The 2011 Rocky Mountain / ACP Internal Medicine Conference Report - 24-27 November, 2011, Banff, Alberta

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Introduction to the 2011 Rocky Mountain /ACP General Internal Medicine Conference

Internists from Western Canada gathered in Banff, Alberta for the annual Rocky Mountain / ACP General Internal Medicine Conference held from November 24-27, 2011. This year's conference continued its tradition of offering the more than 200 attendees a stellar line-up of speakers from academic and regional centres. Keynote presentations and satellite symposia covered a full array of state-of-the-art topics in basic and applied research of interest to general internists. Building on their popularity in previous years, a series of small-group workshops were offered to participants to learn from experts in specific topic areas; these well attended workshops provided a valuable opportunity for collegial discussion and debate.

As a value-added component and in an effort to enhance the educational opportunities at the meeting, this conference report provides a brief summary of topics selected by the scientific committee. A clinical commentary follows each summary to further reflect on and clarify how the findings might impact everyday clinical practice. Clinicians are encouraged to view and download the speaker presentations from this year's conference at the Rocky Mountain Conference website at www.rockymountaininternalmed.com.

KEYNOTE ADDRESS

Top 5 Papers in General Internal Medicine 2010/2011

Presented by Dr. Jake Onrot, University of British Columbia

Every year, hundreds of papers related to general internal medicine are published. This makes staying up-to-date on the latest evidence a formidable challenge for busy internists. Dr. Jake Onrot selected five papers that were published in late 2010 and in 2011 that he believes have had impact on the way internal medicine is practiced. Internists are encouraged to read these papers and familiarize themselves with the context of each trial within the overall literature in its particular field, to balance the pros and cons of each trial, and to apply the trial evidence to their own decision-making. Dr. Onrot introduced each of his selected papers by first presenting it in the context of a clinical case. The key findings and conclusions from the five papers are summarized below:

1. The randomized controlled FEAST trial by Maitland *et al.* does not support the use of any fluid bolus (albumin or saline) in critically ill children with impaired perfusion in resource-limited African countries because both significantly increased 48-hour mortality compared to no bolus.
2. A retrospective review of the VASST trial by Boyd *et al.* supports a positive fluid balance of ~3L at 12 hours in sepsis patients; a more positive fluid balance at 12 hours and at 4 days was associated with significantly increased mortality.
3. A randomized controlled trial by Garcia Pagan *et al.* supports the early use of transjugular intrahepatic portosystemic shunt (TIPS) vs. traditional medical therapy in patients with cirrhosis who were hospitalized for acute variceal bleeding and at high risk for treatment failure.

4. The large randomized controlled ARISTOTLE trial supports the use of apixaban to reduce the risk of hemorrhagic stroke in patients with atrial fibrillation with a number-needed-to-treat (NNT) of 434 compared to standard therapy with warfarin, and a reduced risk of major bleeding (NNT 104).
5. The POET COPD retrospective cohort study supports the use of tiotropium versus salmeterol for the prevention of exacerbations in patients with moderate-to-severe COPD.

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Paper #1: FEAST trial

For pediatric patients in resource-poor countries where malaria is prevalent, clinicians considering fluid management are faced with choosing between guidelines for first-world (60 mL/kg isotonic solution) versus third-world (reserve boluses for advanced shock) settings. FEAST randomized ~3100 children with severe febrile illness and impaired perfusion in sub-Saharan Africa to one of three fluid management strategies: albumin bolus, saline bolus, or no bolus. The primary endpoint of the trial, 48-hour mortality, showed a benefit for no bolus versus either bolus. Malaria (57%) and anemia were prevalent. This result contrasts sharply with Rivers *et al.* (*N Engl J Med* 2001; 345: 1368-77), which favoured early and aggressive fluid administration in adults with septic shock. FEAST raises questions regarding routine administration of fluid boluses in other patient populations with shock.

Paper #2: VASST retrospective review

The question of optimal fluid management in adults with septic shock was assessed in a retrospective analysis of VASST (VAsopressin in Septic Shock Trial). Dr. Onrot reminded the audience of the double-edged sword of fluid resuscitation: inadequate fluid administration may worsen tissue hypoperfusion and ischemia, whereas excessive fluids may cause volume overload, pulmonary edema, capillary leak, and re-perfusion injury. Hypothesizing that both too little fluid AND too much fluid may be harmful, the analysis assessed the relationships between administered fluid volume, central venous pressure (CVP), and mortality. The results showed that a positive fluid balance predicts higher mortality, even after adjusting for baseline illness severity. Patients with the lowest CVP had lower mortality. There was an interaction between survival, CVP, and fluid balance: patients with lower CVP fared better with more fluid administration, whereas patients with higher CVP fared worse with more fluids. Optimal survival occurred in patients with a positive fluid balance of approximately 3L at 12 hours. The authors concluded that in "resuscitated" sepsis, the intravascular fluid deficit and tissue hypoperfusion may be corrected even though hypotension and organ dysfunction may persist. In this setting, giving more fluid may be harmful. The unaddressed question remains precisely when to stop administering fluids in septic shock.

Reviewers' Comments:

These two studies highlight our limited knowledge regarding the optimal level of fluid resuscitation and how we use imperfect indices of tissue perfusion to make iterative adjustments to our sepsis management strategies. We are reminded that a low CVP or JVP is more useful in assessing intravascular volume than is a "normal" or elevated level and that fluid administration is only one part of an early response to sepsis that includes assessment of other markers of tissue perfusion (e.g., MAP, urine output, lactate, cognitive performance, central venous pO2), early administration of antibiotics and source control. Further research is needed to improve our ability to reliably assess intravascular volume (e.g., stroke volume and pulse pressure variability in response to fluid challenge, bedside ultrasound [*J Intensive Care Med* 2009;24:329-37]) and tissue perfusion (e.g. lactate clearance and measures of oxygen transport).

Paper #3: Early TIPS trial

Acute and recurrent variceal bleeding is common in cirrhotic patients with portal hypertension. The early use of TIPS has not been considered a standard part of early management in preventing re-bleeding or death due to concerns about worsening hepatic encephalopathy. The study by Garcia-Pagan *et al.* suggests otherwise. In this study, 63 patients with Child-Pugh class C or B liver failure with persistent bleeding at the time of endoscopic band ligation (EBL) on vasoactive drug therapy were randomized to TIPS within 72 hours or to standard therapy (i.e., vasoactive therapy, beta-blockers, then nitrates as tolerated and serial EBL until variceal eradication). The primary endpoint of failure to control the acute bleed or re-bleed at 1 year was substantially improved in the TIPS group compared to standard therapy (ARR = 47%), as was mortality (ARR = 25%). Dr. Onrot suggested that TIPS should be considered in this patient population, arguing that we are often reluctant to adopt invasive interventions that may turn out to be better than medications.

Reviewers' Comments:

Reservations have been expressed regarding the applicability of this trial, such as its small size; it is a single trial showing benefit when a meta-analysis of related TIPS research is more equivocal; the subjects were highly screened and selected (<20% enrolled); and there were baseline differences between treatment groups, including an asymmetry in encephalopathy. However, large benefits were observed in clinically relevant outcomes (rebleeding, mortality, hepatic function, and time in ICU and hospital) without adverse effects on encephalopathy. Thus, in appropriately selected Child-Pugh B and C patients at high risk of rebleeding, early use of TIPS should be considered along with all standard effective and tolerated therapies (somatostatin analogues, antibiotics, EBL, beta blockers and nitrates) while we await additional confirmatory trials.

Paper #4: ARISTOTLE trial

To avoid redundancy, ARISTOTLE is summarized and discussed in another section of this review.

Paper #5: POET COPD trial

The American Thoracic Society recommends that symptomatic patients with mild or moderate COPD ($FEV_1/FVC<70\%$; $50\%<FEV_1<80\%$) should be offered bronchodilator monotherapy using either long-acting inhaled anticholinergics (LAAC) or long-acting inhaled beta-agonists (LABA), based on patient preference, cost, and adverse effect profile, whereas patients with more severe COPD ($FEV_1<50\%$) should be treated with combination therapy. The question therefore remained, for patients with milder COPD, which monotherapy strategy is preferred? The POET COPD study directly compared tiotropium to salmeterol in more than 7000 patients with COPD exacerbations and FEV_1 <70% for 1 year. The times to first exacerbation, to severe exacerbation, and the number of moderate and severe COPD exacerbations were all improved with tiotropium compared to salmeterol. The effects were consistent across subgroups based on age, sex, COPD severity, smoking status, body mass index, and use of concurrent inhaled glucocorticoids. Dr. Onrot concluded that for mild to moderate COPD requiring monotherapy, a LAAC may be the preferred choice over a LABA.

Reviewers' Comments:

The POET COPD illustrates the large trial size necessary to compare two active treatments using a meaningful outcome such as COPD exacerbations, such that the similarity or small differences can be determined with some degree of certainty. While the differences in outcomes observed in POET COPD are statistically significant, some argue that the absolute size of the differences (a few percentage points) is not large. Even a trial of this size is unable to definitively address questions of cardiac safety that have been raised for both LABA and anticholinergic bronchodilators. Finally, we must never forget that enthusiastic and tenacious efforts to achieve smoking cessation in patients who consume tobacco (like almost half of the POET COPD study population) will achieve a greater mortality benefit at a much lower cost than any or all bronchodilator therapies combined.

AM Edwards Lecture

The Early Diagnosis of Pulmonary Tuberculosis

Dr. Richard Long, University of Alberta

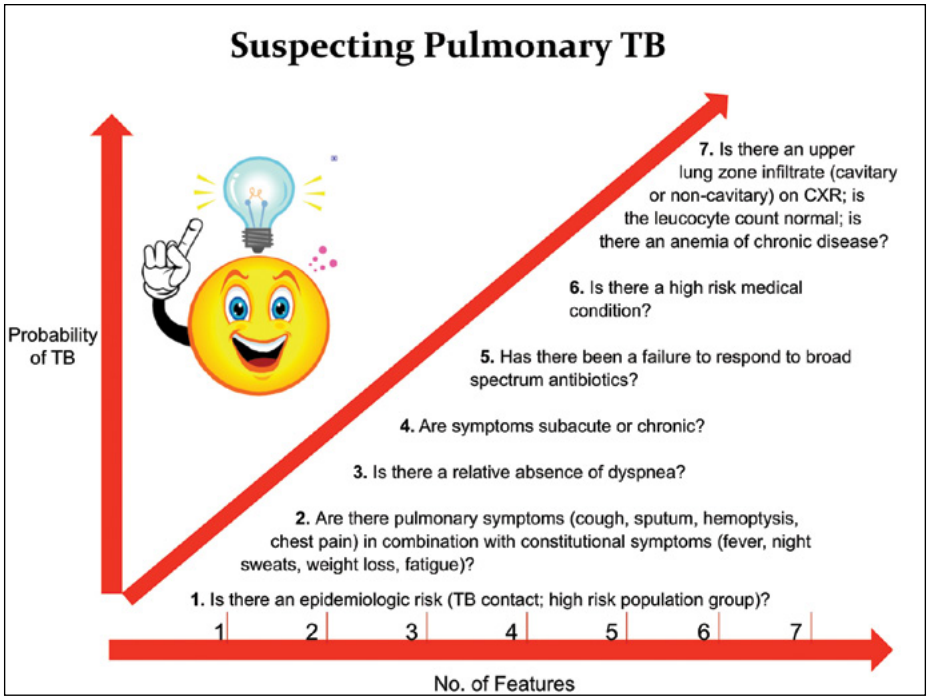
Tuberculosis in Canada is largely a disease that affects two groups: aboriginals from Nunavut and, to a lesser extent, on reserves across the Prairies and foreign-born people coming from high-incidence countries such as Asia and Africa. This is important, given that 20% of the Canadian population is foreign-born. Over 100 years ago, William Osler said that TB is a social disease with a medical aspect, and that remains true in reserve communities today. "Tuberculosis is a very sophisticated pathogen exploiting failures on our part…. Each generation has failed to address social issues that are the basis of this disease," Dr. Long opined. Factors that converge when there is a TB outbreak in a reserve community are: 1) a delay in diagnosis of the source case, 2) large numbers of susceptible contacts (e.g., vulnerable children who have never been exposed to the infection), and 3) an environment that is favourable to transmission (e.g., malnutrition, overcrowding, poorly ventilated homes).

A combination of organ-specific as well as constitutional symptoms is the next clue for suspecting a case of TB. Dyspnea is uncommon in the early presentation of pulmonary TB because of its ability to interrupt both ventilation and perfusion in parallel. In an acutely infected patient, perfusion and ventilation is redistributed to the remaining healthy lung, leading to preserved function and ultimately, a delay in diagnosis. Typically, symptoms are subacute, occurring over weeks or months and sometimes years. The presence of any high-risk condition, including HIV/AIDS, organ transplantation, dialysis-dependent renal failure and patients on immunosuppressants, including systemic steroids, are another clue to diagnosing TB, as these patients are at risk for primary infection and for reactivating latent TB infection.

Leukocytosis is typically a feature of community-acquired pneumonia, whereas anemia is a characteristic feature of chronic TB infection. Also, internists should not

dismiss the value of a plain CXR, which can provide several important diagnostic clues. Dr. Long recommended dividing the lung into an upper and lower half, and assessing for the following four common patterns: 1) upper lobe distribution, 2) cavitation, 3) volume loss, and 4) endobronchial lesions (fluffy, poorly defined nodules are present in virtually all cases of TB). Finally, cases of suspected TB should be confirmed by sputum testing for definitive diagnosis, with molecular epidemiology to link the infection to the source case spatially and temporally. Recovery of the organism through sputum samples is also helpful in tailoring treatment based on drug susceptibility testing.

In Canadian-born patients, drug-resistant TB is rare thanks to the practice of directly observed therapy, which avoids compliance issues. Drug resistance is more commonly found in foreign-born infected individuals. Fluoroquinolones are bactericidal and can be lifesaving in cases of highly drug-resistant TB.



Reviewers' Comments:

Despite medical advances, pulmonary tuberculosis remains an important public health issue today. Dr. Long points out that TB has a disproportionate representation in vulnerable populations in Canada, primarily aboriginal populations and foreign-born immigrants. The importance of its early identification is compounded by its potential to propagate within these communities.

Once suspected, approaches focus on early airborne isolation to prevent the spread of TB. The gold standard for diagnosis remains recovery and culture of the organism. Microscopic detection of AFB by stained sputum smears relates directly to the infectivity of a patient and, if clinical suspicion is high, these should be hastened through a call to the laboratory to ensure prompt diagnosis. In Alberta, all specimens collected are kept for culture of mycobacteria, which although notoriously slow remains critically important as it allows for fingerprinting of the organism, susceptibility testing, and banking of individual strains.

In Dr. Long's second lecture, he explained some of the recent advances in testing for tuberculosis. Two novel methods are becoming widely available and must be understood by internists. The first, known as nucleic acid amplification testing (NAAT), is an automated molecular test for Mycobacterium tuberculosis (MTb), which can be used for rapid diagnosis (within 2h of collection) and to differentiate MTb from other common forms of mycobacterium such as Mycobacterium avian complex (MAC). This test is highly sensitive (~97%) and specific. Moreover, it has also been shown to rapidly identify drug resistant strains of TB through the use of line probe assays, which is increasingly important as the incidence of multi-drug resistant TB (MDR TB), both globally and in Canada, continues to rise. This test was recently endorsed by the WHO and its utility shown in resource poor settings (*N Engl J Med* 2010;363:1005–15). The second diagnostic test is the interferon gamma release assays (IGRAs) for the diagnosis of latent tuberculosis (LTBI). These assays are in-vitro tests of cell-mediated immune response measuring T cell release of interferon-gamma following stimulation by antigens specific to MTb. IGRAs have been shown to be highly specific for LTBI, again ~97%, but are not reliable in active TB infections (sensitivity ~75-90%) and unable to distinguish between latent and active TB infections. Although IGRAs will likely replace tuberculin skin testing for the diagnosis of LTBI, some important questions remain. For example, their utility in immunocompromised hosts and in healthcare worker screening programs is unknown. Lastly, it is not known if a positive IGRA assay will remain positive for the life of the patient, regardless of treatment for LTBI. Despite these questions, IGRAs represent a major advance in the diagnosis of latent TB.

Symposia

Evidence-Based Update in Atrial Fibrillation: Review of Old and New Drugs for Anticoagulation

Presented by Dr. L. Brent Mitchell, Calgary
Co-developed by the RM/ACP Annual Meeting Committee and Bayer Canada

Physicians have been aware of the increased risk of thromboembolic events associated with AFib for over 100 years. Accounting for 15 to 20% of all strokes, AFib is often undiagnosed until after the stroke occurs. Strokes associated with AFib are more severe than those occurring in patients without AFib. Importantly, the risk of stroke is equal for paroxysmal, persistent, and permanent AFib.

The 2010 Canadian Cardiovascular Society (CCS) guidelines for thromboembolism prevention in AFib recommend all patients with AFib be assessed for their risk of stroke, using a tool such as the $CHADS_2$ score, and their risk of bleeding, using a tool such as the HAS-BLED score. In principle, patients with a HAS-BLED score of 3 or more are at an increased risk of major bleeding. However, many of the factors in the $CHADS_2$ score are also included in the HAS-BLED score, making the practical interpretation of an elevated HAS-BLED challenging. Dr. Mitchell recommends that in situations where the HAS-BLED is elevated due to the presence of factors included in the $CHADS_2$ score (i.e., hypertension, prior stroke, and age), then the risk of bleeding is secondary to the increased risk of stroke.

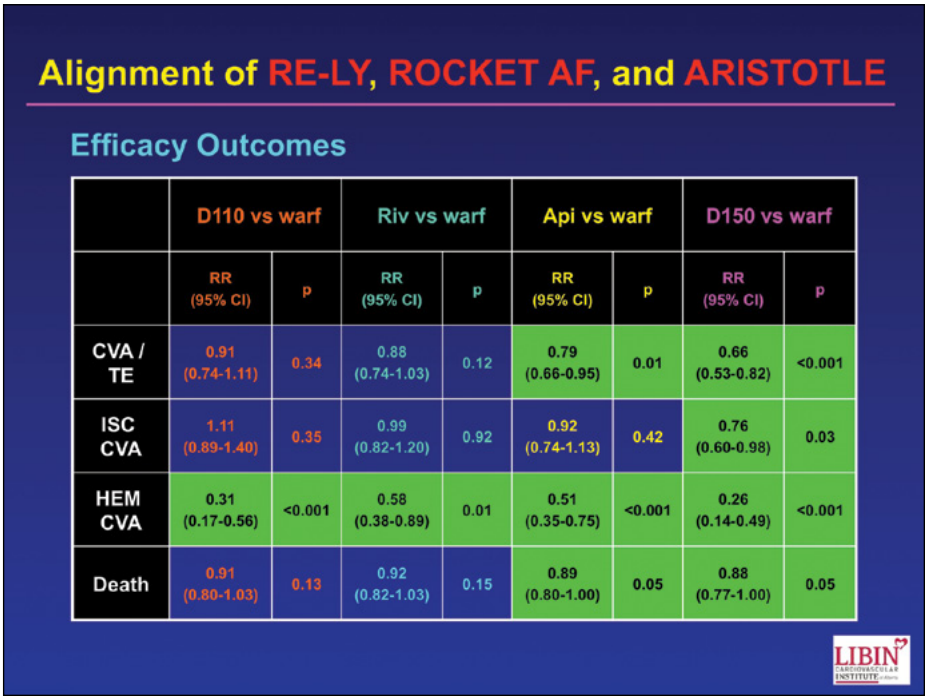
Warfarin has been the foundation for prolonged oral systemic anticoagulant therapy for many years and reduces the risk of stroke in patients with AFib by an impressive 64%. Aspirin offers a smaller benefit that only reaches statistical significance with the addition of other agents such as clopidogrel. Even then, the benefit of the combination does not approach that of warfarin. Based on these findings, the CCS guidelines recommend that only patients at very low risk of stroke (i.e., $CHADS_2 = 0$) should receive aspirin; oral anticoagulant therapy is recommended for all other patients.

Warfarin's characteristics, including a narrow therapeutic window, substantial heterogeneity in individual sensitivity, and multiple interactions with food, herbal agents, and other drugs, complicate its utilization in the clinical setting. A recent meta-analysis[1] found that only 48% of patients with AFib were treated with warfarin, and of those, the mean time in therapeutic range was 55%. As Dr. Mitchell pointed out, these findings tell us that only one quarter of AFib patients are effectively anticoagulated, an important care gap that must be resolved.

Novel anticoagulants that address many of warfarin's limitations are at varying stages of development. Dr. Mitchell presented the key findings from the phase III trials evaluating dabigatran, rivaroxaban, and apixaban versus adjusted-dose warfarin. He noted that each of these three trials was relatively large, enrolled patients with non-valvular AFib and risk factors for stroke (i.e., patients who should be receiving an anticoagulant), defined the primary efficacy endpoint as stroke or systemic embolism, and utilized major bleeding (with varying definitions) as a safety endpoint.

The direct thrombin inhibitor dabigatran was evaluated in RE-LY.[2] Compared to warfarin, the 150 mg dose reduced the risk of stroke with a similar risk of major bleeding and the 110 mg dose had a similar rate of stroke with significantly reduced major bleeding. As a result of these findings, the CCS guidelines now recommend that one of the new oral anticoagulants such as dabigatran is preferred over warfarin in most patients who require anticoagulation. The 150 mg bid dose of dabigatran is generally preferred over the 110 mg bid dose except in the elderly or patients with reduced renal function. Warfarin may be preferred over dabigatran in patients at high risk of an acute coronary event. [Post-conference note: In 2012, CCS published a focused update to the guidelines that i) recommends one of the new agents over warfarin in most patients; and ii) removes the preference for warfarin over one of the new agents in patients at high risk of an acute coronary event.]

Three Factor Xa inhibitors are in the late stages of development. [Post-conference note: rivaroxaban received a Notice of Compliance by Health Canada for this indication in January, 2012.] The ROCKET-AF study[3] evaluated rivaroxaban in patients with at least 2 risk factors for stroke, a higher risk population than was enrolled in RE-LY. Rivaroxaban was found to be non-inferior to warfarin for stroke prevention with similar rates of



major bleeding. Apixaban was compared to warfarin in the ARISTOTLE trial,[4] which enrolled patients at a similar risk for stroke as were studied in RE-LY. Apixaban reduced the risk of stroke compared to warfarin, although the ARR was only 0.34%, which is not clinically meaningful. There were also slightly reduced bleeding rates. Phase III results for edoxaban are expected later this year.

In considering the overall evidence from these studies, Dr. Mitchell emphasized that these new agents are transformative and that healthcare providers will need to weigh the risks and benefits of each as they pertain to individual patients when making treatment decisions.

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Reviewers' Comments:

Dr. Mitchell compared and contrasted the three novel oral anticoagulants that will likely replace warfarin because of their convenience and reliability. Although their absolute clinical benefit is similar to one another and each is comparable to warfarin, their reduced incidence of intracranial hemorrhage and practical advantages are moving guideline committees to recommend that almost all patients with a $CHADS_2$ score of 1 be fully anticoagulated rather than being considered for aspirin prophylaxis.

Dr. Mitchell correctly points out that these novel oral anticoagulants are "game-changers." By the end of the decade, there will be almost a dozen oral anticoagulant agents from which to choose, with widely available tests for therapeutic effect and agents for rapid reversal of their effects. The relative advantages of each agent in any given patient population have yet to be worked out in real life practice.

The adverse cardiac signal seen with dabigatran was not seen in the trials with the Xa inhibitors. Dabigatran and apixaban must be dosed twice daily, whereas rivaroxaban is given only once each day. All need to be dose-adjusted in renal failure.

Finally, one must be careful not to overestimate bleeding risk in the elderly or assume that a bleeding event has the same disutility as a stroke, and in so doing, deny patients the benefits of stroke prevention.

Update on Diabetes: Latest Evidence

Presented by Dr. Stuart Ross, Calgary
Co-developed by the RM/ACP Annual Meeting Committee and Lilly/ Boehringer Ingelheim

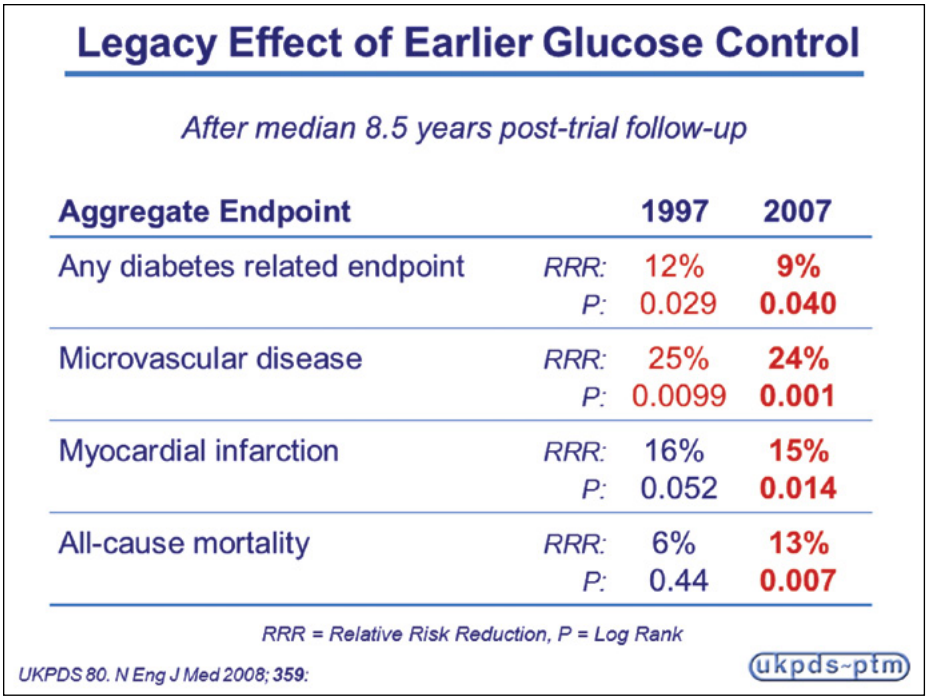
The currently accepted glycemic target of HbA1c ≤7% was derived in large part from the UKPDS study, which showed that this level of control was associated with significant reductions in several diabetes-associated microvascular complications. In a post-trial follow-up of patients 10 years after the trial was completed, patients who had been randomized to intensive control retained a significant advantage over the conventional group, even if glycemic control had deteriorated. This "legacy effect" suggests a major benefit of early intensive glycemic management for both microvascular and macrovascular outcomes.

The benefits and risks of intensive glycemic control continue to be debated in the scientific literature. The intensive glycemic control arm in the ACCORD study (target HbA1c <6%) was stopped early due to a higher incidence of death compared to standard management (target 7.0-7.9%). In contrast, the ADVANCE study reported a significant benefit of intensive glycemic control. A sub-analysis of the ACCORD data showed that patients in the intensive management group who died were generally older, had a longer duration of disease, a longer interval between diagnosis and treatment initiation, a history of cardiovascular disease, rapid correction of elevated HbA1c, had episodes of hypoglycemia, and continued poor glycemic control. In other words, intensive management had failed in these particular patients, even though the mean HbA1c of the entire intensive control arm was 6.5%. These findings support the concept that optimal management of diabetes depends on the "age and stage" of each patient. Reaching a glycemic target of ≤7% in older patients with long-standing diabetes and associated complications may be more difficult – and potentially harmful – compared to achieving this target in younger patients with less advanced disease.

Glycemic variability is another concept that is generating interest in the management of diabetes. Patients who achieve "tighter" glucose control appear to achieve better outcomes than those who experience more frequent swings from hyperglycemia to hypoglycemia. *In vitro* studies have shown that cells exposed to greater variability in glucose concentration have higher rates of cell death than cells exposed to more stable glucose concentrations. Studies have also shown that glycemic variability predicts mortality

in adults in the ICU. A major trial called FLAT-SUGAR will prospectively evaluate the link between glycemic variability and cardiovascular outcomes using continuous glucose monitoring.

Dr. Ross concluded his presentation with a brief discussion of diabetic nephropathy, which continues to be one of the most significant microvascular complications in diabetes patients. Renal impairment increases the risk of hypoglycemia and some oral hypoglycemic agents, such as metformin, are not recommended in patients with impaired renal function. However, evidence from a Cochrane review suggests the risk of lactic acidosis associated with metformin is low and this drug can be safely used in patients with minor reductions in renal function. Sulfonylureas remain the recommended second-line therapy, but are also renally eliminated. Third-line treatment is insulin. DPP-4 and GLP are alternative 3rd line agents in patients who cannot take or refuse insulin. The DPP-4 inhibitors are excreted renally and dose adjustments are necessary in patients with impaired renal function (with the exception of linagliptin, which is excreted primarily through the bile). Finally, Dr. Ross advised that an appropriate glycemic target for an elderly patient with heart disease may not be <7%. "Common sense must remain a big part of clinical acumen."



Reviewers' Comments:

Diabetes continues to represent a very large burden of disease with associated cost and morbidity in Canada. Review of Canadian data in diabetes care reveals discouraging results with respect to achieving combined targets of glycemic control, blood pressure and lipid control (*Can J Cardiol* 2010;26(6):297–302). Dr. Ross' review offered five very practical and evidence-based recommendations for internists to manage their diabetic patients:

1. Early management in newly diagnosed patients offers potentially long lasting beneficial effects in reducing complications (the "Legacy Effect"). HbA1c targets of <7% should ideally be achieved within one year of diagnosis of diabetes.
2. Simultaneous management of all cardiovascular risk factors, including hypertension and dyslipidemia, is paramount.
3. Elderly patients with a long history of diabetes and difficulty achieving glycemic targets may be harmed by overly aggressive management of blood sugar control.
4. High variability in blood glucose levels (glycemic variability) is potentially harmful despite achieving HbA1c targets <7%.
5. The therapeutic pyramid should include metformin as the first line agent, sulfonylureas as second line, and insulin as third line. Insulin is a more effective therapy than oral agents and internists need to be more willing to initiate this therapy in hopes of achieving glycemic targets earlier in the disease process.

Update on Lipids: Cardiovascular Disease Prevention - A Look Ahead

Presented by Dr. Jacques Genest, McGill University
Co-developed by the RM/ACP Annual Meeting Committee and Merck Canada

Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease are updated every 3 years. It is expected that the 2012 version of the guidelines will be largely unchanged in terms of cardiovascular risk assessment and LDL-cholesterol (LDL-C) treatment targets.

Studies suggest that for each 1 mmol/L reduction in LDL-C there is a 2% absolute risk reduction in major atherosclerotic events, regardless of the lipid-lowering agent employed. Whereas evidence continues to accumulate supporting the benefits of aggressive LDL-C lowering, strategies involving modulation of HDL-C mass and function have not borne consistently positive results. The results of ongoing studies evaluating the effects of niacin, dalcetrapib, and anecetrapib on cardiovascular event are eagerly awaited.

Dr. Genest predicted that vascular inflammation may play an increasing role in atherosclerosis research. Inflammatory mediators have a major role in the pathophysiology of atherosclerosis, and patients with chronic inflammatory disorders such as rheumatoid arthritis and psoriatic arthritis have a 2- to 5-fold higher incidence of cardiovascular disease. Emerging evidence suggests that cholesterol crystallization may be an early inflammatory trigger of atherosclerosis. Current models propose that cholesterol crystals activate the inflammasome to generate interleukin (IL)-1β, triggering production of CRP by the liver and ultimately resulting in vascular inflammation. The potential involvement of the inflammasome and the IL-1β pathway opens the door to new molecular targets for the treatment of atherosclerosis.

Reviewers' Comments:

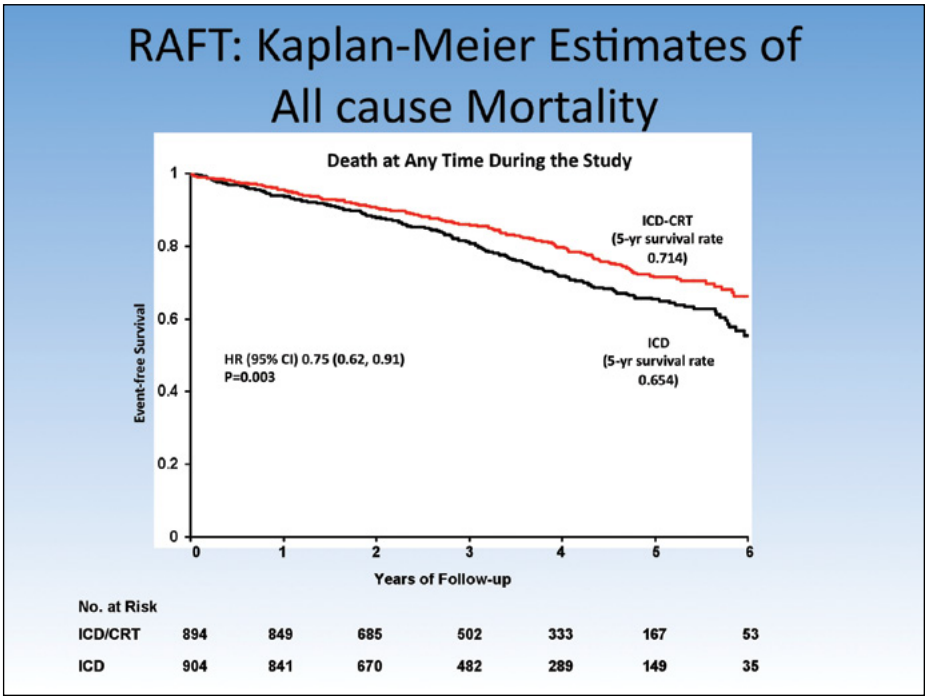
Dr. Genest's talk is an excellent resource to general internists as they navigate this dynamic field. The signal in JUPITER (*Circulation* 2010;121:143:50) regarding hs-CRP indicate that the protein itself is not likely a causal factor in coronary artery disease. Modulation of HDL function may be more important than its mass. This was a hard learned lesson in ILLUMINATE (torcetrapib) (*N Eng J Med* 2007;357:2109–22), and one that has informed forthcoming studies of the next generation of CTEP inhibitors, namely DAL OUTCOMES (dalcetrapib) and REVEAL (anacetrapib). Although the next chapter for niacin remains to be written, HPS-2 THRIVE and AIM-HIGH (*N Eng J Med* 2011;365:2255–67) give credence to the current focus on getting LDL to target. The first advice to pass on to our patients: Eat food. Mostly plants. Not too much (Pollan M. *The Omnivore's Dilemma: A Natural History of Four Meals*. New York, New York: Penguin, 1996).

CRT in the Treatment of Heart Failure

Presented by Dr. Anthony Tang, Victoria, and Dr. Jonathan Howlett, Calgary
Co-developed by the RM/ACP Annual Meeting Committee and Medtronic

While clinical trial evidence supporting cardiac resynchronization therapy (CRT) initially accumulated for the treatment of Class III and IV heart failure patients, recent studies have shown benefits in mildly symptomatic patients. Indeed, the REVERSE, MADIT-CRT and RAFT studies support a reduction in morbidity, mortality, and disease progression in Class I or II heart failure patients.

The REVERSE study demonstrated a trend toward less worsening of a composite endpoint that included all-cause mortality, heart failure hospitalization and heart failure worsening in Class I-II heart failure



patients receiving CRT compared to those with an implanted but inactive device (16% vs. 21%, p=0.10). A significant reduction in the primary composite endpoint of total mortality or heart failure events was demonstrated in Class I-II patients receiving CRT plus an implantable cardiac defibrillator (ICD) compared to ICD alone in the MADIT-CRT study; however, the difference was driven by the reduction in heart failure events, with no significant difference in mortality. Both studies reported a significant reduction in left ventricular (LV) volume and increased ejection fraction (EF) from baseline – so called 'reverse remodeling' of ventricular function.

The RAFT trial, which was largely a Canadian study, supports a significant reduction in a composite endpoint of mortality or hospitalization due to heart failure in Class II-III patients receiving ICD plus CRT. The RAFT trial showed a significant benefit in terms of all-cause mortality, with an absolute reduction of ~6% over 5 years of follow-up. A prespecified subgroup analysis showed that patients with a wider QRS duration or left bundle branch block (LBBB) derived greater benefit from the addition of CRT. Patients with permanent atrial fibrillation (AF) were also included in the RAFT study but there was no significant benefit of CRT added to ICD in this subgroup of patients.

The recently updated Canadian Cardiovascular Society (CCS) heart failure guidelines recommend the use of CRT in combination with an ICD for heart failure patients on optimal medical therapy with Class II symptoms, LEVF <30% and QRS duration of 150 ms. Dr. Howlett pointed out that studies to date have not included patients with planned surgical or interventional procedures, recent myocardial infarction, known cardiomyopathies, end stage renal failure, dementia, or other significant life-limiting co-morbidities. Therefore the benefits and risks of CRT in these patients remain unknown. In conclusion, Dr. Howlett summarized some of the points that argue for and against CRT.

Features that argue for CRT	Features that argue against CRT
Lower ejection fraction	Ejection fraction closer to 35%
Sinus rhythm	Lack of sinus rhythm, lack of pacing potential (e.g., large posterior infarct)
QRS closer to 150 ms	QRS closer to 120 ms
LBBB	Non-LBBB
Stable, chronic heart failure · Dilated DM · Female gender?	Extremes of symptoms · Use of inotropes · Acutely worsening or intermittent symptoms

Reviewers' Comments:

A recently published systematic review and meta-analysis on the subject of CRT (*J Cardiac Fail* 2011;17:860-6) cites 5 studies that compare CRT to medical management of heart failure alone in patients with Class II - IV heart failure. Summarily, these studies show a 4.5% absolute reduction in mortality over the 1-2 years of the running of the trials. Also, in 6 RCTs comparing CRT-ICD versus ICD alone there was a 3.7 % absolute reduction in mortality. These numbers are quite respectable. However, because of the high mortality and morbidity in this cohort, 3-6 times more people died or were admitted to hospital for heart failure despite having the device than benefited from it.

The authors of the 2011 CCS Heart Failure Guidelines statement suggesting that all patients with NYHA Class II-IV heart failure despite optimal medical treatment with an EF < 30% and a QRS duration > 150 msec be considered for placement of CRT-ICD clearly have not examined all of the economic issues relevant to implementing such a costly new technology in this sizable population of patients. Will there be more money for this exciting new technology, or is the verdict in from the 3 trials presented and it's Code BLUE on CRT? Perhaps there is a subset of patients with heart failure where CRT or some better treatment will help them live longer, healthier lives.

Short Snappers

Dementia: A Disease of the Microcirculation

Presented by Dr. Tom Jeerakathil, University of Alberta

Stroke and other vascular risk factors are associated with an increased risk of future dementia. How this occurs and the extent to which cardiovascular risk factors and small vessel disease contribute to dementia is less well established. The findings of a recent meta-analysis of prospective longitudinal studies that examined the impact of white matter changes on outcomes including cognitive decline, dementia, stroke and mortality support an association between small vessel disease and dementia in the general population, although not in 'high risk' subgroups (those with previous stroke, or pre-existing cognitive impairment). While this association would be expected for vascular dementia, it also applied to patients with Alzheimer's disease (AD). The findings are also consistent with the 1997 Nun Study, which showed that in the presence of microinfarcts, smaller plaque burden produced more significant cognitive impairment. Other cardiovascular risk factors have also been associated with a higher risk of dementia and cognitive changes, particularly hypertension.

If dementia is a disease of the microcirculation, can controlling cardiovascular risk factors modulate disease outcomes? The literature shows mixed results, but there is a signal suggesting that modulation of risk factors may be protective. For example, the recent HYVET-COG study showed that aggressive blood pressure reduction (i.e., -15 mmHg) in very elderly patients significantly reduced their risk of dementia. The curves continued to diverge over time, suggesting that dementia might be delayed or prevented by controlling blood pressure over several decades.

Use of Hypertonic Saline in Hyponatremia

Presented by Dr. Irene Ma, University of Calgary

Evidence guiding the optimal management of hyponatremia is limited and is based primarily on consensus from expert panels. Nonetheless, when confronted with a patient with symptomatic severe hyponatremia, few internists would argue against the use of hypertonic saline.

Hypertonic saline is any solution with a higher sodium concentration than the body's normal level of 140 mEq/L. Typically, hypertonic saline solutions are 3% (513 mEq/L) and 5% (856 mEq/L), but they can range as high as 29%. The use of hypertonic saline is generally guided by symptoms. Patients who are most likely to do poorly if undertreated include those with an acute drop in their sodium, women, children, and patients who are hypoxic.

Hyponatremia can be worsened if the saline solution administered does not have a higher sodium concentration than that in the urine. However, when internists are confronted with an acute case of severe hyponatremia, urine indices are not always readily available. Therefore, guidelines suggest empiric treatment with hypertonic saline. There are at least four formulae available to guide the amount of hypertonic saline to administer, with the Androgue-Madias formula being the most commonly used. Dr. Ma recommended a simpler method that yields the same answer as using a formula, but that does not require any memorization on the internist's part. The method involves logically working through the following four questions:

1. How much sodium is in the patient right now? [TBW (L) x existing serum sodium concentration (mEq/L)]
2. How much sodium will be in the patient if 1L of 3% hypertonic saline is administered? [#1 above + 513 mEq]
3. What would the patient's end sodium concentration be? [#1 above + 513] mEq / [TBW + 1] L
4. How quickly do you want to achieve this end concentration?

In order to avoid overtreatment of hyponatremia and the risk of OSD, there are recommended limits based on human data from different sources. While these vary, Dr. Ma suggested that for undifferentiated symptomatic hyponatremia, <12 mEq/L/day is acceptable. Reasonable limits for the treatment of acute severe hyponatremia are to increase sodium by 1-2 mEq/L/hr for the first 3-4 hours, never exceeding 3/hr, with a daily maximum of 8-12 mEq/L.

While there is clearly potential harm to correcting a drop in sodium too rapidly, correcting sodium levels too slowly can also result in negative outcomes. In acute hyponatremia, a correction rate of 2 mmol/hr has been associated with greater survival than correcting sodium more slowly. Studies suggest that end sodium values are overestimated about 75% of the time using the available formulae. There are multiple reasons that may account for over-correction using formulae. For example, formulae do not account for ongoing urine and gastrointestinal sodium losses, dietary intake, and more importantly, for water diuresis. This makes ongoing laboratory testing and monitoring essential in the management of acute hyponatremia. When sodium is over-corrected, hypotonic solutions can be administered (e.g., 1-2 µg IV/SC DDAVP) with monitoring of urine sodium levels every 1-2 hours to ensure they remain in the normal range.

Reviewers' Comments:

Is there any risk to giving 100 ml of 3% NaCl (or 2 ml/kg in smaller adults or children) over 5-10 min, repeating the serum sodium and thereby devising an 'on-the-go' replacement strategy? This can be continued until the patient is asymptomatic (usually after a correction in serum sodium by 4-6 mEq/l), following which no further sodium correction or a slower rate of sodium administration can be undertaken depending upon the cause of the hyponatremia (*Curr Opin Crit Care* 2011;17:581-93). In no instance should the daily correction be greater than 10 mEq/l in the first 24 hours and 18 mEq/l over 48 hours. Indeed, given the frailties of assessing volume, most experts now suggest giving repeated small boluses of hypertonic saline and repeatedly measuring serum sodium to all symptomatic patients that require sodium correction (*Acta Anaesthesiol Scand* 2011; 55:139-48). The key is, and this cannot be overemphasized, choosing the correct solution and reassessing the response to your sodium administration.

What about using normal (0.9%) saline for correction of hyponatremia? If you know the concentration of solute in a bag and can correctly calculate the amount and the rate at which you wish to administer it (information needed regardless of the solution you are choosing), the only difference in giving 100 mEq of Na+ as 0.9% NaCl or 100 mEq of Na+ as 3% NaCl is in the amount of water you are providing along with that solute. The clinical question becomes 'How much water would I like to give to this patient who is already hyponatremic?' This, of course, relates to the overriding cause of the hyponatremia and to the risks inherent in overcorrecting hyponatremia.

If the patient has hypovolemic hyponatremia, and so is deplete of both sodium and water but proportionally more sodium than water, 2 conditions may complicate your correction, particularly when choosing to rehydrate/correct with 0.9% saline. First, and this was discussed by Dr. Ma, if the tonicity (osmolality) of the urine is higher than the tonicity of the solution you are using to correct the hyponatremia, rehydrating/correcting with 0.9% saline may drive the sodium lower and worsen the hyponatremia. Second, given that 0.9% saline has inherently more water than 3% saline, you risk correcting the volume deficit before correcting the sodium deficit. The stimulus causing ADH secretion is lost (ADH is appropriately elevated in hypovolemic hyponatremia) in which case the kidney starts excreting large volumes of dilute urine thereby self-correcting the hyponatremia, irrespective of your best efforts to control solute and water administration. Incidentally, the same problem awaits glucocorticoid administration in hyponatremia due to adrenal insufficiency. Thus, hypertonic saline should be the principal replacement solution early in the treatment of most cases of hyponatremia, irrespective of the cause.

Exercise in Health Promotion

Presented by Dr. Mark Roberts, University of British Columbia

Current epidemiological reports suggest that low fitness levels are responsible for more deaths in Canada and the USA than chronic diseases such as hypertension, obesity and smoking that are expensive to treat and garner much more attention. In Canada, it is estimated that 30,000 deaths can be attributed to the "sedentary death syndrome." Low fitness is not only an important risk factor for mortality, it is also associated with a host of other chronic conditions including dementia, osteoporosis, diabetes, coronary heart disease, colorectal cancer, breast cancer, hypertension, and many others. Given the health benefits of physical fitness and exercise, it might be expected that healthcare professionals would routinely advise their patients on this important matter. Yet studies suggest this is not the case. Indeed, in a study of 330 family physicians across Canada, only 11% counselled their patients on the benefits of exercise, and more alarmingly, only 43% felt they *should* be counselling their patients on this topic. Not surprisingly, the major barriers against counselling were time and education about exercise.

Current exercise recommendations call for at least 30 minutes of moderately intense physical activity at least 5 days per week, and preferably every day. These recommendations are based on evidence suggesting that the benefits of exercise extend beyond weight control and weight loss. Physicians should therefore be actively recommending the minimum amount of exercise to all of their patients. While higher amounts of exercise may be necessary in some circumstances, such as endurance training, there are undeniable health benefits from meeting just the minimum requirements for physical activity each day.

Workshops

Ultrasound Guided Bedside Diagnosis & Procedures

Presented by Dr. Rob McDermid, University of Alberta

Ultrasound (U/S) technology has the potential to assist physicians with a host of procedures and diagnostics, including central venous access, thoracentesis, and many others. Bedside U/S has been shown to be particularly useful for identifying cardiac abnormalities (low ejection fraction, high pulmonary pressure, pericardial effusion, and severe valvular regurgitation or stenosis). These can all be well visualized with bedside U/S. Studies suggest that non-cardiology intensivists can reliably perform goal-directed U/S. For example, a study of six intensivists who received ten 1-hour sessions of U/S training were found to perform with 84% accuracy. Moreover, the information obtained by bedside U/S resulted in a change in management strategy in 37% of cases. Trainees at all levels can learn how to apply bedside U/S-guided diagnosis with appropriate training. For example, first-year medical students have been taught to use bedside U/S to augment diagnosis.

Dr. McDermid utilizes U/S-guided bedside diagnosis 3 to 4 times during a typical night on call. "My practice revolves around U/S because I can get information fast. It helps me improve the care of my patients." Guidelines are currently in development for the training and optimal use of bedside U/S. Meanwhile, the availability and portability of U/S devices is increasing while the development of accurate and affordable U/S probes is an ongoing area of innovation. A hand-held U/S device is now available for approximately $7500.

Reviewers' Comments:

Will bedside US become the new stethoscope of the 21st century? This technology has great potential to augment our physical exam skills and to enhance the safety of some of our common bedside procedures. For example, physical exam findings such as thyroid enlargement or nodules or the presence of a pleural effusion or ascites can be confirmed at the bedside. Central venous catheterization and thoracocentisis are safer when guided by U/S. But, how extensively should internists not formally trained in diagnostic imaging be using this modality of investigation? While very limited research in this area is supportive of the capacity for health care providers at many levels to learn very specific U/S skills, there is much to learn regarding optimal introduction of this new technology into practice. ED physicians and intensivists have moved ahead of internists on introduction of bedside U/S into their practices. Training programs with established curricula (both U/S theory and learning of specific skills) exist. However, the occasion would be rare that a bedside U/S replaces formal and complete diagnostic imaging, when indicated. This technology is undoubtedly useful for many applications and is evolving rapidly – for example, the hand held-device cited above. As internists, it behooves us to keep up to date not only in our knowledge base but also evolving diagnostic skills.

Infection in Pregnancy

Presented by Dr. Eliana Castillo, University of Calgary

Pregnancy can be considered as a "controlled" or contained form of systemic inflammatory response syndrome (SIRS) whereby heart rate is >90 bpm, respiratory rate is >20 breaths/min, PaCO2 is <32 mmHg, white blood cell count is >12,000, and temperature is higher than 38˚C or less than 36˚C. These are normal physiologic changes in pregnancy and women often feel fine despite their presence.

Infections are common complications of pregnancy, occurring in 1 to 10% of pregnant women. In the setting of contained SIRS, a pregnant woman can usually compensate for an infection for a while. However, if she decompensates, it tends to happen rapidly. Sepsis is often not recognized soon enough in pregnant patients because the physiology of pregnancy can mimic the pathophysiology of sepsis. Sepsis continues to rank among the top three causes of maternal morbidity in the United Kingdom and Canada, where data on maternal deaths are tracked and compiled every 3 years. This rich source of epidemiologic information suggests that the median age of women who die from sepsis during pregnancy is ~34 years, and about half of these women were otherwise "healthy" with no associated medical conditions. The pathogens most often associated with maternal sepsis leading to mortality include Group A Streptococcus, E. coli, and influenza. Furthermore, almost 50% of women who died did so within 24 hours of admission, supporting the concept of rapid deterioration when decompensation occurs. These data suggest a failure of taking routine observation, asking for specialist advice early, and importantly, starting empiric antibiotic treatment in pregnant women when sepsis is suspected. Dr. Castillo's own data involving 75 cases of sepsis among pregnant women admitted to the British Columbia Women's Hospital suggest that SpO_2 was measured in only 42% of cases, urine output was recorded only 20% of the time, and lactate was ordered <1% of the time.

Recommendations include considering tachypnea and/or an SpO_2 of less than 94% on room air to be red flags, ensuring that perfusion goals (urine output, lactate) are met, directing investigations toward identifying a source (nasopharyngeal swabs and sputum), and tailoring appropriate antibiotic treatment. With the exception of fluoroquinolones, any antibiotic that would typically be used for the treatment of respiratory infections in non-pregnant patients (e.g., macrobid, azithromycin, 3rd generation cephalosprins) can be considered for pregnant women.

Finally, Dr. Castillo advocated for the recognition of pregnancy as a window of opportunity to promote routine vaccination. Immunization against influenza can significantly reduce maternal morbidity and mortality, and it can also protect newborns from death in the early days of life. Mothers expressing concerns regarding the theoretical risks of vaccination during pregnancy can be reassured that the risk of adverse pregnancy outcomes due to vaccine-preventable infections is much higher. The World Health Organization recommends routine vaccinations during pregnancy including influenza and DTap, as well as specific vaccines based on maternal comorbid medical conditions. Despite this recommendation and the recognized risks of influenza infection during pregnancy, only 15% of all pregnant women are immunized, suggesting an educational need for patients and physicians alike.

Osteoporosis for General Internists

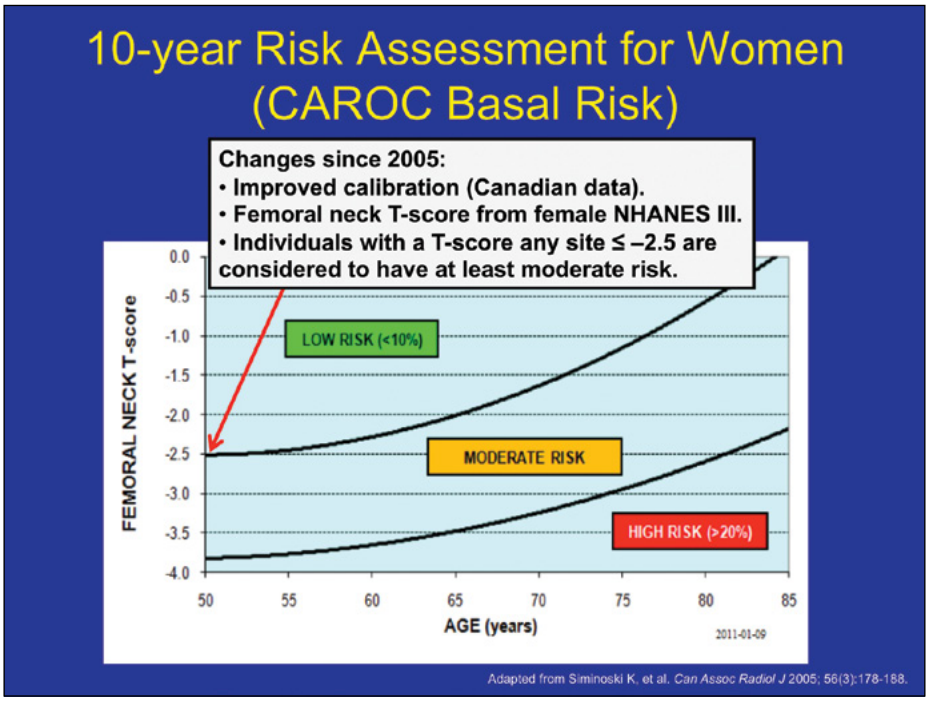
Presented by Dr. Bill Leslie, University of Manitoba

The Osteoporosis Canada clinical practice guidelines for the diagnosis and management of osteoporosis were updated in 2010. Although they continue to emphasize T-scores and bone mineral density (BMD) for the characterization of osteoporosis, the new guidelines also recognize that this disease is complex and multifactorial, and that more than one single risk factor predicts fracture risk. Therefore, the new guidelines have increased their focus on fractures and the clinical impact of fragility fractures.

There continues to be an enormous care gap in post-fracture care and treatment of high-risk patients to prevent secondary fractures. This is in stark contrast to other chronic health conditions. For example, 80% of patients who suffer a heart attack are discharged from hospital with a prescription for beta-blockers, whereas only ~15% of people who fracture are diagnosed and treated for osteoporosis. The consequences of under-recognition of osteoporosis can be considerable to both patients (e.g., subsequent fracture, hospitalization, institutionalization, reduced quality of life) and the healthcare system (i.e., about $1 billion per year in Canada).

The new guidelines endorse the use of the CAROC risk assessment tool that is based on national fracture mortality data and has been tested and validated in Canadian cohorts. This simple tool emphasizes just three risk categories (low, moderate and high) and three risk factors (age, sex and BMD), which are generally sufficient to inform appropriate treatment decisions. Alternatively, Dr. Leslie suggested using the World Health Organization's FRAX system, which considers additional risk factors. A Canadian version is available, which has been directly validated in a Canadian population. Both tools estimate 10-year fracture risk, which aligns with the Osteoporosis Canada treatment guidelines, and are available on the Osteoporosis Canada website (www.osteoporosis.ca).

Patients with a low 10-year risk of fracture (<10%) are unlikely to benefit from treatment; lifestyle counselling should be dispensed and the patient reassessed in 5 years. Patient preference guides treatment decisions for the moderate risk (10-20%) group. These patients should be evaluated for additional risk factors, including height loss or family history of hip fracture, which increases the absolute 10-year risk by 9%. Spinal imaging can be useful in moderate-risk patients; if any undiagnosed vertebral fractures are identified, the patient is re-categorized into a high-risk group that warrants treatment. There is strong evidence to support osteoporosis treatment in high-risk patients (10-year risk >20%). There are several first-line therapies available to choose from. Dr. Leslie noted that while serious adverse events such as osteonecrosis of the jaw and atypical femur fractures have been associated with bisphosphonate therapy, these events are very rare and the risk-benefit ratio remains favourable in high-risk patients. New anabolic treatments that regulate osteoclast function are in development and Dr. Leslie pre-



dicted that "these new drugs will change how we treat osteoporosis in the next 5 to 10 years."

Calcium and vitamin D supplementation as well as weight-bearing exercise remain important components of management for patients with low bone mass. Current recommendations suggest an upper limit of 1200 mg/d of calcium from both dietary sources and supplements, a reduction from previous recommendations of 1500 mg/d. Some studies have suggested that calcium supplements may cause a surge in serum calcium levels that can increase the risk of cardiovascular disease. However, Dr. Leslie cautioned that the evidence for this association is limited to one large study that found a signal using a very narrow definition of myocardial infarction, but the association disappeared when adjudicated definitions were used. Dr. Leslie is comfortable recommending 1200 mg/d, whereas there is no evidence for benefit above this level. He advises vitamin D supplementation at 1000-2000 IU/d, although guideline recommendations vary between 800-4000 IU/d.

A Quick Reference Guide for the 2010 Osteoporosis Canada guidelines is available online at www.osteoporosis.ca.

Reviewers' Comments:

Efforts to reduce the clinical and financial costs of osteoporosis continue to be frustrated by the inability of any single intervention to have a major impact on this multi-factorial problem. However, a systematic approach to diagnosis, categorization and treatment will still be needed for there to be any hope of improving the situation.

The new Osteoporosis Canada guidelines start by recommending formal assessment of osteoporosis risk in all patients with fractures as a first step to avoiding repeat breaks. Both the CAROC risk assessment tool and the World Health Organization's FRAX system provide a 10-year fracture risk, validated for the Canadian population. Those with a > 20% risk merit strong consideration for bisphosphonate therapy.

Dr. Leslie's workshop also reminds us that the most prudent therapy is preventive. Younger patients need encouragement to participate in an active life style that includes weight-bearing exercise and to consider an intake of 1000-2000 IU/d of Vitamin D as well as a total food/supplement intake of 1200 mg/d of calcium. By the time the bone becomes osteoporotic enough to fracture, it may be too late to fully regain its integrity. Therefore, as in many medical diseases, prevention is far more desirable than cure.

Update on Perioperative Medicine

Presented by Dr. Bruce Fisher, University of Alberta

Preoperative consultations are commonly conducted for patients undergoing major non-cardiac surgery. This task involves risk stratification, risk reduction, event surveillance, and dispensing general medical advice. Dr. Bruce Fisher reviewed the benefits – and potential harms – of performing preoperative cardiac risk assessment and preoperative management of medications in patients undergoing non-cardiac surgery.

Several cardiac risk stratification tools are available, among which the ASA (American Society of Anesthesiologists) physical status classification system, Lee criteria, and the revised Cardiac Risk Index (rCRI) are the most commonly employed. Dr. Fisher discussed some of the benefits and limitations of risk assessment tools, which are summarized in the table on the opposite page.

Risk assessment tool	Benefits	Limitations
ASA physical status classification system	· Widely used and recognized	· Not explicitly developed as a risk assessment tool · Clinical acumen required · Derived in a non-contemprary patient population
Lee criteria	· Derived from a large, prospective study · Widely used and recognized · ROC 0.81	· Becoming "stale" (developed 12 years ago) · Underestimates risk · Included only two types of surgical patients (does not reflect orthopedic population) · Does not predict vascular risk very well
VSG-CRI (Vascular Study Group of New England – Cardiac Risk Index)	· Recently developed (2010) · Derived from a large cohort study	· Complicated model · ROC 0.71 · Limited utility for internists who are less likely to consult on vascular surgery patients
rCRI (Erasmus model)	· Stratifies risk by age · ROC increased from 0.63 to 0.85	
Cardiac Risk Calculator	· Recently developed (2011) · Derived from a large database of 250,000 patients · Medical chart review with high quality data extraction · ROC 0.88	· Not a research trial · No preoperative and postoerative evaluations · Average age of cohort ~10 years younger than rCRI cohort · Only included hard cardiac endpoints (MI and cardiac arrest) · ~1/3 were low risk surgeries (laparoscopy, breast surgery) not normally candidates for preoperative consultation · ASA classification embedded in the score (i.e., "a model within a model") · Low sensitivity

ROC: receiver-operator curve

Dr. Fisher noted that the simple and rapid Ankle-Brachial Index (ABI) correlates well with the rCRI, and is probably worth doing to ensure a patient does not have undeclared vascular disease. Among the newer tools and tests on the horizon to improve risk stratification is brain natriuretic peptide (BNP). While studies to date suggest this easy-to-measure biomarker may offer additional prognostic information for mortality and cardiac events after major non-cardiac surgery, this benefit is offset by the lack of understanding regarding what to do with the information. Furthermore, there has been substantial variability between studies evaluating BNP and pro-BNP (e.g., types of surgeries, patients' risk level, mortality rates, etc.) and a threshold BNP level has yet to be defined. While BNP may be a tantalizing idea, Dr. Fisher concluded that it is not "ready for prime time" yet. More definitive data on how to make use of this biomarker is eagerly awaited from the ongoing VISION trial, with results expected in 2013.

Dr. Fisher concluded his workshop by reviewing data from a retrospective cohort study that evaluated outcomes in more than 270,000 patients undergoing major elective non-cardiac surgery in Ontario from 1994 to 2004. In this cohort, 39% of patients had a preoperative consultation at a median of 15 days prior to surgery. Using matched propensity analysis, the investigators showed that patients who received preoperative risk assessment and management had higher 30-day and 1-year mortality, longer hospital stay, increased preoperative testing and pharmaceutical interventions, compared to patients who did not receive a preoperative consultation. A sensitivity analysis showed that risk was increased only when the consultation was carried out by specialists rather than generalists and when the consultation was within 7 days of surgery, suggesting a narrower focus of the consultation and more aggressive interventions close to surgery may increase the risk for harm to patients. Dr. Fisher concluded that "Before you do stuff, you should ask yourself what you'll do with the results, and give yourself enough time to have the intervention work." For example, smoking cessation often takes longer than 2 weeks, beta-blocker initiation within 1-2 weeks of surgery can be dangerous, and statins require several weeks to have an appreciable effect on blood lipids. "As advocates for our patients, we need to actively lobby to stop last-minute management strategies."

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