Reviewing the medical literature: five notable articles in general internal medicine from 2010 and 2011

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➢ **Medicine is confronting an information explosion,** an incredibly "rapid increase in the amount of information available."[1] Although this vast wealth of knowledge has indisputably benefited medical care, it can be difficult to stay abreast of the large volume of information published in both the peer-reviewed and grey literature. Practical strategies to organize the swelling tide of medical literature are essential for providers to recognize and incorporate new information into practice.

One strategy for managing new information is the traditional annual review, in which selected, appraised articles are presented for general consumption.[2,3] Here, we present five notable articles for general internal medicine published from 1 Sept. 2010 to 31 Aug. 2011, with focused summaries of their key findings and supporting clinical vignettes to highlight their significance.

Methods

A hand-search was performed (by CvW) of all manuscript titles and abstracts for primary studies published between 1 Sept. 2010 to 31 Aug. 2011 in the *New England Journal of Medicine,* the *Journal of the American Medical Association*, the *Annals of Internal Medicine*, the *Archives of Internal Medicine*, the *Canadian Medical Association Journal*, the *British Medical Journal*, and *The Lancet*. These seven highly cited general medical journals were chosen on the basis of their broad readership, general visibility, and established reputation for publishing important and high-quality articles. After a preliminary screen, 42 studies were identified as having very significant potential for influencing current practice or policy. Of these, five notable articles were selected on the basis of a combination of factors, including the quality of the study, the prevalence of the medical issue addressed by the study, and the study's possible impact on current treatment paradigms, diagnostic strategies, or health care policy. Similar criteria have previously been proposed to rate the importance of articles.[4] It should be noted that our literature search was conducted by means of a single-person review and that the final selection of articles was based on subjective criteria.

1 Renal ultrasonography for patients with acute kidney injury

Clinical vignette. A 52-year old white woman is admitted to hospital with a 5-day history of nausea, vomiting, and diarrhea. Her past medical history is unremarkable, and she takes no medications. Physical examination is consistent with hypovolemia. Investigations reveal an elevated serum creatinine of 179 μmol/L (with a baseline of 70 μmol/L) and a bland urinalysis. The admitting hospitalist inquires whether renal ultrasonography (RUS) should be ordered for further investigation of acute kidney injury (AKI).

Licurse A, Kim MC, Dziura J, Forman HP, Formica RN, Makarov DV, et al. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. *Arch Intern Med* 2010;170(21):1900–1907. Available from: http://archinte.ama-assn.org/cgi/content/full/170/21/1900

Summary of findings. Licurse and colleagues designed and validated a clinical prediction rule to identify, among patients admitted to hospital with AKI, those who are at low risk of hydronephrosis.[5] This cross-sectional study was conducted at the Yale–New Haven Hospital,from January 2005 to May 2009. A total of 997 patients were assembled by searching through the local imaging database for RUS studies performed on adult inpatients with AKI. Patients were excluded if they were pregnant, had a history of renal transplant, or had a diagnosis of

hydronephrosis in the preceding 30 days. Data from the 200 derivation subjects (a sample consisting of 100 patients with hydronephrosis and another 100 patients without this condition) were used to fit a multivariable prediction model. Seven independent risk factors associated with hydronephrosis were identified; these were assigned scores that were tallied to estimate an individual's risk for hydronephrosis (see Table 1). Three distinct risk groups for hydronephrosis were defined: low risk (< 2 points, 1%–20% prevalence), medium risk (3 points, 20%–40% prevalence), and high risk (> 3 points, > 40% prevalence).

The prediction rule was then applied to 797 subjects from the validation cohort. Classifying patients as low-risk vs mid- and high-risk, the prediction model had a sensitivity of 91.8% (95% confidence interval [CI] 89.9%–93.7%), a specificity of 30.3% (95% CI 27.2%– 33.5%), and a negative likelihood ratio of 0.27 for hydronephrosis. For the outcome of hydronephrosis requiring intervention (i.e., placement of a urologic stent or nephrostomy tube), the sensitivity increased to 96.3% (95% CI 94.9%–97.6%), with a specificity of 28.8% (95% CI 25.7%–32.0%), and a negative likelihood ratio of 0.13. Incidental findings on RUS unrelated to hydronephrosis were rare, and none of these were found in low-risk patients.

This study received no industry funding.

Table 1
Clinical prediction rule for hydronephrosis*

Risk factor	Points
History of hydronephrosis †	High risk
Recurrent urinary tract infections	1
Diagnosis consistent with possible obstruction‡	1
Non-black race	1
Absence of inpatient nephrotoxic medication§ exposure	1
Absence of congestive heart failure	1
Absence of pre-renal acute kidney injury¶	1

* Adapted from Licurse et al. (2010)[5]

† History of hydronephrosis (defined as any documented history of hydronephrosis or any imaging history of hydronephrosis in the previous 2 years) places patient in high-risk category.

‡ Includes benign prostatic hyperplasia, abdominal or pelvic cancer, neurogenic bladder, single functional kidney, or previous pelvic surgery.

§ Defined as acetylsalicylic acid (> 81 mg/d), diuretic, angiotensin-converting enzyme inhibitor, or intravenous vancomycin

¶ Definition of prerenal acute kidney injury based on history of sepsis or use of vasopressors during current hospital admission in the primary model.

Implication and perspectives. Although RUS is safe, noninvasive, and widely available, the indiscriminate use of this test may not necessarily be cost-effective or beneficial. The results of this study help rationalize the diagnostic workup for AKI by identifying patients at low risk of obstruction, therefore conserving some resources without compromising patient care. Although the study population was limited to patients undergoing RUS (a sample enriched with cases of obstruction), the resulting prediction model would be expected to be even more successful at excluding hydronephrosis in unselected populations with AKI (among whom the expected prevalence of obstruction would be lower).

Although the results of this carefully designed study are useful and readily applied to patient care, two important issues remain: first, although the model predicts hydronephrosis requiring intervention, the investigators limited this definition to surgical procedures, thus overlooking important nonsurgical approaches to obstruction (e.g., placement of urinary catheters, discontinuation of anticholinergic drugs, etc.); second, although the results of this study may guide the initial workup of AKI in most patients, clinical judgment should still be used as the evaluation of AKI is a complex and nuanced process based on clinical factors that cannot be captured fully with a simple scoring system alone.

Resolution of clinical vignette. History, examination, and preliminary investigations suggest a pre-renal cause for this patient's AKI. Moreover, the proposed prediction rule suggests that she is at low risk for post-renal obstruction. As such, the admitting physician and patient decide to forgo RUS until other reasonable conservative measures (e.g., adequate volume expansion) are tried first.

2
Risk of recurrence after a first seizure

Clinical vignette. A 32-year-old man is seen in clinic for follow-up after his first unprovoked seizure 6 months earlier. Investigations, including serum chemistries, electroencephalography (EEG), and computed tomography of the brain were unremarkable. He has been free of seizures since then and has not been on any antiepileptic treatment. He asks when he will be able to safely resume driving.

Bonnett LJ, Tudur-Smith C, Williamson PR, Marson AG. Risk of recurrence after a first seizure and implications for driving: further analysis of the Multicentre study of early Epilepsy and Single Seizures. *BMJ* 2010;341:c6477. Available from: www.bmj.com/content/341/bmj.c6477?view=long&pmid=21147743

Summary of findings. Bonnett and colleagues performed a secondary analysis of the Multicentre study of early Epilepsy and Single Seizures (MESS), a randomized

controlled trial conducted from January 1993 to December 2000. MESS determined the effect of early treatment with anti-epileptic drugs compared with no (or delayed) treatment after an unprovoked seizure.[6] This present analysis involved 637 participants aged 16 years and older (i.e., of driving age) without previous anti-epileptic treatment or progressive neurological disease. The authors sought to identify clinical characteristics independently associated with time to recurrent seizure, reporting this model as the probability of recurrent seizure over the next year at various times during follow-up. The final multivariable model included the following variables: a remote symptomatic etiology (i.e., seizure caused by remote disease or event such as head injury, meningitis, encephalitis, or intracranial disease), history of epilepsy in a first-degree relative, seizures only occurring while asleep, EEG showing epileptiform activity with focal or generalized spikes or spike and slow wave activity, neuro-imaging results, and whether the patient initially received anti-epileptic therapy. Estimates of seizure recurrence risk for all possible combination of risk factors from the subgroup analyses are published online (see web appendix, available from www.bmj.com/highwire/filestream/446798/field_highwire_adjunct_files/0).

This study received no industry funding.

Implication and perspectives. There is a dearth of medical evidence to guide clinicians on the risk of seizure recurrence after a first unprovoked seizure. Consequently, existing guidelines have been informed largely by expert opinion and differ widely around the world.[7–9] Importantly, Bonnett and colleagues address a subject with substantial knowledge gaps and present findings that have considerable implications for public policy. The investigators suggest that the study's subgroup analyses provide guidance on individualized risk, and the unadjusted results are informative at the population level.

However, these data should be applied with caution. First, this model has not been externally validated. Second, relying on the seizure-free interval as the sole determinant of driving fitness—one of the most important utilities of such models—may be misleading, since other factors not included in this model (such as the presence of auras and previous driving history) have been reported as important predictors of seizure-related crashes.[10] In addition, the seizure-free interval has not been shown to be related to seizure-related crashes,[11] or to crash fatalities.[12] Therefore, although estimating seizure recurrence risk is indisputably important, this study is limited by the absence of data on motor vehicle collisions (seizure-related or otherwise). Any attempt to apply the results of this study to policy should balance the issues of public safety with individual factors.

Resolution of clinical vignette. On the basis of the study's findings, this patient is reassured that his risk of seizure recurrence in the next 12 months is low. The decision regarding when he may resume driving again should be determined according to national, provincial, or state regulations. For instance, Canadian guidelines recommend that this man should be seen 12 months after his initial seizure to re-evaluate his ability to drive, conditional on him remaining seizure-free with no further signs of epileptiform activity.[9] In contrast, the Driving and Vehicle Licensing Agency in the United Kingdom suggests that he may resume driving now (6 months after his first seizure) because his risk of recurrence is less than 20% in the coming year.[6,13]

3
Cardiac-resynchronization therapy for mild to moderate heart failure

Clinical vignette. A 66-year-old man with heart failure resulting from ischemic cardiomyopathy reports difficulty climbing two flights of stairs because of shortness of breath despite receiving optimal medical therapy. An electrocardiogram confirms a sinus rhythm with a prolonged QRS duration, and a recent echocardiogram revealed an impaired left-ventricular ejection fraction (LVEF) of 25%–30%. He is referred to the heart function clinic to discuss further treatment options.

Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363(25):2385–2395. Available from: www.nejm.org/doi/full/10.1056/NEJMoa1009540

Summary of findings. The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) was a multicentre, double-blinded, randomized controlled trial that enrolled 1798 patients with NYHA class II or III heart failure, a LVEF of ≤ 30%, and a prolonged QRS (i.e., intrinsic duration of ≥ 120 msec, or paced duration of ≥200 msec).[14] In addition to receiving optimal medical therapy, participants were randomly assigned to receive either an implantable cardioverter-defibrillator (ICD) alone (904 patients) or an ICD with cardiac resynchronization therapy (CRT) (894 patients). After a mean follow-up of 40 months, patients in the ICD-CRT group did significantly better with regard to death or hospital admission for heart failure (hazard ratio [HR] 0.75, 95% CI

0.64–0.87, $p < 0.001$), all-cause mortality (ICD-CRT 28.6%; ICD 34.6%; HR 0.75, 95% CI 0.62–0.91, $p = 0.003$), and hospital admission for heart failure (ICD-CRT 19.5%; ICD 26.1%; HR 0.68, 95% CI 0.56–0.83, $p < 0.001$). For the primary outcome, predefined subgroup analyses suggested that ICD-CRT therapy may be more effective in patients with QRS durations ≥ 150 msec (HR 0.59, 95% CI 0.48 to 0.73, $p = 0.003$ for interaction). Patients receiving combination ICD-CRT were more likely to have device-related hospital admissions during the course of the study (20.0% vs 12.2%, $p < 0.001$) and device-related complications within the first 30 days after implantation (13.3% vs 6.8%, $p < 0.001$).

This trial was sponsored by the Canadian Institutes of Health Research and Medtronic of Canada. The latter provided the CRT components but had no role in the conduct of the study, the reporting of the data, or the decision to publish the study results.

Implication and perspectives. In recent decades, the use of pharmacological therapy and medical devices has expanded rapidly to improve the prognosis for patients with heart failure.[15,16] Until now, however, there has been no evidence that CRT confers additional survival benefit when combined with ICD therapy. The results of this trial are particularly important, since most patients who have NYHA class II or II heart failure, impaired LVEF, and widened QRS duration would be suitable candidates for ICD implantation;[17] thus, demonstrating that the combination of ICD with CRT improves survival beyond ICD alone is potentially transformative to routine care. The magnitude of benefit of combination ICD-CRT reported in this rigorously designed study are impressive and clinical relevant. Over 5 years, the number needed to treat (NNT) to prevent 1 death was 14, and the NNT to prevent 1 hospital admission related to heart failure was 11. Although the results were positive overall, the risks of device implantation and its associated complications are not inconsequential (with a number needed to harm of 16). Accordingly, the decision for device implantation should be based on individualized risks and patient preferences after the benefits and risks are weighed.

Resolution of clinical vignette. Although this patient already meets established eligibility criteria for ICD placement for the primary prevention of sudden cardiac death,[17] the results of this study further support the use of CRT in addition to ICD and optimal medical therapy. After the potential risks and expected benefits of implantation are explained to him, the patient consents to ICD-CRT therapy and is listed for device implantation.

4
Apixaban versus warfarin in patients with atrial fibrillation

Clinical vignette. An 82-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 and 3.0). She finds routine monitoring cumbersome and difficult.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981–992. Available from: www.nejm.org/doi/full/10.1056/NEJMoa1107039

Summary of findings. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) investigators designed and performed a multicentre, double-blinded, randomized controlled trial comparing apixaban with warfarin (adjusted to an INR of 2.0 to 3.0) for the prevention of stroke or systemic embolism in the setting of atrial fibrillation.[18] Anticoagulation control in the warfarin group was excellent, with a median time in therapeutic range of 66%. Outcomes analyzed for 18 201 participants from 39 countries demonstrated that apixaban was superior to warfarin in preventing the composite of strokes and systemic embolism (HR 0.79, 95% CI 0.66–0.95, $p = 0.01$), all-cause mortality (HR 0.89, 95% CI 0.80–0.99, $p = 0.047$), and major bleeding (HR 0.69, 95% CI 0.60–0.80, $p < 0.001$). The findings for the primary composite outcome was driven mainly by the large and significant reduction in hemorrhagic stroke rates among apixaban recipients (HR 0.51, 95% CI 0.35–0.75, $p < 0.001$). Liver enzyme abnormalities were similar between the two treatment groups.

This study was supported by Bristol-Myers Squibb and Pfizer. The industry sponsors participated in the design and conduct of the trial, as well as in the reporting of the results. Data analyses were performed at Bristol-Myers Squibb and the Duke Clinical Research Institute.

Implication and perspectives. We have entered a new and exciting era for anticoagulation. In the last several years, novel therapies have emerged as viable alternatives to warfarin for the prevention of cardioembolism among patients with atrial fibrillation. Although warfarin is highly effective at preventing stroke in patients with atrial fibrillation, only about half of patients who would actually benefit from therapy actually receive treatment.[19] Barriers to successful use include its narrow therapeutic window, the associated hemorrhagic

risk, the need for frequent laboratory monitoring, and the plethora of drug-drug and drug-food interactions. In contrast, the new pharmacologic options are potentially safer and more convenient. Notably, the largely positive findings from the trials evaluating apixaban, dabigatran, and rivaroxaban (in comparison with warfarin) have all been driven by impressive reductions in hemorrhagic stroke.[18,20,21] Somewhat surprisingly, only higher-dose dabigatran, when compared with warfarin, has been reported to reduce the risk of ischemic stroke.[21] Although all three drugs appear to have more favourable bleeding profiles in comparison with warfarin,[18,20,21] antidotes are not yet available, which poses problems in the setting of life-threatening hemorrhages or emergency surgeries. Although the general conclusions reached in ARISTOTLE are broadly similar to those of previous trials, this study was uniquely powered to detect a mortality benefit with apixaban,[18] whereas previous studies evaluating dabigatran and rivaroxaban have reported only non-significant trends.[20,21] Although the original task may have been to replace warfarin with a non-inferior alternative, ARISTOTLE boasts that apixaban may be even better.

Resolution of clinical vignette. The physician discusses with the patient the possibility of using a novel oral anticoagulant, rather than warfarin, for systemic anticoagulation, particularly in light of the convenience, safety, and efficacy profiles of these new drugs.

5
Simvastatin and ezetimibe in patients with chronic kidney disease

Clinical vignette. A 68-year-old man with chronic kidney disease and hypertension is referred for cardiovascular risk assessment. His current medications include acetylsalicylic acid 81 mg daily, ramipril 5 mg twice daily, and amlodipine 10 mg daily. Examination is unremarkable, with a blood pressure of 110/70 mmHg. Laboratory investigations reveal a stable creatinine of 180 μmol/L, LDL cholesterol of 2.97 mmol/L, and a urinary albumin-to-creatinine ratio < 30 mg/g.

Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011 25;377(9784):2181-92. Available from: www.sciencedirect.com/science/article/pii/S0140673611607393

Summary of findings. The Study of Heart and Renal Protection (SHARP) was a double-blinded, randomized controlled trial designed to assess the safety and efficacy of reducing LDL cholesterol in 9270 patients with chronic kidney disease.[22] Patients were randomly assigned to receive simvastatin 20 mg daily plus ezetimibe 10 mg daily (4650 patients) vs double-placebo (4620 patients). Over the median follow-up of 4.9 years, the combination of simvastatin and ezetimibe resulted in an average LDL cholesterol reduction of 0.85 mmol/L and a 17% relative risk reduction in the primary outcome of major atherosclerotic events (11.3% simvastatin plus ezetimibe vs 13.4% placebo; absolute risk reduction [ARR] 2.1%; rate ratio [RR] 0.83, 95% CI 0.74—0.94, $p = 0.0021$). Although there were significant differences in non-hemorrhagic stroke (ARR 1.0%; RR 0.75, 95% CI 0.60–0.94, $p = 0.01$) and revascularization rates (ARR 1.5%; RR 0.79, 95% CI 0.68–0.93, $p = 0.0036$) in favour of simvastatin and ezetimibe, there was no difference in the rate of coronary events ($p = 0.37$). Moreover, there was no difference in mortality from any cause ($p = 0.63$). Subgroup analyses suggested that the impact of simvastatin and ezetimibe was similar between patients on dialysis compared with those who were not ($p = 0.25$ for heterogeneity). The use of simvastatin plus ezetimibe appeared safe with no excess risk of cancer, muscle pain, increases in creatinine kinase, hepatitis, or gallstones.

This study was supported by Merck/Schering-Plough Pharmaceuticals, the Australian National Health Medical Research Council, the British Heart Foundation, and the UK Medical Research Council. The authors assert that, although Merck/Schering-Plough Pharmaceuticals participated in the trial design and commented on study reports, none of the funding sources had a role in the conduct of the trial, analysis of data, or reporting of the results.

Implication and perspectives. It has been suggested that, as renal function deteriorates, vascular stiffness and calcification become more important contributors to cardiovascular disease compared with atherosclerosis.[23] As such, there has been uncertainty—and several "negative" trials—surrounding the benefit of LDL-lowering therapy in the setting of renal impairment.[24–26] Addressing this, the SHARP investigators provide evidence that the combination of simvastatin plus ezetimibe is safe and reduces the risk of major atherosclerotic events among patients with chronic kidney disease. The data suggest that for every 1 mmol/L reduction in LDL cholesterol there is an ARR of 2.1% for major atherosclerotic events (NNT 48) over 5 years, thus supporting the use

of LDL-lowering therapy in this high-risk population. The observation that no overall mortality benefit was observed in this trial should not be inherently surprising, given that statins reduce atherosclerotic cardiac death but have little impact on other causes of death, even in the general population.[27] A much larger trial would likely be needed to detect any benefit in vascular mortality from LDL reduction, as coronary heart disease accounted only for a minority (24%) of vascular deaths in SHARP. Nonetheless, this well-conducted study establishes the safety of simvastatin and ezetimibe therapy in this vulnerable population, and further demonstrates therapeutic efficacy.

Resolution of clinical vignette. This patient is started on simvastatin 20 mg daily for primary prevention. If needed, ezetimibe 10 mg daily will be added to target a 1 mmol/L reduction in LDL cholesterol. Beyond his lipid-lowering therapy, he continues to receive attentive blood pressure assessments for his overall cardiovascular health.

Conclusion

The medical community continues to be enriched by valuable research that enhances care, relieves suffering, and guides health policy. However, clinicians will continue to seek easily assessible and reliable synoptic resources to keep up with rapidly expanding information.[1–3] Therefore, the annual review remains an irreplaceable tool to facilitate information delivery. Finally, although the articles that we have highlighted here are indisputably important, we would be remiss not to emphasize that countless other high-quality studies could not be reviewed because because of constraints of space.

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