CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Executive Summary

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; AIS = arterial ischemic stroke; APLA = antiphospolipid antibodies; ASA = acetylsalicylic acid; AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; BMS = bare-metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CDT = catheter-directed thrombosis; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CSVT = cerebral sinovenous thrombosis; CTPH = chronic thromboembolic pulmonary hypertension; CUS = compression ultrasound; CVAD = central venous access device; DES = drug-eluting stent; GCS = graduated compression stockings; HFS = hip fracture surgery; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia complicated by thrombosis; IA = intraarterial; ICH = intracerebral hemorrhage; IE = infective endocarditis; INR = international normalized ratio; IPC = intermittent pneumatic compression; IPCD = intermittent pneumatic compression device; IVC = inferior vena cava; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; LV = left ventricular; MBTS = modified Blalock-Taussig shunt; MR = magnetic resonance; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PFO = patent foramen ovale; PMBV = percutaneous mitral balloon valvotomy; PTS = postthrombotic syndrome; PVT = prosthetic valve thrombosis; r-tPA = recombinant tissue plasminogen activator; RVT = renal vein thrombosis; SC = subcutaneous; TEE = transesophageal echocardiography; THA = total hip arthroplasty; TIA = transient ischemic attack; TKA = total knee arthroplasty; UAC = umbilical arterial catheter; UEDVT = upper-extremity DVT; UFH = unfractionated heparin; US = ultrasound; UVC = umbilical venous catheter; VAD = ventricular assist device; VKA = vitamin K antagonist

The eighth iteration of the American College of Chest Physicians Antithrombotic Guidelines presented, in a paper version, a narrative evidence summary and rationale for the recommendations, a small number of evidence profiles summarizing bodies of evidence, and some articles with quite extensive summary tables of primary studies. In total, this represented 600 recommendations summarized in 968 pages of text. Many readers responded that the result was too voluminous for their liking or practical use.

Cognizant of this feedback, we worked hard to minimize the length of the text for the ninth iteration of the guidelines Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) without sacrificing key content. A number of topic editors found our shortening edits draconian, but we were determined to produce the leanest product possible.

There were, however, a number of obstacles. In what we believe is a key advance in AT9, we conducted a systematic review of what is known about patients' values and preferences regarding antithrombotic therapy and included the results as an article in AT9. In another forward step, we recognized the problems with asymptomatic thrombosis as a surrogate outcome, and devised strategies to estimate reductions in symptomatic DVT and pulmonary embolism with antithrombotic prophylaxis. We felt it important to explain this innovation to users of AT9, and this meant another article.

We included, for the first time, an article on diagnosis addressing patients with symptoms and signs suggesting DVT. We increased the range of interventions we have covered, resulting in additional recommendations. Finally, we produced many summary of findings tables, which offer extremely succinct and informative presentations of best estimates of effect and the confidence associated with those estimates.

If published in the same fashion as the Antithrombotic and Thrombolytic Therapy, 8th ed: American

College of Chest Physicians Antithrombotic Guidelines, this would have resulted in a document with >850 pages of paper text, an unacceptable length. Given this and with the advice of the journal, we decided to adopt a highly focused print version that includes only this executive summary and the following articles:

- An introduction describing the major innovations in AT9
- A methods article explaining how we developed the guidelines (a potential model for other guideline groups interested in optimal rigor)
- Recommendations and grading from each article embedded in the table of contents of each article

Those seeking the rationale for the recommendations, including the supporting evidence, should access the online version of the guideline (http://http://chestjournal.chestpubs.org/content/141/2_suppl) that includes a narrative summaries and supporting summary of findings tables. The numbering indicated beside the recommendations in this summary is aligned with the sections and tables found in the full articles. Those interested in a deeper understanding of the evidence can turn to online data supplements for each of the articles that include recommendations. There, they will find evidence profiles (expanded versions of the summary of findings tables) and some tables summarizing the methods and results, and the risk of bias, associated with the individual studies that contributed to the evidence profiles and summary of findings tables.

The world of medical information is rapidly becoming a world of electronic storage and presentation of primary studies, recommendations, and a wide variety of other information of interest to health care practitioners. Although our abbreviated paper copy presentation represents a necessary response to a challenging situation, it is also a harbinger of the increasingly electronic world of medical information into which future editions of guidelines are destined to move.

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Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

Evidence-Based Management of Anticoagulant Therapy

For further details, see Holbrook et al.[1]

2.1 Loading Dose for Initiation of Vitamin K Antagonist (VKA) Therapy

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C)**.**

2.2 Initial Dose Selection and Pharmacogenetic Testing

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)**.**

2.3 Initiation Overlap for Heparin and VKA

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) therapy rather than waiting for several days to start (Grade 2C)**.**

3.1 Monitoring Frequency for VKAs

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B)**.**

3.2 Management of the Single Out-of-Range INR

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C)**.**

3.3 Bridging for Low INRs

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C)**.**

3.4 Vitamin K Supplementation

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C)**.**

3.5 Anticoagulation Management Services for VKAs

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should 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.

3.6 Patient Self-Testing and Self-Management

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management rather than usual outpatient INR monitoring (Grade 2B)**. For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.**

3.7 Dosing Decision Support

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C)**.**

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8 VKA Drug Interactions to Avoid

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs, including cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, and certain antibiotics (see Table 8 in main article[1]) (Grade 2C)**.**

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C)**.**

4.1 Optimal Therapeutic INR Range

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B)**.**

4.2 Therapeutic Range for High-Risk Groups

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B)**.**

5.0 Discontinuation of Therapy

5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C)**.**

6.1 Unfractionated Heparin (UFH) Dose Adjustment by Weight

6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C)**.**

6.2 Dose Management of Subcutaneous (SC) UFH

6.2. For outpatients with VTE treated with SC UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C)**.**

7.1 Therapeutic Dose of LMWH in Patients With Decreased Renal Function

7.1. For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C)**.**

8.1 Fondaparinux Dose Management by Weight

8.1. For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C)**.**

9.1 Vitamin K for Patients Taking VKAs With High INRs Without Bleeding

9.1.

(a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B)**.**

(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C)**.**

9.2 Clinical Prediction Rules for Bleeding While Taking VKA

9.2. For patients initiating VKA therapy, we suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C)**.**

9.3 Treatment of Anticoagulant-Related Bleeding

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C)**.**

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C)**.**

Prevention of VTE in Nonsurgical Patients

For further details, see Kahn et al.[2]

2.0 Hospitalized Acutely Ill Medical Patients

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B)**.**

Remarks: In choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance, and ease of administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs (eg, prices of various pharmacologic agents in individual hospital formularies).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B)**.**

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, we recommend against anticoagulant thromboprophylaxis (Grade 1B)**.**

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) **or intermittent pneumatic compression (IPC)** (Grade 2C)**, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2B)**.**

Remarks: Patients who are particularly averse to the potential for skin complications, cost, and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis.

2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)**.**

3.0 Critically Ill Patients

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C)**.**

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C)**.**

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C) **until the**

bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (Grade 2C)**.**

4.0 Patients With Cancer in the Outpatient Setting

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and recommend against the prophylactic use of VKAs** (Grade 1B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and suggest against the prophylactic use of VKAs** (Grade 2C)**.**

5.0 Chronically Immobilized Patients

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C)**.**

6.0 Persons Traveling Long-Distance

6.1.1. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C)**.**

6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel (Grade 2C)**. For all other long-distance travelers, we suggest against the use of GCS** (Grade 2C)**.**

6.1.3. For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C)**.**

7.0 Persons With Asymptomatic Thrombophilia

7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)**.**

Prevention of VTE in Nonorthopedic Surgical Patients

For further details, see Gould et al.[3]

3.6 Patients Undergoing General, GI, Urological, Gynecologic, Bariatric, Vascular, Plastic, or Reconstructive Surgery

3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score, < 7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) **or mechanical** (Grade 2C) **prophylaxis be used other than early ambulation.**

3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (~1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C)**.**

3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest LMWH (Grade 2B)**, LDUH** (Grade 2B)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

3.6.4. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, > 10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we

suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C).

3.6.5. For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, ≥5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) **or LDUH** (Grade 1B) **over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis** (Grade 2C).

3.6.6. For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B).

Remarks: Patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient.

3.6.7. For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

3.6.8. For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, ≥5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, we suggest low-dose aspirin (Grade 2C), **fondaparinux** (Grade 2C), **or mechanical prophylaxis, preferably with IPC** (Grade 2C), **over no prophylaxis.**

3.6.9. For general and abdominal-pelvic surgery patients, we suggest that an inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C).

3.6.10. For general and abdominal-pelvic surgery patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C).

4.0 Patients Undergoing Cardiac Surgery

4.4.1. For cardiac surgery patients with an uncomplicated postoperative course, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C).

4.4.2. For cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications, we suggest adding pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis (Grade 2C).

5.0 Patients Undergoing Thoracic Surgery

5.4.1. For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 2B), **LMWH** (Grade 2B), **or mechanical prophylaxis with optimally applied IPC** (Grade 2C) **over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

5.4.2. For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 1B) **or LMWH** (Grade 1B) **over no prophylaxis. In addition, we suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis** (Grade 2C).

5.4.3. For thoracic surgery patients who are at high risk for major bleeding, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

6.0 Patients Undergoing Craniotomy

6.4.1. For craniotomy patients, we suggest that mechanical prophylaxis, preferably with IPC, be used over no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C).

6.4.2. For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant disease), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C).

7.0 Patients Undergoing Spinal Surgery

7.4.1. For patients undergoing spinal surgery, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C), **unfractionated heparin** (Grade 2C), **or LMWH** (Grade 2C).

7.4.2. For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

8.0 Patients With Major Trauma: Traumatic Brain Injury, Acute Spinal Injury, and Traumatic Spine Injury

8.4.1. For major trauma patients, we suggest use of LDUH (Grade 2C)**, LMWH** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

8.4.2. For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury.**

8.4.3. For major trauma patients in whom LMWH and LDUH are contraindicated, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves** (Grade 2C)**.**

8.4.4. For major trauma patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C)**.**

8.4.5. For major trauma patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C)**.**

Prevention of VTE in Orthopedic Surgery Patients

For further details, see Falck-Ytter et al.[4]

2.0 Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS)

2.1.1. In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B)**, or an intermittent pneumatic compression device (IPCD)** (Grade 1C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.1.2. In patients undergoing HFS, we recommend use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all Grade 1B)**, or an IPCD** (Grade 1C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.2. For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, we recommend starting either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B)**.**

2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B)**, adjusted-dose VKA, or aspirin** (all Grade 2C)**.**

Remarks: If started preoperatively, we suggest administering LMWH $\geq$ 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran, and rivaroxaban). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on

its inconvenience are likely to choose an IPCD over the drug options.

2.3.2. In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, LDUH (Grade 2B)**, adjusted-dose VKA, or aspirin** (all Grade 2C)**.**

Remarks: For patients in whom surgery is likely to be delayed, we suggest that LMWH be initiated during the time between hospital admission and surgery but suggest administering LMWH at least 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux) or possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options.

2.4. For patients undergoing major orthopedic surgery, we suggest extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (Grade 2B)**.**

2.5. In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the undesirable consequences associated with prophylaxis with both a pharmacologic agent and an IPCD are likely to decline use of dual prophylaxis.

2.6. In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C)**.**

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the discomfort and inconvenience of IPCD and a low value on avoiding a small absolute increase in bleeding with pharmacologic agents when only one bleeding risk factor is present (in particular the continued use of antiplatelet agents) are likely to choose pharmacologic thromboprophylaxis over IPCD.

2.7. In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B)**.**

2.8. In patients undergoing major orthopedic surgery, we suggest against using IVC filter placement for primary prevention over no thromboprophylaxis in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C)**.**

2.9. For asymptomatic patients following major orthopedic surgery, we recommend against Doppler (or duplex) ultrasound screening before hospital discharge (Grade 1B)**.**

3.0 Patients With Isolated Lower-Leg Injuries Distal to the Knee

3.0. We suggest no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C)**.**

4.0 Patients Undergoing Knee Arthroscopy

4.0. For patients undergoing knee arthroscopy without a history of prior VTE, we suggest no thromboprophylaxis rather than prophylaxis (Grade 2B)**.**

Perioperative Management of Antithrombotic Therapy

For further details, see Douketis et al.[5]

2.1 Interruption of VKAs Before Surgery

2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery *instead of* stopping VKAs a shorter time before surgery (Grade 1C)**.**

2.2 Resumption of VKAs After Surgery

2.2. In patients who require temporary interruption of a VKA before surgery, we recommend

resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs (Grade 2C)**.**

2.4 Bridging Anticoagulation During Interruption of VKA Therapy

2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation *instead of* **no bridging during interruption of VKA therapy** (Grade 2C)**.**

Remarks: Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no bridging *instead of* bridging anticoagulation during interruption of VKA therapy (Grade 2C)**.**

In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.

2.5 Perioperative Management of VKA-Treated Patients Who Require Minor Procedures

2.5. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure *instead of* alternative strategies (Grade 2C)**. In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis *instead of* other strategies** (Grade 2C)**. In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery *instead of* other strategies** (Grade 2C)**.**

3.4 Patients Undergoing a Minor Dental, Dermatologic, or Ophthalmologic Procedure

3.4. In patients who are receiving acetylsalicylic acid (ASA) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure *instead of* stopping ASA 7 to 10 days before the procedure (Grade 2C)**.**

3.5. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C)**. In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery *instead of* continuation of ASA** (Grade 2C)**.**

3.6 Patients Undergoing Coronary Artery Bypass Graft Surgery

3.6. In patients who are receiving ASA and require coronary artery bypass graft (CABG) surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C)**. In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery *instead of* continuing dual antiplatelet therapy around the time of surgery** (Grade 2C)**.**

3.7 Surgical Patients With Coronary Stents

3.7. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent *instead of* undertaking surgery within these time periods (Grade 1C)**. In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery *instead of* stopping dual antiplatelet therapy 7 to 10 days before surgery** (Grade 2C)**.**

Remarks: Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.

4.2 Perioperative Use of IV UFH

4.2. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4 to 6 h before surgery *instead of* closer to surgery (Grade 2C)**.**

4.3 Preoperative Interruption of Therapeutic-Dose Bridging LMWH

4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of* 12 h before surgery (Grade 2C)**.**

4.4 Postoperative Resumption of Therapeutic-Dose Bridging LMWH

4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery *instead of* resuming LMWH within 24 h after surgery (Grade 2C)**.**

Diagnosis of DVT

For further details, see Bates et al.[6]

3.0 Diagnosis of Suspected First Lower Extremity DVT

3.1. In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B)**.**

Remarks: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

3.2. In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer, or (iii) compression ultrasound (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons)**, (ii) venography** (Grade 1B for all comparisons), **or (iii) whole-leg ultrasound (US)** (Grade 2B for all comparisons)**. We suggest initial use of a moderately sensitive** (Grade 2C) **or highly sensitive** (Grade 2B) **D-dimer rather than proximal CUS.**

Remarks: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography** (Grade 1B for all comparisons)**.**

If the D-dimer is positive, we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) **or (ii) venography** (Grade 1B)**. If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography** (Grade 2C)**.**

Remarks: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (eg, a short segment of venous noncompressibility).

3.3. In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than (i) no testing (Grade 1B for all comparisons) **or (ii) venography** (Grade 1B for all comparisons)**. We suggest initial use of a highly sensitive D-dimer rather than US** (Grade 2C)**.**

Remarks: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with

severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the highly sensitive D-dimer is positive, we recommend proximal CUS or whole-leg US rather than no testing** (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

If proximal CUS is chosen as the initial test and is negative, we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) **or venography** (Grade 2B)**. In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**.**

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons)**.**

If whole-leg US is negative, we recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons)**. If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography** (Grade 1B)**. If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are more likely to benefit from treatment over repeat US.

3.4. In patients with a high pretest probability of first lower extremity DVT, we recommend either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and d-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**.**

In patients with a negative proximal CUS, we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) **or venography** (Grade 2B for all comparisons)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**. In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US** (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US)**.**

We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as standalone tests to rule out DVT (Grade 1B)**.**

3.5. If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than (i) no testing (Grade 1B)**, (ii) venography** (Grade 1B)**, or D-dimer testing** (Grade 2B)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

We recommend that patients with a negative proximal CUS undergo testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) **or venography** (Grade 2B)**. In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS** (Grade 2B) **or whole-leg US** (Grade 2C)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing** (Grade 1B for both comparisons)**.**

We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US, no further testing be performed rather than venography (Grade 1B)**.**

If proximal US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**. If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in "Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" are more likely to benefit from treatment over repeat US.

3.6. In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C)**.**

4.1 Venography in Patients With Suspected Recurrent DVT

4.1. In patients suspected of having recurrent lower extremity DVT, we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B)**.**

Remarks: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive, we recommend proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons)**.**

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of <2 mm), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B)**.**

Remarks: In patients with an abnormal proximal CUS at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of <2 mm).

We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B)**.**

If CUS of the proximal veins is positive, we recommend treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a $\geq$4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result)**.**

Remarks: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience

and potential side effects of a venography are likely to choose venography over treatment (in the case of ≥ 4-mm increase in venous diameter).

4.2 Compression Ultrasonography in Patients With Suspected Recurrent DVT

4.2. In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg, an increase in residual venous diameter of < 4 but ≥ 2 mm), we recommend further testing with venography, if available (Grade 1B)**; serial proximal CUS** (Grade 2B) **or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive** (Grade 2B)**, as opposed to other testing strategies or treatment.**

4.3 Pretest Probability Assessment in Patients With Suspected Recurrent DVT

4.3. In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison, we recommend further testing with venography, if available (Grade 1B) **or a highly sensitive D-dimer** (Grade 2B) **over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography** (Grade 2C)**. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence** (Grade 2C)**.**

Remarks: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

5.1 Venography in Pregnancy-Related DVT

5.1. In pregnant patients suspected of having lower extremity DVT, we recommend initial evaluation with proximal CUS over other initial tests, including a whole-leg US (Grade 2C)**, moderately sensitive D-dimer** (Grade 2C)**, highly sensitive D-dimer** (Grade 1B)**, or venography** (Grade 1B)**.**

5.2 Compression Ultrasonography in Pregnancy-Related DVT

5.2. In pregnant patients with suspected DVT in whom initial proximal CUS is negative, we suggest further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) **or a sensitive D-dimer done at the time of presentation** (Grade 2B) **over no further testing for DVT. We recommend that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT** (Grade 1B) **and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7) rather than venography** (Grade 1B) **or whole-leg US** (Grade 2C)**.**

5.3 Pretest Probability in Pregnancy-Related DVT

5.3. In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS, we suggest further testing with either Doppler US of the iliac vein (Grade 2C)**, venography** (Grade 2C)**, or direct MRI** (Grade 2C)**, rather than standard serial CUS of the proximal deep veins.**

6.1 Ultrasonography in Patients With Upper-Extremity DVT (UEDVT)

6.1. In patients suspected of having UEDVT, we suggest initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C)**.**

6.2 Clinical Pretest Probability Assessment in Patients With UEDVT

6.2. In patients with suspected UEDVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT, we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C)**.**

In patients with suspected UEDVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C)**. We suggest that patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms** (Grade 2B)**, in which case testing to evaluate for the presence an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete**

evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography (Grade 2C)**.**

Remarks: Further radiologic testing (serial US or venographic-based imaging or CT/MR to seek an alternative diagnosis) rather than d-dimer testing is preferable in patients with comorbid conditions typically associated with elevated D-dimer levels.

Antithrombotic Therapy for VTE Disease

For further details, see Kearon et al.[7]

2.1 Initial Anticoagulation for Patients With Acute DVT of the Leg

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

2.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for VTE

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

2.3 Anticoagulation in Patients With Isolated Distal DVT

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C)**.**

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C)**.**

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)**.**

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B)**; we suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C)**; we recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B)**.**

2.4 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B)**.**

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH**.**

2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

2.7 At-Home vs In-Hospital Initial Treatment of Patients With DVT

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Remarks: The recommendation is conditional on the adequacy of home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

2.9 Catheter-Directed Thrombolysis for Patients With Acute DVT

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

2.10 Systemic Thrombolytic Therapy for Patients With Acute DVT

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy, are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11 Operative Venous Thrombectomy for Acute DVT

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C).

2.12 Anticoagulation in Patients Who Have Had Any Method of Thrombus Removal Performed

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B).

2.13 Vena Cava Filters for the Initial Treatment of Patients With DVT

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14 Early Ambulation of Patients With Acute DVT

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we suggest the use of compression therapy in these patients.

3.0 Long-term Anticoagulation in Patients With Acute DVT of the Leg

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).

3.1 Duration of Long-term Anticoagulant Therapy

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, or (iii) extended therapy** (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B)**, (ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B)**, and (iii) extended therapy if there is a high bleeding risk** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B).

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) **and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B) **or extended therapy** (Grade 1B regardless of bleeding risk)**.**

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B)**. After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.**

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)**.**

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)**.**

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) **and recommend 3 months of anticoagulant treatment in those with a high bleeding risk** (Grade 1B)**.**

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), **and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B)**.**

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B)**.**

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be given anticoagulants (see section 2.3). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

3.2 Intensity of Anticoagulant Effect

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

3.3 Choice of Anticoagulant Regimen for Long-term Therapy

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2B)**.**

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4 Choice of Anticoagulant Regimen for Extended Therapy

3.4. In patients with DVT of the leg who receive extended therapy, we suggest treatment with the

same anticoagulant chosen for the first 3 months (Grade 2C)**.**

3.5 Treatment of Patients With Asymptomatic DVT of the Leg

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B)**.**

4.1 Compression Stockings and Bandages to Prevent PTS

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2 Physical Treatment of Patients With PTS

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C)**.**

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B)**.**

4.3 Pharmacologic Treatment of Patients With PTS

4.3. In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C)**.**

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.1 Initial Anticoagulation for Patients With Acute Pulmonary Embolism (PE)

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B)**.**

5.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for PE

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C)**.**

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C)**.**

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C)**.**

5.3 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B)**.**

5.4 Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux)**.**

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C)**.**

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5 Early vs Standard Discharge of Patients With Acute PE

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B)**.**

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6 Systemic Thrombolytic Therapy for Patients With PE

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).

5.6.2.2. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

5.7 Catheter-Based Thrombus Removal for the Initial Treatment of Patients With PE

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

5.8 Surgical Embolectomy for the Initial Treatment of Patients With PE

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.9. Vena Cava Filters for the Initial Treatment of Patients With PE

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

6.0 Long-term Treatment of Patients With PE

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **or (iii) extended therapy** (Grade 1B regardless of bleeding risk).

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **and (iii) extended therapy if there is a high bleeding risk** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B).

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). **After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.**

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B)**, and we suggest extended anticoagulant therapy in those with a moderate bleeding risk** (Grade 2B)**.**

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B)**.**

6.4. In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B)**, and if there is a high bleeding risk, we suggest extended anticoagulant therapy** (Grade 2B)**.**

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)**.**

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C)**. For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B)**. In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy** (Grade 2C)**.**

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendation in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C)**.**

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B)**.**

7.1 Pulmonary Thromboendarterectomy, Anticoagulant Therapy, and Vena Cava Filter for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTPH)

7.1.1. In patients with CTPH, we recommend extended anticoagulation over stopping therapy (Grade 1B)**.**

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C)**.**

8.1 Treatment of Patients With Superficial Vein Thrombosis

8.1.1. In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B)**.**

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with superficial vein thrombosis who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)**.**

9.1 Acute Anticoagulation for Patients With UEDVT

9.1.1. In patients with UEDVT that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B)**.**

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B)**.**

9.2 Thrombolytic Therapy for the Initial Treatment of Patients With UEDVT

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C)**.**

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B)**.**

9.3 Long-term Anticoagulation for Patients With UEDVT

9.3.1. In most patients with UEDVT that is associated with a 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)**.**

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B)**.**

Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B)**, and we suggest this in patients with cancer** (Grade 2C)**.**

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C)**, and we suggest this in patients with no cancer** (Grade 2C)**.**

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B)**.**

9.4 Prevention of PTS of the Arm

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C)**.**

9.5 Treatment of Patients With PTS of the Arm

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C)**.**

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C)**.**

10.0 Patients With Splanchnic Vein Thrombosis

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B)**.**

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

11.0 Patients With Hepatic Vein Thrombosis

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C)**.**

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C)**.**

Treatment and Prevention of Heparin-Induced Thrombocytopenia

For further details, see Linkins et al.[8]

2.1 Platelet Count Monitoring Combined With the 4Ts Score for Patients Receiving Heparin/LMWH

2.1.1. For patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C)**.**

2.1.2. For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%, we suggest that platelet counts not be monitored (Grade 2C)**.**

3.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

3.1. In patients with HIT complicated by thrombosis (HITT), we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C)**.**

3.2 Choice of Nonheparin Anticoagulants in Patients With HITT

3.2.1. In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

3.2.2. In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C)**.**

3.3 Platelet Transfusions

3.3 In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C)**.**

3.4 Starting VKAs Before Platelet Recovery

3.4.1. In patients with strongly suspected or confirmed HIT, we recommend against starting VKA until platelets have substantially recovered (ie, usually to at least 150×10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C)**.**

3.4.2. We further suggest that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C)**.**

Remarks: We place a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

3.5 Discontinuation of Thrombin Inhibitor After a Minimum of 5 Days of Overlap With VKAs

3.5. In patients with confirmed HIT, we recommend that that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C)**.**

4.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

4.1. In patients with isolated HIT (HIT without thrombosis), we recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C)**.**

4.2 Choice of Nonheparin Anticoagulants in Patients With Isolated HIT

4.2. In patients with isolated HIT (HIT without thrombosis) who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see Recommendation 3.2.2.

5.1 Patients Who Require Urgent Cardiac Surgery

5.1.1. In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C)**.**

5.1.2. In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. For recommendations for patients with a past history of HIT (>3 months previous) who require cardiac surgery, see section 6.1.

5.2 Patients Who Require Urgent Percutaneous Coronary Interventions

5.2. In patients with acute HIT or subacute HIT who require percutaneous coronary interventions, we suggest the use of bivalirudin (Grade 2B)

or argatroban (Grade 2C) **over other nonheparin anticoagulants.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

5.3 Patients Who Require Renal Replacement Therapy

5.3.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: We acknowledge that the cost of argatroban may be prohibitive at some clinical centers. We further suggest that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

5.3.2. In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, we suggest the use of regional citrate over the use of heparin or LMWH (Grade 2C)**.**

5.4 Pregnant Patients

5.4. In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C)**. We suggest the use of lepirudin or fondaparinux only if danaparoid is not available** (Grade 2C)**.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

6.1 Patients With a History of HIT Who Require Cardiac Surgery

6.1.1. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C)**.**

6.1.2. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see 5.1.1) over heparin or LMWH (Grade 2C)**.**

6.2 Patients Who Require PCI

6.2. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac catheterization or percutaneous coronary interventions, the recommended treatment is the same as 5.2.

6.3 Patients Who Require Prophylaxis or Treatment of Thrombosis

6.3. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved (Grade 2C)**.**

Antithrombotic Therapy for Atrial Fibrillation

For further details, see You et al.[9]

2.1 Patients With Nonrheumatic Atrial Fibrillation (AF)

2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, $CHADS_2$ [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B)**. For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with antithrombotic therapy are likely to choose antithrombotic therapy rather than no antithrombotic therapy. Other factors that may influence the choices above are a consideration of patient-specific bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, $CHADS_2$ score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B)**. We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**. For patients**

who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose oral anticoagulation rather than antiplatelet therapy. Other factors that may influence the choice among antithrombotic therapies are a consideration of bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple additional non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, $CHADS_2$ score = 2), we recommend oral anticoagulation rather than no therapy (Grade 1A)**, aspirin (75 mg to 325 mg once daily)** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)** (Grade 1B)**.**

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B)**.**

Remarks: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less). Clinicians should be aware that there is no antidote for dabigatran.

2.2 Patients With AF and Mitral Stenosis

2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 1B)**. For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone** (Grade 1B)**.**

3.1 Patients With AF and Stable Coronary Artery Disease

3.1. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C)**.**

3.2 Patients With AF and Placement of an Intracoronary Stent

3.2. For patients with AF at high risk of stroke (eg, $CHADS_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C)**. After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone** (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low to intermediate risk of stroke (eg, $CHADS_2$ score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose triple therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.3 Patients With AF and ACS Who Do Not Undergo Intracoronary Stent Placement

3.3. For patients with AF at intermediate to high risk of stroke (eg, $CHADS_2$ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low risk of stroke (eg, $CHADS_2$ score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose adjusted-dose VKA therapy plus single antiplatelet therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.4 Patients With AF Managed by a Rhythm Control Strategy

3.4. For patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (Grade 2C)**.**

3.5 Patients With Atrial Flutter

3.5. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.

4.1 Patients Undergoing Elective Cardioversion of AF

4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Grade 1B)**. We recommend therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke** (Grade 1B)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.1.2. For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (Grade 2C)**. After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.2 Patients Undergoing Urgent Cardioversion for Hemodynamically Unstable AF

4.2. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (Grade 2C)**, but that initiation of anticoagulation must not delay any emergency intervention** (Grade 2C)**. After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations**

for long-term antithrombotic therapy in section 2.1.

4.3 Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter

4.3. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion.

Antithrombotic and Thrombolytic Therapy for Valvular Disease

For further details, see Whitlock et al.[10]

2.0 Patients With Rheumatic Mitral Valve Disease

2.0.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm we suggest not using antiplatelet or VKA therapy (Grade 2C)**.**

2.0.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet (Grade 2C)**.**

2.0.3. For patients with rheumatic mitral valve disease complicated by the presence of left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.0.4. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of atrial fibrillation or previous systemic embolism, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A)**.**

2.1 Patients With Rheumatic Mitral Valve Disease Undergoing Percutaneous Mitral Balloon Valvotomy (PMBV)

2.1.1. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and that VKA therapy (target INR, 3.0; range, 2.5-3.5) be administered until thrombus resolution is documented by repeat TEE over no VKA therapy (Grade 1A)**.**

2.1.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, if the left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1A)**.**

6.2.1. In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C)**.**

6.2 Patients With PFO and Atrial Septal Aneurysm

6.2.2. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A)**.**

6.2.3. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C)**.**

6.2.4. In patients with cryptogenic stroke and PFO, with evidence of DVT, we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) (Grade 1B) **and consideration of device closure over no VKA therapy or aspirin therapy** (Grade 2C)**.**

7.1 Role of Anticoagulants and Antiplatelet Agents in Patients With Native Valve Endocarditis

7.1.1. In patients with infective endocarditis (IE), we recommend against routine anticoagulant therapy, unless a separate indication exists (Grade 1C)**.**

7.1.2. In patients with IE, we recommend against routine antiplatelet therapy, unless a separate indication exists (Grade 1B)**.**

7.2 Role of Anticoagulants in Patients With Prosthetic Valve Endocarditis

7.2. In patients on VKA for a prosthetic valve who develop IE, we suggest VKA be discontinued at the time of initial presentation 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 reinstitution of VKA therapy (Grade 2C)**.**

7.3 Patients With Nonbacterial Thrombotic Endocarditis

7.3. In patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli, we suggest treatment with full-dose IV UFH or SC LMWH over no anticoagulation (Grade 2C)**.**

8.2 Antithrombotic Therapy in the First 3 Months After Surgery

8.2.1. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months (Grade 2C).

8.2.2. In patients with transcatheter aortic bioprosthetic valves, we suggest aspirin (50-100 mg/d) plus clopidogrel (75 mg/d) over VKA therapy and over no antiplatelet therapy in the first 3 months (Grade 2C).

8.2.3. In patients with a bioprosthetic valve in the mitral position, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion (Grade 2C).

8.3 Long-term Antithrombotic Therapy for Patients With Bioprosthetic Valves

8.3. In patients with bioprosthetic valves in normal sinus rhythm, we suggest aspirin therapy over no aspirin therapy after 3 months postoperative (Grade 2C).

9.1 Early Postoperative Bridging to Intermediate/Long-term Therapy (Postoperative Day 0 to 5)

9.1. In patients with mechanical heart valves, we suggest bridging with unfractionated heparin (UFH, prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C).

9.2 Long-term Antithrombotic Therapy for Patients With Mechanical Valves

9.2. In patients with mechanical heart valves, we recommend VKA therapy over no VKA therapy for long-term management (Grade 1B).

9.3 Intensity of VKA Therapy for Patients With Mechanical Aortic Valve Prostheses

9.3.1. In patients with a mechanical aortic valve, we suggest VKA therapy with a target of 2.5 (range, 2.0-3.0) over lower targets (Grade 2C).

9.3.2. In patients with a mechanical aortic valve, we recommend VKA therapy with a target of 2.5 (range 2.0-3.0) over higher targets (Grade 1B).

9.4 Intensity of VKA Therapy for Patients With Mechanical Mitral Valve Prostheses

9.4. In patients with a mechanical mitral valve, we suggest VKA therapy with a target of 3.0 (range, 2.5-3.5) over lower INR targets (Grade 2C).

9.5 Intensity of VKA Therapy in Patients With Double Mechanical Valve or With Additional Risk Factors

9.5. In patients with mechanical heart valves in both the aortic and mitral position, we suggest target INR 3.0 (range 2.5-3.5) over target INR 2.5 (range 2.0-3.0) (Grade 2C).

9.6 Antiplaelet Agent in Addition to VKA Therapy for Patients With Mechanical Aortic or Mitral Valve Prostheses

9.6. In patients with a mechanical mitral or aortic valve at low risk of bleeding, we suggest adding over not adding an antiplatelet agent such as low-dose aspirin (50-100 mg/d) to the VKA therapy (Grade 1B).

Remarks: Caution should be used in patients at increased bleeding risk, such as history of GI bleeding.

9.7 Antiplatelet Agent Therapy Instead of VKA Therapy

9.7. For patients with mechanical aortic or mitral valves we recommend VKA over antiplatelet agents (Grade 1B).

10.1 Antithrombotic Therapy After Mitral Valve Repair

10.1. In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, we suggest the use of antiplatelet therapy for the first 3 months over VKA therapy (Grade 2C).

10.2 Patients Undergoing Aortic Valve Repair

10.2. In patients undergoing aortic valve repair, we suggest aspirin at 50 to 100 mg/d over VKA therapy (Grade 2C).

11.1 Patients With Right-Sided Prosthetic Valve Thrombosis

11.1. For patients with right-sided prosthetic valve thrombosis (PVT), in the absence of contraindications we suggest administration of fibrinolytic therapy over surgical intervention (Grade 2C).

11.2 Patients With Left-Sided Prosthetic Valve Thrombosis

11.2.1. For patients with left-sided PVT and large thrombus area ($\geq$0.8 cm^2), we suggest early surgery over fibrinolytic therapy (Grade 2C). **If contraindications to surgery exist, we suggest the use of fibrinolytic therapy** (Grade 2C).

11.2.2. For patients with left-sided PVT and small thrombus area ($<$0.8 cm^2), we suggest

administration of fibrinolytic therapy over surgery. For very small, nonobstructive thrombus we suggest IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement over other alternatives (Grade 2C)**.**

Antithrombotic and Thrombolytic Therapy for Ischemic Stroke

For further details, see Lansberg et al.[11]

2.1 IV Recombinant Tissue Plasminogen Activator (r-tPA) for Patients With Acute Ischemic Stroke

2.1.1. In patients with acute ischemic stroke in whom treatment can be initiated within 3 h of symptom onset, we recommend IV r-tPA over no IV r-tPA (Grade 1A)**.**

2.1.2. In patients with acute ischemic stroke in whom treatment can be initiated within 4.5 but not within 3 h of symptom onset, we suggest IV r-tPA over no IV r-tPA (Grade 2C)**.**

2.1.3. In patients with acute ischemic stroke in whom treatment cannot be initiated within 4.5 h of symptom onset, we recommend against IV r-tPA (Grade 1B)**.**

2.2 Intraarterial Thrombolysis in Patients With Acute Ischemic Stroke

2.2.1. In patients with acute ischemic stroke due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV r-tPA, we suggest intraarterial (IA) r-tPA initiated within 6 h of symptom onset over no IA r-tPA (Grade 2C)**.**

2.2.2. In patients with acute ischemic stroke we suggest IV r-tPA over the combination IV/IA r-tPA (Grade 2C).

Remarks: Carefully selected patients who value the uncertain benefits of combination IV/IA thrombolysis higher than the associated risks may choose this intervention. Patients who prefer to avoid risk in the setting of uncertain benefits are more likely to choose IV r-tPA alone.

2.3 Mechanical Thrombectomy in Patients With Acute Ischemic Stroke

2.3. In patients with acute ischemic stroke, we suggest against the use of mechanical thrombectomy (Grade 2C)**.**

Remarks: Carefully selected patients who value the uncertain benefit of mechanical thrombectomy higher than the associated risks may choose this intervention.

2.4 Aspirin in Patients With Acute Ischemic Stroke

2.4. In patients with acute ischemic stroke or transient ischemic attack (TIA), we recommend early (within 48 h) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy (Grade 1A)**.**

2.5 Anticoagulation in Patients With Acute Ischemic Stroke

2.5. In patients with acute ischemic stroke or TIA, we recommend early (within 48 h) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A)**.**

3.1 VTE Prevention in Patients With Ischemic Stroke

3.1.1. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose SC UFH or LMWH or intermittent pneumatic compression devices over no prophylaxis (Grade 2B)**.**

3.1.2. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

3.1.3. In patients with acute stroke and restricted mobility, we suggest against elastic compression stockings (Grade 2B)**.**

Remarks: Pharmacologic and mechanical prophylaxis should be initiated as early as possible and should be continued throughout the hospital stay or until the patient has regained mobility. Mechanical devices should be temporarily removed as often as needed to allow for early mobilization and screening for skin complications.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

3.2 VTE Prevention in Patients With Hemorrhagic Stroke

3.2.1. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose SC heparin (UFH or LMWH) started between days 2 and 4 or intermittent pneumatic compression devices over no prophylaxis (Grade 2C)**.**

3.2.2. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B)**.**

3.2.3. In patients with primary intracerebral hemorrhage and restricted mobility, we suggest against elastic compression stockings (Grade 2B)**.**

Remarks: Patients who prefer to avoid a theoretically increased risk of rebleeding with heparin would favor mechanical prophylaxis with intermittent pneumatic compression devices over pharmacologic prophylaxis.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

4.1 Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke

4.1.1. In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A)**, oral anticoagulants** (Grade 1B)**, the combination of clopidogrel plus aspirin** (Grade 1B)**, or triflusal** (grade 2B)**.**

4.1.2. Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) **or cilostazol** (Grade 2C)**.**

Remarks: With long-term use (>5 y), the benefit of clopidogrel over aspirin in preventing major vascular events may be offset by a reduction in cancer-related mortality with regimens that contain aspirin.

4.2 Antithrombotic Therapy for the Secondary Prevention of Cardioembolic Stroke

4.2.1. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we recommend oral anticoagulation over no antithrombotic therapy (Grade 1A)**, aspirin** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**.**

4.2.2. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target range, 2.0-3.0) (Grade 2B)**.**

4.2.3. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel over aspirin (Grade 1B)**.**

Remarks: Patients should be treated (ie, bridged) with aspirin until anticoagulation has reached a therapeutic level.

Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset. Earlier anticoagulation can be considered for patients at low risk of bleeding complications (eg, those with a small infarct burden and no evidence of hemorrhage on brain imaging). Delaying anticoagulation should be considered for patients at high risk of hemorrhagic complications (eg, those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).

Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less).

4.3 Antithrombotic Therapy for Stroke Prevention in Patients With a History of Intracerebral Hemorrhage (ICH)

4.3. In patients with a history of a symptomatic primary ICH, we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke (Grade 2C)**.**

Remarks: Patients who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk (>7% per year) of thromboembolic events (eg, with mechanical heart valves or CHADS2 (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke or TIA) score >4 points).

5.1 Anticoagulation for Patients With Symptomatic Cerebral Venous Sinus Thrombosis

5.1. In patients with cerebral venous sinus thrombosis, we suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases (Grade 2C)**.**

Remarks: Patients with a history of ICH who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk (>7% per year) of cardiac thromboembolic events (eg, with mechanical heart valves or $CHADS_2$ score >4 points).

The Primary and Secondary Prevention of Cardiovascular Disease

For further details, see Vandvik et al.[12]

2.0 Primary Prevention of Cardiovascular Disease

2.1. For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B)**.**

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed will be, if they are in the moderate or high cardiovascular risk group, more likely to choose aspirin.

3.1 Choice of Long-term Antithrombotic Therapy in Patients With Established Coronary Artery Disease (CAD)

3.1.1-3.1.5. For patients with established coronary artery disease (CAD), defined as patients 1-year post-acute coronary syndrome (ACS), with prior revascularization, coronary stenoses >50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing, (including patients after the first year post-ACS and/or with prior coronary artery bypass graft [CABG] surgery):

- **We recommend long-term single antiplatelet therapy with aspirin 75 to 100 mg daily or clopidogrel 75 mg daily over no antiplatelet therapy** (Grade 1A)**.**
- **We suggest *single over* dual antiplatelet therapy with aspirin plus clopidogrel** (Grade 2B)**.**

3.2 Choice of Antithrombotic Therapy Following ACS

3.2.1-3.2.5. For patients in the first year after an ACS who have not undergone percutaneous coronary intervention (PCI):

- **We recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily or clopidogrel 75 mg daily plus low-dose aspirin 75-100 mg daily) over single antiplatelet therapy** (Grade 1B)**.**
- **We suggest ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin** (Grade 2B)**.**

For patients in the first year after an ACS who have undergone PCI with stent placement:

- **We recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily, clopidogrel 75 mg daily plus low-dose aspirin, or prasugrel 10 mg daily plus low-dose aspirin over single antiplatelet therapy)** (Grade 1B)**.**

Remarks: Evidence suggests that prasugrel results in no benefit net harm in patients with a body weight of <60 kg, age >75 years, or with a previous stroke/transient ischemic attack.

- **We suggest ticagrelor 90 mg twice daily plus low-dose aspirin *over* clopidogrel 75 mg daily plus low-dose aspirin** (Grade 2B)**.**

For patients with ACS who undergo PCI with stent placement, we refer to sections 4.3.1 to 4.3.5 for recommendations concerning minimum and prolonged duration of treatment.

3.2.6-3.2.7. For patients with anterior MI and left ventricular (LV) thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who do not undergo stenting:

- **We recommend warfarin (INR 2.0-3.0) plus low-dose aspirin 75 to 100 mg daily over single antiplatelet therapy or dual antiplatelet therapy for the first 3 months** (Grade 1B)**. Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, single antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).**

For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who undergo bare-metal stent (BMS) placement:

- **We suggest triple therapy (warfarin [INR 2.0-3.0], low-dose aspirin, clopidogrel 75 mg daily) for 1 month over dual antiplatelet therapy** (Grade 2C)**.**
- **We suggest warfarin (INR 2.0-3.0) and single antiplatelet therapy for the second and third month post-BMS over alternative regimens and alternative time frames for warfarin use** (Grade 2C)**. Thereafter, we recommend discontinuation of warfarin and use of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).**

For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction < 40%, anteroapical wall motion abnormality) who undergo drug-eluting stent (DES) placement:

- **We suggest triple therapy (warfarin INR 2.0-3.0, low-dose aspirin, clopidogrel 75 mg daily) for 3 to 6 months over alternative regimens and alternative durations of warfarin therapy** (Grade 2C)**. Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).**

4.0 Antithrombotic Therapy Following Elective PCI

4.1.1-4.3.5. For patients who have undergone elective PCI with placement of BMS:

- **For the first month, we recommend dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy** (Grade 1A)**.**
- **For the subsequent 11 months, we suggest dual antiplatelet therapy with combination of low-dose aspirin 75 to 100 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy** (Grade 2C)**.**
- **After 12 months, we recommend single antiplatelet therapy over continuation of dual antiplatelet therapy** (Grade 1B)**.**

For patients who have undergone elective PCI with placement of DES:

- **For the first 3 to 6 months, we recommend dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy** (Grade 1A)**.**

Remarks: Absolute minimum duration will vary based on stent type (in general, 3 months for -limus stents and 6 months for -taxel stents).

- **After 3 to 6 months, we suggest continuation of dual antiplatelet therapy with low-dose aspirin 75 to 100 mg and clopidogrel (75 mg daily) until 12 months over single antiplatelet therapy** (Grade 2C)**.**
- **After 12 months, we recommend single antiplatelet therapy over continuation of dual antiplatelet therapy** (Grade 1B)**. Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).**

For patients who have undergone elective BMS or DES stent placement:

- **We recommend using low-dose aspirin 75 to 100 mg daily and clopidogrel 75 mg daily alone rather than cilostazol in addition to these drugs** (Grade 1B)**.**
- **We suggest aspirin 75 to 100 mg daily or clopidogrel 75 mg daily as part of dual antiplatelet therapy rather than the use of either drug with cilostazol** (Grade 1B)**.**
- **We suggest cilostazol 100 mg twice daily as substitute for either low-dose aspirin 75 to 100 mg daily or clopidogrel 75 mg daily as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class** (Grade 2C)**.**

For patients with CAD undergoing elective PCI but no stent placement:

- **We suggest for the first month dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy** (Grade 2C)**. Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).**

5.0 Antithrombotic Therapy in Patients With Systolic LV Dysfunction

5.1-5.3. For patients with systolic LV dysfunction without established CAD and no LV thrombus, we suggest not to use antiplatelet therapy or warfarin (Grade 2C)**.**

Remarks: Patients who place a high value on an uncertain reduction in stroke and a low value on avoiding an increased risk of GI bleeding are likely to choose to use warfarin.

For patients with systolic LV dysfunction without established CAD with identified acute LV thrombus (eg, Takotsubo cardiomyopathy), we suggest moderate-intensity warfarin (INR 2.0-3.0) for at least 3 months (Grade 2C)**.**

For patients with systolic LV dysfunction and established CAD, recommendations are as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).

Antithrombotic Therapy in Peripheral Artery Disease

For further details, see Alonso-Coello et al.[13]

2.0 Primary Prevention of Cardiovascular Events in Patients with Asymptomatic PAD

2.1. For persons with asymptomatic peripheral arterial disease (PAD), we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B)**.**

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed, if they are in the moderate or high cardiovascular risk group, will be more likely to choose aspirin.

3.0 Secondary Prevention of Cardiovascular Events in Patients with Symptomatic PAD

3.1-3.4. For secondary prevention patients with symptomatic PAD, we recommend one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A)**. We suggest *not to use* dual antiplatelet therapy with aspirin plus clopidogrel** (Grade 2B)**. We recommend *not to use* an antiplatelet agent with moderate-intensity warfarin** (Grade 1B)**.**

4.0 Antithrombotic Therapy for the Management of Patients with Claudication

4.1-4.4. For patients with intermittent claudication refractory to exercise therapy (and smoking cessation), we suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C)**; we suggest against the use of pentoxifylline, heparinoids, or prostanoids** (Grade 2C)**.**

5.0 Patients With Critical Limb Ischemia

5.1. For patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention, we suggest the use of prostanoids in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C)**.**

Values and preferences: Patients who do not value uncertain relief of rest pain and ulcer healing greater than avoidance of a high likelihood of drug-related side effects will be disinclined to take prostanoids.

6.0 Acute Limb Ischemia

6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C)**; we suggest reperfusion therapy (surgery or IA thrombolysis) over no reperfusion therapy** (Grade 2C)**; we recommend surgery over IA thrombolysis** (Grade 1B)**. In patients undergoing IA thrombolysis, we suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase** (Grade 2C)**.**

7.0 Endovascular Revascularization in Patients With Symptomatic PAD

7.1. For patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, we recommend long-term aspirin (75-100 mg/day) or clopidogrel (75 mg/day) (Grade 1A)**. For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, we suggest single rather than dual antiplatelet therapy** (Grade 2C)**.**

Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a definite increased risk of bleeding are more likely to choose to use dual antiplatelet therapy.

8.0 Antithrombotic Therapy Following Peripheral Artery Bypass Graft Surgery

8.1-8.4. We recommend one of the following antithrombotic regimens to be continued long-term following peripheral artery bypass graft surgery over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A)**. We recommend single antiplatelet therapy over antiplatelet therapy and warfarin** (Grade 1B)**. In patients undergoing below-knee bypass graft surgery with prosthetic grafts, we suggest clopidogrel 75 mg/d plus aspirin (75-100 mg/d) over aspirin alone for 1 year** (Grade 2C)**. For all other patients, we suggest single over dual antiplatelet therapy** (Grade 2B)**.**

9.0 Patients With Carotid Artery Stenosis

9.1. For patients with asymptomatic carotid stenosis, we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B)**.**

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis.

9.2-9.3. In patients with symptomatic carotid stenosis (including recent carotid endarterectomy), we recommend long-term antiplatelet therapy with clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) or aspirin (75-100 mg once daily) over no antiplatelet therapy (Grade 1A)**. We suggest either clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) over aspirin (75-100 mg)** (Grade 2B)**.**

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

For further details, see Bates et al.[14]

2.0 Maternal Consequences of Antithrombotic Therapy Use During Pregnancy

2.2.1. For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B)**.**

3.0 Fetal Consequence of Antithrombotic Therapy Use in Pregnant Women

3.0.1. For women receiving anticoagulation for the treatment of VTE who become pregnant, we recommend LMWH over VKAs during the first trimester (Grade 1A)**, in the second and third trimesters** (Grade 1B)**, and during late pregnancy when delivery is imminent** (Grade 1A)**.**

3.0.2. For women requiring long-term VKAs who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and substituting LMWH for VKAs when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Grade 2C)**.**

Remarks: Women who place little value on avoiding the risks, inconvenience, and costs of LMWH therapy of uncertain duration while awaiting pregnancy and a high value on minimizing the risks of early miscarriage associated with VKA therapy are likely to choose LMWH while attempting pregnancy.

3.0.3. For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) who cannot receive danaparoid (Grade 2C)**.**

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C)**.**

4.0 Use of Antithrombotic Therapy in Nursing Women

4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A)**.**

4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B)**.**

4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C)**.**

4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C)**.**

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breast-feed, we suggest continuing this medication (Grade 2C)**.**

5.0 VTE in Patients Using Assisted Reproductive Technology

5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B)**.**

5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C)**.**

Remarks: Women who are averse to taking medication for very small benefit and those who consider self-injecting a considerable burden will be disinclined to use LMWH for extended thrombosis prophylaxis. Given that the absolute benefit decreases as time from the hyperstimulation event increases, such

women will be very disinclined to continue prophylaxis throughout the entire resultant pregnancy.

6.0 VTE Following Cesarean Section

6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B).

6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).

Remarks: The reduced bleeding risk with mechanical prophylaxis should be weighed against the inconvenience of elastic stockings and intermittent pneumatic compression.

6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone (Grade 2C).

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

7.0 Treatment of Patients With Proven Acute VTE During Pregnancy

7.1.1. For pregnant women with acute VTE, we recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH (Grade 1B).

7.1.2. For pregnant women with acute VTE, we recommend LMWH over VKA treatment antenatally (Grade 1A).

7.1.3. 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 3 months) in comparison with shorter durations of treatment (Grade 2C).

7.1.4. For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).

8.0 Prevention of Recurrent VTE in Pregnant Women

8.2.1. For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

8.2.2. For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).

8.2.3. For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

8.2.4. For pregnant women receiving long-term VKAs, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum, rather than prophylactic-dose LMWH (Grade 2C).

9.0 Prevention of VTE in Pregnant Women With Thrompophilia and No Prior VTE

9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).

9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B)**.**

9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C)**.**

10.0 Prevention of Pregnancy Complications in Women With Thrombophilia

10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for antiphospolipid antibodies (APLAs) (Grade 1B)**.**

10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C)**.**

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B)**.**

10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C)**.**

11.0 Prevention of Recurrent Preeclampsia or Pregnancy Loss in Women Without Known Thrombophilia

11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B)**.**

11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B)**.**

12.0 Prevention of Thromboembolism in Pregnant Women With Mechanical Heart Valves

12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A)**:**

(a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous-injection or

(b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval activated partial thromboplastin time at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or

(c) UFH or LMWH (as above) until the 13th week, with substitution by VKAs until close to delivery when UFH or LMWH is resumed.

Remarks: For pregnant women with mechanical heart valves, the decision regarding the choice of anticoagulant regimen is so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that we consider the decision to be completely individualized. Women of childbearing age and pregnant women with mechanical valves, should be counseled about potential maternal and fetal risks associated with various anticoagulant regimens, including continuation of VKAs with substitution by LMWH or UFH close to term, substitution of VKAs by LMWH or UFH until the 13th week and then close to term, and use of LMWH or UFH throughout pregnancy. Usual long-term anticoagulants should be resumed postpartum when adequate hemostasis is assured.

12.1.2. 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 (Grade 2C)**.**

Remarks: Women who place a higher value on avoiding fetal risk than on avoiding maternal complications (eg, catastrophic valve thrombosis) are likely to choose LMWH or UFH over VKAs.

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

Antithrombotic Therapy in Neonates and Children

For further details, see Monagle et al.[15]

1.0. We suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism (Grade 2C)**. When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist** (Grade 2C)**.**

1.1 Heparin in Neonates and Children

1.1. We suggest that therapeutic unfractionated heparin (UFH) in children is titrated to achieve a target range of anti-Xa activity of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C)**. We suggest that when initiating UFH therapy, UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks** (Grade 2C)**. We suggest avoiding long-term use of therapeutic UFH in children** (Grade 2C)**.**

1.2 LMWH in Neonates and Children

1.2. We suggest, for neonates and children receiving either once- or twice-daily therapeutic LMWH that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after SC injection or 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after SC injection (Grade 2C)**.**

1.3 VKAs in Neonates and Children

1.3. We suggest, for children receiving VKAs, that the drug be monitored to a target INR of 2.5 (range, 2.0-3.0), except in the setting of prosthetic cardiac valves where we suggest adherence to the adult recommendations outlined in the article by Whitlock et al in this supplement (Grade 2C)**. We suggest that INR monitoring with point-of-care monitors be made available where resources make this possible** (Grade 2C)**.**

1.5 Aspirin in Children

1.5. We suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C)**.**

2.1 VTE in Neonates

2.1. We suggest that central venous access devices (CVADs) or umbilical venous catheters (UVCs) associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ (Grade 2C)**. We suggest either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up** (Grade 2C)**; however, in previously untreated patients, we recommend the start of anticoagulation if extension occurs** (Grade 2C)**. We suggest that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations** (Grade 2C)**. If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, we suggest a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed** (Grade 2C)**. We suggest against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs** (Grade 2C)**. We suggest if thrombolysis is required, tissue plasminogen activator (tPA) is used rather than other lytic agents** (Grade 2C)**, and we suggest plasminogen (fresh frozen plasma) administration prior to commencing therapy** (Grade 2C)**.**

2.2-2.3 Renal Vein Thrombosis in Neonates

2.2. For unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava (IVC), we suggest either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs we suggest anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, we suggest a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy (Grade 2C)**. For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months** (Grade 2C)**.**

2.3. For bilateral RVT with evidence of renal impairment, we suggest anticoagulation with UFH/LMWH or initial thrombolytic therapy with tPA followed by anticoagulation with UFH/LMWH (Grade 2C)**.**

2.4 CVAD Prophylaxis in Neonates

2.4. For neonates with CVADs, we recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis (Grade 1A) **or intermittent local thrombolysis** (Grade 2C)**. For neonates with blocked CVADs, we suggest local thrombolysis after appropriate clinical assessment** (Grade 2C)**.**

2.6 Thromboprophylaxis for Neonates and Children With Blalock-Taussig Shunts and Modified Blalock-Taussig Shunts (MBTS)

2.6. For neonates and children having modified MBTS, we suggest intraoperative UFH therapy (Grade 2C)**. For neonates and children after MBTS surgery, we suggest either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs** (Grade 2C)**.**

2.9-2.10 Therapy for Femoral Artery Thrombosis in Neonates and Children

2.9. For neonates and children with acute femoral artery thrombosis, we recommend therapeutic doses of IV UFH as initial therapy compared with aspirin or no therapy (Grade 1B) **or LMWH** (Grade 2C)**. We suggest subsequent conversion to LMWH, or else continuation of UFH, to complete 5 to 7 days of therapeutic anticoagulation as compared with a shorter or longer duration** (Grade 2C)**.**

2.10. For neonates and children 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, we recommend thrombolysis (Grade 1C)**. For neonates and children with femoral artery thrombosis, we recommend surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent** (Grade 1C)**.**

2.11 Prophylaxis for Peripheral Arterial Catheters in Neonates and Children

2.11. For neonates and children with peripheral arterial catheters in situ, we recommend UFH continuous infusion at 5 units/mL at 1 mL/h compared with normal saline (Grade 1A)**.**

2.12 Therapy for Peripheral Artery Thrombosis Secondary to Peripheral Artery Catheters in Neonates and Children

2.12. For neonates and children with a peripheral arterial catheter-related thromboembolism, we suggest immediate removal of the catheter (Grade 2B)**. For neonates and children with a symptomatic peripheral arterial catheter-related thromboembolism, we suggest UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy** (Grade 2C)**.**

2.13-2.14 Prophylaxis of Umbilical Arterial Catheters in Neonates

2.13. For neonates with umbilical arterial catheters (UACs), we suggest UAC placement in a high rather than a low position (Grade 2B)**.**

2.14. For neonates with UAC, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency (Grade 2A)**.**

2.16 Prophylaxis for Cardiac Catheterization in Neonates and Children

2.16. For neonates and children requiring cardiac catheterization via an artery, we recommend administration of IV UFH as thromboprophylaxis over no prophylaxis (Grade 1A) **or aspirin** (Grade 1B)**. For neonates and children requiring cardiac catheterization via an artery, we recommend the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus** (Grade 1B)**. In prolonged procedures, we suggest further doses of UFH rather than no further therapy** (Grade 2B)**.**

2.17 Cerebral Sinovenous Thrombosis in Neonates

2.17. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage, we suggest anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration (Grade 2C)**. For neonates with CSVT with significant hemorrhage, we suggest either (1) anticoagulation or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy** (Grade 2C)**.**

2.18-2.20 Arterial Ischemic Stroke in Neonates

2.18. For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented, ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C)**.**

2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C)**.**

2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C)**.**

2.21 Neonates With Purpura Fulminans

2.21. For neonates with clinical presentations of homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of

fresh frozen plasma every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1A)**. For neonates with homozygous protein C deficiency, after initial stabilization, we recommend long-term treatment with VKA** (Grade 1C)**, LMWH** (Grade 1C)**, protein C replacement** (Grade 1B)**, or liver transplantation** (Grade 1C) **compared with no therapy.**

2.22 DVT and PE in Children

2.22.1. In children with first VTE (CVAD and non-CVAD related) we recommend acute anticoagulant therapy with either UFH or LMWH (Grade 1B)**. We recommend initial treatment with UFH or LMWH for at least 5 days** (Grade 1B)**. For ongoing therapy, we recommend LMWH or UFH. 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 compared with no therapy** (Grade 1B)**.**

2.22.2. We suggest that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C)**.**

Values and preferences: Families who place a high value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor and a lower value on avoiding the inconvenience of therapy or potential impact of therapy on growth and development and bleeding risk associated with antithrombotic therapy are likely to choose to continue anticoagulant therapy beyond 6 to 12 months.

2.22.3. In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (Grade 2C) **as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved** (Grade 2C)**.**

2.22.4. In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A)**.**

2.22.5. In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C)**.**

2.22.6. In children with a CVAD in place who have a VTE, if a CVAD 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 rather than no anticoagulation prior to removal** (Grade 2C)**. If CVAD access is required and the CVAD is still functioning, we suggest that the CVAD remain in situ and the patient given anticoagulants** (Grade 2C)**. For children with a first CVAD-related VTE, we suggest initial management as for secondary VTE as previously described.**

2.22.7. In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, we suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C)**. If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE** (Grade 2C)**.**

2.23 Thrombolysis in Pediatric Patients With DVT

2.23. In children with VTE, we suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C)**. If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen** (Grade 2C)**. In children with VTE in whom thrombolysis is used, we suggest systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility.**

2.24 Thrombectomy and IVC Filter Use in Pediatric Patients With DVT

2.24. In children with life-threatening VTE, we suggest thrombectomy (Grade 2C)**. In children who have had a thrombectomy, we suggest anticoagulant therapy as per recommendation (2.22)** (Grade 2C)**. In children > 10 kg body weight with lower-extremity VTE and a contraindication to anticoagulation, we suggest placement of a retrievable IVC filter** (Grade 2C)**. In children who receive a filter, we suggest that the filter be removed as soon as possible if thrombosis is not**

present in the basket of the filter and when contraindication to anticoagulation is resolved (Grade 2C)**. In children who receive an IVC filter, we recommend appropriate anticoagulation for VTE (see 1.2) as soon as the contraindication to anticoagulation is resolved** (Grade 1C)**.**

2.25 DVT in Children With Cancer

2.25. In children with cancer, we suggest that management of VTE follow the general recommendations for management of VTE 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)**.**

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

2.26 Children With APLAs and DVT

2.26. For children with VTE in the setting of APLAs, we suggest management as per general recommendations for VTE management in children.

2.27 Children With DVT and Positive Inherited Thrombophilia Testing

2.27. For children with VTE, independent of the presence or absence of inherited thrombophilic risk factors, we suggest that the duration and intensity of anticoagulant therapy as per 2.22.

2.28 Children With VTE and Structurally Abnormally Venous Systems

2.28. For children with first VTE secondary to structural venous abnormalities, we suggest anticoagulation as per other "spontaneous" VTE (2.22) and consideration of subsequent percutaneous or surgical interventions, depending on patient factors and institutional experience. For children with recurrent VTE secondary to structural venous abnormalities, we suggest indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed (Grade 2C)**.**

2.29 Children With Right Atrial Thrombosis

2.29. For children with right atrial thrombosis related to CVAD, we suggest removal of the CVAD with or without anticoagulation, depending on the individual risk factors, compared with leaving the CVAD in situ (Grade 2C)**. For children with large (> 2 cm) mobile right atrial thrombosis, we suggest anticoagulation, with appropriately timed CVAD removal, and consideration of surgical intervention or thrombolysis based on individualized risk-benefit assessment compared with no anticoagulation therapy** (Grade 2C)**.**

2.30-2.34 Children With CVADs

2.30. For CVADs, we suggest flushing with normal saline or heparin or intermittent recombinant urokinase to maintain patency as compared with no therapy (Grade 2C)**. For blocked CVADs, we suggest tPA or recombinant urokinase to restore patency** (Grade 2C)**. If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, we suggest a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, we suggest radiologic imaging to rule out a CVAD-related thrombosis** (Grade 2C)**.**

2.31. For children with short- or medium-term CVADs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B)**.**

2.34. For children receiving long-term home total parenteral nutrition, we suggest thromboprophylaxis with VKAs (Grade 2C)**.**

2.35 Children Undergoing Glenn Procedure or Bilateral Cavopulmonary Shunt

2.35. For children who have bilateral cavopulmonary shunt, we suggest postoperative UFH (Grade 2C)**.**

2.36 Children Undergoing Fontan Surgery

2.36. For children after Fontan surgery, we recommend aspirin or therapeutic UFH followed by VKAs over no therapy (Grade 1C)**.**

2.37 Insertion of Endovascular Stents in Children

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

2.38 Pediatric Patients With Dilated Cardiomyopathy

2.38. For pediatric patients with cardiomyopathy, we suggest VKAs no later than their activation on a cardiac transplant waiting list (Grade 2C)**.**

Values and preferences: Parents who place a high value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring and a lower value on the uncertain reduction in thrombotic complications are unlikely to choose VKA therapy for their children who are eligible for transplant.

2.39 Children With Primary Pulmonary Hypertension

2.39. For children with primary pulmonary hypertension, we suggest starting anticoagulation with VKAs at the same time as other medical therapy (Grade 2C)**.**

2.40-2.42 Children With Biologic and Mechanical Prosthetic Heart Valves

2.40-2.42. For children with biologic or mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population.

2.44 Children With Ventricular Assist Devices (VADs)

2.44. For children with VADs we suggest administration of UFH (Grade 2C)**. We suggest starting UFH between 8 and 48 h following implantation** (Grade 2C)**. In addition, we suggest antiplatelet therapy (either aspirin or aspirin dipyridamole) to commence within 72 h of VAD placement** (Grade 2C)**. For children with VAD, once clinically stable, we suggest switching from UFH to either LMWH or VKA (target INR 3.0 range, 2.5-3.5) until transplanted or weaned from VAD** (Grade 2C)**.**

2.45-2.46 Primary Prophylaxis for Venous Access Related to Hemodialysis

2.45. For patients undergoing hemodialysis via an arteriovenous fistula, we suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.46. For patients undergoing hemodialysis via CVAD, we suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C)**.**

2.47 Use of UFH or LMWH in Children Undergoing Hemodialysis

2.47. For children having hemodialysis, we suggest the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access (Grade 2C)**.**

2.48-2.50 Children With Kawasaki Disease

2.48. For children with Kawasaki disease, we recommend aspirin in high doses (80-100 mg/kg per day during the acute phase for up to 14 days) as an antiinflammatory agent, then in lower doses (1-5 mg/kg per day for 6 to 8 weeks) as an antiplatelet agent (Grade 1B)**. For children with Kawasaki disease, we recommend IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms** (Grade 1A)**.**

2.49. For children with moderate or giant coronary aneurysms following Kawasaki disease, we suggest that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis (Grade 2C)**.**

2.50. For children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis, we suggest thrombolysis or acute surgical intervention (Grade 2C)**.**

2.51 CSVT in Children

2.51. 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)**. In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, we suggest administration of a further 3 months of anticoagulation** (Grade 2C)**. For children with CSVT with significant hemorrhage, we suggest initial anticoagulation as for children without hemorrhage or radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted at that time** (Grade 2C)**. In children with CSVT and potentially recurrent risk factors (for example, nephrotic syndrome, asparaginase therapy), we suggest prophylactic anticoagulation at times of risk factor recurrence** (Grade 2C)**. 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)**.**

2.52 AIS in Children

2.52. For children with acute AIS, with or without thrombophilia, we recommend UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded (Grade 1C)**. For children with acute AIS, we suggest, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy** (Grade 2C)**. For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs), we suggest changing to clopidogrel or anticoagulant therapy with LMWH or VKA** (Grade 2C)**. For children with AIS, we recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols** (Grade 1C)**.**

2.53 Embolic Stroke in Children

2.53. For AIS secondary to cardioembolic causes, we suggest anticoagulant therapy with LMWH

or VKAs for at least 3 months (Grade 2C)**. For AIS secondary to cardioembolic causes in children with demonstrated right-to-left shunts (eg, PFO), we suggest surgical closure of the shunt** (Grade 2C)**.**

2.54 Cerebral Arterial Dissection Underlying AIS

2.54. For AIS secondary to dissection, we suggest anticoagulant therapy with LMWH or VKAs for at least 6 weeks (Grade 2C)**. Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events.**

2.55 Children With Cerebral Vasculopathies

2.55. For children with acute AIS secondary to non-Moyamoya vasculopathy, we recommend UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment (Grade 1C)**. For children with AIS secondary to non-Moyamoya vasculopathy, we suggest ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging.**

2.56-2.57 Children With Moyamoya Disease

2.56. For children with acute AIS secondary to Moyamoya, we suggest aspirin over no treatment as initial therapy (Grade 2C)**.**

2.57. For children with Moyamoya, we suggest they be referred to an appropriate center for consideration of revascularization.

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