



The 2012 Rocky Mountain/ACP Internal Medicine Conference Report

November 22-25, 2012, Banff, Alberta

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Introduction to the 2012 Rocky Mountain/ACP General Internal Medicine Conference

The 2012 annual Rocky Mountain/ACP General Internal Medicine Conference was held at its usual venue in beautiful Banff, Alberta last November 22-25, 2012. The conference continued its tradition of offering a full array of Internal Medicine topics with a superb lineup of speakers from academic and regional participating members. Keynote presentations and symposia highlighted some of the key issues and emerging data that are shaping the way Internal Medicine is practiced today. Several workshops were available for participants, each providing a valuable opportunity for small-group discussion and peer-to-peer learning.

This conference report aims to review some of the key points from selected presentations, followed by clinical commentaries from the Scientific Review Committee. Speaker presentations are available for download at the Rocky Mountain Conference website at www.rockymountaininternalmed.com.

KEYNOTE ADDRESS

Top 5½ General Internal Medicine Papers 2011/2012

Presented by Dr. Glen Drobot, University of Manitoba

Staying up-to-date on the latest evidence in internal medicine is an ongoing challenge for busy internists. Dr. Glen Drobot was invited to select five papers that were published in the last 12 months that he believes are shaping the practice of internal medicine. Dr. Drobot shared his strategies for staying abreast of the medical literature in the context of his busy clinical life, which include reviewing tables of contents of major internal medicine (IM) journals by email, subscribing to email "news" websites, participating in the McMaster Online Rating of Evidence (MORE), and subscribing to ACP Journal Wise.

The key findings and conclusions from the five (and a half) papers he selected are briefly summarized below:

1. In patients with hypertension and chronic kidney disease, moving at

least one antihypertensive medication to bedtime dosing reduces the rate of cardiovascular events.

2. Antibiotics are a reasonable, safe option in patients with uncomplicated appendicitis, preventing surgery in two thirds of patients.
3. Perioperative statin use is associated with significant reductions in myocardial infarction and atrial fibrillation.
4. The newer oral anticoagulants are at least as efficacious and are slightly safer than warfarin in patients with atrial fibrillation.
5. Aspirin prevents about one in three recurrences after a first episode of unprovoked venous thromboembolism after a course of anticoagulant therapy.



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Paper #1: Bedtime dosing of antihypertensives

Time of dosing of hypertension medications has been shown to affect circadian patterns of blood pressure (BP), but whether this translates into effects on clinical outcomes has been hitherto unknown. In this open-label randomized trial, 661 patients with hypertension and chronic kidney disease (CKD; eGFR <60 mL/min and/or microalbuminuria) on combination antihypertensive therapy were assigned to take all medications

upon awakening or to take at least one at bedtime. Outcome assessors and the study safety committee were blinded to treatment assignment. The primary outcome was total cardiovascular (CV) morbidity and mortality, including all-cause mortality, myocardial infarction, angina, coronary revascularization, heart failure, acute thrombosis, stroke or transient ischemic attack.

Over 5.4 years of follow-up, patients who took at least one antihypertensive at bedtime had a significantly lower risk of total

CV morbidity and mortality compared to those who took all their antihypertensive medications upon awakening (11% vs. 31%, $p < 0.001$), representing a number-needed-to-treat (NNT) of just 5 to prevent one event. Patients on bedtime treatment also had a significantly lower mean sleep-time BP and a higher rate of ambulatory BP control (56% vs. 45%). Every 5 mmHg decrease in sleep-time systolic BP was associated with a 17% relative reduction in risk for CV events.

Reviewers' Comments:

The paper on night-time dosing of antihypertensive agents to patients with hypertension and chronic kidney disease is one of a series of recent publications on this topic by Hermida *et al* under the broader mantra of the MAPEC Study. The strengths of MAPEC are that it uses ABPM and, more importantly, repeated on-treatment ABPM measurements to drive management decisions. We know

that ABPM, and specifically sleep-time sBP and dipping status, are powerful predictors of CV outcome and that these are likely to be facilitated by night-time administration of antihypertensive medications. The outcome differences and NNT in these studies are certainly impressive. On the other hand, MAPEC is a single-centre study and the methodology and outcomes lack clarity and consistency with respect to a number of important issues.

This, along with other data suggesting potential harm, including an increased incidence of acute ischemic and non-ischemic optic neuropathy, particularly in elderly individuals presumably with excessive BP lowering during the night, have led most experts and, indeed, the 2013 Canadian Hypertension Guidelines to adopt a 'wait and see' approach until further confirmatory studies are available.

Paper #2: Antibiotics for appendicitis

Appendectomy has been the mainstay for treatment of acute appendicitis for more than a century. The premise has been that in the absence of surgical intervention, the disease often progresses from uncomplicated to perforated appendicitis. Antibiotic treatment, on the other hand, was considered only as a bridge to surgery in patients with suspected appendicitis but no clear signs of perforation or peritonitis. Has the role of antibiotic treatment of appendicitis been overlooked in the era of less-invasive laparoscopic surgery?

This meta-analysis included four randomized controlled trials (RCTs) with a total of 900 adult patients randomly assigned to intravenous and/or oral antibiotics or appendectomy. Three RCTs were published in the last 6 years, whereas one dated from 1995. The primary outcome was the rate of complications including wound infection, perforated appendicitis or peritonitis. The rate of complications was significantly lower in patients receiving antibiotics compared with surgery (18% vs. 25%, relative risk [RR] 0.69, 95% CI 0.54-0.89, NNT 14). One study reported a protocol violation after randomization and cross-over of patients between treatment groups.

A pre-defined secondary analysis that excluded this trial to avoid selection bias and over-estimation of treatment effects showed the relative risk reduction remained significant (RR 0.61, 95% CI 0.40-0.92, NNT 13). Antibiotic treatment was associated with a 63% success rate (i.e., no surgery) at 1 year. Sixty-five (20%) patients had an appendectomy after readmission and among these, nine had perforated appendicitis and four had gangrenous appendicitis. No significant differences were observed for secondary outcomes including treatment efficacy, length of stay, or risk of developing complicated appendicitis.



Reviewers' Comments:

The paper on antibiotic treatment of appendicitis is interesting in that it suggests a majority of patients with uncomplicated appendicitis can be successfully managed by medical treatment alone. Indeed, a 30-40% lower rate of complications defined as perforated/gangrenous appendicitis, peritonitis or wound infections was observed with antibiotics compared

to surgical management. Antibiotics included in-hospital amoxicillin/clavulin or IV cefotaxime plus metronidazole for 24-48 hours followed by outpatient treatment with a combination of oral fluroquinolone and metronidazole for a further 8-10 days. Approximately 20% crossed over early in the hospital course to appendectomy and a further 15% of those treated with antibiotics were eventually readmitted for

appendectomy. However, these could be reliably predicted using conventional clinical and laboratory findings together with ultrasound and/or CT. These data are consistent with earlier systematic reviews. Our opinion: ready for prime time, but clearly dependent upon establishing strong collaborative links between medical and surgical follow-up.

Paper #3: Perioperative statins and CV events

Surgical interventions are known to precipitate vascular and systemic inflammation – important mediators of perioperative CV events. Statins have pleiotropic properties that may help mitigate the risk of CV events in the perioperative setting.

This meta-analysis included 15 RCTs involving nearly 2,300 patients who were

naïve to statin treatment and randomized pre-operatively to statin therapy or control (placebo [14 trials] or lower-dose statin [1 trial]). Outcomes assessed included death, perioperative MI and atrial fibrillation and length of stay in the intensive care unit (ICU). Perioperative statin treatment significantly reduced the risk of MI (2.7% vs. 7.8%, RR 0.53, 95% CI 0.38-0.74, NNT 24) and atrial fibril-

lation (20% vs. 36%, RR 0.56, 95% CI 0.45-0.69, NNT 7) but not death (11% vs. 31%, RR 0.62, 95% CI 0.34-1.14) or length of stay (standardized mean difference, -0.08 days, 95% CI -0.25 0.10). Perioperative statins administered 3 days prior to surgery and continued 30 days postoperatively may constitute an important risk-reducing intervention with clinical and economic benefits.

Reviewers' Comments:

The meta-analysis on perioperative statins demonstrates the appeal of

this simple intervention. However, one should be mindful of an earlier era where similar systematic reviews and meta-analyses of small trials led

to the adoption of perioperative beta blockers before POISE taught us to be more circumspect and cautious with these agents.

Paper #4: Warfarin and novel oral anticoagulants in atrial fibrillation

Three novel oral anticoagulants (NOACs) have been developed and evaluated as alternatives to warfarin in patients with atrial fibrillation. Data from each of the agents' registration trials (dabigatran: RE-LY trial; apixaban: ARISTOTLE trial; rivaroxaban: ROCKET AF) support their comparable efficacy to warfarin for the primary endpoint of combined stroke and systemic embolism. However, the results with respect to secondary outcomes have been more heterogeneous and inconclusive. This meta-analysis of the three trials included 44,563 patients with atrial fibrillation randomized to a NOAC or warfarin

for at least 1 year. The primary endpoint, combined stroke and systemic embolism, statistically significantly favoured NOACs over warfarin (2.7% vs. 3.5%, RR 0.78, 95% CI 0.67-0.92, NNT 133). Treatment with the NOACs was also associated with statistically significantly lower risk of ischemic stroke (RR 0.87, 95% CI 0.77-0.99), hemorrhagic stroke (RR 0.45, 95% CI 0.31-0.68), all-cause mortality (RR 0.88, 95% CI 0.82-0.95) and vascular mortality (RR 0.87, 95% CI 0.77-0.98). While NOACs have been associated with a significantly lower risk of intracranial bleeding (RR 0.49, 95% CI 0.36-0.66), rates of major bleeding (RR 0.88, 95% CI 0.71-1.09) and gastrointestinal bleed-

ing (RR 1.25, 95% CI 0.91-1.72) were inconclusive. This meta-analysis supports the efficacy and safety of NOACs as an alternative to warfarin; clinical decisions must also take into account patient preference, provincial and private drug coverage, and ability to adhere to regular INR monitoring.



Reviewers' Comments:

The Miller meta-analysis and a second network meta-analysis by Harenberg (*Int Angiol* 2012; 31:330) published a few months later support the generalizability of findings on dabigatran, rivaroxaban and apixaban for thrombo-prophylaxis of patients with atrial fibrillation. The more interesting and important of these observations is the reduction in intracranial hemorrhage (ICH). Intracranial hemorrhage is a feared and devastating complication

of systemic anticoagulation in elderly patients. Intracerebral bleed itself accounts for about half of these with an absolute risk of 0.3-0.6%/year on warfarin treatment and a mortality rate exceeding 50% in most studies. Subdural hematoma makes up another 30-40% with an incidence and mortality of 0.1-0.3%/year and 20-30%, respectively. Despite its relative rarity, the clinical importance of ICH and the fact it is treatment-induced cannot be overstated. Predictors of ICH in atrial fibrillation include assignment

to warfarin (OR 2.9; $p < 0.001$), aspirin use (OR 1.6; $p = 0.01$), previous stroke or TIA (OR 1.9; $p = 0.001$) and age (OR 1.1 per year; $p < 0.001$). Thus, NOACs bring value by removing barriers to effective anticoagulation in this patient group. Indeed, the CCS Clinical Practice Guidelines for Prevention of Stroke in Atrial Fibrillation recommend treating patients with a NOAC rather than warfarin and to treat patients at lower overall risk (CHADS2 score ≥ 1).

Paper #5: ASA for preventing recurrence of VTE

The risk of recurrent venous thromboembolism (VTE) after discontinuation of a course of oral anticoagulant therapy may be high in patients with unprovoked VTE. Extending anticoagulant therapy can reduce this risk, but at the cost of ongoing risk of bleeding. It is common in clinical practice to discontinue anticoagulant therapy after 3 months if the perceived risk of bleeding outweighs the risk of recurrence. While ASA has been shown to be effective in the primary prevention of VTE, its role in prevention of VTE recurrence after a course of oral anticoagulation therapy with warfarin is unclear. The

Warfarin and Aspirin (WARFASA) study aimed to evaluate the clinical benefit of ASA for the prevention of recurrent VTE after a course of warfarin treatment. The study randomized 403 patients to receive ASA 100 mg/d or placebo. The primary efficacy outcome was the incidence of symptomatic, objectively verified recurrent VTE. After more than 2 years of follow-up, ASA was associated with a statistically significantly lower risk of recurrent VTE than placebo (14% vs. 22%, RR 0.66, 95% CI 0.35-0.86, NNT 11). The results of this study contrast those of a similarly designed study published 6 months later by Brighton *et al.* (*N Engl J Med* 2012; 367:1979), which showed a non-significant decrease in recurrent

VTE of 4.8% vs. 6.5% per year (hazard ratio 0.74, $p = 0.09$). However, that study did show a significant decrease in a prespecified secondary outcome of major vascular events (a composite of VTE, MI, stroke, major bleeding or death; HR 0.66, $p = 0.01$). When the results of the two studies were pooled, the primary outcome (recurrence of VTE) was statistically significant (HR 0.68, $p = 0.007$), as was the rate of major vascular events (HR 0.66, $p = 0.002$). Thus, for patients with unprovoked VTE coming off anticoagulant therapy, a continuum of treatment options may be recommended, from continuation of full-dose OAC to moderate intensity anticoagulation to ASA.

Reviewers' Comments:

Previous editions of the Rocky Mountain report have discussed the risk of recurrent VTE following completion of a full course of systemic anticoagulation in patients with idiopathic or unprovoked VTE (in the ASPIRE trial, risk of recurrent VTE was 10% at 1 year,

30% at 10 years for a case fatality rate of around 5-10%). The WARFASA/ASPIRE trials bring important new evidence to bear on this subject. Both trials showed clinically meaningful and, for WARFASA, a statistically significant benefit in the primary outcome as did the pooled analysis of the ASPIRE

and WARFASA results. The absolute risk of bleeding was very low (1%/yr or less), in particular major bleeding. As Dr. Drobot correctly concludes, low-dose ASA provides an option to management of these patients following completion of a usual course of systemic anticoagulation.



High cost treatments/limited resources: Seeking a balance

Presented by Dr. Stuart MacLeod,
University of British Columbia

Similar to health care systems elsewhere in the world, Canadian publicly funded health care systems are facing fiscal challenges that threaten their sustainability. The continued evolution and growth of these systems, argued Dr. MacLeod, depend on a delicate balance between managing large investment risks in settings of uncertain health benefits and the capacity and social preferences to implement innovative new products.

Basic biomedical research is producing new medical technologies, including drugs and diagnostic testing methods, at a fast pace. Not surprisingly, because of the higher price points charged for such new technologies, they are receiving increased scrutiny from stakeholders before being funded and implemented into clinical practice. While patients and physicians may be mostly concerned with what is best for patients, public health decision-makers must evaluate new technologies from the perspective of population health. These different points of view are not necessarily incompatible, but efforts must be made in order to find areas of common ground.

Decision-making in health care is a complex process that must take into account several elements, including the overall environment in which the new technology will be used. Effective management of health care also depends on the accurate assessment of quality and health outcomes, as well as prioritization of human and financial resources. As an example, Dr. MacLeod pointed out that at the present time, there is insufficient human resources trained in applied health research, including implementation and evaluation methods. The lack of expertise in this field constitutes a major challenge in the process of health care innovation in Canada.

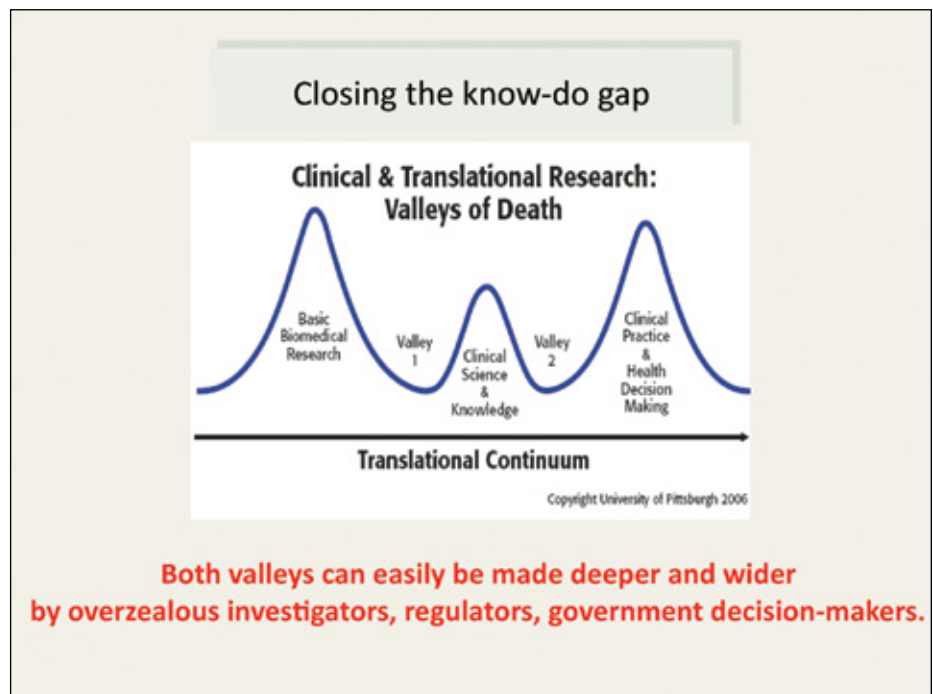
It is essential to maintain a public policy that fosters *incremental* innovation, i.e., small changes that will, in the long-term, lead to major advances in health care. Valuing innovative products should be a process that considers the context (envi-

ronment) and expectations from evidence-based medicine should be tempered to current realities. For instance, the concept of “evidence-informed,” as opposed to “evidence-based” medicine, is gaining popularity. In other words, stakeholders should go beyond the sole analysis of RCTs, that are rarely sufficient, and take into account a broader evidence base that includes comparative effectiveness studies, observational studies, and colloquial evidence in the decision-making process. Initiatives such as the Cochrane Effective Practice and Organization of Care Group (EPOC) and the United Kingdom’s National Institute for Health and Clinical Excellence (NICE), although imperfect, may provide appropriate models on which to base decision-making frameworks in the future.

In 2012, an effort between Health Canada and the Canadian Agency for Drugs and Technology in Health (CADTH) led to the formation of collaborative steering groups involving several stakeholders to review the health technology strategy dating from 2004. Their main goals include increasing transparent decision-making and shifting the focus from health technology *assessment* to effective health technology *management*. This group is concerned with the sustainability of health care systems, contextualization of evidence across

different groups or regions, and training of human resources in technology assessment. Similarly, the Ontario Health Technology Advisory Committee (OHTAC) is a multi-stakeholder group formed to make recommendations about the uptake, diffusion, distribution, and removal of health interventions. Their decisions are based on overall clinical benefits, consistency with expected social values, financial value, and ease of adoption, without being restricted solely to RCT data.

Closing the gap between what we *know* and what we need to *do* will be critical moving forward. Decision-making should consider cost-effectiveness, but should also include factors such as alternative treatments, seriousness of conditions, affordability, equity, social values, and financial implications to governments and the taxpayers who elect them. Following Daniels’ and Sabin’s model of “accountability for reasonableness” (A4R), this process should be transparent, include all stakeholders, offer the possibility of revision or appeal and involve fair-minded individuals in the decision-making process. Dr. MacLeod argued that investing in comparative effectiveness research and learning how to make the best possible decisions with imperfect data is a large part of the solution to ensuring long-term sustainability of Canadian health care systems.



Reviewers' Comments:

Dr. MacLeod has done an excellent job summarizing the overlapping domains of evidence, economics, policy, politics and social values. As a society, most would agree that we want and need to embrace innovation. Yet, among all of the technologies that make optimistic claims of promise, how do we select a favoured few that are most likely to succeed?

We must also recognize our fiscal climate: in this era of modest economic growth, voters have consis-

tently supported tax reductions. Thus, investment in uncertain innovations will have an important opportunity cost – that which we give up, either explicitly (preferable so we know what we're giving up) or implicitly. Further, once a new technology is introduced and funded, robust evidence development usually ceases, public health administrators rarely withdraw public financial support, and manufacturers rarely drop prices without significant resistance. Finally, we need to be reminded there remains low hang-

ing fruit with enormous public health implications, for example, sodium restriction, regular physical exercise, smoking cessation, vaccination and addiction services.

Dr. MacLeod is very much on the right track: under the umbrella of longer term policy guidance, decision-makers need to face the "wall of fear," avoid inertia and accept the fact that promising innovation, even if costly at the outset, needs to be not only supported but fostered.

SYMPOSIA

The influence of type 2 diabetes on cardiovascular disease and glycemic treatment options

*Dr. David Lau, University of Calgary
Co-developed by the RMI/ACP Annual Meeting Committee and Novo Nordisk*

Epidemiological data from Canada and around the world support a rising prevalence of diabetes. The most recent data from Canada (2008/2009) suggest that 6.8% of Canadians have a diagnosis of diabetes and this is expected to rise to 9.9% by 2020. This constitutes a major public health concern, since it is well established that diabetes increases the risk of major micro- and macrovascular complications. Notably, diabetes increases the risk of fatal coronary artery disease (CAD), and this continues despite preventive and interventional therapies.

A growing body of evidence supports a "legacy effect" of early, aggressive glycemic control. The Diabetes Control and Complications Trial (DCCT) showed that patients with type 1 diabetes who received intensive treatment had a 57% reduction in the combined rate of non-fatal MI, stroke or CV death relative to those receiving conventional treatment. Likewise, 10-year follow-up of the UKPDS study showed continued reduction in rates of CV outcomes in patients who

were initially randomized to aggressive glycemic control during the intervention phase. It is not surprising, then, that the 2013 Canadian Diabetes Association (CDA) clinical practice guidelines will likely continue to recommend specific targets for glycemic control, namely A1C \leq 7.0%.

In most cases, 2 to 3 months of lifestyle management are recommended prior to initiating pharmacotherapy. Several classes of glucose-lowering agents are available if A1C targets are not reached. These include metformin, insulin, α -glucosidase inhibitors, incretins, insulin secretagogues, thiazolidinediones, and weight loss agents. When choosing among antihyperglycemic agents, Dr. Lau encouraged clinicians to consider guideline recommendations as well as clinical factors such as efficacy of A1C reduction, glycemic durability, risk of hypoglycemia, effects on weight, long-term tolerability, and more general factors such as cost and patient preference.

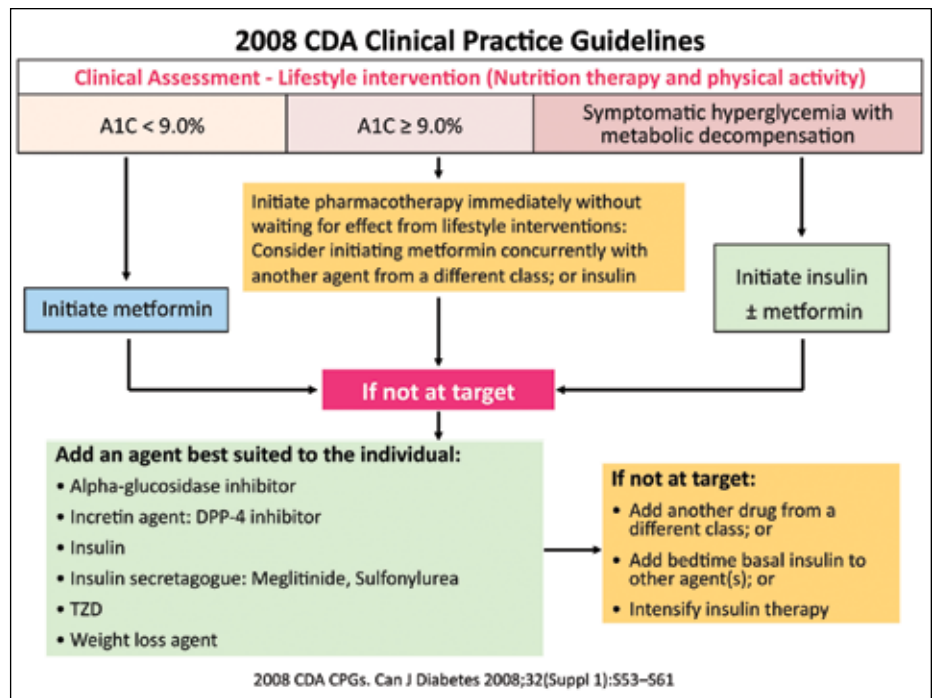
One of the newest classes of antihyperglycemic agents is the incretins, which includes the DPP-4 inhibitors and GLP-1 receptor agonists. These agents reduce glycemia via multiple mechanisms and have been shown to provide reductions in A1C that are comparable to conventional antihyperglycemic agents. In a recent meta-analysis of 20 observational studies representing 1.3 million patients with a median follow-up of 4.6 years,

some sulfonylureas were associated with 11-26% increased risk of CV outcomes compared to metformin. Incretins are associated with a lower risk of hypoglycemia, which has been associated with adverse outcomes and mortality. Other potential beneficial effects of incretins include weight reduction. Dr. Lau also reviewed some of the early studies of GLP-1 agonists and the DPP-4 inhibitors on endothelial dysfunction and myocardial glucose uptake in CHF and following experimental myocardial ischemia. While the results are promising, large RCTs that are powered to evaluate CV outcome endpoints will be needed. Several ongoing trials are underway and should provide further insight into the potential cardioprotective effects of incretin therapies.

Until that time, Dr. Lau encouraged clinicians to continue to follow the evidence-based CDA guidelines. The 2013 update is scheduled to be released in March; notable changes relative to the 2008 guidelines include lowering the A1C threshold for immediate initiation of pharmacotherapy from 9.0% to 8.5% and the addition of GLP-1 receptor agonists to the list of recommended add-on agents. Clinicians should continue to routinely monitor patients for micro- and macrovascular complications as well as A1C control. The benefits of managing multiple CV risk factors have been well



documented; therefore, an individual patient's overall CV risk profile should be established and other appropriate evidence-based therapies added to reach recommended targets (e.g., lipid levels, blood pressure, glycemic control). Inhibition of angiotensin-converting enzyme (ACE) should be offered for vascular protection using either an ACE inhibitor or an angiotensin receptor blocker (ARB). Patients with stable CAD should be offered enteric-coated acetylsalicylic acid. The value of lifestyle factors should not be overlooked; all patients should be encouraged to achieve and maintain a healthy weight and engage in regular exercise. Smoking cessation and moderate alcohol intake should be encouraged to appropriate patients. Finally, Dr. Lau reminded the audience of the value of preventing – rather than treating – diabetes and its complications.



Reviewers' Comments:

Dr. Lau has given us a peak into the upcoming 2013 Canadian Diabetes Guidelines with the notion that glycemic targets (along with other traditional risk factors) will continue to be important and that greater emphasis will be placed on individualized care of the diabetic patient. This is important because better blood sugar control almost always means multiple medications and potentially insulin and

clearly, not all treatments are the same in terms of their risks, associated side effects and cost. For example, weight gain, regardless of extent, may not be acceptable in some patients and hypoglycemia should probably be avoided in all patients with longstanding diabetes mellitus, known cardiovascular disease or hypoglycemia unawareness. Such characteristics are generally ascribed to metformin, α-glycosidase inhibitors and the incretins. Of these,

incretins are more costly, but have limited availability due largely to restrictive pharmacy practices. However, it is likely patients will be increasingly asked to accept greater fiscal responsibility for the various treatments they receive. In this model of care, personal choice balanced against cost is likely to become a more dominating factor in deciding what we do and which treatments we prescribe.

Bleeding management in the era of novel oral anticoagulants

*Dr. Eddy Lang, University of Calgary
Co-developed by the RMIACP Annual Meeting Committee and Bayer*

The novel oral anticoagulants (NOAC) have been shown to be equivalent (rivaroxaban) or superior (dabigatran, apixaban) to warfarin for the prevention of stroke in patients with atrial fibrillation

while demonstrating a statistically significant reduction in rates of intracranial hemorrhage. They also offer a number of pharmacologic advantages, including faster onset, simple, unmonitored dosing, lack of food effect, and shorter offset, although shorter offset may be a disadvantage in the context of non-adherence. These are balanced by more frequent dosing (dabigatran and apixaban), relative difficulty in obtaining laboratory confirm-

ation of degree of anticoagulation, greater dependence on renal clearance, and lack of fully reversing antidotes. The pharmacological profiles of the NOACs require different approaches to supervision and bleeding management that must be considered by clinicians when choosing an oral anticoagulation strategy for their patients.

Pharmacokinetics

Property	Conventional Anticoagulants				New Anticoagulants		
	warfarin	UFH	LMWH	fondaparinux	dabigatran	rivaroxaban	apixaban
Mode of action	vitamin K antagonist	indirect fIIa + Xa inhibitor	indirect fXa (minor IIa) inhibitor	indirect fXa inhibitor	direct factor IIa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
Bioavailability (F _{rel})	100%	100%	100%	100%	6-7%	80%	80%
Peak action (t _{max})	4-5 days	immediate (IV); 0.5 hrs (SC)	2-4 hrs	2-4 hrs	1-3 hrs	1-3 hrs	1-3 hrs
Elimination half-life (t _{1/2})	36-42 hrs	1-1.5 hrs	3-4 hrs	17-21 hrs	14-17 hrs	9-15 hrs	9-14 hrs
Route of clearance	multiple	reticulo-endothelial	>80% renal	100% renal	80% renal	35% renal	25% renal
Involvement of CYP	yes	no	no	no	minor	minor	minor

Douketis JD. *Curr Pharm Des* 2010;16:3436

Laboratory monitoring of patients on NOACs is not as readily available as for warfarin and different approaches are necessary for different agents. For dabigatran, activated partial thromboplastin time (aPTT) is clinically useful for qualitatively assessing anticoagulant effect, whereas the drug has minimal or no effect on prothrombin time (PT) or INR. An aPTT test should be considered as a screening test and a trough level (10-16 hours post-dosing) that is 1.5 times greater than control is considered therapeutic. At this time, thrombin clotting time (TCT) is too sensitive to distinguish different levels of anticoagulation but it can determine whether any dabigatran is present and thus play a role as a confirmation test when the aPTT screen is positive. A dilute TCT (Hemoclot assay) is becoming more widely available and correlates very closely with the concentration of dabigatran in the blood.

Rivaroxaban and apixaban both have measurable effects on PT, but it is not sufficiently reliable to measure their anticoagulant effects. A PT test can therefore be used for screening; if levels are elevated, there is likely some drug effect present. A normal PT suggests no clinically relevant anticoagulation effect; however, for reassurance, an anti-factor Xa assay can be ordered. These are currently calibrated for low-molecular weight heparin (LMWH) and should be calibrated for rivaroxaban or apixaban for greater accuracy.

Bleeding is a recognized risk factor with any anticoagulation therapy. Should bleeding occur in a patient receiving any of the agents used, the following general management steps are recommended:

1. Stop anticoagulation medication and initiate general supportive measures.
2. Order baseline tests including CBC, aPTT, INR, TCT and creatinine, depending on the type of anticoagulant medication.

3. Investigate and treat bleeding.
4. Administer an antidote if available (e.g., fresh frozen plasma and vitamin K for warfarin).
5. Transfuse red blood cells as required.
6. Consider non-specific procoagulant agents (e.g., Amicar/tranexamic acid, platelet transfusion).

Reversal strategies for NOACs are an active area of research and development. Currently, hemodialysis may be considered for removal of dabigatran from the circulation. However, dialysis is a risky procedure in an actively bleeding patient and is not effective for rivaroxaban and apixaban because these drugs are too tightly protein-bound. There is some experimental evidence to support the role of coagulation factor concentrates in reversing the anticoagulant effect of NOACs; however, none to date has been shown effective for reversing NOACs in bleeding patients. Likewise, replacement of clotting factors has not been shown to reverse the effects of dabigatran or rivaroxaban; existing drug will simply inhibit the added clotting factors. Adding factor II (or X) may "overwhelm" this inhibitory effect but this needs to be confirmed in further studies.

Dr. Lang concluded with a few take-home messages for internists. First, use of NOACs is increasing but warfarin will continue to have a place in therapy (e.g., in users with good results and INR monitoring, as well as patients with poor renal function). Second, laboratory monitoring varies according to the anticoagulation agent used. Finally, supportive care is the most relevant strategy for management of bleeding in patients receiving NOACs at this time; full antidotes are eagerly awaited.

Reviewers' Comments:

Warfarin acts indirectly to reduce the rate of coagulation by decreasing the production of vitamin K–dependent clotting proteins. This slow and indirect action is highly influenced by the availability of vitamin K, and susceptibility to multiple drug interactions. The variability of the effect of a given dose of warfarin is so great that INR monitoring is needed every 1 to 4 weeks for potential dose adjustment. Even with methodical monitoring, patients generally spend more than half their time either over- or under-anticoagulated.

For many patients, the reassurance of monitoring is outweighed by the inconvenience and pain of frequent testing. The promise of the novel oral anticoagulants is that “direct anticoag-

ulation” is rapid in onset, unaffected by vitamin K and drug interactions and does not require monitoring.

Because the action of the novel anticoagulants is intrinsically more stable, they appear to have a lower rate of intracranial bleeding. Unfortunately, intracranial bleeds are the least responsive to reversing agents, but the most devastating type of bleed to occur with anticoagulation. Therefore, studies of outcomes with intracranial bleeding have not demonstrated a benefit for warfarin compared to the newer agents. Thus, reversibility would be a poor criterion to persist with warfarin in a patient with unreliable anticoagulation. Going forward, the main reasons to maintain warfarin therapy will be poor renal function and/or a proven track record of reliable

time in therapeutic range in a patient already stabilized on this drug.

What must be remembered is that anticoagulant agents do not cause bleeding, only prolong naturally occurring bleeding events, and that anticoagulation does not completely stop clotting, only delays it. When there is a therapeutic requirement that the risk of intravascular thrombosis clotting be reduced, the risk that the amount of blood lost in any bleeding event must be increased. There will never be an agent that provides clot prevention without bleeding risk. With time, use of the new anticoagulants will become as familiar to clinicians as warfarin or heparin, and they will be comfortable choosing the best agent for their patients' circumstances.

Hypoglycemia in diabetes

*Presented by Dr. Sue Pedersen, C-ENDO
Endocrinology Centre, Calgary
Co-developed by the RM Annual
Meeting Committee and Novo Nordisk*

Hypoglycemia is typically associated with type 1 diabetes. Despite being under-reported by patients with type 2 diabetes, studies using continuous glucose monitoring suggest that up to 83% of patients experience episodes of hypoglycemia. The risk of hypoglycemic episodes increases with intensification of therapy such that among patients with type 2 diabetes treated with insulin for over 5 years, rates of hypoglycemia approximate those for patients with type 1 diabetes.

The consequences of hypoglycemia are well-known; however, other adverse effects are also important. Hypoglycemia-induced activation of the sympathetic nervous system may lead to endothelial dysfunction. There are also important

psychosocial consequences of hypoglycemia, including additional food intake, fear of future hypoglycemic episodes, and interruption of work, school or other activities such as driving.

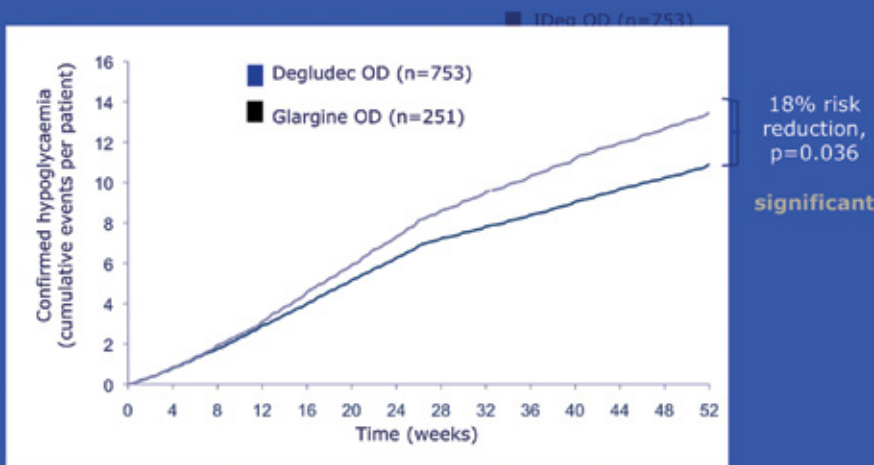
Several risk factors have been associated with hypoglycemia including age, control of glycemia, and type of therapy. DPP-4 inhibitors and GLP-1 mimetics are associated with minimal risks of hypoglycemia since glucose is a necessary cofactor for the insulin-secreting actions of these drugs. Conversely, up to 39% of patients using sulfonylureas self-reported hypoglycemic events. Sulfonylureas vary with respect to their risk of hypoglycemia, with glyburide having the highest risk association. Not surprisingly, patients with type 2 diabetes taking insulin are also at greater risk of hypoglycemia than patients who use other anti-diabetic medications. Given that long-acting insulin analogues more closely match physiologic insulin profiles, there could be an advantage to

long-acting analogues with respect to hypoglycemia.

Degludec, a novel basal insulin recently approved by the FDA, offers several characteristics of an “ideal” basal insulin: a flat profile with a prolonged half-life allowing for continuous insulin action over a 24-hour period, minimal intra-individual variability, and flexible dosing. In patients with type 2 diabetes, degludec reduced the relative risk for hypoglycemia by 18% and nocturnal hypoglycemia by 25% compared to glargine.



T2DM: Confirmed hypoglycemia



SAS
Comparisons: Estimates adjusted for multiple covariates

Garber A. et al. Lancet 2012;379:1498-1507

Other promising medications and technologies are under development for the management of diabetes and are showing promising results with respect to risk of hypoglycemia, including sodium glucose cotransporter 2 (SGLT-2) inhibitors, closed-loop pancreas technologies, insulin pump therapy plus continuous glucose monitoring, and glucose-responsive insulin. Stay tuned for more reports of the efficacy and safety of these and other emerging strategies that may offer tighter glycemic control with a lower risk of hypoglycemia.

Reviewers' Comments:

Dr. Pedersen spoke to the frequency and importance of hypoglycemic episodes in diabetic patients and of newer treatments that might be helpful in mitigating the risks of hypoglycemia. The most common cause of hypoglycemia in patients with type 2 diabetes is iatrogenic administration of excess exogenous insulin or stimulation of release of endogenous insulin by sulfonylureas. Most hypoglycemic episodes are mild and have no serious adverse clinical consequences. Response to glucose administration is prompt and predictable.

Severe hypoglycemia, defined as hypoglycemia requiring assistance from another person, is much less common – on the order of 0-3% per year in adults with type 2 diabetes. Risk is highest for insulins, sulfonylureas and regimens targeting intensive glycaemic control. Patient factors include prior history of hypoglycemia, renal insufficiency, microvascular disease, longer duration of diabetes, low socioeconomic status and education and dementia. There is good evidence that severe hypoglycemia is associated with an increase in all-cause mortality, neurologic events including coma, impaired LOC, seizures and paralysis, hospitalization and ED utilization, and

decreased quality of life. There are data suggesting ACS and stroke are not related to severe hypoglycemia and mixed findings on dementia or cognitive decline (Bloomfield HE. Department of Veterans Affairs, US Government Publications 2012). Pooled estimates of risk for metformin, GLP-1 analogues, DPP-4 inhibitors, insulin detemir, glinides, α -glycosidase inhibitors and TZDs are 0.6% (95% CI 0.3-1.2%) per year, comparable to diet alone. Pooled estimates for sulfonylureas are only slightly above that at 1.2% (95% CI 0.9-1.5%) per year (Bloomfield HE. Department of Veterans Affairs, US Government Publications 2012).

Investigation and treatment of hyponatremic states

Presented by Dr. Daniel Bichet,
University of Montreal
Co-developed by the RM Annual
Meeting Committee and Otsuka

Hyponatremia is characterized by an abnormal ratio of Na⁺ and K⁺ to water.

The recognized threshold for diagnosis of hyponatremia is a sodium concentration of <136 mEq/L. Reports suggest that hyponatremia is present in up to 28% of patients on admission to an adult acute care hospital. The long-term consequences of hyponatremia are considerable: in a 5-year follow-up study, the odds ratio for mortality in patients with persistent

hyponatremia and resolved hyponatremia compared to control subjects was 1.32 and 1.18, respectively.

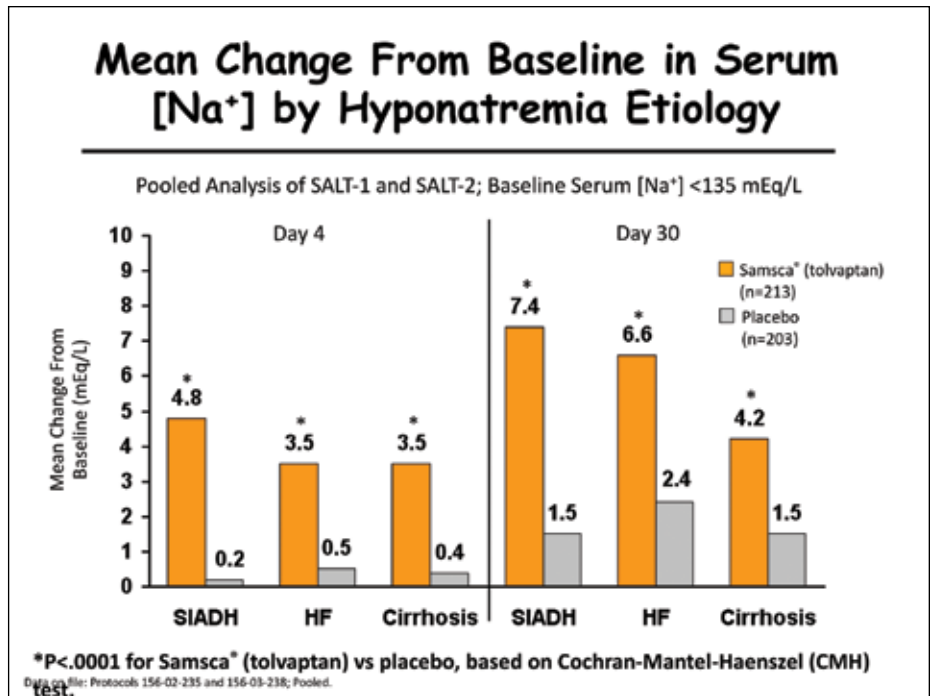
Hyponatremia resulting from loss of body water (depletional hyponatremia) can be readily treated by infusion of saline. Certain medical conditions may lead to hyponatremia with euvolemic or hypervolemic conditions (dilutional hypona-



tremia), for example, congestive heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone (SIADH), adrenal insufficiency, and others. Hyponatremia related to SIADH, heart failure, and cirrhosis is characterized by excessive levels of vasopressin (AVP) despite low plasma osmolality. Vasopressin secretion from the posterior pituitary is normally triggered by elevated plasma sodium concentration as well as low blood pressure. The main function of AVP is to increase reabsorption of water from the renal collecting ducts. Typical treatments include fluid restriction, urea, and hypertonic saline infusion. However, these therapies all carry significant limitations, including partial efficacy in patients with high AVP levels, poor compliance due to thirst (fluid restriction) or bitter taste (urea).

Vasopressin antagonist therapy has emerged as a promising treatment for chronic symptomatic hyponatremia in patients with elevated plasma AVP. Tolvaptan is a reversible inhibitor of vasopressin at the V2 receptors on cells in the renal collecting ducts. In the 1-month, placebo-controlled SALT (Study of Ascending Levels of Tolvaptan in hyponatremia) trials, patients with SIADH, heart failure, or cirrhosis with hyponatremia ($[Na^+]$: 120-135 mEq/L) were treated with tolvaptan 15-60 mg/day. Tolvaptan increased daily average serum $[Na^+]$ at Day 4 and the effect was maintained to Day 30. The improvement in plasma osmolality was also associated with better scores on the mental component of the SF-12 scale.

Cases of severe, symptomatic hyponatremia with seizures, coma, and respiratory distress due to neurogenic pulmonary edema are at very high risk of cerebral edema and should be treated immediately with hypertonic saline. Such acute conditions have been reported in marathon runners (especially females), during psychotic episodes, with the use of ecstasy and in cases of post-operative iatrogenic hyponatremia. According to the "rules of sixes," an increase of 6 mEq/L within 24 hours is safe for mild-to-moderate cases of hyponatremia, while the same increase can be reached within 6 hours for severe



Urine/Plasma electrolyte ratio: $U_{Na} + U_K / P_{Na} + P_K$ to guide water restriction

U/P ratio	Insensible water losses	Expected net water loss	Recommended water consumption
≥ 1.0	800 mL	- 800 mL	0 mL
.5 - 1.0	800 mL	-800 to -1300 mL	Up to 500 mL
< 0.5	800 mL	-1300 to -1800 mL	Up to one liter

The Urine/Plasma Electrolyte Ratio: A Predictive Guide to Water Restriction:
Furst ET AL. American Journal of the Medical Sciences, 2000. 319:240-244.

cases, with no further adjustments until the following day to prevent neurologic injury. Options for chronic, symptomatic, non-reversible causes of hyponatremia include: 1) fluid restriction (see table below for estimation of appropriate level of free water access), 2) oral sodium supplementation (if not hypertensive or at risk of vol-

ume overload from sodium retention), 3) medicinal urea, or 4) tolvaptan. Medicinal urea requires pharmacy compounding of 10 gm urea, 2 gm $NaHCO_3$, 1.5 gm citric acid and 200 mg of sucrose; at a dose of 10-30 gm of urea/day has been shown to be equally effective as tolvaptan.

Reviewers' Comments:

Hyponatremia is common, and even when mild and asymptomatic, is associated with increased prevalence of both falls and fractures from incidental falls, and increased short- and long-term mortality. The SALT studies (*N Engl J Med.* 2006; 355:2099-2112) represented a promising development in the field of hyponatremia, showing that tolvaptan is effective in raising serum sodium in hyponatremic states that have traditionally been the most difficult to treat (SIADH, heart failure, and cirrhosis). Limitations must be considered, however, before widespread use of vasopressin antagonists. Though SALT-1 showed improvements in the mental component of the SF-12 survey with tolvaptan compared to placebo, SALT-2 did not similarly show any statistically significant difference. Neither study reported improvements in the physical component of the survey. Similarly, the EVEREST trial (*JAMA* 2007; 297:1319) showed that although tolvaptan therapy in heart

failure patients resulted in decreased weight and edema compared to the standard therapy group, no difference in morbidity or mortality was found, even in the subgroup with hyponatremia. These studies highlight that despite consistent findings that tolvaptan is effective at increasing serum sodium, its effect on clinically meaningful outcomes, especially morbidity and mortality, remains undetermined. Furthermore, with the high cost of tolvaptan, cost-effectiveness studies are still needed, especially in light of the SALT trials demonstrating that serum sodium returns to baseline within one week after discontinuation of the medication. These results suggest that long-term therapy may be required in patients with chronic hyponatremia from irreversible causes.

Dr. Bichet highlighted important points to remember when using tolvaptan:

1. Tolvaptan has not been studied or approved for treatment of severe, symptomatic hyponatremia. Indeed, it is probably unsafe in that it blocks

AVP, thereby predisposing the patient to overcorrection and osmotic demyelination.

2. Initiation of tolvaptan for treatment of chronic, symptomatic hyponatremia should only be performed in hospital.
3. Fluid restriction should be avoided within the first 24 hours of tolvaptan treatment given the risk of overcorrection.
4. There are important drug interactions to consider because tolvaptan is metabolized by the cytochrome P450 3A system.
5. Tolvaptan may be considered in the treatment of chronic, non-reversible, symptomatic hyponatremia after failure of other traditional treatments such as water restriction, oral sodium, or pharmaceutical urea.
6. There may be other potential uses for this interesting agent in end-stage cirrhosis and congestive heart failure.

Pharmacogenomics: Personalized medicine for optimal outcomes

*Presented by Dr. P. Timothy Pollak,
University of Calgary*

Co-developed by the RMIACP Annual Meeting Committee, the Alberta Medical Association and the Western Canada Chapter of the ACP

Pharmacogenomics is the study of the genetic factors that determine an individual's response to drugs, including their absorption and elimination, and concomitant exposures to foods, other medications and disease.

Key goals of clinical pharmacology are to reduce adverse drug reactions (ADRs) and to avoid treatment failures and overdoses. Many ADRs can be prevented by being mindful of indications and contraindications of drugs, dosing, considerations such as a drug's concentration-time profile and dose-response curve. Contrary

to the notion of "one dose fits all,"

Dr. Pollak remarked that one dose leads to different concentrations in any population of patients depending on interindividual variability in absorption and elimination. These pharmacokinetic processes depend on transport and metabolic processes, all of which are genetically modulated. For instance, the hepatic cytochrome enzyme system (predominantly CYP3A4, CYP2C9 and CYP2D6), which metabolizes many drugs, demonstrates a wide range of genetic variation affecting their level of activity. Thus, different patients may experience a variety of responses to the same dose of a drug, ranging from subtherapeutic to toxic, depending on where they fall in the normal distribution of activity of these enzymes.

Private ventures (such as 23andme) are playing a role in pushing predictive pharmacogenomics to the forefront with promises of 'personalized medicine.'

However, this is occurring in advance of a substantial evidence base to support it. We can expect that tests for single nucleotide polymorphism (SNP) variants in important pharmacogenes will be developed for commercial use in the future and that tools will become increasingly available and affordable for predicting drug response in individual patients. Currently, tests for SNPs that affect metabolic capacity are available for CYP2D6 (codeine, SSRIs, beta-blockers, tamoxifen), CYP2C9 (warfarin, phenytoin), VKORC1 (warfarin), SLCO1B1 (statins) and CYP2C19 (clopidogrel, PPIs, SSRIs), although there are no regulatory bodies advising that these tests should be performed prior to prescribing any of these agents. In some centres, such as London, Ontario, facilities already exist for the practical use of pharmacogenomics to guide personalized medicine (<http://www.uwoclinpharm.ca/pcare.php>).



Reviewers' Comments:

Dr. Pollak identified many of the tensions that are inherent to the emerging field of pharmacogenomics. We amass information at the population level, but apply it to the individual. However, amassing information on the genetic level all too often leads

to the 'discovery' of noise (*Lancet* 2005; 365:454). Nonetheless, several signals are emerging; indeed, tests can be applied at the bedside to effect dosing decisions (e.g., warfarin and CYP2C9/VKORC1 genotype) (*N Engl J Med* 2009; 360:753). In preparing for this coming era, physicians should be

aware of resources such as pharmGKB (www.pharmgkb.org), which curates the state of knowledge pertaining to these genes, summaries of the evidence base that supports changes in clinical action and advice from regulatory bodies (*Clin Pharmacol Ther* 2012; 92:414).

WORKSHOPS

Update on hypertension and ABPM

Presented by Dr. Raj Padwal,
University of Alberta

Ambulatory blood pressure monitoring (ABPM) is now recognized as a gold-standard diagnostic tool for hypertension and should be used if available. Dr. Padwal argued that ABPM needs to be more widely available for three key reasons: 1) it provides additional information, such as blood pressure variability and circadian blood pressure cycle – two factors that are associated with cardiovascular risk; 2) it provides more accurate prognostic information; and 3) ABPM can identify cases of white-coat hypertension or masked hypertension, which cannot be identified solely by office-based measurements. ABPM could also be used to moni-

tor treatment and to guide medication adjustments, timing and/or dosing, based on 24-hour blood pressure variability.

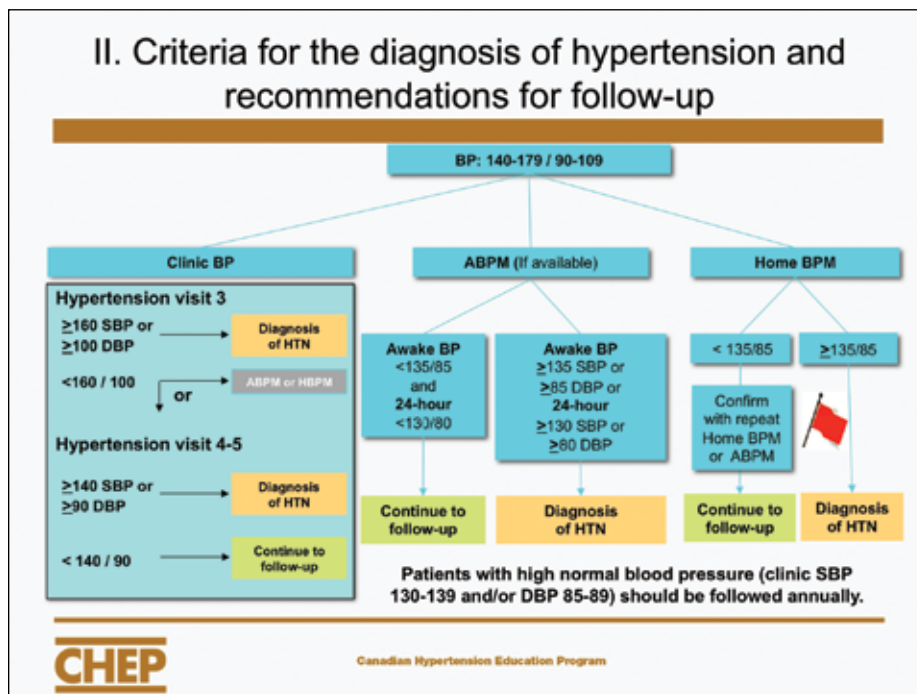
According to recent Canadian guidelines, an average daytime ambulatory blood pressure of 135/85 mm Hg or an average 24-hour ambulatory pressure of 130/80 mm Hg would carry similar risks as a reading of 140/90 mm Hg in the office setting. These thresholds are arbitrary and blood pressure (BP) should therefore be considered as a continuous risk factor. There are only a few contraindications for the use of ABPM including severe obesity, a blood pressure above 220/120 mm Hg, and advanced peripheral vascular disease.

A typical ABPM protocol includes blood pressure readings every 30 minutes during daytime (minimum of 14 readings during waking hours) and hourly readings at night-time, coupled with a patient

diary to accurately determine sleep time. According to current guidelines, ABPM readings should be interpreted based on 24-hour average ambulatory blood pressure daytime average ambulatory blood pressure, and nocturnal dipping. Ideal sleep-time dipping should be between 10 and 20%; non-dipping is associated with a 3-fold increase in cardiovascular risk.

Compared to ABPM, office-based BP readings have average sensitivity and specificity (75% for both). In a recent British study, ABPM showed greater cost-effectiveness than office- and home-based measurements, most likely because ABPM helps to reduce unnecessary treatment. Up to 30% of patients have normal BP during office measurements, but have high BP at home (masked hypertension). In those cases, ABPM becomes an essential diagnostic tool and allows for appropriate initiation of treatment.

Dr. Padwal addressed current controversies in the management of hypertension, including differences between thiazide and non-thiazide diuretics. Several randomized controlled trials and meta-analyses have reported superiority of chlorthalidone over hydrochlorothiazide (HCTZ) in terms of BP reduction and duration of action; however, a definitive answer based on head-to-head data remains elusive. Limitations of chlorthalidone treatment include the need for patients to cut tablets, since the starting dose should be 12.5 mg while the smallest dose available in Canada is 50 mg. Moreover, chlorthalidone is not readily available as a fixed dose combination with other agents. Based on available efficacy data, Dr. Padwal recommends the use of chlorthalidone over HCTZ at a dose of one quarter of a 50 mg tablet daily. However, if a patient is controlled on HCTZ, it is probably not worth switching.



Reviewers' Comments:

Dr. Padwal highlighted the many benefits of ABPM over office-based blood pressure (BP) measurements. The 2013 Canadian Hypertension Education Program (CHEP) guidelines recommend that ABPM be performed for:

1. Diagnosis of hypertension
2. In patients being treated for hypertension when:
 - a. BP remains above target despite

chronic and appropriate use of anti-hypertensives

- b. Hypotension is suspected
- c. Office BPs fluctuate

ABPM also reports BP variability, an area that has garnered widespread interest, given the finding that a blunted nocturnal BP decline (non-dippers) is independently associated with increased risk of target organ damage and cardiovascular events.

However, does bedtime dosing of anti-hypertensives to restore nocturnal dipping reduce this risk? The MAPEC trial (*Chronobiol Int* 2010; 27:1620, *J Am Coll Cardiol* 2011; 58:165) and its limitations were discussed in the top 5 papers. Dr. Padwal also indicated that bedtime dosing for certain anti-hypertensives, such as calcium channel blockers, can result in fewer symptomatic side effects and should therefore be considered.

OSA: Pathogenesis, co-morbidities & outcomes

Presented by Dr. John Reid, University of Saskatchewan

Obstructive sleep apnea (OSA) is under-recognized in research and clinical practice, despite reported prevalence rates of 24% in adult men and 9% in adult women (defined by a score 5 or higher on the Apnea-Hypopnea Index [AHI]). In clinical populations such as cardiology patients, the prevalence of OSA can reach 50%. These figures are likely to increase as the population ages, with consequent reduction in pharyngeal tone and increased neck obesity, in addition to a growing awareness of this condition.

Sleep apnea results from repetitive collapse of the upper airways during sleep, triggering hypoxemia, stress and/or arousals. The consequent sleep loss and fragmentation can lead to excessive daytime sleepiness, the primary complaint among patients with OSA. Other complaints include insomnia, non-restorative sleep, morning headaches, decreased short-term memory and/or irritability. Scores on the AHI may not always correlate with hypoxemia, especially in healthier patients where short periods of apnea may not result in desaturation. Consequently, oximetry has limited utility as a screening tool and is not sensitive enough to rule out OSA.

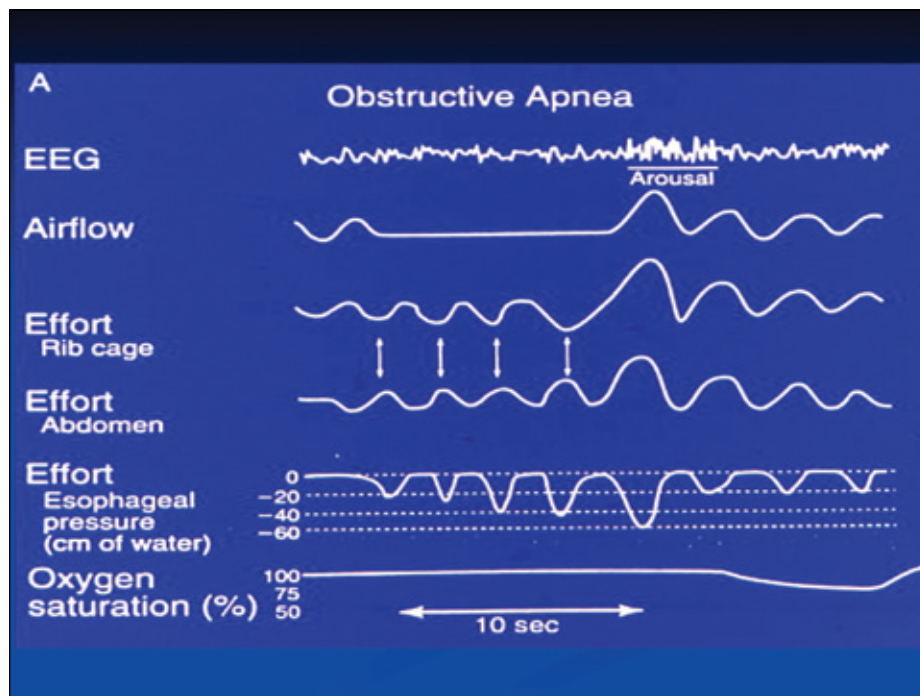
OSA is associated with increased levels of catecholamines, cortisol, and inflamma-

tory cytokines. Thus, OSA may contribute to significant co-morbidity, increasing the risk for hypertension 3-fold, coronary artery disease by 30-40%, stroke by 50%, motor vehicle accidents up to 10-fold, neuropsychological morbidity and possibly type 2 diabetes. Overall, patients with untreated OSA have an estimated 1% per year increase in risk of death compared to treated OSA patients.

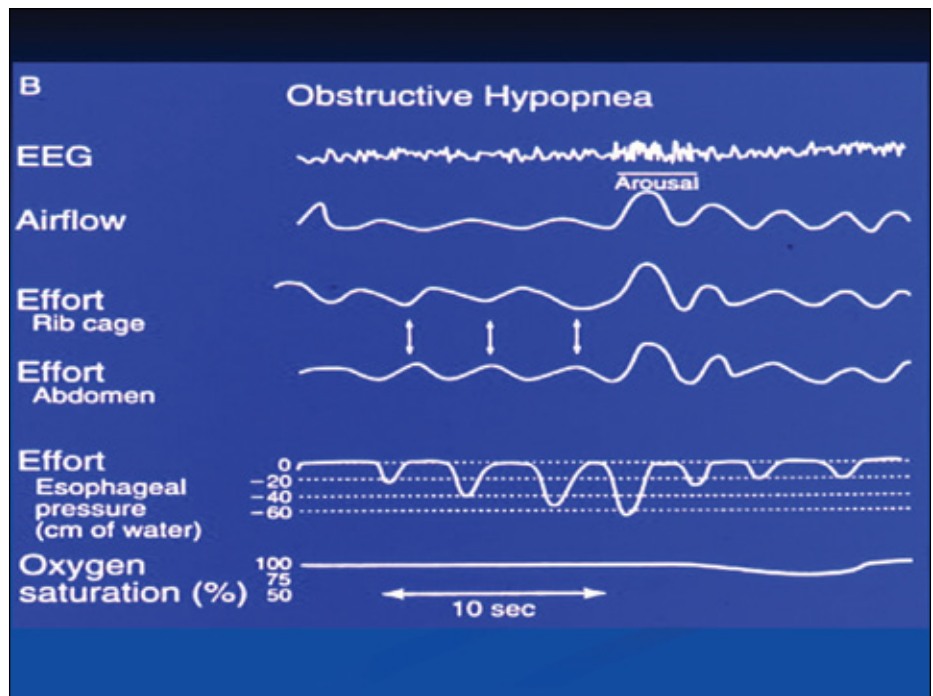
According to current guidelines, OSA is diagnosed based on the number of apnea, hypopnea, or respiratory-effort related arousal (RERA) events per hour during sleep time. Five to 15 events per hour is classified as mild OSA, whereas

more than 30 defines severe OSA. This classification is imperfect and mild events can lead to severe symptoms. Current diagnostic criteria do not take into account the duration of each event and the effect of variability in sleep architecture depending on whether the test was performed at home or in clinic. Furthermore, the classification of events, especially more subtle events such as hypopnea and RERA, is subjective and inter-observer variability is high.

Conservative treatment for OSA includes weight loss, positional therapy, avoidance of alcohol and smoking, and nasal congestion treatment. These strategies



should be recommended for all patients with OSA. There is robust evidence to support the use of continuous positive airways pressure (CPAP) as primary treatment to improve neurophysiologic symptoms in patients with severe OSA; however, the data are inconclusive in milder cases. Dental appliances, oropharyngeal surgery, the Pillar® procedure and nasal expiratory positive airway pressure (EPAP) are available for patients with mild-to-moderate OSA and those who tolerate CPAP poorly, but evidence for their effectiveness is meager.



Reviewers' Comments:

OSA is an exceedingly common and difficult problem in clinical practice. Upwards of 50% of patients with atrial fibrillation have some degree of OSA. The impact of this syndrome on health care costs and transportation

safety is immense. Unfortunately, it remains under-recognized, resources for diagnosis are restricted, and the only reliably proven therapy, CPAP, is often unpopular. Nonetheless, the message here is to clinically screen patients for signs of

sleep apnea if they have hypertension, headaches, atrial fibrillation or daytime somnolence. In this way, more patients will at least have the option to seek treatment or be motivated to change their lifestyle to reverse their OSA.

Management of hepatitis C

*Presented by Dr. Steve Wong,
University of Manitoba*

Hepatitis C virus (HCV) is a prevalent condition that is associated with considerable morbidity and mortality. It is estimated that 25,000 Canadians have chronic HCV and this number grows by 10,000 every year. Notably, up to 21% of infected individuals are not diagnosed because HCV has no or few symptoms, especially in the initial stages of infection. Consequently, diagnosis and treatment are often delayed, which may increase the risk of complications including liver cirrhosis, decompensated hepatitis C, and hepatocellular carcinoma.

All patients presenting with risk factors for HCV infection should be screened.

Traditional risk factors such as intravenous drug use, blood transfusion and medical procedures not using disposable needles account for most HCV cases. However, other risk factors should also be recognized, including poor vaccination practices, cocaine snorting, tattoos, ear and body piercing and fighting. While HCV is not considered a sexually transmitted disease (STD), it is nonetheless transmitted in ~3% of monogamous heterosexual couples and is more common in homosexuals, those with multiple sex partners, and individuals with other STDs. The virus can also be transmitted from mother to child in ~5% of HCV-infected women and in ~15% of mothers co-infected with HIV. Since baby boomers represent 70% of the overall HCV burden and are 5 times more likely to be infected, the

Center for Disease Control and Prevention (CDC) recently recommended that everyone in that cohort be screened for HCV. Clinicians should be aware of extrahepatic manifestations of HCV.

Diagnosis of HCV is relatively simple and inexpensive. Testing for HCV antibodies should be the first screening test, but a positive result only indicates that patients have been exposed to HCV, not necessarily that they have active disease. If positive, further testing for HCV RNA should confirm diagnosis and genotype. Genotype identification is essential, as it is an important factor to predict treatment response.

Approximately 85% of infected patients progress to chronic HCV; 20% of those will develop cirrhosis, which will lead to

death in 1 in 4 cases. Therefore, HCV treatment should aim to prevent the progression to cirrhosis. Liver enzymes should only be used as a surrogate marker since 20-30% of patients with HCV have normal liver enzymes even with active inflammation and fibrosis. Reducing co-infection by vaccination and eliminating alcohol intake is associated with a better prognosis.

New HCV drugs are now available and have improved treatment response rates for genotype 1 HCV, the most common, yet most difficult, genotype to treat. Traditional HCV treatment involves dual therapy with pegylated interferon (IFN) and ribavirin (RBV), with a response rate of 50% (genotype 1) and 80% (genotypes 2 and 3). Recently approved direct-acting antivirals (DAA), telaprevir and boceprevir, work by inhibiting HCV NS3/4A protease, which is essential for viral replication. They offer enhanced virologic response when combined with pegylated IFN and RBV in HCV genotype 1 *only*.

In treatment-naïve patients, response rates with tritherapy are 63-75% (vs. 38-44% with dual therapy). In patients with suboptimal response to dual therapy, treatment with DAAs increases response rates to 29-83%, depending on the level of initial drug response. Treatment with DAAs is associated with clinical challenges, including more severe side effects (e.g., severe anemia and dermatologic rashes), complicated dosing regimens, and pill burden (up to 19 pills daily!), important drug-drug interactions (due to their inhibitory action on CYP3A4), and strong dependence on IFN response. Drug-drug interactions dictate contraindications to DAA-based therapy and common drugs, such as anticonvulsants and statins, should not be used concurrently with telaprevir or boceprevir.

Based on recent data, the Canadian Association for the Study of Liver (CASL) published new HCV treatment guidelines in 2012 advocating that all patients with

Extrahepatic Manifestations of HCV

Immunoglobulin production and/or deposition

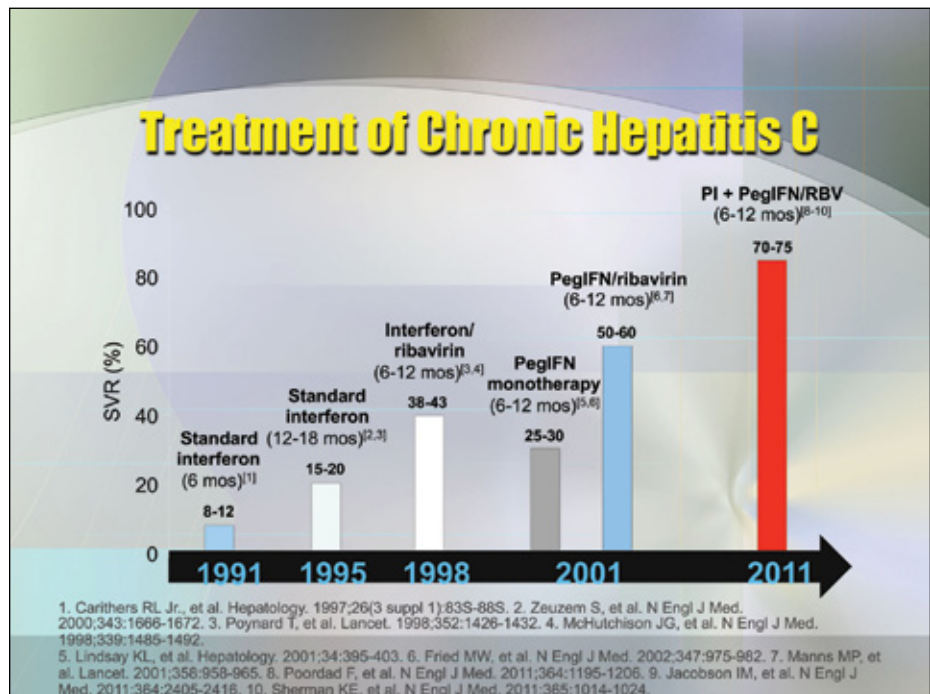
- **Autoantibodies**
- **Mixed cryoglobulinemia**
- **Leukocytoclastic vasculitis**
- **Membranoproliferative glomerulonephritis**
- **B-cell lymphoma**
- **Plasmacytoma**
- **MALT**

Autoimmune

- **Thyroiditis**
- **Sjögren syndrome**
- **Idiopathic thrombocytopenia purpura**
- **Lichen planus**

Unknown mechanism

- **Porphyria cutanea tarda**



HCV be assessed for antiviral therapy (www.hepatology.ca). For patients who are not publicly or privately covered for treatment, Dr. Wong recommended enrollment in clinical trials, biannual monitoring of liver enzymes and

extrahepatic manifestations, and modification of factors accelerating progression or negating treatment response (e.g., alcohol and body mass index).

***Clostridium difficile* infection (CDI): What's new in diagnosis and treatment; target of antibiotic stewardship**

Presented by Dr. Tom Louie,
University of Calgary

There are 30,000 cases of *C. difficile* infection (CDI) every year in Canada. Rates are higher in urban areas, in the elderly population (≥ 65 years old), and regionally in Quebec, British Columbia and Alberta. In the past 10 years, mortality rates from CDI have increased from 1.5% to 5-10%, mostly due to the presence of the 027 strain. This hypervirulent strain is quinolone-resistant, produces hyper spores, and is associated with more severe disease. Most of the worldwide *C. difficile* outbreaks are due to antibiotic-resistant clades, including the 027 strain, which originated in Montreal and Pittsburgh and are now spreading around the globe.

To control CDI in hospital settings, Dr. Louie argued that better diagnostic tools, stringent environmental control (e.g., sanitation, isolation), and more effective primary treatments are essential. In Calgary, the glutamate dehydrogenase

(GDH) test is first used to screen for *C. difficile* and, if positive, diagnosis is confirmed by PCR. At this time, testing for cure is inefficient and should be avoided, as most patients still carry *C. difficile* despite symptomatic improvements.

Data suggest that vancomycin is superior to metronidazole in terms of response (81% vs. 73%) and recurrence rates (23% vs. 36% in patients older than 75 years old). In older patients or in cases complicated by ulcerative colitis and/or Crohn's disease, switching to vancomycin might be required. Drugs used to treat CDI also influence the risk of recurrence. Fidaxomicin, a new drug with a narrower antimicrobial spectrum, has been shown to be as effective as vancomycin for treatment response. Low recurrence rates are mostly due to the ability of fidaxomicin to preserve the normal microbiota, while traditional antibiotic treatments are associated with significant disruption of the colonic bioflora. The benefits of fidaxomicin seem to be restricted to non-027 strains; reduced response rates and higher recurrence rates have been reported for 027 CDI. A further limitation of fidaxomicin is its higher cost compared to traditional antibiotics.

In recurrent cases that are resistant to treatment, evidence suggests that fecal transplant, through enema or oral administration, may be a very effective way to treat CDI. Fecal transplant effectively changes the gut microbiota to match that of the healthy donor and consequently reduces the rate of *C. difficile* relapse in antibiotic non-responders. Interestingly, in an unpublished analysis of 25 donor-patient pairs, Dr. Louie suggested that the following microbes groups are responsible for restoring resistance to *C. difficile*: bacteroidetes, *prevotella* spp., firmicutes, *bifidobacteria* spp. and *desulfovibrio* spp.

C. difficile infection is a disease involving an interplay of host, gut microbiota, pathogens and therapeutics. It is evident that traditional antibiotics, such as vancomycin, considerably disrupt the healthy microbiota, which decreases the host's ability to fight subsequent *C. difficile* infections. Notwithstanding, rigorous hand hygiene practices and transplanting microbes responsible for *C. difficile* resistance into infected hosts may constitute the ultimate probiotic and help break the cycle of CDI recurrence.

Reviewers' Comments:

In this informative talk by Dr. Louie, several points relevant to the practice of the general internist were discussed. The prevalence and associated risk of virulent, hyper spore produc-

ing strains of *C. difficile* is on the rise, and a reasonable action threshold for changing from first line (metronidazole) therapy to vancomycin would be a lack of response in 3-4 days. Clinical response is also the standard for assessing for cure, and we should resist

the notion that repeat antigen testing has any role in assessing response. Evolving treatment strategies aim to limit disruption of the colonic microbiome (fidaxomicin, rifaximin, cecapolid), or to restore it by other means (*N Engl J Med* 2013; 368:407).



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