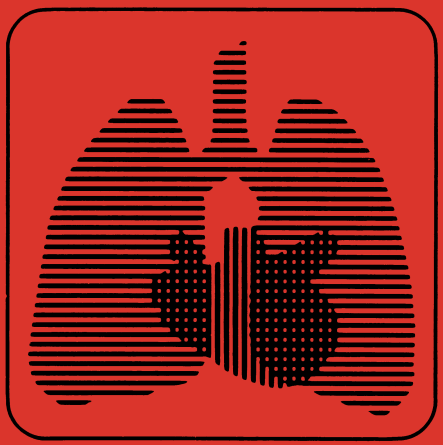
QUICK REFERENCE GUIDE
FOR CLINICIANS



SIXTH ACCP CONSENSUS CONFERENCE ON ANTITHROMBOTIC THERAPY

THE AMERICAN COLLEGE
OF CHEST PHYSICIANS

Division of Health and Science Policy
Committee on Health and Science Policy
Consensus Panel on Antithrombotic Therapy
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See the complete report of the Sixth ACCP Consensus Conference on Antithrombotic Therapy [CHEST Volume 119/1(Suppl.)/January 2001] for a detailed discussion of the items summarized in this Quick Reference Guide, and for reference lists.

AMERICAN COLLEGE OF CHEST PHYSICIANS

Sixth ACCP Consensus Conference on Antithrombotic Therapy

This document is the result of the Sixth ACCP Consensus Conference on Antithrombotic Therapy, held in February 2000.

All recommendations in this document are based upon careful review and grading of evidence in studies published in peer-reviewed journals.

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CONFERENCE OVERVIEW

Major research findings since the 1998 Conference:

- Low doses of aspirin (80 to 325 mg) are as effective as higher doses (500 to 1,000 mg) in cerebrovascular disease.
- The oral antiplatelet agent clopidogrel and the intravenous (IV) glycoprotein (GP) IIb-IIIa antagonists are confirmed as important antithrombotic agents.
- Oral GPIIb/IIIa antagonists have not been found effective in myocardial ischemia.
- Like aspirin and ticlopidine, aspirin and clopidogrel have a synergistic effect in patients with coronary stents.
- Low-molecular-weight heparin (LMWH) is an effective replacement for unfractionated heparin (UFH) in acute coronary ischemic syndromes and in venous thromboembolism (VTE).
- The lower limit of the therapeutic range for oral anticoagulants in atrial fibrillation (AF) is an international normalized ratio (INR) of 2.0.
- Combining low-intensity warfarin (either fixed low-dose, or INR < 2.0) with aspirin has not been proven beneficial in patients with AF.

GRADES OF RECOMMENDATION FOR ANTITHROMBOTIC AGENTS

Gordon Guyatt, MD, MSc; Holger J. Schünemann, MD, PhD; Deborah J. Cook, MD, MSc, FCCP; Roman Jaeschke, MD, MSc; Steven G. Pauker, MD; Heiner Bucher, MD, MPH

If experts are very certain that benefits do, or do not, outweigh risks, they make a strong recommendation — grade 1. If they are less certain of the balance between benefits and risks, they make a weaker grade 2 recommendation. The second part of the grade concerns the methodologic quality of the underlying evidence. Randomized trials with consistent results provide unbiased, grade A recommendations. Randomized trials with inconsistent results or with major methodologic weaknesses warrant grade B recommendations. Grade C recommendations come from observational studies and from generalization from randomized trials in one group of patients to a different group. When experts found the generalization from randomized trials secure, or the data from observational studies overwhelmingly compelling, they chose a C+ grade. Thus, the recommendations receive grades 1A, 1B, 1C, 1C+, 2A, 2B, or 2C.

Grade of Recommendation	Clarity of Risk/Benefit	Methodologic Strength of Supporting Evidence	Implications
1A	Risk/benefit clear	Randomized controlled trials (RCTs) without important limitations	Strong recommendation; can apply to most patients, in most circumstances, without reservation
1B	Risk/benefit clear	RCTs with important limitations (inconsistent results, methodologic flaws*)	Strong recommendation; likely to apply to most patients
1C+	Risk/benefit clear	No RCTs, but RCT results can be unequivocally extrapolated; or, overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1C	Risk/benefit clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence available
2A	Risk/benefit unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ, depending on circumstances or patients' or societal values
2B	Risk/benefit unclear	RCTs with important limitations (inconsistent results, methodologic flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Risk/benefit unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

* *Such situations include RCTs with lack of blinding, and subjective outcomes, in which the risk of bias in measurement of outcomes is high; and RCTs with large loss to follow-up.*

Since studies in categories B and C are flawed, most recommendations in these classes are grade 2. The following considerations influence whether the recommendation is grade 1 or 2: the magnitude and precision of the treatment effect, the patients' risk of the target event being prevented, the nature of the benefit, the magnitude of the risk associated with treatment, variability in patient preferences, variability in regional resource availability and health care delivery practices, and cost considerations. Inevitably, weighing these considerations involves subjective judgment.

CORONARY ARTERY DISEASE

Antithrombotic Agents in Coronary Artery Disease. John A. Cairns, MD; Pierre Théroux, MD; H. Daniel Lewis, Jr., MD; Michael Ezekowitz, MD; Thomas W. Meade, DM

Acute Myocardial Infarction

Anticoagulation

We recommend that all patients with acute myocardial infarction (AMI) be offered anticoagulant therapy (Table 1). Unless a specific contraindication exists, we recommend that all patients receive not less than low-dose heparin (7,500 IU SC q12h), or LMWH, until ambulation, to prevent venous thrombosis (**grade 1A**).

TABLE 1 – ANTICOAGULANT THERAPY FOR AMI

CLINICAL SITUATION	RECOMMENDATION
Patients who have received recombinant tissue-type plasminogen activator (rtPA), reteplase (rPA), or tenecteplase (TNK-PA)	Heparin: about 60 IU/kg IV bolus (maximum 4,000 IU) at initiation of rtPA infusion, or at first bolus of rPA or TNK-PA; initial maintenance 12 IU/kg/h (maximum 1,000 IU); activated partial thromboplastin time (APTT) 1.5 to 2 times control, maintained for 48 h (**grade 2A**)

continued

Table 1 — Continued

CLINICAL SITUATION	RECOMMENDATION
Patients who have received rtPA, rPA, or TNK-PA, and are at high risk for systemic embolism or VTE*	Maintain APTT at 1.5 to 2 times control beyond 48 h; continue the IV heparin regimen, or offer: • Subcutaneous (SC) heparin (initial dose about 17,500 IU q12h, APTT 1.5 to 2 times control) • SC LMWH (all **grade 2A**) • Conversion to warfarin therapy (goal INR 2.5; range, 2.0 to 3.0), for ≤ 3 mo (**grade 2A**); indefinitely, in patients with AF (**grade 1A**)
Patients who have received streptokinase (SK) or anisoylated plasminogen streptokinase activator complex (APSAC) and are at high risk for systemic embolism or VTE*	IV heparin; measure APTT when indication emerges, but not < 4 h after beginning SK or APSAC infusion; if APTT is > 2 times control, repeat measurement as appropriate Begin IV heparin infusion when APTT is < 2 times control, and maintain APTT at 1.5 to 2 times control while the risk for thromboembolism is considered high After 48 h, offer: • SC heparin (initial dose approximately 17,500 IU q12h, APTT 1.5 to 2 times control) • SC LMWH (all **grade 2A**) • Conversion to warfarin therapy (goal INR 2.5; range, 2.0 to 3.0) for ≤ 3 mo (**grade 2A**); indefinitely, in patients with AF (**grade 1A**)
Patients who have not received thrombolytic therapy and are at increased risk for systemic embolism or pulmonary embolism (PE)*	Heparin (about 75 IU/kg IV bolus, initial maintenance 1,000 to 1,200 IU/h IV; APTT 1.5 to 2 times control) (**grade 2A**) Follow with warfarin (goal INR 2.5; range, 2.0 to 3.0) for ≤ 3 mo (**grade 2A**); indefinitely, in patients with AF (**grade 1A**)

* *Anterior Q-wave infarction, severe left ventricular (LV) dysfunction, congestive heart failure (CHF), history of systemic embolism or PE, 2D-echo evidence of mural thrombosis, AF.*

Antiplatelet Therapy

Aspirin doses of 75 to 162.5 mg are effective in all indications and we recommend this dose range. Since low doses delay the onset of full antiplatelet activity, if a rapid response is required, *ie*, in AMI or stroke, clinicians should use a dose of 162.5 mg.

We recommend:

- All patients chew and swallow nonenteric-coated aspirin as soon as possible after the clinical impression of AMI has been formed, whether or not thrombolytic therapy is to be given. Daily aspirin therapy, by mouth, should be continued indefinitely (75 to 162.5 mg/d) (**grade 1A**).
- Patients who are to receive heparin be offered aspirin conjointly (**grade 2A**). If warfarin therapy is begun, aspirin therapy should be discontinued. After warfarin therapy is completed, aspirin therapy should be restarted and continued indefinitely. Aspirin therapy should not be offered with warfarin except in cases of very high risk for embolism or previous failure of either drug used alone (**grade 2C**).
- For long-term therapy, aspirin be offered if embolic risk is low, warfarin if it is high (**grade 2A**). We recommend warfarin for 1 to 3 months after anterior AMI, AMI with severe LV dysfunction, CHF, previous embolism, 2D-echocardiographic evidence of mural thrombosis, or AF (**grade 2A**) and indefinite warfarin therapy for patients with AF (goal INR 2.5; range, 2.0 to 3.0) (**grade 1A**).
- If aspirin is contraindicated, clopidogrel (75 mg/d) be given indefinitely (**grade 1A**). Warfarin (goal INR 2.5; range, 2.0 to 3.0) is an alternative, but involves increased complexity, risk, and cost (**grade 2A**).
- Clinicians offer low-dose aspirin (75 to 80 mg/d) with low-intensity warfarin (goal INR 1.5) to patients with recurrent ischemic episodes following AMI (**grade 2C**).
- Clinicians offer aspirin rather than sulfinpyrazone after AMI (**grade 1C**).

We do **not** recommend:

- Dipyridamole, alone (**grade 2C**) or with aspirin (**grade 2B**) after AMI.

Unstable Angina

We recommend:

- Patients with unstable angina receive nonenteric-coated aspirin (162.5 mg) to chew and swallow as soon as possible after the clinical impression of unstable angina has been formed. Daily aspirin therapy, by mouth, should be continued indefinitely (75 to 162.5 mg/d) (all **grade 1A**).
- Patients with aspirin allergy or intolerance be offered the following alternatives: clopidogrel (75 mg/d) (**grade 1C**), ticlopidine (250 mg bid) (**grade 1A**), triflusal (where available) (**grade 1A**), or warfarin for several months (goal INR 2.5) (**grade 2C**).

- Clinicians do **not** give sulfinpyrazone to patients with unstable angina (**grade 1C**).
- Patients with continuing ischemia, or other high-risk features, receive concomitant administration of IV tirofiban or eptifibatide, with aspirin and heparin, especially if levels of troponin T or I are elevated. The infusion should continue for 48 to 72 h, or until percutaneous intervention (PCI) (**grade 1A**).
- Patients who will undergo PCI in ≤ 24 h receive abciximab for 12 to 24 h (**grade 1A**).
- Patients hospitalized with unstable angina and treated with aspirin receive IV heparin (about 75 IU/kg IV bolus, initial maintenance 1,250 IU/h, APPT 1.5 to 2 times control); or LMWH (dalteparin [120 IU/kg SC q12h], enoxaparin [1 mg/kg SC bid], nadroparin [either 86 anti-Xa IU/kg bid for 4 to 8 d, or the same dose given IV, then SC bid for 14 d]). Administration should continue for ≥ 48 h, or until the unstable pain pattern resolves, which may require other therapy (**grade 1A**).
- Hirudin over heparin in patients with previous heparin-induced thrombocytopenia (HIT) (**grade 1C**).

Primary Prevention of Coronary Artery Disease (CAD)

We do **not** recommend:

- Routine use of aspirin (75 to 162.5 mg/d) in patients < 50 years of age, with no history of AMI, stroke, or transient ischemic attack (TIA) (**grade 2B**).

We recommend:

- Patients > 50 years of age, with at least one major risk factor for CAD (cigarette smoking, hypertension, diabetes mellitus, high cholesterol levels, parental history of infarction) be offered aspirin therapy, in the absence of contraindications (men, **grade 2A**; women, **grade 2C**).
- Men at high risk for cardiovascular events be offered low-intensity warfarin (goal INR 1.5) as an alternative to aspirin (**grade 2A**).
- Men at very high risk for cardiovascular events be offered low-dose aspirin (75 to 80 mg/d) with low-intensity warfarin (goal INR 1.5) as an alternative to either drug alone (**grade 2A**).
- Aggressive blood pressure (BP) control (goal diastolic pressure < 85 mm Hg) whenever antithrombotic therapy is prescribed for primary prevention (**grade 1C**).

Stable Angina and Chronic CAD

We recommend:

- Patients with stable angina (**grade 1A**) receive aspirin indefinitely.
- Patients with clinical or laboratory evidence of CAD (**grade 2C**) be offered aspirin indefinitely.

ISCHEMIC STROKE

Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Gregory W. Albers, MD; Pierre Amarenco, MD; J. Donald Easton, MD; Ralph L. Sacco, MD; Philip Teal, MD

Within 3 Hours of Symptom Onset: Tissue Plasminogen Activator (tPA)

We recommend:

- Patients receive tPA (0.9 mg/kg; maximum 90 mg; 10% as initial bolus, the remainder infused over 60 min) following strict adherence to eligibility criteria (Table 2) (**grade 1A**).
- Clinicians begin therapy as soon as possible (**grade 1C+**).

TABLE 2 – ELIGIBILITY CRITERIA FOR TPA THERAPY

Inclusion Criteria	Age ≥ 18 yr; clinical diagnosis of stroke, with clinically meaningful neurologic deficit; clearly defined onset time of < 180 min before treatment; baseline CT scan showing no evidence of intracranial hemorrhage
Exclusion Criteria*	Minor or rapidly improving symptoms or signs; history or CT-scan signs of intracranial hemorrhage; seizure at stroke onset; stroke or serious head injury < 3 mo; major surgery or serious trauma < 2 wk; GI or urinary tract hemorrhage < 3 wk; systolic blood pressure (SBP) > 185 mm Hg; diastolic blood pressure (DBP) > 110 mm Hg; blood glucose level < 50 or > 400 mg/dL; symptoms of subarachnoid hemorrhage; arterial puncture at a noncompressible site, or lumbar puncture < 1 wk; platelet count < 100,000/mm^3; heparin therapy < 48 h, associated with elevated APTT; clinical presentation suggesting post-myocardial infarct (MI) pericarditis; pregnancy or lactation; current use of oral anticoagulants (INR > 1.7)

* *Thrombolytic therapy should be withheld almost always in patients with evidence of major early signs of infarct (clear evidence of extensive early edema/mass effect) on pretreatment CT scan (**grade 1B**).*

Treatment should be supervised by physicians with expertise in stroke management and CT-scan interpretation. If the time of symptom onset is uncertain, or if symptoms have been present for > 3 h, tPA treatment is **not** recommended. Some experts recommend use of modern neuroimaging techniques in an attempt to identify an intracranial occlusion in a large artery before tPA administration. Treatment should not be unduly delayed to facilitate vascular imaging.

Adequate hospital facilities and personnel are required for administering thrombolytic therapy, monitoring, and managing complications. After tPA administration, BP should be closely monitored and kept below 180/105 mm Hg. Antithrombotic agents should be avoided for 24 h.

Within 3 to 6 Hours of Symptom Onset

We do **not** recommend:

- Clinicians use IV tPA in unselected patients (**grade 2B**).
- Clinicians use streptokinase, except in clinical trials (**grade 1A**).

We recommend:

- Intra-arterial thrombolytic therapy be offered to carefully selected patients with occlusion of the middle cerebral artery, verified by angiography, if the baseline CT scan shows no signs of major early infarction (**grade 2B**).

Patients Ineligible for Thrombolysis

We do **not** recommend:

- Clinicians use full-dose anticoagulation in unselected patients (**grade 2B**).

We recommend:

- Patients with ischemic stroke who are not receiving thrombolytic or anticoagulant therapy receive aspirin (160 to 325 mg/d) (**grade 1A**). Aspirin therapy should be started within 48 h of stroke onset, and may be given with low doses of SC heparin for prophylaxis of deep vein thrombosis (DVT).
- Patients with acute cardioembolic and large-artery ischemic stroke, and with progressing stroke thought to result from ongoing thromboembolism, be offered early anticoagulation (**grade 2B**).
- Early anticoagulation **not** be offered when potential contraindications to anticoagulation are present, such as other bleeding conditions, a large infarction, or uncontrolled hypertension (**grade 1C**). A brain-imaging study should be performed before early anticoagulation, to exclude hemorrhage and to estimate the size of the infarct.
- The following measures to reduce the risk for DVT and PE:

  a) Patients with restricted mobility: prophylactic use of low-dose SC heparin, LMWH, or danaparoid, in the absence of contraindications (**grade 1A**).

  b) Patients with an intracerebral hematoma: prophylactic use of low-dose SC heparin as early as the second day after onset of the hemorrhage (**grade 2C**).

  c) Patients with contraindications to anticoagulants: intermittent pneumatic compression (IPC) devices or elastic stockings (ES) (**grade 1C**).

Stroke Prevention

Noncardioembolic Cerebral Ischemic Events

We recommend:

- After noncardioembolic (atherothrombotic, lacunar, or cryptogenic) stroke, or TIA, patients receive an antiplatelet agent regularly. Aspirin (50 to 325 mg qd), the combination of aspirin and extended-release dipyridamole (25/200 mg bid), or clopidogrel (75 mg qd) are acceptable options for initial therapy (**grade 1A**). Aspirin combined with extended-release dipyridamole (25/200 mg bid) is more effective than aspirin alone (50 to 325 mg qd) (**grade 1A**) and may be more effective than clopidogrel (75 mg) (**grade 2C**).
- Clinicians offer clopidogrel rather than ticlopidine to patients allergic to aspirin (**grade 2C**).
- Clinicians do **not** treat with oral anticoagulants at an INR of 3.0 to 4.5, because the risk for brain hemorrhage outweighs any potential benefit from the use of oral anticoagulants to prevent noncardioembolic stroke (**grade 1A**).

Cardioembolic Cerebral Ischemic Events

We recommend:

- Patients with AF receive long-term oral anticoagulation therapy (goal INR 2.5; range, 2.0 to 3.0) for stroke prevention after a recent stroke or TIA (**grade 1A**).
- Patients with minor-risk cardiac conditions be offered antiplatelet agents (**grade 2C**). Oral anticoagulation is beneficial in preventing stroke recurrence in patients at risk for embolism related to selected high-risk cardiac conditions, *eg,* prosthetic heart valves, valvular heart disease, and CAD (see corresponding section in this reference guide).
- Aspirin therapy (81 to 325 mg/d) before and after carotid endarterectomy (**grade 1A**).

Cerebral Venous Sinus Thrombosis

We recommend:

- Clinicians use UFH (**grade 1A**) or LMWH (**grade 1C**) in acute cerebral venous sinus thrombosis, even in the presence of hemorrhagic infarction secondary to the thrombosis, followed by oral anticoagulation therapy for 3 to 6 months (goal INR 2.5; range, 2.0 to 3.0) (**grade 1C**).

SAPHENOUS VEIN OR INTERNAL MAMMARY ARTERY BYPASS GRAFTS

Antithrombotic Therapy in Patients with Saphenous Vein and Internal Mammary Artery Bypass Grafts. Paul D. Stein, MD, FCCP; James E. Dalen, MD, MPH, FCCP; Steven Goldman, MD; Pierre Théroux, MD

We recommend life-long aspirin therapy for all patients after saphenous vein or internal mammary artery bypass grafting performed for CAD (**grade 1A**).

Saphenous Vein Bypass Graft

We recommend:

- Patients receive aspirin (325 mg/d) 6 h after surgery (**grade 1A**), or, if delayed by bleeding, as soon as possible (**grade 1C+**).
- Clinicians continue aspirin therapy for 1 year, to reduce the frequency of graft closure (**grade 1A**).
- Patients allergic to aspirin be offered a loading dose of clopidogrel (300 mg) 6 h after surgery, followed by additional oral doses (50 to 100 mg/d) (**grade 2C**).
- Clinicians offer oral anticoagulants as sole therapy or with aspirin, if they are simultaneously indicated, *eg*, for heart valve replacement, after coronary artery bypass surgery (**grade 2C**).

Internal Mammary Artery Bypass Graft

We do **not** recommend aspirin therapy when grafting is performed for conditions **other than** CAD (**grade 2C**).

ATRIAL FIBRILLATION

Antithrombotic Therapy in Atrial Fibrillation. Gregory W. Albers, MD; James E. Dalen, MD, MPH, FCCP; Andreas Laupacis, MD; Warren J. Manning, MD; Palle Petersen, MD, DMSc; Daniel E. Singer, MD

We recommend:

- Patients at **high risk** for ischemic stroke (Table 3) receive adjusted-dose warfarin (goal INR 2.5; range, 2.0 to 3.0) rather than aspirin (**grade 1A**). (Specific recommendations for patients with AF and valvular heart disease or prosthetic heart valves are presented in other sections of this reference guide.)
- Patients with **> 1 moderate** risk factor be offered the same therapy as high-risk patients (**grade 2C**).
- Clinicians do **not** use aspirin with fixed low-dose warfarin therapy (**grade 1A**).

TABLE 3 – RECOMMENDATIONS FOR PATIENTS WITH AF CONSIDERED FOR LONG-TERM ORAL ANTICOAGULATION THERAPY

RISK FACTOR	LONG-TERM THERAPY
Any high-risk factor*	Warfarin† (**grade 1A**)
1 moderate-risk factor‡	Aspirin§ or warfarin† (**grade 1A**)
No high-risk or moderate-risk factor, and no clinical or echocardiographic evidence of cardiovascular disease	Aspirin§ (**grade 2C**)

** Previous TIA, systemic embolism, or stroke; history of hypertension; poor LV systolic function; age ≥ 75 years; rheumatic mitral valve disease; prosthetic heart valve.*

† Goal INR 2.5; range, 2.0 to 3.0.

‡ Age 65 to 75 years, diabetes mellitus, CAD with preserved LV systolic function.

§ 325 mg qd.

Cardioversion in Patients With Atrial Fibrillation or Atrial Flutter

We recommend:

- Oral anticoagulants (goal INR 2.5; range, 2.0 to 3.0) be offered 3 weeks before and ≥ 4 weeks after the procedure (**grade 1C+**). Alternatively, patients may be offered oral anticoagulant therapy, then undergo transesophageal echocardiography (TEE), followed without delay by cardioversion, if no thrombi are seen (**grade 1C**). Adjusted-dose warfarin therapy should be continued until normal sinus rhythm (NSR) has been maintained for ≥ 4 weeks.

- Patients with AF for < 48 hours be offered anticoagulation during the pericardioversion period (**grade 2C**).

We do **not** recommend:

- Patients without prior thromboembolism be offered antithrombotic therapy for cardioversion of supraventricular tachycardia (**grade 2C**).

Remark: Treatment of conditions that may precipitate AF (*ie*, thyrotoxicosis, pneumonia, CHF) should be completed before elective DC cardioversion.

PREVENTION OF VENOUS THROMBOEMBOLISM

Prevention of Venous Thromboembolism. William H. Geerts, MD, FCCP; John A. Heit, MD; G. Patrick Clagett, MD; Graham Frederick Pineo, MD; Clifford W. Colwell, Jr., MD; Frederick A. Anderson, Jr., PhD; H. Brownell Wheeler, MD

General recommendations:

Every hospital should develop a written policy or other formal strategy for preventing thromboembolic complications, especially for high-risk patients.

We do **not** recommend prophylactic use of aspirin as a sole prevention strategy, because the measures listed in the tables below are more efficacious (**grade 1A**).

We recommend anticoagulant prophylaxis or therapy should be used with **caution** in all cases involving either spinal puncture or placement of epidural catheters for regional anesthesia or analgesia (**grade 1C+**).

TABLE 4 – GENERAL SURGERY

RISK GROUP	RECOMMENDED PROPHYLAXIS
Low risk (Minor procedure in patients < 40 yr, with no additional risk factors)	Early ambulation (**grade 1C**)
Moderate risk (Minor procedure, with additional risk factors for thrombosis; non-major surgery in patients 40 to 60 yr, with no additional risk factors; major surgery in patients < 40 yr, with no additional risk factors)	Low-dose unfractionated heparin (LDUH), LMWH, ES, or IPC device (**grade 1A**)*

continued

Table 4 — Continued

RISK GROUP	RECOMMENDED PROPHYLAXIS
Higher risk (Non-major surgery in patients > 60 yr, or with additional risk factors; major surgery in patients > 40 yr, or with additional risk factors)	LDUH, LMWH, or IPC device (**grade 1A**)*
Higher risk, with greater-than-usual risk for bleeding	Mechanical prophylaxis with ES or IPC device, at least initially (**grade 1C**)
Very high risk (Multiple risk factors)	Effective pharmacologic method (LDUH or LMWH), combined with mechanical method (ES or IPC device) (**grade 1C**)

* *Compared with no prophylaxis.*

TABLE 5 – GYNECOLOGIC SURGERY

PROCEDURE	RECOMMENDED PROPHYLAXIS
Brief procedure for benign disease	Early mobilization (**grade 1C**)
Major gynecologic surgery for benign disease; no additional risk factors	LDUH bid (**grade 1A**); alternatively, LMWH or IPC device started just before surgery and continued at least several days postoperatively (**grade 1C+**)
Extensive surgery for malignancy	Routine prophylaxis: LDUH tid (**grade 1A**) For possible additional protection: LDUH plus mechanical prophylaxis with ES or IPC device; or higher doses of LMWH (**grade 1C**)

TABLE 6 – UROLOGIC SURGERY

RISK GROUP	RECOMMENDED PROPHYLAXIS
Transurethral surgery, or other low-risk procedure	Prompt mobilization (**grade 1C**)
Major open urologic procedure	Routine prophylaxis: LDUH, ES, IPC device, or LMWH (**grade 1B**)*
Highest-risk patients	ES with or without IPC device added to LDUH or LMWH (**grade 1C**)

* *Compared with no prophylaxis.*

TABLE 7 – MAJOR ORTHOPEDIC SURGERY

PROCEDURE	RECOMMENDED PROPHYLAXIS*
Elective total hip replacement	LMWH therapy (started 12 h before surgery, or 12 to 24 h after surgery; or half the usual high-risk dose 4 to 6 h after surgery, followed by the usual high-risk dose the following day); or adjusted-dose warfarin therapy (goal INR 2.5; range, 2.0 to 3.0), started preoperatively or immediately postoperatively (all **grade 1A**) Alternative, more complex option: adjusted-dose heparin therapy, started preoperatively (**grade 2A**) Adjuvant prophylaxis with ES or IPC device may improve efficacy (**grade 2C**) (We do **not** recommend sole therapy with LDUH, aspirin, dextran, or IPC device)
Elective total knee replacement	LMWH or adjusted-dose warfarin (goal INR 2.5; range, 2.0 to 3.0) (**grade 1A**) Alternative: optimal use of IPC device (**grade 1B**) We do **not** recommended LDUH (**grade 1C+**)
Hip-fracture surgery	LMWH or adjusted-dose warfarin (goal INR 2.5; range, 2.0 to 3.0) (**grade 1B**) Possible alternative: LDUH (**grade 2B**) We do **not** recommend sole therapy with aspirin (**grade 2A**)

** Prophylactic anticoagulant therapy is recommended for at least 7 to 10 d after surgery (**grade 1A**).*

In addition:

- We recommend outpatient prophylaxis with LMWH be offered beyond 7 to 10 d after major orthopedic surgery, at least for high-risk patients (**grade 2A**).
- We do **not** recommend routine duplex ultrasonography screening at hospital discharge or during outpatient follow-up in asymptomatic patients having major orthopedic surgery who have received one of the above prophylaxis regimens (**grade 1A**).

TABLE 8 – NEUROSURGERY, TRAUMA, AND ACUTE SPINAL CORD INJURY

RISK GROUP	RECOMMENDED PROPHYLAXIS
Intracranial neurosurgery	IPC device, with or without ES (**grade 1A**) LDUH or postoperative LMWH may be acceptable alternatives (**grade 2A**) High-risk patients: ES or IPC device with LDUH or postoperative LMWH may be more effective than either prophylactic modality alone (**grade 1B**)
Trauma, with identifiable risk factor for thromboembolism	Prophylaxis with LMWH, as soon as considered safe (**grade 1A**); if delayed, or contraindicated because of bleeding concerns: initial use of ES, or IPC device, or both (**grade 1C**) If prophylaxis is suboptimal, offer screening of high-risk patients with duplex ultrasound (**grade 1C**) If proximal DVT is demonstrated and anticoagulation is contraindicated, we recommend inferior vena cava (IVC) filter insertion (**grade 1C+**), but we do **not** recommend IVC filter insertion as primary prophylaxis (**grade 1C**)
Acute spinal cord injury	Prophylaxis with LMWH (**grade 1B**) We do **not** recommend LDUH, ES, and IPC as sole prophylaxis (**grade 1C**) ES and IPC may be offered in combination with LMWH or LDUH, or if early use of anticoagulants is contraindicated (**grade 2B**) In the rehabilitation phase, we recommend continued LMWH therapy, or full-dose oral anticoagulation (both **grade 1C**)

TABLE 9 – MEDICAL CONDITIONS

CONDITION	RECOMMENDED PROPHYLAXIS
Acute myocardial infarction	Most patients: prophylactic or therapeutic anticoagulant therapy with SC LDUH or IV heparin (**grade 1A**)
Ischemic stroke, with impaired mobility	Routine use of LDUH, LMWH, or danaparoid (**grade 1A**) If anticoagulant prophylaxis is contraindicated: ES or IPC device (**grade 1C+**)
General medical patients with risk factors for VTE (*eg*, cancer, bed rest, heart failure, severe lung disease)	LDUH or LMWH (**grade 1A**)

TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE

Antithrombotic Therapy for Venous Thromboembolic Disease. Thomas M. Hyers, MD, FCCP; Giancarlo Agnelli, MD; Russell D. Hull, MBBS, FCCP; Timothy A. Morris, MD; Michel M. Samama, MD; Victor F. Tapson, MD, FCCP; John G. Weg, MD, FCCP

We recommend:

- Patients in the acute stage of DVT or PE receive LMWH, IV UFH, or adjusted-dose SC heparin (**grade 1A**).
- Clinicians offer LMWH (Table 10) rather than UFH (**grade 2B**). If clinicians use UFH (Table 11), we recommend a dosage that prolongs the APTT to a range that corresponds to a plasma heparin level of 0.2 to 0.4 IU/mL by the plasma protamine paracoagulation test, or 0.3 to 0.6 IU/mL by an amidolytic anti-Xa assay (**grade 1C+**).

TABLE 10 – ALGORITHM FOR ANTICOAGULATION: LMWH

DISEASE	ALGORITHM
Suspected VTE	Obtain baseline APTT, PT, complete blood cell (CBC) count
	Check for contraindication to heparin therapy
	Order imaging study
	Consider giving UFH, 5,000 IU IV; or LMWH
Confirmed VTE	Give LMWH (dalteparin,* enoxaparin,† nadroparin,‡ or tinzaparin§)
	Start warfarin therapy on day 1 at 5 mg; adjust subsequent daily dose according to the INR
	Check platelet count between days 3 and 5
	Stop LMWH therapy after ≥ 4 to 5 d of combined therapy, when INR is > 2.0
	Anticoagulate with warfarin for ≥ 3 mo (goal INR 2.5; range, 2.0 to 3.0)

* *Dalteparin calcium, 200 anti-Xa IU/kg SC daily; single dose should not exceed 8,000 IU (approved in Canada).*

† *Enoxaparin sodium, 1 mg/kg SC q12h; or 1.5 mg/kg SC daily; single daily dose should not exceed 180 mg (approved in the United States and Canada).*

‡ *Nadroparin calcium, 86 anti-Xa IU/kg SC bid for 10 d (approved in Canada).*

§ *Tinzaparin sodium, 175 anti-Xa IU/kg SC daily (approved in the United States and Canada).*

With LMWH regimens, minimal requirements for outpatient therapy include:

- Stable proximal DVT or PE
- Normal vital signs
- Low risk for bleeding
- Absence of severe renal insufficiency
- Availability of a practical system for administering LMWH and warfarin, with appropriate monitoring
- Availability of a practical system for surveillance and treatment of recurrent VTE and bleeding complications

TABLE 11 – ALGORITHM FOR ANTICOAGULATION: UFH*

DISEASE	ALGORITHM
Suspected VTE	Obtain baseline APTT, prothrombin time (PT), CBC count
	Check for contraindication to heparin therapy
	Order imaging study
	Consider giving heparin, 5,000 IU IV
Confirmed VTE	Rebolus with heparin, 80 IU/kg IV; start maintenance infusion at 18 IU/kg
	Check APTT at 6 h, to maintain a range corresponding to a therapeutic heparin level
	Check platelet count between days 3 and 5
	Start warfarin therapy on day 1 at 5 mg; adjust subsequent daily dose according to the INR
	Stop heparin therapy after ≥ 4 to 5 d of combined therapy, when INR is > 2.0
	Anticoagulate with warfarin for ≥ 3 mo (goal INR 2.5; range, 2.0 to 3.0)

** For SC treatment with UFH, give 250 IU/kg q12h to obtain an APPT within therapeutic range at 6 to 8 h.*

Table 12 lists widely used guidelines for dosing and adjusting therapy with IV heparin.

TABLE 12 – BODY WEIGHT-BASED DOSING OF IV HEPARIN*

APTT, s†	DOSE CHANGE, IU/KG/H	ADDITIONAL ACTION	NEXT APTT, H
< 35 (1.2 x mean normal)	+4	Rebolus with 80 IU/kg	6
35 to 45 (1.2 to 1.5 x mean normal)	+2	Rebolus with 40 IU/kg	6
46 to 70‡ (1.5 to 2.3 x mean normal)	0	--	6§
71 to 90 (2.3 to 3.0 x mean normal)	-2	--	6
> 90 (> 3 x mean normal)	-3	Stop infusion 1 h	6

** Initial dosing: loading, 80 IU/kg; maintenance infusion: 18 IU/kg/h (APTT in 6 h).*

† The therapeutic range in seconds should correspond to a plasma heparin level of 0.2 to 0.4 IU/mL by protamine sulfate, or 0.3 to 0.6 IU/mL by amidolytic assay; when APTT is checked at 6 h or longer, steady-state kinetics can be assumed.

‡ Heparin, 25,000 IU in 250 µL D5W; infuse at rate dictated by body weight through an infusion apparatus calibrated for low flow rates.

§ Repeat APTT every 6 h during the first 24 h; thereafter, monitor APTT once every morning, unless it is outside therapeutic range.

Initial Anticoagulation With Heparin

We recommend:

- Patients receive treatment with heparin or LMWH ≥ 5 d, and oral anticoagulation should be overlapped for ≥ 4 to 5 d (**grade 1A**, compared with initial heparin or LMWH treatment for ≥ 10 d). For most patients, treatment with warfarin can start together with heparin or LMWH. Heparin or LMWH therapy can be discontinued on day 5 or 6 if the INR has been within therapeutic range for 2 consecutive days (INR ≥ 2.0).
- Patients with massive PE or severe iliofemoral thrombosis be offered a longer period of heparin therapy, for about 10 days (**grade 1C**).

Long-term Anticoagulation

The recommended duration of long-term anticoagulation varies (Table 13).

TABLE 13 – RECOMMENDED DURATION OF TREATMENT IN VENOUS THROMBOEMBOLIC DISEASE

PATIENT CHARACTERISTICS	LENGTH OF TREATMENT
Most patients	Continue oral anticoagulant therapy for ≥ 3 mo (goal INR 2.5; range, 2.0 to 3.0); if oral anticoagulation is contraindicated or inconvenient, use LMWH or adjusted-dose UFH to prolong the APTT to a time corresponding to a therapeutic plasma heparin level for most of the dosing interval (**grade 1A**)
First event, with a reversible or time-limited risk factor*	Treat ≥ 3 mo (**grade 1A**)
First episode of idiopathic VTE	Treat ≥ 6 mo (**grade 1A**)
Recurrent idiopathic VTE, or a continuing risk factor†	Treat ≥ 12 mo (**grade 1C**)
Symptomatic isolated calf thrombosis	Treat with anticoagulants for ≥ 6 to 12 wk (**grade 1A**); if anticoagulation cannot be given, perform serial noninvasive studies of the lower extremity over the next 10 to 14 d to assess for proximal extension of thrombus (**grade 1C**)

* *Surgery, trauma, immobilization, estrogen use.*

† *Cancer, antithrombin deficiency, anticardiolipin antibody syndrome.*

Thrombolytic Therapy

Use of thrombolytic agents in treating VTE is highly individualized. In general, the best candidates are patients with hemodynamically unstable PE or massive iliofemoral thrombosis.

IVC Filter

We recommend placement of an IVC filter in patients:

- with proximal vein thrombosis or PE or with high risk for these conditions, when anticoagulant therapy is contraindicated or has resulted in a complication (**grade 1C+**).
- with recurrent thromboembolism that occurs despite adequate anticoagulation, with chronic recurrent embolism and pulmonary hypertension, and with the concurrent surgical pulmonary embolectomy or pulmonary thromboendarterectomy (all **grade 1C**).

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Antithrombotic Therapy in Peripheral Arterial Occlusive Disease. Mark R. Jackson, MD; G. Patrick Clagett, MD

We recommend aspirin for patients with clinical evidence of cerebrovascular disease or CAD (**grade 1A**). The recommendations in Table 14 apply to patients without evidence of these conditions.

TABLE 14 – ANTITHROMBOTIC THERAPY IN PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

PATIENT CHARACTERISTICS	RECOMMENDATIONS
Acute Extremity Arterial Insufficiency	
Acute arterial thrombus or embolism	Systemic heparinization (to prevent proximal and distal thrombotic propagation), followed by oral anticoagulants (to prevent recurrent embolism) in patients undergoing thromboembolectomy (**grade 1C**)

continued

Table 14 — Continued

PATIENT CHARACTERISTICS	RECOMMENDATIONS
Acute (< 14 d) thrombotic or embolic occlusive disease	Offer intra-arterial thrombolytic therapy, if risk for myonecrosis during revascularization is low (**grade 2B**)
Chronic Extremity Arterial Insufficiency	
Intermittent claudication* from arteriosclerosis	Aspirin,† alone or in combination with dipyridamole; lifelong aspirin therapy, in the absence of contraindications (**grade 1C+**)
Peripheral vascular disease and/or intermittent claudication*	Offer clopidogrel, which may be superior to aspirin in reducing ischemic complications in such patients (**grade 2A**)
Disabling intermittent claudication*	Offer a trial of cilostazol therapy, especially if lifestyle modification alone is ineffective and revascularization cannot be offered or is declined by the patient (**grade 2A**)
Peripheral Vascular Reconstructive Surgery	
Major vascular reconstructive surgery	Systemic heparinization, when cross-clamps are applied (**grade 1A**); best route of administration (regional vs systemic), optimal dosage, and desirability of using protamine sulfate are not known
Vascular reconstruction of high-flow, low-resistance arteries > 6 mm in diameter	Life-long aspirin therapy,† if indicated for arteriosclerotic disease (**grade 1C+**); do not offer antithrombotic therapy to maintain patency of reconstruction (**grade 1C**)
Prosthetic femoral-popliteal bypass surgery	Aspirin† therapy started preoperatively (**grade 1A**); consider addition of dipyridamole (75 mg tid) (**grade 2B**)
Saphenous vein femoral-popliteal or distal bypass surgery	Lifelong aspirin† therapy (**grade 1C+**); clopidogrel for patients unable to take aspirin (**grade 1C+**)
Infrainguinal bypass	Warfarin with aspirin for patients who are undergoing infrainguinal bypass procedures and are at high risk for graft thrombosis (**grade 1A**)
Carotid Endarterectomy	Aspirin,† given preoperatively and continued indefinitely (**grade 1A**)

** Pentoxifylline should not be used routinely in patients with intermittent claudication (**grade 1B**).*

† 80 to 325 mg/d, unless contraindications are present; such patients are at high risk for stroke and MI.

VALVULAR HEART DISEASE

Antithrombotic Therapy in Valvular Heart Disease. Deeb N. Salem, MD, FCCP; Denise Hartnett Daudelin, RN, MPH; Herbert J. Levine, MD; Stephen G. Pauker, MD; Mark H. Eckman, MD; Joshua Riff, MD

The many variables that influence the risks of thromboembolism and bleeding in patients with valvular heart disease may change with time, and the general guidelines presented in Table 15 may be modified as new clinical data emerge. We recommend reviewing clinical decisions at frequent intervals.

TABLE 15 – ANTITHROMBOTIC THERAPY IN VALVULAR HEART DISEASE

CONCOMITANT CONDITION	RECOMMENDATION
RHEUMATIC MITRAL VALVE DISEASE (MITRAL STENOSIS AND/OR MITRAL REGURGITATION)	
History of systemic embolism, or presence of paroxysmal or chronic AF	Long-term warfarin therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 1C+**)
NSR; left atrial diameter > 5.5 cm	Consider long-term warfarin therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**), based on risk factors for thromboembolism, especially left atrial size, patient's age, and hemodynamic severity of the lesion (**grade 2C**)
Recurrent systemic embolism, despite adequate warfarin therapy	Increase goal INR to 3.0 (range, 2.5 to 3.5), or add aspirin (80 to 100 mg/d) (**grade 1C**); for patients unable to take aspirin, add dipyridamole (400 mg/d); ticlopidine (250 mg po bid); or clopidogrel (75 mg po qd) (all **grade 1C**)
MITRAL VALVE PROLAPSE	
No systemic embolism, unexplained TIA, or AF	We recommend that long-term antithrombotic therapy **not** be given (**grade 1C**)
Documented, unexplained TIA	Long-term, low-dose aspirin therapy (**grade 2C**) (current recommendation is 160 to 325 mg/d)
Documented systemic embolism or recurrent TIA, despite aspirin therapy	Long-term warfarin therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 1C**)
Chronic or paroxysmal AF, despite aspirin therapy	As above (**grade 1A**)

continued

Table 15 — Continued

CONCOMITANT CONDITION	RECOMMENDATION
MITRAL ANNULAR CALCIFICATION	
Systemic embolism, not documented to be calcific embolism	Long-term warfarin therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**)
AF	As above (**grade 1C+**)
NONRHEUMATIC MITRAL REGURGITATION	
AF	Long-term anticoagulation (**grade 1C+**)
History of systemic embolism	
AORTIC VALVE AND AORTIC ARCH DISORDERS	
Mobile aortic atheroma and aortic plaque > 4 mm, measured by TEE	Warfarin therapy (**grade 2C**)
No other indication for anticoagulation	Long-term warfarin therapy is **not** recommended (**grade 2C**)
PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM	
Unexplained systemic embolism or TIA, demonstrable venous thrombosis or PE, and either patent foramen ovale (PFO) or atrial septal aneurysm	Long-term warfarin therapy, unless venous interruption or PFO closure is considered preferable therapy (**grade 1C**)
In selecting therapy, consider the possibility of paradoxic embolism and systemic embolism from the arterial side of the aneurysm.	
INFECTIVE ENDOCARDITIS	
Mechanical prosthetic valve	Continue long-term warfarin therapy, unless specific contraindications exist (**grade 2C**)
The risk of intracranial hemorrhage is substantial; when making the therapeutic decision, consider the presence of comorbid factors and the success of antibiotic therapy.	
NONBACTERIAL THROMBOTIC ENDOCARDITIS	
Systemic embolism or PE	Heparin therapy (**grade 1C**)
Disseminated cancer, or debilitating disease, with aseptic vegetations seen on echocardiography	Heparin therapy (**grade 2C**)

MECHANICAL OR BIOLOGICAL PROSTHETIC HEART VALVES

Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves. Paul D. Stein, MD, FCCP; Joseph S. Alpert, MD, FCCP; Henry I. Bussey, PharmD; James E. Dalen, MD, MPH, FCCP; Alexander G. G. Turpie, MD

Some of the recommendations below may change as new data become available. Treatment should always be based on appraisal of the individual patient and may properly differ from these consensus recommendations.

Mechanical Prosthetic Heart Valves

We recommend that all patients with mechanical prosthetic heart valves receive oral anticoagulants (**grade 1C+**) and that UFH or LMWH be given until the INR is within therapeutic range for 2 consecutive days (**grade 2C**).

TABLE 16 – MECHANICAL PROSTHETIC HEART VALVES

PATIENT CHARACTERISTICS	RECOMMENDATIONS
St. Jude Medical bileaflet aortic valve, left atrium of normal size; NSR	Goal INR 2.5; range, 2.0 to 3.0 (**grade 1A**)
CarboMedics bileaflet aortic valve or Medtronic-Hall tilting disk aortic valve; left atrium of normal size; NSR	As above (**grade 1C+**)
Tilting disk valve; or bileaflet mechanical valve in mitral position; or bileaflet mechanical valve in aortic position and AF	Goal INR 3.0; range, 2.5 to 3.5 (**grade 1C+**)
	Alternative: goal INR 2.5; range, 2.0 to 3.0; and aspirin therapy (80 to 100 mg/d) (**grade 2C**)
Caged ball or caged disk valve	Goal INR 3.0; range, 2.5 to 3.5; and aspirin therapy (80 to 100 mg/d) (**grade 2A**)
Additional risk factors	As above (**grade 1C+**)
Systemic embolism, despite adequate therapy with oral anticoagulants	As above (**grade 1C+**)

TABLE 17 – BIOPROSTHETIC HEART VALVESE

CONCOMITANT CONDITION	RECOMMENDATION
Valve in mitral position	Oral anticoagulants for the first 3 mo after valve insertion (**grade 1C+**)
Valve in aortic position	As above (**grade 2C**)
	Both groups: (goal INR 2.5; range, 2.0 to 3.0) (**grade 1A**)
	Both groups: LMWH or UFH might be used until the INR is within therapeutic range for 2 consecutive days (**grade 2C**)
AF	Long-term oral anticoagulant therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 1C+**)
Evidence of left atrial thrombus at surgery	Long-term oral anticoagulant therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 1C**) (optimal duration of therapy is uncertain)
Permanent pacemaker	Optional use of anticoagulants (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**)
History of systemic embolism	Oral anticoagulants for 3 to 12 mo (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**)
NSR	Long-term aspirin therapy (80 mg/d) (**grade 2C**)

PREGNANT PATIENTS

Use of Antithrombotic Agents During Pregnancy. Jeffrey S. Ginsberg, MD, FCCP; Ian A. Greer, MD; Jack Hirsh, MD, FCCP

The detailed guidelines below reflect important new information on managing thromboembolic complications during pregnancy. Terms used in the tables are defined directly below.

TERM	DEFINITION
UFH	
Mini-dose	5,000 IU SC q12 h
Moderate-dose	Adjusted doses, q12h SC, to target an anti-Xa level of 0.1 to 0.3 IU/mL
Adjusted-dose	Adjusted doses, q12h SC, to target a mid-interval APTT within therapeutic range
LMWH	
Prophylactic	Dalteparin (5,000 IU q24h SC), or enoxaparin (40 mg qd SC), or any qd LMWH adjusted to target a peak anti-Xa level of 0.2 to 0.6 IU/mL
Adjusted-dose	Full, weight-adjusted doses of LMWH; for example, dalteparin (200 IU/kg qd) or enoxaparin (1 mg/kg q12h SC)
POSTPARTUM ANTICOAGULANTS	Warfarin, given 4 to 6 wk (goal INR 2.0 to 3.0), initially overlapped with UFH or LMWH, until the INR is ≥ 2.0
SURVEILLANCE	Clinical vigilance and aggressive investigation of symptoms suggesting DVT or PE

TABLE 18 – PATIENTS AT INCREASED RISK FOR VTE

PATIENT CHARACTERISTICS	RECOMMENDATION
• Prior VTE associated with a transient risk factor; no current risk factors (*eg*, morbid obesity or strict bed rest)	Surveillance and postpartum anticoagulants (**grade 1C**)
• Episode of idiopathic VTE; no current long-term anticoagulant therapy • Episode of VTE; thrombophilia (confirmed laboratory abnormality); no current long-term anticoagulant therapy	Options: surveillance, mini-dose UFH, moderate-dose UFH, or prophylactic LMWH; in addition: postpartum anticoagulants (**grade 1C**)*
No prior VTE; thrombophilia (confirmed laboratory abnormality); no current long-term anticoagulant therapy	Options: surveillance, mini-dose UFH, or prophylactic LMWH; in addition, postpartum anticoagulants; indication for active prophylaxis is strongest in antithrombin-deficient women (**grade 1C**)*
≥ 2 episodes of VTE, and/or long-term anticoagulation (*eg*, single episode of VTE, idiopathic or associated with thrombophilia)	Options: adjusted-dose UFH, prophylactic LMWH, or adjusted-dose LMWH; in addition, long-term postpartum use of anticoagulants (**grade 1C**)*

* *Compared with no surveillance or intervention.*

TABLE 19 – TREATMENT OF VENOUS THROMBOEMBOLISM OF PREGNANCY

PATIENT CHARACTERISTICS	RECOMMENDATION
Average risk for recurrent VTE	Adjusted-dose LMWH throughout pregnancy; or IV UFH bolus, followed by continuous infusion to maintain APTT in therapeutic range for ≥ 5 d; then adjusted-dose UFH until delivery (**grade 1C**) To avoid unwanted anticoagulation during delivery in women receiving adjusted-dose LMWH or UFH, discontinue heparin therapy 24 h before elective induction of labor (**grade 1C**)

continued

Table 19 — Continued

PATIENT CHARACTERISTICS	RECOMMENDATION
Very high risk for recurrent VTE (*eg*, proximal DVT within < 2 wk)	IV UFH, to maintain APTT within therapeutic range; discontinue therapy 4 to 6 h before expected time of delivery; anticoagulants for ≥ 6 wk postpartum or ≥ 3 mo after VTE (**grade 1C**)

Pregnancy in Patients Receiving Long-term Anticoagulant Therapy

Ideally, patients receiving long-term anticoagulant therapy should be counseled before planned or unplanned pregnancy. If pregnancy is desired, we recommend:

- Frequent pregnancy tests can be performed, and adjusted-dose UFH or LMWH substituted for warfarin if pregnancy occurs (**grade 1C**).

Or

- Warfarin can be replaced with UFH or LMWH before conception is attempted (**grade 1C**).

Both options have limitations. We prefer the first because it is convenient and appears to be safe.

Prophylaxis in Patients With Mechanical Heart Valves

We recommend one of the following approaches:

- Aggressive adjusted-dose UFH, given q12h SC throughout pregnancy; mid-interval APTT maintained at ≥ 2 times control levels, or anti-Xa heparin level maintained at 0.35 to 0.70 IU/mL
- LMWH throughout pregnancy, in doses adjusted according to weight, or as necessary to maintain a 4-h post-injection anti-Xa heparin level of about 1.0 IU/mL
- UFH or LMWH, as above, until the 13th week; change to warfarin until the middle of the third trimester, then restart UFH or LMWH therapy until delivery

(all **grade 1C** compared with no treatment)

Long-term anticoagulation should be resumed postpartum.

TABLE 20 – PROPHYLAXIS IN PREGNANT WOMEN WITH INCREASED RISK FOR PREGNANCY LOSS

PATIENT CHARACTERISTICS	RECOMMENDATION
≥ 3 miscarriages	Screen for antiphospholipid antibody (APLA); if a loss occurred in the second trimester, screen for congenital thrombophilia; if prior severe or recurrent preeclampsia, intrauterine growth restriction (IUGR), abruption, or otherwise unexplained intrauterine death occurred: screen for congenital thrombophilia and APLA (**all grade 1C**)
APLA and ≥ 2 early-pregnancy losses, or ≥ 1 late-pregnancy loss, or preeclampsia, IUGR, or abruption	Antepartum aspirin and mini-dose UFH, moderate-dose UFH, or prophylactic LMWH (**grade 1A**)
Homozygous for MTHFR C677T	Folic acid supplements prior to conception or as soon as possible if pregnancy exists (**grade 2C**)
Thrombophilic defects and recurrent miscarriages; a miscarriage during or after the second trimester; or preeclampsia, IUGR, or abruption	Consider low-dose aspirin with either mini-dose heparin or prophylactic LMWH; give anticoagulants postpartum (**grade 2C**)
APLA and a history of venous thrombosis, with current long-term oral anticoagulation	Adjusted-dose LMWH or UFH throughout pregnancy; resume long-term oral anticoagulant therapy postpartum (**grade 2C**)
APLA and no prior VTE or pregnancy loss	Options: surveillance, mini-dose heparin, prophylactic LMWH, or low-dose aspirin (80 to 325 mg)/qd (all **grade 2C**)

PEDIATRIC PATIENTS

Antithrombotic Therapy in Children. Maureen Andrew, MD; Paul Monagle, MBBS; Alan D. Michelson, MD; Edward Bovill, MD

Tables 21 and 22 list indications and recommendations for antithrombotic therapy in children. Guidelines from studies in adults remain the primary source for these recommendations, pending completion of current pediatric trials. Tables 23 and 34 provide heparin and LMWH protocols.

TABLE 21 – INDICATIONS FOR ANTITHROMBOTIC AGENTS IN PEDIATRIC PATIENTS

Treatment	Venous thromboembolic complications Arterial thromboembolic complications
Treatment probable	MI Some forms of stroke
Prophylaxis	Mechanical prosthetic heart valves Biological prosthetic heart valves Cardiac catheterization Central arterial catheters
Prophylaxis probable	Endovascular stents Blalock-Taussig shunts Fontan procedure Central venous catheters Atrial venous fibrillation
Other	Kawasaki disease Cardiopulmonary bypass Extracorporeal membrane oxygenation Hemodialysis Continuous venovenous hemoperfusion

TABLE 22 – RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPY IN PEDIATRIC PATIENTS

PATIENT CHARACTERISTICS	RECOMMENDATION
Age > 2 mo, with first thromboembolism: initial therapy	IV heparin sufficient to prolong the APTT to a range corresponding to an antifactor Xa level of 0.3 to 0.7 IU/mL (**grade 1C+**) Alternative: LMWH sufficient to achieve an antifactor Xa level of 0.5 to 1.0 IU/mL 4 h after injection (**grade 1C+**)
As above: continued therapy	Continue heparin or LMWH therapy for 5 to 10 d; if oral anticoagulant therapy will be used, it can be started as early as day 1 and the heparin or LMWH therapy discontinued on day 6 if the INR is within therapeutic range on 2 consecutive days; consider a longer period of therapy for massive PE or extensive DVT (**grade 1C+**)
As above: long-term therapy	Continue anticoagulant therapy for ≥ 3 mo (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**) Alternative: LMWH, to maintain an antifactor Xa level of 0.5 to 1.0 IU/mL (**grade 2C**)
Idiopathic thromboembolism in children	Treat ≥ 6 mo with oral anticoagulants or LMWH (**grade 2C**)
First DVT, related to a central venous line (CVL)*	Option: after 3 mo of therapy, give prophylactic doses of oral anticoagulants (INR 1.5 to 1.8) or LMWH (antifactor Xa levels of 0.1 to 0.3), until the CVL is removed (**grade 2C**)
Recurrent thromboembolism, non-CVL-related, while not receiving prophylaxis	Treat indefinitely with therapeutic or prophylactic doses of oral anticoagulants or LMWH (**grade 2C**)
Recurrent thromboembolism, CVL-related	Therapeutic doses for 3 mo; then prophylactic doses of oral anticoagulants (INR 1.5 to 1.8) or LMWH (antifactor Xa levels of 0.1 to 0.3) until removal of the CVL (**grade 2C**)

continued

Table 22 — Continued

PATIENT CHARACTERISTICS	RECOMMENDATION
Recurrent thromboembolism, CVL-related, while receiving prophylaxis	Therapeutic doses of oral anticoagulants (INR 2.0 to 3.0) or LMWH (antifactor Xa 0.5 to 1.0) until removal of the CVL or for a minimum of 3 mo (**grade 2C**)
DVT or PE in newborns	Options: conventional anticoagulation in age-appropriate doses, short-term anticoagulation, or close monitoring of the thrombus, using objective tests, and treating with anticoagulants if extension occurs (no specific recommendation) Options, if anticoagulation is used: • IV heparin for 10 to 14 d, APTT within therapeutic range, corresponding to an antifactor Xa level of 0.3 to 0.7 IU/mL • A short course of LMWH, targeting an antifactor Xa level of 0.5 to 1.0 IU/mL (both **grade 2C**, compared with no treatment) Anticoagulant therapy for ≤ 3 mo, with monitoring, may be required, depending on the location and extent of the thrombus; if thrombus extends after heparin therapy is discontinued, we recommend oral anticoagulation or extended LMWH (**grade 2C**)
Thrombolytic therapy for venous thromboembolic disease	There is insufficient evidence to make specific recommendations about the use of thrombolytic agents If thrombolytic therapy is used, we recommend supplementation with plasminogen (fresh frozen plasma) (**grade 2C**)
Homozygous protein C- and S-deficiency	Treat newborns initially with replacement therapy (fresh frozen plasma or protein C concentrate) for 6 to 8 wk, until the skin lesions have healed (**grade 1C+**); then, under cover of replacement therapy, treat with oral anticoagulants (INR 3.0 to 4.5), indefinitely (**grade 2C**)

continued

Table 22 — Continued

PATIENT CHARACTERISTICS	RECOMMENDATION
Homozygous protein C- and S-deficiency	Patients with measurable plasma concentrations of protein C or S, despite deficiency: LMWH is a therapeutic option (**grade 2C**) For long-term prophylaxis or as salvage therapy for recurrent skin lesions or thrombosis in protein C-deficient patients: replacement therapy with protein-C concentrate (**grade 2C**)
Prophylaxis in cardiac catheterization in neonates and children	IV heparin (**grade 1A** compared with no therapy), 100 to 150 IU/kg bolus (**grade 2A**, compared with 50 U/kg); do **not** use aspirin alone (**grade 1B**)
Arterial thromboembolism in neonates and children	Therapeutic doses of IV heparin (**grade 1C**); for patients who have a limb- or organ-threatening arterial thromboembolism and fail to respond: thrombolytic therapy, if no known contraindications exist (**grade 1C**)
Kawasaki disease in children	Gamma globulin (2 g/kg IV, as a single dose), and aspirin (80 to 100 mg/kg/d) for ≤ 14 d, as an anti-inflammatory agent, then aspirin (3 to 5 mg/kg/d) for ≥ 7 wk, to prevent coronary aneurysm thrombosis (**grade 1C**)
Biological prosthetic heart valves in children	Use recommendations for treating adults; follow patients for evidence of valve dysfunction
Mechanical prosthetic heart valves in children	Oral anticoagulation therapy (**grade 1C+**) (target INR 3.0; range, 2.5 to 3.5) (**grade 1C+**) If systemic embolism occurs despite adequate anticoagulation therapy: add aspirin (6 to 20 mg/kg/d) or alternatively dipyridamole (2 to 5 mg/kg/d) (**grade 2C**) If full-dose oral anticoagulant therapy is contraindicated: use sufficient dosage for a goal INR of 2.5 (range, 2.0 to 3.0), in combination with aspirin (6 to 20 mg/kg/d) (**grade 1C+**) and dipyridamole (2 to 5 mg/kg/d) (**grade 2C**)

continued

Table 22 — Continued

PATIENT CHARACTERISTICS	RECOMMENDATION
Blalock-Taussig shunt	Therapeutic doses of heparin, followed by aspirin (3 to 5 mg/kg/d), indefinitely (**grade 2C**)
Fontan procedure	Aspirin or therapeutic doses of heparin, followed by oral anticoagulation therapy (goal INR 2.5; range, 2.0 to 3.0) (**grade 2C**); patients with fenestrations may benefit from treatment until closure

* *We do not recommend primary prophylaxis for VTE in children with a CVL (**grade 2C**). Thrombolytic therapy should be individualized. Plasminogen supplementation should be considered in neonates and infants.*

TABLE 23 – HEPARIN PROTOCOL IN PEDIATRIC PATIENTS

- Loading dose: 75 IU/kg IV over 10 min
- Initial maintenance dose:

  Infants < 1 yr: 28 IU/kg/h
  Children > 1 yr: 20 IU/kg/h
- Adjustment to maintain APTT 60 to 85 s*

APPT, s	Bolus, U/kg	Hold, min	Rate Change	Repeat APTT
< 50	50	0	+10%	4 h
50 to 59	0	0	+10%	4 h
60 to 85	0	0	0	Next day
86 to 95	0	0	-10%	4 h
96 to 120	0	30	-10%	4 h
> 120	0	60	-15%	4 h

- Obtain blood for APTT 4 h after administration of heparin loading dose, and 4 h after every change in infusion rate.
- When APTT is within therapeutic range, obtain a daily CBC count and APTT.

* *Assuming this reflects an antifactor Xa level of 0.30 to 0.70 IU/mL.*

TABLE 24 – LMWH PROTOCOL IN PEDIATRIC PATIENTS

Anti-Factor Xa Level	Hold Next Dose, h	Dose Change	Repeat Anti-Factor Xa Level
< 0.35 U/mL	No	+ 25%	4 h after next dose
0.35 to 0.49 U/mL	No	+ 10%	4 h after next dose
0.5 to 1.0 U/mL	No	0	Next day, then 1 wk later; monthly thereafter, while receiving reviparin treatment (at 4 h after the morning dose)
1.1 to 1.5 U/mL	No	- 20%	Before next dose
1.6 to 2.0 U/mL	3 h	- 30%	Before next dose, then 4 h after next dose
> 2.0 U/mL	Until anti-factor Xa 0.5 U/mL	- 40%	Before next dose; if not < 0.5 U/mL, repeat q12h

INTRAVENOUS THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

Intravenous Thrombolysis in Acute Myocardial Infarction. Eric Magnus Ohman, MD, FCCP; Robert A. Harrington, MD; Christopher P. Cannon, MD; Giancarlo Agnelli, MD; John A. Cairns, MD; J. Ward Kennedy, MD

Presented below are specific recommendations for fibrinolytic therapy, choice of agent, and adjunctive therapy, in patients with AMI.

TABLE 25 – RECOMMENDATIONS FOR FIBRINOLYTIC THERAPY

PATIENT CHARACTERISTICS	RECOMMENDATION
Ischemic symptoms characteristic of AMI for ≤ 12 h; ST-segment elevation or left bundle branch block on the ECG	IV fibrinolytic therapy (unless contraindications exist) (**grade 1A**)
Symptoms characteristic of AMI for 12 to 24 h; ST-segment elevation or left bundle branch block on the ECG	Offer IV fibrinolytic therapy (**grade 2B**)
Prior intracranial hemorrhage, stroke within the past year, or active bleeding	Do **not** give IV fibrinolytic therapy (**grade 1B**)

We also recommend:

- All patients with AMI who receive fibrinolytic therapy be given aspirin (165 to 325 mg) upon hospital arrival and daily thereafter (**grade 1A**).
- All patients with AMI who are candidates for fibrinolytic therapy receive it within 30 minutes of hospital arrival (**grade 1A**).

The choice of fibrinolytic agent is based upon the factors listed in Table 26.

TABLE 26 – CHOICE OF FIBRINOLYTIC AGENT

FACTOR	RECOMMENDATION
Duration of symptoms ≤ 12 h	Streptokinase,* anistreplase, or alteplase (**grade 1A**, compared with placebo)
Duration of symptoms ≤ 6 h	Alteplase† is recommended over streptokinase (**grade 1A**)
Known allergy or sensitivity to streptokinase	Alteplase, tenecteplase, or reteplase (**grade 1C+**)

** Reteplase is equivalent to streptokinase.*

† Tenecteplase is equivalent to alteplase.

TABLE 27 – ADJUNCTIVE THERAPY WITH HEPARIN

FIBRINOLYTIC THERAPY	ADJUNCTIVE THERAPY
Streptokinase	SC UFH* (12,000 IU q 12 h) for 48 h (**grade 2A**)
Streptokinase or anistreplase	IV UFH,* only for patients at high risk of systemic embolism or VTE† (**grade 1C**)
Alteplase	IV UFH for 48 h (**grade 1B**)
Reteplase or tenecteplase	IV UFH for 48 h (**grade 1C**)
IV heparin with alteplase, reteplase, or tenecteplase	Standard-dose UFH (bolus of 5,000 IU, followed by 1,000 IU/h (**grade 1C**); or weight-adjusted dosing (bolus of 60 IU/kg [4,000 IU maximum] followed by 12 IU/kg [1,000 IU/h maximum] (**grade 2C**); adjust dosing to maintain an APTT of 50 to 70 s

** Heparin should not be given ≤ 4 h after fibrinolytic therapy, and should be given when the APTT is < 70 s; goal APTT = 50 to 70 s; continue infusion for ≥ 48 h.*

† Anterior MI, existing heart failure, previous embolus, AF, or LV thrombus.

Direct Thrombin Inhibitors

For patients with known or suspected heparin-induced thrombocytopenia or thrombosis who are receiving fibrinolytic therapy (alteplase or streptokinase), we recommend IV hirudin (lepirudin, 0.1 mg/kg bolus followed by 0.15 mg/h infusion) (**grade 2A**).

USE OF ORAL ANTICOAGULANTS

Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. Jack Hirsh, MD, FCCP; James E. Dalen, MD, MPH, FCCP; David R. Anderson, MD; Leon Poller, DSc, MD; Henry I. Bussey, PharmD; Jack E. Ansell, MD; Daniel Deykin, MD

Evidence from randomized trials continues to support the use of less-intense warfarin treatment for many indications. Within an INR range of 2.0 to 3.0, the lower level generally is safer and equally effective. Recommended therapeutic ranges for the various indications remain unchanged (Table 28). Recent studies do not support the use of fixed low-dose warfarin therapy in patients with AMI or AF.

TABLE 28 – RECOMMENDED THERAPEUTIC RANGE FOR ORAL ANTICOAGULANT THERAPY

INDICATION	INR RANGE
Prophylaxis of venous thrombosis (high-risk surgery) Treatment of venous thrombosis Treatment of PE Prevention of systemic embolism Tissue heart valves AMI (to prevent systemic embolism)* Valvular heart disease AF	2.0 to 3.0
Mechanical prosthetic valves (high risk)	2.5 to 3.5
Bileaflet mechanical valve in aortic position	2.0 to 3.0
Certain patients with thrombosis and the antiphospholipid syndrome	> 2.0 to 3.0

* *If oral anticoagulant therapy is elected to prevent recurrent MI, an INR of 2.5 to 3.5 is recommended, consistent with Food and Drug Administration recommendations.*

MANAGING ORAL ANTICOAGULANT THERAPY

Managing Oral Anticoagulant Therapy. Jack E. Ansell, MD; Jack Hirsh, MD, FCCP; James Dalen, MD, MPH, FCCP; Henry I. Bussey, PharmD; David R. Anderson, MD; Leon Poller, DSc, MD; Alan K. Jacobson, MD; Daniel Deykin, MD; David Matchar, MD

We recommend starting warfarin therapy with an average maintenance dose of 5 mg (**grade 2A**, compared with 10 mg), which usually is sufficient to lower the INR to 2.0 in 4 or 5 d. Lower starting doses may be appropriate in elderly patients, those with liver disease or inadequate nutrition, and those at high risk for bleeding. Larger starting doses, *eg*, 7.5 to 10 mg, may be selected if a rapid effect is urgently needed. A loading dose of warfarin is unnecessary for most patients.

Heparin can be given concurrently for ≥ 4 d if a rapid effect is required. Heparin therapy is usually discontinued when the INR has been within therapeutic range in two measurements taken ≥ 24 h apart.

Approaches for reducing an elevated INR are listed in Table 29.

TABLE 29 – MANAGING PATIENTS WITH HIGH INR VALUES

CLINICAL SITUATION	GUIDELINES
INR > therapeutic range but < 5.0; no significant bleeding	Lower the dose; or omit the next dose, and resume therapy at a lower dose when the INR is within therapeutic range; if the INR is only slightly above therapeutic range, dose reduction may not be necessary (**grade 2C**)
INR > 5.0 but < 9.0; no significant bleeding	Omit the next dose or two, monitor INR more frequently, and resume therapy at a lower dose when the INR is within therapeutic range Alternatively, omit a dose and give vitamin K_1 (1 to 2.5 mg orally), especially if the patient is at increased risk for bleeding Patients requiring more rapid reversal before urgent surgery: vitamin K_1 (2 to 4 mg orally); if INR remains high at 24 h: an additional dose of vitamin K_1 (1 to 2 mg orally) (all **grade 2C**, compared with no treatment)

continued

Table 29 — Continued

CLINICAL SITUATION	GUIDELINES
INR > 9.0; no significant bleeding	Omit warfarin; give vitamin K_1 (3 to 5 mg orally); closely monitor the INR; if the INR is not substantially reduced in 24 to 48 h, monitor the INR more often, giving additional vitamin K_1, if necessary Resume therapy at a lower dose when the INR is within therapeutic range (both **grade 2C**, compared with no treatment)
INR > 20; serious bleeding	Omit warfarin; give vitamin K_1 (10 mg, slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on urgency; vitamin K_1 injections can be repeated every 12 h (**grade 2C**)
Life-threatening bleeding	Omit warfarin; give prothrombin complex concentrate with vitamin K_1 (10 mg by slow IV infusion); repeat if necessary, depending on the INR (**grade 2C**)

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

Full-dose IV UFH has been the standard treatment for providing full anticoagulant protection that can be readily reversed before invasive procedures. Recent studies suggest that LMWH may offer a simple and less-costly alternative for some patients (Table 30).

TABLE 30 – MANAGING ORAL ANTICOAGULATION DURING INVASIVE PROCEDURES

CLINICAL SITUATION	GUIDELINES
Low risk for thromboembolism*	Discontinue warfarin therapy about 4 d before surgery, and allow the INR to return to near-normal levels; if intervention increases a risk for thrombosis: begin short-term low-dose heparin therapy (5,000 IU SC) and resume warfarin therapy (**grade 2C**)
Intermediate risk for thromboembolism	Discontinue warfarin therapy about 4 d before surgery, and allow the INR to fall; about 2 d preoperatively, give either low-dose heparin (5,000 IU SC) or a prophylactic dose of LMWH; postoperatively, give low-dose heparin (or LMWH) and warfarin (**grade 2C**)
High risk for thromboembolism†	Discontinue warfarin therapy about 4 d before surgery, and allow the INR to return to normal range; about 2 d preoperatively, as the INR falls, give full-dose heparin or full-dose LMWH Heparin can be given SC on an outpatient basis, and presurgically, after hospital admission, as a continuous IV infusion, and discontinued 5 h before surgery; alternatively, continue SC heparin or LMWH therapy until 12 to 24 h before surgery (all **grade 2C**)
Low risk for bleeding	Lower the warfarin dose 4 or 5 d before surgery, to reach an INR of 1.3 to 1.5 at time of surgery; resume warfarin therapy postoperatively, supplemented, if necessary, with low-dose heparin (5,000 IU SC) (**grade 2C**)
Dental procedures	Patients at high risk for bleeding: discontinue warfarin therapy Patients not at high risk for bleeding; warfarin therapy should not be discontinued (both **grade 2C**)

continued

Table 30 — Continued

CLINICAL SITUATION	GUIDELINES
Dental procedures, with need to control local bleeding	Administer a mouthwash acid or epsilon amino caproic acid, without interrupting anticoagulant therapy (**grade 2B**)

* *eg, no VTE for > 3 mo; AF, without history of stroke; bileaflet mechanical cardiac valve in the aortic position.*

† *eg, VTE in < 3 mo; history of VTE, mechanical cardiac valve in mitral position; old-model cardiac valve (ball/cage).*

Elderly patients should be carefully monitored to maximize the time within therapeutic range. We recommend that clinicians do **not** withhold anticoagulation because of age if patients are otherwise good candidates (**grade 1C**).

TABLE 31 – MODELS OF ANTICOAGULATION MANAGEMENT

MODEL OF MANAGEMENT	RECOMMENDATION
Usual care vs anticoagulation management service	Use of a systematic process to manage oral anticoagulation dosing that includes a knowledgeable provider, reliable prothrombin-time monitoring, and an organized system of follow up, patient communication, and education (**grade 1C**)
Point-of-care patient self-testing	For selected individuals who are willing and able to perform self-testing, and are suitably trained: offer patient self-testing, as an alternative to a usual care model of INR monitoring and management, to achieve greater time within therapeutic range (**grade 2B**)
Computer program for dose management	Such programs must be considered individually, based on well-designed clinical-outcome studies; offer programs shown to provide dosing decisions equivalent to or better than physician management, especially in high-volume anticoagulation programs (**grade 2B**)

NEW ANTICOAGULANTS

New Anticoagulant Drugs. Jeffrey Weitz, MD, FCCP; Jack Hirsh, MD, FCCP

Anticoagulant strategies to inhibit thrombogenesis have focused on inhibiting thrombin, preventing thrombin generation, or blocking the initiation of coagulation. Thrombin inhibitors block thrombin activity; agents that target clotting enzymes higher in the coagulation pathways prevent thrombin generation. Coagulation factors targeted for inactivation include factor Xa, factor IXa, and the factor VIIa/tissue factor complex. Other approaches to attenuating thrombogenesis include enhancing endogenous anticoagulant pathways or promoting fibrinolysis.

Table 32 lists new anticoagulants in advanced stages of clinical development.

TABLE 32 – NEW ANTICOAGULANTS

TARGET	DRUG	ROUTE	STATUS	INDICATION
VIIa/tissue factor	Tissue factor pathway inhibitor	IV	Phase III	Sepsis
	Nematode anticoagulant peptide c2	SC	Phase II	Thromboprophylaxis (elective knee arthroplasty)
Va/VIIIa	Activated protein C	IV	Phase III	Sepsis
Xa	Pentasaccharide	SC	Phase III	Thromboprophylaxis (elective hip or knee arthroplasty, hip fracture)
				Venous thrombosis
	DX-9065a	IV	Phase II	Unstable angina
Xa/thrombin	SNAC/heparin*	Oral	Phase II	Thromboprophylaxis (elective hip or knee arthroplasty)
Thrombin	Hirudin	IV	Approved	Heparin-induced thrombocytopenia
			Under review	Unstable angina; non-ST-elevation MI
	Bivalirudin	IV	Approved	Alternative to heparin for coronary angioplasty

continued

Table 32 — Continued

TARGET	DRUG	ROUTE	STATUS	INDICATION
	Argatroban	IV	Approved	Heparin-induced thrombocytopenia
	H376/95	Oral	Phase III	Thromboprophylaxis (elective hip or knee arthroplasty)
			Phase II	Alternative to warfarin in atrial fibrillation

* *Sodium N-(8[2-hydroxybenzoyl]amino) caprylate.*

HEMORRHAGIC COMPLICATIONS OF ANTICOAGULANT TREATMENT

Hemorrhagic Complications of Anticoagulant Treatment. Mark N. Levine, MD; Gary Raskob, PhD; Seth Landefeld, MD; Clive Kearon, MD, PhD, FCCP

Oral anticoagulants: The major determinants of bleeding from the use of oral anticoagulants are the intensity of the anticoagulant effect, characteristics of the patient, and length of therapy. The risk for bleeding appears to be reduced with the use of low-intensity oral anticoagulant therapy (goal INR 2.5; range, 2.0 to 3.0). Lower-intensity regimens (INR < 2.0) are associated with further reduction in major bleeding episodes. In selecting therapy, the potential decrease in risk for thromboembolism must be balanced against the potential increase in risk for bleeding.

Heparins: In patients with acute VTE, the risk for bleeding associated with IV heparin is < 3% in recent trials, but appears to increase if higher dosages of heparin are used, and if the patient's age is > 70 years. Use of LMWH, compared with standard heparin, is not associated with an increase in major bleeding episodes in patients with VTE.

Use of standard heparin and LMWH is associated with an increase in major bleeding episodes in ischemic stroke, but not in ischemic coronary syndromes.

USE OF PLATELET-ACTIVE DRUGS

Platelet-Active Drugs: The Relationships Among Dose, Effectiveness, and Side Effects. Carlo Patrono, MD; Barry S. Coller, MD; James E. Dalen, MD, MPH, FCCP; Garret A. Fitzgerald, MD; Valentin Fuster, MD; Michael Gent, DSc; Jack Hirsh, MD, FCCP; Gerald Roth, MD

Studies continue to confirm the effectiveness of platelet-active drugs in treating and preventing thrombotic disorders. Table 33 lists minimum effective doses of aspirin. Clopidogrel, ticlopidine, dipyridamole, and IV GPIIb/III antagonists can be substituted for or combined with aspirin, in some conditions.

TABLE 33 – VASCULAR DISORDERS FOR WHICH ASPIRIN HAS BEEN SHOWN TO BE EFFECTIVE, AND MINIMUM EFFECTIVE DAILY DOSE

CLINICAL SITUATION	MINIMUM EFFECTIVE DAILY DOSE, MG
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
AMI	160
TIA and ischemic stroke*	50
Severe carotid artery stenosis*	75
Acute ischemic stroke*	160

* *Higher doses have not been found to provide greater risk reduction.*

USE OF HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN

Heparin and Low-Molecular-Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety. Jack Hirsh, MD, FCCP; Theodore E. Warkentin, MD; Stephen G. Shaughnessy, PhD; Sonia S. Anand, MD; Jonathan L. Halperin, MD; Robert Raschke, MD, MS; Christopher Granger, MD; Eric Magnus Ohman, MD, FCCP; James E. Dalen, MD, MPH, FCCP

LMWH preparations are at least as effective and safe as UFH, and are more convenient to use. They provide a more predictable relationship between dose and response, offering weight-adjusted dosing without laboratory monitoring. The higher cost of LMWH is likely to be offset by reduced hospital stay.

LMWH is contraindicated in patients with heparin-induced thrombocytopenia (HIT). Table 34 provides guidelines for treating this condition.

TABLE 34 – THERAPY FOR HIT*

CLINICAL CONDITION	RECOMMENDATION
Acute HIT with thrombosis	Danaparoid sodium (**grade 1B**) or lepirudin (**grade 1C**)
Acute HIT without thrombosis (isolated HIT)	Consider danaparoid sodium or lepirudin until the platelet count has recovered (**grade 2C**, compared with no treatment)
HIT with DVT	Do **not** use warfarin alone† (**grade 1C**)

* *LMWH is contraindicated (**grade 1C+**).*

† *Warfarin appears safe in acute HIT in patients receiving adequate anticoagulation with a drug such as danaparoid sodium or lepirudin (**grade 1C**), but administration probably should be delayed until the platelet count has risen to >100x10^9/L (**grade 1C**).*

ANTITHROMBOTIC THERAPY IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention.
Jeffrey J. Popma, MD; Eric Magnus Ohman, MD, FCCP; Jeffrey Weitz, MD, FCCP; A. Michael Lincoff, MD; Robert A. Harrington, MD; Peter B. Berger, MD

Presented below are updated guidelines for the use of oral antiplatelet agents (Table 35), and anticoagulants (*eg*, UFH), to reduce the frequency of early ischemic complications after PCI.

TABLE 35 – RECOMMENDATIONS FOR THERAPY WITH ORAL ANTIPLATELET AGENTS IN PERCUTANEOUS CORONARY INTERVENTION

GOAL	RECOMMENDATION
Reduce incidence of early complications	
• Most patients	Pretreat with aspirin (**grade 1A**) (80 to 325 mg) (**grade 2A**)
• Patients who are undergoing balloon angioplasty or atherectomy alone and cannot tolerate aspirin*	Pretreat with clopidogrel (300 mg oral loading dose and 75 mg/d) (**grade 1A**), or ticlopidine (500 mg loading dose and 250 mg bid) (**grade 2A**)
Secondary prevention	Long-term treatment with aspirin (80 to 325 mg/d) (**grade 1A**)
Provide adjunct to aspirin therapy in patients undergoing stent implantation	Clopidogrel (300 mg oral loading dose and 75 mg/d for 14 to 30 d) (**grade 2A**) or ticlopidine (500 mg loading dose and 250 mg bid for ≥ 10 to 14 d after the procedure) (**grade 2A**)
Reduce incidence of ischemic complications in all patients undergoing PCI, especially those with refractory unstable angina or other high-risk features	Give abciximab, eptifibatide, or tirofiban (**grade 1A**)
Reduce incidence of ischemic complications in patients undergoing primary PCI for AMI	Offer abciximab (**grade 2A**)

* *We recommend that clinicians do not offer dipyridamole as an alternative in aspirin-sensitive patients undergoing PCI (**grade 2A**).*

Use of Heparin

We recommend:

- UFH (ACT 250 to 300 s with the HemoTec device, 300 to 350 s with the Hemochron device); weight-adjusted heparin boluses (70 to 150 IU/kg) can be given to avoid excessive anticoagulation (**grade 1C**).
- If the ACT drops to < 150 to 180 s: early sheath removal, to reduce the incidence of complications at the access site (**grade 1C**).
- When abciximab is given: reduction of the heparin bolus to 50 to 70 IU/kg (goal ACT > 200 s with either the HemoTec or the Hemochron device); removal of femoral sheaths after the procedure or when the ACT falls to < 150 to 180 s (**grade 1A**).

We do **not** recommend:

- Routine postprocedural infusion of heparin in patients undergoing uncomplicated procedures (**grade 1C**).
- Prolonged use of postprocedural low-dose UFH (**grade 1C**) or LMWH to prevent restenosis in patients undergoing uncomplicated PCI (**grade 1A**).

Use of Direct Thrombin Inhibitors

We recommend:

- Patients undergoing PCI be offered bivalirudin as an alternative to heparin (**grade 2A**).
- Patients with known or suspected heparin-induced thrombocytopenia be offered direct thrombin inhibitors as an alternative anticoagulant to UFH (**grade 2A**).

GLOSSARY

AF – atrial fibrillation

AMI – acute myocardial infarction

APLA – antiphospholipid antibody

APSAC – anisoylated plasminogen streptokinase activator complex

APTT – activated partial thromboplastin time

BP – blood pressure

CAD – coronary artery disease

CBC – complete blood cell

CHF – congestive heart failure

CVL – central venous line

DBP – diastolic blood pressure

DVT – deep vein thrombosis

ES – elastic stockings

GP – glycoprotein

HIT – heparin-induced thrombocytopenia

INR – international normalized ratio

IPC – intermittent pneumatic compression

IUGR – intrauterine growth restriction

IV – intravenous

IVC – inferior vena cava

LDUH – low-dose unfractionated heparin

LMWH – low-molecular-weight heparin

LV – left ventricular

MI – myocardial infarction

NSR – normal sinus rhythm

PCI – percutaneous intervention

PE – pulmonary embolism

PFO – patent foramen ovale

PT – prothrombin time

RCT – randomized controlled trial

rPA – reteplase

rtPA – recombinant tissue plasminogen activator

SBP – systolic blood pressure

SC – subcutaneous

SK – streptokinase

TEE – transesophageal echocardiography

TIA – transient ischemic attack

TNK-PA – tenecteplase

tPA – tissue plasminogen activator

UFH – unfractionated heparin

VTE – venous thromboembolism

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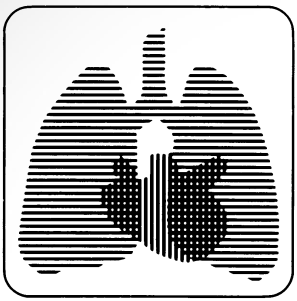

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