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ACCP CLINICAL RESOURCE

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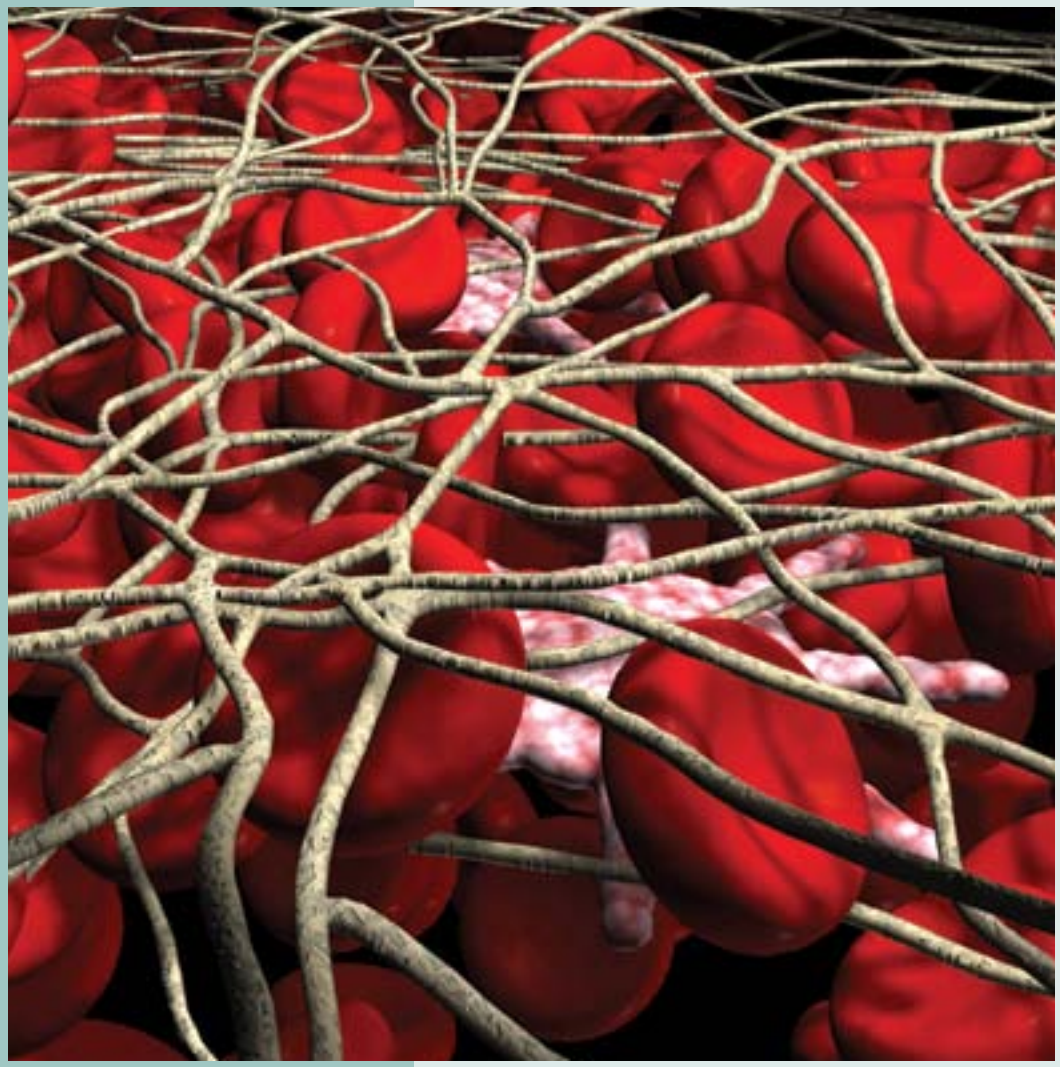
Antithrombotic Therapy and Prevention of Thrombosis

9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines



Antithrombotic Therapy and Prevention of Thrombosis

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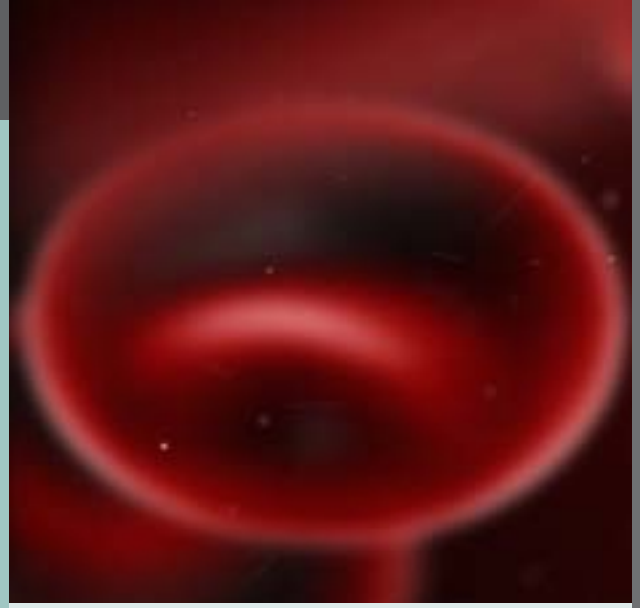
INTRODUCTION

Building on the seminal work of Dr. Jack Hirsh, Dr. Jim Dalen, and their colleagues throughout over 20 years of antithrombotic guidelines, this 9th edition has made a number of changes in process resulting in differences in the approach to making recommendations, and their content. Past iterations of these guidelines have celebrated new, high-quality evidence and the strong recommendations that such evidence warrants. The insights from this 9th edition AT9 include the persisting limitations in evidence quality (particularly with respect to the use of surrogate outcomes in prophylaxis trials) and the appropriateness of weak recommendations that reflect our lack of confidence in effect estimates and the variability in our patients' values and preferences. We believe the objective rigorous application of the science of guideline development will ultimately best serve our patients.

In this quick reference guide, physicians will find all of the recommendations from Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, but in a format that is tabular and easily searchable by key words. The order is reflective of the original guideline chapters and subsections, so users of past editions, including readers of the recent edition of the guidelines, will find the recommendations listed by the familiar topics. This tabular format facilitates easier access to specific recommendations by a simple scan of the first column for the appropriate patient population. The grading of the recommendations follows the ACCP grading system.

Gordon H. Guyatt, Elie A. Akl, Mark Crowther, David D. Gutterman, Holger J. Schuünemann, and for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis: Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2)(suppl):7S-47S.



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ACCP Guideline Disclaimer

The evidence-based practice guidelines published by The American College of Chest Physicians ("ACCP") incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any specific condition. Furthermore, guidelines may not be complete or accurate because new studies that have been published too late in the process of guideline development or after publication are not incorporated into any particular guideline before it is disseminated. The ACCP and its officers, regents, governors, executive committee, members and employees (the "ACCP Parties") disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied. Guideline users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline. The ACCP Parties further disclaim all liability for any damages whatsoever (including, without limitation, direct, indirect, incidental, punitive, or consequential damages) arising out of the use, inability to use, or the results of use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice of the possibility of such damages.

Through a comprehensive and systematic literature review, the ACCP's evidence-based clinical practice guidelines incorporate data from the existing peer-reviewed literature. This literature meets the prespecified inclusion criteria for the clinical research question, which ACCP considers, at the time of publication, to be the best evidence available for general clinical information purposes. This evidence is of varying quality from original studies of varying methodological rigor. The ACCP recommends that performance measures for quality improvement, performance- based reimbursement, and public reporting purposes should be based on rigorously developed guideline recommendations. However, not all recommendations graded highly according to the ACCP grading system (1A, 1B) are necessarily appropriate for development into such performance measures, and each one should be analyzed individually for importance, feasibility, usability, and scientific acceptability (National Quality Forum criteria). Performance measures developers should exercise caution in basing measures on recommendations that are graded 1C, 2A, 2B, and 2C, according to the ACCP Grading System1 as these should generally not be used in performance measures for quality improvement, performance-based reimbursement, and public reporting purposes.

Guyatt G, Gutterman D, Baumann M, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest. 2006;129(1):174-181.

The ACCP Grading System[1]

GRADE OF RECOMMENDATION	BENEFIT VS RISK AND BURDENS	METHODOLOGIC STRENGTH OF SUPPORTING EVIDENCE	IMPLICATIONS
Strong recommendation, High-quality evidence (1A)	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, Moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, Low or very low-quality evidence (1C)	Benefits clearly outweigh risk and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, High-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, Moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, Low or very low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

1. Guyatt G, Gutterman D, Baumann M H, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest. 2006;129(1):174-181.

Benefit vs Risk and Burdens

The ACCP Grading System classifies recommendations into two levels, strong and weak. If there is certainty that benefits do, or do not, outweigh risks and burdens, a strong recommendation, Grade 1 should be written. If there is less certainty or the benefits and risks compared with the burdens are more finely balanced, a weak, Grade 2 recommendation will be offered. In addition, patient and community values and preferences are important in clinical decision-making and, therefore, should be considered in writing clinical practice guideline recommendations and in discussions regarding clinical decisions with individual patients. When the risks clearly outweigh the benefits or vice versa, nearly all patients would have the same preferences. However, for Grade 2 (weaker) recommendations, there may not be consistency in values and preferences across multiple individuals.

Strength of Supporting Evidence

The strength of evidence will be classified into high (Grade A), moderate (Grade B), and low (Grade C) quality. The strongest evidence will be based on one or more well-designed and well-executed randomized control trials (RCTs) yielding consistent directly applicable results. Strong evidence can also come, under unusual circumstances, from observational studies yielding very large effects. Grade B evidence is based on randomized trials with important limitations or exceptionally strong observational studies. Observational studies, and RCTs with multiple serious limitations, make up the lowest category (Grade C) evidence. The HSP Committee has endorsed the principle that all relevant clinical studies published in peer-reviewed journals provide evidence, even though the quality of that evidence can be quite varied. Therefore, there is not use a threshold for "acceptable evidence," as long as it was published in peer-reviewed medical literature.

The following factors should be considered in designating the strength of the recommendation:

Some important limitations possible in RCTs:

1. Poor quality of planning and implementation of the available RCTs suggesting high likelihood of bias
2. Inconsistency of results
3. Indirectness of evidence
4. Sparse evidence
5. Large loss to follow-up

Some important factors that could raise the strength of evidence based on observational studies:

1. Large and consistent magnitude of effect
2. All plausible confounding would reduce a demonstrated effect (ie, the actual treatment effect is very likely to be larger than what the data suggests
3. Dose Response Gradient

Relationship of Strength of the Supporting Evidence to the Balance of Benefits to Risks and Burdens[1]

		Balance of Benefits to Risks and Burdens			
		Benefits Outweigh Risks/Burdens	Risks/Burdens Outweigh Benefits	Closely Balanced	Uncertain
Strength of Evidence	High	1A	1A	2A	
	Moderate	1B	1B	2B	
	Low	1C	1C	2C	2C

Components Used in the Grading of the Strength of the Evidence and Recommendations[1]

A = High	RCTs without important limitations or overwhelming evidence from observational studies	Considerable confidence in the estimate of effect
B = Moderate	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Further research likely to have impact on the confidence in estimate, may change estimate
C = Low	Observational studies or case series	Further research is very likely to have impact on confidence, likely to change the estimate

Balance of Benefits to Risks/Burdens[1]

1 = Benefits clearly outweigh the risks and burdens	Certainty of imbalance	Strong Recommendation (Recommend)
1 = Risks and burdens clearly outweigh the benefits	Certainty of imbalance	Strong Recommendation (Recommend)
2 = The risks/burdens and benefits are closely balanced	Less certainty	Weak Recommendation (Suggest)
2 = The balance of benefits to risks and burdens is uncertain	Uncertainty	Weak Recommendation (Suggest)

1. *Guyatt G, Gutterman D, Baumann M H, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest. 2006;129(1):174-181.*

EVIDENCE-BASED MANAGEMENT OF ANTICOAGULANT THERAPY

This section deals with the evidence regarding managing anticoagulant therapy, that is, oral vitamin K antagonists (VKAs), heparins, and fondaparinux. Separate articles address the pharmacology of these drugs. The questions that we address reflect those commonly posed in clinical practice.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients sufficiently healthy to be treated as outpatients	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	2C

Initial Dose Selection and Pharmacogenetic Testing

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients initiating VKA therapy	Recommend against the routine use of pharmacogenetic testing for guiding doses of VKA	1B

Initiation Overlap for Heparin and VKA

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute VTE	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	2C

Monitoring Frequency for VKAs

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients taking VKA therapy with consistently stable INRs	Suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks	2B

Management of the Single Out-of-Range INR

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic	Suggest continuing the current dose and testing the INR within 1 to 2 weeks	2C

Bridging for Low INRs

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with stable therapeutic INRs presenting with a single subtherapeutic INR value	Suggest against routinely administering bridging with heparin	2C

Vitamin K Supplementation

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients taking VKAs	Suggest against routine use of vitamin K supplementation	2C

Patient Self-Testing and Self-Management

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients treated with VKAs who are motivated and can demonstrate competent self-management strategies including the self-testing equipment	Suggest patient self-management rather than usual outpatient INR monitoring For all other patients, suggest monitoring that includes the safeguards in the previous best practice statement	2B

Dosing Decision Support

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Dosing decisions during maintenance VKA therapy	Suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support	2C
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		
Patients taking VKAs	Suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs, including cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, and certain antibiotics	2C
	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	2C

Optimal Therapeutic INR Range

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients treated with VKAs	Recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2.0) or higher (INR 3.0-5.0) range	1B

Therapeutic Range for High-Risk Groups

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with antiphospholipid syndrome with previous arterial or venous thromboembolism	Suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5)	2B

Discontinuation of Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients eligible to discontinue treatment with VKA	Suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation	2C

Unfractionated Heparin (UFH) Dose Adjustment by Weight

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients starting IV UFH	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/h for VTE; bolus 70 units/kg followed by 15 units/kg/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	2C

Dose Management of Subcutaneous (SC) UFH

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Outpatients with VTE treated with SC UFH	Suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring	2C

Therapeutic Dose of LMWH in Patients With Decreased Renal Function

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min)	Suggest a reduction of the dose rather than using standard doses	2C

Fondaparinux Dose Management by Weight

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with VTE and body weight over 100 kg	Suggest that the treatment dose of fondaparinux be increased from the usual 75 mg to 10 mg daily SC	2C

Vitamin K for Patients Taking VKAs With High INRs Without Bleeding

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding	Suggest against the routine use of vitamin K	2B
Patients taking VKAs with INRs > 10.0 and with no evidence of bleeding	Suggest that oral vitamin K be administered	2C

Clinical Prediction Rules for Bleeding While Taking VKA

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients initiating VKA therapy	Suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy	2C

Treatment of Anticoagulant-Related Bleeding

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with VKA-associated major bleeding	Suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma	2C
	Suggest the additional use of vitamin K, 5 to 10 mg administered by slow IV injection, rather than reversal with coagulation factors alone	2C

PREVENTION OF VTE IN NONSURGICAL PATIENTS

This section focuses on prevention of VTE in nonsurgical populations. Because they are addressed in other chapters in these guidelines, we do not include prevention of VTE in patients with trauma and spinal cord injury and in patients with ischemic and hemorrhagic stroke.

Adverse consequences of unprevented VTE include symptomatic DVT and pulmonary embolism (PE), fatal PE, chronic postthrombotic syndrome, and increased risk of recurrent VTE. We consider the desirable and undesirable consequences of antithrombotic prophylaxis to prevent VTE in the following populations/patient groups: (1) hospitalized acutely ill medical patients; (2) critically ill patients; (3) patients with cancer receiving cancer treatment in the outpatient setting; (4) patients with cancer with indwelling central venous catheters (CVCs); (5) chronically immobilized patients; (6) long-distance travelers; and (7) asymptomatic persons with thrombophilia. We also consider the use of statins (HMG-CoA reductase inhibitors) to prevent VTE.

Hospitalized Acutely Ill Medical Patients

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Acutely ill hospitalized medical patients at increased risk of thrombosis	Recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux	1B
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).		
Acutely ill hospitalized medical patients at low risk of thrombosis	Recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis	1B
Acutely ill hospitalized medical patients who are bleeding or at high risk of bleeding	Recommend against anticoagulant thromboprophylaxis	1B
Acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk major bleeding	Suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS)	2C
	Suggest intermittent pneumatic compression (IPC), rather than no mechanical thromboprophylaxis	2C
	When bleeding risk decreases, and if VTE risk persists, suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis	2B
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.		
Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis	Suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay	2B

Critically Ill Patients

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Critically ill patients	Suggest against routine ultrasound screening for DVT	2C
	Suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis	2C
Critically ill patients who are bleeding or are at high risk of major bleeding	Suggest mechanical thromboprophylaxis with GCS or IPC until the bleeding risk decreases, rather than no mechanical thromboprophylaxis	2C
	When bleeding risk decreases, suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis	2C

Patients With Cancer in the Outpatient Setting

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Outpatients with cancer who have no additional risk factors VTE	Suggest against routine prophylaxis with LMWH or LDUH	2B
	Recommend against the prophylactic use of VKAs	1B

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

Outpatients with solid tumors who have additional risk factors VTE and who are at low risk of bleeding	Suggest prophylactic-dose LMWH or LDUH over no prophylaxis	2B

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

Outpatients with cancer and indwelling central venous catheters	Suggest against routine prophylaxis with LMWH or LDUH	2B
	Suggest against the prophylactic use of VKAs	2C

Chronically Immobilized Patients

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Chronically immobilized persons residing at home or at a nursing home	Suggest against the routine use of thromboprophylaxis	2C

Persons Traveling Long-Distance

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
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)	Suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible	2C
	Suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel	2C
All other long-distance travelers	Suggest against the use of GCS	2C
	Suggest against the use of aspirin or anticoagulants to prevent VTE	2C

Persons With Asymptomatic Thrombophilia

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Persons with asymptomatic thrombophilia (ie, without a previous history of VTE)	Recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE	1C

PREVENTION OF VTE IN NONORTHOPEDIC SURGICAL PATIENTS

VTE is a common cause of preventable death in hospitalized patients. Approximately one-third of the 150,000 to 200,000 VTE-related deaths per year in the United States occur following surgery. The high incidence of postoperative VTE and the availability of effective methods of prevention mandate that thromboprophylaxis should be considered in every surgical patient. We review the literature pertaining to thromboprophylaxis in nonorthopedic surgical patients and make recommendations for VTE prevention after explicitly weighing the trade-offs between the potential benefits and harms of alternative strategies for prophylaxis.

General and Abdominal-pelvic Surgery Patients, Including Those Undergoing GI, Urological, Gynecologic, Bariatric, Vascular, or Plastic and Reconstructive Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
General and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score < 7; Caprini score 0)	Recommend that no specific pharmacologic prophylaxis be used other than early ambulation	1B
	Suggest that no specific mechanical prophylaxis be used other than early ambulation	2C
General and abdominal-pelvic surgery patients at low risk for VTE (~1.5%; Rogers score 7-10; Caprini score 1-2)	Suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis	2C
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	Suggest LMWH over no prophylaxis	2B
	Suggest LDUH over no prophylaxis	2B
	Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis	2C

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

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 whom the consequences of bleeding are thought to be particularly severe	Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis	2C
General and abdominal-pelvic surgery patients at high risk for VTE (approximately 6.0%; Caprini score ≥ 5) who are not at high risk for major bleeding complications	Recommend pharmacologic prophylaxis with LMWH) over no prophylaxis	1B
	Recommend LDUH over no prophylaxis	1B
	Suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis	2C
High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications	Recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis	1B

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.

High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk major for bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe	Suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated	2C
General and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score ≥ 5) whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications	Suggest low-dose aspirin over no prophylaxis	2C
	Suggest fondaparinux over no prophylaxis	2C
	Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis	2C
General and abdominal-pelvic surgery patients	Suggest that an inferior vena cava (IVC) filter should not be used for primary VTE prevention	2C
	Suggest that periodic surveillance with venous compression ultrasound should not be performed	2C

Patients Undergoing Cardiac Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Cardiac surgery patients with an uncomplicated postoperative course	Suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis	2C
	Suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over pharmacologic prophylaxis	2C
Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications	Suggest adding pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis	2C

Patients Undergoing Thoracic Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding	Suggest LDUH over no prophylaxis	2B
	Suggest LMWH over no prophylaxis	2B
	Suggest mechanical prophylaxis with optimally applied IPC over no prophylaxis	2C

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

Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding	Suggest LDUH over no prophylaxis	1B
	Suggest LMWH over no prophylaxis	1B
	Suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis	2C
Thoracic surgery patients who are at high risk for major bleeding	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	2C

Patients Undergoing Craniotomy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Craniotomy patients	Suggest that mechanical prophylaxis, preferably with IPC, be used over no prophylaxis	2C
	Suggest that mechanical prophylaxis, preferably with IPC, be used over pharmacologic prophylaxis	2C
Craniotomy patients at very high risk VTE (eg those undergoing craniotomy for malignant disease)	Suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases	2C

Patients Undergoing Spinal Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing spinal surgery	Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis	2C
	Suggest mechanical prophylaxis, preferably with IPC, over unfractionated heparin	2C
	Suggest mechanical prophylaxis, preferably with IPC, over LMWH	2C
Patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach)	Suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Major trauma patients	Suggest use of LDUH over no prophylaxis	2C
	Suggest use of LMWH over no prophylaxis	2C
	Suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis	2C
	Suggest that an IVC filter should not be used for primary VTE prevention	2C
	Suggest that periodic surveillance with venous compression ultrasound should not be performed	2C
Major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, or spinal surgery trauma)	Suggest adding mechanical prophylaxis to pharmacologic prophylaxis when not contraindicated by lower-extremity injury	2C
Major trauma patients in whom LMWH and LDUH are contraindicated	Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis when not contraindicated by lower-extremity injury	2C
	Suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves	2C

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are performed with increasing frequency, with close to 200,000 procedures for THA alone in the United States each year. The risk for VTE in major orthopedic surgery, in particular THA and hip fracture surgery (HFS), is among the highest for all surgical specialties, and deaths from VTE still occur, albeit very infrequently. This information involves prophylaxis of VTE in patients undergoing orthopedic surgery, including THA, TKA, and HFS; below-knee injuries; and arthroscopic procedures. We have included only the drugs that have been approved by regulatory agencies in more than one country.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing THA or TKA	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, apixiban, dabigatran, rivaroxaban, LDUH, adjusted-dose VKA, aspirin	1B for all comparisons
	Recommend use of intermittent pneumatic compression device (IPCD) for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis	1C
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.		
Patients undergoing HFS	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	1B for all comparisons
	Recommend use of IPCD rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days	1C
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.		
Patients undergoing major orthopedic surgery (THA TKA HFS) and receiving LMWH as thromboprophylaxis	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	1B
Patients undergoing THA or TKA irrespective of the concomitant use of an IPCD or length of treatment	Suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH	2B
If started preoperatively, we suggest administering LMWH ≥ 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.		

Patients undergoing THA or TKA irrespective of the concomitant use of an IPCD or length of treatment	Suggest the use of LMWH in preference to adjusted-dose VKA or aspirin	2C

If started preoperatively, we suggest administering LMWH ≥ 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.

Patients undergoing HFS	Irrespective of the concomitant use of an IPCD or length of treatment, suggest the use of LMWH in preference to the other agents recommended as alternatives: fondaparinux, or LDUH	2B

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.

Patients undergoing HFS	Irrespective of the concomitant use of an IPCD or length of treatment, suggest the use of LMWH in preference to adjusted-dose VKA or aspirin	2C

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.

Patients undergoing major orthopedic surgery	Suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay	2C

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.

Patients undergoing major orthopedic surgery and increased risk of bleeding	Suggest using an IPCD or no prophylaxis rather than pharmacologic treatment	2C

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.

Patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD	Recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis	1B
Patients undergoing major orthopedic surgery	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	2C
Asymptomatic patients following major orthopedic surgery	Recommend against Doppler (or duplex) ultrasound screening before hospital discharge	1B

Patients With Isolated Lower-Leg Injuries Distal to the Knee

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with isolated lower-leg injuries requiring leg immobilization	Suggest no prophylaxis rather than pharmacologic thromboprophylaxis	2C

Patients Undergoing Knee Arthroscopy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing knee arthroscopy without a history of prior VTE	Suggest no thromboprophylaxis rather than prophylaxis	2B

PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY

The primary objectives of this section are the following: (1) to address the perioperative management of patients who are receiving vitamin K antagonists (VKAs) or antiplatelet drugs, such as aspirin and clopidogrel, and require elective surgical or other invasive procedures; and (2) to address the perioperative use of bridging anticoagulation, typically with low-molecular- weight heparin (LMWH) or unfractionated heparin (UFH).

To eliminate the effect of antithrombotic therapy before surgery, treatment should be stopped before surgery (about 5 days for warfarin, 7 to 10 days for antiplatelet drug) with the intent of minimizing the bleeding risk. Administering LMWH or UFH after surgery increases the risk for bleeding; this risk is dependent on the dose of anticoagulant and the proximity to surgery (ie, the risk is higher if given closer to surgery). Delaying the resumption of therapeutic-dose LMWH or UFH (for 48 to 72 h after surgery), decreasing the dose (to low-dose), or avoiding its use after surgery can mitigate the risk for bleeding. For perioperative anticoagulant dosing, low-dose LMWH or UFH is effective in preventing venous thromboembolism (VTE), but evidence is lacking that low-dose treatment is effective in preventing arterial thromboembolism (ATE). In resuming treatment after surgery, it takes 2 to 3 days for an anticoagulant effect to begin after the start of warfarin, 3 to 5 h for a peak anticoagulant effect to occur after the start of LMWH, minutes for an antiplatelet effect to begin after the start of aspirin, and 3 to 7 days for peak inhibition of platelet aggregation after starting a maintenance dose (75 mg) of clopidogrel. Most surgical or other invasive procedures are done out-of-hospital, and potential thromboembolic or bleeding complications usually occur during the initial 2 weeks after surgery while the patient is at home. Close patient follow-up during the early postoperative period allows early detection and treatment of complications.

In patients who are having a major surgical or other major invasive procedure, interruption of antithrombotic therapy is typically required to minimize the risk for perioperative bleeding. Continuation of VKA therapy or aspirin in the perioperative period confers an increased risk for bleeding. In patients who are undergoing minor surgical or invasive procedures, such as dental, skin, or eye procedures, interruption of antithrombotic therapy may not be required.

Should antithrombotic therapy be interrupted prior to surgery, the need for 'bridging anticoagulation' will be driven by the patients' risk for thromboembolism. In patients at high risk for thromboembolism, the need to prevent such events will dominate management, irrespective of bleeding risk; the potential consequences of thromboembolism will justify bridging. Nonetheless, judicious use of postoperative bridging and optimal intraoperative hemostasis is needed to minimizing surgical bleeding that would have the undesired effect of delaying the resumption of antithrombotic therapy after surgery. In patients at moderate risk for thromboembolism, a single perioperative strategy is not dominant, and management will depend on individual patient risk assessment. The need to prevent thromboembolism will have less dominance, and bridging may be less aggressive postoperatively, especially in patients having surgery associated with a high bleeding risk. In patients at low risk for thromboembolism, the need to prevent thromboembolism will be less dominant, and bridging may be avoided; if given, it should be avoided in patients having surgery associated with a high bleeding risk.

Regarding the various degrees of thromboembolic risk stratification for mechanical heart valves, high risk is classified as any mitral valve prosthesis, older (caged-ball or tilting disc) aortic valve prosthesis, or recent (within 6 months time) stroke or transient ischemic attack (TIA). Moderate risk is classified as bileaflet aortic valve and at least one of the following: atrial fibrillation (AF), prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, or being under the age of 75. Low risk is classified as bileaflet aortic valve without AF and having no other risk factors for stroke.

Regarding the various degrees of thromboembolitic risk stratification for AF, high risk is classified as having a $CHADS_2$ score of 5 to 6, recent (within 3 months time) stroke or TIA, or rheumatic valvular heart disease. Moderate risk is classified as having a $CHADS_2$ score of 3 to 4. Low risk is classified as having a $CHADS_2$ score of 0 to 2 (assuming no prior stroke or TIA).

Individual patient characteristics (eg, prior embolic stroke or perioperative stroke/TIA) may override the suggested risk stratification.

Regarding the various degrees of thromboembolic risk stratification for VTE, high risk is classified as the presence of VTE within 3 months time or having severe thrombophilia (eg, deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies). Moderate risk is classified by the occurrence of VTE within the past 3 to 12 months, the presence of nonsevere thrombophilia (eg, heterozygous factor V or factor II mutations), presence of recurrent VTE, or the presence of active cancer (treated within 6 months or palliative). Low risk is classified as having a prior, single VTE episode less than 12 months ago, or no other risk factors.

The following surgical procedures that are associated with high bleeding risk in which postoperative anticoagulation with LMWH or UFH should be delayed or avoided are:

1. Coronary artery bypass or heart valve replacement surgery
2. Intracranial or spinal surgery
3. Major vascular surgery (eg, aortic aneurysm repair, peripheral artery bypass)
4. Major orthopedic surgery (eg, hip or knee replacement)
5. Reconstructive plastic surgery
6. Major cancer surgery
7. Prostate and bladder surgery

Additionally, procedures in which postoperative anticoagulation should be used cautiously are:

1. Colonic polyp resection (bleeding at transected stalk of large polyps)
2. Prostate or kidney biopsy (vascular tissue and endogenous urokinase), and
3. Pacemaker or implantable cardioverter-defibrillator (ICD) implant (unopposed tissues in pocket).

Interruption of VKAs Before Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who require temporary interruption of a VKA before surgery	Recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery	1C

Resumption of VKAs After Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who require temporary interruption of a VKA before surgery	Suggest 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	2C

Bridging Anticoagulation During Interruption of VKA Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism	Suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy	2C
Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.		
Patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism	Suggest no bridging instead of bridging anticoagulation during interruption of VKA therapy	2C
In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen, as in the higher- and lower-risk patients is based on an assessment of individual patient- and surgery-related factors		

Perioperative Management of VKA-Treated Patients Who Require Minor Procedures

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who require a minor dental procedure	Suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies	2C
Patients who require minor dermatologic procedures and are receiving VKA therapy	Suggest continuing VKAs around the time of the procedure and optimizing local hemostasis instead of other strategies	2C
Patients who require cataract surgery and are receiving VKA therapy	Suggest continuing VKAs around the time of the surgery instead of other strategies	2C

Patients Undergoing a Minor Dental, Dermatologic, or Ophthalmologic Procedure

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
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	Suggest continuing ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure	2C
Patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery	Suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery	2C
Patients at low risk for cardiovascular events who are receiving ASA therapy	Suggest stopping ASA 7 to 10 days before surgery instead of continuation of ASA	2C

Patients Undergoing Coronary Artery Bypass Graft Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who are receiving ASA and require coronary artery bypass graft (CABG) surgery	Suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery	2C
Patients who are receiving dual antiplatelet drug therapy and require CABG surgery	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	2C

Surgical Patients With Coronary Stents

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery	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	1C
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	Suggest continuing dual antiplatelet therapy around the time of surgery instead of stopping dual antiplatelet therapy 7 to 10 days before surgery	2C

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.

Perioperative Use of IV UFH

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH	Suggest stopping UFH 4 to 6 h before surgery instead of closer to surgery	2C

Preoperative Interruption of Therapeutic-Dose Bridging LMWH

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH	Suggest administering the last preoperative dose of LMWH approximately 24 h before surgery instead of 12 h before surgery	2C

Postoperative Resumption of Therapeutic-Dose Bridging LMWH

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery	Suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery instead of resuming LMWH within 24 h after surgery	2C

DIAGNOSIS OF DVT

DVT is a common condition that affects approxi- mately one in 1,000 persons per year. Objective testing for DVT is crucial because clinical assessment alone is unreliable, and the consequences of misdiag- nosis are serious, including fatal pulmonary embolism (PE). Although anticoagulant therapy is effective, its unnecessary use entails expense, inconvenience, and risk of major hemorrhage. Only a minority of patients evaluated for suspected DVT actually have the disease. Therefore, diagnostic strategies must be able to correctly rule in DVT when it is present and safely rule out DVT when it is absent.

Three categories of tests are typically used to determine the probability of DVT: (1) clinical probability assessment based on patient history and clinical findings, (2) D-dimer assays, and (3) imaging studies (most commonly venous ultrasonography [US] and less frequently venography, CT scan, or MRI). Diagnostic testing often requires that the results of more than one assessment are combined. The goal of choosing one strategy over another is to improve patient outcomes in the most efficient manner. This article focuses on the identification of optimal strategies for the diagnosis of clinically suspected DVT in adults. Most of the data come from evaluations of patients in the ambulatory setting (ie, outpatient or ED), and our recommendations are most applicable to this patient population.

Diagnosis of Suspected First Lower Extremity DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a suspected first lower extremity DVT	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	2B

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 a weak recommendation.

Patients with a low pretest probability of first lower extremity DVT	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 no diagnostic testing	1B for all comparisons
	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 venography	1B for all comparisons
	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 whole-leg ultrasound (US)	2B for all comparisons
	Suggest initial use of a moderately sensitive D-dimer rather than proximal CUS	2C
	Suggest highly sensitive D-dimer rather than proximal CUS	2B

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

Patients with a low pre test probability and the D-dimer is negative	Recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography	1B for all comparisons

Patients with a low pre test probability and the proximal CUS is negative	Recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography	1B for all comparisons
Patients with a low pre test probability and the D-dimer is positive	Suggest further testing with CUS of the proximal veins rather than whole-leg US	2C
	Suggest further testing with CUS of the proximal veins rather than venography	1B
Patients with a low pre test probability and CUS of the proximal veins is positive	Suggest treating for DVT and performing no further testing over performing confirmatory venography	2C

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).

Patients with a moderate pretest probability of first lower extremity DVT	Recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than no testing	1B for all comparisons
	Recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than venography	1B for all comparisons
	Suggest initial use of a highly sensitive D-dimer rather than US	2C

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.

Patients with a moderate pre-test probability, and the highly sensitive D-dimer is negative	Recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography	1B for all comparisons
Patients with a moderate pre-test probability, and the highly sensitive D-dimer is positive	Recommend proximal CUS or whole-leg US rather than no testing	1B for all comparisons
	Recommend proximal CUS or whole-leg US rather than venography	1B for all comparisons

Patients with a moderate pre-test probability, and proximal CUS is chosen as the initial test and is negative	Recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing	1C
	Recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over venography	2B
Patients with a moderate pre-test probability with a negative proximal CUS but a positive D-dimer	Recommend repeat proximal CUS in 1 week over no further testing	1B
	Recommend repeat proximal CUS in 1 week over venography	2B
Patients with a moderate pretest probability with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer	Recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography	1B for all comparisons
Patients with a moderate pre-test probability, and whole-leg US is negative	Recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography	1B for all comparisons
Patients with a moderate pre-test probability, and proximal CUS is positive	Recommend treating for DVT rather than confirmatory venography	1B
Patients with a moderate pre-test probability, and isolated distal DVT is detected on whole-leg US	Suggest serial testing to rule out proximal extension over treatment	2C

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.

Patients with a high pretest probability of first lower extremity DVT	Recommend either (i) proximal CUS or (ii) whole-leg US over no testing	1B for all comparisons
	Recommend either (i) proximal CUS or (ii) whole-leg US over venography	1B for all comparisons

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.

Patients with a high pretest probability, if proximal CUS or whole-leg US is positive DVT	Recommend treatment rather than confirmatory venography	1B
Patients with a high pretest probability with a negative proximal CUS	Recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing	1B for all comparisons
	Recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over venography	2B for all comparisons
Patients with a high pretest probability with a single negative proximal CUS and positive D-dimer	Recommend that undergo whole-leg US or repeat proximal CUS in 1 week over no further testing	1B
	Recommend that undergo whole-leg US or repeat proximal CUS in 1 week over venography	2B
Patients with a high pretest probability with negative serial proximal CUS, a negative single proximal CUS, and negative highly sensitive D-dimer or a negative whole-leg US	Recommend no further testing over venography or additional US	1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; 2B for negative whole-leg US
Patients with high pretest probability	Recommend that moderately or highly sensitive D-dimer assays should not be used as stand-alone tests to rule out DVT	1B
If risk stratification is not performed, patients with suspected first lower extremity DVT	Recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than no testing	1B
	Recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than venography	1B
	Recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than D-dimer testing	2B

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.

If risk stratification is not performed, patients with suspected first lower extremity DVT with a negative proximal CUS	Recommend testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing	1B
	Recommend testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over venography	2B
	Suggest D-dimer rather than routine serial CUS	2B
	Suggest D-dimer rather than whole-leg US	2C
If risk stratification is not performed, patients with suspected first lower extremity DVT with a single negative proximal CUS and positive D-dimer	Recommend further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing	1B for both comparisons
If risk stratification is not performed, patients with suspected first lower extremity DVT with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US	Recommend no further testing be performed rather than venography	1B
If risk stratification is not performed, patients with suspected first lower extremity DVT if proximal US is positive DVT	Recommend treatment rather than confirmatory venography	1B
If risk stratification is not performed, patients with suspected first lower extremity DVT if isolated distal DVT is detected on whole-leg US	Suggest serial testing to rule out proximal extension over treatment	2C

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.

Diagnosis of Suspected Reccurent Lower Extremity DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients suspected of having recurrent lower extremity DVT	Recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI	1B
Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.		
Patients suspected of having recurrent lower extremity DVT and if the highly sensitive D-dimer is positive	Recommend proximal CUS over venography, CT venography, or MRI	1B for all comparisons
Patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of < 2 mm)	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	2B
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).		
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	Recommend no further testing for suspected recurrent DVT rather than venography	1B

Patients with suspected recurrent lower extremity DVT and the CUS of the proximal veins is positive	Recommend treating for DVT and performing no further testing over performing confirmatory venography	1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, 2B for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result

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).

Patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg an increase residual venous diameter of < 4 but ≥ 2 mm)	Recommend further testing with venography, if available	1B
	Suggest further testing with serial proximal CUS	2B
	Suggest testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive as opposed to other testing strategies or treatment	2B
Patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result comparison	Recommend further testing with venography, if available	1B
	Suggest a highly sensitive D-dimer over serial proximal CUS	2B
Patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result comparison and a negative highly sensitive D-dimer	Suggest no further testing over venography	2C
	Suggest venography if available over empirical treatment of recurrence	2C

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

Diagnosis of Pregnancy Related DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant patients suspected of having lower extremity DVT	Suggest initial evaluation with proximal CUS over other initial tests, including a whole-leg US	2C
	Suggest initial evaluation with proximal CUS over moderately sensitive D-dimer	2C
	Recommend initial evaluation with proximal CUS over highly sensitive D-dimer	1B
	Recommend initial evaluation with proximal CUS over venography	1B
Pregnant patients with suspected DVT whom initial proximal CUS is negative	Recommend further testing with serial proximal CUS (day 3 and day 7)	1B
	Suggest further testing with a sensitive D-dimer done at the time of presentation over no further testing for DVT	2B
Patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS	Recommend no further testing for DVT	1B
Patients with positive D-dimer	Recommend an additional follow-up proximal CUS (day 3 and day 7) rather than venography	1B
	Suggest an additional follow-up proximal CUS (day 3 and day 7) rather than whole-leg US	2C
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	Suggest further testing with Doppler US of the iliac vein	2C
	Suggest further testing with venography	2C
	Suggest further testing with direct MRI rather than standard serial CUS of the proximal deep veins	2C

Diagnosis of Upper Extremity DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients suspected of having UEDVT	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	2C
Patients with suspected UEDVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT	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	2C
Patients with suspected UEDVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI	Recommend no further testing, rather than confirmatory venography	1C
Patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US	Suggest venography rather than no further testing, unless there is an alternative explanation for their symptoms, in which case testing to evaluate for the presence an alternative diagnosis should be performed	2B
Patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation their symptoms	Suggest confirmatory testing and treatment of this alternative explanation rather than venography	2C

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.

Here are recommendations for the use of antithrombotic agents as well as the use of devices or surgical techniques in the treatment of patients with DVT and pulmonary embolism (PE), which are collectively referred to as VTE. We also provide recommendations for patients with (1) post-thrombotic syndrome (PTS), (2) chronic thromboem- bolic pulmonary hypertension (CTPH), (3) incidentally diagnosed (asymptomatic) DVT or PE, (4) acute upper-extremity DVT (UEDVT), (5) superficial vein thrombosis (SVT), (6) splanchnic vein thrombosis, and (7) hepatic vein thrombosis.

Initial Anticoagulation for Patients With Acute DVT of the Leg

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg treated with VKA therapy	Recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment	1B

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a high clinical suspicion of acute VTE	Suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests	2C
Patients with an intermediate clinical suspicion of acute VTE	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	2C
Patients with a low clinical suspicion of acute VTE	Suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h	2C

Anticoagulation for Patients With Isolated Distal DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension	Suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation	2C
Patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension	Suggest initial anticoagulation over serial imaging of the deep veins	2C

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.

Patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation	Recommend using the same approach as for patients with acute proximal DVT	1B

Patients with acute isolated distal DVT of the leg who are managed with serial imaging	Recommend no anticoagulation if the thrombus does not extend	1B
	Suggest anticoagulation if the thrombus extends but remains confined to the distal veins	2C
	Recommend anticoagulation if the thrombus extends into the proximal veins	1B

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg	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	1B

Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg	Suggest LMWH or fondaparinux over IV UFH	2C for all comparisons
	Suggest LMWH or fondaparinux over SC UFH	2B for LMWH; 2C for fondaparinux

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.

Patients with acute DVT of the leg treated with LMWH	Suggest once- over twice-daily administration	2C

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.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg and whose home circumstances are adequate	Recommend initial treatment at home over treatment in hospital	1B

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).

Catheter-Directed Thrombolysis for Patients With Acute DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute proximal DVT of the leg	Suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT)	2C

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.

Systemic Thrombolytic Therapy for Patients With Acute DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute proximal DVT of the leg	Suggest anticoagulant therapy alone over systemic thrombolysis	2C

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.

Operative Venous Thrombectomy for Acute DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute proximal DVT of the leg	Suggest anticoagulant therapy alone over operative venous thrombectomy	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg who undergo thrombosis removal	Recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal	1B

Vena Cava Filters for the Initial Treatment of Patients With DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg	Recommend against the use of an IVC filter in addition to anticoagulants	1B
Patients with acute proximal DVT of the leg and contraindication to anticoagulation	Recommend the use of an IVC filter	1B
Patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation	Suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves	2B

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

Early Ambulation of Patients With Acute DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute DVT of the leg	Suggest early ambulation over initial bed rest	2C

If edema and pain are severe, ambulation may need to be deferred. We suggest the use of compression therapy in these patients. 3.0 Long-term Anticoagulation in Patients With Acute DVT of the Leg

Patients with acute VTE who are treated with anticoagulant therapy	Recommend long-term therapy over stopping anticoagulant therapy after about 1 week of initial therapy	1B

Duration of Long-term Anticoagulant Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a proximal DVT of the leg provoked by surgery	Recommend treatment with anticoagulation for 3 months over treatment of a shorter period	1B
	Recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)	1B
	Recommend treatment with anticoagulation for 3 months over extended therapy	1B regardless of bleeding risk

Patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor	Recommend treatment with anticoagulation for 3 months over treatment of a shorter period	1B
	Recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)	1B
	Recommend treatment with anticoagulation for 3 months over extended therapy if there is a high bleeding risk	1B
	Suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk	2B
Patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor	Suggest treatment with anticoagulation for 3 months over treatment of a shorter period	2C
	Recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)	1B
	Recommend treatment with anticoagulation for 3 months over extended therapy	1B regardless of bleeding risk
Patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal)	Recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration	1B
After 3 months of treatment, patients with unprovoked DVT of the leg	Should be evaluated for the risk-benefit ratio of extended therapy	
Patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk	Suggest extended anticoagulant therapy over 3 months of therapy	2B
Patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk	Recommend 3 months of anticoagulant therapy over extended therapy	1B
Patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark)	Suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk	2B
	Recommend 3 months of anticoagulant treatment in those with a high bleeding risk	1B
Patients with a second unprovoked VTE	Recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk	1B
	Suggest extended anticoagulant therapy in those with a moderate bleeding risk	2B
Patients with a second unprovoked VTE who have a high bleeding risk	Suggest 3 months of anticoagulant therapy over extended therapy	2B

Patients with DVT of the leg and active cancer if the risk of bleeding is not high	Recommend extended anticoagulant therapy over 3 months of therapy	1B
	If there is a high bleeding risk, suggest extended anticoagulant therapy	2B

Remarks: 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 prescribed anticoagulants.

Patients who receive extended anticoagulant therapy	the continuing use of treatment should be reassessed at periodic intervals (eg, annually)	

Intensity of Anticoagulant Effect

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with DVT of the leg who are treated with VKA	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	1B

Choice of Anticoagulant Regimen for Long-term Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with DVT of the leg and no cancer	Suggest VKA therapy over LMWH for long-term therapy	2C
Patients with DVT and no cancer who are not treated with VKA therapy	Suggest LMWH over dabigatran or rivaroxaban for long-term therapy	2C
Patients with DVT of the leg and cancer	Suggest LMWH over VKA therapy	2B
Patients with DVT and cancer who are not treated with LMWH	Suggest VKA over dabigatran or rivaroxaban for long-term therapy	2B

Remarks: 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.

Choice of Anticoagulant Regimen for Extended Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with DVT of the leg who receive extended therapy	Suggest treatment with the same anticoagulant chosen for the first 3 months	2C

Treatment of Patients With Asymptomatic DVT of the Leg

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who are incidentally found to have asymptomatic DVT of the leg	Suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT	2B

Compression Stockings and Bandages to Prevent PTS

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute symptomatic DVT of the leg	Suggest the use of compression stockings	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.

Physical Treatment of Patients With PTS

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with PTS of the leg	Suggest a trial of compression stockings	2C
Patients with severe PTS of the leg that is not adequately relieved by compression stockings	Suggest a trial of an intermittent compression device	2B

Pharmacologic Treatment of Patients With PTS

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with PTS of the leg	Suggest that venoactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used	2C

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

Initial Anticoagulation for Patients With Acute Pulmonary Embolism (PE)

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE	Recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment	1B

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
patients with a high clinical suspicion of acute PE	Suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests	2C
Patients with an intermediate clinical suspicion of acute PE	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	2C
Patients with a low clinical suspicion of acute PE	Suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE	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	1B

Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE	Suggest LMWH or fondaparinux over IV UFH	2C for LMWH; 2B for fondaparinux
	Suggest LMWH or fondaparinux over SC UFH	2B for LMWH; 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.

Patients with acute PE treated with LMWH	Suggest once- over twice-daily administration	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.

Early vs Standard Discharge of Patients With Acute PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with low-risk PE and whose home circumstances are adequate	Suggest early discharge over standard discharge (eg, after first 5 days of treatment)	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.

Systemic Thrombolytic Therapy for Patients With PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk	Suggest systemically administered thrombolytic therapy over no such therapy	2C
Most patients with acute PE not associated with hypotension	Recommend against systemically administered thrombolytic therapy	1C
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	Suggest administration of thrombolytic therapy	2C
Patients with acute PE	When a thrombolytic agent is used, suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion)	2C
Patients with acute PE when a thrombolytic agent is used	Suggest administration through a peripheral vein over a pulmonary artery catheter	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
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	Suggest catheter-assisted thrombus removal over no such intervention	2C

Surgical Embolectomy for the Initial Treatment of Patients With PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE associated with hypotension	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	2C

Vena Cava Filters for the Initial Treatment of Patients With PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute PE who are treated with anticoagulants	Recommend against the use of an IVC filter	1B
Patients with acute PE and contraindication to anticoagulation	Recommend the use of an IVC filter	1B
Patients with acute PE and an IVC filter inserted as an alternative to anticoagulation	Suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves	2B

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

Long-term Treatment of Patients With PE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with PE provoked by surgery	Recommend treatment with anticoagulation for 3 months over treatment of a shorter period	1B
	Recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)	1B
	Recommend treatment with anticoagulation for 3 months over extended therapy	1B regardless of bleeding risk
Patients with PE provoked by a nonsurgical transient risk factor	Recommend treatment with anticoagulation for 3 months over treatment of a shorter period	1B
	Recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months)	1B
	Recommend treatment with anticoagulation for 3 months over extended therapy if there is a high bleeding risk	1B
	Suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk	2B
Patients with an unprovoked PE	Recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration	1B
After 3 months of treatment, patients with unprovoked PE	*Should be evaluated for the risk-benefit ratio of extended therapy*	
Patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk	Suggest extended anticoagulant therapy over 3 months of therapy	2B
Patients with a first VTE that is an unprovoked PE and who have a high bleeding risk	Recommend 3 months of anticoagulant therapy over extended therapy	1B
Patients with a second unprovoked VTE	Recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk	1B
	Suggest extended anticoagulant therapy in those with a moderate bleeding risk	2B
Patients with a second unprovoked VTE who have a high bleeding risk	Suggest 3 months of therapy over extended therapy	2B

Patients with PE and active cancer if there is a low or moderate bleeding risk	Recommend extended anticoagulant therapy over 3 months of therapy	1B
	If there is a high bleeding risk, suggest extended anticoagulant therapy	2B
In all patients who receive extended anticoagulant therapy	The continuing use of treatment should be reassessed at periodic intervals (eg, annually)	
Patients with PE who are treated with VKA	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	1B
Patients with PE and no cancer	Suggest VKA therapy over LMWH for long-term therapy	2C
patients with PE and no cancer who are not treated with VKA therapy	Suggest LMWH over dabigatran or rivaroxaban for long-term therapy	2C
patients with PE and cancer	Suggest LMWH over VKA therapy	2B

Remarks: 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.

Patients with PE and cancer who are not treated with LMWH	Suggest VKA over dabigatran or rivaroxaban for long-term therapy	2C
Patients with PE who receive extended therapy	Suggest treatment with the same anticoagulant chosen for the first 3 months	2C
Patients who are incidentally found to have asymptomatic PE	Suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE	2B

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with CTPH	Recommend extended anticoagulation over stopping therapy	1B
Select patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team	Suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy	2C

Treatment of Patients With Superficial Vein Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with superficial venous thrombosis of the lower limb of at least 5 cm in length	Suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation	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.		
Patients with superficial vethrombosis who are treated with anticoagulation	Suggest fondaparinux 25, mg daily, over a prophylactic dose of LMWH	2C

Acute Anticoagulation for Patients With UEDVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with UEDVT that involves the axillary or more proximal veins	Recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment	1B
Patients with acute UEDVT that involves the axillary or more proximal veins	Suggest LMWH or fondaparinux over IV UFH	2C
	Suggest LMWH or fondaparinux over SC UFH	2B

Thrombolytic Therapy for the Initial Treatment of Patients With UEDVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute UEDVT that involves the axillary or more proximal veins	Suggest anticoagulant therapy alone over thrombolysis	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.		
Patients with UEDVT who undergo thrombolysis	Recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis	1B

Long-term Anticoagulation for Patients With UEDVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Most patients with UEDVT that is associated with a central venous catheter	Suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter	2C
Patients with UEDVT that involves the axillary or more proximal veins	Suggest a minimum duration of anticoagulation of 3 months over a shorter period	2B
Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.		
Patients who have UEDVT that is associated with a central venous catheter that is removed	Recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer	1B
	Suggest 3 months of anticoagulation over a longer duration of therapy in patients with cancer	2C
Patients who have UEDVT that is associated with a central venous catheter that is not removed	Recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer	1C
	Suggest this in patients with no cancer	2C
Patients who have UEDVT that is not associated with a central venous catheter or with cancer	Recommend 3 months of anticoagulation over a longer duration of therapy	1B

Prevention of PTS of the Arm

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute symptomatic UEDVT	Suggest against the use of compression sleeves or venoactive medications	2C

Treatment of Patients With PTS of the Arm

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who have PTS of the arm	Suggest a trial of compression bandages or sleeves to reduce symptoms	2C
Patients with PTS of the arm	Suggest against treatment with venoactive medications	2C

Patients With Splanchnic Vein Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with symptomatic splanchnic vein thrombosis (portal mesenteric and/or splenic vethromboses)	Recommend anticoagulation over no anticoagulation	1B
Patients with incidentally detected splanchnic vein thrombosis (portal mesenteric and/or splenic vethromboses)	Suggest no anticoagulation over anticoagulation	2C

Patients With Hepatic Vein Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with symptomatic hepatic vein thrombosis	Suggest anticoagulation over no anticoagulation	2C
Patients with incidentally detected hepatic vein thrombosis	Suggest no anticoagulation over anticoagulation	2C

TREATMENT AND PREVENTION OF HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction characterized by thrombocytopenia caused by antibodies that recognize complexes of platelet factor 4 (PF4, a constituent of platelet alpha-granules) bound to heparin, resulting in in vivo platelet activation and greatly increased risk of venous and/or arterial thrombotic events. Additionally, HIT is a clinicopathologic syndrome, because the diagnosis is based on both clinical (thrombocytopenia and thrombosis) and serologic grounds (heparin-dependent, platelet-activating IgG against PF4/heparin complexes). Neither thrombocytopenia or thrombosis without the presence of heparin-dependent antibodies, nor the isolated presence of antibodies without thrombocytopenia, thrombosis, or other clinical sequelae, meet the criteria for HIT. Not all anti-PF4/heparin antibodies are able to cause HIT— the "iceberg model of HIT" infers that antibodies that strongly activate platelets are most likely to result in clinical HIT.

Platelet Count Monitoring for Patients Receiving Heparin/LMWH

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be > 1%	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)	2C
Patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%	Suggest that platelet counts not be monitored	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with HITT	Recommend the use of nonheparin antigoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin, or LMWH or initiation/continuation of VKA	1C

Choice of Nonheparin Anticoagulants in Patients With HITT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with HITT who have normal renal function	Suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants	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.		
Patients with HITT and renal insufficiency	Suggest the use of argatroban over other nonheparin anticoagulants	2C

Platelet Transfusions

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with HIT and severe thrombocytopenia	Suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding	2C

Starting VKAs Before Platelet Recovery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with strongly suspected or confirmed HIT	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	1C
If a VKA has already been started, patients diagnosed with HIT	Suggest that vitamin K should be administered	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 parenteral nonheparin anticoagulant.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with confirmed HIT	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	1C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with isolated HIT (HIT without thrombosis)	Recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA	1C

Choice of Nonheparin Anticoagulants in Patients With Isolated HIT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with isolated HIT (HIT without thrombosis) who have normal renal function	Suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants	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.

Patients Who Require Urgent Cardiac Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute HIT (thrombocytopenic HIT antibody-positive) or subacute HIT (platelets recovered but still HIT antibody-positive) who require urgent cardiac surgery	Suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents	2C
Patients with acute HIT who require nonurgent cardiac surgery	Suggest delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative	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.

Patients Who Require Urgent Percutaneous Coronary Interventions

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute HIT or subacute HIT who require percutaneous coronary interventions	Suggest the use of bivalirudin	2B
	Suggest argatroban over other nonheparin anticoagulants	2C

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

Patients Who Require Renal Replacement Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute or subacute HIT who require renal replacement therapy	Suggest the use of argatroban or danaparoid over other nonheparin anticoagulants	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.

Patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking	Suggest the use of regional citrate over the use of heparin or LMWH	2C

Pregnant Patients

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant patients with acute or subacute HIT	Suggest danaparoid over other nonheparin anticoagulants	2C
	Suggest the use of lepirudin or fondaparinux only if danaparoid is not available	2C

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

Patients With a History of HIT Who Require Cardiac Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery	Suggest the use of heparin (short-term use only) over nonheparin anticoagulants	2C
Patients with a history of HIT whom heparin antibodies are still present who require cardiac surgery	Suggest the use of nonheparin anticoagulants over heparin or LMWH	2C

Patients Who Require PCI

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac catheterization or percutaneous coronary interventions	Suggest the use of bivalirudin	2B

Patients Who Require Prophylaxis or Treatment of Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function	Suggest the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved	2C

ANTITHROMBOTIC THERAPY FOR ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is an important risk factor for ischemic stroke. It affects nearly 2.5 million people in the United States, along with a prevalence strongly associated with advancing age culminating in 10% of those 80 years and older, although more prevalent in men than in women at every age. AF increases the risk of stroke fourfold to fivefold across all age groups. Overall, AF accounts for about 15% of all strokes in the United States.

This section deals primarily with stroke prevention in nonvalvular AF when the dysrhythmia is not associated with rheumatic mitral valve disease or prosthetic heart valves.

Patients With Nonrheumatic Atrial Fibrillation (AF)

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF including those with paroxysmal AF who are at low risk of stroke (eg CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score = 0)	Suggest no therapy rather than antithrombotic therapy	2B
Patients who do choose antithrombotic therapy	Suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation	2B
	Suggest aspirin (75 mg to 325 mg once daily) rather than combination therapy with aspirin and clopidogrel	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. The presence of multiple non-CHADS2 risk factors for stroke may favor oral anticoagulation therapy.

Patients with AF including those with paroxysmal AF who are at intermediate risk of stroke (eg CHADS2 score = 1)	Recommend oral anticoagulation rather than no therapy	1B
	Suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)	2B
	Suggest oral anticoagulation rather than combination therapy with aspirin and clopidogrel	2B
Patients who are unsuitable or choose not to take an oral anticoagulant (reasons other than concerns about major bleeding)	Suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)	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. The presence of multiple additional non-CHADS2 risk factors for stroke may favor oral anticoagulation therapy.

Patients with AF including those with paroxysmal AF who are at high risk of stroke (eg CHADS2 score = 2)	Recommend oral anticoagulation rather than no therapy	1A
	Recommend oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)	1B
	Recommend oral anticoagulation rather than combination therapy with aspirin and clopidogrel	1B
Patients who are unsuitable or choose not to take an oral anticoagulant (reasons other than concerns about major bleeding)	Recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)	1B
Patients with AF including those with paroxysmal AF	For recommendations in favor of oral anticoagulation, suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0)	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.

Patients With AF and Mitral Stenosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF and mitral stenosis	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 1B
Patients with AF and mitral stenosis who are unsuitable or choose not to take adjusted-dose VKA therapy (reasons other than concerns about major bleeding)	Recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone	1B

Patients With AF and Stable Coronary Artery Disease

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF and stable coronary artery disease (eg, no acute coronary syndrome with the previous year) and who choose oral anticoagulation	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	2C

Patients With AF and Placement of an Intracoronary Stent

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF at high risk of stroke (eg, CHADS2 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	Suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel)	2C
Patients with AF at high risk of stroke, after this initial period of triple therapy	Suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone	2C
At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease		
Patients with AF at low to intermediate risk of stroke (eg, CHADS2 score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting)	Suggest dual antiplatelet therapy rather than triple therapy	2C
At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease		

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-CHADS2 risk factors for stroke.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF at intermediate to high risk of stroke (eg, CHADS2 score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement	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)	2C
After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease		
Patients with AF at low risk of stroke (eg CHADS2 score of 0)	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)	2C
After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease		

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-CHADS2 risk factors for stroke.

Patients With AF Managed by a Rhythm Control Strategy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation)	Suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF, regardless of the apparent persistence of normal sinus rhythm	2C

Patients With Atrial Flutter

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with atrial flutter	Suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF	

Patients Undergoing Elective Cardioversion of AF

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion	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	1B
	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	1B
Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy.		
Patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic)	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	2C
	Suggest therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk	2C
Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy.		

Patients Undergoing Urgent Cardioversion for Hemodynamically Unstable AF

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic)	Suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible	2C
	But that initiation of anticoagulation must not delay any emergency intervention	2C
	After successful cardioversion to sinus rhythm, suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk	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.

Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion	Suggest that the same approach to thromboprophylaxis be used as for patients with AF undergoing cardioversion	

ANTITHROMBOTIC AND THROMBOLYTIC THERAPY FOR VALVULAR DISEASE

Few complications of valvular heart disease can be more devastating than systemic embolism. Antithrombotic therapy can reduce, but not eliminate, this risk. However, antithrombotic therapy, particularly with heparin or coumarin derivatives, can also carry a substantial bleeding risk. The risks of bleeding and thromboembolism vary with the antithrombotic regimen, the intensity of the anticoagulant effect, and the underlying clinical circumstances in individual patients.

Patients With Rheumatic Mitral Valve Disease

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm	Suggest not using antiplatelet or VKA therapy	2C
	Suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet	2C
Patients with rheumatic mitral valve disease complicated by the presence of left atrial thrombus	Recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy	1A
Patients with rheumatic mitral valve disease complicated singly or combination by the presence of AF or previous systemic embolism	Recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy	1A

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients being considered for PMBV with preprocedural TEE showing left atrial thrombus	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	1A
Patients being considered for PMBV with preprocedural TEE showing left atrial thrombus if the left atrial thrombus does not resolve with VKA therapy	Recommend that PMBV not be performed	1A

Patients With PFO and Atrial Septal Aneurysm

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm	Suggest against antithrombotic therapy	2C
Patients with cryptogenic stroke and PFO or atrial septal aneurysm	Recommend aspirin (50-100 mg/d) over no aspirin	1A
Patients with cryptogenic stroke and PFO or atrial septal aneurysm who experience recurrent events despite aspirin therapy	Suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy	2C
Patients with cryptogenic stroke and PFO with evidence of DVT	Recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0)	1B
	Consideration of device closure over no VKA therapy or aspirin therapy	2C

Role of Anticoagulants and Antiplatelet Agent in Patients With Native Valve Endocarditis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with infective endocarditis (IE)	Recommend against routine anticoagulant therapy, unless a separate indication exists	1C
	Recommend against routine antiplatelet therapy, unless a separate indication exists	1B

Role of Anticoagulants in Patients With Prosthetic Valve Endocarditis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients on VKA for a prosthetic valve who develop IE	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	2C
When the patient is deemed stable without contraindications or neurologic complications	Suggest reinstitution of VKA therapy	2C

Patients With Nonbacterial Thrombotic Endocarditis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli	Suggest treatment with full-dose IV UFH or SC LMWH over no anticoagulation	2C

Antithrombotic Therapy in the First 3 Months After Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with aortic bioprosthetic valves who are in sinus rhythm and have no other indication VKA therapy	Suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months	2C
Patients with transcatheter aortic bioprosthetic valves	Suggest aspirin (50-100 mg/d) plus clopidogrel (75 mg/d) over VKA therapy and over no antiplatelet therapy in the first 3 months	2C
Patients with a bioprosthetic valve in the mitral position	Suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion	2C

Long-term Antithrombotic Therapy for Patients With Bioprosthetic Valves

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with bioprosthetic valves in normal sinus rhythm	Suggest aspirin therapy over no aspirin therapy after 3 months postoperative	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with mechanical heart valves	Suggest bridging with unfractionated heparin (UFH, prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy	2C

Long-term Antithrombotic Therapy for Patients With Mechanical Valves

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with mechanical heart valves	Recommend VKA therapy over no VKA therapy for long-term management	1B

Intensity of VKA Therapy for Patients With Mechanical Aortic Valve Prostheses

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a mechanical aortic valve	Suggest VKA therapy with a target of 2.5 (range, 2.0-3.0) over lower targets	2C
Patients with a mechanical aortic valve	Recommend VKA therapy with a target of 2.5 (range 2.0-3.0) over higher targets	1B

Intensity of VKA Therapy for Patients With Mechanical Mitral Valve Prostheses

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a mechanical mitral valve	Suggest VKA therapy with a target of 3.0 (range, 2.5-3.5) over lower INR targets	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with mechanical heart valves in both the aortic and mitral position	Suggest target INR 3.0 (range, 2.5-3.5) over target INR 2.5 (range, 2.0-3.0)	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a mechanical mitral or aortic valve at low risk of bleeding	Suggest adding over not adding an antiplatelet agent, such as low-dose aspirin (50-100 mg/d), to the VKA therapy	1B

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

Antiplatelet Agent Therapy Instead of VKA Therapy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with mechanical aortic or mitral valves	Recommend VKA over antiplatelet agents	1B

Antithrombotic Therapy After Mitral Valve Repair

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm	Suggest the use of antiplatelet therapy for the first 3 months over VKA therapy	2C

Patients Undergoing Aortic Valve Repair

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing aortic valve repair	Suggest aspirin at 50 to 100 mg/d over VKA therapy	2C

Patients With Right-Sided Prosthetic Valve Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with right-sided prosthetic valve thrombosis (PVT) in the absence of contraindications	Suggest administration of fibrinolytic therapy over surgical intervention	2C

Patients With Left-Sided Prosthetic Valve Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with left-sided PVT and large thrombus area (≥ 0.8 cm^2)	Suggest early surgery over fibrinolytic therapy	2C
	If contraindications to surgery exist, suggest the use of fibrinolytic therapy	2C
Patients with left-sided PVT and small thrombus area (< 0.8 cm^2)	Suggest administration of fibrinolytic therapy over surgery	2C
Patients with left-sided PVT and very small nonobstructive thrombus	Suggest IV UFH accompanied by serial Doppler echocardiography to document thrombus resolution or improvement over other alternatives	2C

ANTITHROMBOTIC AND THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE

Stroke is a brain injury caused by sudden disruption of blood flow to the brain, usually due to a ruptured or blocked artery. Stroke is a leading cause of death and disability in American adults with a prevalence in the United States of 780,000 new strokes per year, 600,000 of which are first attacks. Due to the aging of the population, this rate is anticipated to increase. Stroke is the third most common cause of death, directly causing about 150,000 deaths and the indirect cause of another 150,000 deaths, as well as a leading cause of long-term disability, long-term institutionalization, and negative impacts on the quality of life for both the patient and family. Furthermore, stroke has a large economic impact on health-care costs and lost productivity estimated at roughly 65.5 billion dollars in direct and indirect cost in 2008.

This disease affects men and women of all ages. Although advancing age is the premier risk factor, it also can affect children. About 60% of strokes are in women, and more women die of stroke than from breast cancer. Stroke is particularly common among African Americans, especially at younger ages. There tend to be familial clusters (genetic or environmental).

Common causes of stroke include thrombosis, embolism, atherosclerosis, atrial fibrillation, valve disease, or heart attack. Modifiable behaviors that increase risk include tobacco use, alcohol abuse, and physical inactivity.

The presence of the following medical conditions are also risk factors:

- Hypertension
- Heart disease
- Atrial fibrillation
- High cholesterol
- Diabetes
- Carotid stenosis
- Prior stroke or TIA

The interventions of interest include both drug-based and device-based interventions. The drugs covered include antiplatelet agents, oral anticoagulants, parenteral anticoagulants, and thrombolytic agents. The devices covered include embolectomy devices used for the removal of blood clots from the cerebral circulation and devices used to prevent DVT formation in patients hospitalized for stroke.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke in whom treatment can be initiated within 3 h of symptom onset	Recommend IV r-tPA over no IV r-tPA	1A
Patients with acute ischemic stroke in whom treatment can be initiated within 4.5 but not within 3 h of symptom onset	Suggest IV r-tPA over no IV r-tPA	2C
Patients with acute ischemic stroke in whom treatment cannot be initiated within 4.5 h of symptom onset	Recommend against IV r-tPA	1B

Intraarterial Thrombolysis in Patients With Acute Ischemic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV r-tPA	Suggest intraarterial (IA) r-tPA initiated within 6 h of symptom onset over no IA r-tPA	2C
Patients with acute ischemic stroke	Suggest IV r-tPA over the combination IV/IA r-tPA	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.

Mechanical Thrombectomy in Patients With Acute Ischemic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke	Suggest against the use of mechanical thrombectomy	2C

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

Aspirin in Patients With Acute Ischemic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke or transient ischemic attack (TIA)	Recommend early (within 48 h) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy	1A

Anticoagulation in Patients With Acute Ischemic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke or TIA	Recommend early (within 48 h) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation	1A

VTE Prevention in Patients With Ischemic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute ischemic stroke and restricted mobility	Suggest prophylactic-dose SC UFH or LMWH or intermittent pneumatic compression devices over no prophylaxis	2B
	Suggest prophylactic-dose LMWH over prophylactic-dose UFH	2B
	Suggest against elastic compression stockings	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.

VTE Prevention in Patients With Hemorrhagic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute primary intracerebral hemorrhage and restricted mobility	Suggest prophylactic-dose SC heparin (UFH or LMWH) started between days 2 and 4 or intermittent pneumatic compression devices over no prophylaxis	2C
	Suggest prophylactic-dose LMWH over prophylactic-dose UFH	2B
Patients with primary intracerebral hemorrhage and restricted mobility	Suggest against elastic compression stockings	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.

Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a history of noncardioembolic ischemic stroke or TIA	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	1A
	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 oral anticoagulants	1B
	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 combination of clopidogrel plus aspirin	1B
	Suggest 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 triflusal	2B
Of the recommended antiplatelet regimens	Suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin	2B
	Suggest clopidogrel or aspirin/extended-release dipyridamole over cilostazol	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.

Antithrombotic Therapy for the Secondary Prevention of Cardioembolic Stroke

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a history of ischemic stroke or TIA and AF including paroxysmal AF	Recommend oral anticoagulation over no antithrombotic therapy	1A
	Recommend oral anticoagulation over aspirin	1B
	Recommend oral anticoagulation over combination therapy with aspirin and clopidogrel	1B
	Suggest oral anticoagulation with dabigatran, 150 mg bid, over adjusted-dose VKA therapy therapy (target range, 2.0-3.0)	2B

Patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, who are unsuitable or choose not to take an oral anticoagulant (reasons other than concerns about major bleeding)	Recommend combination therapy with aspirin and clopidogrel over aspirin	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).

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with a history of a symptomatic primary ICH	Suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke	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).

Anticoagulation for Patients With Symptomatic Cerebral Venous Sinus Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with cerebral venous sinus thrombosis	Suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases	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 CHADS2 score > 4 points).

By employing evidence-based antithrombotic strategies, the following goals of therapy can be achieved:

- Prevent myocardial infarction (MI)
- Prevent cardiovascular death
- Prevent cardioembolic events in patients with dilated cardiomyopathy

We consider the desirable and undesirable consequences of antithrombotic treatment in the follow- ing populations and patient groups: (1) persons without established coronary artery disease (CAD); (2) patients with established CAD (established CAD is defined throughout as patients 1-year post ACS, with prior revascularization, coronary stenoses 50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing); including those post- ACS and post-coronary artery bypass graft (CABG) surgery; (3) patients with recent or remote percutaneous coronary intervention (PCI) with or without stents (bare-metal stents [BMS] or drug-eluting stents [DES]); and (4) patients with systolic left ventricular (LV) dysfunction (ischemic and nonischemic).

Primary Prevention of Cardiovascular Disease

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Persons aged 50 years or older without symptomatic cardiovascular disease	Suggest low-dose aspirin, 75 to 100 mg daily, over no aspirin therapy	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.

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
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 of cardiac ischemia on diagnostic testing (including patients after the first year post-ACS and/or with prior coronary artery bypass graft [CABG] surgery)	Recommend long-term single antiplatelet therapy with aspirin, 75 to 100 mg daily, or clopidogrel, 75 mg daily, over no antiplatelet therapy	1A
	Suggest single over dual antiplatelet therapy with aspirin plus clopidogrel	2B

Choice of Antithrombotic Therapy Following ACS

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients the first year after an ACS who have not undergone percutaneous coronary intervention (PCI)	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	1B
	Suggest ticagrelor, 90 mg twice daily, plus low-dose aspirin over clopidogrel, 75 mg twice daily, plus low-dose aspirin	2B

Patients the first year after an ACS who have undergone PCI with stent placement	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)	1B

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

Patients the first year after an ACS who have undergone PCI with stent placement	Suggest ticagrelor, 90 mg twice daily, plus low-dose aspirin; over clopidogrel, 75 mg daily, plus low-dose aspirin	2B
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	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	1B

Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations. After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations.

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	Suggest triple therapy (warfarin [INR 2.0-3.0], low-dose aspirin, clopidogrel, 75 mg daily) for 1 month over dual antiplatelet therapy	2C
	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	2C

Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations. After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations.

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	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	2C

Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations. After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations.

Antithrombotic Therapy Following Elective PCI

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients who have undergone elective PCI with placement of BMS	For the first month, recommend dual antiplatelet therapy with aspirin, 75 to 325 mg daily, and clopidogrel, 75 mg daily, over single antiplatelet therapy	1A
	For the subsequent 11 months, suggest dual antiplatelet therapy with combination of low-dose aspirin, 75 to 100 mg daily, and clopidogrel, 75 mg daily, over single antiplatelet therapy	2C
	After 12 months, recommend single antiplatelet therapy over continuation of dual antiplatelet therapy	1B
Patients who have undergone elective PCI with placement of DES	For the first 3 to 6 months, recommend dual antiplatelet therapy with aspirin, 75 to 325 mg daily; and clopidogrel, 75 mg daily, over single antiplatelet therapy	1A
Remarks: Absolute minimum duration will vary based on stent type (in general, 3 months for -limus stents and 6 months for -taxel stents).		
Patients who have undergone elective PCI with placement of DES	After 3 to 6 months, 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	2C
	After 12 months, recommend single antiplatelet therapy over continuation of dual antiplatelet therapy	1B
Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations.		
Patients who have undergone elective BMS or DES stent placement	Recommend using low-dose aspirin, 75 to 100 mg daily, and clopidogrel, 75 mg daily, alone rather than cilostazol in addition to these drugs	1B
	Recommend 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	1B
	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	2C

Patients with CAD undergoing elective PCI but no stent placement	Suggest for the first month dual antiplatelet therapy with aspirin, 75 to 325 mg daily, and clopidogrel, 75 mg daily, over single antiplatelet therapy	2C

Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations.

Antithrombotic Therapy in Patients With Systolic LV Dysfunction

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with systolic LV dysfunction without established CAD and no LV thrombus	Suggest not to use antiplatelet therapy or warfarin	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.

Patients with systolic LV dysfunction without established CAD with identified acute LV thrombus (eg, Takotsubo cardiomyopathy)	Suggest moderate-intensity warfarin (INR 2.0-3.0) for at least 3 months	2C

For patients with systolic LV dysfunction and established CAD, recommendations are as per the established CAD recommendations.

ANTITHROMBOTIC THERAPY IN PERIPHERAL ARTERY DISEASE

The most common symptom of atherosclerotic peripheral arterial occlusive disease (PAD) is intermittent claudication. Among men over the age of 60 years, 2% to 3% have symptomatic PAD, as do 1% to 2% of women. The prevalence of PAD increases with age, and PAD is a significant cause of hospital admission. The diagnosis of PAD is an important predicator of overall cardiovascular and stroke mortality, which is increased twofold to threefold. Addressing key risk factors, such as smoking, dyslipidemia, and hypertension, will reduce the mortality and morbidity of cardiovascular ischemic events. At the same time, there is a growing body of evidence that treatment of these modifiable risk factors is often neglected in patients with PAD compared with cohorts that present with coronary artery disease (CAD) or stroke.

PAD is associated with a high prevalence of atherosclerosis in other vascular beds. The leading causes of morbidity and mortality in patients with PAD are myocardial infarction (MI) and stroke; therefore, as in patients with coronary artery disease (CAD), the primary benefit of antithrombotic therapy in this patient population is prevention of vascular events and mortality. The patient-important outcomes (ie, total mortality, nonfatal MI, nonfatal stroke, major nonfatal extracranial bleed) are the same outcomes considered for recommendations for CAD and stroke. However, we review the effects of antithrombotic therapy on outcomes specific to PAD (eg, claudication of the limbs, quality of life, or amputation).

Studies evaluating antithrombotic therapy immediately following peripheral bypass graft surgery or percutaneous endovascular procedures generally have used graft patency or reocclusion as the primary end point. These outcomes are surrogates for patient- important outcomes of quality of life and limb amputation, which are seldom reported.

We consider the desirable and undesirable consequences of antithrombotic therapy in the following populations or patient groups: (1) persons with asymptomatic PAD; (2) patients with symptomatic PAD (including those with claudication or critical [chronic] limb ischemia and rest pain or prior peripheral arterial revascularization); (3) patients with acute limb ischemia, threatened limb loss, and critical limb ischemia (CLI); (4) patients following peripheral arterial revascularization; and (5) persons with asymptomatic and symptomatic carotid stenosis.

Primary Prevention of Cardiovascular Events in Patients With Asymptomatic PAD

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Persons with asymptomatic peripheral arterial disease (PAD)	Suggest aspirin, 75 to 100 mg daily, over no aspirin therapy	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.

Secondary Prevention of Cardiovascular Events in Patients With Symptomatic PAD

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Secondary prevention in patients with symptomatic PAD	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 1A
	Suggest not to use dual antiplatelet therapy with aspirin plus clopidogrel	2B
	Recommend not to use an antiplatelet agent with moderate-intensity warfarin	1B

Antithrombotic Therapy for the Management of Patients With Claudication

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with intermittent claudication refractory to exercise therapy (and smoking cessation)	Suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin, 75-100 mg daily, or clopidogrel, 75 mg daily)	2C
	Suggest against the use of pentoxifylline, heparinoids, or prostanoids	2C

Patients With Critical Limb Ischemia

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention	Suggest the use of prostanoids in addition to previously recommended antithrombotic therapies (aspirin, 75-100 mg daily, or clopidogrel, 75 mg daily)	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.

Acute Limb Ischemia

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with acute limb ischemia due to arterial emboli or thrombosis	Suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation	2C
	Suggest reperfusion therapy (surgery or IA thrombolysis) over no reperfusion therapy	2C
	Recommend surgery over IA thrombolysis	1B
Patients undergoing IA thrombolysis	Suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase	2C

Endovascular Revascularization in Patients With Symptomatic PAD

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting	Recommend long-term aspirin (75-100 mg/day) or clopidogrel (75 mg/day)	1A
Patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting	Suggest single rather than dual antiplatelet therapy	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.

Antithrombotic Therapy Following Peripheral Artery Bypass Graft Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients following Peripheral Artery Bypass Graft Surgery	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 1A
	Recommend single antiplatelet therapy over antiplatelet therapy and warfarin	1B
Patients undergoing below-knee bypass graft surgery with prosthetic grafts	Suggest clopidogrel, 75 mg/d, plus aspirin (75-100 mg/d) over aspirin alone for 1 year	2C
All other patients	Suggest single over dual antiplatelet therapy	2B

Patients With Carotid Artery Stenosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with asymptomatic carotid stenosis	Suggest aspirin, 75 to 100 mg daily, over no aspirin therapy	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

Patients with symptomatic carotid stenosis (including recent carotid endarterectomy)	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	1A
	Suggest either clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) over aspirin (75-100 mg)	2B

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of venous thromboembolism (VTE), for the prevention and treatment of systemic embolism in patients with mechanical heart valves and, in combination with aspirin, for the prevention of recurrent pregnancy loss in women with antiphospholipid antibodies (APLAs).

We consider the desirable and undesirable fetal and maternal consequences of antithrombotic therapy, as well as the associated burden of treatment, in the following populations: (1) breastfeeding women, (2) women utilizing assisted reproductive technology, (3) women undergoing cesarean section, (4) pregnant women with newly diagnosed VTE, (5) pregnant women with prior VTE, (6) pregnant women with asymptomatic thrombophilia, (7) pregnant women with a history of pregnancy complications (including pregnancy loss, pre-eclampsia, fetal growth restriction, and placental abruption), and (8) pregnant women with mechanical heart valves.

There is a paucity of high quality studies addressing risk the risks and benefits of antithrombotic therapy during pregnancy. Most recommendations, therefore, are based on low to moderate quality evidence and mirror our limited confidence in relative effect estimates from studies of antithrombotic treatment during pregnancy. In making recommendations; we have placed the burden of proof with those who would claim a benefit of treatment. Therefore, when there is uncertain benefit and a probability of important harm associated with therapy, we generally recommend against intervention. Recommendations in this chapter also reflect our belief that although average women considering antithrombotic therapy will also want to avoid medicalizing their pregnancy, they will put an extremely high value on avoiding fetal risk. For women who do not share these values, some of the recommendations in this chapter may not apply. For most recommendations, optimal decision-making will require that physicians educate patients about their treatment options, including their relative effectiveness, the consequences for both mother and baby, the method of administration and monitoring, the likely side effects, and the uncertainty associated with the estimates of all these effects. Once educated, women can participate in the selection of the treatment regimen that best matches their preferences and values.

When describing the various regimens of unfractionated heparin (UFH) and LMWH, the following short-forms apply:

- Adjusted-dose UFH - UFH subcutaneously every 12 hours in doses adjusted to target a mid-interval activated partial thromboplastin time (aPTT) into the therapeutic range;
- Prophylactic LMWH – e.g., dalteparin 5000 units subcutaneously every 24 hours, tinzaparin 4500 units subcutaneously every 24 hours, nadroparin 2850 units subcutaneously every 24 hours or enoxaparin 40 mg subcutaneously every 24 hours (although at extremes of body weight modification of dose may be required);
- Intermediate-dose LMWH - e.g., dalteparin 5000 units subcutaneously every 12 hours or enoxaparin 40 mg subcutaneously every 12 hours; and
- Adjusted-dose LMWH - weight-adjusted or full treatment doses of LMWH, given once or twice daily (e.g., dalteparin 200 units/kg or tinzaparin 175 units/kg once daily or dalteparin 100 units/kg every 12 hours or enoxaparin 1mg/kg every 12 hours).

Post-partum anticoagulation refers to vitamin K antagonists for six weeks with a target INR of 2.0 to 3.0, with initial UFH or LMWH overlap until the INR is ≥ 2.0 or prophylactic- or intermediate-dose LMWH for six weeks. The term "clinical vigilance" refers to patient and physician alertness to the signs and symptoms of VTE and awareness of the need for timely and appropriate objective investigation of women with symptoms suspicious of DVT or PE. A family history of VTE refers to DVT or PE in a first degree relative.

Maternal Consequences of Antithrombotic Therapy Use During Pregnancy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant patients	Recommend LMWH for the prevention and treatment of VTE, instead of UFH	1B

Fetal Consequence of Antithrombotic Therapy Use in Pregnant Women

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Women receiving anticoagulation for the treatment of VTE who become pregnant	Recommend LMWH over VKAs during the first trimester	1A
	In the second and third trimesters	1B
	During late pregnancy when delivery is imminent	1A
Women requiring long-term VKAs who are attempting pregnancy and are candidates LMWH substitution	Suggest performing frequent pregnancy tests and substituting LMWH for VKAs when pregnancy is achieved rather than switching to LMWH while attempting pregnancy	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.

Pregnant women	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	2C
	Recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors	1C

Use of Antithrombotic Therapy in Nursing Women

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed	Recommend continuing the use of warfarin, acenocoumarol, or UFH	1A
Lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed	Recommend continuing the use of LMWH, danaparoid, or r-hirudin	1B

Breast-feeding women	Suggest alternative anticoagulants rather than fondaparinux	2C
	Recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban)	1C
Lactating women using low-dose aspirin for vascular indications who wish to breast-feed	Suggest continuing this medication	2C

VTE in Patients Using Assisted Reproductive Technology

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Women undergoing assisted reproduction	Recommend against the use of routine thrombosis prophylaxis	1B
Women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome	Suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis	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.

VTE Following Cesarean Section

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Women undergoing cesarean section without additional thrombosis risk factors	Recommend against the use of thrombosis prophylaxis other than early mobilization	1B
Women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors	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	2B

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

Women undergoing cesarean section who are considered to be at very high risk VTE and who have multiple additional risk factors for thromboembolism that persist the puerperium	Suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone	2C
Selected high-risk patients for whom significant risk factors persist following delivery	Suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital	2C
Women undergoing cesarean section without additional thrombosis risk factors	Recommend against the use of thrombosis prophylaxis other than early mobilization	1B

Treatment of Patients With Proven Acute VTE During Pregnancy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant women with acute VTE	Recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH	1B
	Recommend LMWH over VKA treatment antenatally	1A
	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	2C
Pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned	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	1B

Prevention of Recurrent VTE in Pregnant Women

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
All pregnant women with prior VTE	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	2B
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)	Suggest clinical vigilance antepartum rather than antepartum prophylaxis	2C
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)	Suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care	2C

Pregnant women receiving long-term VKAs	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	2C

Prevention of VTE in Pregnant Women With Thrombophilia and No Prior VTE

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant women with no prior history of VTE who are known to be homozygous factor V Leiden or the prothrombin 20210A mutation and have a positive family history of VTE	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	2B
Pregnant women with all other thrombophilias and no prior VTE who have a positive family history of VTE	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	2C
Pregnant women with no prior history of VTE who are known to be homozygous factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history VTE	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	2B
Pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history VTE	Suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis	2C

Prevention of Pregnancy Complications in Women With Thrombophilia

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation)	Recommend screening for antiphospolipid antibodies (APLAs)	1B
Women with a history of pregnancy complications	Suggest not to screen for inherited thrombophilia	2C
Women who fulfill the laboratory criteria of APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses	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	1B
Women with inherited thrombophilia and a history of pregnancy complications	Suggest not to use antithrombotic prophylaxis	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Women considered at risk preeclampsia	Recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment	1B
Women with two or more miscarriages but without APLA or thrombophilia	Recommend against antithrombotic prophylaxis	1B

Prevention of Thromboembolism in Pregnant Women With Mechanical Heart Valves

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pregnant women with mechanical heart valves	Recommend adjusted-dose bid LMWH throughout pregnancy be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous-injection, over no anticoagulation at all	1A
	Recommend adjusted-dose UFH throughout pregnancy be 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, over no anticoagulation at all	1A
	Recommend UFH or LMWH (as above) until the 13th week, with substitution by VKAs until close to delivery when UFH or LMWH is resumed, over no anticoagulation at all	1A

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.

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)	Suggest VKAs throughout pregnancy with replacement by UFH or LMWH close to delivery rather than one of the regimens above	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.

Pregnant women with prosthetic valves at high risk of thromboembolism	Suggest the addition of low-dose aspirin, 75 to 100 mg/d	2C

ANTITHROMBOTIC THERAPY IN NEONATES AND CHILDREN

Thromboembolic disease in neonates and children is increasing in frequency as survival for primary medical and surgical problems in children increases. The following are basic differences that must be considered when using antithrombotic therapy in neonates or children compared with adults:

- Epidemiology of thrombosis is different.
- Coagulation system is different.
- Antithrombotic agents differ in their weight-adjusted dose, impact on monitoring tests, risk: benefit ratio.
- Extrapolation of adult-based guidelines or treatment protocols is likely suboptimal in children.
- Antithrombotic therapy in neonates and children is ideally managed by a pediatric hematologist experienced in the field or by an experienced adult hematologist in conjunction with a neonatologist or pediatrician.
- The evidence base for most of the recommendations in this section remains poor, and further research is encouraged to improve antithrombotic therapy in neonates and children.

Some statements appear in which the evidence is based on generalization of evidence from only remotely similar pediatric and adult clinical situations, combined with the experience of expert authors of these guidelines and the experience of other carefully selected experts in the topic areas. Such statements are intended to provide guidance to physicians in areas where there is minimal direct evidence to guide clinical practice decisions and care management. No weak recommendations should be used for the development of performance measures.

In managing children with antithrombotic therapy, as with any therapy, the values and preferences of the patient and family are crucial to consider in the treatment algorithms. Preliminary studies suggest that these values and preferences can vary widely among families, perhaps related to culture and religion, but certainly reflect the variation in patient and parental personal views and experiences.

Throughout this article, the term "pediatric patients" refers to all neonates and children (birth-18 years). "Neonates" refers to infants from birth to 28 days corrected for gestational age. "Children" refers to patients aged 28 days to 18 years. The age at which adolescents should be considered adults from the perspective of treatment guidelines remains controversial. Young adults (18-25 years) are sparsely represented in most adult data about management of thromboembolism. In other areas of medicine, this demographic is being recognized as a separate entity, which requires specific study. In addition to chronologic age, clinicians need to consider factors such as physical development, stage of puberty, and emotional and intellectual development. Adolescents are transitioned to adult services after they leave school or between 16 and 21 years of age, depending on their local jurisdiction. In addition, there is considerable variation based on individual circumstances.

Where possible, because of the physiologic and pathophysiologic differences, as well as the markedly different implications of therapy, recommendations are presented for neonates and children separately. However, in cases where the available data do not adequately differentiate between the two age groups, the combined recommendations are presented.

General Management of Pediatric Patients with Thromboembolism

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pediatric patients with thromboembolism	Suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism	2C
	When this is not possible, suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist	2C

Heparin in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children being considered for heparin	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	2C
	When initiating UFH therapy, suggest UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks	2C
	Suggest avoiding long-term use of therapeutic UFH in children	2C

LMWH in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates in children being considered for LMWH	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	2C

VKAs in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates in children being considered for VKAs	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 suggest adherence to the adult recommendations outlined in the article by Whitlock et al in this supplement	2C
	Suggest that INR monitoring with point-of-care monitors be made available where resources make this possible	2C

Aspirin in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children being considered for aspirin	Suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day	2C

VTE in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with VTE	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	2C
	Suggest either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up	2C
	Suggest the start of anticoagulation if extension occurs in previously untreated patients	2C
	Suggest that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. Suggest a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations	2C
	Suggest a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed, if either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation	2C
	Suggest against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs	2C
	Suggest if thrombolysis is required, tissue plasminogen activator (tPA) is used rather than other lytic agents	2C

	Suggest plasminogen (fresh frozen plasma) administration prior to commencing therapy	2C

Renal Vein Thrombosis in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with unilateral renal venous thrombosis (RVT) the absence of renal impairment or extension into the inferior vena cava (IVC)	Suggest either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs suggest anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, suggest a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy	2C
Neonates with unilateral RVT that extends into the IVC	Suggest anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months	2C
Neonates with bilateral RVT with evidence of renal impairment	Suggest anticoagulation with UFH/LMWH or initial thrombolytic therapy with tPA followed by anticoagulation with UFH/LMWH	2C

CVAD Prophylaxis in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with CVADs	Recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis	1A
	Recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over intermittent local thrombolysis	2C
Neonates with blocked CVADs	Suggest local thrombolysis after appropriate clinical assessment	2C

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children having MBTS	Suggest intraoperative UFH therapy	2C
Neonates and children after MBTS surgery	Suggest either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs	2C

Therapy for Femoral Artery Thrombosis in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children with acute femoral artery thrombosis	Recommend therapeutic doses of IV UFH as initial therapy compared with aspirin or no therapy	1B
	Suggest therapeutic doses of IV UFH as initial therapy compared with LMWH	2C
	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	2C
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	Recommend thrombolysis	1C
Neonates and children with femoral artery thrombosis	Recommend surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent	1C

Prophylaxis for Peripheral Arterial Catheters in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children with peripheral arterial catheters in situ	Recommend UFH continuous infusion at 5 units/mL at 1 mL/h compared with normal saline	1A

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

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children with a peripheral arterial catheter-related thromboembolism	Suggest immediate removal of the catheter	2B
Neonates and children with a symptomatic peripheral arterial catheter-related thromboembolism	Suggest UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy	2C

Prophylaxis of Umbilical Arterial Catheters in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with umbilical arterial catheters (UACs)	Suggest UAC placement in a high rather than a low position	2B
	Suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1.0 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency	2A

Prophylaxis for Cardiac Catheterization in Neonates and Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates and children requiring cardiac catheterization via an artery	Recommend administration of IV UFH as thromboprophylaxis over no prophylaxis	1A
	Recommend administration of IV UFH as thromboprophylaxis over aspirin	1B
	Recommend the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus	1B
	For prolonged procedures, suggest further doses of UFH rather than no further therapy	2B

Cerebral Sinovenous Thrombosis in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage	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	2C
Neonates with CSVT with significant hemorrhage	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	2C

Arterial Ischemic Stroke in Neonates

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with a first arterial ischemic stroke (AIS) in the absence of a documented ongoing cardioembolic source	Suggest supportive care over anticoagulation or aspirin therapy	2C
Neonates with a first AIS and a documented cardioembolic source	Suggest anticoagulation with UFH or LMWH	2C
Neonates with recurrent AIS	Suggest anticoagulant or aspirin therapy	2C

Neonates With Purpura Fulminans

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Neonates with clinical presentations of homozygous protein C deficiency	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	1A
Neonates with homozygous protein C deficiency after initial stabilization	Recommend long-term treatment with VKA	1C
	Recommend LMWH	1C
	Recommend protein C replacement	1B
	Recommend liver transplantation compared with no therapy	1C

DVT and PE in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with first VTE (CVAD and non-CVAD related)	Recommend acute anticoagulant therapy with either UFH or LMWH	1B
	Recommend initial treatment with UFH or LMWH for at least 5 days	1B
	For ongoing therapy, recommend LMWH	
Patients whom clinicians will subsequently prescribe VKAs	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	1B
Children with idiopathic VTE	Suggest anticoagulant therapy for 6 to 12 months compared with no therapy	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.

Children with secondary VTE (ie VTE that has occurred association with a clinical risk factor) whom the risk factor has resolved	Suggest anticoagulant therapy be administered for 3 months as compared with no further therapy	2C
Children who have ongoing but potentially reversible risk factors such as active nephrotic syndrome or ongoing asparaginase therapy	Suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved	2C
Children with recurrent idiopathic VTE	Recommend indefinite treatment with VKAs	1A

Children with recurrent secondary VTEs with an existing reversible risk factor thrombosis	Suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy	2C
Children with a CVAD place who have a VTE	If a CVAD is no longer required or is nonfunctioning, recommend it be removed	1B
	Suggest at least 3 to 5 days of anticoagulation therapy prior to its removal rather than no anticoagulation prior to removal	2C
	If CVAD access is required and the CVAD is still functioning, suggest that the CVAD remain in situ and the patient given anticoagulants	2C
Children with a first CVAD-related VTE	Suggest initial management as for secondary VTE as previously described	
Children with CVAD in place who have a VTE and in whom the CVAD remains necessary	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	2C
	If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE	2C

Thrombolysis in Pediatric Patients With DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with VTE	Suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis	2C
	If thrombolysis is used the presence of physiologically low levels or pathologic deficiencies of plasminogen, suggest supplementation with plasminogen	2C
Children with VTE in whom thrombolysis is used	Suggest systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility	

Thrombectomy and IVC Filter Use in Pediatric Patients With DVT

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with life-threatening VTE	Suggest thrombectomy	2C
Children who have had a thrombectomy	Suggest anticoagulant therapy as per "DVT and PE in Children" section	2C
Children > 10 kg body weight with lower-extremity VTE and a contraindication to anticoagulation	Suggest placement of a retrievable IVC filter	2C
Children who receive a filter	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	2C
	Recommend appropriate anticoagulation for VTE as soon as the contraindication to anticoagulation is resolved	1C

DVT in Children With Cancer

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with cancer	Suggest that management of VTE follow the general recommendations for management of VTE in children	
	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)	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.

Children With DVT and Positive Inherited Thrombophilia Testing

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with VTE independent of the presence or absence of inherited thrombophilic risk factors	Suggest that the duration and intensity of anticoagulant therapy as per "DVT and PE in Children" section	

Children With VTE and Structurally Abnormal Venous Systems

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with first VTE secondary to structural venous abnormalities	Suggest anticoagulation as per other "spontaneous" VTE and consideration of subsequent percutaneous or surgical interventions, depending on patient factors and institutional experience	
Children with recurrent VTE secondary to structural venous abnormalities	Suggest indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed	2C

Children With Right Atrial Thrombosis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with right atrial thrombosis related to CVAD	Suggest removal of the CVAD with or without anticoagulation, depending on the individual risk factors, compared with leaving the CVAD in situ	2C
Children with large (> 2 cm) mobile right atrial thrombosis	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	2C

Children With CVADs

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with CVADs	Suggest flushing with normal saline or heparin or intermittent recombinant urokinase to maintain patency as compared with no therapy	2C
Children with blocked CVADs	Suggest tPA or recombinant urokinase to restore patency	2C
	If after at least 30 minutes following local thrombolytic instillation CVAD patency is not restored, suggest a second dose be administered	
	If the CVAD remains blocked following two doses of local thrombolytic agent, suggest radiologic imaging to rule out a CVAD-related thrombosis	2C
Children with short- or medium-term CVADs	Recommend against the use of routine systemic thromboprophylaxis	1B
Children receiving long-term home total parenteral nutrition	Suggest thromboprophylaxis with VKAs	2C

Children Undergoing Glenn Procedure or Bilateral Cavopulmonary Shunt

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children who have bilateral cavopulmonary shunt	Suggest postoperative UFH	2C

Children Undergoing Fontan Surgery

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children after Fontan surgery	Recommend aspirin or therapeutic UFH followed by VKAs over no therapy	1C

Insertion of Endovascular Stents in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children having endovascular stents inserted	Suggest administration of UFH perioperatively	2C

Pediatric Patients With Dilated Cardiomyopathy

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Pediatric patients with cardiomyopathy	Suggest VKAs no later than their activation on a cardiac transplant waiting list	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.

Children With Primary Pulmonary Hypertension

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with primary pulmonary hypertension	Suggest starting anticoagulation with VKAs at the same time as other medical therapy	2C

Children With Biologic and Mechanical Prosthetic Heart Valves

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with biologic or mechanical prosthetic heart valves	Recommend that clinicians follow the relevant recommendations from the adult population	

Children With Ventricular Assist Devices (VADs)

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with VADs	Suggest administration of UFH	2C
	Suggest starting UFH between 8 and 48 h following implantation	2C
	Suggest antiplatelet therapy (either aspirin or aspirin and dipyridamole) to commence within 72 h of VAD placement	2C
Children with VAD once clinically stable	Suggest switching from UFH to either LMWH or VKA (target INR 3.0 range, 2.5-3.5) until transplanted or weaned from VAD	2C

Primary Prophylaxis for Venous Access Related to Hemodialysis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients undergoing hemodialysis via an arteriovenous fistula	Suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy	2C
Patients undergoing hemodialysis via CVAD	Suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy	2C

Use of UFH or LMWH in Children During Hemodialysis

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children having hemodialysis	Suggest the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access	2C

Children With Kawasaki Disease

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with Kawasaki disease	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	1B
	Recommend IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms	1A
Children with moderate or giant coronary aneurysms following Kawasaki disease	Suggest that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis	2C
Children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis	Suggest thrombolysis or acute surgical intervention	2C

CSVT in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with CSVT without significant intracranial hemorrhage	Recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation	1B
Children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms	Suggest administration of a further 3 months of anticoagulation	2C
Children with CSVT with significant hemorrhage	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	2C
Children with CSVT and potentially recurrent risk factors (example nephrotic syndrome asparaginase therapy)	Suggest prophylactic anticoagulation at times of risk factor recurrence	2C
	Suggest thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy	2C

AIS in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with acute AIS with or without thrombophilia	Recommend UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded	1C
Children with acute AIS	Suggest, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy	2C
Children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs)	Suggest changing to clopidogrel or anticoagulant therapy with LMWH or VKA	2C
Children with AIS	Recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols	1C

Embolic Stroke in Children

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
AIS secondary to cardioembolic causes	Suggest anticoagulant therapy with LMWH or VKAs for at least 3 months	2C
AIS secondary to cardioembolic causes children with demonstrated right-to-left shunts (eg, PFO)	Suggest surgical closure of the shunt	2C

Cerebral Arterial Dissection Underlying AIS

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
AIS secondary to dissection	Suggest anticoagulant therapy with LMWH or VKAs for at least 6 weeks	2C

Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events

Children With Cerebral Vasculopathies

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with acute AIS secondary to non-Moyamoya vasculopathy	Recommend UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment	1C
Children with AIS secondary to non-Moyamoya vasculopathy	Suggest ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging	

Children With Moyamoya Disease

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Children with acute AIS secondary to Moyamoya	Suggest aspirin over no treatment as initial therapy	2C
Children with Moyamoya	Suggest they be referred to an appropriate center for consideration of revascularization	