Surveying the medical literature:
five notable papers in general internal medicine from 2008/2009

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Abstract

With the vast and growing volume of medical literature, it is essential to develop reliable strategies to identify articles of importance and relevance. Here, we summarize five notable papers for general internal medicine published between 2008 and 2009, and describe the surveillance strategy we used to select these articles.

Introduction

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

Identifying "important" papers need not be haphazard either. Reliably identifying notable high-impact articles may be facilitated by asking four inter-related questions: what is the potential impact on patient outcomes? What are the implications to public health? Is the study easily applicable into current practice? And, does this study herald scientific advancement, or signal a new paradigm?

Here, we highlight five notable papers for general internal medicine published between 2008 to 2009 with an abbreviated presentation of key findings, and focused discussion of salient points. We then provide the strategy we used to select these studies and describe a general approach to survey the vast and growing medical literature for "important" papers, recognizing that the judgment of importance is both personal and subjective.

Paper 1: perioperative beta-blockers in patients undergoing non-cardiac surgery (Bangalore S, et al. Lancet. 2008;6:1962-76).

Summary of findings

The balance of benefits and harms of using beta-blockers prior to non-cardiac surgery has long been a topic of interest for internists involved in preoperative risk assessment. Addressing this topic, Bangalore and colleagues performed a systematic review and meta-analysis of 33 randomized controlled trials evaluating 12,306 patients and found that beta-blockers were not

associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure, but were associated with a 35% reduction (odds ratio, OR 0.65) of nonfatal myocardial infarction (MI) at the expense of a 101% increase (OR 2.16) in nonfatal strokes.[4] There was an absolute risk reduction of nonfatal MI of 1.7% (number needed to treat, NNT 63) balanced against an absolute risk increase of nonfatal strokes of 0.4% (number needed to harm, NNH 275) among patients treated with beta-blockers compared to controls. Beta-blockers were also associated with an increased risk of perioperative bradycardia (NNH 22) and perioperative hypotension requiring treatment (NNH 17) compared to controls. Among the trials included in the analysis, the Perioperative Ischemic Evaluation Study (POISE) trial [5] carried the greatest weight.

Implication and perspectives

This study confirmed what many already suspected: perioperative beta-blockade is associated with a reduced risk of MI at the cost of an increased risk of stroke. More importantly, this study quantified treatment effects in absolute terms. On the population level, for every stroke incurred, more than four MI events may be averted. Consequently, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) have updated their guidelines for the perioperiative cardiovascular evaluation for non-cardiac surgery to reflect the newer data presented in this study.[6] Absolute risk reductions (and NNT) are, however, linked to baseline risks for specific types of events. As a result, there may not be a single over-riding treatment recommendation that applies to all patients. There are specific patient profiles (e.g., patients with documented coronary artery disease with a high risk for ischemic cardiac events) where the potential benefits of beta-blockers may nonetheless be justified, even in light of the more newly-recognized risk of stroke.

Paper 2: management of renal-artery stenosis (Wheatley K, et al. N Engl J Med. 2009;361:1953-62).

Summary of findings

Atherosclerotic renovascular disease is a common condition associated with substantial risk of cardiovascular death.[7] Although treatment has traditionally centered on revascularization, this practice has been questioned.[8] The ASTRAL trial was designed to compare revascularization together with medical therapy versus medical therapy alone for the treatment of atherosclerotic renal artery stenosis.[7] This multicentre, randomized, non-blinded clinical trial followed 806 patients over 5 years and 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 in 31 patients (9%) undergoing revascularization including 19 serious complications (e.g. MI, renal embolization, renal-artery occlusion or perforation, or digital or limb amputation). Late adverse events associated with revascularization (i.e. within 1 month) were reported in 55 patients (20%) including 12 serious complications and 2 deaths.

Implication and perspectives

This study found no significant benefit from attempted revascularization in patients with atherosclerotic renovascular disease, but rather reported substantial risks. The findings of the ASTRAL trial add to the evidence against revascularization therapy [9] beyond medical management for renal artery stenosis (i.e. with statins, antiplatelet agents, and optimal blood-pressure control). It should prompt the internist to consider entirely avoiding potentially harmful

investigations for renal artery stenosis, now that it is becoming clearer that results will *not* lead to an advisable treatment strategy.

Paper 3: a new paradigm in antithrombotic therapy for atrial fibrillation (Connolly SJ, et al. N Engl J Med. 2009;361:1139-51).

Summary of findings

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study group designed and performed a randomized clinical trial comparing warfarin versus dabigatran (110 mg or 150 mg twice daily), a new oral direct thrombin inhibitor, for prevention of cardioembolism in atrial fibrillation.[10] Outcomes were analyzed for 18,113 participants from 44 countries, demonstrating 110 mg of dabigatran was associated with similar rates of stroke and systemic embolism compared to 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 was associated with lower rates of stroke and systemic embolism compared to warfarin (RR 0.66, $p<0.001$ for superiority), with similar rates of major bleeding (RR 0.93, $p=0.31$). However, the hemorrhagic stroke risk was significantly greater among patients treated with warfarin (annual rate 0.38%) compared to dabigatran (0.12% per year with 110 mg dose; 0.10% per year 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 a narrow therapeutic window and associated hemorrhagic risk, thus necessitating frequent laboratory monitoring and caution for interactions with other

drugs and food. This study introduces a new treatment paradigm with dabigatran as an alternative to warfarin for anticoagulation, presenting impressive efficacy and safety evidence favouring dabigatran. The use of this oral direct thrombin inhibitor may simplify previously complex dosing regimens, and mitigate the need for routine monitoring. However, several issues need to be resolved before it can be adopted into widespread clinical practice including balancing the trade-offs between 110 mg versus 150 mg twice daily dosing, acquiring provincial and national approvals for its use, determining the pricing (i.e. affordability to the patient), and assessing its cost-effectiveness (i.e. costs to the system). This trial has intrigued many physicians, and it heralds a new care paradigm.

Paper 4: informing duration of anticoagulation therapy for deep venous thrombosis (Prandoni P, et al. Ann Intern Med. 2009;150:577-85).

Summary of findings

The optimal duration of anticoagulation following initial deep venous thrombosis (DVT) remains unclear. It is uncertain which patients would benefit from prolonged therapy to reduce the risk of recurrence. This Italian trial enrolled 538 outpatients with a first episode of acute proximal DVT.[11] Patients initially received anticoagulation for 3 months for secondary DVT, or 6 months for unprovoked DVT. Patients were then randomized 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) with discontinuation of anticoagulation if veins were recanalized as assessed by ultrasound 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%) compared to fixed-duration anticoagulation (17.2%). There were no significant differences in bleeding complications or death between groups.

Implication and perspectives

Patients with DVT associated with transient, reversible risk factors are commonly anticoagulated for minimum 3 months, and those with unprovoked DVT generally receive at least 6 months of therapy.[12] The presence of persistent venous thrombi [11] and increased D-dimer levels after stopping anticoagulation [13] appear to be predictors of recurrent DVT. The evidence suggests that ultrasonography to detect residual venous thrombosis, and the measurement of persistently elevated D-dimer levels are powerful and promising tools to help identify which patients would benefit most from prolonged anticoagulation. Future areas of research would be to reconcile ultrasound-guided anticoagulation with D-dimer levels in an evidence-based treatment strategy, assess cost-effectiveness of serial ultrasonography, and to determine optimal duration of anticoagulation therapy if recanalization is never achieved. Clearly, for clinicians choosing to adopt an ultrasound-guided approach to treatment, measures should be implemented to ensure that patients are not lost to follow-up.

Paper 5: balancing risk vs. benefit associated with aspirin for the primary and secondary prevention of vascular disease (Baigent C, et al. Lancet. 2009;373:1849-60).

Summary of findings

This systematic review and meta-analysis by the Antithrombotic Trialists' Collaboration aimed to determine the benefits and risks of aspirin therapy.[14] Individual-level data from 6 primary prevention trials (95,456 patients) and 16 secondary prevention trials (17,029 patients)

were analyzed to compare aspirin therapy versus no aspirin with the primary outcomes of interest including serious vascular events (a composite of MI, stroke, and cardiovascular death), major coronary events, stroke, all-cause mortality, and major extracranial bleeding. Meta-analysis of primary prevention trials demonstrated that aspirin reduced serious vascular events compared to no aspirin (0.51% versus 0.57%; NNT 1667). An increase in major bleeding was seen with aspirin (0.10% versus 0.07%; NNH 3333). Aspirin was associated with a greater reduction in serious vascular events when used for secondary prevention (6.7% versus 8.2%; NNT 67), but also resulted in more bleeding (0.25% versus 0.06%; NNH 526).

Implication and perspectives

While it is well established that aspirin reduces thrombotic risk at the expense of increasing bleeding risk, the benefit-risk balance was less certain prior to this study.[15] Here, the Antithrombotic Trialists' Collaboration provides evidence for substantial net benefit of aspirin in secondary prevention, but the magnitude of benefit is less impressive for primary prevention. The balance of risk and benefits can be represented by the 'likelihood of being helped versus harmed' metric (LHH, a ratio of NNH divided by NNT) [16,17] with an LHH of 8 for secondary prevention and 2 for primary prevention. For every 10,000 patients treated with aspirin for secondary prevention, 149 serious vascular events may be prevented at the expense of 19 major bleeding events. Meanwhile, among 10,000 people prescribed aspirin for primary prevention, 6 serious vascular events may be averted, but 3 major bleeding events may occur. This study refines estimates of treatment effects, and clarifies the risk-benefit ratio for specific patient populations.

Caveat lector **(let the reader beware)**

While it is indisputable that the papers selected above are important, they are not necessarily the most important papers from 2008/2009. The adage "beauty is in the eye of the beholder" holds true, and we (AL and WG) are the "beholders." The selection of notable papers arises from personal surveillance strategies of the literature. As high quality healthcare implies practice that is consistent with best evidence, all providers should reflect on their own strategies of incorporating evidence into practice.

Surveillance for important studies

Judging importance is an invaluable skill. Various rating scales have been proposed as tools to assess importance of published articles.[18,19] For example, Lawrence [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 the impact that the new information described is likely to have on health outcomes of those affected by, or at risk for, the disease or condition addressed by the article.[19]

While training clinicians to be "evidence-based practitioners" (to independently retrieve, appraise, and apply best evidence) is appealing, physicians unfortunately face many recognized barriers to this approach.[20]. Most notably, time constraints limit physicians' opportunities to search and review new information in real time to affect decisions in clinical practice [21-23]. Moreover, many physicians admit that they lack the skills required to use literature databases and to properly appraise studies.[22-26] Guyatt and colleagues, leading enthusiasts of evidence-

based medicine, have acknowledged that it is not realistic to expect all providers to be "evidence-based practitioners" who appraise raw evidence from scratch [20]. It is, however, crucial for all providers to gain some fundamental skills to flag and incorporate important evidence as "evidence users."[20]

It is estimated that most internists will spend 4 to 5 hours per week reading medical articles, and read only the abstracts for approximately 2/3 of articles encountered.[27] It also appears that the typical internist relies on journal editors to provide rigorous and useful information.[27] There is a pattern of heavy reliance on summaries and prescreening of articles to survey the literature for relevant information, given the limited time for critical reading. [20,27,28] Reassuringly, "evidence users" that refer to secondary sources of pre-appraised evidence can still become highly competent, up-to-date practitioners, who deliver evidence-based care.[20]

Thus, we recommend using evidence-based, filtered summaries of articles from select journals as a useful surveillance tool to navigate the literature (e.g. *ACP Journal Club*, *ACP Journal Club PLUS*, *Evidence-Based Medicine, Best Evidence*, and *the Cochrane Library*). [20,29] These secondary journals have been developed to identify studies that meet pre-defined criteria of importance,[18] and are then critically appraised. Qualifying studies are screened for relevance to a broad range of medical practice, both for generalists and specialists. It appears that these resources are useful in facilitating continuing medical education, and are directed to identifying the most sound, relevant, and "high-impact" studies.[29] To paraphrase William of Ockham's razor, *lex parsimoniae*, "just keep it simple." It is with the use of these information services that we identified our five notable papers from 2008/2009, as highlighted above.

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Competing interests

None declared.

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Contributors

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