Guidelines for Antithrombotic Therapy

Fifth Edition

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INTRODUCTION

In September 2004, the American College of Chest Physicians (ACCP) published the proceedings of the "Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines." As in the past, the participants have continued to strive to improve the quality of the publication and its clinical relevance. The proceedings of the ACCP Consensus Conference provide an extensive critical review of the literature related to management of thromboembolic disorders, including venous thromboembolism, arterial thrombosis, and systemic arterial embolism. There are also chapters on thrombosis in pregnancy and pediatric thrombosis. As in past issues, each section is concluded by a detailed summary that not only documents the therapeutic recommendations but also assigns a rating for each recommendation.

Clinical thrombosis has come a long way since the first publication of the guidelines in 1986. The number of antithrombotic agents available to the clinician has trebled, the rigor with which they are evaluated has improved dramatically, and the ACCP grading system for making recommendations has been refined. Rigorous studies in most fields have resulted in new and strong evidence-based recommendations. There remains, however, a notable lack of randomized trials in pediatric thrombosis, thrombosis in pregnancy, and thrombosis in valvular heart disease.

The number of participants from outside North America has increased since 2001, reflecting the widespread use of these guidelines internationally. To emphasize the evidence-based approach to making recommendations, the title of the supplement has been changed to "ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines." Major changes have been introduced to strengthen the methodology used for the literature search. The search process is now more comprehensive, transparent, and explicit. The authors provided the clinically relevant questions, and the literature searches were conducted by a team of librarians at the University at Buffalo. The librarians searched the *Cochrane Database of Systematic Reviews*, *Database of Abstracts of Reviews of Effectiveness and Cochrane Register of Controlled Trials*, *ACP Journal Club*, *MEDLINE*, and *Embase* for studies published between 1966 and June 2002 in any language. To filter *MEDLINE* and *Embase* search results for randomized controlled trial evidence, the librarians used the search strategy developed by the Cochrane Collaboration.

The organization of the chapters has also been improved. In each chapter, the clinical question under consideration (eg, prophylaxis in major knee surgery), the clinical trials evaluating the evidence, and the recommendations have now been linked by a numbering scheme common to these three

items. This allows the reader to quickly identify the underlying question associated with each recommendation and the relevant evidence. The recommendations presented here follow the grading system described in 2001.

This short monograph, which is an update of the 1992, 1995, 1998, and 2001 publications, provides a summary of the 2004 ACCP recommendations, together with a brief review of the background data on which the recommendations are based. To keep the document short, no attempt has been made to provide detailed supporting evidence for the recommendations, which can be obtained by referring to the *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines*.

The chapters reviewed in this monograph are listed in the table of contents. All of the chapters with authors of the *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines* are listed at the end of the monograph.

1 GRADES OF RECOMMENDATION FOR ANTITHROMBOTIC DRUGS

Since the 2001 publication, the grading system has been refined further. As in the previous publications, the recommendation to use or not use a treatment is more clearly separated from the methodologic quality of the studies on which the estimate of the treatment effect is made.

RECOMMENDATION TO USE OR NOT USE A TREATMENT

The recommendation to use (or not use) a particular treatment is based on the trade-off between the benefits and the risks and/or costs. If, after weighing all of the evidence, the experts conclude that the benefits outweigh the risks and/or costs, then treatment will be recommended; if the benefits do not outweigh the risks and/or costs, treatment will not be recommended. If experts are very certain that benefits do, or do not, outweigh risks, a **Grade 1 recommendation** is made. If they are less certain of the trade-off between the benefits and the risks, a weaker **Grade 2 recommendation** is made.

METHODOLOGIC QUALITY

There are four methodologic grades: A, B, C, and C+. Grade A recommendations are based on randomized trials with consistent results, Grade B recommendations are based on randomized trials with inconsistent results or with substantial methodologic weaknesses, and Grade C recommendations are based on observational studies or on generalization from randomized

trials from one group of patients to a different group. When experts consider that the generalization from randomized trials is secure or the data from observational studies are overwhelming, then the Grade C recommendation is upgraded to Grade C+.

Several refinements to the grading system have been introduced in the 2004 publication. The methodologic quality of an otherwise sound study is downgraded from A to B if the sample size is small or event rates are low, such that the addition of a small number of adverse events to the treatment arm would render a result nonsignificant. As in the last iteration, studies that produce inconsistent results or are of poor quality are also designated Grade B. A Grade 1 recommendation is downgraded to Grade 2 if the downsides of treatment, as reflected in toxicity, inconvenience, or costs, are such that many people would consider that the benefits of the treatment are offset by the downsides. A terminology has been adopted expressing the strength of the recommendation. Thus, the phrase "we recommend" is used for strong recommendations (**Grade 1A**, 1C+, 1B, 1C), and the phrase "we suggest" is used for weaker recommendations (**Grade 2A**, 2C+, 2B, 2C). The process of making recommendations has also been improved by specifying the values and preferences underlying recommendations where relevant.

2 HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARINS

HEPARIN

Heparin acts as an anticoagulant by catalyzing the inactivation of thrombin and activated factor X (factor Xa) by antithrombin (AT). Heparin catalyzes the inactivation of thrombin by AT by providing a template to which both the enzyme and the inhibitor bind to form a ternary complex. In contrast, the inactivation of factor Xa by the AT-heparin complex does not require ternary complex formation and is achieved by binding of AT activated to factor X (Xa). Heparin binds to lysine sites on AT, producing a conformational change at the arginine reactive center, which converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor. The arginine reactive center on the AT molecule binds covalently to the active center serine of thrombin and other coagulation enzymes, thereby irreversibly inhibiting their procoagulant activity. Heparin then dissociates from the ternary complex and is reused.

Heparin is effective for the prevention and treatment of venous thromboembolism, for the early treatment of patients with unstable angina and

acute myocardial infarction, for the treatment of patients who are having cardiac surgery under cardiopulmonary bypass, and for patients undergoing coronary angioplasty. Although effective clinically, heparin has pharmacokinetic and biophysical limitations. The pharmacokinetic limitations are described below. The biophysical limitations are caused by the reduced ability of heparin to bind to and inactivate thrombin bound to fibrin and factor Xa bound to the platelet surface.

Pharmacokinetics

The mechanism of heparin clearance is complex. Heparin binds to a number of plasma-, platelet-, and endothelial cell–derived proteins that compete with AT for heparin binding. Binding of heparin to plasma proteins contributes to the variability of the anticoagulant response between patients and to the heparin resistance seen in some patients with thromboembolic disorders.

Heparin also binds to macrophages, where it is internalized, depolymerized, and metabolized into smaller and less sulfated forms. At low concentrations, it is cleared rapidly by a saturable cellular mechanism. At higher concentrations, it is cleared by a slower nonsaturable renal clearance mechanism. At therapeutic concentrations, a major proportion of the heparin is cleared by the rapid saturable mechanism.

This complex mechanism of heparin clearance explains why the apparent biologic half-lives of heparin increase from 30 to 60 to 150 minutes with intravenous boluses of 25, 100, and 400 U/kg of heparin, respectively. Heparin has decreased bioavailability when administered subcutaneously in low doses but has approximately 90% bioavailability when administered by subcutaneous injection in high therapeutic doses (eg, 35,000 U/24 h). In practical terms, these pharmacokinetic properties are responsible for the 24-hour delay before steady-state levels are reached with subcutaneous administration of heparin in doses of less than 17,500 U 12 hourly and for the higher heparin requirements when administered by the subcutaneous route. These unfavorable pharmacokinetic properties of heparin provide opportunities for the low-molecular-weight heparins (LMWHs), which show less protein and cellular binding and, as a consequence, have a more predictable dose response, better bioavailability, and a longer plasma half-life.

The anticoagulant response to heparin varies among patients with thromboembolism. This variability is caused by differences among patients in the plasma concentrations of heparin-neutralizing plasma proteins and in the rates of heparin clearance. The risk of heparin-associated bleeding increases with dose and by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects. A relationship has also been reported between the dose of

heparin administered and its efficacy. Therefore, the dose of heparin must be adjusted, usually by monitoring with the activated partial thromboplastin time (APTT) or, when very high doses are given, by activated clotting time. These tests are sensitive mainly to the AT effects of heparin.

There is a wide variation among thromboplastin reagents in responsiveness to the effect of heparin on the APTT. With modern reagents, APTT ratios corresponding to heparin levels of 0.3 to 0.7 anti–factor Xa units range from 1.6 to 2.7 to 3.7 to 6.2 times control. Therefore, the use of a common APTT therapeutic range of 1.5 to 2.5 for all reagents is inappropriate.

A less intense anticoagulant effect is required to prevent venous thrombosis with heparin than to treat established thrombosis. Low-dose heparin, 5,000 U subcutaneously twice or three times daily, is highly effective in preventing venous thrombosis in moderate-risk patients and is administered without laboratory monitoring. However, in very high-risk patients, such as those who undergo hip surgery, the incidence of thrombosis is approximately 25% and of proximal vein thrombosis is 10 to 15% despite low-dose heparin prophylaxis.

Dosing Considerations

A rapid therapeutic heparin effect is achieved in most patients by commencing with a loading dose. Initial dosing of heparin for venous thromboembolism is weight based: an 80 U/kg bolus and an 18 U/kg/h infusion, which is roughly equivalent to a loading dose of 5,000 U and an infusion of 32,000 U/24 h in a 70 kg person. Doses of heparin given to treat coronary thrombosis syndromes are lower than those typically used to treat venous thromboembolism; the recommended dose is a bolus of 60 to 70 U/kg (maximum 5,000 U) and an infusion of 12 to 15 U/kg/h (maximum 1,000 U/h) for unstable angina and non–ST-segment elevation myocardial infarction. Lower doses—60 U/kg bolus (maximum 4,000 U), 12 U/kg infusion (maximum 1,000 U/h)—are recommended in patients receiving a recombinant tissue plasminogen activator (alteplase) for acute ST-segment elevation myocardial infarction.

The APTT should be performed at approximately 6 hours after the bolus and the heparin dosage are adjusted according to the result obtained. Dose adjustment is facilitated by the use of a validated heparin dose adjustment nomogram. In patients undergoing percutaneous coronary intervention, heparin is given in conjunction with glycoprotein (GP) IIb/IIIa inhibitors as a bolus of 70 U/kg, with additional boluses to keep the activated clotting time greater than 200 seconds.

It is also possible to achieve therapeutic heparin levels with subcutaneous injection, but the anticoagulant effect of subcutaneous heparin is delayed for approximately 1 hour, and peak levels occur at approximately

3 hours. If the subcutaneous route is selected, a high initial dose should be used (35,000 U/24 h in two divided doses) to overcome the poor bioavailability of moderate doses. If a rapid effect is required, the subcutaneous injection should be preceded by an intravenous bolus of 5,000 U. Monitoring is performed 6 hours after injection with the aim of maintaining the APTT in the therapeutic range at this time.

LOW-MOLECULAR-WEIGHT HEPARINS

LMWHs are fragments of standard commercial-grade heparin produced by either chemical or enzymatic depolymerization. LMWHs are approximately one-third of the size of heparin. Like heparin, which has a mean molecular weight of 15,000 (range 3,000–30,000), LMWHs are heterogeneous in size, with a mean molecular weight of 4,500 to 5,000 (range 1,000–10,000) (Figure 2-1). Depolymerization of heparin results in a change in its anticoagulant profile, bioavailability, and pharmacokinetics.

Like heparin, LMWHs achieve their major anticoagulant effect by binding to AT through a unique pentasaccharide sequence. Less than 30% of different LMWH preparations have pentasaccharide-containing fragments with 18 or more saccharide units. Therefore, compared with heparin, which has a ratio of anti–factor Xa to anti–factor IIa activity of approximately 1:1, the various commercial LMWHs have anti–factor Xa to anti–factor IIa ratios varying between 4:1 and 2:1 depending on their molecular size distribution.

Pharmacokinetics

The plasma recoveries and pharmacokinetics of LMWHs differ from heparin because of differences in the binding properties of the two sulfated

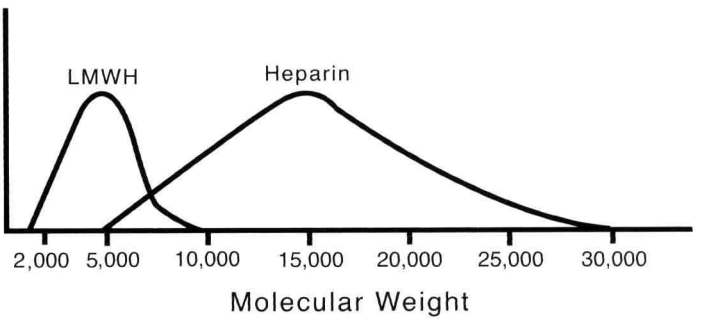

Figure 2-1 Molecular weight distribution of low-molecular-weight heparins (LMWHs) and heparin.

polysaccharides to plasma proteins and endothelial cells. The LMWHs bind much less avidly to heparin-binding proteins than heparin, a property that contributes to the superior bioavailability of LMWHs at low doses and their more predictable anticoagulant response. The LMWHs are cleared by the kidneys and have a longer plasma half-life than heparin, and their clearance is dose independent. The biologic half-life of LMWH is increased in patients with renal failure

LMWHs are typically administered in fixed doses for thromboprophylaxis or in total body weight–adjusted doses when used to obtain a therapeutic effect. Laboratory monitoring is not generally necessary, but monitoring should be considered in patients with renal failure or severe obesity.

The LMWHs are effective in the prevention and treatment of venous thrombosis and in the treatment of patients with unstable angina and non–Q-wave infarction. LMWHs have a number of advantages over heparin. Their use is associated with a lower incidence of heparin-induced thrombocytopenia and heparin-induced osteoporosis. Because they have a longer plasma half-life and a more predictable anticoagulant response than heparin, LMWHs can be administered once daily and without laboratory monitoring. This latter property is particularly useful for the out-of-hospital management of patients with venous thrombosis or unstable angina.

3 ORAL ANTICOAGULANTS (VITAMIN K ANTAGONISTS)

Oral anticoagulants are vitamin K antagonists, which produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3-epoxide (vitamin K epoxide). Inhibition of this process leads to the depletion of vitamin KH_2 and results in the production of hemostatically defective vitamin K–dependent coagulant proteins (prothrombin and factors VII, IX, and X).

Warfarin, a coumarin compound, is the most widely used oral anticoagulant in North America. The drug is administered by the oral route and is rapidly and almost completely absorbed from the gastrointestinal tract. The efficacy and safety of warfarin are closely related to the anticoagulant response achieved. Because the dose-response relationship of warfarin varies widely among individuals, the dose must be monitored closely to prevent overdosing or underdosing. Laboratory monitoring is performed by measuring the prothrombin time (PT). The PT is responsive to depression of three of the four vitamin K–dependent procoagulant clotting factors (prothrombin and factors VII and X), which are reduced at a rate proportionate to their respective half-lives. During the first few days of

warfarin therapy, the PT reflects primarily the depression of factor VII, which has a half-life of only approximately 6 hours. Subsequently, the test is prolonged also by depression of factors X and II. The anticoagulant effect of coumarins can be influenced by genetic and environmental factors; the latter include diet, concomitant drug use, patient compliance, inappropriate dosage adjustments, and the difference in responsiveness of PT reagents.

Commercial PT reagents vary in their responsiveness to a coumarin-induced reduction in clotting factors. This problem is overcome by reporting the PT as the international normalized ratio (INR).

The reliability of warfarin monitoring is improved by ensuring that the patient is educated about the warfarin treatment and that there is good communication between the patient and the health professional responsible for dosage adjustment. The reliability of monitoring is also improved by having the dosage controlled in anticoagulation management services and by using computer-assisted algorithms. The convenience of monitoring can be increased by using point-of-care testing with portable finger-prick monitors. Some of these devices are as accurate as traditional automated methods using citrated plasma. Patient self-management with point-of-care monitors has also been shown to be reliable in the hands of selected patients.

EFFECTIVE LEVELS OF ANTICOAGULATION

Coumarins are effective in the primary and secondary prevention of venous thromboembolism; in the prevention of systemic arterial embolism in patients with tissue and mechanical prosthetic heart valves or with atrial fibrillation; in the prevention of recurrent systemic embolism in patients with atrial fibrillation; in the prevention of acute myocardial infarction in patients with peripheral arterial disease; and in the prevention of stroke, recurrent infarction, and death in patients with acute myocardial infarction. Oral anticoagulants are also indicated in patients with valvular heart disease to prevent systemic arterial embolism, although their effectiveness has never been demonstrated by a randomized clinical trial. A moderate-intensity INR (2.0–3.0) is effective for most indications. The possible exceptions are acute myocardial infarction, in which a higher INR might be superior, and in primary prevention of myocardial infarction in high-risk patients, in which a lower INR is effective. In addition, a lower INR range (1.5–2.0) is effective in patients with venous thrombosis who have received 6 months of full-dose treatment (INR 2.0–3.0), although the lower intensity is less effective than the higher intensity. Fixed-dose warfarin has reduced efficacy or none at all depending on the indication. The optimal intensity for patients with prosthetic heart valves remains uncertain, although there

is evidence that they do not require the very high-intensity regimens that have been used in the past.

PRACTICAL DOSING

If a rapid anticoagulant effect is required, heparin and warfarin should be started at the same time and overlapped for at least 4 days. When the INR has been in the therapeutic range on two measurements approximately 24 hours apart, heparin is discontinued. In previous publications, a starting dose of 5 mg was recommended. This recommendation was based on the results of randomized trials performed in hospitalized patients. More recently, a clinical trial performed in outpatients reported that a therapeutic INR was achieved more rapidly with an initial 10 mg dose for the first 2 days of therapy than with a 5 mg dose, without a difference in the rates of excessive anticoagulation. Thus, selection of the appropriate starting dose of warfarin is influenced by the clinical status of the patient. In otherwise healthy subjects, a starting dose of 7.5 to 10 mg might be appropriate, whereas a lower starting dose (5 mg or less) is likely to be more appropriate in the elderly; in patients with impaired nutrition, liver disease, or congestive heart failure; and in patients at high risk of bleeding. If treatment is not urgent (eg, chronic stable atrial fibrillation), warfarin, without concurrent heparin, can be commenced out of hospital with an anticipated maintenance dose of 4 to 5 mg/d.

MONITORING

In hospitalized patients, INR monitoring is usually performed daily until the therapeutic range has been achieved and maintained for at least 2 consecutive days, then two or three times weekly for 1 to 2 weeks, and then less often, depending on the stability of the INR results. In outpatients started on warfarin, initial monitoring may be reduced to every few days until a stable dose response has been achieved. When the INR response is stable, the frequency of testing can be reduced gradually to intervals as long as every 4 weeks, although there is evidence that testing more frequently than every 4 weeks will lead to greater time in the therapeutic range. If dose adjustments are required, then the cycle of more frequent monitoring is repeated until a stable dose response is again achieved.

MANAGEMENT OF NONTHERAPEUTIC INRs

Various options can be followed for the management of patients whose INR is outside the therapeutic range. Patients whose INR is just outside

the therapeutic range can be managed by either adjusting the dose up or down in 5 to 20% increments based on the cumulative weekly dose of warfarin or by more frequent monitoring, the latter with the expectation that the INR will return to therapeutic levels without a dosage change. High INR values, between 4.0 and 10.0, can be managed by stopping warfarin for a day or more, reducing the weekly dose, and monitoring more frequently. If the patient has a high risk of bleeding or is bleeding, a more active approach should be used to lower the INR more rapidly. The interventions include administering vitamin K_1 and infusing fresh frozen plasma, prothrombin concentrates, or recombinant factor VIIa. If a decision is made to use vitamin K_1, it should be administered in a dose that will quickly lower the INR into a safe but not subtherapeutic range without causing resistance once warfarin is reinstated or without exposing the patient to the risk of anaphylaxis. High doses of vitamin K_1, although effective, may lower the INR more than is necessary and lead to warfarin resistance for up to a week or more. Intravenous injection may be associated with anaphylactic reactions. The response to subcutaneous vitamin K_1 is less predictable than oral vitamin K_1, whereas oral administration is predictably effective and has the advantages of safety and convenience. A dose range of 1.0 to 2.5 mg is effective when the INR is between 5.0 and 9.0, but larger doses (5 mg) are required to correct INR values over 9.0. Vitamin K_1 can also be administered by slow intravenous infusion when there is a greater urgency to reverse anticoagulation.

If continuing warfarin therapy is indicated after high doses of vitamin K_1, then heparin can be given until the effects of vitamin K_1 have been reversed and the patient becomes responsive to warfarin therapy.

FACTORS INFLUENCING ANTICOAGULANT EFFECT OF VITAMIN K ANTAGONISTS

Some patients on long-term warfarin therapy are difficult to manage because they have unexpected fluctuations in dose response. The anticoagulant response to warfarin can be influenced by many factors, including inaccuracies in laboratory testing and reporting, poor communication between the patient and the physician, and inappropriately large changes in the dose of warfarin in response to modest fluctuations in the INR. Concomitant medication with over-the-counter drugs, prescription drugs, and herbal remedies can influence the effect of warfarin on hemostasis by augmenting or inhibiting its anticoagulant effect or by interfering with platelet function. Patients receiving warfarin therapy are also sensitive to fluctuating levels of dietary vitamin K, which is obtained predominantly from leafy green vegetables. Increased intake of dietary vitamin K occurs in patients

on weight reduction diets (rich in green vegetables) and those treated with intravenous (IV) nutritional fluid supplements rich in vitamin K. The effects of warfarin can be potentiated in sick patients with poor vitamin K intake (particularly if they are treated with antibiotics and IV fluids without vitamin K supplementation) and in states of fat malabsorption. Hepatic dysfunction also potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase the responsiveness to warfarin probably by increasing the catabolism of vitamin K–dependent coagulation factors.

A number of drugs can increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the most important because it is present in many over-the-counter preparations and because it has a prolonged effect on hemostasis. Aspirin can also produce gastric erosions, which increase the risk of serious upper gastrointestinal bleeding.

Many other drugs have the potential to influence the effect of warfarin on hemostasis. Therefore, when treatment with any new drug is necessary in patients who are being treated with oral anticoagulants, the PT should be monitored approximately every second day during the initial stages of combined drug therapy, with dose adjustments made as necessary.

The 2004 recommendations[2] for target INR values for the different indications are shown in Table 3-1.

Table 3-1 Recommended Therapeutic Range for Oral Anticoagulant Therapy

Indication	INR
Prophylaxis of venous thrombosis (high-risk surgery)	
Treatment of venous thrombosis	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	2.0–3.0
Valvular heart disease	
Atrial fibrillation	
Recurrent systemic embolism	
Cardiomyopathy	
Mechanical prosthetic valves (high risk)	2.5–3.5
Acute myocardial infarction	

INR = international normalized ratio.

RECOMMENDATIONS

Appropriate Dose for Initiation of Oral Anticoagulants

1. We suggest initiation of oral anticoagulation therapy with either a 5 mg or a 10 mg dose of warfarin for most individuals. Subsequent dosing should be based on the INR response. A lower starting dose may be appropriate in the elderly, patients who are debilitated or malnourished, or patients who have congestive heart failure or liver disease (**Grade 2C**).

Frequency of Monitoring Oral Anticoagulation

1. We suggest that patients who are on a stable dose of oral anticoagulants be monitored at an interval of no longer than every 4 weeks. During initiation and stabilization of therapy, monitoring should be more frequent (**Grade 2C**).

Management of Dosing When the INR Is in the Nontherapeutic Range

We suggest the following:

1. For INRs above the therapeutic range but less than 5.0 and with no significant bleeding, lower or omit the dose, monitor more frequently, and resume at a lower dose when the INR is in the therapeutic range. If only minimally above the therapeutic range, no dose reduction may be required (**Grade 2C**).
2. For INRs > 5.0 but < 9.0 and no significant bleeding, omit the next one or two doses, monitor more frequently, and resume at a lower dose when the INR is in the therapeutic range. Alternatively, omit a dose and give vitamin K_1 (1–2.5 mg) orally, particularly if the patient is at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K_1 ($\leq$ 5 mg) orally can be given with the expectation that a reduction of the INR will occur in 24 hours. If the INR is still high, additional vitamin K_1 (1–2 mg) orally can be given (**Grade 2C**).
3. For INRs > 9.0 and no significant bleeding, hold warfarin and give a higher dose of vitamin K_1 (5–10 mg) orally with the expectation that the INR will be reduced substantially in 24 to 48 hours. Monitor more frequently and use additional vitamin K_1 if necessary. Resume therapy at a lower dose when the INR is in the therapeutic range (**Grade 2C**).
4. We recommend that with serious bleeding and an INR at any level, hold warfarin and give vitamin K_1 (10 mg) by slow IV infusion and supplemented with fresh plasma or prothrombin complex concentrate depending on the urgency of the situation; recombinant factor VIIa may be considered as an alternative to prothrombin complex concentrate. Vitamin K_1 can be repeated every 12 hours (**Grade 1C**).

5. We recommend that for life-threatening bleeding, hold warfarin and give prothrombin complex concentrate supplemented with vitamin K_1, 10 mg by slow IV infusion; recombinant factor VIIa may be considered as an alternative to prothrombin complex concentrate; repeat if necessary depending on the INR (**Grade 1C**).

Method of Vitamin K_1 Administration

1. We recommend that when vitamin K is to be given, it should be administered orally for patients with mildly to moderately elevated INRs without major bleeding (**Grade 1A**). Intravenous vitamin K may be appropriate for patients with major bleeding or excessively elevated INRs.

Management of Dosing When an Invasive Procedure Is Required

1. We suggest that for patients with a low risk of thromboembolism, stop warfarin ~ 4 days before surgery, allow the INR to return to near-normal, briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with low-dose unfractionated heparin (UFH), 5,000 U subcutaneously (SC), or a prophylactic dose of low-molecular-weight heparin (LMWH), and simultaneously begin warfarin therapy. Alternatively, low-dose UFH or prophylactic-dose LMWH can also be used preoperatively (**Grade 2C**).
2. For patients with an intermediate risk of thromboembolism, stop warfarin ~ 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with low-dose UFH, 5,000 U SC, or a prophylactic dose of LMWH, and then commence low-dose UFH (or LMWH) and warfarin postoperatively. Some clinicians would recommend a higher dose of UFH or full-dose LMWH in this setting (**Grade 2C**).
3. For patients with a high risk of thromboembolism, stop warfarin ~ 4 days before surgery, allow the INR to return to normal, and begin therapy with full-dose UFH or full-dose LMWH as the INR falls (~ 2 days preoperatively). UFH can be given as a SC injection as an outpatient; it can then be given as a continuous IV infusion after admission in preparation for surgery and discontinued ~ 5 hours before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. It is also possible to continue with SC UFH or LMWH and to stop therapy 12 to 24 hours before surgery with the expectation that the anticoagulant effect will be very low or will have worn off at the time of surgery (**Grade 2C**).
4. For patients with a low risk of bleeding, continue warfarin at a lower dose and operate at an INR of 1.3 to 1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical