Perioperative Management of Patients on Oral Anticoagulants: A Decision Analysis

Andrew S. Dunn, MD, FACP, Juan Wisnivesky, MD, Warren Ho, MD, Carlton Moore, MD, Thomas McGinn, MD, MPH, Henry S. Sacks, MD, PhD

Background. *To better inform clinicians on the optimal management of patients on oral anticoagulation who need to undergo surgery or invasive procedures, the authors performed a decision analysis examining whether a perioperative aggressive or minimalist strategy results in greater quality-adjusted survival.* ***Methods***. *A decision analysis model was created comparing withholding warfarin (minimalist strategy) to withholding warfarin and administering treatment-dose subcutaneous low-molecular-weight heparin (LMWH) or intravenous heparin perioperatively (aggressive strategy). The base-case analysis examined a hypothetical 60-year-old hypertensive individual with mechanical aortic valve replacement undergoing major abdominal surgery. A probabilistic sensitivity analysis was performed using a Monte Carlo simulation with quality-adjusted life expectancy (QALE) as the outcome. Secondary analyses examined patients with a mechanical mitral valve and atrial fibrillation. Sensitivity analyses were performed for each variable.* ***Results***. *Under the base-case scenario, the minimalist strategy was preferred for 78% of trials in the Monte Carlo simulation, with a mean benefit of 0.003 years (95% confidence interval, –0.005 years to 0.011 years). Sensitivity analyses based on point estimates indicate that the aggressive strategy is preferred when the annual stroke rate is >5.6% or the increase in postoperative major bleeding induced by heparin is <2.0%; however, the benefit is small over the range of plausible values.* ***Conclusions***. *For most patients with a mechanical aortic valve or atrial fibrillation undergoing major surgery, a minimalist strategy of simply withholding oral anticoagulation provides similar QALE as an aggressive strategy of administering perioperative subcutaneous LMWH or intravenous heparin. The aggressive therapy provides greater QALE for patients at higher risk of stroke (e.g., mechanical mitral valves), although the benefit is small.* ***Key words:*** *surgery; anticoagulation; decision analysis; mechanical heart valves; atrial fibrillation; stroke.* ***(Med Decis Making 2005;25:387–397)***

Oral anticoagulants are commonly prescribed for patients with conditions predisposing them to thromboembolism to decrease the risk of life-threatening events, such as stroke. An example of such a condition is atrial fibrillation, which affects 2.3 million Americans and has been projected to affect more than 5.5 million Americans by the year 2050.[1] The perioperative management of patients on oral anticoagulants is problematic, as the medication needs to be discontinued to prevent excessive bleeding for most invasive procedures and surgeries. Substituting treatment-dose subcutaneous low-molecular-weight heparin (LMWH) or intravenous heparin while oral anticoagulants are withheld can decrease the risk of thromboembolism but increases the hospitalization requirement and may increase the risk of postoperative bleeding. In part owing to a lack of randomized trials or rigorous nonrandomized studies, there is no consensus on whether therapeutic anticoagulation should be administered while warfarin is withheld perioperatively.[2,3] The lack of consensus was noted in a survey of physicians, which found that although most would administer perioperative full-dose intravenous heparin or LMWH for patients with mechanical aortic valves,

Received 8 April 2004 from the Division of General Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, New York (ASD, JW, WH, CM, TM); and the Departments of Community and Preventive Medicine, Medicine and Biomathematical Sciences, Mount Sinai School of Medicine, New York, New York (HSS). Presented at the XIX Congress, International Society on Thrombosis and Haemostasis (ISTH), Birmingham, England, July 2003. The authors thank Dr. Al Siu and Dr. Deborah Korenstein for their review of this article and helpful comments. There was no grant support or other external funding for any aspect of the performance of the study or writing of the article. Revision accepted for publication 22 March 2005.

Address correspondence to Andrew S. Dunn, MD, FACP, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1087, New York, NY 10029; e-mail: andrew.dunn@mountsinai.org.

DOI: 10.1177/0272989X05278432

approximately one third would do nothing other than withhold oral anticoagulation.[4]

To better inform clinicians on this decision, we performed a decision analysis comparing 2 distinct strategies: 1) a minimalist strategy consisting of simply withholding oral anticoagulants perioperatively and 2) an aggressive strategy consisting of withholding oral anticoagulants and administering LMWH or intravenous heparin perioperatively. These strategies were chosen, as they are commonly utilized and recommended.[2,5–7]

METHODS

Decision Analytic Model

A decision tree model was constructed to describe the possible outcomes of 2 strategies for the perioperative management of patients on oral anticoagulants (Figure 1). For both strategies, oral anticoagulants were withheld for 4 days prior to the procedure and reinitiated on the evening of the procedure. For the strategy designated as "aggressive," treatment-dose LMWH or intravenous heparin was administered for the 2 days immediately prior to and the 2 days immediately following the procedure. For the strategy designated as "minimalist," therapeutic-dose heparin was not administered. The perioperative period was defined as the 4 days prior to surgery (the preoperative period) and the day of and 4 days following surgery (the postoperative period). Patients are followed in the model until death.

The primary analysis (base case) was based on a 60-year-old individual with a history of hypertension and prosthetic aortic valve replacement undergoing elective major abdominal surgery. To vary the risk of thromboembolic stroke, we assessed as secondary analyses the outcomes of 2 other hypothetical patients undergoing the same surgery: a 60-year-old individual with a history of hypertension and atrial fibrillation (low stroke risk) and a 60-year-old individual with a history of hypertension and prosthetic mitral valve replacement (high stroke risk). To examine the impact of the potential bleeding risk of the procedure, the outcomes for the 3 hypothetical patients were also examined using dental extraction (low bleeding risk) as the elective procedure.

The probability of each event in the model was based on a review of the literature using the MEDLINE (1 January 1966 to 31 December 2003) and Cochrane Collaboration computerized databases. The references of the retrieved articles were examined to further identify studies. Information was extracted from the relevant studies for each input variable. Sensitivity analyses were performed around a wide range of plausible values based on the literature review. Analyses were performed using TreeAge software (TreeAge Software Inc, Williamstown, MA).

Probabilities and Assumptions

The baseline values for probabilities and utilities and ranges for the variables noted in the literature are shown in Table 1.

We assigned the anticoagulation status for each day in the perioperative period as being either "therapeutic" or "subtherapeutic." Preoperatively, the initial 2 days warfarin was withheld were considered therapeutic for both strategies, and the subsequent 2 days were considered therapeutic for the aggressive strategy and subtherapeutic for the minimalist strategy. Postoperatively, the day of surgery was considered subtherapeutic for both strategies, the subsequent 2 days were considered subtherapeutic for the minimalist strategy and therapeutic for the aggressive strategy, and the following 2 days were considered therapeutic for both strategies.

For days in which anticoagulation was considered subtherapeutic, the probability of stroke was considered to be the annual rate of stroke without anticoagulation divided by 365. For days in which the patient was considered anticoagulated, the daily rate was reduced by the relative risk reduction demonstrated in trials of anticoagulation.

The probability of major bleeding in the preoperative period was considered to be the annual rate of major bleeding on oral anticoagulants, as determined in nonsurgical settings, divided by 365, and multiplied by the number of days the patient was considered therapeutically anticoagulated. The probability of preoperative major bleeding on days assigned as subtherapeutic was considered to be negligible, as the daily rate of major bleeding in the absence of anticoagulation or surgery is low.

The probability of stroke for patients with prosthetic mitral valves who are not anticoagulated is unknown. As prosthetic mitral valve thromboembolic events are 1.8 times more common than for prosthetic aortic valves, the stroke rate without anticoagulation for mitral valves was calculated as the stroke rate without anticoagulation for aortic valves multiplied by 1.8.[13]

The increase in postoperative major bleeding due to the administration of treatment-dose LMWH or intravenous heparin soon after procedures or surgery is unknown. Based on the available literature, a 3% increase was used as the baseline estimate for major surgery; however, given the limited nature of the literature, a wide range (0%–10%) was used in a sensitivity analy-

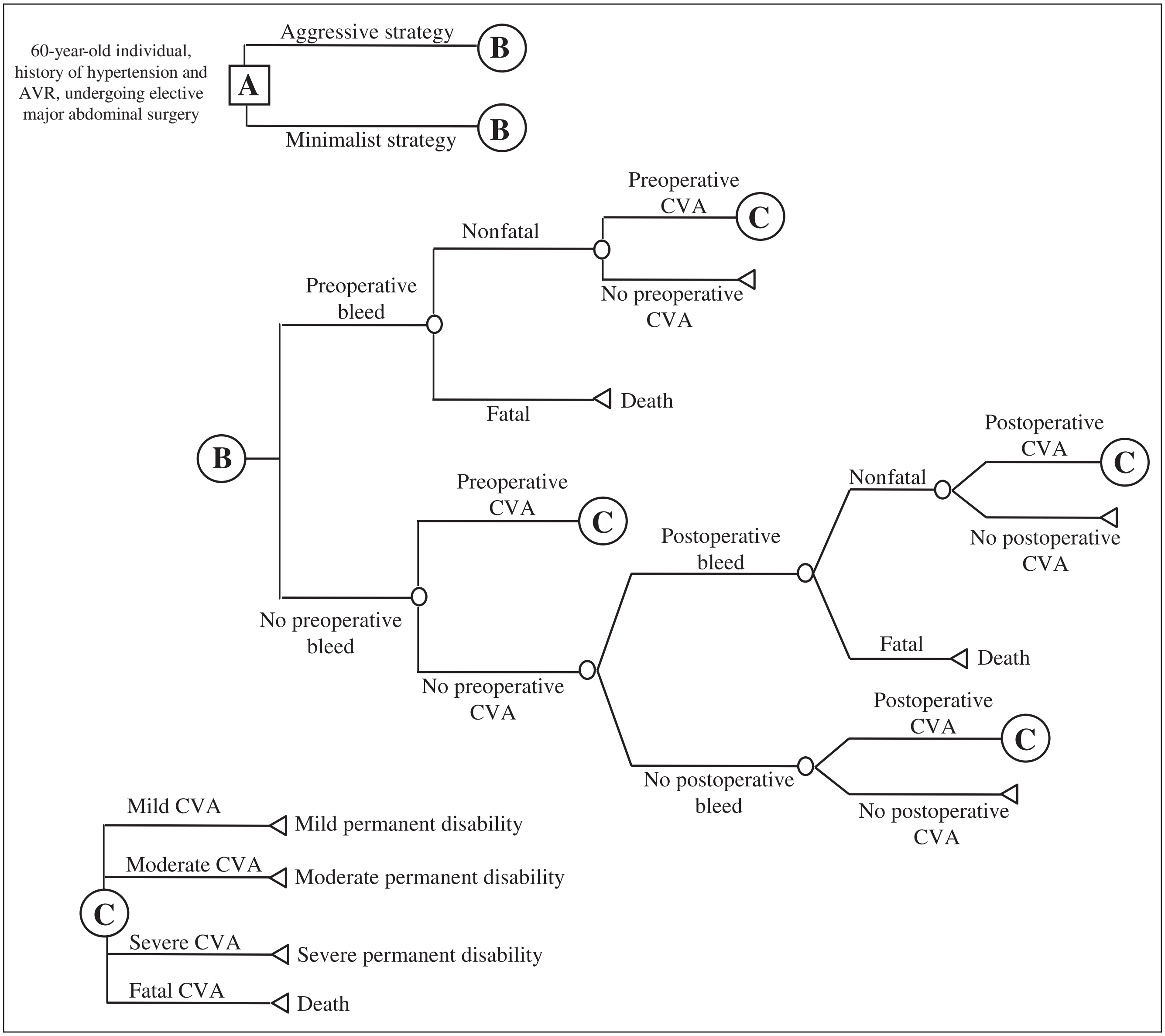

Figure 1 The decision-analysis model. Circles represent chance events. (A) The basic structure of the model. The square represents the choice of 2 treatment strategies: the minimalist strategy, consisting of withholding warfarin perioperatively, and the aggressive strategy, consisting of withholding warfarin and administering treatment-dose low-molecular-weight heparin or intravenous heparin perioperatively. (B) The subtree demonstrates the potential outcomes for the 2 treatment options. (C) The subtree illustrating the 4 potential health states for patients who suffer a stroke. Bleed indicates major bleeding. AVR = mechanical aortic valve replacement; CVA = cerebrovascular accident.

sis.[54–56] For dental extraction, based on a review demonstrating that major bleeding is rare during dental procedures when oral anticoagulation is continued throughout the procedure, it was assumed that major bleeding did not occur in the absence of anticoagulation and that the aggressive strategy results in a 0.2% incidence of major bleeding.[40] As there is no clear evidence for a difference in the rates of perioperative major bleeding and stroke for treatment-dose LMWH and intravenous heparin, we assumed these agents to be equivalent options for the aggressive strategy. Based on studies performed in other settings, however, it is also plausible that LMWH may cause less bleeding than unfractionated heparin.[57–59] The wide range for the bleeding rate chosen for the sensitivity analysis will also allow examination of whether use of a medication with a low bleeding rate impacts whether an aggressive strategy is preferred.

Table 1 Probabilities and Utilities

Input Variable	Base-Case Value %	Range %	References
Probabilities			
Stroke, annual rate without anticoagulation			
Atrial fibrillation	2.8	1–12	8–12
Mechanical valves			
Mitral[a]	7.2	4–12	13
Aortic	4.0	2.9–5.2	13–16
Stroke, annual rate with anticoagulation[b]			
Atrial fibrillation	1.7	0.38–4.6	9, 10, 17
Mechanical valves			
Mitral	1.1	0.9–1.5	13, 18
Aortic	0.7	0.5–0.9	13, 18
Major preoperative bleeding (daily rate on anticoagulation)[c]	0.0082	0.0054–0.0384	19–25
Postoperative major bleeding, without intravenous heparin	3	0–9	26–33
Absolute increase in postoperative major bleeding by intravenous heparin			
Minor and major surgery	3	0–10	34–39
Dental extraction, cataract surgery, and joint aspiration	0	0–2	40–46
Mortality, preoperative major bleed	15	1.5–29	19–22, 30, 47–49
Mortality, postoperative major bleed	1	0–2	26–28, 30, 31, 33
Effectiveness of anticoagulation (relative risk reduction)			
Atrial fibrillation	62	50–75	8–10
Mechanical valves	75	60–85	13, 50
Consequences of thromboembolic stroke			51
Fatal	30.3	20–35	
Mild (Rankin 1–2)	21.1	10–30	
Moderate (Rankin 3)	9.0	5–20	
Severe (Rankin 4–5)	39.6	25–40	
Utilities			
Baseline utility for patients experiencing no events or fully recovering from a perioperative event	1.0	0.5–1.0	
Stroke			52, 53
Minor (Rankin 1–2)	0.76	0–1.0	
Moderate (Rankin 3)	0.39	0–1.0	
Severe (Rankin 4–5)	0.07	0–1.0	

Note: The mortality rate for a major preoperative bleed was considered to be equivalent to the mortality rate for major bleeding determined in nonoperative settings.

a. For mechanical mitral valves, studies examining the stroke rate without anticoagulation are not available. As mitral valve thromboembolic events are approximately 1.8 times more common than aortic valve thromboses, the stroke rate without anticoagulation for mitral valves was calculated as the stroke rate without anticoagulation for aortic valves multiplied by 1.8.

b. For atrial fibrillation, the baseline estimate of the stroke rate on anticoagulation was determined using the stroke rate without anticoagulation multiplied by the relative risk reduction provided by anticoagulation.

c. The daily rate of preoperative major bleeding was calculated based on the annual rate of major bleeding determined in studies of patients receiving oral anticoagulation in nonsurgical settings.

As the surgical milieu or the discontinuation of warfarin inducing a transient hypercoagulable state has not been extensively studied and is not established as increasing the risk for arterial events, the base-case analysis assumed the absence of perioperative hypercoagulability. Perioperative hypercoagulability was considered in a sensitivity analysis, using a "hypercoagulable" variable to modify the daily stroke rate. For example, setting this variable to 2 would examine whether a hypercoagulable state that doubles the risk of stroke in the perioperative period relative to the nonoperative period has an impact on which strategy is preferred.

Stroke was considered to result in death or permanent disability. Stroke severity was classified as minor (minimal or mild residual neurologic deficits corresponding to class 0 or 1 on the modified Rankin scale), moderate (corresponding to class 2 or 3 on the modified Rankin scale), or severe (corresponding to class 4 or 5 on the modified Rankin scale).

Major bleeding was assumed to lead to either death or full recovery. The probability of death after postoperative major bleeding was determined from studies of patients who received anticoagulation for perioperative prophylaxis of venous thromboembolism. The probability of death from major bleeding was not considered to be altered by the anticoagulation status at the time of the event. A permanent disability state due to major bleeding was not included in the model, as this is rare.[2]

In the base-case analysis, we assumed that patients who experienced a preoperative stroke or bleeding event would not undergo surgery in the future. In a secondary analysis, we assumed that patients who suffered a preoperative stroke or major bleeding event from which they fully recovered were given a 2nd attempt at surgery. Under this analysis, if the preoperative event was a stroke, we assumed the patient would receive the aggressive strategy for the 2nd surgery, and if the event was a major hemorrhage, we assumed the patient would receive the minimalist strategy for the 2nd surgery. If the patient suffered an event during the preoperative period of the 2nd attempt at surgery, it was assumed that the patient would not undergo surgery in the future.

We assumed that anticoagulation was held for 1 week after a major bleeding event and that anticoagulation was subtherapeutic during these days.

Outcomes of the Analysis

Quality-adjusted life expectancy (QALE) was used as the measure of health outcomes. The QALEs were obtained by multiplying the appropriate life-years in the different health states with the utility estimate for each health state. Life expectancy was estimated using the declining exponential approximation of life expectancy (DEALE) method.[60,61] The mean mortality rates were estimated based on the US age-specific death rates as reported by the National Center for Health Statistics.[62] The excess annual mortality associated with aortic and mitral prosthetic valves; atrial fibrillation; and hypertension and minimal, moderate, or severe disability following a stroke was estimated based on a review of the literature.[63–71] Quality-adjusted life expectancy was discounted at an annual rate of 3% to account for time preferences.

Quality Adjustments

We adjusted life expectancy to reflect the quality of life for any given state of health by multiplying the life expectancy by the utility for that health state. Death was defined as having a utility of zero, and patients experiencing no events or fully recovering from a perioperative event without permanent disability were defined as having a utility of 1.0. A sensitivity analysis was performed to examine the effect of varying the baseline utility, as the baseline utility for patients experiencing no events or fully recovering from a perioperative event may be substantially less than 1.0, particularly for elderly patients with multiple comorbidities. Utilities for disabilities associated with minor, moderate, and major stroke were assigned based on a study that used the time tradeoff method to elicit these values.[48] For patients who had surgery canceled due to a preoperative event, the utility of living without having had total hip replacement was assigned as 0.6, based on a cost-effectiveness study that included survey data showing a utility difference of 0.4 for living with and without total hip replacement.[72]

Probabilistic Sensitivity Analysis

We conducted a probabilistic sensitivity analysis using a Monte Carlo simulation. For this analysis, each variable in the model was represented by a triangular distribution in which the peak was equal to the base-case value and the lower and upper bounds were equal to the extreme values for the variables found in the literature. We performed 10,000 simulations to generate confidence intervals around the difference in the QALE under the 2 strategies and determine the proportion of trials in which each strategy is favored.

Sensitivity Analyses

One-way sensitivity analyses using point estimates were performed on the base case for all variables presented in Table 1 using the range of values noted in the literature.

RESULTS

For a 60-year-old individual with hypertension and a mechanical aortic valve undergoing elective major abdominal surgery, the expected value for the minimalist strategy was slightly greater than for the aggressive strategy. In a probabilistic sensitivity analysis con-

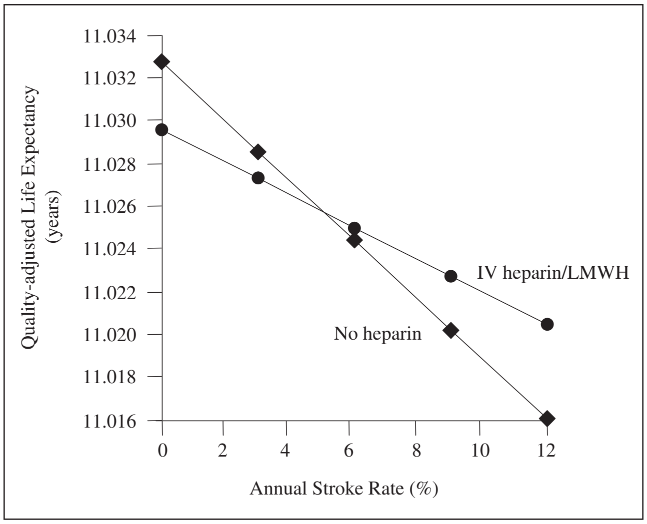

Figure 2 Quality-adjusted life expectancies for the aggressive and minimalist strategies based on the annual risk of stroke without anticoagulation. The minimalist strategy is favored when the annual stroke rate is less than 5.6%. LMWH = low-molecular-weight heparin; IV = intravenous.

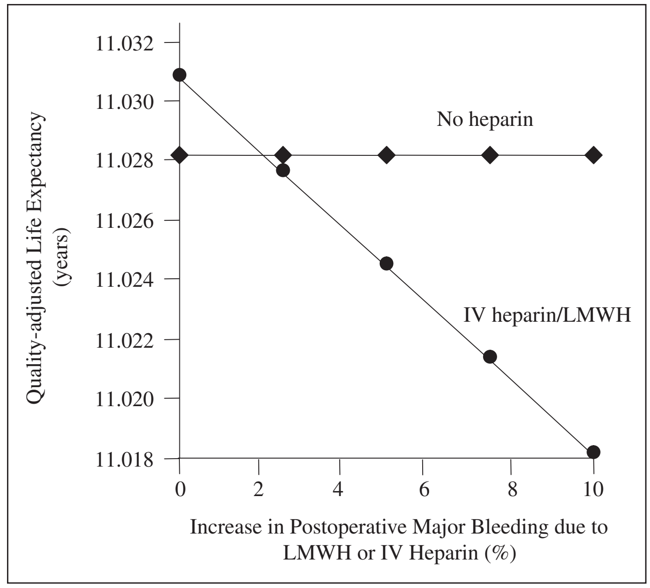

Figure 3 Quality-adjusted life expectancies for the aggressive and minimalist strategies based on the estimated increase in postoperative bleeding due to the administration of treatment-dose low-molecular-weight heparin or intravenous heparin. The minimalist strategy is favored when the increase in bleeding is greater than 2.0%. LMWH = low-molecular-weight heparin; IV = intravenous.

sisting of 10,000 Monte Carlo simulations, the mean difference in QALE for the 2 strategies was 0.003 years favoring the minimalist strategy (95% confidence interval, –0.005 years to 0.011 years). In 22% of the simulations, the difference in the QALE was ≤0 days, indicating that the minimalist strategy was favored for 78% of simulations.

Sensitivity Analyses

One-way sensitivity analyses based on point estimates found that the outcome was insensitive to the preoperative bleeding rate, mortality rate for preoperative major bleeding, effectiveness of anticoagulation, consequences of stroke, life expectancy, baseline utility for patients experiencing no events or fully recovering from a perioperative event, and utility for stroke.

Sensitivity analysis demonstrates that annual stroke rates above 5.6% favor the aggressive strategy (Figure 2). The difference in QALE, however, is small for all estimates of the annual risk of stroke. For example, the benefit of the aggressive strategy when the annual risk of stroke is 20% is 0.014 quality-adjusted life years (QALYs) (5.1 days). The aggressive strategy is also favored when the increase in postoperative major bleeding caused by LMWH or intravenous heparin is less than 2.0% (Figure 3). Again, the difference is small even at the extremes of the bleeding risk range. For example, if there is no increase in major bleeding induced by heparin, the aggressive strategy is favored by 0.003 QALYs (1.1 days). If heparin increases the rate of major bleeding by 10%, the minimalist strategy is favored by 0.010 QALYs (3.7 days).

Figure 4 allows determination of the preferred strategy based on patients' individualized risks of stroke and bleeding. Figure 4 also demonstrates the potential impact of a hypothetical transient hypercoagulable state that doubles the baseline stroke rate in the perioperative period. Under this assumption, the aggressive strategy is favored for most values for stroke and major bleeding, including the values assumed for the base case.

To make the analyses clinically meaningful, 2 additional hypothetical patients on long-term oral anticoagulation were analyzed using the model: a 60-year-old individual with hypertension and atrial fibrillation and a 60-year-old subject with hypertension and a mechanical mitral valve (Table 2). For the base-case and the 2 additional patients, decision analyses were performed for major abdominal surgery and dental extraction. For dental extraction, the aggressive strategy resulted in greater QALE for all 3 individuals because of the minimal risk of major bleeding from periprocedure heparin. The absolute incremental gain in QALE, however, is small for all 3 patients (0.5 to 2.1

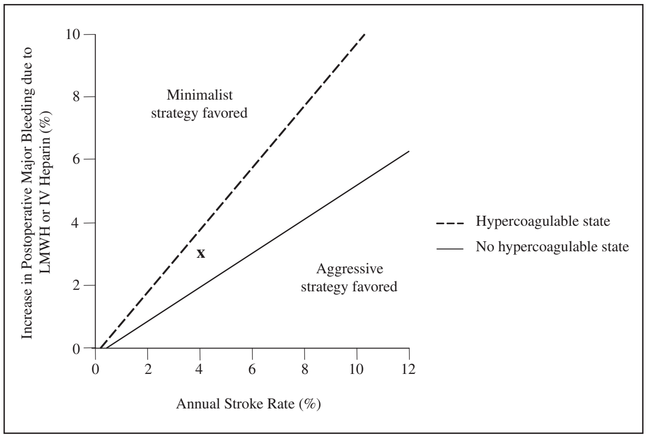

Figure 4 *A 3-way sensitivity analysis allowing determination of the preferred strategy based on the patient's annual risk of stroke without anticoagulation and the estimated increased risk of major postoperative bleeding due to the administration of treatment-dose low-molecular-weight heparin (LMWH) or intravenous (IV) heparin. The solid line represents the baseline assumption of the absence of a perioperative hypercoagulable state that increases the risk for arterial events. The dashed line demonstrates the impact of a hypercoagulable state that doubles the risk of stroke. The patient described in the base-case scenario is marked by the x.*

days). For major abdominal surgery, which has a greater risk of bleeding, the aggressive strategy was beneficial only for the patient with the highest stroke risk (mechanical mitral valve), although the incremental benefit was again noted to be small (0.4 days).

The base-case analysis was also examined using the assumption that a 2nd attempt at surgery is made for patients who fully recover from a preoperative event (e.g., mild stroke or major bleeding). The minimalist strategy remained preferred using this approach.

DISCUSSION

The analysis found that for a patient with a mechanical aortic valve undergoing major surgery, simply withholding warfarin preoperatively and restarting the night of the surgery leads to greater quality-adjusted survival than administering LMWH or intravenous heparin perioperatively. Although the difference is minimal, the result is clinically important, as it indicates that the more expensive and difficult strategy of administering full-dose perioperative anticoagulation is unnecessary and potentially harmful.

Our analysis is limited by the lack of definitive data for several of the variables in the model. To examine uncertainty surrounding the estimates, 1-way sensitivity analyses around wide ranges of values and a probabilistic sensitivity analysis using a Monte Carlo simulation for the base case were performed. The probabilistic sensitivity analysis found the 95% confidence interval for the difference in QALE for the strategies to be from 1.8 days favoring the aggressive strategy to 4.0 days favoring the minimalist strategy. The narrow confidence interval and minimal difference between the strategies across the 95% confidence interval supports the result of the primary analysis that there is no meaningful clinical difference between the strategies.

The sensitivity analyses identified clinical circumstances in which LMWH or intravenous heparin administration is beneficial; the aggressive strategy is favored when the annual stroke rate is greater than 5.6% or when the increase in postoperative major bleeding induced by heparin is less than 2.0%. However, a consistent finding for the 3 indications for long-term anticoagulation (aortic and mitral valve replacement

Table 2 Quality-Adjusted Life Expectancy Differences for the Minimalist and Aggressive Anticoagulation Strategies by Sample Case Scenarios

60-year-old Patient Hypertension	Annual Stroke Rate[a]	Procedure	Increased Risk of Major Bleeding from Low-Molecular-Weight Heparin or Intravenous Heparin	Preferred Strategy	Incremental Difference in Quality-Adjusted Life Expectancy
Mechanical aortic valve	4.0%	Dental extraction	0.2%	Aggressive	0.0024 years (0.9 days)
		Abdominal surgery	3.0%	Minimalist	0.0011 years (0.4 days)
Atrial fibrillation	2.8%	Dental extraction	0.2%	Aggressive	0.0015 years (0.5 days)
		Abdominal surgery	3.0%	Minimalist	0.0020 years (0.7 days)
Mechanical mitral valve	7.2%	Dental extraction	0.2%	Aggressive	0.0058 years (2.1 days)
		Abdominal surgery	3.0%	Aggressive	0.0011 years (0.4 days)

a. Annual stroke rate without anticoagulation.

and atrial fibrillation) is that the difference in QALE between the 2 strategies is small regardless of which strategy is preferred. Analyses examining the extremes of the ranges of the variables reveal that the gain in QALE ranges from half a day to 1 week. To place this finding in context, a report by the Evidence-based Medicine Working Group stated that a gain of 2 or more months of QALE can be considered important, and "a gain of a few days would represent a toss-up."[73]

It is intuitive that because the 2 strategies produce similar QALEs, the patient's preference (i.e., utility for living with a stroke) should have an important impact on the result. We found, however, that the model is insensitive to variations in stroke utilities. The reason for the lack of impact of the utility of stroke on the outcome is the small number of expected strokes; using the baseline estimates, 1 patient will suffer a thromboembolic stroke for every 1515 and 3030 patients treated with the minimalist and aggressive strategies, respectively.

The baseline utility (i.e., utility for patients who have no perioperative events or fully recover from a perioperative event) may vary to a large degree among patients and may be substantially less than 1.0 for elderly patients with multiple comorbidities. Therefore, a wide range of values were examined in a sensitivity analysis to determine whether the baseline utility affects whether an aggressive strategy is preferred. The outcome was insensitive to this variable, indicating that the results are applicable over a broad range of baseline utilities.

A variable with a great impact on which strategy is preferred is the potential presence of a transient perioperative hypercoagulable state. Although most reviews of bridging therapy discount or do not address the possible presence of a hypercoagulable state that impacts the risk of perioperative arterial thromboembolic events, a hypercoagulable state is accepted as leading to an increased risk of venous thromboembolism in the perioperative period and has been estimated as increasing the venous thromboembolism rate by as much as 100-fold.[2,74] Factors postulated as theoretically inducing hypercoagulability in the surgical setting are rebound hypercoagulability after the discontinuation of warfarin and a prothrombotic state induced by the surgical milieu. A theoretical risk of rebound hypercoagulability after the discontinuation of oral anticoagulation has been described based on studies demonstrating increases in markers of thrombin generation, including prothrombin fragments F1+2, thrombin-antithrombin complexes, and d-dimers, and increased levels of factor VIII.[75–77] Similarly, the surgical milieu has been found to induce a hypercoagulable state, including increased levels of plasminogen activator inhibitor-1.[78–80] Although clinical studies examining perioperative bridging therapy have not had sufficient power to make precise determinations of the perioperative stroke rate, most trials have found rates greater than would be expected mathematically.[3,81,82] The base-case analysis indicates that a transient hypercoagulable state that increased the arterial thromboembolic rate more than 1.4 times the baseline rate would result in the aggressive strategy being preferred over the minimalist strategy. For the aggressive strategy to result in a 2-month gain in QALE, however, a hypercoagulable state would have to increase the baseline rate 58-fold. Given the potentially important impact on the decision, future clinical trials need to examine whether the perioperative stroke rate is greater than mathematically predicted due to a hypercoagulable state.

A sensitivity analysis found that the aggressive strategy is favored when the annual stroke rate is greater than 5.6%. Table 2 demonstrates that risk stratification based on the annual risk of stroke can thus identify patients undergoing major surgery who may achieve a benefit, albeit small, from perioperative LMWH or intravenous heparin. Patients at low annual risk (e.g., atrial fibrillation with 0–2 stroke risk factors) and patients at intermediate annual risk (e.g., mechanical aortic valve) do not benefit, and patients at high annual risk (e.g., mechanical mitral valve) achieve a small benefit.

In our study, a sensitivity analysis revealed that the aggressive strategy is also favored when the increase in postoperative major bleeding induced by intravenous heparin is less than 2.0%. Future studies are needed to more precisely determine the rates of postoperative major bleeding for patients treated with therapeutic-dose LMWH or intravenous heparin after surgery. Possibly the greatest difference in practice between the perioperative use of LMWH and unfractionated heparin would be the treatment costs. LMWH can be given subcutaneously and without laboratory monitoring, which allows for home administration for selected patients. The dramatic decrease in health care costs achieved through elimination of the need for additional hospitalization may make this alternative reasonable for patients at high risk for stroke. However, as our analysis indicates that perioperative treatment-dose anticoagulation is not superior to simply withholding and restarting warfarin, a formal cost analysis is unnecessary for most patients on oral anticoagulation.

In conclusion, our analysis found a minimal difference between aggressive and minimalist strategies for the base-case analysis and the secondary analyses, indicating that there is no advantage to complex and costly administration of perioperative heparin and that simply discontinuing oral anticoagulants before surgery and restarting after the procedure is preferred for most patients with mechanical aortic valves and atrial fibrillation. The addition of perioperative LMWH or intravenous heparin is burdensome for patients and physicians and increases health care costs but provides no additional benefit. Although an aggressive strategy provides benefit for certain patients at high risk of stroke (e.g., those with mechanical mitral valves), the magnitude of the benefit is small and of questionable clinical significance. Further studies are needed to determine whether a hypercoagulable state exists, which may substantially impact the perioperative rate of stroke, and the incremental costs for the benefit gained from an aggressive strategy for patients at the highest risk of stroke.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370–5.
2. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997;336;1506–11.
3. Dunn AS, AGG Turpie. Perioperative management of patients on oral anticoagulants: a systematic review. Arch Intern Med. 2003;163:901–8.
4. Douketis JD, Crowther M, Cherian SS, Kearon CB. Physician preferences for perioperative anticoagulation in patients with a mechanical heart valve who are undergoing elective noncardiac surgery. Chest. 1999;116:1240–6.
5. Gerson LB, Gage BF, Owens DK, Triadafilopoulos G. Effect and outcomes of the periendoscopic management of patients who take anticoagulants. Am J Gastroenterol. 2000;95:1717–24.
6. Douketis JD, Johnson JA, Turpie AGG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin. Arch Intern Med. 2004;164:1319–26.
7. Ansell J, Hitsh J, Dalen J, et al. Managing oral anticoagulant therapy. Chest. 2001;119:22S–38S.
8. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131:492–501.
9. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449–57.
10. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study. Final results. Circulation. 1991;84:527–39.
11. EAFT Study Group. Secondary prevention of vascular events in patients with non-rheumatic atrial fibrillation and a recent transient ischaemic attack or minor ischaemic stroke. Lancet. 1993;342:1255–62.
12. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke. Results from the national registry of atrial fibrillation. JAMA. 2001;285:2864–70.
13. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89:635–41.
14. Starr DS, Lawrie GM, Howell JF, Morris GC Jr. Clinical experience with the Smeloff-Cutter prosthesis: 1- to 12-year follow-up. Ann Thorac Surg. 1980;30:448–54.
15. Starr A, Grunkemeier GL, Lambert LE, Thomas DR, Sugimura S, Lefrak LA. Aortic valve replacement: a ten-year follow-up of noncloth-covered vs cloth-covered caged ball prostheses. Circulation. 1977;56(Suppl II):133–8.
16. Larsen GL, Alexander JA, Stanford W. Thromboembolic phenomena in patients with prosthetic aortic valves who did not receive anticoagulants. Ann Thorac Surg. 1977;23:323–6.
17. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II study. Lancet. 1994;343:687–91.
18. Cannegeiter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbrouke JP, Briët E. Optimal oral therapy in patients with mechanical heart valves. N Engl J Med. 1995;333:11–7.
19. The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Arch Intern Med. 1996;156:409–16.
20. McMahon DA, Smith DM, Carey MA, Zhou XH. Risk of major hemorrhage for outpatients treated with warfarin. J Gen Intern Med. 1998;12:311–6.
21. Van der meer FJM, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med. 1993;153:1557–62.
22. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med. 1993;95:315–28.
23. Gitter MJ, Jaeger TM, Petterson TM, Gersh BJ, Silverstein MD. Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. Mayo Clin Proc. 1995;70:725–33.
24. Palareti G, Coccheri S, Poggi M, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Lancet. 1996;348:423–8.
25. Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? Arch Intern Med. 2001;161:1443–7.
26. McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial. Ann Surg. 2001;233:438–44.
27. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318:1162–73.
28. Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet. 1993;341:259–65.
29. Hull RD, Rollin FB, Pineo GF, Stein PD, Raskob GE, Valentine KA. Preoperative versus postoperative initiation of low-molecular-weight heparin prophylaxis against venous thromboembolism in patients undergoing elective hip replacement. Arch Intern Med. 1999;159:137–41.
30. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention trial. Lancet. 2000;355:1295–302.

31. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients. A double-blind, randomized comparison. Arch Intern Med. 2000;160:2199–207.
32. Heit JA, Elliott G, Trowbridge AA, Morrey BF, Gent M, Hirsh J. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2000:132:853–61.
33. Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med. 1986;315:925–9.
34. Michaud GF, Pelosi F, Noble MD, Knight BP, Morady F, Strickberger A. A randomized trial comparing heparin initiation 6 h or 12 h after pacemaker implantation. J Am Col Cardiol. 2000;35;1915–8.
35. Goldstein DJ, Losquadro W, Spotnitz HM. Outpatient pacemaker procedures in orally anticoagulated patients. PACE. 1998;21:1730–4.
36. Otley CC, Fewkes JL, Frank W, Olbricht SM. Complications of cutaneous surgery in patients who are taking warfarin, aspirin, or nonsteroidal anti-inflammatory drugs. Arch Dermatol. 1996;132:161–6.
37. Clark SC, Vitale N, Zacharias J, Forty J. Effect of low molecular weight heparin (Fragmin) on bleeding after cardiac surgery. Ann Thorac Surg. 2000;69:762–5.
38. Patterson BM, Marchand R, Ranawat C. Complications of heparin therapy after total joint arthroplasty. J Bone Joint Surg. 1989;71:1130–4.
39. Della Valle CJ, Jazrawi LM, Idjadi J, et al. Anticoagulant treatment of thromboembolism with intravenous heparin therapy in the early postoperative period following total joint arthroplasty. J Bone Joint Surg. 2000;82:207–12.
40. Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med. 1998;158:1610–6.
41. Gainey SP, Robertson DM, Fay W, Ilstrup D. Ocular surgery on patients receiving long-term warfarin therapy. Am J Ophthalmol. 1989;108:142–6.
42. Hall DL, Steen WH Jr, Drummond JW, Byrd WA. Anticoagulants and cataract surgery. Ophthalmol Surg. 1988;19:221–2.
43. Roberts CW, Woods SM, Turner LS. Cataract surgery in anticoagulated patients. J Cataract Refract Surg. 1991;17:309–12.
44. Carter K, Miller KM. Phacoemulsification and lens implantation in patients treated with aspirin or warfarin. J Cataract Refract Surg. 1998;24:1361–4.
45. Robinson GA, Nylander A. Warfarin and cataract extraction. Br J Ophthalmol. 1989;73:702–3.
46. McMahon LB. Anticoagulants and cataract surgery. J Cataract Refract Surg. 1988;14:569–71.
47. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med. 1989;87:144–52.
48. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Intern Med. 1996;124:970–9.
49. White RH, McKittrick T, Takakuwa J, Callahan C, McDonnell M, Fihn S. Management and prognosis of life-threatening bleeding during warfarin therapy. Arch Intern Med. 1996;156:1197–201.
50. Mok CK, Boey J, Wang R, et al. Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized trial. Circulation. 1985;72:1059–63.
51. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes. A population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062–8.
52. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke. A comprehensive review. Stroke. 2001;32:964–72.
53. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med. 1996;156:1829–36.
54. Maduro JA, Rookstool M, Wease G. The management of patients on chronic coumadin therapy undergoing subsequent surgical procedures. Am J Surg. 1994;60:542–7.
55. Spandorfer JM, Lynch S, Weitz HH, Fertel S, Merli GJ. Use of enoxaparin for the chronically anticoagulated patient before and after procedures. Am J Cardiol. 1999;84:478–80.
56. Kovacs M, Kahn A, Solymoss S, et al. Prospective multicentre trial of bridging therapy with dalteparin for patients who require temporary discontinuation of OAC for prosthetic valves or high risk atrial fibrillation. Blood. 2002;100:149a.
57. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med. 1999;130:800–9.
58. van den Belt AGM, Prins MH, Lensing AWA, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism (Cochrane Review). In: The Cochrane Library, Issue 3. Oxford (UK): Update Software; 2002.
59. Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomized clinical trials. Thromb Haemost. 2000;83:14–9.
60. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. Am J Med. 1982;73:883–8.
61. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). II. Use in medical decision-making. Am J Med. 1982;73:889–97.
62. Anderson RN. United States life tables, 1997. National vital statistics reports. Volume 47, number 28. Hyattsville (MD): National Center for Health Statistics; 1999.
63. Onundarson PT, Thorgeirsson G, Jonmundsson E, et al. Chronic atrial fibrillation—epidemiologic features and 14 year follow-up: a case control study. Eur Heart J. 1987;8:521–7.
64. Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1989;20:828.
65. Cohn LH. The long-term results of aortic valve replacement. Chest. 1984;85:387–96.
66. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. Veterans Affairs Cooperative Study on Valvular Heart Disease. N Engl J Med. 1993;328:1289–96.
67. Prencipe M, Culasso F, Rasura M, et al. Long-term prognosis after a minor stroke: 10-year mortality and major stroke recurrence rates in a hospital-based cohort. Stroke. 1998;29:126–32.
68. Laupacis A, Cuddy TE. Prognosis of individuals with atrial fibrillation. Can J Cardiol. 1996;12(Suppl A):14A–16A.
69. Clausen J, Jensen G. Blood pressure and mortality: an epidemiological survey with 10 years follow-up. J Hum Hypertens. 1992;6(1):53–9.
70. Takagi S, Saitoh S, Nakano M, et al. Relationship between blood pressure level and mortality rate: an 18-year study conducted in two rural communities in Japan. J Hypertens. 2000;18:139–44.
71. Port S, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. Lancet. 2000;355:175–80.

72. Chang RW, Pellissier JM, Hazen GB. A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. JAMA. 1996;275:858–65.
73. Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? JAMA. 1995;273:1610–3.
74. Geerts WH, Heit JA, Clagett PG, et al. Prevention of venous thromboembolism. Chest. 2001;119:132S–175S.
75. Poller L, Thomson J. Evidence for "rebound" hypercoaguability after stopping anticoagulants. Lancet. 1964;2:62–4.
76. Grip L, Blombäck M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial infarction patients. Eur Heart J. 1991;12:1225–33.
77. Genewein U, Haeberli A, Straub PW, Beer JH. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. Br J Haemost. 1996;92:479–85.
78. Palareti G, Legnani C. Warfarin withdrawal. Pharmacokinetic-pharmacodynamic considerations. Clin Phamacokinet. 1996; 30:300–13.
79. Lopez Y, Paramo JA, Valenti JR, Pardo F, Montes R, Rocha E. Hemostatic markers in surgery: a different fibrinolytic activity may be of pathophysiological significance in orthopedic versus abdominal surgery. Int J Clin Lab Res. 1997;27:233–7.
80. Kosir MA, Schmittinger L, Barno-Winarski L, et al. Prospective double-arm study of fibrinolysis in surgical patients. J Surg Res. 1998;74:96–101.
81. Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation. 2004;110:1658–63.
82. Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. Neurology. 2003;;61:964–8.