

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

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**Abstract**

The number of peer-reviewed medical articles published on a regular basis continues to increase. One particularly effective strategy to navigating the growing sea of information is through the tradition of the annual review. Here, we review five notable articles for general internal medicine published between September 1, 2010 and August 31, 2011.

## **Introduction**

Medicine is faced with an information explosion,<sup>1</sup> defined by the incredibly “rapid increase in the amount of information available.”<sup>2</sup> While the vast wealth of knowledge has indisputably benefited medical care, it can be difficult to stay abreast of the large volume of medical information published in both the peer-reviewed and grey literature. Practical strategies to organize the growing tide of medical literature are essential for providers to recognize and incorporate new information into practice.

One particularly effective strategy to managing new information is the traditional annual review where selected, pre-appraised articles are presented for general consumption.<sup>3-4</sup> Here, we present five notable articles for general internal medicine published between September 1, 2010 and August 31, 2011, with focused summaries of their key findings, and supporting clinical vignettes to highlight their significance.

## **Methods**

A comprehensive hand-search was performed for primary studies published between September 1, 2010 to August 31, 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. Of the studies identified, the selection of five notable articles was determined by a combination of factors, including the prevalence of the medical issue addressed by the study and whether the study findings had the potential of changing current treatment paradigms,

diagnostic strategies, or health policy. Similar criteria have been previously proposed to rate the importance of articles.<sup>5</sup>

### **Paper 1: Renal ultrasonography for patients with acute kidney injury**

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 Nov 22;170(21):1900-7. Available from: <http://archinte.ama-assn.org/cgi/content/full/170/21/1900>

#### *Clinical vignette*

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

#### *Summary of findings*

Licurse and colleagues designed and validated a clinical prediction rule to identify patients at low risk of hydronephrosis, among subjects hospitalized with AKI.<sup>6</sup> 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 a diagnosis of hydronephrosis in the previous 30 days. Data from the 200 derivation subjects (a sample consisting of 100 patients with hydronephrosis, and another 100 patients without) 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 (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 intervals [CI], 89.9% to 93.7%), specificity of 30.3% (95% CI, 27.2 to 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 to 97.6%), with a specificity of 28.8% (95% CI, 25.7 to 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 did not receive any industry funding.

#### *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. As such, 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 (where the expected prevalence of obstruction would be less).

While the results of this carefully designed study are useful and easily applied to patient care, two important issues remain: first, while 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 upon clinical factors that cannot be fully captured 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 forego RUS until other reasonable conservative measures (e.g., adequate volume expansion) are tried first.

### **Paper 2: Risk of recurrence after a first seizure**

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 Dec 7;341:c6477. Available from:

<http://www.bmj.com/content/341/bmj.c6477?view=long&pmid=21147743>.

### *Clinical vignette*

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

### *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 to no (or delayed) treatment following an unprovoked seizure.<sup>7</sup> In this present analysis, 637 participants were included consisting of patients 16-years and older (i.e., of driving age) without previous anti-epileptic treatment or progressive neurological disease. The authors sought to identify clinical characteristic 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 results, neuro-imaging results, and whether the patient was initially treated with 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:

[http://www.bmj.com/highwire/filestream/446798/field\\_highwire\\_adjunct\\_files/0](http://www.bmj.com/highwire/filestream/446798/field_highwire_adjunct_files/0)). This study did not receive any industry funding.

### *Implication and perspectives*

There is a dearth of medical evidence to guide clinicians on the risk of seizure recurrence following a first unprovoked seizure. Consequently, existing guidelines have been largely formed by expert opinion, and differ widely around the world.<sup>2, 8-9</sup> 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, there should be cautionary use of these data. 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.<sup>10</sup> In addition, the seizure-free interval has not been shown to be related to seizure-related crashes,<sup>11</sup> or crash fatalities.<sup>12</sup> Therefore, while 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 into 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-wide regulations. For instance, Canadian guidelines recommend that this man should be seen 12 months following his initial seizure to re-evaluate his ability to drive, conditional on him remaining seizure-free with no further signs of epileptiform activity.<sup>2</sup> 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.<sup>7, 13</sup>

### **Paper 3: Cardiac-resynchronization therapy for mild-to-moderate heart failure**

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 Dec 16;363(25):2385-95. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa1009540>.

#### *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. Electrocardiogram confirms a sinus rhythm with a prolonged QRS duration, and a recent echocardiogram reveals an impaired left-ventricular ejection fraction (LVEF) of 25-30%. He is referred to the heart function clinic to discuss further treatment options.

#### *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  $\leq 30\%$ , and a prolonged QRS (i.e., intrinsic duration of

$\geq 120$  msec, or paced duration of  $\geq 200$  msec).<sup>14</sup> 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 did significantly better with regards to death or hospitalization for heart failure (hazard ratio [HR], 0.75; 95% CI, 0.64 to 0.87;  $p < 0.001$ ), all-cause mortality (ICD-CRT: 28.6%; ICD: 34.6%; HR, 0.75; 95% CI, 0.62 to 0.91;  $p = 0.003$ ), and hospitalization for heart failure (ICD-CRT: 19.5%, ICD: 26.1%; HR, 0.68; 95% CI, 0.56 to 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  $\geq 150$  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 hospitalizations (26.1% vs. 19.5%;  $p < 0.001$ ), and device-related complications within the first 30 days post-implantation (13.3% vs. 6.8%;  $p < 0.001$ ). The trial was sponsored by the Canadian Institutes of Health Research and Medtronic of Canada. CRT components were provided by Medtronic of Canada, but it did not have any 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.<sup>15-16</sup> Up until now, however, there has been no evidence showing that CRT confers additional survival benefit when combined with ICD therapy. The results of this well-conducted trial are particularly important since most patients who have NYHA class II or III heart failure, impaired LVEF, and widened QRS duration, would be suitable candidates for ICD implantation;<sup>17</sup> thus, demonstrating that the combination of ICD-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 clinically relevant. Over 5 years, the number needed to treat (NNT) to prevent 1 death was 14, and the NNT to prevent 1 hospitalization related to heart failure was 11. Although the results were overall positive, 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 weighing the benefits and risks.

#### *Resolution of clinical vignette*

While this patient already meets established eligibility criteria for ICD placement for the primary prevention of sudden cardiac death,<sup>17</sup> the results of this study further support the use of CRT in addition to ICD and optimal medical therapy. After explaining the potential risks associated with implantation, and the expected benefits, the patient is agreeable to receiving ICD-CRT therapy, and is listed for device implantation.

#### **Paper 4: Apixaban versus warfarin in patients with atrial fibrillation**

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 Sep 15;365(11):981-92. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa1107039>.

#### *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 to 3.0). She finds routine monitoring cumbersome and difficult.

### *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 vs. 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.<sup>18</sup>

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 to 0.95;  $p = 0.01$ ), all-cause mortality (HR, 0.89; 95% CI, 0.80 to 0.99;  $p = 0.047$ ), and major bleeding (HR, 0.69; 95% CI, 0.60 to 0.80;  $p < 0.001$ ). The findings for the primary composite outcome was mostly driven by the large and significant reduction in hemorrhagic stroke rates among apixaban recipients (HR, 0.51; 95% CI, 0.35 to 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 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 into 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;<sup>19</sup> 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 pharmacological options are potentially safer and more convenient. Notably, the largely positive findings from the trials evaluating apixaban, dabigatran, and rivaroxaban (in comparison to warfarin) have all been driven by impressive reductions in hemorrhagic stroke.<sup>18, 20-21</sup> Somewhat surprisingly, only higher-dose dabigatran, when compared to warfarin, has been reported to reduce the risk of ischemic stroke.<sup>21</sup> Furthermore, all three drugs appear to have more favourable bleeding profiles compared to warfarin.<sup>18, 20-21</sup> Although the general conclusions reached in ARISTOTLE are broadly similar to previous trials, this study was uniquely powered to detect a mortality benefit with apixaban,<sup>20</sup> whereas previous studies evaluating dabigatran and rivaroxaban have only reported non-significant trends.<sup>20-21</sup> While 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 their convenience, safety, and efficacy profiles.

#### **Paper 5: Simvastatin and ezetimibe in patients with chronic kidney disease**

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 Jun 25;377(9784):2181-92. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673611607393>.

### *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  $\mu$ mol/L, LDL cholesterol of 2.97 mmol/L, and a urinary albumin to creatinine ratio <30 mg/g.

### *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.<sup>22</sup> Patients were randomized 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; rate ratio [RR], 0.83; 95% CI, 0.74 to 0.94;  $p = 0.0021$ ). Although there were significant differences in non-hemorrhagic stroke (RR, 0.75; 95% CI, 0.60 to 0.94;  $p = 0.01$ ) and revascularization rates (RR, 0.79; 95% CI, 0.68 to 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 to 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 to atherosclerosis.<sup>23</sup> As such, there has been uncertainty – and several ‘negative’ trials – surrounding the benefit of LDL-lowering therapy in the setting of renal impairment.<sup>24-26</sup> 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 absolute risk reduction 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.<sup>27</sup> A much larger trial would likely be needed to

detect any benefit in vascular mortality from LDL reduction as coronary heart disease only accounted 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 the simvastatin 20mg daily for primary prevention. If needed, ezetimibe 10mg 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 after easily assessable and reliable synoptic resources to keep up with the rapidly expanding information.<sup>1,3</sup> Therefore, the annual review remains an important, invaluable, and irreplaceable tool to facilitate information delivery. Finally, while the articles that we highlighted here are indisputably important, we would be remiss to not emphasize that there are countless other high-quality studies that we could not review because we were constrained to select only five articles.



**Acknowledgments**

This is an invited review based on a plenary presentation entitled “Top 5 Articles in General Internal Medicine 2010/2011” given by Dr. C. van Walraven at the Annual Scientific Meeting of the Canadian Society of Internal Medicine (CSIM) on October 13, 2011.

**Competing interests**

None declared.

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**Contributors**

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

## References

**Table 1.** Clinical prediction rule for hydronephrosis

<b>Risk factor</b>	<b>Points</b>
History of hydronephrosis*	High-risk
Recurrent urinary tract infections	1
Diagnosis consistent with possible obstruction†	1
Nonblack race	1
Absence of inpatient nephrotoxic medication exposure‡	1
Absence of congestive heart failure	1
Absence of prerenal acute kidney injury§	1

Adapted from 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 Nov 22;170(21):1900-7.

\* 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.

† Diagnosis consistent with possible obstruction include benign prostatic hyperplasia, abdominal or pelvic cancer, neurogenic bladder, single functional kidney, or previous pelvic surgery.

‡ Nephrotoxic medications defined as acetylsalicylic acid (>1 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 admission in the primary model.