Introduction to the 2009 Rocky Mountain General Internal Medicine Conference

The 2009 Rocky Mountain/ACP General Internal Medicine Conference provided attendees with another superb line-up of clinically relevant presentations and workshops. The conference was held during the peak of the H1N1 pandemic, which was the focus of a short snapper presentation and was a common topic of discussion throughout the weekend activities.

In response to participant feedback from the 2008 conference, the program featured expert presentations and workshops on wide-ranging topics of interest to general internists, including gout, hyponatremia, and the clinical utility of likelihood ratios. There were also several presentations and symposia on the evolving paradigm of anticoagulation therapy with the development and recent introduction of new oral anticoagulation agents.

This post-conference report aims to highlight some of the key learning points from selected presentations. It uses the same format as previous years, providing a short summary of the topic as presented, followed by a brief commentary emphasizing the clinical impact of the data presented. The goal of this conference report is to provide attendees with further opportunity to reflect on what was learned and stimulate further discussions on some of the more controversial topics that are poised to change the way general internal medicine is practiced today.

To view and download the speaker presentations from this year’s conference, visit the Rocky Mountain Conference website at http://www.ucalgary.ca/gim/rmc.html.
KEYNOTE ADDRESS

Top 5 General Internal Medicine Papers 2008/2009

Presented by Dr. William Ghali, University of Calgary

Dr. William Ghali, Professor of Medicine at the University of Calgary, was invited to present five papers published in the past year that general internists should read. Dr. Ghali’s selection was based on a variety of surveillance strategies, including informal consultation with colleagues; journal clubs; literature searches; journal subscriptions; and notably, the ACP Journal Club, which comments on the most important papers published in the preceding months from an evidence-based perspective. Dr. Ghali’s “Five (Notable) Papers in GIM” included the following:

1. A systematic review and meta-analysis by Bangalore et al. that supports the limited use of perioperative beta blockers in carefully selected patients undergoing non-cardiac surgery.

2. The ASTRAL study that does not support revascularization for renal artery stenosis since this approach provided no benefits over aggressive antihypertensive therapy and was associated with serious complications (24/406), including two procedure-related deaths.

3. The RE-LY trial that supports the use of dabigatran as an alternative to warfarin for stroke prevention in patients with atrial fibrillation.

4. A randomized controlled trial by Prandoni et al. that supports the use of ultrasound as one approach to guide anticoagulation decisions at six months of follow up for patients with deep vein thrombosis (DVT).

5. A meta-analysis using individual-level data by the Antithrombotic Trialists’ Collaboration that provides further support for the benefit of aspirin in secondary prevention of thrombosis.

REFERENCES


Reviewers’ Comments:

General internists should familiarize themselves with these key papers, which are summarized on the Rocky Mountain Conference website at http://www.ucalgary.ca/gim/rmc.html.

The issue of perioperative use of beta-blockers is commonly encountered by internists. The Bangalore meta-analysis concludes that there remains a role for these agents in selected individuals. Both coronary and stroke risk stratification are important in selecting appropriate patients, since the absolute risk reduction of myocardial infarction (MI) of 1.5% was offset by an increased risk of stroke of 0.4%, for a relative trade-off of more than four MIs prevented for every stroke caused. Therefore, patients at high risk of MI and low risk of stroke would be expected to benefit the most from perioperative beta blockade.

The ASTRAL trial results are congruent with those of an earlier and smaller Dutch trial, DRASTIC, and remind us that revascularization of a single vessel in a complex condition may not produce expected benefits and, furthermore, is not without risk. Clinicians should consider these results before embarking on such procedures, particularly if the outcomes are not expected to influence management decisions.

RE-LY is a landmark trial that compared the oral direct thrombin inhibitor dabigatran to warfarin. Its conclusions support the argument that newer oral anticoagulants may finally be poised to change current anticoagulant approaches to stroke prevention for patients with atrial fibrillation. On balance, many patients could benefit from a treatment that results in a high percentage of patients achieving target anticoagulant effects for a greater percentage of time. Unanswered questions remain regarding pricing and cost-effectiveness and an unexpected finding of an increase in non-fatal myocardial infarction. RE-LY is discussed in further detail in a later section of this conference report.

The study by Prandoni et al. helps answer the question of how to manage patients who are treated for DVT at 6 months of follow up. Ultrasound appears to be a helpful tool to guide decisions on whether or not to continue anticoagulation. If ultrasound shows that veins have recanalized, anticoagulation can be safely stopped, whereas if veins have not recanalized, anticoagulation should be continued until recanalization has occurred. This approach remains to be reconciled with the d-dimer approach to guiding anticoagulation decisions, a topic featured at the 2008 Rocky Mountain Conference.

We know that aspirin reduces the risk of thrombosis and increases bleeding risk, but by how much? The ATT (Anti-Thrombosis Trialists) collaborative meta-analysis further refines the estimated magnitude of relative benefits and risks of aspirin in primary and secondary prevention in specific patient populations. The trade-off between benefits (mostly non-fatal MI) and risks of bleeding (mostly GI) are approximately 2:1 for primary prevention and 10:1 for secondary prevention. A more controversial issue remains the benefit-risk ratio of primary prevention for diabetic patients. The equivocal evidence to date for the diabetic population suggests this issue deserves further investigation.
The Very Scary Hypertension (VSHT) Talk: A Thriller in 5 Acts
Presented by Dr. Jake Onrot, University of British Columbia

Hypertensive emergencies are a relatively common problem in clinical practice. There are 4 important questions to consider when seeing a patient with severe hypertension:

1) How high is the blood pressure?
2) What was the patient’s baseline blood pressure?
3) How long has the blood pressure been (severely) elevated to this level?
4) Is the patient symptomatic or is there clinical/biochemical evidence suggesting hypertensive damage in critical vascular territories?

A hypertensive emergency arises when there is severe blood pressure elevation or a significant elevation in blood pressure over baseline levels with symptoms or signs of acute, rapidly-progressive organ damage. A hypertensive urgency occurs when there is a similar blood pressure elevation, but no symptoms, and no progressive organ damage. Examination of the fundi can help classify the severity of the crisis, since this is the only area where the vessels can be directly observed on physical examination.

The setting determines the management strategy, and Dr. Onrot provided an algorithm for managing all types of “very scary hypertension.” Notably, pregnancy is the one situation where the setting does not matter because “things can go wrong really fast when the blood pressure rises above 160/105 mmHg.”

There are several antihypertensive agents available to lower blood pressure, with intravenous sodium nitropresside being the treatment of choice in the setting of an emergency. In general, additional drugs are added until blood pressure is controlled, and only then should clinicians consider removing drugs from the regimen that are believed to be less contributory to BP lowering effects or having untoward effects. Although rapid lowering of blood pressure is the target in hypertensive emergencies to lower the risk of organ damage, there is a risk that too rapid of a decline in any hypertensive crisis can lead to cerebral hypoperfusion and CNS damage. Thus, antihypertensive agents used in the truly emergency setting should be intravenous, rapidly-acting (onset and offset) and titratable. One of the drawbacks of using sublingual captopril or nifedipine is that many patients in this setting have a pressure-induced natriuresis and are volume-depleted, resulting in an exaggerated blood pressure lowering response. Physicians should use repeated small doses of an effective antihypertensive agent in order to achieve a 25% reduction in mean arterial pressure over 1-3 hours in a hypertensive emergency, and the same BP reductions, but over 1-5 days, in a hypertensive urgency.

Useful Drugs

<table>
<thead>
<tr>
<th>Intravenous</th>
<th>PO or Sublingual</th>
<th>Special Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>labetalol</td>
<td>labetalol</td>
<td>phenolamine</td>
</tr>
<tr>
<td>nitroprusside</td>
<td>captopril</td>
<td>trimethopran</td>
</tr>
<tr>
<td>hydralazine</td>
<td>nifedipine</td>
<td>furosemide</td>
</tr>
<tr>
<td>enalaprilat</td>
<td>nitroglycerine</td>
<td>nitroglycerine</td>
</tr>
<tr>
<td>fenoldapam</td>
<td>hydralazine</td>
<td></td>
</tr>
<tr>
<td>nicardipine</td>
<td>Clonidine</td>
<td></td>
</tr>
<tr>
<td>esmolol</td>
<td>urapidil</td>
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Studies suggest that most cases of accelerated hypertension are related to at least one patient factor, usually involving non-adherence. This underscores the importance of proper follow-up and education after patients are discharged.

Reviewers’ Comments:

Dr. Onrot’s “Thriller in 5 Acts” provided Rocky Mountain participants with a great review of how to appropriately manage hypertensive crises. One of the key points from Dr. Onrot’s presentation was that internists should treat the patient, not the pressure, since some patients with very high blood pressure remain functional.

Assessment of the fundi can provide important contributory information in the setting of hypertensive emergencies. However, a normal fundoscopic examination does not exclude hypertensive encephalopathy. When there is advanced retinopathy, internists can assume that the blood pressure is causing the symptoms (i.e., an emergency).
**AM EDWARDS/ACP LECTURE**

** Interruption of Systemic Anticoagulation: To Bridge or Not to Bridge?**

*Presented by Dr. Graham Turpie, McMaster University, Hamilton, Ontario*

The need to manage anticoagulants in the perioperative period is common, with estimates suggesting that one in every 10 patients on warfarin is assessed every year for peri-procedural management. This involves a challenging clinical decision, since the potential risks are significant: arterial and venous thromboembolism if anticoagulants are stopped, balanced against the risk of peri-procedural major bleeding if anticoagulation is continued. Despite the recognized risks, best clinical practices remain to be established, and are limited by a lack of prospective trials. Therefore, anticoagulant bridging at this time is based on numerous “expert-based” recommendations.

Guidelines from both CHEST and International Angiology recommend bridging anticoagulation for patients at high risk of thromboembolism, while bridging should be considered for patients at intermediate risk (bridging is optional for those at low risk). These general recommendations may not provide specific guidance to clinicians for all clinical scenarios, particularly for those patients at moderate risk. Dr. Turpie’s recommendations are to bridge patients in the moderate risk category if the bleeding risk is sufficiently low, and not to bridge those in the low risk category.

The decision to bridge or not depends on both patient- and procedure-specific risk factors. So who is at greatest risk? The following table provides some guidance on risk stratification of patients during the perioperative period.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>High TE risk</th>
<th>Moderate TE risk</th>
<th>Low TE risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical heart valve</td>
<td>Any caged ball valve in the mitral/aortic position</td>
<td>Tilting disc aortic valves</td>
<td>Bileaflet aortic valves without major risk factors</td>
</tr>
<tr>
<td></td>
<td>Any mitral valve prosthesis</td>
<td>Bileaflet aortic valves with major risk factors</td>
<td></td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>CHADS₂ score 4-6</td>
<td>CHADS₂ score 2-3</td>
<td>CHADS₂ score 0-1</td>
</tr>
<tr>
<td>Atrial fibrillation and thromboembolism</td>
<td>Recent (&lt;3 months) stroke or TIA</td>
<td>Valvular heart disease</td>
<td>CHADS₂ score 0-2 (except prior stroke/ TIA)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>VE &lt;3 months</td>
<td>VE 3-12 months</td>
<td>VE &gt;12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS score</th>
<th>Annual Risk</th>
<th>30-day Postoperative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2-3.0)</td>
<td>1.01</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0-3.8)</td>
<td>1.62</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1-5.1)</td>
<td>2.05</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6-7.3)</td>
<td>2.63</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3-11.1)</td>
<td>3.62</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2-17.5)</td>
<td>3.65</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5-27.4)</td>
<td>7.35</td>
</tr>
</tbody>
</table>

Some procedures are recognized as having a high bleeding risk, such as urologic surgery, surgery involving a vascular organ, and procedures with no suturing, a large operative field or at a critical site where bleeding into a closed space such as the CNS or spinal canal can be life-threatening. In these situations or for patients who have known risk factors

**CHADS Score and Risk for Postoperative Stroke in Patients with Atrial Fibrillation**

that increase their risk of bleeding, post-procedure bridging anticoagulation should involve prophylactic doses of LMWH, whereas those at lower risk of bleeding can receive therapeutic doses.

Dr. Turpie noted that the introduction of new oral anticoagulants as alternatives to warfarin may simplify bridging anticoagulation regimens, which currently extend from five days pre-procedure up to one week post-procedure. New agents such as dabigatran and oral factor Xa inhibitors (e.g., rivaroxaban and apixaban) have shorter half-lives, so it may be the case that they can be stopped and restarted more proximal to the procedure. However, optimal timing of cessation and re-introduction of these new agents remain to be determined.

**Reviewers’ Comments:**

The decision to bridge patients on anticoagulation therapy at the time of surgery remains a controversial clinical question. Ultimately, the decision involves balancing the patient-specific and procedure-specific risks of bleeding against the risk of clotting. Today, most clinicians are cognizant of the risk of clotting in the thrombogenic environment of major surgery. Despite a lack of strong evidence supporting the practice, many clinicians opt to bridge their patients on warfarin therapy, usually with a low-molecular weight heparin.

Expert opinion and guideline recommendations encourage the use of bridging anticoagulation therapy in moderate to high risk patients, including patients with mechanical heart valves, recent venous thromboembolic events, and chronic atrial fibrillation with a higher CHADS2 score or history of arterial thromboembolism, particularly stroke. Patients with any mechanical heart valve in the mitral position are at particularly high risk of thromboembolism and should receive bridge anticoagulation.

Clinical judgment will play a necessary role in deciding whether or not to bridge many patients because of the need to assess each individual’s risks for thrombosis and bleeding for any proposed procedure.

Clinicians are encouraged to refer to past Rocky Mountain Conference presentations for further details on perioperative management of patients receiving antiplatelet therapy and those with drug-eluting stents (Dr. Anne Paus lenssen, 2007). The conference report and past presentations can be accessed at [www.ucalgary.ca/gim/rmc/html](http://www.ucalgary.ca/gim/rmc/html).
Advances in Oral Anticoagulation: New Opportunities for Improved Patient Outcomes
Presented by Dr. Graham Turpie, McMaster University, Hamilton, Ontario

Until recently, warfarin has been the only oral anticoagulant available for effective long-term antithrombotic therapy. Although it is widely used, this agent has several limitations that make it difficult to use in practice (e.g., narrow therapeutic window, requirement for routine coagulation monitoring, slow onset/offset of action, numerous food- and drug-drug interactions, and unpredictable response). There are several new oral anticoagulants in development that more specifically target single steps in the coagulation cascade, of which only dabigatran and rivaroxaban are approved in Canada for VTE prophylaxis in patients undergoing hip or knee replacement surgery. Importantly, these alternatives to conventional anticoagulants are administered orally, have no requirements for monitoring, and facilitate extended dosing after hospital discharge.

Anticoagulation therapy significantly reduces the risk of stroke and mortality in high-risk patients with atrial fibrillation. However, studies suggest that oral anticoagulation with a vitamin K antagonist is underutilized in the clinical setting. Indeed, only 34-67% of patients who meet sufficient risk criteria receive warfarin treatment. Many factors play a role in the decision-making process of whether or not to use warfarin, including the patient-specific risk of bleeding, lifestyle factors, patient preferences, the inconvenience of coagulation monitoring, and lack of resources to adequately treat and manage patients on warfarin therapy, particularly at the primary care level.

Trials evaluating the use of new oral anticoagulants in patients with atrial fibrillation have recently been reported (dabigatran) or are currently underway (rivaroxaban and apixaban). The RE-LY trial randomized 18,000 patients with atrial fibrillation and at least one other risk factor for stroke to dabigatran (110 or 150 mg bid) in a blinded fashion versus open-label dose-adjusted warfarin (target INR 2.5, range 2.0-3.0). Approximately half the patients were naive to warfarin therapy.

The results demonstrated that both dosages of dabigatran met the non-inferiority criteria for prevention of stroke or systemic embolism. Annual event rates for dabigatran were 1.53% and 1.11% for the 110 mg and 150 mg doses, respectively, vs. 1.69% for warfarin. The 150 mg dose of dabigatran demonstrated statistical superiority with a 0.58% absolute annual risk reduction over warfarin. These results were consistent whether patients were native to warfarin or had previously received this agent. Both dosages of dabigatran significantly reduced the risk of hemorrhagic stroke (0.12%/year for 110 mg and 0.10%/year for 150 mg vs. 0.38%/year for warfarin, both p<0.001). The 150 mg dose significantly reduced the risk of ischemic stroke (0.92%/year vs. 1.20%/year for warfarin, p=0.03). From a safety perspective, there were significantly fewer major bleeds in patients receiving dabigatran 110 mg vs. warfarin (2.71%/year for 110 mg vs. 3.36%/year for warfarin, p=0.003). The bleeding rate in the dabigatran 150 mg arm was similar to warfarin (3.11%/year, p=0.31 vs. warfarin). Rates of intracranial bleeding were significantly lower with both dosages of dabigatran (0.23% and 0.30% vs. 0.74%, both p<0.001), which constitutes an important concern for patients receiving warfarin.

There was an unexpected increase in the rate of myocardial infarction (0.72%/year and 0.74%/year for the 110 and 150 mg doses, respectively, vs. 0.53%/year for warfarin) that was statistically significant at the higher 150 mg dose. The primary net clinical benefit outcome, which was a composite of vascular events, death and major bleeds, was significantly better for dabigatran 150 mg over warfarin. Importantly, liver enzyme levels were similar across all three treatment groups, which had been an issue with an earlier oral thrombin inhibitor, ximelagatran.

Stroke or systemic embolism

<table>
<thead>
<tr>
<th>Dabigatran 110 mg vs. warfarin</th>
<th>Noninferiority p-value</th>
<th>Superiority p-value</th>
</tr>
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<tbody>
<tr>
<td>&lt;0.001</td>
<td>0.34</td>
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<table>
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<tr>
<th>Dabigatran 150 mg vs. warfarin</th>
<th>Noninferiority p-value</th>
<th>Superiority p-value</th>
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<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.
The most common adverse event associated with dabigatran was dyspepsia (approximately 11% and 6% for dabigatran and warfarin, respectively), which is caused by its acidic formulation. Discontinuation rates were higher with dabigatran than warfarin (21% at 2 years for dabigatran, 17% for warfarin).

Dr. Turpie summarized his presentation with the following conclusion: "I think this is a major advance, and will impact clinical practice. Using a stepwise evaluation of new drugs, we have a new form of antithrombotic therapy that will improve our ability to treat atrial fibrillation and prevent thrombosis."

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**Reviewers’ Comments:**

Over 20 years have passed since warfarin was shown to reduce the risk of stroke by 64% in patients with AF, establishing it as the gold standard for this indication. RE-LY is a landmark trial that now establishes dabigatran as an alternative to warfarin in patients with AF. Dabigatran has demonstrated safety and efficacy similar to warfarin in the controlled environment of a clinical trial. The debate will now begin regarding the appropriate place in therapy for dabigatran.

It is anticipated that many patients will benefit from a new alternative to warfarin; for instance, the large population who cannot or do not wish to take warfarin, as well as those without access to resources for INR monitoring and dose adjustment. Patients in RE-LY who received warfarin were within the target INR range 64% of the time, a result that is consistent with other rigorous trials and reproduced within many dedicated anticoagulation clinics. However, many Canadian patients with AF do not have access to this level of specialized care and thus are not as well-controlled as the patients studied in RE-LY. Indeed, in a recent Canadian study, only 36% of AF patients on warfarin were within therapeutic range – Bungard et al. 2000. It will be incumbent upon physicians to assess their individual communities with respect to the availability of local anticoagulation clinics that are able to manage AF patients, as the situation varies dramatically across the country and will be an important consideration upon future treatment decisions.

Data from the Calgary Anticoagulation Clinic suggest that the pricing breakpoint for a new agent versus the all-in costing of warfarin is approximately $4.00 Canadian daily (unpublished data). At the current costing levels for VTE prophylaxis, dabigatran would not be an attractive option for public reimbursement for stroke prevention in AF. The prices for the studied doses are currently under review and expected to decrease.

Some important considerations relative to dabigatran should be noted. As per the study design, dabigatran should be dosed twice daily for thromboprophylaxis in AF and treatment of existing DVT (recently published RECOVER trial, NEJM, 2009) as opposed to once daily administration in previous studies in VTE. Readers are reminded that there are concerns regarding the efficacy of once daily dosing of dabigatran. Secondly, excretion of the drug is primarily through the renal route; thus it is contraindicated in patients with a creatinine clearance of less than 30 ml per minute. Further information regarding patients with moderate renal impairment will be helpful. There was also a finding of an increase in myocardial infarction with dabigatran, with a Number-Needed-to-Harm of 456, not dissimilar from the Number-Needed-to-Treat of 172 for benefit added by the 150 mg dose of dabigatran in this population (benefit to risk ratio of 2.6:1). Missed dosing of a short half-life drug like dabigatran warrants further exploration and should be taken into account when examining overall net clinical benefit. Finally, this is a completely new treatment paradigm. The absence of an antidote, impact of a missed dose of a short half-life drug, drug interactions, and managing the patient rather than an INR will be very important considerations.

Dabigatran is currently under Health Canada review for this indication. At this stage, we can conclude that dabigatran is a safe and effective anticoagulant with benefits over warfarin that will be an appealing alternative. The discussion over its place in future clinical practice is just beginning.
In October 2009, an update to the 2006 Canadian guidelines for the diagnosis and treatment of dyslipidemia was published. This collaborative effort clarified primary and secondary prevention strategies, simplified target levels, and incorporated evidence-based guidance from randomized controlled trials published since the previous guidelines were released. Dr. David Lau, Professor of Medicine & Biochemistry at the University of Calgary and a researcher at the Julia McFarlane Diabetes Research Centre, highlighted the most important features of the 2009 lipid guidelines for internists:

- Targeted lipid screening of adults is recommended.
- Cardiovascular (CV) risk assessment using the Framingham Risk Score (FRS) is recommended in most patients to estimate overall 10-year CV risk.
- The FRS may underestimate risk, particularly in younger people, females, and those with the metabolic syndrome or a strongly positive family history of atherothrombosis. The Reynolds Risk Score (RRS) includes the effects of family history, diabetes, and C-reactive protein (hsCRP) and may be helpful in assessing some of these individuals. However, the cost-benefit of such a screening algorithm and subsequently treating patients with an intermediate FRS risk, as per the JUPITER trial, have yet to be shown. An analogous strategy whereby patients are upgraded one risk category (from mild to moderate, or moderate to high) for family history of premature coronary artery disease (CAD) (new onset in a first-degree relative before age 60 years) may be as effective without the additional costs of hsCRP screening.
- The primary target for cholesterol reduction is an LDL-C below 2.0 mmol/L, or a 50% reduction from baseline LDL-C levels. An acceptable alternate, if available, would be an apoB level less than 0.80 g/L. At this time, there is little data from a CV risk perspective to support targets employing HDL-C or triglyceride levels.
- Lifestyle interventions are recommended for all patients.
- Treat according to level of risk. Initiate treatment with a statin or other LDL-C lowering medication in all patients at high CV risk; namely, 1) those with known or evident atherothrombosis, 2) all diabetic patients who are male and 45 yrs of age or older, or female and 50 yrs or older, or younger diabetics with at least 1 additional CV risk factor, or 3) patients with a 10-year FRS or RRS greater than 20%.
- Consider treating those in the moderate risk category (10-year FRS between 10 and 19%) if their LDL-C is greater than 3.5 mmol/L or they have risk that could be upgraded to a higher level.
- Monotherapy with statins is generally well tolerated and is able to lower LDL-C to targets of less than 2.0 mmol/L, or achieve a reduction in baseline levels by 50% in most patients. Monotherapy with other agents is generally less effective in LDL-C lowering or may be associated with undesirable side effects. However, combination therapy with niacin, ezetimibe or fibrates may be required for some patients.
- Statin therapy has been shown not to reduce CV risk in patients with end-stage renal disease or advanced congestive heart failure; clinical judgment should be applied.
SHORT SNAPPERS

Gout

Presented by Dr. Dale Sholter,
University of Alberta

Based on participant feedback from the 2008 Rocky Mountain meeting, Dr. Dale Sholter from the University of Alberta was invited to present a “refresher” to internists on the clinical management of gout. Dr. Sholter’s presentation focused on three key pitfalls when managing patients with gouty arthritis:

1. Not establishing or confirming a diagnosis of gout
2. Incorrect implementation of allopurinol
3. Not treating gout aggressively enough

The gold standard for diagnosing gout remains arthrocentesis; asymptomatic knee effusions have a high yield. Serum uric acid levels are unreliable in establishing a diagnosis of gout, and clinicians should appreciate that a swollen big toe is not specific for gout.

Allopurinol is the only effective long term treatment for chronic gout. Patients should be informed that the condition requires lifelong treatment, making adherence during asymptomatic periods an ongoing clinical challenge. Importantly, allopurinol is not effective during acute attacks and dosing should never be started, adjusted, or stopped during an acute flare-up of gout. Instead, patients should be provided with an adequate prophylactic agent and strategies to avoid future flares.

Gout must be treated aggressively to eliminate attacks, which is ultimately the goal of allopurinol treatment. Thus, a secondary objective of treatment is to lower serum uric acid levels to <350 μmol/L. Dr. Sholter suggested that allopurinol is commonly under-dosed. Although this drug should be initiated at a low dose, it should be gradually up-titrated to an effective dose, which can be as high as 800 mg in some patients. Adherence should be addressed in patients who do not improve even at high doses of allopurinol.

Reviewers’ Comments:

While gout has traditionally been regarded as a manageable condition, it is becoming more complicated and is increasingly encountered in patients with comorbid medical conditions. This short snapper provided useful recommendations on how to appropriately diagnose and manage gout, and suggests that allopurinol doses as high as 800 mg/day may be required in order to prevent attacks in some patients. Although most patients respond well to allopurinol, there remains a care gap for those patients who cannot tolerate the drug. Diuretics and aspirin can exacerbate gout, and alternatives should be considered in patients on these medications presenting with gouty arthritis.
Influenza 2009: Not Yet the Perfect Storm
Presented by Dr. Kurt Williams, University of Saskatchewan

At the time of the Rocky Mountain conference, Canada was in the midst of its largest ever vaccination program. H1N1 influenza virus, also known as swine flu, is a novel Type A influenza virus that has redefined the nation’s flu season. Typically, the flu season peaks in February or March, when most individuals have already been vaccinated. This year, pandemic H1N1 positive tests appear to have peaked in late October/early November. According to Dr. Kurt Williams, “We are seeing what happens with a new influenza virus in an unvaccinated population.”

A burning question and controversial issue surrounds who should be vaccinated. Some provinces, such as Alberta, opted for the “herd approach,” with the goal of immunizing to stop the spread of infection. With limited resources and availability of vaccine, other provinces are struggling to fit priorities with current knowledge of the virus, the populations at highest risk, and the morbidity and mortality associated with infection. According to Dr. Williams, we are all at risk of infection, and individuals should respect the prioritization schedule and get vaccinated as soon as it is available for their particular risk category.

Why should we be worried about H1N1? Dr. Williams suggests that the H1N1 pandemic has made influenza more confusing in general; it has provided genetic material for the next human influenza pandemic; and exposure of the virus to antivirals in the setting of poor adherence could be “the perfect storm for mutation against currently effective treatments.”

In a follow-up discussion after his presentation, Dr. Williams summarized the key points that physicians – and their patients – should know about influenza in 2009/2010:

- Infected individuals shed the virus for approximately 5-7 days, unless they are chronically infected.
- Once influenza has been identified in the community and an epidemic situation occurs, empiric use of antiviral medications will be beneficial in about 75% of symptomatic individuals.
- General hygiene, including washing hands, not sharing food or utensils, not touching the eyes, nose or mouth, and cough etiquette, can help prevent infection and spread of influenza.
- The best protection against influenza remains vaccination.
- The risks of vaccination most commonly involve minor swelling and irritation at the injection site.
- More rarely, influenza vaccines have been associated with a risk of Guillain-Barré syndrome. However, the risks of this potentially disabling condition are 5-fold higher in people infected by influenza than in those who are vaccinated.
- Individuals already infected with H1N1 do not require the vaccine.
- Infected individuals should self-isolate until they no longer have a fever and are no longer shedding virus; if shortness of breath develops, medical attention should be sought immediately.

Internists should be prepared to answer questions from their patients. Consult your local and provincial public health agencies and be familiar with their influenza pandemic preparedness plans. For additional information, consult the Public Health Agency of Canada (PHAC) website at http://www.phac-aspc.gc.ca/influenza/hcp-ps-eng.php to obtain up-to-date information on pH1N1. Other useful resources include the PHAC’s FluWatch website (http://www.phac-aspc.gc.ca/fluwatch/index-eng.php), your provincial lab, and Rx Canada Inc.’s H1N1 Antiviral and OTC Weekly Report (https://www.rxcanada.ca/en/phac/).

Reviewers’ Comments:
This year’s flu season is a moving target with information changing on a daily basis. There has been much confusion among the general public and health care providers regarding vaccination in general and who should be prioritized to receive the vaccine in particular.
Thrombolysis for Acute Stroke
Presented by Dr. Michael Hill,
University of Calgary

Dr. Michael Hill from the Calgary Stroke Program and the University of Calgary focused on one point during this short snapper session on the treatment of acute stroke: speed. He summarized his presentation with three key messages:

1. Treat often, treat early, and treat fast

2. The time window between symptom onset and the point where thrombolysis has been demonstrated to be beneficial has been expanded to 4.5 hours

3. Treat disabling stroke

The benefits of tissue plasminogen activator (tPA) administered within 3 hours of the onset of acute stroke are well established. Previous studies such as ECASS-3 have also suggested benefit beyond 3 hours. Two recently published meta-analyses have confirmed a modest benefit of thrombolysis beyond the 3-hour window. One meta-analysis suggests that if 14 patients are treated in the 3-4.5 hour window, seven patients will have good functional outcomes, rather than six if tPA were restricted to the 3-hour window. An updated Cochrane meta-analysis adds confidence to the legitimacy of these results. In this meta-analysis, some benefit was demonstrated for tPA administered in the 3-6 hour window. However, this came at the expense of 70 additional cases of intracerebral hemorrhage (ICH) for every 1,000 patients treated, suggesting that there may be harm to treating patients late. The Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register (SITS-ISTR), which reflects “real-world” practice, confirms the clinical efficacy of thrombolysis within the 3-4.5 hour window.

Reviewers’ Comments:

Speed remains a clinical challenge in appropriately thrombolysing patients with acute stroke. Despite careful protocols, average door to needle times remain suboptimal (in Calgary, the median time from door to needle is closer to 50 minutes), and are likely the result of the sum of several small delays, rather than a single major delay. For clinicians, patient care feels fast in the moment, but when the total time is added up, it becomes apparent how slowly things happen in reality. The data from the presented meta-analyses provide reassurance that patients who do not meet the 3-hour threshold may still derive benefit from thrombolysis. However, this must be balanced against a higher ICH event rate.

Anticoagulation for DVT Prophylaxis
Presented by Dr. Leslie Zypchen,
University of British Columbia

Dr. Leslie Zypchen highlighted seven thromboprophylaxis issues that internists should consider when treating medical patients:

1. Almost all patients admitted to our medical wards should be prophylaxed against the occurrence of in-hospital VTE, since most medical patients have additional risk factors.

2. There is good evidence that pharmacologic prophylaxis is effective – decreasing both symptomatic and asymptomatic DVT.

3. Mechanical prophylaxis has a minor role in VTE prevention – this should be considered as an alternative only in patients who cannot receive pharmacologic prophylaxis, since there is no evidence of efficacy and an increased risk of skin complications in patients treated with compression stockings.

4. Low molecular weight heparin (LMWH) may be more effective than unfractionated heparin (UFH) – although the evidence is equivocal, LMWH is probably safer than UFH.

5. LMWH is more cost effective than UFH – the difference is approximately $90 per patient, due primarily to a lower incidence of bleeding and heparin-induced thrombocytopenia (HIT).

6. Fondaparinux is the only “new” anticoagulant available for prophylaxis of medical patients – although there is growing excitement about oral anticoagulants such as dabigatran and rivaroxaban, there are currently no data available for prophylaxis in medical patients.

7. Extended duration prophylaxis may be appropriate for some patients – the EXCLAIM study suggests that hospitalized medical patients with reduced mobility who are older than 75 years of age or who have a cancer diagnosis or history of VTE, may benefit from a 28-day course of prophylaxis with LMWH.

Reviewers’ Comments:

Today’s hospitalized medical patient typically has multiple risk factors for VTE and is, therefore, at significant risk of developing this condition during hospitalization. Dr. Zypchen’s review of current issues in DVT prophylaxis in medical patients provides a useful follow-up to a presentation at the 2008 Rocky Mountain Conference highlighting the updated CHEST guidelines for DVT prophylaxis. That presentation is available online at [http://www.ucalgary.ca/gim/rmc.html](http://www.ucalgary.ca/gim/rmc.html).
WORKSHOPS
Here to There: Using Likelihood Ratios in Practice
Presented by Dr. Jim Nishikawa, University of Ottawa, Ottawa, Ontario

Likelihood ratios (LRs) can provide compelling evidence to help refine clinical diagnosis. Despite their utility, LRs are often under-utilized in the clinical setting. The LR is defined by the percentage of ill people with a given test result divided by the percentage of well individuals with the same result. LRs greater than 1 (high likelihood ratio) means that a test result is more likely to occur among patients with the disease, whereas a LR less than 1 (low likelihood ratio) is more likely to occur among patients without the disease. LRs near unity have little effect on decision-making, whereas high (>10) or low (<0.1) ratios can shift the estimate of disease and may assist to ‘rule in’ or ‘rule out’ a diagnosis. LR estimates of disease are based on thresholds, which depend on the clinician’s comfort, the consequences of missing a diagnosis or treating an incorrect one, test or treatment risk, benefit and availability, and patient values and preferences.

LRs make a link between pre-test and post-test probabilities of a result. There are four ways to make this link:
1. Do the math – convert the pre-test probability into a pre-test odds ratio, multiply by the LR to give a post-test odds ratio, which is then converted back into a post-test probability.
2. Use a nomogram – this is a simple method that can be used when two of three variables are known (i.e., pre- and post-test probabilities and LR).
3. Use a calculator – available online and for PDA.

LRs are very useful for interpreting the diagnostic value of a lab test and associated results. In contrast to sensitivity and specificity, LRs can be calculated for both dichotomous (positive or negative) tests and for tests with multiple levels of results (e.g., creatinine kinase). For example, labs generally use a statistical definition of “normal” (i.e., mean ± two standard deviations) when reporting results. These “normal” values are based on healthy individuals, which do not make use of all the information available to the physician in a clinical scenario. Information should be interpreted on the basis of what is already known. A positive laboratory result may have vastly different implications in the face of a pretest probability of disease of 80% versus 20%. Thus, likelihood ratios can be very helpful for interpreting results and making rational clinical decisions and diagnoses. The intermediate pre-test probability patients will benefit the most from the use of LRs. Multiple LRs may also be ‘stacked’ in order to strengthen a clinical diagnosis. Combining the objectivity of LRs from ancillary tests with subjective pre-test probabilities is consistent with the principles of evidence based medicine and diagnostic accuracy can be improved in a synergistic manner.

Dr. Nishikawa suggested several resources for accessing information on LRs, including JAMA Evidence (requires a subscription) which also publishes The Rational Clinical Exam textbook with LRs provided in the “Make the Diagnosis” section; SUMSearch – a free, academic online tool that searches multiple databases; PubMed Clinical Queries; and the ACP Journal Club’s clinical prediction guide.

Reviewers’ Comments:
LRs are seldom used today, despite the fact that they represent a powerful tool for making clinical decisions. When combined with an accurate clinical diagnosis, LRs from ancillary tests improve diagnostic accuracy. Dr. Nishikawa’s workshop provided clinicians with hands-on experience on how to use a variety of methods to make use of LRs for clinical decision-making, and importantly, he provided participants with valuable resources on where to find LRs and probabilities to make use of these tools.
Workup and Treatment of Hyponatremia

Presented by Dr. Debbie Rosenbaum, University of British Columbia

Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L, is the most common cause of inpatient electrolyte abnormalities. Yet there are no professional guidelines for the evaluation and treatment of acute or chronic hyponatremia, nor for the reversal or rapid correction of chronic hyponatremia. Dr. Rosenbaum’s case-based workshop provided participants with a useful algorithm for managing hyponatremia:

A common pitfall in the approach to hyponatremia is using volume status as a starting point, since many patients have subclinical volume depletion. Although there are several formulas available to correct electrolyte imbalances, “in practical scenarios, they don’t always work,” cautioned Dr. Rosenbaum. Furthermore, the literature suggests that formulas often over-correct electrolyte levels in hyponatremia.

The best approach in acute hyponatremia is to raise sodium levels quickly using hypertonic saline (e.g., 1-2 ml/kg/h), especially if there are symptoms of cerebral edema. For patients with chronic symptomatic hyponatremia, clinicians should treat the condition emergently (i.e., 5-6 mEq/L in the first 3-6 hours). Conversely, in chronic asymptomatic patients, there is no rush to make a clinical decision, and the etiology can help guide appropriate management (e.g., <8 mEq/L/d or <4 mEq/L/d if high risk for osmotic demyelination syndrome, which can be fatal). Serum sodium and potassium levels as well as urine output should be monitored frequently, whereas urine osmolality and urine sodium levels may be helpful but are not always diagnostic.

A common cause of acute hyponatremia is intake of ecstasy (MDMA) which induces secretion of antidiuretic hormone (ADH), causing excessive thirst, and is a particular concern in young women. Patients at risk of chronic hyponatremia include those on thiazide diuretics or those on a “tea and toast” or low sodium diet.

**Reviewers’ Comments:**

Assessing patients for causes of hyponatremia and implementing treatment is often complex. For the hospitalized patient, often more than one causative factor is at play. Dr. Rosenbaum’s workshop provides useful strategies for the management of this condition. Her full presentation can be accessed on the Rocky Mountain Conference website at [www.ucalgary.ca/gim/rmc.html](http://www.ucalgary.ca/gim/rmc.html).