Longterm Anticoagulation Is Preferable for Patients with Antiphospholipid Antibody Syndrome. Result of a Decision Analysis

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ABSTRACT. ***Objective.*** Patients with antiphospholipid antibody syndrome (APS) have a high risk for rethrombosis. Anticoagulation with warfarin and aspirin reduces the frequency of recurrences. No universally accepted approach regarding the duration and intensity of antithrombotic therapy exists. We investigated the best antithrombotic regimen for patients with APS after the first deep venous thrombosis (DVT).

Methods. We identified 6 anticoagulation regimens used in such patients, the rates of morbidity and mortality associated with bleeding, and the rates of recurrent thrombosis associated with APS by literature search. A decision tree was developed and the expected risks and benefits of each anticoagulation regimen were assessed at 2 different time points: at one year and again 4 years after the initial thrombosis.

Results. Based on the decision analysis, longterm warfarin alone at an international normalization ratio (INR) between 3.0 and 4.0 had the highest expected utility of the 6 antithrombotic regimens, both one year and 4 years after the initial venous thrombotic event. Short term anticoagulation for only 6 months is less beneficial. Combination therapy of warfarin and aspirin (ASA) does not offer an improvement in the expected utility over warfarin alone.

Conclusion. Although the applicability of this analysis to clinical decision-making is not entirely clear, patients with APS presenting with DVT appear to benefit from longterm warfarin (INR 3.0–4.0) that may be superior to warfarin (INR 2.0–3.0). Short term warfarin therapy seems to be less beneficial and the use of ASA does not offer a clear additional benefit. Randomized controlled trials are needed to provide a better basis for recommendations for the treatment APS. (J Rheumatol 2002;29:490–501)

Key Indexing Terms:
DECISION ANALYSIS
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Antiphospholipid antibodies (aPL) are a heterogeneous group of antibodies with specificity for anionic phospholipids and phospholipid-binding proteins[1,2]. Anticardiolipin antibodies (aCL) and lupus anticoagulants are 2 subsets of aPL. They are associated with increased risk for the development of thrombosis, pregnancy loss, and thrombocytopenia[3-6]. If a patient who has persistent aPL develops one or more of these conditions, the diagnosis of antiphospholipid antibody syndrome (APS) is made. Patients diagnosed with APS who develop an initial episode of venous thrombosis have an increased risk of subsequent venous thrombotic events (VTE) and possibly arterial thrombotic events (ATE)[7-9].

Current therapy of patients when they present with an initial episode of VTE is controversial[10] and remains empiric due to lack of well designed large prospective trials, and until recently, the lack of standardization of aPL testing[11,12]. Various preventive therapies have been recommended.

The risk for recurrent thromboses has been reported to be as high as 47%[13,14] and likely depends on multiple factors including the site of the initial thrombosis. Retrospective studies suggest high rates of recurrent of ATE and VTE in aPL positive patients if treated with anticoagulation for only 3 to 6 months after an initial episode[15] and if conventional intensity warfarin at international normalization ratios

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(INR) between 1.5 and 2.0 is used. Therefore longterm warfarin at INR between 2.0 and 3.0 is widely used[10]. Others have recommended more vigorous anticoagulation, targeting an INR between 3.0 and 4.0[11,12]. Because recurrent events can be venous or arterial, it has been suggested that warfarin alone may not suffice and that patients with APS should be treated with warfarin plus low dose aspirin (ASA)[15], the rationale being that the addition of ASA might prevent ATE.

The main risk associated with anticoagulation is bleeding. Although most hemorrhages are not life-threatening and do not result in permanent morbidity, death may occur. Every year 1–5% of patients receiving longterm anticoagulation will bleed sufficiently to require hospitalization[16]. Even in the absence of bleeding, patients must alter their lifestyle, which has the potential to decrease their quality of life. They must avoid major trauma, contact sports, and some drugs, and require regular INR assessments to measure the antithrombotic effect of warfarin.

The decision to employ and continue anticoagulant therapy rests primarily on its efficacy to prevent recurrent thromboembolisms compared to the risk of precipitating a hemorrhagic event. The recurrence risk and the site of recurrent events are likely dependent on the site of the initial VTE[17]. Decision analysis has been used to compare the risks and benefits of therapeutic approaches, and if possible to identify an overall preferred treatment strategy. The aim of our decision analysis is to identify the best therapeutic anticoagulation regimen in patients with APS after their first deep vein thrombosis (DVT).

MATERIALS AND METHODS

A systematic literature search using Medline was performed to identify articles published between 1966 and 1998. The MeSH headings and keywords "antiphospholipids," "lupus anticoagulant," "anticardiolipin antibodies," "therapy," "anticoagulation," "thrombosis," "deep vein thrombosis," "pulmonary embolus," "stroke," "utility," "standard gamble," and "time tradeoff" were used to identify relevant literature in English. These articles and their references were examined for the presence of the following information: (1) Composition and duration of antithrombotic regimens for patients with APS. (2) The rate of recurrent thromboses, types of recurrent events (e.g., deep venous thromboses, pulmonary emboli, and cerebrovascular accidents, etc), and the morbidity and mortality associated with recurrent events. (3) Rates of bleeding, severity of bleeding, and the morbidity and mortality associated with bleeding. (4) Location and frequency of recurrent thromboses and bleeding complications. (5) Utility (as a measure of health related quality of life) associated with anticoagulation therapy, with complications from anticoagulation, and with recurrent thrombotic events.

Values of utility range between 0 and 1.

The value 0 is the assigned utility of death, and 1 is the utility assigned to perfect health. All utilities used in the decision analysis were determined by time tradeoff or standard gamble techniques. The standard gamble[18] is the classic method of measuring health state preferences and is frequently referred to as the gold standard. The standard gamble measures utility as the probability of death that one would risk in order to live the rest of one's natural life in perfect health. Similarly, when using the time tradeoff technique[19] to measure preferences towards a health state, a patient trades a certain number of expected life years in exchange for perfect health during the remaining (shorter) life span. The utility of the health state of interest is calculated based on the number of life years a patient is willing to give up.

We used a decision analytic approach to weigh the benefits and risks involved in anticoagulation of aPL positive patients presenting with a first episode of a DVT. Decision analysis is a useful methodology for analyzing alternative treatment strategies[20,21]. Using Data3D software (TreeAge Software Inc., Williamstown, MA, USA) we developed a simple decision tree to measure the utility of the 6 most widely recommended treatment regimens at one year and again 4 years after the initial DVT. Despite the large number of reports in this field, only a few publications were suitable for use in the decision analysis for the following reasons: the patient population was not defined well, and the intensity and duration of the anticoagulation regimens were often unclear.

As a first step, we identified published therapeutic regimens used in patients with APS after their initial episode of a DVT. The baseline values of probability of recurrence and probability of complications of anticoagulation were determined by calculating (unweighted) averages of the values found in the literature. The extreme values we identified in the literature were used as the ranges tested in sensitivity analysis.

Next, the most frequent and most relevant sites of recurrent thromboses were selected. The occurrence of these events and the frequency of complications associated with them were determined, again using the relevant literature.

Subsequently the utilities for the different longterm health states (decomposed utilities) were identified in the literature. These decomposed utilities of the single longterm health states were multiplied to determine the combined utility of the longterm health states when more than one of these longterm health states were modeled in a certain decision tree branch. The relevant utilities of all short term health states were set to 0 for the duration of the short term health state[22]. The integrated utility, which measures the overall benefit from an antithrombotic therapy (which in this case may be considered the payoff for each strategy), was determined by subtracting the relevant utilities of the short term health states from the combined utilities of the longterm health states. All integrated utilities were assessed for their face validity, as suggested[22].

In a robust decision analysis, the preferred outcome does not significantly change when its variables are tested throughout the range of possible values. To test for the robustness (stability) of our decision analysis, we tested all probabilities and utilities in one-way and 2-way sensitivity analysis. One-way and 2-way sensitivity analyses aim to identify variables with threshold effects, that is, variables for which changing the value within the plausible range leads to a change in the preferred treatment strategy. Clinically relevant decision trees should be robust, i.e., not contain important threshold effects.

We also calculated the size of the marginal values. Marginal values are the differences in the overall benefits of treatment strategies with adjacent ranks. If the outcomes (expected utilities) of the different treatment strategies do not differ much, i.e., the marginal values of the utilities are small, then a so-called "toss-up" occurs[21,22]. This means that, on a clinical level, a preferable strategy cannot be identified when using the decision model.

Structure of the decision tree. Six commonly used antithrombotic regimens were identified: (1) longterm warfarin (INR 2–3), (2) longterm warfarin (INR 3–4), (3) warfarin (INR 2–3) for 6 months, or (4) warfarin (INR 3–4) for 6 months. As well, (5) longterm warfarin (INR 2–3) and (6) warfarin (INR 2–3) for 6 months are sometimes combined with ASA to enhance the efficacy of the anticoagulation effect in the arterial arm (Figure 1). The structure of the branches of the decision tree following the initial treatment decision is identical for all 6 antithrombotic regimens.

In our model, during the chosen time frames of one and 4 years, it was assumed that a patient could only have one single recurrent thrombosis or remain asymptomatic. The recurrent thrombosis could be arterial or venous (Figure 2). Only the 2 most common types of VTE were modeled in the decision tree, deep venous thromboses (DVT) and pulmonary emboli (PE)[8]. In the included studies, DVT were diagnosed by venogram or noncompressibility on duplex ultrasound, and PE by pulmonary angiogram

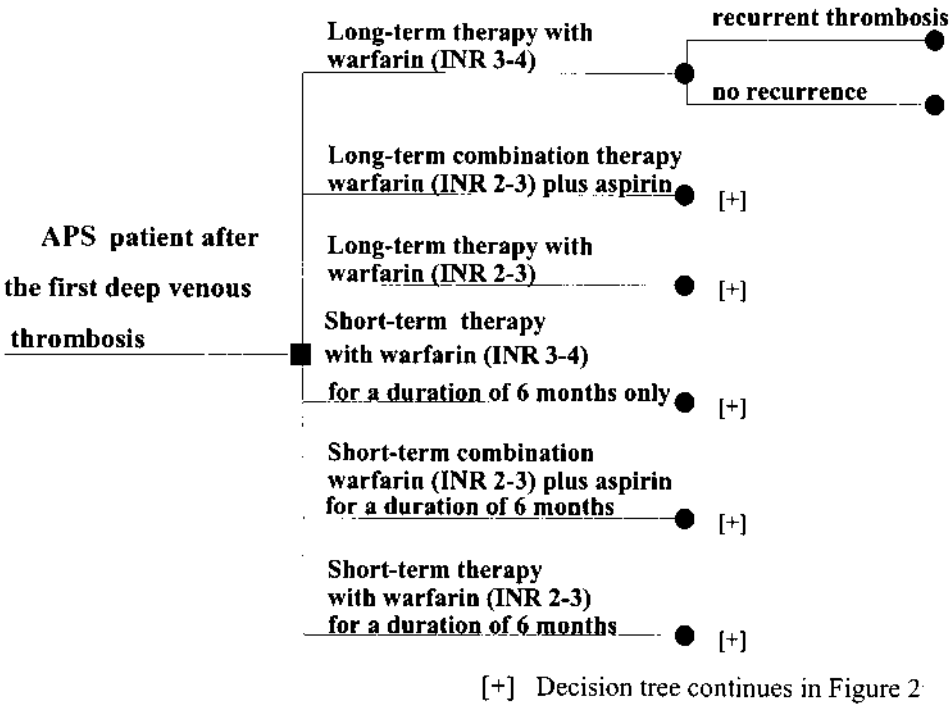

Figure 1. The decision model of 6 commonly used antithrombotic regimens in patients diagnosed with antiphospholipid antibody syndrome (APS) after an initial deep venous thrombosis. Warfarin therapy was tested when targeting an international normalization ratio between 2.0 and 3.0 (INR 2–3) or when using a higher intensity warfarin regimen with a target INR between 3.0 and 4.0. In clinical practice warfarin INR 2–3 is sometimes combined with low dose aspirin to protect from arterial thromboses. In addition, short term regimens using anticoagulant therapy for 6 months only were considered. The basic structure of the decision tree following the initial treatment decision is identical for all antithrombotic regimens; depending on the regimen chosen, patients have certain risks of recurrent thromboses and bleeding complications.

or high probability ventilation/perfusion scans. Recurrences in the arterial arm were only modeled as strokes, because strokes are the most frequent and most severe type of ATE observed in APS[8,23].

Bleeding was the only complication of anticoagulation considered in the decision tree (Figure 3). Although rare, bleeding complications can be lethal and major hemorrhages requiring hospitalization and/or blood transfusions result in short term and possibly longterm morbidity. Minor hemorrhages were not associated with short term or longterm morbidity.

Probabilities for thromboses and side effects from anticoagulation. The recurrence risk for thrombotic events was extracted from retrospective case series[7-9,15] and prospective cohort studies[11-13,24-26], as well as from one meta-analysis[17]. The risk of recurrent thromboses decreases over time and was estimated to be 21.1% per year at baseline[8,12] without prophylactic therapy for the one-year time frame, and overall 39%[14,15,24-26] for the 4-year time frame.

PE and DVT as sites of recurrent VTE (Figure 2) could be lethal, but only DVT were modeled to be associated with longterm morbidity due to postthrombotic syndrome. At baseline, 71% of the recurrences were estimated to be VTE[7,9]. The baseline probability of a recurrent event in the form of a PE was estimated to be 21.4%[17] and was associated with a mortality of 2.3%. The probability of a recurrent DVT with longterm morbidity was thought to be 12%[14,25,26] (Table 1).

Recurrence as ATE (Figure 2), modeled as a being a stroke, led to instantaneous death in 24%[27,28] (Table 1) of the cases at baseline. Sixty-one percent were major strokes[27,29], 39% were minor strokes. In the decision model short term neurological deficits, occurring after both major and minor strokes, resolved over a period of 6 weeks (short term morbidity). Twenty-four percent of all strokes also led to longterm morbidity.

The effectiveness of warfarin (INR 3–4) was estimated to be 96% and therefore 49% higher than that of the warfarin therapy (INR 2–3) for which a baseline effectiveness of 64.45% was used[7-9,11]. Combination therapy of warfarin (INR 2–3) plus ASA increased the effectiveness of warfarin (INR 2–3) by 5%[7-9,30] at baseline (Table 1).

In the decision tree, longterm warfarin (INR 2–3) had an associated baseline risk of major hemorrhage (Figure 3) requiring hospitalization and blood transfusions of 2.4% per year[31,32] (Table 2). This baseline risk was 50% higher for patients taking warfarin (INR 3–4), and therefore was set to 3.6% per year[30-34]. The addition of ASA increased the risk of major hemorrhage to 3% per year[30,34]. The risk of longterm morbidity associated with major bleeding events was estimated to be 5%[28]. The mortality associated with bleeding while treated with warfarin (INR 2–3 or INR 3–4) was 0.3% per year[30-34], and the mortality with combination therapies of warfarin (INR 2–3) plus ASA was 0.375% per year at baseline[30,34].

Values of outcomes. All decomposed utilities for the longterm health states were determined by standard gamble or time tradeoff techniques (Table 3). Because medication intake even in the absence of major side effect is often associated with limitations in the patient's quality of life, the utility associated with warfarin intake was 0.988[27] and that associated with ASA was 0.998[27] compared to a utility of 1 without medication intake. The utility of longterm morbidity due to DVT was estimated to be 0.982 at baseline[35]. The utility for all (acute) short term health states was estimated to be zero for the entire duration of the short term health state[22]. A period of one week was chosen as the duration of the short term health state following a PE, 2 weeks for that of a DVT, 3 days for that of a major hemorrhage, and the duration of the short term morbidity following any stroke was estimated to be 6 weeks. The integrated utilities of all 372 possible outcomes modeled

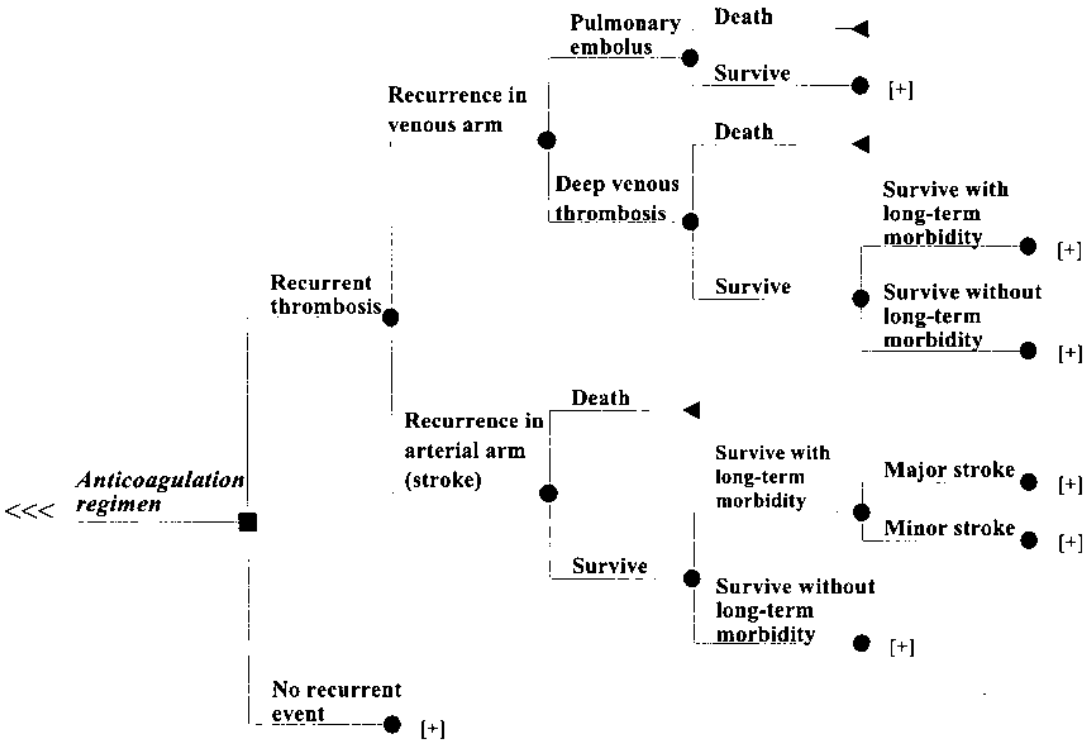

Figure 2. Depending on the anticoagulation regimen chosen patients will be at certain risks of recurrent thrombotic events in either the venous arm or the arterial system. DVT and pulmonary emboli were modeled as possible sites of venous recurrences, while only minor and major strokes were modeled as possible arterial recurrences.

for the one-year and the 4-year time frame had face validity[21]. When using the 4-year time frame, for example, the global utility of patients who experienced a DVT and subsequently a postthrombotic syndrome despite anticoagulation with warfarin (INR 2–3) was lower (global utility = 0.938) than that of patients undergoing similar antithrombotic therapy who had no recurrent thrombosis but did have longterm complications from a major hemorrhage (global utility = 0.972).

Some assumptions of the decision analytical model. This decision model is mainly applicable to adults without additional risk factors of thromboses such as obesity, hypertension, pregnancy, high age, or estrogen-containing

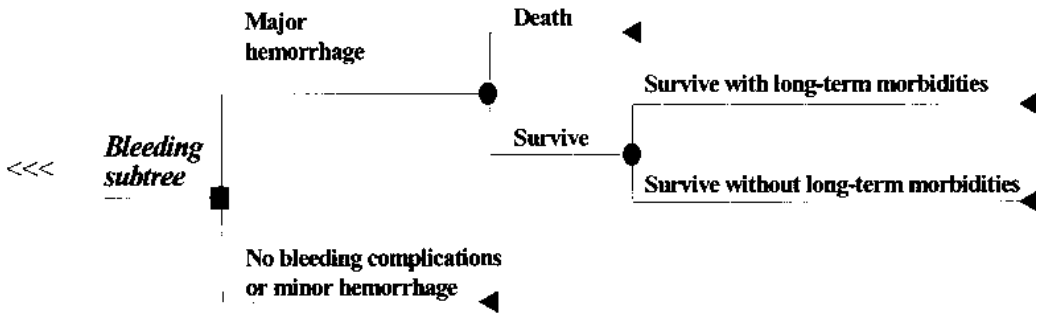

Figure 3. Subtree to model bleeding complications due to antithrombotic therapy. Complications can occur whether a patient has a recurrent thrombotic event or not. Risk of dying after a major hemorrhage was modeled as the same for patients undergoing warfarin therapy INR 2–3 as for those on warfarin INR 3–4. Uncontrollable bleeding is more likely with combination therapy consisting of warfarin INR 2–3 plus low dose aspirin, because both the coagulation system and platelet function are compromised. Thus the risk of dying was modeled as being increased by 25% in patients treated with combination therapy at baseline compared to those receiving warfarin INR 2–3 alone.

Table 1. Probabilities of recurrent thrombotic events. The ranges of the probability values are based on values reported in the literature. For the baseline probabilities the unweighted average estimates of the included studies were used.

Event	Baseline Value	Range	Reference	No. of Patients and/or Patient-years and/or Followup Time Included in Baseline and Range Values
Effectiveness of warfarin (INR 2–3)	0.6445	0.5–1	7–9	40.9 pt-yrs[7] 67 pts/141 pt-yrs[8] 63 pt-yrs[9]
Increase of effectiveness of warfarin (INR 2–3) when aspirin is added	1.05	1–1.55	7–9	5.3 pt-yrs[7] 14 pts/31.4 pt-yrs[8] 30.6 pt-yrs[9]
Effectivness of warfarin (INR 3–4)	0.960	0.6445–1	7, 8	110 pt-yrs[7] 64 pts/197.3 pt-yrs[8]
Annual recurrence risk in first year after initial venous thrombosis without prophylaxis	0.211	0.086–0.47	8,11–13, 15, 24	67 pts/141 pt-yrs[8] 11 pts/2.8 mo[11] 412 pts/4 yrs[12] 230 pts/followed mean of 7.7 yrs (SD 4.7 yrs)[13] 19 pts/median followup 8.4 yrs[15] 21 pts/median followup 8 yrs[24]
Recurrence risk within first 4 years after an initial venous thrombosis without prophylaxis	0.39	0.3–0.59	8, 12	67 pts/approx. 24 pts were followed for 4 yrs[8] 116 pts/followed 4 yrs[12]
Recurrent event in venous arm	0.71	0.33–0.91	7–9	33 pts/161.2 pt-yrs[7] 145 pts/370 pt-yrs[8] 61 pts/median followup 6.4 yrs[9]
Probability of DVT with longterm morbidity as 2nd event	0.12	0.08–0.24	14, 25, 26	120 pts/followup 4 yrs[14] 355 pts/followup 8 yrs[25] 4222 pts/followup 0.5–12 yrs[26]
Probability of pulmonary embolus as 2nd event	0.214	0–0.5	17	4221 pts (metaanalysis)[17]
Stroke reduction due to use of lowdose aspirin	1	0.25–1	30	186 pts/mean followup 2.5 yrs[30]
Probability of death due to DVT	0.004	0.002–0.006	17	4221 pts (metaanalysis)[17]
Probability of death due to pulmonary embolus	0.023	0.015–0.032	17	4221 pts (metaanalysis)[17]
Probability of death due to stroke	0.24	0.08–0.3	27, 28	Decision analysis; patient-specific data not available[23,28]
Probability of major stroke	0.61	0.5–0.8	27, 29	Decision analysis; patient-specific data not available[27] 31 pts[30]
Probability of longterm morbidity after any stroke	0.24	0.2–0.35	27, 28	Decision analysis; patient-specific data not available[27,28]

INR: international normalization ratio, DVT: deep venous thrombosis.

contraceptive medications. The decision model considered the possibility of only one recurrent event within the assessment time frame of either one or 4 years, and as such imitates clinical practice by which patients with multiple recurrent thromboses are generally committed to longterm anticoagulation.

It was assumed that the risk of a recurrent thrombosis when treated with any of the short term regimens was equal to the sum of 1/2 the annual recurrence risk despite therapy plus 1/2 the annual risk of thrombosis without prophylaxis for the one-year time frame. Accordingly, when using short term therapy in the 4-year time frame, effective therapy was provided for 1/8 of the 4-year time period. The overall thrombosis risk was calculated as follows: 1/8 multiplied by the recurrence risk associated with effective therapy plus 7/8 times the risk of thrombosis without prophylaxis during a period of 4 years.

For the one-year time frame we assumed that, on average, all events (recurrences and bleeding complications) occurred around 6 months after an initial thrombosis. Therefore, for example, the integrated utility for the health state (u-int) at one year for a patient taking longterm warfarin (utility of warfarin therapy: u-war) with a recurrent DVT associated with longterm complications (u-dvt-ltm) and also a major hemorrhage resulting in longterm moribidity (u-hem-maj-ltm) would be calculated by:

$$\text{u-int (1 year)} = 0.5 \times \text{u-war} \times (1 + \text{u-dvt-ltm} \times \text{u-hem-maj-ltm}) - (1 - \text{u-dvt-stm}) - (1 - \text{u-hem-maj-stm})$$

with u-dvt-stm being the utility of the short term health state associated with a DVT and u-hem-maj-stm being the utility of the short term health state associated with a major hemorrhage.

Similarly, the integrated utility of the 4-year model assumed that all recurrences occurred, on average, at 6 months after the initial event, and thus the integrated utility of the example health state outlined above in the 4-year decision model was as follows[22]:

$$\text{u-int (4 years)} = 0.125 \times \text{u-war} \times (1 + 7\ \text{u-dvt-ltm} \times \text{u-hem-maj-ltm}) - (1 - \text{u-dvt-stm}) - (1 - \text{u-hem-maj-stm})$$

Table 2. Probability of side effects of antithrombotic therapy.

Event	Baseline Value	Range	Reference	No. of Patients and/or Patient-years and/or Followup Time Included in Baseline and Range Values
Probability of major hemorrhage taking warfarin (INR 2–3)	0.024	0–0.168	31, 32	541 pts (review article)[31] 111 pts/followup 4 yrs[32]
Probability of major hemorrhage taking warfarin (INR 3–4)	0.036	0.024–0.048	30–34	184 pts/mean followup 2.5 yrs[30] 541 pts (review article)[31] 227 pts/followup 4 yrs[32] 101 pts/mean followup 3 yrs[33] 245 pts/median followup 1.9 yrs[34]
Probability of death due to bleeding taking warfarin (INR 2–3) or (INR 3–4)	0.003	0–0.036	30–34	184 pts/mean followup 2.5 yrs[30] 541 pts (review article)[31] 412 pts/followup 4 yrs[32] 205 pts/followup 4 yrs[33] 245 pts/median followup 1.9 yrs[34]
Probability or longterm morbidity secondary to major hemorrhage	0.05	0.02–0.15	28	Decision analysis; patient-specific data not available[28]
Factor of increased risk of major hemorrhage if aspirin is added to warfarin (INR 2–3)	1.25	1–1.5	30, 34	370 pts/mean followup 2.5 yrs[30] 503 pts/median followup 1.9 yrs[34]

INR: international normalization ratio.

There are, however, no standardized rules for how best to calculate integrated utilities. Thus a separate exploratory analysis was performed, as some investigators have[21,36], where utilities for short term health states were not considered and only the health state with the lowest utility of a decision tree branch was used to calculate the utility associated with a treatment strategy. For example, if a patient had a major hemorrhage and also a major stroke with longterm morbidity then only the utility of the major stroke in the long term was considered as an outcome. In this exploratory analysis we did not consider the major hemorrhagic event, because the utility of a major stroke with longterm morbidity is the lower of the 2 complications.

RESULTS

Results of the decision analytical model using the one-year time frame. Longterm anticoagulation with warfarin (INR 3–4) ranked first, followed by the corresponding short term regimen of equal intensity (Table 4). For outcomes at one year, the marginal values between the 6 different regimens were very small, and therefore do not support the recommendation that one of the chosen antithrombotic therapies is

Table 3. Decomposed utilities of the encountered health states. The decomposed utilities of the longterm and short term health states were combined to calculate the integrated wtilities (payoffs) of a certain antithrombotic therapy. All decomposed utilities of the longterm utilities were elicited by time tradeoff or by standard gamble technique. For the short term health states, conservative estimates were chosen by using a utility of 0 for the duration of the acute health state.

Event	Utility	Range	Reference	No. of Patients and/or Patient-years and/or Followup Time Included in Baseline and Range Values
Daily intake of aral aspirin	0.998	0.96–1.0	27	74 pts[27]
Daily intake of oral warfarin	0.988	0.92–1.0	27	74 pts[27]
DVT with longterm morbidity	0.982	0.9–1.0	35	36 pts[35]
Major stroke with longterm morbidity	0.450	0–1.0	29	31 pts[29]
Minor stroke with longterm morbidity	0.810	0.3–1.0	29	31 pts[29]
Major hemorrhage with longterm morbidity	0.760	0.5–0.99	27	74 pts[27]
Short term morbidity due to pulmonary embolus	0.981	0.9–1.0		—
Short term morbidity due to DVT	0.961	0.9–1.0		—
Short term morbidity due to any stroke	0.885	0.846–0.92		—
Short term morbidity due to major hemorrhage	0.990	0.981–1.0		—

DVT: deep venous thrombosis

Table 4. Ranking of the antithrombotic regimens according to their utilities for the one year time frame. Longterm anticoagulation targeting an INR between 3.0 and 4.0 ranks first at one year after an initial venous thrombotic event. The marginal values of the different regimens are small. The addition of aspirin does not offer substantial benefit, even if aspirin decreased the number of strokes by 75%.

Prophylactic Regimen	1-year Rank	1-year Utility	1-year Marginal Value*	1-year Rank Considering 75% Stroke Reduction with Aspirin	1-year Utility Considering 75% Stroke Reduction with Aspirin
Longterm warfarin (INR 3–4)	1	0.986		1	—
Anticoagulation for 6 mo with warfarin (INR 3–4)	2	0.979	0.007	3	—
Longterm warfarin (INR 2–3)	3	0.978	0.001	5	—
Longterm warfarin (INR 2–3) plus aspirin	4	0.976	0.001	2	0.981
Anticoagulation for 6 mo with warfarin (INR 2–3)	5	0.974	0.002	6	—
Anticoagulation for 6 mo with warfarin (INR 2–3) plus aspirin	6	0.973	0.001	4	0.976

INR: international normalization ratio.
* Marginal value: difference of utility between antithrombotic regimens with adjacent ranks.

clinically preferable over the others (toss-up situation). Threshold effects were present only for extreme values within the possible value range for the effectiveness of warfarin (INR 2–3), the additional benefit of higher intensity anticoagulation using warfarin (INR 3–4) over warfarin (INR 2–3), and the baseline recurrence risk (Table 5). There were no threshold effects with regard to bleeding complications associated with anticoagulation.

Results of the decision analytical model using the 4-year time frame. Longterm anticoagulation with warfarin (INR 3–4) ranked first, followed by longterm warfarin (INR 2–3) and longterm combination therapy of warfarin plus ASA (Table 6). The differences of the expected utility between therapy with warfarin (INR 3–4) and the other 2 longterm regimens were larger than for the one-year time frame. Nonetheless, this likely does not allow a clear recommendation[36] for which of the 3 longterm antithrombotic regimens is preferable. However, all short term regimens had much lower utilities compared to all longterm regimens. Thus, based on the relatively large differences in the expected utility, short term regimens seemed to be clinically inferior to longterm regimens. The only threshold value for the model using the 4-year time frame was the baseline effec-

Table 5. Variables with thresholds within the ranges of possible values in the one-year time frame. For the one-year time frame 4 threshold values of the decision model were identified by one-way sensitivity analysis. The threshold value for effectiveness of warfarin (INR 2–3) and that of the increased effectiveness of warfarin (INR 3–4) compared to warfarin (INR 2–3) are both at the extremes of the possible ranges considered. If warfarin (INR 2–3) was at least 99% effective to prevent recurrences, then higher intensity anticoagulation would not provide an additional benefit to patients. Similarly, warfarin (INR 3–4) would only be beneficial to patients if it were at least 2% more effect than warfarin (INR 2–3). If the utility of warfarin therapy were < 0.97, then 6 month warfarin (INR 3–4) would be the preferable prophylactic regimen. No threshold effects were present for variables concerning bleeding complications.

Variable	Range	Threshold Value(s) Within Range	Preferred Antithrombotic Therapy
Effectiveness of warfarin (INR 2–3)	0.5–1	0.5–0.99	Longterm warfarin (INR 3–4)
		0.99–1	Longterm warfarin (INR 2–3)
Factor by which warfarin (INR 3–4) is more effective than warfarin (INR 2–3)	1–2	1–1.02	Longterm warfarin (INR 2–3)
		1.02–2	Longterm warfarin (INR 3–4)
Recurrence risk without anticoagulation, %	8.6–21	8.6–10	Anticoagulation for 6 mo with warfarin (INR 3–4)
		10–21	Longterm warfarin (INR 3–4)
Utility associated with warfarin therapy	0.92–1	0.92–0.97	Anticoagulation for 6 mo with warfarin (INR 3–4)
		0.97–1	Longterm warfarin (INR 3–4)

INR: international normalization ratio.

Table 6. Ranking of antithrombotic regimens according to their utilities for the 4-year time frame. Assessing the benefits of antcoagulation 4 years after an initial deep venous thrombosis, utilities of all longterm regimens are much higher compared to those of 6 month prophylactic regimens. Although longterm anticoagulation with warfarin (INR 3–4) ranks first, the difference between its utility and that of warfarin (INR 2–3) is not very large. Therefore a clear recommendation regarding the intensity of longterm anticoagulation is not possible. The addition of aspirin does not provide substantial longterm benefit even if aspirin was stroke-protective.

Prophylactic Regimen	4-year Rank	4-year Utility	4-year Marginal Value	4-year Rank Considering 75% Stroke Reduction with Aspirin	4-year Utility Considering 75% Stroke Reduction with Aspirin
Longterm warfarin (INR 3–4)	1	0.982		1	—
Lonterm warfarin (INR 2–3)	2	0.966	0.016	3	—
Longterm warfarin (INR 2–3) plus aspirin	3	0.965	0.001	2	0.974
Anticoagulation for 6 mo with warfarin (INR 3–4)	4	0.854	0.111	5	—
Anticoagulation for 6 mo with warfarin (INR 2–3)	5	0.853	0.001	6	—
Anticoagulation for 6 mo with warfarin (INR 2–3) plus aspirin	6	0.846	0.007	4	0.856

INR: international normalization ratio.

tiveness of warfarin therapy (INR 2–3). If warfarin (INR 2–3) were already 99% (baseline 64.45%) protective against recurrences, then higher intensity warfarin (INR 3–4) would not offer an additional benefit to the patients (Figure 4).

Two-way sensitivity analyses. Two-way sensitivity analyses were performed for all possible variable combinations. When using the one-year time frame, the decision model was also sensitive to the combined change of the thrombosis recurrence risk and the effectiveness of warfarin therapy (Figure 5). Depending on the assumed risk of recurrence without therapy and the concomitant effectiveness of warfarin therapy, 6-month warfarin (INR 3–4), longterm warfarin (INR 2–3), or longterm warfarin (INR 3–4) would be the best treatment for a patient.

If there was no mortality associated with recurrent thromboses, i.e., the probability of death from DVT, PE, or stroke was 0, then the mortality associated with a major hemorrhage had to exceed 6% and 21% using the one-year and the 4-year time frame, respectively, to replace longterm warfarin (INR 3–4) as the preferred treatment strategy.

Combination therapy with aspirin. ASA has been found to decrease the risk of recurrent strokes by up to 75% in patients after heart valve replacement[30]. Whether there is a similar benefit of ASA in aPL positive patients is unknown. Under our baseline assumptions, ASA intake was associated with both an increased effectiveness of the antithrombotic regimen and with an increase of bleeding complications, while possible stroke-protective properties of ASA were not considered. Using these assumptions, the addition of ASA to warfarin did not result in a substantial benefit to the patient.

In secondary analyses, ASA was also modeled as being associated with a reduction of strokes by up to 75%. Even then, longterm warfarin (INR 3–4) would be the preferred treatment strategy for both the one-year and 4-year time frame, because of increased bleeding complications associated with ASA (Tables 4 and 6).

For the 4-year time frame, an exploratory analysis was performed using only the lowest utility of the longterm health states (see above) for a given treatment strategy. Again, when using this approach longterm warfarin (INR 3–4) ranked first (expected utility = 0.985) followed by longterm warfarin (INR 2–3) (expected utility = 0.973) and longterm warfarin (INR 2–3) plus ASA (expected utility without consideration of stroke protection = 0.972; expected utility under consideration of 75% stroke protection when using ASA = 0.981). All short term anticoagulation regimens were associated with much lower benefits of patients (utilities all < 0.964).

DISCUSSION

Appropriate therapy of aPL positive patients after an initial VTE is controversial in terms of type, intensity, and duration of appropriate antithrombotic prophylaxis. We developed a robust decision analytical model to weigh the risks and benefits associated with 6 commonly used antithrombotic regimens at one year and again 4 years after an initial thrombosis. Longterm anticoagulation with warfarin (INR 3–4) ranked first at one year and 4 years after an initial event. Overall, longterm therapy was preferable to short term (6 month duration) anticoagulation. The addition of ASA to warfarin did not lead to a substantial benefit compared to warfarin alone.

About 6 to 10% of the general population tests positive for aPL[3]. aPL positivity is associated with diseases such as systemic lupus erythematosus, Behçet's syndrome, idiopathic inflammatory myopathy, and rheumatoid arthritis[37]. APS is associated with significant longterm morbidity and increased mortality, irrespective of whether aPL occur in

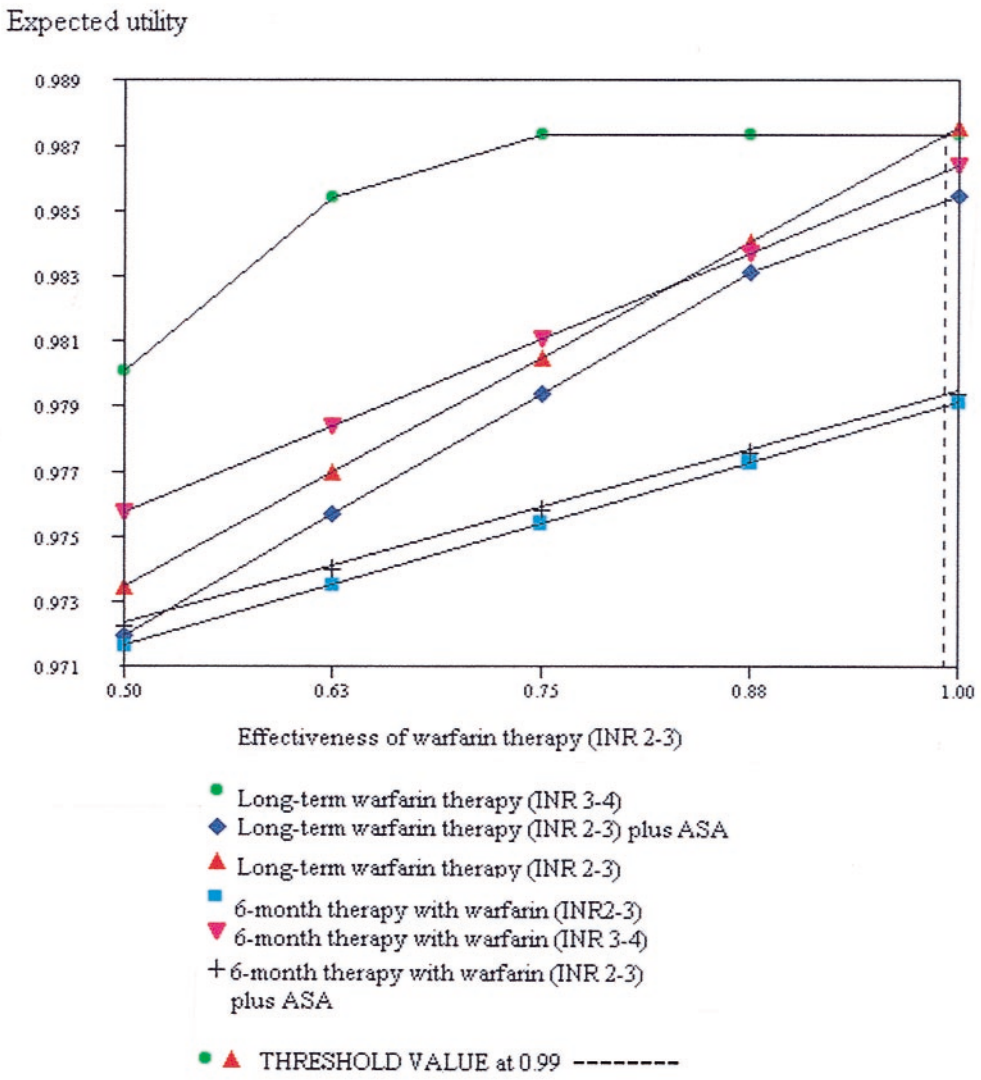

Figure 4. One-way sensitivity analysis on the effectiveness of warfarin INR 2–3 therapy for the 4 year time frame. Longterm warfarin INR 3–4 is the preferable treatment strategy provided warfarin INR 2–3 is less than 99% effective to prevent a recurrent thrombosis. If the efficacy of warfarin therapy INR 2–3 exceeded 99%, then even more effective high intensity anticoagulation would not be expected to lead to an additional benefit, because more bleeding complications are expected to occur with warfarin INR 3–4 compared to warfarin INR 2–3.

combination with other diseases or not[4,5,7]. Although a significant number of patients are diagnosed with APS and are at risk, there is no agreement about the best prophylactic therapy against rethromboses[10].

It has been suggested[17] that aPL positive patients whose initial thrombosis is venous are more likely to have a venous rather than an arterial recurrence, and that patients who initially present with a DVT are less likely to have recurrent thromboses and to develop PE. Conversely, an aPL positive patient with an initial ATE has a higher risk for arterial recurrences. The current decision analysis evaluates the therapeutic regimens of aPL positive patients presenting with a DVT, which is the most frequent site of thrombosis.

We found that longterm anticoagulation is more beneficial than short term regimens. Assessing the different antithrombotic regimens at one year after the initial DVT, the benefits of longterm versus short term anticoagulation are small, because — at one year — patients on short term therapy have only been off prophylactic therapy for 6 months. The recurrence risk for thromboses decreases over time. Therefore one could speculate that prolonged anticoagulation with its ongoing risk of bleeding might not be beneficial. It has been suggested that the minimal important difference in utility values is 0.054[38]. Thus the 4-year decision model supports previous reports[8,9,15,32], because longterm anticoagulation was superior to short term antithrombotic therapies (marginal utility values between short term and longterm regimens > 0.111).

Decision models cannot accommodate the entire spectrum of possible findings and complications of patients with

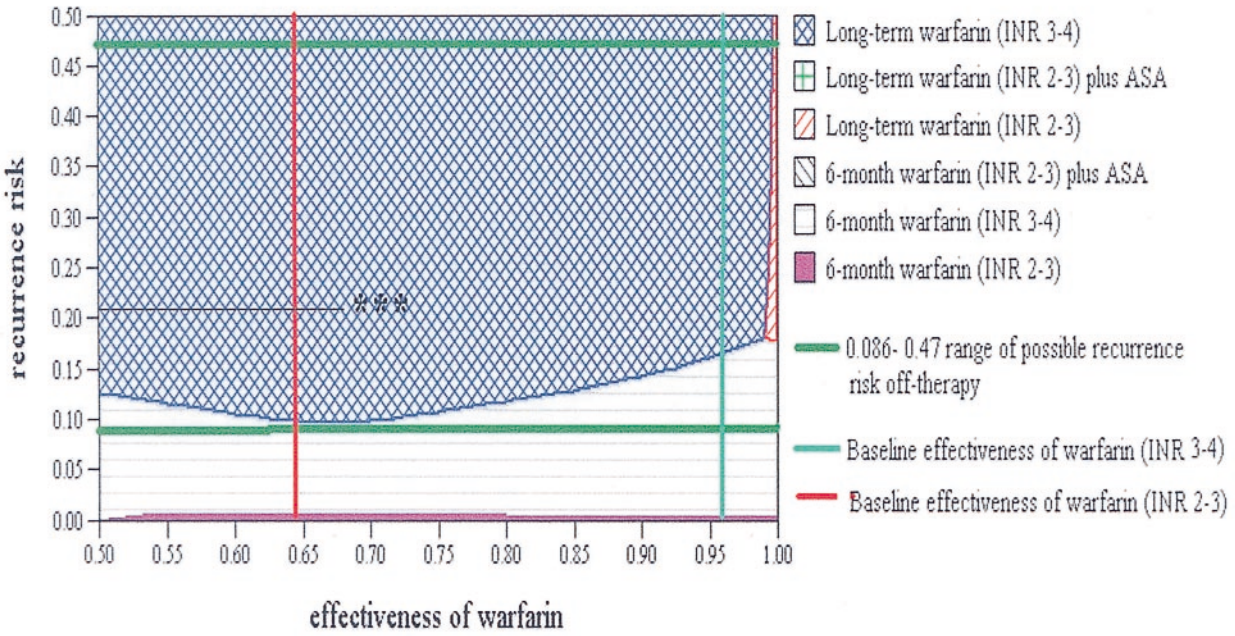

Figure 5. Using the baseline assumptions of recurrence risk = 0.21 and effectiveness of warfarin INR 2–3 = 0.6445, longterm warfarin INR 3–4 offers the highest benefit. Using 2 way sensitivity analysis in a one-year model, the assumptions about the effectiveness of warfarin (INR 2–3) and the recurrence risk are simultaneously changed throughout the ranges of possible values. Depending on the assumed recurrence risk and the concomitant assumption about the effectiveness of warfarin, either short term warfarin INR 3–4 or longterm warfarin INR 2–3 or longterm warfarin INR 3–4 is the preferable treatment for patients with APS. For example, if the recurrence risk is only 0.05 then short term warfarin INR 3–4 would be the preferred treatment strategy irrespective of the effectiveness of warfarin INR 2–3 (range 0.5–1.0). Other treatments considered in the decision model, such as short term or longterm anticoagulation using warfarin INR 2–3 in combination with ASA or short term warfarin INR 2–3, are inferior irrespective of the assumptions about recurrence risk or the effectiveness of warfarin INR 2–3. ***: Baseline recurrence risk of thrombosis without prophylaxis with a one-year time frame.

APS. The quality of a decision analysis is only as good as the quality of the data that go into it. Unfortunately, there are no good randomized controlled trials examining the treatment of recurrent thromboses in APS. Based on current knowledge, however, the optimal intensity of anticoagulation in APS remains to be determined (small differences in the utility values between longterm regimens). It is possible that longterm warfarin at an INR of 2.5 or 3.5 may result in the best outcome. As anticoagulation using warfarin and ASA has not been prospectively tested in large patient populations, further studies are required to evaluate the benefits of this combination therapy for patients with APS.

There are not sufficient data currently to estimate the optimal duration of anticoagulation in APS beyond 4 years after the initial presentation. The duration of any longterm regimen will be influenced by its associated risk of major hemorrhages. Bleeding risk is higher in older patients, especially in those with comorbid conditions including a history of strokes[31,39,40]. Severe hemorrhages are also more frequent in patients with large fluctuations in the anticoagulation levels. The risk of bleeding seems to increase significantly once the INR is elevated beyond 4[31]. For regimens below this level the increase in bleeding risk seems to increase by a factor of 0.5 for an increase of the INR by 1 unit. However, beyond an INR of 4.0 this factor rises to 4.5 for each unit increase of the INR[31].

The rate of bleeding complications reported in the literature varies significantly, even in studies with similar anticoagulation intensity[13]. An explanation of this phenomenon may be (besides differences of the comorbidity spectrum of the patients) that the monitoring of anticoagulation levels used in the different studies varied and that major bleeds often occur in patients with extremely high INR[7]. Thus, it is conceivable that strict monitoring of any antithrombotic therapy will lead to a decreased risk of serious bleeding complications even if target INR between 3.0 and 4.0 are used. Similarly, the effectiveness of anticoagulation therapy is likely influenced by the monitoring regimens chosen. Information regarding the frequency of anticoagulation monitoring to maintain target INR levels is rarely reported. This constitutes a general problem in the literature on APS therapy and might have influenced the result of the current decision model.

The current decision model is very robust, especially when using the clinically more relevant 4-year time frame. It is only sensitive to the effectiveness of warfarin (INR 2–3). In some studies with close monitoring of the anticoagulant therapy, no patient taking warfarin (INR 2–3) had recurrent thrombotic events[8]. However, even if the baseline effectiveness of warfarin (INR 2–3) exceeded 99%, then all 3 longterm antithrombotic regimens would still be preferable to the examined short term regimens.

Limitations of this study are that some of the utilities and probabilities for bleeding complications used in the decision tree were not derived from patients with APS. We assumed that the utilities of APS patients are similar to those who had similar complications but who did not have aPL — as long as the health states and ages of the patients are comparable. For instance, it is likely that the effect on health related quality of life (utility) of having to take warfarin for thrombosis prophylaxis is similar for all patients of similar age whether they have APS or not. Similarly, the bleeding risk of patients with APS was thought to be the same as that of other patients treated with warfarin[7,31,39].

We chose the format of a simple decision analysis. Often, Markov based decision analyses are used to model the variability of event times and to simulate the clinical situation more realistically. We considered a simple decision model was more appropriate, considering the sparsity of data that were mostly gathered for one-year and 4-year followup periods. Markov based models are used to model recurrent events; however, aPL positive patients with multiple recurrent thromboses are committed to life-long anticoagulation and were not considered in the decision model. In addition, evaluation of utilities of medication intake over time has not been well examined. It is conceivable that the utility of warfarin intake may rise over time as a patient gets used to the alteration of lifestyle, or conversely the burden of warfarin therapy could increase over time based on ongoing fear of major hemorrhage, blood draws, and hospitalizations[41]. Given this lack of knowledge additional arbitrary assumptions would have been necessary for a Markov based decision model. In addition, simple decision models mostly come to quite similar overall results compared to Markov based models[42,43]. To support our strategy, a secondary analysis was done (data not shown) where the times of recurrent events and bleeding complications were changed to 9, 12, 24, and 36 months after the initial VTE. Using these altered occurrence times of events in the one-year and/or in the 4-year decision model, the rankings of the treatment regimens remained the same and the marginal values between longterm and short term regimens were similar (all > 0.1) to the baseline models.

Another limitation of the decision model may be that some of the studies were performed prior to the adoption of consensus criteria for APS[44]. Therefore patients may have been included into studies that would not fulfill criteria for APS using the current standards. However, it is unlikely this influenced the results of the decision model much and could only have led to underestimation of the benefits from anticoagulation in APS. Also, new evidence is emerging that certain subtypes of aPL, such as antibodies against $ß_2$-glycoprotein I or prothrombin, may be associated with higher risks of arterial or venous thromboses[45,46]. However, it is unclear at present whether and how this may affect prophylactic therapies of aPL positive patients.

The utility of warfarin therapy has a threshold at 0.97 for the one-year decision model. This means that at one year, short term anticoagulation would be preferable to longterm anticoagulation for values that are lower than 0.97. However, a utility of 0.97 is relatively low and many other decision models involving anticoagulation strategies with warfarin used baseline estimates between 0.99 and 1 and ranges of warfarin utilities between 0.95 and 1[41,47-49]. Utility estimates depend largely upon the method used for their measurement. The standard gamble and the time tradeoff techniques are regarded as the traditional methods for utility determination[18], and therefore this decision model only considered utilities elicited using these techniques. In contrast, reported baseline utility values for warfarin at 0.99–1.0 were not derived by standard gamble or time tradeoff techniques and thus they were not considered in the current model. For the 4-year model the utility associated with warfarin intake had no threshold effect.

The current decision model allows us to explicitly examine important factors and outcomes associated with treatment strategies of aPL positive patients after an initial DVT. The advantage of longterm anticoagulation over short term therapies of 6 months duration increases with longer followup (i.e., larger marginal values between short term and longterm regimens are seen after 4 years of followup). This suggests that patients with APS benefit from anticoagulation for at least 4 years after the initial event. The marginal value between warfarin (INR 3–4) and all the other treatment regimens increases with the duration of anticoagulation in the present decision model. Thus one may speculate that high intensity therapy (first rank) may be better than warfarin (INR 2–3) (second rank) with even longer followup. Additional data from larger prospective studies are necessary to make exact treatment recommendations for aPL positive patients after an initial thrombotic event. In particular, based on the results of our decision analysis, prospective testing of high intensity warfarin therapy may be warranted.

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