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Official publication of the American College of Chest Physicians



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Chest 2008;133;71-109
DOI 10.1378/chest.08-0693

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Executive Summary*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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(CHEST 2008; 133:71S–105S)

Key words: guidelines; recommendations

Abbreviations: ACCP = American College of Chest Physicians; ACS = acute coronary syndromes; AF = atrial fibrillation; AIS = arterial ischemic stroke; APTT = activated partial thromboplastin time; CABG = coronary artery bypass grafting; CrCl = creatinine clearance; CSVT = cerebral sinovenous thrombosis; CTPH = chronic thromboembolic pulmonary hypertension; CVL = central venous line; DVT = deep vein thrombosis; GCS = graduated compression stockings; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; IPC = intermittent pneumatic compression; INR = international normalized ratio; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; MVP = mitral valve prolapse; NSTEMI = non-ST-segment elevation; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PMBV = percutaneous mitral valve balloon valvotomy; PTS = postthrombotic syndrome; PVT = prosthetic valve thrombosis; SC = subcutaneous; SCI = spinal cord injury; TEE = transesophageal echocardiography; tPA = tissue plasminogen activator; UAC = umbilical artery catheter; UFH = unfractionated heparin; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism

This executive summary accompanies the publication of 8th edition of “Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines.” These guidelines provide an extensive

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Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0693

critical review of the literature related to management of thromboembolic disorders.

In each chapter, the clinical question under consideration, the clinical trials evaluating the evidence, and the recommendations are linked by a numbering scheme common to these three items. The recommendations are included at the beginning of the chapters and are presented in this executive summary.

The grading system in the 8th edition of the ACCP guidelines reflects the system adopted for all ACCP guidelines, and is similar to the GRADE system, which is being widely adopted by many guideline groups. The strength of any recommendation depends on two factors: the trade-off between benefits, risks, burden, and cost, and the level of confidence in estimates of those benefits and risks. If benefits do or do not outweigh risks, burden, and costs, a strong recommendation is designated as Grade 1. If there is less certainty about the magnitude of the benefits and risks, burden, and costs, a weaker Grade 2 recommendation is made. Support for these recommendations may come from high-quality, moderate-quality, or low-quality evidence, labeled, respectively, A, B, and C. The phrase “we recommend” is used for strong recommendations (Grade 1A, 1B, 1C) and “we suggest” for weaker recommendations (2A, 2B, 2C). The full set of recommendations follows.

PARENTERAL ANTICOAGULANTS

2.2.3 Monitoring Antithrombotic Effect

2.2.3. In patients treated with low-molecular-weight heparin (LMWH), we recommend against routine coagulation monitoring (Grade 1C). In pregnant women treated with therapeutic doses of LMWH, we recommend monitoring of anti-Xa levels (Grade 1C).

2.2.4 Dosing and Monitoring in Special Situations

2.2.4. In obese patients receiving LMWH prophylaxis or treatment, we suggest weight-based dosing (Grade 2C). In patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min) who require therapeutic anticoagulation, we suggest the use of unfractionated heparin (UFH) instead of LMWH (Grade 2C). If LMWH is used in patients with severe renal insufficiency (CrCl < 30 mL/min) who require therapeutic anticoagulation, we suggest using 50% of the recommended dose (Grade 2C).

3.0 Direct Thrombin Inhibitors

3.0. In patients who receive either lepirudin or desirudin and have renal insufficiency (CrCl < 60 mL/min but > 30 mL/min), we recommend that the dose be reduced and the drug monitored using the activated partial thromboplastin time (APTT) [Grade 1C]. In patients with a CrCl < 30 mL/min, we recommend against the use of lepirudin or desirudin (Grade 1C). In patients who require anticoagulation and have previously received lepirudin or desirudin, we recommend against repeated use of these drugs because of the risk of anaphylaxis (Grade 1C).

3.1 Monitoring of Direct Thrombin Inhibitors

3.1. In patients receiving argatroban who are being transitioned to a vitamin K antagonist (VKA), we suggest that factor X levels, measured using a chromogenic assay, be used to adjust the dose of the VKA (Grade 2C).

PHARMACOLOGY AND MANAGEMENT OF VKAS

2.1 Initiation and Maintenance Dosing

2.1.1. In patients beginning VKA therapy, we recommend the initiation of oral anticoagulation with doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 1B). At the present time, for patients beginning VKA therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C).

2.2 Initiation of Anticoagulation in the Elderly or Other Populations

2.2.1. In elderly patients or patients who are debilitated, are malnourished, have congestive

heart failure, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (eg, amiodarone), we recommend the use of a starting dose of ≤ 5 mg (Grade 1C), with subsequent dosing based on the INR response.

2.3 Frequency of Monitoring

2.3.1. In patients beginning VKA therapy, we suggest that INR monitoring should be started after the initial two or three doses of oral anticoagulation therapy (Grade 2C).

2.3.2. For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks (Grade 2C).

2.4 Management of Nontherapeutic INRs

2.4.1. For patients with INRs above the therapeutic range, but < 5.0 and with no significant bleeding, we recommend lowering the dose or omitting a dose, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level. If only minimally above therapeutic range, or associated with a transient causative factor, no dose reduction may be required (all Grade 1C).

2.4.2. For patients with INRs ≥ 5.0 but < 9.0 and no significant bleeding, we recommend omitting the next one or two doses, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level (Grade 1C). Alternatively, we suggest omitting a dose and administering vitamin K (1 to 2.5 mg) orally, particularly if the patient is at increased risk of bleeding (Grade 2A). If more rapid reversal is required because the patient requires urgent surgery, we suggest vitamin K (≤ 5 mg) orally, with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, we suggest additional vitamin K (1 to 2 mg) orally (Grade 2C).

2.4.3. For patients with INRs of > 9.0 and no significant bleeding, we recommend holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with the expectation that the INR will be reduced substantially in 24 to 48 h (Grade 1B). Clinicians should monitor the INR more frequently, administer additional vitamin K if necessary, and resume therapy at an appropriately adjusted dose when the INR reaches the therapeutic range.

2.4.4. In patients with serious bleeding and elevated INR, regardless of the magnitude of the

elevation, we recommend holding warfarin therapy and giving vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. We recommend repeating vitamin K administration every 12 h for persistent INR elevation (all Grade 1C).

2.4.5. In patients with life-threatening bleeding (eg, intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and administering fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa supplemented with vitamin K, 10 mg by slow IV infusion, repeated, if necessary, depending on the INR (Grade 1C).

2.4.6. In patients with mild-to-moderately elevated INRs without major bleeding, we recommend that when vitamin K is to be given, it be administered orally rather than subcutaneously (Grade 1A).

2.5 Management of Variable INRs

2.5.1. For patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability, we suggest a trial of daily low-dose oral vitamin K (100 to 200 µg) with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K (Grade 2B).

2.7 Management of INRs in Antiphospholipid Syndrome

2.7.1. In patients who have a lupus inhibitor, who have no additional risk factors, and no lack of response to therapy, we recommend a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 1A]. In patients who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thromboembolic events, we suggest a target INR of 3.0 (INR range, 2.5 to 3.5) [Grade 2C].

4.1 Optimal Management of VKA Therapy

4.1.1. For health-care providers who manage oral anticoagulation therapy, we recommend that they do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions as occurs in an anticoagulation management service (Grade 1B).

4.3 Patient Self-Testing and Patient Self-Management

4.3.1. Patient self-management is a choice made by patients and health-care providers that depends on many factors. In patients who are suitably selected and trained, patient self-testing and patient self-management is an effective alternative treatment model. We suggest that such therapeutic management be implemented where suitable (Grade 2B).

PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY

2.0 Perioperative Management of Patients Who Are Receiving VKAs

2.1. In patients who require temporary interruption of a VKA before surgery or a procedure and require normalization of the INR for the surgery or procedure, we recommend stopping VKAs approximately 5 days before surgery over stopping VKAs within a shorter time interval before surgery to allow adequate time for the INR to normalize (Grade 1B).

2.2. In patients who have had temporary interruption of a VKA before surgery or a procedure, we recommend resuming VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery and when there is adequate hemostasis over resumption of VKAs closer to surgery (Grade 1C).

2.3. In patients who require temporary interruption of a VKA before surgery or a procedure and whose INR is still elevated (ie, ≥ 1.5) 1 to 2 days before surgery, we suggest administering low-dose (ie, 1 to 2 mg) oral vitamin K to normalize the INR instead of not administering vitamin K (Grade 2C).

2.4. In patients with a mechanical heart valve or atrial fibrillation (AF) or venous thromboembolism (VTE) at high risk for thromboembolism, we recommend bridging anticoagulation with therapeutic-dose subcutaneous (SC) LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 1C); we suggest therapeutic-dose SC LMWH over IV UFH (Grade 2C). In patients with a mechanical heart valve or AT or VTE at moderate risk for thromboembolism, we suggest bridging anticoagulation with therapeutic-dose SC LMWH, therapeutic-dose IV UFH, or low-dose SC LMWH over no bridging during temporary interruption of VKA therapy (Grade 2C); we suggest therapeutic-dose SC LMWH over other management options (Grade 2C). In

patients with a mechanical heart valve or AF or VTE at low risk for thromboembolism, we suggest low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH (Grade 2C).

Underlying values and preferences: In patients at high or moderate risk for thromboembolism, the recommendations reflect a relatively high value on preventing thromboembolism and a relatively low value is on preventing bleeding; in patients at low risk for thromboembolism, the recommendations reflect a relatively high value on preventing bleeding and a relatively low value on preventing thromboembolism.

3.0 Perioperative Management of Patients Who Are Receiving Bridging Anticoagulation

3.1. In patients who require temporary interruption of VKAs and are to receive bridging anticoagulation, from a cost-containment perspective we recommend the use of SC LMWH administered in an outpatient setting where feasible instead of inpatient administration of IV UFH (Grade 1C).

Underlying values and preferences: This recommendation reflects a consideration not only of the trade-off between the advantages and disadvantages of SC LMWH and IV UFH as reflected in their effects on clinical outcomes (LMWH at least as good, possibly better), but also the implications in terms of resource use (costs) in a representative group of countries (substantially less resource use with LMWH).

3.2. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we recommend administering the last dose of LMWH 24 h before surgery or a procedure over administering LMWH closer to surgery (Grade 1C); for the last preoperative dose of LMWH, we recommend administering approximately half the total daily dose instead of 100% of the total daily dose (Grade 1C). In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we recommend stopping UFH approximately 4 h before surgery over stopping UFH closer to surgery (Grade 1C).

3.3. In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic-dose LMWH, we recommend resuming this regimen approximately 24 h after (eg, the day after) the procedure when there is adequate hemostasis over a shorter (eg, < 12 h) time interval (Grade 1C). In patients undergoing major surgery or a high bleeding risk surgery/procedure and for whom postoperative therapeutic-dose LMWH/UFH is planned, we recommend either delaying

the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured, administering low-dose LMWH/UFH after surgery when hemostasis is secured, or completely avoiding LMWH or UFH after surgery over the administration of therapeutic-dose LMWH/UFH in close proximity to surgery (Grade 1C). We recommend considering the anticipated bleeding risk and adequacy of postoperative hemostasis in individual patients to determine the timing of LMWH or UFH resumption after surgery instead of resuming LMWH or UFH at a fixed time after surgery in all patients (Grade 1C).

3.4. In patients who are receiving bridging anticoagulation with LMWH, we suggest against the routine use of anti-factor Xa levels to monitor the anticoagulant effect of LMWHs (Grade 2C).

4.0 Perioperative Management of Patients Who Are Receiving Antiplatelet Therapy

4.2. In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure, we suggest stopping this treatment 7 to 10 days before the procedure over stopping this treatment closer to surgery (Grade 2C).

4.3. In patients who have had temporary interruption of aspirin therapy because of surgery or a procedure, we suggest resuming aspirin approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming aspirin closer to surgery (Grade 2C). In patients who have had temporary interruption of clopidogrel because of surgery or a procedure, we suggest resuming clopidogrel approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming clopidogrel closer to surgery (Grade 2C).

4.4. In patients who are receiving antiplatelet drugs, we suggest against the routine use of platelet function assays to monitor the anti-thrombotic effect of aspirin or clopidogrel (Grade 2C).

4.5. For patients who are not at high risk for cardiac events, we recommend interruption of antiplatelet drugs (Grade 1C). For patients at high risk of cardiac events (exclusive of coronary stents) scheduled for noncardiac surgery, we suggest continuing aspirin up to and beyond the time of surgery (Grade 2C); if patients are receiving clopidogrel, we suggest interrupting clopidogrel at least 5 days and, preferably,

within 10 days prior to surgery (Grade 2C). In patients scheduled for coronary artery bypass grafting (CABG), we recommend continuing aspirin up to and beyond the time of CABG (Grade 1C); if aspirin is interrupted, we recommend it be reinitiated between 6 h and 48 h after CABG (Grade 1C). In patients scheduled for CABG, we recommend interrupting clopidogrel at least 5 days and, preferably, 10 days prior to surgery (Grade 1C). In patients scheduled for percutaneous coronary intervention (PCI), we suggest continuing aspirin up to and beyond the time of the procedure; if clopidogrel is interrupted prior to PCI, we suggest resuming clopidogrel after PCI with a loading dose of 300 to 600 mg (Grade 2C).

4.6. In patients with a bare metal coronary stent who require surgery within 6 weeks of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C). In patients with a drug-eluting coronary stent who require surgery within 12 months of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C). In patients with a coronary stent who have interruption of antiplatelet therapy before surgery, we suggest against the routine use of bridging therapy with UFH, LMWH, direct thrombin inhibitors, or glycoprotein (GP) IIb/IIIa inhibitors (Grade 2C).

Underlying values and preferences: These recommendations reflect a relatively high value placed on preventing stent-related coronary thrombosis, a consideration of complexity and costs of administering bridging therapy in the absence of efficacy and safety data in this clinical setting, and a relatively low value on avoiding the unknown but potentially large increase in bleeding risk associated with the concomitant administration of aspirin and clopidogrel during surgery.

5.0 Perioperative Management of Antithrombotic Therapy in Patients Who Require Dental, Dermatologic, or Ophthalmologic Procedures

5.1. In patients who are undergoing minor dental procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure and coadministering an oral prohemostatic agent (Grade 1B). In patients who are undergoing minor dental procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure (Grade 1C). In patients who are undergoing minor dental procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.

5.2. In patients who are undergoing minor dermatologic procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C). In patients who are undergoing minor dermatologic procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure (Grade 1C). In patients who are undergoing minor dermatologic procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.

5.3. In patients who are undergoing cataract removal and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C). In patients who are undergoing cataract removal and are receiving aspirin, we recommend continuing aspirin around the time of the procedure (Grade 1C). In patients who are undergoing cataract removal and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.

6.0 Perioperative Management of Antithrombotic Therapy Patients Who Require Urgent Surgical or Other Invasive Procedures

6.1. In patients who are receiving VKAs and require reversal of the anticoagulant effect for an urgent surgical or other invasive procedure, we recommend treatment with low-dose (2.5 to 5.0 mg) IV or oral vitamin K (Grade 1C). For more immediate reversal of the anticoagulant effect, we suggest treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose IV or oral vitamin K (Grade 2C).

6.2. For patients receiving aspirin, clopidogrel, or both, are undergoing surgery and have excessive or life-threatening perioperative bleeding, we suggest transfusion of platelets or administration of other prohemostatic agents (Grade 2C).

TREATMENT AND PREVENTION OF HEPARIN-INDUCED THROMBOCYTOPENIA

1.0 Recognition of Heparin-Induced Thrombocytopenia

1.1 Platelet Count Monitoring for HIT

1.1. For patients receiving heparin in whom the clinician considers the risk of heparin-induced thrombocytopenia (HIT) to be > 1.0%, we recommend platelet count monitoring over no platelet count monitoring (Grade 1C). For patients receiving heparin who have an estimated risk of HIT of 0.1 to 1.0%, we suggest platelet count monitoring over no platelet count monitoring (Grade 2C).

1.1.1 Platelet Count Monitoring of Patients Recently Treated With Heparin

1.1.1. For patients who are starting UFH or LMWH treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, we recommend obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin over not obtaining a repeat platelet count (Grade 1C).

1.1.2 Anaphylactoid Reactions After IV UFH Bolus

1.1.2. For patients in whom acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs develop within 30 min following an IV UFH bolus, we recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, over not performing a platelet count (Grade 1C).

1.1.3 Platelet Count Monitoring in Patients Receiving Therapeutic-Dose UFH

1.1.3. For patients who are receiving therapeutic-dose UFH, we suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) over less frequent platelet count monitoring (Grade 2C).

1.1.4 Platelet Count Monitoring in Postoperative Patients Receiving UFH Antithrombotic Prophylaxis (Highest Risk Group for HIT)

1.1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH, *ie*, the patient population at highest risk for HIT (HIT risk > 1%), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14 (or until UFH is stopped, whichever occurs first) over less frequent platelet count monitoring (Grade 2C).

1.1.5 Platelet Count Monitoring in Patients in Whom HIT Is Infrequent (0.1 to 1%)

1.1.5. For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH “flushes,” or medical/obstetrical patients receiving LMWH after first receiving UFH (estimated HIT risk, 0.1 to 1%), we suggest

platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical, over less frequent platelet count monitoring (Grade 2C).

1.1.6 Platelet Count Monitoring When HIT Is Rare (< 0.1%): UFH and LMWH

1.1.6. For medical/obstetrical patients who are receiving only LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk < 0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C).

1.1.7 Platelet Count Monitoring When HIT Is Rare (< 0.1%): Fondaparinux

1.1.7. For patients who are receiving fondaparinux thromboprophylaxis or treatment, we recommend that clinicians do not use routine platelet count monitoring (Grade 1C).

1.1.8 Management of Patients in Whom Platelet Counts Are Not Monitored

1.1.8. In outpatients who will receive heparin prophylaxis or treatment, informed consent should include HIT and its typical sequelae (new thrombosis, skin lesions), and the patient should be advised to seek medical advice if these events occur (Grade 2C).

1.1.9 Screening for Subclinical HIT Antibody Seroconversion

1.1.9. In patients who receive heparin, or in whom heparin treatment is planned (*eg*, for cardiac or vascular surgery), we recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT (Grade 1C).

1.1.10 When Should HIT Be Suspected?

1.1.10. For patients who are receiving heparin or have received heparin within the previous 2 weeks, we recommend investigating for a diagnosis of HIT if the platelet count falls by $\geq 50\%$, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred (Grade 1C).

1.2 Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring After Cardiac Surgery

1.2. For postoperative cardiac surgery patients, we recommend investigating for HIT antibodies if the platelet count falls by $\geq 50\%$, and/or a thrombotic event occurs, between postoperative days 5 and 14 (inclusive; day of cardiac surgery = day 0) [Grade 1C].

2.0 Treatment of HIT

2.1 Nonheparin Anticoagulants for Treating HIT (With or Without Thrombosis)

2.1.1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], bivalirudin [Grade 2C]) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA (Grade 1B).

2.1.2. For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h (patients with creatinine $< 90 \mu\text{mol/L}$), with lower infusion rates for patients with higher serum creatinine levels (creatinine, 90 to 140 $\mu\text{mol/L}$: starting infusion rate, 0.05 mg/kg/h; creatinine, 140 to 400 $\mu\text{mol/L}$: starting infusion rate, 0.01 mg/kg/h; creatinine $> 400 \mu\text{mol/L}$: starting infusion rate, 0.005 mg/kg/h) [Grade 1C]. Furthermore, we recommend that the initial IV bolus either be omitted or, in case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg) [Grade 1C]. Further, we recommend that APTT monitoring be performed at 4-h intervals until it is apparent that steady state within the normal range (1.5 to 2.5 times patient baseline [or mean laboratory] APTT) is achieved (Grade 1C).

2.1.3. When argatroban is used to treat patients who have heart failure, multiple organ system failure, or severe anasarca, or who are postcardiac surgery, we suggest beginning the initial infusion at a rate between 0.5 and 1.2 $\mu\text{g/kg/min}$, with subsequent adjustments using the APTT, over the usual recommended starting dose of 2.0 $\mu\text{g/kg/min}$ (Grade 2C).

2.1.4. When danaparoid is used to treat patients with strongly suspected (or confirmed) HIT, we recommend a therapeutic-dose regimen (see text) administered (at least initially)

by the IV route over prophylactic-dose regimens or initial SC administration (Grade 1B). **2.1.5.** For patients with strongly suspected or confirmed HIT, whether or not there is clinical evidence of lower-limb deep vein thrombosis (DVT), we recommend routine ultrasonography of the lower-limb veins for investigation of DVT over not performing routine ultrasonography (Grade 1C).

2.2 VKAs

2.2.1 Management of Direct Thrombin Inhibitor-VKA Overlap

2.1.1. For patients with strongly suspected or confirmed HIT, we recommend against the use of VKA (coumarin) therapy until after the platelet count has substantially recovered (*ie*, usually to at least $150 \times 10^9/\text{L}$) over starting VKA therapy at a lower platelet count (Grade 1B); that VKA therapy be started only with low, maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) rather than with higher initial doses (Grade 1B); and the nonheparin anticoagulant (*eg*, lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the INR has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and VKA therapy rather than a shorter overlap (Grade 1B).

2.2.2 Reversal of VKA Anticoagulation

2.2.2. For patients receiving a VKA at the time of diagnosis of HIT, we recommend use of vitamin K (10 mg po or 5 to 10 mg IV) [Grade 1C].

2.3 LMWH for HIT

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

2.4 Prophylactic Platelet Transfusions for HIT

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

3.0 Special Patient Populations

3.1 Patients With Previous HIT Undergoing Cardiac or Vascular Surgery

3.1.1. For patients with a history of HIT who are HIT antibody negative and require cardiac sur-

gery, we recommend the use of UFH over a nonheparin anticoagulant (Grade 1B).

3.1.2. For patients with a history of HIT who are antibody positive by platelet factor 4-dependent enzyme immunosorbent assay but antibody negative by washed platelet activation assay, we recommend the use of UFH over a nonheparin anticoagulant (Grade 2C).

Remark: Preoperative and postoperative anticoagulation, if indicated, should be given with a nonheparin anticoagulant.

3.2 Patients With Acute or Subacute HIT Undergoing Cardiac Surgery

3.2.1. 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 has resolved and antibodies are negative (then see Recommendation 3.1.1.) or weakly positive (then see Recommendation 3.1.2.) [Grade 1B]; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if techniques of cardiac surgery and anesthesiology have been adapted to the unique features of bivalirudin pharmacology) [Grade 1B] or during “off-pump” cardiac surgery (Grade 1B); using lepirudin for intraoperative anticoagulation (if ECT is available and patient has normal renal function and is judged to be at low risk for postcardiac surgery renal dysfunction) [Grade 2C]; using UFH plus the antiplatelet agent epoprostenol (if ECT 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 for off-pump CABG (Grade 2C) over performing the surgery with UFH when platelet-activating anti-platelet factor 4/heparin antibodies are known to be present in a patient with acute or recent HIT.

3.2.2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody positive), we recommend delaying surgery (if possible) until HIT antibodies (washed platelet activation assay) are negative, then using heparin (see Recommendation 3.1.1.) over using a nonheparin anticoagulant (Grade 1C). If surgery cannot be delayed, we suggest the use of a nonheparin anticoagulant (see Recommendation 3.2.1.) over the use of UFH (Grade 2C).

3.3 PCIs

3.3.1. For patients with strongly suspected (or confirmed) acute HIT who require cardiac catheterization or PCI, we recommend a nonheparin anticoagulant (bivalirudin [Grade 1B], argatroban [Grade 1C], lepirudin [Grade 1C], or danaparoid [Grade 1C]) over UFH or LMWH (Grade 1B).

3.3.2. For patients with previous HIT (who are antibody negative) who require cardiac catheterization or PCI, we suggest use of a nonheparin anticoagulant (see Recommendation 3.3.1.) over UFH or LMWH (Grade 2C).

PREVENTION OF VTE

1.0 GENERAL RECOMMENDATIONS

Hospital Thromboprophylaxis Policy

1.2.1. For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed (Grade 1A).

1.2.2. We recommend that the local thromboprophylaxis strategy be in the form of a written, institution-wide thromboprophylaxis policy (Grade 1C).

1.2.3. We recommend the use of strategies shown to increase thromboprophylaxis adherence, including the use of computer decision support systems (Grade 1A), preprinted orders (Grade 1B), and periodic audit and feedback (Grade 1C). Passive methods such as distribution of educational materials or educational meetings are not recommended as sole strategies to increase adherence to thromboprophylaxis (Grade 1B).

Mechanical Methods of Thromboprophylaxis

1.4.3.1. We recommend that mechanical methods of thromboprophylaxis be used primarily in patients at high risk of bleeding (Grade 1A), or possibly as an adjunct to anticoagulant-based thromboprophylaxis (Grade 2A).

1.4.3.2. For patients receiving mechanical methods of thromboprophylaxis, we recommend that careful attention be directed toward ensuring the proper use of, and optimal adherence with, these methods (Grade 1A).

Aspirin as Thromboprophylaxis

1.4.4. We recommend against the use of aspirin alone as thromboprophylaxis against VTE for any patient group (Grade 1A).

Anticoagulant Dosing

1.4.5. For each of the antithrombotic agents, we recommend that clinicians follow manufacturer-suggested dosing guidelines (Grade 1C).

Renal Impairment and Anticoagulant Dosing

1.4.6. We recommend that renal function be considered when making decisions about the use and/or the dose of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those at high risk for bleeding (Grade 1A). Depending on the circumstances, we recommend one of the following options in this situation: avoiding the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent, or monitoring the drug level or its anticoagulant effect (Grade 1B).

Antithrombotic Drugs and Neuraxial Anesthesia/Analgesia or Peripheral Nerve Blocks

1.5.1. For all patients undergoing neuraxial anesthesia or analgesia, we recommend appropriate patient selection and caution when using anticoagulant thromboprophylaxis (Grade 1A).

1.5.2. For patients receiving deep peripheral nerve blocks, we recommend that the same cautions considered for neuraxial techniques be applied when using anticoagulant thromboprophylaxis (Grade 1C).

2.0 GENERAL, VASCULAR, GYNECOLOGIC, UROLOGIC, LAPAROSCOPIC, BARIATRIC, THORACIC, AND CABG SURGERY

2.1 General Surgery

2.1.1. For low-risk general surgery patients who are undergoing minor procedures and have no additional thromboembolic risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A).

2.1.2. For moderate-risk general surgery patients who are undergoing a major procedure for benign disease, we recommend thromboprophylaxis with LMWH, low-dose UFH (LDUH), or fondaparinux (each Grade 1A).

2.1.3. For higher-risk general surgery patients who are undergoing a major procedure for cancer, we recommend thromboprophylaxis with LMWH, LDUH tid, or fondaparinux (each Grade 1A).

2.1.4. For general surgery patients with multiple risk factors for VTE who are thought to be at particularly high risk, we recommend that a pharmacologic method (*ie*, LMWH, LDUH tid, or fondaparinux) be combined with the optimal use of a mechanical method (*ie*, graduated compression stockings [GCS] and/or intermittent pneumatic compression [IPC]) [Grade 1C].

2.1.5. For general surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS or IPC (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

2.1.6. For patients undergoing major general surgical procedures, we recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered (Grade 2A).

2.2 Vascular Surgery

2.2.1. For patients undergoing vascular surgery, who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2B).

2.2.2. For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (Grade 1C).

2.3 Gynecologic Surgery

2.3.1. For low-risk gynecologic surgery patients who are undergoing minor procedures and have no additional risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A).

2.3.2. For gynecology patients undergoing entirely laparoscopic procedures, we recommend against routine thromboprophylaxis, other than early and frequent ambulation (Grade 1B).

2.3.3. For gynecology patients undergoing entirely laparoscopic procedures in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, IPC, or GCS (Grade 1C).

2.3.4. For all patients undergoing major gynecologic surgery, we recommend that thromboprophylaxis be used routinely (Grade 1A).

2.3.5 For patients undergoing major gynecologic surgery for benign disease, without additional risk factors, we recommend LMWH (Grade 1A), LDUH (Grade 1A), or IPC started just before surgery and used continuously while the patient is not ambulating (Grade 1B).

2.3.6. For patients undergoing extensive surgery for malignancy, and for patients with additional VTE risk factors, we recommend routine thromboprophylaxis with LMWH (Grade 1A), or LDUH three times daily (Grade 1A), or IPC, started just before surgery and used continuously while the patient is not ambulating (Grade 1A). Alternative considerations include a combination of LMWH or LDUH plus mechanical thromboprophylaxis with GCS or IPC, or fondaparinux (all Grade 1C).

2.3.7. For patients undergoing major gynecologic procedures, we recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). For selected high-risk gynecology patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered (Grade 2C).

2.4 Urologic Surgery

2.4.1. For patients undergoing transurethral or other low-risk urologic procedures, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A).

2.4.2. For all patients undergoing major, open urologic procedures, we recommend that thromboprophylaxis be used routinely (Grade 1A).

2.4.3. For patients undergoing major, open urologic procedures, we recommend routine thromboprophylaxis with LDUH bid or tid (Grade 1B), GCS, and/or IPC started just before surgery and used continuously while the patient is not ambulating (Grade 1B), LMWH (Grade 1C), fondaparinux (Grade 1C), or the combination of a pharmacologic method (*ie*, LMWH, LDUH, or fondaparinux) with the optimal use of a mechanical method (*ie*, GCS and/or IPC) [Grade 1C].

2.4.4. For urologic surgery patients who are actively bleeding, or who are at very high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases

(Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

2.5 Laparoscopic Surgery

2.5.1. For patients undergoing entirely laparoscopic procedures who do not have additional thromboembolic risk factors, we recommend against the routine use of thromboprophylaxis, other than early and frequent ambulation (Grade 1B).

2.5.2. For patients undergoing laparoscopic procedures, in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, fondaparinux, IPC, or GCS (all Grade 1C).

2.6 Bariatric Surgery

2.6.1. For patients undergoing in-patient bariatric surgery, we recommend routine thromboprophylaxis with LMWH, LDUH tid, fondaparinux, or the combination of one of these pharmacologic methods with optimally used IPC (each Grade 1C).

2.6.2. For patients undergoing inpatient bariatric surgery, we suggest that higher doses of LMWH or LDUH than usual for nonobese patients be used (Grade 2C).

2.7 Thoracic Surgery

2.7.1. For patients undergoing major thoracic surgery, we recommend routine thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1C).

2.7.2. For thoracic surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS and/or IPC (Grade 1C).

2.8 Coronary Bypass Surgery

2.8.1. For patients undergoing CABG, we recommend the use of thromboprophylaxis with LMWH, LDUH, or optimally used bilateral GCS or IPC (Grade 1C).

2.8.2. For patients undergoing CABG, we suggest the use of LMWH over LDUH (Grade 2B).

2.8.3. For patients undergoing CABG with a high risk of bleeding, we recommend the opti-

mal use of mechanical thromboprophylaxis with properly fitted bilateral GCS or IPC (Grade 1C).

3.0 ORTHOPEDIC SURGERY

3.1 Elective Hip Replacement

3.1.1. For patients undergoing elective total hip replacement, we recommend the routine use of one of the following anticoagulant options: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6 to 24 h after surgery); or (3) adjusted-dose VKA started preoperatively or the evening of the surgical day (INR target, 2.5; INR range, 2.0 to 3.0) [all Grade 1A].

3.1.2. For patients undergoing total hip replacement, we recommended against the use of any of the following: aspirin, dextran, LDUH, GCS, or venous foot pump (VFP) as the sole method of thromboprophylaxis (all Grade 1A).

3.1.3. For patients undergoing total hip replacement who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with the VFP or IPC (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

3.2 Elective Knee Replacement

3.2.1. For patients undergoing total knee replacement, we recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0) [all Grade 1A].

3.2.2. For patients undergoing total knee replacement, the optimal use of IPC is an alternative option to anticoagulant thromboprophylaxis (Grade 1B).

3.2.3. For patients undergoing total knee replacement, we recommend against the use of any of the following as the only method of thromboprophylaxis: aspirin (Grade 1A), LDUH (Grade 1A), or VFP (Grade 1B).

3.2.4. For patients undergoing total knee replacement who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with IPC (Grade 1A) or VFP (Grade 1B). When the high bleeding risk decreases, we recommend that pharmaco-

logic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

3.3 Knee Arthroscopy

3.3.1. For patients undergoing knee arthroscopy who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use thromboprophylaxis other than early mobilization (Grade 2B).

3.3.2. For patients undergoing arthroscopic knee surgery who have additional thromboembolic risk factors or following a complicated procedure, we recommend thromboprophylaxis with LMWH (Grade 1B).

3.4 Hip Fracture Surgery

3.4.1. For patients undergoing hip fracture surgery, we recommend routine thromboprophylaxis using fondaparinux (Grade 1A), LMWH (Grade 1B), adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0) [Grade 1B], or LDUH (Grade 1B).

3.4.2. For patients undergoing hip fracture surgery, we recommend against the use of aspirin alone (Grade 1A).

3.4.3. For patients undergoing hip fracture surgery in whom surgery is likely to be delayed, we recommend that thromboprophylaxis with LMWH or LDUH be initiated during the time between hospital admission and surgery (Grade 1C).

3.4.4. For patients undergoing hip fracture surgery who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

3.5 Other Thromboprophylaxis Issues in Major Orthopedic Surgery

Commencement of Thromboprophylaxis

3.5.1.1. For patients receiving LMWH as thromboprophylaxis in major orthopedic surgery, we recommend starting either preoperatively or postoperatively (Grade 1A).

3.5.1.2. For patients receiving fondaparinux as thromboprophylaxis in major orthopedic surgery, we recommend starting either 6 to 8 h after surgery or the next day (Grade 1A).

3.5.2. For asymptomatic patients following major orthopedic surgery, we recommend against the routine use of DUS screening before hospital discharge (Grade 1A).

Duration of Thromboprophylaxis

3.5.3.1. For patients undergoing total hip replacement, total knee replacement, or hip fracture surgery, we recommend thromboprophylaxis with one of the recommended options for at least 10 days (Grade 1A).

3.5.3.2. For patients undergoing total hip replacement, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A). The recommended options for extended thromboprophylaxis in total hip replacement include LMWH (Grade 1A), a VKA (Grade 1B), or fondaparinux (Grade 1C).

3.5.3.3. For patients undergoing total knee replacement, we suggest that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 2B). The recommended options for extended thromboprophylaxis in total knee replacement include LMWH (Grade 1C), a VKA (Grade 1C), or fondaparinux (Grade 1C).

3.5.3.4. For patients undergoing hip fracture surgery, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A). The recommended options for extended thromboprophylaxis in hip fracture surgery include fondaparinux (Grade 1A), LMWH (Grade 1C), or a VKA (Grade 1C).

3.6 Elective Spine Surgery

3.6.1. For patients undergoing spine surgery who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2C).

3.6.2. For patients undergoing spine surgery who have additional thromboembolic risk factors, such as advanced age, malignancy, presence of a neurologic deficit, previous VTE, or an anterior surgical approach, we recommend that one of the following thromboprophylaxis options be used: postoperative LDUH (Grade 1B), postoperative LMWH (Grade 1B), or optimal use of perioperative IPC (Grade 1B). An alternative consideration is GCS (Grade 2B).

3.6.3. For patients undergoing spine surgery who have multiple risk factors for VTE, we

suggest that a pharmacologic method (*ie*, LDUH or LMWH) be combined with the optimal use of a mechanical method (*ie*, GCS and/or IPC) [Grade 2C].

3.7 Isolated Lower-Extremity Injuries Distal to the Knee

3.7.1. For patients with isolated lower-extremity injuries distal to the knee, we suggest that clinicians do not routinely use thromboprophylaxis (Grade 2A).

4.0 NEUROSURGERY

4.0.1. For patients undergoing major neurosurgery, we recommend that thromboprophylaxis be used routinely (Grade 1A), with optimal use of IPC (Grade 1A). Acceptable alternatives to IPC are postoperative LMWH (Grade 2A) or LDUH (Grade 2B).

4.0.2. For patients undergoing major neurosurgery who have a particularly high thrombosis risk, we suggest that a mechanical method (*ie*, GCS and/or IPC) be combined with a pharmacologic method (*ie*, postoperative LMWH or LDUH) [Grade 2B].

5.0 TRAUMA, SPINAL CORD INJURY, BURNS

5.1 Trauma

5.1.1. For all major trauma patients, we recommend routine thromboprophylaxis, if possible (Grade 1A).

5.1.2. For major trauma patients, in the absence of a major contraindication, we recommend that clinicians use LMWH thromboprophylaxis starting as soon as it is considered safe to do so (Grade 1A). An acceptable alternative is the combination of LMWH and the optimal use of a mechanical method of thromboprophylaxis (Grade 1B).

5.1.3. For major trauma patients, if LMWH thromboprophylaxis is contraindicated due to active bleeding or high risk for clinically important bleeding, we recommend that mechanical thromboprophylaxis with IPC, or possibly with GCS alone, be used (Grade 1B). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

5.1.4. In trauma patients, we recommend against

routine DUS screening for asymptomatic DVT (Grade 1B). We do recommend DUS screening in patients who are at high risk for VTE (eg, in the presence of a spinal cord injury [SCI], lower-extremity or pelvic fracture, or major head injury) and who have received suboptimal thromboprophylaxis or no thromboprophylaxis (Grade 1C).

5.1.5. For trauma patients, we recommend against the use of an inferior vena cava filter as thromboprophylaxis (Grade 1C).

5.1.6. For major trauma patients, we recommend the continuation of thromboprophylaxis until hospital discharge (Grade 1C). For trauma patients with impaired mobility who undergo inpatient rehabilitation, we suggest continuing thromboprophylaxis with LMWH or a VKA (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C].

5.2 Acute SCI

5.2.1. For all patients with acute SCI, we recommend that routine thromboprophylaxis be provided (Grade 1A).

5.2.2. For patients with acute SCI, we recommend thromboprophylaxis with LMWH, commenced once primary hemostasis is evident (Grade 1B). Alternatives include the combined use of IPC and either LDUH (Grade 1B) or LMWH (Grade 1C).

5.2.3. For patients with acute SCI, we recommend the optimal use of IPC and/or GCS if anticoagulant thromboprophylaxis is contraindicated because of high bleeding risk early after injury (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

5.2.4. For patients with an incomplete SCI associated with evidence of a spinal hematoma on CT or MRI, we recommend the use of mechanical thromboprophylaxis instead of anticoagulant thromboprophylaxis at least for the first few days after injury (Grade 1C).

5.2.5. Following acute SCI, we recommend against the use of LDUH alone (Grade 1A).

5.2.6. For patients with SCI, we recommend against the use of an inferior vena cava filter as thromboprophylaxis (Grade 1C).

5.2.7. For patients undergoing rehabilitation following acute SCI, we recommend the continuation of LMWH thromboprophylaxis or conversion to an oral VKA (INR target, 2.5; range, 2.0 to 3.0) [Grade 1C].

5.3 Burns

5.3.1. For burn patients who have 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 a femoral venous catheter, and/or prolonged immobility, we recommend routine thromboprophylaxis if possible (Grade 1A).

5.3.2. For burn patients who have additional risk factors for VTE, if there are no contraindications, we recommend the use of either LMWH or LDUH, starting as soon as it is considered safe to do so (Grade 1C).

5.3.3. For burn patients who have a high bleeding risk, we recommend mechanical thromboprophylaxis with GCS and/or IPC until the bleeding risk decreases (Grade 1A).

6.0 MEDICAL CONDITIONS

6.0.1. For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A), LDUH (Grade 1A), or fondaparinux (Grade 1A).

6.0.2. For medical patients with risk factors for VTE, and in whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with GCS or IPC (Grade 1A).

7.0 CANCER PATIENTS

7.0.1. For cancer patients undergoing surgical procedures, we recommend routine thromboprophylaxis that is appropriate for the type of surgery (Grade 1A). Refer to the recommendations in the relevant surgical subsections.

7.0.2. For cancer patients who are bedridden with an acute medical illness, we recommend routine thromboprophylaxis as for other high-risk medical patients (Grade 1A). Refer to the recommendations in Section 6.0.

7.0.3. For cancer patients with indwelling central venous catheters, we recommend that clinicians not use either prophylactic doses of LMWH (Grade 1B) or mini-dose warfarin (Grade 1B) to try to prevent catheter-related thrombosis.

7.0.4. For cancer patients receiving chemotherapy or hormonal therapy, we recommend against the routine use of thromboprophylaxis for the primary prevention of VTE (Grade 1C).

7.0.5. For cancer patients, we recommend against the routine use of primary thromboprophylaxis to try to improve survival (Grade 1B).

8.0 CRITICAL CARE

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).

8.2. For critical care patients who are at moderate risk for VTE (*eg*, medically ill or postoperative general surgery patients), we recommend using LMWH or LDUH thromboprophylaxis (Grade 1A).

8.3. For critical care patients who are at higher risk (*eg*, following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A).

8.4. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

9.0 LONG-DISTANCE TRAVEL

9.1. For travelers who are taking flights > 8 h, we recommend the following general measures: avoidance of constrictive clothing around the lower extremities or waist, maintenance of adequate hydration, and frequent calf muscle contraction (Grade 1C).

9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general measures listed above. If active thromboprophylaxis is considered because of a perceived high risk of VTE, we suggest the use of properly fitted, below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (Grade 2C), or a single prophylactic dose of LMWH, injected prior to departure (Grade 2C).

9.3. For long-distance travelers, we recommend against the use of aspirin for VTE prevention (Grade 1B).

ANTITHROMBOTIC THERAPY FOR VENOUS THROMBOEMBOLIC DISEASE

1.1 Initial Anticoagulation of Acute DVT of the Leg

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH (Grade 1A), IV UFH (Grade 1A), monitored SC UFH (Grade 1A), fixed-dose SC UFH (Grade 1A), or SC fondaparinux (Grade 1A) rather than no such acute treatment.

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C).

1.1.3. In patients with acute DVT, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for 24 h (Grade 1C).

1.1.4. In patients with acute DVT, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A).

1.2 IV UFH for the Initial Treatment of DVT

1.2.1. In patients with acute DVT, if IV UFH is chosen, we recommend that, after an initial IV bolus (80 U/kg or 5,000 U) it be administered by continuous infusion (initially at a dose of 18 U/kg/h or 1,300 U/h) with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C).

1.3 SC UFH Compared With IV Heparin for the Initial Treatment of DVT

1.3.1. In patients with acute DVT, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of about 250 U/kg, bid, with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (Grade 1C) [see also Section 1.5].

1.3.2. In patients with acute DVT, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/kg followed by a twice-daily dose of 250 U/kg rather than nonweight-based dosing (Grade 1C) [see also Section 1.5].

1.4 LMWH for the Initial Treatment of DVT

1.4.1. In patients with acute DVT, we recommend initial treatment with LMWH SC once or twice daily, as an outpatient if possible (Grade 1C) or as an inpatient if necessary (Grade 1A), rather than treatment with IV UFH.

1.4.2. In patients with acute DVT treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A).

1.4.3. In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C).

1.9 Catheter-Directed Thrombolysis for Acute DVT

1.9.1. In selected patients with extensive acute proximal DVT (*eg*, iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year) who have a low risk of bleeding, we suggest that catheter-directed thrombolysis may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B).

1.9.2. After successful catheter-directed thrombolysis in patients with acute DVT, we suggest correction of underlying venous lesions using balloon angioplasty and stents (Grade 2C).

1.9.3. We suggest pharmacomechanical thrombolysis (*eg*, with inclusion of thrombus fragmentation and/or aspiration) in preference to catheter-directed thrombolysis alone to shorten treatment time if appropriate expertise and resources are available (Grade 2C).

1.9.4. After successful catheter-directed thrombolysis in patients with acute DVT, we recommend the same intensity and duration of anticoagulant therapy as for comparable patients who do not undergo catheter-directed thrombolysis (Grade 1C).

1.10 Systemic Thrombolytic Therapy for Acute DVT

1.10.1. In selected patients with extensive proximal DVT (*eg*, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year) who have a low risk of bleeding, we suggest that systemic thrombolytic therapy may be used to reduce acute symptoms and postthrombotic morbidity if catheter-directed thrombolysis is not available (Grade 2C).

1.11 Percutaneous Venous Thrombectomy

1.11.1. In patients with acute DVT, we suggest that they should not be treated with percutaneous mechanical thrombectomy alone (Grade 2C).

1.12 Operative Venous Thrombectomy for Acute DVT

1.12.1. In selected patients with acute iliofemoral DVT (*eg*, symptoms for < 7 days, good functional status, and life expectancy of ≥ 1 year), we suggest that operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B). If such patients do not have a high risk of bleeding, we suggest that catheter-directed thrombolysis is usually preferable to operative venous thrombectomy (Grade 2C).

1.12.2. In patients who undergo operative venous thrombectomy, we recommend the same intensity and duration of anticoagulant therapy afterwards as for comparable patients who do not undergo venous thrombectomy (Grade 1C).

1.13 Vena Caval Filters for the Initial Treatment of DVT

1.13.1. For patients with DVT, we recommend against the routine use of a vena cava filter in addition to anticoagulants (Grade 1A).

1.13.2. For patients with acute proximal DVT, if anticoagulant therapy is not possible because of the risk of bleeding, we recommend placement of an inferior vena cava filter (Grade 1C).

1.13.3. For patients with acute DVT who have an inferior vena cava filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).

1.14 Immobilization for the Treatment of Acute DVT

1.14.1. In patients with acute DVT, we recommend early ambulation in preference to initial bed rest when this is feasible (Grade 1A).

2.1 Duration of Anticoagulant Therapy

2.1.1. For patients with DVT secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A).

2.1.2. For patients with unprovoked DVT, we recommend treatment with a VKA for at least 3 months (Grade 1A). We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-benefit ratio of long-term therapy (Grade 1C). For patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment (Grade 1A).

Underlying values and preferences: This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A). For patients with a first isolated distal DVT that is unprovoked, we suggest that 3 months of anticoagulant therapy is sufficient rather than indefinite therapy (Grade 2B).

2.1.3. 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 subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4) [Grade 1C].

2.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C).

2.2 Intensity of Anticoagulant Effect

2.2.1. In patients with DVT, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A). For patients with unprovoked DVT who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of conventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (INR range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment (Grade 1A). We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared to an INR range of 2.0 to 3.0 (Grade 1A).

2.6 Treatment of Asymptomatic DVT of the Leg

2.6.1. In patients who are unexpectedly found to have asymptomatic DVT, we recommend the

same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 1C).

3.1 Elastic Stockings and Compression Bandages To Prevent Postthrombotic Syndrome

3.1.1. For a patient who has had a symptomatic proximal DVT, we recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A). Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum of 2 years, and longer if patients have symptoms of the postthrombotic syndrome (PTS). (Note: feasibility, both short and long term, refers to ability of patients and their caregivers to apply and remove stockings.)

Underlying values and preferences: This recommendation attaches a relatively high value to long-term prevention of the postthrombotic syndrome (PTS) and a low value to the burden (*eg*, inconvenience or discomfort) associated with wearing stockings.

3.2 Physical Treatment of PTS Without Venous Leg Ulcers

3.2.1. For patients with severe edema of the leg due to PTS, we suggest a course of IPC (Grade 2B).

3.2.2. For patients with mild edema of the leg due to PTS, we suggest the use of elastic compression stockings (Grade 2C).

3.3 Physical Treatment of Venous Leg Ulcers

3.3.1. In patients with venous ulcers resistant to healing with wound care and compression, we suggest the addition of IPC (Grade 2B).

3.4 Hyperbaric Oxygen and the Management of Patients With Venous Ulcers

3.4.1. For patients with venous ulcers, we suggest that hyperbaric oxygen not be used (Grade 2B).

3.5.1 Pentoxifylline

3.5.1. In patients with venous leg ulcers, we suggest pentoxifylline, 400 mg po tid, in addition to local care and compression and/or IPC (Grade 2B).

3.5.2 Micronized Purified Flavonoid Fraction or Sulodexide for the Treatment of Venous Leg Ulcers

3.5.2. In patients with persistent venous ulcers, we suggest that rutosides, in the form of micronized purified flavonoid fraction given orally, or sulodexide administered intramuscularly and then orally, be added to local care and compression (Grade 2B).

4.1 IV or SC UFH, SC LMWH, SC Fondaparinux, and VKA for the Initial Treatment of Pulmonary Embolism

4.1.1. For patients with objectively confirmed pulmonary embolism (PE), we recommend short-term treatment with SC LMWH (Grade 1A), IV UFH (Grade 1A), monitored SC UFH (Grade 1A), fixed-dose SC UFH (Grade 1A), or SC fondaparinux (Grade 1A) rather than no such acute treatment. Patients with acute PE should also be routinely assessed for treatment with thrombolytic therapy (see Section 4.3 for related discussion and recommendations).

4.1.2. For patients in whom there is a high clinical suspicion of PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade 1C).

4.1.3. In patients with acute PE, we recommend initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥ 2.0 for at least 24 h (Grade 1C).

4.1.4. In patients with acute PE, we recommend initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA (Grade 1A).

4.1.5. In patients with acute PE, if IV UFH is chosen, we recommend that after an initial IV bolus (80 U/kg or 5,000 U), it is administered by continuous infusion (initially at dose of 18 U/kg/h or 1,300 U/h) with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay rather than administration as IV boluses throughout treatment, or administration without coagulation monitoring (Grade 1C).

4.1.6. In patients with acute PE, if monitored SC UFH is chosen, we recommend an initial dose of 17,500 U, or a weight-adjusted dose of about 250 U/kg, bid, with dose adjustment to achieve and maintain an APTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity when measured 6 h after injection rather than starting with a smaller initial dose (Grade 1C).

4.1.7. In patients with acute PE, if fixed-dose, unmonitored SC UFH is chosen, we recommend an initial dose of 333 U/Kg followed by a twice-daily dose of 250 U/kg rather than non-weight-based dosing (Grade 1C).

4.1.8. In patients with acute nonmassive PE, we recommend initial treatment with LMWH over IV UFH (Grade 1A). In patients with massive PE, in other situations where there is concern about SC absorption, or in patients in whom thrombolytic therapy is being considered or planned, we suggest IV UFH over SC LMWH, SC fondaparinux, or SC UFH (Grade 2C).

4.1.9. In patients with acute PE treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (Grade 1A).

4.1.10. In patients with acute PE and severe renal failure, we suggest UFH over LMWH (Grade 2C).

4.3 Systemically and Locally Administered Thrombolytic Therapy for PE

4.3.1. All PE patients should undergo rapid risk stratification (Grade 1C). For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk (Grade 1B). Thrombolysis in these patients should not be delayed, because irreversible cardiogenic shock may ensue. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (Grade 2B). The decision to use thrombolytic therapy depends on the clinician's assessment of PE severity, prognosis, and risk of bleeding. For the majority of patients with PE, we recommend against using thrombolytic therapy (Grade 1B).

4.3.2. In patients with acute PE, when a thrombolytic agent is used, we recommend that treatment be administered via a peripheral vein rather than placing a pulmonary artery catheter to administer treatment (Grade 1B).

4.3.3. In patients with acute PE, with administration of thrombolytic therapy, we recommend use of regimens with short infusion times (eg, a 2-h infusion) over those with prolonged infusion times (eg, a 24-h infusion) [Grade 1B].

4.4 Catheter Extraction or Fragmentation for the Initial Treatment of PE

4.4.1. For most patients with PE, we recommend against use of interventional catheteriza-

tion techniques (Grade 1C). In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest use of interventional catheterization techniques if appropriate expertise is available (Grade 2C).

4.5 Pulmonary Embolectomy for the Initial Treatment of PE

4.5.1. In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest that pulmonary embolectomy may be used if appropriate expertise is available (Grade 2C).

4.6 Vena Caval Filters for the Initial Treatment of PE

4.6.1. For most patients with PE, we recommend against the routine use of a vena caval filter in addition to anticoagulants (Grade 1A).

4.6.2. In patients with acute PE, if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an inferior vena caval filter (Grade 1C).

4.6.3. For patients with acute PE who have an inferior vena caval filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).

5.0 LONG-TERM TREATMENT OF ACUTE PE

5.1.1. For patients with PE secondary to a transient (reversible) risk factor, we recommend treatment with a VKA for 3 months over treatment for shorter periods (Grade 1A).

5.1.2. For patients with unprovoked PE, we recommend treatment with a VKA for at least 3 months (Grade 1A). We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked PE should be evaluated for the risk-benefit ratio of long-term therapy (Grade 1C). For patients with a first unprovoked episode of VTE that is a PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, we recommend long-term treatment (Grade 1A). *Underlying values and preferences:* This recommendation attaches a relatively high value to prevention

of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

For patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1A).

5.1.3. For patients with PE and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (Grade 1C).

5.1.4. In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade 1C).

5.1.5. In patients with PE, we recommend that the dose of VKA be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations (Grade 1A). For patients with unprovoked PE who have a strong preference for less frequent INR testing to monitor their therapy, after the first 3 months of conventional-intensity anticoagulation (INR range, 2.0 to 3.0), we recommend low-intensity therapy (INR range, 1.5 to 1.9) with less frequent INR monitoring over stopping treatment (Grade 1A). We recommend against high-intensity VKA therapy (INR range, 3.1 to 4.0) compared with an INR range of 2.0 to 3.0 (Grade 1A).

5.1.6. In patients who are unexpectedly found to have asymptomatic PE, we recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 1C).

6.1 Pulmonary Thromboendarterectomy, VKA, and Vena Caval Filter for the Treatment of CTPH

6.1.1. In selected patients with chronic thromboembolic pulmonary hypertension (CTPH), such as those with central disease under the care of an experienced surgical/medical team, we recommend pulmonary thromboendarterectomy (Grade 1C).

6.1.2. For all patients with CTPH, we recommend life-long treatment with a VKA targeted to an INR of 2.0 to 3.0 (Grade 1C).

6.1.3. For patients with CTPH undergoing pulmonary thromboendarterectomy, we suggest the placement of a permanent vena caval filter before or at the time of the procedure (Grade 2C).

6.1.4. For patients with inoperable CTPH, we suggest referral to a center with expertise in

pulmonary hypertension so that patients can be evaluated for alternative treatments, such as vasodilator therapy or balloon pulmonary angioplasty (Grade 2C).

7.1 Treatment of Infusion Thrombophlebitis

7.1.1. For patients with symptomatic infusion thrombophlebitis as a complication of IV infusion, we suggest oral diclofenac or another nonsteroidal antiinflammatory drug (Grade 2B), topical diclofenac gel (Grade 2B), or heparin gel (Grade 2B) until resolution of symptoms or for up to 2 weeks. We recommend against the use of systemic anticoagulation (Grade 1C).

7.2 Treatment of Superficial Vein Thrombosis

7.2.1. For patients with spontaneous superficial vein thrombosis, we suggest prophylactic or intermediate doses of LMWH (Grade 2B) or intermediate doses of UFH (Grade 2B) for at least 4 weeks. We suggest that as an alternative to 4 weeks of LMWH or UFH, VKA (target INR, 2.5; range, 2.0 to 3.0) can be overlapped with 5 days of UFH and LMWH and continued for 4 weeks (Grade 2C). We suggest that oral nonsteroidal antiinflammatory drugs should not be used in addition to anticoagulation (Grade 2B). We recommend medical treatment with anticoagulants over surgical treatment (Grade 1B).

Remark: It is likely that less extensive superficial vein thrombosis (*ie*, where the affected venous segment is short in length or further from the saphenofemoral junction) does not require treatment with anticoagulants. It is reasonable to use oral or topical nonsteroidal antiinflammatory drugs for symptom control in such cases.

8.1 IV UFH or LMWH for the Initial Treatment of UEDVT

8.1.1. For patients with acute upper-extremity DVT, we recommend initial treatment with therapeutic doses of LMWH, UFH, or fondaparinux as described for leg DVT (see Section 1) [Grade 1C].

8.2 Thrombolytic Therapy for the Initial Treatment of UEDVT

8.2.1. For most patients with acute upper-extremity DVT, we recommend against the routine use of systemic or catheter-directed thrombolytic therapy (Grade 1C).

8.2.2. In selected patients with acute upper-

extremity DVT (*eg*, in those with a low risk of bleeding and severe symptoms of recent onset) we suggest a short course of catheter-directed thrombolytic therapy may be used for initial treatment if appropriate expertise and resources are available (Grade 2C).

8.3 Catheter Extraction, Surgical Thrombectomy, Transluminal Angioplasty, Stent Placement, Staged Approach of Lysis Followed by Interventional or Surgical Procedure, and Superior Vena Cava Filter Insertion, for the Initial Treatment of UEDVT

8.3.1. For most patients with acute upper-extremity DVT, we recommend against the routine use of catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, or superior vena cava filter placement (Grade 1C).

8.3.2. In selected patients with acute upper-extremity DVT (*eg*, those with primary upper-extremity DVT and failure of anticoagulant or thrombolytic treatment who have severe persistent symptoms), we suggest that catheter extraction, surgical thrombectomy, transluminal angioplasty, or a staged approach of lysis followed by a vascular interventional or surgical procedure may be used, if appropriate expertise and resources are available (all Grade 2C).

8.3.3. In selected patients with acute upper-extremity DVT (*eg*, those in whom anticoagulant treatment is contraindicated and there is clear evidence of DVT progression or clinically significant PE), we suggest placement of a superior vena cava filter (Grade 2C).

8.4 Anticoagulants for the Long-term Treatment of UEDVT

8.4.1. For patients with acute upper-extremity DVT, we recommend treatment with a VKA for ≥ 3 months (Grade 1C).

Remark: A similar process as for lower-extremity DVT (see Section 2) should be used to determine the optimal duration of anticoagulation.

8.4.2. For most patients with upper-extremity DVT in association with an indwelling central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C).

8.4.3. For patients who have upper-extremity DVT in association with an indwelling central venous catheter that is removed, we do not recommend that the duration of long-term anticoagulant treatment be shortened to < 3 months (Grade 2C).

8.5 Prevention of PTS of the Arm

8.5.1. For patients at risk for PTS after upper-extremity DVT, we do not suggest routine use of elastic compression or venoactive medications (Grade 2C).

8.6 Treatment of PTS of the Arm

8.6.1. In patients with upper-extremity DVT who have persistent edema and pain, we suggest elastic bandages or elastic compression sleeves to reduce symptoms of PTS of the upper extremity (Grade 2C).

ANTITHROMBOTIC THERAPY IN AF

1.1 AF

1.1.1. In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, transient ischemic attack, or systemic embolism, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). Timing of the initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short-term risk of recurrent ischemic stroke and is addressed in “Ischemic Stroke” chapter by Albers et al in this supplement.

1.1.2. In patients with AF, including those with paroxysmal AF, who have two or more of the following risk factors for future ischemic stroke, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the increased risk of future ischemic stroke faced by this set of patients (Grade 1A). Two or more of the following risk factors apply: (1) age > 75 years, (2) history of hypertension, (3) diabetes mellitus, and (4) moderately or severely impaired left ventricular systolic function and/or heart failure.

Remark: Recommendations 1.1.1 and 1.1.2 correspond to a recommendation of oral VKA therapy for individuals with a score ≥ 2 using the CHADS₂ classification. For these and all other recommendations of long-term therapy in this chapter, “long-term” means lifelong unless a contraindication emerges.

1.1.3. In patients with AF, including those with paroxysmal AF, with only one of the risk factors listed below, we recommend long-term antithrombotic therapy (Grade 1A), either as anticoag-

ulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) [Grade 1A], or as aspirin, at a dose of 75 to 325 mg/d (Grade 1B). For these patients at intermediate risk of ischemic stroke, we suggest a VKA rather than aspirin (Grade 2A). This set of patients with AF is defined by having one of the following risk factors: (1) age > 75 years, (2) history of hypertension, (3) diabetes mellitus, and (4) moderately or severely impaired left ventricular systolic function and/or heart failure.

1.1.4. In patients with AF, including those with paroxysmal AF, aged ≤ 75 years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75 to 325 mg/d (Grade 1B) because of their low risk of ischemic stroke.

Underlying values and preferences: Anticoagulation with oral VKAs, such as warfarin, has far greater efficacy than aspirin in preventing stroke, and particularly in preventing severe ischemic stroke, in AF. We recommend the option of aspirin therapy for lower risk groups in 1.1.3 and 1.1.4, above, estimating the absolute expected benefit of anticoagulant therapy may not be worth the increased hemorrhagic risk and burden of anticoagulation. Individual lower-risk patients may rationally choose anticoagulation over aspirin therapy to gain greater protection against ischemic stroke if they value protection against stroke much more highly than reducing risk of hemorrhage and the burden of managing anticoagulation. Our recommendations assume that the patient is not at high risk for bleeding and that good control of anticoagulation will occur.

Remarks: These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute pulmonary infection. The optimal dose of aspirin for patients with AF is unclear. The largest effect of aspirin was seen in the first Stroke Prevention in AF (SPAF I) trial, which used aspirin at 325 mg/d. However, generalizing from trials of aspirin for all antithrombotic indications and from physiologic studies, we feel the best balance of efficacy and safety is achieved at low doses of aspirin, *ie*, 75 to 100 mg/d (see the “Antiplatelet Drugs” chapter by Patrono et al in this supplement).

1.2 Atrial Flutter

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

1.3 Valvular Heart Disease and AF

1.3.1. For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA, such as warfarin (target INR 2.5; range, 2.0 to 3.0) [Grade 1B].

1.3.2. For patients with AF and prosthetic heart valves, we recommend long-term anticoagulation with an oral VKA, such as warfarin, at a dose intensity appropriate for the specific type of prosthesis (Grade 1B). See the “Valvular and Structural Heart Disease” chapter by Salem et al for antithrombotic management of patients with valvular heart disease and AF.

1.4 AF Following Cardiac Surgery

1.4. For patients with AF occurring shortly after open-heart surgery and lasting ≥ 48 h, we suggest anticoagulation with an oral VKA, such as warfarin, if bleeding risks are acceptable (Grade 2C). The target INR is 2.5 (range, 2.0 to 3.0). We suggest continuing anticoagulation for 4 weeks following reversion to and maintenance of normal sinus rhythm, particularly if patients have risk factors for thromboembolism (Grade 2C).

2.1 Anticoagulation for Elective Cardioversion of AF

2.1.1. For patients with AF of ≥ 48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, at a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C).

Remark: This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.2. For patients with AF of ≥ 48 h or of unknown duration who are undergoing pharmacologic or electrical cardioversion, we recommend either immediate anticoagulation with IV UFH (target PTT, 60 s; range, 50 to 70 s), or LMWH (at full DVT treatment doses), or at least 5 days of warfarin (target INR of 2.5; range, 2.0 to 3.0) at the time of cardioversion

and performance of a screening multiplane TEE. If no thrombus is seen, cardioversion is successful, and sinus rhythm is maintained, we recommend anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (all Grade 1B addressing the equivalence of TEE-guided vs non-TEE-guided cardioversion; see Recommendation 2.1.1, above).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.3. For patients with AF of known duration < 48 h, we suggest that cardioversion be performed without prolonged anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin (target PTT, 60 s; range, 50 to 70 s) or LMWH (at full DVT treatment doses) at presentation (Grade 2C).

Remark: For patients with risk factors for stroke, it is particularly important to be confident that the duration of AF is < 48 h. In such patients with risk factors, a TEE-guided approach (see section 2.12, previously) is a reasonable alternative strategy. Post-cardioversion anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.4. For emergency cardioversion in the hemodynamically unstable patient, we suggest that IV UFH (target PTT of 60 s with a target range of 50 to 70 s) or LMWH (at full DVT treatment doses) be started as soon as possible, followed by at least 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR of 2.5; range, 2.0 to 3.0) if cardioversion is successful and sinus rhythm is maintained (Grade 2C).

Remark: Long-term continuation of anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients experiencing more than one episode of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.5. 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).

VALVULAR AND STRUCTURAL HEART DISEASE

1.1.1. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of AF, previous systemic embolism, or left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1A].

1.1.2. For patients with rheumatic mitral valve disease with AF who suffer systemic embolism or have left atrial thrombus while receiving VKAs at a therapeutic INR, we suggest the addition of low-dose aspirin (50 to 100 mg/d) therapy after consideration of the additional hemorrhagic risks (Grade 2C). An alternative strategy might be the adjustment of VKA dosing to achieve a higher target INR (target INR, 3.0; range, 2.5 to 3.5) [Grade 2C].

1.2.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with the left atrial diameter > 55 mm, we suggest VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C].

Underlying values and preferences: This recommendation places a relatively high value on preventing systemic embolism and its consequences, and a relatively low value on avoiding the bleeding risk and inconvenience associated with VKA therapy.

1.2.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm, we do not suggest antithrombotic therapy, unless a separate indication exists (Grade 2C).

1.3.1. For patients being considered for percutaneous mitral balloon valvotomy (PMBV), we recommend a preprocedural transesophageal echocardiography (TEE) to exclude left atrial thrombus (Grade 1C).

1.3.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and VKA therapy (target INR 3.0; range, 2.5 to 3.5) until thrombus resolution is documented by repeat TEE (Grade 1C). If left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1C).

2.0.1. In patients with mitral valve prolapse (MVP) who have not experienced systemic embolism, unexplained transient ischemic attacks or ischemic

stroke, and do not have AF, we recommend against any antithrombotic therapy (Grade 1C).

2.0.2. In patients with MVP who have documented but unexplained transient ischemic attacks or ischemic stroke, we recommend long-term aspirin therapy (50 to 100 mg/d) [Grade 1B].

2.0.3. In patients with MVP who have AF, documented systemic embolism or recurrent transient ischemic attacks despite aspirin therapy, we suggest long-term VKA therapy (target INR, 2.5; range 2.0 to 3.0) [Grade 2C].

3.0.1. In patients with mitral annular calcification complicated by systemic embolism, ischemic stroke, or transient ischemic attack, who do not have AF, we recommend aspirin (50 to 100 mg/d) [Grade 1B]. For recurrent events despite aspirin therapy, we suggest treatment with VKA therapy be considered (target INR, 2.5; range, 2.0 to 3.0) [Grade 2C]. In patients with mitral annular calcification who have a single embolus documented to be calcific, the data are not sufficient to allow recommendation for or against antithrombotic therapy.

3.0.2. In patients with mitral annular calcification and AF, we recommend long-term VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C].

4.1.1. In patients with isolated calcific aortic valve disease who have not had ischemic stroke or transient ischemic attack, we suggest against antithrombotic therapy (Grade 2C).

4.1.2. In patients with isolated calcific aortic valve disease who have experienced ischemic stroke or transient ischemic attack not attributable to another source, we suggest aspirin (50 to 100 mg/d) [Grade 2C].

4.2.1. In patients with ischemic stroke associated with aortic atherosclerotic lesions, we recommend low-dose aspirin (50 to 100 mg/d) over no therapy (Grade 1C). For patients with ischemic stroke associated with mobile aortic arch thrombi, we suggest therapy with either VKAs (target INR, 2.5; range, 2.0 to 3.0) or low-dose aspirin (50 to 100 mg/d) [Grade 2C].

5.0.1. In patients with ischemic stroke and a patent foramen ovale, we recommend antiplatelet agent therapy (Grade 1A), and suggest antiplatelet agent therapy over VKA therapy (Grade 2A).

5.0.2. In patients with cryptogenic ischemic stroke and patent foramen ovale, with evidence of DVT or another indication for VKA therapy, such as AF or an underlying hypercoagulable state, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C].

6.0.1. In patients with mechanical heart valves, we recommend VKA therapy (Grade 1A). In patients immediately following mechanical valve replacement, and as dictated by clinical concerns regarding postoperative bleeding, we suggest administration of IV UFH or SC LMWH until the INR is stable and at a therapeutic level for 2 consecutive days (Grade 2C).

6.0.2. In patients with a bileaflet mechanical valve or a Medtronic Hall tilting disk valve in the aortic position who are in sinus rhythm and without left atrial enlargement, we recommend long-term VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].

6.0.3. In patients with a tilting disk or bileaflet mechanical valve in the mitral position, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.4. In patients with a caged ball or caged disk valve, we recommend long-term VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.5. In patients with mechanical heart valves in either or both the aortic or mitral positions, and additional risk factors for thromboembolism, such as AF, anterior-apical ST-segment elevation myocardial infarction, left atrial enlargement, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 3.0; range, 2.5 to 3.5) [Grade 1B].

6.0.6. In patients with mechanical heart valves who have additional risk factors for thromboembolism, such as AF, hypercoagulable state, or low ejection fraction, or who have a history of atherosclerotic vascular disease, we recommend the addition of low-dose aspirin (50 to 100 mg/d) to long-term VKA therapy (Grade 1B). We suggest aspirin not be added to VKA therapy in patients with mechanical heart valves who are at particularly high risk of bleeding; such as in patients with history of GI bleed or in patients > 80 years of age (Grade 2C).

6.0.7. In patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, we suggest the addition of aspirin (50 to 100 mg/d) if not previously provided and/or upward titration of VKA therapy to achieve a higher target INR. For a previous target INR of 2.5, we suggest the VKA dose be increased to achieve a target INR of 3.0 (range, 2.5 to 3.5). For a previous target INR of 3.0, we suggest the VKA dose be increased to achieve a target INR of 3.5 (range, 3.0 to 4.0) [Grade 2C].

7.0.1. In patients with a bioprosthetic valve in the mitral position, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for the

first 3 months after valve insertion (Grade 1B). In the early postoperative period, in the absence of concerns for significant bleeding, we suggest administration of IV UFH or SC LMWH until the INR is at therapeutic levels for 2 consecutive days (Grade 2C). After the first 3 months, in patients who are in sinus rhythm and have no other indication for VKA therapy, we recommend aspirin (50 to 100 mg/d) [Grade 1B].

7.0.2. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we recommend aspirin (50 to 100 mg/d) [Grade 1B].

7.0.3. In patients with bioprosthetic valves who have a prior history of systemic embolism, we recommend VKA therapy (target INR 2.5; range, 2.0 to 3.0) for at least 3 months after valve insertion, followed by clinical reassessment (Grade 1C).

7.0.4. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) until documented thrombus resolution (Grade 1C).

7.0.5. In patients with bioprosthetic valves who have additional risk factors for thromboembolism, including AF, hypercoagulable state, or low ejection fraction, we recommend VKA therapy (target INR, 2.5; range, 2.0 to 3.0) [Grade 1C]. We suggest the addition of low-dose aspirin (50 to 100 mg/d) be considered, particularly in patients with history of atherosclerotic vascular disease (Grade 2C). We suggest aspirin not be added to long-term VKA therapy patients with bioprosthetic heart valves who are at particularly high risk of bleeding, such as patients with history of GI bleed or in patients > 80 years of age (Grade 2C).

8.0.1. For patients with right-sided prosthetic valve thrombosis (PVT) with large thrombus size or New York Heart Association functional class III to IV, we recommend administration of fibrinolytic therapy (Grade 1C).

8.0.2. For patients with left-sided PVT, New York Heart Association functional class I to II, and small thrombus area (< 0.8 cm²), we suggest administration of fibrinolytic therapy. Alternatively, administration of IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement, can be considered for very small nonobstructive thrombus [Grade 2C].

8.0.3. For patients with left-sided PVT, New York Heart Association functional class III to IV, and small thrombus area (< 0.8 cm²), we

suggest fibrinolytic therapy (Grade 2C).

8.0.4. For patients with left-sided PVT and large thrombus area ($\geq 0.8 \text{ cm}^2$), we suggest emergency surgery be considered. If surgery is not available or considered high-risk, we suggest fibrinolytic therapy (Grade 2C).

8.0.5. For patients who have had successful resolution of PVT, we suggest initiation of IV UFH and VKA therapy. We suggest IV UFH be continued until a therapeutic INR is achieved. For a mechanical valve in the aortic position, we suggest maintaining a higher INR (target, 3.5; range, 3.0 to 4.0) plus aspirin (50 to 100 mg/d). For a mechanical valve in the mitral position, we suggest maintaining a higher INR (target 4.0; range 3.5 to 4.5) plus aspirin (50 to 100 mg/d) [Grade 2C].

9.1.1. In patients with infective endocarditis, we recommend against routine antithrombotic therapy, unless a separate indication exists (Grade 1B).

9.1.2. In the patient treated with VKA therapy who has infective endocarditis, we suggest VKA be discontinued at the time of initial presentation and UFH substituted, until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, we suggest reinstatement of long-term VKA therapy (Grade 2C).

9.2.1. In patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli, we recommend treatment with full-dose IV UFH or SC LMWH (Grade 1C).

9.2.2. In patients with disseminated cancer or debilitating disease with aseptic vegetations, we suggest administration of full-dose IV UFH or SC LMWH (Grade 2C).

ANTITHROMBOTIC THERAPY AND THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE

1.1 IV Tissue Plasminogen Activator for Acute Ischemic Stroke Within 3 h of Symptom Onset

1.1.1. For eligible patients (see inclusion and exclusion criteria listed below) we recommend administration of IV tissue plasminogen activator (tPA) 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 min, provided that treatment is initiated within 3 h of clearly defined symptom onset (Grade 1A).

Underlying values and preferences: This recom-

mendation places relatively more weight on overall prospects for long-term functional improvement despite the increased risk of symptomatic intracerebral hemorrhage in the immediate peristroke period.

1.1.2. We recommend that patients who are eligible for tPA be treated as quickly as possible within the 3-h time limit (Grade 1A).

Remark: All unnecessary delays must be avoided as the benefits of tPA therapy diminish rapidly over time.

1.1.3. For patients with extensive ($> 1/3$ of the middle cerebral artery territory) and clearly identifiable hypodensity on CT, we suggest not using of tPA (Grade 2B).

1.2 IV tPA for Acute Ischemic Stroke Between 3 h and 6 h of Symptom Onset

1.2. For patients with acute ischemic stroke of > 3 h but < 4.5 h, we suggest clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h we recommend against the use of IV tPA (Grade 1A).

Underlying values and preferences: This recommendation assumes a relatively low value on small increases in long-term functional improvement, a relatively high value on avoiding acute intracranial hemorrhage and death, and a relatively high degree of risk aversion.

1.3 IV Streptokinase for Acute Ischemic Stroke Between 0 h and 6 h of Symptom Onset

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

1.4 Intraarterial Thrombolysis for Acute Ischemic Stroke

1.4.1. For patients with angiographically demonstrated middle cerebral artery occlusion and without signs major early infarct signs on the baseline CT or MRI scan, who can be treated within 6 h of symptom onset, we suggest intraarterial thrombolytic therapy with tPA for selected patients in centers with the appropriate neurologic and interventional expertise (Grade 2C).

1.4.2. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, we suggest either intraarterial or IV thrombolysis with tPA depending on available resources and capabilities (Grade 2C).

2.1 Anticoagulants for Altering Outcomes Among Acute Stroke in Patients Not Eligible for Thrombolysis

2.1. For patients with acute ischemic stroke, we recommend against full-dose anticoagulation with IV, SC, or LMWHs or heparinoids (Grade 1B).

2.2 Antiplatelet Agents for Altering Outcomes in Acute Stroke Patients Not Eligible for Thrombolysis

2.2. For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (initial dose of 150 to 325 mg) [Grade 1A].

2.3 Antithrombotic Therapy for Prevention of DVT and PE in Acute Ischemic Stroke

2.3.1. For acute stroke patients with restricted mobility, we recommend prophylactic low-dose SC heparin or LMWHs (Grade 1A).

2.3.2. For patients who have contraindications to anticoagulants, we recommend IPC devices or elastic stockings (Grade 1B).

3.1 IPC for DVT/PE Prophylaxis in Patients With Intracerebral Hematoma

3.1. In patients with an acute intracerebral hematoma, we recommend the initial use of IPC devices (Grade 1B).

3.2 Heparin for DVT/PE Prophylaxis in Patients With Intracerebral Hematoma

3.2. In stable patients, we suggest low-dose SC heparin as soon as the second day after the onset of the hemorrhage (Grade 2C).

Underlying values and preferences: Given the uncertainty about the risk of heparin in this setting, this recommendation places a relatively high value on reducing the consequences of thromboembolism and a relatively lower value on minimizing the risk of cerebral rebleeding.

4.1 Prevention of Cerebral Ischemic Events in Patients With Noncardioembolic Transient Ischemic Attack or Stroke: Antiplatelet Drugs vs Placebo or vs an Alternative Antiplatelet Drug

4.1.1. In patients who have experienced a noncardioembolic stroke or transient ischemic attack (ie, atherothrombotic, lacunar, or cryptogenic), we recommend treatment with an

antiplatelet drug (Grade 1A). Aspirin, the combination of aspirin (25 mg) and extended-release dipyridamole (200 mg bid) and clopidogrel (75 qd) are all acceptable options for initial therapy. We recommend an aspirin dose of 50–100 mg/d over higher aspirin doses (Grade 1B).

4.1.2. In patients who have experienced a noncardioembolic stroke or transient ischemic attack, we recommend using the combination of aspirin and extended-release dipyridamole (25/200 mg bid) over aspirin (Grade 1A) and suggest clopidogrel over aspirin (Grade 2B).

Underlying values and preferences: The implementation of the recommendation to use the combination of aspirin and extended-release dipyridamole over aspirin may vary based on cost, tolerability, availability, ease of use, and absolute risk.

4.1.3. In most patients with a noncardioembolic stroke or transient ischemic attack, we recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B). In those with a recent acute myocardial infarction, other acute coronary syndrome, or a recently placed coronary stent, we recommend clopidogrel plus aspirin (75–100 mg) [Grade 1A]. The optimal duration of dual antiplatelet therapy depends on the specific cardiac indication (see other articles in this supplement) for recommended for specific indications.

4.1.4. For patients who are allergic to aspirin, we recommend clopidogrel (Grade 1A).

4.2 Prevention of Noncardioembolic Cerebral Ischemic Events: Oral Anticoagulants

4.2.1. For patients with noncardioembolic stroke or transient ischemic attack, we recommend antiplatelet agents over oral anticoagulation (Grade 1A).

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

4.3. In patients undergoing carotid endarterectomy, we recommend aspirin (50 to 100 mg/d) prior to and following the procedure (Grade 1A).

4.4 Prevention of Cardioembolic Cerebral Ischemic Events

4.4.1. In patients with AF who have suffered a recent stroke or transient ischemic attack, we

recommend long-term oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) [Grade 1A].

4.4.2. For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin at a dose of 75–325 mg/d (Grade 1B).

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

4.4.4. In patients with cryptogenic ischemic stroke and a patent foramen ovale, we recommend antiplatelet therapy over no therapy (Grade 1A) and suggest antiplatelet agents over anticoagulation (Grade 2A).

4.4.5. In patients with mitral valve strands or prolapse, who have a history of transient ischemic attack or stroke, we recommend antiplatelet therapy (Grade 1A).

5.1 Anticoagulation for Cerebral Venous Sinus Thrombosis

5.1. In patients with venous sinus thrombosis, we recommend that clinicians use UFH (Grade 1B) or LMWH (Grade 1B) over no anticoagulant therapy during the acute phase, even in the presence of hemorrhagic infarction. In these patients, we recommend continued use of VKA therapy for up to 12 months (target INR, 2.5; range, 2.0–3.0) [Grade 1B].

ANTITHROMBOTIC THERAPY FOR NON-ST-SEGMENT ACUTE CORONARY SYNDROMES

Antiplatelet Therapies

1. For all patients presenting with NSTEMI ACS, without a clear allergy to aspirin, we recommend immediate aspirin (162 to 325 mg po) and then daily oral aspirin (75 to 100 mg) [Grade 1A].
2. For all NSTEMI ACS patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300 mg po bolus, followed by 75 mg/d indefinitely (Grade 1A).
3. For NSTEMI ACS patients who are at moderate or greater risk (eg, ongoing chest pain, hemodynamic instability, positive troponin, or dynamic ECG changes) for an ischemic event and who will undergo an early invasive management strategy (ie, diagnostic catheterization followed by anatomy-driven revascularization), we recommend:
 - a. “Upstream” treatment either with clopidogrel (300 mg po bolus, followed by 75 mg/d) or a small-molecule IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A]
 - b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2A). Scrupulous attention to weight- and renal-based dosing algorithms must be part of eptifibatide or tirofiban administration
 - c. For patients presenting with NSTEMI ACS, we recommend against abciximab as initial treatment except when coronary anatomy is known and PCI is planned within 24 h (Grade 1A).
4. For NSTEMI ACS patients who are at moderate or greater risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used:
 - a. We recommend upstream treatment with clopidogrel (300 mg po bolus, followed by 75 mg/d) [Grade 1A]
 - b. We suggest upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor (Grade 2B).
5. For NSTEMI ACS patients who undergo PCI, we recommend treatment with both clopidogrel and an IV GP IIb/IIIa inhibitor (Grade 1A),
 - a. We recommend a loading dose of 600 mg of clopidogrel given at least 2 h prior to planned PCI followed by 75 mg/d (Grade 1B)
 - b. If ticlopidine is given, we suggest that a loading dose of 500 mg be given at least 6 h before planned PCI (Grade 2C)
 - c. For PCI patients who cannot tolerate aspirin, we suggest that the loading dose of clopidogrel (600 mg) or ticlopidine (500 mg) be given at least 24 h prior to planned PCI (Grade 2C)
 - d. We recommend use of a GP IIb/IIIa antagonist (abciximab or eptifibatide) [Grade 1A] for all NSTEMI ACS patients with at least moderate risk features undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream; we recommend administration of abciximab as a 0.25 mg/kg bolus followed by a 12-h infusion at a rate of

10 µg/min (Grade 1A) and eptifibatide as a double bolus (each 180 µg/kg, given 10 min apart) followed by an 18-h infusion of 2.0 µg/kg/min (Grade 1A). Appropriate dose reduction of eptifibatide must be based on renal function

- e. In patients undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream, we recommend against the use of tirofiban as an alternative to abciximab (Grade 1B).
6. For NSTEMI ACS patients who have received clopidogrel and are scheduled for CABG, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).

Anticoagulant Therapies

1. For all patients presenting with NSTEMI ACS, we recommend anticoagulation with UFH or LMWH or bivalirudin or fondaparinux over no anticoagulation (Grade 1A).
 - a. We recommend weight-based dosing of UFH and maintenance of the APTT between 50 s and 70 s (Grade 1B)
 - b. We recommend against routine monitoring of the anticoagulant effect of LMWH (Grade 1C). Careful attention is needed to appropriately adjust LMWH dose in patients with renal insufficiency.
2. For NSTEMI ACS patients who will undergo an early invasive strategy of management (*ie*, diagnostic catheterization followed by anatomy-driven revascularization),
 - a. We recommend UFH (with a GP IIb/IIIa inhibitor) over either LMWH or fondaparinux (Grade 1B)
 - b. We suggest bivalirudin over UFH in combination with a thienopyridine as an initial antithrombotic strategy in patients with moderate-to-high risk features presenting with a NSTEMI ACS and scheduled for very early coronary angiography (< 6 h) [Grade 2B].
3. For NSTEMI ACS patients in whom an early conservative or a delayed invasive strategy of management is to be used:
 - a. We recommend fondaparinux over enoxaparin (Grade 1A). For patients treated with upstream fondaparinux and undergoing PCI, we recommend that additional IV boluses of UFH be given at the time of the procedure (for example, 50 to

60 U/kg) as well as additional IV doses of fondaparinux (2.5 mg if also receiving a GP IIb/IIIa inhibitor and 5 mg if not) [Grade 1B]. Additionally, PCI operators should regularly flush the catheters with UFH during the procedure as well

- b. We recommend LMWH over UFH (Grade 1B). We recommend continuing LMWH during PCI treatment of patients with NSTEMI ACS when LMWH has been started as the upstream anticoagulant (Grade 1B). If the last dose of enoxaparin was given ≤ 8 h prior to PCI, we recommend no additional anticoagulant therapy (Grade 1B). If the last dose of enoxaparin was given 8 to 12 h before PCI, we recommend a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI (Grade 1B).
4. In low-to-moderate risk patients with NSTEMI ACS undergoing PCI, we recommend either bivalirudin with provisional (“bail-out”) GP IIb/IIIa inhibitors or UFH plus a GP IIb/IIIa inhibitor over alternative antithrombotic regimens (Grade 1B).

ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

1.0 REPERFUSION THERAPY

1.0.1. For patients with ischemic symptoms characteristic of acute myocardial infarction of ≤ 12 h duration and persistent ST-segment elevation, we recommend that all undergo rapid evaluation for reperfusion (primary PCI or fibrinolytic) therapy and have a reperfusion strategy implemented promptly after contact with the health-care system (Grade 1A).

1.1 Fibrinolysis

1.1.1. In patients with acute myocardial infarction who are candidates for fibrinolytic therapy, we recommend administration as soon as possible (ideally within 30 min) after arrival to the hospital or first contact with the health-care system (Grade 1A).

1.1.2. In health-care settings where prehospital administration of fibrinolytic therapy is feasible, we recommend prehospital administration of fibrinolytic therapy (Grade 1A).

1.1.3. For patients with ischemic symptoms

characteristic of acute myocardial infarction of ≤ 12 h duration, and persistent ST-segment elevation, we recommend administration of streptokinase, anistreplase, alteplase, reteplase, or tenecteplase over no fibrinolytic therapy (all Grade 1A).

1.1.4. For patients with symptom duration ≤ 6 h, we recommend the administration of alteplase (Grade 1A) or tenecteplase (Grade 1A), and suggest reteplase (Grade 2B) over streptokinase.

1.1.5. For patients receiving fibrinolytic therapy, we suggest the use of a bolus agent (eg, tenecteplase) to facilitate the ease of administration and potentially reduce the risk of non-intracranial hemorrhage-related bleeding (tenecteplase) [Grade 2A].

1.1.6. For patients with ischemic symptoms characteristic of acute myocardial infarction of ≤ 12 h duration, and left bundle-branch block with associated ST-segment changes, we recommend fibrinolytic therapy if primary PCI is not readily available (Grade 1B).

1.1.7. For patients with ischemic symptoms characteristic of acute myocardial infarction of ≤ 12 h duration and ECG findings consistent with a true posterior myocardial infarction, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.8. For high-risk patients with ongoing symptoms characteristic of acute myocardial infarction or hemodynamic compromise and duration of 12 to 24 h who have persistent ST-segment elevation or left bundle-branch block with ST-segment changes, we suggest fibrinolytic therapy if primary PCI is not readily available (Grade 2B).

1.1.9. In patients with any history of intracranial hemorrhage, or with history of head trauma, or with ischemic stroke within the past 6 months, we recommend against administration of fibrinolytic therapy (Grade 1C).

2.0 ANTIPLATELET/ANTITHROMBOTIC THERAPY

2.1 Aspirin

2.1.1. For patients with acute ST-segment elevation myocardial infarction whether or not they receive fibrinolytic therapy, we recommend aspirin (160 to 325 mg po) over no aspirin therapy at initial evaluation by health-care personnel (Grade 1A) followed by indefinite therapy (75 mg to 162 mg/d po) [Grade 1A].

2.2 Clopidogrel

2.2.1. For patients with acute ST-segment elevation myocardial infarction, we recommend clopidogrel in addition to aspirin (Grade 1A). The recommended dosing for clopidogrel is 300 mg po for patients age ≤ 75 years and 75 mg po for patients age > 75 years if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/d po for up to 28 days (Grade 1A).

2.2.2. For patients with acute ST-segment elevation myocardial infarction who have not received a coronary stent, we suggest that clopidogrel 75 mg/d could be continued beyond 28 days and up to 1 year (Grade 2B).

2.2.3. For patients undergoing primary PCI, we suggest clopidogrel in addition to aspirin with a recommended initial dosing of at least 300 mg (Grade 1B), followed by 75 mg daily (for duration of therapy, see chapter by Becker et al in this supplement).

2.3 Antithrombin Therapy

2.3.1. For patients with acute ST-segment elevation myocardial infarction, in addition to aspirin and other antiplatelet therapies, we recommend the use of antithrombin therapy over no antithrombin therapy (Grade 1A), including for those patients receiving fibrinolysis (and regardless of which lytic agent is administered), primary PCI, or patients not receiving reperfusion therapy.

2.4 UFH

2.4.1. For patients receiving streptokinase, we suggest administration of either IV UFH (5,000-U bolus followed by 1,000 U/h for patients > 80 kg, 800 U/h for < 80 kg) with a target APTT of 50 to 75 s or SC UFH (12,500 U q12h) over no UFH therapy for 48 h (both Grade 1B).

2.4.2. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis in acute myocardial infarction, 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 50 to 70 s for 48 h (Grade 1B).

2.4.3. For patients with ST-segment elevation myocardial infarction undergoing primary PCI, we recommend administration of IV UFH over no UFH therapy (Grade 1C). The recommended periprocedural dosing in patients receiving a GP IIb/IIIa inhibitor is 50 to 70 U/kg (target

activated clotting time > 200 s); in patients not receiving a GP IIb/IIIa inhibitor, the recommended periprocedural dosing is 60 to 100 U/kg (target activated clottint time, 250 to 350 s).

2.5 LMWH

2.5.1. For patients with acute ST-segment elevation myocardial infarction, regardless of whether or not they receive reperfusion therapy, we recommend the use of reviparin over no therapy (Grade 1B). Recommended dosing for reviparin is 3,436 IU for < 50 kg, 5,153 IU for 50 to 75 kg, or 6,871 IU for > 75 kg q12h SC up to 7 days. For patients undergoing primary PCI, UFH should be used periprocedurally and reviparin initiated 1 h after sheath removal.

2.5.2. For patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy who have preserved renal function (> 2.5 mg/dL [220 μ mol/L] in males and < 2.0 md/dL [175 μ mol/L] in females), we recommend the use of enoxaparin over UFH, continued up to 8 days (Grade 2A). Recommended dosing for enoxaparin is for age < 75 years, 30 mg IV bolus followed by 1 mg/kg SC q12h (maximum 100 mg for the first two SC doses); and for age \geq 75 years, no IV bolus, 0.75 mg/kg SC q12h (maximum, 75 mg for the first two SC doses).

2.6 Fondaparinux

2.6.1. For patients with acute ST-segment elevation myocardial infarction and not receiving reperfusion therapy, we recommend fondaparinux over no therapy (Grade 1A). Recommended dosing for fondaparinux is 2.5 mg IV for the first dose and then SC once daily up to 9 days.

2.6.2. For patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy and thought not to have an indication for anticoagulation, we recommend fondaparinux over no therapy (2.5 mg IV for the first dose and then SC qd up to 9 days) [Grade 1B].

2.6.3. For patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy and thought to have an indication for anticoagulation, we suggest fondaparinux (2.5 mg IV for the first dose and then SC qd up to 9 days) could be used as an alternative to UFH (Grade 2B).

2.6.4. For patients with acute ST-segment elevation myocardial infarction and undergo-

ing primary PCI, we recommend against using fondaparinux (Grade 1A).

2.7 Direct Thrombin Inhibitors

2.7.1. For patients with acute ST-segment elevation myocardial infarction treated with streptokinase, we suggest clinicians not use bivalirudin as an alternative to UFH (Grade 2B).

Underlying values and preferences: This recommendation places a relatively higher value on avoiding excess of major bleeding and a relatively lower value on avoiding reinfarction. Recommended dosing for bivalirudin is 0.25 mg/kg IV bolus followed by an infusion of 0.5 mg/kg/h for the first 12 h and then 0.25 mg/kg/h for the subsequent 36 h; APTTs should be measured at 12 h and 24 h with potential dose reductions as noted (see previous text).

2.8 GP IIb/IIIa Inhibitors

2.8.1. For patients with acute ST-segment elevation myocardial infarction, we recommend against the combination of standard-dose abciximab and half-dose reteplase or tenecteplase with low-dose IV UFH over standard-dose reteplase or tenecteplase (Grade 1B).

2.8.2. For patients with acute ST-segment elevation myocardial infarction, we suggest clinicians not use the combination of streptokinase and any GP IIb/IIIa inhibitor (Grade 2B).

2.8.3. For patients with acute ST-segment elevation myocardial infarction undergoing primary PCI (with or without stenting), we recommend the use of abciximab (Grade 1B). Recommended dosing for abciximab is 0.25 mg/kg IV bolus followed by 0.125 μ g/kg/min (maximum, 10 μ g/min) for 12 h.

3.0 FACILITATED PCI

3.0.1. For patients with acute ST-segment elevation myocardial infarction undergoing primary PCI, we recommend against the use of fibrinolysis, with or without a GP IIb/IIIa inhibitor (Grade 1B).

3.0.2. For patients with acute ST-segment elevation myocardial infarction who are to undergo primary PCI, we suggest administration of a GP IIb/IIIa inhibitor prior to coronary angiography (Grade 2B). The largest number of patients studied in this setting received abciximab 0.25 mg/kg IV bolus followed by 0.125 μ g/kg/min (maximum 10 μ g/min) for 12 h; rec-

ommended dosing for eptifibatide is two 180 µg IV boluses (10 min apart) followed by 2.0 µg/kg/min infusion for 12–24 h; recommended dosing for tirofiban is 25 µg/kg IV bolus followed by 0.15 µg/kg/min for 24 h.

4.0 RESCUE PCI

4.0.1. For patients with ST-segment elevation myocardial infarction who have received fibrinolysis but who have persistent ST-segment elevation (< 50% resolution 90 min after treatment initiation compared with the pretreatment ECG), we recommend rescue PCI should be performed over repeat fibrinolysis or no additional reperfusion therapy (Grade 1B), and suggest as soon as possible and within 2 h of identification of lack of ST-segment elevation resolution (Grade 2C).

THE PRIMARY AND SECONDARY PREVENTION OF CHRONIC CORONARY ARTERY DISEASE

1.1.1. For patients with ACS with and without ST-segment elevation, we recommend aspirin given initially at a dose of 75–162 mg and then indefinitely at a dose of 75–100 mg/d (Grade 1A).

1.1.2. For patients with ST-segment elevation ACS, with or without fibrinolytic therapy, we recommend clopidogrel, administered as a 300-mg po loading dose for patients ≤ 75 years of age and 75-mg starting dose for those > 75 years of age and continued at a daily dose of 75 mg for 2–4 weeks (Grade 1A). We suggest continuing clopidogrel for up to 12 months following hospital discharge (Grade 2B).

1.1.3. For patients with NSTEMI ACS, we recommend combination therapy with aspirin (75–100 mg/d) and clopidogrel (75 mg/d) for 12 months (Grade 1A).

1.1.4. For patients in whom aspirin is contraindicated or not tolerated, we recommend clopidogrel monotherapy (75 mg/d) [Grade 1A].

1.1.5. For patients with symptomatic coronary artery disease, we suggest aspirin (75–100 mg/d) in combination with clopidogrel (75 mg/d) [Grade 2B].

Underlying values and preferences: This recommendation places a high value on the probable small reduction in arterial vascular risk consequent on adding clopidogrel to aspirin and a low value on avoiding the additional bleeding and high cost associated with clopidogrel.

2.1. For most patients (all except the high-risk

group described in recommendation 2.2 below) in most health-care settings, following ACS, we recommend aspirin alone (75–100 mg/d) over oral VKA alone or in combination with aspirin (Grade 1B).

Underlying values and preferences: This recommendation places a relatively low value on prevention of thromboembolism, and a relatively high value on avoiding the inconvenience, expense, and bleeding risk associated with VKA therapy.

2.1.1. For most patients after myocardial infarction, in health-care settings in which meticulous INR monitoring and highly skilled VKA dose titration are expected and widely accessible, we suggest long-term (up to 4 years) high-intensity oral VKA (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral VKA (target INR, 2.5; range, 2.0 to 3.0) with aspirin (≤ 100 mg/d) over aspirin alone (both Grade 2B).

2.2. For high-risk patients with myocardial infarction, including those with a large anterior myocardial infarction, those with significant heart failure, those with intracardiac thrombus visible on transthoracic echocardiography, those with AF, and those with a history of a thromboembolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral VKA plus low-dose aspirin (≤ 100 mg/d) for at least 3 months after the MI (Grade 2A).

2.4. For long-term treatment of patients after PCI, we recommend aspirin at a dose of 75–100 mg/d (Grade 1A).

2.4.1. For patients undergoing PCI with bare metal stent placement, we recommend aspirin (75–100 mg/d) plus clopidogrel over aspirin alone (Grade 1A).

2.4.1.1. For patients undergoing PCI with bare metal stent placement following ACS, we recommend 12 months of aspirin (75–100 mg/d) plus clopidogrel (75 mg/d) over aspirin alone (Grade 1A).

2.4.1.2. For patients undergoing PCI with drug-eluting stents, we recommend aspirin (75–100 mg/d) plus clopidogrel (75 mg/d for at least 12 months) [Grade 1A for 3 to 4 months; Grade 1B for 4 to 12 months]. Beyond 1 year, we suggest continued treatment with aspirin plus clopidogrel indefinitely if no bleeding or other tolerability issues (Grade 2C).

2.4.2. For patients undergoing stent placement with a strong concomitant indication for VKA, we suggest triple antithrombotic therapy (Grade 2C).

We suggest 4 weeks of clopidogrel following bare metal stents and 1 year following drug-eluting stents (Grade 2C).

Underlying values and preferences: This recommendation places a high value on the prevention of thromboembolism, including stent thrombosis, and a lower value on minimizing bleeding risk.

For recommendations of use of antiplatelet agents in other patient populations with AF, see “Atrial Fibrillation” chapter by Singer et al (reviewed in *CHEST* 2007 Guidelines).

2.5. For patients after stent placement, we suggest clopidogrel (Grade 1A) or ticlopidine (Grade 2B) over cilostazol. We recommend clopidogrel over ticlopidine (Grade 1A).

2.5.1. For aspirin-intolerant patients undergoing PCI, we recommend use of a thienopyridine derivative rather than dipyridamole (Grade 1B).

2.6. For patients who undergo PCI with no other indication for VKA, we recommend against VKA (Grade 1A).

3.1. In patients with congestive heart failure due to a nonischemic etiology, we recommend against routine use of aspirin or oral VKA (Grade 1B).

4.1.5. For all patients with coronary artery disease undergoing CABG, we recommend aspirin, 75 to 100 mg/d, indefinitely (Grade 1A). We suggest that the aspirin be started postoperatively (Grade 2A).

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

4.1.8. For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po indefinitely (Grade 1B).

4.1.8.1. In patients who undergo CABG following NSTEMI ACS, we suggest clopidogrel, 75 mg/d, for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 2B).

4.1.8.2. For patients who have received clopidogrel for ACS and are scheduled for CABG, we suggest discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A).

4.1.10. For patients undergoing CABG who have no other indication for VKA, we recommend clinicians not administer VKAs (Grade 1C).

4.1.10.1. For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C).

4.2.1. For all patients with coronary artery disease who undergo internal mammary artery bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (Grade 1A).

4.2.2. For all patients undergoing internal mammary artery bypass grafting who have no other indication for VKAs, we recommend against using VKAs (Grade 1C).

5.0. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend 75–100 mg/d of aspirin over either no antithrombotic therapy or VKA (Grade 2A).

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

5.3. For all patients we recommend against the routine addition of clopidogrel to aspirin therapy in primary prevention (Grade 1A). For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, we recommend monotherapy with clopidogrel (Grade 1B).

5.4. For women < 65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2A).

5.4.1. For women > 65 years of age at risk for ischemic stroke or myocardial infarction, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2B).

Underlying values and preferences: The recommendation of aspirin over VKA places a relatively low value on a small absolute reduction in coronary events and deaths and a relatively high value on avoiding the inconvenience, cost, and minor bleeding risk associated with oral VKA. The low target INR value required in primary prevention typically mandates less frequent monitoring; on average every 2 to 3 months and is associated with lower risk of bleeding.

Patients, particularly those in the highest risk groups for whom systems permitting meticulous monitoring of anticoagulant therapy are available, who place a relatively high value on small absolute risk reductions in coronary events and are not influenced by an element of inconvenience and potential bleeding risk associated with VKA are likely to derive the greatest overall benefit from administration of VKA rather than aspirin.

1.0 CHRONIC LIMB ISCHEMIA AND
INTERMITTENT CLAUDICATION

1.1.1.1. In peripheral artery occlusive disease patients with clinically manifest coronary or cerebrovascular disease, we recommend lifelong antiplatelet therapy in comparison to no antiplatelet therapy (Grade 1A).

1.1.1.2. In those without clinically manifest coronary or cerebrovascular disease, we suggest aspirin (75–100 mg/d) over clopidogrel (Grade 2B). In patients who are aspirin intolerant, we recommend clopidogrel over ticlopidine (Grade 1B).

Underlying values and preferences: This recommendation places a relatively high value on avoiding large expenditures to achieve uncertain, small reductions in vascular events.

1.1.2. In patients with peripheral artery occlusive disease and intermittent claudication, we recommend against the use of anticoagulants to prevent vascular mortality or cardiovascular events (Grade 1A).

1.1.4. For patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, we recommend cilostazol (Grade 1A). We suggest that clinicians not use cilostazol in those with less disabling claudication (Grade 2A). We recommend against the use of pentoxifylline (Grade 2B).

Underlying values and preferences: Because of the cost of cilostazol therapy, and the safety and efficacy of an exercise program, we recommend cilostazol treatment be reserved for patients with moderate-to-severe claudication who have tried and failed an exercise program, and are not candidates for vascular surgical or endovascular procedures.

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

1.1.6. For patients with limb ischemia, we suggest clinicians do not use prostaglandins (Grade 2B).

2.1. In patients who suffer from acute arterial emboli or thrombosis, we recommend immediate systemic anticoagulation with UFH, over no anticoagulation (Grade 1C). In patients undergoing embolectomy, we suggest following systemic anticoagulation with UFH with long-term anticoagulation with VKA (Grade 2C).

2.2. In patients with short-term (< 14 days)

thrombotic or embolic disease, we suggest intraarterial thrombolytic therapy (Grade 2B), provided patients are at low risk of myonecrosis and ischemic nerve damage developing during the time to achieve revascularization by this method.

Underlying values and preferences: This recommendation places relatively little value on small reductions in the need for surgical intervention and relatively high value on avoiding large expenditures and possible major hemorrhagic complications.

3.1. For patients undergoing major vascular reconstructive procedures, we recommend IV UFH, prior to the application of vascular cross clamps (Grade 1A).

3.2. For all patients undergoing infrainguinal arterial reconstruction, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We recommend against the routine use of perioperative dextran, heparin, or long-term anticoagulation with VKA for all extremity reconstructions (Grade 1B).

3.3. For patients receiving routine autogenous vein infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We suggest that VKA not be used routinely in patients undergoing infrainguinal vein bypass (Grade 2B). For those at high risk of bypass occlusion and limb loss, we suggest VKA plus aspirin (Grade 2B).

Underlying values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

3.4. For patients receiving routine prosthetic infrainguinal bypass, we recommend aspirin (75–100 mg, begun preoperatively) [Grade 1A]. We suggest that VKA not be used routinely in patients undergoing prosthetic infrainguinal bypass (Grade 2A).

Underlying values and preferences: These recommendations place relatively little value on small increases in long-term patency that may be statistically uncertain, and a relatively high value on avoiding hemorrhagic complications.

4.0. In patients undergoing carotid endarterectomy, we recommend that aspirin, 75–100 mg, preoperatively to prevent perioperative ischemic neurologic events. We recommend lifelong postoperative aspirin (75–100 mg/d) [Grade 1A].

5.0. In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), we recommend lifelong aspirin, 75–100 mg/d (Grade 1C). In this patient group, we recommend against dual antiplatelet therapy with aspirin and clopidogrel (Grade 1B).

6.0. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend long-term aspirin (75–100 mg/d) [Grade 1C]. For patients undergoing lower-extremity balloon angioplasty (with or without stenting), we recommend against anticoagulation with heparin or VKA (Grade 1A).

VTE, THROMBOPHILIA, ANTITHROMBOTIC THERAPY, AND PREGNANCY

2.1 VKA Exposure in Utero

2.1.1. For women receiving anticoagulation for the management of VTE who become pregnant, we recommend that VKAs be substituted with UFH or LMWH (Grade 1A).

2.1.2. For women with mechanical valves who become pregnant, we suggest either adjusted-dose bid LMWH or UFH throughout pregnancy or adjusted-dose bid LMWH or UFH until the thirteenth week with substitution by VKAs until LMWH or UFH are resumed close to delivery (Grade 1C). In pregnant women with high-risk mechanical valves (eg, older-generation valve in the mitral position or history of thromboembolism), we suggest the use of oral anticoagulants over heparin (Grade 2C).

Underlying values and preferences: The suggestion to utilize VKAs during the first 12 weeks of pregnancy places similar value on avoiding maternal thromboembolic complications as on avoiding fetal risks.

2.2 Management of Women Receiving Long-term VKAs Who Are Considering Pregnancy

2.2.1. For women requiring long-term VKAs who are attempting pregnancy and are candidates for UFH or LMWH substitution, we suggest performing frequent pregnancy tests and substituting UFH or LMWH for VKAs when pregnancy is achieved (Grade 2C).

Underlying values and preferences: This recommendation places a higher value on avoiding the risks, inconvenience, and costs of UFH or LMWH therapy of uncertain duration while awaiting pregnancy compared to minimizing the risks of early miscarriage associated with VKA therapy.

3.6 Pentasaccharide Exposure During Breastfeeding

3.6.1. For lactating women using warfarin or UFH who wish to breastfeed, we recommend continuing these medications (Grade 1A).

3.6.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, we suggest continuing these medications (Grade 2C).

3.6.3. For breastfeeding women, we suggest alternative anticoagulants rather than pentasaccharides (Grade 2C).

4.2 LMWH Therapy

4.2.1. For pregnant patients, we suggest LMWH over UFH for the prevention and treatment of VTE (Grade 2C).

5.1 Risk of VTE Following Cesarean Section

5.1.1. We suggest that a thrombosis risk assessment be carried out in all women undergoing cesarean section to determine the need for thromboprophylaxis (Grade 2C).

5.1.2. In patients without additional thrombosis risk factors undergoing cesarean section, we recommend against the use of specific thromboprophylaxis other than early mobilization (Grade 1B).

5.2 Thromboprophylaxis Following cesarean Section

5.2.1. For women considered at increased risk of VTE after cesarean section because of the presence of at least one risk factor in addition to pregnancy and cesarean section, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH or UFH) or mechanical prophylaxis (GCS or IPC) while in hospital following delivery (Grade 2C).

5.2.2. For women with multiple additional risk factors for thromboembolism who are undergoing cesarean section and are considered to be at very high risk of VTE, we suggest that pharmacologic prophylaxis be combined with the use of GCS and/or IPC (Grade 2C).

5.2.3. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 4 to 6 weeks after delivery) following discharge from the hospital (Grade 2C).

6.1 Treatment of VTE During Pregnancy

6.1.1. For pregnant women with acute VTE, we recommend initial therapy with either adjusted-dose SC LMWH or adjusted-dose UFH (IV bolus, followed by a continuous infusion to maintain the APTT within the therapeutic range or SC therapy adjusted to maintain the

APTT 6 h after injection into the therapeutic APTT range) for at least 5 days (Grade 1A).

6.1.2. For pregnant women with acute VTE, after initial therapy, we recommend that SC LMWH or UFH should be continued throughout pregnancy (Grade 1B).

6.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 6 months) [Grade 2C].

6.1.4. For pregnant women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuation of the heparin at least 24 h prior to elective induction of labor (Grade 1C).

7.2 Prevention of Recurrent VTE in Pregnant Women

7.2.1. For pregnant women with a single episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, we recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum (Grade 1C).

7.2.2. If the transient risk factor associated with a previous VTE event is pregnancy or estrogen related, we suggest antepartum clinical surveillance or prophylaxis (prophylactic LMWH/UFH or intermediate-dose LMWH/UFH) plus postpartum prophylaxis, rather than routine care (Grade 2C).

7.2.3. For pregnant women with a single idiopathic episode of VTE but without thrombophilia and who are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants (Grade 1C).

7.2.4. For pregnant women with thrombophilia (confirmed laboratory abnormality) who have had a single prior episode of VTE and are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care or adjusted-dose anticoagulation: antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH or clinical surveillance throughout pregnancy; plus postpartum anticoagulants (Grade 1C).

7.2.5. For women with “higher-risk” thrombophilias (eg, antithrombin deficiency, persistent positivity for the presence of antiphospholipid antibodies; compound heterozygosity for prothrombin G20210A variant and factor V Leiden or homozygosity for these conditions) who have had a single prior episode of VTE and are not

receiving long-term anticoagulants, we suggest, in addition to postpartum prophylaxis, antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH, rather than clinical surveillance (Grade 2C).

7.2.6. For pregnant women with multiple (≥ 2) episodes of VTE not receiving long-term anticoagulants, we suggest antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH or prophylactic, intermediate-dose or adjusted-dose UFH followed by postpartum anticoagulants rather than clinical surveillance (Grade 2C).

7.2.7. For pregnant women receiving long-term anticoagulants for prior VTE, we recommend LMWH or UFH throughout pregnancy (either adjusted-dose LMWH or UFH, 75% of adjusted-dose LMWH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum (Grade 1C).

7.2.8. For all pregnant women with previous DVT, we suggest the use of GCS both antepartum and postpartum (Grade 2C).

Underlying values and preferences: This recommendation places a high value on uncertain incremental benefit with stockings and a low value on avoiding discomfort and inconvenience.

8.1 Risk of Pregnancy-Related VTE in Women With Thrombophilia

8.1.1. For pregnant patients with thrombophilia but no prior VTE, we recommend that physicians do not use routine pharmacologic antepartum prophylaxis but instead perform an individualized risk assessment (Grade 1C).

8.2 Prevention of Pregnancy-Related VTE in Women With Thrombophilia

8.2.1. For pregnant women with no history of VTE but antithrombin deficiency, we suggest antepartum and postpartum prophylaxis (Grade 2C).

8.2.2. For all other pregnant women with thrombophilia and no prior VTE, we suggest antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants (Grade 2C).

9.1 Risk of Pregnancy Complications in Women With Thrombophilia

9.1.1. For women with recurrent early pregnancy loss (three or more miscarriages) or unexplained late pregnancy loss, we recommend screening for antiphospholipid antibodies (Grade 1A).

9.1.2. For women with severe or recurrent

preeclampsia or IUGR, we suggest screening for antiphospholipid antibodies (Grade 2C).

9.2 Prevention of Pregnancy Complications in Women With Thrombophilia

9.2.1. For women with antiphospholipid antibodies and recurrent (three or more) pregnancy loss or late pregnancy loss and no history of venous or arterial thrombosis, we recommend antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin (Grade 1B).

10.1 Prevention of Recurrent Preeclampsia in Women Without Thrombophilia

10.1.1. For women considered high risk for preeclampsia, we recommend low-dose aspirin therapy throughout pregnancy (Grade 1B).

10.1.2. For women with a history of preeclampsia, we suggest that UFH and LMWH should not be used as prophylaxis in subsequent pregnancies (Grade 2C).

11.1 Anticoagulant Management of Mechanical Prosthetic Valves in Pregnant Women

11.1.1. For pregnant women with mechanical heart valves we recommend that the decision about anticoagulant management during pregnancy include an assessment of additional risk factors for thromboembolism including valve type, position, and history of thromboembolism and that the decision should also be influenced strongly by patient preferences (Grade 1C).

11.1.2. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation:

- a. **Adjusted-dose bid LMWH throughout pregnancy (Grade 1C); we suggest that doses be adjusted to achieve the manufacturer peak anti-Xa LMWH 4 h after SC injection (Grade 2C)**
- b. **Adjusted-dose UFH throughout pregnancy administered SC q12h in doses adjusted to keep the mid-interval APTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (Grade 1C)**
- c. **UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed (Grade 1C).**

In women judged to be at very high risk of

thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older-generation prosthesis in the mitral position or history of thromboembolism), we suggest VKAs throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery, rather than one of the regimens above; after a thorough discussion of the potential risks and benefits of this approach (Grade 2C).

Underlying values and preferences: In contrast to our other recommendations, which place a high value on avoiding fetal risk, the recommendation for women at very high risk of thromboembolism places equal value on avoiding maternal complications.

Remark: For all the recommendations above, usual long-term anticoagulants should be resumed postpartum.

11.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we recommend the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C).

ANTITHROMBOTIC THERAPY IN NEONATES AND CHILDREN

In Neonates With VTE (CVL and Non-CVL Related)

1.1.1. We suggest that central venous lines (CVL) or UVCs associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation (Grade 2C).

1.1.2. We suggest either initial anticoagulation, or supportive care with radiologic monitoring (Grade 2C); however, we recommend subsequent anticoagulation if extension of the thrombosis occurs during supportive care (Grade 1B).

1.1.3. We suggest anticoagulation should be with either of the following: (1) LMWH given bid and adjusted to achieve an anti-FXa level of 0.5–1.0 U/mL; or (2) UFH for 3 to 5 days adjusted to achieve an anti-FXa of 0.35 to 0.7 U/mL or a corresponding APTT range, followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months (Grade 2C).

1.1.4. We suggest that if either a CVL or a UVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH be given to prevent recurrent VTE until such time as the CVL or UVC is removed (Grade 2C).

1.1.5. We recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 1B).

1.1.6. We suggest that if thrombolysis is required the clinician use tPA and supplement with plasminogen (fresh frozen plasma) prior to commencing therapy (Grade 2C).

In Children With DVT

1.2.1. We recommend anticoagulant therapy with either UFH or LMWH (Grade 1B). For additional information, see Section 1.2 (DVT in Children).

1.2.2. We recommend initial treatment with UFH or LMWH for at least 5 to 10 days (Grade 1B). For patients in whom clinicians will subsequently prescribe VKAs, we recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the INR has not exceeded 2.0 (Grade 1B). After the initial 5- to 10-day treatment period, we suggest LMWH rather than VKA therapy if therapeutic levels are difficult to maintain on VKA therapy or if VKA therapy is challenging for the child and family (Grade 2C).

1.2.3. We suggest children with idiopathic thromboembolism receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C).

Underlying values and preferences: The suggestion to use anticoagulation therapy to treat idiopathic DVTs in children for at least 6 months rather than on a lifelong basis places a relatively high value on avoiding the inconvenience and bleeding risk associated with antithrombotic therapy, and a relative low value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor.

1.2.4. In children with secondary thrombosis in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for at least 3 months using VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C).

1.2.5. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing l-asparaginase therapy, we suggest continuing anticoagulant therapy in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C).

1.2.6. For children with recurrent idiopathic thrombosis, we recommend indefinite treatment with VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 1A].

Remark: For some patients, long-term LMWH

may be preferable; however, there are little or no data about the safety of long-term LMWH in children.

1.2.7. For children with recurrent secondary thromboembolisms with an existing reversible risk factor for thrombosis, we suggest anticoagulation until the removal of the precipitating factor but for a minimum of 3 months (Grade 2C).

1.2.8. If a CVL is no longer required, or is nonfunctioning, we recommend it be removed (Grade 1B). We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal (Grade 2C). If CVL access is required and the CVL is still functioning, we suggest that the CVL remain *in situ* and the patient be anticoagulated (Grade 2C).

1.2.9. For children with a first CVL-related DVT, we suggest initial management as for secondary thromboembolism as previously described. We suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range 1.5 to 1.9) or LMWH (anti-FXa level range, 0.1 to 0.3) be given until the CVL is removed (Grade 2C). If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed but at least for a minimum of 3 months (Grade 2C).

1.3.1. In children with DVT, we suggest that thrombolysis therapy not be used routinely (Grade 2C). If thrombolysis is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (Grade 2C).

1.4.1. If life-threatening VTE is present, we suggest thrombectomy (Grade 2C).

1.4.2. We suggest, following thrombectomy, anticoagulant therapy be initiated (Grade 2C).

1.4.3. In children > 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, we suggest placement of a temporary inferior vena cava filter (Grade 2C).

1.4.4. We suggest that temporary inferior vena cava filters be removed as soon as possible if thrombosis is not present in the basket of the filter and when the risk of anticoagulation decreases (Grade 2C).

1.4.5. In children who receive an inferior vena cava filter, we recommend appropriate anticoagulation for DVT (see Section 1.2) as soon as the contraindication to anticoagulation is resolved (Grade 1B).

1.5.1. In children with cancer, we suggest management of VTE follow the general recommen-

dations for management of DVT in children. We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) [Grade 2C].

Remark: The presence of cancer, and the need for surgery, chemotherapy, or other treatments may modify the risk benefit ratio for treatment of DVT, and clinicians should consider these factors on an individual basis.

1.5.2. We suggest clinicians not use primary anti-thrombotic prophylaxis in children with cancer and central venous access devices (Grade 2C).

1.6. For children with VTE, in the setting of antiphospholipid antibodies, we suggest management as per general recommendations for VTE management in children.

Remark: Depending on the age of the patient, it may be more appropriate to follow adult guidelines for management of VTE in the setting of antiphospholipid antibodies.

1.7.1. For neonates or children with unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava, we suggest supportive care with monitoring of the RVT for extension or anticoagulation with UFH/LMWH or LMWH in therapeutic doses; we suggest continuation for 3 months (Grade 2C).

1.7.2. For unilateral RVT that extends into the inferior vena cava, we suggest anticoagulation with UFH/LMWH or LMWH for 3 months (Grade 2C).

1.7.3. For bilateral RVT with various degrees of renal failure, we suggest anticoagulation with UFH and initial thrombolytic therapy with tPA, followed by anticoagulation with UFH/LMWH (Grade 2C).

Remark: LMWH therapy requires careful monitoring in the presence of significant renal impairment.

1.8.1. In children with CVLs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B).

1.8.2. In children receiving long-term home total parenteral nutrition, we suggest thromboprophylaxis with VKAs with a target INR of 2.5 (range 2.0–3.0) [Grade 2C].

1.8.3. For blocked CVLs, we suggest tPA or recombinant urokinase to restore patency (Grade 2C). If 30 min following local thrombolytic instillation CVL patency is not restored, we suggest a second dose be administered. If the CVL remains blocked following two doses of local thrombolytic agent, we suggest investigations to rule out a CVL-related thrombosis be initiated (Grade 2C).

1.9. For pediatric patients having a modified Blalock-Taussig shunt, we suggest intraoperative therapy with UFH followed by either aspirin (1–5 mg/kg/d) or no further antithrombotic therapy compared to prolonged LMWH or VKAs (Grade 2C).

1.10. For patients who underwent the Norwood procedure, we suggest UFH immediately after the procedure, with or without ongoing antiplatelet therapy (Grade 2C).

1.11. In patients who have bilateral cavopulmonary shunts, we suggest postoperative UFH (Grade 2C). For additional information, see Section 1.11 (Primary Prophylaxis for Glenn or Bilateral Cavopulmonary Shunts in Children).

1.12. For children after Fontan surgery, we recommend aspirin (1–5 mg/kg/d) or therapeutic UFH followed by VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) [Grade 1B].

Remark: The optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

1.13. For children having endovascular stents inserted, we suggest administration of UFH perioperatively (Grade 2C).

1.14. We suggest that pediatric patients with cardiomyopathy receive VKAs to achieve a target INR of 2.5 (range, 2.0 to 3.0) no later than their activation on a cardiac transplant waiting list (Grade 2C).

Underlying values and preferences: Our suggestion for administration of VKAs places a high value on avoiding thrombotic complications, and a relatively low value on avoiding the inconvenience, discomfort and limitations of anticoagulant monitoring, in children who are eligible for transplant, which is a potentially curative therapy.

1.15. In children with primary pulmonary hypertension, we suggest anticoagulation with VKAs commencing when other medical therapy is commenced (Grade 2C).

1.16. For children with biological prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population.

1.17. For children with mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population with respect to the intensity of anticoagulation therapy.

1.17.2. For children with mechanical prosthetic heart valves who have had thrombotic events while on therapeutic antithrombotic therapy or in

patients in whom there is a contraindication to full-dose VKAs, we suggest adding aspirin therapy (Grade 2C).

1.18.1. Following ventricular assistance device (VAD) placement, in the absence of bleeding we suggest administration of UFH targeted to an anti-factor Xa of 0.35 to 0.7 u/mL (Grade 2C). We suggest starting UFH between 8 h and 48 h following implantation (Grade 2C).

1.18.2. We suggest antiplatelet therapy (either aspirin, 1 to 5 mg/kg/d, and/or dipyridamole, 3 to 10 mg/kg/d) to commence within 72 h of VAD placement (Grade 2C).

1.18.3. We suggest that once clinically stable, pediatric patients be weaned from UFH to either LMWH (target anti-FXa 0.5–1.0 U/mL) or VKA (target INR, 3.0; range, 2.5–3.5) until transplanted or weaned from ventricular assistance device (Grade 2C).

1.19.1. For neonates and children requiring CC via an artery, we recommend administration of IV UFH prophylaxis (Grade 1A).

1.19.2. We recommend the use of UFH doses of 100 to 150 U/kg as a bolus (Grade 1B). We suggest further doses of UFH rather than no further therapy in prolonged procedures (Grade 2B).

1.19.3. We recommend against the use of aspirin therapy for prophylaxis for cardiac catheterization (Grade 1B).

1.20.1. For pediatric patients with a femoral artery thrombosis, we recommend therapeutic doses of IV UFH (Grade 1B). We suggest treatment for at least 5–7 days (Grade 2C).

1.20.2. We recommend administration of thrombolytic therapy for pediatric patients with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications (Grade 1B).

1.20.3. For children with femoral artery thrombosis, we suggest surgical intervention when there is a contraindication to thrombolytic therapy and organ or limb death is imminent (Grade 2C).

1.20.4. We suggest that for children in whom thrombolysis or surgery is not required, conversion to LMWH to complete 5 to 7 days of treatment (Grade 2C).

1.21.1. For pediatric patients with peripheral arterial catheters *in situ*, we recommend UFH through the catheter, preferably by continuous infusion (5 U/mL at 1 mL/h) [Grade 1A].

1.21.2. For children with a peripheral arterial catheter-related thromboembolism, we suggest immediate removal of the catheter (Grade 1B).

We suggest UFH anticoagulation with or without thrombolysis, or surgical thrombectomy (Grade 2C).

1.22.1 To maintain umbilical artery catheter (UAC) patency, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25–1 U/mL) [Grade 2A].

1.22.2. For neonates with UAC-related thrombosis, we suggest therapy with UFH or LMWH for at least 10 days (Grade 2C).

1.22.3. For neonates with UAC-related thrombosis, we recommend UAC removal (Grade 1B).

1.22.4. For neonates with UAC-related thrombosis with potentially life-, limb-, or organ-threatening symptoms, we suggest thrombolysis with tPA. When thrombolysis is contraindicated, we suggest surgical thrombectomy (Grade 2C).

1.23. We suggest UACs placement in a high position rather than a low position (Grade 2B).

1.24 Neonatal Aortic Thrombosis–Spontaneous. For additional information, see Section 1.24 “Neonatal Aortic Thrombosis–Spontaneous”

1.25. In patients undergoing hemodialysis, we suggest against routine use of VKAs or LMWH for prevention of thrombosis related to central venous lines or fistulas (Grade 2C).

1.26. We suggest the use of UFH or LMWH in hemodialysis (Grade 2C).

1.27.1. In children with Kawasaki disease, we recommend aspirin in high doses (80 to 100 mg/kg/d during the acute phase, for up to 14 days) as an antiinflammatory agent, then in lower doses (1 to 5 mg/kg/d for 6 to 8 weeks) as an antiplatelet agent (Grade 1B).

1.27.2. In children with Kawasaki disease, we suggest against concomitant use of ibuprofen or other nonsteroidal antiinflammatory drugs during aspirin therapy (Grade 2C).

1.27.3. In children with Kawasaki disease, we recommend IV gamma globulin (2 g/kg, single dose) within 10 days of the onset of symptoms (Grade 1A).

1.27.4. In children with giant coronary aneurysms following Kawasaki disease, we suggest warfarin (target INR, 2.5; INR range, 2.0 to 3.0) in addition to therapy with low-dose aspirin be given as primary thromboprophylaxis (Grade 2C).

1.28.1. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage, we suggest anticoagulation, initially with UFH, or LMWH and subsequently with LMWH or VKA for a minimum of 6 weeks, and no longer than 3 months (Grade 2C).

1.28.2. For children with cerebral sinovenous thrombosis (CSVT) with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus propagation is noted (Grade 2C).

1.29.1. For children with CSVT without significant intracranial hemorrhage, we recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation (Grade 1B).

1.29.2. We suggest that if after 3 months of therapy there is incomplete radiologic recanalisation of CSVT or ongoing symptoms, administration of a further 3 months of anticoagulation (Grade 2C).

1.29.3. For children with CSVT with significant hemorrhage, we suggest radiologic monitoring of the thrombosis at 5 to 7 days. If thrombus propagation is noted at that time, we suggest anticoagulation (Grade 2C).

1.29.4. We suggest children with CSVT in the context of a potentially recurrent risk factors (for example nephrotic syndrome, L-asparaginase therapy) should receive prophylactic anticoagulation at times of risk factor recurrence (Grade 2C).

1.29.5. We suggest thrombolysis thrombectomy or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy (Grade 2C).

1.30.1. In the absence of a documented ongoing cardioembolic source, we recommend against anticoagulation or aspirin therapy for neonates with a first arterial ischemic stroke (AIS) (Grade 1B).

1.30.2. In neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C).

1.31.1. For children with non-sickle-cell disease-related acute AIS, we recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded (Grade 1B).

1.31.2. We recommend, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis (1–5 mg/kg/d) for a minimum of 2 years (Grade 1B).

1.31.3. We suggest for AIS secondary to dissection or cardioembolic causes, anticoagulant therapy with LMWH or VKAs for at least 6 weeks, with ongoing treatment dependent on radiologic assessment (Grade 2C).

1.31.4. We recommend against the use of thrombolysis (tPA) for AIS in children, outside of specific research protocols (Grade 1B).

1.31.5. We recommend for children with sickle-cell disease and AIS, IV hydration and exchange transfusion to reduce sickle hemoglobin levels to at least < 30% total hemoglobin (Grade 1B).

1.31.6. For children with sickle-cell disease and AIS, after initial exchange transfusion we recommend a long-term transfusion program (Grade 1B).

1.31.7. In children with sickle-cell anemia who have transcranial Doppler velocities > 200 cm/s on screening, we recommend regular blood transfusion, which should be continued indefinitely (Grade 1B).

1.31.8. We recommend that children with moyamoya be referred to an appropriate center for consideration of revascularization (Grade 1B).

1.31.9. For children receiving aspirin who have recurrent AIS or transient ischemic attack, we suggest changing to clopidogrel or anticoagulant (LMWH or VKA) therapy (Grade 2C).

1.32.1. For neonates with homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of fresh frozen plasma q12h or protein C concentrate, when available, at 20 to 60 U/kg until the clinical lesions resolve (Grade 1B).

1.31.2. We suggest long-term treatment with VKAs (Grade 2C), LMWH (Grade 2C), protein C replacement (Grade 1B), or liver transplantation (Grade 2C).

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Holger J. Schönemann
Chest 2008;133;71-109
DOI 10.1378/chest.08-0693

This information is current as of June 24, 2008

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