CLINICAL PRACTICE

Care of Patients Receiving Long-Term Anticoagulant Therapy

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 75-year-old man with diabetes mellitus is found to have chronic atrial fibrillation, and warfarin therapy is begun for the prevention of thromboembolic stroke. How should the anticoagulant therapy be initiated and managed?

THE CLINICAL PROBLEM

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For more than 50 years, the availability of vitamin K antagonists[1] has made possible effective primary and secondary prevention of arterial and venous thromboembolism. Although such drugs are often referred to as oral anticoagulants, the term "vitamin K antagonists" is preferable, since it distinguishes these drugs from selective coagulation factor inhibitors (such as oral inhibitors of activated factor X [factor Xa] and oral thrombin inhibitors), which are currently in clinical trials but are not discussed here.

The indications for long-term anticoagulation and the natural course of several conditions in the absence of anticoagulant therapy are listed in Table 1. Additional indications are the primary prevention of myocardial infarction in patients at particularly high risk[10] and secondary prevention after systemic embolism in patients with rheumatic mitral-valve disease, mitral-valve prolapse, mitral annular calcification, nonrheumatic mitral regurgitation, or mobile aortic atheromas or aortic plaques larger than 4 mm.[13] Controversial indications are peripheral arterial disease,[21] heart failure in sinus rhythm,[22] and dissecting carotid-artery aneurysm.[23]

The problem inherent in any anticoagulant therapy is the risk of hemorrhage. The annual incidence of major hemorrhage (usually defined as intracranial hemorrhage or hemorrhage causing death or necessitating transfusion or hospitalization) has ranged between 1.2 and 7.0 episodes per 100 patients in different cohort studies,[24] whereas in clinical trials with selected patient populations, it has ranged between 0.5 and 4.2 per 100 patients.[25] Minor bleeding episodes are those that have no costs or consequences; the annual incidence of such bleeding is 2 to 24 episodes per 100 patients. The risk of hemorrhage is closely related to the intensity of anticoagulation. With an increasing duration of treatment, the risk of major hemorrhage increases cumulatively.[25] Although this issue is subject to debate, the risk of bleeding may be higher during the first month of anticoagulant therapy and then decrease gradually, owing to the fact that the prothrombin time fluctuates more initially.[24] Other predictors of hemorrhage include poor control of the degree of anticoagulation, peripheral vascular disease, cerebrovascular disease, and, in some studies, old age.[26] When anticoagulant therapy is initiated, bleeding often occurs at the site of preexisting anatomical lesions.

It is thus important to define the range of prothrombin times, usually expressed in terms of the international normalized ratio (INR), within which a highly protective antithrombotic effect is combined with an acceptable risk of bleeding. For conditions in which the risk of thromboembolic complications declines over time, such as venous

Table 1. Indications for and Effect of Long-Term Anticoagulation.*

Indication	Incidence of Thromboembolism	Absolute Risk Reduction with Anticoagulation Alone	Intensity of Treatment
	percent	*percentage points*	*target INR*
Prevention of systemic embolism			
Mechanical prosthetic heart valve[2,3]	8.6/yr[4]	4–8[2,4]	2.0–3.5[2,3]†
Bioprosthetic heart valve[2,3]	5–6 in first 3 mo[5]	Controversial[2]	2.0–3.0[2]
Nonvalvular atrial fibrillation[6,7]	4.5/yr[8]	3[9]	2.0–3.0[6]
Myocardial infarction[10]	1.2–2.6/yr[11]	1–2[12]	2.0–3.0[10]
Mitral-valve disease in sinus rhythm[13]	8/yr[14]	6[15]	2.0–3.0[13]
Prevention of recurrent disease			
Ischemic stroke in atrial fibrillation[9]	12/yr[16]	8[16]	2.0–3.0[6]
Myocardial infarction[10]	5–7/yr[11]	Approximately 4[11,12]	2.0–3.0[10] or 2.5–3.5[17]‡
Venous thromboembolism[18]	22–29 in first 3 mo[19,20]	≤22[19]	2.0–3.0[18]

* INR denotes international normalized ratio. References cited in the table provide more detailed information.
† The target INR may be split into narrower recommended ranges according to the risk associated with the valve position (lower with aortic than with mitral and lower with mitral than with both) and type of valve prosthesis (lower with a bileaflet valve than with a tilting disk and lower with a tilting disk than with a caged ball or caged disk).
‡ The recommendation for a target INR of 2.5 to 3.5 refers to anticoagulation without the addition of aspirin.

thromboembolism and perhaps myocardial infarction, anticoagulant therapy should be discontinued when the risk of recurrent thromboembolic events is surpassed by the risk of major hemorrhage.

Additional hurdles to overcome in achieving satisfactory anticoagulation are the multitude of interactions between vitamin K antagonists and other drugs or foods, problems with monitoring the degree of anticoagulation, and lack of knowledge about how to adjust the dose. Few patients have completely stable INR values over a period of several months, and frequent laboratory monitoring and dose adjustments are necessary but time-consuming.

STRATEGIES AND EVIDENCE

EFFICACY OF VITAMIN K ANTAGONISTS

The absolute reduction in risk provided by vitamin K antagonists for various indications is shown in Table 1. The efficacy of these agents is generally superior to that of aspirin,[12,27,28] but the use of the two in combination is even more effective in arterial disease[12,29] and permits the intensity of vitamin K antagonist therapy to be reduced. This difference in the treatment of venous and arterial disease is explained by the formation of platelet aggregates as an important constituent of the clots in arterial disease. In conditions associated with a low risk of thromboembolism, aspirin is preferred. Examples are the presence of a bioprosthetic heart valve in patients in sinus rhythm more than three months after surgery,[2] atrial fibrillation in patients less than 65 years of age and probably also in those 65 to 75 years of age who have no additional risk factors,[6] and myocardial infarction with a low risk of recurrence.[10]

INITIATION OF THERAPY

In situations in which the risk of new, progressive, or recurrent thromboembolism is high (e.g., immediately after prosthetic-valve surgery or when deep-vein thrombosis or pulmonary embolism has occurred), heparin is indicated until anticoagulation with the vitamin K antagonist reaches its full effect — in any case, for at least four to five days. Introduction of the two agents simultaneously does not lead to more recurrences or hemorrhages than does delayed initiation of the vitamin K antagonist. Simultaneous introduction also reduces the duration of treatment with heparin by a mean of four days, thus decreasing the risk of heparin-induced thrombocytopenia.[30] A starting dose of 15 mg of warfarin daily, given until an INR of approximately 1.9 is achieved, appears to be effective and safe and reduces the du-

ration of heparin treatment by one day as compared with the time required with lower initial doses.[31]

A starting dose of 5 mg[32] may be more prudent when there is a high risk of bleeding — for example, after recent surgery or trauma — and is absolutely indicated for patients with a known deficiency of protein C or protein S, in order to minimize the risk of skin necrosis.[33] In such patients, who make up about 3 percent of all patients with venous thromboembolism, the deficiency aggravates the imbalance between these severely depressed inhibitors and mildly depressed coagulation factors during the initiation of therapy with a vitamin K antagonist. The hypercoagulability is manifested as fibrin deposits in small veins and venules of the dermis and subcutaneous fat, with surrounding hemorrhage and necrosis.

Vitamin K antagonist therapy may be started without concomitant heparin in patients without protein C or protein S deficiency who have conditions that are not acute, such as chronic atrial fibrillation. Laboratory monitoring is performed every one to two days until the therapeutic INR range has been reached. Nomograms may be used to guide the initial dosage; an example is shown in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

INTENSITY OF TREATMENT

The range of INR values at which the combined incidence of thromboembolism and major hemorrhage is lowest varies for different indications (Table 1). In patients with systemic lupus erythematosus, phospholipid antibodies, and thrombosis, a higher intensity (target INR, 3.0 to 4.0) has been recommended, though this recommendation is controversial.[34]

The risk of the progression or recurrence of venous thromboembolism decreases as the thrombus resolves or is covered by endothelium and as the activation of coagulation subsides. Thus, a lower intensity of anticoagulation, corresponding to an INR of 1.5 to 2.0, may suffice after the initial 3 to 12 months at standard intensity. Less intense anticoagulant therapy may reduce the risk of major bleeding[35]; however, another study, reported elsewhere in this issue of the *Journal*,[36] seems to contradict this hypothesis, as discussed below.

DURATION OF ANTICOAGULANT THERAPY

For some patients, such as those with mechanical prosthetic heart valves, treatment must be lifelong or it must be continued at least until the risk of hemorrhage becomes unacceptably high and aspirin becomes an alternative (as in the case of atrial fibrillation). For patients with bioprosthetic heart valves who do not have atrial fibrillation, three months seems sufficient.[2] After myocardial infarction, three months of anticoagulation has been recommended,[10] but for patients with a high risk of recurrent infarction, several years of treatment should be considered, on the basis of trials in this field.[10,12] The presence of atrial fibrillation in combination with any of these conditions usually justifies anticoagulation for an indefinite period.

The risk of recurrence of venous thromboembolism is influenced by the anatomical location and extension of the thrombus; by whether risk factors are reversible or permanent (e.g., cancer or genetic or biochemical thrombogenic abnormalities); and, to some extent, by the number of thromboembolic events and perhaps by the resolution of thrombotic obstructions and the normalization of hemostatic hyperactivity. Table 2 presents suggestions for the appropriate duration of anticoagulation, according to such risk factors.

Recent studies of venous thromboembolism suggest that the provision of therapy for more than 6 to 12 months is safe and effective. Continued low-intensity warfarin (target INR, 1.5 to 2.0) given for a mean of 2.1 years after an initial 6-month course significantly reduced the risk of recurrent thromboembolism, as compared with placebo, without a significant increase in major bleeding.[35] In the study in this issue of the *Journal*,[36] ongoing warfarin therapy (mean duration of treatment, 2.4 years) with a higher target INR (2.0 to 3.0) led to greater reductions in recurrent thromboembolism than lower-intensity anticoagulation, with no increase in major bleeding.

However, the risk of recurrent venous thromboembolism after the discontinuation of anticoagulant therapy appears to be the same whether therapy lasts for 6, 12, or 24 months. Continuing anticoagulant therapy eliminates this risk, but other factors should be considered, including costs, possible effects on the quality of life, the risk of bleeding, the patient's compliance with therapy, any coexisting disease, and the severity of the thromboembolic event. Ongoing therapy should be reevaluated at least annually.

The disadvantages associated with vitamin K antagonists — including numerous drug interactions, the need for frequent venipuncture for monitoring, and complex dose adjustments in patients under-

Table 2. Suggested Duration of Anticoagulation after Venous Thromboembolism.

Type of Event or Condition	Duration	Source of Evidence
No identified thrombophilic abnormalities		
First event, distal deep-vein thrombosis, provoked by temporary risk factor	6 Wk	Schulman et al.[37]
First event, distal deep-vein thrombosis with idiopathic or permanent risk factor; or any proximal deep-vein thrombosis or pulmonary embolism	≥6 Mo*	Ridker et al.,[35] Kearon et al.,[36] Schulman et al.,[37] Pinede et al.[38]
As above, with increased risk of bleeding	3 Mo	
Single life-threatening event	≥12 Mo*	
First event, active cancer	Until cancer resolved	Hutten et al.[39]
Second event, contralateral deep-vein thrombosis	≥6 Mo (as a first event)	Schulman et al.[40]
Second event, ipsilateral or pulmonary embolism	≥12 Mo*	Schulman et al.,[40] Prandoni et al.[41]
Third or subsequent event	Indefinite	
Thrombophilic defects identified†		
Deficiency of antithrombin	Indefinite	Case series, Lane et al.[42]
Deficiency of protein C or protein S	≥12 Mo	van den Belt et al.[43]
Homozygous form of thrombophilic defect	Indefinite‡	Case reports, Procare Group[44]
Heterozygous for two thrombophilic defects	Indefinite	De Stefano et al.[45]
Antiphospholipid-antibody syndrome	Years	Khamashta et al.[34]
Hyperhomocysteinemia	Variable§	Schnyder et al.[46]
Elevated factor VIII activity (>2.3 IU/ml)	≥6 Mo	Kyrle et al.[47]
Factor V Leiden mutation, heterozygous	As without	Lindmarker et al.[48]
Prothrombin polymorphism, heterozygous	As without	Lindmarker et al.[48]
Life-threatening event and any defect	Indefinite	Lane et al.[42]

* Some recent data[35,36] suggest that the benefit of indefinite anticoagulation outweighs the risk after isolated venous thrombosis, even without identifiable thrombophilia.
† The presence of the defects listed is independent of provocation of the event by a temporary or permanent risk factor, whenever the thrombophilic defect is permanent.
‡ This recommendation may not pertain to the homozygous form of the prothrombin polymorphism.
§ The duration depends on factors other than the biochemical defect. Hyperhomocysteinemia does not affect the duration of anticoagulation, but after anticoagulation is completed, treatment with B vitamins should probably be given.

going surgery or biopsy procedures — are magnified in patients who are receiving active treatment for cancer. Low-molecular-weight heparin may then be practical and possibly safer for secondary prophylaxis.[49] It may also be considered when anticoagulation is needed for only six weeks or when it has been impossible to stabilize the INR within the therapeutic range. Anticoagulant therapy begun after venous thromboembolism may be discontinued either abruptly or gradually, since no difference in the risk of clinical events between the two strategies has been demonstrated.[50]

INTERACTIONS WITH VITAMIN K ANTAGONISTS

An important step toward safer anticoagulation is greater awareness on the part of the treating physician and the patient regarding important interactions with other drugs and foods. The list of drugs that interact with vitamin K antagonists is constantly expanding,[24] and every change in a patient's medications should prompt a glance at such a list (Table 3). Avocado and foods rich in vitamin K may inhibit the anticoagulant effect, but quite substantial amounts are needed. Thus, 250 g of spinach or broccoli, eaten on a single occasion, does not affect

the prothrombin time,[51] whereas higher amounts do.[51,52] Furthermore, St. John's wort, ginseng, and garlic may lower the concentration of warfarin in blood, and ginkgo is associated with bleeding when combined with warfarin.[53] This information is important, since the use of alternative medicines has increased and patients are rarely made aware of possible interactions.

Patients should be provided with information about these interactions, but the message should be carefully balanced so as to avoid a misunderstanding that might lead to the complete exclusion of vegetables from the diet. Brand-name warfarin can be safely replaced by at least one generic agent,[54] but since substitution with some formulations has been reported to cause changes in the INR,[54] more frequent laboratory monitoring is recommended during the first weeks after the change has been made.

Table 3. Major Drug Interactions with Warfarin.*

Anticoagulant Response Increased	Anticoagulant Response Decreased
Acetaminophen	Antithyroid drugs
Amiodarone	Barbiturates
Androgens (17-alkyl)	Carbamazepine
Cimetidine	Cholestyramine
Clofibrate	Dichloralphenazone
Disulfiram	Glutethimide
Erythromycin	Sucralfate
Fluconazole	
Fluoxetine	
Glucagon	
Metronidazole	
Oxyphenbutazone	
Phenylbutazone	
Salicylates (high dose)	
Sulfinpyrazone	
Tamoxifen	
Thyroid hormone	
Trimethoprim–sulfamethoxazole	

* An extensive list of drug interactions can be found in Schulman.[24]

THE QUALITY OF MONITORING OF ANTICOAGULATION

The stability of therapy with vitamin K antagonists also depends on the quality of laboratory monitoring and dose adjustment. The adoption of the INR system and the local calibration of reagents and instruments have made possible more standardized anticoagulant therapy and provide assurance that the target level is comparable to that referred to in clinical trials.

Various tools to improve the selection of the initial and maintenance dosage of vitamin K antagonists have been evaluated — for example, computers,[55] nomograms, and flexible protocols.[56] Generally, such tools — in the hands of inexperienced physicians as well as specialists — have reduced the number of measured INR values that are above the therapeutic range, shortened the time to the achievement of a steady state, or reduced the number of dose adjustments that are necessary.[57] Clinical end points were not evaluated in these studies.

Dose adjustments may be delegated to nonphysician medical staff such as pharmacists[58] or to patients without compromising quality, so long as they have received proper instruction. The optimal type of outpatient clinic for monitoring the level of anticoagulation has not been evaluated in randomized trials. In one study, patients followed at a specialized clinic had fewer recurrences of thrombosis and fewer episodes of major bleeding than those receiving usual care.[59] With appropriate education, sufficient experience, and supportive tools, an adequate quality of anticoagulation can probably be achieved in a variety of clinical settings.

Alternatively, patients can be taught to monitor the prothrombin time themselves, using a portable instrument, and to adjust the dose of vitamin K antagonist, with support from a nomogram. In a trial involving 600 patients, there was an absolute decrease of 0.9 percentage point per patient-year in the rate of thrombotic and major hemorrhagic events in the group randomly assigned to point-of-care analysis, as compared with patients assigned to routine care.[60] Structured training of the patient is required, and several countries have a curriculum for this purpose.[61] Only a minority of patients have sufficient motivation to learn and practice testing and dose adjustment, especially if they are not reimbursed for the cost of the instrument and the reagents. Whether patients are reimbursed for the cost of these products varies among countries and indications; in the United States and Germany, patients receiving anticoagulation because they have a mechanical heart-valve prosthesis may be reimbursed, whereas this is not the case in Sweden and Canada, for example.

REVERSAL OF ANTICOAGULATION

In case of overanticoagulation (INR, >4) without bleeding, omission of one or several doses until the therapeutic range is reached may suffice. Correction is achieved substantially faster if a small dose of vitamin K_1 is administered, most conveniently as 1 mg given orally; this also reduces the risk of at least

minor hemorrhages.[62] Alternatively, 0.5 mg of vitamin K_1 may be injected intravenously.[63] Higher doses should be avoided, as they may lead to overcorrection and resistance to vitamin K antagonists for several days. Subcutaneous injection is not recommended because of variable absorption.

For overanticoagulation associated with major bleeding, administration of vitamin K_1 is inadequate, since its full effect occurs after 12 to 24 hours. The volume of plasma required for reversal is almost invariably too large to be infused safely, whereas prothrombin-complex concentrates are effective and convenient (Fig. 1).[64] These products are virally inactivated and therefore safer than plasma with respect to the transmission of the human immunodeficiency virus, hepatitis B virus, or hepatitis C virus, but a thrombogenic effect has occasionally been reported. Bleeding in a patient whose INR is within the therapeutic range should raise the suspicion of cancer or another pathologic process at the site of bleeding and may require a temporary lowering of the target INR to approximately 1.5.

Step 1. Decide on Target INR.

Clinical Situation	Target INR
Moderate bleeding, high risk of thrombosis	2.0–2.1
Serious bleeding, moderate risk of thrombosis	1.5
Serious or life-threatening bleeding, low risk of thrombosis	1.0

Step 2. Convert INR to Prothrombin Complex (expressed as a percentage of normal plasma).

	INR	Approximate %
Overanticoagulation	>5	5
	4.0–4.9	10
Therapeutic range	2.6–3.2	15
	2.2–2.5	20
	1.9–2.1	25
Subtherapeutic range	1.7–1.8	30
	1.4–1.6	40
Complete reversal to normal	1.0	100

Step 3. Calculate the Dose.

Formula for calculating the dose:

(target level as a percentage − present level as a percentage) × body weight in kg = ml of plasma or IU of prothrombin-complex concentrate

Example: a patient with pulmonary embolism 3 months ago now has major intestinal bleeding; present INR = 7.5, target INR = 1.5, body weight = 80 kg:

(40 − 5) × 80 = dose of 2800 ml or IU

Figure 1. Calculation of the Volume of Plasma (in Milliliters) or the Dose of Prothrombin-Complex Concentrate (in International Units) Required for the Reversal of the Effects of a Vitamin K Antagonist in Case of Bleeding.

INR denotes international normalized ratio. Calculation of the required replacement dose on the basis of INR levels is performed with a formula that is complicated to use without a calculator. The "percentage method" is based on the principle that 1 ml of normal plasma contains 1 unit of each coagulation factor and that prothrombin complex, expressed as a percentage of normal plasma, corresponds to the mean level of the vitamin K–dependent coagulation factors.

SURGERY DURING ANTICOAGULANT THERAPY

During the first few months after a thromboembolic event, the high risk of recurrence makes a temporary reduction in the intensity of anticoagulant therapy undesirable. Dental extraction may be performed safely while the intensity of anticoagulation is maintained, provided that the mouth is rinsed with an antifibrinolytic agent, such as 500 mg of tranexamic acid, for two minutes every six hours for seven days.[65] Dermatologic surgery and injections or aspirations from soft tissues also appear to be safe without a reduction in anticoagulation.[24] For most major surgery and high-risk endoscopic procedures, the intensity of anticoagulation should be lowered and then increased again as soon as circumstances allow, in view of the increased risk of thromboembolism associated with surgical trauma and immobilization. There are several examples of protocols[66,67] or strategies[68] that can be used for adjusting anticoagulant therapy.

AREAS OF UNCERTAINTY

Anticoagulation during pregnancy is problematic, because of concern about possible teratogenic effects of vitamin K antagonists. Problems related to the management of anticoagulation in pregnant women with artificial heart valves have recently been addressed.[69] The optimal duration of anticoagulation after venous thromboembolism also remains controversial. Although mutations in the factor IX gene and polymorphisms in the cytochrome P-450 CYP2C9 gene have been associated with an increased risk of hemorrhage during treatment with vitamin K antagonists,[24] it is not known to what extent genetic factors contribute to bleeding complications, and tests for such variants are not used in routine clinical practice.

GUIDELINES

The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy updated guidelines on anticoagulant therapy in 2001 (http://www.chestjournal.org/content/vol119/1_suppl/). Disease-specific guidelines have been issued for

valvular heart disease,[3] atrial fibrillation,[7] and myocardial infarction.[70] There are procedure-specific guidelines for endoscopy[67] and recommendations for management by patients of anticoagulation with vitamin K antagonists, including discussions of suitable patients and quality control.[61]

CONCLUSIONS AND RECOMMENDATIONS

The benefit of anticoagulation with vitamin K antagonists has been convincingly demonstrated for patients with mechanical prosthetic heart valves, mitral-valve disease, atrial fibrillation, and venous thromboembolism. The intensity of anticoagulation and the duration of treatment should be tailored according to the indication for treatment and the presence or absence of risk factors. For a patient with atrial fibrillation and other risk factors for thromboembolism, as in the case described in the vignette, oral anticoagulation with a vitamin K antagonist is appropriate and should be targeted to achieve an INR of 2.0 to 3.0. It is preferable to use a nomogram to determine the appropriate initial dose and not to give concomitant heparin. Dose adjustments to maintain the INR in the therapeutic range may be facilitated by the use of a nomogram or another supportive tool; once the INR appears to be stable, monthly tests of the prothrombin time should be sufficient.

All patients taking vitamin K antagonists should be educated about potential interactions with other medications, herbal preparations, and foods and about the importance of monitoring. Prompt reversal of overanticoagulation with small doses of vitamin K (1 mg given orally or 0.5 mg given intravenously) appears to be safe and reduces the incidence of bleeding.

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REFERENCES

1. Allen EV, Barker NW, Waugh JM. A preparation from spoiled sweet clover: [3.3′-methylene-bis-(4-hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood: a clinical study. JAMA 1942;120:1009-15.
2. Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AGG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001;119:Suppl:220S-227S. [Erratum, Chest 2001;120:1044.]
3. Gohlke-Bärwolf C, Acar J, Oakley C, et al. Guidelines for prevention of thromboembolic events in valvular heart disease. Eur Heart J 1995;16:1320-30.
4. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-41.
5. Heras M, Chesebro JH, Fuster V, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol 1995;25:1111-9.
6. Albers GW, Dalen JE, Laupacis A, Manning WJ , Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest 2001;119:Suppl:194S-206S.
7. Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol 2001;38:1231-66.
8. Koefoed BG, Petersen P. Oral anticoagulation in nonvalvular atrial fibrillation. J Intern Med 1999;245:375-81.
9. 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. [Erratum, Arch Intern Med 1994;154:2254.]
10. Cairns JA, Théroux P, Lewis HD Jr, Ezekowits M, Meade TW. Antithrombotic agents in coronary artery disease. Chest 2001;119:Suppl:228S-252S. [Erratum, Chest 2001;120:1427.]
11. Smith P. Oral anticoagulants are effective long-term after acute myocardial infarction. J Intern Med 1999;245:383-7.
12. Hurlen M, Abdelnoor M, Smith P, Eriksen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74.
13. Salem DN, Daudelin HD, Levine HJ, Pauker SG, Eckman MH, Riff J. Antithrombotic therapy in valvular heart disease. Chest 2001;119:Suppl:207S-219S.
14. Coulshed N, Epstein EJ, McKendrick CS, Galloway RW, Walker E. Systemic embolism in mitral valve disease. Br Heart J 1970;32:26-34.
15. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. BMJ 1964;1:1209-12.
16. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-62.
17. Becker RC. Antithrombotic therapy after myocardial infarction. N Engl J Med 2002;347:1019-22.
18. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119:Suppl:176S-193S.
19. Lagerstedt CI, Olsson CG, Fagher BO, Öqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985;2:515-8.
20. Rosenbeck-Hansen JV, Valdorf-Hansen F, Dige-Petersen H, Hansen W. En kontrolleret undersøgelse af antikoagulationsbehandlingens effekt ved dyb venetrombose og lungeemboli. Nordisk Med 1968;80:1305-6.
21. Kretschmer G, Hölzenbein TJ. Oral anticoagulation in peripheral vascular surgery: how intense, for how long, or at all? J Intern Med 1999;245:389-97.
22. Lip GY, Gibbs CR. Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm. Cochrane Database Syst Rev 2001;4:CD003333.
23. Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. Cochrane Database Syst Rev 2000;4:CD000255.
24. Schulman S. Oral anticoagulation. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, eds. Williams hematology. 6th ed. New York: McGraw-Hill, 2001:1777-92.
25. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. Chest 2001;119:Suppl:108S-121S.
26. 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.

27. Mok CK, Boey J, Wang R, et al. Warfarin versus dipyridamole-aspirin and pentoxiphylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. Circulation 1985; 72:1059-63.
28. 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.
29. Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients wtih prosthetic heart valves: a meta-analysis. J Am Coll Cardiol 2001;37: 569-78.
30. Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. Lancet 1986; 2:1293-6.
31. Schulman S, Lockner D, Bergström K, Blombäck M. Intensive initial oral anticoagulation and shorter heparin treatment in deep vein thrombosis. Thromb Haemost 1984;52: 276-80.
32. Harrison L, Johnston M, Massicotte MP, 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.
33. Jillella AP, Lutcher CL. Reinstituting warfarin in patients who develop warfarin skin necrosis. Am J Hematol 1996;52:117-9.
34. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993-7.
35. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348: 1425-34.
36. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349:631-9.
37. Schulman S, Duration of Anticoagulation Study Group. The effect of the duration of anticoagulation and other risk factors on the recurrence of venous thromboembolisms. Wien Med Wochenschr 1999;149:66-9.
38. Pinede L, Duhaut P, Cucherat M, Ninet J, Pasquier J, Boissel JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. J Intern Med 2000;247:553-62.
39. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JGP, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000; 18:3078-83.
40. Schulman S, Granqvist S, Holmström M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med 1997;336:393-8.
41. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125:1-7.
42. Lane DA, Mannucci PM, Bauer KA, et al. Inherited thrombophilia. Thromb Haemost 1996;76:651-62.
43. van den Belt AGM, Sanson B-J, Simioni P, et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. Arch Intern Med 1997;157:2227-32.
44. Procare Group. Comparison of thrombotic risk between 85 homozygotes and 481 heterozygotes carriers of the factor V Leiden mutation: retrospective analysis from the Procare Study. Blood Coagul Fibrinolysis 2000;11:511-8.
45. De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 1999;341: 801-6.
46. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 2001;345:1593-600.
47. Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med 2000;343:457-62.
48. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. Thromb Haemost 1999;81:684-9.
49. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 2002;162:1729-35.
50. Ascani A, Iorio A, Agnelli G. Withdrawal of warfarin after deep vein thrombosis: effects of a low fixed dose on rebound thrombin generation. Blood Coagul Fibrinolysis 1999;10:291-5.
51. Karlson B, Leijd B, Hellström K. On the influence of vitamin K-rich vegetables and wine on the effectiveness of warfarin treatment. Acta Med Scand 1986;220:347-50.
52. Pedersen FM, Hamberg O, Hess K, Ovesen L. The effect of dietary vitamin K on warfarin-induced anticoagulation. J Intern Med 1991;229:517-20.
53. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs 2001;61:2163-75.
54. Milligan PE, Banet GA, Waterman AD, Gatchel SK, Gage BF. Substitution of generic warfarin for Coumadin in an HMO setting. Ann Pharmacother 2002;36:764-8.
55. Poller L, Shiach CR, MacCallum PK, et al. Multicentre randomised study of computerised anticoagulant dosage. Lancet 1998;352: 1505-9.
56. Doecke CJ, Cosh DG, Gallus AS. Standardised initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomised trial, and risk factors for an excessive warfarin response. Aust N Z J Med 1991;21:319-24.
57. Ageno W, Turpie AG. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. Thromb Res 1998;91: 237-40.
58. Chenella FC, Klotz TA, Gill MA, et al. Comparison of physician and pharmacist management of anticoagulant therapy of inpatients. Am J Hosp Pharm 1983;40:1642-5.
59. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 1998;158:1641-7.
60. Körtke H, Körfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? Ann Thorac Surg 2001; 72:44-8.
61. Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self management of oral anticoagulation. BMJ 2001; 323:985-9.
62. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet 2000;356:1551-3.
63. Nee R, Doppenschmidt D, Donovan DJ, Andrews TC. Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. Am J Cardiol 1999;83:286-8, A6-A7.
64. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston FE. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thromb Haemost 1997; 77:477-80.
65. Ramström G, Sindet-Pedersen S, Hall G, Blombäck M, Ålander U. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. J Oral Maxillofac Surg 1993; 51:1211-6.
66. Vigano'D'Angelo S, Tsoureli E, Crippa L, Tomassini L, D'Angelo A. Prevalence of hemorrhagic and thrombotic complications in patients requiring oral anticoagulation and submitted to elective surgery: a study of 197 consecutive patients. Thromb Res 1998;91: Suppl 1:S100. abstract.
67. Eisen GM, Baron TH, Dominitz JA, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc 2002;55: 775-9.
68. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997;336:1506-11.

69. Reimold SC, Rutherford JD. Valvular heart disease in pregnancy. N Engl J Med 2003;349:52-9.
70. Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999;100:1016-30.