Guidelines for
Antithrombotic Therapy

Fifth Edition

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Notice: The authors and publisher have made every effort to ensure that the patient care recommended herein, including choice of drugs and drug dosages, is in accord with the accepted standard and practice at the time of publication. However, since research and regulation constantly change clinical standards, the reader is urged to check the product information sheet included in the package of each drug, which includes recommended doses, warnings, and contraindications. This is particularly important with new or infrequently used drugs. Any treatment regimen, particularly one involving medication, involves inherent risk that must be weighed on a case-by-case basis against the benefits anticipated. The reader is cautioned that the purpose of this book is to inform and enlighten; the information contained herein is not intended as, and should not be employed as, a substitute for individual diagnosis and treatment.

CONTENTS

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

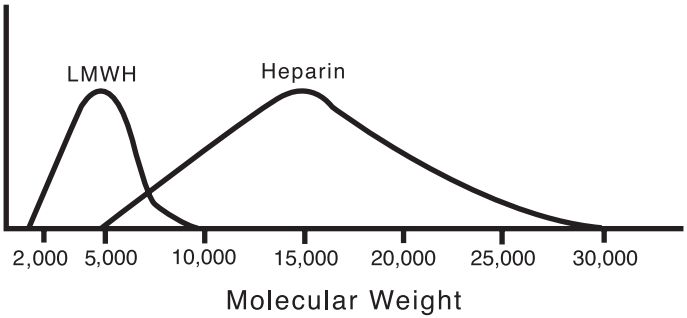

Figure 2-1 Molecular weight distribution of low-molecular-weight heparins (LMWHs) and heparin.

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 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

patients. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy can then be restarted postoperatively, supplemented with low-dose UFH (5,000 U SC) or a prophylactic dose of LMWH if necessary (**Grade 2C**).

Therapeutic Range in the Presence of a Lupus Inhibitor

1. We suggest aiming for a therapeutic INR range of 2.0 to 3.0 in patients with a lupus inhibitor (or antiphospholipid antibody syndrome) unless there is a reason for a higher range (eg, the patient also has a prosthetic mechanical valve, is post–myocardial infarction, or has recurrent thromboembolism when in the therapeutic range) (**Grade 2B**).

Models of Anticoagulation Monitoring and Management

1. We recommend that physicians who manage oral anticoagulation do so in a systematic and coordinated fashion, incorporating patient education; systematic INR testing, tracking, and follow-up; and good patient communication of results and dosing decisionss (**Grade 1C+**).

4 PLATELET-ACTIVE DRUGS

The platelet-active drugs that are effective in the prevention and treatment of arterial thrombosis are aspirin, ticlopidine, clopidogrel, dipyridamole, abciximab, and the small-molecular-weight glycoprotein (GP) IIb/IIIa antagonists, tirofiban and eptifibatide. Since the last report in 2001, new information has been published suggesting that (1) the benefit-risk profile of GP IIb/IIIa antagonists is uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization; (2) the combination of aspirin and clopidogrel is effective for the long-term management of high-risk patients; and (3) the use of a bolus of clopidogrel pre–percutaneous coronary intervention (PCI) might obviate the need for GP IIb/IIIa antagonists in non–high-risk PCI patients.

ASPIRIN AND OTHER CYCLOOXYGENASE INHIBITORS

Aspirin is an effective antithrombotic agent that inhibits the production of thromboxane A_2 (TXA_2), a potent inducer of platelet aggregation and vasoconstriction, by inhibiting platelet cyclooxygenase (COX)-1. Aspirin prevents vascular death by approximately 15% and nonfatal vascular events by about 30%.

Mechanism of Action

Aspirin permanently inactivates prostaglandin H synthase 1 and 2 (also referred to as COX-1 and COX-2). The COX isozymes catalyze the con-

version of arachidonic acid to prostaglandin H_2 (PGH_2), which is the precursor of a variety of prostaglandins, including TXA_2 and prostacylin (prostaglandin I_2 [PGI_2]). Aspirin is approximately 50- to 100-fold more potent in inhibiting platelet COX-1 than COX-2 in monocytes and other inflammatory cells. Consequently, the COX-2–dependent anti-inflammatory effects of aspirin require larger doses of the drug because of (1) a decreased sensitivity of COX-2 to aspirin and (2) a much more short-lived inhibitory effect of aspirin on inflammatory cells because these nucleated cells rapidly resynthesize the enzyme. Aspirin produces a permanent defect in a TXA_2-dependent function in platelets because these anucleated cells are incapable of synthesizing new COX-1. Aspirin also inactivates COX-1 in relatively mature megakaryocytes. Given that only 10% of the platelet pool is replenished each day, once-a-day dosing of aspirin is able to maintain virtually complete inhibition of platelet TXA_2 production.

Human platelets and vascular endothelial cells process PGH_2 to produce TXA_2 and PGI_2, respectively. TXA_2 induces platelet aggregation and vasoconstriction, whereas PGI_2 inhibits platelet aggregation and induces vasodilatation. TXA_2 is mostly a COX-1–derived platelet product, whereas vascular PGI_2 can derive from both COX-1 and COX-2. Low and even moderate doses of aspirin do not inhibit PGI_2 synthesis substantially because the effect of aspirin on endothelial cell–derived COX-1 is short-lived and COX-2 is largely insensitive to aspirin inhibition at conventional antiplatelet doses. Although it is not established that more profound suppression of PGI_2 formation by high doses of aspirin predisposes the patient to thrombosis, studies with mice deficient in the gene encoding the PGI_2 receptor support the importance of this prostanoid in the prevention of arterial thrombosis.

Effects Not Related to TXA_2

Aspirin has been reported to have effects on hemostasis that are unrelated to its ability to inactivate platelet COX-1. These include dose-dependent inhibition of platelet function, enhancement of fibrinolysis, and suppression of plasma coagulation. None of these effects have been shown to contribute to the antithrombotic effect of aspirin. In contrast, there is overwhelming evidence that the antithrombotic effect of aspirin is largely derived from its ability to inhibit COX-1 in platelets.

Pharmacokinetics

Aspirin is rapidly absorbed in the stomach and upper intestine and has a short half-life (15–20 minutes) in the human circulation. Peak plasma levels occur 30 to 40 minutes after aspirin ingestion, and inhibition of platelet function is evident by 1 hour. In contrast, it can take up to 3 to 4 hours to reach peak plasma levels after administration of enteric-coated aspirin. If

only enteric-coated tablets are available and a rapid effect is required, the tablets should be chewed. The oral bioavailability of regular aspirin tablets is approximately 40 to 50% over a wide range of doses. A considerably lower bioavailability has been reported for enteric-coated tablets and sustained-release, microencapsulated preparations. Because platelet COX-1 is acetylated in the presystemic circulation, the antiplatelet effect of aspirin is largely independent of systemic bioavailability.

Aspirin reduces the incidence of myocardial infarction and/or death in the following groups of patients: those with silent myocardial ischemia or stable angina; those with unstable angina and non–Q-wave infarction; those with acute myocardial infarction; in patients after angioplasty and aortocoronary bypass surgery; and in patients with cerebrovascular disease.

There is also evidence that aspirin prevents myocardial infarction in asymptomatic males and females over the age of 50 years, although the relative risks and benefits in asymptomatic individuals are less certain than in those with overt evidence of atherosclerotic vascular disease. Therefore, the risks of aspirin must be weighed carefully against the small benefits in asymptomatic persons. For patients with acute myocardial infarction, prior infarction, or prior stroke, aspirin prevents between 35 and 40 events per 1,000 patients treated. In contrast, when used in asymptomatic patients, aspirin prevents only four events per 1,000 patients treated. Low-dose aspirin does not reduce maternal and fetal complications in pregnant women with hypertension, past or present preeclampsia, renal disease, or a history of intrauterine growth retardation. The addition of aspirin (100 mg) to warfarin increases the efficacy of warfarin in preventing systemic embolism and vascular death in patients with mechanical prosthetic heart valves but at an increased risk of bleeding. Other effective aspirin combinations are (1) aspirin and dipyridamole in a patient with stroke, (2) low-dose aspirin with heparin to prevent recurrent miscarriages in pregnant women with antiphospholipid antibody syndrome, and (3) aspirin and clopidogrel to prevent acute thrombosis of coronary stents and in patients with unstable angina or non–ST-segment elevation myocardial infarction.

Aspirin produces a very small increase in the risk of cerebral hemorrhage, which is more than overcome by its much greater beneficial effects in reducing ischemic stroke in high-risk patients.

The antithrombotic effects of a range of doses of aspirin have been evaluated. Aspirin is effective when used in doses between 50 and 1,500 mg/d, and there is no evidence that low doses (50–100 mg/d) are less effective than high doses (650–1,500 mg/d). Doses of approximately 300 mg/d produce fewer gastrointestinal side effects than doses of approximately 1,200 mg/d. In the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) trial, patients with acute coronary syndromes receiving aspirin ≤ 100 mg daily had

the lowest rate of major or life-threatening bleeding complications without any loss in efficacy. Because the gastrointestinal toxicity of aspirin and bleeding appear to be dose related, the lowest dose of aspirin shown to be effective in each clinical setting is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit-risk profile.

Aspirin-resistant TXA_2 biosynthesis has recently been related to the occurrence of treatment failure. From the therapeutic standpoint, it is important to establish whether aspirin resistance can be overcome by increasing the dose of aspirin, but, at present, few data bear directly on this issue.

DIPYRIDAMOLE

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. Dipyridamole inhibits platelet function by elevating platelet cyclic adenosine monophosphate (AMP) levels by (1) inhibition of cyclic nucleotide phosphodiesterase, the enzyme that degrades cyclic AMP to 5'-AMP, and (2) blockade of the uptake of adenosine, thereby stimulating platelet adenylyl cyclase.

The absorption of dipyridamole from conventional formulations is quite variable and may result in low systemic bioavailability of the drug. A modified-release formulation of dipyridamole with improved bioavailability has been developed and has been evaluated in association with low-dose aspirin. Dipyridamole is eliminated primarily by biliary excretion as a glucuronide conjugate and is subject to enterohepatic recirculation. A terminal half-life of 10 hours has been reported. This is consistent with the twice-daily regimen used in recent clinical studies.

The efficacy of dipyridamole, alone or in combination with aspirin, has been questioned in the past, but this issue has been reopened by the results of the European Stroke Prevention Study (ESPS)-2. In this study of 6,602 patients with prior stroke or transient ischemic attack, stroke risk in comparison with placebo was reduced by dipyridamole alone and by aspirin plus dipyridamole. Whether the favorable results obtained in the ESPS-2 reflect the higher dose (400 vs 225 mg daily) of dipyridamole or the improved systemic bioavailability of modified-release dipyridamole compared with conventional formulations is uncertain. The combination of modified-release dipyridamole and low-dose aspirin was recently approved by the US Food and Drug Administration (FDA).

THIENOPYRIDINES

Ticlopidine and clopidogrel are structurally related thienopyridines that selectively inhibit adenosine diphosphate (ADP)-induced platelet aggrega-

tion. Both drugs derive their antiplatelet effect through their hepatic transformation in vivo to an active metabolite(s). Platelets contain three receptors for ADP: a ligand-gated ion channel ($P2X_1$), a G protein–linked receptor ($P2Y_1$), and a third less well-characterized receptor ($P2Y_{12}$). Clopidogrel and ticlopidine induce irreversible (permanent) alterations to this third ADP receptor, which is postulated to mediate the inhibition of stimulated adenylyl cyclase activity. The irreversible modification of this ADP receptor site has been attributed to the formation of a disulfide bridge(s) between the reactive thiol group of the active metabolite of clopidogrel and that of a cysteine residue(s) of the platelet $P2Y_{12}$ receptor. The onset of action of the thienopyridines is delayed until the compounds are biotransformed to their active metabolites, and the recovery of platelet function is delayed until the metabolites are cleared and new unaffected platelets enter the circulation.

Up to 90% of a single oral dose of ticlopidine is rapidly absorbed in humans. Peak plasma concentrations occur 1 to 3 hours after a single oral dose of 250 mg. Plasma levels of ticlopidine increase by approximately threefold on repeated twice-daily dosing over 2 to 3 weeks because of drug accumulation.

Ticlopidine is transformed rapidly and extensively to a variety of metabolites, one of which (the 2-keto derivative) is more potent than the parent compound in inhibiting ADP-induced platelet aggregation. Because of its delayed onset of action, ticlopidine is not useful when a rapid antiplatelet effect is required.

Ticlopidine as a single agent has been shown to be efffective in a number of randomized clinical trials. Its clinical benefit, however, is offset by two important side effects: hypercholesterolemia and neutropenia. The reported rate of incidence for neutropenia is 2.4% for a neutrophil count of $< 1.2 \times 10^9$/L and 0.8% for a neutrophil count of $< 0.45 \times 10^9$/L. Ticlopidine has also been associated with thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura (TTP). Ticlopidine is approved for clinical use in patients with cerebral ischemia when aspirin has failed, cannot be tolerated, or is contraindicated, although this limitation does not apply to all countries in which the drug is registered.

Several studies have demonstrated the superiority of the combination of ticlopidine and aspirin compared with aspirin alone, or aspirin plus warfarin, in preventing thrombotic complications after coronary artery stent placement. However, the better safety profile of clopidogrel has resulted in the substitution of clopidogrel for ticlopidine in many centers for this indication (see below).

Clopidogrel is rapidly absorbed and metabolized to its carboxylic acid derivative, SR 26334. The plasma elimination half-life of SR 26334 is

approximately 8 hours. The onset of the inhibition of platelet aggregation with clopidogrel is more rapid than that observed with ticlopidine. Thus, inhibition of platelet aggregation is detectable as soon as 2 hours after an oral loading dose of 300 mg and remains relatively stable up to 48 hours. Inhibition of ADP-induced platelet aggregation occurs in a dose-dependent fashion with an apparent ceiling effect of 40% inhibition after a single oral loading dose. On repeated daily administration of low doses, there is cumulative inhibition of platelet function with a return to normal 7 days after the last dose of clopidogrel.

The optimal timing and size of the loading dose for achieving a prompt antiplatelet effect in the acute setting are still under investigation, and doses up to 600 mg are currently being used as a loading dose of clopidogrel pre-PCI. In one recent trial in moderate-risk patients, the clinical outcome was similar with or without abciximab when a 600 mg loading dose of clopidogrel prior to PCI was used.

Patients exhibit marked interindividual variability to the effect of clopidogrel on the ADP-inhibiting effects on platelets. Three separate studies suggest that concurrent treatment with lipophilic statins that are substrates of CYP3A4 (eg, atorvastatin and simvastatin) may interfere with the inhibitory effects of clopidogrel on platelet function. Many drugs are metabolized by CYP3A4, so it is possible that other drugs may modify the systemic bioavailability of the active metabolite of clopidogrel and affect its clinical efficacy.

The efficacy and safety of clopidogrel have been compared with aspirin in a single, very large phase III trial, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), in patients who had experienced a recent stroke or recent myocardial infarction and those presenting with symptomatic peripheral arterial disease.

CAPRIE showed a modest benefit in effectiveness in favor of clopidogrel. Both clopidogrel and medium-dose aspirin therapy were well tolerated in the CAPRIE study. The frequency of severe rash and severe diarrhea was higher with clopidogrel than with aspirin, whereas gastrointestinal discomfort and hemorrhage were more frequent with aspirin than with clopidogrel. No excess neutropenia was found in the clopidogrel group. Based on these findings, clopidogrel has been approved for the reduction of atherosclerotic events in patients with recent stroke, recent myocardial infarction, or established peripheral arterial disease. TTP can occur after the initiation of clopidogrel therapy, often within the first 2 weeks of treatment; this is likely to be a very rare complication.

The efficacy and safety of the combination of aspirin and clopidogrel have been evaluated in high-risk clinical settings. The results of the CURE trial demonstrated that the combination was about 20% more effective than

aspirin in patients with acute coronary syndromes without ST-segment elevation. The benefit of clopidogrel was apparent within the first 30 days after randomization and remained constant during the 12 months of the study. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs 2.7%; $p = .001$). A subgroup analysis of the CURE trial based on the daily dose of prescribed aspirin revealed a clear dose-related effect on major bleeding in both treatment groups. Those patients receiving the lowest dose (100 mg) of aspirin combined with clopidogrel had virtually the same rate of major bleeding complications (3.0%) as those receiving higher doses of aspirin and placebo. The safety advantage of lower doses of aspirin was not associated with any loss of efficacy.

More recently, the results of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial demonstrated that long-term (1 year) clopidogrel therapy significantly reduces the risk of major vascular events following PCI. Numerous randomized clinical trials are currently under way to further evaluate the efficacy and safety of clopidogrel and aspirin in a variety of high-risk clinical settings.

INTEGRIN IIBβ_3 (GP IIB/IIIA) RECEPTOR ANTAGONISTS

The expression of functionally active integrin IIbβ_3 (GP IIb/IIIa) on the platelet surface is the final common pathway of platelet aggregation. The GP IIb/IIIa antagonists include monoclonal antibodies against the receptor, synthetic RGD- or Lys-Gly-Asp sequence (KGD)-containing peptides, and peptidomimetic and nonpeptide RGD mimetics that compete with fibrinogen and von Willebrand factor for occupancy of the platelet receptor.

ABCIXIMAB

Abciximab (ReoPro), the first GP IIb/IIIa antagonist developed for clinical use, is a mouse/human chimeric 7E3 Fab antibody. Platelet aggregation is inhibited significantly at antibody doses that decrease the number of available receptors to < 50% of normal. Platelet aggregation is nearly completely abolished at approximately 80% receptor blockade, but the bleeding time is only mildly affected at this level of receptor blockade. In contrast, the bleeding time is markedly prolonged with > 90% receptor blockade. Abciximab is unique among the GP IIb/IIIa antagonists in also blocking the $\alpha V\beta_3$ receptor at therapeutic doses and binding to an activated form of the leukocyte $\alpha M\beta_2$ receptor; it is unclear whether any of the beneficial clinical effects of abciximab are due to inhibition of these receptors.

Following intravenous bolus administration, free plasma concentrations decrease rapidly (initial half-life of about 30 minutes) as a result of rapid

binding to platelet GP IIb/IIIa receptors, with approximately 65% of the injected antibody becoming attached to platelets in the circulation and spleen. Platelet function is impaired rapidly, with gradual recovery over time. Platelet aggregation in response to 20 M ADP returns to 50% of baseline within 24 hours in most patients and within 48 hours in nearly all patients. Small amounts of abciximab can be detected on circulating platelets as late as 14 days after administration, presumably as a result of antibody redistribution from platelet to platelet.

TIROFIBAN

Tirofiban (MK-383; Aggrastat) is a nonpeptide derivative of tyrosine that selectively inhibits the GP IIb/IIIa receptor. When administered to humans at 0.15 g/kg/min for 4 hours, tirofiban produced a 2.5-fold increase in bleeding time and 97% inhibition of ADP-induced platelet aggregation. Its half-life in plasma is 1.6 hours. After stopping tirofiban therapy, within 4 hours, bleeding times return to normal, and inhibition of platelet aggregation declines to approximately 20%. When administered with aspirin, the bleeding time increased 1. 5-fold.

EPTIFIBATIDE

Eptifibatide (Integrilin) is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the KGD sequence found in the snake venom disintegrin obtained from *Sistrurus m. barbouri* (barbourin) and has a high specificity for inhibition of GP IIb/IIIa. The elimination of eptifibatide depends principally on plasma clearance. Two hours after discontinuing an eptifibatide infusion, there is a substantial return of platelet function and return of more than half of the baseline aggregation response in all groups after 4 hours.

EFFICACY AND SAFETY

The efficacy and safety of abciximab and the small-molecular-weight antagonists have been demonstrated in patients undergoing PCI. Over 20,000 patients have been enrolled in nine studies of abciximab, eptifibatide, and tirofiban. The first of these phase III trials, the Evaluation in Preventing Ischemic Complications (EPIC) trial, resulted in approval in many countries of abciximab for PCI patients at high risk of developing ischemic complication. The c7E3 Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial demonstrated the efficacy of an 18- to 24-hour abciximab treatment prior to PCI in patients with unstable angina refractory to conventional antithrombotic and antianginal therapy. The EPILOG trial demon-

strated the efficacy of abciximab in a broad patient population undergoing PCI, not just high-risk patients, as enrolled in the EPIC and CAPTURE trials. The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial demonstrated that abciximab decreases the frequency of ischemic complications of PCI associated with stent insertion during the first 30 days.

A meta-analysis of all major randomized clinical trials of GP IIb/IIIa antagonists in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularization reported a 9% reduction in the odds of death or myocardial infarction at 30 days. The 1% absolute difference in death or myocardial infarction was balanced by an absolute excess of 1% in major bleeding complications associated with GP IIb/IIIa antagonists versus a control.

Both eptifibatide and tirofiban have received approval from the FDA for the treatment of acute coronary syndromes, including patients who are to be managed medically and those undergoing PCI. Abciximab previously received approval for the treatment of patients with refractory unstable angina who are expected to undergo PCI within 18 to 24 hours of beginning abciximab treatment.

Abciximab was compared with tirofiban as treatment for PCI in the Tirofiban And Reopro Give similar Efficacy Trial (TARGET). Abciximab treatment was found to be associated with a statistically significant lower rate of ischemic complications after 30 days; at 6 months, the differences were less apparent.

After phase II trials in acute myocardial infarction suggested potential benefits of GP IIb/IIIa blockade as an adjunct to thrombolysis, the Global Use of Studies to Open Occluded Coronary Arteries Trial was performed. This trial compared the efficacy and safety of half-dose reteplase and full-dose abciximab versus standard-dose reteplase in 16,588 patients in the first 6 hours of evolving ST-segment elevation myocardial infarction. The primary end point of 30-day mortality was similar in the two treatment groups (5.6 vs 5.9%). Combination therapy led to a consistent reduction in secondary complications of myocardial infarction, including reinfarction, which was partly counterbalanced by increased extracranial bleeding. There was no mortality benefit of combined therapy after 1 year.

ORAL GP IIB/IIIA ANTAGONISTS

Orally active nonpeptide GP IIb/IIIa inhibitors have been developed for long-term use. The results of these studies, which included over 40,000 patients who had recovered from acute coronary ischemia, have been disappointing. The consistent finding of these large-scale trials is that oral GP IIb/IIIa antagonists (xemilofiban, orbofiban, sibrafiban, and lotrafiban) are not more effective than

aspirin or, when combined with aspirin, are not superior to placebo and may, in fact, increase mortality. Several mechanisms have been put forward to explain these results. One is that the poor oral bioavailability of these compounds, combined with a target of 50% inhibition of platelet aggregation, resulted in trivial antiplatelet activity in many patients. An alternative (or additional) explanation is that GP IIb/IIIa antagonists can activate platelets.

5 NEW ANTICOAGULANTS

The limitations of established anticoagulants have prompted the development of a variety of new anticoagulant agents that target various specific steps in the coagulation mechanism.

INHIBITORS OF INITIATION OF COAGULATION

Three drugs that target the factor VIIa–tissue factor complex have been evaluated in clinical trials. These are recombinant tissue factor pathway inhibitor (TFPI), recombinant nematode anticoagulant peptide (NAPc2), and active-site blocked factor VIIa (factor VIIai).

Tissue Factor Pathway Inhibitor

A recombinant form of TFPI, tifacogin, has been evaluated in patients with sepsis. TFPI binds to factor Xa, and the bimolecular complex then binds to and inactivates the factor VIIa–tissue factor complex. The promising results of a phase II trial were not observed in a large phase III trial, and further development of TFPI for sepsis has been stopped.

Recombinant Nematode Anticoagulant Peptide

NAPc2 is a polypeptide originally isolated from the canine hookworm and now available as a recombinant molecule. NAPc2 binds to a noncatalytic site on factor X or factor Xa. Once bound to factor Xa, the NAPc2–factor Xa complex inhibits factor VIIa within the tissue factor. Because it binds to factor X with high affinity, NAPc2 has a half-life of approximately 50 hours after subcutaneous injection. NAPc2 has been evaluated in a phase II study in patients undergoing elective knee arthroplasty with promising results. It is now being evaluated in a series of phase II clinical trials in patients with unstable angina or non–ST-segment elevation myocardial infarction and in those undergoing percutaneous coronary interventions.

Factor VIIai

Inactivated factor VIIa competes with factor VIIa for tissue factor binding, thereby modulating initiation of coagulation by the factor VIIa–tissue

factor complex. Factor VIIai has been evaluated in a small study of patients undergoing elective percutaneous coronary interventions. The results were not sufficiently promising to continue its development for treatment of arterial thrombosis.

INHIBITORS OF PROPAGATION OF COAGULATION

Drugs that inactivate factors Xa, VIIIa, and Va inhibit the propagation of coagulation. New factor Xa inhibitors block factor Xa indirectly or directly. The indirect inhibitors fondaparinux and idraparinux act by catalyzing factor Xa inhibition by antithrombin, whereas the direct factor Xa inhibitors, DX9065a and DPC 906, bind directly to the active site of factor Xa. Unlike the indirect inhibitors, direct factor Xa inhibitors not only inhibit free factor Xa but also inactivate factor Xa bound to platelets within the prothrombinase complex.

Inhibition of factors Va and VIIIa is effected by activated protein C. From a therapeutic standpoint, this can be achieved by recombinant activated protein C or recombinant soluble thrombomodulin.

Fondaparinux

Fondaparinux is a synthetic analog of the antithrombin-binding pentasaccharide sequence found in heparin. Fondaparinux binds antithrombin and enhances its reactivity with factor Xa. Fondaparinux has no activity against thrombin.

Fondaparinux has excellent bioavailability after subcutaneous injection. It has a plasma half-life of about 17 hours and is administered subcutaneously once daily. The drug is excreted unchanged in the urine. Fondaparinux does not bind to platelets or platelet factor 4 (PF4) and therefore does not cause heparin-induced thrombocytopenia. It has been evaluated for prevention and treatment of venous thromboembolism and for treatment of arterial thrombosis.

Based on four large phase III trials comparing fondaparinux with enoxaparin for thromboprophylaxis in patients undergoing surgery for hip fracture or elective hip or knee arthroplasty, fondaparinux has been licensed for these indications. Fondaparinux was also shown to be effective and safe when used for extended thromboprophylaxis patients undergoing surgery for hip fracture and for prophylaxis in general medical and general surgical patients. Fondaparinux also has been evaluated in two trials for initial treatment of venous thrombosis and pulmonary embolism. In both of these clinical trials, fondaparinux was as effective and safe as low-molecular-weight heparin and unfractionated heparin, respectively. Finally, fondaparinux is being evaluated in two phase III studies in patients with ST-segment elevation and non–ST-segment elevation myocardial infarction.

Idraparinux

Idraparinux is a more highly sulfated derivative of fondaparinux. It has very high affinity to antithrombin, and, as a result, it has a plasma half-life of 130 hours, thereby allowing it to be administered subcutaneously on a once-weekly basis. Idraparinux has been compared with warfarin in a phase II trial in patients with proximal deep vein thrombosis and is being evaluated in phase III clinical trials.

DX 9065a

DX 9065a is a nonpeptidic arginine derivative that binds reversibly to the active site of factor Xa. It was given as a continuous intravenous infusion in a small phase II trial in patients with stable coronary artery disease to assess safety. Additional phase II studies are under way comparing DX 9065a with heparin in patients undergoing percutaneous coronary interventions.

DPC 906

An orally active agent, DPC 906 must be given twice daily. In a phase II dose-finding study, DPC 906 was compared with enoxaparin in patients undergoing knee arthroplasty. Based on promising results, a phase III study is being planned.

Activated Protein C

Recombinant activated protein C, drotrecogin alfa (activated), has been shown to be effective in a phase III study in patients with severe sepsis. Based on this study, activated protein C has been licensed in North America for treatment of patients with severe sepsis.

Soluble Thrombomodulin

Soluble thrombomodulin is a recombinant analog of the extracellular domain of thrombomodulin. It binds thrombin and induces a conformation change in the active site of the enzyme that converts it into a potent activator of protein C. Soluble thrombomodulin has been evaluated in a phase II dose-ranging study in patients undergoing elective hip arthroplasty. The results were promising.

INHIBITORS OF FIBRIN FORMATION

Direct Thrombin Inhibitors

There are two classes of direct thrombin inhibitors: bivalent and active-site inhibitors. Of the four thrombin inhibitors, three are parenteral and one is oral. Direct thrombin inhibitors act independently of antithrombin.

Direct thrombin inhibitors have three potential mechanistic advantages over indirect thrombin inhibitors, such as heparin. First, they have a predictable anticoagulant response and do not require anticoagulant monitoring. Second, they do not bind to PF4 and therefore are unaffected by the large quantities of PF4 released in the vicinity of platelet-rich thrombi. Third, they inactivate fibrin-bound thrombin, as well as fluid-phase thrombin.

Three parenteral direct thrombin inhibitors (hirudin, argatroban, and bivalirudin) have been licensed in North America for limited indications. Hirudin and argatroban are approved for treatment of patients with heparin-induced thrombocytopenia, whereas bivalirudin is licensed as an alternative to heparin in patients undergoing percutaneous coronary interventions. Ximelagatran, a prodrug of melagatran, is the first orally available direct thrombin inhibitor to undergo evaluation in phase III studies.

Hirudin is a 65–amino acid polypeptide now available through recombinant deoxyribonucleic acid (DNA) technology. Hirudin is a bivalent inhibitor; it has a plasma half-life of 60 minutes after intravenous injection and 120 minutes after subcutaneous injection. Hirudin is cleared via the kidneys and should not be used in patients with renal insufficiency.

Recombinant hirudin (lepirudin) has been evaluated in acute coronary syndromes and, to a lesser extent, for prevention and treatment of venous thrombosis. Despite some promise, hirudin has not been licensed for these indications.

Bivalirudin is a synthetic peptide that, like hirudin, is a bivalent inhibitor. Active-site inhibition by bivalirudin is transient because, once complexed, thrombin can slowly cleave bivalirudin, thereby converting it to a weaker, monovalent inhibitor.

Bivalirudin has been evaluated in patients undergoing percutaneous coronary interventions and as an adjunct to streptokinase in patients with acute myocardial infarction. It is licensed as an alternative to heparin in patients undergoing percutaneous coronary angioplasty and was approved for this indication based on the results of a phase III study that compared bivalirudin with heparin in patients undergoing coronary angioplasty for unstable or postinfarction angina. Bivalirudin has also been evaluated as a possible replacement for glycoprotein IIb/IIIa antagonists in patients undergoing percutaneous coronary intervention and as an adjunct to streptokinase in patients with acute ST-segment elevation myocardial infarction.

Ximelagatran

Ximelagatran is a prodrug of the active site–directed thrombin inhibitor melagatran. Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran. Ximelagatran has a plasma half-life of 3 to 4 hours and is administered orally twice daily. Because ximelagatran produces a pre-

dictable anticoagulant response, coagulation monitoring is unnecessary. Melagatran, the active agent, is eliminated via the kidneys.

Ximelagatran has been evaluated for thromboprophylaxis in high-risk orthopedic patients, treatment of venous thromboembolism, prevention of cardioembolic events in patients with nonvalvular atrial fibrillation, and prevention of recurrent ischemia in patients with recent myocardial infarction. It has been shown to be effective for the prevention and treatment of venous thrombosis and for the prevention of stroke in atrial fibrillation. The clinical trial in recent myocardial infarction was a dose-finding study.

The most important side effect of ximelagatran is elevation of liver enzymes. Overall, approximately 4 to 9% of patients treated with long-term ximelagatran develop an increase in alanine aminotransferase. Typically, this problem occurs after 6 weeks to 4 months of treatment. Although the increase in alanine aminotransferase is usually asymptomatic and reversible, more information is needed to determine the impact of this side effect on its clinical development.

6 HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse effect of heparin. It is important because of its strong association with venous and arterial thrombosis. The frequency of HIT among patients exposed to heparin is higher with heparin than with low-molecular-weight heparin (LMWH), is higher in surgical patients than medical patients, and is very low in pregnancy. These differences in risk influence the required frequency of platelet count monitoring.

A diagnosis of HIT should be suspected if (1) the platelet count fall exceeds 50% of baseline during 5 to 10 days of heparin treatment; (2) if thrombotic complications or other sequelae, such as heparin-induced skin lesions, occur during or soon after heparin treatment; or (3) an acute systemic reaction occurs following an intravenous bolus dose of heparin. Although, in HIT patients, the platelet count usually begins to fall 5 to 10 days after commencing heparin, there are also other patterns of platelet count fall. Thus, in about 25 to 30% of patients, the platelet count falls abruptly on beginning heparin; typically, these patients have recently been exposed to heparin and have HIT antibodies. In a much smaller percentage of patients, the onset of thrombocytopenia begins several days after heparin has been stopped. The diagnosis of HIT is confirmed by detecting HIT antibodies on serologic testing.

HIT is an intensely prothrombotic state. The thrombotic tendency in HIT is caused by immune-mediated platelet activation; exposure of tissue

factor on endothelial cells and monocytes might also contribute. The thrombotic manifestations include venous and arterial thrombosis.

When HIT is suspected, heparin should be discontinued, and if anticoagulant therapy is indicated, heparin should be replaced with an anticoagulant that does not cross-react with HIT antibodies. Currently, four anticoagulants are available that do not cross-react with HIT antibodies. Of these, two direct thrombin inhibitors, argatroban and lepirudin (hirudin), are approved for treatment of HIT in the United States. Two others, bivalirudin, a direct thrombin inhibitor, and fondaparinux, an antithrombin-dependent factor Xa inhibitor, are being used off-label to a limited extent. A fifth agent, danaparoid, which exhibits minimal cross-reactivity with HIT antibodies, was recently withdrawn from the US and UK markets but is approved for treatment and prevention of HIT-associated thrombosis in other countries.

Patients with HIT and complicating thrombosis should be treated with either lepirudin or argatroban. The optimal management of HIT without thrombosis remains uncertain. Many of these patients either have silent venous thrombosis or are at risk of developing venous thrombosis in the ensuing days. The use of vitamin K antagonists (without a thrombin inhibitor) to treat such patients should be avoided because it carries a risk of venous gangrene. If anticoagulation is indicated, a direct thrombin inhibitor should be used and continued until the platelet count has returned to normal levels, and the introduction of warfarin should be delayed until there has been substantial recovery of thrombocytopenia.

Platelet transfusions are not indicated for the prevention of bleeding in patients with acute HIT because bleeding is very uncommon in HIT, and it is possible that platelet transfusions could contribute to the risk of thrombotic events.

RECOMMENDATIONS

Recognition of HIT

Platelet Count Monitoring for HIT

1. *For patients receiving heparin in whom the risk of HIT is considered to be > 0.1%,* we recommend platelet count monitoring over no platelet count monitoring (**Grade 1C**).
2. *For patients who are starting unfractionated heparin (UFH) or LMWH treatment and who have received UFH within the past 100 days, or for those patients in whom the exposure history is uncertain,* we suggest obtaining a baseline platelet count and then a repeat platelet count within 24 hours of starting heparin (**Grade 2C**).

3. *For patients who develop acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 minutes following an intravenous UFH bolus,* we recommend performing an immediate platelet count measurement and comparing this value with recent prior platelet counts in comparison with not performing a platelet count measure (**Grade 1C**).
4. *For patients who are receiving therapeutic-dose UFH,* we suggest at least every-other-day platelet count monitoring until day 14 (or until UFH is stopped) (**Grade 2C**).
5. *For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk > 1%),* we suggest at least every-other-day platelet count monitoring between postoperative days 4 and 14 (or until UFH is stopped) (**Grade 2C**).
6. *For medical or obstetric patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH "flushes," or medical or obstetric patients receiving LMWH after first receiving UFH (HIT risk 0.1–1%),* we suggest platelet count monitoring every 2 or 3 days from day 4 to day 14 (or until heparin is stopped) when practical (**Grade 2C**).
7. *For medical or obstetric patients who are receiving only LMWH or medical patients who are receiving only intravascular catheter UFH "flushes" (HIT risk < 0.1%),* we suggest that clinicians do not use routine platelet count monitoring (**Grade 2C**).

Screening for Subclinical HIT Antibody Seroconversion

1. In patients who receive heparin, we recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other sequelae of HIT (**Grade 1C**).

When Should HIT Be Suspected?

1. *For patients receiving heparin or who have received heparin within the previous 2 weeks,* we recommend excluding a diagnosis of HIT if the platelet count falls by 50% or more and/or a thrombotic event occurs between days 4 and 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred (**Grade 1C**).

Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring Post–Cardiac Surgery

1. *For postoperative cardiac surgery patients,* we recommend excluding a diagnosis of HIT if the platelet count falls by 50% or more (and/or a thrombotic event occurs) between postoperative days 4 and 14 (day of cardiac surgery = day 0) (**Grade 1C**).

Treatment of HIT

Nonheparin Anticoagulants for HIT

1. *For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis,* we recommend use of an alternative, nonheparin anticoagulant, such as lepirudin (**Grade 1C+**), argatroban (**Grade 1C**), bivalirudin (**Grade 2C**), or danaparoid (**Grade 1B**), over further UFH or LMWH therapy and over no further anticoagulation (with or without a vena cava filter).
2. *For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb deep venous thrombosis (DVT),* we recommend routine ultrasonography of the lower-limb veins for investigation of DVT over not performing routine ultrasonography (**Grade 1C**).

Vitamin K Antagonists

Management of Vitamin K Antagonist Overlap

1. *For patients with strongly suspected or confirmed HIT,* we recommend against the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (eg, to at least 100×10^9/L and, preferably, 150×10^9/L); that the vitamin K antagonist be given only during overlapping alternative anticoagulation (minimum 5-day overlap) and begun with low maintenance doses (maximum 5 mg warfarin and 6 mg phenprocoumon); and that the alternative anticoagulant not be stopped until the platelet count has reached a stable plateau, with at least the last 2 days in the target therapeutic range (all **Grade 1C**).

Reversal of Vitamin K Antagonist Anticoagulation

1. *For patients receiving vitamin K antagonists at the time of diagnosis of HIT,* we recommend use of vitamin K (**Grade 2C**).

LMWH for HIT

1. *For patients with strongly suspected HIT, whether or not complicated by thrombosis,* we recommend against the use of LMWH (**Grade 1C+**).

Prophylactic Platelet Transfusions for HIT

1. *For patients with strongly suspected or confirmed HIT who do not have active bleeding,* we suggest that prophylactic platelet transfusions not be given (**Grade 2C**).

Special Patient Populations

Patients with Previous HIT Undergoing Cardiac or Vascular Surgery

1. *For patients with a history of HIT who are HIT antibody negative and require cardiac surgery,* we recommend the use of UFH over a nonheparin anticoagulant (**Grade 1C**).

Patients with Acute or Subacute HIT Undergoing Cardiac Surgery

1. *For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery,* we recommend one of the following alternative anticoagulant approaches (in descending order of preference): delaying surgery (if possible) until HIT antibodies are negative (**Grade 1C**); using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if the ecarin clotting time is available) (**Grade 1C**) or during "off-pump" cardiac surgery (**Grade 1C+**); using lepirudin for intraoperative anticoagulation (if the ecarin clotting time is available and the patient has normal renal function) (**Grade 1C**); using UFH plus the antiplatelet agent epoprostenol (if the ecarin clotting time monitoring is not available or renal insufficiency precludes lepirudin use) (**Grade 2C**); using UFH plus the antiplatelet agent tirofiban (**Grade 2C**); or using danaparoid for intraoperative anticoagulation (if anti–factor Xa levels are available) (**Grade 2C**).
2. *For patients with subacute HIT (platelet count recovery but continuing HIT antibody positive),* we recommend delaying surgery (if possible) until HIT antibodies are negative and then using heparin (**Grade 1C**). Alternatively, we suggest the use of a nonheparin anticoagulant (**Grade 2C**).

Percutaneous Coronary Interventions

1. *For patients with acute or previous HIT who require cardiac catheterization or percutaneous coronary intervention,* we recommend use of an alternative anticoagulant, such as argatroban (**Grade 1C**), bivalirudin (**Grade 1C**), lepirudin (**Grade 1C**), or danaparoid (**Grade 2C**), over the use of heparin.

Prevention of HIT

Reducing HIT Antibody Formation and Clinical HIT

UFH versus LMWH

1. *For postoperative orthopedic surgery patients,* we recommend the use of LMWH over UFH (**Grade 1A**).

Bovine versus Porcine UFH

1. *For the treatment of patients with thrombosis,* we recommend against the use of bovine UFH rather than porcine UFH or LMWH (**Grade 1A**).
2. *For patients undergoing cardiac surgery,* we recommend the use of porcine UFH for intraoperative anticoagulation rather than bovine UFH (**Grade 1B**).

7 PREVENTION OF VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is a major cause of morbidity and mortality among hospitalized patients. Pulmonary embolism (PE) has been estimated to cause death in over 100,000 patients each year in North America and to contribute to death in another 100,000 patients per year.

The important clinical risk factors include advanced age, prolonged immobility or paralysis, previous VTE, cancer, extensive surgery, orthopedic surgery of the lower limb leg, hip or pelvic fracture, major trauma, stroke, obesity, varicose veins, and heart failure. Many patients have multiple risk factors, and the risks are cumulative.

The first manifestation of the disease can be fatal PE. Therefore, a strategy of effective primary prophylaxis is preferred over clinical or noninvasive screening as an approach to prevent fatal PE in patients at risk.

There is persuasive evidence that primary thromboprophylaxis reduces deep venous thromboembolism, PE, and fatal PE. PE is the most common cause of preventable death in hospitalized patients. VTE can be prevented either by reducing venous stasis with external pneumatic compression, the venous foot pump, or graduated compression stockings (GCSs) or by counteracting increased blood coagulability with heparin, oral anticoagulants, low-molecular-weight heparins (LMWHs), fondaparinux, and other new anticoagulants.

GENERAL SURGERY

Patients undergoing general surgery, gynecologic surgery, vascular surgery, and laparoscopic surgery can be classified into various risk categories. For those at low risk, prophylaxis is limited to early mobilization. Active prophylaxis is indicated for all other risk categories. Low-dose heparin, external pneumatic compression, GCSs, LMWHs, oral anticoagulants, and fondaparinux have all been shown to be effective in various patient groups. Only low-dose heparin and LMWHs have been shown to reduce mortality in surgical patients; LMWHs used in contemporary dosages appear to be equivalent to or only slightly better than low-dose heparin, with slightly

less bleeding. GCSs have not been evaluated adequately in high-risk patients, but they appear to augment the effects of low-dose heparin.

ORTHOPEDIC SURGERY

For elective hip surgery patients, LMWHs, oral anticoagulants, and fondaparinux are most effective. Of these three methods, fondaparinux is more effective than LMWH, LMWH is more effective than warfarin or low-dose heparin, and warfarin is more effective than aspirin. For elective major knee surgery (total knee replacement) patients, LMWH is more effective than low-dose heparin or warfarin, and fondaparinux is more effective than LMWH, but at the cost of an increase in bleeding. For patients with hip fracture, fondaparinux is most effective, and warfarin is more effective than aspirin; data on LMWHs are sparse in hip fracture patients.

Contemporary studies have shown that patients undergoing elective hip surgery or surgery for hip fracture remain at substantial risk of postoperative thrombosis (detected by venography) despite the use of all present methods of prophylaxis for 7 to 10 days postoperatively. Although most of these thrombi are clinically silent, about one in seven are clinically symptomatic. The use of LMWH for up to 35 days postoperatively is effective in reducing the rate of these delayed thrombi in elective hip surgery, and the use of fondaparinux for 30 days is effective in reducing delayed thrombosis in hip fracture patients. Warfarin is also effective as extended prophylaxis in total hip replacement patients, but its use is associated with more bleeding than LMWH.

NEUROSURGERY

Both external pneumatic compression and LMWHs are effective in preventing thrombosis in neurosurgery patients. If available, the first approach is probably preferred because it does not carry an increased risk of bleeding. LMWH is more effective than low-dose heparin in reducing venous thrombosis in patients with stroke.

For patients with spinal cord injury, LMWH appears to be effective, whereas low-dose heparin, intermittent pneumatic compression (IPC), and GCSs provide inadequate protection.

MEDICAL CONDITIONS

Over 50% of symptomatic thromboembolic events and over 70% of fatal PEs occur in nonsurgical patients. Hospitalization for an acute medical illness is associated with about an eightfold increased relative risk of VTE.

Therefore, appropriate prophylaxis of medical inpatients is important. Both LMWH and low-dose heparin are effective methods of prophylaxis in medical patients.

RECOMMENDATIONS

General Issues

1. We recommend that mechanical methods of prophylaxis be used primarily *in patients at high risk of bleeding* (**Grade 1C+**) *or as an adjunct to anticoagulant-based prophylaxis* (**Grade 2A**). We recommend that careful attention be directed toward ensuring proper use of and optimal compliance with the mechanical device (**Grade 1C+**).
2. We recommend against the use of aspirin alone as prophylaxis against VTE for any patient group (**Grade 1A**).
3. For each of the antithrombotic agents, we recommend that clinicians consider the manufacturers' suggested dosing guidelines (**Grade 1C**).
4. We recommend *consideration of potential effects of renal impairment* when deciding on doses of LMWH, fondaparinux, the direct thrombin inhibitors, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients and those at high risk of bleeding (**Grade 1C+**).
5. *In all patients undergoing neuraxial anesthesia or analgesia,* we recommend special caution when using anticoagulant prophylaxis (**Grade 1C+**).

General Surgery

1. *In low-risk general surgery patients*, we recommend against the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).
2. *In moderate-risk general surgery patients*, we recommend prophylaxis with low-dose unfractionated heparin (LDUH) (5,000 U twice daily) or LMWH (< 3,400 U once daily) (both **Grade 1A**).
3. *In higher-risk general surgery patients,* we recommend thromboprophylaxis with LDUH (5,000 U three times daily) or LMWH (> 3,400 U daily) (both **Grade 1A**).
4. *In high-risk general surgery patients with multiple risk factors,* we recommend that pharmacologic methods (LDUH three times daily or LMWH > 3,400 U daily) be combined with GCSs and/or IPC (**Grade 1C+**).
5. *For general surgery patients with a high risk of bleeding,* we recommend the use of mechanical prophylaxis with properly fitted GCSs or IPC, at least initially until the risk of bleeding decreases (**Grade 1A**).

6. *For selected high-risk general surgery patients, including those who have undergone major cancer surgery,* we suggest postdischarge prophylaxis with LMWH (**Grade 2A**).

Vascular Surgery

1. *For patients who do not have additional thromboembolism risk factors,* we suggest that clinicians do not routinely use thromboprophylaxis (**Grade 2B**).
2. *For patients who have additional thromboembolic risk factors,* we recommend prophylaxis with LDUH or LMWH (**Grade 1C+**).

Gynecologic Surgery

1. *For patients undergoing brief procedures of 30 minutes or less for benign disease,* we recommend against the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).
2. *For patients undergoing laparoscopic gynecologic procedures, in whom additional VTE risk factors are present,* we recommend the use of thromboprophylaxis with one or more of LDUH, LMWH, IPC, or GCSs (all **Grade 1C**).
3. *For major gynecologic surgery patients,* we recommend that thromboprophylaxis be used (**Grade 1A**).
4. *For patients undergoing major gynecologic surgery for benign disease, without additional risk factors,* we recommend LDUH 5,000 U twice daily (**Grade 1A**). Alternatives include once-daily LMWH (< 3,400 U/d) (**Grade 1C+**) or IPC started just before surgery and used continuously while the patient is not ambulating (**Grade 1B**).
5. *For patients undergoing extensive surgery for malignancy and for patients with additional VTE risk factors,* we recommend routine prophylaxis with LDUH 5,000 U three times daily (**Grade 1A**) or higher doses of LMWH (> 3,400 U/d) (**Grade 1A**). Alternative considerations include IPC alone continued until discharge (**Grade 1A**) or a combination of LDUH or LMWH plus mechanical prophylaxis with GCSs or IPC (all **Grade 1C**).
6. *For patients undergoing major gynecologic procedures,* we suggest that prophylaxis continue until discharge from hospital (**Grade 1C**).
7. *For patients at particularly high risk, including those with cancer surgery and age greater than 60 years or previous VTE*, we suggest continuing prophylaxis for 2 to 4 weeks after discharge (**Grade 2C**).

Urologic Surgery

1. *For patients undergoing transurethral or other low-risk urologic procedures,* we recommend against the use of specific prophylaxis other than early and persistent mobilization (**Grade 1C+**).

2. *For patients undergoing major, open urologic procedures,* we recommend routine prophylaxis with twice-daily or three-times-daily LDUH (**Grade 1A**). Acceptable alternatives include IPC and/or GCSs (**Grade 1B**) or LMWH (**Grade 1C+**).
3. *For urologic surgery patients who are actively bleeding or at very high risk of bleeding,* we recommend the use of mechanical prophylaxis with GCSs and/or IPC at least until the risk of bleeding decreases (**Grade 1C+**).
4. *For patients with multiple risk factors,* we recommend combining GCSs and/or IPC with LDUH or LMWH (**Grade 1C+**).

Laparoscopic Surgery

1. *For patients without additional risk factors,* we recommend against routine thromboprophylaxis, other than aggressive mobilization (**Grade 1A**).
2. *For patients with additional thromboembolic risk factors,* we recommend the use of thromboprophylaxis with one or more of LDUH, LMWH, IPC, or GCSs (**Grade 1C+**).

Elective Hip Arthroplasty

1. *For patients undergoing elective total hip replacement,* we recommend the routine use of one of three anticoagulants: (a) LMWH (at a usual high-risk dose, started 12 hours before surgery or 12 to 24 hours after surgery or 4 to 6 hours after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (b) fondaparinux (2.5 mg started 6 to 8 hours after surgery); or (c) adjusted-dose vitamin K antagonist (target international normalized ratio [INR] 2.5, range 2.0–3.0; started preoperatively or the evening after surgery) (all **Grade 1A**). We recommended against the use of aspirin, dextran, LDUH, GCSs, IPC, or venous foot pump as the only method of thromboprophylaxis in these patients (**Grade 1A**).

Elective Knee Arthroplasty

1. We recommend routine thromboprophylaxis using either LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose vitamin K antagonist (target INR 2.5, range 2.0–3.0) (all **Grade 1A**).
2. We recommend optimal use of IPC as an alternative option to anticoagulant prophylaxis (**Grade 1B**).
3. We recommend against the use of any of the following as sole methods of thromboprophylaxis: aspirin (**Grade 1A**), LDUH (**Grade 1A**), or venous foot pump (**Grade 1B**).

Knee Arthroscopy

1. We suggest that routine thromboprophylaxis not be used in these patients, other than early mobilization (**Grade 2B**).

2. *For patients undergoing arthroscopic knee surgery and who are at higher than usual risk, based on preexisting VTE risk factors or following a prolonged or complicated procedure*, we suggest thromboprophylaxis with LMWH (**Grade 2B**).

Hip Fracture Surgery

1. We recommend the routine use of fondaparinux (**Grade 1A**), LMWH at the usual high-risk dose (**Grade 1C+**).
2. We suggest an adjusted-dose vitamin K antagonist with a target INR of 2.5 and a range of 2.0 to 3.0 (**Grade 2B**) or LDUH (**Grade 1B**).
3. We recommend against the use of aspirin alone (**Grade 1A**).
4. If surgery will likely be delayed, we recommend that prophylaxis with either LDUH or LMWH be initiated during the time between admission and surgery (**Grade 1C+**).
4. We recommend mechanical prophylaxis if anticoagulant prophylaxis is contraindicated because of a high risk of bleeding (**Grade 1C+**).

Other Prophylaxis Issues in Major Orthopedic Surgery

1. We recommend *that a decision about the timing of initiation of pharmacologic prophylaxis be based on the efficacy-to-bleeding trade-offs for that particular agent* (**Grade 1A**). For LMWH, either a preoperative or a postoperative start is acceptable (**Grade 1A**).
2. We recommend *against the routine use of duplex ultrasonography screening at the time of hospital discharge in asymptomatic patients following major orthopedic surgery* (**Grade 1A**).
3. We recommend that patients *undergoing total hip replacement, total knee arthroplasty, or hip fracture surgery* receive thromboprophylaxis with LMWH (using a high-risk dose), fondaparinux (2.5 mg daily), or a vitamin K antagonist (target INR 2.5, range 2.0–3.0) for at least 10 days (**Grade 1A**).
4. We recommend that patients undergoing *total hip replacement or hip fracture surgery* be given extended prophylaxis for up to 28 to 35 days after surgery (**Grade 1A**). The recommended options for total hip replacement include LMWH (**Grade 1A**), a vitamin K antagonist (**Grade 1A**), or fondaparinux (**Grade 1C+**). The recommended options following hip fracture surgery are fondaparinux (**Grade 1A**), LMWH (**Grade 1C+**), or a vitamin K antagonist (**Grade 1C+**).

Elective Spine Surgery

1. *For patients with no additional risk factors,* we recommend against the routine use of any thromboprophylaxis modality, apart from early and persistent mobilization (**Grade 1C**).

2. We recommend that some form of prophylaxis be used *in patients undergoing spinal surgery and who exhibit additional risk factors, such as advanced age, known malignancy, the presence of a neurologic deficit, previous VTE, or an anterior surgical approach* (**Grade 1B**).
3. *For patients with additional risk factors,* we recommend any of the following prophylaxis options: postoperative LDUH alone (**Grade 1C+**), postoperative LMWH alone (**Grade 1B**), or perioperative IPC alone (**Grade 1B**); we suggest perioperative GCSs alone (**Grade 2B**) or perioperative IPC combined with GCSs (**Grade 2C**). *In patients with multiple risk factors for VTE,* we recommend combining LDUH or LMWH with GCSs and/or IPC (**Grade 1C+**).

Isolated Lower Extremity Injuries

1. We suggest that clinicians not use thromboprophylaxis routinely in patients with isolated lower extremity injuries (**Grade 2A**).

Neurosurgery

1. We recommend that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (**Grade 1A**).
2. We recommend the use of IPC plus or minus GCSs in patients undergoing intracranial neurosurgery (**Grade 1A**).
3. We suggest as acceptable alternatives to the above LDUH (**Grade 2B**) or postoperative LMWH (**Grade 2A**).
4. *For high-risk neurosurgery patients,* we suggest the combination of mechanical (ie, GCSs and/or IPC) and pharmacologic (ie, LDUH or LMWH) prophylaxis.

Trauma

1. We recommend that all trauma patients *with at least one risk factor for VTE* receive thromboprophylaxis if possible (**Grade 1A**).
2. In the absence of a major contraindication, we recommend LMWH, to be started as soon as it is considered safe to do so (**Grade 1A**).
3. We recommend that mechanical prophylaxis with IPC or GCSs be used if LMWH prophylaxis is delayed or is currently contraindicated owing to active bleeding or a high risk of hemorrhage (**Grade 1B**).
4. We recommend duplex ultrasonography screening in patients *at high risk of VTE (eg, presence of a spinal cord injury, lower extremity or pelvic fracture, major head injury, or an indwelling femoral venous line) who have received suboptimal or no prophylaxis* (**Grade 1C**).
5. We recommend against inferior vena cava filters as primary prophylaxis in trauma patients (**Grade 1C**).
6. We recommend continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (**Grade 1C+**).

7. We suggest continuing prophylaxis after hospital discharge with LMWH or a vitamin K antagonist (target INR 2.5, range 2.0–3.0) in patients with major impaired mobility (**Grade 2C**).

Acute Spinal Cord Injury

1. We recommend that thromboprophylaxis be provided for all patients with acute spinal cord injuries (**Grade 1A**).
2. We recommend against the use of LDUH, GCSs, or IPC as single-prophylaxis modalities (**Grade 1A**).
3. We recommend prophylaxis with LMWH, to be commenced once primary hemostasis is evident (**Grade 1B**).
4. We suggest the combined use of IPC and either LDUH (**Grade 2B**) or LWMH (**Grade 2C**) as alternatives to LMWH.
5. We recommend IPC and/or GCSs when anticoagulant prophylaxis is contraindicated early after injury (**Grade 1C+**).
6. We recommend against the use of an inferior vena cava filter as primary prophylaxis against PE (**Grade 1C**).
7. During the rehabilitation phase following acute spinal cord injury, we recommend the continuation of LMWH prophylaxis or conversion to an oral vitamin K antagonist (INR target 2.5, range 2.0–3.0) (**Grade 1C**).

Burns

1. We recommend thromboprophylaxis, if possible, *for burn patients with additional risk factors for VTE, including one or more of the following: advanced age, morbid obesity, extensive or lower extremity burns, concomitant lower extremity trauma, use of central venous catheters, and/or prolonged immobility* (**Grade 1C+**).
2. *If there are no contraindications,* we recommend the use of either LDUH or LMWH, starting as soon as it is considered safe to do so (**Grade 1C+**).

Medical Conditions

1. *For high-risk acutely ill medical patients,* we recommend prophylaxis with LDUH (**Grade 1A**) or LMWH (**Grade 1A**).
2. *For patients at high risk and with contraindication to anticoagulant prophylaxis,* we recommend the use of mechanical prophylaxis with GCSs or IPC (**Grade 1C+**).

Cancer Patients

1. We recommend that cancer patients *undergoing surgical procedures* receive prophylaxis that is appropriate for their current risk state (**Grade 1A**). Refer to the recommendations in the relevant surgical subsections.
2. We recommend that hospitalized *cancer patients who are bedridden with an acute medical illness* receive prophylaxis that is appropriate for their cur-

rent risk state (**Grade 1A**). Refer to the recommendations in the section dealing with medical patients.
3. *For cancer patients with long-term indwelling central venous catheters,* we suggest that clinicians not routinely use prophylaxis to prevent catheter-related thrombosis (**Grade 2B**).

Critical Care

1. We recommend that, on admission to critical care, all patients be assessed for their risk of VTE. Accordingly, most should receive thromboprophylaxis (**Grade 1A**).
2. *For patients at high risk of bleeding,* we recommend mechanical prophylaxis with GCSs and/or IPC until the risk of bleeding decreases (**Grade 1C+**).
3. *For intensive care unit patients at moderate risk of VTE*, we recommend using LDUH or LMWH (**Grade 1A**).
4. *For high-risk intensive care unit patients,* we recommend LMWH (**Grade 1A**).

Long-Distance Travel

1. We recommend the following general measures for long-distance travelers (flights longer than 6 hours): avoiding constrictive clothing around the lower extremities or waist, avoiding dehydration, and frequent calf muscle stretching (**Grade 1C**).
2. For long-distance travelers with other risk factors for VTE, we recommend the general strategies listed above. If active prophylaxis is considered because of perceived increased risk of venous thrombosis, we suggest preflight, properly fitted, below-knee GCSs providing 15 to 30 mm Hg of pressure at the ankle (**Grade 2B**) or a single prophylactic dose of LMWH injected prior to departure (**Grade 2B**).
3. We recommend against the use of aspirin for VTE prevention associated with travel (**Grade 1B**).

8 TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE

ANTICOAGULANTS

Patients with venous thromboembolism (VTE) have a high risk of recurrence if untreated or if treated with subtherapeutic doses of anticoagulants. On the other hand, the risk of recurrence is low if anticoagulants are started promptly and in appropriate dosages. The objectives of anticoagu-

lant therapy are to prevent thrombus extension, early and late recurrences, and pulmonary embolism (PE).

Patients with VTE should be treated with anticoagulants as soon as the diagnosis is confirmed by objective testing. If the clinical suspicion is high and there is a delay before the diagnosis can be confirmed by objective tests, then treatment should be commenced while awaiting confirmation. Treatment should be continued only if the diagnosis is confirmed by reliable diagnostic tests. Three options are available for the initial treatment of deep venous thrombosis (DVT): (1) body weight–adjusted low-molecular-weight heparin (LMWH) given subcutaneously without monitoring, (2) intravenous unfractionated heparin (UFH), or (3) subcutaneous UFH given with monitoring and subsequent dose adjustments.

Of these three options, LMWH (using the recommended and approved therapeutric weight–adjusted doses) is preferred because of the lack of need for anticoagulant monitoring, the benefits of convenient dosing, and the option of out-of-hospital treatment. Treatment with either LMWH or heparin should be continued for a minimum of 5 days.

If LMWH is used, it should be administered in a dose of either 100 anti–factor Xa U/kg twice daily or 150 to 200 anti–factor Xa U daily (depending on the manufacturer's dosing instructions). If heparin is used, it should be given either as a bolus dose of 5,000 U, followed by a continuous infusion of at least 30,000 U for the first 24 hours or as a weight-adjusted regimen of 80 U/kg bolus followed by 18 U/kg/h. Subsequent doses should be adjusted using a standard or weight-based nomogram to rapidly reach and maintain an activated partial thromboplastin time (APTT) at levels corresponding to therapeutic heparin levels. Alternatively, heparin can be given by subcutaneous injection in a dose of 17,500 U 12 hourly. The anticoagulant effect of heparin should be monitored by the APTT. Because APTT reagents vary in their responsiveness to heparin, it is inappropriate to use a lower limit of the therapeutic range for the APTT of 1.5 times control. Instead, the heparin dose should be adjusted to correspond to a heparin level (ex vivo) of 0.2 to 0.4 U/mL by protamine titration or to an anti–factor Xa level of 0.3 to 0.7 U/mL. Warfarin can be commenced on the first day, overlapped with LMWH or heparin for a minimum of 5 days, and continued for 3 months or longer. LMWH or heparin should be continued until the international normalized ratio (INR) is stable at 2.0 or higher. For patients with major PE or extensive iliofemoral vein thrombosis, heparin should be administered for longer than 5 days.

The optimal duration for anticoagulant therapy with warfarin is influenced by the risk of recurrence if anticoagulants are stopped and the risk of bleeding during anticoagulant therapy. The risk of recurrence when anticoagulants are discontinued is influenced by the nature of the VTE

episode, based on the following categories: (1) first-episode VTE secondary to a transient risk factor, (2) first-episode VTE and concurrent cancer, (3) first episode of idiopathic VTE, and (4) first episode of VTE associated with a prothrombotic genotype or a prognostic marker for an increased risk of recurrent thromboembolism.

Patients with a first episode of DVT (both proximal vein and calf vein) secondary to a transient (reversible) risk factor should be treated for at least 3 months. If there are problems with continuing treatment, it is reasonable to consider discontinuing anticoagulant treatment after 6 weeks in patients with isolated calf vein thrombosis.

Patients with a first episode of idiopathic DVT should be treated for at least 6 to 12 months. The rates of recurrence when anticoagulants are discontinued are similar after treatment for 6, 12, or 24 months of anticoagulant therapy and are between 7 and 10%. Therefore, indefinite anticoagulant therapy is reasonable in patients with a low risk of bleeding and good compliance if they prefer to remain on anticoagulants. Patients with a first episode of DVT who have documented antiphospholipid antibodies or who have one or more inherited thrombophilic defects or two or more episodes of objectively documented idiopathic VTE should also be considered for indefinite anticoagulant therapy.

Patients with DVT and cancer should be treated with LMWH for at least the first 3 to 6 months of long-term treatment. Treatment with vitamin K antagonists (VKAs) should then be continued indefinitely.

THROMBOLYTIC THERAPY

The indications for thrombolytic therapy are not entirely clear. Thrombolytic therapy should be considered for patients with recent-onset (3 days or less) proximal vein thrombosis who are relatively young and those with major PE and hemodynamic instability, provided that there are no contraindications.

INFERIOR VENA CAVA PROCEDURES

The major indications for placement of an inferior vena cava filter are contraindications to or complications of anticoagulation in patients with proximal vein thrombosis. Less common indications are recurrent thromboembolism despite adequate anticoagulation, chronic recurrent embolism with pulmonary hypertension, surgical pulmonary embolectomy, or pulmonary endarterectomy.

Resumption of anticoagulation is recommended as soon as possible after insertion of a filter.

PULMONARY EMBOLECTOMY

Pulmonary embolectomy can be lifesaving in patients with acute massive PE with hemodynamic instability despite heparin or thrombolytic therapy. Pulmonary thromboendarterectomy is also indicated in selected patients with chronic thromboembolic pulmonary hypertension.

RECOMMENDATIONS

Treatment of DVT

Initial Treatment of Acute DVT

1. For patients with objectively confirmed DVT, we recommend acute treatment with subcutaneous LMWH or intravenous or subcutaneous UFH (all **Grade 1A**).
2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).
3. We recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).
4. We recommend initiation of a VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and above 2.0 (**Grade 1A**).

Intravenous UFH for Initial Treatment of DVT

1. *If intravenous UFH is chosen,* we recommend administration by continuous infusion with dose adjustment to achieve and maintain an APTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti–factor Xa activity by the amidolytic assay (**Grade 1C+**).
2. *In patients requiring large daily doses of UFH without achieving a therapeutic APTT,* we recommend the measurement of the anti–factor Xa level for dose guidance (**Grade 1B**).

Subcutaneous UFH for Initial Treatment of DVT

1. We recommend that UFH administered subcutaneously can be used as an adequate alternative to intravenous UFH (**Grade 1A**).
2. We recommend an initial dose of 35,000 U/24 h subcutaneously, with subsequent dosing to maintain the APTT in the therapeutic range (**Grade 1C+**).

LMWH for Initial Treatment of DVT

1. We recommend initial treatment with LMWH subcutaneously once or twice a day over UFH as an outpatient if possible (**Grade 1C**) and

as an inpatient if outpatient treatment is not possible or feasible (**Grade 1A**).
2. We recommend against routine monitoring with anti–factor Xa level measurements (**Grade 1A**).
3. In patients with severe renal failure, we suggest intravenous UFH over LMWH (**Grade 2C**).

Systemically Administered Thrombolysis in Initial Treatment of DVT

1. In patients with DVT, we recommend against the routine use of intravenous thrombolytic treatment (**Grade 1A**).
2. *In selected patients such as those with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion,* we suggest intravenous thrombolytic treatment (**Grade 2C**).

Catheter-Directed Thrombolysis in Initial Treatment of DVT

1. In patients with DVT, we recommend against the routine use of catheter-directed thrombolysis (**Grade 1C**).
2. We suggest that this treatment be confined to selected patients, such as those requiring limb salvage (**Grade 2C**).

Catheter Extraction or Fragmentation and Surgical Thrombectomy for Initial Treatment of DVT

1. In patients with DVT, we recommend against the routine use of venous thrombectomy (**Grade 1C**).
2. In selected patients, such as patients with massive ileofemoral DVT at risk of limb gangrene secondary to venous occlusion, we suggest venous thrombectomy (**Grade 2C**).

Vena Cava Interruption for Initial Treatment of DVT

1. For most patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (**Grade 1A**).
2. We suggest the placement of an inferior vena cava filter in patients with a contraindication for or a complication of anticoagulant treatment (**Grade 2C**), as well as in those with recurrent thromboembolism despite adequate anticoagulation (**Grade 2C**).

Nonsteroidal Anti-inflammatory Agents for Initial Treatment of DVT

1. We recommend against the use of nonsteroidal anti-inflammatory agents (**Grade 2B**).

Immobilization

1. For patients with DVT, we recommend ambulation as tolerated (**Grade 1B**).

Long-Term Treatment of Acute DVT of the Leg

Vitamin K Antagonists

1. For patients with a *first episode of DVT secondary to a transient (reversible) risk factor,* we recommend long-term treatment with a VKA for 3 months over treatment for shorter periods (**Grade 1A**).
2. For patients with a first episode of idiopathic DVT, we recommend treatment with a VKA for at least 6 to 12 months (**Grade 1A**).
3. We suggest that patients with first-episode idiopathic DVT be considered for indefinite anticoagulant therapy (**Grade 2A**).
4. For patients *with DVT and cancer,* we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (**Grade 1A**). For these patients, we recommend anticoagulant therapy indefinitely or until the cancer is resolved (**Grade 1C**).
5. For patients *with a first episode of DVT who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations),* we recommend treatment for 12 months (**Grade 1C+**). We suggest indefinite anticoagulant therapy in these patients (**Grade 2C**).
6. For patients *with a first episode of DVT who have documented deficiency of antithrombin, deficiency of protein C or protein S, the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal),* we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy, as for patients with unprovoked thrombosis (**Grade 2C**).
7. For patients *with two or more episodes of objectively documented DVT*, we suggest indefinite treatment (**Grade 2A**).
8. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range 2.0–3.0) for all treatment durations (**Grade 1A**). We recommend against high-intensity VKA therapy (INR range 3.1–4.0) (**Grade 1A**). We recommend against low-intensity therapy (INR range 1.5–1.9) compared with an INR range of 2.0 to 3.0 (**Grade 1A**).
9. In patients *who receive indefinite anticoagulant treatment,* we recommend that the risk and benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (**Grade 1C**).
10. We suggest repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of a plasma D-dimer as a guide to selecting the duration of treatment (**Grade 2C**).

LMWH for Long-Term Treatment of DVT in Cancer Patients

1. For most patients *with DVT and cancer,* we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**).

Post-Thrombotic Syndrome

Elastic Stockings for Prevention

1. We recommend the use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle for 2 years after an episode of DVT (**Grade 1A**).

Physical Treatment

1. We suggest a course of intermittent pneumatic compression for patients with severe edema of the leg owing to the syndrome (**Grade 2B**).
2. We suggest the use of elastic compression stockings for patients with leg edema owing to the syndrome (**Grade 2C**).

Drug Treatment

1. In patients *with mild edema owing to the syndrome*, we suggest administration of rutosides (**Grade 2B**).

Initial Treatment of Acute PE

Intravenous UFH or LMWH

1. For patients with objectively confirmed *nonmassive PE*, we recommend acute treatment with subcutaneous LMWH or intravenous UFH (both **Grade 1A**).
2. For patients with *a high clinical suspicion of PE,* we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).
3. In patients *with acute nonmassive PE*, we recommend LMWH over UFH (**Grade 1A**).
4. In patients *with acute nonmassive PE*, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).
5. In patients *with acute nonmassive PE treated with LMWH*, we recommend against routine monitoring with anti–factor Xa levels (**Grade 1A**).
6. In patients *with severe renal failure,* we suggest intravenous UFH over LMWH (**Grade 2C**).

7. If intravenous UFH is chosen, we recommend administration by continuous infusion with dose adjustment to achieve and maintain an APTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti–factor Xa activity by the amidolytic assay (**Grade 1C+**).
8. In patients *requiring large daily doses of UFH without achieving a therapeutic APTT,* we recommend the measurement of the anti–factor Xa level for dose guidance (**Grade 1B**).
9. We recommend initiation of a VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and above 2.0 (**Grade 1A**).

Systemically and Locally Administered Thrombolytic Drugs

1. For *most patients with PE,* we recommend that clinicians do not use systemic thrombolytic therapy (**Grade 1A**). In *selected patients,* we suggest systemic administration of thrombolytic therapy (**Grade 2B**). For patients *who are hemodynamically unstable,* we suggest the use of thrombolytic therapy (**Grade 2B**).
2. We suggest that clinicians do not use local administration of thrombolytic therapy via a catheter (**Grade 1C**).
3. For patients with PE who receive thrombolytic regimens, we suggest use of thrombolytic regimens with a short infusion time over those with prolonged infusion times (**Grade 2C**).

Catheter Extraction or Fragmentation

1. For *most patients with PE,* we recommend against use of mechanical approaches (**Grade 1C**). *In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy patients,* we suggest use of mechanical approaches (**Grade 2C**).

Pulmonary Embolectomy

1. For most patients with PE, we recommend against pulmonary embolectomy (**Grade 1C**). In *selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy,* we suggest that pulmonary embolectomy should be considered (**Grade 2C**).

Vena Cava Interruption

1. In PE *patients with a contraindication for or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate*

anticoagulation, we suggest that clinicians consider the placement of an inferior vena cava filter (both **Grade 2C**).

Long-Term Treatment of Acute PE

Vitamin K Antagonists

1. For patients *with a first episode of PE secondary to a transient (reversible) risk factor,* we recommend long-term treatment with a VKA for at least 3 months (**Grade 1A**).
2. For patients with a first episode of idiopathic PE, we recommend treatment with a VKA for at least 6 to 12 months (**Grade 1A**).
3. We suggest that patients *with first-episode idiopathic PE* be considered for indefinite anticoagulant therapy (**Grade 2A**).
4. For patients *with PE and cancer*, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (**Grade 1A**). These patients should then receive anticoagulant therapy indefinitely or until the cancer is resolved (**Grade 1C**).
5. For patients *with a first episode of PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations),* we recommend treatment for 12 months (**Grade 1C+**). For these patients, we suggest indefinite anticoagulant therapy (**Grade 2C**).
6. For patients with *a first episode of PE who have documented deficiency of antithrombin, deficiency of protein C or protein S, the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (> 90th percentile of normal),* we recommend treatment for 6 to 12 months (**Grade 1A**). We suggest indefinite therapy, as for patients with idiopathic PE (**Grade 2C**)
7. For patients *with two or more episodes of objectively documented PE,* we suggest indefinite treatment (**Grade 2A**).
8. We recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (range 2.0–3.0) for all treatment durations (**Grade 1A**). We recommend against high-intensity VKA therapy (INR range 3.1–4.0) (**Grade 1A**). We recommend against low-intensity therapy (INR range 1.5–1.9 compared with 2.0–3.0) (**Grade 1A**).
9. In patients *who receive indefinite anticoagulant treatment,* we recommend that the risk and benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (**Grade 1C**).

Low-Molecular-Weight Heparin

1. *For most patients with PE and concurrent cancer*, we recommend treatment with LMWH for at least the first 3 to 6 months of long-term treatment (**Grade 1A**).

Chronic Thromboembolic Pulmonary Hypertension

Pulmonary Thromboendarterectomy, VKAs, and Vena Cava Filter

1. *In selected patients with chronic thromboembolic pulmonary hypertension (CTPH), that is, patients with central disease under the care of an experienced surgical or medical team,* we recommend pulmonary thromboendarterectomy (**Grade 1C**).
2. We recommend that lifelong treatment with a VKA to an INR of 2.0 to 3.0 be administered following pulmonary thromboendarterectomy and also be administered to patients with CTPH who are ineligible for pulmonary thromboendarterectomy (**Grade 1C**).
3. We suggest the placement of a vena cava filter before or at the time of pulmonary thromboendarterectomy for CTPH (**Grade 2C**).

Treatment of Superficial Thrombophlebitis

1. For patients with superficial thrombophlebitis as a complication of an infusion, we suggest topical diclofenac gel (**Grade 1B**) or oral diclofenac (**Grade 2B**).
2. For patients with spontaneous superficial thrombophlebitis, we suggest intermediate dosages of UFH or LMWH for at least 4 weeks (**Grade 2B**).

Acute Upper Extremity DVT

Intravenous UFH or LMWH for Initial Treatment

1. For patients with acute upper extremity DVT, we recommend initial treatment with UFH (**Grade 1C+**) or LMWH (**Grade 1C+**).

Thrombolytic Therapy for Initial Treatment

1. In selected patients with acute upper extremity DVT, for example, in those with a low risk of bleeding and symptoms of recent onset, we suggest a short course of thrombolytic therapy (**Grade 2C**).

Catheter Extraction, Surgical Thrombectomy, or Superior Vena Cava Filter for Initial Treatment

1. In selected patients with acute upper extremity DVT, for example, those with failure of anticoagulant or thrombolytic treatment and persistent symptoms, we suggest surgical embolectomy (**Grade 2C**) or catheter extraction (**Grade 2C**).
2. In selected patients with acute upper extremity DVT, for example, those in whom anticoagulant treatment is contraindicated, a superior vena cava filter (**Grade 2C**) could be considered for initial treatment.

Anticoagulants for Long-Term Treatment

1. For patients with acute upper extremity DVT, we recommend long-term treatment with a VKA (**Grade 1C+**).

Elastic Bandages for Long-Term Treatment

1. In patients with upper extremity DVT who have persistent edema and pain, we suggest elastic bandages for symptomatic relief (**Grade 2C**).

9 ATRIAL FIBRILLATION

Atrial fibrillation (AF) is an important independent risk factor for stroke. It is present in about 2.5 million people in the United States. AF is uncommon among individuals younger than age 50 years, and its prevalence rises rapidly after age 65, to about 10% in people over age 80. The median age of patients with AF is 72 years.

The overall incidence of stroke in AF is about 5% per year. Subgroup analysis of contemporary clinical trials has identified the following risk factors for stroke in patients with AF: prior transient ischemic attack, systemic embolus, or stroke; a history of hypertension; poor left ventricular function; age > 75 years; rheumatic mitral valve disease; and prosthetic heart valves (Table 9-1). In these patient groups, the risk of stroke in AF is high in the absence of antithrombotic therapy, and anticoagulant therapy is usually indicated. Other more moderate risk factors are age 65 to75 years, diabetes mellitus, and coronary artery disease.

Table 9-1 Risk Factors for Embolic Events in Atrial Fibrillation

High-Risk Factors	Moderate-Risk Factors
Prior transient ischemic attack	Age 65–75 yr
Systemic embolus or stroke	Diabetes mellitus
History of hypertension	Coronary artery disease
Poor left ventricular function	
Age > 75 yr	
Rheumatic mitral valve disease	
Prosthetic heart valve	

EFFICACY AND SAFETY OF THERAPY

The efficacy and safety of adjusted-dose warfarin have been compared with a variety of different treatment regimens. The results are summarized below.

Oral Anticoagulation versus Control

Five randomized primary prevention controlled trials compared subjects receiving oral anticoagulation treatment with untreated control subjects. The annual stroke rate was 4.5% for the control patients and 1.4% for the adjusted-dose warfarin patients (risk reduction 68%). There was no significant increase in major bleeding events in patients treated with adjusted-dose warfarin. Anticoagulation lowered the death rate by 33% and lowered the combined outcome of stroke, systemic embolism, or death by 48%.

Aspirin versus Placebo or Control

The evidence supporting aspirin's efficacy is much weaker than the evidence supporting warfarin. Five studies compared aspirin with a control. There was a risk reduction of 21% with aspirin, with wide confidence intervals.

Adjusted-Dose Anticoagulation versus Aspirin

Six studies have compared vitamin K antagonists with aspirin. Vitamin K antagonist therapy is more effective than aspirin, with a reported reduction of 46% (95% CI 29–57%). Major hemorrhage was increased 1.7-fold with vitamin K antagonists. On balance, treating 1,000 patients with AF for 1 year with adjusted-dose oral anticoagulants rather than aspirin would avoid 23 ischemic strokes while causing 9 additional major bleeds.

Oral Anticoagulation versus Low-Dose Oral Anticoagulation and Aspirin

Two studies compared adjusted-dose oral anticoagulation with the combination of low-dose oral anticoagulation and aspirin. The low-intensity anticoagulation-aspirin combination was found to be much less effective than adjusted-dose oral anticoagulation.

Oral Anticoagulation versus Low-Dose Anticoagulation

Three studies have compared adjusted-dose anticoagulation with lower doses of oral anticoagulation. There was a risk reduction of 38% in favor of adjusted-dose oral anticoagulation.

Oral Anticoagulation versus Other Nonaspirin Antiplatelet Agents

Adjusted-dose warfarin has been compared with indobufen. There was no significant difference in the incidence of primary events (stroke, myocardial infarction, pulmonary embolism, or vascular death) between the two groups (12% in the indobufen group vs 10% in the warfarin group; $p = .47$).

Summary

Based on the results of these studies, anticoagulants are considered to be indicated in the patients with AF and the presence of either a major risk factor or more than one moderate risk factor. The decision whether to use anticoagulants or aspirin is optional when only one moderate risk factor is present. Although low-risk patients should be treated with aspirin, the risk of stroke is only about 1% per year in patients without risk factors. Aspirin is also indicated in patients at risk of stroke when warfarin is contraindicated.

OTHER CONDITIONS

Paroxysmal Atrial Fibrillation

Paroxysmal atrial fibrillation (PAF) appears to be associated with a risk of stroke similar to that of constant AF. Patients with PAF tend to be younger and have a lower incidence of associated cardiovascular disorders than those with constant AF; therefore, their absolute stroke rate is lower. The relative risk reduction provided by warfarin appears to be similar for patients with both PAF and constant AF.

Atrial Flutter

The risk of stroke in patients with atrial flutter may be higher than previously assumed. Although it has not been evaluated in patients with atrial flutter, antithrombotic therapy should be considered in these patients for stroke prevention.

Thyrotoxicosis

The risk of systemic embolism in patients with thyrotoxicosis and AF is similar to that in euthyroid patients with AF. The indications for antithrombotic therapy are therefore dictated by the presence or absence of other risk factors.

Cardioversion

The risk of systemic embolism is increased during electrical cardioversion and can be reduced by the use of prophylactic warfarin administered before and after cardioversion.

RECOMMENDATIONS

Long-Term Antithrombotic Therapy

Chronic AF

1. *In patients with persistent or paroxysmal or intermittent AF at high risk of stroke (ie, having any of the following features: prior ischemic stroke, transient*

ischemic attack, or systemic embolism; age > 75 years old; moderately or severely impaired left ventricular systolic function and/or congestive heart failure; a history of hypertension; or diabetes mellitus), we recommend anticoagulation with an oral vitamin K antagonist (target international normalized ratio [INR] 2.5, range 2.0–3.0) (**Grade 1A**).

2. *In patients with persistent or paroxysmal AF, age 65 to 75 years (intermediate risk of stroke), in the absence of other risk factors,* we recommend antithrombotic therapy with either a vitamin K antagonist (target INR 2.5, range 2.0–3.0) or aspirin, 325 mg/d (**Grade 1A**).
3. *In patients with persistent or paroxysmal AF under age 65 years and with no other risk factors,* we recommend aspirin at 325 mg/d (**Grade 1B**).

Atrial Flutter

1. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (**Grade 2C**).

Valvular Heart Disease and AF

1. *For patients with AF and mitral stenosis,* we recommend anticoagulation with an oral vitamin K antagonist (target INR 2.5, range 2.0–3.0) (**Grade 1C+**).
2. *For patients with AF and prosthetic heart valves,* we recommend anticoagulation with an oral vitamin K antagonist (target intensity of anticoagulation INR 3.0, range 2.5–3.5) (**Grade 1C+**).

AF following Cardiac Surgery

1. *For AF occurring shortly after open heart surgery and lasting more than 48 hours,* we suggest anticoagulation with an oral vitamin K antagonist if bleeding risks are acceptable. The target INR is 2.5 (range 2.0–3.0) (**Grade 2C**).
2. We suggest continuing anticoagulation for several weeks following reversion to sinus rhythm, particularly if patients have risk factors for thromboembolism (**Grade 2C**).

Elective Cardioversion in AF and Atrial Flutter

1. *For patients with AF of > 48 hours or of unknown duration for whom pharmacologic or electrical cardioversion is planned,* we recommend anticoagulation with an oral vitamin K antagonist (target INR 2.5, range 2.0–3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after successful cardioversion (**Grade 1C+**).
2. *For patients with AF of > 48 hours or of unknown duration undergoing pharmacologic or electrical cardioversio*n, we also recommend anticoagulation (immediate unfractionated intravenous heparin with a target partial

thromboplastin time [PTT] of 60 seconds, range 50–70 seconds, or at least 5 days of warfarin with a target INR of 2.5, range 2.0–3.0, at the time of cardioversion) and the performance of screening multiplane transesophageal echocardiography (TEE). *If no thrombus is seen and cardioversion is successful,* we recommend anticoagulation (target INR 2.5, range 2.0–3.0) for at least 4 weeks. *If a thrombus is seen on TEE, then* we recommend that cardioversion be postponed and anticoagulation be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (all **Grade 1B**).

3. *For patients with AF of known duration < 48 hours*, we suggest that cardioversion be performed without anticoagulation (**Grade 2C**). However, in patients without contraindications to anticoagulation, we suggest beginning intravenous heparin (target PTT of 60 seconds, range 50–70 seconds) or LMWH (at full deep venous thrombosis treatment doses) at presentation (**Grade 2C**).
4. *For emergency cardioversion in which a TEE-guided approach is not possible,* we suggest that intravenous unfractionated heparin (target PTT of 60 seconds with a target range of 50–70 seconds) be started as soon as possible, followed by 4 weeks of anticoagulation with an oral vitamin K antagonist, such as warfarin (target INR 2.5, range 2.0–3.0), if normal sinus rhythm persists after cardioversion (**Grade 2C**).
5. *For cardioversion of patients with atrial flutter,* we suggest use of anticoagulants in the same way as for cardioversion of patients with AF (**Grade 2C**).

10 VALVULAR HEART DISEASE

RHEUMATIC MITRAL VALVE DISEASE (MITRAL STENOSIS AND/OR MITRAL REGURGITATION)

The risk of systemic embolism is greater in rheumatic mitral valve disease than in any other common form of valvular heart disease. It has been estimated that patients with rheumatic mitral valve disease have about a 20% lifetime risk of developing systemic embolism. The incidence of systemic emboli increases dramatically with the development of atrial fibrillation (AF). The risk of thromboembolism also increases with age. There is, however, controversy as to whether a dilated left atrial chamber contributes to the risk of thromboembolism. Mitral valvuloplasty does not appear to eliminate the risk of thromboembolism, although it might reduce it. Other risk factors for systemic embolism include the presence of a left atrial thrombus, low cardiac output, and significant aortic regurgitation.

Patients who suffer a first embolus are at high risk of recurrent embolism. This risk is not eliminated by mitral valvuloplasty. Thus, a successful mitral valvuloplasty does not obviate the need for anticoagulation in patients who required long-term anticoagulation prior to the procedure.

Although never evaluated by a randomized trial, there is a very strong impression that long-term anticoagulant therapy is effective in reducing the incidence of systemic emboli in patients with rheumatic mitral valve disease and AF, but the decision to use long-term anticoagulation in patients with sinus rhythm is uncertain.

Percutaneous balloon mitral valvuloplasty is being used with increasing frequency to treat mitral stenosis. In some centers, it is common practice to treat all such patients with warfarin for a minimum of 3 weeks before the balloon valvuloplasty, regardless of the presence or absence of AF. An alternate strategy might be to perform transesophageal echocardiography (TEE) just prior to balloon mitral valvuloplasty, and if the examination does not reveal a left atrial clot, anticoagulation prior to the valvuloplasty can be avoided. It would be prudent, however, to give anticoagulation therapy to most patients after balloon mitral valvuloplasty for at least 4 weeks.

MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP) is the most common form of valve disease in adults. About 6% of the female population and 4% of the male population have MVP. The risk of stroke in young adults with MVP is very low (only 1/6,000/yr). Clinical trials of antithrombotic therapy have not been reported in this disorder, so treatment decisions are based on extrapolation from the results of studies in patients with related disorders. Long-term warfarin therapy is appropriate for those patients with AF and for those who continue to have cerebral ischemic events despite aspirin therapy.

MITRAL ANNULAR CALCIFICATION

Mitral annular calcification (MAC) may be associated with mitral stenosis and regurgitation, calcific aortic stenosis, conduction disturbances, arrhythmias, embolic phenomena, and endocarditis. Emboli can arise from thrombi on the calcific valve, or they can be calcified spicules. Most patients are elderly (mean age 73–75 years).

MAC is an independent risk factor for stroke, and the prevalence of AF is 12 times greater in patients with MAC than in those without MAC. Clinical trials with antithrombotic therapy have not been reported.

AORTIC VALVE AND AORTIC ARCH DISORDERS

Systemic embolism in patients with aortic valve disease is uncommon in the absence of AF. When embolism does occur, it may be calcific in nature.

Patients with atherosclerotic plaques of the aortic arch and ascending aorta detected by TEE have an increased risk of ischemic stroke. Mobile aortic plaques or plaques ≥ 4 mm in thickness are associated with an increased risk of vascular events; this risk is further increased by a lack of plaque calcification. Oral anticoagulants appear to be more effective than antiplatelet agents in preventing systemic embolism in these patients.

PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM

Patent foramen ovale (PFO) is observed at autopsy in about 28% of otherwise normal hearts. Paradoxical embolism through a patent PFO is well documented, as is thrombus on the arterial side of an atrial septal aneurysm. However, the importance of these conditions as causes of stroke remains uncertain.

Surgical repair of atrial septal aneurysm has been suggested when there is associated systemic embolism, but the evidence for this remains unclear. The indications for antithrombotic therapy in both isolated PFO and in atrial septal aneurysm are also uncertain.

In patients with unexplained cerebral ischemia or stroke, the demonstration of right-to-left shunting through a PFO warrants a search for deep venous thrombosis, which, if found, provides a strong indication for long-term anticoagulation or, in some cases, closure of the PFO or atrial septal defect.

MECHANICAL AND BIOPROSTHETIC VALVES

Patients with prosthetic heart valve replacements are at risk of systemic embolism. The risk of systemic embolism is greater with mechanical than with bioprosthetic valves, with prosthetic mitral than with aortic valves, and if there is associated AF. In addition, the newer mechanical valves appear to be less thrombogenic than older valves. For patients with tissue prosthetic valves who are in sinus rhythm, the risk of embolism is largely confined to the first 3 months after valve insertion. In contrast, the risk is lifelong in patients with mechanical prosthetic valves (particularly in the mitral position).

Mechanical Prosthetic Valves

Randomized trials have shown that warfarin is effective in reducing the risk of systemic embolism in patients with mechanical prosthetic valves

when given at a lower intensity than has been used in the past. A target international normalized ratio (INR) of 2.0 to 3.0 appears to be satisfactory for patients with St. Jude bileaflet and Medtronic-Hall tilting disk mechanical valves in the aortic position, provided that they are in sinus rhythm and the left atrium is not enlarged, whereas a target INR of 2.5 to 3.5 is suggested for tilting disk valves and bileaflet prosthetic valves in the mitral position. The addition of aspirin to warfarin reduces the risk of stroke and vascular death when compared with warfarin alone but at an increased risk of bleeding. If embolic complications occur at the recommended intensity, then either aspirin 80 mg/d or dipyridamole 300 mg/d should be added to warfarin because both antiplatelet agents augment the efficacy of warfarin when used for this indication.

Bioprosthetic Valves

The risk of thromboembolism is less with uncomplicated bioprosthetic valves than with mechanical valves. Warfarin is just as effective but much safer when used at a target INR of 2.0 to 3.0 than when used at an INR of 3.0 to 4.5. Consequently, the less intense therapeutic range of 2.0 to 3.0 is indicated. Although the risk of thromboembolism is limited mainly to the first 3 months postoperatively in the uncomplicated patient, it is present indefinitely if there is associated AF. Consequently, in uncomplicated patients with mitral bioprosthetic valves, warfarin treatment is limited to 3 months. The risk of systemic embolism is less in patients with aortic bioprosthetic valves, so the case for oral anticoagulants is less compelling. Longer-term therapy is indicated in patients with AF and those with an atrial thrombus detected at echocardiography.

INFECTIVE ENDOCARDITIS

Patients with infective endocarditis are at high risk of systemic embolism, but the use of anticoagulants in these patients is problematic because they are at high risk of intracranial bleeding. Embolic risk is increased in the following circumstances: (1) in acute endocarditis versus subacute endocarditis, (2) in mitral valve endocarditis versus aortic valve endocarditis, and (3) in mechanical prosthetic valve endocarditis versus native valve or bioprosthetic valve endocarditis.

In general, anticoagulants are not indicated in patients with native valve or bioprosthetic valve endocarditis because the risk of intracranial bleeding is thought to outweigh the benefits of treatment. However, in the higher-risk mechanical bioprosthetic valve endocarditis, discontinuation of anticoagulant therapy is not recommended because the risk of cerebral embolism in untreated patients is thought to be greater than the risk of intracranial hemorrhage.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

Nonbacterial thrombotic endocarditis (NBTE) occurs in patients with malignancies, other chronic debilitating diseases, and acute fulminant diseases, such as septicemia or burns. Systemic embolism occurs in about 40% of patients with NBTE. The diagnosis of NBTE is difficult. Cardiac murmurs are often absent, and echocardiography is less sensitive for the detection of NBTE than it is for bacterial endocarditis. Heparin appears to be effective in preventing embolic events in these patients, whereas limited data suggest that warfarin is ineffective.

RECOMMENDATIONS

Rheumatic Mitral Valve Disease

1. *For patients with rheumatic mital valve disease and AF or a history of previous systemic embolism,* we recommend long-term oral anticoagulant therapy (target INR 2.5, range 2.0–3.0) (**Grade 1C+**).
2. *For patients with rheumatic mitral valve disease with AF or a history of systemic embolism,* we suggest that clinicians not use concomitant therapy with an oral anticoagulant and an antiplatelet agent (**Grade 2C**).
3. *For patients with rheumatic mitral valve disease with AF or a history of systemic embolism while receiving warfarin at a therapeutic INR,* we recommend adding aspirin (80–100 mg/d) (**Grade 1C**). For those patients unable to take aspirin, we recommend adding dipyridamole (400 mg/d), clopidogrel, or ticlopidine (**Grade 1C**).
4. *In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter in excess of 5.5 cm,* we suggest long-term warfarin therapy with a target INR of 2.5 (range 2.0–3.0) (**Grade 2C**).
5. *In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter less than 5.5 cm,* we suggest that clinicians not use antithrombotic therapy (**Grade 2C**).

Mitral Valvuloplasty

1. We suggest that patients undergoing mitral valvuloplasty receive anticoagulation with warfarin with a target INR of 2.0 to 3.0 for 3 weeks prior to the procedure and for 4 weeks after the procedure (**Grade 2C**).

Mitral Valve Prolapse

1. *In patients with MVP who have not experienced systemic embolism, unexplained transient ischemic attacks (TIAs), or AF,* we recommend against any antithrombotic therapy (**Grade 1C**).

2. *In patients with MVP who have documented but unexplained TIAs,* we suggest long-term aspirin therapy (50–325 mg/d) (**Grade 1A**).
3. *In patients with MVP who have documented systemic embolism or recurrent TIAs despite aspirin therapy,* we recommend long-term oral anticoagulant therapy (target INR 2.5) (**Grade 2C**).

Mitral Annular Calcification and Nonrheumatic Mitral Regurgitation

1. *In patients with MAC complicated by systemic embolism, not documented to be calcific embolism,* we suggest treatment with long-term oral anticoagulant therapy (target INR 2.5) (**Grade 2C**).

Aortic Valve Disease

1. We suggest that clinicians not use long-term oral anticoagulant therapy in patients with aortic valve disease (**Grade 2C**).

Aortic Arch Disorders

1. *In patients with mobile aortic atheromas and aortic plaques > 4 mm, as measured by TEE,* we suggest that oral anticoagulant therapy be considered (**Grade 2C**).

Prosthetic Heart Valves

Mechanical Prosthetic Heart Valves

1. We suggest that all patients with mechanical prosthetic heart valves receive vitamin K antagonists (**Grade 1C+**).
2. F*or patients with a St. Jude Medical bileaflet valve in the aortic position, w*e suggest a target INR of 2.5 (range 2.0–3.0) (**Grade 1A**).
3. *For patients with tilting disk valves and bileaflet mechanical valves in the mitral position,* we suggest a target INR of 3.0 (range 2.5–3.5) (**Grade 1C+**).
4. *For patients with CarboMedics bileaflet valve or Medtronic Hall tilting disk mechanical valves in the aortic position, provided that the left atrium is normal size and the patient is in sinus rhythm*, we suggest a target INR of 2.5 (range 2.0–3.0) (**Grade 1C+**).
5. *In patients who have mechanical valves and additional risk factors, such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction,* we suggest a target INR of 3.0 (range 2.5–3.5), combined with low doses of aspirin (80–100 mg/d) (**Grade 1C+**).
6. *For patients with caged ball or caged disk valves,* we suggest a target INR of 3.0 (range 2.5–3.5) in combination with aspirin 80 to 100 mg/d (**Grade 2A**).

7. *For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR,* we suggest aspirin 80 to 100 mg/d in addition to vitamin K antagonists and maintenance of the INR at a target of 3.0 (range 2.5–3.5) (**Grade 1C+**).
8. *In the event that a vitamin K antagonist needs to be discontinued*, we recommend low-molecular-weight heparin (LMWH) *in nonpregnant patients* (**Grade 1C**) and adjusted-dose LMWH (factor Xa monitored) *in pregnant patients* (**Grade 1C**).

Bioprosthetic Heart Valves

1. *Mitral position.* We suggest that patients should be treated for the first 3 months after valve insertion with vitamin K antagonists (**Grade 1C+**).
2. *Aortic position.* We suggest that patients should be treated for the first 3 months after valve insertion with vitamin K antagonists (**Grade 2C**).
3. We suggest a target INR of 2.5 (range 2.0–3.0) during the first 3 months after operation in patients with bioprosthetic valves in the mitral or aortic position (**Grade 1C+**).
4. We suggest concomitant treatment with a vitamin K antagonist and either heparin or LMWH until the INR is at therapeutic levels for 2 consecutive days (**Grade 2C**).
5. We suggest that patients with bioprosthetic valves who have a history of systemic embolism be treated with vitamin K antagonists for 3 to 12 months (**Grade 1C**).
6. *In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery,* we suggest vitamin K antagonists with a dose sufficient to prolong the INR to a target of 2.5 (range 2.0–3.0) (**Grade 1C**).
7. *For patients with bioprosthetic valves who have AF,* we suggest long-term vitamin K antagonists with an INR of 2.5 (range 2.0–3.0) (**Grade 1C+**).
8. *For patients with bioprosthetic valves who are in sinus rhythm and do not have one of the above-mentioned conditions,* we suggest long-term therapy with aspirin 80 to 100 mg/d (**Grade 1C+**).

Infective Endocarditis and NBTE

1. *For patients with endocarditis on a mechanical prosthetic valve,* we suggest that long-term oral anticoagulant therapy be continued unless there are specific contraindications (**Grade 2C**).
2. *For patients with NBTE and systemic or pulmonary emboli,* we recommend treatment with heparin (**Grade 1C**).
3. *For patients with disseminated cancer or debilitating disease who are found to have aseptic vegetations on echocardiographic study,* we suggest that full-dose unfractionated heparin therapy be considered (**Grade 2C**).

11 ANTITHROMBOTIC AND THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE

The management of stroke can be problematic because optimal antithrombotic treatment requires knowledge of the cause of stroke, and the cause of the stroke can sometimes be difficult to determine with certainty. Atherosclerosis of both small and large arteries supplying the brain is the most common cause of ischemic stroke. About 20% of ischemic strokes are due to cardiogenic embolism, most commonly from atrial fibrillation (AF). Lipohyalinosis and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, subcortical "lacunar" infarcts, whereas about 30% of ischemic strokes remain cryptogenic and are thought to be caused by transient embolic or thrombotic obstruction.

Strokes caused by large-artery atherosclerosis have the worst prognosis. The risk of early recurrence in patients with cardioembolic strokes is related to the underlying cardiac lesion. Lacunar strokes have the lowest early recurrence risk and the best survival rates.

Cardiogenic embolism occurs in AF, mitral stenosis, mechanical prosthetic valves, recent myocardial infarction (MI), left ventricular mural thrombus, atrial myxoma, dilated cardiomyopathies, infective endocarditis, and marantic endocarditis. The occurrence of multiple infarctions in different vascular territories or the history of systemic emboli increases the likelihood of a cardiac mechanism.

Cryptogenic infarcts are thought to be cardioembolic, although other causes, such as hypercoagulable states, paradoxical emboli through a patent foramen ovale, unrecognized arterial lesions (dissections, mild atherosclerosis), or aortic arch atherosclerosis, must be considered.

TREATMENT OF STROKE

Thrombolytic therapy and antithrombotic therapy are effective in selected patients with stroke. Most stroke patients are not eligible for intravenous (IV) recombinant tissue plasminogen activator (t-PA) therapy and are treated with antithrombotic agents.

Thrombolytic Therapy

Thrombolytic therapy has been evaluated in carefully selected ischemic stroke patients in randomized placebo-controlled trials using IV recombinant t-PA, streptokinase, or intra-arterial recombinant prourokinase. When administered to selected patients within 3 hours of acute ischemic stroke onset, IV t-PA improves outcome at 3 months. Although the risk of symptomatic cerebral hemorrhage is increased with t-PA treatment, this serious

side effect is more than offset by a reduction in the incidence of severe disability or death and an increase in the number of patients with a good functional outcome, provided that treatment is commenced within 3 hours of stroke onset. The risk factors for cerebral hemorrhage are the severity of neurologic deficit and brain edema or mass effect on the pretreatment computed tomography (CT) scan. In addition, patients with uncontrolled hypertension are ineligible for t-PA treatment. In contrast to the results with t-PA, the use of streptokinase is associated with an increased incidence of adverse outcomes (mortality and cerebral hemorrhage). Regulatory approval for t-PA use in stroke has been issued in the United States and Canada.

Antithrombotic Agents (Heparin, Low-Molecular-Weight Heparin, Heparinoid, and Antiplatelet Agents)

A variety of antithrombotic agents, including heparin, low-molecular-weight heparins (LMWHs), heparinoids, and aspirin, have been evaluated for acute cerebral infarction patients who are not eligible for thrombolytic therapy. In general, the results with anticoagulants have been disappointing, but they have been more promising with aspirin.

In the large international stroke trial, 19,435 patients with suspected acute ischemic stroke treated with subcutaneous heparin (5,000 U twice daily [bid] or 12,500 U bid) showed no significant difference in 14-day mortality or 6-month outcome when compared with non–heparin-treated patients. Those patients receiving the higher dose of subcutaneous heparin (12,500 U bid) had more systemic bleeding, hemorrhagic strokes, and a significantly increased risk of death or nonfatal stroke at 14 days. The low-dose heparin regimen (5,000 U bid) did, however, significantly reduce the composite of early death or nonfatal stroke, with only a slight and nonsignificant excess of bleeding side effects, although the absolute benefit was small. Patients who received both low-dose heparin and aspirin had the lowest rate of stroke recurrence and no significant increase in bleeding risk (compared with patients who received low-dose heparin without aspirin).

Neither the LMWH nadroparin nor the low-molecular-weight heparinoid danaparoid was shown to be effective in stroke patients in recent trials.

A meta-analysis from 41,325 subjects enrolled in eight trials evaluated the efficacy of antiplatelet agents. For every 1,000 acute strokes treated with aspirin, about 7 fewer early recurrent ischemic strokes were observed and 13 fewer patients died or were dependent at 6 months at the expense of 2 more intracranial hemorrhages.

Stroke Prevention

Antiplatelet Agents

Aspirin, ticlopidine, and clopidogrel are effective for prevention of stroke and other vascular events in patients with cerebrovascular disease. Dipyridamole (particularly when combined with aspirin) also is effective for prevention of stroke.

In an analysis of 144,051 patients with previous MI, acute MI, previous transient ischemic attack (TIA) or stroke, acute stroke, and other patients at increased risk of atherothrombotic events, antiplatelet agents reduce the odds of the composite outcome of stroke, MI, or vascular death by about 25%. The odds reduction attributable to aspirin alone was 23%. Antiplatelet drugs reduced the odds of a nonfatal stroke by 25%, nonfatal MI by about 34%, and vascular mortality by 15%.

For patients with prior stroke or TIA, aspirin use reduced the odds for the composite outcome of stroke, MI, or vascular death by only 16%. The efficacy of aspirin appears to be independent of aspirin dose, although a recent study in patients undergoing carotid endarterectomy reported that low-dose aspirin is more effective than high-dose aspirin.

Ticlopidine is also effective in stroke patients (relative risk reduction 30%) and more effective than aspirin (relative risk reduction 21%). Clopidogrel is marginally more effective than aspirin in stroke patients (relative risk reduction 8%). Slow-release dipyridamole is effective when used alone (relative risk reduction 23%), and the combination of dipyridamole and aspirin is more effective than aspirin alone (relative risk reduction 23%).

Vitamin K Antagonists

Vitamin K antagonists are effective for both primary and secondary prevention of stroke in patients with AF and other conditions associated with cardiogenic embolism. In contrast, there is no evidence that coumarins are effective in noncardioembolic stroke, but there is evidence that when used at a target international normalized ratio (INR) of 3.0 to 4.5, oral anticoagulant therapy causes unacceptably high rates of intracranial hemorrhage. In the one trial comparing warfarin (INR range 1.4–2.8) with aspirin, no differences were observed between the two antithrombotic agents.

OTHER CAUSES OF EMBOLIC STROKE

Aortic Atheromata

Complex atherosclerotic aortic plaques are an independent risk factor for embolic stroke. Plaques of greater than 4 to 5 mm in thickness, ulcerated plaques, and those with mobile components are more likely to be associ-

ated with stroke. Information on the effectiveness of antithrombotic therapy in preventing stroke associated with aortic atherosclerosis is sparse.

Patent Foramen Ovale

A patent foramen ovale (PFO) is a potential cause of cryptogenic stroke in young patients. Patients with a complex PFO (eg, the combination of a large PFO and an atrial septal aneurysm) may be at higher risk of recurrent stroke, although the data are not consistent.

Mitral Valve Prolapse

Recent population-based prospective studies failed to find an increased risk of ischemic stroke associated with this common echocardiographic finding.

CEREBRAL VENOUS SINUS THROMBOSIS

Cerebral venous sinus thrombosis (CVST) can present as headache, focal neurologic deficits, seizures, alterations of consciousness, and papilledema with a sudden or progressive onset. The risk factors include pregnancy, estrogens, and inherited thrombophilic disorders. The diagnosis is made by imaging studies. There is an increased risk of CVST in carriers of prothrombin and factor V gene mutations and in hyperhomocysteinemia; this risk is increased further in women who are taking oral contraceptives. The prognosis of CVST is good with treatment but poor without treatment. Both unfractionated heparin and LMWHs are safe and effective in these patients. There is controversy regarding the benefit-to-risk ratio in patients with large hemorrhagic venous infarcts with associated hematomas. In patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options, such as local intrathrombus infusion of a thrombolytic agent, together with intravenous heparin, are under investigation.

RECOMMENDATIONS

Acute Ischemic Stroke: Thrombolytic Therapy

IV t-PA within 3 Hours of Symptom Onset

1. *For eligible patients,* we recommend administration of IV t-PA in a dose of 0.9 mg/kg (maximum of 90 mg), with 10% of the total dose given as an initial bolus and the remainder infused over 60 minutes, provided that treatment is initiated within 3 hours of clearly defined symptom onset (**Grade 1A**).

2. *For patients with extensive (greater than one-third of the middle cerebral artery territory) and clearly identifiable hypodensity on CT,* we recommend against thrombolytic therapy (**Grade 1B**).

IV t-PA between 3 and 6 Hours of Symptom Onset

1. *For unselected patients with acute ischemic stroke of greater than 3 hours but less than 6 hours,* we suggest that clinicians do not use IV t-PA (**Grade 2A**).

IV Streptokinase between 0 and 6 Hours of Symptom Onset

1. *For patients with acute ischemic stroke,* we recommend against streptokinase (**Grade 1A**).

Intra-arterial Thrombolysis

1. *For patients with angiographically demonstrated middle cerebral artery occlusion and no signs of major early infarction on the baseline CT scan who can be treated within 6 hours of symptom onset,* we suggest use of intra-arterial thrombolytic therapy with a t-PA (**Grade 2C**).
2. *For patients with acute basilar artery thrombosis and without major CT or magnetic resonance imaging evidence of infarction,* we suggest intra-arterial thrombolysis with a t-PA (**Grade 2C**).

Acute Ischemic Stroke: Patients Not Eligible for Thrombolysis

Anticoagulants

1. *For patients with acute ischemic stroke,* we suggest that clinicians do not use full-dose anticoagulation with IV, subcutaneous, or low-molecular-weight heparins or heparinoids (**Grade 2B**).

Antiplatelet Agents

1. *For patients with ischemic stroke who are not receiving thrombolysis,* we recommend early aspirin therapy (160–325 mg/d) (**Grade 1A**).

Antithrombotic Therapy for Prevention of Deep Venous Thrombosis and Pulmonary Embolism

1. *For acute stroke patients with restricted mobility*, we recommend prophylactic low-dose subcutaneous heparin or low-molecular-weight heparins or heparinoids (**Grade 1A**).
2. *For patients who have contraindications to anticoagulants*, we recommend use of intermittent pneumatic compression devices or elastic stockings (**Grade 1C**).

Deep Venous Thrombosis and Pulmonary Embolism Prophylaxis in Patients with Intracerebral Hematoma

1. *In patients with an acute intracerebral hematoma,* we recommend the initial use of intermittent pneumatic compression (**Grade 1C+**) for the prevention of deep venous thrombosis and pulmonary embolism. In stable patients, we suggest that low-dose subcutaneous heparin be initiated as soon as the second day after the onset of the hemorrhage (**Grade 2C**).

Stroke Prevention

Prevention of Cerebral Ischemic Events in Patients with Noncardioembolic TIA or Stroke: Antiplatelet Drugs

1. *In patients who have experienced a noncardioembolic stroke or TIA,* we recommend treatment with an antiplatelet agent (**Grade 1A**). Aspirin at a dose of 50 to 325 mg daily; the combination of aspirin, 25 mg, and extended-release dipyridamole, 200 mg bid; and clopidogrel (75 mg daily) are all acceptable options for initial therapy.
2. *In patients who are at moderate to high risk of gastrointestinal bleeding complications,* we recommend using low doses of aspirin, that is, 50 to 100 mg daily (**Grade 1C+**).
3. *In patients who have experienced a noncardioembolic stroke or TIA,* we suggest use of the combination of aspirin (25 mg bid) and extended-release dipyridamole (200 mg bid) over aspirin (**Grade 2A**) and clopidogrel over aspirin (**Grade 2B**).
4. *For patients who are allergic to aspirin,* we recommend clopidogrel (**Grade 1C+**).
5. *For patients with a history of risk factors for bleeding who are being treated with aspirin,* we recommend use of low doses of aspirin (< 100 mg daily) (**Grade 1C+**).

Prevention of Noncardioembolic Cerebral Ischemic Events: Oral Anticoagulants

1. *For most patients with noncardioembolic stroke or TIA,* we recommend antiplatelet agents over oral anticoagulation (**Grade 1A**).
2. *For patients with well-documented prothrombotic disorders,* we suggest oral anticoagulation over antiplatelet agents (**Grade 2C**).

Prevention of Cerebral Ischemic Events in Patients Undergoing Carotid Endarterectomy: Antiplatelet Agents

1. *In patients undergoing carotid endarterectomy,* we recommend aspirin (81–325 mg/d) prior to and following the procedure (**Grade 1A**).

Prevention of Cardioembolic Cerebral Ischemic Events

1. *In patients with AF who have suffered a recent stroke or TIA,* we recommend long-term oral anticoagulation (target INR 2.5, range 2.0–3.0) (**Grade 1A**).
2. *For patients with cardioembolic stroke who have contraindications to anticoagulant therapy,* we recommend aspirin (**Grade 1A**).

Patients with Aortic Atheromata

1. *In patients with stroke associated with aortic atherosclerotic lesions,* we recommend antiplatelet therapy over no therapy (**Grade 1C+**).
2. *For patients with cryptogenic stroke associated with mobile aortic arch thrombi,* we suggest either oral anticoagulation or antiplatelet agents (**Grade 2C**).

Patients with PFO

1. *In patients with cryptogenic ischemic stroke and a PFO,* we recommend antiplatelet therapy over no therapy (**Grade 1C+**) and suggest antiplatelet agents over anticoagulation (**Grade 2A**).

Mitral Valve Strands and Prolapse

1. *In patients with mitral valve strands or prolapse who have a history of TIA or stroke,* we recommend antiplatelet therapy (**Grade 1C+**).

Cerebral Venous Sinus Thrombosis

1. *In patients with CVST,* we recommend that clinicians use unfractionated heparin (**Grade 1B**) or LMWH (**Grade 1B**) over no anticoagulant therapy during the acute phase, even in the presence of hemorrhagic infarction.
2. *In these patients,* we recommend that oral anticoagulation therapy be continued for 3 to 6 months (target INR 2.5, range 2.0–3.0) (**Grade 1C**).

12 ANTITHROMBOTIC THERAPY FOR CORONARY ARTERY DISEASE

This chapter on coronary artery disease covers (1) patients presenting with non–ST-segment elevation (NSTE) acute coronary syndromes (ACSs), (2) those with post–myocardial infarction (MI) and ACS, (3) patients with chronic stable coronary artery disease (CAD), (4) those with congestive heart failure, and (5) those without a clinical diagnosis of CAD.

NON–ST-SEGMENT ELEVATION ACSs

Patients presenting with symptoms consistent with acute ischemic chest pain are differentiated by their electrocardiogram as having an ACS with or

without persistent ST-segment elevation. Those without ST-segment elevation are then further risk-stratified and treated with appropriate antiplatelet and antithrombin therapies.

ACUTE MANAGEMENT

Antiplatelet Therapies

Aspirin

Aspirin is an important part of first-line management of NSTE ACS. In the recent Antithrombotic Trialists' Collaboration, which included 5,031 patients with unstable angina, treatment with aspirin was associated with an odds reduction in vascular events of 46%. The benefits of aspirin were consistent across a wide range of doses, whereas gastrointestinal bleeding, which was reported in about 0.9%, was dose related. Some patients develop gastrointestinal intolerance to aspirin, whereas about 2% are allergic to the drug.

Thienopyridines

Clopidogrel has a more favorable safety profile than ticlopidine. Both are effective in patients with coronary heart disease. In the CURE study, the addition of clopidogrel to aspirin in unstable angina patients proved to be more effective than aspirin (relative risk 0.80). Major bleeding was significantly more common in clopidogrel-treated patients (relative risk 1.38), but there was no excess rate of fatal bleeding, bleeding that required surgical intervention, or hemorrhagic stroke. Bleeding associated with coronary artery bypass graft was increased among patients receiving clopidogrel within 5 days of surgery.

Glycoprotein IIb/IIIa Inhibitors

Abciximab and eptifibatide are indicated as adjunctive antithrombotics in patients undergoing percutaneous coronary intervention (PCI), whereas eptifibatide and tirofiban are approved among patients presenting with NSTE ACSs. A recent systematic overview reported that the use of glycoprotein (GP) IIb/IIIa inhibitors in patients with NSTE ACS resulted in a small but significant 1.2% absolute decrease in the 30-day incidence of death or MI (5.7 vs 6.9%). The benefit appeared to be confined to troponin-positive patients. Although GP IIb/IIIa inhibitors add clinical value on the background therapy of aspirin and heparin, the incremental value of adding GP IIb/IIIa inhibitors to aspirin, heparin, and clopidogrel remains uncertain.

Antithrombin Therapies

Unfractionated Heparin

The addition of unfractionated heparin (UFH) to aspirin improves efficacy among patients with unstable angina and NSTE MI (relative risk of 0.44 for death or MI with combination aspirin and UFH therapy compared with aspirin alone). A weight-adjusted dosing with an initial bolus of 60 to 70 U/kg (maximum 5,000 U) and an initial infusion of 12 to 15 U/kg/h (maximum 1,000 U/h) titrated to a target activated partial thromboplastin time (APTT) of 50 to 75 seconds is recommended.

Low-Molecular-Weight Heparin

Placebo-controlled trials indicate that low-molecular-weight heparin (LMWH) preparations are effective for the treatment of NSTE ACS. Comparison of either fragmin or nadroparin and UFH showed no difference in MI or death or secondary outcomes. In contrast, studies comparing enoxaparin with UFH reported a risk reduction in the composite outcome of death or nonfatal MI of about 20% in favor of enoxaparin. There is now evidence that LMWH can be administered safely in patients who are assigned early PCI. There is limited evidence that extended LMWH treatment might benefit high-risk patients with unstable angina. There are also data indicating that LMWH can be used in place of UFH in patients who receive a GP IIb/IIIa inhibitor.

POST–MYOCARDIAL INFARCTION AND POST-ACS

Antiplatelet Therapies

Short-Term Trials

There is conclusive evidence that short-term aspirin therapy for acute MI decreases mortality and reinfarction, has benefits in addition to those of fibrinolysis, and prevents the increase in reinfarction that occurs after fibrinolytic therapy. These benefits were achieved with an aspirin dose of 160 mg/d. Although associated with an increased rate of minor bleeding from 1.9 to 2.5%, aspirin therapy was not associated with any significant increase in the risk of major bleeding, including hemorrhagic stroke.

Long-Term Trials

The Antiplatelet Trialists' Collaboration update reported a 22% odds reduction in serious vascular disease in patients allocated to receive antiplatelet therapy versus control patients ($p = .0001$). Antiplatelet therapy was associated with a 15% reduction in vascular deaths in nonfatal MI

(34%) and stroke (25%). Overall, the proportional risk of experiencing a major intracranial hemorrhage was increased 50% with antiplatelet therapy.

Among 18,788 patients with a history of MI, allocation to antiplatelet therapy was associated with a 25% reduction in serious vascular events. The overall benefits were larger than the excess risk of major extracerebral hemorrhage (3 per 1,000 or 1 per 1,000 patients per year).

In the CAPRIE trial, which included 19,185 patients with a history of MI, stroke, or peripheral vascular disease, patients receiving clopidogrel had 10% fewer serious vascular events than patients receiving aspirin.

Anticoagulant Therapies

Short-Term Trials

In patients receiving aspirin and fibrinolytic therapy, the addition of heparin leads to a more modest benefit of about five fewer deaths per 1,000 patients, three fewer reinfarctions, and one less pulmonary embolus. This benefit is balanced against three additional episodes of major bleeding.

Long-Term Trials

There is good evidence that combining aspirin with moderate-intensity (international normalized ratio [INR] range 2.0–3.0) oral anticoagulation therapy (vitamin K antagonists [VKAs]) is superior to treatment with aspirin alone and that high-intensity oral anticoagulation therapy (VKAs) is superior to treatment with aspirin alone. The relative efficacy and safety of moderate-intensity anticoagulation therapy compared with aspirin are uncertain. The benefits of anticoagulation therapy (either alone or when combined with aspirin) over aspirin alone come at a cost of increased bleeding.

CHRONIC STABLE CAD

Antiplatelet Therapy

Antiplatelet treatment (predominantly aspirin) is associated with about a 33% reduction in vascular events (14.1 vs 9.9%) in patients with chronic stable angina. There are few data on the efficacy of anticoagulant therapy in patients with chronic stable angina.

Primary Prevention: Aspirin, VKA, or Both

When used for primary prevention, aspirin produces a relative risk reduction of 15% in all cardiovascular events and a relative risk reduction of 30% in MI. This benefit comes at a cost of a modest increase in bleeding complications. It has been estimated that aspirin is safe and worthwhile for pri-

mary prevention when the risk of a major coronary episode is 1.5% per annum but of limited value at a coronary event risk of 1.0% per annum and unsafe at a risk of 0.5%.

Low dose-adjusted warfarin at an INR of 1.5 is also effective in primary prevention, producing about a 20% reduction in all cardiovascular events and a mortality reduction of 17%. Whereas the beneficial effect of aspirin appears to be mainly in nonfatal events, the benefits of adjusted-dose warfarin (INR 1.5) are mainly from fatal events. Warfarin causes a modest increase in bleeding similar to that of aspirin. The combination of warfarin (INR 1.5) and aspirin is more effective than either group alone but at a cost of a small increase in intracranial bleeding.

RECOMMENDATIONS

Acute Management of NSTE ACS

Antiplatelet Therapies

Aspirin

1. *For all patients presenting with an NSTE ACS, without a clear allergy to acetylsalicylic acid (ASA)*, we recommend immediate ASA (75–325 mg orally) and then daily oral ASA (75–162 mg) (**Grade 1A**).

Thienopyridines

1. *For all NSTE ACS patients with an ASA allergy,* we recommend immediate treatment with clopidogrel, 300 mg oral bolus, followed by 75 mg daily indefinitely (**Grade 1A**).
2. *In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until > 5 days following coronary angiography,* we recommend that clopidogrel be given immediately as bolus therapy (300 mg), followed by 75 mg daily for 9 to 12 months in addition to aspirin (**Grade 1A**).
3. *In NSTE ACS patients in whom angiography will take place rapidly (< 24 hours),* we suggest beginning clopidogrel after coronary anatomy has been determined (**Grade 2A**).
4. *For patients who have received clopidogrel and are scheduled for coronary bypass surgery,* we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

GP IIb/IIIa Inhibitors

1. *In moderate- to high-risk patients presenting with NSTE ACS,* we recommend either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin (**Grade 1A**).

2. *In moderate- to high-risk patients who are also receiving clopidogrel*, we recommend eptifibatide or tirofiban as additional initial treatment (**Grade 2A**).
3. *For patients presenting with NSTE ACS,* we recommend against abciximab as initial treatment except when the coronary anatomy is known and the PCI is planned within 24 hours (**Grade 1A**).

Antithrombin Therapies

Unfractionated Heparin

1. *For patients presenting with NSTE ACS,* we recommend UFH over no heparin therapy for acute use with antiplatelet therapies (**Grade 1A**). We recommend weight-based dosing of UFH and maintenance of the APTT between 50 and 75 seconds (**Grade 1C+**).

Low-Molecular-Weight Heparin

1. *For the acute treatment of patients with NSTE ACS,* we recommend LMWHs over UFH (**Grade 1B**)
2. We recommend against routine monitoring of the anticoagulant effect of the LMWHs (**Grade 1C**).
3. We suggest continuing LMWHs during PCI treatment of the NSTE ACS patient when it has been started as the "upstream" anticoagulant (**Grade 2C**).
4. *For patients receiving GP IIb/IIIa inhibitors as "upstream" treatment of NSTE ACS,* we suggest LMWH over UFH as the anticoagulant of choice (**Grade 2B**).

Direct Thrombin Inhibitors

1. *In patients presenting with NSTE ACS,* we recommend against direct thrombin inhibitors as routine initial antithrombin therapy (**Grade 1B**).

Post–Myocardial Infarction and Post-ACS

Antiplatelet Therapies

1. *For patients with ACSs with and without ST-segment elevation*, we recommend ASA in initial doses of 160 to 325 mg and then indefinite aspirin in doses of 75 to 162 mg daily (**Grade 1A**).
2. *For patients with a history of ASA-induced bleeding or with risk factors for bleeding,* we recommend lower doses (100 mg) of aspirin (**Grade 1C+**).
3. *For patients in whom ASA is contraindicated or not tolerated,* we recommend clopidogrel for long-term administration (75 mg daily) (**Grade 1A**).

Comparisons of Antiplatelet and Anticoagulant Therapy and/or Combinations of Aspirin and Warfarin

1. *In most health care settings, for moderate- and low-risk patients with an MI,* we recommend ASA alone over oral VKAs plus aspirin (**Grade 2B**).
2. *In health care settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after MI,* we recommend a long-term (up to 4 years) high-intensity oral VKA (target INR 3.5, range 3.0–4.0) without concomitant aspirin or a moderate-intensity oral VKA (target INR 2.5, range 2.0–3.0) with aspirin (both **Grade 2B**).
3. *For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event,* we suggest the combined use of a moderate-intensity (INR range 2.0–3.0) oral VKA plus low-dose aspirin (≤ 100 mg daily) for 3 months after the MI (**Grade 2A**).

Chronic Stable CAD

Antiplatelet Agents

1. *For all patients with chronic stable CAD*, we recommend the administration of oral aspirin in a dose of 75 to 162 mg (**Grade 1A**). We suggest that aspirin be continued indefinitely (**Grade 2C**).
2. *For patients with stable chronic CAD with a risk profile indicating a high likelihood of development of acute MI,* we suggest chronic therapy with clopidogrel in addition to aspirin (**Grade 2C**).

Vitamin K Antagonists

1. *For patients with chronic CAD without prior MI*, we suggest that clinicians do not use a chronic oral VKA (**Grade 2C**).

Congestive Heart Failure with and without CAD

1. *In patients with congestive heart failure owing to a nonischemic etiology,* we recommend against routine use of aspirin or an oral VKA (**Grade 1B**).
2. We recommend that, when otherwise indicated, patients receive ASA whether or not they are receiving angiotensin-converting enzyme inhibitors (**Grade 1C+**).

Primary Prevention: Aspirin, VKA, or Both

1. *For patients with at least moderate risk of a coronary event (based on age and a cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%),* we suggest 75 to 162 mg aspirin daily over either no antithrombotic therapy or a VKA (**Grade 2A**).

2. *For patients at particularly high risk of events in whom the INR can be monitored without difficulty,* we suggest a low-dose VKA with a target INR of approximately 1.5 (**Grade 2A**).

13 INTRAVENOUS THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

THROMBOLYTIC AGENTS

Acute ST-segment elevation myocardial infarction (MI) is usually caused by an occlusive thrombosis of the infarct-related artery. Timely fibrinolytic therapy can reestablish coronary flow and salvage jeopardized myocardium. A number of large randomized clinical trials have clearly demonstrated impressive mortality benefit from fibrinolytic (thrombolytic) therapy in this clinical setting. Despite evidence that primary angioplasty is more effective for acute MI, thrombolysis is the most common form of reperfusion treatment worldwide.

Streptokinase versus Placebo

For acute MI patients treated with streptokinase within 6 hours, the absolute reduction in mortality was 30 lives saved per 1,000 patients treated, and for patients treated within the first 7 to 12 hours after symptom onset, it was 20 lives saved per 1,000 patients treated. For patients treated between 13 and 18 hours after symptom onset, there was an uncertain trend toward mortality reduction of about 10 lives saved per 1,000 patients treated. Fibrinolytic therapy was associated with about 4 extra strokes per 1,000 patients treated, most of which occurred within 2 days. Fibrinolytic therapy results in a 25% relative reduction and a 2% absolute reduction in mortality compared with placebo—an important benefit that clearly outweighs the risks for most patients who present with acute MI within 12 hours of symptom onset.

Streptokinase versus Tissue Plasminogen Activator

Initial trials comparing streptokinase with recombinant tissue plasminogen activator (t-PA) in acute MI did not demonstrate differences in efficacy and safety between these two agents. Subsequently, the GUSTO I trial (which used an accelerated recombinant t-PA regimen and intravenous heparin) reported a significantly lower mortality in the recombinant t-PA (alteplase) arm than in the streptokinase arm. The relative reduction in mortality was 14%, and the absolute reduction in mortality was 1%. The incidence of intracranial hemorrhage was 0.5% and 0.7% in the streptokinase and recombinant t-PA patients, respectively.

Bolus Thrombolytic Agents

Two t-PA variants (reteplase and tenecteplase) with a longer half-life than t-PA have been developed for use as bolus injections. Both have been approved by the US Food and Drug Administration.

Double-bolus reteplase was shown to have an efficacy similar to that of streptokinase and t-PA.

Weight-adjusted, single-bolus tenecteplase was shown to be equivalent to alteplase in reducing mortality. Patients treated more than 4 hours after symptom onset had improved outcomes when treated with tenecteplase compared with alteplase. The rates of major bleeding, total bleeding, and bleeding requiring transfusion were significantly lower with tenecteplase, whereas the rates of intracranial hemorrhage and overall stroke were nearly identical for tenecteplase and alteplase.

Bolus fibrinolytic agents have convenience advantages over agents that are administered by infusion. This advantage has the potential to allow earlier administration of the bolus agents, particularly their use in a prehospital setting—an approach that has been shown to be more effective than administration after hospital admission.

ANTIPLATELET AGENTS

Adjunctive Treatment with Aspirin

In the ISIS 2 trial, assignment to 162.5 mg of aspirin (first dose crushed or chewed) resulted in a treatment effect of 25 early lives saved per 1,000 patients treated. Treatment with aspirin also prevented 10 nonfatal reinfarctions and 3 nonfatal strokes per 1,000 patients treated.

Treatment with aspirin should be initiated as early as possible, at the time of initial contact with health care personnel. Treatment with aspirin at a dose of 75 to 162 mg should be continued indefinitely.

Clopidogrel

There are currently few data regarding the safety and efficacy of combining clopidogrel with fibrinolytic therapy. It could be considered as an alternative to aspirin in the patient with a serious allergic reaction to aspirin or documented aspirin resistance.

Adjunctive Therapy with Glycoprotein IIb/IIIa Receptor Blockers

Full-dose fibrinolytic therapy with either reteplase or tenecteplase has been compared with the combination of half-dose fibrinolytic therapy with abciximab. The results are difficult to interpret because of the asymmetric design (different doses of unfractionated heparin in the two groups). Com-

bined treatment appears to show an advantage in reduced levels of reinfarction but at the cost of increased bleeding (particularly in the elderly).

ANTICOAGULANTS (ANTITHROMBINS)

Adjunctive Treatment with Unfractionated Heparin or Low-Molecular-Weight Heparin

The clinical data supporting use of adjunctive unfractionated heparin in the setting of streptokinase and aspirin are weak. An increase in bleeding with adjunctive heparin is not matched by a mortality benefit at 35 days or 6 months. The benefit of adding unfractionated heparin to t-PA and aspirin is also uncertain, although it is used routinely in this setting. Adjunctive heparin increases the risk of intracranial hemorrhage, a risk that appears to be dosage sensitive; this resulted in a reduction in dosing of adjunctive heparin. Direct comparisons between unfractionated heparin and low-molecular-weight heparin (LMWH) as adjuncts to fibrinolytic therapy are limited, and there is no good evidence supporting the use of one anticoagulant over the other in this setting.

Adjunctive Treatment with Direct Thrombin Inhibitors

The direct thrombin inhibitors hirudin and bivalirudin have slightly better efficacy and reduced safety than heparin as adjuncts to fibrinolytic therapy. The use of either of these two direct thrombin inhibitors is limited to their role as an alternative to heparin in the setting of ST-segment elevation MI when heparin-induced thrombocytopenia is present or suspected.

PRIMARY ANGIOPLASTY VERSUS THROMBOLYSIS

Coronary angioplasty is more effective than fibrinolysis in the setting of acute ST-segment elevation MI. Significant benefit is observed in the rates of death, non-fatal MI, and intracranial hemorrhage. Despite the benefits of primary angioplasty, fibrinolytic therapy will continue to be an important form of treatment for patients with ST-segment elevation MI because access to primary angioplasty is limited.

RECOMMENDATIONS

Thrombolysis

Thrombolysis with Streptokinase, t-PA, Anistreplase, Reteplase, and Tenecteplase

1. *For patients with ischemic symptoms characteristic of acute MI of < 12 hours duration and ST-segment elevation or left bundle branch block (of unknown*

duration) on electrocardiography (ECG), we recommend administration of any approved fibrinolytic agent (**Grade 1A**).
2. We recommend the use of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase (all **Grade 1A**).
3. *For patients with symptom duration < 6 hours,* we recommend the administration of alteplase over streptokinase (**Grade 1A**).
4. *For patients with known allergy or sensitivity to streptokinase,* we recommend alteplase, reteplase, or tenecteplase (**Grade 1A**).
5. *For patients with recurrent acute MI,* we suggest that clinicians do not use repeat administration of streptokinase (**Grade 2C**).
6. *For patients with ischemic symptoms characteristic of acute MI of < 12 hours duration and 12-lead ECG findings consistent with a true posterior MI,* we suggest fibrinolytic therapy (**Grade 2C**).
7. *For high-risk patients with ongoing symptoms characteristic of acute MI or hemodynamic compromise and duration of 12 to 24 hours who have ST-segment elevation or left bundle branch block,* we suggest administration of intravenous fibrinolytic therapy (**Grade 2B**).
8. *In health care settings in which prehospital administration of fibrinolytic therapy is feasible and primary angioplasty is not available,* we recommend prehospital administration of fibrinolytic therapy only (**Grade 1A**).
9. *For patients with acute MI who are candidates for fibrinolytic therapy,* we recommend administration within 30 minutes of arrival at the hospital or at the first contact with the health care system (**Grade 1A**).
10. *In patients with any history of intracranial hemorrhage, closed head trauma, or ischemic stroke within the past 3 months,* we recommend against administration of fibrinolytic therapy (**Grade 1C+**).

Adjunctive Treatment with Antithrombotic Agents in Patients Receiving Fibrinolysis

Aspirin

1. *For patients with acute ST-segment elevation MI, whether or not they receive fibrinolytic therapy*, we recommend aspirin (160–325 mg orally) at initial evaluation by health care personnel followed by indefinite therapy (75–162 mg orally daily) (both **Grade 1A**).

Clopidogrel

1. *In patients who are allergic to aspirin,* we suggest administration of clopidogrel with a loading dose of 300 mg and a maintenance dose of 75 mg daily as an alternative therapy to aspirin (**Grade 2C**).

Unfractionated Heparin

1. *For patients receiving streptokinase,* we suggest administration of either intravenous unfractionated heparin 5,000 U bolus followed by 1,000 U/h for patients > 80 kg and 800 U/h for patients < 80 kg with a target activated partial thromboplastin time (APTT) of 50 to 75 seconds (**Grade 2C**) or subcutaneous unfractionated heparin (12,500 U every 12 hours for 48 hours) (**Grade 2A**).
2. *For all patients at high risk of systemic or venous thromboembolism (anterior MI, pump failure, previous embolus, atrial fibrillation, or left ventricular thrombus),* we recommend administration of intravenous unfractionated heparin while receiving streptokinase (**Grade 1C+**).
3. *For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis in acute MI,* we recommend administration of weight-adjusted heparin (60 U/kg bolus for a maximum of 4,000 U) followed by 12 U/kg/h (1,000 U/h maximum) adjusted to maintain an APTT of 50 to 75 seconds for 48 hours (**Grade 1C**).

Low-Molecular-Weight Heparin

1. *For patients aged < 75 years with preserved renal function (Cr < 2.5 mg/dL in males and < 2.0 mg/dL in females) who receive tenecteplase*, we suggest use of enoxaparin (30 mg bolus followed by 1 mg subcutaneously every 12 hours) as an alternative to unfractionated heparin up to 7 days (**Grade 2B**).

Glycoprotein IIb/IIIa Receptor Blockers

1. We recommend against the use of either a combination of standard-dose abciximab and half-dose reteplase or half-dose tenectaplase with low-dose intravenous unfractionated heparin over standard-dose reteplase or tenecteplase for routine use (**Grade 1B**).
2. We suggest that clinicians do not use the combination of streptokinase and any glycoprotein IIb/IIIa inhibitor (**Grade 2B**).

Direct Thrombin Inhibitors

1. *For patients with acute ST-segment elevation MI treated with streptokinase,* we suggest that clinicians do not use bivalirudin on a routine basis (**Grade 2A**).
2. *For patients with known or suspected heparin-induced thrombocytopenia who are receiving fibrinolytic therapy,* we recommend administration of hirudin with t-PA (**Grade 1A**) and bivalirudin with streptokinase (**Grade 2A**).

14 ANTITHROMBOTIC THERAPY IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

In the United States, the use of percutaneous coronary intervention (PCI) now exceeds coronary artery bypass surgery in patients with ischemic heart disease. PCI was performed in more than 900,000 patients in 2003. Based on technologic improvements such as drug-eluting stents, periprocedural adjunctive pharmacology, and other advances, PCI is now a much more effective and safe procedure than it was a decade ago.

The introduction of coronary stents has reduced the risk of acute closure and recurrent symptoms owing to restenosis. This latter complication has been reduced further with the use of new drug-eluting stents. Because of these results, coronary stents are now used in > 90% of patients undergoing PCI.

Although antithrombotic therapy reduces the risk of acute thrombosis, none of the antithrombotic regimens tested to date have had a significant effect on restenosis.

ORAL ANTIPLATELET THERAPY

Aspirin

Aspirin is effective in reducing the risk of periprocedural myocardial infarction (MI). There appears to be no added benefit in adding dipyridamole to aspirin. In contrast to its effects on periprocedural thrombosis, there is no evidence that aspirin influences the rate of restenosis.

Thienopyridine Derivatives

Combined antiplatelet therapy with aspirin and a thienopyridine is superior to aspirin alone or aspirin and a vitamin K antagonist for prevention of acute complications after coronary stent insertion. Clopidogrel is safer than and as effective as ticlopidine. There is evidence that pretreatment with clopidogrel at least 6 hours prior to PCI is effective in high-risk patients and that extended treatment with the combination of aspirin and clopidogrel after PCI reduces the rate of ischemic events. This beneficial effect is associated with a small increase in bleeding.

Glycoprotein IIb/IIIa Inhibitors

Three intravenous inhibitors of the glycoprotein (GP) IIb/IIIa receptor, abciximab, eptifibatide, and tirofiban, are licensed in North America, and these agents produce a 35 to 50% reduction in clinical events in patients with acute coronary syndromes.

In a meta-analysis, 30-day mortality was reduced by about 30% with GP IIb/IIIa inhibition. GP IIb/IIIa inhibitors do not appear to influence restenosis. Abciximab was more effective than tirofiban in one trial, possibly because of suboptimal dosing with tirofiban.

ANTICOAGULANTS

Unfractionated Heparin

In the absence of adjunctive GP IIb/IIIa inhibition, heparin is usually given in doses of 60 to 100 IU/kg and a target activated clotting time (ACT) between 250 and 350 seconds. In contrast, when heparin is given in conjunction with a GP IIb/IIIa inhibitor, a target ACT of 200 seconds is advocated. Removal of the femoral sheath should be delayed until the ACT is between 150 and 180 seconds. Routine use of intravenous heparin after PCI is no longer recommended because it is of doubtful benefit and increases the risk of bleeding.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) can be used instead of heparin.

Direct Thrombin Inhibitors

Three direct thrombin inhibitors, hirudin, bivalirudin, and argatroban, have been evaluated as alternatives to heparin during PCI. Promising results have been obtained with bivalirudin.

Vitamin K Antagonists

Warfarin provides little incremental benefit over aspirin alone on early outcomes, and long-term warfarin does not reduce restenosis after PCI.

RECOMMENDATIONS

Oral Antiplatelet Therapy

Aspirin

1. *For patients undergoing PCI,* we recommend pretreatment with aspirin (**Grade 1A**).
2. *For long-term treatment after PCI,* we recommend aspirin (**Grade 1A**).
3. *For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin,* we recommend lower-dose aspirin (75–100 mg daily) (**Grade 1C+**).

Pretreatment with Thienopyridine Derivatives prior to Stenting

1. We recommend a loading dose of 300 mg of clopidogrel given at least 6 hours prior to planned PCI (**Grade 1B**). If clopidogrel is started less than 6 hours prior to PCI, we suggest a 600 mg loading dose of clopidogrel (**Grade 2C**).
2. *If ticlopidine is given,* we recommend a loading dose of 500 mg at least 6 hours before planned PCI (**Grade 2C**).

Thienopyridine after Stent Placement

1. We recommend the combination of aspirin and a thienopyridine derivative (ticlopidine or clopidogrel) over systemic anticoagulation therapy (**Grade 1A**).
2. We recommend clopidogrel over ticlopidine (**Grade 1A**).

Aspirin-Intolerant Patients

1. *For PCI patients who cannot tolerate aspirin,* we recommend that the loading dose of clopidogrel (300 mg) or ticlopidine (500 mg) be given at least 24 hours prior to planned PCI (**Grade 2C**).

Duration of Thienopyridine Therapy after Stent Placement

1. *After PCI,* we recommend that, in addition to aspirin, clopidogrel (75 mg daily) be given for at least 9 to 12 months (**Grade 1A**).
2. *If ticlopidine is used in place of clopidogrel after PCI,* we recommend ticlopidine for 2 weeks after placement of a bare metal stent in addition to aspirin (**Grade 1B**).
3. *In patients with isolated coronary lesions,* we recommend clopidogrel for at least 2 weeks after placement of a bare metal stent (**Grade 1A**), for 2 to 3 months after placement of a sirolimus-eluting stent (**Grade 1C+**), and 6 months after placement of a paclitaxel-eluting stent (**Grade 1C**).

Other Oral Antiplatelet Agents

1. For patients after stent placement, we suggest ticlopidine (**Grade 1B**) or clopidogrel (**Grade 1C**) over cilostazol.
2. In aspirin-intolerant patients undergoing PCI, we suggest that clinicians do not use dipyridamole (**Grade 2C**).

GP IIb/IIIa Inhibitors

1. *For all patients undergoing PCI, particularly those undergoing primary PCI or those with refractory unstable angina (UA) or other high-risk features,* we recommend use of a GP IIb/IIIa antagonist (abciximab or eptifibatide) (**Grade 1A**).

2. *In patients undergoing PCI for ST-segment elevation MI,* we recommend abciximab over eptifibatide (**Grade 1B**).
3. We recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12-hour infusion at a rate of 10 μg/min (**Grade 1A**) and eptifibatide as a double bolus (each of 180 μg/kg given 10 minutes apart) followed by an 18-hour infusion of 2.0 μg/kg/min (**Grade 1A**).
4. *In patients undergoing PCI,* we recommend against the use of tirofiban as an alternative to abciximab or eptifibatide (**Grade 1A**).
5. *For patients with non–ST-segment elevation (NSTE) MI or UA who are designated as moderate to high risk based on TIMI score,* we recommend that upstream use of a GP IIb/IIIa antagonist (either eptifibatide or tirofiban) be started as soon as possible prior to PCI (**Grade 1A**).
6. *In NSTE MI or UA patients who receive upstream treatment with tirofiban,* we recommend that PCI be deferred for at least 4 hours after initiating the tirofiban infusion (**Grade 2C**).
7. *With planned PCI in NSTE MI or UA patients with an elevated troponin level,* we recommend that abciximab be started within 24 hours prior to the intervention (**Grade 1A**).

Unfractionated Heparin

1. *In patients receiving a GP IIb/IIIa inhibitor,* we recommend a heparin bolus of 50 to 70 IU/kg to achieve a target ACT over 200 seconds (**Grade 1C**).
2. *In patients not receiving a GP IIb–IIIa inhibitor, we recommend that heparin be given in doses sufficient to produce an ACT of 250 to 350 seconds* (**Grade 1C+**). We suggest a weight-adjusted heparin bolus of 60 to 100 IU/kg (**Grade 2C**).
3. *In patients after uncomplicated PCI,* we recommend against routine post-procedural infusion of heparin (**Grade 1A**).

Low-Molecular-Weight Heparin

1. *In patients who have received LMWH prior to PCI,* we recommend that administration of additional anticoagulant therapy depend on the timing of the last dose of LMWH (**Grade 1C**). If the last dose of LMWH was given 8 hours or less prior to PCI, we suggest no additional anticoagulant therapy (**Grade 2C**). If the last dose of LMWH was given more than 8 hours prior to PCI, we suggest the usual doses of intravenous heparin or LMWH (enoxaparin 3 mg/kg) at the time of PCI (**Grade 2C**).

Direct Thrombin Inhibitors

1. *For patients undergoing PCI who are not treated with a GP IIb/IIIa antagonist or heparin*, we recommend bivalirudin (0.75 mg/kg bolus followed

by an infusion of 1.75 mg/kg/h for the duration of PCI) during PCI (**Grade 1A**).
2. *In PCI patients who are at high risk of bleeding,* we recommend bivalirudin over heparin as an adjunct to GP IIb/IIIa antagonists (**Grade 1B**).

Vitamin K Antagonists

1. *In patients who undergo PCI with no other indication for systemic anticoagulation therapy,* we recommend against routine use of warfarin (or other vitamin K antagonists) after PCI (**Grade 1A**).

15 CORONARY ARTERY BYPASS GRAFTS

Coronary bypass grafts (CABGs) can be complicated by early thrombotic occlusion or late occlusion owing to complicating atherosclerotic narrowing with or without associated thrombosis. Two forms of grafts are used: saphenous vein grafts and internal mammary arterial grafts. The saphenous vein grafts are more thrombogenic than internal mammary artery grafts.

SAPHENOUS VEIN BYPASS GRAFTS

Saphenous veins are vulnerable to early thrombotic occlusion because immediately after harvesting the vein, the endothelium is lost, leaving an exposed thrombogenic surface. Graft patency is influenced by several graft-related factors. These include the nature of the graft, its size, and its location. Graft patency is reduced if the operation time exceeded 5 hours, the bypass time exceeded 2 hours, the cross-clamp time exceeded 80 minutes, and the temperature of the vein preservation solution exceeded 5°C. Grafts of 1.5 mm diameter or larger have a higher patency rate after 1 year than smaller grafts. Aggressive lowering of low-density lipoprotein cholesterol reduces graft occlusion.

Aspirin 75 to 325 mg/d begun within 6 hours after operation increases early saphenous vein graft patency but does not influence the long-term patency rate after 1 year. The addition of dipyridamole to aspirin does not add to the benefit of aspirin. Preoperative aspirin is associated with increased bleeding, a complication that is likely to be reduced by starting aspirin on the first postoperative day. Ticlopidine and clopidogrel have also been shown to be effective in maintaining graft patency.

INTERNAL MAMMARY GRAFTS

Without treatment, the patency of internal mammary grafts is 96 to 100% at 3 months to 1 year and 92% at 3 years. Antiplatelet agents have not

been shown to improve patency, possibly because the room for improvement is small.

RECOMMENDATIONS

Prevention of Saphenous Vein Graft Occlusion following CABG

Antiplatelet Agents

Aspirin

1. *For all patients with coronary artery disease,* we recommend aspirin (75–162 mg daily) indefinitely (**Grade 1A**).
2. *For patients undergoing CABG,* we recommend aspirin (75–162 mg daily) starting 6 hours after operation over preoperative aspirin (**Grade 1A**).
3. *In patients in whom bleeding prevents the administration of aspirin at 6 hours after CABG,* we recommend starting aspirin as soon as possible thereafter (**Grade 1C**).

Aspirin in Combination with Dipyridamole

1. *For patients undergoing CABG,* we recommend against the addition of dipyridamole to aspirin therapy (**Grade 1A**).

Clopidogrel

1. *For patients with coronary artery disease undergoing CABG who are allergic to aspirin,* we recommend clopidogrel 300 mg as a loading dose 6 hours after operation followed by 75 mg daily by mouth (**Grade 1C+**).
2. *In patients who undergo CABG for non–ST-segment elevation acute coronary syndrome,* we recommend clopidogrel at 75 mg daily for 9 to 12 months following the procedure in addition to treatment with aspirin (**Grade 1A**).
3. *For patients who have received clopidogrel for acute coronary syndrome and are scheduled for coronary bypass surgery,* we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (**Grade 2A**).

Vitamin K Antagonists

1. *For patients undergoing CABG who have no other indication for vitamin K antagonists (VKAs),* we suggest that clinicians not administer VKAs (**Grade 2B**).
2. *For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement,* we suggest that clinicians administer a VKA in addition to aspirin (**Grade 2C**).

Prevention of Internal Mammary Bypass Graft Occlusion following CABG

Aspirin with and without Dipyridamole

1. For all patients with coronary artery disease who undergo internal mammary artery bypass grafting, we recommend aspirin (75–162 mg daily) indefinitely (**Grade 1A**).

Vitamin K Antagonists

1. For all patients undergoing internal mammary artery bypass grafting who have no other indication for VKAs, we suggest that clinicians do not use VKAs (**Grade 2C**).

16 ANTITHROMBOTIC THERAPY IN PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

CHRONIC LIMB ISCHEMIA

Peripheral arterial occlusive disease (PAOD) can be symptomatic or asymptomatic. Intermittent claudication (symptomatic ischemia) occurs in 2 to 3% of men and 1 to 2% of women over the age of 60 years. Asymptomatic PAOD is three to four times more common than symptomatic PAOD. On long-term follow-up, about 20 to 30% of patients with intermittent claudication have progression of symptoms and 10% require amputation. The remainder either are unchanged or show some improvement. Risk factors for progression include multilevel arterial involvement, low ankle-to-brachial pressure indexes, chronic renal insufficiency, diabetes mellitus, and heavy smoking.

Patients with PAOD have a two- to threefold increase in mortality from coronary or cerebrovascular complications. Exercise improves maximal walking time. In addition, some improvement in outcome might be achieved by modifying key risk factors for atherosclerotic disease, such as smoking, diabetes, dyslipidemia, and hypertension.

Antiplatelet Therapy

Antiplatelet therapy reduces the incidence of death and disability from stroke and myocardial infarction (MI). Aspirin may also reduce the risk of thrombotic occlusion in the affected lower extremity. A single randomized controlled trial reported that aspirin, alone or combined with dipyridamole, delayed the progression of established arterial occlusive disease as assessed by serial angiography. This improvement was likely caused by a

reduction in thrombotic occlusion rather than a reversal of the atherosclerotic process.

Ticlopidine reduces fatal and nonfatal cardiovascular events in patients with intermittent claudication and has a modest effect on relieving symptoms and increasing walking distance. In a subgroup analysis of the CAPRIE trial, a larger benefit of clopidogrel over aspirin was observed in patients with symptomatic PAOD than those with cardiac or cerebrovascular disease.

Prostaglandin I_2 may provide temporary relief of rest pain in nondiabetic patients with severe arterial insufficiency and may promote healing of ischemic ulcers when given intra-arterially. However, it is doubtful that such therapy will ultimately prevent amputation in patients with end-stage vascular disease.

Other Agents

Two agents, pentoxifylline and cilostazol, have been approved by the US Food and Drug Administration for treatment of intermittent claudication. Pentoxifylline decreases whole blood viscosity by decreasing red blood cell deformity. The results of studies with pentoxifylline have been inconclusive and do not justify the added expense for most patients. Cilostazol, a type III phosphodiesterase inhibitor, possesses antiplatelet and vasodilating properties and has been shown to be more effective than placebo or pentoxifylline in improving walking distance.

ACUTE EXTREMITY ARTERIAL INSUFFICIENCY

Nontraumatic acute arterial occlusion is either embolic or thrombotic. Emboli usually arise from a cardiac source but can also arise from an arterial aneurysm, ulcerated atherosclerotic plaques, recent vascular surgery, and paradoxical emboli from venous thrombi in the lower extremities.

Treatment is influenced by the nature of the occlusion. Acute embolism in a healthy artery is treated with embolectomy by a Fogarty balloon catheter. Percutaneous thromboembolectomy with the aid of an aspiration catheter or of a thrombectomy device is an alternative approach.

Thrombotic occlusions of arteries are usually associated with advanced atherosclerosis. Consequently, these vessels often have a well-developed collateral blood supply, and the acute thrombotic occlusion is not an emergency in most patients.

Thrombolytic therapy has been evaluated in numerous clinical trials involving patients with thrombotic or embolic occlusions. Regional or intra-arterial thrombolytic therapy is more effective than systemic therapy in achieving lysis but causes more bleeding. Regional thrombolysis is no more effective than surgical intervention.

PERIPHERAL VASCULAR RECONSTRUCTIVE SURGERY

Vein Grafts and Arterial Prostheses

Saphenous vein grafts are more effective than prosthetic grafts with expanded polytetrafluoroethylene prostheses for lower extremity arterial occlusion.

The 5- to 10-year patency rates range from 80 to 90% in vascular reconstructions involving high-flow, low-resistance arteries greater than 6 mm in diameter (aortoiliac, femoral, major visceral, renal, and proximal brachiocephalic vessels). In contrast, reconstructed small arteries with flow rates of less than 200 mL/min are prone to thrombosis; therefore, antithrombotic therapy has a potential role in these patients.

INTRAOPERATIVE ANTICOAGULATION DURING VASCULAR RECONSTRUCTIONS

Intravenous unfractionated heparin (UFH) is traditionally given prior to clamping arteries and interrupting flow. UFH was shown to be more effective than a control in reducing the risk of MI in patients undergoing elective abdominal aortic aneurysm repair. There was no difference in the incidence of blood loss, transfusion requirement, or arterial thrombosis in either group. A regimen of 100 to 150 U/kg intravenously before application of cross-clamps supplemented every 45 to 50 minutes with 50 U/kg until cross-clamps are removed and circulation is reestablished was used.

Antiplatelet Agents

The results of a meta-analysis demonstrated that antiplatelet therapy reduced the risk of graft occlusion by 32%. Antiplatelet therapy was most effective in patients with prosthetic grafts, but the results were inconclusive in patients with venous grafts. In the Dutch BOA study comparing vitamin K antagonists (VKAs) with aspirin, aspirin was found to be more effective in improving the patency of prosthetic grafts. Aspirin should be started before surgery.

Anticoagulants

Studies evaluating the relative benefit and risk of warfarin versus aspirin have yielded inconsistent results. Low-intensity oral anticoagulant therapy (international normalized ratio [INR] range 1.5–2) combined with low-dose aspirin therapy (80–325 mg) was reported to be no more effective in achieving patency than aspirin, although the combination of warfarin and aspirin appeared to be more effective for infrainguinal vein bypass grafts. In a comparison of high-intensity oral anticoagulation (INR 3.0–4.5) with

aspirin, the results of subgroup analysis suggested that oral anticoagulants might be beneficial in patients with vein grafts, whereas aspirin might be beneficial for nonvenous grafts. In all studies, anticoagulant therapy increased the incidence of wound hematoma.

LMWH has been shown to be more effective than aspirin and dipyridamole in patients undergoing femoropopliteal bypass.

Most surgeons do not routinely use therapeutic heparin or other anticoagulants beyond the intraoperative period.

CAROTID ENDARTERECTOMY

Perioperative aspirin therapy, 81 to 325 mg daily, is effective in patients undergoing carotid endarterectomy. Therapy should be started at the time of clinical presentation and continued through the perioperative period. In contrast, there is uncertainty as to whether aspirin reduces the stroke rate in asymptomatic patients with 50% or greater carotid stenosis. The combination of aspirin and dipyridamole does not appear to prevent recurrent stenosis after carotid endarterectomy.

Lower Extremity Endovascular Procedures

Transluminal angioplasty has become standard treatment for selected patients with focal stenotic lesions of the iliac and femoropopliteal arteries. Self-expanding metallic stents are also being used, although evidence for their effectiveness is lacking. Lifelong antiplatelet therapy is recommended for all patients with PAOD because they are at increased risk of coronary and cerebrovascular events. Based on the data with coronary angioplasty and stenting, it is reasonable to consider combinations of aspirin and thienopyridines in high-risk, small-diameter tibial artery angioplasty.

RECOMMENDATIONS

Chronic Limb Ischemia

Aspirin

1. We recommend lifelong aspirin therapy (75–162 mg/d) in comparison with no antiplatelet therapy in both patients with clinically manifest coronary or cerebrovascular disease (**Grade 1A**) and those without clinically manifest coronary or cerebrovascular disease (**Grade 1C+**).

Ticlopidine

1. We recommend clopidogrel over ticlopidine (**Grade 1C+**).

Clopidogrel

1. We recommend clopidogrel in comparison with no antiplatelet therapy (**Grade 1C+**) but suggest that aspirin be used instead of clopidogrel (**Grade 2A**).

Cilostazol

1. For patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention, we suggest cilostazol (**Grade 2A**). We suggest that clinicians not use cilostazol in patients with less disabling claudication (**Grade 2A**).

Pentoxifylline

1. We recommend against the use of pentoxifylline (**Grade 1B**).

Prostaglandins

1. For limb ischemia, we suggest that clinicians do not use prostaglandins (**Grade 2B**).

Anticoagulants

1. In patients with intermittent claudication, we recommend against the use of anticoagulants (**Grade 1A**).

Acute Limb Ischemia

Heparin

1. *In patients who suffer from acute arterial emboli or thrombosis,* we recommend immediate systemic anticoagulation with UFH (**Grade 1C**).
2. *In patients who suffer from acute arterial emboli and undergo embolectomy,* we recommend immediate systemic anticoagulation with UFH followed by a long-term VKA to prevent recurrent embolism (**Grade 1C**).

Thrombolysis

1. *In patients with recent (< 14 days) thrombotic or embolic disease with a low risk of myonecrosis,* we suggest intra-arterial thrombolytic therapy (**Grade 2B**).

Vascular Grafts

1. *For patients undergoing major vascular reconstructive procedures,* we recommend UFH at the time of application of vascular cross-clamps (**Grade 1A**).

Antiplatelet Agents

1. *In patients undergoing prosthetic infrainguinal bypass,* we recommend aspirin (**Grade 1A**).

Vitamin K Antagonists

1. *In patients undergoing infrainguinal femoropopliteal or distal vein bypass,* we suggest that VKA not be used routinely (**Grade 2A**).

VKA plus Aspirin

1. *For routine patients undergoing infrainguinal bypass without special risk factors for occlusion,* we recommend against VKA plus aspirin (**Grade 1A**).
2. *For patients at high risk of bypass occlusion and limb loss,* we suggest a VKA plus aspirin (**Grade 2B**).

Carotid Endarterectomy

Aspirin

1. We recommend that aspirin, 75 to 325 mg daily, be given preoperatively and continued indefinitely (75–162 mg/d) in patients undergoing carotid endarterectomy (**Grade 1A**).

Asymptomatic and Recurrent Carotid Stenosis

1. We recommend lifelong aspirin, 75 to 162 mg daily (**Grade 1C+**).

Lower Extremity Endovascular Procedures

1. *For all patients undergoing extremity balloon angioplasty (with or without stenting),* we recommend long-term aspirin, 75 to 162 mg daily (**Grade 1C+**).

17 ANTITHROMBOTIC THERAPY DURING PREGNANCY

Pulmonary embolism is a leading cause of maternal mortality in the Western world. Since our last review, new information has been published on the management of pregnant women with prior venous thromboembolism (VTE), the management of VTE in pregnancy, the safety of low-molecular-weight heparin (LMWH) during pregnancy (particularly with regard to osteoporosis), the difficulties of managing pregnant women with prosthetic heart valves, and the relationship between thrombophilia and fetal loss, intrauterine growth restriction, and preeclampsia. Antithrombotic therapy is indicated during pregnancy for the prevention and treatment of VTE, for the prevention of systemic embolism in certain patients with valvular heart disease, and for the prevention of fetal growth retardation. Fetal

growth retardation and recurrent miscarriages can occur as a result of placental infarction in preeclampsia, antiphospholipid antibody (APLA) syndrome, and, possibly, a number of inherited thrombophilic disorders.

ANTICOAGULANTS

The use of coumarins such as warfarin is controversial during pregnancy because it crosses the placenta and enters the fetal circulation. It is particularly problematic during the first trimester of pregnancy because it is teratogenic. Warfarin is also contraindicated within 2 weeks of vaginal delivery because it produces a coagulopathy in the fetus, thereby exposing it to the risk of serious bleeding during delivery. Warfarin may also be fetopathic in more advanced pregnancy and therefore should also be avoided if at all possible even after the first trimester. However, the incidence of fetopathic effects in the second and third trimesters is likely to be very low, and the use of warfarin may be considered at these times in high-risk situations (such as patients with prosthetic heart valves) if heparin cannot be used. Before warfarin is considered during pregnancy, the patient should be informed about the potential risks and of the clear statement made in the package insert, by the manufacturers of warfarin, that warfarin is contraindicated during pregnancy.

In contrast to warfarin, neither heparin nor LMWH crosses the placenta, and, in general, if anticoagulants are indicated during pregnancy, one of these two parenteral anticoagulants should be used. Long-term use of heparin can be complicated by osteopenia and, uncommonly, by symptomatic osteoporosis. This complication occurs less frequently with LMWH. Therefore, LMWHs should be considered in preference to heparin in patients with a history of heparin-induced osteoporosis.

Adjusted-dose heparin has been reported to provide inadequate protection in patients with mechanical prosthetic heart valves, as has weight-adjusted LMWH. Whether the reported failures with heparin or LMWH were caused by inadequate dosing or an inherent limitation of these anticoagulants in pregnant women with prosthetic heart valve patients is uncertain. However, the present state of uncertainty provides justification for the use of warfarin in the second trimester and the first half of the third trimester in pregnant women with high-risk prosthetic heart valves. If heparin is used in patients with high-risk prosthetic heart valves, it should be administered in high doses with careful laboratory monitoring. If LMWH is used, it should be given in therapeutic weight-adjusted doses, administered twice daily to achieve anti–factor Xa levels of 1.0 to 1.2 U/mL 4 to 6 hours after subcutaneous injection. Coumarins do not pass into breast milk and are not contraindicated in the nursing mother.

ASPIRIN

Aspirin administered in the second and third trimesters was initially reported to be effective in preventing pregnancy-induced hypertension and the complicating fetal growth retardation. However, the results of a recent large study failed to demonstrate a beneficial effect of aspirin. The combination of low-dose heparin and aspirin is more effective than aspirin alone in preventing recurrent abortions in patients with APLAs. The results of a number of studies suggest that maternal aspirin ingestion is safe for the fetus, although there is some evidence that aspirin might be teratogenic in humans if used in the first trimester. In addition, there might be a small increase in the risk of neonatal bleeding if aspirin is used close to term in doses of 325 mg or more per day.

RECOMMENDATIONS

Management of Women Receiving Long-Term Vitamin K Antagonist Therapy Who Are Considering Pregnancy

1. We suggest that women requiring long-term vitamin K antagonist therapy who are attempting pregnancy perform frequent pregnancy tests and substitute unfractionated heparin (UFH) or LMWH for warfarin when pregnancy is achieved (**Grade 2C**).

Treatment of VTE during Pregnancy

1. We recommend either adjusted-dose LMWH throughout pregnancy or intravenous UFH (bolus followed by a continuous infusion to maintain the activated partial thromboplastin time in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Postpartum anticoagulants should be given for at least 6 weeks (**Grade 1C+**).
2. We recommend discontinuing the heparin 24 hours prior to elective induction of labor (**Grade 1C**).

Prevention of VTE during Pregnancy

Prior VTE and Pregnancy

1. *For a single episode of VTE associated with a transient risk factor that is no longer present,* we recommend clinical surveillance and postpartum anticoagulants (**Grade 1C**). If the previous event occurred during pregnancy or was estrogen related, or there are additional risk factors (such a obesity), we suggest antenatal anticoagulant prophylaxis (**Grade 2C**).

2. *For a single idiopathic episode of VTE and a patient not on long-term anticoagulants,* we suggest prophylactic LMWH or minidose UFH or moderate-dose UFH or clinical surveillance plus postpartum anticoagulants (**Grade 2C**).
3. *For a single episode of VTE and thrombophilia (confirmed laboratory abnormality) or a strong family history of thrombosis and a patient not on long-term anticoagulants,* we suggest prophylactic or intermediate-dose LMWH or mini- or moderate-dose UFH plus postpartum anticoagulants (**Grade 2C**).
4. We suggest that intermediate-dose LMWH prophylaxis or moderate-dose UFH be used *in antithrombin-deficient women, compound heterozygotes for prothrombin G20210A and factor V Leiden, and homozygotes for these conditions* (**Grade 2C**).
5. *For multiple (two or more) episodes of VTE and/or women receiving long-term anticoagulants (eg, a single episode of VTE either idiopathic or associated with thrombophilia),* we suggest adjusted-dose UFH or adjusted-dose LMWH followed by resumption of long-term anticoagulants postpartum (**Grade 2C**).
6. We suggest that graduated elastic compression stockings be considered *in all women with previous deep venous thrombosis* (**Grade 2C**).

Thrombophilia and No Prior Thromboembolism

1. *In patients with no prior VTE and thrombophilia (confirmed laboratory abnormality),* we suggest surveillance or prophylactic LMWH or minidose UFH plus postpartum anticoagulants (**Grade 2C**).
2. *For antithrombin-deficient women, compound heterozygotes for prothrombin G20210A, and factor V Leiden homozygotes,* we suggest active prophylaxis (**Grade 2C**).

Thrombophilia and Pregnancy Complications

1. We suggest screening *women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death for congenital thrombophilia and APLAs* (**Grade 2C**).
2. We suggest that *women with APLAs and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses or preeclampsia, intrauterine growth restriction, or abruption* should receive antepartum aspirin plus mini- or moderate-dose UFH or prophylactic LMWH (**Grade 2B**).
3. We suggest that *women found to be homozygous for a thermolabile variant (C677T) of MTHFR* should be treated with folic acid supplements prior to conception or, if the patient is already pregnant, as soon as possible, and this should be continued throughout the pregnancy (**Grade 2C**).

4. We suggest that *women with a congenital thrombophilic deficit and recurrent miscarriages, a second-trimester or later loss, or severe or recurrent preeclampsia or abruption* should receive low-dose aspirin therapy plus either minidose heparin or prophylactic LMWH therapy (**Grade 2C**). We also suggest that postpartum anticoagulants be administered to these women (**Grade 2C**).
5. *In patients with APLAs and a history of venous thrombosis who are on long-term oral anticoagulant therapy,* we recommend adjusted-dose LMWH or UFH therapy plus low-dose aspirin and resumption of long-term oral anticoagulation therapy postpartum (**Grade 1C**).
6. *In patients with APLAs and no prior VTE or pregnancy loss,* we suggest one of the following approaches: surveillance, minidose heparin, prophylactic LMWH, and/or low-dose aspirin, 80 to 325 mg daily (**Grade 2C**).

Prophylaxis in Patients with Mechanical Heart Valves

One of three approaches is recommended:

1. Adjusted-dose twice-daily LMWH throughout pregnancy in doses adjusted either to keep a 4-hour postinjection anti–factor Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight (**Grade 1C**)
2. Aggressive adjusted-dose UFH throughout pregnancy: that is, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval activated partial thromboplastin time at least twice that of the control or to attain an anti–factor Xa heparin level of 0.35 to 0.70 U/mL (**Grade 1C**)
3. UFH or LMWH (as above) until the thirteenth week, a change to warfarin until the middle of the third trimester, and then restarting UFH or LMWH (**Grade 1C**). Long-term anticoagulants should be resumed postpartum with all regimens.
4. We suggest that the addition of low-dose aspirin (80–150 mg once a day) be considered in high-risk patients (**Grade 2C**).

18 ANTITHROMBOTIC THERAPY IN CHILDREN

Compared with the adult population, thromboembolism (TE) is uncommon in children, yet when TE complications occur, they can be devastating. There are very few clinical trials in the prevention and treatment of TE in children to guide clinicians, so most recommendations for antithrombotic therapy in pediatric patients have been extrapolated from the results of clinical trials performed in adults. Dosing and choice of antithrombotic agents are influenced by many factors that are specific to the pediatric population. These include pharmacokinetics, pharmacodynamics, and dif-

ficulties in compliance, venous access, and obtaining pediatric formulations of a number of agents.

SYSTEMIC VENOUS THROMBOEMBOLISM IN NEONATES

Over 80% of venous thromboembolic (VTE) events are secondary to central venous lines (CVLs). These lines are placed into the umbilical or upper arm veins and lead to complicating thrombosis in over 10% of neonates. The effectiveness of anticoagulants in preventing acute or chronic complications of CVL thrombosis has not been evaluated.

SYSTEMIC VTE IN CHILDREN

The risk of systemic VTE in children is much lower than it is in adults. Most episodes of VTE in children occur in association with risk factors such as cancer, trauma or surgery, congenital heart disease, and systemic lupus erythematosus. Over 50% of venous thrombi complicate CVL and occur in arm veins, and the majority of the rest occur in leg veins. One randomized trial compared unfractionated heparin (UFH) plus warfarin with the low-molecular-weight heparin (LMWH) rivaparin. The study was terminated prior to completion, at which time, the recurrence rate was 5.6% in the rivaparin arm and 12.5% in the heparin + warfarin arm (a nonsignificant trend in favor of LMWH).

RENAL VEIN THROMBOSIS

Renal vein thrombosis (RVT) is responsible for 10% of VTE in neonates and is the most common cause of non–catheter-related VTE in neonates. Data on the effect of antithrombotic therapy are sparse.

Prevention of CVL Thrombosis

The effects of fixed-dose warfarin (1 mg) and of LMWH on preventing CVL thrombosis have been compared with no treatment in a number of small clinical trials. The results have been inconsistent. One multicenter trial failed to show a difference in the rate of venographic thrombosis between the LMWH rivaparin and a nontreated control.

Primary Prophylaxis in Special High-Risk Groups

A number of disorders in neonates are associated with an increased risk of thrombosis, but data are sparse on the relative efficacy and safety of antithrombotic therapy for a variety of procedures performed to correct congenital heart abnormalities. For children with prosthetic heart

valves, recommendations are based on extrapolation from the results of trials in adults.

Primary Prophylaxis for Cardiac Catheterization

In the absence of prophylaxis, cardiac catheterization can be complicated by femoral artery thrombosis. Symptomatic TE events have been reported in 40% of children. Aspirin does not reduce the risk of TE complications, but heparin reduces the incidence by more than 75%.

Treatment of Femoral Artery Thrombosis after Cardiac Catheterization

Children with established femoral vein thrombosis are usually treated with heparin or thrombolytic therapy. There have been no studies evaluating the efficacy of these agents.

Umbilical Artery Catheters

The umbilical artery is often the site of catheterization in sick newborns who require blood gas analysis and other monitoring. These neonates can develop thromboembolic complications, including aortic thrombosis. Data on the prevention and treatment of umbilical artery thrombosis are sparse.

Kawasaki Disease

During the acute stage, children suffering from Kawasaki disease can develop medium- and large-vessel arteritis and arterial aneurysms that can lead to arterial stenosis and thrombosis. There is evidence that intravenous gamma-globulin is effective. Aspirin in anti-inflammatory doses is also effective.

Cerebral Venous Thrombosis

Cerebral vein thrombosis can occur in neonates and in children. The role of anticoagulants in neonates is controversial, whereas anticoagulants are considered to be appropriate in children, provided that there is no intracranial bleeding.

Arterial Ischemic Stroke

Arterial ischemic stroke (AIS) can occur in neonates and in children. The role of antithrombotic therapy is uncertain, but it is recommended in children with AIS.

Purpura Fulminans

This disorder occurs in homozygous protein C deficiency and less frequently in homozygous protein S deficiency. Patients are treated acutely with replacement therapy and long term with replacement therapy and warfarin.

RECOMMENDATIONS

Venous Thromboembolism

In neonates with VTE,

1. We suggest treatment with either UFH or low-molecular-weight heparin (LMWH) or monitoring radiographically and an anticoagulant if extension occurs (**Grade 2C**).
2. We suggest that if they elect to begin anticoagulation therapy, clinicians administer UFH or LMWH and subsequently administer LMWH for 10 days to 3 months (**Grade 2C**).
3. We suggest that clinicians adjust the dose of UFH to prolong the activated partial thromboplastin time (APPT) corresponding to an anti–factor Xa level of 0.35 to 0.7 U/mL (**Grade 2C**).
4. We suggest that clinicians adjust the dose of LMWH to achieve an anti–factor Xa level of 0.5 to 1.0 U/mL (**Grade 2C**).
5. We suggest that if the thrombus extends following discontinuation of heparin therapy, clinicians administer vitamin K antagonists or extended LMWH therapy (**Grade 2C**).
6. We suggest that clinicians **not** use thrombolytic therapy for VTE in neonates unless there is major vessel occlusion that is causing critical compromise of organs or limbs (**Grade 2C**). If thrombolytic therapy is used, we suggest supplementation with plasminogen (fresh frozen plasma) immediately prior to thrombolysis (**Grade 2C**).
7. We suggest that, in general, clinicians should remove either CVLs or UVCs that are in situ. However if either CVLs or UVCs are still in place at the completion of the above therapy, we suggest prophylactic dosing with LMWH to prevent recurrent VTE until such time as the CVL or UVC is removed (both **Grade 2C**).

Systemic Venous Thromboembolic Disease in Children

First Thromboembolic Event

For children (over 2 months of age) with an initial TE,

1. We recommend treatment with intravenous heparin sufficient to prolong the APTT to a range that corresponds to an anti–factor Xa level of 0.35 to 0.7 U/mL or LMWH sufficient to achieve an anti–factor Xa level of 0.5 to 1.0 U/mL 4 hours after an injection (**Grade 1C+**).
2. We recommend initial treatment with heparin or LMWH for 5 to 10 days (**Grade 1C+**). For patients in whom subsequent vitamin K antagonists will be used, we recommend beginning oral therapy as early as day 1 and discontinuing heparin/LWMH on day 6 if the international normalized ratio (INR) is therapeutic on 2 consecutive days (**Grade**

1C+). For massive pulmonary embolism or extensive deep venous thrombosis (DVT), we recommend a longer period of heparin or LMWH therapy (**Grade 1C+**).

3. We suggest continuing anticoagulant therapy for idiopathic TEs for at least 6 months using vitamin K antagonists to achieve a target INR of 2.5 (range 2.0–3.0) or LMWH to maintain an anti–factor Xa level of 0.5 to 1.0 U/mL (**Grade 2C**). *Underlying values and preferences:* The suggestion to anticoagulate idiopathic DVT in children for at least 6 months rather than lifelong places a relatively high value on avoiding the known risk of bleeding secondary to anticoagulant therapy in young active adults and less importance on the unknown risk of recurrence in the absence of an ongoing clinical precipitating factor.
4. We suggest that for secondary TEs, anticoagulant therapy be continued for a least 3 months using vitamin K antagonists to achieve a target INR of 2.5 (range 2.0–3.0) or LMWH to maintain an anti–factor Xa level of 0.5 to 1.0 U/mL (**Grade 2C**).
5. We suggest that in the presence of ongoing risk factors, such as active nephritic syndrome, ongoing asparaginase therapy, or a lupus anticoagulant, anticoagulant therapy, in either therapeutic or prophylactic doses, be continued until the risk factor has resolved (**Grade 2C**).
6. We suggest that clinicians not use thrombolytic therapy routinely for venous TE in children (**Grade 2C**). Treatment needs to be individualized, based on the size and location of the thrombus and the degree of organ compromise. If thrombolytic therapy is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (fresh frozen plasma) (**Grade 2C**).

Recurrent Thromboembolic Event

For children with recurrent idiopathic TEs,

1. We recommend indefinite therapy with either therapeutic or prophylactic doses of vitamin K antagonists (**Grade 1C+**). We suggest LMWH as an alternative if vitamin K antagonist therapy is too difficult (**Grade 2C**).

For children with recurrent secondary TEs.

1. We suggest that, following the initial 3 months of therapy, anticoagulation therapy be continued for at least a further 3 months or until removal of any precipitating factors (**Grade 2C**).

CVL-Related Thrombosis

There are two aspects to the management of CVL-related thrombosis: management of the CVL itself and anticoagulation therapy.

1. We suggest that if the CVL is no longer required or is nonfunctioning, it be removed (**Grade 2C**). We suggest at least 3 to 5 days of anticoagulation therapy prior to removal. If CVL access is required and the CVL involved is still functioning, we suggest that the CVL remain in situ (**Grade 2C**).
2. For children with a first CVL-related DVT after the initial 3 months of therapy, we suggest that prophylactic doses of vitamin K antagonists (INR range 1.5–1.8) or LMWH (anti–factor Xa levels of 0.1 to 0.3) be given until the CVL is removed (**Grade 2C**).
3. For children with recurrent CVL-related TEs after the initial 3 months of therapy, we suggest that prophylactic doses of vitamin K antagonists (INR range 1.5–1.8) or LMWH (anti–factor Xa levels of 0.1 to 0.3) be continued until removal of the CVL. If the recurrence occurs while the patient is on prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed or for a minimum of 3 months (**Grade 2C**).

Renal Vein Thrombosis

1. For unilateral RVT in the absence of uremia and in the absence of extension into the inferior vena cava, we suggest supportive care with careful monitoring of the RVT for extension (**Grade 2C**). Alternatively, we suggest anticoagulation therapy with UFH or LMWH (**Grade 2C**).
2. For unilateral RVT that does extend into the inferior vena cava, we suggest anticoagulation therapy with UFH or LMWH for 6 weeks to 3 months (**Grade 2C**).
3. Remark: The therapeutic range is as for venous thrombosis.
4. For bilateral RVT with various degrees of renal failure, we suggest UFH (and not LMWH) and thrombolytic therapy (**Grade 2C**).

CVL Prophylaxis

1. For children with CVLs, we recommend against routine primary prophylaxis (**Grade 1B**).
2. For children having long-term home total parenteral nutrition therapy, we suggest antithrombotic prophylaxis therapy. We suggest vitamin K antagonists with a target INR of 2 to 2.5 continuously or for the first 3 months after each CVL is inserted (all **Grade 2C**).
3. Remark: The optimal drug and dose are unknown.

Primary Prophylaxis for Blalock-Taussig (BT) Shunts in Neonates

1. For neonates having BT shunts, we suggest intraoperative heparin followed by either aspirin (5 mg/kg/d) or no further anticoagulant therapy (**Grade 2C**).

Primary Prophlyaxis for Stage 1 Norwood Procedure in Neonates

1. For patients who have undergone the Norwood procedure, we suggest heparin immediately after the procedure (**Grade 2C**).

Primary Prophylaxis for Fontan Surgery in Children

1. For children after Fontan surgery, we suggest aspirin (5 mg/kg/d) or therapeutic heparin followed by vitamin K antagonists to achieve a target INR of 2.5 (range 2–3) (**Grade 2C**).

Primary Prophylaxis for Endovascular Stents in Children

1. For children having endovascular stents inserted, we suggest administration of heparin perioperatively (**Grade 2C**).

Primary Prophylaxis for Dilated Cardiomyopathy in Neonates and Children

1. Children with cardiomyopathy should receive vitamin K antagonists to achieve a target INR of 2.5 (range 2–3) no later than activation on a cardiac transplant waiting list (**Grade 2C**).

Primary Prophylaxis for Biologic Prosthetic Heart Valves in Children

1. For children with biologic prosthetic heart valves, we recommend treatment according to the adult guidelines (**Grade 1C+**).

Primary Prophylaxis for Mechanical Prosthetic Heart Valves in Children

1. For children with mechanical prosthetic heart valves, we recommend administration of vitamin K antagonists following adult guidelines (**Grade 1C+**).
2. For children in whom additional antithrombotic therapy is required owing to the failure of vitamin K antagonists or a contraindication to full-dose vitamin K antagonists, we suggest adding aspirin (6–20 mg/kg/d) (**Grade 2C**).

Thromboprophylaxis for Cardiac Catheterization in Neonates and Children

1. For neonates and children requiring cardiac catheterization via an artery, we recommend intravenous heparin prophylaxis (**Grade 1A**).
2. We suggest use of heparin doses of 100 to 150 U/kg as a bolus. Further doses may be required in prolonged procedures (both **Grade 2B**).
3. For prophylaxis for cardiac catheterization, we recommend against aspirin therapy (**Grade 1B**).

Femoral Artery Thrombosis

1. For children or neonates with femoral artery thrombosis, we recommend therapeutic doses of intravenous heparin (**Grade 1C**). We suggest treatment for at least 5 to 7 days (**Grade 2C**).
2. For children or neonates with limb- or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial heparin therapy and who have no known contraindications, we recommend administration of thrombolytic therapy (**Grade 1C**).
3. For children with femoral artery thrombosis, in selected cases, we suggest surgical intervention, in particular when there is a contraindication to thrombolytic therapy or organ or limb death is imminent (**Grade 2C**).

Peripheral Artery Thrombosis

1. For neonates and children with peripheral arterial catheters in situ, we recommend administration of low-dose heparin through the catheter, preferably by continuous infusion, to prolong the catheter patency (**Grade 1A**).
2. For children with a peripheral arterial catheter-related TE, we suggest immediate removal of the catheter (**Grade 2C**). We suggest subsequent anticoagulation with or without thrombolysis, depending on the clinical situation (**Grade 2C**).

Aortic Thrombosis Secondary to Umbilical Artery Catheters in Neonates

1. For neonates with umbilical artery catheters, we suggest low-dose heparin infusion (1–5 U/h) (**Grade 2A**).
2. We suggest that aortic thrombosis secondary to umbilical artery catheters is managed by the same principles as femoral artery thrombosis secondary to cardiac catheters. If there is evidence or renal failure, then urgent restoration of renal blood flow is required, and we suggest thrombolysis or thromboectomy (all **Grade 2C**).

Spontaneous Aortic Thrombosis in Neonates

1. For children suffering from spontaneous aortic thrombosis with evidence of renal ischemia, we suggest urgent, aggressive use of thrombolytic or surgical therapy, supported by anticoagulation therapy with heparin or LMWH (**Grade 2C**).

Kawasaki Disease

In children with Kawasaki disease,

1. We recommend aspirin in high doses (80–100 mg/kg/d during the acute phase, up to 14 days) as an anti-inflammatory agent and then in lower doses as an antiplatelet agent (3–5 mg/kg/d for 7 weeks or longer) (**Grade 1C+**).
2. We recommend intravenous gammaglobulin (2 g/kg single dose) within 10 days of onset of symptoms (**Grade 1A**).

Anticoagulation for Kawasaki Disease with Giant Aneurysms

1. In children with giant coronary aneurysms following Kawasaki disease, we suggest warfarin, at a target INR of 2.5 (range 2.0–3.0), in addition to low-dose aspirin (**Grade 2C**).

Sinovenous Thrombosis in Neonates

1. For neonates with cerebral venous thrombosis, without large ischemic infarct or intracranial hemorrhage, we suggest initial treatment with either UFH or LMWH followed by LMWH for 3 months (**Grade 2C**).
2. For neonates with cerebral venous thrombosis, without large ischemic infarct or intracranial hemorrhage, we suggest radiographic monitoring and commencement of anticoagulation if extension occurs (**Grade 2C**).

Sinovenous Thrombosis in Children

1. For children with cerebral venous thrombosis, we suggest treatment for 5 to 7 days with either UFH or LMWH followed by LMWH or vitamin K antagonists with a target INR of 2.5 (range 2.0–3.0) for 3 to 6 months even in the presence of a localized hemorrhagic infarct (**Grade 2C**).

AIS in Neonates

1. For neonates with noncardioembolic AIS, we suggest that clinicians do not use anticoagulation therapy or aspirin (**Grade 2C**).
2. For neonates with cardioembolic AIS, we suggest anticoagulation therapy with either UFH or LMWH for 3 months (**Grade 2C**).

AIS in Children

1. For children with AIS, we suggest treatment with UFH or LMWH for 5 to 7 days and until cardioembolic stroke or vascular dissection has been excluded (**Grade 2C**).
2. For children with AIS and cardioembolic stroke or vascular dissection, we suggest treatment for 5 to 7 days with UFH or LMWH followed by LMWH or vitamin K antagonists for 3 to 6 months (**Grade 2C**).
3. For all children with AIS, we suggest treatment with 2 to 5 mg/kg/d aspirin after anticoagulation has been discontinued (**Grade 2C**).
4. For children with sickle cell disease over 2 years of age, we recommend screening for stroke during transcranial Doppler ultrasonography. If transcranial Doppler ultrasonography is unavailable, we recommend intermittent screening with magnetic resonance imaging (**Grade 1C**).
5. For children with sickle cell disease who have AIS, we recommend intravenous hydration and exchange transfusion to reduce hemoglobin S to < 30% total hemoglobin (**Grade 1C**).
6. For children with sickle cell disease who have AIS, after initial exchange transfusion, we suggest a chronic transfusion program (**Grade 2C**).

Purpura Fulminans

1. For neonates with homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of fresh frozen plasma every 12 hours or protein C concentrate, when available, at 20 to 60 U/kg until the clinical lesions resolve (**Grade 1C+**).
2. We suggest long-term treatment with vitamin K antagonists (**Grade 2C**), LMWH (**Grade 2C**), protein C replacement (**Grade 1C+**), or liver transplant (**Grade 2C**).

SEVENTH ACCP CONFERENCE ON ANTITHROMBOTIC AND THROMBOEMBOLYTIC THERAPY: EVIDENCE-BASED GUIDELINES CHAPTER LISTING

Title	Chair and Co-Authors
Introduction – The Seventh (2003) ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines	Jack Hirsh, MD, FCCP Gord Guyatt, MD, MSc Greg Albers, MD Holger J. Schunemann, MD, PhD
Methodology for Guideline Development for the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy	Holger J. Schünemann, MD, PhD Heather Munger, MLS Stewart Brower, MLIS Martin O'Donnell, MD Mark Crowther, MD, MSc Deborah Cook, MD, MSc Gordon Guyatt, MD, MSc
Applying the Grades of Recommendation for Antithrombotic and Thrombolytic Therapy	Gordon Guyatt, MD, MSc Holger Schunemann, MD, PhD Deborah Cook, MD, MSc Roman Jaeschke, MD Stephen Pauker, MD
Heparin and Low-Molecular-Weight Heparin	Jack Hirsh, MD, FCCP Robert Raschke, MD, MS
The Pharmacology and Management of the Vitamin K Antagonists	Jack E. Ansell, MD Jack Hirsh, MD, FCCP Leon Poller, MD Henry Bussey Alan Jacobson Elaine Hylek
Platelet- Active Drugs: The Relationships Among Dose Effectiveness and Side Effects	Carlo Patrono, MD Barry Coller, MD Garret FitzGerald, MD Jack Hirsh, MD, FCCP Gerald Roth, MD
New Anticoagulant Drugs	Jeffrey I. Weitz, MD, FCCP Jack Hirsh, MD, FCCP Meyer M. Samama
Hemorrhagic Complications of Anticoagulant Treatment	Mark N. Levine, MD Gary Raskob, PhD Rebecca Beyth, MD, MSc Clive Kearon, MD, PhD, FCCP Sam Schulman, MD, PhD

Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention	Theodore Warkentin, MD Andreas Greinacher, MD
Prevention of Venous Thromboembolism	William H. Geerts, MD, FCCP Graham Pineo, MD John Heit, MD David Bergqvist, MD, PhD, FRCS Michael Lassen, MD Clifford Colwell, MD Joel Ray, MD, MSc
Antithrombotic Therapy for Venous Thromboembolic Disease	Harry R. Buller, MD Giancarlo Agnelli, MD Russel Hull, MBBS, MSc, FCCP Thomas Hyers, MD, FCCP Martin Prins, MD Gary Raskob, PhD
Antithrombotic Therapy in Atrial Fibrillation	Daniel E. Singer, MD Gregory Albers, MD James Dalen, MD, MPH Alan Go, MD Jonathan Halperin, MD Warren Manning, MD
Antithrombotic Therapy in Valvular Disease: Native and Prosthetic	Deeb N. Salem, MD, FCCP Paul Stein, MD, FCCP Amin Al-Ahmad, MD Henry Bussey, PharmD, FCCP Dieter Horstkotte, MD, FESC Nancy Miller, RN Stephen Pauker, MD
Antithrombotic Therapy and Thrombolytic Therapy for Ischemic Stroke	Gregory W. Albers, MD Pierre Amarenco, MD J. Donald Easton, MD Ralph Sacco, MD Philip Teal, MD
Antithrombotic Therapy in Coronary Artery Disease	Robert A. Harrington, MD Richard Becker, MD Michael Ezekowitz, MD Thomas Meade, DM Christopher O'Connor, MD David Vorchheimer, MD Gordon Guyatt, MD, FCCP
Intravenous Thrombolysis in Acute Myocardial Infarction	Venu Menon, MD, FACC Robert Harrington, MD, FACC Judith Hochman, MD, FACC Christopher Cannon, MD, FACC Shaun Goodman, MD, FACC

	Robert Wilcox, MD Holger Schunemann, MD, PhD E. Magnus Ohman, MD, FCCP
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