Evidence-Based Medicine

EBM NOTEBOOK

Applying the results of trials and systematic reviews to individual patients

Your patient is a 60-year-old hypertensive, alcoholic woman whose symptomless atrial fibrillation was first documented 3 months ago. An echocardiogram shows an enlarged left atrium, rendering successful cardioversion unlikely. She tells you that both of her parents had severe strokes that made the last years of their lives horrible, and she is terrified of having a stroke. You know that a meta-analysis of 5 randomized trials of warfarin in nonvalvular atrial fibrillation demonstrated a 68% relative risk reduction (RRR) in stroke (1). You consider prescribing warfarin for this patient but know that she would not have qualified for the study because alcoholism increases her risk for major hemorrhage (2).

Patients' presentations define problems that clinicians must help resolve. Evidence on the effects of alternate courses of action helps us determine what is likely to work best. But we must consider the evidence in light of practical constraints and a patient's particular biology, circumstances, and values. Moving from evidence to action, therefore, involves judging how to apply the evidence to the individual patient. We offer 4 questions clinicians might find useful when making this judgment. Our discussion, which we will illustrate using the above scenario, has evolved from other expositions on the issues of applicability that we have published elsewhere (3–6).

Is my patient so different from those in the study that results cannot be applied?

One approach to applying the results of a randomized trial would be to demand that your patient meets all the inclusion criteria (including the site of care) and violates none of the exclusion criteria of the original study. One can see the needless rigidity of this approach, for example, by considering whether the findings of a trial that enrolled patients 40 to 70 years of age apply to a patient 71 years of age. Therefore, we suggest asking the following question: Is the underlying pathobiology in my patient so different that the study cannot give any guidance? For most differences in patient groups (older or younger, somewhat less or more sick, presence of comorbid conditions) the answer is "no," and we should instead think about how these factors might shift the balance of benefits and harms of treatment.

Differences between our patients and those we read about in trials tend to be quantitative (e.g., matters of degree in risk and responsiveness) rather than qualitative (no response or adverse response). A few exceptions to this rule exist because the same disease may affect patients in important pathobiological, pharmacodynamic, or pharmacogenetic ways. For example, a recent systematic review (7) suggests that tricyclic antidepressants have little effect in children or adolescents; another study (8) showed that differing pharmacogenetic features of drugs, such as acetylation rates, may radically alter treatment response.

For your patient, the issue is complex. Patients with factors that increase the risk for bleeding, including alcoholism, were excluded from the randomized trials of warfarin for atrial fibrillation, so your patient would not have qualified. However, there is no pathobiological reason that warfarin would exert a qualitatively different impact on reducing cardiac embolism in this patient, and hypertensive patients with atrial fibrillation are at higher risk for stroke yet respond quite well to warfarin (1). Thus, it is reasonable to expect that your patient would achieve a large absolute reduction in the risk for embolic stroke with appropriately adjusted doses of warfarin.

But this is only one side of the benefit–harm balance sheet. The major downside of warfarin administration is increased risk for bleeding. Patients who received warfarin in the randomized trials had an absolute risk for major bleeding of approximately 1.4% per year, which was 0.6% higher than those who did not. In population-based studies of patients receiving warfarin outside of trials (9), however, the excess risk for bleeding has been higher—around 3%. This patient's alcoholism puts her at still greater risk for serious bleeding, perhaps as high as 2.7-fold (2).

Is the treatment feasible in my setting?

Barriers to care include geography, economics, and how services are organized. If you live in a rural part of a developing country, you may be unable to offer this patient regular monitoring of her anticoagulation status or provide adequate services for handling adverse events. Even if drugs and services are available, you can only provide her with what she can afford. These factors can lead either to an increased risk for bleeding from anticoagulation (at full doses) or a decreased chance of stroke (at lower, "safer" doses) (10). If extreme, these barriers may force you to offer your patient aspirin, despite the evidence that it is less effective than warfarin.

What are the likely benefits and harms from the treatment?

Once you've decided that the results of a trial or systematic review are both broadly applicable and feasible, you need to individualize the treatment's benefits and risks to the patient. We know that among patients with atrial fibrillation, anticoagulation generates an RRR for stroke of 68%* and that the RRR is constant over subgroups of patients with different risks on entry to the trials. Predictably, this "baseline risk" (expressed in increased control event rates [CERs]) and the absolute risk reduction (ARR) from warfarin increases and the associated number needed to treat (NNT) (1/ARR or the number of patients with atrial fibrillation needed to treat to prevent 1 additional stroke) decreases.

*For definitions and derivations of this and other measures of benefit and risk, please refer to the Glossary.

Fortunately, the trial reports provide CERs for various risk factor subgroups (1). For instance, patients with nonvalvular atrial fibrillation who are younger than 65 years of age; have normal echocardiograms; and are free of hypertension, heart failure, and previous embolic episodes have a stroke risk, if left untreated, of just 1% per year (CER = 0.01). In such low-risk patients, even a perfectly efficacious treatment (RRR = 100%) could only produce an ARR of 1% (ARR = 0.01) and a corresponding NNT of 100. As it happens, the best estimate of the effect of warfarin in this subgroup (and others) is 68%, which generates an ARR of 0.007 and an NNT of 147.

Your patient's hypertension, if left untreated, places her at moderate risk for stroke—about 5% per year. Thus, the NNT to prevent 1 additional stroke in patients like her is 30. To complete the picture, the stroke risk among untreated high-risk patients, such as persons older than 75 years of age who have additional risk factors, is 8.1%, generating a corresponding NNT of 18. Thus, the higher the patients' risk for the target event, the smaller the NNT and the more favorable the trade-off between benefit and harm.

On the other hand, treatment increases the risk for harm, and we must bear that in mind as well. Assuming a yearly excess risk for major and fatal hemorrhage from warfarin of 0.3% (inside the trials) and 2% (outside the trials) (1, 9), the numbers needed to harm (NNH) are 333 and 50, respectively. Applying the NNH of 50 to the above NNTs for the different subgroups, the price to be paid for preventing 1 additional stroke would be about 3 serious bleeding episodes among low-risk patients, 1 episode among moderate-risk patients, and one third of an episode among high-risk patients.

Finally, any discussion of benefits and harms must consider the effects of low compliance. For example, we need to consider whether 1 or both are dose-dependent.

How will my patient's values influence the decision?

Practicing evidence-based medicine requires the integration of evidence with each patient's values and expectations (5). The patient's alcoholism may increase her bleeding risk substantially—at least 2.7-fold (2), generating an NNH of $1/(2.7 \times 0.02)$, or about 19 (remember, she had an NNT of 30). In such patients, the price for preventing 1 stroke is 1.6 severe bleeding episodes. Who is to say whether a serious bleeding episode is a fair price to pay to prevent a stroke? Most readers of this journal would probably consider the patient to be the best judge of that.

How can we incorporate our patient's values into this decision? In addition to the time-honored verbal approaches in general use, several efforts are under way to provide patients with visual (11) or numerical representations (12) of the benefits and risks of therapy (the latter ranges from formal decision analysis [13] to simple bedside demonstrations of the likelihood of being helped or harmed [6]). In any event, we suggest that energy currently devoted to agonizing over the minutiae of the inclusion and exclusion criteria used to generate the research evidence is better spent considering how it can be applied to the special situations and values of our patients. We hope the above 4 questions will help this work.

Paul Glasziou, MBBS, PhD
Gordon H. Guyatt, MD
Antonio L. Dans, MD, MSc
Leonila F. Dans, MD, MSc
Sharon Straus, MD
David L. Sackett, MD

References

1. Risk factors for stroke and efficacy o antithrombotic therapy in atrial fibrillation Analysis of pooled data from five random ized controlled trials. Arch Intern Med 1994;154;1449-57.
2. **McMahan DA, Smith DM, Carey MA, Zhou XH.** Risk of major hemorrhage fo outpatients treated with warfarin. J Gen In tern Med. 1998;13:311-6.
3. **Dans AL, Dans LF, Guyatt GH, Richarc S.** User's guides to the medical literature XIV. How to decide on the applicability o clinical trial results to your patient. Evi dence-Based Medicine Working Group JAMA. 1998;279:545-9.
4. **Glasziou PP, Irwig LM.** An evidence-based approach to individualising treatment. BMJ 1995;311:1356-9.
5. **Sackett DL, Rosenberg WM, Gray JA Haynes RB, Richardson WS.** Evidence-based medicine: what it is and what it isn't BMJ. 1996;312:71-2.
6. **Straus SE, Sackett DL.** The likelihood of being helped versus harmed—a new method of presenting information to patients about the risks and benefits of therapy. Presented at the Third Cochrane Colloquium, Amsterdam October 1997.
7. **Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D.** Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. BMJ. 1995;310. 897-901.
8. **Schaefer O.** Adverse reactions to drugs and metabolic problems perceived in Northern Canadian Indians and Eskimos. Prog Clin Biol Res. 1986;214:77-83.
9. **Landefeld CS, Beyth RJ.** Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315-28.
10. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet. 1996;348:633-8.
11. **O'Connor AM, Tugwell P, Wells GA, et al.** A decision aid for women considering hormone therapy after menopause: decision support framework and evaluation. Patient Educ Couns. 1998;33:267-79.
12. **Sackett DL.** On some clinically useful measures of the effects of treatment [EBM Note]. Evidence-Based Medicine. 1996 Jan-Feb;1:37-8.
13. **Weinstein MC, Fineberg HV.** Clinical Decision Analysis. Philadelphia: WB Saunders; 1980.

This EBM Note was also published in *ACP Journal Club*. 1998;129:A-17.