Surveying the medical literature: five notable articles in general internal medicine from 2008 and 2009

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Evidence-based medicine has been promoted as an ideal in medical practice.[1,2] Clinicians are encouraged to search the literature, to retrieve and critique articles, and ultimately to apply their conclusions to bedside decisions.[3] However, given the tremendous volume of medical literature, this is no easy task.

Here, we highlight 5 notable articles for general internal medicine published in 2008 and 2009, with summaries of their key findings and focused discussion of salient points. For each article, a clinical vignette is used to illustrate how physicians might apply the findings of the study to their own practices. We then describe the strategy we used to select the studies, along with a general approach to surveying the vast and growing medical literature for "important" papers, recognizing that the judgment of importance is both personal and subjective.

Use of beta-blockers during noncardiac surgery

Clinical vignette. A 54-year-old man is seen for preoperative medical assessment before elective total arthroplasty of the left knee. He has type 2 diabetes mellitus, which is managed with insulin therapy. He is not taking any other medications and, notably, is naive for beta-blockers. He has no known history of coronary artery disease or renal insufficiency, and his functional capacity is normal. He inquires about strategies to lower his perioperative cardiovascular risk.

Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative ß blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet* 2008;372(9654):1962–1976. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2808%2961560-3/fulltext.

Summary of findings. The balance between the benefits and harms of using beta-blockers before noncardiac surgery has long been a topic of interest for internists involved in preoperative risk assessment. To address this topic, Bangalore and colleagues performed a systematic review and meta-analysis of 33 randomized controlled trials that evaluated a total of 12 306 patients and found that beta-blockers (either given to beta-blocker-naive patients, or continued versus discontinued in trials that included patients with pre-existing beta-blocker therapy) were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality or heart failure. However, they were associated with a 35% reduction (odds ratio [OR] 0.65) of nonfatal myocardial infarction at the expense of a 101% increase (OR 2.16) in nonfatal stroke.[4] In a comparison of patients treated with beta-blockers and controls, there was an absolute reduction in the risk of nonfatal myocardial infarction of 1.7% (number needed to treat [NNT] 63) but an absolute increase in the risk of nonfatal stroke of 0.4% (number needed to harm [NNH] 275). Relative to controls, beta-blockers were also associated with a greater risk of perioperative bradycardia (NNH 22) and perioperative hypotension requiring treatment (NNH 17). Among the trials included in the analysis, the Perioperative Ischemic Evaluation Study (POISE) trial[5] carried the greatest weight. There were no sponsors for this meta-analysis.

Implication and perspectives. This study confirmed what some already suspected on the basis of the POISE trial:[5] that perioperative beta-blockade is associated with a reduced risk of myocardial infarction at the cost of an increased risk of stroke. More importantly, this study

quantified the treatment effects in absolute terms. At the population level, for every stroke incurred, more than 4 myocardial infarction events may be averted with beta-blocker therapy. The American College of Cardiology Foundation and the American Heart Association have now updated their guidelines for perioperative cardiovascular evaluation for noncardiac surgery[6] to reflect the newer data presented in this study. Absolute risk reductions (and NNTs) are, however, linked to baseline risks for specific types of events. As a result, there may not be a single overriding treatment recommendation that applies to all patients. The findings of this study may allow clinicians to more meaningfully discuss the benefits and risks of beta-blocker therapy with patients while negotiating a mutually agreeable treatment plan. There are specific patient profiles (e.g., documented coronary artery disease with a high risk of ischemic cardiac events) for which the potential benefits of beta-blockers may nonetheless be justified, even in light of this newly recognized risk of stroke.

Resolution of the clinical vignette. For most patients undergoing noncardiac surgery, current evidence does not support starting beta-blocker therapy as a strategy to lower perioperative cardiovascular risk. However, in individuals at high risk for ischemic heart disease, the benefit of beta-blockers may outweigh the risk of stroke and possible death. The patient in this vignette is estimated to have only an intermediate risk of perioperative myocardial infarction, given the planned orthopedic surgery and his history of diabetes mellitus.[6] In this context, the anticipated benefit compared to risk is probably not high enough to warrant beta-blocker therapy. However, beta-blocker therapy might be appropriate for a patient with higher risk of ischemic cardiac events.

Revascularization for renal artery stenosis

Clinical vignette. A 62-year-old woman is referred for evaluation of severe hypertension. There is ultrasonographic evidence of a small and atrophic right kidney. Her family physician suspects unilateral renal artery stenosis.

Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;361(20):1953–1962. Available from: http://content.nejm.org/cgi/content/full/361/20/1953.

Summary of findings. Atherosclerotic renovascular disease is a common condition associated with substantial risk of cardiovascular death.[7] Although treatment has traditionally centred on revascularization, this practice has been questioned.[8] The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial was designed to compare the combination of revascularization and medical therapy with medical therapy alone for the treatment of this condition.[7] This study was supported by research grants from the Medical Research Council UK, Kidney Research UK and Medtronic. In this multicentre, randomized, nonblinded clinical trial, 806 patients were followed over 5 years. The investigators found similar rates of renal deterioration, renal events (i.e., acute kidney injury, initiation of dialysis, renal transplantation, nephrectomy or death from renal failure), major cardiovascular death and all-cause mortality. Early periprocedural complications (i.e., occurring within 24 hours) were reported for 31 (9%) of the 359 patients who underwent revascularization; these included 19 serious complications (e.g., myocardial infarction, renal embolization, occlusion or perforation of the renal artery, or digital or limb amputation). Late adverse events associated with revascularization (i.e., after 24 hours but within 1 month) were reported in 55 patients (20%), and these included 12 serious complications (including 2 deaths).

Implication and perspectives. The authors of this study found no significant benefit of attempted revascularization in patients with atherosclerotic renovascular disease; rather, they reported substantial risks. The findings of the ASTRAL trial add to the evidence against combining revascularization therapy[9] with medical management for renal artery stenosis (i.e., statins, antiplatelet agents and optimal control of blood pressure). These findings indicate that the potentially harmful and costly investigations used to diagnose renal artery stenosis (e.g., computed tomography with intravenous administration of contrast agent, catheter angiography, and magnetic resonance imaging with administration of gadolinium) will not lead to an advisable treatment strategy. As such, internists should consider avoiding such investigations entirely.

Resolution of clinical vignette. This patient likely has atherosclerotic stenosis of the renal artery, complicated by hypertension. In contrast to the traditional practice of revascularization, the focus of this patient's management should be to treat modifiable cardiovascular risk factors and to optimize blood-pressure control. On the basis of this new evidence, further investigation for renal artery stenosis is discouraged.

Dabigatran for atrial fibrillation

Clinical vignette. An 80-year-old woman is receiving warfarin for atrial fibrillation. However, she struggles to maintain the international normalized ratio (INR) within the therapeutic range (between 2.0 to 3.0). She finds routine monitoring cumbersome and difficult.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151. Available from: http://content.nejm.org/cgi/content/full/361/12/1139.

Summary of findings. Dabigatran is a new oral direct thrombin inhibitor. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study group designed and performed a randomized clinical trial comparing warfarin with dabigatran (110 mg or 150 mg twice daily) for the prevention of cardioembolism in atrial fibrillation.[10] This study was supported by a grant from Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, Ont., Canada), which "independently managed the database and performed the primary data analyses."[10] Warfarin was adjusted locally to an INR of 2.0 to 3.0, and the INR was measured at least monthly. Outcomes analyzed for 18 113 participants from 44 countries demonstrated that dabigatran 110 mg twice daily was associated with rates of stroke and systemic embolism similar to those obtained with warfarin (relative risk [RR] 0.91, $p < 0.001$ for noninferiority) and lower rates of major bleeding (RR 0.80, $p = 0.003$). Dabigatran at a dose of 150 mg twice daily was associated with lower rates of stroke and systemic embolism than warfarin (absolute risk reduction [ARR] 0.58% per year, RR 0.66, $p < 0.001$ for superiority), with similar rates of major bleeding (RR 0.93, $p = 0.31$). However, the risk of hemorrhagic stroke was significantly greater among patients treated with warfarin (annual rate 0.38%) than among those treated with dabigatran at either dose (0.12% per year, RR 0.31, $p < 0.001$ with 110-mg dose, 0.10% per year, RR 0.26, $p < 0.001$ with 150-mg dose).

Implication and perspectives. Warfarin, a vitamin K antagonist, has been the cornerstone of antithrombotic therapy for patients at high risk of cardioembolism in the setting of atrial fibrillation. However, warfarin therapy is cumbersome because of its narrow therapeutic window and the associated hemorrhagic risk. As a result, frequent laboratory monitoring is required, and the patient must be cautious about potential interactions with other drugs and food. This study introduces a new treatment paradigm, with dabigatran as an alternative to warfarin for anticoagulation, and presents impressive efficacy and safety evidence favouring the new drug. The use of this oral direct thrombin inhibitor may simplify previously complex dosing regimens, and it may mitigate the need for routine monitoring. However, several issues need to be resolved before this drug can be adopted into widespread clinical practice: the balance between relative benefits and harms of the 2 doses must be determined; provincial and national approvals must be obtained; pricing must be determined to ensure affordability for the patient; and cost-effectiveness must be assessed (i.e., net costs to the system).

Resolution of clinical vignette. The physician discusses with the patient the possibility of using dabigatran, rather than warfarin, for systemic anticoagulation. However, given the uncertainty about the issues described above, this patient decides to continue her warfarin therapy for now.

Duration of anticoagulation for deep venous thrombosis

Clinical vignette. A 22-year-old female college student presents to the anticoagulation clinic for follow-up recommendations after completing 6 months of therapeutic anticoagulation for idiopathic deep venous thrombosis (DVT).

Prandoni P, Prins MH, Lensing AWA, Ghirarduzzi A, Ageno W, Imberti D, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med* 2009;150(9):577–585. Available from: http://www.annals.org/content/150/9/577.full.

Summary of findings. The optimal duration of anticoagulation after initial DVT remains unclear, and it is uncertain which patients would benefit from prolonged therapy to reduce the risk of recurrence. This Italian trial enrolled 538 consecutive outpatients with a first episode of acute proximal DVT.[11] The study had no external sources of funding. Patients initially received anticoagulation for 3 months (if they had secondary DVT) or 6 months (for unprovoked DVT). Patients were then randomly assigned to fixed-duration anticoagulation (i.e., no further treatment) or flexible-duration anticoagulation guided by ultrasonographic evidence of residual thrombi (i.e., up to 9 months for secondary DVT or 21 months for unprovoked DVT). Anticoagulation was discontinued if the veins were recanalized, as indicated by ultrasonography at 3, 9, 15 and 21 months. Outcome assessment for recurrent venothromboembolism revealed a decreased risk (adjusted hazard ratio [HR] 0.64) associated with

ultrasound-guided anticoagulation (11.9%) relative to fixed-duration anticoagulation (17.2%). Among patients with unprovoked DVT, pulmonary embolism (PE) occurred in 8 patients (5%) treated with flexible-duration anticoagulation and in 7 patients (5%) treated with fixed-duration anticoagulation. Among patients with secondary DVT, PE occurred in 1 patient (1%) treated with flexible-duration anticoagulation and 3 patients (3%) with fixed-duration anticoagulation. The occurrence of incident pulmonary embolism appeared to be similar between the groups. There were no significant differences between the groups in bleeding complications or death.

Implication and perspectives. Patients with DVT associated with transient, reversible risk factors commonly receive anticoagulation for a minimum of 3 months, and those with unprovoked DVT generally receive at least 6 months of therapy.[12] The evidence from this study suggests that ultrasonography to detect residual venous thrombosis is a powerful and promising tool to help identify which patients would benefit most from prolonged anticoagulation.[11] Future areas of research would be reconciliation of ultrasound-guided anticoagulation with increased D-dimer levels (another predictor of recurrent DVT)[13] in an evidence-based treatment strategy, assessment of the cost-effectiveness of serial ultrasonography, and determination of the optimal duration of anticoagulation therapy if recanalization is never achieved. Clearly, for clinicians adopting an ultrasound-guided approach to treatment, measures should be implemented to ensure that patients are not lost to follow-up.

Resolution of clinical vignette. For this patient, follow-up ultrasonography is ordered after 6 months of therapeutic anticoagulation to determine if there is evidence of a residual thrombus with or without recanalization. In the absence of recanalization, anticoagulation therapy should be extended, with repeat ultrasonography scheduled in another 3 months to reassess for recanalization and to determine whether anticoagulation therapy should be continued any longer.

Acetylsalicylic acid for prevention of vascular disease

Clinical vignette. A healthy 48-year-old woman has been taking low-dose, over-the-counter acetylsalicylic acid (ASA) because she read an article in a popular magazine recommending low-dose ASA toprotect against strokes and heart attacks. She asks her physician for advice.

Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373(9678):1849–1860. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2809%2960503-1/fulltext.

Summary of findings. This systematic review and meta-analysis by the Antithrombotic Trialists' Collaboration aimed to determine the benefits and risks of ASA therapy.[14] Individual-level data from 6 primary prevention trials (assessing ASA doses ranging from 100 mg to 500 mg in 95 456 patients) and 16 secondary prevention trials (17 029 patients) were analyzed to compare outcomes for ASA therapy and no ASA. The primary outcomes of interest were serious vascular events (a composite of myocardial infarction, stroke and cardiovascular death), major coronary events, stroke, all-cause mortality and major extracranial bleeding. Meta-analysis of the primary prevention trials revealed that ASA was associated with a lower rate of serious vascular events than no ASA (absolute event rate 0.51% v. 0.57% per year; NNT 1667). The rate of major bleeding was greater with ASA (absolute event rate 0.10% v. 0.07% per year; NNH 3333). ASA was associated with fewer serious vascular events when used for secondary prevention (absolute event rate 6.7% v. 8.2% per year; NNT 67) but also resulted in more bleeding (0.25% v. 0.06% absolute event rate per year; NNH 526). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation or writing of the paper. The sources of funding for each individual trial were described in the original publications. This meta-analysis was not funded.

Implication and perspectives. Although it is well established that ASA reduces the risk of thrombosis at the expense of increasing the risk of bleeding, the balance between benefit and risk was less certain before this study.[15] Here, the Antithrombotic Trialists' Collaboration provides evidence for substantial net benefit of ASA in secondary prevention, but the magnitude of benefit was less impressive for primary prevention. The balance of risks and benefits can be represented by the "likelihood of being helped versus harmed" metric (LHH, a ratio of NNH divided by NNT):[16,17] in this study, the LHH was 8 for secondary prevention and 2 for primary prevention. For every 10 000 patients treated with ASA for secondary prevention, 149 serious vascular events may be prevented at the expense of 19 major bleeding events. Conversely, among 10000 people who take ASA for primary prevention, 6 serious vascular events may be averted, but 3 major bleeding events may occur. This study

refines the estimates of treatment effects and clarifies the risk–benefit ratio for specific patient populations. The findings validate that the benefits of ASA for secondary prevention of cardiovascular events exceed the bleeding hazards, irrespective of age or sex. However, this article raises questions about the value of ASA in primary prevention.

Resolution of clinical vignette. The physician advises the patient that, given her current risk, the expected absolute benefit of ASA therapy for primary prevention is small and must be weighed against the increased risk of major bleeding. The physician concludes that, at present, there is no compelling reason that this patient should continue low-dose ASA therapy.

Surveillance for important studies

Judging importance is an invaluable skill. Various rating scales have been proposed as tools to assess the importance of published articles. For example, Lawrence and colleagues[18] proposed 6 dimensions relevant to rating the importance of articles: importance to one's own clinical practice (i.e., relevance); importance to clinical practice in general; importance from a local, national or international public health perspective; importance to the general advancement of our collective medical knowledge; ease with which the new information can be applied to current practice; and impact that the new information is likely to have on the health outcomes of those affected by, or at risk of, the disease or condition addressed by the study.

Although the concept of training clinicians to be "evidence-based practitioners" (i.e., to independently retrieve, appraise and apply best evidence) is appealing, physicians unfortunately face many recognized barriers to this approach.[19] Most notably, time constraints limit their opportunities to search and review, in real time, new information that is likely to affect decisions in clinical practice.[20–22] Moreover, many physicians admit that they lack the skills required to use literature databases and to properly appraise studies.[21–25] Guyatt and colleagues,[19] leading enthusiasts of evidence-based medicine, have acknowledged that it is unrealistic to expect all care providers to be "evidence-based practitioners" who are able to appraise raw evidence from scratch. It is, however, crucial for all providers, as "evidence users," to gain some fundamental skills in flagging important evidence and incorporating it into practice.[19]

It is estimated that most internists spend 4 to 5 hours per week reading medical articles, and that they read only the abstracts for about two-thirds of the articles they encounter.[26] It also appears that the typical internist relies on journal editors to provide rigorous and useful information.[26] As such, given internists' limited time for critical reading, there is a pattern of heavy reliance on summaries and prescreened articles, as provided by others, to survey the literature for relevant information.[19,26,27] Reassuringly, "evidence users" who refer to secondary sources for pre-appraised evidence can still become highly competent, up-to-date practitioners who are able to deliver evidence-based care.[19]

We recommend the use of evidence-based, filtered summaries of articles from selected journals (e.g., *ACP Journal Club* and ACP Journal Club PLUS [www.acpjc.org], *Evidence-Based Medicine for Primary Care and Internal Medicine* [ebm.bmj.com] and *The Cochrane Library* [http://www.thecochranelibrary.com/view/0/index.html]) for surveillance of the literature.[20,28] These secondary sources have been developed to identify studies that meet predefined criteria of importance,[18] which are then critically appraised by clinical experts. Qualifying studies are screened for relevance to a broad range of medical practices, both for generalists and specialists. These resources appear to be useful in facilitating continuing medical education and focus on identifying the most sound, most relevant and "highest-impact" studies.[28] To paraphrase Ockham's razor ("*Lex parsimoniae*"), just keep it simple.

We used these information services and considered the rating scale of Lawrence and colleagues[18] to identify the 5 notable articles published in 2008 and 2009 in the discipline of general internal medicine that we highlighted and summarized above. Although it is indisputable that the articles we selected are important, they are not necessarily the most important papers from this 2-year period. The adage that "beauty is in the eye of the beholder" holds true here, and in this instance, we (AAL and WAG) are the "beholders." The selection of these particular notable papers arises from our own personal strategies for surveillance of the literature, which are based on the principles we have outlined here. High-quality health care implies practice that is consistent with best evidence, and all providers should develop their own strategies for incorporating evidence into practice.

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