Cost considerations surrounding current and future anticoagulant therapies

MARGARET C. FANG, MD, MPH; TRACY MINICHIELLO, MD; AND ANDREW D. AUERBACH, MD, MPH

ABSTRACT

Because the costs of anticoagulation therapy are substantial and the difference between the risks and benefits of this therapy are often narrow, economic analyses are particularly valuable when weighing anticoagulation options. Economic analyses to date suggest that anticoagulation is most effective and results in the greatest cost savings when applied to populations at highest risk for thrombotic events. They also suggest that in situations where a more costly anticoagulant agent is available, that agent is cost-effective only if it is clearly more efficacious or if it substantially reduces costs in other areas, such as hospitalization. These principles should guide clinicians' choices of anticoagulation strategies.

Economic analyses are particularly important in anticoagulation because the difference between the risks and benefits of therapy can be quite narrow in relative terms, and because the costs of therapy are substantial, especially since therapy may be required for the rest of a patient's life.

For these reasons, standardized, systematic analyses that compare the risks, benefits, and costs of therapy can be valuable for the appropriate selection and use of anticoagulant medications. Empiric methods for comparing anticoagulation strategies will become even more relevant as new and equally effective but more costly anticoagulants become available.

This article addresses cost considerations for several common uses of anticoagulant drugs—the prevention of stroke in patients with nonvalvular atrial fibrillation and the treatment and prevention of venous thromboembolism. We also explore the evidence supporting differing systems for anticoagulation management and discuss cost-effectiveness considerations for new anticoagulant drugs.

From the Department of Medicine Hospitalist Group, University of California, San Francisco.

Address: Andrew D. Auerbach, MD, MPH, UCSF Box 0131, 505 Parnassus Avenue, University of California, San Francisco, San Francisco, CA 94143–0131; ada@medicine.ucsf.edu.

OVERVIEW OF ECONOMIC ANALYSES

Economic analyses help to prioritize health care decisions made at the *societal level*,[1] a perspective that is critical when considering anticoagulants, given the large numbers of patients potentially affected. In addition, the costs for anticoagulants are often borne by society (eg, via Medicare), making empiric comparison of costs and outcomes critically important. We suggest that readers gauge the quality and applicability of economic analyses to their individual practice using several simple questions outlined below and expanded in **Table 1**.[2]

Was the analysis explained clearly?

Economic models cannot account for individual patients' clinical situations but instead apply to "average" patients; thus, it is important to identify the assumptions on which the models are based. Assumptions should be clearly explained and represent accepted standards of practice.

Did the authors use the most broadly representative data available?

Examples of data sources include population-based trials or publicly available sources such as Medicare cost data; these data provide more useful estimates of effectiveness and cost than data from smaller studies and allow cross-comparability of findings across different regions or health care systems.

What kind of economic analysis was performed?

Cost-effectiveness analyses quantify effectiveness using quality-adjusted life-years (QALYs), which range from 0 (dead) to 1 (perfect health). The QALY weight for a year on warfarin therapy is surprisingly high (0.987, or 1.3% less than perfect health).[3,4] A high QALY weight for warfarin therapy is consistent with studies suggesting that patients rate quality of

TABLE 1
Elements of economic analyses that should guide decisions about anticoagulation

Does the analysis. . .	Points relevant to anticoagulation decisions
Clearly describe its patient population?	What were the characteristics of the hypothetical cohort in terms of age, indication for anticoagulation, and risks for benefits/adverse outcomes of therapy?
Compare strategies that are both effective and broadly acceptable in practice?	Strategies that are not considered effective or do not represent standard practice are not appropriate for economic analyses
Clearly explain its assumptions?	While simplifying assumptions is often necessary, assure yourself that the scenario studied would be reproducible in your clinic
Maintain a societal perspective?	Analyses that use data from small or single-site studies limit the generalizability of the results; population-derived data provide more stable and broadly useful information
Express results in quality-adjusted life-years (QALYs) (cost-effectiveness analysis) or costs per event (cost-benefit analysis)?	QALYs are a standard metric of effectiveness that allows for explicit comparisons of events that may have different clinical impact (eg, cerebral hemorrhage vs minor bleeding events)
Calculate incremental cost-effectiveness ratios (ICERs)?	ICERs using QALYs provide an estimate of how much more money it will cost to preserve one additional life at perfect health. ICERs using the costs required to prevent an event can be useful but do not include the potential differing impact of events.
Perform sensitivity analyses to test uncertainty in the source data and assumptions?	Sensitivity analyses provide a sense of which clinical variables influence cost-effectiveness most powerfully; these analyses provide data that clinicians can apply to patients more broadly

life on warfarin highly, and higher than their physicians do.[5–7] From a societal perspective, it is consistent with preference for avoiding stroke with permanent sequelae (eg, QALY weight = 0.6).[3,4]

Cost-benefit analyses, in contrast, express effectiveness in terms of the cost incurred per event (either prevented or caused by therapy). Cost-benefit analyses do not balance preferences for specific disease states (eg, intracranial hemorrhage and minor bleeding events are treated equally) and do not account for the impact of events that happen at different ages (eg, a paralyzing stroke at age 30 is equivalent to a death at age 90).

Were incremental cost-effectiveness ratios used to compare strategies?

When two therapies are being compared, the relevant metric is the incremental cost-effectiveness, ie, the additional costs incurred to achieve another year of perfect health (cost-effectiveness analyses) or to avert an adverse event (cost-benefit analyses). In cost-effectiveness analyses, incremental costs less than $50,000 per QALY gained are considered low cost, those between $50,000 and $100,000 per QALY gained are considered intermediate cost, and those greater than $100,000 per QALY gained are considered high cost. There are no standards for evaluating incremental cost-effectiveness ratios calculated in cost-benefit analyses; the relative value of events and costs in these analyses are left to readers to interpret.

Were sensitivity analyses done to test uncertainty in the model, its data inputs, or its assumptions?

Sensitivity analyses test the results by inputting broad ranges of key variables, thereby providing insight into how differing assumptions (or the use of estimates of risk/benefit from different trials) can influence the study's conclusions.

ANTICOAGULATION IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Cost-effectiveness analyses are particularly appropriate for helping clinicians decide on optimal strategies to prevent stroke in patients with nonvalvular atrial fibrillation (AF), given that AF patients are generally older and at higher risk for adverse events related to therapy or to AF itself. In addition, treatment is generally lifelong, with patients exposed to the risks, benefits, and costs of treatment for longer periods of time.

Several authors have examined the cost-effectiveness of anticoagulation for prevention of stroke in patients with AF.[8–13]

Gage et al[9] compared warfarin, aspirin, and no therapy in a hypothetical cohort of 65-year-olds with chronic AF. For high-risk patients (those with an annual stroke rate of 4.9% to 17.6%), warfarin was both more effective and more cost-saving than either aspirin or no therapy. Among patients at medium risk (annual stroke rate of 2.6% to 4.6%), warfarin was better than aspirin in terms of quality-adjusted survival but cost more than aspirin, incurring an additional $8,000 per QALY saved. For patients at low risk of stroke, warfarin and aspirin were comparable in terms of quality-adjusted survival (and both were better than no therapy), but warfarin cost an additional $370,000 per QALY saved in the base case. The incremental costs of warfarin would be even higher if aspirin produced more than a 22% reduction in stroke risk, if hemorrhage rates on warfarin therapy were substantially higher than reported in randomized trial settings, or if warfarin resulted in greater disutility than the authors' base case assumptions.

Thomson et al[13] conducted a decision analysis to advise clinicians about appropriate treatment for AF by modeling various combinations of risk factors among people with AF using data inputs from a rigorous systematic review of the literature. Comparing only warfarin and no therapy, the results were consistent with those of Gage et al[9] in that warfarin led to both QALY gains and lower costs compared with no therapy in patients at high stroke risk, such as those with three or more stroke risk factors, and for most other combinations of risk factors. Again, this model was particularly sensitive to changes in patient quality of life on warfarin.

How does age affect cost-effectiveness?

Cost-effectiveness analyses have also examined how age influences the cost-effectiveness of anticoagulation. Desbiens[8] evaluated the costs of anticoagulation for AF and its impact on quality of life in older patients (up to age 100 years), comparing warfarin with no therapy. Despite assuming annual intracranial hemorrhage rates of 5.0% for patients aged 100 years, the analysis showed that warfarin resulted in improved quality-adjusted survival even among the "oldest old" who possessed significant risk factors for stroke. Warfarin led to worse or equivocal outcomes in younger patients and in older patients with fewer stroke risk factors. Notably, this study assumed fairly high rates of intracranial hemorrhage among older patients and acknowledged the need for more precise data on hemorrhagic complications and AF outcomes among the oldest old.

Conclusions

Studies of the cost-effectiveness of anticoagulation in patients with AF consistently suggest that warfarin improves quality-adjusted survival and reduces costs in patients at high risk for stroke; in patients at low risk for stroke, aspirin is a cost-effective alternative. For patients at moderate stroke risk, warfarin continues to be a cost-effective therapy compared with aspirin. Cost-effectiveness analyses of anticoagulation for AF in older patients are supported by fewer data, particularly because there are few studies of the risks and benefits of warfarin in the very old. However, warfarin does appear to be generally cost-effective in older patients because they are often at high risk for stroke. Notably, these studies were based on assumptions that strokes occurring on and off warfarin therapy result in equivalent decrements in quality of life and cost. Recent evidence suggesting that strokes that occur during warfarin therapy result in lower morbidity and mortality than those occurring off warfarin[14] would further tilt the balance in warfarin's favor.

ANTICOAGULATION FOR PREVENTION OF VENOUS THROMBOEMBOLISM

Surgical patients

Cost-effectiveness analyses of strategies for the prevention of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), in surgical patients have largely focused on warfarin and low-molecular-weight heparins (LMWHs) such as enoxaparin, as well as synthetic pentasaccharides such as fondaparinux. Cost-effectiveness analyses are particularly relevant in these cases because LMWHs are far more expensive but only slightly more effective than warfarin.

LMWH vs warfarin. Several published decision analyses of short-term prophylaxis (4 to 15 days) examining enoxaparin suggest that this balance is in enoxaparin's favor. One study suggested that the expected cost per VTE event avoided was $2,525 less and $87,201 less with enoxaparin than with warfarin for each DVT and PE prevented, respectively.[15] A cost-effectiveness analysis by Garcia-Zozaya[16] found that the overall cost of care for 15 days of prophylactic therapy in joint replacement patients was slightly lower with enoxaparin than with warfarin ($925 vs $972), but these results were not reported in QALYs or in cost-benefit terms. A recent cost-effectiveness analysis comparing 7 days of prophylaxis with warfarin 5 mg daily or enoxaparin 30 mg twice daily in hypothetical US patients undergoing hip replacement suggested that enoxaparin was associated with an incremental cost of $3,733 per QALY saved if only

short-term outcomes were considered.[17] When long-term complications were included, enoxaparin was both less expensive and more effective than warfarin ($89 lower costs per patient with net QALY benefits of 0.16 per patient).

Fondaparinux vs LMWH. A number of decision analyses have compared fondaparinux and enoxaparin for VTE prevention in the orthopedic population. A recent Canadian decision analysis[18] found that the use of fondaparinux in patients undergoing hip or knee surgery would prevent an additional 16 VTE events per 1,000 patients compared with enoxaparin, resulting in a cost savings of $55 (Canadian dollars) per patient. A cost-effectiveness analysis by Spruill et al[19] suggested that prophylactic fondaparinux resulted in an incremental cost savings of $1,081 per VTE event avoided compared with enoxaparin 30 mg twice daily; the incremental cost per life-year gained was $5,437 for enoxaparin and $4,925 for fondaparinux. Another decision analysis in joint replacement and hip fracture patients concluded that fondaparinux would be less costly overall than enoxaparin, largely owing to fewer VTE events and fewer VTE-related deaths.[20]

Prolonged prophylaxis. Recent recommendations from the American College of Chest Physicians[21] add yet another wrinkle to VTE prevention in surgical patients by advising prolonged VTE prophylaxis (28 to 35 days) in patients undergoing hip surgery. Sarasin et al[22] used a decision analysis to evaluate this strategy in patients undergoing hip replacement. Among patients without increased bleeding risks, extending prophylaxis with warfarin, LMWH, or aspirin to 4 weeks after discharge was cost-effective. LMWH was the most clinically effective regimen, and aspirin was the most cost-effective. The results of this analysis were most sensitive to the bleeding complication rate.

Medical patients

Although VTE prophylaxis in medical patients has gained prominence only recently, it has been the subject of a number of decision analyses. Four separate cost-benefit analyses suggest that, compared with aspirin or no therapy, LMWHs prevent VTE at reasonable additional cost;[23–26] those analyses conducted in North America suggest that the incremental cost to avoid a VTE ranges from $87 to $3,088. One cost-effectiveness analysis suggested that, compared with no prophylaxis, the incremental cost to avert a VTE-related death with enoxaparin 40 mg daily was $9,100.[27] In this analysis, enoxaparin was more cost-effective than unfractionated heparin 5,000 U twice daily because of greater efficacy and reduced costs of complications.

Conclusions

Most of the evidence for the cost-effectiveness of VTE prevention in surgical patients has focused on orthopedic patients, in whom enoxaparin appears to be more cost-effective than warfarin. In these same patients, fondaparinux appears to prevent VTE at a reasonably low cost, but there are few data to describe the effectiveness of fondaparinux in terms of QALYs. For prolonged prophylaxis in surgical patients, fondaparinux appears to be less costly and more effective than enoxaparin; again, these results are based more on cost-benefit methods than on QALY-based cost-effectiveness analysis.

Although LMWHs are less well studied in medical patients than in surgical patients, they appear to have similar advantages when used for VTE prevention in medical patients, where their higher costs relative to aspirin and unfractionated heparin are offset by cost savings due to VTE events averted.

ANTICOAGULATION FOR ACUTE MANAGEMENT OF VENOUS THROMBOEMBOLISM

The initial treatment of VTE is now dominated by anticoagulants that can be given subcutaneously and do not require laboratory monitoring—specifically, enoxaparin and fondaparinux. Use of these drugs has moved VTE treatment to the outpatient setting, avoiding the costs of lengthy hospital stays. A cost-effectiveness analysis by Gould et al[28] found that an enoxaparin-based approach is quite cost-effective when compared with usual (ie, inpatient) care with unfractionated heparin, incurring an incremental cost of $7,280 per QALY gained.

There are currently no data available for evaluating the cost-effectiveness of fondaparinux relative to enoxaparin for acute VTE treatment.

Conclusions

LMWH therapy is more expensive than older therapies but is more cost-effective, almost entirely because it obviates the need for prolonged hospital admission, not because of improved effectiveness.

ANTICOAGULATION FOR CHRONIC MANAGEMENT OF VENOUS THROMBOEMBOLISM

Recurrence of VTE is common, particularly among patients with idiopathic thromboses or predisposing hypercoagulable conditions. While longer courses of anticoagulation reduce recurrence, they also increase the costs of therapy and monitoring. In addition, patients with indications for lifelong anticoagulation (such as those with certain prothrombotic disorders)

TABLE 2
Summary of economic analyses of anticoagulation

Indication	Summary of evidence
Stroke prevention in patients with nonvalvular atrial fibrillation (AF)	Compared with aspirin, warfarin is cost-effective at an incremental cost of < $100,000 per QALY gained in patients at high and moderate risk for AF-related stroke. Warfarin is not as cost-effective in patients at low risk for AF-related stroke.
Prevention of venous thromboembolism	• *Surgical patients:* Enoxaparin is superior to unfractionated heparin for prophylaxis (incremental cost < $100,000 per QALY gained) in orthopedic surgical patients; fondaparinux is potentially cost-saving vs enoxaparin for short-term prophylaxis. For prolonged prophylaxis, use of any agent is cost-effective relative to usual care; enoxaparin may prevent additional events at reasonable cost. • *Medical patients:* Enoxaparin is superior to unfractionated heparin in high-risk medical patients
Acute treatment of venous thromboembolism	Enoxaparin is cost-effective relative to usual care, largely due to avoidance of hospital costs
Secondary prevention of venous thromboembolism	Little data to support cost-effectiveness of any anticoagulation approach; strategies that use warfarin in patients at highest risk for recurrence appear to be cost-effective
Anticoagulation management strategies (clinics, patient self-testing)	Mixed results—likely fewer emergency visits with anticoagulation clinics, but effectiveness of other strategies is sensitive to uncertainty in efficacy data

QALY = quality-adjusted life-year

tend to be younger, exposing them to risk for therapy-related adverse events for a longer time than patients with AF, for example. Once the decision is made to embark on long-term anticoagulation, warfarin remains standard therapy, as other options (eg, heparin pumps, LMWHs) are supported by too few data to allow cost-effectiveness analysis. The few studies examining secondary prevention suggest that the risk-benefit ratio of long-term warfarin therapy in these patients is influenced primarily by the baseline risk of VTE recurrence and lifetime risk for adverse events, and that long-term anticoagulation is less effective (and cost-effective) in patients at low risk for recurrence.[29,30]

ANTICOAGULATION CLINICS AND COST

Strategies for long-term oral anticoagulation management, such as the establishment of anticoagulation clinics or patient self-testing with home capillary blood monitors, are attractive options because they reduce patients' need for repeated clinic visits or hospitalizations. As such, they have been the subject of several economic analyses.

Chiquette et al[31] compared hospitalization and emergency department costs of hypothetical patients in an anticoagulation clinic with anticoagulated patients receiving usual medical care and found that anticoagulation clinics saved $1,620 per patient per year, largely owing to fewer hemorrhages and thromboembolic events. This study did not report results in terms of QALYs or the incremental cost of managing an anticoagulation clinic.

Another analysis compared usual care, care in an anticoagulation clinic, and patient self-testing; it assumed that patients would be in therapeutic international normalized ratio (INR) range 50% of the time with usual care, 65% of the time with anticoagulation clinic care, and 89% of the time with self-testing.[32] Using these assumptions, the authors calculated the anticipated number of hemorrhages and thromboembolic events and also tabulated costs from the patient, provider, and societal perspectives. Not surprisingly, costs in this study were highly sensitive to the perspective chosen and the type of costs included in the model (eg, direct medical costs only, or inclusion of indirect costs of traveling to clinic appointments). For instance, changing from usual care to an anticoagulation clinic was cost-saving from the individual provider perspective but shifted costs to the patient; changing to patient self-testing was cost-effective from the individual patient perspective because it reduced clinic visits and indirect costs. In general, more definitive data on outcomes associated with each strategy are needed before valid cost comparisons can be made.

INVESTIGATIONAL ANTICOAGULANTS

The orally administered direct thrombin inhibitor ximelagatran has been studied as an alternative to warfarin for several indications, notably stroke pre-

vention in patients with AF, chronic VTE treatment, and postoperative prevention of VTE.[33,34] Ximelagatran has substantial potential advantages over warfarin in that it does not require INR monitoring, has no known interactions with drugs metabolized via the cytochrome P450 isoenzyme, and produces reliable anticoagulation at fixed doses.

However, the US Food and Drug Administration has not approved the use of ximelagatran because of concerns about liver toxicity and coronary events. Even if eventually approved, ximelagatran is unlikely to be cost-effective compared with warfarin for most patients with AF. The exceptions may be patients who have low quality of life with warfarin therapy and those whose intracranial hemorrhage rates are lower on ximelagatran than on warfarin.[35] However, current cost-effectiveness analyses are limited by the lack of longer follow-up studies detailing the incidence of adverse events on ximelagatran therapy.

SUMMARY AND IMPLICATIONS

Results from a variety of economic analyses (summarized in **Table 2**) of anticoagulation for various indications suggest a couple of general themes:

- Anticoagulation is most effective and results in the greatest cost savings when applied to populations at highest risk for thrombotic events, a consistent finding in studies examining anticoagulation for nonvalvular AF.
- In situations where a more costly agent is available (eg, enoxaparin vs unfractionated heparin), the more costly agent is cost-effective only if it is truly more efficacious or if it can substantially reduce costs in other areas, such as by avoiding hospitalizations for treatment of VTE.

As newer anticoagulant agents become available, clinicians should consider these themes to maximize the cost-effectiveness of their anticoagulation strategies.

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