Appreciating the medical literature: five notable articles in general internal medicine from 2009 and 2010

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Funding: Alexander Leung is supported by an Alberta Innovates Health Solutions Clinical Fellowship Award and a Canadian Institutes for Health Research Fellowship Award. William Ghali is funded by a Canada Research Chair in Health Services Research and a Senior Health Scholar Award from Alberta Innovates Health Solutions.

Competing interests: William Ghali is an associate editor at *Open Medicine*; he was not involved in inviting this article for publication or deciding on its acceptance for publication. No conflict of interest reported for Alexander Leung.

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The volume of information that is presented to practitioners is increasing at an incredible pace. Addressing this, we previously described some practical surveillance strategies for providers to flag important evidence and keep up to date on the current state of medical knowledge.[1] Using these strategies, we identified five notable articles for general internal medicine published in late 2009 and in 2010. Here, we present a focused summary of these articles, supported by clinical vignettes to highlight the importance of their findings. We then reflect on the rich and ongoing advances made to the global body of medical knowledge by investigators and collaborators worldwide.

Target rate control in patients with atrial fibrillation

Clinical vignette. A 76-year-old woman with chronic atrial fibrillation receives long-term rate control with metoprolol at a dose of 50 mg b.i.d. She has a normal exercise tolerance. On examination, she is asymptomatic with a resting heart rate of 90–110 beats/minute and blood pressure (BP) of 110/70 mmHg. Should her rate control therapy be modified?

Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;362(15):1363–1373. Available from: www.nejm.org/doi/full/10.1056/NEJMoa1001337.

Summary of findings. The RACE II trial (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) was a multicentre, prospective, randomized, open-label, non-inferiority trial designed to compare two rate control strategies in patients with chronic atrial fibrillation.[2] Six hundred and fourteen (614) patients were randomly assigned to receive either a lenient rate control strategy (target resting heart rate < 110 beats/minute), or a strict rate control strategy (target resting heart rate < 80 beats/minute and < 110 beats/minute during moderate exercise). Targets were achieved in 304 of 311 patients (97.7%) in the lenient rate control group, as compared with 203 of 303 patients (67.0%) in the strict rate control group. Lenient rate control did not differ significantly from strict rate control for the primary outcome, a composite of cardiovascular mortality, hospital admission for heart failure, stroke, systemic embolism, major bleeding, and arrhythmic events at 3 years (hazard ratio [HR] 0.84; 90% confidence interval [CI] 0.58–1.21; p = 0.001 for non-inferiority). Individually, the outcomes of all-cause mortality, cardiovascular death, heart failure, bleeding, hospital admissions and adverse drug events were not statistically different between groups. However, a significant difference in stroke rates was observed in favour of lenient rate control (HR 0.35; 90% CI 0.13–0.92). The study was funded by the Netherlands Heart Foundation, AstraZeneca, Biotronik, Boehringer Ingelheim, Boston Scientific, Medtronic, Roche and Sanofi Aventis France. The authors assert that none of the sponsors was involved in the study design, data collection, data analysis or manuscript preparation.

Implication and perspectives. The results of this trial are both surprising and potentially transformative to care recommendations for atrial fibrillation. Strict rate control has been widely recommended by guidelines for the management of chronic atrial fibrillation.[3] However, with the first randomized controlled trial (RCT) on this topic, the RACE II investigators concluded that a lenient

rate control strategy was non-inferior to a strict rate control strategy in terms of important major clinical outcomes. The interpretability of the primary outcome of interest is challenging because it was a complex composite of diverse events, many of which do not directly relate to heart rate (e.g., major bleeding). Further, symptom assessment and quality-of-life measures were not included. Nonetheless, individual components relating to rate control, such as hospital admissions for heart failure, arrhythmic events and cardiovascular death were similar between the two treatment groups. The results of this well-conducted study should guide clinical management. Lenient rate control appears to be an advisable treatment strategy for the majority of asymptomatic patients with chronic atrial fibrillation. In contrast, strict rate control may be inconvenient and undesirable for some patients and providers because of the frequent outpatient examinations required to achieve targets, the potential increased risk of medication-related side effects, and the possible increased risk of stroke. Finally, although the results of this study pertain to the management of chronic atrial fibrillation, they might not necessarily apply to patients with new-onset atrial fibrillation.

Resolution of clinical vignette. In the absence of symptoms, the findings of this trial suggest that no changes should be made to this patient's medication list, whereas the prior approach would have been to increase her dose of metoprolol. Therefore, she continues on her current dose of metoprolol to maintain a resting heart rate of < 110 beats/minute.

Preventing surgical-site infections in carriers of S. aureus

Clinical vignette. A recent local hospital-wide audit reveals that 18% of admitted patients are nasal carriers for methicillin-sensitive *Staphylococcus aureus*, and the prevalence of *S. aureus*–associated nosocomial infections is reported to be as high as 10%. Hospital infection control practitioners wonder whether anything can be done to address these challenges.

Bode LG, Kluytmans JA, Wertheim HF, Bogaers D, Vandenbroucke-Grauls CM, Roosendaal R, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010;362(1):9–17. Available from: www.nejm.org/doi/full/10.1056/NEJMoa0808939.

Summary of findings. Bode and colleagues conducted a randomized, placebo-controlled trial across 5 hospitals in the Netherlands, evaluating the benefit of targeted decolonization in preventing *S. aureus*–associated nosocomial infections.[4] Nine hundred and seventeen (917) participants were identified after 6771 patients were screened for the presence of *S. aureus* by real-time polymerase chain reaction assay. They were then randomly assigned to receive active treatment (with 2% mupirocin nasal ointment applied twice daily in combination with chlorhexidine soap for daily total-body wash), or double placebo for a total treatment course of 5 days with repeated treatments, if necessary, for longer hospital stays at 3 and 6 weeks. Participants were followed for 6 weeks after discharge. The cumulative incidence of hospital-associated *S. aureus* infections was significantly lower in the mupirocin-chlorhexidine group than in the placebo group (absolute event rates 3.4% v. 7.7%; relative risk [RR] 0.42; 95% CI 0.23–0.75; number needed to treat [NNT] 23) with no significant difference between surgical and nonsurgical patients after adjustment. Treatment with mupirocin-chlorhexidine versus placebo was associated with fewer infections from endogenous sources, as determined by molecular typing (RR 0.39; 95% CI 0.20–0.77), fewer deep surgical site infections (RR 0.21; 95% CI 0.07–0.62), and shorter hospital stays (mean 12.2 days v. 14.0 days; $p = 0.04$). The study was inadequately powered to detect a significant difference in mortality. This study was supported by grants from ZonMw, Mölnlycke Health Care, GlaxoSmithKline, Roche, bioMérieux and 3M. The authors assert that the sponsors did not influence the study design, data collection, analysis or writing of the manuscript.

Implication and perspectives. Bode and colleagues introduce a novel hospital-care paradigm with tremendous potential for reducing rates of *S. aureus*–associated nosocomial infections. The strength of association and magnitude of benefit reported with this intervention are impressive. However, several issues remain unresolved: can the results of this study be generalized to populations with a greater prevalence of methicillin-resistant *S. aureus*; will nonselective decolonization be effective against non–*S. aureus* pathogens; and, is targeted decolonization cost effective? This study is likely to inspire further patient-safety research to inform policy-makers and providers.

Resolution of clinical vignette. A hospital-wide protocol for targeted decolonization of nasal carriers of *S. aureus* is considered for the hospital in question, although site administrators agree that an analysis of the local cost implications and potential savings is needed.

Systolic blood pressure targets in patients with type 2 diabetes

Clinical vignette. A 45-year-old man with type 2 diabetes and hypertension is seen in follow-up. He has no evidence of renal disease. His blood pressure medications are ramipril 2.5 mg b.i.d. and amlodipine 5 mg q.d. He denies any side-effects from treatment. On examination, he has a BP of 128/74 with no postural change. His physician ponders whether his BP is on target.

ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362(17):1575–1585. Available from: www.nejm.org/doi/full/10.1056/NEJMoa1001286.

Summary of findings. The ACCORD BP trial (Action to Control Cardiovascular Risk in Diabetes blood pressure) was an open-label, randomized controlled trial conducted at 77 centres in the United States and Canada, involving 4733 patients with type 2 diabetes and hypertension.[5] Participants were randomly assigned to receive intensive antihypertensive therapy with a target systolic BP < 120 mmHg (2362 patients) or standard therapy with a target systolic BP < 140 mmHg (2371 patients). Mean blood pressures achieved at 1 year were 119 mmHg and 134 mmHg in the intensive and standard control groups, respectively, and these levels were maintained throughout the trial. Intensive therapy and standard therapy were similar for the primary outcome, a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (absolute event rates 1.87%/year v. 2.09%/year; HR 0.88; 95% CI 0.73–1.06; $p = 0.20$) with a mean follow-up of 4.7 years. No statistical difference was observed in the individual rates of nonfatal myocardial infarction, major coronary disease, heart failure or death. However, a significant reduction in stroke was reported with intensive therapy v. standard therapy (HR 0.59; 95% CI 0.39–0.89; $p = 0.01$; NNT 95). Patients receiving intensive control were more likely to have serious adverse drug events ($p < 0.001$), hypokalemia ($p < 0.01$) and elevated creatinine levels ($p < 0.001$), but less macroalbuminuria ($p = 0.009$). The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Drugs were donated by Abbott Laboratories, AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, King Pharmaceuticals, Sanofi-Aventis U.S. and Novartis Pharmaceuticals. Sphygmomanometers were donated by Omron Healthcare. The authors assert that these companies had no role in the design of the study, the accrual or analysis of the data or the preparation of the manuscript.

Implication and perspectives. High-quality evidence to support existing recommendations to target systolic BP < 130 mmHg for patients with diabetes is lacking.[6,7] Although ACCORD BP does not conclusively determine the optimal systolic BP target for patients with diabetes, its results are nonetheless informative. This study was the first rigorously conducted trial to compare two different BP treatment strategies in patients with diabetes at high cardiovascular risk, and found that intensive antihypertensive therapy did not significantly reduce a composite of major adverse cardiovascular events more than standard therapy.[5] However, these conclusions must be interpreted with caution. First, the trial was designed to detect a 20% reduction of the rate of the primary composite outcome in the intensive-therapy group compared with the standard-therapy group, assuming an event rate of 4% per year among those receiving standard therapy. In fact, the observed event rate was almost 50% lower than expected among those receiving standard therapy. Consequently, the reduced power (resulting in relatively wide confidence intervals) does not exclude a 12% relative risk reduction for the primary outcome. Moreover, follow-up beyond 5 years may be needed to observe a significant cardioprotective benefit, as seen in other antihypertensive trials. Second, the statistically significant 41% relative risk reduction reported for strokes in those receiving intensive therapy is neither clinically insignificant nor inconsequential. Therefore, it is important to emphasize that, although this trial was inadequately powered to detect a significant reduction in composite cardiovascular events, intensive BP control lowers stroke risk at the expense of more serious adverse drug events. Accordingly, when applying this evidence to the bedside, providers need to weigh the benefits and risks of intensive therapy according to individualized risks and patient preferences.

Resolution of clinical vignette. Although this trial's results leave some questions unanswered, the findings still point to some potential benefit for tight blood pressure control, particularly in patients such as this one, for whom drug dosages are modest and there are no medication side-effects relating to current therapy. Therefore, this patient's dosage of ramipril is increased to 5 mg b.i.d. in an effort to lower his blood pressure further and reduce future risk of ischemic stroke. The patient is agreeable to this plan, as he is currently free from medication-related side-effects.

Use of fluvastatin in patients undergoing vascular surgery

Clinical vignette. A 52-year-old man with severe, symptomatic peripheral arterial disease is seen in the preoperative assessment clinic in preparation for a femoral popliteal bypass scheduled in 6 weeks. He takes low-dose acetylsalicylic acid and metoprolol. He inquires about other strategies to lower his perioperative cardiovascular risk.

Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, et al. **Fluvastatin and perioperative events in patients undergoing vascular surgery.** *N Engl J Med* 2009;361(10):980–989. Available from: www.nejm.org/doi/full/10.1056/NEJMoa0808207.

Summary of findings. This Dutch study was a randomized placebo-controlled trial of 497 patients scheduled for vascular surgery, designed to evaluate the benefit of perioperative fluvastatin in reducing the incidence of cardiac events.[8] Patients were randomly assigned to receive either 80 mg of extended-release fluvastatin, or placebo (median 37 days before surgery); those not already receiving beta-blocker therapy were also started on bisoprolol 2.5 mg once daily at the time of randomization. Treatment was continued for at least 30 days postoperatively. Patients receiving fluvastatin v. placebo had a decreased risk of myocardial ischemia, as defined by transient ischemic changes on electrocardiogram, elevation of troponin T, or both (absolute event rates within 30 days of surgery 10.8% v. 19.0%; HR 0.55; p = 0.01; NNT 12), and a decreased risk for the composite outcome of cardiovascular death and myocardial infarction (absolute event rates within 30 days of surgery, 4.8% v. 10.1%, HR 0.47; p = 0.03; NNT 19). There were no reports of myopathy or rhabdomyolysis in either group. This study was supported by unrestricted grants from Novartis, the Netherlands Organization for Health Research and Development, the Erasmus Medical Center, Stichting Lijfen Leven and the Netherlands Heart Foundation. The authors assert that none of the funding sources had a role in the design or conduct of the trial, analysis of data or reporting of the results.

Implication and perspectives. The findings of this study strengthen existing recommendations for perioperative statin therapy for patients undergoing vascular surgery who are at high risk for cardiac complications.[9] This study offers RCT evidence for the benefit of statin therapy over and above concomitant beta-blockade in the setting of vascular surgery. Although a significant proportion of patients with peripheral arterial disease will already be on statins given the demonstrated benefits from long-term statin therapy in such patients,[10] this trial calls attention to the relatively short-term, but important, benefits of perioperative treatment. Therefore, scheduled preoperative encounters with patients prior to planned vascular surgeries may provide meaningful opportunities for clinicians to improve perioperative and long-term outcomes with a simple intervention, especially for those not already on existing statin treatment. Although these findings can likely be generalized to all statins, further research is required to define the optimal time to initiate statin therapy in the preoperative setting.

Resolution of clinical vignette. In the absence of any contraindications to statin therapy, this man is started on fluvastatin 80 mg once daily preoperatively in addition to his current medications and is continued on long-term statin therapy.

The use of A1C for the screening and diagnosis of type 2 diabetes

Clinical vignette. A 68-year-old man is referred for interpretation of laboratory blood tests performed by his family physician. He has a single fasting plasma glucose measurement of 5.2 mmol/L and a hemoglobin A1C of 6.4%.

Lu ZX, Walker KZ, O'Dea K, Sikaris KA, Shaw JE. **A1C for screening and diagnosis of type 2 diabetes in routine clinical practice.** *Diabetes Care* 2010;33(4):817–819. Available from: http://care.diabetesjournals.org/content/33/4/817.full.

Summary of findings. Lu and colleagues evaluated the use of A1C as a screening and diagnostic tool for type 2 diabetes in a clinic-based cohort of 2494 patients from Melbourne, Australia, and a population-based cohort of 6015 patients derived from the national AusDiab study.[11] A1C levels were standardized to Diabetes Control and Complications Trial (DCCT)–aligned values. All participants concurrently received an oral glucose tolerance test (OGTT) as the gold standard diagnostic test and were classified according to the American Diabetes Association (ADA) criteria for the presence or absence of diabetes.[12] Among patients without diabetes in the clinic-based cohort, A1C levels of 5.6% and 6.9% corresponded to the 2.5th and 97.5th percentiles, respectively. Thus, an A1C ≤ 5.5% was identified as a strong threshold for "ruling out" diabetes, and ≥ 7.0% for "ruling in"

(i.e., diagnosing) diabetes. When applied to both study cohorts, these two cutoffs were associated with moderate to high sensitivities (83.5% and 97.8%), high specificities (98.2% and 100%), high negative predictive values (NPV) (95.8% and 99.0%), and high positive predictive values (PPV) (92.9% and 100%). In contrast, when various A1C cutoffs were tested, a value of 6.2% was found to be the single most discriminating cut-point, and associated with a sensitivity of 82.2%, specificity of 78.8%, NPV of 89.3%, PPV of 67.2%, positive likelihood ratio (LR+) of 3.9, and negative likelihood ratio (LR–) of 0.2. Although no direct funding was reported for this study, funding sources for the original AusDiab study were clearly disclosed in the original publication.[13]

Implication and perspectives. For decades, the diagnosis of diabetes has been based on conventional glucose measurements.[12] However, current evidence supports the use of A1C as an acceptable and convenient alternative. Here,[11] Lu and colleagues uniquely demonstrated that the use of two A1C cutoffs offered superior diagnostic characteristics compared to a single cutoff of 6.5% as recommended by the International Expert Committee and the ADA guidelines.[12,14] Importantly, this study highlights that A1C values > 5.5% are associated with escalating risks for impaired fasting glucose, impaired glucose tolerance, and diabetes. These findings are in broad agreement with other reports that describe similar gradients of increasing risk for diabetes, microvascular and macrovascular complications, and all-cause mortality associated with increasing A1C.[15,16] Although it appears that A1C cutoffs of ≤ 5.5% and ≥ 7.0% accurately rule out and rule in diabetes, respectively, individuals with "impaired" A1C levels between 5.5% and 7.0% should also be considered to be at risk for dysglycemia and its associated complications.

Resolution of clinical vignette. Strictly speaking, this patient does not meet the current criteria for the diagnosis of diabetes because his A1C is below 6.5%.[12] However, his A1C level is above the optimal discriminating threshold of 6.2%. Thus, some experts may still consider him to have diabetes on that basis. Others, however, would point out that, regardless of where he sits relative to the proposed thresholds that dichotomize diabetes into two discrete groups (yes v. no), the patient has an abnormal glucose metabolism and is at a higher risk for developing associated microvascular and macrovascular complications. Therefore, he is referred for a 75-g oral glucose tolerance test and, regardless of its result, receives attentive lipid and blood pressure assessments and management. He is also provided with appropriate advice for lifestyle modification.

Marvelling at advances in medical knowledge

This is truly an exciting era! We are witnessing unprecedented growth in scientific discovery and an impressive uptake of new knowledge. Indeed, the medical research community is highly productive and vibrant.

In particular, the introduction of clinical trials and evidence-informed medicine has resulted in a vast wealth of medical literature. The first randomized clinical trial in 1948, which compared streptomycin with placebo in the treatment of pulmonary tuberculosis, left a legacy through which subsequent clinical trials were conducted,[17,18] providing much of the rational evidence for current treatment policies. Further, the widespread adoption of trial results into clinical practice has resulted in an exponential growth in the number of clinical trials being conducted worldwide. Various trial registries have been established to facilitate accessibility, improve research transparency and ultimately strengthen the global scientific evidence base (e.g., clinicaltrials.gov, isrctn.com and controlled-trials.com). There are now impressively over 100 000 trials registered to *ClinicalTrials.gov* alone.

The tremendous productivity in the research community is the result of the incredible work of diligent investigators, inquisitive minds posing practice-changing questions (e.g., Is strict rate control optimal for patients with permanent atrial fibrillation? — a truly important yet basic question that, intriguingly, has only been posed now, well into the 21st century after decades of therapy provided by practitioners in a void of evidence), and the emergence of hybrid funding strategies to support intensive investigation (through a combination of government agencies, industry, charitable foundations and philanthropic donations). Also importantly, proponents of evidence-informed medicine have been instrumental in the promotion of information uptake through education, the dissemination of literature, and the creation of knowledge repositories. With the continual flow of new information, we gain greater insights into medicine, refine our practices, and explore new paradigms of care.

Finally, although the five articles that we have highlighted here are indisputably important, we would be remiss not to emphasize that countless other high-quality and important articles were published during the period covered by our selection. All users of evidence are greatly indebted to the many investigators who have facilitated

the growth of medical knowledge through the publication of their research. Their work will certainly save lives and enhance care, and we should all applaud them for their impressive work.

Contributors: Both authors contributed to the drafting and revision of the manuscript and read and approved the final manuscript for publication.

Acknowledgments. This is an invited review based on a plenary presentation entitled "Top 5 Articles in General Internal Medicine 2009/2010" given by Dr. W.A. Ghali at the Annual Scientific Meeting of the Canadian Society of Internal Medicine (CSIM) and the Rocky Mountain Chapter of the American College of Physicians (ACP) on 28 October 2010.

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Citation: Leung AA, Ghali WA. Appreciating the medical literature: five notable articles in general internal medicine from 2009 and 2010. *Open Med* 2011;5(1):e49-e54

Published: 8 March 2011.