident cardiac stem cells after an MI.
NATURAL HISTORY STUDIES OF HYPERTROPHIC CARDIOMYOPATHY (HCM) by the Mayo Clinic and others show that this disorder is associated with considerable prognostic heterogeneity. The majority of patients in the community will have normal longevity with this disorder, even if they are symptomatic. Dr. Bernard Gersh, a clinical researcher at the Mayo Clinic, reviewed the medical and surgical management of symptomatic treatment of patients with HCM.

The cornerstones of the medical management of hypertrophic obstructive cardiomyopathy (HOCM) include beta-blockers, calcium channel blockers such as verapamil and diltiazem, and disopyramide, which Dr. Gersh advised should only be used in the hospital setting. Dr. Gersh recommended stress testing at baseline and again at follow-up, to objectively determine a patient’s exercise tolerance so that symptomatic improvement with medical therapy can be assessed. One to three months should be a sufficient trial of medical therapy, and evidence suggests that two thirds of patients with HCM will be controlled with medication. When maximal doses of medical therapies fail, surgical approaches are indicated. While pacing strategies had previously been considered a potential approach to managing HCM, a RCT conducted at the Mayo Clinic showed that the benefits of pacing strategies appear to be due to placebo effects.

Myectomy has been a surgical approach to the management of HCM for more than 50 years. At the Mayo Clinic, this procedure is reserved for patients with persistent NYHA class 3 or 4 symptoms after a trial of medical therapy. Current observational data suggest that myectomy provides symptomatic reduction, improves patient prognosis and may reduce rates of sudden cardiac death and prolong survival, although data from RCTs are lacking. Dr. Gersh also noted that evidence supporting septal myectomy is dominated by single-centre studies and reflects a strong institutional level of expertise, putting into question whether or not the results can be generalized to lower-volume centres.

Septal alcohol ablation was developed as an alternative approach to the management of HCM in 1985, and is generally reserved for patients who are suboptimal candidates for myectomy. Although septal alcohol ablation has been shown to be effective, it is not free of complications, and like myectomy, there is a learning curve involved. Moreover, the long-term outcomes after alcohol septal ablation remain unknown at this time. A recent MRI study comparing anatomic consequences after myectomy or alcohol septal ablation raised concerns over the area of ablated tissue and the ragged edges resulting from the ablative procedure. Dr. Gersh noted that as the volume of alcohol used in septal ablation continues to be reduced, these effects may be diminished.

Guidelines are forthcoming, and should assist clinicians in making therapeutic decisions surrounding the optimal management of HCM.

CURRENT EVIDENCE SUPPORTING TRANSCATHETER AORTIC VALVE INTERVENTIONS (TAVI) FOR SYMPTOMATIC SEVERE AORTIC STENOSIS

Surgical management of aortic stenosis can improve survival, yet almost one third of patients with severe disease are never referred for an intervention, frequently because of advanced age and/or the presence of comorbidities. Yet evidence suggests that such patients can also benefit from conventional surgical approaches to aortic stenosis management. Dr. James Velianou, from McMaster University, reviewed current evidence for new devices that are balloon-expandable and can be delivered percutaneously. The PARTNER trial is the largest aortic valve RCT, and randomized very high-risk or inoperable patients with symptomatic aortic stenosis to either standard therapy (usually balloon aortic valvuloplasty) or to transcatheter aortic valve implantation (TAVI). In this group of high-risk patients, mortality was significantly reduced in the TAVI group, with an impressive number-needed-to-treat of only five. Repeat hospitalization was also significantly reduced in the TAVI group compared to standard therapy.
The 30-day incidence of stroke or TIA was high (6.7%), and likewise, vascular complications and major bleeding were significantly higher with TAVI versus standard therapy. Dr. Velianou predicted that these rates will decrease as newer devices become available and as the TAVI technology is refined to produce less trauma around the aortic arch. Survivors who received TAVI significantly improved their NYHA class after the procedure, and this outcome continued to improve out to 1 year. Notably, patient measures such as the 6-minute walk test were also significantly improved, suggesting that patients feel better after this procedure.

A multicentre Canadian observational study is following all patients who receive TAVI. Mortality rates at 30 days were ~10% but unlike the PARTNER trial, the 30-day incidence of stroke was very low (0.6%). Over the longer term, mortality was ~25% at 1 year and 35% at 2 years, which is consistent with results of observational studies conducted in other countries. Factors that were predictive of mortality included pulmonary hypertension, COPD, severe mitral regurgitation, need for periprocedural hemodynamic support due to vascular complications, and high baseline SDS-PROM score.

Dr. Velianou concluded that surgery remains the best option for most patients with severe aortic stenosis, and despite the encouraging results of the PARTNER trial and observational studies, patients who are at moderate risk and who are surgical candidates should not be offered TAVI at this time.
Dr. Jean Rouleau is an internationally recognized clinician scientist and Dean of the Faculty of Medicine at the University of Montréal. He was invited to deliver the inaugural ACC Lake Louise Annual Lecture on a subject of increasing importance to clinicians: ethical considerations when treating frail elderly patients.

Frailty has been described as a decrease in performance and functional reserve, and can be conceptualized as the triangulated elements of mobility, cognition and function. While it is typically associated with advancing age, it can also occur in much younger patients with chronic diseases such as renal dysfunction, heart failure, and others. There is also a vicious cycle between frailty and cardiovascular risk, whereby the prevalence of frailty increases in older people with CVD, and mortality increases in frail elders with severe CVD.

Section 15.1 of Canada’s Charter of Rights protects individuals from discrimination based on several factors, including age. People of advanced age should not be presumed to lack abilities that they may in fact possess. As it relates to the healthcare setting, Dr. Rouleau suggested that clinicians must be very careful in how they assess their patients. The Supreme Court of Canada has recognized that while we must guard against age discrimination, it also acknowledged that “there are often solid grounds for importing benefits on one age group over another in the development of broad social schemes and in allocating benefits.” Dr. Rouleau concluded that clinicians must be very careful and give every opportunity to elderly patients to benefit from medical treatment, since “when making recommendations, the benefit of the individual patient takes precedence over societal needs.”

Dr. Rouleau quoted two papers that address important ethical issues as they relate to the frail elderly. Del Vecchio & Locatelli (2009) stated that “the final shared decision should be the result of weighing beneficence (to maximize good) with non-maleficence (to not cause harm).” In the presence of severe medical conditions and/or mental impairment, clinicians have the responsibility to weigh the true benefits to patients, since a treatment may in fact represent the prolongation of death rather than life, and may not offer an appropriate balance of benefits relative to its down-sides (e.g., dialysis in the frail elderly with renal disease). Similarly, Rocker (2003) suggested that a key issue in critical care decisions is the “reversibility or otherwise of an acute illness and where this illness sits in the trajectory of that individual’s life and possibly death.” In such cases, Dr. Rouleau advised that clinicians should provide families with the best information possible so that they can make informed decisions.

How do ethical considerations impact on decisions surrounding invasive procedures in the frail elderly in clinical practice? Evidence suggests that age alone does not predict functional outcomes after acute MI at 1-year follow-up. Dr. Rouleau commented that “When looking at a patient in front of you, age is a risk factor, but it doesn’t necessarily relate to outcomes at 1 year.”

In terms of cardiovascular procedures, age alone does not predict in-hospital mortality. However, the incidence of comorbidities that are recognized risk factors for
in-hospital mortality (e.g., hypertension) tends to increase with advancing age. Evidence suggests that octogenarians respond well to PCI, bypass or aortic valve surgery. Indeed, 5-year survival rates are the same in octogenarians who received PCI, CABG or aortic valve surgery, as they are in octogenarian controls who do not receive coronary interventions. However, there is great heterogeneity in terms of in-hospital mortality in older patients, leading Dr. Rouleau to advise that when considering invasive interventions for elderly patients, they should be referred to centres with established experience in treating higher-risk patients.

Dr. Rouleau concluded his presentation by suggesting that clinicians must put into perspective the risks of interventions in individual patients, which can potentially be fewer in an elderly patient than in a younger patient with early frailty caused by comorbidities such as chronic kidney disease or diabetes. When assessing elderly patients for cardiac surgery, it can be helpful to consider the “5 A’s” which can perhaps be more important than frailty itself:

- Age (chronologic / physiologic)
- Activity (prior normal activity)
- Attitude / courage (includes realistic understanding of risk and expectations)
- Associated diseases
- Ability to tolerate medical therapy

Dr. Rouleau’s parting words were that “The final decisions regarding invasive cardiac procedures in frail and elderly patients belong to the patient and their family. Our role is to best assess and present the risks and benefits of all options to the patients and their family in order to permit them to make the best decision possible, for them. We must then accompany them, as best we can, throughout the process and after the procedure, whether it involves prolonged intensive, and/or multidisciplinary care.”

**HEART FAILURE AND DYSLIPIDEMIA**

**SHIFTING EMPHASIS IN HEART FAILURE: GIVING PATIENTS A NEW LIFE RAFT**

Dr. Peter Liu, from the University of Toronto, reviewed some of the recent landmark heart failure trials that have revived much interest in this area. Until recently, guidelines had changed very little and there were few effective treatment options available for the majority of HF patients. Now, the results of a few key trials are poised to change the way heart failure is managed.

Aldosterone antagonists such as eplerenone were first evaluated for the management of diastolic HF based on their ability to reduce myocardial fibrosis and increase elastin production. The results of the large EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy & SUrvival Study) showed that the addition of eplerenone to standard treatment reduced mortality by 15% and HF hospitalization/CV mortality by 13% compared with placebo in patients who had transient HF or depressed ejection fraction post-MI. These benefits were consistent in a subgroup analysis of patients with LVEF ≤30%, “showing quite impressive results for a population we generally consider to be relatively well treated already,” remarked Dr. Liu. These positive results were carried forward in the EMPHASIS trial, which evaluated eplerenone versus placebo added to standard therapy in patients with milder HF (NYHA class II), a population of patients commonly seen in clinical practice. Results showed a dramatic 37% reduction in the primary endpoint of CV death/HF hospitalization, with consistent positive benefits across all endpoints except sudden cardiac death. The 42% reduction in HF hospitalization suggests there could potentially be substantial impact on costs as well as important benefits in terms of patient quality of life. Although there was a significantly higher incidence of hyperkalemia among the eplerenone-treated patients, this effect did not result in a higher rate of drug discontinuation. Dr. Liu concluded that “with close monitoring, we can safely use this medication in patients with class II heart failure.”

Dr. Liu shifted gears and reviewed the evidence for heart rate reduction as a target for the management of heart failure. Ivabradine is a novel agent that acts in the sinus node to block I_{f} channels, thereby reducing heart rate.
An early study, BEAUTIFUL, suggested this agent was beneficial in patients with depressed cardiac function and a history of ischemic heart disease by reducing the rate of recurrent MI and unstable angina. This led to the SHIFT trial, which compared ivabradine versus placebo in patients with NYHA class II-III heart failure, depressed LVEF and heart rate ≥70 bpm. Despite patients being on the best available background therapy, with approximately 90% on the highest tolerated dose of beta-blockers and 60% on aldosterone antagonists, the mean heart rate was reduced by about 10 bpm in the ivabradine group. The primary endpoint of CV death/HF hospitalization was significantly reduced by 18% in the ivabradine group compared with placebo, which was mostly driven by a 26% reduction in HF hospitalization. Although all-cause mortality was not statistically significantly different between the groups, there was a trend towards lower mortality in patients randomized to ivabradine (HR 0.90, 95% CI 0.80, 1.02; p=0.092). Patients achieving the greatest reductions in heart rate benefited from the greatest treatment effects, leading Dr. Liu to comment that “slowing the heart rate further helped stabilize the patient … despite optimal background therapy including beta-blockers… this suggests that heart rate is not only an indicator but possibly a modifiable risk factor [for heart failure].”

Dr. Liu briefly reviewed the results of the RAFT study, which were previously addressed by Dr. Brent Mitchell during an earlier presentation at the ACC Lake Louise. This Canadian-led study supports the benefits of cardiac resynchronization therapy in patients with NYHA class II or III heart failure in terms of death or hospitalization due to HF. This effect was consistent in patients with class II heart failure, a group commonly encountered in clinical practice.

Dr. Liu concluded his presentation by commenting that these recent trials in HF suggest that “these agents that can modify the disease progression will change the natural history of systolic heart failure, even in patients with only very mild symptoms.”
In recent years, a plethora of new biomarkers have been evaluated for their potential ability to predict cardiovascular risk. Many of these were recently reviewed in the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, however none received a Class I recommendation (indicating the treatment/procedure should be utilized) and only a few received Class IIa recommendations (indicating it is reasonable to utilize the treatment/procedure in some patients). Dr. Jacques Genest, a cardiovascular researcher at McGill University, summarized the important points that clinicians can derive from these recent recommendations. First, while biomarkers may be useful to predict disease, their use in preventing disease is much less well established, limiting their clinical usefulness at the current time. Second, all asymptomatic adults should be targeted for total CVD risk assessment using established global risk scores unless there is a very compelling reason not to do so. Dr. Genest noted that many risk scores are available and concord very well, therefore “it doesn’t matter which one you use as long as you identify the patients who are in the high-risk category.” Third, additional information on family history should be sought, since CV risk is doubled for individuals with a first-degree relative aged <60 years who is affected.

Despite their recognized usefulness, current risk assessment tools remain imperfect. The question is, therefore, can we do better? Among the hundreds of serum or plasma biomarkers that have been identified to date, only high-sensitivity C-reactive protein (hsCRP) is recommended (Class IIb), based on the very narrow indication from the JUPITER trial (i.e., in patients with Framingham Risk Score [FRS] 10-19% and LDL-cholesterol <3.4 mmol/L in men aged <50 years and women aged >60 years). Notably, the panel did not recommend apolipoproteins – including LDL and HDL particle size – as reliable biomarkers for CV risk. This suggests that all the information required for risk assessment is contained in the lipid profile, which should facilitate clinical practice.

Inflammatory markers of plaque instability have not yet been shown to be useful at predicting CV events, particularly ACS. Noninvasive imaging techniques are appealing, however only resting ECG, ankle-brachial index, as well as carotid IMT and coronary calcium score (in patients with intermediate FRS of 10-19%) have met criteria for Class IIb recommendation. Dr. Genest predicted that changes to current practice might be restricted to identifying patients in the intermediate risk category, where there is subclinical atherosclerosis. Despite the positive recommendation, imaging techniques such as cIMT remain limited by technological aspects including suboptimal quality and reliability, particularly in non-university centres, and moreover, there remains a lack of outcome data on imaging-based techniques. Dr. Genest also pointed to the risks of exposing patients to cumulative doses of radiation using some types of imaging modalities. Finally, while it is recognized that up to 5% of CVD is attributable to monogenic disorders such as familial hypercholesterolemia, genetic contributions to multifactorial or complex diseases such as diabetes and heart disease are much more difficult to investigate. To date, single nucleotide polymorphisms (SNP) on chromosome 9p21 have shown a consistent association with heart disease risk, however, the risk association is much lower than for traditional risk factors such as smoking. Dr. Genest advocated for a common sense approach to the use of genetic biomarkers, and opined
that there is no role for commercial genetic testing because it does not change clinical decisions. At this point, family history is much more informative than genetic profiling, although the latter remains an area of active research and interest.

Dr. Genest concluded his presentation by stating that the following guideline should be applied: “the initial step in risk assessment in individual patients involves the ascertainment of a global risk score (Framingham, Reynolds, etc.) and the elucidation of a family history of atherosclerotic CVD. These Class I recommendations, which are simple and inexpensive, determine subsequent strategies to be undertaken. Persons at low risk do not require further testing for risk assessment, as more intensive interventions are considered unwarranted, and those already documented to be at high risk (established CHD or coronary risk equivalents) are already candidates for intensive preventive interventions, so that added testing will not provide incremental benefit.”

**EMERGING NON-STATIN DRUGS**

The question of whether “lower is better” in terms of targets in patients with diabetes was reviewed by Dr. Todd Anderson at this year’s ACC Lake Louise meeting. Dr. Jacques Genest, from McGill University, focused on whether targeting residual risk once LDL-cholesterol is at target levels is an appropriate strategy in patients with dyslipidemia. He also highlighted some of the novel drugs in the dyslipidemia pipeline.

Several approaches have been established for the reduction of LDL cholesterol, including diet, statins, ezetimibe, and bile acid sequestrants. The body of evidence to date suggests that the actual method of LDL lowering is irrelevant – all of these strategies have been shown to reduce CV events. Once LDL target levels have been achieved, adjusting lipid-lowering therapy to optimize one or more secondary targets (e.g., total cholesterol:HDL ratio, non-HDL levels, Apo B/AI ratio, triglycerides and hsCRP) in high-risk patients has not yet been proven to modulate patient outcomes. Therefore, clinicians should exercise expert judgment and caution when considering further treatment intensification in secondary prevention or in high-risk primary prevention.

Dr. Genest predicted that HDL-modulating drugs are the next frontier in preventive cardiology and are the subject of several ongoing trials. For example, AIM-HIGH and HPS-2 THRIVE are evaluating the benefits of adding niacin to treatment with statins with or without ezetimibe. The ACCORD study demonstrated that the addition of fibrates to statin therapy in diabetes patients had no effect on LDL, but dramatically reduced triglycerides and modestly increased HDL, however there was no apparent effect on patient outcomes. There may be a role for fibrates in subgroups of patients with high baseline triglycerides and low HDL, but this has yet to be conclusively demonstrated. Meta-analyses suggest that while fibrates may reduce CV endpoints, there is no effect on all-cause mortality, and furthermore, there is a consistent increase in non-vascular death that approaches statistical significance.

The SHARP study evaluated the effects of ezetimibe plus a statin in patients with chronic kidney disease, and confirms that lowering LDL reduces major CV events, with no apparent effect on kidney disease progression and with a favourable safety profile. Ongoing studies such as IMPROVE-IT should add to the body of information on the effects of ezetimibe on clinical outcomes.

Novel therapies such as Apo B antisense molecules, PCSK9 inhibitors, squalene synthase inhibitors, microsomal triglyceride transfer protein inhibitors, and the Chinese herb, berberine, have been or are currently under evaluation. The HDL-raising CETP inhibitors, anacetrapib and dalcetrapib, are both entering large scale clinical trials and will be the first real test of the HDL hypothesis. Results should start to become available in 2013. Dr. Genest commented that for the foreseeable future, pharmacologic treatment options for dyslipidemia will remain LDL-lowering agents, with statins as first-line agents, ezetimibe as a second-line option, and bile acid sequestrants third-line.
Cardiology is an area of very active research, with more than 18,000 ongoing clinical trials. Dr. Todd Anderson, Director of the Libin Cardiovascular Institute, reviewed some of the currently ongoing clinical trials whose results are eagerly awaited in the coming weeks, months and years, or whose results have been presented at recent cardiology meetings. Many of the trials were reviewed in greater detail during other plenary presentations at this year’s ACC Lake Louise meeting; readers are encouraged to visit the conference website at www.acclakelouise.com to view the complete slide presentations of interest.

### Ongoing ‘Major’ Clinical Trials that Will Impact Cardiology in Canada

<table>
<thead>
<tr>
<th>Area of cardiovascular medicine</th>
<th>Ongoing or recently completed clinical trials that will impact cardiology in Canada</th>
<th>Primary endpoint</th>
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| **Cholesterol & atherosclerosis** | - **AIM-HIGH**: Simvastatin (+ ezetimibe) vs. simvastatin (+ ezetimibe) and ER niacin in high-risk patients with CAD and metabolic syndrome or diabetes  
- **HPS2-THRIVE**: simvastatin + placebo vs. simvastatin + ER niacin in high-risk atherosclerosis patients  
- **dal-OUTCOMES**: dalceptrapib vs. placebo in patients with recent ACS hospitalization  
- **DEFINE**: anacetrapib vs. placebo in patients with CAD or high-risk on statin Rx  
- **IMPROVE-IT**: simvastatin vs. simvastatin + ezetimibe in patients stabilized post-ACS <10 days and dyslipidemia  
- **SOLID TIMI 52**: darapladib vs. placebo in ACS patients | - MACE  
- MVE  
- CV events  
- LDL-C  
- Composite of CV events  
- MACE |
| **Arrhythmia** | - **REFINE ICD**: ICD vs. usual care in post-MI patients with EF 0.36-0.49 and impaired HRT and abnormal TWA  
- **RAFT**: ICD vs. ICD + CRT in patients with EF <30% and QRS >120  
- **CABANA**: ablation vs. best medical therapy in patients with AFib (AFFIRM type population) | - Mortality  
- Mortality/CHF hospitalization  
- Mortality |
| **CHF** | - **STICH**: CABG vs. medical therapy in patients with class II-IV CHE and EF<35%  
- **EVEREST 2**: Mitra-clip E valve vs. conventional surgery in patients with severe MR seeking surgery for symptoms  
- **Acute decompensated CHF**: furosemide administered continuously IV; bid IV at previous oral dose; high-dose IV | - All-cause mortality  
- Freedom from surgery for valve dysfunction, death or 3-4 plus MR  
- Global assessment of feeling or creatinine in 72 hrs |
| **Atrial fibrillation: anticoagulation** | - **AVERROES**: apixaban vs. ASA in patients at increased risk for stroke and unsuitable for vitamin K antagonists  
- **ARISTOTLE**: warfarin vs. apixaban in patients with AF and CHADS2 ≥1  
- **ROCKET AFIB**: rivaroxaban vs. warfarin in high-risk patients with AF and CHADS2 ≥3  
- **ENGAGE AFIB TIMI 48**: edoxaban 30 or 60 mg in patients with CHADS2 ≥2 | - Stroke or systemic embolism  
- Stroke or systemic embolism  
- CVA and systemic embolism  
- Stroke/systemic embolism/mortality |

* Trial results have been presented or recently published
Many ongoing cardiovascular clinical trials have participation of Canadian centres, including substantial research activity at the Canadian VIGOUR Centre at the University of Alberta, the Montreal Heart Institute, and the Population Health Research Institute in Hamilton, Ontario, among others.

Dr. Anderson concluded that “cardiovascular clinical trials continue to provide excellent evidence for practice guidelines… and Canadian groups are world leaders in this area.” He encouraged conference participants to take advantage of the many opportunities to be involved in high-quality clinical trials.

Among some of the top trials in cardiology in 2010, the topics of atheroproteective mechanisms of HDL, atherosclerosis in general, lipid parameters for measuring risk of CVD, and obesity and inflammation, figured prominently. Dr. Jacques Genest, from McGill University, synthesized a few knowledge snippets relating specifically to HDL as a therapeutic target in CVD management, and obesity.

Recent meta-analyses suggest that LDL and HDL particle size are not predictive of CV events and are thus no longer considered as a component in patient risk stratification. Evidence continues to suggest that HDL is strongly inversely related to coronary heart disease even after adjustment for age, sex, and several risk factors. However, in patients whose LDL levels are well controlled on high-dose statin therapy, HDL does not predict risk of death or coronary events, as demonstrated in several large RCTs including PROVE-IT, TNT and JUPITER. HDL is thought to protect the vascular system through pleiotropic effects such as mediating reverse cholesterol transport; antioxidant, anti-inflammatory, anti-thrombotic and anti-apoptotic effects; promotion of vascular endothelial cells; and improvements in vascular endothelial function. Data from ongoing clinical studies evaluating the CETP inhibitors, dalcetrapib and anacetrapib, may help elucidate the role of some of these pleiotropic effects of HDL. Dr. Genest commented that modulation of HDL function for the prevention and treatment of CVD shows great promise, but that positive findings from outcome-driven clinical trials will be required before HDL is adopted as a therapeutic target in the management of dyslipidemia.

Shifting gears to recent findings in the field of obesity research, Dr. Genest reviewed a recently published analysis of 58 prospective studies that included more than 220,000 people. It had previously been widely believed that abdominal adiposity was a risk factor for CVD, and that measures of waist circumference and waist-to-hip ratio might therefore be better predictors of CVD than measures of body mass index (BMI). However, this analysis showed that each of these three measures, analyzed separately or in combination, had similar hazard ratios, suggesting that no single measure of obesity is more predictive than another. The authors concluded that “BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, do not importantly improve cardiovascular disease risk prediction in people in developed countries when additional information is available for systolic blood pressure, history of diabetes, and lipids.” In short, apples and pears in this regard appear to be equivalent.
RESULTS OF RECENT HEART FAILURE TRIALS: IMPACT ON CURRENT MANAGEMENT

The impressive results of recent clinical trials in heart failure were reviewed during several plenary presentations at the ACC Lake Louise 2011. Dr. Anique Ducharme, from the Montreal Heart Institute, was tasked with addressing the clinical integration of current knowledge and future possibilities for the management of HF.

One of the important questions arising from the EMPHASIS, SHIFT and RAFT studies, is whether or not the patients studied are comparable to the patients physicians typically manage in routine clinical practice. Although the SHIFT study suggests that ivabradine improves outcomes when added to optimal medical therapy by further reducing heart rate, Dr. Ducharme pointed out that only about one quarter of patients were receiving beta-blockers at a target dose. When the study results were re-analyzed for the subgroup of patients who were at ≥50% of their target beta-blocker dose, the primary composite outcome was no longer statistically significant and neither was cardiovascular death, although the benefit in terms of HF hospitalization remained. Dr. Ducharme opined that “Ivabradine is an excellent alternate treatment for patients who cannot tolerate high-dose beta-blockers.”

The EMPHASIS-HF study demonstrated that the addition of eplerenone to standard care (i.e., ACE inhibitors, ARBs, beta-blockers, and/or loop diuretics) in patients with Class II HF significantly reduced all-cause mortality. Notably, the curves began to diverge after 1 year and continued to diverge afterwards, supporting a positive effect of eplerenone on the remodeling process. While there are very clear potential benefits of this therapy, there is also an increased risk of hyperkalemia with aldosterone inhibitors. In a retrospective analysis of the SOLVD trials, several risk factors for hyperkalemia were identified, including the presence of renal dysfunction, baseline serum potassium level, diabetes, atrial fibrillation, NYHA functional class, and treatment with an ACE inhibitor. The authors recommended that patients with estimated glomerular filtration rate (eGFR) <60 mL/min be closely monitored for serum potassium levels. Dr. Ducharme also pointed out that there were few patients in the EMPHASIS-HF study who were on CRT at baseline, yet many patients are receiving pacing and defibrillator devices in current practice today. From a practical perspective, patients who are on standard HF therapies should discontinue potassium supplementation when eplerenone is added on to their treatment regimen. While it might be tempting to extend the results of EMPHASIS-HF to other (less expensive) aldosterone inhibitors such as spironolactone, Dr. Ducharme commented that two molecules that look very similar can have quite different biological effects. While eplerenone and spironolactone have not been directly compared in head-to-head trials, the two agents have different side effect profiles. In the EMPHASIS-HF study, eplerenone was well tolerated. Indeed, the withdrawal rate due to adverse events was 13% in the eplerenone arm compared to 16% in the placebo arm.
The RAFT study demonstrated a very impressive reduction in death or hospitalization for HF in patients receiving CRT in addition to ICD compared with ICD alone. Dr. Ducharme suggested that referral to an electrophysiologist for a CRT device would be appropriate for patients who remain symptomatic (NYHA class II or higher) and with a LVEF <35% despite optimized medical therapy including beta-blockers and eplerenone.

Dr. Ducharme concluded that the results of recent trials in HF have filled some important gaps in clinical knowledge, but now the challenge is for clinicians to learn how to properly use these new agents, much as was the case 10-15 years ago with beta-blockers. She suggested that a rational management approach to CHF is to first up-titrate beta-blockers if possible. In patients who do not tolerate target doses, ivabradine is a good treatment option. Aldosterone antagonists should be used in the majority of HF patients unless contraindicated, with close monitoring of electrolytes, BUN and creatinine. Finally, while optimization is well accepted in the realm of pharmacotherapy, Dr. Ducharme suggested that optimization should apply to device therapy as well.

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**Heart Failure**

**STUDY DATA ALONG THE HF SPECTRUM**

<table>
<thead>
<tr>
<th>ACE-I</th>
<th>AIRE/SAVETRACE (ramipril/captopril/trandol)</th>
<th>SCLVD Treatment (enalapril)</th>
<th>CONSENSUS (enalapril)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blocker</td>
<td>CAPRICORN (carvedilol)</td>
<td>US Carvedilol/PERIC/IBIS (carvedilol/metoprolol/bisoprolol)</td>
<td>COPERNICUS (carvedilol)</td>
</tr>
<tr>
<td>Aldosterone Blocker</td>
<td>EPHUSIS (eplerenone)</td>
<td>EMPHASIS-HF (eplerenone)</td>
<td>NYHA II mild CHF</td>
</tr>
<tr>
<td>ARB</td>
<td>OPTIMAAL (Losartan)</td>
<td>ELITE (Losartan)</td>
<td>Valsartan/CHARM (Valsartan/Candesartan)</td>
</tr>
<tr>
<td>(\beta) inhibitor</td>
<td>(\beta) inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHIFT</td>
<td>(\beta) inhibitor (Ivabradine)</td>
<td>RAFT, MADIIT-CRT</td>
<td>CRT</td>
</tr>
<tr>
<td>DEVICES</td>
<td>RAFT, MADIIT-CRT</td>
<td>CRT</td>
<td>CARE-HF, MIRACLE, COMPANION</td>
</tr>
<tr>
<td>HM-II</td>
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</tbody>
</table>

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**BASIC SCIENCE BREAKTHROUGHS THAT WILL IMPACT CLINICIANS IN THE FUTURE**

Several important scientific advances in the field of cardiology have been made in the past decade. Dr. Gary Lopaschuk, Scientific Director of the Mazankowski Alberta Heart Institute, reviewed a few of the recent advances in basic science that are impacting practice, with a focus on his own area of interest, optimizing cardiac energy metabolism.

The topic of stem cell therapy and its potential for repairing myocardial and vascular tissue and for improving cardiac function was addressed in an earlier presentation by Dr. Bernard Gersh. While large studies such as STAR-heart demonstrate the feasibility of using stem cells in patients with chronic LV dysfunction, several obstacles remain. For example, there is little evidence to support that myocardial regeneration takes place; modest functional and clinical benefits are attributed to the ‘paracrine effect’; arrhythmogenicity; teratoma issues; and immune issues. Using a patient’s own somatic cells to generate inducible pluripotent stem (iPS) cells could overcome the ethical roadblocks and problems with immune rejection, and may prove to be an acceptable alternative to the use of embryonic and bone marrow stem cells.

One of the most important challenges to overcome will involve making the ischemic myocardium a less hostile environment so that stem cells have a greater chance of surviving. Mature contracting myocytes are highly dependent on mitochondrial oxidation for energy production, with the majority of ATP generated through fatty acid oxidation and glucose oxidation.
Conversely, highly proliferative cells including stem cells, fetal cells and tumour cells, primarily derive their energy through glycolysis. The transition of stem cells to cardiomyocytes therefore requires the development of a mitochondrial oxidative capacity to increase energy production. Manipulation of metabolic pathways to maintain glycolysis and inhibit mitochondrial respiration could be a strategy to facilitate stem cell survival in the hypoxic post-MI environment. Once the stem cells are established and maturation progresses, efforts will need to shift towards increasing myocardial metabolism and reducing tumorigenesis. Dr. Lopaschuk commented that metabolic strategies will need to be applied at the proper time to manipulate the transition of stem cells to cardiomyocytes.

A relative newcomer to the field of basic cardiology science that is generating much interest is microRNA (miRNA) biology. miRNAs are short, single-stranded RNAs that inhibit the expression of specific RNAs. Dysregulation of miRNAs has been shown to be associated with several cardiac pathologies, including ischemic heart disease, arrhythmias, fibrosis, hypertrophy remodeling, and metabolic disorders. Several miRNAs are involved in energy metabolism at the mitochondrial level and may have therapeutic potential in acute MI. They may also help to optimize the pluripotency and survival of stem cells. Since 2006, there has been explosive research interest in miRNAs, and Dr. Lopaschuk predicted that the field will rapidly advance towards therapeutic use.

**PRACTICAL APPLICATION OF THE NEW CANADIAN CHOLESTEROL GUIDELINES**

Dr. Jacques Genest, the lead author of the 2009 guidelines for the diagnosis and management of dyslipidemia and prevention of cardiovascular disease, briefly reviewed some of the recent evidence that has been published since the guidelines were released.

A sub-analysis of the JUPITER trial suggests that achieving LDL <50 mg/dL is associated with improved outcomes including the primary endpoint, as well as all-cause mortality and MI/stroke/CV death. Moreover, achieving this lower LDL target was safe, with adverse events occurring at a similar rate as in those patients who did not reach the lower target.

In a meta-analysis of six RCTs including JUPITER, statins were shown to be highly effective in the primary prevention of cardiovascular events in women. Dr. Genest commented that “We can now set aside the concept that primary prevention in women with statins does not work.”

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Meta-analysis of Exclusively Primary Prevention Statin Trials in Women
Current efforts are underway to harmonize several clinical practice guidelines into one comprehensive guideline for cardiovascular disease prevention; these are expected to be available in 2012. Until that time, the current guidelines continue to recommend risk assessment, lifestyle modifications including smoking cessation, and treatment according to level of risk.

### Risk Assessment and Treatment Targets

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>Initiate/consider treatment if any of the following:</th>
<th>Primary Target LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH FRS ≥ 20%</td>
<td>• CAD • PVD • Atherosclerosis • Most Diabetic Patients</td>
<td>&lt; 2 mmol/L or LDL-C 50%</td>
</tr>
<tr>
<td>RRS ≥ 20%</td>
<td>(consider treatment in all patients)</td>
<td></td>
</tr>
<tr>
<td>Moderate FRS 10-19%</td>
<td>• LDL-C &gt; 3.5 mmol/L • TG/HDL-C &gt; 5.0 • hsCRP &gt; 2 mg/L • Family history</td>
<td>A</td>
</tr>
<tr>
<td>LOW FRS &lt; 10%</td>
<td>• LDL-C &gt; 5.0 mmol/L</td>
<td>A</td>
</tr>
</tbody>
</table>
WE ARE PLEASED TO ADVISE YOU THAT IN 2012, THE ACC LAKE LOUISE MEETING IS MOVING TO ITS NEW HOME AT THE RIMROCK HOTEL IN BANFF, ALBERTA. TO REFLECT THIS EVOLUTION, THE NAME OF THE CONFERENCE HAS BEEN CHANGED TO THE ACC ROCKIES.

PLEASE JOIN US MARCH 11 – 14, 2012 IN BANFF FOR THE ACC ROCKIES MEETING. FURTHER DETAILS AND REGISTRATION INFORMATION WILL BE FORTHCOMING AT THE CONFERENCE WEBSITE: WWW.ACCROCKIES.COM.