ORIGINAL INVESTIGATION

Prophylactic Antithrombotic Therapy for Patients With Systemic Lupus Erythematosus With or Without Antiphospholipid Antibodies

Do the Benefits Outweigh the Risks? A Decision Analysis

Denis G. Wahl, MD, PhD; Henri Bounameaux, MD; Philippe de Moerloose, MD; François P. Sarasin, MD

Background: A high incidence of both arterial and venous thromboembolic events has been reported in patients with systemic lupus erythematosus (SLE), but the risks and benefits of primary prophylactic antithrombotic therapy have not been assessed. We measured the clinical benefit of 3 antithrombotic regimens in patients with SLE without antiphospholipid antibodies, with anticardiolipin antibodies, or with lupus anticoagulant.

Methods: A Markov decision analysis was used to evaluate prophylactic aspirin therapy, prophylactic oral anticoagulant therapy, and observation. Input data were obtained by literature review. Clinical practice was simulated in a hypothetical cohort of patients with SLE who had not experienced any previous episode of arterial or venous thromboembolic events. For each strategy, we measured numbers of thromboembolic events prevented and major bleeding episodes induced, and quality-adjusted survival years.

Results: Prophylactic aspirin therapy was the preferred strategy in all settings, the number of prevented thrombotic events exceeding that of induced bleeding episodes. In the baseline analysis (40-year-old patients with SLE), the gain in quality-adjusted survival years achieved by prophylactic aspirin compared with observation ranged from 3 months in patients without antiphospholipid antibodies to 11 months in patients with anticardiolipin antibodies or lupus anticoagulant. Prophylactic oral anticoagulant therapy provided better results than prophylactic aspirin only in patients with lupus anticoagulant and an estimated bleeding risk of 1% per year or less.

Conclusions: Prophylactic aspirin should be given to all patients with SLE to prevent both arterial and venous thrombotic manifestations, especially in patients with antiphospholipid antibodies. In selected patients with lupus anticoagulant and a low bleeding risk, prophylactic oral anticoagulant therapy may provide a higher utility.

Arch Intern Med. 2000;160:2042-2048

From the Division of Angiology and Hemostasis (Drs Wahl, Bounameaux, and de Moerloose), and Clinique de Médecine 1 (Dr Sarasin), Department of Internal Medicine, Hôpitaux Universitaires de Genève, Geneva, Switzerland. Dr Wahl is now with the Service de Médecine Interne H, Centre Hospitalier Universitaire, Nancy, and Faculté de Médecine, Vandoeuvre-Les-Nancy, France.

More than 200 000 Americans are estimated[1] to have suspected or definite systemic lupus erythematosus (SLE). Both arterial and venous thromboembolic events have been reported in a substantial proportion of these patients. The prevalence of these events is higher than 10% and may even exceed 50% in some high-risk patients.[2] Several mechanisms have been proposed to explain this thrombotic tendency, including the presence of the so-called antiphospholipid antibodies (aPLA), particularly anticardiolipin antibodies and the lupus anticoagulant (LA).[2-6] Several environmental or genetic factors may increase this tendency.[7,8]

While most authors advocate the use of antithrombotic therapy only in patients with aPLA and thromboembolic events,[9] there is no consensus as to whether patients who have not yet experienced any thrombotic event might also be given prophylaxis.[10] Since there are no large controlled trials that address these issues, we used a decision analysis model to evaluate 2 possible prophylactic strategies (using aspirin or oral anticoagulants) in patients with SLE compared with observation alone. Specifically, we addressed the following questions: (1) based on the available evidence from the literature, what is the net clinical benefit of prophylactic antithrombotic agents? (2) Are there identifiable subgroups of patients who might achieve greater benefit from these therapeutic modalities?

RESULTS

BASELINE ANALYSIS

We compared clinical outcomes after 5 years in a cohort of 40-year-old patients as a function of different risks of arterial

MATERIALS AND METHODS

Decision analysis explicates the logic of a choice among alternate strategies. To analyze a decision, one defines possible strategies, describes plausible and important clinical events associated with each strategy, and specifies the probability of each event. One estimates the value of each possible state of health resulting from each strategy and calculates the average expected value of pursuing each strategy. The axioms of decision analysis dictate that the strategy with the greatest expected value is preferred. We describe the structure of this analysis in general below.

ASSUMPTIONS

The absence of published information required assumptions on several points. These assumptions are listed below.

(1) We assumed that the daily dosage of aspirin was 100 to 325 mg. For patients taking oral anticoagulants: (2) we assumed the targeted international normalized ratio to be between 2.0 and 3.0; (3) we considered only the risks of major hemorrhagic events (intracranial, retroperitoneal, or those that resulted in hospital admission or transfusion), some of them leading to death; and (4) we assumed the risk of major bleeding to be constant while patients are receiving anticoagulant therapy, ignoring the potentially higher risk of bleeding at treatment initiation and possible variation of this risk with age (analysis restricted to patients aged 20 to 60 years). (5) For patients receiving oral anticoagulant therapy and surviving a major bleeding event without having previously suffered a thromboembolic event (arterial and/or venous), we assumed that prophylactic oral anticoagulant therapy was discontinued permanently, or (6) for patients recovering from venous and/or arterial embolic events who suffer a nonfatal hemorrhage, that anticoagulant therapy was discontinued for 1 month and then was resumed. (7) Patients sustaining long-term morbidity from an event (eg, arterial embolism) were still subject to the risks of future events (eg, bleeding), and (8) finally, we did not take into consideration long-term morbidity from deep venous thrombosis (the postthrombotic syndrome) and from nonfatal pulmonary embolism (secondary pulmonary arterial hypertension).

DECISION TREE

The choice between the 3 competing strategies is depicted by the square shaded node on the left in **Figure 1**, A. These strategies include (1) observation, in which prolonged oral anticoagulant therapy is started in patients having suffered and survived a clinically apparent thromboembolic event; (2) prophylactic aspirin, in which aspirin is started before the occurrence of any thromboembolic event and is switched for oral anticoagulants if a thromboembolic event occurs; and (3) prophylactic oral anticoagulant therapy, in which oral anticoagulant therapy is started before the occurrence of any clinically apparent thromboembolic event.

We used a Markov subtree[11-13] to model repetitive clinical events beyond the patient's and physician's control. In a Markov process, patients move between various health states depending on the chance events modeled in the decision tree and the probability of those events. States of health are long-term (eg, morbidity after systemic embolism), or short-term (eg, discontinuation of anticoagulant therapy after the occurrence of a major bleeding episode). Patients may move from one health state to another with each "tick of the clock" or cycle. In this model, each cycle is 1 month long, to allow switching to another therapy (eg, from prophylactic oral anticoagulant therapy to observation) in case of occurrence of an adverse event. We calculated the average value (expected utility) of each strategy by tracking how much time is spent in each health state and the consequences of being in that health state (eg, quality-adjustment factor). The states are listed in Figure 1, A.

At the beginning of the Markov process, patients are well and are in one of the following states: taking oral anticoagulant therapy (well while taking oral anticoagulants), taking oral aspirin (well while taking aspirin), or not taking any prophylactic therapy (well without antithrombotics). In each case, 3 groups of events are possible: thromboembolic events (venous and/or arterial), major bleeding events, and death from demographic and comorbidity-related causes (Figure 1, B and C). Patients face the risk of these same events during each cycle but at different probabilities, depending on the initial strategy. In each cycle, more than 1 event may occur (eg, long-term morbidity after arterial thromboembolism and long-term morbidity after bleeding). Thus, in each cycle, 1 of the 9 mutually exclusive outcomes will occur, resulting in a new distribution across the health states shown in Figure 1, A.

PROBABILITIES AND RATES USED IN THE ANALYSIS

Table 1 summarizes the rates and probabilities used in the analysis derived from published systematic reviews and meta-analyses. Estimates that could not be derived by an explicit approach were obtained by either individual studies or consensus statements. The range of estimates used in sensitivity analyses are included. (Additional information is available from the authors upon request.)

ANALYSIS OF OUTCOMES

In this analysis, we measured the outcome of each strategy (1) by tracking the number of thromboembolic events prevented and the number of major bleeding events induced in the 3 strategies and (2) in terms of quality-adjusted life years (QALYs).[29,30] The QALY addresses both longevity and quality of life. As life expectancy is calculated by the Markov process, it is adjusted for the loss of quality experienced by the patient with each strategy. Quality of life is diminished by reducing functional capabilities in both the short and long term. A month spent in the patient's baseline state of health is assigned 1 full quality-adjusted month, and months in which the patient has morbidity (such as hemiplegia) are given values between 0 and 1. **Table 2** lists the baseline long-term quality-of-life adjustments used in the analysis.

and/or venous thromboembolic complications. Specifically, the number of arterial and venous embolic episodes prevented by prophylactic aspirin and prophylactic oral anticoagulant therapy compared with observation was balanced against the number of major hemorrhages induced by these strategies. This relationship is depicted in **Figure 2**. Prophylactic aspirin was the preferred strategy, as the number of arterial and venous

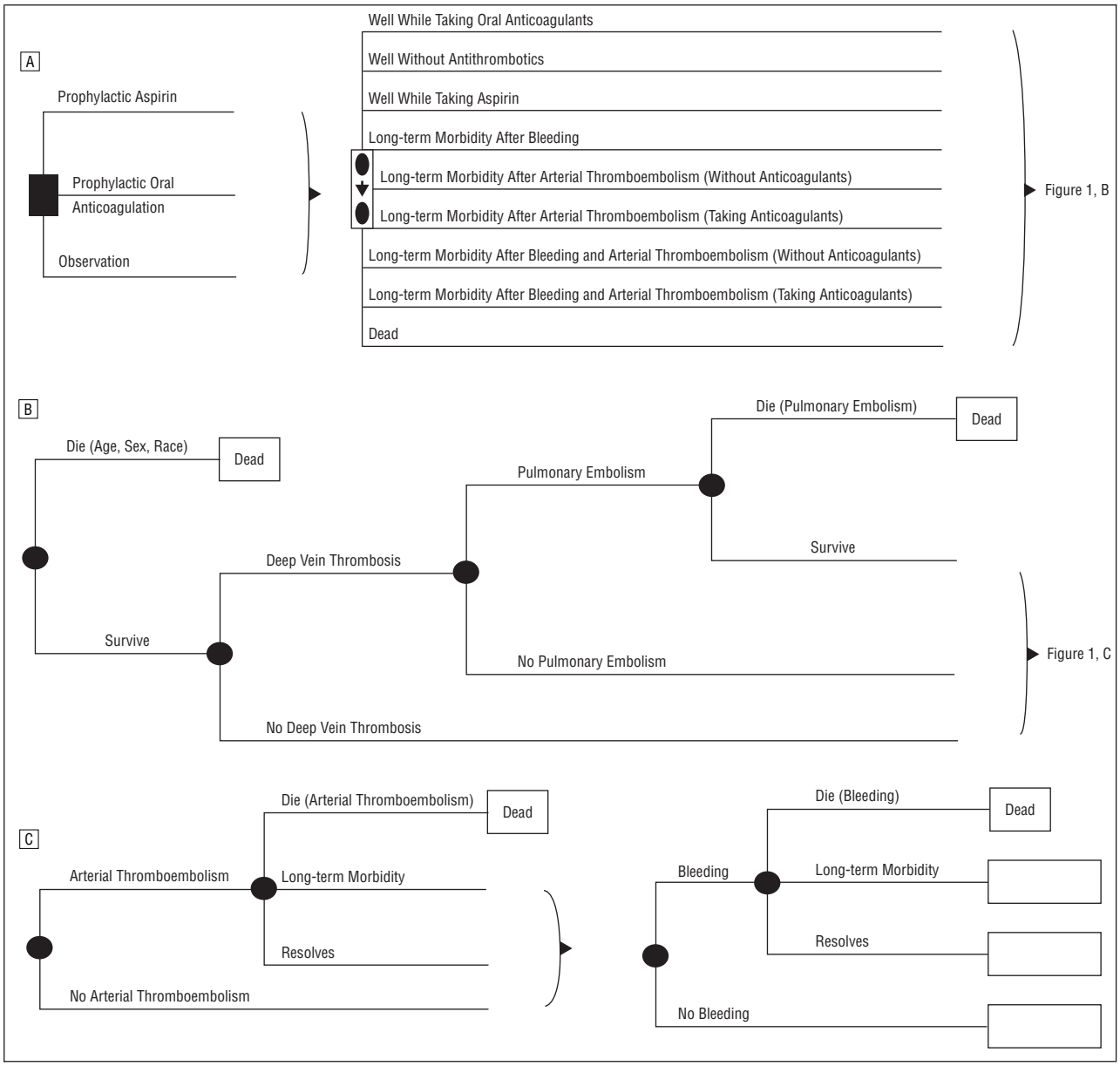

Figure 1. *The decision tree. The square node (A) represents the choice between the 3 strategies: prophylactic aspirin therapy, prophylactic oral anticoagulant therapy, and observation. The figure is divided into 3 subtrees that represent the initial decision and the Markov states of health (A), complications from venous thromboembolic events (B), and complications from arterial thromboembolic events and bleeding events (C).*

thromboembolic events prevented by this option exceeded that of major bleeding episodes induced in all risk scenarios. In addition, the overall number of disabling events (related to hemorrhage and thrombosis) associated with this strategy was smaller than in the other strategies. The number of arterial and venous thromboembolic events prevented by prophylactic oral anticoagulant therapy overwhelmed that of major bleeding events compared with observation, only for patients with a high thrombotic tendency (LA+). However, this option was associated with more disabling events than prophylactic aspirin.

For the clinical scenario of a 40-year-old patient with a low thrombotic tendency (aPLA–), prophylactic aspirin provided the greatest quality-adjusted life expectancy (29 QALYs). This represented an additional 3 months of quality-adjusted survival compared with observation (28.7 QALYs), and 2.5 years compared with prophylactic oral anticoagulant therapy (26.3 QALYs). As expected, when the thrombotic tendency increased, the gain in QALYs provided by prophylactic aspirin increased compared with the observation. For a 40-year-old patient with an intermediate risk of arterial or venous thromboembolism (positive for anticardiolipin antibodies), the expected number of QALYs provided by prophylactic aspirin was 24.6. This represented a gain of 11 months compared with observation (23.7 QALYs), and of 17 months compared with prophylactic oral anticoagulant therapy (23.2 QALYs). Finally, in the setting of high thromboembolic risk (LA+), prophylactic aspirin–related survival was 21.7 QALYs, representing a gain of 11 months compared with observation (20.8 QALYs),

Table 1. Probabilities and Rates Used in the Analysis*

Variable	Baseline Value, %	Range, %	References
Thromboembolism			
Rate of VTE in patients without aPLA†	1	0.5-2	3-5, 14
Rate of VTE in patients with LA†	6.3	3.7-10.8	5, 6, 15
Rate of VTE in patients with aCL†	2.5	1.5-4.2	5, 6, 15
Rate of ATE in patients without aPLA†	1	0.5-2	3-5, 14
Rate of ATE in patients with LA†	6.2	4.2-9.3	5, 6, 15
Rate of ATE in patients with aCL†	3.7	2.4-5.7	5, 6, 15
PE in patients with treated VTE‡	1.7	1.3-2	16
Death in patients with treated VTE‡	12	7-18	16
Death from ATE‡	25	8-35	17, 18
Permanent disability for survivors of ATE‡	44	35-71	17, 18
Efficacy of antithrombotic agents			
Efficacy of oral anticoagulation in preventing VTE§	50	11-72	19-21
Efficacy of aspirin in preventing VTE§	23	10-43	22
Efficacy of oral anticoagulation in preventing ATE§	34	10-60	19-21, 23
Efficacy of aspirin in preventing ATE§	25	21-29	23, 24
Major bleeding events			
Rate in patients taking oral anticoagulants†	2.7	1-5	25, 26
Rate in patients taking aspirin†	0.3	0.1-1	22, 24
Death from major bleeding‡	20.6	15-27	25
Morbidity in survivors of major bleeding‡	11	2.8-19	25
Excess annual mortality rate of SLE‖	1	1-6	27, 28

*VTE indicates venous thromboembolism; aPLA, antiphospholipid antibodies; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; ATE, arterial thromboembolism; PE, pulmonary embolism; and SLE, systemic lupus erythematosus.

†Monthly transition probabilities were calculated for the Markov simulation from annual rates by means of the following formula: monthly probability = 1–e(–annual rate/12)

‡Probabilities.

§Efficacy = (events in untreated patients – events in treated patients)/events in untreated patients.

‖With the use of the assumption of a declining exponential approximation to survival, the annual excess mortality can be expressed as the reciprocal of life expectancy.[29,30]

Table 2. Quality-of-Life Adjustment Factors Used in the Analysis*

Utilities	Baseline Value	Range	References
Long-term morbidity after disabling ATE	0.50	0.25-0.75	17, 18
Long-term morbidity after disabling major bleeding	0.29	0.13-0.45	31
Long-term morbidity after disabling ATE and major bleeding	0.15	0.06-0.23	17, 18, 31
Oral anticoagulation	0.99	0.95-1.00	17, 18
Quality of life of patients with SLE	0.55	0.37-0.77	32

*ATE indicates arterial thromboembolism; SLE, systemic lupus erythematosus.

and 9 months compared with prophylactic oral anticoagulant therapy (21 QALYs).

SENSITIVITY ANALYSIS

The previously described results depend largely on the baseline values used in the model, but estimates of these variables vary in the published literature. After sensitivity analyses were performed on all variables in the model, 3 critical variables emerged, in addition to the venous and/or arterial embolic risk profile: the incidence of treatment-related complications (major bleeding), treatment efficacy, and patient age. In patients with a high thrombotic tendency (LA+), prophylactic oral anticoagulant therapy became the preferred strategy when the rate of major hemorrhage was below 1% per year, or when the efficacy of oral anticoagulant therapy in preventing thromboembolism was above 51% ("threshold" values). **Table 3** depicts the threshold values of these 2 variables in different clinical settings. **Table 4** represents the gain in QALYs achieved by prophylactic aspirin therapy compared with observation for different age groups. Primary prophylaxis with aspirin remained the preferred strategy over the whole range from 20 to 60 years of age.

The effect of varying 2 variables simultaneously (2-way sensitivity analysis) can be assessed. **Figure 3** and **Figure 4** represent 2-way sensitivity analyses. In Figure 3 the horizontal axis represents the rate of thromboembolic events, whereas the vertical axis represents efficacy of aspirin. In Figure 4 the horizontal axis represents the rate of major bleeding with aspirin, whereas the vertical axis represents efficacy of aspirin. Thus, any point in these graphs represents a specific pair of values for different rate of thromboembolism (Figure 3) or aspirin-related complications (Figure 4) and for different treatment efficacy (vertical axis). For combinations falling in the upper left region (low rate of complications and high

efficacy), prophylactic aspirin therapy is preferred to observation. On the opposite, for values falling toward the lower right region (high rate of complications and low efficacy), the observation strategy is preferred. All points falling on one of the lines yielded the same QALYs for the 2 strategies.

COMMENT

The benefit of primary prophylaxis with aspirin outweighs its risks in patients with SLE. This benefit is proportional to the thrombotic tendency, becomes quite substantial in patients with aPLA, and translates into a gain in life expectancy. For example, in the case of a 30-year-old patient with aPLA, the quality-adjusted survival gain provided exceeds 1 year. Prophylactic oral anticoagulant therapy may also be an option but only in a well-defined subgroup, namely, patients with a high thrombotic tendency (LA+) and a low bleeding risk. The latter (≤1% per year) has only been approached in the setting of some anticoagulant clinics and in patient groups that might differ from those with SLE.[26,33] Thus, a 20-year-old LA+ patient without comorbidity might be a good candidate for oral anticoagulant therapy. Moreover, the advantage of this option might be further increased by reducing the international normalized ratio to 1.5 to 2.0.[23] However, there are insufficient data to support the latter recommendation at the present time.

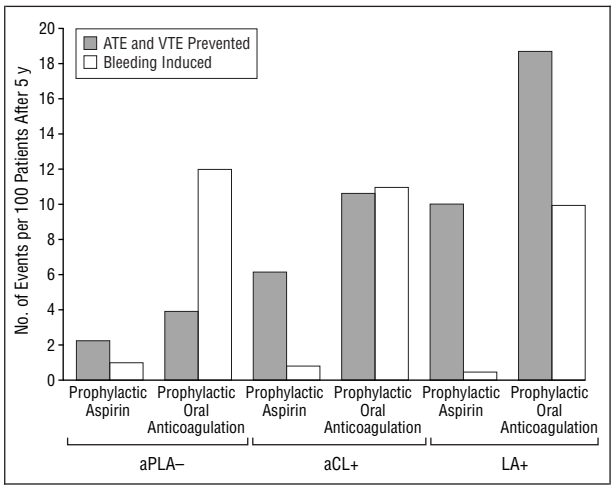

Figure 2. *Balance between the number of embolic events prevented and bleeding events induced by different types of prophylaxis compared with observation during a 5-year period. ATE indicates arterial thromboembolic events; VTE, venous thromboembolic events; aPLA–, patients without antiphospholipid antibodies; aCL+, patients with anticardiolipin antibodies; and LA+, patients with lupus anticoagulant.*

Our results favor primary antithrombotic prophylaxis (aspirin or oral anticoagulants), despite the fact that we consistently biased our analysis against these 2 strategies. Specifically, we underestimated the efficacy of both aspirin and oral anticoagulants and used rather high estimates for the bleeding risks. However, these figures may, over time, underestimate the bleeding risks, especially that of oral anticoagulant therapy, because patients with SLE may have multiple medications and comorbidities that may increase the hemorrhagic tendency. Moreover, this risk has to be viewed in the perspective of a long-term treatment.

These results are important in daily practice because of the uncertainty of physicians in charge of these patients. Indeed, current therapeutic approaches are based mainly on clinicians' best judgment. Of course, our analysis cannot replace longitudinal trials and certainly should not be used as a formal guideline. However, clinical studies designed to assess the risk of thromboembolic complications and the efficacy of various treatments in asymptomatic patients will probably not be available in the near future. In the meantime, our model may represent a useful tool for clinicians to facilitate decision making. Given the reported prevalence of SLE or SLE-like disease in the United States (40 to 50 cases per 100 000 persons), around 240 000 Americans have suspected or definite SLE[1] and might benefit from prophylaxis if they have not experienced previous thrombotic events. The low cost of aspirin prevented us from performing a formal cost-effectiveness analysis. However, it can be anticipated that such a strategy would even be cost saving because of the high costs induced by thromboembolic complications.

The limitations of our study also warrant comments. First, the efficacy of aspirin has not been established in the setting of SLE, and our estimates were obtained from randomized trials and overviews in general medical patients. However, we performed sensitivity analyses in which efficacy was varied over wide ranges, which did not affect the ranking of strategies. Second, our classification of the thrombotic risk relying on the presence of anticardiolipin antibodies and LA does not take into consideration more refined patient characteristics, such as prothrombin or β_2-glycoprotein I binding

Table 3. Threshold Values of Variables Affecting the Choice Among Treatment Strategies*

Strategy	Variable	Lupus Anticoagulant, %	Anticardiolipin Antibodies, %	Patients Without aPLA, %
Observation vs prophylactic aspirin	Rate of bleeding (aspirin)	2.3	1.5	0.4
	Efficacy (aspirin)	3.0	3.7	16.0
Observation vs prophylactic OAC	Rate of bleeding (OAC)	3.0	1.9	0.5
	Efficacy (OAC)	29.0	47.0	NT
Prophylactic aspirin vs prophylactic OAC	Rate of bleeding (OAC)	1.0	0.8	0.4
	Rate of bleeding (aspirin)	1.9	2.2	2.6
	Efficacy (OAC)	51.0	67.0	NT
	Efficacy (aspirin)	7.0	NT	NT

**aPLA indicates antiphospholipid antibodies; OAC, oral anticoagulation; and NT, no threshold.*

Table 4. Quality-Adjusted Survival Gains Provided by Prophylactic Aspirin Compared With Observation in Patients With Low (Patients without aPLA), Intermediate (Patients With aCL), and High (Patients With LA) Thrombotic Tendency*

Clinical Setting	Age at Treatment Initiation, y				
	20	30	40	50	60
Patients without aPLA	6.4	4.7	3.0	2.1	1.1
Patients with aCL	14.7	12.6	11.0	7.5	4.9
Patients with LA	14.0	12.7	11.0	8.6	6.0

**Quality-adjusted survival gains are given in months. aPLA indicates antiphospholipid antibodies; aCL, anticardiolipin antibodies; and LA, lupus anticoagulant.*

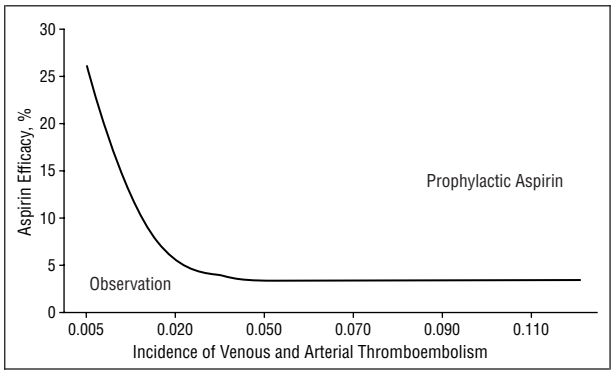

Figure 3. *Two-way sensitivity analysis showing the threshold curve between observation and prophylactic aspirin. The horizontal axis represents the incidence of venous and arterial thromboembolism, and the vertical axis, efficacy of aspirin. For values below the curve, observation is the preferred strategy; for example, a patient with a 4% annual rate of arterial or venous thromboembolism will benefit from prophylactic aspirin if treatment efficacy is 5%. Conversely, a patient with a 1% annual rate of arterial or venous thromboembolism will achieve greater benefit with observation if treatment efficacy is 20%.*

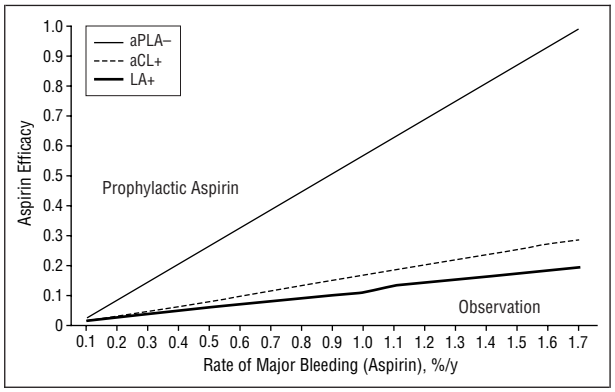

Figure 4. *Two-way sensitivity analysis showing several threshold curves between observation and prophylactic aspirin therapy. The horizontal axis represents the rate of major bleeding, and the vertical axis, efficacy of aspirin. For values below each curve (patients with lupus anticoagulant [LA+] or anticardiolipin antibodies [aCL+] or patients without antiphospholipid antibodies [aPLA–]), observation is the preferred strategy.*

antibodies,[4,5,34] associated inherited thrombophilia,[8,35] or evidence of a prothrombotic state as assessed by activation markers such as abnormal levels of prothrombin fragment 1+2.[9] Third, comorbidities that are frequent in SLE may influence both thrombotic and hemorrhagic risks; for example, concomitant use of nonsteroidal anti-inflammatory drugs may potentiate gastrointestinal tract side effects of aspirin.[36,37] Conversely , a highly inflammatory state might increase the thromboembolic risk.

In conclusion, SLE is a complex disease with a wide spectrum of thrombotic and hemorrhagic tendency. Our decision analysis model handles part of this complexity and suggests that primary prophylaxis with aspirin is beneficial to all patients with SLE who have not yet experienced any thrombotic event. Under special circumstances, prophylactic oral anticoagulant therapy might provide a higher benefit. Ideally, this hypothesis should be confirmed in randomized controlled trials, which, however, would be difficult to set up because of the complexity of the issues.

Accepted for publication January 28, 2000.

Reprints: Denis G. Wahl, MD, PhD, Service de Médecine H, Hôpital Central, CO#34, 29, avenue de Lattre de Tassigny, F54035 Nancy, France (e-mail: dwahl @club-internet.fr).

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-779.
2. Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders: prevalence and clinical significance. *Ann Intern Med.* 1990;112:682-698.
3. Petri M, Roubenoff R, Dallal GE, Nadeau MR, Selhub J, Rosenberg IH. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet.* 1996;348:1120-1124.
4. Puurunen M, Vaarala O, Julkunen H, Aho K, Palosuo T. Antibodies to phospholipid-binding plasma proteins and occurrence of thrombosis in patients with systemic lupus erythematosus. *Clin Immunol Immunopathol.* 1996;80:16-22.
5. Horbach DA, van Oort E, Donders RCJM, Derksen RHWM, de Groot PG. Lupus anticoagulant is the strongest risk factor for both venous and arterial thrombosis in patients with systemic lupus erythematosus. *Thromb Haemost.* 1996;76:916-924.
6. Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus: a meta-analysis. *Lupus.* 1997;6:467-473.
7. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med.* 1992;93:513-519.
8. Fijnheer R, Horbach DA, Donders RCJM, et al. Factor V Leiden, antiphospholipid antibodies and thrombosis in systemic lupus erythematosus. *Thromb Haemost.* 1996;76:514-517.
9. Shapiro SS. The lupus anticoagulant/antiphospholipid syndrome. *Annu Rev Med.* 1996;47:533-553.
10. McCrae KR. Antiphospholipid antibody associated thrombosis: a consensus for treatment? *Lupus.* 1996;5:560-570.
11. Pauker SG, Sonnenberg FA, Wong JB. *Decision Maker 7.05.* Boston, Mass: Pratt Medical Group; 1996.
12. Beck JR, Pauker SG. The Markov model in medical prognosis. *Med Decis Making.* 1983;12:419-458.
13. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making.* 1993;13:322-338.
14. Alarcon-Segovia D, Perez-Vazquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. *Semin Arthritis Rheum.* 1992;21:275-286.
15. Nojima J, Suehisa E, Akita N, et al. Risk of arterial thrombosis in patients with anticardiolipin antibodies and the lupus anticoagulant. *Br J Haematol.* 1997;96:447-450.
16. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA.* 1998;279:458-462.
17. Eckman MH, Levine HJ, Salem DN, Pauker SG. Making decisions about antithrombotic therapy in heart disease: decision analytic and cost-effectiveness issues. *Chest.* 1998;114(suppl):699S-714S.
18. Disch DL, Greenberg ML, Holtzberger PT, Malenka DK, Birkmeyer JD. Manag-

ing chronic atrial fibrillation: a Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. *Ann Intern Med*. 1994;120:449-457.
19. Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med*. 1992;117:303-308.
20. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995;332:993-997.
21. Krnic-Barrie S, O'Connor CR, Looney SW, Pierangeli SS, Harris EN. A retrospective review of 61 patients with antiphospholipid syndrome: analysis of factors influencing thrombosis. *Arch Intern Med*. 1997;157:2101-2108.
22. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ*. 1994;308:235-246.
23. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet*. 1998;35:233-241.
24. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994; 308:81-108.
25. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91-99.
26. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet*. 1998;348:423-428.
27. Gladman DD, Hochberg MC. Epidemiology of systemic lupus erythematosus. In: Lahita RG, ed. *Systemic Lupus Erythematosus*. 3rd ed. San Diego, Calif: Academic Press; 1999:537-550.
28. Silverstein MD, Albert DA, Hadler NM, Ropes MW. Prognosis in SLE: comparison of Markov model to life table analysis. *J Clin Epidemiol*. 1988;41:623-633.
29. Beck JR, Pauker SG, Gottlieb JE, Klein K, Kassirer JP. A convenient approximation of life expectancy (the "DEALE"), II: use in decision-making. *Am J Med*. 1982; 73:889-897.
30. National Center for Health Statistics. *Vital Statistics of the United States, 1988, Vol II, Mortality, Part A*. Washington, DC: Public Health Service; 1991.
31. O'Meara JJ, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. *N Engl J Med*. 1994;330:1864-1869.
32. Fortin PR, Abrahamowicz M, Neville C, et al. Impact of disease activity and cumulative damage on the health of lupus patients. *Lupus*. 1998;7:101-107.
33. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med*. 1998;158:1641-1647.
34. Wahl DG, de Maistre E, Guillemin F, Regnault V, Perret-Guillaume C, Lecompte T. Antibodies against phospholipids and β_2-glycoprotein I increase the risk of recurrent venous thromboembolism in patients without systemic lupus erythematosus. *QJM*. 1998;91:125-130.
35. Sarasin FP, Bounameaux H. Decision analysis model of prolonged oral anticoagulant treatment in factor V Leiden carriers with first episode of deep vein thrombosis. *BMJ*. 1998;316:95-99.
36. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med*. 1986;104: 390-398.
37. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med*. 1991;115:787-796.