

The Economics of Anticoagulation: What are the Issues?

Discussions of anticoagulation therapy often begin with a review of 3 rather noncontroversial facts. As summarized here, these might be dubbed “the Good Fact,” “the Bad Fact,” and “the Ugly Fact.”

The Good

First, evidence that anticoagulation therapy reduces the risk of major and costly medical events is overwhelming. Meta-analyses indicate that oral anticoagulation with dose-adjusted warfarin reduces the risk of stroke by about 60% versus placebo in patients with atrial fibrillation (AF).^{1,2} By comparison, aspirin offers only modest protection (approximately 20% risk reduction) against future stroke in these patients.²⁻⁴ Similarly, therapy with heparin for 1 week plus oral anticoagulation continuing for at least 3 months has been shown to reduce the risk of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) by about 80% to 90%.⁵ Extended therapy with warfarin further reduces the risk of venous thromboembolism.⁶⁻⁸

The Bad

Second, although the benefits of oral anticoagulation in patients are clear, the risk of bleeding and the potential for serious intracranial hemorrhage are equally well documented. In particular, the risks of warfarin-related major bleeding increases as the intensity of anticoagulation increases and is higher in the elderly, in patients with a history of bleeding, and in patients with serious comorbid conditions.^{9,10} To balance the benefits and risks of anticoagulation, therapeutic monitoring has become a necessary adjunct to warfarin therapy. Recommendations on how to select patients and make the crucial periodic adjustments of warfarin dosage in individual patients with varying degrees of thrombotic and bleeding risk—

and how to combine oral anticoagulation with concomitant therapy, such as rate control in AF or heparin in DVT/PE—are now spelled out in various anticoagulation treatment guidelines.¹¹⁻¹⁴

The Ugly

The third fact about anticoagulation that will not often be disputed is that healthcare providers still do not provide sufficient anticoagulation for some patients. Only about half of eligible AF patients, for example, receive anticoagulation.¹⁵ A recent review of 9 studies found the rate of warfarin use in eligible high-risk patients ranges from 22% to 79%.¹⁶ Equally troubling was the finding that up to 60% of those receiving warfarin had international normalized ratios (INRs) below the recommended therapeutic range.¹⁶ The barriers to the initiation and proper long-term use of dose-adjusted warfarin therapy include: the fear of bleeding events, the inconvenience of continuous prothrombin time monitoring, and the possibility of drug interactions and complex interindividual pharmacokinetics that will further confound dosing. From the patient's perspective, the need for continuous anticoagulation monitoring contributes to widespread noncompliance, especially in patients with language barriers, disabilities, or rural residences.

To help overcome these barriers to evidence-based oral anticoagulation, a variety of approaches have been adopted, with anticoagulation clinics and patient education with self-testing and/or self-management being commonly employed tactics. Anticoagulation clinics now represent the gold standard for long-term warfarin therapy—essentially coming closest to emulating the efficacy rates seen in the randomized clinical trial settings—and these clinics are acknowledged to improve quality, reduce complications, and reduce total health sys-

tem costs.¹⁷⁻²¹ One recent 2004 analysis in a large health maintenance organization in Georgia calculated the per member per month costs for an outpatient pharmacy anticoagulation service for AF patients to be \$62, an amount that the authors concluded was justified based on the percent of time patients were kept within their INR goal (60%) and the cost savings because of prevented complications, such as stroke or intracranial bleeding.²¹ Although less established, patient self-management of warfarin therapy has recently emerged as an alternative or an add-on to anticoagulation clinics. These innovative strategies, which have included home use of portable coagulometers and creation of Web-based virtual anticoagulation clinics, have in some cases been found to be safe and cost-effective alternatives to usual care or to the classic anticoagulation clinic model.²²⁻²⁵

Having recited these 3 facts, many discussions and review articles on anticoagulation end at this point, perhaps adding a call for investments in research, anticoagulation programs, or improvements in efforts to boost warfarin adherence.

The Costs

From the health system perspective, the costs of therapy, monitoring, and related anticoagulation management programs must now become a critical part of the extended discussion. The economic rationale for investing in the primary and secondary prevention of stroke and DVT/PE has always been clear. After all, the clinical and economic burdens of stroke and PE are known to be huge. On a national level, the direct costs of stroke alone have been estimated at \$33 billion per year.²⁶ A recent review of international studies indicated that the long-term per-patient costs of stroke ranged from \$18 538 to over \$200 000, with severe strokes costing 11% to 71% more than minor strokes because of longer acute care stays.²⁷ In the United States, the increasing size of the elderly population, a group at much higher risk of AF and stroke, makes the cost-effectiveness argument for anticoagulation even stronger.¹⁶

However, although the possibility of cost-effective, if not cost-saving, warfarin preven-

tive therapy might seem intuitive with such high disease-related costs, the various pharmacoeconomic studies evaluating this question show that the actual cost effectiveness depends on an amalgam of factors, such as stroke risk, bleeding risk, patient preferences, patient age, rates of appropriate use, and local costs of anticoagulation management.^{16,28-32} In the end, health systems must base their decisions to invest in stroke and venous thromboembolism prevention on their analysis of local demographics, event rates, costs, and available anticoagulation resources and talent. As made clear in the few ambitious attempts to develop a decision-making tool for anticoagulation management costs and outcomes,^{33,34} estimating the cost effectiveness of any single health system's anticoagulation program can be an extraordinarily complex undertaking. With warfarin as the sole oral agent, further investments in anticoagulation education soon reach a point of diminishing returns.

The economics of anticoagulation may quickly be radically altered by the introduction of new anticoagulant and antiplatelet therapies now emerging from clinical trials. Agents such as the oral direct thrombin inhibitor ximelagatran, the subcutaneously injected synthetic pentasaccharide idraparinux, and the combination of clopidogrel and aspirin are now being tested against dose-adjusted warfarin. If these therapies are proved to be safer than and as effective as warfarin, they may eliminate the need for therapeutic monitoring and thereby greatly increase the willingness of both clinicians and patients to initiate and maintain long-term anticoagulation therapy. One or more of these agents may soon signal the end of an era for warfarin.³⁵ But as newer therapies enter the clinic and pharmacy, questions about the cost effectiveness of anticoagulation will remain. In fact, because the new agents may improve anticoagulation initiation and adherence rates (vs health system investments in anticoagulation clinics or patient education), discussions about the economics of anticoagulation have never been more relevant.

Clinicians and administrators in managed care settings need to anticipate the arrival of these new agents by assessing their current

situation. This assessment should include an honest appraisal of the current institutional rates of anticoagulation in key populations and the local resources already being spent to improve this rate (eg, staff for anticoagulation clinic or patient education and self-monitoring programs). A baseline assessment of missed prevention opportunities (eg, percent of warfarin-eligible patients not receiving anticoagulation) will provide an objective measure of the potential upside for improved outcomes with the new anticoagulants. Although these new therapies will be more costly than warfarin, they may also cut overall medical budgets by reducing the need for therapeutic monitoring and avoiding adverse events. Costs for treatment of certain bleeding side effects may also be reduced. Finally, and most important, if the promise of early trials is borne out, the new nonwarfarin anticoagulants may also eventually ease clinician hesitancy to prescribe anticoagulants and, in the process, increase overall population anticoagulation usage and adherence and thereby reduce event rates and event severity. This potential for improvement in patient outcome—fewer serious strokes and PEs—is where real economic gains will likely be found.

This supplement to *The American Journal of Managed Care* was based on a roundtable discussion on the healthcare economics of effective anticoagulation. The discussion was held on April 2, 2004, in San Francisco. The purpose of the discussion was to provide readers with a starting point to undertake their own local and institutional discussions of issues related to the economics of anticoagulation.

The review article by Ann K. Wittkowsky, PharmD, CACP, FASHP, provides details on the epidemiologic and economic scope of stroke and PE and formally introduces the above-mentioned essential facts about anticoagulation. Dr Wittkowsky emphasizes the current extent of suboptimal warfarin use, reminding readers that this gap between anticoagulation guidelines and clinical practice can be measured in 2 distinct ways: underutilization (the number of eligible patients not receiving warfarin) and undercoagulation (the percentage of patients taking warfarin but not at INR goal). As director

of anticoagulation services at the University of Washington Medical Center, long-time author and educator in the field of antithrombotic pharmacotherapy, and recipient of the 2003 American Society of Health-System Pharmacists Drug Therapy Research Award for her work in the pharmacogenomics of warfarin, Dr Wittkowsky was a natural choice to chair the session and set the stage for discussion.

The roundtable of experts was then invited to share their ideas on the economic consequences of stroke and DVT/PE, the extent and the costs of nonadherence to national guidelines for anticoagulation, the primary causes of anticoagulant underuse, and the best ways to improve adherence to anticoagulation guidelines. The edited summary of this discussion provides managed care decision makers with a diverse range of opinions and insights on the stubborn challenges with the anticoagulation services prevalent in most healthcare settings today.

In a post-meeting interview, Jaime Caro, MDCM, was given an opportunity to expand on his comments related to the economics of anticoagulation. In particular, he shared the results of a new Medicare-based study measuring the national economic burden of stroke in AF. In describing a related study, Dr Caro explains how he compared the national cost outcomes in typical clinical scenarios, including care with anticoagulation clinics, usual medical care, and no anticoagulation. His conclusion that only 11% of the potential anticoagulation benefit is currently being obtained supports his belief that it will be difficult to overcome the inherent difficulties of prescribing warfarin in clinical practice.

Finally, in the concluding article by Dr Wittkowsky, the main pharmacologic agents currently being evaluated as possible replacements for warfarin are briefly reviewed. The arrival of these agents may powerfully reshape the clinical and economic status quo with warfarin-based anticoagulation. The new anticoagulants are, as one discussant termed it, “a disruptive technology” that just might close the longstanding gap between the promise of anticoagulation as demonstrated in clinical studies and the current practice of anticoagulation as evi-

denced in underutilization and undercoagulation. Will direct thrombin inhibitors really replace warfarin as a first-line anticoagulant to prevent stroke and DVT/PE? Will more than half of patients with AF finally get proper preventive therapy? Uptake of these new agents will depend on the final evidence of safety and efficacy, but it will also hinge on discussions about the economics of anticoagulation that are just now beginning in managed care organizations around the country.

REFERENCES

1. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687-691.
2. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131:492-501.
3. Go AS. Efficacy of anticoagulation for stroke prevention and risk stratification in atrial fibrillation: translating trials into clinical practice. *Am J Manag Care*. 2004;10(3 suppl):S58-S65.
4. AFI. The Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. The Atrial Fibrillation Investigators. *Arch Intern Med*. 1997;157:1237-1240.
5. Hyers TM. Venous thromboembolism. *Am J Respir Crit Care Med*. 1999;159:1-14.
6. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med*. 1999;340:901-907.
7. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1997;336:393-398.
8. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425-1434.
9. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ*. 2002;325:1073-1075.
10. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest*. 2001;119(1 suppl):108S-121S.
11. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation): developed in Collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol*. 2001;38:1231-1266.
12. Snow V, Weiss KB, LeFevre M, et al. Management of newly detected atrial fibrillation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med*. 2003;139:1009-1017.
13. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest*. 2001;119(1 suppl):132S-175S.
14. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2003;41:1633-1652.
15. Buckingham TA, Hatala R. Anticoagulants for atrial fibrillation: why is the treatment rate so low? *Clin Cardiol*. 2002;25:447-454.
16. Bushnell CD, Matchar DB. Pharmacoeconomics of atrial fibrillation and stroke prevention. *Am J Manag Care*. 2004;10(3 suppl):S66-S71.
17. Hamby L, Weeks WB, Malikowski C. Complications of warfarin therapy: causes, costs, and the role of the anticoagulation clinic. *Eff Clin Pract*. 2000;3:179-184.
18. Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. *J Thromb Thrombolysis*. 2000;9:283-292.
19. Macik BG. The future of anticoagulation clinics. *J Thromb Thrombolysis*. 2003;16:55-59.
20. Gill JM, Landis MK. Benefits of a mobile, point-of-care anticoagulation therapy management program. *Jt Comm J Qual Improv*. 2002;28:625-630.
21. Anderson RJ. Cost analysis of a managed care decentralized outpatient pharmacy anticoagulation service. *J Manag Care Pharm*. 2004;10:159-165.
22. Lafata JE, Martin SA, Kaatz S, Ward RE. Anticoagulation clinics and patient self-testing for patients on chronic warfarin therapy: a cost-effectiveness analysis. *J Thromb Thrombolysis*. 2000;9(suppl 1):S13-S19.
23. Cheung DS, Heizer D, Wilson J, Gage BF. Cost-savings analysis of using a portable coagulometer for monitoring homebound elderly patients taking warfarin. *Am J Geriatr Cardiol*. 2003;12:283-287.
24. Kelly JJ, Sweigard KW, Shields K, Schneider D. John M. Eisenberg Patient Safety Awards. Safety, effectiveness, and efficiency: a Web-based virtual anticoagulation clinic. *Jt Comm J Qual Saf*. 2003;29:646-651.
25. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs management by specialized anticoagulation clinics: positive effects on quality of life. *J Thromb Haemost*. 2004;2:584-591.
26. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, Tex: American Heart Association; 2003.
27. Payne K, Huybrechts K, Caro JJ. The economic burden of stroke: an international review of long-term cost-of-illness estimates. Abstract presented at: 5th World Stroke Congress; June 25, 2004; Vancouver British Columbia, Canada.
28. Gustafsson C, Asplund K, Britton M, Norrving B, Olsson B, Marke LA. Cost effectiveness of primary stroke prevention in atrial fibrillation: Swedish national perspective. *BMJ*. 1992;305:1457-1460.

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- 29. Gage BF, Cardinalli AB, Albers GW, Owens DK.** Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*. 1995;274:1839-1845.
- 30. Eckman MH, Falk RH, Pauker SG.** Cost-effectiveness of therapies for patients with nonvalvular atrial fibrillation. *Arch Intern Med*. 1998;158:1669-1677.
- 31. Lightowlers S, McGuire A.** Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke*. 1998;29:1827-1832.
- 32. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB.** Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998;158:229-234.
- 33. Samsa GP, Matchar DB, Phillips DL, McGrann J.** Which approach to anticoagulation management is best? Illustration of an interactive mathematical model to support informed decision making. *J Thromb Thrombolysis*. 2002;14:103-111.
- 34. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A.** Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet*. 2000;355:956-962.
- 35. Donnan GA, Dewey HM, Chambers BR.** Warfarin for atrial fibrillation: the end of an era? *Lancet Neurol*. 2004;3:305-308.