



The 2010 Canadian Society of Internal Medicine (CSIM)/Rocky Mountain Conference Report

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Introduction to the 2010 CSIM Annual Scientific Meeting & Rocky Mountain /ACP General Internal Medicine Conference

Every four years, the Canadian Society of Internal Medicine (CSIM) and the Rocky Mountain / ACP General Internal Medicine Conference join forces for their annual scientific meeting. This year, conference attendees from across the country gathered in Vancouver and were presented with an outstanding line-up of national and international experts specialized in a broad range of disciplines. Plenary presentations and small group workshops explored the most current information and trends

in internal medicine that are clinically relevant and germane to practicing internists.

During a keynote address at this year's conference, internists were exposed to the benefits of team-based research and the importance of knowledge translation. This post-conference newsletter aims to strengthen the knowledge gained by conference attendees by providing a summary of some of the most relevant topics and

discussion points. A clinical commentary follows each summary to further reflect

on and clarify how the findings might impact everyday practice.

Clinicians are encouraged to view and download the speaker presentations from this year's conference at the CSIM website at

www.csimonline.com or the Rocky Mountain Conference website at www.ucalgary.ca/gim/rmc.html.



Dr. Robert Herman
Director, Rocky Mountain Conference



Dr. Finlay McAlister
President, CSIM



KEYNOTE ADDRESS

Top 5 General Internal Medicine Papers 2009/2010

Presented by Dr. William Ghali, Calgary

Staying up-to-date on the latest evidence can be a formidable challenge for practicing internists. Dr. William Ghali selected five papers that were published in late 2009 and in 2010 that were influential according to the following criteria: the potential to impact on patient outcomes and on public health; the ease of applicability of the findings; and the extent to which the paper signals a new paradigm. According to Dr. Ghali's survey

of the recent literature, general internists should make the time to read the following articles:

1. Two large cohort studies by Lu et al. and by Selvin et al. support A1c as a useful screening test for type 2 diabetes in routine clinical practice and is particularly powerful at discriminating between diabetics and nondiabetics at the extremes of <5.5% and >7.0%.
2. A randomized controlled trial by Schouten et al. supports perioperative use of fluvastatin for protection against cardiovascular outcomes in patients receiving beta-blockers who are undergoing vascular surgery.
3. The RACE II randomized trial does not support strict rate control for atrial fibrillation (HR <80 bpm) since it may invoke a higher risk than lenient rate control (HR <110 bpm) of major cardiac outcomes, death or bleeding.
4. A randomized controlled trial by Bode et al. supports screening and decolonization of surgical or medical patients who are nasal carriers of *Staphylococcus aureus* to reduce the rate of nosocomial infections.
5. The ACCORD-BP study does not support intensive blood pressure control (<120 mmHg systolic) in patients with type 2 diabetes.

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Reviewers' Comments:

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently introduced HbA1c as a clinical screening tool to diagnose diabetes mellitus into their 2011 Clinical Practice Guidelines, setting an HbA1c level of >6.5% as sufficient to diagnose diabetes. This is something that general internists and all physicians caring for diabetic patients need to be aware of. For most patients, Dr. Ghali's point is correct that an HbA1c <5% excludes and an HbA1c >7% supports the diagnosis of diabetes. However, the notion that HbA1c is useful or is even an appropriate test for establishing diabetes in the clinical setting is much more complicated. HbA1c represents glycation of hemoglobin.

Besides circulating blood sugar, erythrocyte turnover, cell membrane permeability to glucose, hemoglobin glycation/deglycation and a myriad of other processes potentially affect HbA1c levels. Moreover, HbA1c and blood sugars are not concordant tests, and probably identify differing populations of patients. This was most evident in a sub-analysis of the US National Health and Nutrition Survey (NHANES) where 50-60% of patients with a fasting blood sugar (FBS) ≥ 7.0 mmol/L had an HbA1c <6.5% (Saudek CD et al., 2008). If tested only using HbA1c, large numbers of these patients would have been diagnosed as prediabetic (in the HbA1c range of 5.1-6.4%, whatever that designation means in the HbA1c domain) or not having diabetes at all. Furthermore, there are a number of other conditions

that can alter the measurement of HbA1c. Indeed, the use of HbA1c as the sole measure to diagnose diabetes could lead to over-diagnosis "among the elderly, blacks, subjects with iron deficiency, and individuals genetically predisposed to greater levels of [hemoglobin] glycation, whereas [pregnant females], or those with anemia, renal insufficiency, and many hemoglobinopathies ... [may] be incorrectly told that they do not have diabetes." (Bloomgarden ZT, 2009). Thus, the important questions are: 1) will physicians be aware of these issues and sufficiently skilled in interpreting an HbA1c, and 2) has this test proven its validity, cost effectiveness (with all the other testing that may be necessary) and clinical utility in order to accurately and reliably diagnose diabetes in our hospitals and clinics?

The DECREASE III trial enrolled 499 patients with high cardiovascular risk and randomized them to 80 mg of extended-release fluvastatin or placebo, in addition to a beta-blocker before undergoing vascular surgery. They found a significant 47% relative risk reduction for the endpoint of perioperative myocardial ischemia (10.8% vs. 19.0%, HR 0.55; 95% CI 0.34-0.88; $p=0.01$) and a 53% relative risk reduction for the combined endpoint of nonfatal myocardial infarction and cardiovascular death (4.8% vs. 10.1%, HR 0.47; 95% CI 0.24-0.94; $p=0.03$). Dr. Ghali makes the point that the numbers of events in this study were quite small, but the overall clinical benefit was impressive with a number-needed-to-treat (NNT) to prevent each adverse outcome of 13 and 19, respectively. Also, the effect is consistent with the effects of statins in other clinical scenarios and in keeping with the notion that all statins possess an anti-atherothrombotic effect. Currently, it is not known when perioperative treatment with these agents should be started and how long they must be continued postoperatively. Certainly, patients already receiving statin therapy should continue to receive these agents in the perioperative period because discontinuation may lead to a higher rate of complications. Large randomized controlled trials will be necessary in order to evaluate the efficacy and the safety of perioperative statin use in patients with low or intermediate cardiovascular risk profiles.

The RACE II Trial, likewise, was a small study of 624 patients with persistent atrial fibrillation with a very small number of outcome events

and a short study interval of only 2 years. The mean on-treatment resting heart rate was 85 bpm in the lenient and 75 bpm in the strict treatment strategy arms. The mean absolute difference in the primary composite endpoint of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, bleeding or other life-threatening events between the two groups was 2%, with the hazard ratio slightly favouring the lenient treatment arm (HR 0.84; 90% CI 0.58-1.21). Given the number of physician visits was far lower for the lenient strategy, yet the symptoms and adverse events in the two groups were similar, the authors concluded that lenient rate control in atrial fibrillation was as effective and easier to achieve. However, physicians should be reminded that the internal validity of a trial is dictated by the magnitude of the clinical differences between the groups and the number of events. In this context, the results favouring the more lenient treatment are unexpected and unexplained. Thus, we recommend caution in implementing any change in practice on the basis of this trial until the findings can be supported by larger studies.

The study by Bode et al. (2010) on testing and de-colonizing nasal carriers of *Staphylococcus aureus* to reduce surgical site infections is clearly a step forward in our understanding and approach to prevention of infection in the perioperative period. It is well-known that nasal carriers of *S. aureus* have a high risk of health care-associated infection with this organism, and that more than 80% of these infections are endogenous (Bode et al., 2010), meaning they arise from the host infection and not the

healthcare facility, itself. Moreover, this organism is a virulent pathogen that is responsible for a substantial proportion of serious surgical-site infections across the entire spectrum of surgical procedures and patient risk. The approach included real-time PCR identification of carriers, and immediate treatment consisting of 2% mupirocin ointment applied twice daily to the nares and chlorhexidine gluconate soap, 40 mg/mL, once daily total-body wash, both given for a 5-day duration of treatment. Second and third treatment courses were given to patients at 3 weeks and 6 weeks, if their hospitalizations were prolonged. The effect size in the surgical group was a 79% reduction in rates of infection with *S. aureus* (HR 0.21; 95% CI 0.07-0.62) and a mean reduction in hospitalization of almost 2 days, from 14.0 to 12.2 days ($p=0.04$). The NNT to detect and prevent one *S. aureus* infection was 250 and 23 patients, respectively. All-cause in-hospital mortality favoured (not significantly) mupirocin/ chlorhexidine treatment, but the study was not adequately powered to address this issue. Important questions asked in response to the article were: 1) whether this approach might be effective in hospitals with a much higher rate of MRSA (the prevalence of MRSA in the Netherlands, where the study was conducted, is only 0.03%), and 2) whether such treatment might lead to mupirocin resistance. The answers: most isolates of MRSA are sensitive to mupirocin, and several studies suggest short-term use of mupirocin is not associated with emergence of resistance.

The ACCORD trial tests our understanding of the statistical nuances of looking for differences



and finding none, versus testing for sameness and finding such to be true. Accordingly, ACCORD has two flaws that weaken its conclusions and limit its clinical applicability, substantially. In the first instance, the study was designed as a superiority trial (testing for differences) with an a priori power to detect a 20% reduction in the rate of the primary composite outcome of 94%, given an outcome in the comparison arm of at least 4% per year. Unfortunately, the observed event rate in the standard treatment arm was half (2.09%/yr) the expected rate, with the consequence that the study was badly underpowered (finding no difference) and unable to test the original hypothesis with the numbers enrolled. It was not designed nor powered as an equivalency trial (testing for sameness), so there was

no test and no evidence the two treatment strategies were the same. Indeed, it could be argued that the statistically significant 37% reduction in the annual rate of nonfatal stroke and the non-significant 13% reduction in nonfatal MI favouring the intensive BP-lowering arm in the study are exactly in the range of what has been seen in other large trials of effective BP-lowering treatment. Of all the primary and secondary outcomes included in the analyses, only death from any cause and death from cardiovascular cause numerically favoured standard treatment, and the important diabetic renal parameters of urinary albumin/creatinine ratio and macroalbuminuria statistically favoured the lower SBP target. On the second matter of clinical applicability, the target chosen for aggressive SBP lowering in the ACCORD study (<120

mmHg) is lower than the current Canadian, or any other national BP-lowering recommendation. Thus, the study doesn't test the guidance, just the principle, of aggressive BP reduction. There have long been concerns regarding lowering BP too far, particularly in elderly patients. An SBP <120 mmHg may be simply too low in diabetes. Finally, three other trials; namely, JATOS (JATOS Study Group, 2008), Cardio-Sis (Verdecchia P, et al., 2009) and the ESCAPE trial (The ESCAPE Trial Group, 2009) further inform the decision of aggressive versus standard SBP targets and led the 2011 CHEP Guidelines Taskforce to conclude there was insufficient evidence to change existing guidelines in diabetic and renal patients targeting a treatment goal BP <130/80 mmHg.

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KEYNOTE ADDRESS

Canadian Cardiovascular Outcomes Research Team (CCORT): Lessons Learned

Dr. David Sackett Senior Investigator Award Winner 2010, Dr. Jack Tu, Toronto

Medical research has historically been conducted by scientists working independently in a lab, but as research becomes more and more complex, future discoveries will increasingly rely on teamwork and multidisciplinary collaboration. The CCORT was formed in 2001, bringing together a national team of investigators with the initial goal of

providing "report cards" to hospitals on the quality of care delivered to cardiac patients across the country. The CCORT later focused on issues surrounding access to care, which were prominent at the time the CCORT was applying for funding.

One of the original mandates of the CCORT was to translate the knowledge gained through research and measure the impact of the findings on patient outcomes. The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study randomized 86 hospitals across Ontario to receive either early or delayed feedback of a public report card on

their performance on national acute myocardial infarction (MI) and congestive heart failure (CHF) process of care quality indicators (e.g., speed of delivery of drugs to STEMI patients, use of statins, ACE inhibitors [ACEi], beta-blockers, etc.). Changes in performance indicators and the impact on various patient outcomes were then reassessed after the report cards were released. One of the major effects of early feedback related to hospital policies surrounding door-to-needle times. Twenty-four percent of hospitals in the early feedback group introduced policies allowing the use of lytics by emergency physicians rather



than waiting for the patient to see a specialist, and this resulted in a 2.5% absolute reduction in mortality rates at 30 days. Hospitals receiving late feedback also made significant policy changes in an effort to improve quality of care, even before public release of their own performance scores. However, this did not affect outcomes. One year after the release of the report cards, no differences were seen. In the case of practice standards for patients with CHF, a trend for improvement in outcomes at 30 days and at 1 year were seen in those hospitals that received report cards, suggesting that changes in hospital policies had a positive impact on important patient outcomes.

Report cards, interactive maps and heart failure risk calculators are posted on www.ccort.ca, providing public access to “grey literature” and information that is not necessarily published in journals or promoted by the media.

CCORT EFFECT Study
Mean Change in Hospital-Specific Mortality Rates after Publication of Report Cards for Early Feedback Arm

All-Cause Mortality	Early Feedback Hospitals (N=42)		Delayed Feedback Hospitals (N=39)		Absolute Difference* Early vs Delayed % (95% CI)	P Value
	Baseline	Follow up	Baseline	Follow up		
AMI patients						
30 day	11.7%	9.8%	12.2%	12.2%	-2.5 (-4.9 to -0.1)	0.045
1 year	19.2%	19.4%	20.2%	22.5%	-3.1 (-6.4 to 0.2)	0.06
STEMI patients						
30 day	11.5%	8.3%	11.9%	11.4%	-3.1 (-6.0 to -0.2)	0.04
1 year	16.0%	13.5%	17.2%	17.4%	-4.0 (-8.0 to -0.1)	0.045
CHF patients						
30 day	11.3%	9.6%	10.4%	10.6%	-1.1 (-3.2 to 0.9)	0.26
1 year	32.6%	30.3%	33.2%	32.9%	-2.8 (-6.0 to 0.5)	0.10

*Absolute difference represents the mean relative improvement in each mortality indicator in the early feedback hospitals as compared with the delayed feedback hospitals in the follow-up patient cohort after adjusting for performance in the baseline patient cohort and type of hospital. Negative values indicate better performance in the early feedback hospitals.

Tu JV, Donovan LR, Lee DS, et al. Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. JAMA 2009;302:2230-7

Reviewers' Comments:

Dr. Jack Tu, a co-team leader for the CCORT, shared some of his observations and lessons learned over the past decade with his involvement in team-based research. One of his key observations is that working with stakeholders for knowledge translation is an effective way to disseminate information from

research trials to a broader audience. The Internet is also a powerful agent for dissemination of findings and has been a valuable vehicle for knowledge translation for the CCORT. Other important lessons Dr. Tu learned about team-based research through his involvement with the CCORT include the importance of developing personal relationships; identifying and leveraging individual strengths

and weaknesses; choosing research projects that benefit from multi-investigator input; ensuring good writing and data analysis skills within the team; choosing collaborators; and investing in students. Dr. Tu concluded by stating that “Being part of the ‘right’ research team can be a lot of fun and can lead to many life-long friendships as well as publications.”

AM Edwards Lecture

Evidence-based Physical Diagnosis

Presented by Dr. Steven McGee, Seattle

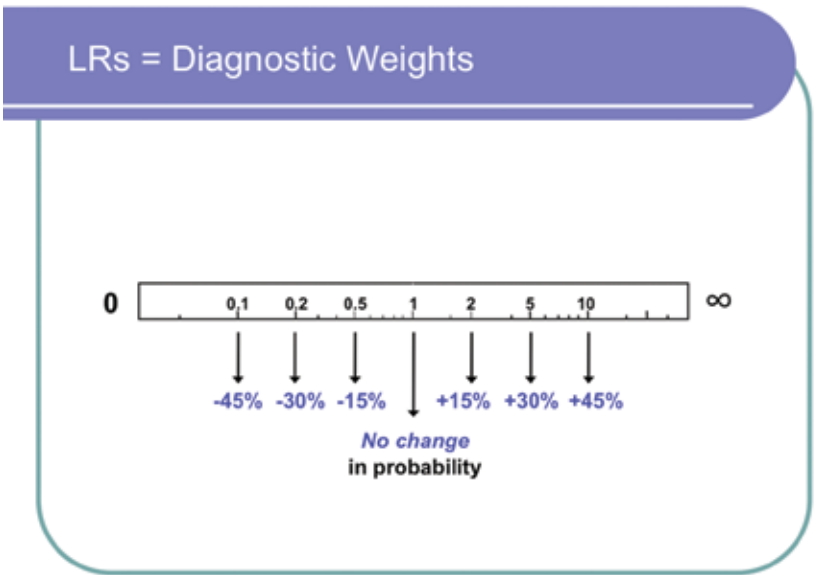
Patients’ problems are traditionally categorized and weighted according to what is seen, heard and felt at the bedside, backed by imaging and laboratory testing. Today, the majority of conditions encountered by internists

are complex and multi-system disorders where errors in diagnosis and misinterpretation of test results can lead to less than optimal outcomes. Physical diagnosis is an important tool and knowing which findings are accurate and which are not can help clinicians estimate the probability of the presence or absence of a specific disease diagnosis. Likewise, each test that is performed carries a certain accuracy supporting

or refuting the primary diagnosis or other important considerations for management, including prognosis and likelihood of therapeutic benefit. Linkage of the multiple approaches, including history taking, physical diagnosis and laboratory or imaging testing, through principles of probabilistic thinking, greatly enhances the certainty with which the internist can approach difficult diagnostic cases.



Sensitivity and specificity have traditionally been considered the best standard of diagnostic accuracy. However, these measures can be difficult to apply and interpret at the bedside. Dr. Steven McGee argues that a preferable way to assess the accuracy of clinical diagnosis at the bedside is to use likelihood ratios (LRs). A positive LR is useful for estimating the probability of the presence of a condition and represents the probability of a particular finding showing up in patients with the diagnosis of interest divided by the probability of the same finding showing up in patients without the diagnosis of interest. Reciprocally, a negative LR is useful for estimating the absence of a condition and is the proportion of patients with the condition of interest who do not demonstrate the physical sign of interest, divided by the proportion of patients who do not have the condition of interest and who also lack the physical sign. Likelihood ratios can be interpreted as belonging to three diagnostic categories: findings with a LR <1 decrease the post-test probability of the diagnosis of interest (this can be useful for excluding disease); values >1 increase the post-test probability of the diagnosis (most useful for confirming a diagnosis); and values close to 1 are not helpful because they do not change the pre-test probability of the diagnosis. The absolute diagnostic gain of a positive or negative LR depends not only on the value of the LR, but also on the pre-test likelihood. As an example, when the pre-test probability is 50%, a physical finding whose LR is 2, 5 or 10 increases the absolute probability of the diagnosis by 15%, 30% or 45%, respectively, whereas the inverse values (0.5, 0.2 and 0.1) decrease the probability by 15%, 30% and 45%, respectively. Internists should not ignore those clinical findings whose LRs fall in the grey zones of the Figure below (i.e., LRs of >3 or <0.3) because they may significantly increase or decrease the probability of the diagnosis by 20-25% or more. Conversely, findings whose LRs fall in the white zone (LR=0.3-3.0) do not sufficiently change the diagnostic probability to be useful.



- ### Findings With Surprising Accuracy
- **Conjunctival rim pallor, detecting Hb < 11 gm/dL**
Pallor present 16.7, borderline 2.3, absent 0.6
 - **Characteristic diastolic murmur of AR**
Presence of murmur, LR = 9.9 for mild AR or worse
Absence of murmur, LR = 0.1 for moderate AR or worse
 - **Palpable nontender gallbladder in patients with jaundice, detecting extrahepatic obstruction:**
LR+ = 26.0, LR- = 0.7
 - **Pulsus paradoxus, detecting cardiac tamponade**
LR+ = 5.9, LR- = 0.03

Dr. McGee illustrated how to use an evidence-based approach to address four clinical questions using LRs:

1. Does a patient with chest pain or dyspnea have elevated left atrial pressure?
2. Does a patient with acute abdominal pain have peritonitis?
3. Does a patient with shoulder pain have a torn rotator cuff?
4. Does a patient with acute respiratory complaints have pneumonia?

As an example of how simple physical findings can be combined in the form of a prognostic clinical decision rule, the CURB-65 was presented. This tool

has largely replaced the more complex pneumonia severity index (PSI) to augment decision-making regarding whether or not to admit a patient with pneumonia to hospital. It is based on the probability for 30-day mortality based on five independent bedside findings: confusion, high blood urea nitrogen, respiratory rate ≥ 30 breaths/min, low blood pressure, and age >65 years.

One of the key benefits of LRs is that they provide clinicians with a handy summary based on a wealth of clinical experience. According to Dr. McGee, "It's as though you personally examined those [hundreds or thousands of] patients [from the clinical studies used to derive the

likelihood ratios] and remembered what you learned.” Also, the LR for the pretest probability of a diagnosis can be directly multiplied by the positive – or negative – predictive value of each independent test for the diagnosis to calculate a post-test probability of disease.

Findings at the bedside exam can inform not only a patient’s diagnosis, but also the prognosis, appropriate treatment selection, and treatment response.

Dr. McGee referenced his book, *Evidence Based Physical Diagnosis* (2nd Edition, Saunders Elsevier,

2007) and summarized his lecture by recommending that internists should use an evidence-based approach to physical diagnosis so that “We can start making decisions from where they should be made, which is, of course, at the patient’s bedside.”

Reviewers’ Comments:

Dr. McGee’s book, *Evidence Based Physical Diagnosis*, is a valuable tool for a wide variety of healthcare professionals, from internists to family practitioners, nurse practitioners, physician assistants and medical students. It is a clinical reference that takes an evidence-based approach to the physical examination so that healthcare professionals can diagnose with

confidence. This book is written in an easy-to-reference manner, making it simple to find the available scientific evidence concerning the diagnostic significance and accuracy of physical examination findings.

A good illustrative and highly relevant example of some of the strengths and limitations of simple historical symptoms and physical signs that is outlined in McGee’s book is that of pulmonary embolism. Of 15 physical exam findings related to

vital signs, pulmonary, cardiac and chest wall findings, the highest LRs are around 2.0 (respiratory rate >30 and unilateral calf findings) and none are so low that PE can be confidently excluded. Yet, in combination with historical symptoms, simple clinical features can be combined, such as Well’s Score for Pulmonary Embolism, to produce positive and negative LRs (5.0 and 0.2) that may often help guide subsequent diagnostic decision-making.

Satellite Symposium

Optimizing Patient Outcomes in ACS

Presented by Dr. Robert Welsh, Edmonton, and Dr. Hector Baillie, Nanaimo

Antiplatelet therapy is the standard of care in Canada for the acute management of patients with acute coronary syndromes (ACS) and as a management strategy for patients post-percutaneous coronary intervention (PCI) with bare metal stents. Despite the compelling evidence that antiplatelet therapy can improve patient outcomes, its optimal use remains a clinical challenge.

Dr. Hector Baillie set the stage for this discussion by presenting a case scenario that illustrated the complexity of risk assessment for ACS in the community hospital setting. Although clinicians often have ‘clinical gestalt’ concerning patient risk stratification, available evidence suggests that many high-risk patients are not correctly identified. Risk estimation can be improved using tools such as the

GRACE ACS risk prediction model or the TIMI risk score, and both are superior to using EKG and troponin findings at presentation. Such tools can be useful for tracking a patient’s status over time, and for facilitating the identification of patients who become higher-risk and require urgent transfer for an invasive strategy. Tools are also available to estimate a patient’s risk of bleeding, which needs to be balanced against the risk of cardiac events or death.

Dr. Robert Welsh presented findings from recent trials that are informing clinicians’ decisions on optimal antiplatelet therapy. Landmark studies such as the CURE trial and CURRENT OASIS 7 have demonstrated the benefits of dual antiplatelet therapy (DAPT) using ASA and clopidogrel in ACS patients managed medically or in those receiving a PCI or coronary artery bypass grafting (CABG).


Prasugrel is a newer antiplatelet agent that was recently approved in Canada. It offers higher potency than clopidogrel with a faster onset of action and more

predictable pharmacokinetics. Its efficacy and safety were evaluated in the TRITON TIMI 38 trial, which randomized ACS patients with planned PCI to either prasugrel or clopidogrel once their coronary anatomy had been assessed via angiography. Prasugrel demonstrated a significant reduction in ischemic endpoints that was driven mainly by a reduction in the rate of re-infarction (7.4% vs. 9.7% for clopidogrel, $p < 0.001$), as well as a significant reduction in stent thrombosis (1.1% vs. 2.4%, $p < 0.001$). Prasugrel was associated with an increased risk of bleeding (major bleeding 2.4% vs. 1.8% for clopidogrel [$p = 0.03$], and fatal bleeding 0.4% vs. 0.1% [$p = 0.002$]), a finding that was associated with specific subgroups of patients; namely, those aged 75 years or older, those weighing <60 kg, or those with a history of stroke or transient ischemic attack.

Ticagrelor is another novel antiplatelet agent that internists are likely to encounter in the clinical setting. It is an oral reversible agent that does not



require metabolic activation, offering a rapid onset of action, higher potency than clopidogrel and reversible platelet inhibition. The PLATO trial compared ticagrelor to clopidogrel in patients with a broad spectrum of ACS, including unstable angina, NSTEMI, medically managed STEMI, or STEMI patients undergoing PCI or CABG who had not received thrombolytic therapy. Ticagrelor significantly reduced the risk of the combined primary endpoint of cardiovascular death, MI and stroke (9.8% vs. 11.7% for clopidogrel, $p < 0.001$), as well as MI or cardiovascular death considered separately (5.8% vs. 6.9% [$p = 0.005$] and 4.0% vs. 5.1% [$p = 0.001$], respectively). This is the first study showing a significant reduction in the risk of CV death with antiplatelet therapy. Similar outcomes were reported in the subgroup of patients undergoing CABG. The risk of major bleeding with ticagrelor was similar to clopidogrel (11.6% vs 11.2% respectively, $p = 0.434$). There was a significantly higher rate of dyspnea in the ticagrelor group (13.8% vs. 7.8% for clopidogrel, $p < 0.001$) resulting in a greater number of treatment discontinuations due to this effect (0.9% vs. 0.1%, $p < 0.001$). This off-



CLINICAL Summary - P2Y12 Inhibitors

	TRITON Prasugrel	CURRENT (PCI) High dose Clopidogrel	PLATO Ticagrelor
CV death, MI , stroke	9.9% vs. 12.1% ($p < 0.001$) ↓ 19% (ARR 2.2%)	3.9% vs. 4.5% ($p = 0.039$) ↓ 14% (ARR 0.6%)	9.8% vs. 11.7% ($p < 0.001$) ↓ 16% (ARR 1.9%)
CV death	2.1% vs. 2.4% ($p = NS$)	1.9% vs. 1.9% ($p = NS$)	4.0% vs. 5.1% ($p = 0.005$) ↓ 21% (ARR 1.1%)
MI	7.3% vs. 9.5% ($p < 0.001$) ↓ 24% (ARR 2.2%)	2.0% vs. 2.6% ($p = 0.018$) ↓ 22% (ARR 0.6%)	5.8% vs. 6.9% ($p = 0.001$) ↓ 16% (ARR 1.1%)
Stroke	1.0% vs. 1.0% ($p = NS$)	0.4% vs. 0.4% ($p = NS$)	1.5% vs. 1.3% ($p = NS$)
Stent thrombosis	1.1% vs. 2.4% ($p < 0.001$) ↓ 52% (ARR 1.3%)	1.2% vs. 0.7% ($p = 0.0001$) ↑ 46% (ARR 0.5%)	1.3% vs. 1.9% ($p = 0.009$) ↓ 33% (ARR 0.6%)
Non-CABG related TIMI major bleeding	2.4% vs. 1.8% ($p = 0.03$) ↑ 32% (ARR 0.6%)	1.0% vs. 0.7% ($p = NS$)	2.8% vs. 2.2% ($p = 0.03$) ↑ 25% (ARR 0.6%)
CABG related bleeding	13.4% vs. 3.2% ($p < 0.001$) ↑ 473% (ARR 10.2%)	0.1% vs. 0.07% ($p = NS$)	5.3% vs. 5.8% ($p = NS$)

target treatment effect warrants further evaluation in registry studies. Clinicians now find themselves in the era where individual risk factors – both for ischemic events and for major bleeding – must be taken into consideration when selecting the most appropriate antiplatelet treatment strategy. Dr. Welsh

concluded by commenting that the CV mortality benefit observed with ticagrelor is “difficult to deny” and that newer antiplatelet agents “will be protocol changing” as they potentially position themselves to replace clopidogrel as the standard antiplatelet therapy.

Reviewers' Comments:

The new antiplatelet agents address some of the shortcomings of previous inhibitors of the P2Y12 adenosine diphosphate platelet receptors. Just as clopidogrel offered reduced incidence of neutropenia over ticlopidine, these new agents offer more reliable availability of

active compound over clopidogrel (without CYP 2C19 dependence) and still lower rates of neutropenia. Nonetheless, the heritage of these new thienopyridine compounds must be remembered, as the incidence of neutropenia is still not zero. It should also be noted that prasugrel has a more limited indication for use than clopidogrel and is currently

only approved to reduce thrombotic events in patients with ACS who are to be managed with PCI. The short duration of action of ticagrelor will make it more suitable for in-hospital, perioperative use than for outpatient therapy. As with many other newer agents, cost considerations will have a major effect on their rate of adoption into everyday practice.

Short Snappers

Glycemic Targets in Diabetes

Presented by Dr. Ann Colbourne, Edmonton

The Canadian Diabetes Association currently recommends that patients with type 2 diabetes be treated to maintain

adequate glycemic control, defined by an A1c level of < 7.0 for most patients, and as low as < 6.0 if it can be safely achieved. Four large-scale studies have evaluated whether more intensive glycemic control confers advantages over standard glycemic targets: the

UKPDS, ACCORD, ADVANCE and VADT trials. Important differences between the studies in terms of patient demographics and disease characteristics, treatment interventions, duration of follow-up, A1c levels at baseline and at study completion, and the incidence



of hypoglycemia, complicate their interpretation. A systematic review by Kelly et al. recently published in the Annals of Internal Medicine suggests that there may be modest benefits of tighter glycemic control in terms of cardiovascular disease, coronary heart disease, and nonfatal MI, which must be balanced against a higher risk of severe hypoglycemia and of death from any cause emerging after 3 years in the ACCORD study.

Dr. Ann Colbourne reflected on how these trials inform clinicians with respect to management of patients with type 2

diabetes. Firstly, the trials suggest that patients take several medications for diabetes control and for other comorbid conditions. Secondly, the rate of A1c decline may influence the safety of intensive glycemic control. Notably, those patients who had the most difficulty achieving intensive glycemic targets accounted for the majority of excessive deaths. Thirdly, intensive glycemic control strategies are associated with a higher rate of severe hypoglycemia. This is particularly relevant since the body's response to hypoglycemia is mediated through the release of epinephrine,

cortisol, glucagon, interleukin-6, endothelin-1 and other mediators, which are well-known to precipitate acute vascular events. Lastly, non-pharmacologic strategies such as weight loss, smoking cessation and physical activity are important mediators of cardiovascular risk through their effects on glycemic control, blood pressure and lipids, and need to be considered in the overall management of patients with type 2 diabetes.

Dr. Colbourne reminded the audience that current guidelines for glycemic targets remain unchanged.

Reviewers' Comments:

Dr. Colbourne provided an excellent review of the evidence that supports currently recommended glycemic targets, reminding us that some clinical trials suggest overall increases in death rates in people with type 2 diabetes with more aggressive glycemic targets. Proteinuria and

retinopathy (microvascular diseases) may be improved by achieving normoglycemic levels, but reduction in vascular events appears to level off at A1c levels <8.5 with current medications. Some subgroups of people with diabetes may benefit from more aggressive reductions in glucose, but given the risk of increased mortality, these benefits

need to be defined by future trials. In the meantime, overall management strategies such as treatment of increased blood pressure, dyslipidemia, poor dietary habits and lack of activity, have shown remarkable reductions in death rates and this should be the clinical focus.

Atrial Fibrillation

Presented by Dr. P. Timothy Pollak, Calgary

Atrial fibrillation is a problem of aging that can result not only from diseases of valves and atrial anatomy, but more commonly from the "unholy trinity" of obesity, hypertension and obstructive sleep apnea. These three conditions have metabolic and inflammatory effects that promote cardiovascular disease, including atrial fibrillation. In the last two decades, it has been recognized that the therapy of atrial fibrillation can be greatly improved by effective anticoagulation therapies to substantially reduce the risk of stroke in these patients. While warfarin has long been the standard of care in oral anticoagulation therapy, dabigatran has recently received regulatory approval in Canada for this indication. Dabigatran offers improved efficacy over warfarin without the burden of INR testing to

A Fib – Treat the Symptoms

• Use Rate & Rhythm control to treat symptoms

Favors Rate Control	Favors Rhythm Control
Persistent AF	Paroxysmal AF
Less Symptomatic	More Symptomatic
>65 years of age	< 65 years of age
Hypertension	No Hypertension
No History of Congestive Heart Failure	Congestive Heart Failure clearly exacerbated by AF
Previous Antiarrhythmic Drug Failure	No Previous Antiarrhythmic Drug Failure



consistently maintain an adequate level of anticoagulation. Other new agents, including rivaroxaban and apixaban, are also being evaluated in this setting. Dr. Pollak provided guidance to clinicians on how these newer therapies might influence the management of atrial fibrillation.

Foremost, Dr. Pollak encouraged clinicians to systematically record the indications for therapy in individual patients. This involves making therapeutic decisions to address thromboembolic risk, cardiac function, and the patient's symptoms. Useful tools to help clinicians assess indications and risks in patients with atrial fibrillation include the CHADS2 score to estimate

the risk of stroke; HAS-BLED to quantify bleeding risk; and CCS-SAF for evaluating symptom severity. A new risk prediction tool, the CHA2DS2-VASc, may improve on the CHADS2 score by expanding the age criteria and adding vascular disease and female gender as additional risk factors, theoretically resulting in better discrimination between risk levels.

The main goals of treatment should be to prevent stroke and to "make patients feel more comfortable." This may require anticoagulation as well as both rate and rhythm control to address symptoms. New antiarrhythmic medications such as dronedarone are now available, but their use may be limited by cost and

tolerability. Other amiodarone analogues are currently under development and may offer improved tolerability. Ablation procedures for selected patients with atrial fibrillation will continue to be limited by availability of resources for next decade, but efforts are underway to make these procedures more cost-effective and easier to access.

The Canadian Cardiovascular Society's updated guidelines on atrial fibrillation were recently released and are available at www.ccsguidelineprograms.ca/index.php. European and American updates will also become available in the coming months.

Reviewers' Comments:

Dr. Pollak's summary provides an excellent overview of the subject and the potential benefits conferred through the newly available oral anticoagulant agents. Our only caution is his reference to the use of the CHA2DS2-VASc score for

predicting risk of thromboembolic events in patients with atrial fibrillation. We would remind readers that despite its recent recommendation in an update of the European Society of Cardiology Guidelines, this score has not been appropriately validated in clinical studies (Singer D, et al., 2010) and

simply expands the indications for systemic anticoagulation to women over the age of 65 years and, indeed, all patients over the age of 75 years with atrial fibrillation. While we agree that better risk prediction algorithms for stroke are needed, it is our opinion the CHA2DS2-VASc is not ready for clinical use.

REFERENCES

Singer DE, Fang MC, Go AS. CHA2DS2-VASc risk scheme. Not ready for clinical use. *Chest* 2010; doi 10.1378/chest.10-0875.

Workshops

When Two plus Two Equals Ten (or Maybe Zero): Drug Interactions for the Internist

Presented by Dr. David Juurlink, Toronto

With the vast array of drugs available today and the prevalence of polypharmacy, drug-drug interactions (DDIs) are very common and even the most diligent clinician cannot be expected to stay on top of them all. Dr. David Juurlink presented a case-based approach to dealing with the most common DDIs.

The two main types of DDIs are pharmacokinetic interactions, where one

drug increases or decreases the level of another drug; and pharmacodynamic interactions, where two drugs have similar (or opposing) clinical effects. In general, clinicians fear toxicity caused by DDIs more than the loss of clinical effect of a drug, however, both are cause for concern and can lead to negative patient outcomes. Pharmacokinetic interactions often involve the cytochrome P-450 enzymes, primarily those involving CYP 2D6, 3A4, 2C9 and 1A2, since these metabolize the majority of drugs. Dr. Juurlink recommended the following strategies to avoid DDIs:

1. Commit a short list of 'precipitant' drugs to memory: E.g., antibiotics,

SSRIs, verapamil / diltiazem, tramadol, antiretrovirals

2. Be wary in patients taking the following high-risk drugs: warfarin, digoxin, sulfonyleureas, statins, calcium channel blockers, anticonvulsants, lithium, theophylline, immunosuppressants
3. When possible, choose safer alternatives to high-risk drugs: azithromycin, beta-lactams, pravastatin / rosuvastatin, citalopram / venlafaxine
4. Use external resources: E.g., a good pharmacist, PDAs such as ePocrates or LexiDrugs, www.drug-interactions.com
5. Informed patients = safer patients

Common DDIs to be aware of:

- Glyburide + antibiotics → hypoglycemia due to inhibition of CYP 2D9
- Grapefruit juice + statins → rhabdomyolysis due to CYP 3A4 inhibition in the small intestine
- Paroxetine + codeine → loss of analgesic effect due to inhibition of CYP 2D6
- Antibiotics + codeine → profound sedation due to inhibition of CYP 3A4 and gene duplication of CYP 2D6
- Clarithromycin + digoxin → atrial fibrillation due to inhibition of p-glycoprotein
- Acetaminophen + warfarin → increased bleeding risk due to pharmacodynamic interaction AND inhibition of gamma-carboxylase
- Citalopram + tramadol → serotonin syndrome due to inhibition of CYP 2D6
- Many drugs can cause hyperkalemia in patients with renal insufficiency; usual suspects include NSAIDs, beta-blockers, salt substitutes and TMP-SMX

Reviewers' Comments:

Clinicians need to be aware that in this day and age, drug interactions are likely taking place. Many are benign however, in a patient taking multiple medications, the addition of one more drug to the mix may potentially "tip the apple cart." Therefore, clinicians must always be sure the indication for a particular drug has potential benefits in a given patient that outweigh the potential risks. The corollary also holds true: the more dangerous the drug, the more compelling the benefit should be before it is prescribed.

Both pharmacokinetic and pharmacodynamic DDIs can theoretically be overcome by altering the administration and dosing of the agent responsible for a potential interaction. One of the best ways for clinicians to avoid DDIs is to keep a short list of potentially devastating or life-threatening interactions as well as those drugs that frequently cause DDIs. DDIs are potentially serious if they can cause the following:

- Anticoagulation (bleeding risk)
- Hypoglycemia
- Hemodynamic instability (bradycardia and/or hypotension)
- Altered renal function (hyper- or

hypokalemia)

- CNS active drugs that can result in coma and/or seizure
- Clinicians should also keep in mind that certain dietary and complementary and alternative medicine agents can cause interactions (e.g., grapefruit juice, St. John's wort). Patients may not consider these agents as drugs and therefore may not inform their physicians and/or pharmacists unless specifically questioned about their use.

Late Breaking Topics in General Internal Medicine

The Risk of Hypotension Following Co-prescription of Macrolide Antibiotics and Calcium Channel Blockers

Presented by Dr. Alissa Wright, Vancouver

Macrolides and calcium channel blockers (CCBs) are among the most commonly prescribed medications. There is a potential risk of drug-drug interactions (DDIs) when these agents are co-prescribed, since many CCBs are metabolized in part by CYP 3A4 and some macrolides (clarithromycin and erythromycin, but not azithromycin) inhibit CYP 3A4. While most CYP-

mediated metabolism occurs in the liver, CYP 3A4-mediated interactions can also occur at the level of the small intestine. Inhibition of CYP 3A4 in both the liver and enterocytes has the potential to increase the amount of active drug that enters the circulation from the lumen.

Dr. Alissa Wright was an investigator in a study examining the consequences of macrolide-CCB interactions in a community-dwelling population of older individuals. A large discharge abstract database was examined for patients receiving a CCB and admitted with a diagnosis of hypotension or shock by ICD 9/10 codes. Using a case-crossover design, each subject served as both a case and his or her own control, thereby

controlling for confounding factors such as age, gender, comorbidity, etc. Clarithromycin and erythromycin were significantly more likely to be used during the risk interval (i.e., 7 days prior to hospitalization) than during a 7-day control interval (4 weeks prior to hospitalization), whereas azithromycin was found to be used equally during the risk and control intervals. Based on the known pharmacology of the drugs, these observations were likely due to the inhibition of CYP 3A4.

These observations suggest that when a macrolide is indicated in older patients who are receiving a CCB, azithromycin should be used preferentially when clinically appropriate.



Reviewers' Comments:

This is an observational study that informs physicians regarding a potentially common drug interaction between CCBs and treatment with

non azithromycin-based macrolide antibiotics. However, before a concrete recommendation such as preferential selection of azithromycin can be justified, a properly conducted randomized controlled trial is

required. This should be easy to do and would be an excellent research project for anyone anticipating a career in General Internal Medicine.

Should We Prescribe ACEI / ARB for Atherosclerotic Patients with Normal Blood Pressure?

Presented by Dr. Finlay McAlister, University of Alberta

Reduction of systolic blood pressure in hypertensive patients has been shown in large randomized controlled trials to significantly reduce the risk of coronary heart disease (CHD) and stroke. If "lower is better" for hypertensive patients, would there also be benefit to reducing blood pressure in patients with – or who are at high risk for – atherosclerosis if they are 'normotensive' (defined as <140/90 mmHg by current Canadian guidelines)?

A systematic review recently addressed this question. Primary data were evaluated from 12 placebo-controlled randomized trials that enrolled at least 1,000 subjects with or at risk of atherosclerotic

vascular disease and who were treated with an ACEi or an ARB for at least 12 months with prospective assessment for cardiovascular endpoints. Subjects were stratified by baseline systolic blood pressure (SBP) of <130 mmHg, 130-139 mmHg or >140 mmHg. The primary outcome of CV death or nonfatal MI or nonfatal stroke was significantly reduced by 13% overall (range 11-16% across the various SBP strata). The NNT to prevent one event was approximately 86 in normotensive subjects compared to 71 in hypertensive subjects.

A meta-regression was performed to evaluate whether baseline variables could predict benefit of treatment with ACEi or ARB. Results suggest that age, gender, baseline SBP, degree of SBP reduction, use of an ACEi or ARB, and trial duration had no influence on the results, and

that no matter which subgroup was considered, there was no evidence that benefits of ACEi or ARB varied by baseline SBP. There was a significant overall benefit even among subjects with a SBP <120 mmHg, however, there were too few events to adequately stratify by subgroups or component events. Benefits of ACEi or ARB treatment were apparent within 6 months and accrued over time for up to 3 years.

These results suggest that ACEi or ARB treatment is beneficial in high-risk patients with SBP in the normotensive range, and that clinicians should consider a patient's overall cardiovascular risk, cost and potential adverse effects when considering prescription of these agents, rather than basing decisions on their blood pressure alone.

Reviewers' Comments:

ACEi and ARB are the foundation upon which drug therapy for many cardiovascular diseases is based, including heart failure and diabetic proteinuria. This is not surprising given prolonged stress is bad for the cardiovascular system, and that angiotensin and catecholamines are the chief mediators of the stress response. Physicians have been using beta-blocking agents for years to prevent the negative

effects of catecholamines in non-hypertensive patients. Moreover, BP, lipids and blood glucose, to name a few, are continuous variables and do not necessary conform to our prevailing dichotomous definitions of normal and abnormal. The use of statins to lower cholesterol in 'non-hyperlipidemic' individuals at high cardiovascular risk is another cogent example where treatment of risk dominates over the presence or absence of a laboratory parameter. Therefore, as noted by Dr. McAlister,

blood pressure management is only one potential indication for the use these cardiovascular protective agents and their use in normotensive patients with high cardiovascular risk may be beneficial. Again, the data are observational and a well designed RCT is needed. The NNT, NNH, costs, potential adverse effects, and other considerations seen in such a trial would then appropriately inform physicians and their patients regarding this exciting concept.



Risk of Intraoperative Hypotension with Loop Diuretics: A Randomized Controlled Trial

Presented by Dr. NA Khan, Vancouver

Intraoperative hypotension is associated with adverse patient outcomes including a higher risk of postoperative cardiovascular events, renal dysfunction, and mortality. The POISE study demonstrated that an untitrated, high dose of a beta-blocker initiated in the immediate preoperative period increased the risk of hypotension during surgery. Other antihypertensive agents associated with a risk of intraoperative hypotension (e.g., ARBs) are now often held prior to surgery.

Dr. Nadia Khan presented the results of a placebo-controlled trial that evaluated whether loop diuretics, which have a relatively rapid onset of action and potent diuretic effects, might also induce perioperative hypotension. Secondary outcomes included the risk of in-hospital cardiovascular outcomes, renal dysfunction, and electrolyte disturbances.

The study included a heterogeneous group of 212 subjects undergoing non-cardiac elective surgery who were receiving a loop diuretic on a regular basis for the treatment of peripheral edema, hypertension, heart failure and/or renal dysfunction. All subjects were instructed to withhold their loop diuretic on the morning of surgery. Subjects were then randomized to either placebo or furosemide at a dose corresponding to their regularly scheduled oral dose of loop diuretic on the morning of surgery. Hypotension was defined as either SBP <90 mmHg for at least 5 minutes; a 35% drop in mean arterial pressure; or use of any vasopressor agent to treat hypotension.

Results showed that the risk of intraoperative hypotension was similar with furosemide or placebo. Systolic BP and mean arterial pressure were almost identical between the groups. So, too, was the use of intraoperative fluid replacement and inotropes. Among the small number of discrete secondary outcome events, there was a non-significant trend towards an increased risk of heart failure or cardiac events and a lower risk of mortality in

the furosemide group. However, the trial was not powered to detect differences in these outcomes. Other secondary endpoints were also similar between the groups, including electrolytes, markers of kidney function, and hemoglobin levels. A multivariate analysis adjusting for age, type of anesthetic, use of other antihypertensives, and medical centre, showed no significant differences between subjects receiving furosemide or placebo. Only one subgroup analysis based on the type of surgery (major versus minor) showed evidence of a significant interaction, which can credibly be attributed to the play of chance.

Dr. Khan concluded that there is no evidence to support the theoretical risk of intraoperative hypotension with the perioperative use of loop diuretics. Withholding or continuing loop diuretics did not appreciably affect intraoperative hemodynamics, vasopressor use or volume of intraoperative fluids. The study investigators will next evaluate whether ACE inhibitors or ARBs should be withheld prior to surgery.

Reviewers' Comments:

Dr. Khan and colleagues have tackled one of the many important but largely unanswered questions regarding appropriate medication management during the perioperative period. Perioperative studies, especially ones that include careful physiological assessments as outcome measures in the chaotic and time-pressed perioperative environment, are very difficult to conduct and thus the investigators are to be commended for their high-quality work. The multiple modes of assessing volume status employed by Khan et al. (outlined in more detail in the published manuscript) all provide reassurance that hemodynamic status remains relatively stable, whether furosemide is given or not.

A few deliberative comments are appropriate. First, the study is relatively

small and therefore clinically meaningful differences in both rates of intraoperative hypotension and more importantly, postoperative clinical events (whether benefit, no effect or harm) cannot be excluded. Second, among the subjects recruited to the trial, the most common indication for use of furosemide was peripheral edema (only 20% had heart failure) and the daily dose was modest (<40 mg/day). Thus, applying the results to those at greatest risk of the clinical sequelae of such a decision, for example, heart failure patients with moderate to severe LV dysfunction and lower blood pressure, may remain a tenuous judgment call because such patients may be underrepresented. Finally, we have been humbled by the complexity of the data regarding perioperative beta-blocker use, despite the publication of numerous high-quality randomized trials. As such, it is unrealistic to expect one trial to

completely answer the many variations on what first seems like a straightforward question.

The results of this study are both perplexing and reassuring, in that there is no signal of perioperative risk associated with loop diuretics that is large enough to be detected with a study of this size. However, it should be remembered that in the early days of ACEi therapy, the dreaded "first dose effect" was related to hypovolemia and activation of the renin-angiotensin system. Thus, if loop diuretics are used in combination with angiotensin blockade, there may still be a risk of perioperative hypotension with attendant organ hypoperfusion. Although there is more work to do, Dr. Khan's study is a great start. The proposed studies of perioperative ACEi/ARB will be of interest.



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