Review Article

Current Concepts

Management of Anticoagulation before and after Elective Surgery

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THE most common indications for warfarin therapy are atrial fibrillation, the presence of a mechanical heart valve, and venous thromboembolism.[1,2] Treatment with warfarin presents a problem if patients with these indications need surgery, because the interruption of anticoagulant therapy increases the risk of thromboembolism. After warfarin therapy is discontinued, it takes several days for its antithrombotic effect to recede, and when it is resumed, several days are needed to reestablish therapeutic anticoagulation.

There is no consensus on the appropriate perioperative management of anticoagulation for patients who have been receiving long-term warfarin therapy. Rational decisions about the treatment of such patients can be made only if one can quantify the risks of thrombosis and bleeding associated with the various alternatives. In this review, we will consider the expected risks and benefits of different approaches to anticoagulation in patients who require warfarin because of atrial fibrillation, a mechanical heart valve, or a history of venous thromboembolism. Our assessment of the consequences of arterial and venous thromboembolism and postoperative bleeding is then used as the basis for an approach to management designed to maximize the patient's safety and the efficient use of health care resources.

We quantified the estimated risks and benefits of two different strategies: an aggressive approach, in which intravenous heparin is given for two days before and two days after surgery; and a minimalist strategy, under which patients receive no heparin immediately before or after surgery. These two approaches were chosen because they are widely used in clinical practice, conceptually clear, and likely to be associated with the most divergent levels of risk of thromboembolism and bleeding. Whenever possible, our estimates of risk and benefit are based on data from randomized trials or prospective studies.

Risks Associated with Temporarily Stopping Warfarin Therapy

After warfarin therapy is stopped, it takes about four days for the international normalized ratio (INR) to reach 1.5 in almost all patients[3]; once the INR reaches 1.5, surgery can be safely performed.[3-8] After warfarin therapy is restarted, it takes about three days for the INR to reach 2.0.[9] Therefore, if warfarin is withheld for four days before surgery and treatment is restarted as soon as possible after surgery, patients can be expected to have a subtherapeutic INR for approximately two days before surgery, and two days after surgery. However, because the INR will be elevated to some extent for much of this period, patients can still be expected to have partial protection against thromboembolism.[10-12] The temporary discontinuation of warfarin thus exposes patients to a risk of thromboembolism equivalent to one day without anticoagulation before surgery and another day without anticoagulation after surgery. Regardless of the approach to perioperative anticoagulation used, patients need to have a normal or nearly normal state of coagulation during surgery, so some increase in the risk of thromboembolism is unavoidable.

Independently of the intensity of anticoagulation, the perioperative risk of thromboembolism may be increased by other factors, in particular a rebound hypercoagulable state caused by the discontinuation of warfarin and the prothrombotic effect of the surgery itself. Although there is biochemical evidence suggestive of a rebound hypercoagulable state after therapy with oral anticoagulants is stopped,[13-18] the phenomenon has yet to be seen clinically.[19] Surgery can induce hemostatic changes that may increase the risk of thromboembolism.[20] Although there is good evidence that surgery increases the risk of venous thromboembolism,[21,22] there is no evidence that surgery increases the risk of arterial embolism in patients with atrial fibrillation or mechanical heart valves.

Consequently, for patients whose INR returns to normal shortly after stopping warfarin therapy, we have assumed that the risk of preoperative arterial thromboembolism, postoperative arterial thromboembolism, and preoperative venous thromboembolism will be similar to that which is expected in the absence of anticoagulation. However, the risk of postoperative venous thromboembolism will be

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greatly increased. Calculating a risk of pulmonary embolism of 1.7 percent per year for patients with previous venous thromboembolism who do not undergo surgery[23] and a risk of 6.4 percent in the two weeks after operation for surgical patients with the same history (on the basis of a 1.6 percent risk for surgical patients,[24] multiplied by 4 because of the previous episode of venous thromboembolism[25]), we estimate that major surgery increases the short-term risk of recurrence 100-fold.

RISKS OF THROMBOEMBOLISM IN SPECIFIC SETTINGS

Venous Thromboembolism

After an acute episode of venous thromboembolism, the risk of recurrence declines rapidly over the following three months[26] (Table 1). The risk of recurrent venous thromboembolism in the three months after proximal deep-vein thrombosis is approximately 50 percent in the absence of anticoagulation[27]; one month of warfarin therapy reduces this risk to about 10 percent,[28,29] and three months of warfarin therapy reduces it to about 5 percent.[27-29] On the basis of these data, we estimate that stopping anticoagulation in the first month after an acute event is associated with a very high risk of recurrent venous thromboembolism (40 percent in a one-month interval) and that the risk becomes intermediate if anticoagulants are not stopped until the second or third month (10 percent in a two-month interval).

Long-term anticoagulation is usually reserved for patients with multiple episodes of venous thromboembolism, a hereditary hypercoagulable state, or active cancer. In these patients, discontinuation of warfarin is estimated to be associated with a much lower risk of thromboembolism (15 percent per year).[30]

Anticoagulation reduces the risk of recurrent venous thromboembolism by about 80 percent.[23,27,29,31,32]

Arterial Thromboembolism

Patients with nonvalvular atrial fibrillation who do not receive antithrombotic therapy have an average risk of systemic embolism of 4.5 percent per year.[33] The risk for an individual patient varies from about 1 percent to 20 percent depending on the presence of risk factors[33]; in patients with previous cerebral embolism it is approximately 12 percent per year.[34] Less reliable data suggest that the risk of recurrent embolism from any cardiac source is approximately 0.5 percent per day in the first month after an acute event.[35] Anticoagulation reduces the risk of embolism by 66 percent in patients with nonvalvular atrial fibrillation.[33,34]

Mechanical Heart Valves

The average rate of major thromboembolism in patients with mechanical heart valves who are not given anticoagulant therapy is estimated at 8 percent; there is evidence that anticoagulation reduces this risk by 75 percent.[36,37]

RISK OF BLEEDING

A two-day course of intravenous heparin before surgery is unlikely to cause much bleeding. However, if heparin therapy is resumed immediately after surgery, there is likely to be a marked increase in the risk of major bleeding.[38-45] The size of this increase is uncertain, although in one study the reported incidence of major bleeding in patients with deep-vein thrombosis who were judged to be at high risk for bleeding was 11 percent during the first five days of intravenous heparin therapy.[46] We therefore estimate that two days of intravenous heparin therapy will increase the absolute rate of major postoperative bleeding by about 3 percent.

CONSEQUENCES OF THROMBOSIS AND BLEEDING

It is important to consider the consequences of venous and arterial thromboembolism, and of bleeding, in addition to the rates at which these outcomes occur. Six percent of recurrent episodes of venous thromboembolism are expected to be fatal.[23,28,29] A small group of patients with recurrent events, perhaps 2 percent, will have serious permanent disability, though the majority will make a good recovery. The consequences of arterial thromboembolism are

TABLE 1. ESTIMATED RATES OF THROMBOEMBOLISM ASSOCIATED WITH VARIOUS INDICATIONS FOR ORAL ANTICOAGULATION, AND THE REDUCTION IN RISK DUE TO ANTICOAGULANT THERAPY.

INDICATION	RATE WITHOUT THERAPY	RISK REDUCTION WITH THERAPY
	percent	
Acute venous thromboembolism*		
Month 1	40	80
Months 2 and 3	10	80
Recurrent venous thromboembolism*†	15‡	80
Nonvalvular atrial fibrillation	4.5‡	66
Nonvalvular atrial fibrillation and previous embolism	12‡	66
Mechanical heart valve	8‡	75
Acute arterial embolism		
Month 1	15	66

*The increase in the risk of venous thromboembolism associated with surgery (estimated to be 100-fold) is not included in these rates.

†The term refers to patients whose last episode of venous thromboembolism occurred more than three months before evaluation but who require long-term anticoagulation because of a high risk of recurrence.

‡The rate shown is per year.

much more serious; approximately 20 percent of these episodes are fatal, and 40 percent result in serious permanent disability.[33,34,47,48] Approximately 3 percent of episodes of major postoperative bleeding are fatal,[38,49] but most patients make a full recovery, despite the need for reoperation in as many as 50 percent of them.[49] Rarely, perhaps half as often as they are fatal, episodes of major postoperative bleeding result in permanent disability.

RISKS AND BENEFITS OF PERIOPERATIVE INTRAVENOUS HEPARIN

We will now provide estimates of the net effect, in terms of the frequency of major disability, of administering intravenous heparin for two days before and two days after surgery in patients with different indications for anticoagulation.

Venous Thromboembolism

In the first month after an acute episode of venous thromboembolism, each day without anticoagulation is associated with a 1.0 percent absolute increase in the risk of recurrence. Despite doubling the rate of bleeding, postoperative intravenous heparin therapy results in a net reduction in serious morbidity in these patients, because the risk of postoperative venous thromboembolism is extremely high. Preoperative intravenous heparin is also warranted while the INR is subtherapeutic (Table 2).

In the second and third months after an acute episode of venous thromboembolism, the risk of recurrence has dropped sufficiently that preoperative intravenous heparin therapy is not justified unless the patient has other risk factors for thromboembolism (e.g., hospitalization). However, because of the expected 100-fold increase in the risk of venous thromboembolism after surgery, postoperative therapy with intravenous heparin is indicated (Table 2).

More than three months after an acute episode of venous thromboembolism, preoperative anticoagulation is not warranted. In these circumstances, the argument for postoperative intravenous heparin is also weak because of the marked decline over time in the absolute risk of venous thromboembolism. In this setting, postoperative intravenous heparin can be expected to cause as many episodes of major bleeding as it will prevent major thromboembolic events (Table 2). Because the consequences of venous thromboembolism are usually more severe than those of bleeding, the use of postoperative intravenous heparin will thus produce a small net decrease in severe morbidity. However, prophylactic measures that are associated with a lower risk of bleeding than intravenous heparin (for instance, subcutaneous low-molecular-weight heparin, given with or without the use of graduated-compression stockings and intermittent pneumatic compression) are likely to be a safer alternative for such patients.

TABLE 2. ADVERSE EVENTS CAUSED OR PREVENTED BY THE PREOPERATIVE AND POSTOPERATIVE ADMINISTRATION OF INTRAVENOUS HEPARIN, ACCORDING TO THE INDICATION FOR ANTICOAGULATION.*

INDICATION FOR HEPARIN	THROMBOEMBOLISM	MAJOR BLEEDING	DEATH OR DISABILITY
	no. of events caused or prevented/10,000 patients		
Acute venous thromboembolism			
Month 1	−7162†	+300	−559
Months 2 and 3	−1328†	+300	−93
Recurrent venous thromboembolism‡	−332†	+300	−13
Nonvalvular atrial fibrillation	−2	+300	+12
Nonvalvular atrial fibrillation and previous embolism	−4	+300	+11
Mechanical heart valve	−3	+300	+12
Arterial embolism			
Month 1	−65	+300	−26

*Values shown are estimated numbers of major events caused (+) or prevented (−) if therapy is administered to 10,000 patients undergoing major surgery.

†A 100-fold increase in the postoperative rate of venous thromboembolism has been assumed, to reflect the added risk associated with major surgery.

‡The term refers to patients whose last episode of venous thromboembolism occurred more than three months before evaluation but who require long-term anticoagulation because of a high risk of recurrence.

Arterial Thromboembolism

For patients at risk of arterial thromboembolism, there is a stronger argument in favor of preoperative intravenous heparin than there is for postoperative therapy. The risk of thromboembolism is similar before and after surgery, but the risk of bleeding is much higher after surgery.

In the first month after an acute episode of arterial thromboembolism, preoperative intravenous heparin is indicated. However, the reduction in the rate of long-term disability achieved by intravenous heparin therapy after major surgery is small and is gained at the expense of a large number of episodes of less serious major bleeding (Table 2). Consequently, we think it reasonable to recommend postoperative therapy with intravenous heparin only for patients undergoing minor surgery in which the risk of bleeding is low.

In conditions associated with a lesser risk of arterial thromboembolism (e.g., atrial fibrillation or the presence of a mechanical heart valve in patients with no recent embolism), our analysis suggests that postoperative intravenous heparin therapy increases rather than decreases serious morbidity. This is because the risks associated with postoperative thromboembolism are lower than the risks associated with heparin-induced bleeding (Table 2). Although preoperative heparin therapy should reduce morbidity due to thromboembolism, the achieved benefit is

small, because the absolute risk of embolism during the short period of subtherapeutic anticoagulation is extremely low.

QUALIFYING REMARKS

The validity of our recommendations depends on the validity of our assumptions. It was often not possible in our analysis to estimate rates of thromboembolism and bleeding on the basis of randomized trials. Among our analytic estimates, those involving postoperative bleeding causing death or disability are the least certain. We estimated that two days of postoperative intravenous heparin therapy will cause 3 percent of patients to have episodes of major bleeding, of which 3 percent will be fatal or disabling. On the basis of the frequency of major bleeding observed in high-risk patients during initial heparin therapy[46] and the case fatality rate among patients with postoperative bleeding in trials that evaluated prophylactic doses of heparin,[38,49] these estimates appear reasonable.

To examine the robustness of our conclusions, we performed sensitivity analyses in which our assumed rates of thromboembolism and bleeding were, alternatively, doubled and halved. Even when we doubled the estimated rate of thromboembolism and halved the rate of bleeding, none of our ultimate recommendations needed to be changed. Similarly, although the risks of thromboembolism[33,37,50,51] and bleeding[52,53] for individual patients may differ from the average values we used, this fact is unlikely to alter our recommendations.

We analyzed two options, one at each end of the therapeutic spectrum. There is, of course, a middle ground. We certainly recognize that other forms of perioperative antithrombotic therapy may be reasonable for patients whose INR has returned to normal, even if intravenous heparin is not indicated. Low-dose heparin is routinely recommended as prophylaxis against venous thromboembolism after major surgery.[38] Low-molecular-weight heparin is more effective than low-dose heparin in orthopedic patients who are at high risk for venous thromboembolism, does not increase the risk of bleeding any more than low-dose heparin, and is convenient for hospital use.[54,55] These forms of heparin may also lessen the risk of arterial thromboembolism. Consequently, we recommend these antithrombotic regimens for all patients who require long-term anticoagulation but in whom perioperative intravenous heparin is not justified.

Mechanical techniques, such as those involving graduated-compression stockings or intermittent pneumatic compression, should also be used to make prophylaxis against venous thromboembolism more effective.[56-58] The insertion of a vena caval filter to prevent pulmonary embolism should be considered if the risk of venous thromboembolism is very high (for instance, in a patient with a very recent venous thromboembolism) and effective anticoagulation cannot be undertaken.[59,60]

Although the subcutaneous administration of therapeutic doses of heparin or low-molecular-weight heparin to outpatients may appear attractive, the approach has limitations. The procedure is difficult to arrange on an outpatient basis. Moreover, the action of subcutaneous heparin is more prolonged and its clearance less predictable than is the case with intravenous heparin.[61] This makes it difficult to time the last preoperative injection and complicates the management of any bleeding.

Considerations other than those we evaluated may influence the management of anticoagulation, such as a perhaps disproportionate fear of thromboembolism or bleeding on the part of patients or their physicians.[62] There are also legal issues that may arise, although adherence to clinical-practice guidelines is one way to limit any potential liability.[63,64]

Our overall conclusion is that although there is justification for the perioperative use of intravenous heparin, particularly in patients who have had an acute episode of venous thromboembolism in the three months before surgery, it is not indicated for most patients who are being given long-term oral anticoagulant therapy. The absolute risk of thromboembolism associated with a few days of perioperative subtherapeutic anticoagulation is generally very low, and the risk of bleeding associated with postoperative intravenous heparin therapy is often relatively high.

RECOMMENDATIONS

We offer a number of recommendations for the perioperative management of anticoagulation in patients who are taking oral anticoagulants (Table 3). If a patient's INR is between 2.0 and 3.0, four scheduled doses of warfarin should be withheld to allow the INR to fall spontaneously to 1.5 or less before surgery. Warfarin should be withheld for a longer period if the INR is normally maintained above 3.0 or if it is necessary to keep it at a lower level (i.e., <1.3). The INR should be measured a day before surgery to ensure adequate progress in the reversal of anticoagulation; the physician then has the option of administering a small dose (1 mg, subcutaneously) of vitamin K, if required (that is, if the INR is 1.8 or higher). Alternative preoperative or postoperative prophylaxis, or both, against thromboembolism should be considered for the period during which the INR is less than 2.0 (Table 3).

Patients with a History of Venous Thromboembolism

Elective surgery should be avoided in the first month after an acute episode of venous thromboembolism. If this is not possible, intravenous heparin should be given before and after the procedure while the INR is below 2.0. If the activated partial-thromboplastin time is in the therapeutic range,

TABLE 3. RECOMMENDATIONS FOR PREOPERATIVE AND POSTOPERATIVE ANTICOAGULATION IN PATIENTS WHO ARE TAKING ORAL ANTICOAGULANTS.*

INDICATION	BEFORE SURGERY	AFTER SURGERY
Acute venous thromboembolism		
Month 1	IV heparin†	IV heparin†
Months 2 and 3	No change‡	IV heparin
Recurrent venous thromboembolism§	No change‡	SC heparin
Acute arterial embolism		
Month 1	IV heparin	IV heparin¶
Mechanical heart valve	No change‡	SC heparin
Nonvalvular atrial fibrillation	No change‡	SC heparin

*IV heparin denotes intravenous heparin at therapeutic doses, and SC heparin subcutaneous unfractionated or low-molecular-weight heparin in doses recommended for prophylaxis against venous thromboembolism in high-risk patients.

†A vena caval filter should be considered if acute venous thromboembolism has occurred within two weeks or if the risk of bleeding during intravenous heparin therapy is high.

‡If patients are hospitalized, subcutaneous heparin may be administered, but hospitalization is not recommended solely for this purpose.

§The term refers to patients whose last episode of venous thromboembolism occurred more than three months before evaluation but who require long-term anticoagulation because of a high risk of recurrence.

¶Intravenous heparin should be used after surgery only if the risk of bleeding is low.

stopping continuous intravenous heparin therapy six hours before surgery should be sufficient for heparin to be cleared before surgery.

Heparin therapy should not be restarted until 12 hours after major surgery and should be delayed even longer if there is any evidence of bleeding from the surgical site. Heparin should be restarted without a bolus, at no more than the expected maintenance infusion rate.[65] The activated partial-thromboplastin time should be checked 12 hours after restarting therapy to allow time for a stable anticoagulant response.

If the patient has been receiving anticoagulant therapy for less than two weeks after a pulmonary embolism or a proximal deep-vein thrombosis or if the risk of bleeding during intravenous heparin therapy is considered unacceptable, a vena caval filter should be inserted.

If the patient has been receiving anticoagulant therapy for acute venous thromboembolism for more than one month but less than three months, preoperative intravenous heparin therapy is not justified unless there are additional risk factors for recurrent venous thromboembolism, such as the patient's having been hospitalized for acute illness. However, postoperative intravenous heparin is recommended for such patients until warfarin therapy is resumed and the INR is above 2.0.

Patients who have been receiving anticoagulants for more than three months since their last episode of acute venous thromboembolism do not need preoperative heparin. They should receive postoperative prophylaxis, as recommended for patients at high risk for venous thromboembolism (e.g., with low-molecular-weight heparin),[66] until oral anticoagulation is reestablished (an INR of 2.0 or higher). This therapy should be combined with mechanical methods of prophylaxis, such as graduated-compression stockings or intermittent pneumatic compression. Intravenous heparin therapy is an acceptable postoperative alternative.

Patients at Risk for Arterial Thromboembolism

Elective surgery should be avoided in the first month after an arterial embolism, but if surgery is essential, preoperative intravenous heparin should be administered. Postoperative heparin therapy is recommended for such patients only if the risk of postoperative bleeding is low.

In all other patients who receive anticoagulants to prevent arterial embolism, such as those with mechanical heart valves or a history of nonvalvular atrial fibrillation, the risk of embolism is not high enough to warrant either preoperative or postoperative therapy with intravenous heparin. Intravenous heparin therapy should, in fact, be avoided after major surgery because of the high risk of bleeding. Subcutaneous low-dose heparin or low-molecular-weight heparin, in the dosage used for prophylaxis against venous thromboembolism in high-risk patients,[66] is recommended for hospitalized patients whose risk of arterial embolism does not justify the use of intravenous heparin. However, neither hospitalization to administer subcutaneous heparin nor the administration of subcutaneous heparin to outpatients appears to be justified.

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REFERENCES

1. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1995;108:Suppl:231S-246S.
2. Becker RC, Ansell J. Antithrombotic therapy: an abbreviated reference for clinicians. Arch Intern Med 1995;155:149-61.
3. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995;122:40-2.
4. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses: observations in 180 operations. JAMA 1978;239:738-9.
5. Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S. Two-step warfarin therapy: prevention of postoperative venous thrombosis without excessive bleeding. JAMA 1983;249:374-8.
6. Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis. BMJ 1978;1:272-4.
7. Rustad H, Myhre E. Surgery during anticoagulant treatment: the risk of increased bleeding in patients on oral anticoagulant treatment. Acta Med Scand 1963;173:115-9.
8. Francis CW, Pellegrini VD Jr, Leibert KM, et al. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. Thromb Haemost 1996;75:706-11.

9. Harrison L, Johnston M, Massicotte P, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997;126:133-6.
10. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. Ann Intern Med 1990;112:423-8.
11. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994;343:886-9.
12. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 1996;348:633-8.
13. Poller L, Thomson J. Evidence for "rebound" hypercoagulability after stopping anticoagulants. Lancet 1964;2:62-4.
14. Grip L, Blomback M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. Eur Heart J 1991;12:1225-33.
15. Palareti G, Legnani C, Guazzaloca G, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants — a prospective study. Thromb Haemost 1994;72:222-6.
16. Valles J, Aznar J, Santos T, Villa P, Fernandez A. Platelet function in patients with chronic coronary heart disease on long-term anticoagulant therapy: effect of anticoagulant stopping. Haemostasis 1993;23:212-8.
17. Raskob GE, Durica SS, Morrissey JH, Owen WL, Comp PC. Effect of treatment with low-dose warfarin-aspirin on activated factor VII. Blood 1995;85:3034-9.
18. Genewein U, Haeberli A, Straub PW, Beer JH. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. Br J Haematol 1996;92:479-85.
19. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. Clin Pharmacokinet 1996;30:300-13.
20. Kluft C, Verheijen JH, Jie AF, et al. The postoperative fibrinolytic shutdown: a rapidly reverting acute phase pattern for the fast-acting inhibitor or tissue-type plasminogen activator after trauma. Scand J Clin Lab Invest 1985;45:605-10.
21. Flanc C, Kakkar VV, Clarke MB. The detection of venous thrombosis of the legs using 125-I-labeled fibrinogen. Br J Surg 1968;55:742-7.
22. Carter CJ. The pathophysiology of venous thrombosis. Prog Cardiovasc Dis 1994;36:439-46.
23. Schulman S, Rhedin A-S, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995;332:1661-5.
24. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients: results of meta-analysis. Ann Surg 1988;208:227-40.
25. Kakkar VV, Howe CT, Nicolaides AN, Renney JT, Clarke MB. Deep vein thrombosis of the leg: is there a "high risk" group? Am J Surg 1970; 120:527-30.
26. Coon WW, Willis PW III. Recurrence of venous thromboembolism. Surgery 1973;73:823-7.
27. Hull R, Delmore T, Genton E, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979;301:855-8.
28. Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Lancet 1992;340:873-6.
29. Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost 1995;74:606-11.
30. Hull RD, Carter CJ, Jay RM, et al. The diagnosis of acute, recurrent, deep-vein thrombosis: a diagnostic challenge. Circulation 1983;67:901-6.
31. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1960;1:1309-12.
32. Lagerstedt CJ, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985;2:515-8.
33. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized trials. Arch Intern Med 1994;154:1449-57. [Erratum, Arch Intern Med 1994;154:2254.]
34. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-62.
35. Cerebral Embolism Task Force. Cardiogenic brain embolism. Arch Neurol 1986;43:71-84.
36. 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 clinical trial. Circulation 1985;72:1059-63.
37. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-41.
38. 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.
39. Levine MN, Hirsh J, Gent M. Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. Ann Intern Med 1991;114:545-51.
40. Coon WW, Willis PW III. Hemorrhagic complications of anticoagulant therapy. Arch Intern Med 1974;133:386-92.
41. Green RM, DeWeese JA, Rob CG. Arterial embolectomy before and after the Fogarty catheter. Surgery 1975;77:24-33.
42. Treiman RL, Cossman DV, Foran RF, Levin PM, Cohen JL, Wagner WH. The influence of neutralizing heparin after carotid endarterectomy on postoperative stroke and wound hematoma. J Vasc Surg 1990;12:440-6.
43. Wilson JR, Lampman J. Heparin therapy: a randomized prospective study. Am Heart J 1979;97:155-8.
44. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood 1991;78:2337-43.
45. Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972;287:324-7.
46. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990;322:1260-4.
47. Caplan LR, Hier DB, D'Cruz I. Cerebral embolism in the Michael Reese Stroke Registry. Stroke 1983;14:530-6.
48. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Stroke 1994; 25:1935-44.
49. Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. Lancet 1993;341:259-65.
50. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. II. Echocardiographic features of patients at risk. Ann Intern Med 1992;116:6-12.
51. Stein PD, Alpert JS, Copeland J, Dalen JE, Goldman S, Turpie AGG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1995;108:Suppl:371S-379S.
52. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995;108:Suppl:276S-290S.
53. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315-28.
54. Leizorovicz A, Haugh MC, Chapuis F-R, Samama MM, Boissel JP. Low molecular weight heparin in prevention of perioperative thrombosis. BMJ 1992;305:913-20.
55. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet 1992;340:152-6.
56. Wille-Jorgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. Br J Surg 1985;72:579-81.
57. Torngren S. Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. Br J Surg 1980;67:482-4.
58. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. Chest 1996;109:82-5.
59. Bergqvist D. The role of vena caval interruption in patients with venous thromboembolism. Prog Cardiovasc Dis 1994;37:25-37.
60. Decousus H. Efficacy and safety of permanent inferior vena cava filters and of a low molecular weight heparin (enoxaparin) in proximal deep venous thrombosis. Haemostasis 1996;26:Suppl 3:177. abstract.
61. Anderson DR, Ginsberg JS, Burrows R, Brill-Edwards P. Subcutaneous heparin therapy during pregnancy: a need for concern at the time of delivery. Thromb Haemost 1991;65:248-50.
62. Feinstein AR. The 'chagrin factor' and qualitative decision analysis. Arch Intern Med 1985;145:1257-9.
63. Hyams AL, Brandenburg JA, Lipsitz SR, Shapiro DW, Brennan TA. Practice guidelines and malpractice litigation: a two-way street. Ann Intern Med 1995;122:450-5.
64. McIntyre KM. Medicolegal implications of consensus statements. Chest 1995;108:Suppl:502S-505S.
65. Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 1995;108:Suppl:258S-275S.
66. Clagett GP, Anderson FA Jr, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboembolism. Chest 1995;108:Suppl:312S-334S.